12 December 2019
EMA/23630/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Beovu

International non-proprietary name: brolucizumab

Procedure No. EMEA/H/C/004913/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Beovu
Applicant:	Novartis Europharm Limited Vista Building Elm Park Merrion Road Dublin 4 IRELAND
Active substance:	BROLUCIZUMAB
International Non-proprietary Name/Common Name:	brolucizumab
Pharmaco-therapeutic group (ATC Code):	S01LA06
Therapeutic indication(s):	Beovu is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD).
Pharmaceutical form(s):	Solution for injection
Strength(s):	120 mg/ml
Route(s) of administration:	Intravitreal use
Packaging:	pre-filled syringe (glass) and vial (glass)
Package size(s):	1 pre-filled syringe and 1 vial + 1 needle

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List of abbreviations

ADA	Anti-drug antibody
AEX	Anion exchange chromatography
AUC	Analytical ultracentrifugation
BDP	Bulk drug product
$BREC_S$	Bovine retinal endothelial cells
CD	Circular dichroism
CE-SDS	Capillary electrophoresis-sodium dodecyl sulfate
Cmax	The observed maximum serum concentration following drug administration
CNV	Choroidal neovascularization
CPP	Critical Process Parameter
DLS	Dynamic Light Scattering
DP	Drug Product
DS	Drug Substance
ECH	Ethylene chlorohydrin
ELISA	Enzyme-linked Immunosorbent assay
ERG	Electroretinogram
ETO	Ethylene oxide
EU	Endotoxin Unit
FT-IR	Fourier transform infrared
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GMT	Geometric mean
HCP	Host cell protein
HRECs	Human retinal endothelial cells
HUVEC	Human umbilical vein endothelial cells
hVEGF	Human vascular endothelial growth factor
IOP	Intraocular pressure
IP	Intraperitoneal

IPTG	Isopropyl β-D-1-thiogalactopyranoside
IVT	Intravitreal
LIVCA	Limit of in vitro cell age
MCB	Master Cell Bank
nAMD	Neovascular age related macular degeneration
NOAEL	No observed adverse effect level
NOR	Normal acceptable range
NV	Neovascularization
OD	Ocularis dexter
OIR	Oxygen induced retinopathy
OS	Ocularis sinister
PAR	Proven acceptable range
PFS	Prefilled syringe
PTFE	Polytetrafluoroethylene
QTPP	Quality target product profile
scFv	monoclonal single-chain Fv fragment
SCT	Safety Concern Threshold
SD	Standard deviation
SDS-PAGE	sodium dodecyl sulfate-polyacrylamide gel electrophoresis
SEC	Size exclusion chromatography
SPR	Surface Plasmon Resonance
SST	System Suitability Test
UF/DF	Ultrafiltration/Diafiltration
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor
VP-DSC	Valerian-Plotnikov differential scanning calorimetry
WCB	Working Cell Bank
WFI	Water for injections

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Limited submitted on 6 February 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Beovu through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 September 2017.

The applicant applied for the following indication: indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (nAMD).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/0001/2015 on the granting of a class waiver.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance brolucizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific Advice on the development for the indication 'treatment of neovascular age-related macular degeneration' from the CHMP on 19 September 2013. The Scientific Advice pertained to the following quality, preclinical and clinical aspects of the dossier.

To summarise, the applicant asked for advice concerning

- Evidence for comparability following manufacturing changes, specification, and stability
- Approaches regarding ocular and systemic toxicity, carcinogenicity and reproductive toxicity

- Pharmacokinetic studies, proposed dose and regimen, number and design of the confirmatory clinical trials, including timing and nature of the primary endpoint, non-inferiority margin, masking, and the submission plan.

12 October 2017, the applicant returned for follow-up advice on quality aspects regarding comparability evidence regarding manufacturing changes, and stability.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau, Co-Rapporteur: Maria Concepcion Prieto Yerro

The application was received by the EMA on	6 February 2019
The procedure started on	28 February 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	27 May 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	30 May 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	3 June 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 June 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 August 2019
The Rapporteurs circulated the D150 Joint Assessment Report on the responses to the List of Questions to all CHMP members on	24 September 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	2 October 2019
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	17 October 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	12 November 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	28 November 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Beovu on	12 December 2019

2. Scientific discussion

2.1. Problem statement

Age-related macular degeneration (AMD) is a chronic eye disease characterized by progressive degenerative abnormalities in the central retina (macula).

2.1.1. Disease or condition

Age-related macular degeneration (AMD) is a chronic eye disease characterized by progressive degenerative abnormalities in the central retina (macula).

Two stages are known for this disease:

- early AMD, which is characterized by drusen and pigmentary changes,
- late AMD, which can be distinguished in 2 subtypes — geographic atrophy (GA) and choroidal neovascularization (CNV). The neovascular subtype of AMD (neovascular AMD or wet AMD) is known to cause particularly rapid and devastating vision loss for these individuals. Vision loss results from the abnormal growth and leakage of blood vessels in the macula, leading to legally blindness.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Neovascular AMD (nAMD) is the leading cause of severe vision loss worldwide, affecting 10% to 13% of individuals over the age of 65 in North America, Europe, and Australia. It is suggested that almost 16% of patients with nAMD would become legally blind in 2 years without treatment and that the prevalence rates of late AMD are in European is around 2.5%.

Although the neovascular form of the disease is only present in about 10% of all AMD cases, it accounted for approximately 90% of the severe vision loss from AMD prior to the introduction of anti-vascular endothelial growth factor (VEGF) treatments.

Neovascular AMD generally onsets in individuals older than 50 years of age. It is suggested that 10% of individuals aged 65 to 74 years, and 30% of those aged 75 to 85 years, show signs of AMD.

Major observed risk factors include cigarette smoking, nutritional factors, cardiovascular diseases, and genetic predisposition.

2.1.3. Aetiology and pathogenesis

Although aetiology and pathogenesis remain not fully elucidated, main factor of progression of AMD remains age genetic predisposition and cigarette smoking.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

AMD is a disease of the photoreceptors and the retinal pigment epithelium (RPE). In the aging eye, Bruch's membrane composition changes, and RPE function diminishes. Because of reduced RPE function, drusen deposits at the level of the RPE and photoreceptors accumulate. Drusen contain lipofuscin and other toxic waste products of metabolism.

In AMD, Bruch's membrane ruptures associated with a localized inflammatory response and vascular endothelial growth factor (VEGF) is released, which induces choroidal neovascularization (CNV). The CNV is a membrane of abnormal and leaky blood vessels, growing from the choroid through the defects in Bruch's membrane underneath the RPE and the retina. These new, immature blood vessels leak lipids, fluid and blood. This causes oedema and elevation of the retina, resulting in blurring and distortion of vision. Onset of visual dysfunction in nAMD is acute and progresses within a few weeks or even more accelerated particularly if bleeding occurs. With bleeding under the retina or persistent oedema, the loss of central vision becomes permanent leading to patients who are not able to read, watch TV, drive a car or recognize faces.

The damage to the retina due to neovascularisation results in progressive, severe, and irreversible vision loss, metamorphopsia, scotoma, photopsia, and difficulties in dark adaptation. Without treatment, most affected eyes will have poor central vision (20/200) within 12 months.

Neovascular AMD is classified into three subtypes: classic, occult, and minimally classic lesions. However, it seems that progression of neovascular lesion sizes appears to be independent of lesion subtypes.

The main determinant of choroidal neovascularization lesion size enlargement is the duration of exudative disease. The gold standard to diagnostic nAMD is the fluorescein angiography. Additionally, optical coherence tomography (OCT) is a useful complementary imagery which allow to identify the presence of subretinal fluid and the central retinal thickness.

2.1.5. Management

To date, intravitreal anti-VEGF therapies are the standard of care. Two anti-VEGF therapies authorized in the treatment of neovascular AMD are available on the market: ranibizumab (Lucentis®) and aflibercept (Eylea®).

Previous therapy approaches such as surgical therapies, radiotherapy or laser photocoagulation, or even photodynamic therapy (PDT) using verteporfin are not frequently used anymore.

VEGF are angiogenic factors which are found elevated in patients with nAMD. They play a key role in the neovascularization process. Anti-VEGF inhibit VEGF signalling pathways and have been shown to halt the growth of neovascular lesions and resolve retinal oedema in patients with nAMD.

Ranibizumab

Lucentis® is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A).

The treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity. Initially, three or more consecutive, monthly injections may be needed. Thereafter, monitoring and treatment intervals should be determined by the physician.

Aflibercept

Eylea® is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1, bidding VEGFA, VEGFB and PlGF.

Aflibercept is initiated with a launching phase of 3 monthly injections. The treatment interval is then extended to two months. Based on the physician's judgement of visual acuity and/or anatomic parameters, the treatment interval may be maintained at two months or further extended.

About the product

Brolucizumab (RTH258, ESBA1008, AL-86810) is a humanized single-chain Fv (scFv) antibody fragment with a molecular weight of ~26 kDa which inhibits vascular endothelial growth factor A (VEGF-A) binding to VEGF receptors VEGFR1 and VEGFR2. Inhibition of the VEGF pathway has been shown to inhibit the growth of neovascular lesions and resolve retinal oedema in patients with nAMD resulting in improved and/or maintained visual function.

Brolucizumab is developed for ophthalmic use and is administered by intravitreal injection. The smaller molecular size of the scFvs as compared to whole antibodies or larger antibody fragments enables delivery of a high molar dose to the limited volume of the vitreous body, which may enable better tissue penetration at the retina and prolong the therapeutic effect. It is intended to maintain long-term efficacy while reducing the frequency of treatment and monitoring visits, thereby reducing the treatment and monitoring burden.

Aspects on development

CHMP Guidance

There is no CHMP guidance for the development of drugs in this pathology and target population.

Clinical development

The brolucizumab clinical development program provides extensive clinical data of up to 2 years treatment duration in 2202 subjects with neovascular age-related macular degeneration in 7 clinical trials, including 1355 subjects who received brolucizumab. The results of the two studies in the Phase I/II program (C-10-083 [SEE study]) and Study C- 12-006 [OSPREY study]) were used to support the dose and regimen selection for the Phase III trials. The Phase III program is based on 2 randomized, double-masked, multicentre, active-control (versus aflibercept 2 mg) pivotal studies (RTH258-C001 [HAWK study] and RTH258-C002 [HARRIER study]) to evaluate the safety and efficacy of brolucizumab administrated intravitreally. Two doses were investigated, 3 mg and 6 mg.

2.2. Quality aspects

2.2.1. Introduction

The finished product (FP) Beovu is presented as a solution for injection containing 6 mg (120 mg/mL) of brolucizumab as active substance.

Other ingredients are: sucrose, sodium citrate, polysorbate 80, sodium hydroxide and water for injections.

The product is available in a vial (Type 1 glass, colourless) with a coated rubber stopper sealed with an aluminium cap with a purple plastic flip-off disk. The product is also available in a pre-filled syringe consisting of a long clear, colourless glass syringe, rubber plunger stopper, an a tamper-evident closure system containing a rubber tip cap and a purple finger grip. The injected volume is 0.05 mL per eye.

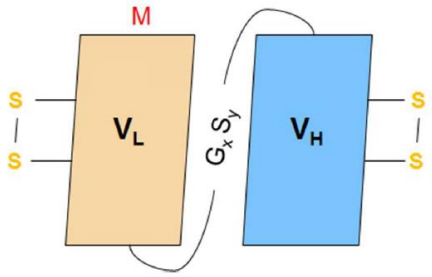
Although this dossier is not considered a Quality by Design application, certain elements of an enhanced approached were applied.

2.2.2. Active substance

General information

Brolucizumab is a recombinant humanised single-chain Fv (scFv) antibody fragment which inhibits vascular endothelial growth factor-A (VEGF-A) binding to its receptors VEGFR1 and VEGFR2. It is expressed in an *E. coli* BL21(DE3) and consists of a light chain fragment and a heavy chain fragment, which belong to the human kappa and VH3 subtypes respectively. Both chains are connected via a flexible glycine / serine linker. The molecular sum formula of brolucizumab is $C_{1164}H_{1768}N_{310}O372S_8$.

Figure 1: Brolucizumab single-chain Fv (scFv)



Manufacture, process controls and characterisation

Brolucizumab active substance is manufactured by Lonza AG, Visp in Switzerland. All relevant active substance sites have valid manufacturing authorisations or valid GMP certificates.

Brolucizumab solution for injection in a prefilled syringe is manufactured by Alcon-Couvreur N.V., Belgium. The solution for injection in a glass vial is manufactured in Novartis Pharma Stein AG, Switzerland.

Description of manufacturing process and process controls

Brolucizumab active substance manufacturing process has been adequately described. Main steps are fermentation, harvest and inclusion body (IB) solubilisation and isolation, several chromatographic purifications, filtration and filling. The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step. The active substance manufacturing process is considered acceptable.

Description of the manufacturing process and controls are appropriately detailed with a satisfactory list of process parameters and in-process controls (IPCs). Definition of batch and its scale are provided.

Brolucizumab active substance is manufactured according to a fed batch mode culture. The upstream process (USP) starts with the thawing of one vial of working cell bank (WCB) followed by expansion steps and then culture in the production bioreactor (15000 L). At a defined cell density, the induction of protein expression is triggered. After incubation, the cells are separated from the fermentation media by disc stack centrifugation. The inclusion bodies are then isolated by various washes followed by a centrifugation step each time. The isolated IBs can be stored at 4 – 12°C for up to 168 hours prior to solubilisation. The protein is then solubilised and reduced followed by renaturation of the unfolded protein by dilution into a refolding buffer. The refolded protein may be stored at 15-25°C for up to 48 hours. After the refolding step the protein solution is filtered through a depth and bioburden reduction filter before starting the first purification step.

The downstream manufacturing process (DSP) includes 3 chromatography steps, 2 ultrafiltration/diafiltration steps and one last ultrafiltration to further concentrate the protein solution.

At the end of the manufacturing process, the active substance is pre-formulated with sodium citrate, sucrose and 0.01g/L polysorbate 80. It is then filtered through a 0.2 μm filter into PETG bottles, stored at $\leq$-65° C and shipped to the finished product manufacturing sites. No reprocessing is foreseen.

The active substance is stored in 1L PETG bottle fitted with a HDPE screw cap. The bottles and caps are sterilised via validated gamma radiation within the range 20-45 kGy. They are compliant with the corresponding Ph. Eur. Monographs.

Critical steps of the brolucizumab active substance manufacturing process are controlled by in-processs controls (IPC) with action limits or acceptance criteria. A justification based on the results obtained from process development, process characterisation at small scale, control strategy and manufacturing process capabilities, was submitted for the action limits and the acceptance criteria.

In the upstream process there are no IPCs with action limit and two IPCs with acceptance criteria, i.e. culture purity and culture identity at the seed fermentation and at the main fermentation. In the downstream process no IPCs are monitored with acceptance criteria. The endotoxin and bioburden are controlled with action limits at each step. This classification is acceptable.

For both the upstream and downstream processes the process parameters (PP) are classified as critical (CPP) and non-critical (non-CPP). The non-CPP are further classified into key-PP (KPP) and non-KPP, KPP being a non-CPP which has an impact on process performance indicator but not on critical quality attributes and which should be monitored or controlled to ensure process performance or consistency. A non-KPP is a non-CPP whose considered variability has no impact on either a CQA or a performance indicator. Both CPPs and non-CPPs are defined by acceptable ranges (AR) that correspond to an interval over which a parameter may vary in the process without leading to unexpected product quality and process performance regardless of their classification.

In the process characterisation studies it can be seen that the AR applied to the process parameters correspond to proven acceptable ranges (PAR), which is acceptable.

Control of materials

Cells of the BL21 (DE3) *E. coli* strain were used as parental cell line, from which the brolucizumab production cell line and cell banks for the expression of the protein of interest were derived. The competent cells were purchased from Invitrogen (Carlsbad, USA). The gene sequence coding for brolucizumab was genetically engineered by grafting the complementarity determining regions (CDRs) and specific framework residues from heavy and light chain variable region sequences of a monoclonal rabbit anti-human VEGF antibody to human heavy and light chain variable region frameworks, covalently linked by a flexible amino acid sequence consisting of glycine and serine. For cloning of the brolucizumab expression vector pGMP ESBA1008, the vector backbone of pET-24d(+), a commercially available *E. coli* expression vector from Novagen, was used. The insert was synthetically created. The cloning of the expression vector, pGMP ESBA1008, was done in several sequential steps described in the dossier.

Plasmid pGMP ESBA1008 with the coding sequence of brolucizumab was transformed into commercially available competent *E. coli* BL21 (DE3) cells by heat shock transformation to generate the brolucizumab production cell line.

A detailed listing of raw materials, filters and membranes used in the active substance manufacturing process is presented. Raw materials are tested according to European Pharmacopeia, USP or in-house monographs. Regarding the non compendial raw materials, the specifications are given. The composition of the different culture media used for the inoculum, the expansion and the main fermentation is also presented. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

Cell banks

Information on the origin of the host cell line, on the development genetics (including origin of the gene, description of the gene construct) and on the establishment of the cell banks is provided. A two-tiered system cell banking was established for commercial production. The banking procedure was adequately presented and characterisation was performed in accordance with ICH Q5D guideline. The protocol of establishment for new WCBs was also provided. The genetic cell bank stability of the production cell line was appropriately demonstrated.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the brolucizumab active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified. There are no active substance intermediates isolated in the manufacturing process of brolucizumab.

The control strategy presented was based on quality attributes, criticality, process control capability and the testing strategy. The integrated control strategy incorporated also control elements including process parameters, in-process controls, release specifications, and periodic testing controls (e.g., validation, comparability, stability) of the active substance and finished product. This reflects knowledge of CQAs and their potential to impact patient safety and product efficacy, as well as an understanding of the means by which these attributes are controlled during manufacturing and through shelf-life. A list of brolucizumab CQAs provided with the control elements in place to control each CQA was provided. The information provided regarding assigned CQAs and the control strategy is sufficient.

Prior to execution of the process characterisation studies, a FMEA (Failure mode and effects analysis) risk assessment was performed for each unit operation of the brolucizumab active substance manufacturing process to identify potential critical process parameters and / or potential key process parameters. The assessment was performed based on experiences gained during early phase process development, clinical manufacturing, experience on platform knowledge, or described in general literature. Then the potential KPP/CPPs were further analysed in the process characterisation studies based on univariate and multivariate small-scale studies. Statistical significance and extent of impact (sensitivity) on the output parameters (process performance and / or critical quality attributes) of each process parameter within its PAR were evaluated.

Based on the statistical analysis the process parameters were classified as KPP or CPP. The proposed classification was not entirely endorsed. Indeed for a process parameter that can have an impact between 10%-30% on an output parameter, the score is 3 if $p>0.1$ (meaning no impact) and 3 if p is between 0.05 and 0.1 (meaning moderate impact); in both cases the parameter is classified as a non-KPP. From a general point of view, if a process parameter impacts a CQA, it should be considered as a CPP even if the impact is

low (ICH Q8(R2)). However, taking into account that these parameters are mentioned and controlled in section S.2.2, no concern was raised.

Process validation

Process validation consisted of analysing three consecutive full-scale batches of brolucizumab, for the different steps of the upstream and downstream processes. An additional commercial batch corresponding to cells cultured at the extended cell age, was also analysed to validate the LIVCA (Limit of In Vitro Cell Age) corresponding to the number of generations from the MCB.

Critical and key process parameters, as well as in-process controls and additional tests were investigated in this validation. Validation batch data were generally well aligned within narrow ranges, well above/below/within the acceptable ranges, acceptance criteria or action limits. These results showed that the active substance manufacturing process will ensure consistency in production at commercial scale.

Detailed reports were also adequately provided for the scale down model (SDM) used for the impurities depletion studies and in the proces characterisation studies.

To assess the depletion capacity of the manufacturing process for process-related impurities (HCP, host cell DNA, culture media and buffer components removal), validation studies for removal of those impurities were performed and samples taken from different process steps were monitored. Spiking studies were also performed for the HCP and host cell DNA. The current manufacturing process was found capable of effectively and consistently reducing these impurities to low levels. Most of the process-related impurities were below the LOQ and below the safety concern threshold (SCT) of 1.5µg/day.

As regards the extractables and leachables, a risk assessment including a toxicological assessment was performed for the materials that are in contact with the product, process pools, buffers, media or solutions used for the manufacturing of brolucizumab active substance. Based on the comprehensive risk assessment, and the simulated in-use leachable study, it can be concluded that materials used in the manufacturing and storage of brolucizumab active substance have no risk of leachables in the active substance.

Manufacturing process development

The process development history is described in sufficient detail. Five versions of the active substance manufacturing process have been used during the clinical development: Process A (toxicological, clinical phase 1), Process B (toxicological), Process C (clinical phase 2), Process F (toxicological, clinical phase 3) and Process G (clinical phase 3 extension study, commercial). Processes D and E were used for research purposes. No batches from these two processes were used in non-clinical or clinical studies.

Major changes to the USP mainly focused on the need of increasing the production scale.

Major changes to the DSP were mainly triggered by active substance formulation change and adaptions needed due to manufacturing site change. During early phase clinical development, a maximum dose of 6 mg per eye was targeted using a 100 µL injection volume. In order to reduce the injection volume to 50 µL per eye, the active substance protein concentration was increased from 60 mg/mL (process A) to 127 mg/mL. The active substance formulation buffer composition was also changed to accommodate the higher protein concentration. As a risk mitigation strategy during process development, the active substance formulation was changed first without drastically increasing the protein concentration (process B). The active substance protein concentration was subsequently increased to 127 mg/mL (process C). After the process was transferred from Biomeva GmbH, Heidelberg, Germany site to Lonza AG, Visp, Switzerland site, the DSP was further adapted to accommodate equipment differences (process F). Subsequently, active substance

composition was modified to support the finished product manufacturing. DSP was adapted to support the composition change, as well as to accommodate the increase of production scale (process G). Process G is the intended commercial manufacturing process.

Comparability between processes F and G was assessed according to ICH Q5E, by analytical testing with a focus on process performance analysis, release testing, characterisation and comparative stability studies.

Five process F active substance batches and three process G active substance batches were used. Although minor differences were detected reasonably explained, the comparability exercise is considered approvable based on the totality of data.

Characterisation

Brolucizumab has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a humanised single-chain Fv (scFv) antibody fragment. The analytical results are consistent with the proposed structure. Furthermore, heterogeneity of the active substance was adequately characterised by analysing size and charge variants, and other product-related substances and impurities. Biological characterisation of Brolucizumab indicates that this antibody has the ability to bind human VEGF with high affinity as expected. Potency of brolucizumab was determined by its capacity to inhibit VEGF-induced proliferation of human umbilical vein endothelial cells (HUVECs). In summary, the characterisation is considered appropriate for this type of molecule.

Biochemical, biophysical, and biological characterisation of Brolucizumab was conducted to provide a comprehensive understanding of the structural (primary and higher order structure, heterogeneity pattern, purity and impurities) and functional properties and to enable an assessment of the product quality attributes. The characterisation studies were completed in the responses to LoQ with the amino acid composition analysis, the N-terminal and C-terminal amino-acid sequencing and the extinction coefficient. Forced degradation studies were performed to reveal potential degradation pathways.

Brolucizumab binding to antigen VEGF was demonstrated by the ELISA assay. High affinity binding of brolucizumab active substance batches was characterized using the cell based potency assay, ELISA potency assay and surface plasmon resonance binding assays. The ability of brolucizumab to bind to VEGF-A isoforms was determined by the SPR while no binding was observed for VEGF-C, VEGF-D and PlGF (Placenta growth factor). The potency assay corresponds to a cell-based assay which determined the capacity of brolucizumab to inhibit VEGF-induced proliferation of HUVEC cells.

Forced degradation studies were performed on brolucizumab active substance and finished product for elucidation of degradation pathways of brolucizumab after exposure to acidic pH, basic pH, temperature, oxidative agents, light, freeze/thaw and shaking stress. These studies identified the product-related substances and product related impurities. The potency assay has been demonstrated to be sensitive to molecular changes induced by thermal stress and UV light stress. Instead, samples subjected to acidic and basic pH stressed thermal, oxidative stress retained potency.

Specification

The specifications for brolucizumab active substance are: appearance (turbidimetry, colour, pH, osmolality), Identity (AEX, peptide mapping), purity and impurities (SEC, AEX, CE-SDS), potency (proliferation assay) and Quantity (UV, polysorbate 80).

The active substance specifications are based on clinical and toxicological manufacturing experience, process validation data, analytical method capabilities, characterisation of brolucizumab, release and stability testing results, release and end of shelf life specifications, statistical analysis and ICH and USP/Ph.Eur./JP monographs guidelines.

In order to establish the acceptance criteria of brolucizumab active substance, the applicant proposed a statistical analysis of the data based on the calculated tolerance intervals (95/99.9), obtained using historical data. The TI applied is considered acceptable based on the historical data used. Most of the active substance acceptance criteria were found satisfactory.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. Regarding the non-compendial analytical methods, additional data and justifications were provided in the responses to the LoQ and are considered satisfactory.

Batch analysis

Batch analyses are presented for batches manufactured according to all processes used in clinical trials, toxicological studies, primary stability studies, process validation and/or intended for commercial use, with using historical bathes. The information provided on the batches is sufficient. All data comply with the active substance commercial specification and results were close between batches, which demonstrates consistency in the active substance manufacturing process.

Reference materials

A two-tier reference standard was established for the control of brolucizumab active substance and finished product. The current primary reference standard (PRS) was produced from active substance manufactured according to commercial process and tested against the previous PRS. The specification of the PRS complies with the commercial active substance specification except for: the HCP, the polysorbate 80, the microbial enumeration test and bacterial endotoxin test which are not tested and the potency acceptance criteria which is tightener. The testing strategy of the company is endorsed. Appropriate extensive characterisation studies were also performed and submitted showing comparability to the previous PRS. The current working (WRS) was manufactured according to commercial process and tested and released against the current PRS. To qualify future primary and working reference standards, including the potency assignment, the Applicant's proposal was completed in response to the LoQ and is now considered appropriate.

Stability

The company claims a 2-year shelf-life for the active substance, when stored below -60°C.

This claim is based on the data obtained from three clinical active substance batches manufactured according to the proposed commercial process for which 24 months data are available. Stability data were also provided for the process validation active substance batches for which 6 months were available under the long term storage conditions. In addition, accelerated (5±3°C) studies were also conducted for all batches and stressed studies (25°C ± 2°C/60% ± 5%RH) only for the clinical batches.

Under the accelerated conditions, 6-month data are available for all batches. Under the stress conditions, 6-month data are also available. The trends were similar for the three batches.

In conclusion, a 2-year shelf-life below -60ºC for active substance can be granted. The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container.

Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Vials

Brolucizumab finished product is supplied as a sterile, single-use, preservative-free, colourless to slightly brownish yellow solution for injection in a vial. The Type I glass vial is closed with a rubber stopper and sealed with an aluminium cap with a flip-off disk. The vial is co-packaged with a filter needle. Another presentation, a prefilled syringe, is also available and is described in a separate 3.2.P section. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The composition of the intended commercial formulation is 120 mg/mL brolucizumab, polysorbate 80 (0.02%), sodium citrate (10 mM), sucrose (5.8%), and Water for Injection. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

The quality target product profile (QTPP) of the finished product was presented, as well as the quality attributes based on it. For each quality attribute, a criticality score was calculated based on a criticality assessment. For the API-related (i.e. product-related variants) quality attribute scoring, please refer to the comments related to the active substance. The non API-related and FP-related attributes are bioburden, endotoxin, HCP, DNA, colour, safety relevant soluble raw materials (process-related impurities and leachables), turbidity / clarity, container closure integrity, sterility, subvisible particles, visible particles, API concentration, polysorbate 80 concentration, extractable volume, osmolality, pH, sucrose and citrate concentrations.

There is no overage in the finished product. An overfill is present to allow for the minimal delivered volume. The chosen volume (0.230 mL ± 4%) was justified based on a handling study showing that for the worst-case users, 220 µL is needed to allow the withdrawal of minimum 50.1 µL. This justification is deemed acceptable.

During development, three formulations were successively used. The initial formulation used in the phase 1 clinical trial was changed for a new formulation (formulation A) at 120 mg/mL, to avoid aggregation, which was used for phase 2 and phase 3 clinical trials. Then formulation B was developed to prevent the formation of visible particles during storage, by increasing the pH and by decreasing the polysorbate concentration. This last formulation, with active substance from process G (commercial process), was used during the phase 3 extension clinical trial. Between the phase 3 extension and the intended commercial process and formulation, the only change is the manufacturing scale. A comparability study between batches of formulation A and formulation B (pilot scale and commercial scale) was performed and confirmed that, apart from the improved stability profile, no other quality difference is noted.

Pharmaceutical development was based on laboratory scale studies and robustness studies conducted on the pre-validation batches manufactured in worst-case conditions. The provided data were completed in the responses to the LoQ with data regarding stirring parameters, flushing volumes, crystallised and aggregated protein.

Leachables from Pt-cured silicone and PTFE tubing materials as well as the microbial and sterile filters were measured using 0.1% polysorbate 20 solution and were all lower than the safety concern threshold of 1.5 µg/ 100 µL.

To justify the appropriateness of the container closure system, the absence of adsorption of the active substance on the container materials was confirmed during stability studies in inverted vials, by protein content measurement. An extractable study was performed with a 0.1% polysorbate 20 surrogate solution. All the extracted compound concentrations were below the safety concern threshold (1.5 µg / 100 µL finished product). Moreover, the vials containing the surrogate solution were stored inverted for 36 months at 2-8°C. Analysis of leachables, elements and silicone showed no compound with concentrations exceeding the safety concern threshold. A summary of the risk assessment for elemental impurities, as requested in ICH Q3D, was provided in the responses to the LoQ. These data are considered sufficient.

In-use stability and compatibility were verified with several delivery devices (polypropylene/polystyrene, polypropylene, or polycarbonate syringes, blunt filter needle, 32G or 30G injection needle). All the results were comparable before and after incubation in the container plus incubation in the syringes, showing compatibility with all the tested configurations.

Prefilled syringe

Finished product in prefilled syringe has the same qualitative and quantitative composition as in vials. The primary packaging consists in Type I glass barrel closed with a plunger stopper and a tamper evident closure system.

The QTPP of the finished product in prefilled syringe is identical to the QTPP for the vial with additional attributes (outer sterility of the prefilled syringe, ethylene oxide, break out and sliding force, residual silicone), which were all classified as critical.

The proposed overfill (target fill volume of 165 µL) covers the dead volume of the assembly of injection needle and syringe, plus the volume for priming and the volume remaining in the tip cap. The dosing accuracy was satisfactory at temperatures ranging from 15 to 30°C.

The manufacturing process development of the prefilled syringe was based on the work performed for the finished product in vial. The manufacturing process differences are principally related to site adaptations (batch size, compounding parameters, filtration through sterile filters) or related to additional steps (prefilled syringe assembly, blistering, sterilization of the outer surface of the syringes). A comparability study between finished product in vials and in prefilled syringe was provided: no quality differences were noted.

Unlike finished product in vials, the slight filter adsorption has no final impact on the product as the filtered BDP is collected in a vessel and stirred before filling. Filtration studies confirming the pressure range were also performed.

Manufacturing process development studies were also performed on siliconization of the syringe barrel and of the plunger stopper, the correct placement of the tip cap on the glass barrel, the confirmation of the filling process, and the appropriate position of the plunger stopper. The process parameters for blister sealing were qualified.

As regards development of the outer surface sterilisation of the prefilled syringe, the sensitivity of the finished product to heat had to be taken into account into the sterilisation process settings. Decrease of ETO sterilisation temperature with increased contact time were used and qualified based on ISO 11135:2014. It was confirmed that the quality of the product (including stability) was maintained when using the worst case conditions of the setting. The provided data and information are satisfactory. Moreover, the Applicant justified in the responses to LoQ that only ETO sterilisation was found capable to sterilise while preserving the quality of the product.

Leachables from tubing materials and from filters were measured and were all lower than the safety concern threshold of 1.5 µg/ treatment. This is acceptable. Physico-chemical hold times were confirmed on a pre-validation batch. As for the vials, robustness studies showed that turbid vials can be detected and contain some proteinaceous particles, leading to the definition of controls for the 100% visual inspection, which were detailed upon request.

The container closure system was confirmed to be suitable as regards absence of protein adsorption, absence of extractable compounds above the safety concern threshold, and elemental impurities in accordance to ICH Q3D.

Compatibility of finished product in prefilled syringe with tungsten (from tungsten pin used to form the syringe bore), silicone oil, and ethylene oxide was confirmed by spiking studies. The spiked levels are considered sufficiently justified. The long term stability of the spiked finished product was also confirmed.

Compatibility of the finished product with the injection needles was confirmed with finished product in vials, which is sufficient.

Manufacture of the product and process controls

The finished product in vials is manufactured at Novartis Pharma AG (Stein, Switzerland) while the prefilled syringes are manufactured in Alcon-Couvreur N.V. (Belgium). Manufacturing authorizations and GMP certificates can be found on EudraGMP.

The batch formula was provided for the target batch size of bulk finished product (BFP), which is in line with the batch size of the validation batches.

The manufacturing process consists of thawing of active substance, dilution with an excipient dilution solution and pH adjustment, adding of WFI to reach the final batch size and pH adjustment, pre-filtration, sterile filtration, filling, capping and sealing of the vials, which are 100% inspected. The process parameters and in-process controls were provided with associated targets and ranges. Chemical and microbiological hold times were also defined. Overall the manufacturing process description was adequately completed.

The critical steps were defined with process parameters / in-process controls involved in the control of the quality of the product. They included speed and time after each addition in the BFP, control of pH and endotoxins, filter integrity test after sterile filtration and fill weight.

Classification and justification for PARs, if wider than NORs, were listed for each process step.

Validation batches at commercial scale were manufactured most of which met the acceptance criteria. Process validation was completed with the following studies: filter retention capacity; validation of vial crimping machine; media fill tests; sterilisation and depyrogenation of the vials and sterilisation of the stoppers. It has been demonstrated that the manufacturing process is capable of producing finished product of the intended quality in a reproducible manner. The in-process controls are adequate.

Maximal hold times were validated on a pre-validation batch at commercial scale, except for filter contact time. The filter contact time was studied during the filter retention capacity test in the bulk product, confirming that the microbiological hold time is acceptable. The maximal active substance hold time and compounding hold time were used during the first validation batch, confirming the proposed limits for these hold times.

Transportation of the packaged finished product was validated by temperature excursion studies and qualification of the shipping containers showing adequate quality after worst case configuration of transportation conditions.

Product specification

All excipients are compendial. Specifications for excipients have additional endotoxin and microbial tests performed on sucrose, sodium citrate and polysorbate 80. Peroxide limit for polysorbate 80 is tighter than the compendial limit.

Release and shelf-life specifications for the finished product, as well as description of the analytical procedures were provided.

The proposed acceptance criteria are appropriately justified. The primary and secondary packaging components were described. For each component, the material of construction, supplier, compliance status, specifications, batch analysis data and drawings were provided.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch analyses were presented for historical batches. It was confirmed upon request that pooling of active substance batches will be performed in routine.

Justification of acceptance criteria was based on formulation A and B batches or on formulation B batches only, depending on the impact of the formulation on each parameter. Statistical analysis was used to determine whether a significant slope was present during long-term storage. Acceptance criteria based on tolerance intervals (95/99.9) were proposed for some parameters. The acceptance criteria were tightened according to batch results.

The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

The reference standard used for release and stability testing of the finished products is the same adopted for the release and stability testing of brolucizumab active substance.

Stability of the product

The company claims a 24 month shelf-life for both presentations, when stored 2 – 8 °C protected from light.

