EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 February 2022
EMA/CHMP/180855/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

IPIQUE

International non-proprietary name: bevacizumab

Procedure No. EMEA/H/C/005433/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Quality

µDSC	Micro Differential Scanning Calorimetry
aa	Amino Acid
ADCC	Antibody Dependent Cell Mediated Cytotoxicity
AEX	Anion Exchange Chromatography
BDS	Bulk Drug Substance
BLI	Biolayer interferometry
CCIT	Container Closure Integrity Test
CD	Circular Dichroism
CDC	Complement Dependent Cytotoxicity
CE	Capillary Electrophoresis
CE-SDS	Capillary Electrophoresis in Sodium Dodecyl Sulfate
CFU	Colony Forming Units
CHO	Chinese Hamster Ovary
cIEF	Capillary Isoelectric Focusing
CIEX/CEX	Cation Exchange Chromatography
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
Cys	Cysteine
DF/UF	Diafiltration / Ultrafiltration
DLS	Dynamic Light Scattering
DoE	Design of Experiment
DP	Drug Product
DS	Drug Substance
DSC	Differential Scanning Microcalorimetry
ELISA	Enzyme-Linked Immunosorbent Assay
EoPCB	End of Production Cell Bank
ESI	ElectroSpray Ionisation
EU	Endotoxin Unit
FA2	Glycoform diantennary w/o 2 β-Gal w Fuc or G0F
Fab	Fragment Antigen Binding
Fc	Fragment Crystallisable
FcRn	Fc Receptor Neonatal
FcγR	Fc Gamma Receptor
FLR	Fluorescence (detection)
FMEA	Failure Mode and Effects Analysis

F/T	Freeze-Thaw
GC	Gas Chromatography
GMP	Good Manufacturing Practice
GPP	General Process Parameter
HC	Heavy Chain
HCCF	Harvested Cell Culture Fluid
HCP	Host Cell Protein
HDPE	High Density Polyethylene
HDX	Hydrogen/deuterium exchange
HHL	Heavy Light (chain fragment)
HILIC-UPLC	Hydrophilic Interaction Ultra Performance Liquid Chromatography
HMW	High Molecular Weight
HPLC	High Performance Liquid Chromatography
HUVEC	Human Umbilical Vein Endothelial Cells
IEX	Ion Exchange Chromatography
Ig	Immunoglobulin
IPC	In-Process Control
IPP	In-Process Parameter
IPT	In-Process Testing
kDa	Kilo Dalton
LC	Light Chain
LMV	Low Molecular Weight
LOQ	Limit of Quantitation
MA	Material Attribute
mAb	Monoclonal Antibody
Man5	Mannose 5
DS	Drug Substance
DP	Drug Product
MCB	Master Cell Bank
MFI	Microflow Imaging
MMV/MVM	Mouse Minute Virus
MoA	Mechanism of Action
MS	Mass Spectrometry
NCPP	Non-Critical Process Parameter
NeuAc	N-Acetylneuraminic acid
NeuGc	N-Glycolylneuraminic acid
NR	Non-Reduced

OFAT	One Factor At Time
PAR	Proven Acceptable Range
PD	Pharmacodynamics
PETG	Polyethylene Terephthalate Glycol
PK	Pharmacokinetics
PlGF	Placenta Growth Factor
PO	Polyolefin
PP	Process Parameter
PPQ	Process Performance Qualification
QA	Quality Attribute
QbD	Quality by Design
QC	Quality Control
QTPP	Quality Target Product Profile
R	Reduced
RMP	Reference Medicinal Product
RP HPLC	Reverse Phase High Performance Liquid Chromatography
RPLC	Reverse Phase Liquid Chromatography
SD	Standard Deviation
SDM	Scale-Down Model
SDS-PAGE	Sodium Dodecyl Sulphate – Polyacrylamide Gel Electrophoresis
SEC	Size Exclusion Chromatography
SE HPLC	Size Exclusion High Performance Liquid Chromatography
SPR	Surface Plasmon Resonance
SST	System Suitability Test
svAUC	Sedimentation Velocity Analytical Ultracentrifugation
t1/2	half-life
TOF	Time-of-flight
TVCN	Total Viable Cell Number
Tyr	Tyrosine
TAMC	Total Aerobic Microbial Count
TSE	Transmittable Spongiform Encephalopathy
TYMC	Total Yeast and Mould Count
UF/DF	Ultrafiltration/Diafiltration
UHPLC	Ultrahigh Performance Liquid Chromatography
UV	Ultraviolet
VEGF	Vascular Endothelial Growth Factor
WCB	Working Cell Bank

WC-CPP	Well Controlled-Critical Process Parameter
WFI	Water For Injections

Non-Clinical and Clinical

ADCC	Antibody dependent cell cytotoxicity
ADME	Absorption-Distribution-Metabolism-Excretion
AH	Aqueous humour
AlphaLISA	Alpha-linked immunosorbent assay
AMD	Age-related macular degeneration
AUC	Area under the curve
BLI	Biolayer interferometry
BSA	Bovine serum albumin
CDC	Complement dependent cytotoxicity
CE-SDS	Capillary electrophoresis-sodium dodecyl sulphate
CEX	Cation exchange chromatography
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
DMO	Diabetic macular oedema
ELISA	Enzyme-linked immuno sorbent assay
EP	European Pharmacopeia
ERA	Environmental risk assessment
EU	European Union
Fab	Fragment antigen binding
Fc	Fragment crystallisable
FcRn	Neonatal Fc receptor
FcγRI	Fc gamma receptor I
FcγRIIa	Fc gamma receptor IIa
FcγRIIIa	Fc gamma receptor IIIa
GLP	Good laboratory practice
GMP	Good manufacturing practice
HPLC	High pressure liquid chromatography
HUVEC	Human umbilical vein endothelial cell
ICH	International Conference on Harmonization
IEF	Isoelectric focusing
INN	International non-proprietary name
KD	Equilibrium dissociation constant
KDa	Kilodalton

KDR	Kinase insert domain receptor
kg	Kilogram
L	Litre
LC-MS	Liquid chromatography-Mass spectrometry
LC-MS/MS	Liquid chromatography-Mass spectrometry/Mass spectrometry
LMIC	Low- and middle-income countries
LOQ	Limit of quantification
MAA	Marketing authorisation application
µL	Microlitre
mg	Milligram
mL	Millilitre
MOA	Method of analysis
NA	Not Applicable
ND	Not done
ng	Nanogram
nm	Nanometre
PCR	Polymerase chain reaction
pg	Picogram
Ph. Eur	European Pharmacopoeia
R&D	Research and development
RMP	Reference medicinal product
RP	Relative potency
RP- HPLC	Reversed phase-high performance liquid chromatography
SD	Standard Deviation
SDS-PAGE	Sodium dodecyl sulfate–polyacrylamide gel electrophoresis
SEC	Size exclusion chromatography
SOP	Standard operating procedure
SPR	Surface plasmon resonance
TEM	Transmission electron microscopy
USP	United States Pharmacopoeia
UV	Ultra Violet
VEGF	Vascular endothelial growth factor
VH	Vitreous humour
WEU	Well-established use
WHO	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Rotterdam Biologics B.V. submitted on 10 March 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Ipique, 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 25 July 2019.

The applicant initially applied for the following indication: adults for the treatment of neovascular macular degeneration associated with aging and diabetes.

The proposed indication was subsequently specified to include treatment of neovascular (wet) age-related macular degeneration (AMD) and treatment of visual impairment due to diabetic macular oedema (DME). The DME indication was subsequently withdrawn by the applicant following concerns over deficiencies in the data submitted.

During the procedure, the applicant has also proposed to add the indication "*treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO)*", submitting supporting data. The addition of the RVO indication was not accepted. The data were considered given their potential to be informative on the AMD indication, despite the fact that the assessment performed revealed that they would have been clearly insufficient for an RVO indication. In any event, the overarching lack of adequate bridge between Ipique and the bevacizumab used to generate the data present in the literature (see below) also apply to this indication.

The final indication proposed by the applicant only included AMD. However, data submitted in support of the DME and RVO indications were taken into consideration as far as they were considered as supportive information of the efficacy and safety of bevacizumab in AMD.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10a of Directive 2001/83/EC – relating to applications relying on well-established medicinal use supported by scientific literature

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 test(s) or study(ies).

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised

orphan medicinal products. However, in view of the indication finally applied for, considerations pursuant to Commission Regulation (EC) No 847/2000 no longer apply.

1.5. Scientific advice

The applicant received scientific advice from the CHMP on 27 February 2020. The scientific advice pertained to the following quality and clinical aspects:

Quality: The level of similarity testing required between Avastin and Ipique to be able to claim the extensive literature data on the efficacy and safety of bevacizumab in retinal neovascularisation.

Clinical: The approach to show well-established use based on a critical and unbiased assessment of literature data.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Andrea Laslop Co-Rapporteur: Maria Concepcion Prieto Yerro

The application was received by the EMA on	10 March 2020
The procedure started on	21 May 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 August 2020
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	11 August 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 August 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 September 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 March 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	27 April 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	06 May 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	20 May 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	14 September 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	29 September 2021

The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	7 October 2021
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	12 October 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Ipique on	11 November 2021

1.7. Steps taken for the re-examination procedure

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

Rapporteur: Jayne Crowe Co-Rapporteur: Armando Genazzani

The applicant submitted written notice to the EMA, to request a re-examination of Ipique CHMP opinion of 11 November 2021, on	26 November 2021
The CHMP appointed Jayne Crowe as Rapporteur and Armando Genazzani as Co-Rapporteur on	17 January 2022
The applicant submitted the detailed grounds for the re-examination on	14 January 2022
The re-examination procedure started on	17 January 2022
The Rapporteur's re-examination assessment report was circulated to all CHMP members on	11 February 2022
The Co-Rapporteur's assessment report was circulated to all CHMP members on	12 February 2022
Expert group were convened to address questions raised by the CHMP on The CHMP considered the views of the Expert group as presented in the minutes of this meeting	16 February 2022
The Rapporteurs circulated the Joint Assessment Report on the detailed grounds for re-examination to all CHMP members on	18 February 2022
The detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP on	23 February 2022
The CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the standard marketing authorisation on	24 February 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The target indication is treatment of neovascular (wet) age-related macular degeneration (AMD). AMD is a degenerative disease of the central portion of the retina (the macula) that results primarily in loss of central vision. Central vision is required for activities such as driving, reading, watching television, and performing activities of daily living. AMD is classified as dry (atrophic) or wet (neovascular or exudative) for clinical purposes. Wet AMD is characterised by growth of abnormal vessels into the subretinal space, usually from the choroidal circulation and less frequently from the retinal circulation. These abnormal blood vessels leak, leading to collections of subretinal fluid and/or blood beneath the retina. The abnormal blood vessels emanating from the choroid are also referred to as choroidal neovascularisation. Although wet AMD is found in only 10 to 15 percent of patients with AMD, wet AMD accounts for more than 80 percent of cases with severe visual loss or legal blindness. Wet AMD is characterised by rapid distortion and loss of central vision over a period of days to weeks. The contralateral eye is at high risk of developing neovascularisation.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Prevalence

Age-related macular degeneration (AMD) has been reported in many different populations, and its prevalence varies among racial and ethnic groups. AMD is more common in older adults. Focal and geographic areas of RPE atrophy appear as AMD progresses. These areas represent thinning and loss of tissue in a focal or more geographic pattern in the macula. Depending upon the location of the RPE atrophy, central vision or pericentral vision may be affected.

The global prevalence was estimated to be around 170 million in 2016 (Pennington K.L and DeAngelis M 2016). Q Li et al. estimated in 2019 that approximately 67 million people in the EU are currently affected by any AMD and, due to population ageing, this number is expected to increase by 15% until 2050. Colijn et al. 2017 published that in Europe, the prevalence of early AMD increased from 3.5% (95% confidence interval [CI] 2.1%-5.0%) in those aged 55-59 years to 17.6% (95% CI 13.6%-21.5%) in those aged ≥85 years; for late AMD these figures were 0.1% (95% CI 0.04%-0.3%) and 9.8% (95% CI 6.3%-13.3%), respectively.

AMD was identified in 1.6 percent of 14,752 people (aged 43 to 99) from the United States, the Netherlands, and Australia [Smith et al. 2001]. Prevalence rates for people aged <55, 55 to 64, 65 to 74, 75 to 84, and >84 were 0.0, 0.2, 0.9, 4.6, and 13.1 percent, respectively. Overall, dry AMD was found in 0.5 percent of the population, and wet AMD was found in 0.9 percent. Forecast data have indicated an increasing prevalence of AMD.

Incidence

The incidence of AMD is higher in older adults but appears to be decreasing with each new generation. The Beaver Dam Eye Study longitudinally followed 4000 people aged 43 to 86 at baseline, with eye examinations every five years for 15 years [Klein et al. 2007]. The cumulative incidence of early AMD was 14.3 percent, and the cumulative incidence of late AMD was 3.1 percent overall and 7.6 percent in

those who were ≥75 years at baseline. However, the risk of developing AMD has declined in birth cohorts followed in this study throughout the 20 century [Cruickshanks et al. 2017].

Risk Factors

A variety of clinical risk factors for age-related macular degeneration (AMD) have been identified. These include:

- Ethnicity – AMD appears to be more prevalent in whites than in blacks, with an intermediate prevalence in Hispanics and Chinese.
- Smoking – Smoking increases the risk of dry and wet AMD, with relative risks (RR) ranging from 2 to 4 compared with people who never smoked.
- Alcohol use – Heavy alcohol use (more than three drinks per day) is associated with an increased risk for early AMD.
- Diet – Observational studies suggest that a healthy diet including fruits, vegetables, and fish may be associated with a lower risk of AMD.
- Family history – There appears to be an increased risk in patients with a family history of AMD
- Chronic medical conditions Cardiovascular disease, AIDS, Chronic myeloproliferative diseases Cataract surgery and certain medications (e.g. Aspirin) are associated with an increased risk.

Prevention

Healthy lifestyle habits may be helpful in preventing AMD. Healthy diet and physical activity have been discussed as preventive measures.

2.1.3. Biologic features and aetiology and pathogenesis

Choroidal neovascularisation is controlled by a dynamic balance between membrane bound and diffusible substances with properties that either promote or inhibit blood vessel development. Several isoforms of VEGF, with different binding affinities for the VEGF receptors, have been identified as factors. VEGF-A is most strongly associated with angiogenesis and is the target of most current anti-VEGF treatments.

Genetic polymorphisms in several genes have been identified that could account for more than half of all cases of AMD.

Many of the identified genetic polymorphisms support a role for local inflammation and complement activation in the aetiology of AMD.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Clinical Presentation

Wet AMD may present as acute visual distortion or loss of central vision as a result of subretinal haemorrhage or fluid accumulation. Symptoms of wet AMD usually appear in one eye, although the disease is often present in both eyes. Once advanced AMD develops in one eye, there is a greater than 40 percent risk of development in the other eye within five years.

Distortion of straight lines (metamorphopsia) is one of the earliest changes with wet AMD. Patients may perceive straight edges (such as doors or window blinds) as curved or distorted. Most patients

with advanced AMD lose central vision, but they rarely lose their peripheral vision; nonetheless, significant visual loss results in disability and clinical depression in over one-third of patients.

Diagnosis

Patients with an acute distortion or loss of central vision may represent wet age related macular degeneration (AMD). AMD is a clinical diagnosis based upon the presence of characteristic findings on dilated eye examination using a slit-lamp instrument (biomicroscopy): In wet AMD, dilated examination may reveal subretinal fluid and/or haemorrhage. Neovascularisation appears as a greyish-green discoloration in the macular area. The presence of subretinal haemorrhage or a grey subretinal membrane is strongly suggestive of a subretinal choroidal membrane.

These patients require an office-based fluorescein angiogram delineate and characterise the neovascular membrane and optical coherence tomography (OCT) to identify the presence of subretinal fluid or retinal oedema. Optical coherence tomography is a non-invasive imaging technique that produces high-resolution cross-sectional images of the retina, posterior vitreous, retina, retinal pigment epithelium and anterior choroid. These images can be used to identify retinal oedema and/or subretinal fluid. Fundus autofluorescence is a new imaging technique that allows identification of lipofuscin accumulation, a sign of cellular metabolism and aging, and can be used to characterise and follow the progression of geographic atrophy.

2.1.5. Management

Age-related macular degeneration (AMD) is a progressive blinding disease with no cure at present. Effective therapies for exudative or wet age-related macular degeneration (AMD) include intravitreous injection of a vascular endothelial growth factor (VEGF) inhibitor, photodynamic therapy (PDT). Supplementation with zinc and antioxidant vitamins as well as visual aids are suggested.

Aflibercept (Eylea), Ranibizumab (Lucentis) and Brolucizumab (Beovu) are approved and available across the union.

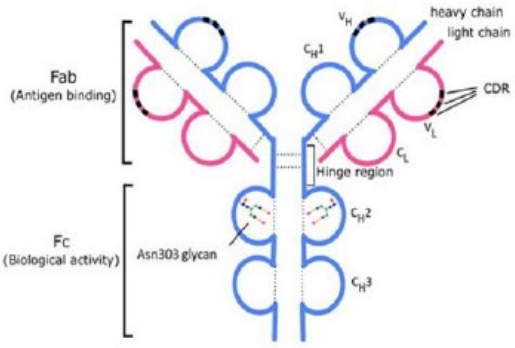
2.2. About the product

Active substance: bevacizumab

Therapeutic indication: Ipique is proposed for treatment of neovascular (wet) age-related macular degeneration (AMD).

Mechanism of action: Bevacizumab binds with high affinity to the VEGF-A isoforms, thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, pathologic myopia and CNV or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to RVO.

Figure 1: Structure



recombinant humanised monoclonal antibody of the IgG1κ isotype

Class of biological product: Monoclonal antibody

2.3. Type of Application and aspects on development

The legal basis for this application refers to Article 10a of Directive 2001/83/EC– relating to applications relying on well-established medicinal use supported by scientific literature.

The Application was based on the demonstration of well-established use of Avastin in the claimed indications, including the demonstration of efficacy and safety through literature data and on the demonstration that the evidence submitted is relevant for Ipique.

In the following paragraphs, the legal requirements for a claim under well-established use will be discussed.

In accordance with the provisions of Annex I of Directive 2001/83/EC as amended, evidence is needed that bevacizumab has been extensively used for more than a decade and has recognised efficacy and an acceptable safety in the proposed indication.

Furthermore, Annex I also states that: *'The non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences.'*

Related to the above, it also bears noting that Volume 2A of Chapter 1 of the Notice to Applicants further clarifies that "[i]*n certain cases, studies may be provided only to support the relevance of the literature (used to demonstrate safety and efficacy of the active substance(s)), to the product intended for marketing*".

In other words, when the evidence on safety and efficacy submitted for the purpose of demonstrating WEU was obtained with a product different from that being applied for marketing authorisation (the studied product): (a) the applicant must explain how said evidence is relevant, or, putting it differently, applicable, to the candidate product; and (b) a scientific judgment must be made on the applicability of the evidence submitted to conclude on the safety and efficacy of the candidate product in the applied indication despite any differences vis-à-vis the studied product.

The requirements of article 10a application are discussed below.

a) Factors which have been taken into account in order to establish a well-established use

- ***Time*** *over which a substance has been used (minimum requirement: 10 years)*

Literature relevant to this application started to be published in the mid-00 years, indicating a more than 10 year time span since start of intravitreal use of bevacizumab in wet age-related macular degeneration (AMD). Since when the substance has been used 'regularly' or 'with regular application' is hard to determine for the target indication, because the extent of use cannot be estimated for any given point/period of time (in the past). No thorough literature overview has been provided by the applicant and no discussion on regularity of use has been provided. Overall, the extent of use of bevacizumab can be considered acceptable for AMD.

- Quantitative aspects *of the use of the substance*

- Extent of use in terms of quantitative aspects

Based on patient numbers reported in Solomon et al. 2019 around 1621 patients had received bevacizumab for neovascular AMD during RCTs meeting eligibility criteria to be included in the Cochrane review. Cumulative patient numbers outside of the scope of this Cochrane review were not discussed.

Besides controlled and uncontrolled studies, single arm trials and case series, also the use outside of study settings is of interest for the assessment of well-established use. For example, it would have been of interest to understand the proportion of bevacizumab doses sold and used for each indication during the last 10 years. Data on the use of bevacizumab in the intended indications from specialised centres and institutions could have been used.

The applicant has supplied guidelines that to some extent substantiate significant use.

Overall, the criterion could be considered accepted for AMD.

- Extent of use in terms of geographical aspects

The pivotal reference in support of efficacy of the AMD indication (Solomon et al. 2019) included data from North and South America, Europe, Asia, and Australia. It is currently unclear what data stem from what country or what products have been used in the respective studies (presumably EU or US Avastin).

The CHMP also noted the therapeutics guidelines from different Member States that indicate the use of bevacizumab in AMD, although the extent of the use cannot be quantified based on these documents.

Despite the limitations of the data provided, it can be concluded that bevacizumab has been sufficiently used in different territories of the Union.

Consequently, the provided data can be considered acceptable for the AMD indication.

- Scientific interest *reflected in the published scientific literature*

Based on the data referred to by the applicant and relevant data available in the public domain, scientific interest for the use of bevacizumab in macular degeneration can be reasonably assumed. This criterion is considered demonstrated.

- Coherence *of scientific assessments*

The Cochrane reviews resulted in quite consistent conclusions supporting efficacy of the substance in the target indication. The publications considered pivotal for this assessment are: Solomon et al 2019 (*Anti-vascular endothelial growth factor for neovascular age-related macular degeneration (Cochrane Review)*), Virgili et al 2017 (*Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis (Cochrane Review)*) and Thulliez et al. 2018 (*Overview of Systematic Reviews and Meta-analyses on Systemic Adverse Events Associated With Intravitreal Anti–Vascular Endothelial*

Growth Factor Medication Use). However, no comprehensive literature review has been provided by the applicant and no discussion of favourable and/or unfavourable data is available. Coherence of scientific assessment cannot be completely determined without a comprehensive literature search and a thorough discussion of literature data, therefore there is remaining uncertainty if the totality of data has been considered to support the AMD indication in this procedure. This partial deficiency will be considered when assessing the uncertainties around the risk-benefit.

b) As stated above*,* no comprehensive literature review has been provided by the applicant and no discussion of favourable and/or unfavourable data is available, therefore there is remaining uncertainty if the totality of data has been considered to support the AMD indication in this procedure. This partial deficiency will be considered when assessing the uncertainties around the risk-benefit.

c) Despite the lack of some studies and the lack of provision by the applicant of a comprehensive review, it can be concluded that acceptable levels of safety and efficacy were demonstrated for the bevacizumab used to generate the data presented in the literature given the following considerations: (i) coherent results from independent reviews and meta-analyses; (ii) widespread recommendations in treatment guidelines; (iii) comparability of the mechanism of action with the mechanism of action of approved products.

d) Similarity of the product studied and of that for which application for a marketing authorisation has been made

The applicant provided a rationale and data to support the relevance of data submitted concerning the product reviewed in the literature for Ipique. The applicant used analytical comparability of Avastin and a biosimilar of Avastin recently approved in the EU claimed to be the same bevacizumab as Ipique) to support bridging to the literature data on use of bevacizumab in retinal neovascularisation. The fact that the bevacizumab used to generate the literature in this indication is presumed to be mostly EU- and US- sourced Avastin can be accepted. However, due to the complexity of the monoclonal antibody structure and the potential impact of aberrations between products on the clinical performance, similarity on a quality level alone is not considered sufficient to conclude that the clinical data obtained with Avastin can be extrapolated to Ipique. The applicant also submitted a clinical trial comparing a biosimilar of Avastin recently approved in the EU to Avastin which was performed in the clinical setting of an intravenous administration in an oncological indication. This study was not considered sufficient to establish the bridge between Ipique and the product referred to in the literature in AMD and establish the efficacy and safety of Ipique owing to the differences in the claimed indication and route of administration.

The need of an appropriate clinical comparison in the intended indication and route of administration to demonstrate that Ipique and the medicinal product referred to in the literature are similar has been discussed further in the report.

e) Extent of monitoring (post-marketing experience with products containing the same constituents is of particular importance and applicants should have put a special emphasis on this issue)

The extent of post marketing experience with bevacizumab for the target indication has been discussed to some extent. Since the applicant is not the MAH of the bevacizumab described in literature nor has Ipique ever been used in the claimed indication the amount of post marketing data available to the applicant is expected to be limited. The provided information is considered acceptable by the CHMP.

Further, in this report, the quality section will discuss the quality data specific to Ipique, while sections on Non-Clinical and Clinical Efficacy and Safety will mainly discuss the efficacy and safety of the Bevacizumab used in the literature (sometimes also referred to as "Avastin"). The sections on Benefits and Risks will take into account all aspects to conclude on the balance between benefits and risks of Ipique.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as solution for injection containing 25 mg/mL of bevacizumab as active substance. The product is supplied in one presentation, i.e. 100 mg/4 mL single-use vials (8 mL).