Long-term (5±3°C) and accelerated (25±2°C / 60±5% RH and 30±2°C / 75±5% RH) stability studies are ongoing for 3 pilot batches, differing from commercial batches only by the batch size, and for the 3 validation batches. Comparability between the pilot and the commercial batches was demonstrated. Trends were observed, but all the results remained well within the finished product shelf-life specifications. Changes to purity levels seen at accelerated (25°C ± 2°C / 60% ± 5% RH and 30°C ± 2°C / 75% ± 5% RH) storage conditions are in the range expected for these conditions. Furthermore, the stability behaviour and degradation profiles are comparable for all three registration batches. So, the claimed 24-month shelf-life can be granted.

Stability of the product upon shaking and temperature excursions before long term storage was demonstrated. Photostability was studied, showing that the product should be stored protected from light in the secondary packaging. The in-use stability study confirmed that the finished product can be stored for 24 hours at ambient temperature with normal office light. Consequently, the SmpC contains the following instruction: Prior to use, the unopened blister which contains the pre-filled syringe, or the unopened vial may be kept at room temperature (below 25°C) for up to 24 hours.

The parameters tested for all stability studies were appearance and description, purity by CE-SDS, AEX and SEC, Assay by UV, and potency by activity/inhibition.

Based on available stability data, the shelf-life of 24 month at 2 – 8 °C as stated in the SmPC are acceptable.

Medical device issues

The filter needle provided with the finished product in vials is a class I sterile medical device. The CE number was provided as well as the declaration of conformity.

Adventitious agents

The active substance, brolucizumab protein is a fusion protein manufactured via microbial fermentation utilizing recombinant *E. coli* BL 21 (DE3) host cells. No materials of human, animal or recombinant origin were used during the generation of brolucizumab master cell bank and working cell banks. Some compounds (yeast extract and Tryptone) used in the manufacturing process and consumables are tallow-derived and comply with EMA's Guidance (EMA/410/01 vers 3). The data provided are satisfactory concerning the viral adventitious aspect and the TSE risk.

GMO

Not applicable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product is expected to have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

In support of the MAA, the applicant submitted a full non-clinical dossier, in accordance with ICH M3 (R2) and ICHS6 (R1), investigating the pharmacological, pharmacokinetic and toxicological profiles of Brolucizumab.

2.3.2. Pharmacology

The pharmacology program included in vitro studies designed to characterize the binding affinity and specificity of brolucizumab to VEGF-A.

Table 1: List of in vitro pharmacology studies

Study Type	Test Species	Study Number	GLP status
Potency	*In vitro* human and bovine endothelial cells	[ESBATech study RDR_AssMo_0017.01 version 2.0]	non-GLP
		[Alcon study TDOC-0013037]	non-GLP
		[RD-2018-00365]	non-GLP
			non-GLP
Efficacy	Rat and mouse	[Alcon study TDOC-0013037]	non-GLP
Binding parameters affinity	*In vitro*	[ESBATech study RDR_AssMo_0017.01 version 2.0]	non-GLP
neutralizing potential	*In vitro*	[ESBATech study RDR_AssMo_0017.01 version 2.0]	non-GLP
isoform selectivity	*In vitro*	[ESBATech study RDR_AssMo_0016.01]	non-GLP
species specificity	*In vitro*	[ESBATech study	non-GLP
affinity & potency	*In vitro*	RDR_AssMo_0007.01]	non-GLP
		[RD-2018-00365]	non-GLP
		[RD-2018-00360]	non-GLP

Brolucizumab binds to the predominant isoform of human VEGF-A, VEGF165, as well as to two shorter VEGF-A isoforms (VEGF121, and VEGF110).

Characterization of the binding affinity of brolucizumab to three of the VEGF-A isoforms (VEGF165, VEGF121, and VEGF110) was performed by SPR analysis in an isoform selectivity study (ESBATech Study RDR_AssMo_0016.01). These isoforms correspond to the 3 major soluble forms of biologically active VEGF found in vivo.

Surface Plasmon Resonance (SPR) was used to determine the binding kinetics of brolucizumab for non-glycosylated and glycosylated rhVEGF-165 (ESBATech study RDR_AssMo_0017.01 version 2.0), which is the most abundant isoform of VEGF-A. For comparison, the binding kinetics of ranibizumab (Lucentis) to glycosylated rhVEGF-165 was also determined by Surface Plasmon Resonance (SPR)using the same analytical methods is (ESBATech study RDR_AssMo_0017.01 version 2.0). Blocking of the interaction of human VEGF165 with VEGFR-2 and VEGFR-1 by brolucizumab, therefore testing the neutralising potential was also studied by the applicant (ESBATech study RDR_AssMo_0017.01 version 2.0). In this study, Binding of

hVEGF-165 to plate immobilized VEGFR-2/Fc and VEGFR-1/Fc was measured in presence of a constant amount of rhVEGF-165 (1.3 nM and 5.2 nM, respectively) and varying concentrations of brolucizumab or ranibizumab (Lucentis).

Potency and affinity of brolucizumab in comparison with marketed anti VEGF inhibitors ranibizumab, bevacizumab and aflibercept was studied (Study RD-2018-00365). To evaluate potency, the anti-VEGFs were analysed for their ability to inhibit binding of VEGF-A to the VEGFR2 receptor and inhibit VEGF-A induced proliferation of human retinal endothelial cells (HREC). The binding kinetics and affinity were measured by SPR.

Complex formation of brolucizumab with human VEGF was analyzed by fluorescence emission spectroscopy (Study RD-2018-00360). Brolucizumab and human VEGF were diluted with dilution buffer to 1.02 and 0.96 µM respectively. In second step, brolucizumab was further diluted 1:20 to yield a final solution of 50 nM.

Species specificity (ESBATech study RDR_AssMo_0007.01) regarding VEGF sequence was also studied in order to determine the most relevant species for toxicology studies. Cross-reactivity of brolucizumab towards human, mouse, porcine, feline, and rabbit VEGF, in a direct ELISA test was performed. This study highlighted that brolucizumab did not bind to rabbit VEGF. These results showing a cross-reactivity towards mouse and rat VEGF allow assessment of ESBA 1008 efficacy in rat and mouse animal models such as the laser-induced CNV (choroidal neovascularization) during in vivo pharmacology studies. Moreover, since similarity of sequence has been demonstrated between human and primate, monkey was selected as the relevant species for toxicity studies. The affinity and kinetics of the interaction between brolucizumab and mouse, rat, rabbit, porcine, canine and feline VEGF were characterized using SPR technology.

The ability of brolucizumab to neutralize the biological activity of VEGF in cell cultures was demonstrated using endothelial cells from different sources, human umbilical vein endothelial cells (HUVECs) and human or bovine retinal endothelial cells (HRECs or BRECs) using standard assay methods. Similarly to ranibizumab, brolucizumab blocked VEGF induced proliferation of HUVECs and BRECs in a dose-dependent manner. IC50 values found in the HUVEC proliferation assay were 0.49 nM (12.7 ng/mL) for brolucizumab and 0.62 nM (29.8 ng/mL) for ranibizumab with glycosylated VEGF165. Compared to HUVECs, IC50 values determined in BRECs were slightly higher, 0.77 nM (20.0 ng/mL) for brolucizumab and 0.64 nM (30.7 ng/mL) for ranibizumab. In line with the proliferation assays, the potency of brolucizumab to inhibit VEGF-induced migration in HRECs is similar to that of ranibizumab IC50 of 0.09 nM (2.3 ng/mL) for brolucizumab and IC50 of 0.11 nM (5.3 ng/mL) for ranibizumab.

In addition to binding to human VEGF-A, brolucizumab also binds to rodent VEGF-A allowing for evaluation in rodent efficacy models.

The in vivo pharmacology of brolucizumab was assessed in three different surrogate rodent models (mice and neonatal and adult rats). All the in vivo models are aimed to reproduce the features of VEGF-induced vascular permeability and neovascularisation in the different tissues of the eye. All models were deemed appropriate.

Efficacy of brolucizumab against VEGF-induced retinal vascular permeability in adult rats (*Alcon study TDOC-0013037*)

Brolucizumab concentrations of 0.1, 0.3 and 1 µg/µl, administered IVT and pre-dosed 1 day before the VEGF challenge, probed to significantly reduce the VEGF-induced retinal vascular permeability in adult rats. In this same model, a time-dependent decrease in the efficacy of brolucizumab was detected when the product was single administered at different days pre-insult (1, 3, 7 and 14 days) with VEGF.

The second aspect of this *in vivo* study was to investigate time-dependency/ duration of effect, of brolucizumab or the comparator Lucentis *via* a single IVT dose of 10 mole equivalents of VEGF. Challenge with VEGF was performed 1, 3, 7 or 14 days later. Positive controls received vehicle and VEGF; negative controls, two doses of vehicle. Results of inhibition are summarized in Table 2.

Table 2: Intravitreal time-course of brolucizumab in the Rat VEGF Model

Day of VEGH challenge	Treatment group	Mean permeability	% inhibition (vs. VEGF treated)
Day 1	OD (VEGF)	7.911	
	OS (0.1% BSA)	1.477	
	Brolucizumab (10x)	1.742	95.9
	Lucentis (10x)	2.239	88.2
Day 3	OD (VEGF)	6.809	
	OS (0.1% BSA)	1.000	
	Brolucizumab (10x)	5.215	27.4
	Lucentis (10x)	5.039	30.5
Day 7	OD (VEGF)	6.805	
	OS (0.1% BSA)	1.000	
	Brolucizumab (10x)	5.254	26.7
	Lucentis (10x)	4.584	38.3
Day 14	OD (VEGF)	4.806	
	OS (0.1% BSA)	1.231	
	Brolucizumab (10x)	4.086	20.1
	Lucentis (10x)	4.140	18.6

Brolucizumab and Lucentis have demonstrated near complete (99.5% and 88.2%, respectively) and statistically significant inhibition when dosed 24 hours prior to VEGF challenge. When injected into the vitreous from 3 to 14 days prior to VEGF challenge, both products exhibited a time-dependent decrease in efficacy. Indeed 14 days after administration, no significant inhibition was observed for both products.

Efficacy of brolucizumab in neonatal rat model of oxygen-induced retinopathy (*Alcon study TDOC-0013037*)

Similar results were found in the oxygen-induced retinopathy (OIR) and neovascularization (NV) model in neonatal rats (Alcon study TDOC-0013037). Data showed that brolucizumab prevented preretinal neovascularisation in the rat OIR model in a dose-dependent manner when administered on days 14 and 17 postpartum while a single IVT injection on day 14 (15 µg and 46 µg) or day 17 (100 µg and 300 µg) postpartum did not show any effect.

However, in this assay double IVT administration of the product was required (with the second injection 3 days after inducing the lesion) to observe a protective effect, as single injection failed to prevent the pre-retinal neovascularisation.

In regression experiments conducted in the same model, brolucizumab failed to reverse the pathologic neovascularisation, even at doses of 60 µg/µl, in single IVT administration, conducted 3-4 days after the animals were exposed to the toxic insult and when the damage has already developed. These results indicate that administration of brolucizumab immediately or concomitant to the damage, followed by additional administrations at later time points might be necessary to observe a preventive, measurable effect in neovascularisation, as reversion of the pre-existing NV was not achieved using single, high doses of brolucizumab, administered days after exposure to the injury.

Efficacy of brolucizumab against laser-induced choroidal neovascularisation in adult mice (*Alcon study TDOC-0013037*)

The applicant has also conducted in vivo studies in mice, using a model of laser-induced choroidal neovascularisation (Alcon study TDOC-0013037). In this case, IP administration of the product prior to the laser-induced damage and sustained after the insult, resulted in prevention of the choroidal NV, but always to a lesser extent than the effects seen in the controls (anti-VEFG tyrosine kinase inhibitors). The dosage of the VEGF inhibitor in one of the assays (CNV-10-003) required daily IP administration of the drug, compared to brolucizumab which was employed in this assay at a concentration of 6 mg/kg, Q3D. When brolucizumab was administered IVT immediately after laser-induced damage and re-dosed after 3 or 7 days, protection up to some extent against choroidal NV was detected in a dose-dependent fashion, indicating again the need of concomitant to the injury and repeated administration of the product.

Secondary pharmacodynamic studies

No dedicated studies, including tissue cross-reactivity, have been conducted with brolucizumab. The justification for the absence of the aforementioned studies relies on the nature of the product (a humanized antibody fragment) and the route of administration (IVT), resulting in specific target engagement and lower systemic concentrations after treatment, respectively.

Safety pharmacology program

Lack of dedicated safety pharmacology studies was justified by the incorporation of safety pharmacology endpoints in repeat-dose toxicity studies, and the human systemic exposure being below levels where any meaningful effect of a VEGF-related activity is expected. No effect on respiratory function or cardiovascular function, and no effects on the central nervous system were detected in toxicological studies.

Pharmacodynamic drug interactions

Drug-drug interactions between antibody-based biologics and low molecular weight drugs were not investigated because hepatic metabolizing enzymes are generally not involved in metabolism and elimination of monoclonal antibodies. Antibody fragments such as brolucizumab are not expected to change either the cytokine profile or the expression of hepatic metabolizing enzymes. Therefore, section 4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical) of the e-CTD structure is not included.

2.3.3. Pharmacokinetics

The pharmacokinetic parameters (PK) of brolucizumab following intravenous and intravitreal (IVT) administration were evaluated in rabbits and cynomolgus monkeys. While brolucizumab does not bind to rabbit VEGF, the rabbit was chosen because it is commonly used for preliminary PK assessment of drugs

administered locally to the eye. The cynomolgus monkey was chosen because brolucizumab binds to monkey VEGF, itis pharmacologically active in this species and it was used in the toxicology evaluations. The formulations used in the PK studies were consistent with the formulations used in the Toxicology studies.

Following IVT administration, it appeared that free brolucizumab was cleared in parallel from all the evaluated ocular tissues and serum with a terminal half-life ranging from 59 to 82 hours in rabbits and 50 to 78 hours in cynomolgus monkeys. The serum half-life of brolucizumab in monkeys was prolonged after IVT administration compared to intravenous injection where the serum half-life was approximately 6 hours. The parallel elimination from all analysed ocular tissues and serum indicated that brolucizumab distributed from the vitreous humor to the adjacent compartments and serum. Free brolucizumab penetrated rapidly into the retina with concentrations similar to vitreous humor levels in cynomolgus monkeys, while in rabbits, the vitreous humor concentrations were approximately three times higher than those found in the retina. Following IVT administration, systemic (serum) exposure of free brolucizumab in rabbits and cynomolgus monkeys was found to be >20000-fold and >7000-fold lower than in vitreous humor.

IVT injections of increasing doses of brolucizumab (0.5 mg to 6 mg/eye) in monkeys resulted in systemic exposures to free brolucizumab in serum that increased dose proportionally to slightly greater than dose proportionally.

Absence of metabolism, excretion, and PK drug interaction studies are considered acceptable due to the nature of the product.

2.3.4. Toxicology

The non-clinical safety of up to 6 mg brolucizumab was established for intravitreal IVT in cynomolgus monkeys and rabbits in three non-GLP single dose toxicity studies (study E-12-015 and study E-13-001 in NZ rabbits, and study E-10-029 in cynomolgus), two non-pivotal non-GLP-regulated repeated-dose studies (Study E-10-003 and Study E-10-043 in cynomolgus) and three pivotal GLP-regulated repeated-dose studies (Alcon Study N-14-007, Alcon Study N-10-104 and Alcon Study N-12-042 in cynomolgus).

Single dose toxicity studies via IVT did not reveal any major findings regarding excipients and/or brolucizumab. The non-pivotal/non-GLP study in cynomolgus monkeys, has shown ocular inflammation in animals. However, this effect was not considered to be related to brolucizumab, but to the level of endotoxin in the employed large-scale batch of ESBA1008. Overall brolucizumab appeared to be well tolerated in rabbits and monkeys under the tested conditions.

3 GLP repeat-dose studies (Study N-10-104, Study N-12-042 and Study N-14-007) were conducted with the GMP material to determine the potential ocular toxicity, tolerability, and systemic exposure of brolucizumab in Cynomolgus monkeys after repeated IVT injections. Cynomolgus monkeys were chosen as they are the only species in which brolucizumab is both pharmacologically active and possessing a similar ocular anatomy to humans. Animals were dosed unilaterally (to provide an untreated contralateral control) with up to 6 mg/50 µL injection volume using a dosing interval designed to mimic or exaggerate clinical use.

Overall, results of the different studies revealed that brolucizumab was well tolerated with a NOAEL value of 6 mg/eye corresponding to the highest tested dose and no systemic toxicity was observed.

IVT administration of 6 mg brolucizumab to cynomolgus monkeys resulted in systemic exposure, with a Cmax of 0.577 µg/mL and AUC of 30.3 µg·h/mL. Serum free brolucizumab AUC increased dose-proportionally to slightly greater than dose-proportionally. Some potential accumulation was observed in serum after repeated brolucizumab administration at the highest tested dose of 6 mg.

The proposed human dosing is up to every 12 weeks following three monthly loading doses of 50 µL IVT injections of 6 mg/eye brolucizumab. Non-clinical toxicity data provides a 2-fold ocular margin of safety based on comparative ocular volume for the recommended dose in patients, and 12- and 6-fold systemic margins of safety based on Cmax and AUC, respectively.

No genotoxicity, carcinogenicity and reproductive-developmental studies were conducted by the applicant.

Local tolerance was assessed as a part of the repeated dose-toxicity studies and immunogenicity was evaluated either during the course of repeated-dose toxicity studies and in dedicated T-cell proliferation assay. It was concluded that brolucizumab was weakly immunogenic.

ADA response was assessed in the in vivo studies. Although antibodies were detected in all the studied groups, no effects were detected in brolucizumab exposure. This approach is acceptable from the non-clinical perspective as the predictive value of the data is limited and relevant antigenicity data is obtained in the clinical trials.

Other toxicity studies

2.3.5. Ecotoxicity/environmental risk assessment

Brolucizumab is a humanized single-chain Fv (scFv) antibody fragment with a molecular weight of ~26 kDa which inhibits vascular endothelial growth factor A (VEGF-A) binding to its receptors VEGFR1 and VEGFR2. It has been developed for the treatment of neovascular age-related macular degeneration (nAMD). Inhibition of the VEGF pathway has been shown to inhibit the growth of neovascular lesions and resolve retinal oedema in patients with nAMD. Any active pharmaceutical ingredient that reaches water streams after use in patients, via eventual spills during brolucizumab application or after disposal of unused drug is expected to be very rapidly degraded by microbial activity.

Therefore, there is no appreciable risk for the environment emerging from the introduction of brolucizumab for the treatment of neovascular age-related macular degeneration in the EU market. It is therefore deemed unnecessary to perform a detailed environmental risk assessment.

2.3.6. Discussion on non-clinical aspects

Pharmacological program conducted by the applicant relies on in vitro and in vivo studies for primary pharmacodynamics. Brolucizumab has shown to be as efficient as ranibizumab in neutralization the binding of VEGF165 to its two receptors VEGFR1 and VEGFR2. Affinity of brolucizumab to VEGF165 is similar to ranibizumab, but differences in the binding kinetics were observed. Brolucizumab binds to hVEGF165, hVEGF121 and hVEGF110 isoforms with high and similar affinities. The ability of brolucizumab to block the interaction of VEGF to its receptors and to inhibit VEGF-induced cells proliferation and migration (HUVECs, BRECs and HRECs) was demonstrated. In HUVECs, brolucizumab has demonstrated similar EC50 to ranibizumab (~20 nM) for non-glycosylated VEGF. However, for both molecules, an increase in EC50 value was observed for glycosylated VEGF. Brolucizumab and ranibizumab provided dose-dependent inhibition of VEGF-induced BREC proliferation with EC50 values of 0.77 and 0.64 nM respectively. In HRECs complete inhibition were observed for brolucizumab (0.3-0.6 nM) and ranibizumab (1 nM).

Difference in binding kinetic has been observed between brolucizumab and ranibizumab. The key step is based on the dissociation step with VEGF165. The applicant has highlighted that temperature has an effect on KD values and especially it was observed that KD increases with an increase in temperature for brolucizumab,

bevacizumab and aflibercept. At 25°C, brolucizumab and aflibercept have roughly similar KD values whereas KD value for bevacizumab was at least 40 foldr higher. This is related to a faster binding kinetic of bevacizumab upon VEGF165. At 37°C, the difference observed is more pronounced between brolucizumab and aflibercept, this is in relation with the decomplexation step. Regarding bevacizumab, the difference observed with brolucizumab regarding the KD value is more distinct at 37°C.

In addition, the applicant has demonstrated for brolucizumab and aflibercept, that IC50 values were not correlated with incubation time whereas incubation time has an impact on IC50 for bevacizumab and ranibizumab wherein IC50 values decreased with time of incubation. Thus, if incubation period was limited to 1 hr. then brolucizumab and aflibercept are better inhibitors. Decreases observed in IC50 values with incubation time are correlated to KD with VEGF165.

Species cross-reactivity study of brolucizumab towards human, mouse, porcine, feline, and rabbit VEGF has shown that brolucizumab binds to human, mouse, porcine, feline VEGF with similar affinity. However, this study did highlight that Brolucizumab did not bind to rabbit VEGF. These results showing cross-reactivity towards mouse and rat VEGF allows assessment of ESBA 1008 efficacy in rat and mouse animal models such as the laser-induced CNV (choroidal neovascularization) during in vivo pharmacology studies. Moreover, since similarity of sequence has been demonstrated between human and primate, monkey was selected as the relevant species for toxicity studies.

In vivo studies were performed to characterize the efficacy of brolucizumab in preventing pathological neovascularization and vascular permeability in relevant animal models of ocular vascular disease.

In vivo studies showed a preventive action of brolucizumab on retinal vascular permeability, choroidal neovascularisation (both by IVT administration) and preretinal neovascularisation (IVT and IP administration). It is noted that in the VEGF-induced retinal vascular permeability assays in adult rats the concentrations employed are expressed as mole equivalents to VEGF rather than in standard weight/volume of the product. Mole equivalent were provided to allow for direct comparison of the same number of molecules of brolucizumab and ranibizumab. Accordingly, 10-times molar equivalent to dimeric VEGF of brolucizumab corresponded to 0.345 µg/µl and for ranibizumab, represented 0.628 µg/µl. After adjustement with the molar weight (26.3 KDa and 48 KDa for brolucizumab and ranibizumab, respectively) concentrations are 13 µM for each. Therefore, it has been concluded that brolucizumab shows similar efficacy and effect duration for the inhibition of VEGF-induced retinal vascular permeability when applied at the same molar dose.

In the rat oxygen-induced retinopathy and neovascularisation model, the results indicate that administration of brolucizumab immediately or concomitant to the damage, followed by additional administrations at later time points might be necessary to observe a preventive, measurable effect in neovascularisation, as reversion of the pre-existing NV was not achieved using single, high doses of brolucizumab, administered days after exposure to the injury. The lack of effect of brolucizumab in the regression assays presented as part of this study may be expected upon treatment with the product, as according to the Applicant, no regression of the already formed blood vessels may be expected after treatment with anti- VEGF therapy, applied several days after the insult. For the current evaluation of brolucizumab in the treatment of neovascular AMD (nAMD) this is considered of no relevance, but it could be significant for other indications, i.e. the new indication of Lucentis (retinopathy of prematurity), recently granted positive opinion at the CHMP. For this new indication, the rat OIR model is considered a relevant non-clinical model and it should be noted as well that Lucentis has been used extensively in the developmental plan of brolucizumab as a comparator.

No dedicated study has been performed by the applicant in order to investigate the off-target effects. However, the applicant has presented the potential risks associated with the use of anti-VEGF compounds. Indeed, VEGF inhibitors are known to increase blood pressure, thromboembolic events (stroke and myocardial infarction) after systemic administration. Systemic exposure was estimated to be low after IVT administration, based on PK and TK data and no effects on the cardiac system or blood pressure were observed during repeated dose toxicity studies with brolucizumab.

The absence of systemic toxicity at exposure levels above maximum clinical exposure is reassuring. Therefore, the lack of dedicated safety pharmacology and pharmacodynamic drug interactions studies is accepted.

PK program developed by the applicant relies mainly in studies performed in cynomolgus species except one distribution study in NZ rabbits. Although in vitro pharmacological studies have shown that brolucizumab did not cross-react with rabbit VEGF, ocular distribution of brolucizumab in NZ rabbits following single IVT was studied. Brolucizumab did penetrate in RPE-choroid after IVT administration and was cleared via the aqueous humor to the systemic circulation. Exposures in vitreous humor > retina> RPE-choroid > aqueous humor > serum (AUC vitreous humor >30000 x AUC serum).

A rabbit ocular PK study was performed as an initial preliminary investigation of the ocular and serum PK of brolucizumab. This study was not GLP-compliant, and the bioanalytical method was not formally validated. However, the concentration of brolucizumab in serum and ocular fluids/tissues was analysed using an adequate protocol.

In cynomolgus, it was observed after single IVT administration that brolucizumab distributed rapidly into ocular tissues with exposure levels central retina> peripheral retina> vitreous humor> aqueous humor> peripheral choroid> central choroid. As shown in rabbits, the systemic exposure of brolucizumab was low in serum and AUC vitreous humor >9200 x AUC serum. Overall, it has been shown in the two species that brolucizumab distributed rapidly into ocular tissues and systemic exposure was negligible, as compared to ocular tissues.

Intravitreal administration of brolucizumab in cynomolgus resulted in prolonged half-life compared with IV injection.

Since, brolucizumab is expected to be metabolised and degraded to small peptides and individual amino acids, no biotransformation studies have been performed by the applicant. This is acceptable regarding ICHS6 (R1).

Dedicated studies on excretion were not performed by the applicant since expected elimination after systemic administration is very rapid compared to full IgG and after IVT administration it was demonstrated that systemic exposure was low.

Regarding brolucizumab, the IVT route has been selected for administration. It is believed that PK interactions of brolucizumab and small drugs will be limited and the lack of studies on PK drug interactions is accepted.

No pharmacokinetic studies have been conducted with brolucizumab in pregnant or lactating animals. Lack of dedicated studies is accepted based on the points raised by the applicant regarding the fact that brolucizumab (~26 kDa) is much larger than the <600 Da which is the molecular weight limit generally accepted for passive transport across the placenta or into breast milk. Moreover, the following sentence: "breast-feeding is not recommended during treatment and for at least one month after the last dose when stopping treatment" is stated in the 4.6 section of the SmPC.

Overall, the PK program proposed by the applicant is satisfactory.

Single dose toxicity studies via IVT did not reveal any major findings regarding excipients and/or brolucizumab. The non-pivotal/non-GLP study in cynomolgus monkeys, has shown ocular inflammation in animals. However, this effect was not considered to be related to brolucizumab, but to the level of endotoxin in the employed large-scale batch of ESBA1008. Overall, brolucizumab appeared to be well tolerated in rabbits and monkeys under the tested conditions.

No systemic toxicity has been observed in the two non-pivotal repeated dose toxicity studies. Only findings at the target organ (eye) were observed in both studies, such as ocular inflammation, retinal degeneration (dose-dependency). Severe ocular inflammations seemed to be the results of higher levels of endotoxin on the animals tested with pilot mock ESBA1008 and lab-batch ESBA1008.Since it has not been observed any related ocular findings with the clinical GMP batch therefore it may be considered that the observed effects were related to the manufacturing process. Thus, pivotal repeated dose toxicity studies were then conducted with the GMP manufactured product.

All the 3 conducted studies have demonstrated systemic exposure in all treated groups. Whereas retinal degeneration was observed in non-pivotal repeated toxicity studies, it was not observed in the pivotal ones. Only right eye inflammation corresponding to cell infiltrates was observed but was not test article-related but correlated with the IVT technique. No test-article changes in body weight, haematology parameters, clinical chemistry parameters, ERGs and ECGs were observed during pivotal studies. Histopathology was not performed in Alcon Study N-14-007, therefore it was reported if spleen lymphoid depletion occurred, as reported in Alcon Study N-10-104 and Alcon Study N-12-042. Since VEGF inhibitors may have adverse effect on overall lymphoid depletion, extra investigation by external pathologist was conducted in order to reanalyse the observed effect on spleen. It was concluded that there was no test-article related effect on spleen because increase in spleen weights were not statistically significant and no effect were observed on thymus or lymph node and no test article-related effects on haematology parameters were underlined.

Alcon Study N-12-047 was performed in order to demonstrate similarity between the drug substances from Biomeva and Lonza. Only one dose was selected corresponding to the highest dose of Alcon Study N-12-042 i.e. 6mg/eye. Similar conclusion could be made between tolerances of the two drug substances. Nevertheless, it has to be underlined that no histopathology was conducted in Alcon Study N-14-007, therefore "comparability" was assed via indirect ophthalmic evaluation (IOP, eye observation for swelling, inflammation…). Overall the Lonza drug substance was well tolerated at the dose of 6 mg/eye. In addition, during scientific advices, the applicant was told that toxicity study on its own would not be sufficient to compare the two drug substances and comparability would require sufficient quality data.

As previously stated, systemic exposure based on free brolucizumab was observed in all treated groups. In Alcon Study N-10-104, no statistically significant differences in the serum Cmax and AUC0_168h values between Day 1, Day 22 and Day 43 and therefore no accumulation of free brolucizumab was observed. In Alcon Study N-12-042, no statistically significant gender differences in the Cmax or AUC0-168 h values and therefore values were combined, and no accumulation was observed following repeated administrations. Dose proportional increases were observed in Cmax whereas it was less than dose proportional increase regarding AUC values. Whereas no gender difference in term of Cmax or AUC values were observed in the other pivotal studies, slightly higher values in mean Cmax and AUC were observed for female in Alcon Study N-14-007 (Lonza drug substance). There was no systemic accumulation of test article.

Pre-existing ADA were detected in all the studies before administration of brolucizumab. Indeed, in Alcon Study N-10-104 pre-existing anti-drug ADA were detected in 27% of animals, 16.7% in Alcon Study N-12-

042 and finally 8.3% of the total animals (1/12) in Alcon Study N-14-007. Since pre-existing brolucizumab ADA have been measured, the specificity of the method to identify brolucizumab-ADA is questionable although correlation from animal to Human is difficult. In addition, pre-existing brolucizumab ADA have been measured in Human during the clinical trials up to 43.7% (884/2023 of the subjects). Regarding levels of ADA during pivotal repeated dose toxicity studies, increase was observed after the final injection (6 IVT) in Alcon Study N-12-042, wherein ADA levels were up to 47% (17/36 animals). However, no dose-response relationship and no correlation between ADA titers and systemic exposure were observed. In Alcon Study N-14-007, 1/6 animals in each group (untreated and treated) was ADA positive, showing the non-specificity of the method. Although, the ELISA method designed to detect anti-brolucizumab seems to lack of specificity, no systemic toxicity has been observed in the 3-pivotal repeated dose toxicity studies.

No genotoxicity studies have been conducted. Since brolucizumab is an antibody fragment, the lack of genotoxicity studies is in accordance with the available guideline ICH S6 (R1) and this point is accepted. Similarly, no carcinogenicity studies have been conducted with brolucizumab, as noted in ICH S6 (R1), standard carcinogenicity bioassays are generally not performed for biotechnology-derived pharmaceuticals.

Based on its mechanism of action (VEGF inhibitor), brolucizumab has the potential to impair fertility and embryo-foetal development in relation to the degree of systemic VEGF-inhibition. Nevertheless, the absence of reproductive and developmental toxicity studies is considered as acceptable in view of the low systemic exposure levels after IVT dosing, and the age of the patient population undergoing treatment for neovascular (wet) age-related macular degeneration. Potential pharmacologically related effects on fertility and embryo-fetal development are clearly mentioned in SPC section 4.6, as well as the recommendation for women of childbearing potential (WOCBP) which may be treated by brolucizumab to use effective contraception.

The lack of dedicated local tolerance studies is accepted since this endpoint has been investigated during repeated-dose toxicity studies after IVT administration.

T-cell proliferation assay was selected by the applicant to estimate immunogenicity of brolucizumab. Nevertheless, the test article of this assay was not brolucizumab (ESBA1008) but with a variant ESBA1008-DHP. Modification of the surface by increasing/decreasing hydrophobicity would modify immunogenicity. Modification was introduced by mutation on various amino acid positions. Similar approach was used with structure-related monoclonal antibody ESBA903 (see Table 31) wherein surface residue was modified in order to generate compound ESBA903-DHP. No immunogenic response higher than background response rate was observed. It was therefore concluded that the tested monoclonal antibody was weakly immunogenic.

Concerning studies on impurities, no dedicated studies apart from one of the non-pivotal repeated dose toxicity which included groups treated with impurities from pilot batches, have been conducted by the applicant.

Concentrations of free brolucizumab in the vitreous humour were assessed in two different toxicology studies. In the first one (TDOC-0011462), vitreous humour was collected 43 days after the second injection (Day 79 of the study). In all the analysed samples, the concentration of brolucizumab was below the lower limit of quantification. In the second study (TDOC-0012707), vitreous humour was collected 21 days after the third injection (Day 64 or 65 of the study). Concentrations of brolucizumab were determined using a validated method of detection showing that free brolucizumab concentrations in the vitreous humour increased with the dose. Similarly, the detection of free brolucizumab three weeks after the last dose indicated that the eye of the cynomolgus monkey was exposed to brolucizumab throughout the dose interval.

The proposed clinical dosing regimen is repeated IVT injections of 6 mg brolucizumab. Nonclinical safety data provides a 2-fold ocular margin of safety for the recommended human dose and a 12- and 6-fold systemic

margin of safety, based on Cmax and AUC respectively (NOAEL corresponds to the highest tested dose in Alcon study N-12-042 i.e. 6 mg/eye). The nonclinical studies cover the use of brolucizumab at IVT doses of up to 6 mg/eye administered every 3 to 4 weeks.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical data were considered by the CHMP sufficient to support the application for a marketing authorisation of Beovu in the treatment of neovascular (wet) age-related macular degeneration (AMD).

The CHMP furthermore concluded that Beovu was not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 3: Tabular overview of clinical studies

Protocol No., Study Dates, Countries & Publication	**Study Design & Purpose Population Studied**	**Total No.& Race (w,b,a,o)** **Age Range (mean) Group No. & Sex (m,f)**	**Treatment, Route, Regimen, Duration of Therapy, Dosage**
protocol: [RTH258-C001] **countries:** Argentina, Australia, Canada, Colombia, Israel, Japan, Mexico, Panama, United States **start:** 8Dec2014 **end:** 28Mar2018 **publ.:** none	**design, goal & population**: A two-year, randomized, double-masked, multicentre, three-arm study comparing the efficacy and safety of RTH258 versus aflibercept in subjects with neovascular age-related macular degeneration **efficacy:** BCVA using ETDRS methodology, spectral domain optical coherence tomography (SD-OCT), fluorescein angiography (FA), anatomical parameters of disease activity including central subfield thickness (CSFT), CNV area and	**total**: 1078 (874w, 3b, 158a, 43o) **age**: 50-97 (76.5) years **groups**: 3 (469m, 609f) Arm 1: 358 (148m, 210f) Arm 2: 360 (155m, 205f) Arm 3: 360 (166m, 194f)	**form(s)**: 3 mg RTH258 in 50 µL (60 mg/mL formulation) 6 mg RTH258 in 50 µL (120 mg/mL formulation) Aflibercept, 2 mg/50 µL **duration**: 96 weeks **doses**: intravitreal (IVT) injection Arm 1: RTH258 3 mg initially injected 3 times every 4 weeks then every 12 weeks (q12w) unless there is disease activity. If disease activity is identified injections given every 8 weeks (q8w)

Protocol No., Study Dates, Countries & Publication	Study Design & Purpose Population Studied	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage
	presence of subretinal, intraretinal, and subRPE fluid, disease activity assessments/q12w status, National Eye Institute Visual Function Questionaire-25 (VFQ-25) **safety:** physical exam, vital signs, laboratory parameters (blood chemistry, hematology, urinalysis), anti- drug antibody (ADA) assessments, systemic RTH258 assessments, complete ophthalmic exam (slit-lamp exam, IOP measurement, fundus exam), post-injection assessments, TEAEs, AESIs, SAEs **Diagnostic:** color fundus photography, Indocyanine green (ICG) imaging, fundus autofluorescence		Arm 2: RTH258 6 mg initially injected 3 times every 4 weeks then every 12 weeks (q12w) unless there is disease activity. If disease activity is identified injections given every 8 weeks (q8w) Arm 3: 2 mg aflibercept injected 3 times at 4 week intervals followed by injections every 8 weeks (q8w)
protocol: [RTH258-C002] **countries:** Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Malaysia, Netherlands, Norway, Poland, Portugal, Russia, Singapore, Slovakia, South Korea, Spain, Sweden, Switzerland, Taiwan, Turkey,	**design, goal & population**: A two-year, randomized, double-masked, multicentre, two-arm study comparing the efficacy and safety of RTH258 6 mg versus aflibercept in subjects with neovascular age-related macular degeneration **efficacy:** BCVA using ETDRS methodology, spectral domain optical coherence tomography (SD-OCT), fluorescein angiography (FA), anatomical parameters of disease activity including central subfield thickness (CSFT), CNV area and presence of subretinal, intraretinal, and subRPE fluid, disease activity assessments/q12w status, National	**total:** 739 (681w, 1b, 45a, 12o) **age:** 50-95 (75.1) years **groups:** 2 (317m, 422f) Arm 1: 370 (160m, 210f) Arm 2: 369 (157m, 212f)	**form(s)**: RTH258 6 mg in 50 µL (120 mg/mL formulation) Aflibercept 2 mg / 50 µL **duration:** 96 weeks **doses:** IVT injection Arm 1: RTH258 6 mg initially injected 3 times every 4 weeks then every 12 weeks (q12w) unless there is disease activity. If disease activity is identified injections given every 8 weeks (q8w) Arm 2: 2 mg aflibercept injected 3 times at 4 week intervals followed by injections every 8 weeks (q8w)

Protocol No., Study Dates, Countries & Publication	**Study Design & Purpose Population Studied**	**Total No.& Race (w,b,a,o)** **Age Range (mean) Group No. & Sex (m,f)**	**Treatment, Route, Regimen, Duration of Therapy, Dosage**
United Kingdom, Vietnam **start:** 28 Jul 2015 **end:** 7 Mar 2018 **publ.:** none	Eye Institute Visual Function Questionnaire-25 (VFQ-25) **safety:** physical exam, vital signs, laboratory parameters (blood chemistry, hematology, urinalysis), anti- drug antibody (ADA) assessments, systemic RTH258 assessments, complete ophthalmic exam (slit-lamp exam, IOP measurement, fundus exam), post injection assessments, TEAEs, AESIs, SAEs **Other:** color fundus photography, fundus autofluorenscence		

Protocol No., Study Dates, Countries & Publication	**Study Design & Purpose Population Studied**	**Total No.& Race (w,b,a,o)** **Age Range (mean) Group No. & Sex (m,f)**	**Treatment, Route, Regimen, Duration of Therapy, Dosage**
protocol: [C-12-006] **countries:** United States **start:** 11-Mar-2013 **end:** 18-Aug-2014 **publ.:** Dugel PU, Jaffe GJ, Sallstig P, et al (2017). Brolucizumab versus aflibercept in participants with neovascular age-related macular degeneration: a randomized trial. Ophthalmology; 124:1296- 304.	**design, goal & population:** Prospective, randomized, double-masked, multicenter, two-arm study comparing the efficacy and safety of ESBA1008 versus EYLEA in subjects with exudative age-related macular degeneration **efficacy:** BCVA, CSFT using SD-OCT imaging, investigator assessment of CSFT, presence of hyperreflective material, subretinal fluid, and intraretinal fluid cystoid oedema **safety:** AEs/SAEs, AESIs, ocular and systemic parameters (physical examination, vital signs, clinical chemistry, hematology, and urinalysis), ophthalmic examination (slit lamp biomicroscopy, IOP, and dilated fundus examinations), postinjection assessments (gross visual acuity, central retinal artery status, presence of retinal detachment/new intraocular hemorrhage). Additional post-hoc analysis safety parameters included presence of geographic atrophy and/or fibrosis using color fundus photographs.	**total:** 89 (86w, 1b, 2a) **age:** 55-96 (78.0) years **groups:** 2 (36m, 53f) 36 (16m, 20f) 53 (28m, 25f)	**form(s):** ESBA1008 (6 mg/50 µL) EYLEA (2 mg/50 µL) **duration:** 44 to 48 weeks with follow up to Week 56 **doses:** IVT eye injection ESBA1008 (6 mg/50 µL) EYLEA (2 mg/50 µL)
protocol: **[C-10-083]** **countries:**	**design, goal & population:** Safety and efficacy study of ESBA1008 versus	**total:** 194 (193w) **age:** 51-95 (76.5) years	**form(s):** ESBA1008 0.5 ESBA1008 3.0

Protocol No., Study Dates, Countries & Publication	**Study Design & Purpose Population Studied**	**Total No.& Race (w,b,a,o)** **Age Range (mean) Group No. & Sex (m,f)**	**Treatment, Route, Regimen, Duration of Therapy, Dosage**
Australia, Austria, Denmark, France, Germany, Israel, Italy, Netherlands, Portugal, Spain, United Kingdom, United States **start:** 03-Oct-2010 **end:** 13-Mar-2013 **publ.:** Holz FG, Dugel PU, Weissgerber G, et al (2016). Single-chain antibody fragment VEGF inhibitor RTH258 for neovascular age-related macular degeneration. Ophthalmology; 123:1080- 89.	LUCENTIS for the treatment of exudative age-related macular degeneration **efficacy:** CSFT and BCVA **safety:** AEs/SAEs, general physical examinations, vital signs, hematology, serum chemistry, serum pregnancy, urinalysis, complete ophthalmic examination ESBA1008 serum exposure, antidrug serum antibodies, postinjection evaluations of the study eye, fundus photography, fluorescein angiography Pharmacokinetics: blood serum exam Immunogenicity: Anti-ESBA1008 Antibodies	**groups: 5** (88m, 106f 10 (4m, 6f) 35 (20m, 15) 48 (21m, 27f) 40 (15m, 25f) 61 (28m, 33f)	ESBA1008 4.5 ESBA1008 6.0 Ranibizumab(LUCENTIS) **duration:** Single intravitreal injection with follow-up for 6 months **doses:** intravetreal (IVT) injection 0.5 mg (0.05 mL of 10 mg/mL ESBA1008) 3.0 mg (0.05 mL of 60 mg/mL ESBA1008) 4.5 mg (0.075 mL of 60 mg/mL ESBA1008) 6 mg (0.10 mL of 60 mg/mL ESBA1008) Single intravitreal injection 0.5 mg (0.05 mL of 10 mg/mL Ranibizumab, LUCENTIS)
protocol: **[C-13-001]** **countries:** Australia, Dominican Republic, United States **start:** 20-Jul-2014 **end:** 23-Jan-2015 **publ.:** None	**design, goal & population:** A prospective, two-staged, single-masked study to evaluate the effect of ESBA1008 applied by microvolume injection or infusion in subjects with exudative age-related macular degeneration **efficacy:** BCVA and CSFT	**total:** 52 (50w, 0b, 1a, 1o) **age:** 70-84 (77.7) years groups: 4 (28m, 24f) 13 (9m, 4f) 13 (5m, 8f) 13 (6m, 7f) 13 (8m, 5f)	**form(s):** ESBA1008 solution for intravitreal injection/infusion, 60 mg/mL, 120 mg/mL, Lucentis 0.5 mg in 50 µL **duration:** 2 administrations (Day 0 and Day 28) **doses:** single intravitreal infusion <u>Stage 1/Cohort1</u> ESBA1008 single intravitreal injection of 1.2 mg in 10 µL at Day 0; single injection of 6 mg in 50 µL

Protocol No., Study Dates, Countries & Publication	Study Design & Purpose Population Studied	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage
	safety: AEs/SAEs, slit-lamp biomicroscopy, IOP measurements, dilated fundus evaluation, vital signs, postinjection and postinfusion assessments, and physical examination findings		at Day 28 Lucentis single injection 0.5 mg in 50 µL at Day 0 and Day 28 <u>Stage 1/Cohort 2</u> ESBA1008 single infusion of 1.0.mg in 8.3 µL at Day 0; single injection of 6 mg in 50 µL at Day 28 Lucentis single injection 0.5 mg in 50 µL at Day 0 and Day 28 <u>Stage 2/Cohort 3</u> ESBA1008 single injection of 0.6.mg in 10 µL at Day 0; single injection of 6 mg in 50 µL at Day 28 Lucentis single injection 50 µL or infusion 0.5 mg at Day 0 and Day 28 <u>Stage 2/Cohort 4</u> ESBA1008 single infusion of 0.5 mg in 8.3 µL at Day 0; single injection of 6 mg in 50 µL at Day 28 Lucentis single injection 50 µL or infusion 0.5 mg at Day 0 and Day 28.

2.4.2. Pharmacokinetics

Considering the local administration of the drug and the local acting within the eye, traditional ADME is not appropriate. The below sections describe the systemic exposure of brolucizumab after IVT injection.

As it is not feasible to collect retina, RPE-choroid and other relevant ocular samples from patients, neither the bioavailability nor the distribution in ocular tissues was determined. The bioavailability was considered 100% in the vitreous. Also, no specific studies on distribution or to assess the plasma protein binding have been performed, nor were they required.

Rich PK sampling was performed in phase I and II studies in order to assess the systemic exposure and calculate PK parameters of brolucizumab in Caucasian and Japanese patients with nAMD (Study RTH258-E003). Sparse PK data to confirm systemic exposure (without calculation of PK parameters) were also available in subjects with nAMD in the pivotal Phase III studies RTH258-C001 RTH258-C002.

Table 4: Overview of the Clinical Studies providing PK data of brolucizumab.

Study	Phase	Design and Objectives	Dose Regimen	Age in years (Range)	Enrolled number of subjects	Subjects received brolucizumab
Studies with pharmacokinetic and immunogenicity endpoints in nAMD subjects						
RTH258-C-10-083	Phase I	Prospective, randomized, double-masked, multi-center, single ascending dose, active-controlled, parallel-group study evaluating safety and efficacy of brolucizumab vs. ranibizumab in subjects with subfoveal CNV secondary to AMD	0.5 mg, 3 mg, 4.5 mg, 6 mg IVT, single dose	51-95	194	133
RTH258-E003	Phase II	Randomized, double-masked, multi-center study evaluating pharmacokinetics, safety, and immunogenicity of brolucizumab in subjects with active CNV secondary to AMD	3 mg, 6 mg IVT repeat (3) dose	55-88	50	50
Studies with immunogenicity endpoints in nAMD subjects						
RTH258-C001	Phase III	Phase III, randomized, double-masked, multi-center study evaluating efficacy and safety of brolucizumab vs. aflibercept in subjects with nAMD	3 mg, 6 mg	50-97	N=1082 Brolucizumab 3 mg: N=360 Brolucizumab 6 mg: N=360 Aflibercept 2 mg: N=361	720
RTH258-C002	Phase III	Phase III, randomized, double-masked, multi-center study evaluating efficacy and safety of brolucizumab vs. aflibercept in subjects with nAMD	6 mg	50-95	N=743 Brolucizumab 6 mg: N=372 Aflibercept 2 mg: N=371	372
RTH2582301E1	Phase III	Phase III, double-masked, two-arm extension study to collect data on safety and efficacy of the brolucizumab 6 mg drug product intended for commercialization in subjects previously treated in Study RTH258-C001 to support comparability to the brolucizumab 6 mg drug product used in Phase III clinical studies	6 mg	52-98	N=150 Brolucizumab 6 mg: N=100 Aflibercept 2 mg: N=50	100

Systemic exposure

In initial phase I and II studies (RTH258-C-10-083 and RTH258-E003, respectively) that enrolled patients with nAMD, rich PK sampling was performed to document the systemic exposure and calculate PK parameters of brolucizumab after IVT injection. Additionally, sparse PK data (trough concentrations at various time-points up to two-year treatment) were available to confirm the systemic exposure of brolucizumab in patients with nAMD during the pivotal phase III studies (RTH258-C001, RTH258-C002 and A2301E1).

Two distinct analytical methods were used, throughout the clinical development, to quantify free brolucizumab in human serum. An ELISA assay was first used in patients which participated to phase I study RTH258-C-10-083, then the IA-LC-MS/MS method was used to measure free brolucizumab for all other studies. The two applied analytical methods (ELISA and IA-LC-MS/MS) appear to be adequate and comply with acceptance criteria of the bioanalytical method validation EMA Guideline. Description and validation reports were provided with satisfactory results regarding precision, accuracy, selectivity and sensitivity, short and long-term stability and ISR data.No cross-validation study was performed between the two methods since interference testing (free serum VEGF and ADA) was not investigated with the ELISA method. The applicant's proposal to avoid a direct comparison of PK data from phase I study C-10-083 and others PK studies is agreed.

Although the applied methods to detect and quantify ADA and NAb of brolucizumab are satisfactory in terms of sensitivity, accuracy and precision, a high proportion of subjects regardless of which treatment they subsequently received (43.7% 884/2023 across all studies) were positive for pre-existing anti-brolucizumab antibodies. High proportion of positive ADA titers prior to the first injection is not unexpected and has been detected in drug-naïve subjects for a variety of antibody fragments of similar structure, such as nanobodies and single domain antibodies. Both types of antibody fragments show high prevalence (50% or higher) because of epitopes in these constructs being similar to cryptic epitopes that are revealed through the catabolism/degradation of immunoglobulins. The lack of selectivity of the ADA method precludes the inclusion of positive pre-existing ADA patients in the assessment of the immunogenicity potential of brolucizumab. Therefore, the immunogenicity potential of brolucizumab could only be reliably estimated in negative pre-existing ADA patients

PK data were analysed using non-compartmental approach (NCA). Analyses were performed using the software WinNonlin® Enterprise (version 6.2, Pharsight Corporation). Pharmacokinetic variables, e.g. AUC_{last}, AUC_{inf}, C_{max}, C_{min}, t_{max}, and $t_{1/2}$, with standard summary statistics (*means, median, SD, CV etc…*) were calculated.

The commercial formulation B (solution 120 mg/mL) appears to be different from formulation A used in pivotal phase III for efficacy and safety demonstration and for assessment of the systemic exposure in phase II study RTH258-E003 (60 and 120 mg/mL). Indeed, in comparison the phase III formulation, the concentration of polysorbate 80 is reduced by more than a half (0.02 versus 0.05%) and the pH is not the same (7.2 instead of 6.8). The PK/clinical impact of such differences could not be estimated. However, based on the quality analytical similarity between the two products (please refer to the quality assessment report), these differences are not deemed to significantly impact the PK/clinical drug profile. Thus, conclusions with regards to the systemic exposure observed with drug product used in phase II and III studies could be extrapolated to the commercial product.

To note, no formal PK comparability with regards to local bioavailability/distribution of brolucizumab could be made between the to-be marketed product and the phase III/II formulation, as no ocular samples could be collected.

Study RTH258-C-10-083

This was a SAD study to evaluate the safety and efficacy of brolucizumab administered by a single IVT injection compared with ranibizumab in patients with nAMD. Overall, 191 subjects completed the study: 10, 35, 48 and 40 subjects were in the brolucizumab 0.5, 3, 4.5 and 6 mg group, respectively; and 61 in the ranibizumab group.

Overall, the systemic brolucizumab levels were low but quantifiable for up to two weeks post-dose in most patients. The peak serum brolucizumab concentration was observed in the first time point after dosing (day 1). Then brolucizumab levels demonstrated a mono-exponential decay with mean (±SD) T1/2 of 5.01(±2.97) days.

For the 6mg dose (relevant dose in clinical practice), the mean (±SD) Cmax and AUClast were 8.53 (±7.27) ng/mL and 64.18 (51.41) ng*d/mL, respectively. The highest Cmax value was 42.10 ng/mL. All samples collected at day 30 post-dose were below the LLoQ (0.5 ng/mL) except for 5 patients with the highest value at D30 being 1.94 ng/mL.

Study RTH258-E003 (SHRIKE)

This is a pivotal PK study to assess the systemic exposure, ocular and systemic safety, and immunogenicity of brolucizumab after IVT injection in patients (Japanese and non-Japanese ancestry) with nAMD.

The study evaluated 2 doses (3 and 6 mg) of brolucizumab in 50 patients (25 in each group), including 26 subjects of Japanese ancestry (13 in each treatment group). In each arm, 3 repeated brolucizumab dose was injected monthly on Days 0, 28, and 56.

PK after the first dose

Following IVT injection of brolucizumab, the systemic levels were low but quantifiable for up to four weeks post-dose in most subjects. The peak serum brolucizumab concentration was low and generally observed within the first day following dosing (ie, at either 6- or 24-hours after injection). After that, the drug concentration declined in a mono-exponential fashion with a harmonic mean T1/2 of approximately 4.5 days. Pre-existing ADA status had no impact on the half-life of free brolucizumab.

The overall mean serum brolucizumab concentration versus time profiles are plotted in Figure 2. Descriptive statistics for the overall PK parameters are presented in Table 5.

Figure 2: Line Plots of Geo. Mean (+/- SE) brolucizumab Serum Concentration (ng/mL) following a single IVT injection.

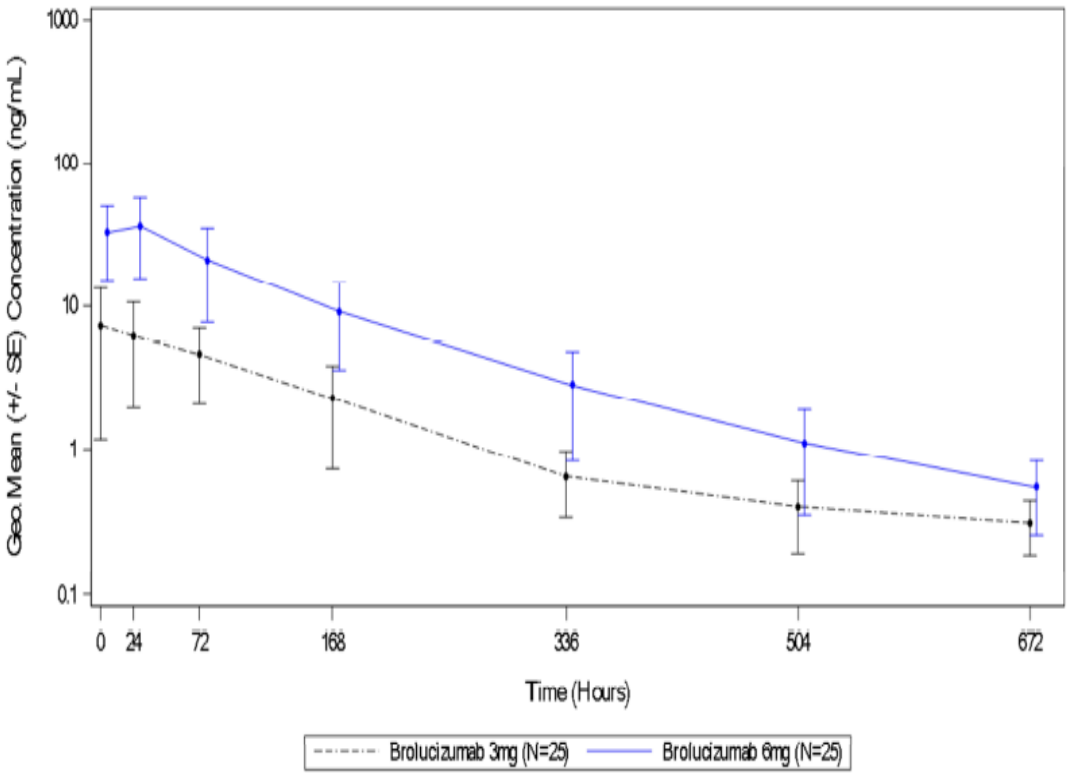


Table 5: Descriptive statistics for brolucizumab PK parameters after single IVT injection.

Treatment: Brolucizumab 3mg

PK Parameters	n	Mean	SD	Geo.Mean	Min	Median	Max	Harmonic Mean(SD)
Day 1, C24hr (ng/mL)	24	13.5	20.0	7.14	1.31	6.50	77.0	
Day 57, C24hr (ng/mL)	22	12.4	21.8	5.81	0.584	6.12	102	
Cmax (ng/mL)	25	20.7	29.4	9.76	0.514	8.33	105	
AUC(0-tlast) (hr*ng/mL)	25	2480	5470	977	18.5	961	27600	
AUC(0-inf) (hr*ng/mL)	17	3380	6860	1710	634	1330	29400	
Tmax (hr)	25	20.3	24.6	11.4	5.02	5.70	74.9	
t1/2(hr)*	18	122	43.0	115	57.6	117	223	108(40.7)

Treatment: Brolucizumab 6mg

PK Parameters	n	Mean	SD	Geo.Mean	Min	Median	Max	Harmonic Mean(SD)
Day 1, C24hr (ng/mL)	25	65.7	107	35.9	8.02	31.3	548	
Day 57, C24hr (ng/mL)	25	45.0	59.9	27.9	4.87	25.1	299	
Cmax (ng/mL)	25	77.6	105	49.0	8.97	59.2	548	
AUC(0-tlast) (hr*ng/mL)	25	9160	12300	5320	910	4450	59400	
AUC(0-inf) (hr*ng/mL)	24	9770	12600	6000	1420	5580	60400	
Tmax (hr)	25	17.4	14.7	12.7	5.05	21.7	73.0	
t1/2(hr)*	24	123	50.8	113	38.0	122	245	103(52.5)

For the 6mg dose (relevant dose in clinical practice), the mean (±SD) Cmax and AUClast were 77.6 (±106) ng/mL and 9160 (±12300) ng*d/mL, respectively. These reflects a high inter-individual variability of the systemic exposure and a non-Gaussian distribution (medians for Cmax and AUClast of 59.2 ng/mL and 4450 ng*d/mL, respectively different from means). The inter-subject variability (%CV) for brolucizumab could be estimated to range between 128 to 210% for Cmax and AUCs. The highest Cmax value was 548 ng/mL and highest AUClast was 59400 ng*d/mL. The geometric mean (±SE) concentrations of bromucizumab at D28 (C28d) was 0.6 ng/mL (±0.116) with the highest measured value at D28 being 5.32 ng/mL.

Based on the findings of study RTH258-E003 in patients with nAMD, the systemic exposure (Cmax, AUCs) of free brolucizumab appears to increase in a greater than dose proportional manner following IVT injection of brolucizumab doses (3 and 6 mg). Indeed, the geometric means of Cmax increased by 5- fold (9.76 to 49 ng/mL) while those of AUCinf increased by more than 3-fold (1710 to from 6000 ng*h/mL) with a 2-fold increase in dose (3 to 6 mg).

Accumulation

To provide some information about the potential systemic accumulation of brolucizumab after repeated IVT dosing, the free brolucizumab concentration 24 hours (C24h, taken as reflect of Cmax) after the third dose (Day 57) was compared with the concentration of brolucizumab 24 hours after the first dose (Day 1). For both the 3 and 6 mg dose levels, the geometric means of C24h ratios (dose 3/dose1) were slightly below 1: 0.69 and 0.78, respectively. Similarly, scatter plot of the values of C24h Day 57 versus those of Day 1 shows the time points to be well distributed about the identity line with no clustering by either dose (3 mg vs 6 mg)

or ancestry (Japanese or non-Japanese). This suggests that no meaningful systemic accumulation of brolucizumab was observed between the first and third injection for patients with nAMD regardless of dose (3 mg vs 6 mg). This finding appears to be confirmed by the very low geometric mean (±SE) concentrations of brolucizumab at D84 (D28 after third dose) found to be 0.556 (± 0.112) ng/mL (close to LLoQ =0.5 ng/mL) and comparable to levels at D28 after the first injection (0.601 ng/mL ±0.116).

Studies RTH258-C001 and C002

In these pivotal phase III, two-year studies designed to compare efficacy and safety of brolucizumab 6 mg (and 3 mg for study RTH258-C001) with aflibercept 2 mg in subjects with nAMD, ssubjects received 3 monthly loading doses followed by q12w/q8w maintenance regimen for brolucizumab 6 or 3 mg up to two years. To note, this is the recommended dosing regimen in the SmPC.

Sparse trough brolucizumab serum concentrations for subjects receiving brolucizumab were collected prior to dosing and at Week 12, Week 24, Week 36, Week 48, Week 68 and Week 88 (plus Week 4, Week 12 for RTH258-C001).

Descriptive statistics for free brolucizumab serum concentration (ng/mL) are displayed in Table 6 and Table 7, respectively for study RTH258-C001 and C002.

Table 6: Descriptive statistics for free brolucizumab serum concentration (ng/mL) in Study RTH258-C001

Nominal/Timepoint	n	Geo. Mean	Median	Min	Max
Brolucizumab 3 mg					
Week 4	239	BLQ	BLQ	BLQ	11.2
Week 12	350	BLQ	BLQ	BLQ	7.18
Week 24	334	BLQ	BLQ	BLQ	9.13
Week 36	327	BLQ	BLQ	BLQ	3.82
Week 48	317	BLQ	BLQ	BLQ	7.57
Week 68	300	BLQ	BLQ	BLQ	5.11
Week 88	293	BLQ	BLQ	BLQ	2.70
Brolucizumab 6 mg					
Week 4	251	BLQ	BLQ	BLQ	27.2
Week 12	343	BLQ	BLQ	BLQ	12.3
Week 24	336	BLQ	BLQ	BLQ	41.0
Week 36	327	BLQ	BLQ	BLQ	117
Week 48	319	BLQ	BLQ	BLQ	56.8
Week 68	294	BLQ	BLQ	BLQ	3.31
Week 88	288	BLQ	BLQ	BLQ	8.88

Table 7: Descriptive statistics for free brolucizumab serum concentration (ng/mL) in study Study RTH258-C002

Nominal/Timepoint	n	Geo. Mean	Geo. SE	Median	Min	Max
Brolucizumab 6 mg						
Week 12	353	0.537	0.0319	BLQ	BLQ	38.9
Week 24	351	BLQ	-	BLQ	BLQ	34.0
Week 36	348	BLQ	-	BLQ	BLQ	24.9
Week 48	346	BLQ	-	BLQ	BLQ	19.9
Week 68	337	BLQ	-	BLQ	BLQ	3.18
Week 88	322	BLQ	-	BLQ	BLQ	44.3

BLQ = Below the limit of quantification (<0.5 ng/mL).

BLQ values are replaced by one half of the LLOQ (0.25 ng/mL) in the calculation of the summary statistics. If the calculated value is less than 0.5, then "BLQ" is displayed instead.

Overall, the free brolucizumab serum concentrations appear to be low. In both studies, the geometric mean and the median concentration were below the LLoQ across the various time-points, except for the time-point Week 12 in study RTH258-C002. The maximum concentration observed at each time-point ranged between 2.70 ng/mL to 117 ng/mL (RTH258-C001) and between 3.18 ng/mL to 44.3 ng/mL (RTH258-C002) with no consistent change in trough brolucizumab concentration across the time-points.

Conclusively, PK data from study RTH258-E003 and pivotal phase III studies in patients with nAMD supported a low systemic exposure following IVT injection of Brolucizumab. In clinical practice, brolucizumab is to be administered monthly for the first three doses and thereafter every 8 or 12 weeks. No systemic accumulation of free brolucizumab is expected after repeated administration (up to two-year treatment).

Special populations

No formal study investigating the effect of renal impairment on the systemic exposure of brolucizumab after IVT injection has been performed.

In study RTH258-E003, the systemic exposure of brolucizumab was evaluated by renal impairment status using creatinine clearance (calculated using the MDRD equation) as a measure of renal function. The mean systemic clearance of brolucizumab (CL= 1690 mL/h) in subjects with mild (50-79 mL/min [n=13]) renal impairment was found within 15% of the mean clearance rate (CL =1910 mL/h) for subjects with normal renal function (≥80 mL/min [n=25]). Subjects with moderate (30-49 mL/min (n=3) renal impairment had a mean systemic clearance (CL= 1320 mL/h) approximately 30 % lower than subjects with normal renal function. Based on these results, the applicant proposes to not adjust the dosing regimen for mild and moderate renal impairment. Based on the results of an additional analysis following re-grading patients according to the recommended renal impairment classification as per EU guideline EMA/CHMP/83874/2014 (normal ≥ 90 mL/min, mild 60- <90 mL/min and moderate renal impairment 30- <60 mL/min), it could be agreed that no significant impact of mild and moderate renal impairment on the overall systemic exposure of brolucizumab is to be expected. For severe renal impairment, no PK/ clinical data were available. The lack of such data in this subgroup is clearly implemented in the SmPC.

No formal study investigating the effect of hepatic impairment on the PK of Brolucizumab has been performed, and no study is requested. Mild and moderate hepatic impairment is not expected to impact the systemic exposure of brolucizumab and no dose adjustment is required in this subgroup of patients.

Gender is unlikely to influence the systemic exposure of this product applied in the eye or eyes. RTH258-E003: no consistent difference in the systemic exposure (Cmax and AUC inf) of brolucizumab were shown between males and females.

Similarly, weight is unlikely to influence the systemic exposure of this product applied in the eye or eyes.

The impact of race on the systemic exposure brolucizumab was investigated study RTH258-E003. Of the 50 patients enrolled, n= 26 Japanese (13 subjects in each dose group 3 and 6 mg) and n =24 non-Japanese (12 subjects in each dose group) ancestry were included.

Following IVT injection of brolucizumab, serum drug concentrations versus time curves show no marked or consistent difference between subjects of Japanese and non-Japanese ancestry. Similarly, comparison of PK parameters based on ancestry showed no consistent or meaningful differences. Indeed, the distribution of these parameters (Cmax, AUCs) by ancestry confirms that any differences in the mean PK parameters are driven by individual differences between subjects, rather than reflecting any systematic effect of ancestry on the PK of brolucizumab. Overall, these results support that the systemic exposure of brolucizumab was comparable between Japanese and Caucasian patients.

In study RTH258-E003 (n=50), most of subjects were in the age categories of 65 to 74 years (n= 22, 44.0%) or 75 to 84 years (n= 18, 36.0%). Only 3 patients were aged 85 years or above. To explore the potential impact of age on the systemic exposure of brolucizumab after IVT injection descriptive statistics and box plots of free serum brolucizumab Cmax and AUCs by age groups were provided. Based on these data, and despite the scarcity of the sample size in each group, the systemic exposure of brolucizumab appears to be comparable to marginally lower in the oldest patient groups. Importantly, no systemic overexposure in the oldest groups (65 to 74 years, 75 to 84 years and age > 85 years) was observed compared to patients <65 years old. Overall, taking into account the comparable systemic exposure levels of brolucizumab across age groups and the fact that no significant overexposure in the oldest patient groups (on the contrary a trend to a lower exposure was observed), it could be agreed that age is not expected to have a significant impact on the systemic brolucizumab exposure.

Pharmacokinetics was not assessed in the paediatric population, since nAMD does not occur in this population.

Table 8

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	22	18	3

Pharmacokinetic interaction studies

Brolucizumab and VEGF do not bind to cytokines that modulate the expression of CYP450 isozymes or drug transporters and therefore should not have the potential to indirectly alter the clearance rate of small molecule drugs that are metabolized or transported by these pathways. Therefore, no specific drug-drug interaction studies were performed.

2.4.3. Pharmacodynamics

Mechanism of action

The key functional property of brolucizumab is its ability to bind to human VEGF-A and prevent VEGF-A binding to the VEGF receptors VEGFR1 and VEGFR2, thereby neutralizing its activity by halting the growth of neovascular lesion and to reducing retinal thickness. Brolucizumab was designed by grafting the binding regions of a novel anti-VEGF antibody onto a proprietary human scFv scaffold, combining optimized biophysical properties with potent, high-affinity anti-VEGF attributes.

Primary and Secondary pharmacology

No dedicated studies have been performed by the Applicant to investigate pharmacodynamic as the concentration of VEGF in the serum is not known to be directly associated with the VEGF concentration in the eye.

However, an anatomical evaluation has been performed along the Phase III studies showing an improvement in anatomical parameters (i.e., CSFT, SRF, IRF, sub-RPE fluid).

Additionally, nonclinical studies have demonstrated the PD effect of brolucizumab on retinal vascular permeability and choroidal neovascularisation.

Discussion on clinical pharmacology

Brolucizumab is a humanized single-chain Fv antibody fragment inhibitor of VEGF with a molecular weight of ~26 kDa developed for the treatment of nAMD.

Subjects with nAMD have elevated ocular concentrations of vascular endothelial growth factor (VEGF), which is thought to play a key role in the neovascularization process. The key functional property of brolucizumab is its ability to bind to human VEGF-A and prevent VEGF-A binding to the VEGF receptors VEGFR1 and VEGFR2, thereby neutralizing its activity.

Some concerns were raised with regards to bioanalysis methods (including long term stability data). In the responses to Day 120 list of questions, the applicant confirms that all samples for the pivotal PK study were performed within the demonstrated stability of 538 days, although in study RTH258-C002, 99.9% of the samples and 95.8% of the samples in RTH258-C001 are covered by the established 538 days of long term stability (LTS). According to the applicant, additional LTS experiment is ongoing. The issue can be considered as resolved.

The lack investigations on metabolism and excretory pathways is acceptable, as metabolism and elimination of brolucizumab is assumed to be similar to other proteins, which are mainly eliminated by renal route, and catabolized by lysosomal proteolysis (to small peptides or amino acids) and then eliminated (no specific route), with limited effect of single organs on the overall elimination.

Based on these results of study RTH258-E003, no significant impact of mild and moderate renal impairment on the overall systemic exposure of brolucizumab is expected. For severe renal impairment, no PK/ clinical data were available. The lack of such data in this subgroup is clearly implemented in the SmPC.

Overall, considering the comparable systemic exposure levels of brolucizumab across age groups and the fact that no significant overexposure in the oldest patient groups was observed, it could be agreed that age is not expected to have a significant impact on the systemic brolucizumab exposure.

No dedicated pharmacodynamics (PD) studies have been conducted, as the concentration of VEGF in the serum is not known to be directly associated with the VEGF concentration in the eye. However, an anatomical evaluation had been performed along the Phase III studies showing an improvement in anatomical parameters (i.e., CSFT, SRF, IRF, sub-RPE fluid). Additionally, nonclinical studies have demonstrated the PD effect of brolucizumab on retinal vascular permeability and choroidal neovascularisation.

Serum concentrations of brolucizumab in this study were measured using an ELISA method which was subsequently found to no longer be reliable. This was due to lack of standard curve ruggedness and selectivity as the original lot of biotinylated detection antibody was no longer available. Moreover, this study used an initial drug product which is different from formulation A used in phase III for efficacy and safety demonstration and from the commercial product. Therefore, PK data from this study are to be interpreted with caution and to not be combined with other PK data as no cross-validation data were provided between the analytical methods.

2.4.4. Conclusions on clinical pharmacology

Overall the pharmacokinetics of brolucizumab have been thoroughly investigated and well described.