Other ingredients are: α,α-trehalose dihydrate, sodium phosphate (monobasic sodium phosphate monohydrate and disodium phosphate), polysorbate 20, and water for injections.

The product is available in Type I glass vials closed with a chlorobutyl stopper and an aluminium seal with a polypropylene flip-off cap.

The Ipique application is submitted following the well-established use pathway (Article 10a of Directive 2001/83/EC). Based on the analytical comparability study against Avastin (EMEA/H/C/000582) and published data on off-label treatment of AMD by intravitreal administration of Avastin, the applicant intends to demonstrate that Ipique can be safely and effectively used in the targeted indication. It should be noted that the Module 3 submitted for Ipique is based on that of a bevacizumab developed as biosimilar to Avastin.

2.4.2. Active substance

2.4.2.1. General Information

The active substance is bevacizumab, a recombinant humanised IgG1 kappa monoclonal antibody directed against VEGF-A. Binding of bevacizumab to VEGF-A neutralises the biological activity of VEGF-A by blocking binding of VEGF-A to its receptors. Bevacizumab does not display Fc effector functions. Ipique is produced from a mammalian Chinese hamster ovarian (CHO) cell line. It consists of 2 heavy chains (HC) of the lgG1 subclass (453 aa) and 2 light chains (LC) of the kappa subclass (214 aa) connected by intra- and interchain disulphide bonds. The N-glycosylation site is located at amino acid position Asn303 on the heavy chain. The theoretical molecular mass of the fully assembled antibody is 149199.86 Da (main glycoform G0F/G0F).

2.4.2.2. Manufacture, process controls and characterisation

The active substance is manufactured in accordance with current good manufacturing practices (GMP).

The active substance is expressed in a CHO cell line using a fed-batch process. Manufacture of a batch starts from a single vial of the working cell bank (WCB). After thawing the cells are expanded under controlled conditions in multiple steps to obtain sufficient cells for inoculation of the single-use production bioreactors. The unprocessed bulk from the end of production bioreactors step is clarified through a series of depth filters

The active substance is purified by a series of column chromatography steps The manufacturing process includes two dedicated, orthogonal virus clearance steps, i.e. virus inactivation and virus removal. The formulated active substance is filtered, filled into bottles and stored.

Overall, the process parameters and in-process controls in combination with the other control measures appear sufficient to ensure quality and safety of the active substance and to monitor process consistency. The process parameters, which are classified into critical process parameters (CPP), well-

controlled critical process parameters (WC-CPP), non-critical (NCPP) process parameters, and general process parameters (GPP), are based on enhanced knowledge gained by process experience throughout process development, manufacture of clinical batches, and process characterisation at small scale. Three categories of in-process tests have been defined by the applicant. The in-process tests and their limits have been derived from process understanding and under consideration of safety aspects. The proposed controls appear sufficient to ensure adequate quality of the active substance.

Control of Materials

Raw materials are of compendial quality or adequate in-house specifications have been established. Composition and preparation of cell culture media and buffer solutions are sufficiently described. Significant single-use materials as well as relevant processing materials are described. No direct animal-derived materials but some materials of indirect animal origin are used during manufacture the active substance (please refer to section on adventitious agents below).

The construction of the expression vector and its genetic elements are described in sufficient detail. The origin of the antibody sequence is briefly described and the correct nucleotide and amino acid sequence was confirmed. The information provided on the origin and history of the parental CHO cell line and generation of the final production clone is acceptable. The applicant has established a two-tiered cell bank system with Master Cell Bank (MCB) and Working Cell Bank (WCB). Cell banking procedures are adequately described. A protocol describing manufacture and qualification of new WCBs has been registered. Characterisation of the expression construct and cell substrate including MCB, WCB, and End of Production Cell Bank (EoPCB) is in line with ICH guidelines Q5A, Q5B and Q5D.

Process Validation

The applicant follows a process validation lifecycle strategy as described in Guideline EMA/CHMP/BWP/187338/2014 comprising process characterisation (see section below), process verification/process performance qualification (PPQ), and ongoing process verification throughout the lifecycle. A traditional approach was chosen to verify process performance at commercial scale. The prospective process verification encompassed manufacture of three consecutive process validation batches according to the intended commercial process at the intended commercial manufacturing site and scale. Confirmation of adequate removal of process- and product related impurities and of hold times for process intermediate pools were part of the validation activities. The validation results, which were all within their specified acceptance criteria, demonstrate that the process performs consistently and delivers active substance complying with the release specifications under commercial operating conditions. The results confirm that the process-related impurities are consistently reduced to low levels/below the limit of quantification (LOQ) and that product-related impurities are controlled at low level. Potential leachables originating from single-use equipment have been addressed. Overall, the data on re-use of the chromatography resins support the proposed life time.

A summary of the shipping validation has been presented.

Manufacturing Process Development

Early development was performed at 500 L scale and comprehensively presented. Based on experience gained, the process was further developed, optimised and scaled-up to the intended scale at the intended manufacturing site for the European market. In the main, the proposed commercial manufacturing process resembles the previous 500 L process. Prior to manufacture of active substance for the pivotal clinical trials in the oncology indications of the biosimilar the process was further optimised. In addition, during production of active substance for the pivotal phase III study for the oncology indications of the biosimilar the UF/DF step was optimised to improve the adjustment of the protein concentration.

The applicant followed an enhanced development approach using existing knowledge, process development and manufacturing experience, risk assessment tools, and process characterisation studies to develop a control strategy as outlined in ICH Q11 and EMA/CHMP/BWP/187338/2014.

A comprehensive set of product variants, process-related impurities and so called `obligatory´ quality attributes (i.e. protein content, general and microbial attributes) that cover the relevant attributes of the active substance was assessed and an impact score based on impact on biological activity, PK/PD, immunogenicity and safety was assigned to each quality attribute. The criticality score was determined from the impact score and the uncertainty score using a quantitative risk ranking matrix. The relevant CQA of bevacizumab have been identified; the individual impact and uncertainty scores as well as justifications for the scoring are agreeable.

Process characterisation studies were used to systematically evaluate process parameters with regard to their impact on process performance and product quality and inform regression models for determination of proven acceptable ranges (PAR).

Comparability of active substance from the 500 L and the commercial scale process was not directly evaluated but the finished product from the site used to manufacture clinical material or intended commercial site using active substance from the 500 L and commercial process, respectively, was shown to be comparable (refer to finished product section). The pivotal clinical phase I and phase III studies conducted for the biosimilar in its oncology indications were performed with active substance manufactured with the intended commercial process (except for the modified UF/DF step which was implemented during the pivotal comparative phase III study).

Characterisation

The applicant comprehensively characterised the structure and biological properties of the active substance using orthogonal, state-of-the art analytical methods. The amino acid sequence was experimentally confirmed by peptide mapping with 100% sequence coverage. Presence of C- and N-terminal variants (pyroglutamate, Lys-clipping), oxidation, and deamidation is presented. The higher order structure was evaluated by a combination of disulphide bridge mapping, far-UV CD, hydrogen/deuterium exchange mass spectrometry, µDSC, and DLS. Charge and size variants were determined using complementary analytical methods (CEX-HPLC, cIEF and CE-SDS, SE-HPLC, respectively). Glycoanalysis comprised the identification of the oligosaccharide pattern and site occupancy by peptide mapping and HILIC-UPLC-FLR; in addition, sialic acid content (NeuAc and NeuGc) was determined by UHPL-FLR. The absence of alpha-1,3-galactose structures has been demonstrated. The biological characterisation included an assessment of binding to VEGF-A_{121}, -B_{167}, C, -D and PlGF (by biolayer interferometry) and to VEGF-A_{165} by ELISA as well as of functional activity in cell-based assays (HUVEC). In addition, absence of Fc effector functions (ADCC and CDC) was confirmed in cell-based assays. The presented data confirm the expected structural and functional characteristics of bevacizumab**.**

Product-related variants and impurities detected by SEC- and CEX-HPLC were identified and characterised using relevant orthogonal methods. Functional characterisation of the variants/impurities included determination of VEGF binding by competitive ELISA.

The levels of HHL fragments, as observed by non-reducing CE-SDS, were demonstrated to be higher in the active substance as compared to Avastin. Detailed analyses by peptide mapping and mass spectrometry revealed amino acid substitutions with relevant substitution levels (>1%) only occurring at position HC226. Extensive experiments support the applicant´s conclusion that the amino acid substitution is metabolic. As demonstrated in the analytical comparability assessment (please refer to discussion of analytical comparability) higher order structure and biological activity was highly comparable between the biosimilar and Avastin further indicating that the amino acid replacements

have no impact on efficacy. Immunogenicity may potentially be affected by the replacement; however, the clinical data from the oncology study for the biosimilar do not hint at immunogenicity issues with the biosimilar. Absolute quantitation based on stable isotope labelling revealed low levels of amino acid substitution at HC226. The chemistry behind the change (probably codon misuse due to similar codon sequences) has been sufficiently discussed by the applicant.

The applicant described future options to minimise the amino acid substitution in the commercial process and submitted a post approval change management protocol (PACMP) for implementation of an optimised active substance manufacturing process.

2.4.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

The proposed set of quality attributes included in the specifications for release and stability testing of the active substance complies with ICH Q6B, Ph. Eur. 2031 and EMA/CHMP/BWP/532517/2008, and is acceptable. The release specification comprises tests for identity, purity and impurities, potency, quantity, microbiological attributes and general attributes.

Potency is determined by a combination of a competitive VEGF-binding ELISA and a relevant cell-based assay that measures inhibition of proliferation.

In addition to manufacturing process capability, batch release and stability data (including clinical batches for the oncology indications of the biosimilar), data from the analytical comparability exercise against Avastin, and characterisation data, the applicant took into account regulatory requirements from the Ph. Eur. and relevant guidelines to justify the specifications.

The proposed specification limits are generally considered acceptable. However, the justification of the endotoxin limits needs to be revised. This issue remains to be resolved. In addition, the applicant committed to re-evaluate several limits after at least 30 commercial batches have been manufactured.

Analytical Methods

The analytical methods are sufficiently described and appear adequate. For determination of HCP, a commercial generic test kit is used. However, the applicant committed to implement a process specific HCP method. The implemented system suitability tests (SST) and sample acceptance criteria appear suitable to provide adequate control over analytical method performance.

Overall, the presented analytical method validations are adequate and demonstrate the suitability of the analytical procedures for their intended use. The relevant analytical method parameters have been assessed in accordance with ICH Q2(R1). Robustness of the methods has been sufficiently demonstrated by extensive robustness data.

Reference Standards

The history of reference standards used throughout development of the active substance is presented. Recently, a two-tiered system with primary reference standard and secondary reference standards has been implemented. The reference materials were adequately qualified according to the development phase using release and additional characterisation tests. The procedures for assignment and stability monitoring of potency of the reference standards are acceptable.

Batch Analyses

Batch release data are presented for active substance batches manufactured according to the intended commercial manufacturing process at the intended commercial site. The batches were used in pivotal clinical studies conducted for the biosimilar in its oncology indications, for demonstration of analytical

similarity, in stability studies as well as for process validation purposes. All results comply with the specifications at time of testing and the commercial specifications. The presented results demonstrate that the manufacturing process reliably delivers active substance with consistent quality.

Container closure

The active substance is stored in bottles with screw cap closures. The materials comply with Ph. Eur. and/or USP requirements and Commission Regulation (EU) No. 10/2011 on plastic materials and articles in contact with food. Compatibility has been demonstrated by stability studies and additional compatibility studies.

2.4.2.4. Stability

The applicant presented a shelf-life claim.

The ongoing stability studies are conducted at long-term storage conditions as well as under accelerated conditions using active substance batches that were manufactured according to the intended commercial manufacturing process at the intended commercial site. In addition, forced degradation studies applying several stress conditions were performed with.

The design of the studies is in accordance with ICH Q5C. The samples are stored in bottles representative of the commercial container closure system and were filled to the same level as the commercial container closure. Overall, the analytical programme follows the proposed active substance specifications and includes stability-indicating methods.

Results were statistically evaluated for trends. At long-term and accelerated conditions, all results comply with the acceptance criteria for the studies as well as the proposed commercial specification limits. No obvious relevant trends are present at long-term conditions.

No major effects on quality of the active substance were observed in the forced degradation studies. Further comparative stress stability studies were conducted as part of the analytical similarity exercise.

In conclusion, the presented data support the proposed shelf life in the described container closure system.

A commitment to complete the currently ongoing stability studies as well as the schedule for annual stability studies are provided.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and Pharmaceutical Development

Description and composition

The finished product is a sterile, preservative-free solution for injection containing 25 mg/mL of bevacizumab as active substance and is supplied in single-use vials of 100 mg/4 mL.

Bevacizumab is formulated with trehalose dihydrate, sodium phosphate (as monobasic sodium phosphate monohydrate and as disodium phosphate), polysorbate 20 and water for injections. The formulation is identical to that of Avastin.

Pharmaceutical development

The excipients used are of compendial quality and the same as the excipients used in EU-authorised Avastin. The excipients include a buffering agent to stabilise pH, non-reducing disaccharide as

lyo/cryo-protectant and stabiliser against thermal stress, and a surfactant for preventing aggregation upon mechanical and freeze-thaw stresses.

The formulation is identical to that of Avastin and the biosimilar for oncology indications. The suitability of the formulation was justified by data derived from stability studies. Furthermore, formulation robustness was assessed under accelerated/stress/freeze-thaw conditions. The proposed formulation is considered suitable.

The finished product does not contain any overages. To ensure that each vial contains a volume sufficient for withdrawal, the applicant is proposing a target fill volume of 4.30 mL for the 100 mg/4 mL presentation. The proposed target fill volume appears sufficiently justified. As described in the SmPC, 0.05 mL of the finished product will be injected intravitreally and the remainder volume must be discarded. To prevent potential misuse and administration errors, a product format more relevant to the current posology applied should be developed. The applicant states that a new presentation will be developed.

Manufacturing process development

Manufacture of the finished product includes thawing and pooling of active substance, sterile filtration, aseptic filling into vials and packaging.

The process development activities addressed defining the quality target product profile (QTPP), identifying CQAs, risk assessment and identification of CPPs, and establishing a process control strategy to ensure that CQAs are met.

The process control strategy was based on the evaluation of CQAs and CPPs. The following control elements are included: control of excipients and raw materials, in-process testing, release testing, characterisation of impurities, stability monitoring, process performance qualification, and control of environmental factors and adventitious agents. A clear link of each control element to each CQA has been provided. Taken together, the control strategy appears adequate.

The applicant has outlined a summary of manufacturing process changes that occurred between early phase clinical development and late phase clinical development (for the biosimilar) and commercial production.

The potential impact of manufacturing process changes to the quality of the finished product has been evaluated in three comparability studies:

Comparability study 1 and 2 compared early phase clinical material to late phase/pivotal clinical development. Comparability study 1 includes extensive physicochemical and biological characterisation studies while Comparability study 2 includes forced/stressed degradation studies. These comparability studies have demonstrated that the early and late phase/pivotal clinical materials are comparable.

Comparability Study 3 compared the finished product manufactured at the proposed commercial manufacturing site using the filling Line 1 versus filling Line 2. Comparability was assessed by evaluating release data and extended characterisation studies. The provided data indicate comparability of material manufactured using filling Line 1 vs. filling Line 2.

Container closure system

The container closure system consists of 8 mL vials. These containers comprise a clear, sterilised Type I borosilicate glass vial, closed with Type I chlorobutyl rubber stopper and an aluminium seal fitted with a plastic flip-off cap. The vial, stopper and seal components are compliant with appropriate Ph. Eur. monographs for primary containers and closures.

The suitability of the container closure system used for storage, transportation and use of the finished product was demonstrated by the studies assessing the appropriateness of materials (compliance to standards and extractable assessment), compatibility of materials of construction with dosage form (leachable assessment), functional performance, and container closure integrity. The long-term compatibility of the finished product with the container closure system is demonstrated by stability data.

Preliminary data of the ongoing extractables and leachables study have been provided. The applicant committed to present the results of the ongoing leachables study when the study is finalised**.**

As regards elemental impurities, the applicant provided a risk assessment for elemental impurities in accordance with ICH Q3D. The risk assessment appears reasonable, and overall the risk arising from elemental impurities can be considered as negligible. Elemental impurities are further assessed as part of the ongoing leachables study, and the applicant committed to also present these data when the study is finalised**.**

For administration, the finished product is withdrawn from the vial into a 1 mL syringe using a 5 µm filter needle, and the filter needle is replaced by an injection needle. These medical devices are not co-packed but must be provided by the ophthalmologist. Compatibility of the active substance with various materials has been demonstrated. However, further compatibility data is expected. This issue remains to be resolved.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured, packaged, controlled and released in accordance with the current Good Manufacturing Practices (GMP). Certificates confirming GMP compliance have been provided or are available via EudraGMDP.

The finished product is manufactured according to a standard manufacturing process including active substance thawing and pooling (Step 1 and Step 2), bioburden reduction filtration (Step 3), sterilizing filtration/aseptic filling (Step 4), visual inspection (Step 5), and secondary packaging & storage (Step 6).

The control strategy has been established to ensure that CQAs consistently remain within acceptable limits. Critical in-process parameters are either controlled via in-process controls (IPCs) or in-process tests (IPTs). Critical process parameters are controlled or monitored with an acceptable range, which has been defined based on product development studies and existing product knowledge.

Process validation

The process validation studies were performed according to a classical approach.

Batches with minimum and maximum batch sizes were manufactured. Process parameters were set based on results obtained in manufacturing process development studies according to normal operating ranges.

The in-process test results met pre-defined acceptance criteria in most instances. Excursions have been adequately investigated and addressed.

Analytical release testing was performed in line with specifications proposed for release of commercial batches. The release test results were well within pre-defined specifications for all process validation batches.

Taken together, the process validation data overall indicate that the manufacturing process consistently yields finished product meeting its pre-determined quality attributes.

Furthermore, the applicant provided a risk assessment as regards potential leachables from the single-use equipment, and the associated risk can be considered as negligible.

Sterile filter validation was performed.

The applicant presented data on media fills, which gave satisfactory results. Based on the results obtained, the maximum aseptic process time, is considered sufficiently validated.

Transport of the finished product has been adequately validated, and a respective summary has been included in the dossier.

2.4.3.3. Product specification, analytical procedures, batch analysis

The specifications proposed for release and stability testing of the finished product comply with ICH Q6B, Ph. Eur. 2031, and EMA/CHMP/BWP/532517/2008 GL. The specifications include tests for appearance, general tests, identity, purity/product-related impurities, biological activity, quantity, contaminants, and container closure integrity. Two assays are included in the finished product specification to measure biological activity: competitive binding by ELISA and HUVEC bioassay of potency. The proposed acceptance criteria are considered acceptable.

The proposed acceptance criteria for the general tests, identity and general tests/contaminants are found acceptable. The proposed acceptance criteria for subvisible particles comply with Ph. Eur. 2.9.19. However, for a state-of-the–art product for intravitreal application more stringent limits for sub-visible particles should be considered. The available release and stability data for Ipique generally show subvisible particle levels well below the limits defined in Ph. Eur. 2.9.19 which may indirectly support the conclusion that Ipique does not pose an elevated risk (compared to off-label use of Avastin) regarding subvisible particles. In addition, Ipique will be transferred from the vial into the syringe used for administration using a 5 µm filter needle and hence, reduction of subvisible particle levels by the filter needle can be expected. Furthermore, only a small fraction of the filled product volume is eventually administered. Thus, under the provision that a reduction of subvisible particles by the filter needle to low levels is demonstrated by the applicant (see outstanding issue above), the proposed specification limit for subvisible particles for the current vial presentation is deemed acceptable. The justification for the acceptance criteria for endotoxin still needs revision. This issue remains to be resolved.

In line with the active substance, the applicant committed to re-evaluate several limits after at least 30 batches of commercial material have been manufactured.

A risk evaluation concerning the presence of nitrosamine impurities was missing in the initial application and this was raised as a major objection. The requested information was submitted and the respective risk is considered negligible. No additional controls are needed in this regard as part of the finished product specification.

Analytical procedures

With the exception of the finished product specific general tests all analytical methods are common for active substance and finished product. These common methods are described and discussed in the respective active substance section. The finished product specific general tests are performed according to Ph. Eur. and USP.

Batch analyses

Batch analyses data are presented for batches manufactured with the clinical and with the proposed commercial processes. The respective results comply with the specifications valid at time of release testing, and indicate a consistent manufacturing process.

Container closure system

The primary packaging material has been well described, including specifications, and schematic drawings and supplier certificates have been provided. The vials and rubber stoppers are in compliance with the Ph. Eur. Monographs for primary containers and closures.

2.4.3.4. Stability of the product

Based on the updated stability data, the applicant is proposing a shelf-life of 30 months when stored at the intended long-term condition (i.e. 2-8°C, protected from light).

The ongoing stability studies are performed in accordance with ICH Q5C. The container closure system used was the same as that intended for commercial batches. Data up to 30 months are available for primary and supportive batches of the finished product. Additional stability data are available for additional clinical batches which have also been used for clinical studies in the oncology indications and for the PPQ batches. Stability data at accelerated conditions (25ºC ± 2ºC/60% ± 5% RH) are available for most batches.

Degradation over time was observed for some quality attributes under long-term and accelerated conditions However, all batches remained within shelf-life specifications when stored at the long-term condition. Degradation pathways have been evaluated in forced degradation studies.

Photostability testing was conducted in line with ICH Q1B. Based on the study results, it can be concluded that the finished product should be stored protected from light.

Furthermore, stress stability of finished product was studied in the secondary packing to reflect real-life conditions. The provided data indicate that finished product is stable upon short term excursion at high temperature or low temperature (40ºC / 60% RH or -20ºC for 3 days), upon agitation (300 rpm), freeze and thaw and exposure to ambient and UV light while enclosed in the secondary package.

Taken together, the provided data indicate that the finished product is stable when stored for up to 30 months at the intended storage conditions (i.e. 2-8°C, protected from light).

2.4.3.5. Analytical comparability to Avastin

Based on the analytical comparability study against EU-Avastin that was performed for the biosimilar and published data on off-label treatment of AMD by intravitreal administration of Avastin, the applicant intends to demonstrate that Ipique can be safely and effectively used in the targeted indication. The clinical studies referred by the applicant have been conducted for the biosimilar in its oncology indications.

Analytical comparability was assessed in a comprehensive comparability exercise against EU-sourced Avastin. The approach and methodology of the analytical comparability assessment is sufficiently described and overall acceptable.

Several finished product lots were included in the analytical comparability exercise. The active substance batches were manufactured according to the intended commercial process at the intended commercial site, the corresponding finished product lots have been manufactured at the intended commercial site. The finished batches/lots have been used in the pivotal clinical studies conducted to support the licensure of the biosimilar in oncology indications and for active substance/finished product

process validation and stability studies The lot-to-lot variability is considered to be sufficiently reflected.

EU-Avastin batches for the comparability exercise were procured over an extended period. Several lots, including most of the lots used in the comparative clinical studies conducted for the oncology indications of the biosimilar, were analysed. The number of lots is expected to sufficiently reflect variability and appears adequate for evaluation of similarity. In addition to EU-sourced Avastin, US-sourced Avastin have been included. A broad range of lot ages is covered for the finished product and Avastin with sufficient overlap between both products.

The applicant followed a tiered approach to demonstrate analytical comparability. Based on their criticality, quality attributes/corresponding analytical methods were assigned to three tiers with assessment criteria of different stringency. Tier 1 included QAs with highest risk ranking directly related to the mechanism of action, quantitative attributes not directly related to the mechanism of action (MoA) were assigned to Tier 2, and Tier 3 comprised QAs with lowest risk ranking and QAs not amenable to quantitation. The comparability ranges were based on analytical characterisation of EU-Avastin and set to mean ± 2 SD (Tier 1) and mean ± 3 SD (Tier 2; for highly variable Tier 2 methods: mean ± 2 SD), respectively; for several Tier 2 parameters a pre-defined limit derived from method capability was used (e.g. mass spectrometry). For Tier 3 attributes, data were visually compared. In principle, the applicant's approach to set the comparability ranges based on ± x SD is acceptable if data are normally distributed and are not impacted by few extreme results. It is noted that justification for the statistical approach is limited. However, the applicant provided graphical and tabular presentations of individual analytical results as well as descriptive statistics, which enable also an assessment independent of the defined quality ranges.