No specific pharmacodynamic studies were conducted with brolucizumab. It is intended that intravitreal injection would allow adequate vitreous concentration to bind ocular VEGF. Nonclinical studies together with anatomical evaluation in Phase III studies suggest that brolucizumab, by binding VEGF, has a PD effect on neovascular lesions and retinal thickness.

2.5. Clinical efficacy

The clinical study program consists of 2 randomized, double-masked, multicentre, active-controlled (versus aflibercept 2 mg) studies (RTH258-C001 [HAWK study] and RTH258-C002 [HARRIER study]) trials to evaluate the safety and efficacy of brolucizumab administrated intravitreally.

2.5.1. Dose response studies

The selection of the dose of brolucizumab is based on a Phase I study (C-10-083 – SEE study) and a Phase II study (C-12-006 – OSPREY study), with the additional consideration that from the quality point of view brolucizumab cannot be formulated to deliver a concentration of more than 6 mg in a 50 µl dose.

C-10-083 (SEE study)

SEE Study is a multicenter, double-masked, randomized, single ascending dose (0.5, 3.0, 4.5, and 6 mg), active-controlled, parallel-group Phase I study, intended to evaluate the safety and efficacy of a single intravitreal administration of brolucizumab solution at different doses, compared with ranibizumab 0.5 mg in subjects with primary subfoveal choroidal neovascularization secondary to AMD. Patients received a single dose at D0 followed by visits scheduled at Day 1, then every two weeks until Month 3, and monthly until Month 6.

The study population included males and females who were 50 years of age and older and were diagnosed with primary CNV secondary to AMD in the study eye. Subjects (n=194) were randomized within dosing

cohorts to receive either brolucizumab 0.5mg (n=10), 3.0mg (n=35), 4.5mg (n=48) and 6.0mg (n=40), or ranibizumab 0.5mg (n=61). The same number of patients were evaluable for intent-to-treat analysis.

The primary efficacy endpoint was the change from Baseline to Month 1 in central subfield thickness (CSFT) as measured by SD-OCT analysed in a non-inferiority setting. The secondary efficacy endpoint was the duration of effect measured by time from randomization to receipt of standard of care (SOC) as determined by the Investigator using protocol-specified criteria. Change from baseline in best corrected visual acuity (BCVA) had been also measured for supportive outcomes.

As the maximum benefit, for instance in visual function (BCVA) was not expected to be reached with a single dose, this study cannot be considered as true dose-response study. Together with the limited number of patients (especially for 0.5 mg brolucizumab group, n=10) and the early primary endpoint, provided outcomes are preliminary dose response tendencies.

IVT injections of single doses of brolucizumab were associated with improvements in CSFT and in BCVA at Month 1. The non-inferiority versus ranibizumab 0.5 mg was met for the 4.5 mg and the 6 mg dose. However, differences in CSFT between 3 mg, 4.5 mg and 6 mg versus ranibizumab were numerically small (with 90% CI, respectively 23.82 µm [-6.58, 54.23], 22.86 µm [-9.28, 54.99] and 19.40 µm [-9.00, 47.80]). Similarly, small differences were measured for the 3 tested drug concentrations (3 mg, 4.5 mg and 6 mg), in BCVA at Month 1.5 respectively 6.7, 7.2 and 10.4 letters, respectively. Although CSFT outcomes were numerically in favour of the 4.5 mg dose, BCVA was numerically in favour of the 6 mg dose. Usually, it is preferred to select the lowest dose to minimise adverse effects that is commensurate with adequate efficacy.

A trend towards a longer duration of effect (secondary efficacy endpoint) was observed in each brolucizumab group relative to the ranibizumab group. The median times to receiving SOC for subjects in the brolucizumab 3.0, 4.5, and 6.0 mg groups were 75.0, 67.5, and 75.0 days, respectively; the median time to receiving SOC for subjects in the ranibizumab group was 45.0 days.

The mean changes from Baseline in BCVA (a supportive efficacy parameter in this study) observed were consistently larger in the brolucizumab 6.0 mg group than that observed in the ranibizumab group and all brolucizumab lower doses (e.g., mean change in BCVA at Month 1.5 was 6.0, 6.7, 7.2 and 10.4 letters in the 0.5, 3, 4.5 and 6 mg brolucizumab doses, respectively).

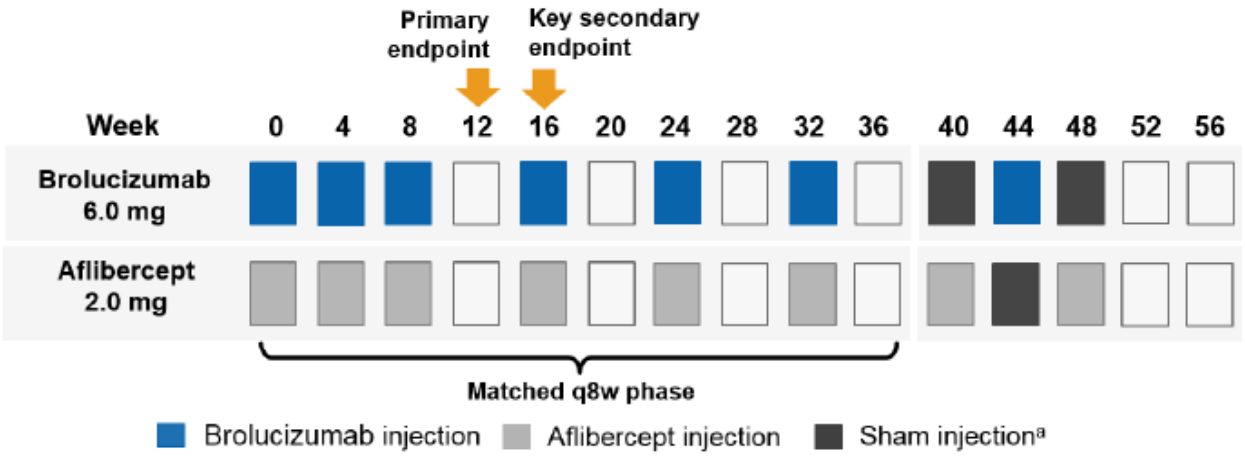
C-12-006 (OSPREY study)

C-12-006 was a prospective, randomized (1:1), double-masked, multicentre, two-arm study to further assess efficacy and safety of treatment with brolucizumab at a dose of 6 mg compared to aflibercept 2 mg. The total duration of the study was 56 weeks.

The study population was comprised of 90 subjects who were ≥ 50 years of age with untreated active choroidal neovascularization due to AMD in the study eye.

After a loading phase of 3 monthly injections (q4w), subjects were treated every 8 weeks (q8w) up to Week 32. After Week 32, subjects randomized to aflibercept 2 mg continued a q8w interval, (i.e., received 2 injections at Weeks 40 and 48), while subjects randomized to brolucizumab were switched to a quarterly regimen (q12w) receiving only one additional injection at Week 44.

Figure 3: Visit schedule and drug administration in Study C-12-006



All subjects were evaluated every month. If the Investigator believed that a subject required treatment at a visit in which an injection was not scheduled, the subject could receive an additional treatment at that visit.
[a]Investigators were allowed to administer the injection from Week 40 onward, so masking may have been incomplete.

The primary efficacy endpoint was the change in BCVA from baseline at Week 12. The statistical hypothesis for the primary efficacy endpoint was to demonstrate non-inferiority of brolucizumab to aflibercept using a non-inferiority margin of 5 letters and a 1-sided alpha of 0.1, in subjects with primary subfoveal choroidal neovascularization secondary to AMD. Superiority was evaluated at a 1-sided alpha of 0.1 once non-inferiority was concluded.

The key secondary efficacy endpoint was the change in BCVA from baseline at Week 16. The statistical hypothesis for the key secondary efficacy endpoint was to demonstrate non-inferiority of brolucizumab to aflibercept.

Incidence and size of hemorrhages secondary to AMD had been also assessed for supportive outcomes.

Regarding the primary objective, the least squares (LS) estimate of the mean BCVA change from Baseline to Week 12 was 5.75 letters in the brolucizumab 6 mg arm and 6.89 letters in the aflibercept 2 mg arm. The LS estimate of the mean difference between treatment arms in BCVA changes from Baseline to Week 12 was −1.13 letters, with the lower limit of the 80% CI being −4.19 letters. Thus, non-inferiority was met.

Table 9: Least Square Estimates for BCVA Change from Baseline (No. of Letters) to Week 12 (Full Analysis Set/As Treated - LOCF)

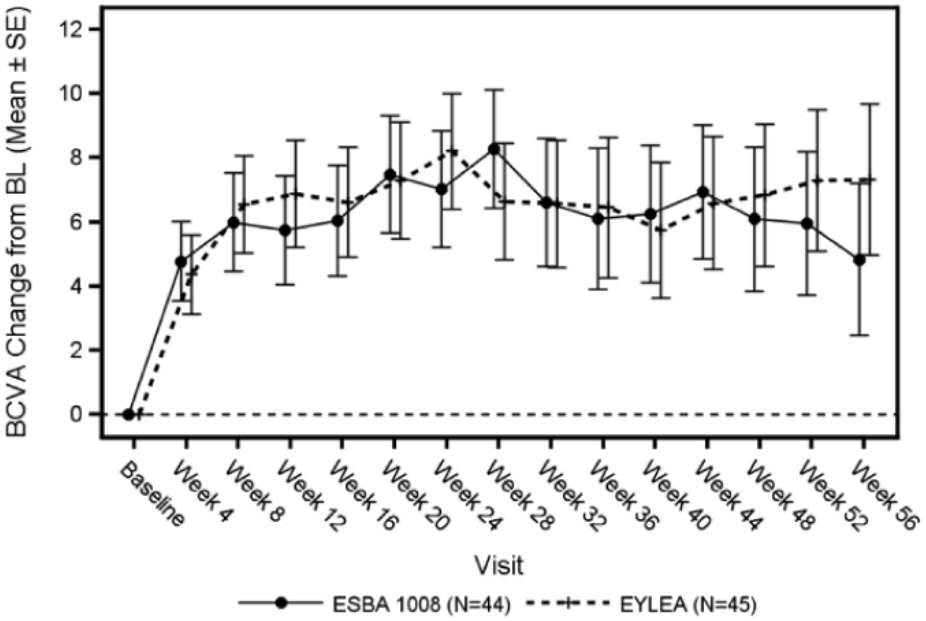
	ESBA 1008 (N=44)	EYLEA (N=45)	Difference (ESBA-EYLEA) 80% CI	p-value*
Mean	5.75	6.89	-1.13 (-4.19, 1.93)	0.6335
(SE)	(1.68)	(1.67)		

ESBA 1008 = ESBA 1008 6 mg/50µL
EYLEA = EYLEA 2 mg/50µL
SE = Standard Error; CI = Confidence Interval
Note: Estimates were based on the Analysis of Variance model. Baseline BCVA (<55 letters and ≥55 letters) included as class variable in the model and using observed weights
*p-values related to the treatment difference
Analysis using actual treatment received

Regarding the secondary study objectives, the LS estimate of the mean BCVA change from Baseline to Week 16 was 6.04 letters in the brolucizumab 6 mg group and 6.62 letters in the aflibercept 2 mg arm. The LS estimate of the mean difference between treatment arms in the BCVA changes from Baseline at Week 16 was −0.58 letters, with the lower limit of the 80% CI being −3.72 letters. Thus, non-inferiority of brolucizumab 6 mg to aflibercept 2 mg was demonstrated.

Below are presented the LS estimates of the mean BCVA change from Baseline over the all duration of the study.

Figure 4: Least Square Estimates for BCVA Change from Baseline (No. of Letters) by Visit Using ANOVA Including BCVA Categories as class variable (Full Analysis Set/As Treated - LOCF)



A further secondary efficacy endpoint was change in central subfield thickness (CSFT) from baseline by visit up to Week 40 (= study period allowing for head to head comparison based on the same treatment schedule).The LS mean changes from Baseline in CSFT in the brolucizumab 6 mg group during the q8w period ranged from −209.90 to −182.25 µm and in the aflibercept 2 mg group from −201.95 to −155.34 µm.

These Phase II results provide support for the regimens selected for Phase III (launching phase, q8w and q12W).

2.5.2. Main studies

RTH258-C001 (HAWK study) and RTH258-C002 (HARRIER study)

Methods

The design of these both Phase III studies is globally similar: randomized, double-masked, multicentre, active-controlled clinical trials to compare the efficacy and safety of brolucizumab 6 mg versus aflibercept 2 mg (Eylea®) in subjects with CNV due to AMD who had not received prior anti-VEGF treatments.

The total studies duration was 96 weeks.

The main differences in study design were that the HAWK study included a brolucizumab 3 mg treatment arm in addition to the 6 mg arm, and HARRIER study included additional disease activity assessments for potential adjusting from q12w to q8w.

It is to emphasize that the selected comparator for the both studies is aflibercept 2 mg IVT (Eylea®). Contrary to the initial development plan, as presented in the Scientific Advice EMA/CHMPA/SAWP/550707/2013, ranibizumab 0.5 mg IVT (Lucentis®) had been fully discarded. The efficacy of aflibercept had been demonstrated through 2 Phase III studies (VIEW 1 and VIEW 2) in a non-inferiority setting versus ranibizumab. There is thus a potential risk of biocreep. Indeed, in the hypothesis that aflibercept would be slightly inferior to ranibizumab, although in the non-inferiority margin, and that brolucizumab would be slightly inferior to aflibercept, although in the non-inferiority margin, this could lead at the end of the day to a lower efficacy. However, it is acknowledged that aflibercept 2 mg is considered to date as a standard of care as ranibizumab 0.5 mg. Thus, it is unlikely that demonstrating that brolucizumab is non-inferior to aflibercept lead to a loss of efficacy. Additionally, the applicant justified the choice of aflibercept as comparator for the both Phase III studies by the fact that:

- The use of the same comparator in both Phase III studies allowed for confirmation and external validation of the study results;

- Ranibizumab had a different posology in the US (monthly injections) than in other countries including Europe (3-times monthly loading doses followed by a pro-re-nata regimen).

The regimen for aflibercept was fixed after the loading phase to every 2 months. No personalised treatment was allowed, even after Month 12, despite that it was authorized at the time of the studies in the Summary of Product Characteristic of Eylea® from the second year. The total number of injections was thus maintained in the control groups regardless of the disease activity of the patients, contrary to the brolucizumab groups for which every 3 months administration was permitted. Consequently, the clinical development does not allow to demonstrate strong conclusion on the reduction of the treatment burden of brolucizumab 3 mg or 6 mg compared to a standard of care.

Study Participants

The study population consisted of subjects ≥ 50 years of age with active CNV due to AMD who were not previously treated with anti-VEGF therapy. The inclusion and the exclusion criteria were consistent with the target population.

Main ocular inclusion criteria were:

- Active CNV lesions secondary to AMD that affected the central subfield (including retinal angiomatous proliferation lesions with a CNV component) in the study eye at Screening and confirmed by the Central Reading Center (CRC),
- Total area of CNV (including both classic and occult components) must have comprised > 50% of the total lesion area in the study eye at Screening and confirmed by the CRC,
- Intraretinal and/or subretinal fluid (SRF) affecting the central subfield of the study eye at Screening and confirmed by the CRC,
- BCVA between 78 and 23 letters, inclusive, in the study eye at Screening and Baseline using Early Treatment Diabetic Retinopathy Study (ETDRS) testing.

Subjects who received any approved or investigational treatment for nAMD (other than vitamin supplements) in the study eye at any time were excluded of the studies.

HAWK study was conducted in centres in North America, Latin America, Japan, Australia, New Zealand and Israel, whereas HARRIER study was conducted in centres in the EU, Middle East, Asia and Russia.

Overall, in HAWK study approximately 990 subjects (330 per treatment arm) were planned for randomization across approximately 320 study centres. In HARRIER study approximately 660 subjects (330 per treatment arm) were planned for randomization across approximately 200 study centres. In both studies subjects who discontinued the study were not replaced.

The upper baseline BCVA limit for inclusion was 78 letters. It is supported that source population should reflect current usual practice where patients can be treated early in the course of the disease despite a mild impairment only. Nonetheless, given that 84 letters is equivalent to a 20/20 visual acuity, these patients have less amplitude for improvement, inferior to the effect size observed in the more impaired patients. Therefore, the limited room for improvement may not allow to observe a difference between aflibercept and brolucizumab if exists. To that extent, subset analysis by BCVA at Baseline will be of importance, showing that non inferiority is met while removing less impaired patients. It is also noted that the upper limit of 73 letters had been used in VIEW 1 and VIEW 2 studies to demonstrate the non-inferiority of Eylea® compared to Lucentis®.

Additionally only naïve patients were enrolled in the phase III studies. Subjects having not received any approved treatment for wAMD were excluded.

Treatments

The doses for Phases III were chosen based on the results of the Phase I SEE study (assessing the 0.5, 3.0, 4.5, and 6 mg doses) and the Phase II OSPREY study (assessing the 6 mg dose). It was observed that brolucizumab doses below 3 mg had an inferior efficacy at Month 1 compared to ranibizumab 0.5 mg.

The 6 mg dose was tested in both studies, whereas the 3 mg dose was tested in the HAWK study only

Patients in all treatment arms received 3 monthly loading doses (Day 0, Week 4 and Week 8) based on the fact that the efficacy of this regimen had been demonstrated for other anti VEGF products used in AMD. Additionally, supportive data had been also provided along the Phase II OSPREY study results.

The loading phase was followed by maintenance regimens:

• brolucizumab 3 mg, every 12 weeks (q12w)/every 8 weeks (q8w) (HAWK study only),

• brolucizumab 6 mg, q12w/q8w,

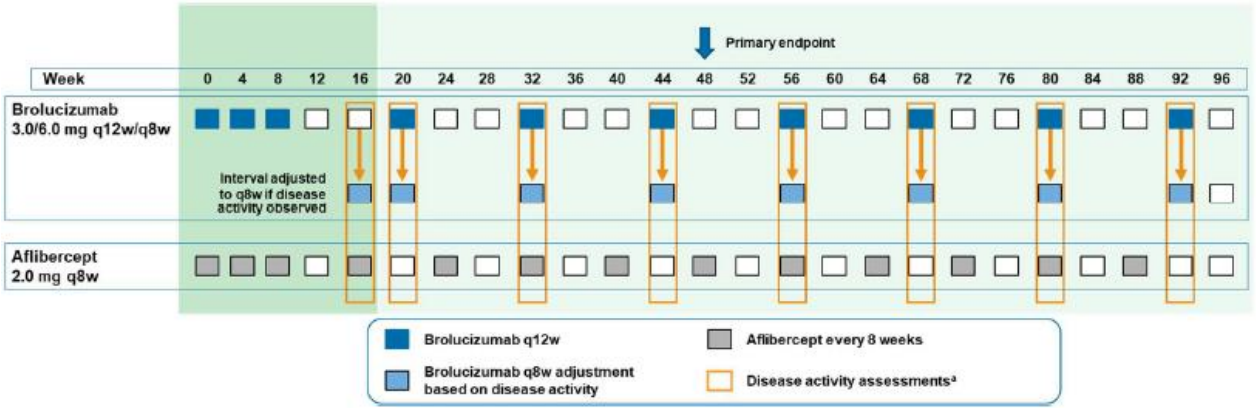
• aflibercept 2 mg, q8w.

"Q12w/q8w" maintenance regimen represents a treatment regimen where the interval could be adjusted according to the subject's individual treatment need as identified by disease activity assessments (DAAs) performed by the masked investigator at pre-specified visits (week 16, week 20, week 32, week 44, week 56, week 68, week 80 and week 92 in HAWK study and week 16, week 20, week 28, week 32, week 40, week 44, week 52, week 56, week 64, week 68, week 76, week 80, week 88, and week 92 in HARRIER study).

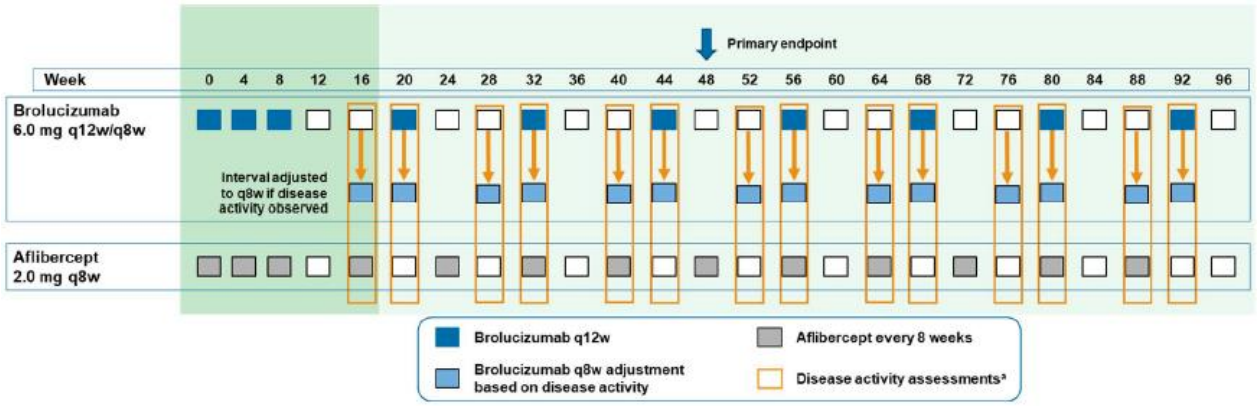
Within the q12w/q8w regimen, the initial treatment after the loading phase was q12w. If disease activity was identified by the masked investigator in brolucizumab-treated patients at any of the DAAs, dosing was adjusted to q8w ("q12w/q8w regimen"). Once subjects were adjusted to a q8w interval, they stayed on that interval until the end of the study (Week 96/Exit).

Figure 5: Study design

a) HAWK study



b) HARRIER study



The regimen every 8 weeks (q8w) and every 12 weeks (q12w) is supported. However, it is to note that patients switched to q8w were not able to switch back on q12w. If this design is appropriate to assess the probability to stay on q12w over the time (see section regarding objectives), this might be not representative of the real-life conditions where intervals between treatments can be re-extended.

Additionally, individualized regimen, Pro Re Nata (PRN) or Treat-and-Extend (T-&-E), had not been investigated in neither of the two-Phase III studies.

Disease activity guidance criteria at Week 16 were:

• Decrease in BCVA of ≥ 5 letters compared with Baseline,

• Decrease in BCVA of ≥ 3 letters and CSFT increase ≥ 75 µm compared with Week 12,

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

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

Disease activity guidance criterion at Weeks 20, 28, 32, 40, and 44 was:

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

Disease activity guidance criterion at Weeks 52, 56, 64, 68, 76, 80, 88, and 92 was:

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

Guidance criteria for disease activity at Week 16 are acceptable. Nonetheless, those were less stringent for visits from Week 20. It is not clear why the criteria were not same over the entire duration of the study, and whether this change might influence the estimation of the probability for a patient to remain on q12w regimen.

Objectives

- Primary objective

The primary objective was to demonstrate that the efficacy brolucizumab 6 mg (additional 3 mg arm in HAWK study) is not inferior to aflibercept 2 mg, which is a standard of care medication, which is supported despite the concerns raised above regarding the choice of the comparator.

- Secondary objectives

Key secondary objectives assessed the maintenance of patients treated with brolucizumab on q12w regimen, globally ("maintaining on q12w") and in subjects with no need of q8w at Week 16 or Week 20 ("remaining on q12w").

Additional secondary objectives were to assess the safety and tolerability of brolucizumab relative to aflibercept and to assess anatomical parameters of disease activity.

Besides, following Week 48 results in the HARRIER study, additional hypotheses testing for superiority of brolucizumab versus aflibercept were added in HAWK study. For each dose (3mg and 6 mg) change in CSFT from baseline and retinal fluid status were assessed at Week 16, Week 48 and the period Week 36 through Week 48. Disease activity was assessed at Week 16 and at Week 48. However, the selection of these outcomes and timepoints over others for superiority testing were not justified and visual acuity had not been chosen.

Outcomes/endpoints

The primary endpoint was mean BCVA change from Baseline to Week 48.

The second and third key secondary endpoints were as follows:

- The proportion of subjects receiving q12w (1 injection every 12 weeks) up to Week 48 in the brolucizumab 6 mg treatment arm ("maintaining on q12w"),

- The predictive value of the first ("initial") q12w cycle for maintenance of q12w treatment up to Week 48 in the brolucizumab 6 mg treatment arm ("remaining on q12w").

Further secondary or exploratory endpoints were changes up to Week 96 of BCVA, responder analysis in visual acuity, and anatomical parameters of disease activity including central subfield thickness (CSFT), CNV area, and retinal fluids. Exploratory endpoints included also assessment of the Quality of life assessed through the VFQ-25 questionnaire.

Sample size

A sample size of 297 subjects per treatment arm was considered sufficient to demonstrate non-inferiority (margin = 4 letters) of brolucizumab 3 mg/6 mg versus aflibercept 2 mg with respect to the change in BCVA from Baseline to Week 48 at a 2-sided alpha level of 0.05 with a power of approximately 90%, assuming equal efficacy and a common SD of 15 letters.

A power of at least 90% can be expected for the first key secondary efficacy endpoint, assuming that averaging over the 4 time points would not lead to an increase in the SD.

To account for a dropout rate of 10%, a total of 330 subjects were planned for randomization into each treatment arm. A total of 990 subjects was planned for randomisation in HAWK study (3mg group, 6 mg group and aflibercept group), and a total of 660 subject was planned for randomisation in HAWK study (6 mg group and aflibercept group).

Randomisation

After confirmation of eligibility at Baseline, subjects were randomized centrally, using an Interactive Response Technology, to brolucizumab 3mg (HAWK study only), brolucizumab 6 mg and aflibercept 2 mg in a respectively 1:1:1 ratio and 1:1 ratio.

At Baseline, all eligible subjects were randomized centrally using an Interactive Response Technology (IRT) system in a (1:)1:1 ratio to receive one of the study treatments. The unmasked injecting Investigator or his/her unmasked delegate contacted the IRT after confirming that the subject met all the inclusion and none of the exclusion criteria. The IRT assigned a randomization number to the subject, which was used to link the subject to a treatment arm and specified a unique medication number for the first package of study treatment to be administered to the subject. The randomization number was not communicated to unmasked staff.

A member of the Statistical Programming group who was not part of the study team generated the randomized allocation for the study treatment assignment based on a randomization plan that provided study specific criteria for randomization, including block size and randomization ratio.

Central randomization, without stratification by investigational site, was employed.

Subjects who discontinued the study were not replaced.

Blinding (masking)

This was a double-masked study. The subjects, investigators, study centre staff (except for the unmasked study centre personnel and unmasked injecting physician), Sponsor personnel (except for those who have been delegated responsibility for working with the study treatment), and data analysts remained masked to the identity of the treatment from the time of randomization until Week 48 and final database locks.

Sham injections were administered to establish an identical monthly injection schedule across treatment arms given the differences of regimen. To maintain the masking and data integrity, at least 2 investigators (and corresponding study centre staff) were involved in the study at each study centre: 1 masked (evaluating) investigator performed all assessments and captured data in the electronic data capture system, and 1 unmasked (treating) investigator administered the randomized study treatment according to the protocol. The investigators were to maintain the same role throughout the study.

Statistical methods

Related to the primary objective, the statistical analysis plan for both studies specified 4 and 2 non-inferiority hypotheses (for HAWK and HARRIER respectively) to be tested hierarchically, in a pre-specified order. Each of these 4 non-inferiority hypotheses exceeded the threshold for statistical significance (one-sided $p<0.025$).

Non-inferiority testing related to the primary efficacy parameter BCVA was based on a margin of 4 letters. This is acceptable since it is generally admitted that a change in BCVA is clinically significant from 5 letters.

FAS and PPS were properly used to assess primary endpoint, according to guidelines on non-inferiority testing. Moreover, the definition of the analysis population is appropriate:

- The full analysis set (FAS)

FAS included all randomized subjects who received at least 1 IVT injection of study treatment. The FAS served as the primary analysis set for all efficacy analyses and represented the analysis set that was as close as possible to the intent-to-treat principle of including all randomized subjects. The subjects in the FAS were analysed according to the treatment arm they were assigned at randomization.

- The per protocol analysis set (PPS)

PPS was a subset of the FAS that excluded subjects with protocol deviations and violations of analysis requirements that were expected to majorly affect the validity of the assessment of efficacy at Week 48. These violations included, but were not limited to, lack of compliance (including study treatment misallocation), missing data, use of prohibited concomitant medications, and deviations from the inclusion/exclusion criteria. Discontinuation from study treatment due to a lack of efficacy did not constitute a reason for exclusion from the PPS. Supportive analyses of the primary and secondary efficacy endpoints were performed using the PPS. The subjects in the PPS were analysed according to the treatment arm they were assigned at randomization.

- The safety analysis set (SAF)

SAF included all subjects who received at least 1 IVT injection. Subjects in the SAF were analysed according to the study treatment from which they received a majority of treatments up to and including Week 44.

No alpha adjustment was applied for testing the hypotheses for the primary and first key secondary efficacy analyses. However, a hierarchically procedure, in a pre-specified order, has been set to handle multiple comparison in primary and first key secondary endpoint.

Sensitivity analysis used a mixed model repeated measures (MMRM) approach (without LOCF imputation). Co-factor were the age, BCVA at Baseline, visits and interaction treatment x visits.

Taking anti-VEGF rescue therapy in the treated eye was a cause of censoring the response to treatment (BCVA score). A complementary analysis not considering this intercurrent event would have been welcome in order to evaluate this treatment intake in terms of care strategy. Unfortunately, it is unclear whether the BCVA score was assessed beyond the event during the 96-weeks follow-up. Furthermore, and according to tables 14.3-4.6a of the HAWK study and HARRIER CSRs, it seems that few subjects used this type of alternative during the study (2 to 3%). However, in order to detail a bit further this possible strategy of care, the following descriptive statistics per arm in the concerned patients should be provided: average time of onset of anti-VEGF rescue in the treated eye through the 96-weeks follow-up as well as the variation of BCVA score at 48 and 96 weeks. Nonetheless, due to the lack of information on taking anti-VEGF rescue therapy after the 48-week efficacy study window, the requested analyses could not be provided by the Applicant. Rescue therapy was a strong reason for patient discontinuation because it was a censoring event in Applicant's phase 3 trials. This missing information would be of important matter because the 96 weeks treatment could have allowed a more complete exploration of the treatment efficacy as a treatment policy.

The choice of the subgroups, as listed below, were appropriate:

- Age category (< 75 years and ≥ 75 years),
- Sex (male and female),
- Baseline BCVA categories (≤ 55, 56-70, and ≥ 71 letters),

- Baseline CSFT category (< 400 and ≥ 400 μm),
- Baseline lesion type (predominantly classic, minimally classic, occult),
- Baseline CNV lesion size (tertiles),
- Baseline lesion size by lesion type (predominant classic vs minimally classic/occult) (tertiles),
- Baseline fluid status (IRF, SRF, sub-RPE fluid),
- Japanese ethnicity: Japanese versus non-Japanese,
- Baseline polyp status (present/absent) from ICG assessment at Screening (study centres in Japan only).

The subgroup analyses were performed for the primary and key secondary efficacy variables. The FAS with missing/censored values imputed using LOCF and observed case analyses were used for the subgroup analyses.

Results

Participant flow

HAWK study

Of the 1775 subjects who were screened, 693 were screen failures. Overall, 1082 subjects were randomized 1:1:1 into the study as follows: 360 into the brolucizumab 3 mg arm, 361 into the brolucizumab 6 mg arm, and 361 into the aflibercept 2 mg arm. Four subjects were randomized but did not receive treatment.

HARRIER study

Of the 1048 subjects who were screened, 305 were screen failures. 743 subjects were randomized 1:1 into the study as follows: 372 into the brolucizumab 6 mg arm and 371 into the aflibercept 2 mg arm. Four subjects were randomized but did not receive treatment.

Recruitment

HAWK study

The first subject for this study was screened on 08-Dec-2014 and treated on 11-Dec-2014. The last subject completed the Week 48 visit on 22-Apr-2017. The last subject completed the Week 96 visit on 28-Mar-18.

HARRIER study

The first subject for this study was screened on 28-Jul-2015 and treated on 31-Jul-2015. The last subject completed the Week 48 visit on 05-Apr-2017. The last subject completed the Week 96 visit on 08-Mar-2018.

Conduct of the study

HAWK study

The SAP for this study was amended based on the outcome from study RTH258–C002. This amendment was finalized prior to the DBL. The amendment introduced additional hypotheses testing for superiority of brolucizumab versus aflibercept related to CSFT, retinal fluid, and disease activity. Correspondingly, the analysis plan also pre-specified a proper management of the global alpha-level in relation to the resulting multiple testing. As these hypotheses were derived from an independent source (HARRIER study) and were pre-specified prior to unmasking of this study all related statistical significances for superiority provide confirmatory evidence.

HARRIER study

The study protocol was amended 3 times. The Applicants stated that these amendments were not considered to have affected the interpretation of study results as they were minor and occurred prior to study unmasking.

Baseline data

Disease characteristics were well balanced among groups. The mean BCVA at baseline was 60.6 letters and 61.2 letters respectively in HAWK study and HARRIER study. Mean CSFT was 462.5 µm and 469.5 µm. Lesion subtypes were also balanced across study groups as reported above with a predominance of occult lesions in all groups.

Likewise, there were no concerns about demographics.

It is to note that the area of lesion associated with CNV was higher in the HAWK study, 4.5 mm2, rather than in the HARRIER study, 2.8 mm2. However, the size was well balanced across the arms within each study.

The time since diagnosis of nAMD was well balanced among groups, large majority of the patients having a diagnosis inferior to 3 months. This is reassuring since duration of exudative disease is one of the main factors associated with choroidal neovascularization lesion size enlargement.

Polypoidal Choroidal Vasculopathy (PCV) is a subtype of nAMD known to be more prevalent in the East Asian population than in the European population. These patients had been enrolled only in the HAWK study and in a very limited proportion. Therefore, there are no concerns about the impact of this subgroup on the overall results.

The demographic characteristics in FAS population are presented below.

Table 10: Demographic characteristics (FAS) – Week 48 Analysis

	Study RTH258-C001			Study RTH258-C002	
Demographic Characteristics	**Brolucizumab 3mg (N=358)**	**Brolucizumab 6mg (N=360)**	**Aflibercept 2mg (N=360)**	**Brolucizumab 6mg (N=370)**	**Aflibercept 2mg (N=369)**
Age (years)					
n	358	360	360	370	369
Mean (SD)	76.7 (8.28)	76.7 (8.95)	76.2 (8.80)	74.8 (8.58)	75.5 (7.87)
Median	78.0	78.0	77.0	75.0	76.0
Minimum-Maximum	50-96	51-97	51-96	50-94	52-95
Age group – m (%)					
n	358	360	360	370	369
<50 Years	0	0	0	0 (0.0)	0 (0.0)
50-64 Years	31 (8.7)	35 (9.7)	37 (10.3)	44 (11.9)	28 (7.6)
65-74 Years	103 (28.8)	103 (28.6)	112 (31.1)	124 (33.5)	126 (34.1)
75-84 Years	162 (45.3)	155 (43.1)	148 (41.1)	150 (40.5)	167 (45.3)
>=85 Years	62 (17.3)	67 (18.6)	63 (17.5)	52 (14.1)	48 (13.0)
Sex – m (%)					
n	358	360	360	370	369
Male	148 (41.3)	155(43.1)	166(46.1)	160 (43.2)	157 (42.5)
Female	210 (58.7)	205(56.9)	194(53.9)	210 (56.8)	212 (57.5)
Race – m (%)					
n	358	360	360	370	369
White	302(84.4)	285(79.2)	287(79.7)	340 (91.9)	341 (92.4)
Black Or African American	1(0.3)	1(0.3)	1(0.3)	1 (0.3)	0 (0.0)
American Indian Or Alaska Native	1(0.3)	1(0.3)	1(0.3)	0 (0.0)	0 (0.0)
Asian	44(12.3)	61(16.9)	53(14.7)	22 (5.9)	23 (6.2)
Native Hawaiian Or Other Pacific Islander	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	0 (0.0)
Other	9(2.5)	9(2.5)	17(4.7)	5 (1.4)	4 (1.1)
Multiple	1(0.3)	3(0.8)	1(0.3)	2 (0.5)	1 (0.3)
Ethnicity – m (%)					
n	358	360	360	370	369
Hispanic/Latino	32(8.9)	29(8.1)	40(11.1)	23 (6.2)	25 (6.8)
Not Hispanic Or Latino	323(90.2)	329(91.4)	319(88.6)	321 (86.8)	322 (87.3)
Not Reported	1(0.3)	1(0.3)	0(0.0)	8 (2.2)	5 (1.4)
Unknown	2(0.6)	1(0.3)	1(0.3)	18 (4.9)	17 (4.6)
Japanese Ancestry– m (%)					
n	358	360	360	n.a.	n.a.
Japanese	41 (11.5)	60 (16.7)	53 (14.7)	n.a.	n.a.
Non-Japanese	317 (88.5)	300 (83.3)	307 (85.3)	n.a.	n.a.

*Week 48 analysis was based on database locked for the Week 48 analysis
n = Number of subjects with an assessment.
m = Number of subjects with assessment meeting the criterion for the given categorical variables.
Percentages (%) are calculated based on n.

The baseline ocular characteristics in FAS population are presented below.

Table 11: Baseline ocular characteristics (FAS) – Week 48 Analysis

	Study RTH258-C001			Study RTH258-C002	
Baseline characteristic	Brolucizumab 3mg (N=358)	Brolucizumab 6mg (N=360)	Aflibercept 2mg (N=360)	Brolucizumab 6mg (N=370)	Aflibercept 2mg (N=369)
Time since diagnosis of nAMD - m (%)					
n	358	360	360	369	369
< 1 month	155 (43.3)	159 (44.2)	154 (42.8)	136 (36.9)	139 (37.7)
1 – 3 months	183 (51.1)	184 (51.1)	190 (52.8)	191 (51.8)	197 (53.4)
> 3 months	20 (5.6)	17 (4.7)	16 (4.4)	42 (11.4)	33 (8.9)
Unilateral versus bilateral nAMD – m (%)					
n	358	360	360	370	369
Unilateral	269 (75.1)	271 (75.3)	268 (74.4)	268 (72.4)	255 (69.1)
Bilateral	89 (24.9)	89 (24.7)	92 (25.6)	102 (27.6)	114 (30.9)
BCVA (letters read)					
n	358	360	360	370	369
Mean (SD)	61.0 (13.57)	60.8 (13.66)	60.0 (13.92)	61.5 (12.59)	60.8 (12.93)
Med	64.5	64.0	63.0	64.0	64.0
Min-Max	23-85	23-85	16-83	22-78	23-79
BCVA (letters read) – m (%)					
n	358	360	360	370	369
<=55 letters	109 (30.4)	101 (28.1)	116 (32.2)	102 (27.6)	107 (29.0)
56-70 letters	138 (38.5)	157 (43.6)	153 (42.5)	171 (46.2)	170 (46.1)
>=71 letters	111 (31.0)	102 (28.3)	91 (25.3)	97 (26.2)	92 (24.9)
CSFT-total (µm)					
n	358	360	360	370	369
Mean (SD)	466.6 (167.42)	463.1 (166.62)	457.9 (146.37)	473.6 (171.39)	465.3 (151.21)
Med	426.5	416.5	425.0	433.5	442.0
Min-Max	168-1392	217-1204	215-1082	200-1192	206-1319
CSFT-total (µm) – m (%)					
n	358	360	360	370	369
<400 micrometer	157 (43.9)	157 (43.6)	146 (40.6)	148 (40.0)	130 (35.2)
>=400 micrometer	201 (56.1)	203 (56.4)	214 (59.4)	222 (60.0)	239 (64.8)
Type of CNV - m (%)					
n	358	360	359	370	365
Predominantly classic	122 (34.1)	113 (31.4)	116 (32.3)	154 (41.6)	144 (39.5)
Minimally classic	32 (8.9)	39 (10.8)	34 (9.5)	33 (8.9)	34 (9.3)
Occult	204 (57.0)	208 (57.8)	209 (58.2)	183 (49.5)	187 (51.2)
Area of Lesion associated with CNV (mm^2) – n (%)					
n	358	360	359	370	369
Mean (SD)	4.5 (4.70)	4.6 (4.08)	4.4 (3.72)	2.6 (2.76)	2.9 (3.95)
Med	3.2	3.4	3.7	1.5	1.6
Min-Max	0-28	0-20	0-19	0.022-14	0-33.6
Presence of subretinal fluid - m (%)					
n	358	360	360	370	369
Present	244 (68.2)	250 (69.4)	245 (68.1)	251 (67.8)	268 (72.6)
Absent	114 (31.8)	110 (30.6)	115 (31.9)	119 (32.2)	101 (27.4)

Baseline characteristic	Study RTH258-C001			Study RTH258-C002	
	Brolucizumab 3mg (N=358)	Brolucizumab 6mg (N=360)	Aflibercept 2mg (N=360)	Brolucizumab 6mg (N=370)	Aflibercept 2mg (N=369)
Presence of intraretinal fluid/cyst - m (%)					
n	358	360	360	370	369
Present	196 (54.7)	194 (53.9)	194 (53.9)	149 (40.3)	139 (37.7)
Absent	162 (45.3)	166 (46.1)	166 (46.1)	221 (59.7)	230 (62.3)
Presence of SRF and IRF - m (%)					
n	358	360	360	370	369
Present	330 (92.2)	334 (92.8)	336 (93.3)	330 (89.2)	332 (90.0)
Absent	28 (7.8)	26 (7.2)	24 (6.7)	40 (10.8)	37 (10.0)
Presence of sub RPE fluid - m (%)					
n	358	360	360	370	369
Present	147 (41.1)	168 (46.7)	158 (43.9)	125 (33.8)	127 (34.4)
Absent	211 (58.9)	192 (53.3)	202 (56.1)	245 (66.2)	242 (65.6)
Presence of PCV (Japan subjects only)					
n	40	59	53	n.a.	n.a.
Present	20 (50.0)	39 (66.1)	30 (56.6)	-	-
Absent	20 (50.0)	20 (33.9)	23 (43.4)	-	-

n = Number of subjects with an assessment.
m = Number of subjects with assessment meeting the criterion for the given categorical variables.
Percentages (%) are calculated based on n.
n.a. = not applicable. PCV: polypoidal choroidal vasculopathy
Occult is considered present if at least one of the three sub-types (Fibrovascular PED, Serous PED and Late Leakage) is present (PED: pigment epithelial detachment)
"Predominantly classic" category includes both "Predominantly classic" and "Pure classic" sub-categories.

Numbers analysed

Number of subject analysed is presented below.

Table 12: Subject disposition in HAWK study

	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg
Number Randomised	360	361	361
Full Analysis Set	358 (99.4%)	360 (99.7%)	360 (99.7%)
Per protocol Set	325 (90.3%)	328 (90.9%)	312 (86.4%)
Completed Week 48	334 (92.8%)	333 (92.2%)	327 (90.6%)
Completed Week 96	310 (86.1%)	304 (84.2%)	297 (82.3%)
Subjects with at least one protocol deviation	58 (16.1%)	46 (12.7%)	52 (14.4%)

Table 13: Subject disposition in HARRIER study

	Brolucizumab 6 mg	Aflibercept 2 mg
Number Randomised	372	371
Full Analysis Set	370 (99.5%)	369 (99.5%)
Per protocol Set	351 (94.4%)	341 (91.9%)
Completed Week 48	354 (95.2%)	352 (94.9%)
Completed Week 96	342 (91.9%)	329 (88.7%)
Subjects with at least one protocol deviation	43 (11.6%)	43 (11.6%)

The number of patients analysed in FAS and PPS is acceptable having regard of the total number of subjects enrolled. Differences between FAS population size and PPS population size remained limited.

Outcomes and estimation

Primary endpoint

Change in BCVA from Baseline to Week 48

According to the primary analysis, in FAS as well as in PPS, the non-inferiority of all brolucizumab groups (3 mg and 6mg) over the aflibercept group was demonstrated in HAWK and HARRIER studies. Analysis in FAS and PPS were consistent. Indeed, all the lower limits of the 95% CI of the difference of the LS mean change in mean BCVA from baseline between brolucizumab and aflibercept were superior to -4 letters.

Table 14: Best-corrected visual acuity (letters read): summary statistics and ANOVA for change from Baseline at Week 48 (FAS – LOCF)

	Study RTH258-C001			Study RTH258-C002	
	Brolucizumab 3mg (N = 358)	Brolucizumab 6mg (N = 360)	Aflibercept 2mg (N = 360)	Brolucizumab 6mg (N = 370)	Aflibercept 2mg (N = 369)
Descriptive statistics					
n	358	360	360	370	369
Mean (SD)	5.9 (13.49)	6.4 (14.40)	7.0 (13.16)	6.9 (11.47)	7.6 (12.47)
SE	0.71	0.76	0.69	0.60	0.65
Median	7.0	7.5	8.0	8.0	8.0
Min, Max	-57, 51	-69, 52	-57, 54	-57 , 38	-37 , 50
95% CI for mean[1]	(4.5, 7.3)	(4.9, 7.9)	(5.6, 8.3)	(5.8, 8.1)	(6.3, 8.9)
Pairwise ANOVA [2]					
LS mean estimate (BRO3 vs. AFL2)					
LS mean (SE)	6.1 (0.69)		6.8 (0.69)	-	-
95% CI for LS mean	(4.8, 7.5)		(5.4, 8.1)	-	-
LS mean estimate (BRO6 vs. AFL2)					
LS mean (SE)		6.6 (0.71)	6.8 (0.71)	6.9 (0.61)	7.6 (0.61)
95% CI for LS mean		(5.2, 8.0)	(5.4, 8.2)	(5.7 , 8.1)	(6.4 , 8.8)
LS mean difference (Brolucizumab - Aflibercept)					
Difference (SE)	-0.6 (0.98)	-0.2 (1.00)		-0.7 (0.86)	
95% CI for treatment difference	(-2.5,1.3)	(-2.1,1.8)		(-2.4 , 1.0)	
p-value for treatment difference (2-sided)	0.5237	0.8695		0.4199	
p-value for noninferiority (4 letter margin)(1-sided)	0.0003	<0.0001		<0.0001	

BRO3 = Brolucizumab 3 mg; BRO6 = Brolucizumab 6 mg; AFL2 = Aflibercept 2 mg.
n is the number of subjects with data used in the model.

[1] 95% CI for the mean are based on t-distribution.
[2] Analyzed using ANOVA model with Baseline BCVA categories (<=55, 56-70, >=71 letters), age categories (<75, >=75 years) and treatment as fixed effect factors.
BCVA assessments after start of alternative anti-VEGF treatment in the study eye are censored and imputed by the last value prior to start of this alternative treatment.

	Study RTH258-C001			Study RTH258-C002	
	Brolucizumab 3mg (N = 325)	Brolucizumab 6mg (N = 328)	Aflibercept 2mg (N = 312)	Brolucizumab 6mg (N = 351)	Aflibercept 2mg (N = 341)
Descriptive statistics					
n	325	328	312	351	341
Mean (SD)	6.3 (13.37)	6.6 (14.68)	7.4 (12.71)	7.0 (11.24)	7.8 (12.49)
SE	0.74	0.81	0.72	0.60	0.68
Median	7.0	8.0	8.0	8.0	8.0
Min, Max	-56, 51	-69, 52	-57, 51	-57 , 38	-35 , 50
95% CI for mean[1]	(4.9, 7.8)	(5.0, 8.2)	(6.0, 8.8)	(5.8, 8.2)	(6.5, 9.1)
Pairwise ANOVA [2]					
LS mean estimate (BRO3 vs. AFL2)					
LS mean (SE)	6.5 (0.71)		7.2 (0.73)	-	-
95% CI for LS mean	(5.1, 7.9)		(5.7, 8.6)	-	-
LS mean estimate (BRO6 vs. AFL2)					
LS mean (SE)		6.9 (0.74)	7.1 (0.76)	7.0 (0.62)	7.8 (0.63)
95% CI for LS mean		(5.4, 8.3)	(5.7, 8.6)	(5.8, 8.2)	(6.6, 9.0)
LS mean difference (Brolucizumab - Aflibercept)					
Difference (SE)	-0.6 (1.02)	-0.3 (1.06)		-0.8 (0.88)	
95% CI for treatment difference	(-2.6, 1.4)	(-2.4, 1.8)		(-2.5, 1.0)	
p-value for treatment difference (2-sided)	0.5355	0.7844		0.3771	
p-value for noninferiority (4 letter margin) (1-sided)	0.0005	0.0003		0.0001	

BRO3 = Brolucizumab 3 mg; BRO6 = Brolucizumab 6 mg; AFL2 = Aflibercept 2 mg.
n is the number of subjects with data used in the model.
[1] 95% CI for the mean are based on t-distribution.
[2] Analyzed using ANOVA model with Baseline BCVA categories (<=55, 56-70, >=71 letters), age categories (<75, >=75 years) and treatment as fixed effect factors.
BCVA assessments after start of alternative anti-VEGF treatment in the study eye are censored and imputed by the last value prior to start of this alternative treatment.

In HAWK study, regarding FAS population, the mean change in BCVA from Baseline at Week 48, with 95% CI, for brolucizumab 3 mg, brolucizumab 6 mg and Aflibercept were respectively 6.3 [4.5,7.3], 6.6 [4.9,7.9] and 7.4 [5.6,8.3] letters. In pairwise ANOVA, the non-inferiority of brolucizumab 3 mg and brolucizumab 6 mg compared to Aflibercept were demonstrated with a LS mean difference of 0.6 (95% C.I.: -2.5,1.3; P=0.0003) and -0.2 (95% C.I.: -2.1,1.8; P<0.0001) respectively.

In HARRIER study, regarding FAS population, the mean change in BCVA from Baseline at Week 48, with 95% CI, for brolucizumab 6 mg and aflibercept were respectively 7.0 [5.8,8.1] and 7.8 [6.3,8.9] letters. In pairwise ANOVA, the non-inferiority of brolucizumab 6 mg compared to aflibercept were demonstrated with a LS mean difference of -0.7 (95% C.I.: -2.4,1.0; P<0.0001).

Overall, differences between 3 mg and 6 mg doses across primary and secondary endpoints were numerically very limited and not clinically significant.

First secondary endpoint

Average change in BCVA from Baseline over the period Week 36 through Week 48 (first key secondary endpoint)

Primary endpoint was supported by the first key secondary endpoint, average change in BCVA from Baseline over the period Week 36 through Week 48, for which non-inferiority was met for all brolucizumab groups. Likewise, effect size was similar to the ones observed in primary endpoint. Indeed, regarding FAS population, in HAWK study, the LS mean difference between the brolucizumab and Aflibercept arms was -0.5 letters for brolucizumab 3 mg (with a lower limit of the 95% CI = -2.4, p=0.0001 for non-inferiority testing) and 0.0 letters for brolucizumab 6 mg (with a lower limit of the 95% CI = -1.9 letters, p<0.0001 for non-inferiority testing) and. In Study RTH258-C002, the LS mean difference between the brolucizumab 6 mg and Aflibercept 2 mg arm was -1.2 letters (with a lower limit of the 95% CI = -2.8 letters, p=0.0003 for non-inferiority testing).

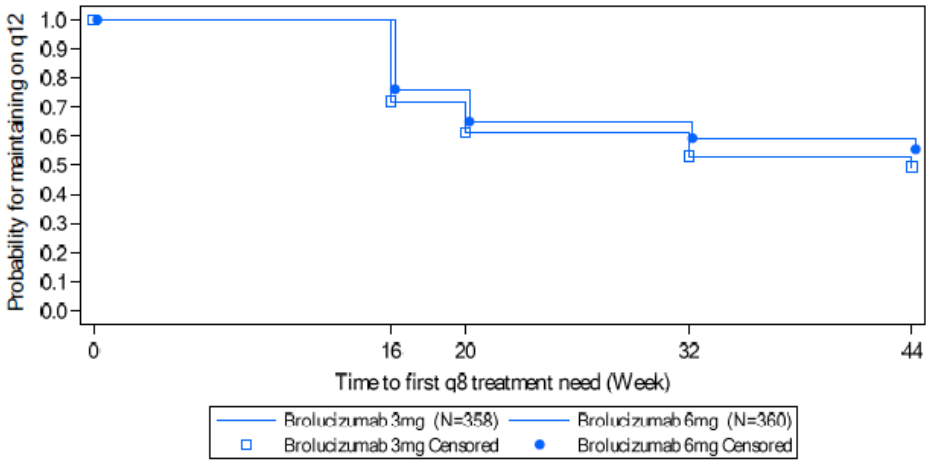
Second and third secondary endpoint

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

Second key secondary endpoint estimated that the probability for a subject to be maintained on the q12w regimen up to the disease activity assessment at Week 44, with 95% CI, was 49.4% (43.9, 54.6) in the brolucizumab 3 mg arm versus 55.6% (50.1, 60.7) and 51.0% (45.6, 56.1) in the brolucizumab 6 mg arm in respectively HAWK study and HARRIER study. So, almost half of the patients only could remain on the q12w regimen through the first year with limited numerically differences between 3 mg group and 6 mg group.

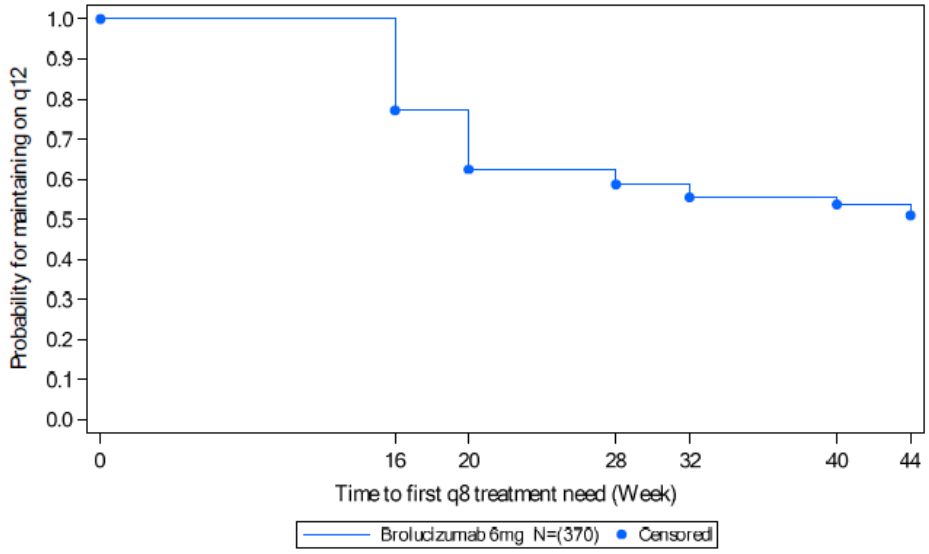
Figure 6: Time-to-first q8w treatment need: Kaplan-Meier plot for brolucizumab 6 mg subjects (FAS - 'efficacy/safety' approach)

a) HAWK study



Censored: subjects are considered to be not anymore under risk for a q8w need identification at later visits.
Efficacy/Safety approach: censored data attributable to lack of efficacy and/or safety are imputed with q8w need = Yes at the next DAA visit.

b) HARRIER



Censored: subjects are considered to be not anymore under risk for a q8w need identification at later visits.
Efficacy/Safety approach: censored data attributable to lack of efficacy and/or safety are imputed with q8w need = Yes at the next disease activity assessment visit.

Predictive value of the initial q12w cycle: q12 status at Week 48 (44) for brolucizumab subjects with no q8w need during the initial q12w cycle ("remaining on q12w")

The third key secondary endpoint allowed specification of patients susceptible to remain on q12w are mainly identified after the first cycle following launching phase. Inversely, patient with a need for a q8w regimen were mainly identified at Week 16 or Week 20.

Among subjects with no q8w need during the initial q12w cycle, the estimate for the probability of remaining on q12w regimen up to DAA at Week 44 was 80.8% for the 3 mg dose and, 85.3% and 81.7% for the 6 mg dose in respectively HAWK study and HARRIER study. The Applicant stated that the absence of disease activity during the initial q12w cycle was a strong predictor for remaining on q12w dosing interval up to Week 44.

Table 15: Summary for brolucizumab subjects with no q8w need during the initial q12w cycle (FAS "efficacy/safety" approach)

a) HAWK study

Time (week)	Number of subjects with first q8w need at visit	Number of subjects under risk at this visit	Number censored at the visit	Prob. of remaining on q12w (survival)	95% CI for prob. of remaining on q12w
			Brolucizumab 3 mg (N = 208)		
20	0	208	12	1.0000	1.0000, 1.0000
32	26	196	8	0.8673	0.8113, 0.9077
44	11	162	151	0.8085	0.7454, 0.8574
			Brolucizumab 6 mg (N = 222)		
20	0	222	5	1.0000	1.0000, 1.0000
32	19	217	11	0.9124	0.8662, 0.9432
44	12	187	175	0.8539	0.7987, 0.8950

Censored: subjects are considered to be not anymore under risk for a q8w need identification at later visits.

Efficacy/Safety approach: censored/confounded data attributable to lack of efficacy and/or safety are imputed with q8w need = Yes at the next DAA visit.

b) HARRIER study

			Brolucizumab 6 mg (N = 220)		
Time (week)	Number of subjects with first q8w need at visit	Number of subjects under risk at this visit	Number censored at the visit	Probability of maintaining on q12w (survival)	95% CI for probability of remaining on q12w
20	0	220	1	1.0000	1.0000, 1.0000
28	13	219	6	0.9406	0.9000, 0.9651
32	11	200	1	0.8889	0.8388, 0.9241
40	6	188	4	0.8605	0.8066, 0.9004
44	9	178	169	0.8170	0.7582, 0.8629

Censored: subjects are considered to be not anymore under risk for a q8w need identification at later visits.

Efficacy/Safety Approach: censored data attributable to lack of efficacy and/or safety are imputed with q8w need = Yes at the next disease activity assessment visit.

Ancillary analyses

BCVA-related secondary endpoints

An overview of the selected BCVA-related endpoints at, and up to, Week 48 is presented below. Results in these other secondary endpoints about BCVA, as responder analysis (i.e.: proportion of patients having a gain of at least 15 letters from Baseline or a BCVA >= 84 letters at Week 48), are consistent with primary outcomes.

Table 16: Results of selected secondary endpoints related to BCVA up to Week 48 (FAS – LOCF)

a) HAWK study

Secondary BCVA Endpoint	BRO Dose	BRO LSMean	AFL 2 mg LSMean	Difference	95% CI for Difference	p-value (2-sided)
Average change from Baseline over the period Week 4 through Week 48	3 mg	5.9	6.3	-0.4	(-1.9, 1.1)	0.6275
	6 mg	6.3	6.3	0.0	(-1.5, 1.6)	0.9647
Average change from Baseline over the period Week 12 through Week 48	3 mg	6.1	6.5	-0.4	(-2.0, 1.2)	0.6185
	6 mg	6.6	6.6	0.1	(-1.6, 1.8)	0.9235
">= 15 letters gain from Baseline or BCVA of >=84 letters at Week 48"	3 mg	25.2	25.5	-0.2	(-6.8, 6.1)	0.9480
	6 mg	33.6	25.4	8.2	(2.2,15.0)	0.0136
" >=15 letters loss from Baseline at Week 48"	3 mg	5.9	5.6	0.3	(-3.2, 3.9)	0.8583
	6 mg	6.4	5.5	0.9	(-2.7, 4.3)	0.6198
"BCVA >= 73 letters at Week 48"	3 mg	48.5	52.0	-3.5	(-9.5, 2.3)	0.2455
	6 mg	49.5	51.9	-2.4	(-8.6, 3.6)	0.4442

BRO = Brolucizumab; AFL = Aflibercept.

ANOVA (for continuous variables) and logistic regression (for categorical variables) models with Baseline BCVA categories (<=55, 56-70, >=71 letters), age categories (<75, >=75 years) and treatment as fixed effect factors are used.

BCVA assessments after start of alternative anti-VEGF treatment in the study eye are censored and imputed by the last value prior to start of this alternative treatment.

b) HARRIER study

Secondary BCVA Endpoint	Brolucizumab 6 mg Mean	Aflibercept 2 mg Mean	Difference	95% CI for Difference	p-value (2-sided)
Average change from Baseline over the period Week 4 through Week 48	5.8	6.9	-1.1	(-2.4, 0.3)	0.1191
Average change from Baseline over the period Week 12 through Week 48	6.1	7.2	-1.1	(-2.5, 0.4)	0.1429
>=15 letters gain from Baseline or BCVA of >=84 letters at Week 48	29.3	29.9	-0.6	(-7.1, 5.8)	0.8600
>=15 letters loss from Baseline at Week 48	3.8	4.8	-1.0	(-3.9, 2.2)	0.5079
BCVA >=73 letters at Week 48	50.7	50.3	0.4	(-5.4, 6.1)	0.8922

ANOVA (for continuous variables) and logistic regression (for categorical variables) models with Baseline BCVA categories (<=55, 56-70, >=71 letters), age categories (<75, >=75 years) and treatment as fixed effect factors are used. 95% CI for the treatment difference estimated using bootstrap method.

BCVA assessments after start of alternative anti-VEGF treatment in the study eye are censored and imputed by the last value prior to start of this alternative treatment.

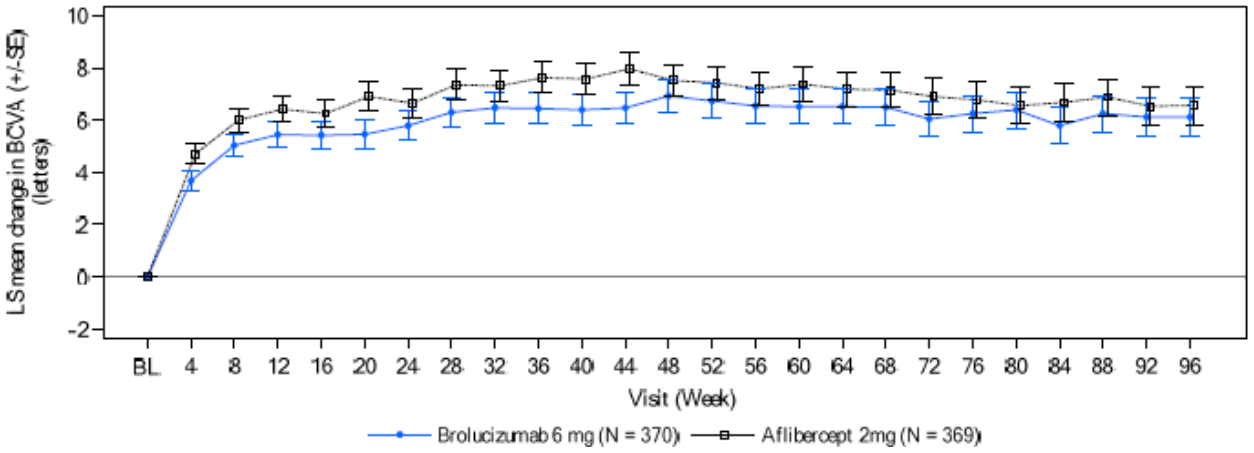
Maintenance of the benefit

Maintenance of the benefit of brolucizumab 3 mg and 6 mg treatments over the time had been addressed through functional endpoint (BCVA) as well as anatomical endpoints (changes in CSFT, CNV lesion, retinal fluids) providing positive outcomes at Week 96. Indeed, in HAWK study, regarding FAS population, the mean change in BCVA from Baseline at Week 96, with 95% CI, for brolucizumab 3 mg, brolucizumab 6 mg and

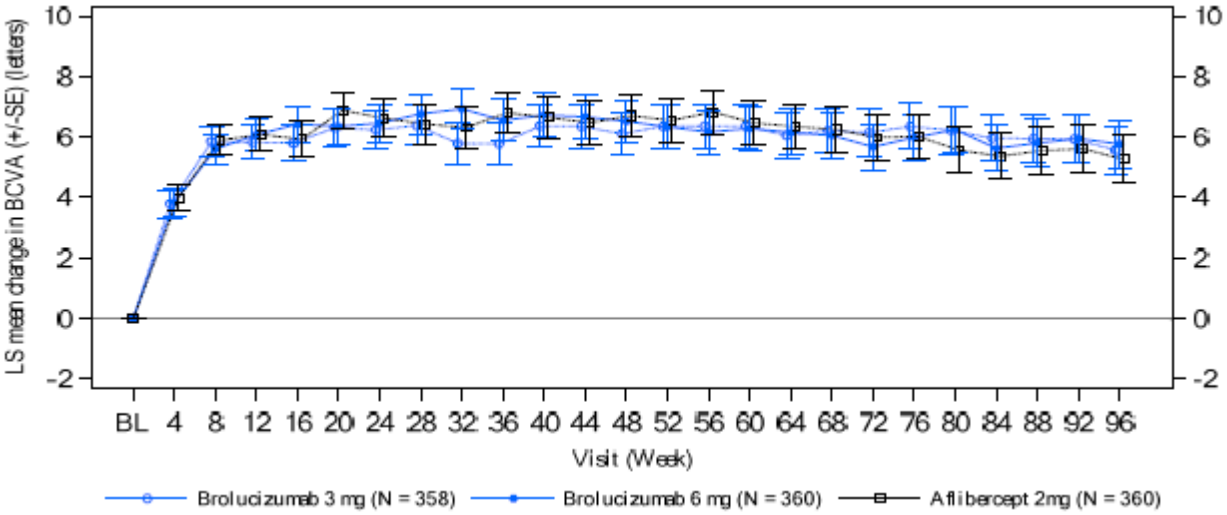
aflibercept were respectively 5.4 [3.7,7.0], 5.6 [4.0,7.3] and 5.6 [4.0,7.1] letters. In HARRIER study, regarding FAS population, the mean change in BCVA from Baseline at Week 96, with 95% CI, for brolucizumab 6 mg and aflibercept were respectively 6.1 [4.7,7.6] and 6.6 [5.1,8.1] letters.

Figure 7: Best-Corrected Visual Acuity (Letters) for Mean Change (Plus/Minus SE) from Baseline by Visit for the Study Eye FAS – LOCF

a) HAWK study



b) HARRIER study

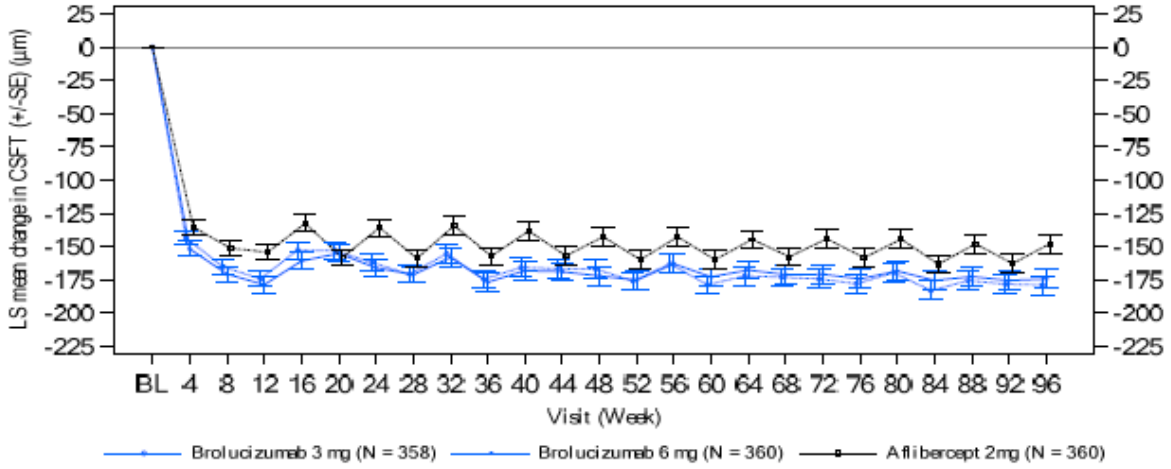


Anatomical parameters

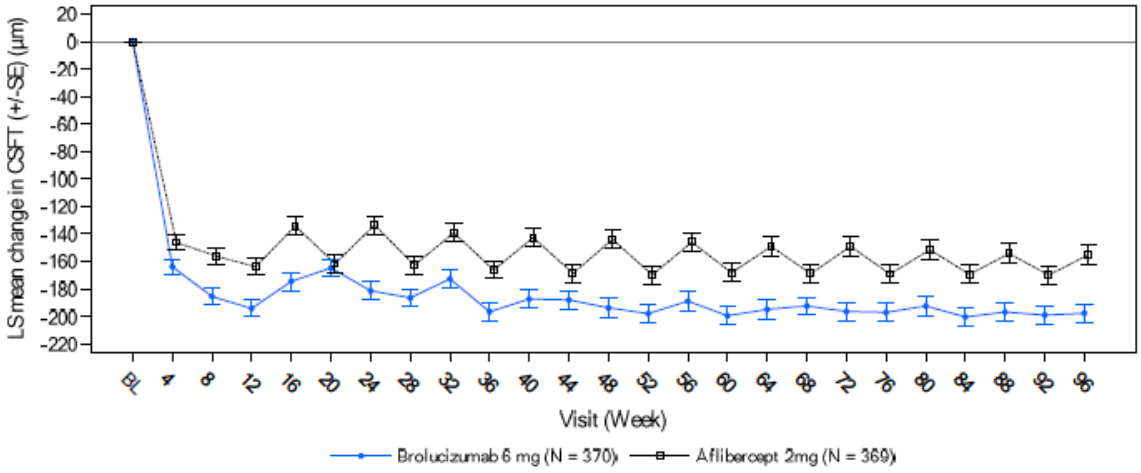
Outcomes in anatomical parameters, for instance mean change in CSFTtot from Baseline, mean change in CNV lesion size from Baseline and proportion of subjects with presence of sub-RPE fluid at Week 48, also supported non-inferiority of both brolucizumab 3 mg and 6 mg compared to aflibercept. The reduction in CSFT observed at the end of the first year of treatment was overall maintained through Week 96.