The selected comprehensive set of orthogonal state-of-the–art analytical methods, which covers primary and higher order structure, post-translational modifications, size and charge variants, larger aggregates, general attributes, as well as Fab- or Fc-mediated biological functions, appears adequate to address the relevant quality attributes of bevacizumab. The Fab-mediated MoA was evaluated by a range of biological assays at different levels (binding to various VEGF isoforms, HUVEC anti-proliferation assay, VEGF blocker reporter gene assay, receptor dimerisation assay). Biological characteristics were further compared with regard to Fc receptor and mannose receptor binding, C1q binding, and CDC and ADCC activity. Adequate descriptions and qualification data have been provided for the analytical methods used for the analytical comparability exercise.

For many quality attributes, the finished product was demonstrated to be analytically highly comparable to EU-Avastin. The primary structure attributes molecular mass, amino acid sequence (low level metabolic amino acid substitutions were detected, see discussion below), post translational modifications (oxidation, isomerisation, deamidation, O-glycosylation), extinction coefficient, protein concentration as well as the higher order structure (disulphide structure, CD, Fluorescence, HDX, µDSC, DLS) were shown to be highly comparable. Concerning biological activity, comparability was demonstrated for the mechanism of action (VEGF binding including the relevant isoforms, VEGF neutralisation, anti-proliferation) as well as for binding to FcγRIIa, FcγRIIb, FcγRIIIa V/F (by SPR), FcRn, mannose receptors and C1q. Lack of CDC and ADCC activity was confirmed for both MB02 and Avastin.

Results from several analytical methods show differences between the finished product and EU-Avastin:

Compared to EU-Avastin slightly lower glycation levels were observed for the finished product. Biological activity is not impacted by the different glycation levels.

Minor differences are observed between the finished product and EU-Avastin regarding N- and C-terminal integrity. Effect on clinical performance is not likely.

A higher level of free thiols is present in the finished product compared to EU-Avastin which was initially explained by metabolic amino acid substitutions present in the finished product. However, further analysis revealed that the higher level of free thiols cannot only be attributed to the amino acid substitution. No impact on VEGF binding was observed for fractions enriched for HHL and biological activity of the finished product and EU-Avastin is similar. A potential effect on immunogenicity cannot be excluded, but the clinical data for the biosimilar do not indicate an issue with immunogenicity upon intravenous administration. Absolute quantitation of the amino acid substitution revealed a low substitution level. Overall, it is concluded that the substitution does not preclude comparability.

Minor differences in distribution of charge variants are evident between the finished product and EU-Avastin. Overall, the differences are small and characterisation of the individual peaks did not corroborate any significant differences between the finished product and EU-Avastin. While no relevant effect on clinical performance is expected when the products are administered systemically, relevant clinical consequences when used intravitreally can only be confirmed or ruled out by appropriate clinical studies.

The distribution of the glycoforms (HILIC-UHPLC-FLR analyses) differs between the finished product and EU-Avastin. It is unlikely that these differences have an impact on immunogenicity. Considering the MoA of bevacizumab and that the finished product and EU-Avastin show similar Fab- and Fc-related biological activities including mannose receptor binding, these differences are not expected to impact clinical performance. The clinical efficacy and safety data from the clinical NSCLC study support these conclusions. However, while no relevant effect on clinical performance is observed when the products are administered systemically, potential relevant clinical consequences when used intravitreally can only be confirmed or ruled out by appropriate clinical studies.

Compared to EU-Avastin no new size variants are observed for the finished product by the different techniques applied. SEC-HPLC shows a higher purity of finished product and a lower aggregate content compared to EU-Avastin. Reduced CE-SDS reveals a slightly higher content of HC+LC for the finished product associated with lower levels of NGHC. On the contrary, under non-reducing conditions CE-SDS for the finished product a lower IgG content and higher levels of a HHL fragment are detected. In addition, the content of LC and LMW variants is slightly increased for the finished product when analysed by non-reducing CE-SDS. Analytical ultracentrifugation also reveals a slightly higher monomer content for the finished product associated with lower levels of HMWS1 species. No obvious differences between the finished product and EU-Avastin were noted by SDS-PAGE (reduced, non-reduced) and DLS. A higher purity (lower level of aggregates, higher monomer/HC+LC content) is observed by SE-HPLC, CE-SDS reduced, and svAUC. As discussed above, the higher level of the HHL fragment is not expected to impact efficacy Nevertheless, while no relevant effect on clinical performance is observed when the products are administered systemically, potential relevant clinical consequences when used intravitreally can only be confirmed or ruled out by appropriate clinical studies.

A broader range of activity is observed for the finished product in the cell based reporter gene assay. However, it should be noted that the applicant identified one out-of-trend result for EU-Avastin that was excluded from the analysis. In addition, comparable activity of the finished product and EU-Avastin was demonstrated in the other VEGF binding and bioassays.

Compared to EU-Avastin, the finished product shows a slightly higher relative binding affinity to FcγRI. However, the difference is small and the KD is highly comparable for finished product and EU-Avastin.

When analysed by AlphaLISA, relative binding to both FcγRIII V and F variant differed between the finished product and EU-Avastin The difference in binding could be correlated to the different levels of G0 present in the finished product and EU-Avastin. A noticeable difference in binding or affinity between finished product and Avastin was not detected with an orthogonal method (i.e. SPR). Taking into account that ADCC is not a MoA for bevacizumab and absence of ADCC activity has been demonstrated for finished product and Avastin it is agreed that these differences are not clinically relevant.

Comparative forced degradation studies were conducted to further demonstrate comparability of finished product and EU-Avastin (one lot each of the finished product, EU-Avastin, and US-Avastin were included). Using a set of stability indicating analytical methods including additional characterisation methods, comparable degradation profiles and kinetics were observed for finished product and Avastin under thermal, mechanical, low/high pH, and light stress. Overall, the presented stress stability data support the conclusion of analytical comparability.

In summary, the presented data (Table 1) support analytical comparability between finished product and Avastin. The analytical differences have been assessed and justified by the applicant with regard to their potential impact on clinical performance of the product. Clinical data obtained in a comparative NSCLC study support this conclusion. However, given the intravitreal route of administration and the targeted indication for Ipique, some uncertainty remains that cannot be excluded based on analytical data alone (please refer to the discussion in the clinical section). This issue remains to be resolved.

Table 1: Summary of analytical comparability assessment between EU approved biosimilar and EU-Avastin

Molecular parameter	Attribute	Methods for control and characterisation	Key findings
General test	Extinction coefficient	Amino acid analysis	Similar extinction coefficients
	Protein content	UV	Similar protein concentration in finished product
Primary structure	Intact mass	RPLC-UV/MS	Comparable mass profile
	Reduced and de-N-glycosylated (LC and HC)	RPLC-UV/MS	Comparable mass profile
	Glycation (HC and LC)	RPLC-UV/MS	Slightly lower levels for the finished product; not clinically meaningful
	Primary structure confirmation by reduced peptide mapping with multiple enzymatic digestions	Reducing peptide mapping by RPLC-ESI-TOF MS/MS	100% sequence coverage, Identical
	Primary structure confirmation by reduced tryptic peptide mapping	Reducing peptide mapping by RPLC-UV-MS	100% sequence coverage, identical

Molecular parameter	Attribute	Methods for control and characterisation	Key findings
	N- and C-terminal integrity	Tryptic peptide mapping by RPLC-UV-MS	Marginal differences; not expected to be clinically meaningful
Higher order structure	Disulphide bridges	Non Reduced Peptide mapping	Comparable mapping profile
	Free Thiols	Ellmans test	Slightly higher levels; not expected to be clinically meaningful
	Secondary Structure	CD	Similar content in structural components and Similar CD spectra
	Tertiary Structure	Fluorescence	Similar fluorescence spectra
	Higher Order Structure	HDX-MS at peptide and intact level	Same higher order structure
	Epitope mapping	HDX-MS	Same amino acids compose the epitope binding site
	Colloidal stability	DLS	Similar colloidal stability
	Structural stability	µDSC	Similar thermal stability (Tm)
Post-translational modifications	Charge variants	CEX HPLC chromatogram profile and data	Slight difference in one finished product basic peak and minor difference in distribution of charge variants (age dependent); unlikely to be clinically meaningful
	Charge variants	cIEF electropherogram profile and data	Similar profile and similar isoelectric point
	Oxidation/Deamidation/Aspartate isomerisation	Peptide mapping (LC-ESI MS/MS)	Similar levels of deamidation, oxidation and aspartate isomerisation
	O-glycosylation	Peptide mapping	No O-glycosylation for either Avastin or the finished product
	Site of N-glycosylation	Peptide mapping	Identical site of N-glycosylation on N303
	Monosaccharides content	GC-MS	Level of galactose is higher
	Sialic Acids content	UHPLC-FLR	Slightly higher sialic acids content for the finished product; levels are very low;

Molecular parameter	Attribute	Methods for control and characterisation	Key findings
			difference is not significant from clinical perspective
	Glycosylation assessment	HILIC-UHPLC-FLR Overall N-glycosylation HILIC profile	Similar N-glycans identity and distribution; comparable biological activity demonstrated impact on clinical efficacy rather unlikely
	Glycosylation assessment	LC-MS	Comparable masses of G0F and G1F
Purity	Size heterogeneity	SE HPLC chromatogram profile and data	Similar profile, slightly lower HMW species (higher purity); minor differences not clinically meaningful
	Size heterogeneity	CE SDS R and NR electropherogram profile and data	Similar profiles, slightly higher levels of HC+LC and lower levels of NGHC (R), slightly lower levels of IgG and higher levels of HHL peak (forms under denaturing conditions) (NR); clinical impact unlikely
	Size heterogeneity	SDS-PAGE R and NR	Similar band profiles
	Aggregate assessment	sv-AUC	Similar monomer content (slightly higher for the finished product)
	Aggregate assessment	Isothermal DLS	Similar hydrodynamic size of predominant peak
Biological activity (Fab region)	Binding to VEGF-A_{165}	Competitive binding ELISA	Highly similar relative binding
	Binding to VEGF-A_{165}	SPR	Highly similar relative affinity and KD
	Binding to VEGF-A_{121}, -A_{189}, and -A_{206}	ELISA	Highly similar relative binding
	VEGF B, C and D variants and PlGF	BLI	Absence of binding for both the finished product and Avastin
	Antiproliferation bioassay	HUVEC assay	Similar relative potency
	VEGF neutralisation	VEGF blocker reporter assay	Similar relative potency

Molecular parameter	Attribute	Methods for control and characterisation	Key findings
	Blockade of KDR signalisation pathway	KDR/KDR dimerisation bioassay	Similar relative potency
Biological activity (Fc region)	ADCC and CDC activity	ADCC and CDC bioassays	No ADCC and CDC activity
	Binding to C1q	ELISA	Highly similar relative binding
	Binding to FcγRI	SPR	Slightly higher relative affinity, similar KD; minor difference not clinically meaningful
	Binding to FcγRIIa	SPR	Highly similar relative affinity and KD
	Binding to FcγRIIb	SPR	Highly similar relative affinity and KD
	Binding to FcγRIIIa V variant	SPR	Highly similar relative affinity and KD
	Binding to FcγRIIIa V variant	AlphaLISA	Differences in relative binding; minor differences unlikely to be clinically meaningful
	Binding to FcγRIIIa F variant	SPR	Highly similar relative affinity and KD
	Binding to FcγRIIIa F variant	AlphaLISA	Differences in relative binding; minor differences unlikely to be clinically meaningful
	Binding to macrophage mannose receptor	BLI	Similar KD in the 10^{-8} M range
	Binding to FcRn	SPR	Highly similar relative affinity and KD
	Binding to FcRn	ELISA	Similar relative binding

Note: While no relevant effect on clinical performance is expected when the products are administered systemically, potential relevant clinical consequences when used intravitreally can only be confirmed or ruled out by appropriate clinical studies.

2.4.3.6. Adventitious agents

Overall, the risk of contamination of Ipique with adventitious agents is considered low. The applicant implemented multiple complementary measures to ensure product safety with regard to non-viral and viral adventitious agents. The measures include selection of materials, testing of cell banks and

process intermediates, testing of microbial attributes at release, and implementation and validation of dedicated virus clearance steps and steps contributing to virus reduction:

- Ipique is manufactured from a CHO cell line without materials of direct animal or human origin. Based on the information provided the risk with regard to TSE or viral contamination is low.
- The production cell line, the MCB, as well as the WCB have been manufactured without using materials of direct animal or human origin. The cell banks have been tested for the absence of adventitious viruses and microbial contamination.
- Each unprocessed harvest is routinely tested for the absence of adventitious viruses and mycoplasma.
- Endotoxin levels and bioburden/sterility are controlled throughout the manufacturing process and at active substance and finished product release.

Robust and effective overall virus clearance by five orthogonal manufacturing process steps has been demonstrated using validated down-scaled models. The manufacturing process includes two dedicated virus clearance steps that are effective against enveloped and non-enveloped viruses. The viral clearance capacity of the purification process was validated in accordance with ICH Q5A(R1). Overall, a satisfactory viral clearance capability of the manufacturing process was demonstrated.

2.4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Module 3 of the Ipique application is largely based on Module 3 of the EU authorised bevacizumab biosimilar. A major objection was raised during the procedure in relation to the need to adequately reflect the targeted indications using the intravitreal route of administration, the presentation intended to be marketed, and the legal basis (Well Established Use). In response, multiple sections of Module 3 have been revised to tailor the dossier specifically to Ipique. The major objection was thereby considered resolved. The applicant intends to demonstrate that Ipique can be safely and effectively used in the targeted indication based on an analytical comparability study against EU-Avastin, results from a comparative Efficacy/Safety NSCLC study conducted for the EU authorised bevacizumab biosimilar, and published data on use of bevacizumab in AMD by intravitreal administration.

Active substance

The active substance is manufactured using a typical manufacturing process for monoclonal antibodies. The manufacturing process has been described in sufficient detail. Raw materials and starting materials used in the manufacture of active substance are listed identifying where each material is used in the process. Sufficient information on the quality and control of these materials has been provided. The cell banks are adequately described and characterised. Overall, the control strategy seems to be adequate and ensures a consistent routine manufacture of active substance with adequate quality.

The process validation in combination with manufacture of three verification batches support the conclusion that the manufacturing process for active substance reliably generates active substance (and finished product) meeting its predetermined specifications and quality attributes.

The provided batch analyses data shows consistency of active substance batches.

Development of the active substance manufacturing process is adequately described.

Structural and functional characteristics of the active substance have been investigated using orthogonal state-of-the-art analytical methods. A specific HHL fragment was detected that originates

from metabolic partial amino acid substitutions. A PACMP for an intended change of the active substance manufacturing has been submitted during the procedure. The intended change is expected to reduce the level of amino acid substitution and is as such endorsed.

The proposed active substance specifications are generally acceptable. However, the justification of the endotoxin limit is not accurate and should be revised accordingly (outstanding issue). The applicant also committed to re-evaluate several limits based on at least 30 commercial batches. Overall, the analytical methods are suitable and adequately validated. The applicant committed to implement a process specific HCP method.

The available stability data support the claimed shelf life of the active substance.

Finished product

The finished product is a sterile, preservative-free solution for injection containing 25 mg/mL of bevacizumab as active substance and is supplied in single-use vials with 100 mg/4 mL. The primary packaging components (i.e. type I glass vial and chlorobutyl rubber stopper) comply with Ph. Eur. The applicant committed to develop a new product presentation that is more relevant to the posology applied.

MB02 is formulated with α,α-trehalose dihydrate, sodium phosphate (as monobasic sodium phosphate monohydrate and as disodium phosphate), polysorbate 20 and water for injections. The formulation is identical to that of Avastin. The excipients used are of compendial quality and are known from other EU-authorised medicinal products intended for intravitreal administration.

The finished product manufacturing process includes thawing of the active substance, pooling and mixing, bioburden reduction filtration, sterilising filtration/filling/stoppering, visual inspection and storage/secondary packaging, and is adequately described. CQAs have been defined under consideration of the proposed route of administration, and the respective control strategy is considered appropriate. Process characterisation, process validation, and batch data indicate that the manufacturing process reliably generates finished product meeting its predetermined specifications and quality attributes. Leachables, extractables and elemental impurities are addressed in the dossier, and adequate risk assessments have been provided. For leachables/elemental impurities testing, the applicant committed to present the final study report when the respective study is finalised.

A risk evaluation concerning the presence of nitrosamine impurities was missing in the initial application and this was raised as a major objection. The requested information was submitted and the respective risk is considered negligible. No additional controls are needed in this regard as part of the finished product specification.

The finished product specifications are deemed sufficiently justified. However, the justification of the endotoxin limit is not accurate and should be revised accordingly (outstanding issue). The acceptance criterion for subvisible particles is based on the Ph. Eur. requirements for parenteral drugs. Generally, a tighter control of subvisible particles is expected for intravitreal products. However, considering that a filter needle is used during preparation for administration of Ipique and that only a small fraction of the product volume is administered, the proposed specification limit would be acceptable provided that the filter needle is capable to reduce subvisible particles to low levels (outstanding issue). Further compatibility data is expected (outstanding issue). Furthermore, the applicant committed to re-evaluate several limits after at least 30 batches of commercial material have been manufactured.

The applicant has outlined a summary of manufacturing process changes that occurred between early phase clinical development and late phase clinical development and commercial production.

The proposed shelf life of 30 months when stored at the intended long-term condition (i.e. 2 – 8 °C, protected from light) is considered sufficiently justified based on stability data provided.

Comparability to Avastin

The applicant used analytical comparability between Ipique and Avastin to support bridging to the literature data on use of bevacizumab in retinal neovascularisation.

Concerning the demonstration of analytical comparability, the applicant performed a sound and comprehensive analytical comparability exercise. A sufficient number of lots that can be expected to sufficiently reflect product variability of both Ipique and Avastin was included in the analytical comparability exercise. The chosen tiered approach with assessment criteria of different stringency is acceptable. Analytical results for the individual batches have been provided.

The relevant quality attributes of the bevacizumab molecule were assessed using a broad panel of orthogonal standard and state-of-the art techniques. Analysis covered the primary sequence and higher order structure, post-translational modifications and other modifications, as well as charge- and size heterogeneity. Functional activity was compared by a large panel of cell-based biological assays and binding assays covering the mode of action for the targeted indication as well as other biological activities. The comparability assessment is complemented by side-by-side analysis, forced degradation studies and detailed characterisation of molecule variants. These complementary studies are adequately designed to support the conclusion drawn.

For many quality attributes including those related to the mechanism of action, the applicant demonstrated that Ipique and Avastin are highly comparable. Several minor analytical differences have been observed. While no relevant effect on clinical performance is expected when the products are administered systemically, potential relevant clinical consequences when used intravitreally can only be confirmed or ruled out by appropriate clinical studies.

Conclusion

The quality assessment identifies differences between the bevacizumab used to generate the data present in the literature and Ipique whose significance in the claimed indication could have only been characterised by appropriate clinical comparison.

2.5. Non-clinical aspects

2.5.1. Pharmacology

The present submission of MAA for Ipique is based on a well-established use application in accordance with Article 10a of Directive 2001/83. The regulation in this case specifies that certain test and trial results may be replaced by appropriate scientific literature. Hence, relevant non-clinical literature is provided in Module 4 to substantiate the non-clinical aspects of the risk-benefit profile of intravitreal bevacizumab in conditions of retinal neovascularisation.

In order to allow the bridging of the literature data collected on intravitreal administration of the monoclonal antibody Avastin to Ipique it is necessary to establish stringent and comprehensive comparability on all relevant levels of the biological products.

Ipique was developed as a medicinal product with a degree of similarity to Avastin, as evidenced by biophysical, biochemical and functional comparability data presented in Module 3 of this MAA. Non-clinical aspects of the comparative in vitro results are briefly discussed and information from the literature on the non-clinical pharmacology of intravitreal bevacizumab is summarised.

The efficacy of Ipique is based on the binding of all major VEGF-A isoforms with resulting neutralisation of activity by prevention of their binding to the VEGF-receptors on endothelial cells. During

development the binding of the active substance bevacizumab (Ipique) was shown to be highly comparable to Avastin in ELISA and SPR assays. Furthermore, Ipique and Avastin were demonstrated to have similar relative potency and elicit similar responses in a variety of bioassays (antiproliferation bioassay using HUVECs, VEGF blocker reporter bioassay and PathHunter KDR/KDR dimerisation bioassay).

Altogether, it can be considered that Ipique and Avastin products have the same mechanisms of action involving Fab-related functions as well as Fc-related binding resulting in similar in vitro biological potencies.

Evidence for the in vivo activity of bevacizumab as provided by the applicant is limited to two non-clinical studies, which demonstrated that intravitreal injection into both normal and vitrectomised eyes of cynomolgus monkeys resulted in a transient but practically complete suppression of VEGF levels in the aqueous humour. No further literature studies on the *in vivo* pharmacology of bevacizumab or Avastin have been submitted. In a rapid search in PubMed some additional publications of non-clinical *in vivo* pharmacology studies of intravitreal or topical bevacizumab in choroid neovascularisation models in the mouse (Bock et al, 2007), rat (Lu et al, 2009, Sahan et al, 2020), or monkey (Lichtlen et al, 2010; Olvera-Montaño et al, 2019) could be identified, some comparing the activity of bevacizumab with other anti-VEGF drugs. There is, however, some evidence that rodent and rabbit CNV (choroid neovascularisation) models are not appropriate for intravitreal bevacizumab activity assessment (Lu et al, 2009; Yu et al, 2008) probably due to differences in retinal anatomy and the narrow species specificity of anti-VEGF antibodies. Hence, the *in vivo* pharmacologic effects of bevacizumab can only be studied in primate models.

In a study in cynomolgus monkeys by Lichtlen and colleagues (Lichtlen et al, 2010), animals (3/sex/group) were administered 50 µL of Avastin (20 mg/mL, 1 mg total dose per injection), control (PBS) or other antibodies by bilateral intravitreal injection on Days 1 (8 days pre-CNV), 15 and 29 of the study. Experimental CNV in both eyes of each animal was induced by laser on Day 8 of the study. Intravitreal bevacizumab completely blocked the formation of grade 4 lesions at all times and was most effective in CNV pathology prevention, resulting primarily in grade 1 lesions, a median lesion grade of 1, and a range of lesions from grade 1 to grade 3. However, although additional information regarding the *in vivo* pharmacology of bevacizumab can be found in the literature, considering the extensive clinical experience with Avastin in macular degeneration, no further discussion is deemed necessary.

Secondary pharmacology, safety pharmacology and pharmacodynamic drug interaction studies are not considered necessary due to the nature of the product, its high specificity for VEGF, the expected low systemic exposure as well as the presence of abundant clinical experience that displaces the need for retrospective non-clinical investigation. Therefore, the restriction or lack of submission of these non-clinical data is not seen critical for determination of the benefit-risk profile of Ipique.

2.5.2. Pharmacokinetics

In accordance with an application under Article 10a of Directive 2001/83/EC for well-established use, non-clinical studies specifically investigating the pharmacokinetics of Ipique were not submitted by the applicant and this is considered acceptable.

In the initial submission, the applicant has provided a short table, based on some references from published literature on the pharmacokinetics of Avastin after intravitreal administration. This information was considered too limited, insufficient and not fully accurate. After another review of the literature the applicant has identified 2 additional publications and all selected publications concerning original research in animals about the PK/PD and biodistribution of intravitreal bevacizumab have now been provided. The table summarizing the main aspects of several of the pharmacokinetic studies has

been up-dated and expanded by addition of the analytical methods of detection, the source of bevacizumab and parameters of vitreal kinetics together with the serum kinetics, as available. In general, much more information could have been included upon revision of these publications, in view of the type of application and the mandatory requirements regarding the dossier, but the data presented, although scarce, are overall acceptable. Still, an amendment in the table was agreed by the applicant regarding the reference Christoforidis et al 2017, where only 4 animals per group were employed and therefore only 4 owl monkeys (not 40) received Avastin. No comparison among data produced and reported in the same species has been performed, yet considering the limited relevance of this information for the clinical use in patients this issue was not considered central.

The methods of analysis used in the pharmacokinetic studies mentioned in the literature references comprise immunoassay, ELISA and PET/CT autoradiography. In all studies that were included by the applicant in the table summarising the pharmacokinetics of bevacizumab, Cmax detected in the vitreous was well above the limit of quantification of the analytical methods, confirming the informative value of these measurements.

Limitations in the published literature can be identified as regards the unknown source of bevacizumab and its comparability to Avastin, including the potential influence on PK values of different excipients. It is also important to mention the generally low number of animals investigated, as those studies were largely conducted in the context of research and not for regulatory purposes. These aspects limit the validity of the published literature to support the current MAA.