Figure 8: Central subfield thickness-total (Micro m) of LS mean change (Plus/Minus SE) from Baseline by visit (FAS – LOCF)

a) HAWK study



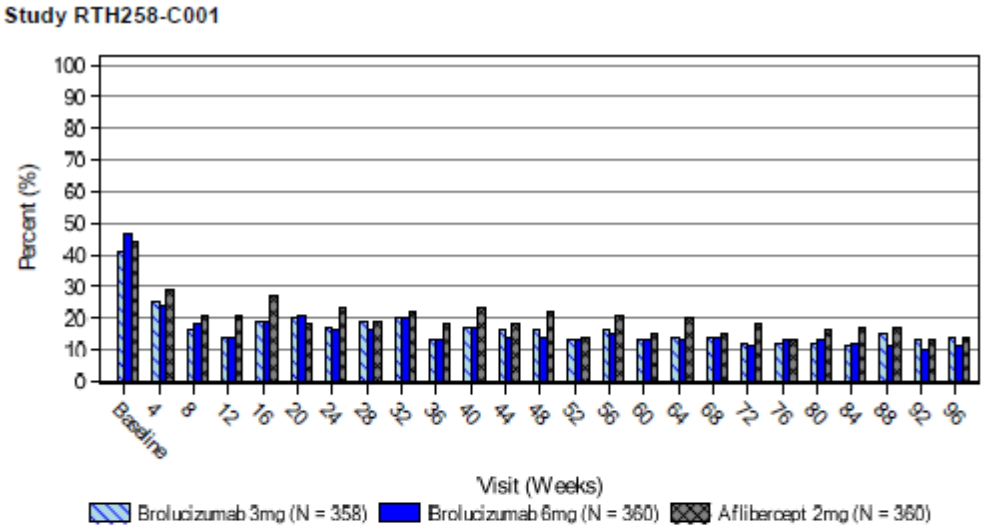
b) HARRIER study

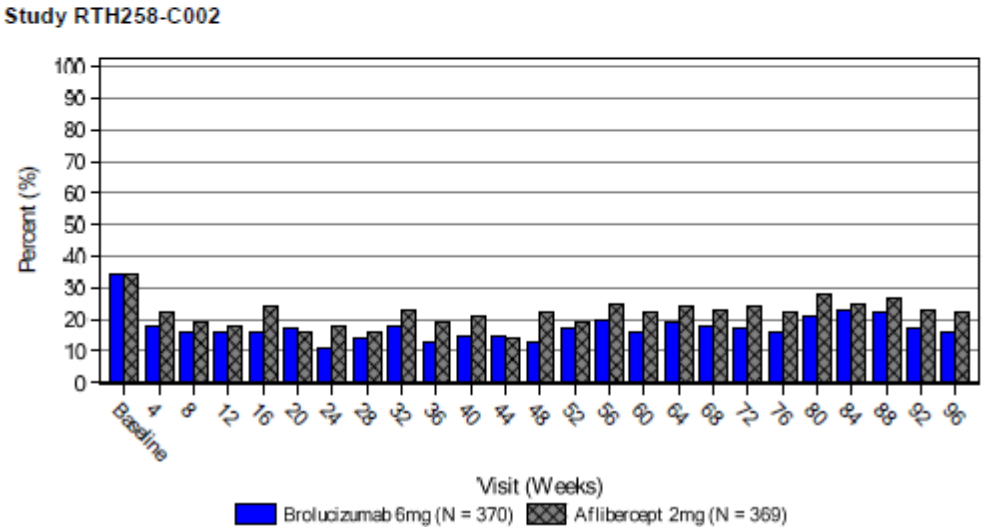


CNV lesion size, in HAWK study, the mean change from Baseline to Week 48 was -3.9 mm2 and -4.0 mm2 in the brolucizumab 3 mg and 6 mg arms, and -3.5 mm2 in the aflibercept 2 mg arm. In HARRIER study, the mean change in CNV lesion size from Baseline to Week 48 was -2.3 mm2 in the brolucizumab 6 mg arm and -2.5 mm2 in the aflibercept 2 mg arm.

The percentage of subjects with presence of sub-RPE fluid in the study eye at each post-baseline visit up to Week 96 is presented in below figure.

Figure 9: Subretinal pigment epithelium (sub-RPE) fluid percentages of subjects with presence of sub-RPE by visit up to Week 96 (FAS – LOCF)





Quality of Life

In HAWK study, the mean change from Baseline (improvement) in the VFQ-25 composite score at respectively Week 24 and Week 72 was 3.9 then 5.0 (n=354) in the brolucizumab 6 mg arm, and 3.5 then 3.2 (n=355) in the aflibercept 2 mg arm.

In HARRIER study, the mean change from Baseline (improvement) in the VFQ-25 composite score at respectively Week 24 and Week 72 was 3.9 then 5.0 (n=354) in the brolucizumab 6 mg arm, and 3.5 then 3.2 (n=355) in the aflibercept 2 mg arm.

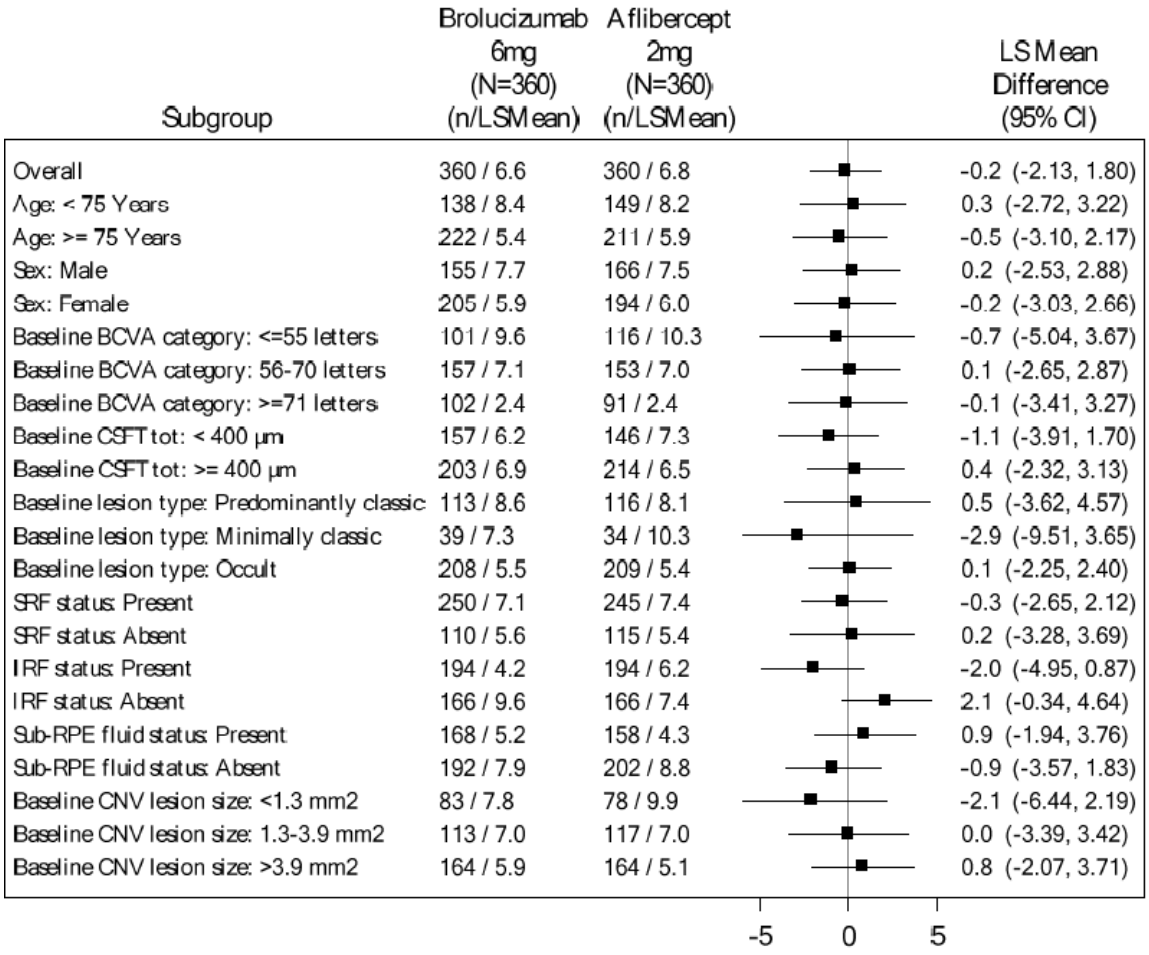
Subset analysis

Overall, subset analysis showed some heterogeneity of the treatment effect across some subgroups. For instance, seeing mean change in BCVA from Baseline at Week 48, a greater difference in disfavour of brolucizumab is observed for patient with a BCVA at Baseline <= 55 letters in both studies. This alters a bit the demonstration of the non-inferiority but does not compromise the studies' conclusions on efficacy.

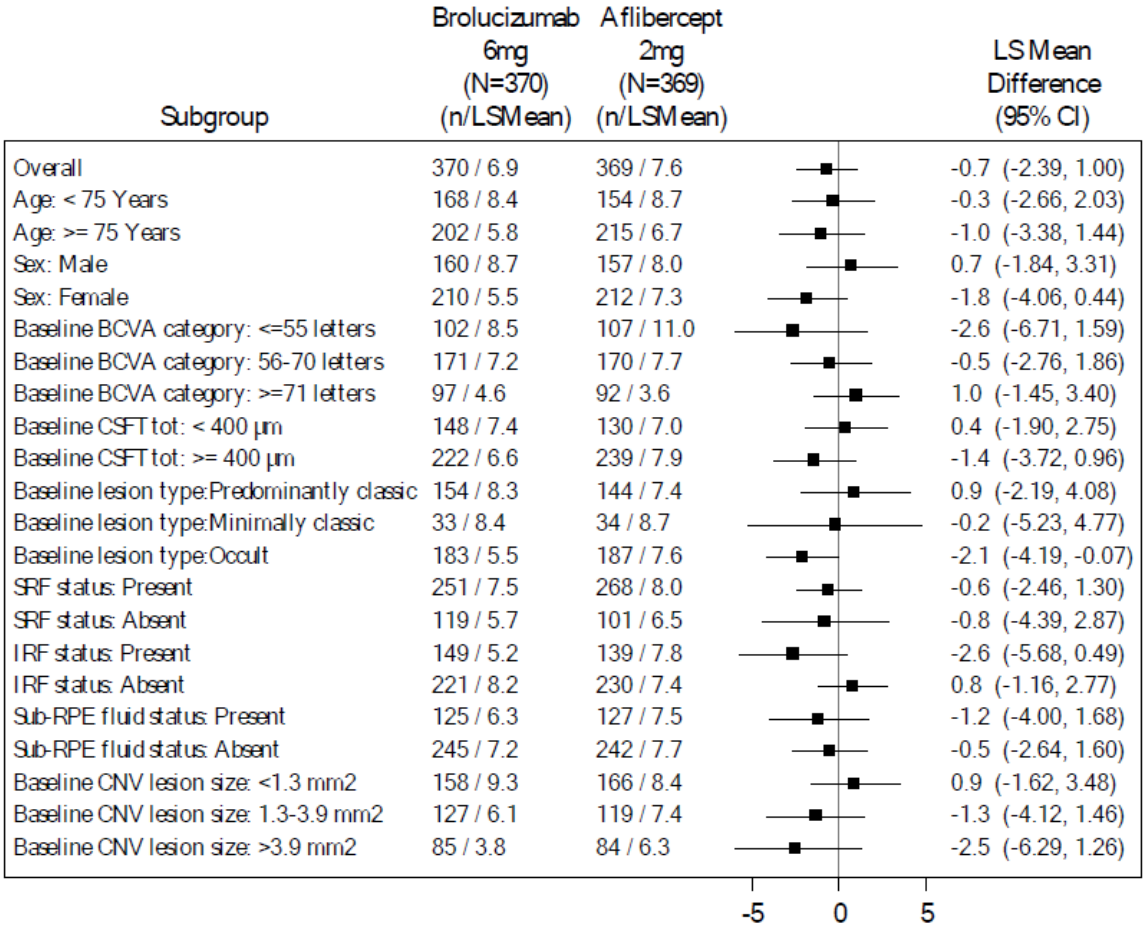
Subset analysis of the primary endpoint is presented in the following figure.

Figure 10: Best-corrected visual acuity (letters): forest plot of change from Baseline at Week 48 (primary endpoint) by subgroups of interest (FAS – LOCF)

a) HAWK study



b) HARRIER study



Treatment burden

Assessment of disease activity in HAWK at Week 16 indicated that 28.1% and 24.0% for the brolucizumab 3 mg and 6 mg subjects, respectively, compared 34.5% for the aflibercept 2 mg. In HARRIER study, the proportion was 22.7% for brolucizumab 6 mg compared to 32.2% for aflibercept. Thus, the posology claimed should reflect that a substantial part of patients was not at any time of the study on the q12w regimen.

Table 17: Disease activity assessment: proportion of subjects with q8 treatment need as assessed by the Investigator at Week 16 (FAS – "efficacy/safety" approach)

	Comparison of Brolucizumab vs. Aflibercept [1]			
Study RTH258-C001				
Treatment	**BRO (%)**	**AFL (%)**	**Difference (95% CI) (%)**	**p-value (1-sided / 2-sided)**
BRO3 (N=358)	28.1	34.5	-6.5 (-13.2, 0.3)	0.0331 / 0.0662
BRO6 (N=360)	24.0	34.5	-10.5 (-17.1, -3.5)	0.0013 / 0.0025
AFL2 (N=360)				
Study RTH258-C002				
Treatment	**BRO (%)**	**AFL (%)**	**Difference (95% CI) (%)**	**p-value (1-sided / 2-sided**
BRO6 (N=370)	22.7	32.2	-9.5 (-15.8, -3.1)	0.0021 / 0.0042
AFL2 (N=369)				

*1-sided p-values were calculated based on the 2-sided p-values provided in the source table.

BRO3 = Brolucizumab 3 mg; BRO6 = Brolucizumab 6mg; AFL2 = Aflibercept 2mg.
n = number of subjects satisfying the criteria of the response variable.
M = number of subjects with an assessment of the criterion.
[1] Statistical model used logistic regression adjusting for age categories (<75, >=75 years) and treatment as fixed effect factors. 95% CI for the treatment difference estimated using bootstrap method.

Efficacy/Safety Approach: censored data at Week 16 attributable to lack of efficacy and/or safety are imputed with q8 need = Yes at Week 16.

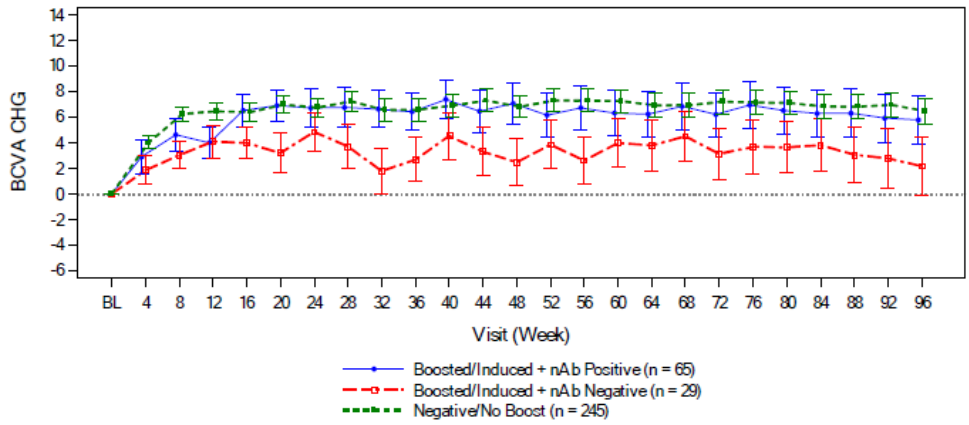
The total number of injections is similar between the 3 mg group and the 6 mg group. This number was slightly higher for aflibercept (6.5 for aflibercept versus 6.1 both brolucizumab group in HAWK study, and 6.8 versus 6.2 in HARRIER study). However, patients of aflibercept groups were not permitted to extend the interval between injections until 3 months. Additionally, the estimated probability to remain on q12w regimen at Week 92 slightly decrease compared to Week 44, with 39.7% (34.2,45.1) for brolucizumab 3 mg and, 45.4% (39.8, 50.7) (HAWK study) and 38.6.0% (33.4, 43.7) (HARRIER study) for brolucizumab 6 mg arm.

Neutralizing antibodies

Regarding ADA, mean change in BCVA from baseline up to Week 96 did not show a reduction of the efficacy in patient having neutralizing antibodies.

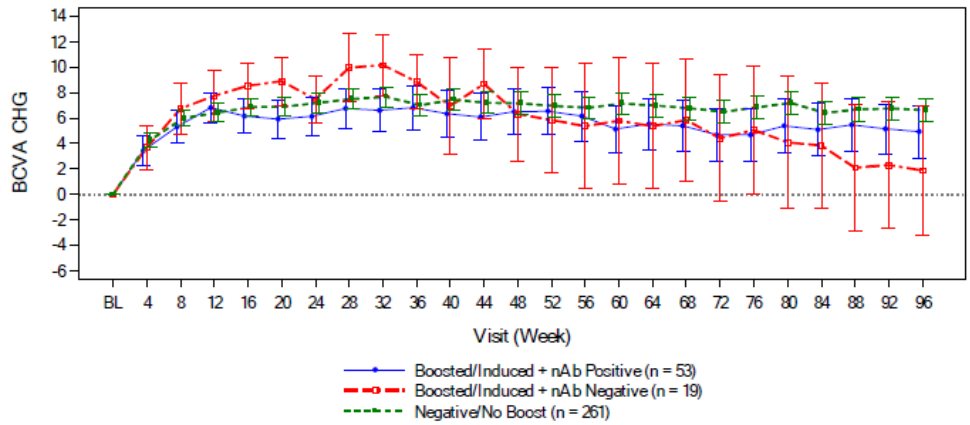
Figure 11: Integrated treatment-emergent status and post-dose nAb status up to Week 88 and BCVA (study eye) in subjects with no intraocular inflammation adverse events

RTH258-C001 Brolucizumab 3 mg



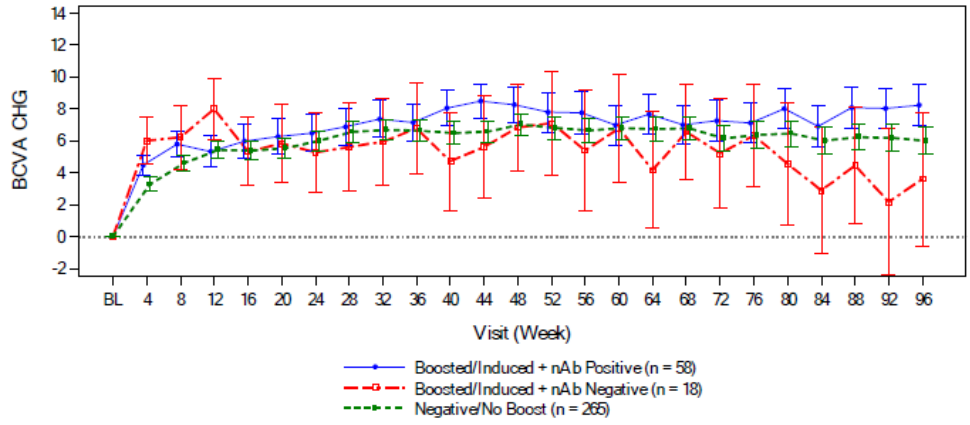
nAb Positive = At least one positive nAb status post-baseline; nAb Negative = Negative nAb at all post-baseline visits.

RTH258-C001 Brolucizumab 6 mg



nAb Positive = At least one positive nAb status post-baseline; nAb Negative = Negative nAb at all post-baseline visits.

RTH258-C002 Brolucizumab 6 mg



nAb Positive = At least one positive nAb status post-baseline; nAb Negative = Negative nAb at all post-baseline visits.

Whiskers (error bars) represent standard error

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18: Summary of efficacy for trial RTH258-C001(HAWK)

Title: A two-year, randomized, double-masked, multicentre, three-arm study comparing the efficacy and safety of RTH258 versus aflibercept in subjects with neovascular age-related macular degeneration			
Study identifier	RTH258-C001(HAWK)		
Design	Prospective, randomized, double-masked, multicenter study designed to compare the efficacy and safety of brolucizumab 3 mg and 6 mg with aflibercept 2 mg		
	Duration of main phase: Duration of Extension phase: (Study CRTH258A2301E1)		96 weeks 24 weeks
Hypothesis	Demonstrate that brolucizumab is not inferior to aflibercept with respect to the change in best-corrected visual acuity (BCVA) from Baseline to Week 48.		
Treatments groups	Brolucizumab 3mg		D0, W4, W8 (qW12/qW8) N= 334
	Brolucizumab 6 mg		D0, W4, W8 (qW12/qW8) N= 333
	Aflibercept 2 mg		D0, W4, W8 (qW8) N= 327
Endpoints and definitions	Primary endpoint	Mean change in best-corrected visual acuity (BCVA) from Baseline to Week 48	
	Secondary endpoint:	Mean change in BCVA from Baseline averaged over the period Week 36 to Week 48	

	Secondary endpoint:	Proportion of q12W treatment status at W48 for subjects randomized to brolucizumab (maintaining on q12W)		
	Secondary endpoint:	Predictive value of initial q12W cycle at W48 with no q8W need during the initial q12W cycle (remaining on q12W)		
Database lock	23-04-2018			
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	FAS (patients received study treatment with LOCF imputation of missing BCVA values) =1078			
Descriptive statistics and estimate variability	Treatment group	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg
	Number of subject	358	360	360
	Primary endpoint Mean change in best-corrected visual acuity (BCVA) from Baseline to Week 48	Mean : 5.9 (SD): (13.49) SE: 0.71 Median: 7.0 Min, Max: -57, 51 95%CI for mean: (4.5, 7.3)	Mean : 6.4 (SD):(14.40) SE: 0.76 Median: 7.5 Min, Max: -69, 52 95%CI for mean: (4.9, 7.9)	Mean : 7.0 (SD):(13.16) SE: 0.69 Median: 8.0 Min, Max: -57, 54 95%CI for mean: (5.6, 8.3)
	Secondary endpoint Mean change in BCVA from Baseline averaged over the period Week 36 to Week 48	Mean : 6.0 (SD): (13.37) SE: 0.71 Median: 7.0 Min, Max: -64, 54 95%CI for mean: (4.6, 7.4)	Mean : 6.5 (SD):(13.85) SE: 0.73 Median: 7.3 Min, Max: -67, 50 95%CI for mean: (5.1, 8.0)	Mean : 6.9 (SD):(12.61) SE: 0.66 Median: 7.6 Min, Max: -53, 52 95%CI for mean: (5.6, 8.2)

	Secondary endpoint Proportion of qW12 at W48 (maintaining on qW12)	Probability of maintaining on qW12 (survival) W44: 0.4939 95%CI: 0.4393, 0.5461	Probability of maintaining on qW12 (survival) W44: 0.5563 95%CI: 0.5016, 0.6075	
	Predictive value of initial q12W cycle at W48 with no q8W need during the initial q12W	Probability of maintaining on qW12 (survival) at W44: 0.8085 95%CI:0.7454, 0.8574	Probability of maintaining on qW12 (survival) at W44: 0.8539 95%CI: 0.7987, 0.8950	

Effect estimate per comparison	Primary endpoint	Comparison groups Pairwise ANOVA	
		(BRO3 vs AFL2)	LS mean (SE) 6.1 (0.69) – 6.8 (0.69) 95% CI for LS mean (4.8, 7.5) – (5.4,
		(BRO6 vs AFL2)	LS mean (SE) 6.6 (0.71) – 6.8 (0.71) 95% CI for LS mean (5.2, 8.0) – (5.4,
		(BRO vs AFL)	Difference (SE) BRO3 -0.6 (0.98) BRO6 -0.2 (1.00) 95CI% for treat Difference BRO3 (-2.5, 1.3) BRO6 (-2.1, 1.8) P value for treat Difference (2 sided) BRO3 0.5237 BRO6 0.8695
Notes	Robustness of the results from the primary analysis was assessed based on the per protocol set (PPS; subset of the FAS that excluded subjects with protocol deviations and violations of analysis requirements that were expected to majorly affect the validity of the assessment of efficacy at Week 48). The analysis of the primary endpoint based on the PPS (BRO3mg: N= 325, BRO6mg: N=328, AFL2mg: N=312) were consistent with the corresponding primary efficacy analysis		

Table 19: Summary of efficacy for trial RTH258-C002 (HARRIER)

Title: A two-year, randomized, double-masked, multicentre, two-arm study comparing the efficacy and safety of RTH258 versus aflibercept in subjects with neovascular age-related macular degeneration		
Study identifier	RTH258-C002 (HARRIER)	
Design	Prospective, randomized, double-masked, multicenter study designed to compare the efficacy and safety of brolucizumab 6 mg with aflibercept 2 mg	
	Duration of main phase:	96 weeks
Hypothesis	Demonstrate that brolucizumab is not inferior to aflibercept with respect to the change in best-corrected visual acuity (BCVA) from Baseline to Week 48.	
	Brolucizumab 6 mg	D0, W4, W8 (qW12/qW8) N= 372

	Aflibercept 2 mg		D0, W4, W8 (qW8) N= 371
Endpoints and definitions	Primary endpoint	Mean change in best-corrected visual acuity (BCVA) from Baseline to Week 48	
	Secondary endpoint:	Mean change in BCVA from Baseline averaged over the period Week 36 to Week 48	
	Secondary endpoint:	Proportion of q12W treatment status at W48 for subjects randomized to brolucizumab (maintaining on q12W)	
	Secondary endpoint:	Predictive value of initial q12W cycle at W48 with no q8W need during the initial q12W cycle (remaining on q12W)	
Database lock	28-03-2018		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point	FAS (patients received study treatment with LOCF imputation of missing BCVA values) = 739		

Descriptive statistics and estimate variability	Treatment group	Brolucizumab 6 mg	Aflibercept 2 mg
	Number of subject	370	369
	Primary endpoint Mean change in best-corrected visual acuity (BCVA) from Baseline to Week 48	Mean : 6.9 (SD):(11.47) SE: 0.60 Median: 8.0 Min, Max: -57, 38 95%CI for mean: (5.8, 8.1)	Mean : 7.6 (SD):(12.47) SE: 0.65 Median: 8.0 Min, Max: -37, 50 95%CI for mean: (6.3, 8.9)
	Secondary endpoint Mean change in BCVA from Baseline averaged over the period Week 36 to Week 48	Mean : 6.6 (SD):(11.10) SE: 0.58 Median: 7.5 Min, Max: -58, 37 95%CI for mean: (5.4, 7.7)	Mean : 7.7 (SD):(11.81) SE: 0.61 Median: 8.3 Min, Max: -38, 47 95%CI for mean: (6.5,8.9)
	Proportion of q12W treatment status at W48 for subjects randomized to brolucizumab (maintaining on q12W)	Probability of maintaining on qW12 (survival) W44: 0.5101 95%CI: 0.4567, 0.5610	
	Predictive value of initial q12W cycle at W48 with no q8W need during the initial q12W cycle (remaining on q12W)	Probability of maintaining on qW12 (survival) W44: 0.81.70 95%CI: 0.7582, 0.8629	
Effect estimate per comparison	Primary endpoint	Comparison groups Pairwise ANOVA	
		(BRO6 vs AFL2)	LS mean (SE) 6.9(0.61) – 7.6 (0.61) 95% CI for LS mean (5.7, 8.1) – (6.4, 8.8)

		(BRO vs AFL)	Difference (SE) -0.7 95CI% for treat Difference (-2.4, 1.0) P value for treat Difference (2 sided) 0.4199 P value non-inferiority (4 letter margin) <0.0001 (1-sided)
Notes	Robustness of the results from the primary analysis was assessed based on the per protocol set (PPS; subset of the FAS that excluded subjects with protocol deviations and violations of analysis requirements that were expected to majorly affect the validity of the assessment of efficacy at Week 48). The analysis of the primary endpoint based on the PPS (BRO6mg: N=351, AFL2mg: N=341) was consistent with the corresponding primary efficacy analysis using FAS.		

Clinical studies in special populations

No special population were formally studied. Nevertheless, in the two pivotal studies (HAWK and HARRIER studies) patients aged over 85 had been enrolled. Subset analysis showed similar outcomes in BCVA across ages groups (old than 75 years). Additionally, based on the non-clinical outcomes, the absence of specific studies is acceptable.

Supportive studies

CRTH258A2301E1

The CRTH258A2301E1 study consists of a double-masked, multicentre, two-arm 24-week extension study of the HAWK study. The objective was to collect safety and efficacy data on brolucizumab 6 mg drug product intended for commercialization.

A subgroup of 150 subjects have enrolled in the US, who completed Week 96. Subjects who were treated with brolucizumab 3 mg (n=62) or 6 mg (n=45) in the core study received brolucizumab 6 mg (2xq8w+1xq12w/q8w) in the extension study and subjects with aflibercept 2 mg (n=43) remained on aflibercept. For the brolucizumab core 6 mg, while a trend towards slight decrease in BCVA was observed in the second year of the core study, the time course during the extension study suggests stabilization. For the brolucizumab core 3 mg, the trend observed during the second year of the core study continued in the extension study. Overall, the reduction in CSFTtot observed at the end of the core study was maintained throughout this extension study.

Results in the maintenance of the benefit in the second year were consistent with outcomes of the pivotal studies. Together with the conclusion of the Quality, these results provide sufficient evidence about efficacy of the formulation intended for commercialization.

C-13-001

C-13-001 was 2-month, 4-cohort, prospective, single-masked, multicentre, randomized study. The stage 1 was to demonstrate a treatment effect of brolucizumab 120 mg/mL applied as a single microvolume injection or single infusion on retinal function and morphology in subjects with nAMD. The stage 2 investigated brolucizumab 60 mg/ml as a single microvolume injection or single infusion.

Overall, 52 subjects, randomized in 4 cohorts (120 mg/mL injection, 120 mg/mL infusion, 60 mg/mL injection, 60 mg/mL infusion), received study treatment.

The primary efficacy hypothesis was that the responder rate for subjects treated with brolucizumab was > 15%. A patient was responder if at least 3 out of the following 4 criteria were fulfilled in comparison with baseline: ≥ 4-letter gain in BCVA at Day 14; ≥ 4-letter gain in BCVA at Day 28; ≥ 80-µ m decrease in CSFT at Day 14; ≥ 80-µ m decrease in CSFT at Day 28. The primary endpoint was met (the proportion of responders range from 60 to 80 % across the 4 cohorts.

C-13-001 provided additional supportive data in favour of the efficacy of brolucizumab.

RTH258-E003

RTH258-E003 was a randomized, double masked, multicentre, PK (systemic pharmacokinetics) and safety study evaluating 2 doses (3 mg and 6 mg) of brolucizumab administrated by intravitreal injection in subjects (Japanese and non-Japanese ancestry) with nAMD. The regimen was 3 IVT injections administered 4-weeks apart.

The Applicant concluded that serum PK data from this study supported a low systemic exposure following IVT injection of brolucizumab and were comparable between subjects of Japanese ancestry and subjects of non-Japanese ancestry. No systemic accumulation of free brolucizumab was observed. It stated also the brolucizumab 3mg and brolucizumab 6mg were generally safe and well tolerated in this study.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development of brolucizumab is based on two randomized, double-masked, multicentre, active-controlled, pivotal studies (HAWK study and HARRIER study). Overall, the design of both these Phase III studies was adequate.

The selection criteria were globally consistent with the target population, and morphological criteria related to nAMD were reasonable. The upper baseline BCVA limit for inclusion was 78 letters. There is a possibility that the inclusion of patients with mild impairment leaves less room for improvement which may not allow detection of a difference between aflibercept and brolucizumab in this subpopulation if exists and consequently to drive non-inferiority. Additionally, only naïve patients had been included in pivotal studies. It is knowledge that patients already treated may not have a room for further improvement. Excluding this population is thus in disfavour of the non-inferiority hypothesis and appears to be a more conservative approach. However, switching from an anti-VEGF to another one is a common practice for patients with loss of benefit over the time, and it is unknown if the reported response will be reached in patients with more advanced/pre-treated condition. Finally, HAWK study did not include any patient from the European Union. However, European subjects were well enrolled in the HARRIER study. Considering the substantial sample

size of the HARRIER study, together with the fact that the main proportion of the HAWK patients were from US with a high proportion of Caucasian subjects, this is acceptable.

The blinding using monthly sham injection for the visit without treatment administration was acceptable.

Two doses were tested in the HAWK study, 3 mg and 6 mg, whereas only the 6 mg dose was investigated in HARRIER study. The 6 mg dose (the higher dose tested in Phase I) was selected expecting a longer effect, despite that no formal dose selection study was performed. The 3 mg dose was added following recommendations of the CHMP in the Scientific Advice EMA/CHMPA/SAWP/550707/2013. Indeed, the assumption that a higher dose lead to a longer effect or a larger effect size should have been demonstrated.

Contrary to the initial development plan presented during the Scientific Advice discussion at the EMA (EMA/CHMPA/SAWP/550707/2013), instead of ranibizumab 0.5 mg IVT (Lucentis®), aflibercept (Eylea®) was chosen as comparator for the both pivotal studies, however, it was justified by the fact that ranibizumab had a different posology in the US than in other countries including Europe.

As the efficacy of aflibercept had been demonstrated in a non-inferiority setting versus ranibizumab, there is a potential risk of biocreep. Indeed, in the hypothesis that aflibercept would be slightly inferior to ranibizumab, although within the non-inferiority margin, and that brolucizumab would be slightly inferior to aflibercept, although within the non-inferiority margin, this could lead to a lower efficacy. However, this is mitigated by the fact that to date aflibercept is considered as a standard of care.

Additionally, pivotal studies haven't investigated personalized regimen (pro re nata or Treat-and-Extend), as recommended in the Scientific Advice, even though such treatment strategies are largely used in common practice to manage anti-VEGF IVT medication. Indeed, personalized treatments allow reduction in the number of injections, and, consequently, the risk linked to intravitreal injection and the patient burden. However, a Phase IIIb study investing treat-&-extend regimen is planned by the Applicant.

After the launching phase (3 monthly injections), patients were assessed at Week 16 to undergo a q8w regimen, in case of disease activity, or a q12w regimen, in absence of disease activity, with the possibility to switch on q8w regimen in necessary at the following visits. Disease activity guidance criteria at Week 16 where more stringent than real life, compared to the following visits in order to select patients to have a higher chance to remain on q12w regimen over the time. Therefore, in real life, more patient could be put on q12w treatment after lauding phase, but the probability for a patient to remain on q12w regimen could thus be lower than in Phase III studies.

It is also to note that patients from brolucizumab groups were not permitted to switch on q12w once being on q8w regimen. Therefore extension/re-extension of the interval between injections was not assessed. The regimen in aflibercept groups was fixed in both studies, q8w, despite that personalized treatment from the second year was authorized at the time of the studies. Finally, it was not possible to draw conclusion on the treatment burden of brolucizumab 3 mg and 6 mg compared to the current standard of care.

Demonstrating the efficacy of a new anti-VEGF IVT in the treatment of the nAMD using non-inferiority setting versus one of the current standard of care (aflibercept) was appropriate. The mean change in BCVA from baseline at Week 48 was an acceptable primary endpoint. Nonetheless, Week 48 assessment was favourable to patients on q12w regimen. Indeed, BCVA assessment was performed 1 month after the last injection, with potentially a higher benefit, contrary to patients on q8w regimen for which assessment was performed 2 months after the last injection. Therefore, the timepoint was favourable to brolucizumab given that patients treated with aflibercept were not permitted to be on q12w regimen. However, the first key secondary

endpoint, being the mean change in BCVA from Baseline averaged over the period Week 36 to Week 48, could overcome the problem of a single timepoint in the context of multiple regimens.

The non-inferiority margin of 4 letters was acceptable.

Second and third key secondary endpoints were appropriate to assess the relevance of the q12w regimen. Additionally, to visual acuity, anatomical parameters (changes in CSFT, CNV lesion, retinal fluids) and Quality of Life were explored in other secondary endpoints. Additional secondary timepoint at Week 96 allowed investigation of the maintenance of the benefit over the time.

ETDRS procedure was appropriate to assess BCVA, whereas fluorescein angiography and OCT were suitable for anatomical parameters.

Regarding superiority testing, it is not understandable why visual acuity had not been selected despite it represents the primary endpoint's variable and the first key secondary. Moreover, as additional secondary endpoints, no hierarchy testing strategy had been set, and neither has a control been set for the risk alpha. Therefore, these superiority testing are considered only as exploratory, and cannot be the basis for claims in the product information.

The primary and first key secondary endpoints were analysed based on the FAS with LOCF imputation of missing / censored (after start of alternative anti-VEGF treatment) BCVA values.

Definition of the FAS and the PPS was appropriate. The analysis based on the PPS was considered supportive. In this respect, the analysis based on ITT principles may not always be conservative and, therefore the per-protocol analysis would have been preferable as the primary analysis. At least, PP results should be consistent with the primary analysis. A hierarchical procedure, in a pre-specified order, has been set to handle multiple comparison in primary and first key secondary endpoint. Sensitivity analyses using a MMRM model and observed data were also conducted.

It is known that imputation by the LOCF is not a satisfying method to replacing missing data. The use of this method in the main analysis can be questionable when the treatment is supposed to slow down a progressive disease and, in this case, the inevitable degradation of the visual acuity over time. However, the Applicant provided within the answers a sensitivity analysis using multivariate imputation method assuming data missing at random. Outcomes of this sensitivity analysis in primary endpoint were positive and consistent with the analysis performed using LOCF.

Efficacy data and additional analyses

According to the primary analysis, brolucizumab 3 mg and brolucizumab 6 mg were both non-inferior to aflibercept 2 mg. Results in FAS and in PPS were consistent in both studies. These outcomes were supported by the first key secondary endpoint, average change in BCVA from Baseline over the period Week 36 through Week 48, for which non-inferiority was also met.

Likewise, outcomes in anatomical parameters, for instance mean change in CSFTtot from Baseline, mean change in CNV lesion size from Baseline and proportion of subjects with presence of sub-RPE fluid at Week 48, were also in favor of the non-inferiority of brolucizumab 3 m and 6 mg compared to aflibercept.

Positives outcomes at Week 96 in both functional endpoints (BCVA) and anatomical endpoints provide evidences having regards of the maintenance of the benefit over the time.

Some heterogeneities were observed in some subgroups in subset analysis, but not to an extent to impact the overall conclusion on efficacy.

Regarding the q12w regimen, it was estimated that patients who did not meet disease activity criteria at Week 16 or 20 had a high probability to remain on this regimen. However, more than 20 % of the patients were never eligible to the q12w regimen, and globally half of the subjects only could remain on the q12w regimen for the entire first year. This raise concerns on the generalibility of the q12w regiment, and thus recommendation for posology in the Product Information. At this end, the PI has been updated to reflect the fact that patients with disease activity at Week 16 should be treated directly with a q8w regimen.

Overall, differences between 3 mg and 6 mg doses across primary and secondary endpoints were numerically very limited and not clinically significant. However, considering that nAMD is a chronic disease together with the fact that intravitreal injection constitutes a substantial burden, the difference, although limited, between the 2 doses in proportion of patients remaining in q12w regimen may be ultimately considered as an advantage in favour of the 6 mg dose.

2.5.4. Conclusions on the clinical efficacy

Overall, the clinical development was acceptable and the design of the both pivotal Phase III studies was appropriate. Outcomes bring evidences of the demonstration of the non-inferiority of brolucizumab 3 mg and 6 mg compared to aflibercept at Week 48 and was maintained up to 2 years

Differences between 3 mg and 6 mg doses across primary and secondary endpoints were numerically very limited and not clinically significant. However, the slightly higher proportion of patients remaining in q12w regimen may be ultimately considered as an advantage in favour of the higher dose. Additionally, there is a lack of data regarding personalised regimen (i.e.: PRN, Treat-&-Extend), despite the fact that these treatment strategies primordial in clinical practice, especially to reduce the treatment burden. Moreover, there was concerns on the generability of the q12w regimen and recommendation for posology to be done in Product Information.

The fact that the small molecule size of brolucizumab could facilitate the penetration in tissues resulting in an improved response and longer duration of the effect was suggested but the results provided do not sustained it. While slightly better results in anatomical outcomes were reported with brolucizumab compared to aflibercept, visual acuity gain favoured aflibercept over brolucizumab.

Based on the totality of presented evidence, the CHMP considered that efficacy of brolucizumab was demonstrated for treatment of neovascular (wet) age-related macular degeneration (AMD) in adults.

2.6. Clinical safety

Patient exposure

Safety has been assessed of 2 pivotal Phase III studies of 96 weeks duration (HAWK: RTH258- C001 and HARRIER: RTH258-C002), while supportive safety data are provided from 3 Phase II studies (C-12-006, C-13-001, and RTH258-E003) and 1 Phase I study (C-10-083).

The study design of the two pivotal studies was largely similar: a 3-month loading phase (q4w), followed by a q12w/q8w regimen.

Two different pooled safety databases (S-db) were used to analyse the safety data. In each database, data from brolucizumab 6mg arm are compared to data from aflibercept 2mg group. In 2 studies (one phase II and one phase III: HAWK), a brolucizumab 3mg arm has been studied.

- Monthly loading S-db:

This pool was used to assess the safety of brolucizumab in the loading phase, i.e. during a period of monthly intravitreal injections (3 doses administered at Baseline, Week 4, and Week 8). It consisted of all nAMD studies with a duration of at least 12 weeks and a treatment group with brolucizumab 6 mg/50 µL, 3xq4w injections during the first 12 weeks, corresponding to 3, monthly loading doses.

This S-db consisted of 4 studies (RTH258-E003, C-12-006, RTH258-C001 and RTH258-C002) and collected data from 1956 patients (383 in brolucizumab 3mg; 799 in brolucizumab 6mg; 774 in aflibercept 2mg).

-Target posology long-term S-db:

This pool was used to assess the long-term safety of brolucizumab and consisted of all nAMD studies with a study duration of at least 96 weeks and a treatment group with brolucizumab 6 mg/50 µL, 3xq4w intravitreal injections (monthly loading) during the first 12 weeks followed by q12w/q8w. This S-db consisted of the 2 pivotal Phase III studies (RTH258-C001 and RTH258-C002) and collected data from 1817 patients (358 in brolucizumab 3mg; 730 in brolucizumab 6mg; 729 in aflibercept 2mg).

In the monthly loading S-db, the majority of subjects (> 96%) across treatment groups received 3 active injections from Baseline to Week 12, which were to be administered at Baseline, Week 4, and Week 8.

In the targeted posology long-term S-db, from Baseline to Week 96, the mean number of administered active injections was quite similar between treatment groups: 10.5 injections in both brolucizumab groups vs 11.7 injections in the aflibercept 2 mg group. However, the highest frequency in subjects receiving brolucizumab was 10 injections (36.7% in the pooled brolucizumab 6 mg group) and the highest frequency was 13 injections in aflibercept group (73.1%).

Patient's demographics appear to reflect the general European nAMD population and are consistent across treatment groups. There were slightly more female than male, mean age was 76 years old and more white patients were represented.

A quarter of patients had bilateral disease which seems representative according to published data (A. Rasmussen et al, 2017) with an estimated rate between 20% to 42%. In addition, according to another published article, between 19% to 68% of patients with unilateral disease will progress to bilateral disease within five years (Joachim N et al, 2017).

Extension study data

The Applicant conducted a 24-week, double-masked, multicentre, two-arm extension study to collect safety and efficacy data on brolucizumab 6 mg drug product intended for commercialization in patients with neovascular age-related macular degeneration who have completed the RTH258-C001 study.

Overall, 150 subjects were enrolled into this extension study. Out of 150 subjects enrolled, 107 were treated with brolucizumab 6 mg (62 subjects from the brolucizumab core 3 mg group and 45 subjects from the brolucizumab core 6 mg group) and 43 were treated with aflibercept 2 mg.

In this extension study, no relevant difference was observed compared to the last 6 months of the core study.

Overall, the safety profile was in line with the one identified in phase III clinical trial. No new information emerged except that cases of intraocular inflammation could also occur 2 years after treatment initiation.

Safety beyond 2 years is a safety concern that has been included in the RMP by the Applicant and will be further monitored in post-marketing.

Adverse events

- **Overview of AE**

Monthly loading S-db

The overall incidence of AE was similar in the brolucizumab 6 mg and aflibercept 2 mg groups (48.8% and 47.3%); the AE incidence in the brolucizumab 3 mg group was 54.3%.

SAE in the study eye leading to permanent discontinuation of study drug or to permanent discontinuation of the study occurred in ≤ 1% of subjects in all treatment groups.

Target posology long-term S-db

The incidence of deaths, SAE, and AE leading to permanent discontinuation of study drug or of the study was similar across treatment groups.

- **Most reported AE**

OCULAR AE

Monthly loading S-db

The most frequently reported SOC was Eye disorders which is numerically slightly higher in brolucizumab groups (27.9% in the brolucizumab 3 mg group, 23.4% in the brolucizumab 6 mg group, and 20.0% in the aflibercept 2 mg group).

Conjunctival hemorrhage was the most commonly reported AE which occurred in 5.7% of subjects in the brolucizumab 3 mg group, 4.0% of subjects in the brolucizumab 6 mg group, and 3.1% of subjects in the aflibercept 2 mg group. This AE is a known AE of anti-VEGF drugs by IVT route.

In the monthly loading S-db, 15.9% of subjects in the brolucizumab 3 mg group, 11.6% of subjects in the brolucizumab 6 mg group, and 8.5% of subjects in the aflibercept 2 mg group had at least 1 AE suspected by the Investigator to be related to study drug and/or study drug administration procedure, whereby the majority of those AE were assessed as being suspected to be related to the study drug administration procedure (in 13.6%, 9.1%, and 6.7% of subjects in the brolucizumab 3 mg, brolucizumab 6 mg and aflibercept 2 mg groups, respectively).

The most frequently reported ocular AE suspected by the Investigator to be related to the study drug administration procedure was conjunctival haemorrhage, which was reported for 5.2% (brolucizumab 3 mg group), 3.1% (brolucizumab 6 mg group) and 2.1% (aflibercept 2 mg group) of the subjects.

Target posology long-term S-db

The most frequently reported SOC across all treatment groups was Eye disorders, which is numerically slightly higher in brolucizumab groups (57.0% in brolucizumab 3mg group, 50.5% in the pooled brolucizumab 6 mg group, and 48.0% in the pooled aflibercept 2 mg group). This AE is a known AE of anti-VEGF drugs by IVT route.

The most frequently reported ocular AE in the study eye by preferred term in the pooled brolucizumab 6 mg group was visual acuity reduced. Incidence of this AE was similar in both pooled treatment groups. Conjunctival hemorrhage was the second most frequently reported ocular AE in the pooled brolucizumab 6 mg group and had a similar incidence rate in both pooled treatment groups.

Ocular AE incidence in brolucizumab 3mg group is numerically slightly higher than in brolucizumab 6mg in both safety databases which could be explained by a higher rate of ocular comorbidities at baseline in phase III study HAWK compared to HARRIER since main data from brolucizumab 3mg arm were collected from HAWK study.

The proportion of subjects with ocular AE in the study eye suspected by the Investigator to be related to study drug and/or study drug administration procedure was similar in both pooled treatment groups of the target posology long-term S-db (23.2% for pooled brolucizumab 6 mg, 22.1% for pooled aflibercept 2 mg) and in the brolucizumab 3 mg group (27.1%). The majority of AE in the study eye were suspected by the Investigator to be related to the study drug administration procedure (18.9% for pooled brolucizumab 6 mg and 18.7% for pooled aflibercept 2 mg; 22.6% for brolucizumab 3 mg) rather than suspected to be related to study drug (7.4% for pooled brolucizumab 6 mg, 4.8% for pooled aflibercept 2 mg; 6.4% for brolucizumab 3 mg).

Overall, the most frequently reported ocular AE of the study eye suspected by the Investigator to be related to study drug was retinal pigment epithelial tear, which was reported for a similar proportion of subjects across treatment groups (0.8% in the brolucizumab 3 mg group of Study RTH258-C001, 1.1% in the pooled brolucizumab 6 mg group, 1.0% in the pooled aflibercept 2 mg group).

NON-OCULAR AE

Monthly loading S-db

The proportion of subjects across treatment groups experiencing at least 1 non-ocular AE was 35.0% in the brolucizumab 3 mg group, 28.7% in the brolucizumab 6 mg group, and 30.9% in the aflibercept 2 mg group. The incidence of non-ocular AE by preferred term was similar across treatment groups.

The most frequently reported SOC was Infections and infestations (11.7% in the brolucizumab 3 mg group, 9.0% in the brolucizumab 6 mg group, and 11.0% in the aflibercept 2 mg group).

Nasopharyngitis was the most frequently reported AE with similar rates between treatments groups. This AE is considered as a common AE in elderly population and unrelated to brolucizumab.

In the monthly loading S-db, 1 subject (0.3%) in the brolucizumab 3 mg group, 4 subjects (0.5%) in the brolucizumab 6 mg group, and 0 subject in the aflibercept 2 mg group had non-ocular AE that were suspected by the Investigator to be related to study drug and/or to the study drug administration procedure and included myocardial ischemia, headache, rash, hypertension.

Target posology long-term S-db

A similar proportion of subjects in the pooled brolucizumab 6 mg and the pooled aflibercept 2 mg groups experienced at least 1 non-ocular AE (77.4% and 78.1%, respectively).

All non-ocular AE by primary SOC were reported by a similar or lower proportion of subjects in the pooled brolucizumab 6 mg group compared to the pooled aflibercept 2 mg group.

The most frequently reported non-ocular AE by preferred term in any treatment group was nasopharyngitis which occurred in a similar proportion of subjects across treatment groups.

The proportion of subjects with non-ocular AE suspected by the Investigator to be related to study drug and/or study drug administration procedure was similar in both pooled treatment pooled aflibercept 2 mg and in the brolucizumab 3 mg group of Study RTH258-C001 (1.7%).

In the pooled treatment groups, non-ocular AE suspected by the Investigator to be related to study drug were reported for 6 subjects (0.8%) in the pooled brolucizumab 6 mg group and 4 subjects (0.5%) in the pooled aflibercept 2 mg group and included the following events for brolucizumab 6mg: gamma-glutamyltransferase increased, headache, dizziness, transient ischaemic attack and hypertension. In the brolucizumab 3 mg group, non-ocular AE suspected by the Investigator to be related to study drug were reported for 6 subjects (1.7%) and included the following events: coronary artery disease, ventricular extrasystoles, colitis ischaemic, blood urea increased, blood urea nitrogen/creatinine ratio increased, cerebral infarction and cerebrovascular accident.

Serious adverse event/deaths/other significant events

- **SERIOUS OCULAR AE**

Monthly loading S-db

A total of 14 subjects experienced at least 1 SAE in the study eye, with a similar proportion across treatment groups (all $\leq$ 1%). The most frequently reported SOC across treatment groups was Eye disorders, which occurred in 0 subject in the brolucizumab 3 mg group, 6 subjects (0.8%) in the brolucizumab 6 mg group, and 3 subjects (0.4%) in the aflibercept 2 mg group.

Overall, the most frequently reported SAE in the study eye by preferred term was endophthalmitis (reported for 3 subjects (0.8%) in the brolucizumab 3 mg group), followed by retinal artery thrombosis (reported for 2 subjects (0.3%) in the brolucizumab 6 mg group).

Target posology long-term S-db

A numerically slightly higher proportion of subjects in the pooled brolucizumab 6 mg group than in the pooled aflibercept 2 mg group and the brolucizumab 3 mg group experienced at least 1 SAE in the study eye (3.4% vs 1.5% and 1.7%, respectively).

The most frequently reported SOC across treatment groups was Eye disorders (1.1% of subjects in the brolucizumab 3 mg group, 2.7% of subjects in the pooled brolucizumab 6 mg group, and 1.4% of subjects in the pooled aflibercept 2 mg group).

The most frequently reported SAE in the study eye was endophthalmitis (8 subjects overall) with a frequency of <1% in each treatment group; followed by uveitis (6 subjects overall), retinal artery occlusion/thrombosis (6 subjects), retinal detachment (5 subjects overall) and visual acuity reduced (5 subjects overall). All of them are known to be induced by anti-VEGF drugs by IVT route except for retinal artery occlusion.

- **SERIOUS NON-OCULAR AE**

Monthly loading S-db

A similar proportion of subjects across treatment groups experienced at least 1 non-ocular SAE (3.4% in the brolucizumab 3 mg group, 3.9% in the brolucizumab 6 mg group, and 3.7% in the aflibercept 2 mg group).

The most frequently reported primary SOC was Cardiac disorders, with a similar proportion of subjects across treatment groups (0.5% in the brolucizumab 3 mg group, 1.0% in the brolucizumab 6 mg group, and 0.6% in the aflibercept 2 mg group).

The most frequently reported non-ocular SAE by preferred term was pneumonia, which was experienced by 5 subjects overall (2 subjects (0.5%) in the brolucizumab 3 mg group, 1 subject (0.1%) in the brolucizumab 6 mg group, and 2 subjects (0.3%) in the aflibercept 2 mg group). In the brolucizumab 3 mg and aflibercept 2 mg groups, no other serious non-ocular AE occurred in > 1 subject; in the brolucizumab 6 mg group, cardiac failure congestive, arrhythmia, and syncope were reported for 2 subjects each.

Target posology long-term S-db

A similar proportion of subjects across treatment groups experienced at least 1 non-ocular SAE (24.3% in the brolucizumab 3 mg group, 21.0% in the pooled brolucizumab 6 mg group, and 26.6% in the pooled aflibercept 2 mg group).

The most frequently reported non-ocular SAE by primary SOC was Cardiac disorders (5.6% of subjects in the brolucizumab 3 mg group, 4.0% of subjects in the pooled brolucizumab 6 mg group, and 4.0% of subjects in the pooled aflibercept 2 mg group, respectively) followed by Infections and infestations (4.7%, 4.5%, and 5.2%, respectively).

The most frequently reported non-ocular SAE by preferred term was pneumonia (36 subjects overall), with similar incidences in the pooled treatment groups (1.6% in the pooled brolucizumab 6 mg group, and 2.3% in the pooled aflibercept 2 mg group).

Other preferred terms reported for ≥ 5 subjects in the pooled brolucizumab 6 mg group included chronic obstructive pulmonary disease (1.1% in brolucizumab 6 mg group, and 0.7% in aflibercept 2 mg group), cardiac failure congestive (0.8% in brolucizumab 6 mg group, and 0.7% in aflibercept 2 mg group), syncope (0.7% in brolucizumab 6 mg group, and 0.7% in aflibercept 2 mg group), sepsis ((0.7% in brolucizumab 6 mg group, and 0.3% in aflibercept 2 mg group), and atrial fibrillation (0.7% in brolucizumab 6 mg group, and 0.3%)in aflibercept 2 mg group).

- **DEATH**

Monthly loading S-db

No subject in the brolucizumab 3 mg group, 3 subjects (0.4%) in the brolucizumab 6 mg group, and 2 subjects (0.3%) in the aflibercept 2 mg group died up to Week 12.

The only preferred term reported for > 1 subject overall was myocardial infarction, which was reported for 2 subjects overall (1 subject each in the brolucizumab 6 mg group and in the aflibercept 2 mg group).

Death was suspected to be related to study drug by the Investigator for 1 subject in the brolucizumab 6 mg group in Study C-12-006, who died of myocardial ischemia 18 days following the third dose of study drug. The death was considered by the Investigator to be study drug related, as causality could not be ruled out.

Target posology long-term S-db

12 subjects (1.6%) in the pooled brolucizumab 6 mg group, 19 subjects (2.6%) in the pooled aflibercept 2 mg group, and 9 subjects (2.5%) in the brolucizumab 3 mg group died up to Week 96.

The most frequently reported SOC was Cardiac disorders, particularly the preferred term cardiac arrest, which was reported for 1 subject in the brolucizumab 3 mg group, 1 subject in the pooled brolucizumab 6 mg group, and 3 subjects in the pooled aflibercept 2 mg group.

One death was suspected by the Investigator to be related to study drug (event of cerebrovascular accident in the brolucizumab 3 mg group).

Overall, in brolucizumab arms, 4 cases of fatal arterial-thromboembolic events (3 cerebrovascular accident and 1 myocardial infarction) were reported with a compatible chronology (time to onset from last dose <30 days). Indeed, considering systemic half-life of brolucizumab of 4.4 days and pharmacological plausibility of anti-VEGF in ATE occurrence, a contributory role of brolucizumab in ATE cannot be excluded despite cardiovascular risk factors reported in these patients. However, pharmacokinetic and pharmacodynamics data reported rapid clearance of brolucizumab, absence of accumulation and free VEGF of short duration. This is not expected to result in any clinical consequence.

- **AE OF POTENTIAL RELEVANCE TO INTRAVITREAL ANTI-VEGF**

For each of these topics, only the data for the target posology long-term S-db are being presented since no specific safety signal was identified from the data of the monthly loading S-db.

OCULAR AE

In the target posology long-term S-db, there was no relevant difference in the overall incidence of ocular AE of potential relevance to intravitreal anti-VEGF for the study eye between the pooled brolucizumab 6 mg and the pooled aflibercept 2 mg groups (14.4% and 11.8%) and the brolucizumab 3 mg group (16.5%) at Week 96.

Endophtalmitis

The number of subjects with at least one event categorized under endophthalmitis in the target posology long-term S-db was low. Among the 10 subjects with at least one event categorized under endophthalmitis in the study eye up to Week 96, 5 subjects (0.7%; 95%CI 0.00-1.67) were in the pooled brolucizumab 6 mg group and 1 subject (0.1%; 95% CI 0.00-0.54) in the pooled aflibercept 2 mg group (risk difference for pooled brolucizumab 6 mg – aflibercept 2 mg: 0.5% (95% CI -0.27, 1.67) and 4 subjects (1.1%) were in the brolucizumab 3 mg group. The marketing of the pre-filled syringe alone will allow to reduce this risk.

Intraocular inflammation

AE categorized under intraocular inflammation were reported with a higher incidence in the brolucizumab treatment groups compared to the aflibercept 2 mg group at Week 96. The percentage of subjects with at least one intraocular inflammation event was 4.4% (95% CI 2.30-7.08) for pooled brolucizumab 6 mg vs. 0.8% (95% CI 0.14-1.63) for pooled aflibercept 2 mg, with a risk difference for pooled brolucizumab 6 mg – pooled aflibercept 2 mg of 3.6% (95% CI 1.08-6.53).

The percentage of subjects with at least one intraocular inflammation event was 4.5% in the brolucizumab 3 mg group which is similar to brolucizumab 6mg group. In order to limit the bias observed at baseline regarding ocular morbidities and discussed above (more ocular morbidities observed at baseline in HAWK compared to HARRIER study), intraocular inflammation rate for brolucizumab 3mg and 6mg has been compared in individual safety report of HAWK study. Similar rates were reported between brolucizumab 6mg and 3mg (5.8% vs 4.7%).

Most frequently PT terms retrieved were uveitis, iritis and vitritis. Most of these events were mild and moderate (~94%) and were observed in the 6 first months of treatment. Majority of cases resolved (81.3% in brolucizumab 6mg and 83.3% in brolucizumab 3mg) and some resolved with sequelae (9.4% in brolucizumab 6mg and 12.5% in brolucizumab 3mg).

An extensive review of the intraocular inflammation AE was performed by the Applicant to identify possible underlying causes and a higher incidence for intraocular inflammation AE was found in female subjects compared to male subjects and for subjects of Japanese ancestry vs subjects of non-Japanese ancestry.

Considering this higher rate in brolucizumab group compared to aflibercept and that 31.3% of cases led to drug withdrawn in brolucizumab 6mg group, a warning in the EU product information has been included by the Applicant as an AE related to intravitreal injections. This AE need to be closely monitored in post-marketing setting.

ATE and retinal artery occlusion

Ocular ATE were reported in both treatment groups of brolucizumab 3mg, 6mg and aflibercept 2 mg (1.1% and 1.2% vs 0.4% respectively) as well as retinal artery occlusive events (1.1% and 0.8% vs 0.1% respectively) with numerically slightly higher rate for brolucizumab groups.

Despite cardiovascular risk factors reported in all patients, time to onset from last dose (2 cases occurred the day of the injection) is in favor of a causal role of anti-VEGF in retinal artery occlusion occurrence in the study eye. The Applicant reported cases in clinical trials mostly reported with concomitant intraocular inflammation and proposed that the inflammation might have led to a direct compression of the artery or to a periphlebitis that subsequently caused the interruption of the blood flow leading to a retinal artery occlusion. Considering the common frequency of intraocular inflammation with brolucizumab, its higher rate compared to aflibercept and the necessity of prompt medical care for retinal artery occlusion, a warning has been added in section 4.4 of the SmPC to bring to the attention of the healthcare professionals and of the patients in addition to the listedness of this AE in section 4.8.

Further discussions were introduced concerning retinal artery occlusion in the fellow eye. No relevant differences were observed between brolucizumab and aflibercept and considering absence of direct vascular link between the two eyes, brolucizumab would need to come via the systemic circulation. At this stage, due to uncertainties related to systemic profile in case of bilateral treatment (see discussion below), causal role of retinal artery occlusion in fellow eyes is unknown and this topic should be closely monitored in post-marketing setting through PSUR.

Other ocular AE related to IVT procedure

Other AE related to injection procedure were reported with similar rates between brolucizumab 3mg and 6 mg and aflibercept such as IOP increased (5.0% , 3.8% and 4.5% respectively), retinal pigment epithelial tears (1.4%, 0.5% and 1.2% respectively), retinal detachment (0.6%, 1.6% and 1.0% respectively) and traumatic cataract (0%, 0.1% and 0% respectively).

NON-OCULAR AE

Arterial thromboembolic events (ATE)

The proportion of subjects with ATE up to Week 96 in the target posology long-term S-db was similar between the brolucizumab 3 mg group and the pooled brolucizumab 6 mg group (5.9% vs 4.5%). There was no meaningful difference in the overall incidence of non-ocular ATE between the pooled brolucizumab 6 mg and the pooled aflibercept 2 mg groups of the target posology long-term S-db (3.0% and 4.1%; risk difference for pooled brolucizumab 6 mg – aflibercept 2 mg of −1.1% (95% CI −3.19, 0.82).

Narratives were provided by the Applicant and in 16 cases, despite cardiovascular risk factors reported in all cases, a compatible chronology (time to onset from last dose <30 days taking into account systemic half-life of brolucizumab of 4.4 days) do not allow to exclude a contributory role of brolucizumab in ATE occurrence.

VEGF inhibition may predispose to thromboembolic events by reduction of PGI2 and nitric oxide and to thrombosis by increasing haematocrit and blood viscosity via overproduction of erythropoietin (Kamba et al, 2007; Spivak et al, 2002).

Systemic safety profile of anti-VEGF drugs by intravitreal route is of concern in Europe and systemic AE are not excluded since one ongoing signal procedure related to aortic dissection and aneurysm with anti-VEGF drugs has included drugs administered by IVT route (EPITT N°19330).

Pharmacokinetic data in patients with nAMD support generally a low systemic exposure after IVT injection of brolucizumab. In fact, the short systemic half-life (around 4,5 days) suggests an almost complete systemic clearance of brolucizumab before the next injection (monthly), and even more so if the time interval is increased to 2 or 3 months. Importantly, the mean free brolucizumab concentration over time appears to fall below both IC50 for VEGFR2 and VEGFR1 by approximately three days post dose. Overall, after intravitreal brolucizumab administration, a free VEGF suppression would be partial and of very short duration which is not expected to result in any clinical consequence. However, the systemic exposure in case of bilateral treatment could not be confidently predicted due to absence of PK data at 12mg and has not been investigated in clinical trials with brolucizumab. More data needed in post-marketing setting to confirm absence of clinical consequences in case of bilateral treatment. The Applicant has accepted to add a warning in section 4.4 of the SmPC related to bilateral treatment stating that this practice has not been studied in clinical trial. In addition, a warning in the product information as well as a mention related to this theoretical risk has been added as requested in sections 4.4 and 4.8 of the SmPC as it is already mentioned for other anti-VEGF drugs administered by IVT route (ranibizumab and aflibercept).

Other known risks of anti-VEGF by IV route

Similar rates between brolucizumab 3mg and 6mg groups and aflibercept 2mg group were reported for venous thromboembolic events (1.1%, 0.7% and 1.2% respectively), hypertension (11.7%, 9.2% and 9.9% respectively) and non-ocular haemorrhage (9.2%, 7.1% and 7.8%).

Similarly to ATE, VEGF inhibition may predispose to these events but more data are needed to confirm them due to low systemic exposure.

Due to low number of cases reported, it is difficult to compare ATE, VTE, hypertension and non-ocular haemorrhage rates between brolucizumab 3mg and 6mg groups.

Laboratory findings

Overall, no safety concerns were identified based on clinical laboratory assessments such as vital signs, BCVA, geographic atrophy, fibrosis and IOP in any study.

No pooled analyses were performed for clinical laboratory evaluations.

Safety in special populations

- **Intrinsic factors**

Monthly loading S-db

There were no relevant differences in exposure to study drug from Baseline to Week 12 across subgroups by age, gender, race, and ethnicity.

There were no clinically relevant differences in the incidence of ocular AE in the study eye and non-ocular AE from Baseline to Week 12 across subgroups by age, race, and ethnicity.

However, ocular AE occurred in a numerically higher proportion of females (34.7% in the brolucizumab 3 mg group, 26.0% in brolucizumab 6 mg group and 23.2%, in aflibercept 2 mg group) than males (23.8% in the brolucizumab 3 mg, 24.3% in the brolucizumab 6 mg group and 17.8% in the aflibercept 2 mg group).

Target posology long-term S-db

In this S-db, any comparison has to be interpreted with caution since the brolucizumab 3 mg group was only included in Study RTH258-C001, while the pooled brolucizumab 6 mg and pooled aflibercept 2 mg results are obtained from the pooled pivotal studies (RTH258-C001 and RTH258-C002).

Generally, the mean exposure to study drug from Baseline to Week 96 was slightly lower for both the pooled brolucizumab 6 mg and the brolucizumab 3 mg group than for the pooled aflibercept 2 mg group in all subgroups by age, gender, race, and ethnicity, where the number of subjects in the subgroup was large enough to allow for a meaningful comparison.

There were no clinically relevant differences from Baseline to Week 96 in the incidence of ocular AE in the study eye for age and ethnicity and of non-ocular AE across subgroups by race, gender and ethnicity.

However, differences of ocular AE were reported for gender (numerically higher proportion of female vs male in brolucizumab 3mg group: 65.2% in females vs 54.1% in males) and ethnicity (numerically higher proportion of Asian subjects especially for cataract and dry eye in brolucizumab 6mg vs aflibercept).

In addition, differences of reported for age groups in the <65 group, 12.9%, 10.1% and 16.9 % of subjects experienced SAE, respectively, in the brolucizumab 3 mg group, in the pooled brolucizumab 6 mg group and in the pooled aflibercept 2 mg group.

For the 65-74 group, these proportions increased to 18.4%, 19.8 % and 19.3 %, respectively.

For the 75-84 group, these proportions further increased to 29.0%, 21.3% and 28.6 %.

In the >85 group, 27.4%, 29.4% and 42.3% of subjects experienced SAE, respectively in the brolucizumab 3 mg group, in the pooled brolucizumab 6 mg group and in the pooled aflibercept 2 mg groups. An increase of the incidence of non-ocular SAE with age may be explained in the AMD population which gather most elderly subjects.

- **Extrinsic factors**

No subgroup analyses by extrinsic factors were performed by the Applicant.

Immunological events

Pre-existing anti-brolucizumab antibodies were assessed including all subjects for whom ADA data was available. Across all studies and dose groups just under half (884/2023, 43.7%) of the subjects regardless of which treatment they subsequently received, were positive for pre-existing anti-brolucizumab antibodies.

Indeed, the detection method of an immune response appears to be non-specific not only to brolucizumab but also to other antibody fragments of similar structure such as nanobodies and single domain antibodies. This can be because they share the cryptic epitopes that are revealed through the catabolism/degradation of immunoglobulins.

Separated data on patients without pre-existing ADA status at baseline (treatment induced ADA status) and patients with pre-existing ADA status at baseline (treatment boosted ADA status) were presented in Pharmacology section. Subjects who were negative for pre-existing ADA were two to three times more likely to develop brolucizumab antibodies as compared to subjects who were positive for pre-existing ADA. Positive pre-existing ADA status did not increase the likelihood of subsequently developing a treatment-emergent ADA response.

The rate of positive ADA in phase III clinical studies in patients without pre-existing ADA status at baseline was 33.2% (205/617 patients) at Week 88 for brolucizumab with no major difference between the two experimental doses. Half of them were transient (15.9% 98/617 patients).

No impact of antibodies, whether they were neutralizing or not, was observed on the incidence of non-ocular AE including systemic hypersensitivity but a correlation between ADA status and occurrence of intraocular inflammation was made since:

- most subjects with a treatment-emergent ADA status and with an intraocular inflammation AE were associated with ADA titers $\geq$270.

- a higher incidence of intraocular inflammation AE was observed in subjects with a persistent integrated induced or boosted ADA status versus a transient status.

Thus, it could be assumed that brolucizumab has a potential for immunogenicity and a mention has been added in the SmPC in section 4.4 in addition to the mention already proposed in section 4.8 of the SmPC by the Applicant. Impact on safety will be further monitored as part of routine pharmacovigilance setting.

Safety related to drug-drug interactions and other interactions

No specific drug interaction studies were performed with brolucizumab.

Discontinuation due to adverse events

- **OCULAR AE**

<u>Monthly loading S-db</u>

A total of 16 subjects in all treatment groups, experienced at least 1 AE in the study eye that led to permanent study drug discontinuation: 4 subjects (1.0%) in the brolucizumab 3 mg group, 8 subjects (1.0%) in the brolucizumab 6 mg group, and 4 subjects (0.5%) in the aflibercept 2 mg group.

Endophthalmitis was the most frequently reported ocular AE leading to permanent study drug discontinuation (3 subjects overall, all in the brolucizumab 3 mg group (0.8%)). Reported preferred terms in the brolucizumab 6 mg group included iritis, retinal artery thrombosis, uveitis (2 subjects, 0.3% each), anterior chamber inflammation, retinal artery embolism, and retinal pigment epithelial tear (1 subject, 0.1% each).

Target posology long-term S-db

A similar proportion of subjects across treatment groups experienced at least 1 AE in the study eye leading to permanent discontinuation of study drug. The most frequently reported ocular AE leading to permanent discontinuation of study drug was uveitis, which was reported more frequently in the pooled brolucizumab 6 mg group (6 subjects, 0.8%; brolucizumab 3 mg: 1 subject, 0.3%) than in the pooled aflibercept 2 mg (0 subject) group.

- **NON-OCULAR AE**

Monthly loading S-db

A total of 3 subjects experienced at least 1 non-ocular AE that led to permanent discontinuation of study drug (2 subjects (0.3%) in the brolucizumab 6 mg group and 1 subject (0.1%) in the aflibercept 2 mg group). Reported preferred terms included amnesia and colon cancer in the brolucizumab 6 mg group (1 subject, 0.3%, each) and spinal fracture in the aflibercept 2 mg group (1 subject, 0.1%).

Target posology long-term S-db

Less than 2% of subjects in each treatment group experienced at least 1 non-ocular AE that led to permanent discontinuation of study drug. The most frequently reported preferred terms, each reported for 3 subjects overall, were ischaemic stroke (2 subjects in the pooled brolucizumab 6 mg group and 1 subject in the pooled aflibercept 2 mg group) and dementia (1 subject in each treatment group).

Post marketing experience

Not Applicable

2.6.1. Discussion on clinical safety

The clinical safety analysis is based on data pooled from two Phase III studies (HAWK and HARRIER) and two-Phase II studies which have been analysed into two databases: one for the loading phase (3 monthly injections) and one for the long-term treatment (96 weeks). In these databases, brolucizumab 6 mg treatment is compared to aflibercept 2mg treatment. In 2 studies (one phase II and one phase III HAWK), a brolucizumab 3mg arm has been studied. In general, the Applicant's approach for safety assessment is considered acceptable. Of note, given the lack of a placebo arm in the studies conducted, the safety profile of brolucizumab cannot be considered fully characterised.