The applicant has identified publications in which Avastin, bevacizumab of unknown origin and animal homologues, such as anti-murine VEGF monoclonal antibodies, were employed. The main argument provided by the applicant for using the references in support of Ipique relies on the fact that the majority of the articles used Avastin, for which similarity with Ipique is claimed. The further reasoning of the applicant that in some instances use of Avastin can be assumed because the studies were performed when biosimilars were not yet available, can be followed. Although a comprehensive and critical discussion on the validity of the published literature has not been performed, the issue will not be further pursued and the submitted non-clinical evidence on the pharmacokinetics of bevacizumab when administered by intravitreal injection is accepted as sufficient information for this bibliographic application.

In agreement with current regulatory guidelines (ICH S6 (R1)) and attending to the nature of the product (an antibody which is expected to be degraded to small peptides and amino acids), no metabolism studies are required. Due to the nature of the product, no dedicated studies or bibliographical references are deemed necessary to assess the excretion of the product.

As systemic bevacizumab levels in patients treated with intravitreal injections are expected to be low, no interactions with other drugs are expected and no non-clinical studies are deemed necessary.

2.5.3. Toxicology

In line with the type of application, no dedicated studies with Ipique were submitted. In this context, bibliographical data on the toxicology of bevacizumab is deemed essential. The applicant has conducted a review of animal studies of intravitreal bevacizumab and identified 23 safety studies in adult mice, rats, rabbits, pigs and monkeys. Similarly to the bibliographic literature on pharmacokinetics discussed above, these studies were very briefly summarised in a table and the publications have been provided.

Although presenting a number of limitations, like the often small number of animals, the sometimes unclear source of bevacizumab with potentially different formulation compared to Avastin and non-GLP

compliant studies with experimental approaches that do not meet stringent regulatory requirements, the available published literature enables to build up a dossier where the safety of bevacizumab upon intravitreal administration can be examined. As indicated, the source of bevacizumab in many cases is the oncological pharmaceutical form of Avastin, while in some other instances, like already argued in the pharmacokinetic section above, the use of Avastin is assumed due to the lack of biosimilars at the time of conduct of these studies. In a limited number of cases animal homologues of bevacizumab were used such as anti-murine VEGF monoclonal antibodies and all products had the same formulation as Avastin.

The applicant emphasises the systemic and local safety of intravitreally injected bevacizumab revealed by the consistent lack of adverse effects. In fact, the claimed consistency in the various investigations is not obvious. There are conflicting results in terms of observed effects in the eye, although many studies report no changes detected after macroscopic or light microscopy evaluations. There are, however, alterations reported in electron microscopy investigations, as well as changes in biochemical and electrophysiological parameters. Notably, many of the studies only investigated a single intravitreal application of bevacizumab and found no adverse events observed with this single dosing scheme. In contrast, two studies with repeat administration of bevacizumab for e.g. three times on monthly or weekly intervals (Avci et al, 2009; Romano et al, 2012) led to detection of apoptosis and neuronal cell loss in rabbit or rat eyes, respectively. On the other hand, one study of repeat injections in rabbit eyes did not result in histopathological or functional compromise of retinal structures (Zayitt-Soudry et al, 2010). Taking into account the repeat administration scheme of long-term bevacizumab treatment foreseen in patients, the non-clinical studies investigating several doses of intravitreal bevacizumab appear most relevant in order to determine the safety profile of bevacizumab from the non-clinical perspective. Based on satisfactory comparability between Ipique and Avastin and considering the claimed well-established use in the intended medical conditions, non-clinical published studies assessing the toxicology of bevacizumab upon intravitreal administration can suffice to evaluate the safety profile of the product. In line with the results reported therein, a thorough discussion and appropriate wording to reflect the potential toxic effects in section 5.3 of the SmPC after (repeated) intravitreal injection of bevacizumab was provided by the applicant.

Some information regarding doses and their safety margins with the planned human dose and frequency of administration or posology can be found in the publications provided by the applicant. The human equivalent dose (HED) based on vitreal volume of the non-clinical studies with intravitreal bevacizumab discussed in the literature review is >1 in all cases, and up to 20 times the HED in mice (Heiduschka et al, 2008), 12 in rabbits (Feiner et al, 2006), 3 in pigs (Olsen et al, 2011) and 3 in monkeys (Peters et al, 2007). As already referred to, repeated intravitreal bevacizumab administration to rats (Romano et al, 2012) and rabbits (Avci et al, 2009) was associated with apoptosis and neuronal loss but at doses higher than the doses intended for human treatment. These findings are reflected in the section 5.3 of the SmPC.

The absence of genotoxicity studies is considered acceptable due to the nature of the product (an antibody composed of naturally occurring amino acids with no additional modifications). No interaction with cellular DNA is expected and no studies are required in accordance with regulatory guidelines (ICH S6 (R1). Likewise, the absence of carcinogenicity studies is acceptable according to the ICH S6 (R1) regulatory guideline, as carcinogenicity studies are not appropriate for biotechnology products when there is no cause of concern.

More discussion is needed on the aspects of reproductive and developmental toxicity, especially in view of the fact that upon intravitreal injection systemic levels of bevacizumab have been detected and quantified in several of the cited bibliographical references. The applicant refers to Avastin SmPC, with the product tested upon intravenous injections, and has proposed a similar wording for section 4.6 of the SmPC of Ipique. This can be seen as generally acceptable, taking into account the fact that after

intravitreal bevacizumab application suppression of VEGF not only locally, but also in the systemic circulation was measured (Dinc et al, 2013; Dinc et al, 2015).

Considering the similarity between Ipique and Avastin, a comparison between the doses described in the Avastin EPAR, associated to reproductive and developmental toxicity, and the bevacizumab systemic levels described in the published literature, achieved after intravitreal injection, would appear important to justify proper safety margins for Ipique's expected exposure.

No proper discussion on the safety margins for reproductive and developmental toxicity has been provided by the applicant. According to the Avastin EPAR, DART studies concluded on a maternal NOAEL of 10mg/kg and a fetal NOAEL of <10 mg/kg. All the studies were conducted following intravenous administration and led to a HED of 3.22 mg/kg . The intended dose for Ipique is 1.25 mg bevacizumab in 0.05 mL, the same dose that is used in nearly all clinical trials in the literature with Avastin 20 mg/mL and in clinical practice for intravitreal injection. Assuming a single injection in one eye, a total dose of 1.25 mg will be administered for a person of 60 kg, leading to a dose of 0.020 mg/kg. This is 161 times lower than the HED calculated from the DART studies. As only a fraction of the intravitreal dose of 1.25 mg is expected to reach the systemic circulation, the safety margin is increased even more.

Adverse events that may impair fertility (inhibition of the maturation of ovarian follicles, decreases in corpora lutea, in ovarian and uterus weight as well as in the number of menstrual cycles) and serious embryotoxic and teratogenic effects have been described in cynomolgus monkeys and rabbits for the approval of Avastin in oncology. As mentioned in the Avastin SmPC, "Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits". Similarly, "IgGs are known to cross the placenta, and Avastin is anticipated to inhibit angiogenesis in the foetus, and thus is suspected to cause serious birth defects when administered during pregnancy".

The only teratogenicity study presented in the responses of the applicant (Bamdad et al, 2017) evaluated intravitreal treatment of pregnant rats with 14.3 the HED of Avastin in 3 groups at different time-points (on days 2, 10 and 18 after insemination in groups 1, 2 and 3, respectively), representing the 3 trimesters of pregnancy. In group 1, fetal and placental weights were reduced and two cases of gastroschisis were observed; group 2 showed decreased fetal weight, shorter crown-rump length and one case of a cleft in the skull. Only group 3 remained free of morphological anomalies, confirming fetal toxicity during the periods corresponding to the first and second trimester of pregnancy. These results are reflected in the SmPC in sections 4.6 *Fertility, pregnancy and lactation* and 5.3 *Preclinical safety data*, respectively.

There is clinical experience with bevacizumab in children (Warminski and He, 2012). In this context the applicant's literature review of the non-clinical studies of intravitreal bevacizumab yielded four studies of safety in newborn animals. According to the submitted references, which investigated the safety of bevacizumab in newborn or very young mice and rabbits (Jo et al, 2016; Cam et al, 2017; Zayit-Soudry et al, 2011 and Axer-Siegel et al, 2009), the highest evaluated human equivalent dose (HED) in these studies corresponds to 3.2 fold, which is considered a rather small safety margin. While results did not reveal overt signs of local and systemic adverse events or histological changes in structural and functional integrity of various ocular compartments including the retina, there is evidence of retinal toxicity in terms of increased apoptosis, as shown by positive TUNEL staining in all retinal layers, as well as compromised retinal vasculogenesis in newborn rabbits. Temporary whitening of brown fat with reduced vascular density, lower levels of VEGF and decreased expression of various genes in brown fat was detected in neonatal mice in response to treatment with a murine analogue of bevacizumab. The findings of peripheral reduction of VEGF levels, together with the fact that these changes occurred even after single intravitreal injection raise further concerns on potential toxic effects of bevacizumab after repeated administration, as foreseen for the clinical treatment situation. Local tolerance is of

utmost importance for a product to be injected into the vitreous cavity. As indicated above, the literature review conducted by the applicant resulted in 23 studies in 5 different species regarding the safety aspects of local treatment with intravitreal bevacizumab.

The applicant's statement that none of the studies revealed any specific local adverse events is challenged, and so is the notion that signs of inflammation could be considered associated per se with the trauma caused by the intravitreal injection. While indeed several studies did not report specific adverse events after macroscopic or histological assessment of morphology and function (e.g. Dinc et al, 2015; Cardiakidis-Myers et al, 2012; Johnson-Soriano et al, 2011; Bakri et al, 2006; Thaler et al, 2010; Arraes et al, 2009; Zayitt-Soudry et al, 2010, Schlichtenbrede et al, 2009; Avci et al, 2009; Heiduschka et al, 2008; Iriyama et al, 2007; Inan et al, 2007; Feiner et al, 2006; Kim et al, 2008; Shahar et al, 2006), it has to be recognised that practically all of these studies investigated only a single intravitreal application of bevacizumab, which is in fact not fully representative of the repeat injections necessary for treatment of the clinical conditions. On the other hand, studies which also evaluated single administrations, have indicated pathological responses with induction of retinal vein thrombosis, local formation of immune complexes and clumps of thrombocytes in cynomolgus monkeys (Schraermeyer et al, 2013; similarly in Peters et al, 2007). Vitreous inflammation was also observed in one eye in the high dose bevacizumab group (5 mg) of a rabbit study (Manzano et al, 2006), one rabbit in another study developed uveitis (Inan et al, 2007) and vitreitis and vasculitis, possibly due to an altered immune response was detected in a number of pig eyes (Olsen et al, 2011). Alterations at the functional level, as investigated by electroretinography in rabbits (Cardiakidis-Myers et al, 2012) and rats (Sancho-Tello et al, 2008), damage of mitochondria in photoreceptors revealed by electron microscopy (Inan et al, 2007) and signs of increased apoptosis in rabbits (Inan et al, 2007; Avci et al, 2009) were seen after single intravitreal injections of bevacizumab.

Few studies also employed repeat-dosing schemes; importantly in two of these studies apoptosis in the retina of rabbits (Avci et al, 2009) and rats (Romano et al, 2012) was even more pronounced than after single administration. In contrast, one other study with repeat injections in rabbit eyes did not result in histopathological or functional compromise of retinal structures (Zayitt-Soudry et al, 2010).

Taken together, a number of adverse findings observed in several of the non-clinical studies provided by the applicant indicate the potential for local, systemic as well as reproductive and developmental harm due to (long-term) intravitreal treatment with bevacizumab. This was summarised and discussed by the applicant and it was reflected in section 5.3 of the proposed SmPC.

Given the nature of the product, the development of ADAs is expected. However, no discussion of relevant available animal studies could be found in the responses provided by the applicant (one publication, which does not add non-clinical information relevant for the assessment of the product, was erroneously included in the references tabled in Table 6 *Other animal studies* and therefore agreed to be deleted by the applicant). Immunogenicity of bevacizumab in non-clinical models is not fully predictive for the human scenario and therefore it would have needed to be assessed from a clinical perspective. Although no information was provided by the applicant on the presence of ADAs in animals and how it could affect the exposure and the calculated human safety margin, this issue is not further pursued in view of the clinical experience with bevacizumab.

Considering the biotechnology-derived nature of the product and the claimed well-established use, the absence of dedicated studies addressing immunotoxicity, dependence, metabolites, impurities and other toxicity studies is deemed acceptable.

2.5.4. Ecotoxicity/environmental risk assessment

The active substance bevacizumab in Ipique belongs to the components for which according to the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2[1]*) the ERA can be replaced by justification for not submitting ERA studies, as they are unlikely by nature to result in a significant risk to the environment.

2.5.5. Discussion on non-clinical aspects

In accordance with an application under Article 10a of Directive 2001/83/EC for well-established use, non-clinical studies specifically investigating the pharmacokinetics and pharmacodynamics of Ipique were not submitted by the applicant and this is considered acceptable.

Evidence for the pharmacodynamic effects of bevacizumab and hence also of Ipique comes from the comparative in vitro studies conducted to demonstrate the similarity of Avastin and Ipique at the physicochemical and functional level. In addition, a number of publications investigating in vivo animal models of uveitis or choroidal neovascularisation have been included to illustrate the efficacy of bevacizumab in the eyes of several different species. The relevance of these studies for the clinical effects in various diseases involving vascular leakage and neovascularisation may however be viewed as limited.

The applicant has conducted a literature search as required in order to provide the non-clinical in vivo evidence on the PK/biodistribution and safety after intravitreal application of bevacizumab to juvenile and adult animals, yet it remains somewhat unclear how the selection criteria for this search were chosen. Especially the condition to ask for full papers being available in the repositories of the Dutch universities, cannot be followed. Various services that provide requested literature in response to specific orders are commonly available and could have been used by the applicant. Also, the relevance for the efficacy and safety of bevacizumab for the treatment of neovascularisation associated with AMD, DME and RVO is not directly understood as being essential for identification of non-clinical scientific publications related to various aspects of bevacizumab applied intravitreally. Therefore, the comprehensiveness of the conducted literature search cannot be judged, however, the 42 papers finally selected may in principle be seen as sufficiently representative of non-clinical data on intravitreal bevacizumab available in the public domain.

Overall it can be agreed with the applicant that the great majority of studies were performed with the originator product Avastin, to which the formulation in Ipique is claimed to be similar.

The table summarising the main factors of several of the pharmacokinetic studies has been up-dated and expanded by addition of the analytical methods of detection, the source of bevacizumab and parameters of vitreal kinetics together with the serum kinetics, as available. In general, much more information could have been included upon revision of these publications, in view of the type of application and the mandatory requirements regarding the dossier, but the data presented, although scarce, are overall acceptable.

While it is agreed that some aspects of the non-clinical toxicology programme can be abbreviated or exempted in view of an application for a biological protein product, several toxicological characteristics deserve a thorough discussion. In this regard the applicant has conducted a review of animal studies of single and repeat dose intravitreal bevacizumab and identified 23 safety studies in adult mice, rats, rabbits, pigs and monkeys. Similarly to the bibliographic literature on pharmacokinetics discussed above, these studies were very briefly summarised in a table and the publications have been provided.

The applicant emphasises the lack of systemic and local safety concerns of intravitreally injected bevacizumab in line with the outcome that many studies did not report toxicological signs at the

macroscopic or light microscopy level. However, electron microscopy investigations as well as biochemical assays and electrophysiological measurements reported changes in a variety of parameters, including amongst others mitochondrial damage of photoreceptors, markers of apoptosis and neuronal cell damage and formation of thrombotic vessel occlusions. Notably, many of the studies only investigated a single intravitreal application of bevacizumab and found no adverse events observed with this single dosing scheme, whereas two studies with repeat administration of bevacizumab indicated apoptotic cell loss in rabbit or rat eyes. Taking into account the repeat administration scheme of long-term bevacizumab treatment foreseen in patients, the non-clinical studies investigating several doses of intravitreal bevacizumab appear most relevant in order to determine the safety profile of bevacizumab from the non-clinical perspective.

It is agreed that the local intravitreal use of bevacizumab/Ipique in much lower doses than those used for the systemic treatment in cancer indications bears a lower risk for systemic adverse events. Nevertheless, serum levels of bevacizumab after intravitreal injection of 1.25 mg may still amount to concentrations at or higher than those leading to blockade of known physiological effects of VEGF. A teratogenicity study in pregnant rats conducted with intravitreal Avastin on different days during pregnancy at doses with a HED of 14.3, revealed fetal morphological changes, reduced fetal and placental weight and smaller crown-rump length, confirming the embryo-fetotoxic potential of bevacizumab when applied intravitreally.

Another highly relevant aspect is the local tolerance of the proposed treatment and like already pointed out above, a more extensive search of the literature database yielded additional information. It is acknowledged that local tolerance in general was described as unremarkable in a number of publications. However, in other studies local inflammatory, thrombotic and apoptotic reactions were observed.

Taken together, a number of adverse findings observed in several of the non-clinical studies provided by the applicant indicate the potential for local, systemic as well as reproductive and developmental harm due to (long-term) intravitreal treatment with bevacizumab.

The potential development of ADAs in non-clinical models is not fully predictive for the human situation and therefore is superseded by assessment from the clinical perspective.

2.5.6. Conclusion on the non-clinical aspects

The non-clinical data submitted for the current application for intravitreal treatment of macular neovascularisation with Ipique is satisfactory, except for the concerns identified above on sections 5.3 and 4.6 of the SmPC.

2.6. Clinical aspects

2.6.1. Clinical pharmacology

2.6.1.1. Pharmacokinetics

Bevacizumab is a full-length recombinant humanised monoclonal antibody (149 kDa) which binds to all human vascular endothelial growth factor A (VEGF-A) isoforms.

Ipique containing bevacizumab as active substance is intended for ophthalmic use and administered by intravitreal injection. The product for registration is provided in solution 25 mg/mL (in vials of 4 ml

containing 100 mg). The recommended dose is 1.25 mg (0.05 mL) every 4 weeks for the first three (or more) doses, then administered according disease activity.

No pharmacokinetic studies were performed with Ipique. The pharmacokinetic data presented were collected from the literature (Table 2). These data are relatively limited because pharmacokinetic studies after intravitreal injection are restricted by the number of sampling possible. Therefore, the pharmacokinetic studies with intravitreal bevacizumab in humans were performed in patients who underwent surgical procedures for treatment of various eye conditions.

Table 2: Overview of the clinical studies providing PK data of bevacizumab

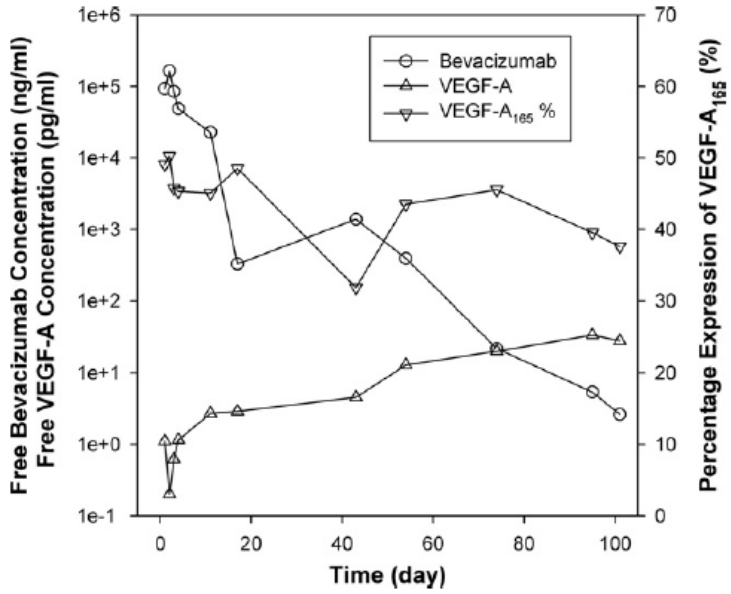
Study	Subjects	Conditions	Treatment	Assessment	Method
Krohne 2008	N= 30 eyes	AMD (n=6), DME (n=14), RVO (n=10)	BCZ 1.5 mg IVT (single dose)	BCZ levels in aqueous humor. Samples collected during elective cataract surgery	ELISA (detection range 5-500 ng/ml)
Meyer 2011	N= 29 eyes Group A 1.5 mg n=13 Group B 3.0 mg n=16	AMD (n=6), DME (n=14), RVO (n=10)	BCZ 1.5 mg IVT BCZ 3.0 mg IVT (single dose in the same eye)	BCZ levels in aqueous humor. Samples collected during elective cataract surgery	ELISA (detection range 5-500 ng/ml)
Moisseiev 2014	N = 22 eyes Group 1 BCZ top n=8 Group 2 BCZ top n=8 Group 3 BCZ IVT 1.25 n=3 Group 4 None n=3			BCZ levels in vitreous humor. Samples collected during elective cataract surgery	ELISA (detection range 6.25-300 ng/ml)
Zhu 2008	N= 11 eyes	AMD (n=11)	BCZ 1.25 mg IVT (single dose)	BCZ and VEGF-A levels in vitreous humor. Samples collected during vitrectomy.	BCZ levels (ELISA) VEGF-A levels (microsphere-based immunoassay)
Avery 2014	N= 56 patients	AMD (n=56),	BCZ 1.25 mg n=15 RBZ 0.5 mg n=20 AFB 2.0 mg n= 21 1 dose IVT/mth 3 months	BCZ, RBZ, AFB and VEGF-A serum levels. Samples collected baseline, +3 h, D1, D3, D7 and D28 following dose1 and dose3.	ELISA LLOQ RBZ 15.0 pg/mL, BCZ 313 pg/mL, and AFB 1000 pg/mL.
Avery 2017	N= 157 patients	AMD (n=57), DME (n=46), RVO (n=48)	BCZ 1.25 mg n=15 RBZ 0.3/0.5 mg n=20 AFB 2.0 mg n= 21 1 dose IVT/mth 3 months	BCZ, RBZ, AFB and VEGF-A serum levels. Samples collected baseline, +3 h, D1, D3, D7 and D28 following dose1 and dose3.	ELISA LLOQ RBZ 15.0 pg/mL, BCZ 313 pg/mL, and AFB 1000 pg/mL.

AMD: Age-related macular degeneration DME: diabetic macular edema; RVO: retinal vein occlusion BCZ: Bevacizumab; RBZ: Ranibizumab AFB: Aflibercept VEGF-E; LLOQ: Lower limit of quantitation

- **Absorption**

After intravitreal administration of a single dose of 1.25 mg bevacizumab to 11 eyes (11 patients) with age-related macular degeneration prior to vitrectomy the peak vitreal concentration 165 µg/mL was reached on the second day after the injection (Zhu et al 2008). Bevacizumab could be detected in all cases, ranging from 2.63 ng/ml to 165 ng/ml. Vitreous free VEGF-A levels ranged from 0.2 to 33.9 pg/ml and showed a negative correlation with the bevacizumab concentration (P<0.001; r =-0.955) and a positive correlation with time (P<0.001; r = 0.964).

Figure 2: Changes of vitreous free bevacizumab, free vascular endothelial growth factor-A (VEGF-A) and percentage expression of VEGF-A165 after intravitreal bevacizumab administration (n = 11; 1-101 days)

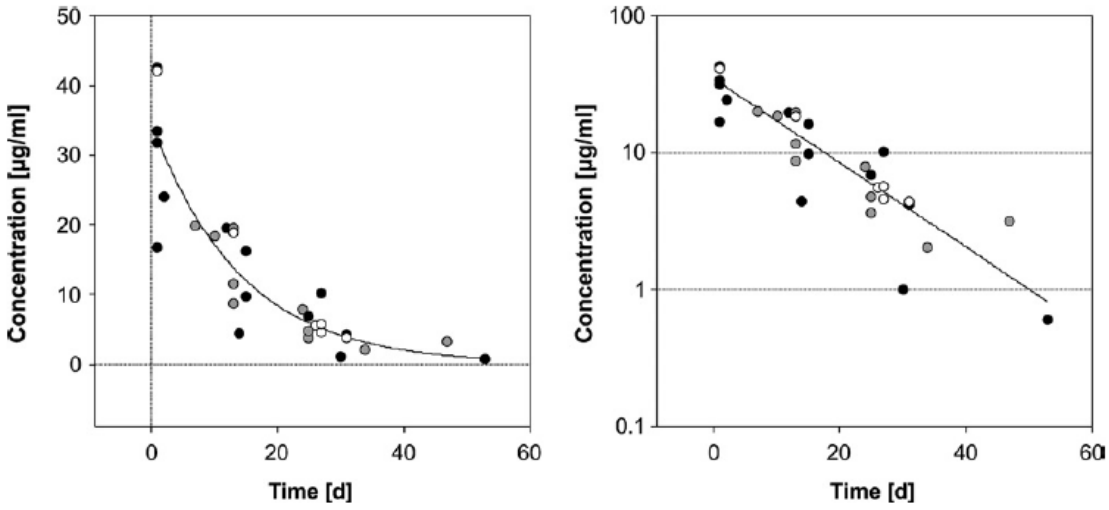


Vitreous free VEGF-A levels showed bevacizumab- and time-related changes (P<0.001, r=-0.955; P<0.001, r=0.964), as well as the percentage expression of VEGF-A165 (P=0.032, r =0.645; P=0.007, r=-0.755).