Patient exposure: The monthly loading safety-database (S-db) collected data from 1956 patients (383 in brolucizumab 3mg; 799 in brolucizumab 6mg; 774 in aflibercept 2mg) and the targeted posology long-term safety-database collected data from 1817 patients (358 in brolucizumab 3mg; 730 in brolucizumab 6mg; 729

in aflibercept 2mg). Mean number of injections was quite similar between all groups in the long-term S-db (10.5 vs 10.5 vs 11.7 respectively).

Patient's demographics reflect the general European nAMD population and it is consistent across treatment groups. There were slightly more female than male subjects, mean age was 76 years old, and white patients were better represented.

Long-term data: Limited long-term data are available. An extension study of HAWK allows to collect additional data over 24-weeks. This extension study enrolled 150 subjects including 107 treated with brolucizumab (62 with brolucizumab 3mg and 45 with brolucizumab 6mg). In this study, the intended drug product for commercialisation was used. Analytical studies support the conclusion that the drug products in both formulation solutions are comparable. No additional clinical studies are needed.

In this extension study, no relevant difference was observed compared to the last 6 months of the core study. Safety beyond 2 years is a safety concern that has been included in the RMP as missing information.

Adverse events (AE): Overall, AE incidence was similar between brolucizumab 6mg and aflibercept 2mg groups in both safety databases (48.8% vs 47.3% and 89.7% vs 89.6% respectively).

Ocular AE: Incidence of ocular AE in brolucizumab 6mg group is numerically slightly higher than in aflibercept group in both safety databases (25.3% vs 20.8% and 53.4% vs 51.0% respectively). The most commonly reported AE were conjunctival haemorrhage in the monthly loading S-db and reduced visual acuity in the targeted posology long-term S-db with similar rates between aflibercept and brolucizumab arms. These AE are known effects of anti-VEGF drugs by IVT route.

The AE for which a higher difference was observed between brolucizumab (3mg and 6mg) and aflibercept was intraocular inflammation (4.5% and 4.4% vs 0.8% respectively) in the targeted posology long-term S-db with a risk difference for pooled brolucizumab 6 mg – pooled aflibercept 2 mg of 3.6% (95% CI 1.08-6.53). Most of these events were mild and moderate (~94%) and were observed in the 6 first months of treatment. Most frequently preferred terms retrieved were uveitis, iritis and vitritis. Majority of cases resolved (81.3% in brolucizumab 6mg and 75% in brolucizumab 3mg) and some resolved with sequelae (9.4% in brolucizumab 6mg and 12.5% in brolucizumab 3mg). Some cases necessitated a temporary interruption of the treatment (12.5% in brolucizumab 6mg and 43.8% in brolucizumab 3mg) or drug withdrawal (31.3% in brolucizumab 6mg and 12.5% in brolucizumab 3mg). The Applicant identified gender (female subjects reported higher incidence than males) and ethnicity (Japanese ancestry subjects reported events more frequently than non-Japanese ancestry) as possible risk factors. Hypothesis of immunogenicity was put forward by the Applicant for intraocular inflammation occurrence since a higher number of cases were observed among patients with treatment-emergent AE antibodies (ADA). Hypothesis of difference in formulation between brolucizumab and aflibercept has been ruled out due to standard excipients with a well-known safety profile. Intraocular inflammation will be further investigated in post-marketing setting through PSUR.

Regarding brolucizumab dosing, a numerically slightly higher rate of ocular AE was reported in 3mg group compared to 6mg group in both safety databases (30% vs 25.3% and 60.6% vs 53.4% respectively) which could be explained by a higher rate of ocular comorbidities at baseline in study HAWK compared to HARRIER (main data from brolucizumab 3mg arm were collected from HAWK study). In study HAWK which compared the two dosages in patients with similar ocular morbidities, ocular AE were reported with similar rate between both groups (48.9% vs 49.7%) as well as for intraocular inflammation for both dosages of brolucizumab (5.8% vs 4.7%).

Ocular arterial-thromboembolic events and retinal artery occlusions (RAO) were recorded in brolucizumab 3mg and 6mg arms with a slightly higher rate compared to aflibercept (ATE: 1.1% and 1.2% vs 0.4% with aflibercept; retinal artery occlusive events: 1.1% and 0.8% vs 0.1% with aflibercept). These AE are not listed in the product information of other anti-VEGF drugs by IVT route. Among retinal artery occlusion cases reported in the study eye, most events were reported following intraocular inflammation events such as iritis, vitritis and iridocyclitis. The mechanism of action proposed by the Applicant is a direct compression by inflammation of the artery that causes interruption to the blood flow. Other hypothesis has been proposed in literature with anti-VEGF agents such as vasoconstriction of retinal arterioles and retinal whitening by complete inhibition in eyes, post-injection rise of intraocular pressure and patient stress as a result of this procedure (Mansour et al, 2012; Kida et al, 2016). Considering the common frequency of intraocular inflammation with brolucizumab, its higher rate compared to aflibercept, pharmacological mechanisms and the necessity of prompt medical care for RAO, this information need to be brought to the attention of the healthcare professionals and to the patients. A mention in sections 4.4 and 4.8 of the SmPC and in section 2 of the PIL has thus been added by the Applicant as requested.

Concerning retinal artery occlusion cases in the fellow eyes, no relevant difference was observed between brolucizumab and aflibercept treated patients. Considering absence of direct vascular link between the two eyes, brolucizumab would need to come via the systemic circulation to reach the fellow eye. Therefore, at this stage, due to uncertainties related to systemic profile in case of bilateral treatment, causal role of RAO in fellow eyes is unknown and this topic should be closely monitored in post-marketing setting through PSUR.

Other AE known to be induced by anti-VEGF agents by IVT route and related to injection procedure were also reported with similar rates between both groups such as endophtalmitis, IOP increase, traumatic cataract, retinal pigment epithelial tears and retinal tear/detachment. Marketing of the pre-filled syringe alone will allow to reduce the risk of endophtalmitis.

Non-ocular AE: Incidence of non-ocular AE was similar between brolucizumab 6mg and aflibercept groups in both safety databases (28.7% vs 30.9% and 77.4% vs 78.1%).

Nasopharyngitis was the most frequently reported AE but commonly reported in elderly population and thus unrelated to brolucizumab and aflibercept.

Regarding **arterial thromboembolic events (ATE)**, similar rates were reported in the targeted posology long-term S-db between brolucizumab 6mg and aflibercept (4.5% vs 4.7%). These events are difficult to assess because of the treated population who are elderly patients with many cardiovascular risk factors considered as confounding factors. However, in 16 cases from clinical trials, a compatible chronology (time to onset from last dose <30 days taking into account systemic half-life of brolucizumab of 4.4 days) do not allow to exclude a contributory role of brolucizumab in ATE occurrence due to pharmacological plausibility despite cardiovascular risk factors reported. In addition, considering that causal role of these systemic AE has not been excluded at this stage with aflibercept, similar rates reported in clinical trials do not allow to exclude these risks with brolucizumab. Indeed, ATE risks are still included in the RMP of EYLEA as important potential risks and are closely monitored through PSUR.

Regarding **venous thromboembolic events (VTE),** hypertension and non-ocular haemorrhage, known risks of anti-VEGF agents, similar rates were also reported between both groups. Similarly, to ATE these risks cannot be excluded for brolucizumab.

Pharmacokinetic data in patients with nAMD support generally a low systemic exposure after IVT injection of brolucizumab. The short systemic half-life suggests an almost complete systemic clearance of brolucizumab before the next injection (monthly). In addition, the mean free brolucizumab concentrations over time

appears to fall below both IC50 for VEGFR2 and VEGFR1 by approximately three days post dose and thus, a free VEGF suppression would be partial and of very short duration after intravitreal brolucizumab administration which is not expected to result in any clinical consequence. However, the systemic exposure in case of bilateral treatment could not be confidently predicted due to absence of pharmacokinetic data at 12mg and need to be closely monitored in post-marketing setting.

Discontinuation due to AE: In the monthly loading S-db, subject's decision was the first cause of treatment discontinuation in brolucizumab 6 mg (1.5%) and aflibercept 2 mg (1.2%) treated patients. In the long-term S-db, withdrawal by subject (6.3% and 5.8%, respectively) followed by adverse events (4.4% and 3.0%, respectively) were reported in the pivotal phase III studies C001 and C002.

No concerns are raised by discontinuations occurred in either the initial loading or long-term phases.

Immunogenicity: The impact of ADA on safety was investigated. A positive pre-existing ADA status did not increase the likelihood of subsequently developing a treatment-emergent ADA response. No increased incidence of systemic hypersensitivity was observed in patients with treatment-induced or boosted ADA. However, a higher incidence of intraocular inflammation events was reported among the patients with induced/boosted ADA with respect to those who were negative or positive or boosted ADA. No clear impact on efficacy in terms of visual acuity and maintenance of the trimonthly dosing regimen was also observed.

Overall, there is a potential for immunogenicity (in presence or absence of pre-existing non-specific antibodies) which will be further monitored in post-marketing surveillance and a mention has been added in sections 4.4 and 4.8 of the SmPC.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of brolucizumab seems similar to aflibercept, except for intraocular inflammations and ocular occlusive events which are more frequently reported with brolucizumab.

As with other anti-VEGF drugs by IVT route, concerns were raised regarding the potential role of brolucizumab on systemic AE occurrence such as arterial thromboembolic events, venous thromboembolic events, hypertension and non-ocular haemorrhage. Despite reassuring pharmacokinetic and pharmacodynamic data, the claimed systemic profile in case of bilateral treatment with brolucizumab 6mg, a common practice, cannot be supported by pharmacokinetic data at 12 mg and should be closely monitored in post-marketing setting.

2.7. Risk Management Plan

Safety concerns

Table 20: Part II SVIII.1: Summary of safety concerns

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

Pharmacovigilance plan

The PRAC and CHMP agreed that routine pharmacovigilance activities, including collection and reporting of adverse reactions, and signal detection are considered sufficient to monitor the safety of the medicinal product in the licensed indication. No additional pharmacovigilance activities are deemed necessary.

However, the PRAC recommended that the Applicant propose and discuss the conduction of a feasibility study of a PASS to address the important identified and potential risks as well as missing information (e.g. ATE, VTE, hypertension and non-ocular haemorrhage, bilateral treatment), but following discussion at the CHMP, it has been decided that based on large experience from similar class products, including with bilateral treatment, the PASS study was deemed not necessary. Therefore, the need for a feasibility study has been dismissed.

Risk minimisation measures

Table 21: Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Intraocular inflammation	Routine risk minimization: SmPC Sections 4.2, 4.3, 4.4, 4.8. PL Sections 2, 4. Additional Risk Minimization Measures: Patient educational materials	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up using targeted checklist. Additional pharmacovigilance activities: None
Endophthalmitis	Routine risk minimization: SmPC Sections 4.2, 4.4, 4.8. PL Section 4. Additional Risk Minimization Measures: Patient educational materials	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Transient intraocular pressure increased	Routine risk minimization: SmPC Sections 4.2, 4.4, 4.8, 4.9. PL Sections 2, 4. Additional Risk Minimization Measures: Patient educational materials	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Retinal detachment/ tear	Routine risk minimization: SmPC Sections 4.4, 4.8. PL Sections 2, 4. Additional Risk Minimization Measures: Patient educational materials	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Non-ocular events (ATE, VTE, non-ocular haemorrhage, and hypertension)	Routine risk minimization: SmPC Sections 4.4, 4.8. PL Sections 2, 4. Additional Risk Minimization Measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Safety beyond two years of treatment	Routine risk minimization: None Additional Risk Minimization Measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Non-ocular safety after bilateral treatment	Routine risk minimization: SmPC Section 4.4. PL Section 2. Additional Risk Minimization Measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 07.10.2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that brolucizumab has not been previously authorised in a medicinal product in the European Union. The CHMP, based on the available data, considers brolucizumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Beovu (brolucizumab) is included in the additional monitoring list as a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Age-related macular degeneration (AMD) is a chronic eye disease characterized by progressive degenerative abnormalities in the central retina (macula). In the aging eye, Bruch's membrane composition changes, and retinal pigment epithelium (RPE) function diminishes. As a consequence of reduced RPE function, drusen deposits at the level of the RPE photoreceptors accumulate. Drusen contain lipofuscin and other toxic waste products of metabolism. Two stages are known for this disease:

- early AMD, which is characterized by drusen and pigmentary changes,
- late AMD, which can be distinguished in 2 subtypes — geographic atrophy (GA) and choroidal neovascularization (CNV). The neovascular subtype of AMD is known to cause particularly rapid and devastating vision loss for these individuals. Vision loss results from the abnormal growth and leakage of blood vessels in the macula, leading to legally blindness.

Neovascular AMD is the leading cause of severe vision loss worldwide, affecting 10% to 13% of individuals over the age of 65 in North America, Europe, and Australia. It is suggested that almost 16% of patients with nAMD would become legally blind in 2 years without treatment and that the prevalence rates of late AMD are in European is around 2.5%.

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

3.1.2. Available therapies and unmet medical need

To date, intravitreal anti-VEGF therapies are the standard of care. Two anti-VEGF therapies authorized in the treatment of neovascular AMD are available on the market: ranibizumab (Lucentis®) and aflibercept (Eylea®).

However, intravitreal anti-VEGF treatments can be a significant burden to patients. Thus, there is a need to develop therapies with a longer effect. Additionally, in the context where the efficacy of an anti-VEGF can reduce over the time and requires a switch to another anti-VEGF together with the fact some patients have a poor treatment effect to available therapies lead a need of additional alternatives therapies.

3.1.3. Main clinical studies

The clinical study program for the sought indication consists of 2 randomized, double-masked, multicentre, active-control (versus aflibercept 2 mg) studies (RTH258-C001 [HAWK study] and RTH258-C002 [HARRIER

study]) to evaluate the safety and efficacy of brolucizumab administrated intravitreally. Two doses were investigated, 3 mg and 6 mg. The volume of injection used in pivotal studies is 50 µl (0.05 mL) regardless the dose. In both studies, following 3 loading doses at 4-week intervals, each subject treated with brolucizumab was injected every 12-weeks (q12w) up to Week 92 unless there was disease activity identified by the masked Investigator, in which case the subject was assigned to receive injections every 8 weeks (q8w) for the remainder of the study. Aflibercept subjects were treated every 8 weeks (q8w) after the loading phase (3 monthly injections).

3.2. Favourable effects

Demonstration on the non-inferiority in efficacy

In both pivotal Phase III studies, brolucizumab 3 mg and brolucizumab 6 mg demonstrated non-inferiority to aflibercept 2 mg in the treatment of the neovascular AMD. The primary endpoint was met in FAS as well in PPS analysis with consistent outcomes.

In HAWK study, regarding FAS population, the mean change in BCVA from Baseline at Week 48, with 95% CI, for brolucizumab 3 mg, brolucizumab 6 mg and aflibercept were respectively 6.3 [4.5,7.3], 6.6 [4.9,7.9] and 7.4 [5.6,8.3] letters. In pairwise ANOVA, the non-inferiority of brolucizumab 3 mg and brolucizumab 6 mg compared to Aflibercept were demonstrated with a LS mean difference of -0.6 (95% C.I.: -2.5,1.3 respectively; P=0.0003) and -0.2 (95% C.I.: -2.1,1.8; P<0.0001). In HARRIER study, regarding FAS population, the mean change in BCVA from Baseline at Week 48, with 95% CI, for brolucizumab 6 mg and aflibercept were respectively 7.0 [5.8,8.1] and 7.8 [6.3,8.9] letters. In pairwise ANOVA, the non-inferiority of Brolucizumab 6 mg compared to Aflibercept were demonstrated with a LS mean difference of -0.7 (95% C.I.: -2.4,1.0; P<0.0001).

Primary outcomes were supported by the first key secondary endpoint, average change in BCVA from Baseline over the period Week 36 through Week 48. Regarding FAS population, in HAWK study, the LS mean difference between brolucizumab and aflibercept arms was -0.5 letters for the dose of 3 mg (with a lower limit of the 95% CI = -2.4, p=0.0001 for non-inferiority testing) and 0.0 letters for the dose of 6 mg (with a lower limit of the 95% CI = -1.9 letters, p<0.0001 for non-inferiority testing).

In HARRIER study, the LS mean difference between the brolucizumab 6 mg and aflibercept 2 mg arm was -1.2 letters (with a lower limit of the 95% CI = -2.8 letters, p=0.0003 for non-inferiority testing).

Analysis of the other secondary endpoints related to anatomical parameters and Quality of Life provided supportive and consistent outcomes, giving reassurance on the efficacy of brolucizumab (3mg and 6 mg).

Support of the regimen

Secondary outcomes showed maintenance of the benefit over the time with positive outcomes at Week 96. Indeed, in HAWK study, regarding FAS population, the mean change in BCVA from Baseline at Week 96, with 95% CI, for brolucizumab 3 mg, brolucizumab 6 mg and Aflibercept were respectively 5.4 [3.7,7.0], 5.6 [4.0,7.3] and 5.6 [4.0,7.1] letters. In HARRIER study, regarding FAS population, the mean change in BCVA from Baseline at Week 96, with 95% CI, for brolucizumab 6 mg and aflibercept were respectively 6.1 [4.7,7.6] and 6.6 [5.1,8.1] letters.

Second and third key secondary endpoints were designed to assess the q12w regimen recommended after launching phase of 3 monthly injections. Regarding FAS population, in HAWK study, the estimate of the probability for a subject to be maintained on the q12w regimen up to the Disease Activity Assessment (DAA),

with CI 95%, at Week 44 was 49.4% (43.9, 54.6) for brolucizumab 3 mg and 55.6% (50.1, 60.7) for brolucizumab 6 mg. In HARRIER study, the probability was 51.0% (45.6, 56.1) for brolucizumab 6 mg.

Additionally, in subjects with no q8w need during the initial q12w cycle, the estimate for the probability of remaining on q12w regimen up to DAA at Week 44 was 80.8% (74.5, 85.7) for brolucizumab 3 mg dose and 85.3% (79.9,89.5) for brolucizumab 6 mg in HAWK study. In HARRIER study, the probability was 81.7% (75.8,86.3) for brolucizumab 6 mg.

3.3. Uncertainties and limitations about favourable effects

Demonstration of the non-inferiority in efficacy

Aflibercept has been chosen as comparator for the both pivotal Phase III studies. Given that the efficacy of aflibercept had been demonstrated in a non-inferiority setting versus ranibizumab together with the fact that the efficacy of brolucizumab has been assessed in a non-inferiority setting, there is a potential risk of biocreep. Indeed, in the hypothesis that aflibercept would be slightly inferior to ranibizumab, although in the non-inferiority margin, and that brolucizumab would be slightly inferior to aflibercept, although in the non-inferiority margin, this could lead at the end of the day to a lower efficacy. However, this is mitigated by the fact that to date aflibercept is considered as a standard of care.

Whereas the non-inferiority between brolucizumab and aflibercept was proven in both pivotal trials visual improvement was numerically larger in aflibercept treated patients.

The primary timepoint was set at Week 48. BCVA assessment for primary endpoint was thus performed 1 month after the last injection for patients on the q12w regimen, and 2 months after the last injection for patients on the q8w regimen. Given that only patients of brolucizumab groups were permitted to receive q12w, patients of Aflibercept groups remaining necessarily on the q8w regimen, together with the fact that Week 48 assessment was favorable to patients on the q12w regimen, primary timepoint was advantageous to brolucizumab. However, this is mitigated by the first key secondary endpoint, mean change in BCVA from Baseline averaged over the period Week 36 to Week 48, which could overcome the problem of a single timepoint in the context of multiple regimens.

Imputation of the missing data has been addressed with LOCF method in the main analysis. This can be questionable when the treatment is supposed to slow down a progressive disease and, in this case, the inevitable degradation of the visual acuity over time. However, sensibility analysis using multiple imputation, provided within the responses, give positive outcomes which are consistent with analysis using LOCF.

Overall, differences between 3 mg and 6 mg doses across primary and secondary endpoints were numerically very limited and not clinically significant. In that perspective, there are no strong evidences leading to support the choice of the 6 mg dose over the 3 mg dose for Marketing Authorisation.

Only naïve patient was included in the brolucizumab clinical development. Good outcomes are expected in the selected population, recently diagnosed (< 3 months) with a relevant percentage of patients with preserved visual acuity. It is unknown if the reported response will be reached in patients with more advanced/pretreated condition. However, given that brolucizumab was compared (non-inferiority) with aflibercept in the pivotal trial a similar efficacy in the intended population can reasonably be assumed.

Support of the regimen

Disease activity guidance criteria, used to assess the need of q8w regimen instead of q12w, were more stringent at Week 16 compared to the following visit, in order to select patients to have more chance to

remain on q12w regiment. The Applicant explained that criteria at Week 16 were also more stringent than real life practice. Therefore, in real life, the probability for a patient to remain on q12w regimen could be lower than in Phase III studies.

A substantial part of patients (more than 20 %) treated by brolucizumab were not eligible to q12w injections and never underwent this regimen. Together with the fact that more than 40 % of the patients were not on q12w anymore by the first year of treatment, concerns are raised on the generability of the q12w regimen as the reference posology. However, Product Information has been updated to reflect that patients with disease activity at week 16 should be treated directly with a q8w regimen.

Additionally, neither studies investigated personalized regimen (pro re nata or Treat-and-Extend). This raises concerns on the management of the patient since such treatment strategies are largely used in common practice to manage anti-VEGF IVT medication. Indeed, personalized treatments allow reduction of the number of injections, and, consequently, the risk linked to intravitreal injection and the patient burden.

3.4. Unfavourable effects

Ocular safety profile of brolucizumab seems similar to aflibercept except for intraocular inflammation and ocular occlusive events.

Most common AE reported with brolucizumab 6mg pertained to SOC Eye disorders and the most reported AE was conjunctival haemorrhage (4% in the loading phase and 6.3% at 96 weeks) and reduced visual acuity (2% in the loading phase and 7.3% at 96 weeks). Similar rates were reported in aflibercept group.

Other AE related to injection procedure were reported such as endophthalmitis (0.7%), IOP increased (3.8%), retinal pigment epithelial tears (2.7%), retinal detachment (1.6%) and traumatic cataract (0.1%) with no difference compared to aflibercept group.

The main difference observed between aflibercept and brolucizumab 6mg group is for intraocular inflammations which was reported with a higher incidence in brolucizumab group (4.4%vs 0.8%) with a risk difference for 3.6% (95% CI 1.08-6.53).

Most of these events were mild and moderate (~94%) and were observed in the 6 first months of treatment. Most frequently preferred terms retrieved were uveitis, iritis and vitritis. Majority of cases resolved (81.3%) and some resolved with sequelae (9.4%). No action was necessary in 65.6% of cases but drug was temporary interrupted in 12.5% of cases and withdrawn in 31.3% of cases.

Cases of retinal artery occlusion (RAO) which is an ophthalmological emergency were also reported with brolucizumab in the study eyes with a higher incidence compared to aflibercept (0.8% vs 0.1%). These AE are not listed in the product information of other anti-VEGF drugs by IVT route. The mechanism of action proposed is a direct compression by inflammation of the artery and considering the common frequency of intraocular inflammation with brolucizumab and the need of prompt medical care in case of RAO occurrence, a warning has been introduced in the product information to alert healthcare professionals and patients. For cases in the fellow eyes, brolucizumab would need to come via the systemic circulation in order to reach the fellow eye in absence of direct vascular link between the two eyes. At this stage, due to uncertainties related to systemic profile in case of bilateral treatment, causal role of RAO in fellow eyes is unknown and this topic need to be closely monitored in post-marketing setting through PSUR.

3.5. Uncertainties and limitations about unfavourable effects

Long-term data

Limited long-term data is available despite an extension study of HAWK to collect additional data over 24-weeks. In this Study no relevant difference was observed compared to the last 6 months of the core study. Safety data beyond 2 years has thus been included in the RMP as missing information.

Systemic safety profile

As with other anti-VEGF drugs by IVT route, concerns are raised by the PRAC and CHMP Rapporteurs about potential risk of systemic AE especially arterial thromboembolic events (ATE) due to pharmacological plausibility.

ATE cases were reported with no major difference between brolucizumab and aflibercept groups (1.2% vs 0.4% respectively) despite low rate reported which do make the comparison difficult to assess. The fact that the population treated is elderly with an elevated risk for cardiovascular events, and the absence of placebo-controlled group make the evaluation difficult. The fact that systemic AE are still closely monitored for aflibercept and that their causal role has not be ruled out at this stage, do not allow consideration of lower risk for brolucizumab.

In 16 cases reported from clinical trials, a compatible chronology (time to onset from last dose <30 days considering systemic half-life of brolucizumab of 4.4 days) do not allow to exclude a contributory role of brolucizumab in ATE occurrence despite cardiovascular risk factors identified in all cases.

Similar observations were reported for brolucizumab 6 mg compared to aflibercept for other AE known to be induced by anti-VEGF drugs by IV route such as venous thromboembolic events (0.7% vs 1.2% respectively), hypertension (9.2% vs 9.9% respectively) and non-ocular haemorrhage (7.1% vs 7.8%).

Pharmacokinetic and pharmacodynamic data revealing rapid clearance of brolucizumab, absence of accumulation and free VEGF suppression of short duration after brolucizumab injection are quite reassuring.

However, the CHMP considers that the claimed systemic profile is unknown in case of bilateral treatment which is a common practice in real life conditions and has not been studied with brolucizumab. Published data reported bilateral disease in 20 to 42% of AMD population (A. Rasmussen et al, 2017) and between 19% to 68% of AMD patients with unilateral disease will progress to bilateral disease within five years (Joachim N et al, 2017). Bilateral treatment would necessitate total dose of 12 mg for which no non-clinical and pharmacokinetic data are available. This point is of concern and need to be closely monitored in post-marketing setting.

Dose of 6mg

Uncertainties have been initially raised on the choice of the dose of 6 mg. Among the two phase III clinical studies, brolucizumab 3mg was tested in only one study (HAWK study, not tested in HARRIER).

Indeed, efficacy data revealed a comparable profile for brolucizumab 3 mg and 6 mg.

According to the safety data, ocular safety profile seemed to be comparable for doses 3 mg and 6 mg. Regarding, systemic safety profile, as mentioned above, there is a theoretical risk of systemic event due to pharmacological plausibility but considering confounding factors in the treated population and the low systemic exposure in case of intravitreal administration, this risk is not confirmed.

Pharmacokinetic and pharmacodynamics data are reassuring at 6mg but this safety profile is also to be considered in the context of bilateral treatment which would necessitate total dose of 12 mg for which no pharmacokinetic data are available. The choice of the lower dose would be a precautionary measure but considering that the Applicant want to maintain the dose of 6mg, a close monitoring is needed in post-marketing to confirm absence of systemic AE in case of bilateral treatment.

3.6. Effects Table

Table 22: Effects Table for brolucizumab for nAMD indication (data cut-off: January 2019)

Effect	Short Description	Unit	brolucizumab 6mg	aflibercept	Uncertainties/ Strength of evidence	References
Favourable Effects						
Mean change in best-corrected visual acuity (BCVA) from Baseline to Week 48	Primary endpoint (95% CI)	Letters (EDTRS)	6.4 (4.9, 7.9)	7.0 (5.6, 8.3)	- Consistent with PPS analysis - Supported by other secondary endpoints (BCVA and anatomical parameters) and long term analysis	HAWK study
			6.9 (5.8, 8.1)	7.6 (6.3, 8.9)		HARRIER study
Secondary endpoint Mean change in BCVA from Baseline averaged over the period Week 36 to Week 48	First key secondary endpoint (95% CI)	Letters (EDTRS)	6.5 (5.1, 8.0)	6.9 (5.6, 8.2)		HAWK study
			6.6 (5.4, 7.7)	7.7 (6.5,8.9)	- Difference versus the 3 mg dose numerically very limited and not clinically significant - Primary timepoint favorable to brolucizumab for patient on q12w - Imputation by LOCF questionable - No demonstration versus ranibizumab	HARRIER study
Proportion of q12W treatment status at W48	Probability for a subject to maintain on the q12w	%	0.5563 (0.5016, 0.6075)	/	- Disease activity guidance criteria less	HAWK study

Effect	Short Description	Unit	brolucizumab 6mg	aflibercept	Uncertainties/ Strength of evidence	References
for subjects randomized to brolucizumab	interval up to the disease activity assessment at Week 44 (95% CI)		0.5101 (0.4567, 0.5610)	/	stringent from Week 20 compared to Week 16. - A substantial part of patients (more than 20 %) treated by brolucizumab were not eligible to q12w. - Individualized treatment not investigated.	HARRIER study
Predictive value of initial q12W cycle at W48 with no q8W need during the initial q12W cycle	Probability to remain on q12w cycle among subjects with no q8w need at Week 16 and Week 20 (95% CI)	%	0.8539 (0.7987, 0.8950)	/		HAWK study
			0.81.70 (0.7582, 0.8629)	/		HARRIER study
Unfavourable Effects						
Conjunctival haemorrhage	Incidence	%	6.3%	7%	Most reported AE	(1)
Visual acuity reduced	Incidence	%	7.3%	7.4%		
Endophtalmitis, IOP increased, retinal pigment epithelial tears, retinal detachment and traumatic cataract	Incidence	%	0.7 3.8 2.7 2.7 0.1	0.1 4.5 1.1 1.0 0	AE related to injection procedure	(1)
Intraocular inflammation	Incidence	%	4.4	0.8	AE reported with a higher incidence compared to aflibercept and a risk difference for 3.6% (95% CI 1.08-6.53)	(1)

Effect	Short Description	Unit	brolucizumab 6mg	aflibercept	Uncertainties/ Strength of evidence	References
Retinal artery occlusion	Incidence	%	0.8	0.1	AE associated with brolucizumab and not listed with other anti-VEGF drugs by IVT route	(1)
ATE VTE Hypertension Non-ocular haemorrhage	AE known to be induced by anti-VEGF drugs by IVT route	%	1.2 0.7 9.2 7.1	0.4 1.2 9.9 7.8	Potential AE of concern. Not confirmed due to low systemic exposure but compatible chronology in 16 cases for ATE and pharmacological plausibility do not allow to exclude a contributory role of brolucizumab	(1)
Bilateral treatment	Prevalence of bilateral disease in AMD population	%	20-42		Common practice in real life conditions. Absence of non-clinical, pharmacokinetic and clinical data at 12 mg	(2)

Notes:

(1) Pooled safety data from targeted posology long-term s-db

(2) A. Rasmussen et al, 2017

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The fact that the small molecule size of brolucizumab would facilitate the tissue penetration and would result in an improved and prolonged effect has not been sustained with the results provided. While slightly better results in anatomical outcomes were reported with brolucizumab compared to aflibercept, visual acuity gain favoured aflibercept over brolucizumab.

Brolucizumab (3 mg and 6 mg) demonstrated a similar benefit profile with the comparator, aflibercept. The non-inferiority was largely met in the primary and the first key secondary endpoint. As required in such context, analysis in FAS population and PPS population were consistent. The size of the effect in visual function (BCVA) was very close across the treatment groups. Moreover, long term data (2 years) provided a sufficient level of evidence on the maintenance of the benefit over the time. Additionally, endpoints related to

anatomical parameters and Quality of Life brought reassurance on the efficacy of brolucizumab in the treatment of the patient having neovascular AMD.

The proposed dose regimen may represent a benefit with respect to other more frequently administered anti-VEGF therapies (e.g. bevacizumab) in reducing the burden of treatment. Otherwise, it is unknown how brolucizumab compares with existing flexible dose regimens (e.g. ranibizumab or aflibercept treat-and-extend dosing regimen). In principle, no clear advantage can be anticipated without further investigations on flexible dose regimens.

Ocular safety profile of brolucizumab appears to be similar to other anti-VEGF drugs by IVT route. The most commonly reported AE were conjunctival haemorrhage and visual acuity reduced with similar rates between aflibercept and brolucizumab arms.

Other AE known to be induced by anti-VEGF agents by IVT route and related to injection procedure were also reported with similar rates between both groups such as endophthalmitis, IOP increase, traumatic cataract, retinal pigment epithelial tears and retinal tear/detachment.

Compared to aflibercept, two AE were reported with a higher incidence for brolucizumab: intraocular inflammations and retinal artery occlusive events. For intraocular inflammations, no action was necessary in most cases but one third necessitated a withdrawal of treatment. Warnings have been introduced in the SmPC for both events and a close monitoring is requested in post-marketing setting to further investigate these events.

As with other anti-VEGF drug products administered by intravitreal injections, concerns are shared by the CHMP and the PRAC Rapporteurs on potential role of brolucizumab in systemic AE occurrence despite low systemic exposure, especially arterial thromboembolic events, venous thromboembolic events, hypertension and non-ocular haemorrhage which are known risks of anti-VEGF drugs by IV route due to pharmacological plausibility. Similar rates were reported compared to aflibercept for which this topic is still of concern and is closely monitored through PSUR. For ATE, a relationship to brolucizumab is difficult to assess because of the treated population who are elderly patients with many cardiovascular risk factors considered as confounding factors. In 16 cases from phase III clinical trials, a compatible chronology does not allow to exclude a contributory role of brolucizumab in ATE occurrence despite cardiovascular risk factors reported in all cases.

Pharmacokinetic and pharmacodynamic data revealing rapid clearance of brolucizumab, absence of accumulation and free VEGF suppression of short duration after brolucizumab injection are quite reassuring. However, the CHMP considers that the claimed systemic profile in case of bilateral treatment need to be better investigated and closely monitored in post-marketing due to absence of PK data at 12mg.

3.7.2. Balance of benefits and risks

The favourable effects demonstrated in the pivotal clinical studies provided evidence on the efficacy of brolucizumab, in visual function as well as in anatomical parameters, in the treatment of patient with neovascular AMD. Additionally, the ocular safety profile of brolucizumab seems to be similar to other anti-VEGF drugs by IVT route.

It is to emphasize that the benefit-risk balance is positive for both 3 mg and 6 mg doses. No strong evidence has been provided by the Applicant to clearly support the choice of the higher dose. However, the 6 mg dose could be untimely accepted based on limited numerical differences in efficacy and the similarity of the safety

profile in unilateral administration between the 2 doses. Nonetheless, considering absence of supportive pharmacokinetic data at 12 mg, systemic profile for this dose need to be better investigated and closely monitored in post-marketing setting.

3.7.3. Additional considerations on the benefit-risk balance

Not Applicable

3.8. Conclusions

The overall B/R of Beovu is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Beovu is favourable in the following indication:

Indicated in adults for the treatment of neovascular (wet) age-related macular degeneration. (AMD).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch in each Member State the MAH shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, following discussions and agreements with the National Competent Authority in each Member State where Beovu is marketed, all ophthalmological clinics where Beovu is expected to be used are provided with a patient guide in written and audio format, including the following key elements:

- What is neovascular (wet) age-related macular degeneration
- What is Beovu, how does it work, how is it administered and what to expect from the treatment
- What are the steps following treatment with Beovu
- Description of the risks, including increased intraocular pressure, intraocular inflammation, retinal detachment & retinal tear and endophthalmitis, and their key signs and symptoms; signs and symptoms of immunogenicity
- Recommendations for monitoring and required examinations: Following intravitreal injection: measurement of increased intraocular pressure and perfusion of the optic nerve
- When and how to seek urgent attention from the health care provider

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

The applicant requested the active substance brolucizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.