In another study the vitreous half-life ranged between 2.5 and 7.3 days, with a mean of 4.9 days, after the administration of 1.25 mg/0.05 mL while using a one-compartmental model. The vitreous samples were taken during pars plana vitrectomy (Moisseiev 2014).

Aqueous half-life was estimated to be 9.82 days in humans by non-compartmental analysis. A total of 30 patients with neovascular age-related macular degeneration, diabetic macular edema, and central or branch retinal vein occlusion with secondary macular edema received a single intravitreal injection of 1.5 mg bevacizumab and within 53 days after the injection, an aqueous humour sample was obtained during cataract surgery. Bevacizumab concentration peaked on the first day, with a mean concentration 33.3 µg/mL (Krohne 2008)

Figure 3: Graphs demonstrating bevacizumab concentrations in aqueous humor after intravitreal delivery of 1.5 mg



Samples were obtained from 30 patients treated for neovascular age-related macular degeneration (O), diabetic macular edema (●), and central or branch retinal vein occlusion with secondary macular edema (●). Mean values of triplet measurements are plotted both (Left) arithmetically and (Right) semilogarithmically. Regression analysis determined a half-time (t1/2) of 9.82 days (R^2 =0.81) for elimination of bevacizumab from aqueous humor.(6)

Following an intravitreal dose of 1.25 mg of bevacizumab the peak serum bevacizumab concentration was reached at 7.0 days with a serum half-life of 18.7 days (Avery 2014). Intravitreal injection of 0.5 mg ranibizumab and 2.0 mg aflibercept were also administered in the study. Systemic exposure was assessed by Cmax, AUC over 28 days (AUC0–28, AUC60–88), and Cmin at 1 month after dosing. The systemic exposure of bevacizumab was greater than that of ranibizumab or aflibercept, with a serum concentration of 1.58 nM, which is higher than the estimated inhibitory concentration (IC50= 0.668 nM) for VEGF factor (Yu 2011).

Figure 4: Serum concentration–time curves for ranibizumab, bevacizumab, or aflibercept following intravitreal injection in patients with age-related macular degeneration

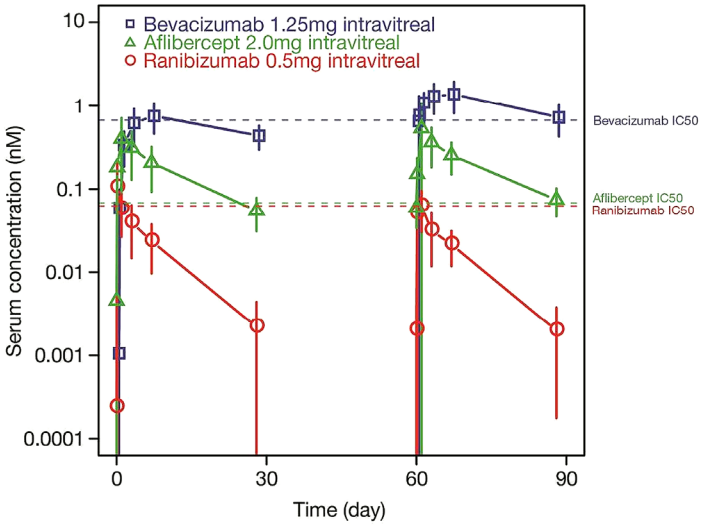


Table 3: Mean (SD) systemic exposures of bevacizumab, ranibizumab and aflibercept

	Bevacizumab	Ranibizumab	Aflibercept	Geometric mean ratio	
				Bevacizumab/ ranibizumab (95% CI)	Aflibercept/ ranibizumab (95% CI)
First dose					
C_{max}, nM	0.76 (0.31) n=15	0.11 (0.13) n=20	0.45 (0.29) n=21	8.80 (5.59 to 13.8)	4.65 (3.07 to 7.05)
C_{min}, nM	0.44 (0.14) n=14	0.002 (0.002) n=19	0.05 (0.02) n=20	310 (188 to 511)	37.3 (23.7 to 58.7)
AUC_{0-28}, nM*h	15.73 (5.76) n=14	0.46 (0.24) n=19	4.32 (1.77) n=20	34.9 (26.4 to 46.1)	9.49 (7.4 to 12.2)
Third dose					
C_{max}, nM	1.47 (0.55) n=15	0.07 (0.05) n=18	0.58 (0.52) n=21	22.7 (14.8 to 34.8)	7.28 (4.91 to 10.8)
C_{min}, nM	0.70 (0.29) n=14	0.002 (0.002) n=18	0.07 (0.03) n=21	500 (304 to 822)	52.9 (33.8 to 82.8)
AUC_{60-88}, nM*h	29.12 (10.35) n=14	0.41 (0.17) n=18	5.38 (1.77) n=21	72.4 (55.4 to 94.8)	13.5 (10.6 to 17.3)

AUC, area under curve; C_{max}, maximum serum concentration; C_{min}, minimum serum concentration.

- **Distribution**

A 2-compartment model has been described for intravitreal bevacizumab (Zou 2008) with an initial rapid distribution phase (first phase) and a subsequent elimination phase (second phase).

The initial apparent volume of the central compartment (V1) was 0.62 ml, and the volume of distribution at steady state (Vss) was 3.17 ml. This volume approximates the vitreous volume in human eyes (4.5 ml). When the distribution between the central and peripheral compartment was assessed the ratio of k12/k21 was 2.7, which indicated a fast distribution of intravitreal bevacizumab from the central compartment (vitreous) into the peripheral compartment (retina, choroid, anterior chamber, serum, etc). Additionally, the dramatic drop might also reflect the rapid binding between bevacizumab and VEGF-A.

The clearance of intravitreal bevacizumab followed first-order kinetics (second phase) with an estimated half-life of 6.7 days. Even after 101 days, there was still a low level of bevacizumab (2.63 ng/ml) detectable.

- **Elimination**

The clearance of proteins is mainly determined by non-metabolic elimination pathways.

With respect to bevacizumab and considering the larger molecular weight (149 kDa18), its penetration into the retina and its clearance from the vitreous may be slower compared with the smaller ranibizumab molecule (48 kDa19). In addition, Fc-containing molecules such as bevacizumab and aflibercept are recycled by binding endothelial cell FcRn receptors to protect them from the default degradative pathway within endosomes. This recycling decreases the rate of systemic clearance. Ranibizumab, by contrast, was designed without the Fc domain to allow for rapid systemic clearance. (Avery 2014)

- **Dose proportionality**

Bevacizumab 1.5 mg was compared to a higher dose of 3 mg (Meyer 2011).

After intravitreal administration of 1.5 mg the unbound bevacizumab concentration (Cmax) peaked 1 day post injection at 17.5 mg/mL. The estimated half-time (t1/2) of bevacizumab elimination from aqueous humor was 7.85 days (95% confidence interval, 4.8–19.7 days).

After intravitreal administration of 3 mg the peak bevacizumab concentration (Cmax) 1 day postinjection was 27.9 mg/mL. The estimated half-time (t1/2) of bevacizumab elimination from aqueous humor was 11.17 days (95% confidence interval, 8.7–18.2 days).

- **Time dependency**

Systemic accumulation was observed following the third dose of 1.25 mg bevacizumab with an accumulation ratio between the third and first doses of 1.56 (95% CI 1.15 to 2.12), 1.95 (95% CI 1.43 to 2.68), and 1.84 (95% CI 1.37 to 2.48), based on the dose 3/dose 1 geometric mean ratio of Cmin, Cmax, and AUC28, respectively (Avery 2014).

- **Pharmacokinetics in target population**

The systemic exposure of bevacizumab, ranibizumab and aflibercept after intravitreal administration was documented in patients with AMD, patients with DME and patients with RVO (Avery 2014).

No relevant differences were observed by indication. Systemic exposure was consistently highest with bevacizumab, followed by aflibercept, and lowest with ranibizumab.

No information on PK according to the age groups proposed in the table below is available.

Table 4: PK in selected age groups

	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	n/a	n/a	n/a

2.6.1.2. Pharmacodynamics

Bevacizumab is licensed in the EU as Avastin (Roche) since 2005 and is a humanised monoclonal antibody inhibiting VEGF binding to its cognate receptors, which leads to a reduction in the growth of both normal and tumour microvasculature. It is authorised for the treatment of various cancers, such as metastatic carcinoma of the colon or rectum, metastatic breast cancer, metastatic or recurrent non-squamous non-small cell lung cancer, advanced and/or metastatic renal cell cancer, advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer.

The information on bevacizumab pharmacological activity, especially in relation to the claimed indication, is derived from literature but also from the Avastin SmPC.

VEGF is an important growth factor for angiogenesis and has been shown to be necessary in normal vascular development. VEGF is highly selective for vascular endothelial cells and induces angiogenesis by serving as a potent endothelial cell mitogen. It has been shown to be secreted by hypoxic retinal pigmented epithelium (RPE) cells and induces endothelial cell proliferation and retinal vascular permeability. VEGF has also been shown to be necessary and sufficient for the development of retinal and iris neovascularisation in experimental models. Bevacizumab binds to soluble VEGF and inhibits the binding of VEGF molecules to its receptors on the surface of endothelial cells. Bevacizumab is a nonspecific VEGF inhibitor with two binding sites per molecule. Bevacizumab prevents all VEGF-A isoforms from binding to endothelial cell receptors. Reduction in activity of VEGF inhibits angiogenesis and vascular permeability.

The intravitreal administration of bevacizumab appeared to produce significant suppression of free plasma VEGF to a mean of <10 pg/mL following the first dose, and to below the LLOQ between 1 and 7

days following the third dose (Day 60). This increased suppression of free VEGF levels was associated with higher measured serum concentrations of bevacizumab following the third dose. (Avery 2014)

The mean baseline free VEGF levels were 22.5 pg/mL (95% CI 17.3 to 27.6 pg/mL). When comparing the in vitro IC50 values for VEGF based on bovine retinal microvascular endothelial cell proliferation assay, mean serum bevacizumab concentrations were higher than its IC50 (0.668 nM) at day 3 and day 7 after the first injection, and at all observed time points after the third injection through day 88.

Systemic exposure for each anti-VEGF therapeutic did not seem to differ by indication and was consistently highest with bevacizumab (Avery 2017). Mean serum concentrations of bevacizumab were also above its reported IC50 (0.668 nM) at most time points after Dose 3 for all indications.

The wording in SmPC section 5.1 is:

'Bevacizumab is a humanised recombinant monoclonal antibody targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms (VEGF165, VEGF121 & VEGF110), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, pathologic myopia and CNV or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to RVO.'

As of secondary pharmacology, other physiological effects on vasculature have been demonstrated, such as a reduction in tumour interstitial pressure, which may underlie its demonstrated antitumour effects.

These biological actions may also play a role in initiating some of the specific toxic effects observed in patients treated with Avastin, including hypertension, proteinuria and nephrosis, hemorrhage, gastrointestinal perforations, and impaired wound healing.

No formal studies have been performed on pharmacodynamic drug interactions after intravitreal injection with bevacizumab. The applicant claims that since systemic exposure of bevacizumab after ophthalmic use is very low, the risk for systemic drug interactions is low as well.

2.6.2. Discussion on clinical pharmacology

PK

No pharmacokinetic studies were performed with Ipique.

The pharmacokinetic properties of intravitreally used bevacizumab in adults are investigated by several studies and some relevant information is contained in the submitted literature on the topic. The preparation of the clinical pharmacology part of the submitted dossier was done in a rather superficial way. Although relevant publications are submitted as full texts, and a distinct literature review seems to have been conducted, several aspects of PK (and PD) relevant to this application are rather superficially discussed. Details on how the submitted literature was identified/selected are sparse. Although several relevant articles were provided, the database on bevacizumab PK with intravitreal application could be considerably larger, as indicated by reference lists of the respective articles. It cannot be excluded that more, probably high quality evidence has been generated in that field. On the other hand, there seems to be a population overlap between the studies/publications submitted. Relevant information can only be accounted for once for the B/R assessment of the product.

Due to the nature of the application (bibliographical application) in depth assessment of analytical methods used for PK characterisation, PK data analysis and statistical methods is not possible (no

source data provided). However, some relevant information is included in the individual publications and it seems that, overall, measures used were appropriate at the time of study conduct. The applicant has not discussed these issues.

Absorption

Information on absorption after intravitreal injection of bevacizumab were derived from patients e.g. by an aqueous humour sample obtained during elective cataract surgery or via vitrectomy. Peak concentrations reported are different in terms of time point (first day after injection vs. second day) and magnitude of exposure depending on the data source. Robustness in terms of quality of the evidence and applicability of data for this submission were not discussed.

Distribution

Distribution after intravitreal use was not discussed. Some of the authors reported data on the distribution of bevacizumab after intravitreal application (e.g. Zhu et al 2008).

Elimination

Vitreous half-life was reported by different authors based on different datasets using different methods. However, the results were rather comparable and vitreous half-life is estimated to be around 5-7 days with the proposed dose.

After 3 intravitreal 1.25mg doses a serum half-life of 18.7 days was estimated. The systemic exposure was greater than that of ranibizumab or aflibercept, with a serum concentration of 1.58 nM, which is higher than the estimated inhibitory concentration (IC50) for VEGF factor (IC50 = 0.668 nM)[5] suggesting possible systemic adverse effects and that bevacizumab might have the greatest potential for systemic side effects. The meaningfulness of systemic exposure after intravitreal application in relation to anti VEGF-activity is still not fully clear.

Metabolism

No specific information has been provided, but in the SmPC of Avastin biotransformation of bevacizumab is described as comparable to native IgG molecule which does not bind VEGF: The metabolism and elimination of bevacizumab is reported to be '*similar to endogenous IgG i.e. primarily via proteolytic catabolism throughout the body, including endothelial cells, and does not rely primarily on elimination through the kidneys and liver.'*

Dose proportionality

No dose escalation studies were included in the application and no respective literature data are available. It is however reported that an intravitreal dose of 1.5 mg was compared to a double dose of 3 mg with a maximum concentration in the aqueous humour at one day post-injection and an aqueous half-life of 7.85 and 11.69 days for the 1.5 and 3 mg doses, respectively. The pharmacokinetic of bevacizumab was linear at doses ranging from 1 to 10 mg/kg with intravenous application.

Information on time dependency, intra- and inter-individual variability based on intrinsic or extrinsic factors, impact of gender, race, weight or age has not been discussed.

The relationship between serum and ocular concentrations is not well established. In these circumstances, it is difficult to determine the relationship between the plasma exposure to bevacizumab and the local response within the eye. Whether differences between anti-VEGF treatments in plasma VEGF suppression may have an impact on the effect achieved is difficult to judge and might only be evident after long follow-up.

The challenges of evaluating PK after intravitreal application in relation to sampling are acknowledged. Although the relevance of PK data obtained from patients with conditions other than the target

indications has not been conclusively argued, it seems likely that data obtained e.g. in glaucoma patients could still be used to characterise intravitreal PK of bevacizumab.

It is agreed with the applicant that comparison/merging of data across different studies is complicated. But given the circumstances of this submission and the nature of a well-established use application, it would have been appreciated to make further efforts and adequately summarise and discuss the available data in a distinct PK table displaying pharmacokinetic parameters in a comprehensive manner. However, this issue was not further pursued as this issue was not considered essential to conclude on the B/R balance.

No specific data on Drug-Drug interactions are provided. The relevance for interactions might be lower for intravitreally used bevacizumab compared to i.v. use, also due to the lower dose and number of applications (lower exposure, fewer application time points). A risk for local interactions with other products applied to the eye is not discussed and no data seem available.

The applicant has not provided a thorough discussion on the PK of bevacizumab with intravitreous application in special populations. No pop PK analyses seem to have been performed according to the literature data provided. Inter-individual or intra-individual variability in PK was not discussed. Some information is mentioned in the SmPC based on data for i.v. use (Avastin). Use of intravitreal bevacizumab in paediatric patients might be less relevant because of the indication not occurring in these young age subsets. PK in elderly patients has not been specifically addressed, but it is acknowledged that a lot of the data are generated in elderly individuals. Influence of weight, race, gender on the PK have not been discussed.

Overall, the amount of available data on bevacizumab PK after intravitreal use is rather sparse in this procedure which introduces some uncertainty to the benefit/risk.

PD

The applicant's dossier does include a short discussion on pharmacodynamic effects of bevacizumab in relation to the targeted indications. No respective literature data are discussed and it is unknown if a literature search has been conducted.

The mechanism of action of bevacizumab is well known - it binds to vascular endothelial growth factor (VEGF) and thereby neutralises its biological activity. VEGF is a key driver of vasculogenesis and angiogenesis. Anti-VEGF therapy is suspected to inhibit endothelial cell proliferation and neovascularisation, as well as vascular leakage and thus believed to inhibit disease progression in AMD and DME.

No PD marker has been established for bevacizumab in the cancer indications, and no potential biomarker for the ocular indications has been proposed by the applicant. VEGF levels can be measured in the blood, which could per se be a good indicator of effect, but a respective discussion is missing.

Pharmacodynamic interactions have been considered irrelevant based on a literature search conducted by the applicant (no details on the conduct of the search or the results are available). Due to the fact that relevant systemic levels are reached with intravitreal administration, interactions with other systemic products cannot be excluded, however.

The intravitreal administration of bevacizumab appeared to produce significant suppression of free plasma VEGF. Mean serum concentrations of bevacizumab were above its reported IC50 (0.668 nM) at most time points after the third administered dose. Systemic exposure for each anti-VEGF therapeutic did not seem to differ by indication and was consistently highest with bevacizumab compared with other VEGF inhibitors.

The role of VEGF-activity as indicator of effect and potential 'biomarker' has not been thoroughly discussed. The comparability of the VEGF binding capacity between Avastin and Ipique would also support the clinical comparability, but such data are not available.

SmPC

The applicant has not argued what information has been chosen to be displayed in section 5.1 and 5.2 of the SmPC and why. Several amendments in the SmPC were recommended but remain outstanding.

2.6.2.1. Conclusions on clinical pharmacology

The dossier is fragmentary regarding documentation of bevacizumab PK and PD with intravitreal use, although the overarching mechanism of action (VEGF-inhibition) is well understood. The selection of submitted literature is unclear. There are some gaps in the knowledge of PK, PD, PK/PD relationship and the optimal dose regimen in the target population, which introduce some minor uncertainty for the B/R. The intravitreal administration of bevacizumab appeared to produce significant suppression of free plasma VEGF, indicating a potential for systemic effects.

2.6.3. Clinical efficacy

No efficacy studies on Ipique have been conducted. The data presented below relates to the claim that the efficacy of bevacizumab used in the target indication can be inferred from the published literature studies with bevacizumab in line with the type of application (article 10a of Directive 2001/83/EC).

Initially the applicant proposed the following indications: treatment of neovascular (wet) age-related macular degeneration (AMD) and visual impairment due to diabetic macular oedema (DME).

was developed as a medicinal product with a high degree of similarity to Avastin. According to the applicant, the efficacy of intravitreal Avastin in neovascular macular degeneration has been demonstrated in a number of large randomised controlled clinical trials and confirmed in a number of Cochrane analyses.

The two most recent Cochrane review regarding the efficacy of anti-VEGF in age and diabetes associated retinal vascularisation were Solomon SD et al. 2019 regarding AMD and Virgili et al. (2018) regarding treatment of visual impairment due to diabetic macular oedema (DME).

During the course of the procedure, the applicant proposed a new target indication 'treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO)', and has submitted three publications in support: A recent Cochrane review by Shalchi et al. 2020 and two publications by Spooner et al. 2019, one addressing branch and the other one addressing central retinal vein occlusion (see discussion on clinical efficacy below).

At the final stage of the procedure, the applicant only pursued the indication 'treatment of AMD'. The data presented and respective assessment for other indications discussed in the course of this procedure (DME, RVO) are nevertheless considered informative/supportive for this application and are reflected in this report also for the sake of transparency.

2.6.3.1. Dose response study(ies)

No dose response studies or literature data on dose response have been provided.

2.6.3.2. Main study(ies)

Methods

In view of the legal basis of this submission, the main studies are derived from the literature. Two recent Cochrane reviews are available to support efficacy of bevacizumab in AMD and DME and both reviews contain data on several relevant studies on the matter. Both reviews are based on earlier reviews on the matter which were not submitted with the dossier and are not discussed here.

AMD

Review title: **Anti-vascular endothelial growth factor for neovascular age-related macular degeneration (Cochrane Review, Solomon et al 2019)**

DME

Review title: **Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis (Cochrane Review, Virgili et al 2017)**

Study Participants

AMD

Trials in which participants had neovascular AMD as defined by study investigators were included.

DME

People with DME for whom anti-VEGF treatment is indicated were included (as defined by the investigators).

Treatments

AMD

Studies that compared anti-VEGF treatment versus another treatment, sham treatment, or no treatment were included. Studies comparing different doses of one anti-VEGF treatment, studies that included no control or comparator group, or studies that used anti-VEGF agents in combination with other treatments were not included. Studies with aflibercept (VEGF Trap-Eye/EYLEA solution) or studies that compared different treatment schedules (e.g. monthly vs as needed dosing) were not included. Other Cochrane reviews have evaluated these interventions (Li 2016; Sarwar 2016).

DME

Included was any antiangiogenic drug with anti-VEGF modalities compared with another drug with anti-VEGF modalities, laser treatment, sham treatment or no treatment. Steroids may be compared with anti-VEGF drugs but this needs a different approach, specifically patient subgroups and timing, and their inclusion could lead to violation of similarity in a review aiming to compare different anti-VEGF drugs such as this. Regarding drug dose and monitoring/retreatment regimen, efficacy schemes that are either on-label or commonly used in clinical practice were used.

Objectives

AMD

• To investigate ocular and systemic effects of, and quality of life associated with, intravitreous injection of three anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) versus no anti-VEGF treatment for patients with neovascular AMD

• To compare the relative effects of one of these anti-VEGF agents versus another when administered in comparable dosages and regimens

DME

The objective of this updated review is to compare the effectiveness and safety of the different anti-VEGF drugs in preserving and improving vision and quality of life using network meta-analysis methods.

Outcomes/endpoints

AMD

Primary outcomes

The primary outcome was based on best-corrected visual acuity (BCVA) at one-year follow-up. All included RCTs randomised only one eye per participant (i.e. the study eye); therefore the primary outcome for the comparison of treatments was defined as the proportion of participants who gained 15 or more letters (three lines) of BCVA in the study eye when BCVA was measured on a visual acuity chart with a LogMAR scale.

Secondary outcomes

Visual acuity outcomes

• Proportion of participants who gained 15 or more letters of BCVA in the study eye as measured at two-year follow-up

• Proportion of participants who lost fewer than 15 letters of visual acuity at one year and at two years

• Proportion of participants who lost fewer than 30 letters of visual acuity at one year and at two years

• Proportion of participants for whom blindness was avoided in the study eye, defined as eyes with visual acuity better than 20/200 at one year and at two years

• Proportion of participants maintaining visual acuity, defined as a gain of zero or more letters (i.e. no loss of BCVA from baseline) at one year and at two years

• Mean change in visual acuity from baseline to one year and to two years

Other secondary outcomes

• Contrast sensitivity, reading speed, or any other validated measure of visual function as measured in the included studies

• Assessment of morphologic characteristics by fluorescein angiography or OCT, including mean change in size of CNV, mean change in size of total lesion, and mean change in central retinal thickness (CRT)

• Quality of life measures, as assessed with any validated measurement scale

• Economic data, such as comparative cost analyses

• Ocular or systemic adverse outcomes

Follow-up

We included only trials in which participants were followed for at least one year. We also included outcomes at two-year follow-up when these data were available.

DME

Primary outcomes

Best-corrected visual acuity (BCVA) expressed as the proportion of participants with at least 15 ETDRS letters (3 ETDRS lines or 0.3 logMAR) of improvement in BCVA from baseline to 12 months.

Secondary outcomes

• Mean change in BCVA from baseline to 12 months, measured using ETDRS charts.

• Mean change in central retinal thickness (CRT), from baseline to 12 months, measured using optical coherence tomography (OCT).

• Mean change in quality of life from baseline to 12 months, measured using a validated instrument.

Randomisation and blinding (masking)

AMD

Only randomised trials were included.

Masking (performance bias and detection bias): Most of the included studies were considered to be at low risk of performance bias and detection bias. Only one study was an open-label study that employed no form of masking (Sacu 2009, N=14 in bevacizumab group and N=14 in photodynamic therapy + intravitreal triamcinolone acetonide group).

DME

Only randomised trials were included.

The unit of randomisation was the eye of individual participants.

One cross-over study comparing ranibizumab and bevacizumab was included and treated as a parallel arm study (Wiley 2016), which equals to assume a moderate (0.5) correlation within-person. However, relative drug safety is impossible to assess with a paired design.

Masking of participants and outcome assessors was obtained in 14 and 12 trials respectively, and was unclear in seven and nine trials respectively. Three trials (LUCIDATE 2014, READ2 2009 and RESPOND 2013) were unmasked.

Statistical methods

AMD

Data analysis was guided by Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2011). The primary outcome and many secondary outcomes for this review relied

on measurements of best-corrected visual acuity (BCVA) of the study eye. BCVA measured on LogMAR charts, was analysed as both dichotomous and continuous outcomes. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes.

Measures to deal with missing data were standardised. Statistical heterogeneity was assessed based on the ChiX test, the IX statistic, and the overlap of confidence intervals in forest plots. Studies were not combined in meta-analysis when clinical or methodological heterogeneity was identified. Selective outcome reporting was assessed for each study by comparing outcomes specified in a protocol, research plan, or clinical trial registry with reported results. No subgroup analyses or sensitivity analyses were conducted.

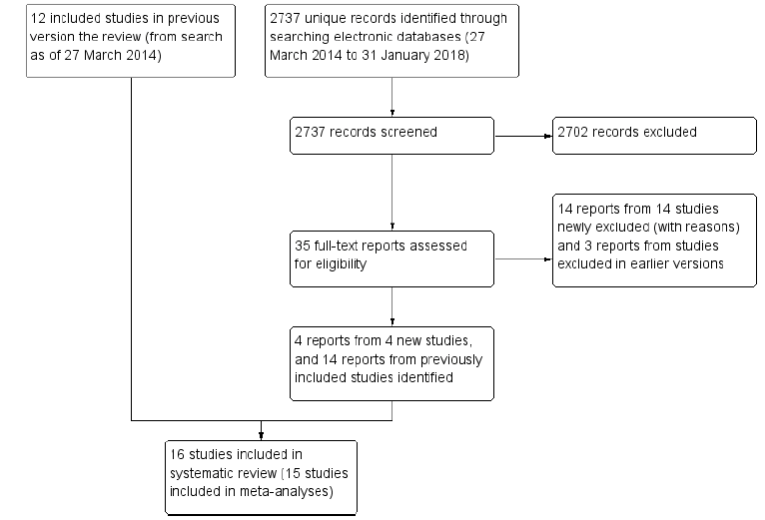
DME

Data analysis was guided by Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2011). For dichotomous outcomes, a summary risk ratio (RR) was calculated. For continuous outcome, the mean difference (MD) was calculated. Ranking measures were not used in this review, since the main interest was to compare only three drugs: aflibercept, bevacizumab and ranibizumab. Measures to deal with missing data were standardised. To investigate small-study bias at the network level the comparison-adjusted funnel plot was employed, which is an adaptation of the funnel plot. From each study-specific effect size the mean of meta-analysis of the study-specific comparison was subtracted and plotted against the study's standard error (Chaimani 2013). If there was no substantial statistical heterogeneity, and if there was no clinical heterogeneity between the trials, the results were combined in a meta-analysis using a random-effects model. A fixed effect model was used if the number of trials was three or less. In the case of substantial statistical heterogeneity (that is I^2 value more than 50%) or clinical heterogeneity, the results were combined in a meta-analysis using a random-effects model if the individual trial results were all consistent in the direction of the effect (that is the RR or MD and confidence intervals largely fall on one side of the null line); when the individual trial results were inconsistent in the direction of the effect, study results were not combined but presented a narrative or tabulated summary of each study. Network meta-analysis was performed using the methodology of the multivariate meta-analysis model where different treatment comparisons are treated as different outcomes (Salanti 2012). In standard pairwise meta-analyses, heterogeneity variances were estimated for each direct comparison. The presence of heterogeneity was statistically assessed within each pairwise comparison using the I^2 statistic (Higgins 2011b). To evaluate the presence of inconsistency locally, the node-splitting approach was used (Dias 2010). To check the assumption of consistency in the entire network, the 'design-by-treatment' model was used using the 'network' command in STATA (White 2015). Sensitivity analyses were not planned but it was decided post-hoc to conduct one excluding studies which were assessed as being at overall high or unclear risk of bias.

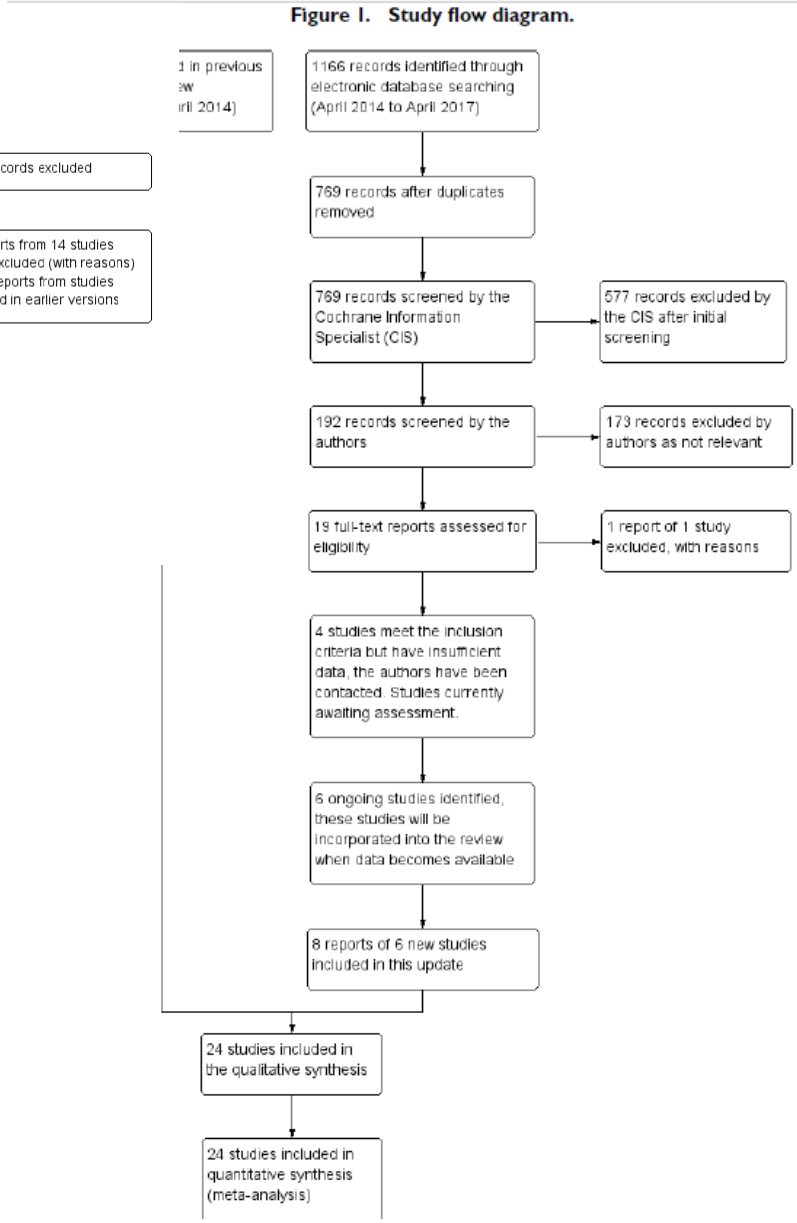
Results

Figure 5: Study flow diagram

AMD



DME



Baseline data

AMD

The included trials were similar in that all enrolled both men and women 50 years of age or older who had subfoveal CNV secondary to AMD. Among the included trials, reports describe variation in types of eligible neovascular lesions (e.g. predominantly classic CNV, minimally classic CNV, occult CNV), lesion sizes, and baseline visual acuities of participants). A majority of participants in most trials were women, but one trial enrolled a greater number of men than women (Subramanian 2010). All trials

predefined visual acuity eligibility criteria for the study eye of each participant. BCVA eligibility criteria varied between the studies.

Some trials included only participants who had received no previous treatment for CNV or AMD.

DME

Trials included participants with DMO diagnosed clinically, and often these trials used OCT for confirming macular centre involvement. Baseline visual acuity of participants was generally between 20/200 and 20/40. Most trials required a three- to six-month interval from previous central or peripheral laser, and a few small studies required that participants had not received previous antiangiogenic treatment

Numbers analysed

The following numbers consider only the comparison with bevacizumab (other treatments were evaluated in the reviews, however):

AMD: 1542 patients receiving bevacizumab were included in this review (1602 patients received ranibizumab and 80 other control treatments including sham).

DME: Data were collected on drugs of direct interest from eight studies on bevacizumab (515 eyes) (three studies on aflibercept (975 eyes) and 14 studies on ranibizumab (1518 eyes) are also included in the review).

Outcomes and estimation

AMD

Visual acuity outcomes after bevacizumab and ranibizumab were similar when the same RCTs compared the same regimens with respect to gain of 15 or more letters of visual acuity (RR 0.95, 95% CI 0.81 to 1.12; high-certainty evidence) and loss of fewer than 15 letters of visual acuity (RR 1.00, 95% CI 0.98 to 1.02; high-certainty evidence); results showed similar mean improvement in visual acuity (mean difference [MD] -0.5 letters, 95% CI -1.5 to 0.5; high-certainty evidence) after one year of follow-up. Reduction in central retinal thickness was less among bevacizumab-treated participants than among ranibizumab-treated participants after one year (MD -11.6 Qm, 95% CI -21.6 to -1.7; high-certainty evidence); however, this difference is within the range of measurement error, and was not interpreted to be clinically meaningful.

DME

Aflibercept, bevacizumab and ranibizumab were all more effective than laser for improving vision by 3 or more lines after one year (high certainty evidence). Approximately one in 10 people improve vision with laser, and about three in 10 people improve with anti-VEGF treatment: risk ratio (RR) versus laser 3.66 (95% confidence interval (CI) 2.79 to 4.79) for aflibercept; RR 2.47 (95% CI 1.81 to 3.37) for bevacizumab; RR 2.76 (95% CI 2.12 to 3.59) for ranibizumab. On average there was no change in visual acuity (VA) with laser after one year, compared with a gain of 1 or 2 lines with anti-VEGF treatment: laser versus aflibercept mean difference (MD) −0.20 (95% CI −0.22 to −0.17) logMAR; versus bevacizumab MD −0.12 (95% CI −0.15 to −0.09) logMAR; versus ranibizumab MD −0.12 (95% CI −0.14 to −0.10) logMAR. The certainty of the evidence was high for the comparison of aflibercept and ranibizumab with laser and moderate for bevacizumab comparison with laser due to inconsistency between the indirect and direct evidence. Ranibizumab and bevacizumab were comparable with respect

to aflibercept and did not differ in terms of VA: RR of gain of 3 or more lines of VA at one year 1.11 (95% CI 0.87 to 1.43), moderate-certainty evidence, and difference in change in VA was 0.00 (95% CI −0.02 to 0.03) logMAR, moderate-certainty evidence. CRT reduction favoured ranibizumab by −29 µm (95% CI −58 µm to −1 µm, low-certainty evidence).

Two-year data were available and reported in only four RCTs in this review. Most industry-sponsored studies were open-label after one year. One large publicly-funded study compared the three drugs at two years and found no difference.

Ancillary analyses

N/A

2.6.3.1. Summary of main efficacy results

AMD

Table 5: Summary of findings: bevacizumab vs ranibizumab

Bevacizumab versus ranibizumab for neovascular age-related macular degeneration

Participant or population: people with neovascular age-related macular degeneration

Settings: clinical centers

Intervention: intravitreal injections of bevacizumab

Comparison: intravitreal injections of ranibizumab

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk Ranibizumab	Corresponding risk Bevacizumab				
Gain of 15 or more letters visual acuity at 1 year	**252 per 1000**	**239 per 1000** (204 to 282)	**RR 0.95** (0.81 to 1.12)	3144 (8)	⊕⊕⊕⊕ **High**	
Loss of fewer than 15 letters visual acuity at 1 year	**944 per 1000**	**944 per 1000** (926 to 963)	**RR 1.00** (0.98 to 1.02)	3144 (8)	⊕⊕⊕⊕ **High**	
Mean change in visual acuity at 1 year (number of letters)	Mean change across ranibizumab groups ranged from **gains of 3 to 8 letters**	Mean change in visual acuity in bevacizumab groups was on average **0.58 fewer letters gained** (95% CI 1.55 fewer letters to 0.40 more letters)	**MD -0.6** (-1.6 to 0.4)	3190 (9)	⊕⊕⊕⊕ **High**	
Reduction in central retinal thickness at 1 year	Mean reduction in central retinal thickness across ranibizumab groups ranged from **30 to 182 µm**	Mean reduction in central retinal thickness in bevacizumab groups was on average **11.61 µm less** (95% CI 21.55 less to 1.66 less)	**MD -11.6** (-21.6 to -1.7)	2693 (6)	⊕⊕⊕⊕ **High**	Three additional trials reported no differences between groups for this outcome; however, these data were not reported in formats that could be included in meta-analysis
No problems in quality of life domains at 1 year	Range of **591 per 1000** to **861 per 1000** across 5 quality of life domains	Range of **608 per 1000** to **828 per 1000** across 5 quality of life domains	Range of **RR 0.96** (0.90 to 1.04) to **1.02** (0.89 to 1.17)	548 (1)	⊕⊕⊕⊖ **Moderate**[a]	Quality of life domains included mobility, self-care, usual activities, pain/discomfort, anxiety/depression

*The basis for the **assumed risk** is estimated by the proportion with the event in the ranibizumab group. The **corresponding risk** (and its 95% CI) is based on assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; MD: mean difference; RR: risk ratio.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence.
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Quality of life and adverse event outcomes downgraded to moderate quality as not all eligible trials reported these outcomes, and numbers of some adverse events were small (< 1%).
[b]A Cochrane review on systemic safety of bevacizumab versus ranibizumab includes more complete data for this finding (Moja 2014). Please refer to Moja 2014 for the most complete information on systemic safety for bevacizumab versus ranibizumab.

Figure 6: Forest plot of comparison: 4 Bevacizumab versus ranibizumab, outcome: 4.1 Gain of 15 or more letters visual acuity at 1 year

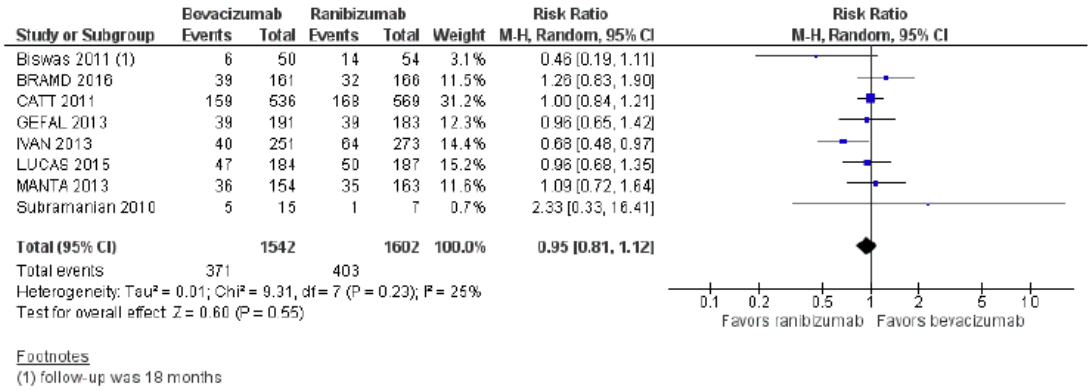


Figure 7: Forest plot of comparison: 4 Bevacizumab versus ranibizumab, outcome: 4.2 Gain of 15 or more letters visual acuity at 2 years

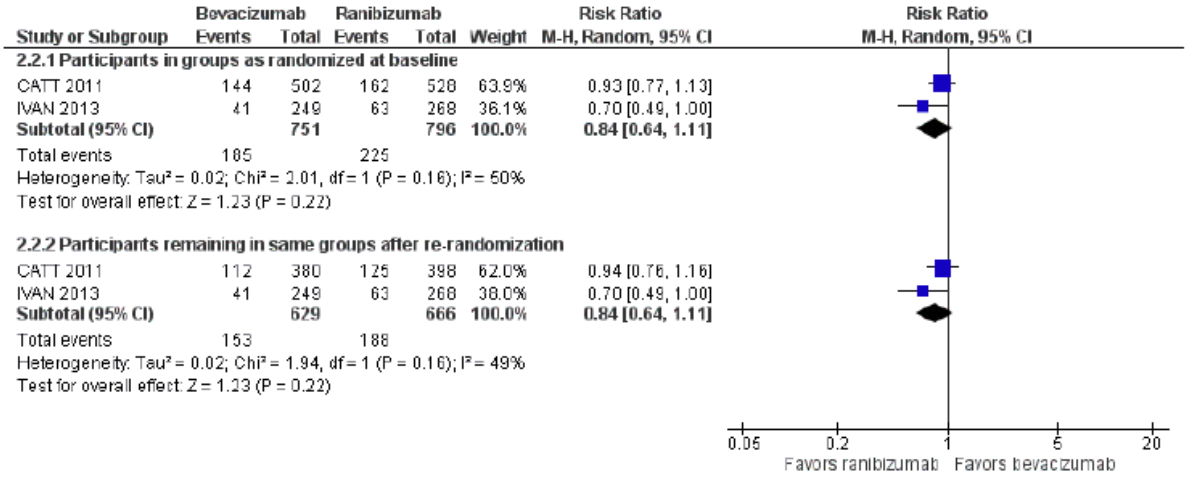


Figure 8: Analysis 2.3. Comparison 2 Bevacizumab versus ranibizumab, outcome 3 loss of fever than 15 letters visual acuity at 1 year

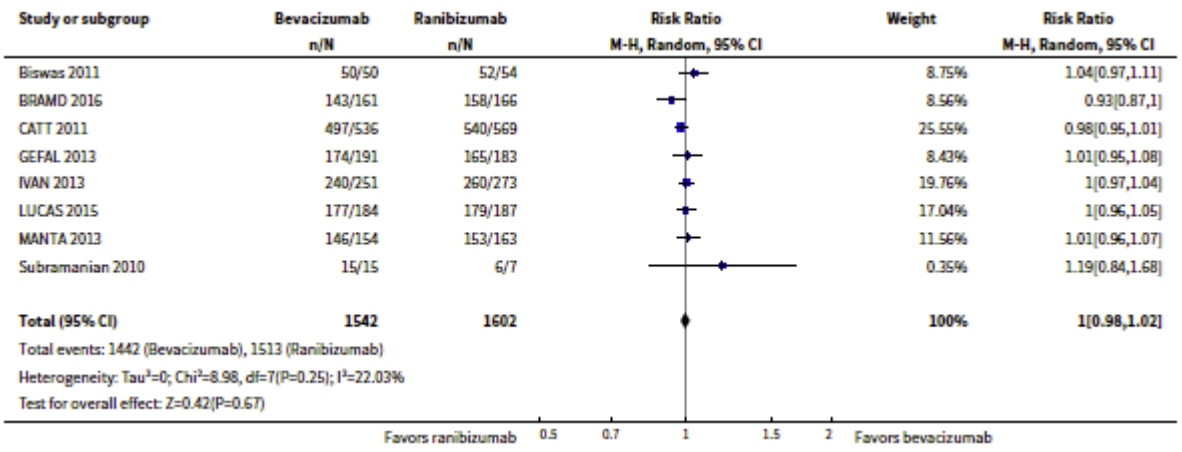
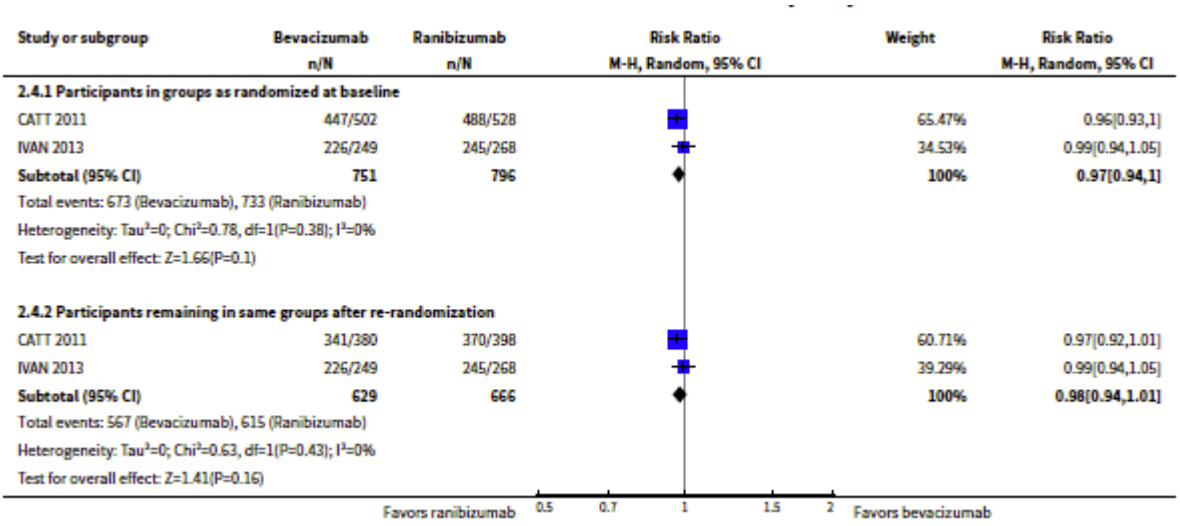


Figure 9: Analysis 2.4. Comparison 2 Bevacizumab versus ranibizumab, outcome 4 loss of fever than 15 letters visual acuity at 2 years



Further results of individual comparisons can be found in the Clinical Assessment Report.

DME

Table 6: Ranibizumab versus bevacizumab for diabetic macular oedema

Ranibizumab versus bevacizumab for diabetic macular oedema

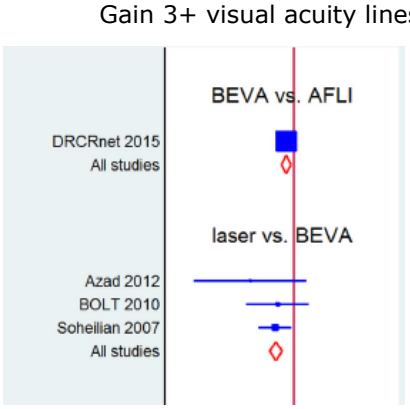
Patient or population: people with diabetic macular oedema
Settings: ophthalmology clinics
Interventions: bevacizumab, ranibizumab

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI), mixed evidence**	Certainty of the evidence (GRADE)	Reason for downgrading certainty of evidence
	Assumed risk	Corresponding risk			
	Bevacizumab	Ranibizumab			
Gain 3+ lines of visual acuity at 1 year	**300 per 1000**	**333 per 1000** (261 to 429)	**RR 1.11** (0.87 to 1.43)	⊕⊕⊕ moderate	Imprecise estimate (−1)
Visual acuity change at 1 year Measured on the logMAR scale, range −1.3 to 1. 3. Higher values represent worse visual acuity.	On average visual acuity improved by **−0.19 logMAR units** in the bevacizumab group between the start of treatment and 1 year	Average change in visual acuity was**0.00 (−0.02 to 0.03) logMAR** units (same) with ranibizumab compared with bevacizumab		⊕⊕⊕ moderate	Unclear risk of bias (−1)
Central retinal thickness (CRT) change at 1 year The aim of treatment is to reduce central macular thickness so thinner is better.	On average CRT changed by **−98 μm** in the bevacizumab group between the start of treatment and 1 year (became thinner)	Average change in CRT was **−29 (−58 to −1) μm more (thinner) with ranibizumab** compared with bevacizumab		⊕⊕ low	Unclear risk of bias (−1) Imprecise estimate (−1)
Quality of life at 1 year	No data available				

The **assumed risk** in the bevacizumab group was estimated as the row sum of the events divided by the row sum of the participants (eyes) for dichotomous variables, and as the (unweighted) median change of visual acuity or central retina thickness
The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** The risk ratio was estimated from mixed (direct and indirect) comparisons.
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High-certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate-certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-certainty: we are very uncertain about the estimate.

Figure 10: All direct and mixed comparisons: gain of 3 or more lines of visual acuity at 1 year



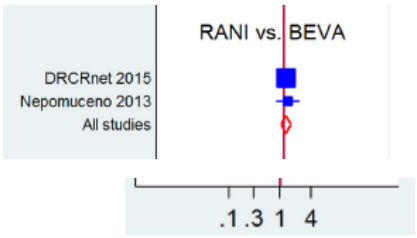


Figure 11: All direct and mixed comparisons: mean change in visual acuity at 1 year

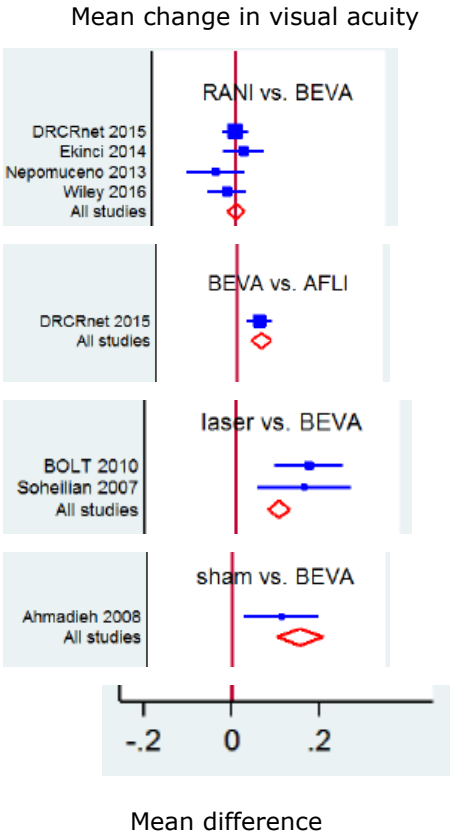
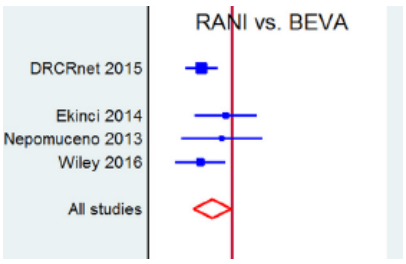
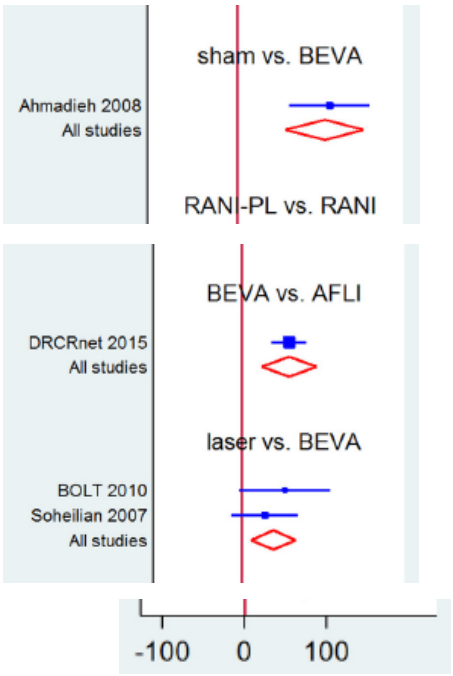


Figure 12: All direct and mixed comparisons: mean change in central retinal thickness at 1 year (micron)





Mean difference (micron)

The following tables summarise the efficacy results from the meta-analyses 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 7: Summary of efficacy for AMD

Title: Anti-vascular endothelial growth factor for neovascular age-related macular degeneration (Cochrane Review (Solomon et al 2019))			
Study identifier	N/A		
Design	Meta analysis, only RCTs were included		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		1 year not applicable 1 year or longer
Hypothesis	Equivalence		
Treatments groups	group descriptor		Bevacizumab (Beva), 1 year, N=1542
	group descriptor		Ranibizumab (Rani), 1 year, N=1602
Endpoints and definitions	Primary endpoint	Best-corrected visual acuity (BCVA)	The proportion of participants who gained 15 or more letters (three lines) of BCVA in the study eye

	Secondary endpoint	Best-corrected visual acuity (BCVA)	Proportion of participants who gained 15 or more letters of BCVA in the study eye as measured at two-year follow-up
	Secondary endpoint	Best-corrected visual acuity (BCVA)	Proportion of participants who lost fewer than 15 letters of visual acuity at one year and at two years
Database lock	January 31, 2018		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	men and women 50 years of age or older with AMD as defined by study investigator 1 year/2 years		
Effect estimate per comparison	Primary EP: Gain of ≥ 15 letters or more in BCVA at 1 year	Comparison groups	Bevacizumab vs Ranibizumab
		RR	**0.95**
		95% CI	0.01 to 1.12
	Secondary EP: Gain of ≥ 15 letters or more in BCVA at 2 years	Comparison groups	Bevacizumab vs Ranibizumab
		RR	**0.84**
		95% CI	0.64 to 1.11
	Secondary EP: loss of < 15 letters in BCVA at 1 year	Comparison groups	Bevacizumab vs Ranibizumab
		RR	**1.00**
		95% CI	0.98 to 1.02
Notes			
Analysis description	standard methodological procedures expected by Cochrane were used		

Table 8: Summary of efficacy for DME

Title: Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis (Cochrane Review (Virgili et al 2017))		
Study identifier	N/A	
Design	Meta analysis, only RCTs were included	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	1 year not applicable 1 year or longer
Hypothesis	Equivalence	
Treatments groups	group descriptor	Bevacizumab (Beva), 1 year, N=515 eyes
	group descriptor	Ranibizumab (Rani), 1 year, N=1518

Endpoints and definitions	Primary endpoint	Best-corrected visual acuity (BCVA)	The proportion of participants who gained 3 lines (15 letters) of BCVA at 1 year
	Secondary endpoint	Best-corrected visual acuity (BCVA)	Mean change in BCVA from baseline to 12 months, measured using ETDRS charts. Measured on the logMAR scale (higher values represent worse visual acuity)
	Secondary endpoint	central retinal thickness (CRT)	Mean change in central retinal thickness (CRT), from baseline to 12 months, measured using optical coherence tomography (OCT). Aim of therapy is to reduce CRT (in µm)
Database lock	26 April 2017		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	People with DME for whom anti-VEGF treatment is indicated as decided by study investigator 1 year/2 years		
Effect estimate per comparison	Primary EP: Gain of ≥ 15 letters or more in BCVA at 1 year	Comparison groups	Bevacizumab vs Ranibizumab
		RR	**1.1**
		95% CI	0.87 to 1.43
	Mean change in BCVA after 1 year measured on the logMAR scale	Comparison groups	Bevacizumab vs Ranibizumab
		Average change	**0.0**
			(-0.02 to 0.03)
		On average visual acuity improved by **−0.19 logMAR** units in the bevacizumab group between the start of treatment and 1 year	
	Mean change in central retinal thickness (CRT) after 1 year in µm	Comparison groups	Ranibizumab vs Bevacizumab
		Average change	**-29 µm** thinner with Rani compared to Beva
			(-58 to -1)

		On average CRT changed by **−98 µm** in the bevacizumab group between the start of treatment and 1 year (became thinner)	
Notes			
Analysis description	standard methodological procedures expected by Cochrane were used		

A short summary and discussion of the **RVO** indication (introduced by the applicant at during the course of the procedure) is in the below discussion on clinical efficacy.

2.6.3.2. Analysis performed across trials (pooled analyses and meta-analysis)

The Cochrane reviews summarising relevant studies discussed above provide analyses across relevant trials, taking into account differences in objectives and study designs, level of potential bias and, in general, robustness of results.

2.6.3.3. Guidelines

The applicant has submitted a number of Guidelines, bearing some lower evidentiary value regarding a claim of recognised safety and efficacy and supporting a well-established use.

Guidelines

Table 9: Summary of national and international guidelines for management of nAMD

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation
European Society of Retina Specialists (EURETINA)	2014	EU	The CATT and IVAN results indicate that ranibizumab and bevacizumab both confer solid visual function benefits. With monthly use of both drugs, non inferiority (NI) has been proven with optimal visual outcomes. Direct comparison among as-needed treatments also demonstrated NI, although on a generally lower level. Bevacizumab, as needed, failed to meet NI equivalence to monthly ranibizumab, that is, bevacizumab used in a PRN regimen did not reach the superior visual outcome achievable with monthly ranibizumab. Therefore, choice of the fixed monthly regimen is relevant when off-label bevacizumab is used. How much reduction in ocular efficacy one would be willing to sacrifice for reducing the number of injections and/or costs might depend on individual circumstances. Bevacizumab's impact on plasma concentrations of VEGF and its prolonged half-life in the circulation are proven. Therefore, the individual physical condition of each patient should be considered in the choice of therapy. Informed consent after discussing the optimal benefit, comfort and risks and the off-label status of the drug is mandatory. *(Evidence level I).*
American Academy of Ophthalmology	2019	USA	In patients with neovascular AMD, early detection and prompt treatment improves the visual outcome. Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment.

			Symptoms suggestive of postinjection endophthalmitis or retinal detachment require prompt evaluation.
NICE	2018	UK	Intravitreal anti-vascular endothelial growth factor (VEGF) treatment is recommended for late AMD (under predefined circumstances) No clinically significant differences in effectiveness and safety between the different anti-VEGF treatments have been seen in the trials taken into account for the guideline. RBZ or AFB is recommended as an option. Pegaptanib is not recommended. BCZ is considered an unlicensed medication in, this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the prescribing decision. Informed consent would need to be obtained and documented. The guideline committee's view is that there is equivalent clinical effectiveness and safety of different anti-VEGF agents (aflibercept, bevacizumab and ranibizumab) Stopping rules for antiangiogenic treatment for late AMD (wet) are discussed

Table 10: Summary of national and international guidelines for management of DME

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation
European Society of Retina Specialists (EURETINA)	2017	EU	The comparative trial from the DRCR.net has provided data about efficacy and safety for bevacizumab, aflibercept, and ranibizumab. According to these results, the choice of treatment for DME depends on the baseline BCVA letter score. While aflibercept and ranibizumab are the drugs of choice for BCVA letter score of less than 69, all three medications are equivalent in improving vision in eyes with a baseline BCVA letter score of 69 or more. The numbers of serious adverse events were altogether small, but the follow-up was short. The much lower cost of off-label use of intravitreal bevacizumab is indisputable, but all three medications should be available to ophthalmologists who are responsible for tailoring the treatment for each patient with DME.
American Academy of Ophthalmology	2019	USA	Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents are effective in the treatment of center-involved diabetic macular edema with vision loss. At this time, laser photocoagulation surgery remains the preferred treatment for non-center-involved diabetic macular edema and pan-retinal photocoagulation (PRP) surgery remains the mainstay treatment for proliferative diabetic retinopathy (PDR). The DRCR.net Protocol T demonstrated that anti-VEGF therapy using either bevacizumab,

			ranibizumab, or aflibercept is effective treatment for CI-DME. The 2-year results did not reveal a statistical difference among the three drugs in serious adverse events and all three treatments provided substantial visual acuity improvement. In eyes with visual acuity of 20/40 or better, there were no visual acuity differences between treatment regimens. In eyes 20/50 or worse, aflibercept was superior to ranibizumab and bevacizumab at year 1. However, at year 2, the mean visual acuity in the aflibercept group was superior only to the bevacizumab group.
International Council of Ophthalmology	2017	International	Central-involved DME and good visual acuity (better than 6/9 or 20/30): 3 treatment options being evaluated in an ongoing clinical trial: (1) careful follow-up with anti-VEGF treatment only for worsening DME; (2) intravitreal anti- VEGF injections or (3) laser photocoagulation with anti-VEGF, if necessary. Central-involved DME and associated vision loss (6/9 or 20/30 or worse): intravitreal anti-VEGF treatment (e.g., with ranibizumab [Lucentis] 0.3 or 0.5mg, bevacizumab [Avastin] 1.25mg, or aflibercept [Eylea]) 2mg therapy). Treatment with aflibercept may provide the best visual outcomes over 1 year, especially in eyes with baseline visual acuity of 6/15 (20/50) or worse. However, by 2 years of therapy, ranibizumab-treated eyes achieve similar visual results to those given aflibercept. Consideration should be given to monthly injections followed by treatment interruption and re-initiation based on visual stability and OCT. Patients should be monitored almost monthly with OCT to consider the need for treatment. Typically, the number of injections is 8-10 in the first year, 2 or 3 during the second year, 1 to 2 during the third year, and 0 to 1 in the fourth and fifth years of treatment. For eyes with persistent retinal thickening despite anti-VEGF therapy, consider laser treatment after 24 weeks. Treatment with intravitreal triamcinolone may also be considered, especially in pseudophakic eyes. Injections are given 3.5 to 4 mm behind the limbus in the inferotemporal quadrant under topical anesthesia using a sterile technique. DME associated with proliferative DR: monotherapy with intravitreal anti-VEGF therapy

			should be considered with re-evaluation for need for PRP versus continued anti-VEGF once the DME resolves.

2.6.4. Discussion on clinical efficacy

This is an application based on Article 10a of Directive 2001/83/EC for a monoclonal antibody, bevacizumab, in the treatment of neovascular age-related macular degeneration (AMD) relying on *'well established use'* in the EU for at least 10 years.

Initially the applicant pursued the indications 'treatment of neovascular (wet) age-related macular degeneration (AMD) and visual impairment due to diabetic macular oedema (DME)'. During the course of the procedure, the applicant proposed a new target indication, 'treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO)', but was not accepted (see section *Submission of the dossier*, above). During the procedure the applicant withdrew the DME indication and only pursued the AMD indication DME (and RVO) data are considered supportive also for the AMD indication, and are discussed in this report.

In order to rely on the literature data generated with Avastin, similarity between Ipique and the product used in the literature (EU or US Avastin) need to be established. This bridge is of particular importance in the context of biological medicinal products where minor differences in the active substance could translate in significant clinical differences on the efficacy and/or safety. Ipique should be comparable to the product used in the historical studies in physicochemical, biological and functional terms.

Due to the complexity of the monoclonal antibody structure and the potential impact of aberrations between products on the clinical performance, similarity on a quality level alone is not considered sufficient to conclude that the clinical data obtained with Avastin can be extrapolated to Ipique.

Furthermore, the quality comparability assessment shows differences between the two products, including in glycosylation levels and in the presence of incomplete molecules (HHL) in finished product due to a amino acid substitution. The potential impact of these (and other, including unknown) differences on the clinical performance of Ipique, especially in terms of safety when used intravitreally, cannot be predicted from the quality data alone. In addition, the safety and efficacy profile of biologicals in general may be influenced by factors such as e.g. the manufacturing process and micro-heterogeneity of products that would not be detected during the quality comparability exercise. The irrelevance of known (e.g. subvisible particles, different levels of glycosylation, different distribution of glycophorms, higher level of the HHL fragment) and unknown differences would need to be adequately demonstrated with appropriate (i.e. in this case, with intravitreal use) clinical studies before clinical comparability for the intended use could be assumed. It is taken into account that the intravitreal administration implies specific risks regarding the risk of inflammation, immunogenicity, and that sub-visible particles – for which differences are observed and other might be present but are unknown - may accumulate in the vitreous body. Hence, comparative clinical studies only aiming to establish the bridge between Ipique and the medicinal product used in the published literature (presumably EU or US Avastin) would have been necessary to support the relevance of the literature in this procedure.

It is concluded that the characteristics of safety and efficacy of the product referred to in the literature cannot be used to infer of safety and efficacy of Ipique in indications requiring intravitreal use.

The data submitted on Ipique, a bevacizumab that recently achieved a positive opinion by CHMP and which is considered identical to Ipique, have been taken into account. It related to a study was conducted in Subjects with Stage IIIB/IV Non-squamous Non-Small Cell Lung Cancer (NSCLC). Efficacy

outcomes of this study (randomised, multicenter, multinational, double-blind, support the notion of a similar VEGF-binding effect of the two tested products. However, the difference in route of administration does not allow to rely only on this bridging exercise. It is considered necessary to demonstrate that there are no clinically relevant differences in efficacy between Ipique and the product(s) used in the provided literature when administered into the vitreous.

To establish such bridge, the applicant could consider a clinical comparability study in AMD to directly contextualise efficacy and safety of intravitreally used Ipique in addition to the quality comparability exercise.

Discussion of literature data

At the initial submission for this procedure, two recent Cochrane reviews were the basis for the assessment of efficacy of bevacizumab in both initially claimed indications (Solomon et al 2019 for AMD and Virgili et al. 2017 for DME).

The proposed dose for Ipique in AMD is 1.25 mg per intravitreal injection, with an initial 'loading dose' phase of at least three monthly injections, followed by a 'pro re nata' approach. The posology section 4.2 in the SmPC is worded along the lines of the respective section of Lucentis (ranibizumab). Indeed, in clinical practice, bevacizumab seems to be used in a comparable way and therefore this approach is acceptable.

Design of studies and conduct of meta-analyses

Search methods, selection criteria, objectives and methodology of analyses are comprehensible and agreeable for both Cochrane reviews (AMD and DME). Only RCTs were included in both data reviews, which is a good basis for robust outcomes of the meta-analyses. The majority of studies was masked.

As inclusion/exclusion criteria were not always consistent within the included trials, the evidence is generated based on data from a broad patient collective. This could be beneficial for the external validity of data but could also introduce heterogeneity and thus complicate the assessment.

In the review on AMD, other anti-VEGF treatments, sham treatment, or no treatment were included. No studies on aflibercept (Eylea) were included as no trial was found that compared aflibercept versus bevacizumab injections into the eye up to November 30, 2015. In the review on DME (indication no longer pursued) other anti-VEGF treatments were compared with each other, laser treatment, sham treatment or no treatment.

Both, aflibercept and ranibizumab (Lucentis) are licensed for the treatment of AMD and the treatment of visual impairment due to DME.

It is noted that in AMD data on pegaptanib was also used for the comparison of anti VEGF-performance but 'Macugen' is no longer authorised in the EU. Other comparators such as laser, sham procedures and other are also available but represent a smaller part of the evidence. The active comparators used in the reviews are considered standard of care at the time.

The primary endpoint in both reviews was defined as the proportion of participants who gained 15 or more letters (three lines) of BCVA in the study eye after one year. BCVA addresses visual function and has regulatory precedence as pivotal primary outcome measure as both, Eylea and Lucentis (and also Macugen) were approved based on changes in BCVA. Both products however were authorised based on BCVA worsening less than 15 letters after one year (this was also assessed as secondary endpoint by Cochrane). Thus, the chosen primary outcome measure in the reviews approaches from a different perspective. However, while the responder threshold of 15 letters has regulatory precedence, its clinical meaningfulness (for either evaluation) is not well justified to date.

In many of the studies included in the reviews continuous outcomes were the primary endpoints, and these are considered more informative compared to the responder analyses used by Cochrane. Continuous outcomes were used as secondary objectives also in the Cochrane reviews.

Efficacy data and additional analyses

Relevant data were collected over a duration of one year in all studies in AMD and DME and some studies also reported two year data. Long term data are considered important to evaluate maintenance of effect as the diseases are chronic and progressive and the treatment likely exceeds a one year period in clinical practice. For the interpretation of the two year data it has to be taken into account, that a certain selection of patients with an overall higher benefit of treatment (compared to the mean patient) is likely (patient with poor tolerability or unsatisfactory response are likely to discontinue treatment earlier).

1542 patients receiving bevacizumab for AMD were included in the Cochrane review (1602 patients received ranibizumab and 80 other control treatments including sham) in ten trials. For DME data were collected from eight studies on bevacizumab (515 eyes) (three studies on aflibercept (975 eyes) and 14 studies on ranibizumab (1518 eyes). The numbers analysed seem sufficiently large to allow for meaningful interpretation of the meta-analyses results. The numbers indicate that bevacizumab use is not rare in the target indications. However, a true assessment on extent of use cannot be made based on these numbers as studies were selected based on other criteria than sample size for these reviews.

The majority of trials enrolled both men and women 50 years of age or older who had subfoveal CNV secondary to AMD. Different types of neovascular lesions (e.g. predominantly classic CNV, minimally classic CNV, occult CNV), lesion sizes, and baseline visual acuities of participants have been reported. Visual acuity criteria in more sized clinical trials recruited patients with BCVA ranged from 20/25 to 20/320. Most trials included only participants who had received no previous treatment for DME or AMD. Additional subgroups efficacy results for potential prognostic factors of interest were asked from the applicant based on the historic literature. The applicant referred to a review-study from Ashraf et al. (2018) and summarised several morphological and demographic prognostic indicators that can predict response to therapy in wet AMD. The applicant has not discussed whether this has any consequences for recommendations outlined in the SmPC.

AMD

In two trials (ABC 2010, Sacu 2009) bevacizumab was compared with the standard therapy available at that moment (verteporfin with or without triamcinolone or pegaptanib). However, none of them can be currently considered as first line therapy; this comparison is of limited value for assessing the efficacy of bevacizumab. Direct comparison of bevacizumab to placebo/sham is not available. One of the comparators besides verteporfin PDT was pegabtanib and it is unclear why these data were not considered for the overall comparison with anti-VEGF treatments in the review. Not many secondary outcomes were reported to support the conclusion of the primary objective, but the overall notion of a beneficial effect of bevacizumab is supported by two small studies (ABC 2010 and Sacu 2009).

In the remaining 10 studies bevacizumab was compared with ranibizumab. Therefore, only relative efficacy is available. This is in line with the clinical development of aflibercept (VIEW 1 and 2 studies) and brolucizumab (HAWK and HARRIER studies), where the main comparison was performed with ranibizumab and aflibercept, respectively. In principle, it can be considered acceptable as they both are considered as standard therapy. However, there is potential risk of biocreep. This could be relevant as a non-inferiority margin of 5 letters (higher than that usually accepted from a regulatory point of view)

was frequently established and most of studies were analysed under ITT principles, less conservative for concluding non-inferiority.

Comparative data on visual acuity, visual function, morphological outcomes and QoL outcomes overall revealed no difference in the performance between bevacizumab and ranibizumab after one or two years. Still, some uncertainties were identified by the Rapporteurs:

- The origin of the bevacizumab product used in individual studies is unclear, the applicability of results for Ipique, based on a required scientific bridge, is not clear.

- Two year data were available only from a few studies

- Maintenance of visual acuity was reported as endpoint only in two small studies. Only one trial that compared bevacizumab with ranibizumab reported visual function outcomes

- Visual function: participants in the ranibizumab group had slightly better (8%-6%) near LogMAR visual acuity than those in the bevacizumab group after one and two years, respectively.

- some endpoints potentially meaningful such as e.g. reading speed, contrast sensitivity, visual field or perimetric measures were not measured/reported.

- The choice of endpoints reported by Cochrane is not explained and it seems unlikely that all endpoints from all individual studies are reflected in the publication by Solomon et al 2019.

- Participants treated with bevacizumab showed less reduction in CRT compared with those treated with ranibizumab in six trials (MD -11.6 µm, 95% CI -21.6 to -1.7)

- Quality of life was evaluated only in one study.

While most of the conclusions were graded as high certainty evidence, some secondary outcomes were considered only of moderate robustness due to different reasons.

Some differences were observed between the largest studies submitted. The CATT study demonstrated a head-to-head equivalent effect on visual acuity at 1 year when bevacizumab and ranibizumab were compared. However, some differences were observed when they were administered monthly (RBZ +8.5 vs BCZ +8.0 letters) and as-needed (RBZ +6.8 vs BCZ +5.9 letters). The results of IVAN study were considered as inconclusive when a similar comparison was established. The difference between drugs (bevacizumab vs ranibizumab) was -1.99 letters (95% CI, -4.04 to 0.06). Discontinuous (PRN) vs continuous (monthly) regimen showed a difference of -0.35 letters (95% CI, -2.40 to 1.70). LUCAS 2015 exploring a "treat and extend" scheme found bevacizumab non-inferior to ranibizumab (RBZ +8.2 vs BCZ +7.9) with the confidence interval within the predefined limits (-2.4 to 2.9; p=0.845).

Factors such as the initial level of visual acuity or the use of different injection schemes, including the criteria established for retreatment may have an influence on the effect or the population obtaining benefit from the treatment.

The conclusions of the Cochrane review is that (1) intravitreous injection of (pegaptanib,) ranibizumab, and bevacizumab has beneficial effects on best corrected visual acuity in eyes with neovascular age-related macular degeneration, and that (2) ranibizumab and bevacizumab have comparable safety and effectiveness in such eyes. These conclusions can be largely supported based on the data provided.

DME

(This indication was no longer pursued at D181.)

The studies included in the review by Virgili et al. 2018 were in general small (most of the studies included <100 patients). Only DRCR net 2015 may be considered as a sufficiently sized study.

In one trial bevacizumab was compared with sham. Three trials included a comparison versus laser and four studies compared bevacizumab with ranibizumab (in one of them aflibercept was also tested). One (Wiley 2016) was a cross-over study but treated for the review as a parallel-arm trial. There are doubts on the suitability of a cross-over design in this chronic, progressive condition, when treatments with extended effect are compared. Evaluation of the results may be inconclusive so that parallel-group trials remain the gold standard for comparing these therapies.

The role of bevacizumab as first line therapy for DME in the submitted studies does not appear to be clearly determined as many patients were treated with laser therapy prior to bevacizumab in the submitted studies. Upon request the applicant has discussed the results from two papers (Soheilian 2009 and Soheilian 2012). The number of naïve patients treated with bevacizumab in the submitted studies was reduced (n=50; only 39 eyes remained at 2 year-follow-up) and the schedule used does not correspond to that proposed in the SmPC so that the concerns still remain.

Several clinical trials comparing intravitreal bevacizumab and corticosteroids have been conducted and published. The comparison with intravitreal corticosteroids was neither considered in the meta-analysis nor discussed by the applicant. Some of the studies included only one eye per patients but at least in four studies (Ahmadieh 2007, Nepomuceno 2013, Soheilian 2007 and Wiley 2016) some patients received treatment in both eyes.

Bevacizumab was more effective than laser for improving vision by 3 or more lines after one year (RR 2.47 [95% CI 1.81 to 3.37]). It was non inferior to ranibizumab (RR 1.1 [95% CI 0.87 to 1.43]) and inferior to aflibercept (RR 0.68 [95% CI 0.52 to 0.90]). Unfortunately, only RR values are available. In general, this pattern was consistent for the vision-related outcomes (difference in mean VA change versus ranibizumab 0.00 [95% CI −0.02 to 0.03] logMAR). With respect to anatomic outcomes, significant improvements were observed with both treatments but small (29 µm difference in central retinal thickness [95% CI −58.2 to −0.70]) relative estimated benefit of ranibizumab compared with bevacizumab was shown.

Aflibercept showed the best responses at 1 year of treatment, and DRCR net 2015 study showed different magnitudes of improvement according the initial level of visual acuity. Aflibercept was more effective at improving vision at worse levels of initial visual acuity. It is unknown the determining factors for these differences (differences in structure, growth factor specificity, VEGF-binding affinity). This different behaviour according visual acuity was not observed with bevacizumab, which otherwise showed numerically the lowest effect. According to the results provided by the meta-analysis published by Virgili (2018) bevacizumab improved mean visual acuity and central macular thickness at one year in patients with DME. However, studies considered for the systematic review were heterogeneous in the dosing regimen administered, baseline characteristics of patients included and duration of the follow-up. The use of different injection schemes along with a short follow-up duration of 6 months and limited sample size of a relevant number of studies can be considered to be shortcomings of the dossier for this indication so that it is questionable that they are sufficiently supportive of the effect of bevacizumab in this condition. As the DME indication is no longer pursued, no question is raised.

Only two studies reported 2 year data and the data were considered unsuitable for a network meta-analysis.

No data were reported for bevacizumab in relation to quality of life.

Level of evidence/risk of bias

The risk of bias in general was low in the included trials according to the authors. A judgement about the methodological quality of the included studies was incorporated in both data reviews, the certainty of the evidence was graded in both reviews and results were overall considered very robust. There is no reason to doubt these statements.

At this point it is noted that the objectives of such reviews cannot be translated 1:1 to the objective of a registrational phase III study that would usually be the basis for drug approval. While the level of evidence of a meta-analysis has to be considered higher compared to a single study, the research questions might not be fully applicable in view of the establishment of a benefit/risk for a certain population. It is furthermore criticised that the outcome measures (and responder definitions) chosen to be displayed in the Cochrane reviews have not been discussed as to their clinical relevance by the authors or the applicant. However, it is acknowledged that the performance of bevacizumab was overall comparable to ranibizumab in all evaluated endpoints in both target indications. Both products seemed sufficiently equal regarding their efficacy performance. In general, an improvement of visual acuity in a potentially progressive disease has to be interpreted as clinical benefit.

It is noted that bevacizumab is currently mentioned on the WHO Model Lists of Essential Medicines as "Ophthalmological preparations - Anti-vascular endothelial growth factor (VEGF) preparations" (21th version, 2019) and mentioned also in other treatment guidelines, e.g. by the European Society of Retina Specialists (EURETINA), NICE, the UK Royal College of Ophthalmologists, the Dutch Ophthalmology Society or the American Academy of Ophthalmology.

Comments in the SmPC, especially related to the display of information in section 5.1, were also raised.

Claim for an additional target indication by the applicant during the course of the procedure:

In the response to MO 116 at D121 on the indication wording the applicant introduced *'the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO).'* as additional target indication for Ipique. The addition of the RVO indication was not accepted. The data were considered, given their potential to be informative on the AMD indication, despite the fact that the assessment performed revealed that they would have been clearly insufficient for an RVO indication. In any event, the overarching lack of adequate bridge between Ipique and the bevacizumab used to generate the data present in the literature (see below) also apply to this indication.

To support this new indication, three publications were submitted; a recent Cochrane review by Shalchi et al. 2020 on branch retinal vein occlusion, and two publications by Spooner et al. 2019 (one addressing branch and one addressing central retinal vein occlusion). Hemiretinal vein occlusion (HRVO) is not addressed in either publication and was not mentioned by the applicant in the updated documents.

It is noted that RVO is included in the labels for Lucentis and Eylea (other anti VEGF-factors).

A thorough presentation of the respective data and a clinical overview (and summary) was not submitted. The publications by Ramezani et al. 2012 and Higashyana 2012 (the only two studies included in the Cochrane review by Shalchi et al. 2020 were bevacizumab was used) were not included in Module 5.

Salchi et al. 2020 Cochrane Analysis BRVO

Approach and methods of the data review by Salchi et al. 2020 seem compliant with what would be expected from Cochrane, only RCTs were included. However, it needs to be considered that the primary objective of the review was not to establish a B/R profile for bevacizumab in the claimed indication (but to evaluate 'anti-VEGF factors' in general, in a more narrow indication (BRVO) than sought by the applicant for Ipique (RVO)). Comparative data on patients treated with bevacizumab are available for BRVO but no subgroup analysis evaluating bevacizumab efficacy alone were conducted. The authors judged the bevacizumab studies of moderate-high or unclear risk of bias. Two small studies on bevacizumab use were included in the Cochrane review; Higashiyama 2013 and Ramezani 2012.

Higashiyama 2013; N=22 patients received bevacizumab (compared to N=21 who received intravitreal triamcinolone) with a 12 month follow-up.

The risk of performance and detection bias was considered high for Higashiyama 2013 by Cochrane. Treating doctors were not masked. Four bevacizumab participants were lost to follow-up. These were not analysed in the 12-month results, regardless of reason for discontinuation.

The protocol for Higashiyama 2013 was not available and it was not possible to exclude the possibility of selective reporting.

Ramezani 2012; N= 43 eyes were treated with bevacizumab and compared to n=43 eyes which received intravitreal triamcinolone, the primary outcome was the change in BCVA at six months. The study showed unclear risk of performance bias; the study group masked participants to their treatment; however, since triamcinolone might cause floaters they do not consider this study as a double-masked one. One participant in the bevacizumab group was lost to follow-up at six months.

The bevacizumab effect is overall considered favourable in the studies of Higashiyama 2013 and Ramezani 2012. The two relevant studies were small and the risk of bias was high. The amount of data (and information on individual studies) is not deemed sufficient to base regulatory decisions on.

Spooner et al 2019 (1) is a Meta-Analysis that evaluated anti-VEGF therapy in the Treatment of Macular Oedema Secondary to Branch Retinal Vein Occlusions. Randomised controlled trials and observational studies were included. 15 studies examined the effectiveness of bevacizumab [see references 18, 22, 23, 27-38 in the publication]. 654 eyes were treated with bevacizumab. Available analyses favoured anti-VEGF treatments. It is unclear how many of the 15 trials were randomised or controlled and probably none of them was.

The mean improvement in BCVA for ranibizumab and bevacizumab groups was comparable (both 13 letters), whereas those in the aflibercept group had a greater mean BCVA gain of 19.0 letters (95% CI 16.6 to 21.4) at 12 months.

According to the authors the main limitation of the meta-analysis is that publication bias could not be excluded. Further limitations include differences in baseline characteristics between different studies, including visual acuity and indicators of retinal thickness, central retinal thickness, central macular thickness and CFT. There were also varying sample sizes and study designs. Longer-term data are required as BRVO can be a chronic disorder, and, consequently, long-term perspective evaluations are needed. Nevertheless, the findings indicate that anti-VEGF therapy offers substantial gains in vision and reduction in macular oedema.

Spooner et al 2019 (2) is the only data source in support of Central Retinal Vein Occlusions. This meta-analysis evaluated the current anti–vascular endothelial growth factor (anti-VEGF) treatments for

macular edema due to central retinal vein occlusions. The search for the meta-analysis was limited to clinical studies available in peer reviewed English language publications, and those published between January 2013 and June 2018. Randomised controlled trials, and real-world prospective and retrospective clinical studies were included, but no RCT with bevacizumab is available. The number of patients (eyes) treated with bevacizumab is unclear.

The pooled mean improvement in BCVA was 16.5 letters (95% CI, 12.6–22.9, P < 0.001) for eyes treated with bevacizumab, 18.2 letters (95% CI, 10.1–22.9, P < 0.001) for aflibercept, and 8.5 letters gained (95% CI, 3.0–14.0, P < 0.001) for ranibizumab at 12 months, indicating a beneficial effect.

Limitations of submitted literature/studies were not adequately discussed by the applicant and data were not presented to allow for investigation of the bevacizumab effect.

2.6.5. Conclusions on clinical efficacy

Intravitreal bevacizumab seems non-inferior to the approved anti-VEGF inhibitor ranibizumab in the target indication AMD according to one well conducted, comprehensive Cochrane review. Also, superiority over sham or no treatment is supported by some data. There are some limitations inherent to the publications such as the heterogeneity of the studies in terms of selection of patients, outcome measures, etc. that represent challenges for the interpretation of the overall effect, but overall the conclusion on a beneficial effect of Avastin in AMD is acceptable. As no comprehensive literature review has been provided to support efficacy, there is remaining uncertainty whether the totality of data has been considered for the procedure.

However, in the absence of evidence in intravitreal use establishing similarity of Ipique and the bevacizumab referred to in the literature, the efficacy results cannot be extrapolated to Ipique in AMD. The need for evidence establishing similarity between medicinal products is of particular importance for biological medicinal products where minor differences in their active substances may result in significant differences in efficacy.

2.7. Clinical safety

2.7.1 Patient exposure

No clinical trial in an ophthalmological setting has been performed using PIQUE (bevacizumab). The information for safety is based solely on the presented literature references. The applicant claims that, based on comparable efficacy and safety, bevacizumab via intravitreal injection has been used increasingly over the last decade as cheaper alternative to ranibizumab (Lucentis) for the treatment of (wet) age-related macular degeneration (AMD) and diabetic macular oedema (DME).

In order to support the claim of comparable safety between bevacizumab and ranibizumab a **list of 11 publications** has been provided (Table 11 and Table 12). In the majority of the listed publications several anti-VEGF treatments (bevacizumab, ranibizumab (Lucentis), aflibercept (Eylea) and VEGF-trap (Macugen)) have been combined in order to perform a review of their effectiveness in different disease settings and different indications. Five have been provided in the initial target population of Ipique: patients with AMD or DME.

During the course of the procedure, the applicant also added treatment of macular oedema secondary to retinal vein occlusion (RVO) as intended indication. However, the data submitted in support of this indication add very limited information to the characterisation of the safety of bevacizumab in AMD.

In the final stage of the procedure, the applicant only pursued the indication for the treatment of AMD. The data initially presented for DME patients is included as supportive information since the exposure to bevacizumab of DME patients is considered informative to establish the safety profile of bevacizumab in AMD patients.

Upon repeated request the applicant performed a more comprehensive literature search, adding new publications and a respective representation of patient exposure was provided at D181 (Table 13). However, information on exact dose, treatment duration and discontinuations were not provided.

Table 11: Cochrane meta-analyses and systematic reviews of anti-VEGF efficacy and safety after intravitreal injection

Year	Authors	Condition	Numbers of Patients included	Outcome
2019	Solomon et al.	AMD	6347 patients	Effectiveness of anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) in terms of maintaining visual acuity; studies show that ranibizumab and bevacizumab improved visual acuity and were equally effective. There was no higher incidence of potentially vision-threatening complications with intravitreous injection of anti-VEGF agents compared with control interventions.
2018	Shankar et al.	Retinopathy of prematurity	383 infants	Intravitreal bevacizumab/ranibizumab reduces the risk of refractive errors during childhood but does not reduce the risk of retinal detachment or recurrence of ROP in infants with type 1 ROP.
2018	Virgili et al.	Diabetic Macular Edema	6007 patients	Anti-VEGF drugs are effective at improving vision in people with DMO. We found no signals of differences in overall safety between the three antiangiogenic drugs.
2016	Zhu et al.	Neovascularization in myopia	594 patients	There is low to moderate-certainty evidence for the efficacy of anti-VEGF agents to treat mCNV at one year and two years. Moderate-certainty evidence suggests ranibizumab and bevacizumab are equivalent in terms of efficacy. Adverse effects occurred rarely and the trials included here were underpowered to assess these.
2016	Zheng et al.	Wound healing in glaucoma surgery	175 patients/177 eyes	Evidence is currently of low quality which is insufficient to refute or support anti-VEGF subconjunctival injection for control of wound healing in glaucoma surgery. The effect on IOP control of anti-VEGF agents in glaucoma patients undergoing trabeculectomy is still uncertain.
2016	Solomon et al.	AMD	2809 patients	No important difference in effectiveness or safety between bevacizumab and ranibizumab for NVAMD treatment but a large cost difference.
2015	Smith et al.	Prevention of postoperative vitreous cavity haemorrhage	654 eyes	The use of pre- or intraoperative bevacizumab lowers the incidence of early POVCH. The reported complications from its use appear to be low.
2014	Solomon et al.	AMD	5496 patients	The results indicate the effectiveness of anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) in terms of maintaining visual acuity; ranibizumab and bevacizumab were also shown to improve visual acuity. The information available on the adverse effects of each medication do not suggest a higher incidence of potentially vision-threatening complications with intravitreal injection compared with control interventions.
2014	Braithwaite et al.	Central retinal Vein occlusion	937 patients	Repeated intravitreal injection of anti-VEGF agents including bevacuzumab in eyes with CRVO macular oedema improved visual outcomes at six months. All agents were relatively well tolerated with a low incidence of adverse effects.
2011	Smith et al.	Prevention of postoperative vitreous cavity hemorrhage	202 eyes of 198 participants	Results from one of the included studies support the use of preoperative intravitreal bevacizumab to reduce the incidence of early POVCH.

Table 12: Additional meta-analysis of systematic review of anti-VEGF safety after intravitreal injection

Year	Authors	Condition	Number of systematic reviews included	Outcome
2018	Thulliez et al.	Multiple	21	Anti-VEGF treatments do not increase the risk of systemic adverse events

Table 13: Treatment and safety monitoring in RCTs (as available from the literature)

Study Duration	Exposure	Control	Number of patients analyzed	Safety in study monitored
RCT's studying intravitreal bevacizumab versus non-anti-VEGF controls				
SACU 2009 1 year	1.0 mg beva monthly for 3 months then as needed	Verteporfine/laser plus triamcinolone	Beva n=14 Ver/triam n=14	Adverse events monitored monthly
ABC 2010 1 year	1.25 mg beva 3 times every 6 weeks. Further as needed	Pegatinib Verteporfine/laser Sham injection	Beva n=65 Pega n=38 Ver n=16 Sham n=13	Intervals at which safety assessed: 1 week; 6, 12, 18, 24, 30, 36, 42, 48 and 54 weeks)
RCT's studying intravitreal bevacizumab compared with ranibizumab				
CATT 2011 2 years with re-randomisation after 1 year	1.25 mg monthly or as needed. After 1 year monthly group randomised to monthly or as needed	0.5 mg ranibizumab monthly for 1 Year or as needed; at 1 year, re-randomisation monthly group to ranibizumab monthly or variable dosing	265 in bevacizumab monthly group, 284 in ranibizumab monthly group, 271 in bevacizumab as needed group, and 285 in ranibizumab as needed group	Incidence of ocular and systemic adverse events, assessed: weeks 4, 12, 24, 36, and 52 during first and second year
IVAN 2013 2 years	1.25 mg beva monthly or as needed	0.5 mg rani monthly or as needed	At one year n=136 in beva monthly N=138 as needed; 141 ranibi monthly and 146 in ranibi as needed At 2-year follow-up: 127 in continued bevacizumab group; 127 in discontinued bevacizumab group; 134 in continued ranibizumab group; and 137 in discontinued ranibizumab group	Frequency of adverse effects at intervals at which outcomes were assessed: monthly through 24 months
BISWASS 2011 18 months	1.25 mg beva monthly for 3 months, then as needed	0.5 mg rani monthly for 3 months, then as needed	Beva n=50 Ranibi n=54	Adverse assessed: monthly through 18 months
BRAMD 2016 1 year	1.25 mg beva monthly for 1 Year	0.5 mg ranibi monthly for 1 Year	Beva n=161 Ranibi n=166	Secondary outcome occurrence of (serious) adverse events during 12 months of the study
GEFAL 2013 1 year	1.25 mg bevacizumab; maximum of 1 injection per month	1.25 mg bevacizumab; maximum of 1 injection per month	Beva n=246 Ranibi n=239	Secondary outcomes, as defined in trial registry proportions of ocular and systemic adverse events at intervals at which outcomes were assessed: monthly through 12 months
LUCAS 2015 1 year	1.25 mg bevacizumab; treat and extend protocol	1.25 mg bevacizumab; treat and extend protocol	Beva n= 184 Rani n=187	Safety outcome: occurrence of arteriothrombotic events Intervals at which outcomes were assessed is unclear
MANTA 2013 1 year	1.25 mg bevacizumab monthly for 3 months, then as needed	1.25 mg bevacizumab monthly for 3 months, then as needed	Beva n=154 Rani n=163	Adverse events defined as outcome Assessed monthly through 12 months

Study Duration	Exposure	Control	Number of patients analyzed	Safety in study monitored
SAVE-AMD 2017 1 year	1.25 mg bevacizumab at day 1 and at week 4, then as needed	1.25 mg bevacizumab at day 1 and at week 4, then as needed	Beva n=23	Trial was designed to test effect in different stages of AMD
SCHOLLER 2014 1 year	1.25 mg bevacizumab for 3 months, at 30-day intervals, then as needed	1.25 mg bevacizumab for 3 months, at 30-day intervals, then as needed	Beva n=20 Rani n=26	Adverse events (Y/N): yes;
SABRAMANIAN 2010 1 year	0.05 mL bevacizumab monthly for 3 months, then as needed	0.05 mL bevacizumab monthly for 3 months, then as needed	Beva n=15 Rani n=7	Intervals at which outcome assessed: 1 week after injections to assess adverse events; and monthly through 12 months

2.7.2 Adverse events

Initially no overview was provided about which and how frequent adverse events have been observed during treatment. The applicant did not provide a discussion about adverse events and the expected summary documents in the dossier only include the following three statements concerning the most recent Cochrane reviews:

> In the Cochrane review of Solomons et al. (2019) concerning the effect of anti-VEGF treatment in AMD, the conclusion on safety was: "Inflammation and increased pressure in the eye were the most common unwanted effects caused by anti-VEGF agents. Investigators reported endophthalmitis (infection in the inner part of the eye, which can cause blindness) in less than 1% of anti-VEGF-treated eyes and observed no cases among those not treated with anti-VEGF agents. The occurrence of serious side effects, such as high blood pressure and internal bleeding, was low and was similar between anti-VEGF-treated groups and groups that did not receive anti-VEGFs. The number of total side effects was very small, so it is impossible to tell which drug may have caused the most harmful effects"
>
> In the Cochrane review by Virgili et al. (2018) concerning the effect of anti-VEGF in neovascularisation associated with diabetic retinal oedema the conclusion on safety was: "The previous version of this review found moderate-certainty evidence of good safety of antiangiogenic drugs versus control. This update used data at the longest available follow-up (one or two years) and found that aflibercept, ranibizumab and bevacizumab do not differ regarding systemic serious adverse events (SSAEs) (moderate- or high-certainty evidence). However, risk of bias was variable, loop inconsistency could be found and estimates were not precise enough on relative safety regarding less frequent events such as arterial thromboembolic events or death (low- or very low-certainty evidence)."
>
> The systemic side effects of intravitreal injection of anti-VEGF treatment was recently reviewed in JAMA Ophthalmology by Thulliez et al. (2018) with as conclusion:" Anti-VEGF treatments did not increase the risk of systemic adverse events when compared with control regimens; similarly, there was no increase in systematic adverse events when treatment was given on a monthly schedule vs an as-needed regimen. Compared with ranibizumab, bevacizumab did not appear to be associated with an increase in the risk of systemic adverse events in the most recent and exhaustive reviews".

In the following sections, the available data from the presented literature sources are described for the target indication AMD. Initially the applicant applied for an indication including the treatment of DME and presented respective data. Although the applicant did not pursue this indication any more, the respective data is considered informative to establish the safety profile of bevacizumab in AMD patients and is therefore included as supportive information in the respective sections. The presented literature

in other indications is not relevant for the characterisation of the safety profile of bevacizumab due to quality of safety reporting, the presented indication or redundancy of data.

In addition to the literature data, the adverse events included in the SmPC are presented. The presented SmPC is largely identical to the SmPC of Lucentis. The applicant did however not discuss why certain events have been included in the SmPC and whether the reported frequencies also apply to IPique, which has been requested repeatedly.

Initially no information about monitoring of adverse events in the included studies has been provided. At D181, the applicant provided a brief overview for the main studies, which is included in Table 13 above.

Adverse events in AMD and DME reported in the submitted literature:

Patients with AMD or DME are included in five of the presented reviews: Solomon et al (2019, 2016, 2014), Virgili et al 2018 and Thulliez 2018. The results of Solomon et al 2016 and 2014 are redundant with the data presented for Solomon et al 2019 and are therefore not presented here.

Solomon 2019: Anti-vascular endothelial growth factor for neovascular age-related macular degeneration (Review)

The authors included 16 RCTs that had enrolled a total of 6347 participants with neovascular AMD (the number of participants per trial ranged from 23 to 1208). Six trials compared anti-VEGF treatment (pegaptanib, ranibizumab, or bevacizumab) versus control, and 10 trials compared bevacizumab versus ranibizumab. In this document only the comparison between bevacizumab versus ranibizumab is presented. Details about the comparisons vs control can be found in the clinical assessment report.

Overall, ocular inflammation and increased intraocular pressure (IOP) after intravitreal injection were the most frequently reported serious ocular adverse events. Investigators reported endophthalmitis (infection in the inner part of the eye, which can cause blindness) in less than 1% of anti-VEGF-treated eyes and observed no cases among those not treated with anti-VEGF agents.

- Bevacizumab versus ranibizumab

Ten trials compared bevacizumab for non-inferiority versus ranibizumab. In addition to the primary comparison of the two agents, two studies compared monthly injections of anti-VEGF agents with an "as-needed" regimen after three initial injections of the assigned agent. Four studies used the latter treatment regimen (a 0.5 mg dose of ranibizumab and a 1.25 mg dose of bevacizumab) to compare the two anti-VEGF agents. One study each used a monthly injection schedule, and a "treat-and-extend" protocol for both drugs. In a newly included study investigators did not specify the hypothesis and treated participants with an "as-needed" regimen after three initial injections of the assigned agent. In another more recent study researchers gave intravitreous injections after the initial two injections PRN for the remainder of the one-year follow-up period.

Although all ten trials provided information related to adverse events, data reported varied by study regarding the types and specificity of adverse events.

At one year, investigators from four trials reported no *serious ocular events*. Minor adverse events reported from three of these trials included subconjunctival hemorrhage, increased IOP, transient postinjection pain, and mild ocular inflammation; investigators did not report the numbers of participants who experienced these adverse events. No case of endophthalmitis or retinal detachment was reported from the four trials. In four other trials, less than 1% of participants had endophthalmitis, retinal detachment, retinal pigment epithelial tear, traumatic cataract, or uveitis

(Table 14). Another study reported two eyes with subretinal bleeding, both treated with ranibizumab. For one study no ocular adverse events were mentioned. As a result of the small numbers of events, risk estimates for these adverse events are imprecise.

One study did not assess *systemic adverse events*. At one year, one study reported no serious systemic adverse events. Two others did report events (transient ischemic attack, thromboembolitic events) but did not specify the applied treatment. The remaining six trials reported that 18% of participants in the bevacizumab groups versus 16% in the ranibizumab groups experienced at least one serious adverse event (RR 1.15, 95% CI 0.99 to 1.34). Mortality from any cause was approximately 2% in the bevacizumab and ranibizumab groups during the first year of follow-up (RR 1.10, 95% CI 0.66 to 1.83). Less than 1% of participants experienced myocardial infarction, stroke or cerebral infarction, transient ischemic attack, or a venous thrombotic event (Table 14). Rates were comparable between bevacizumab and ranibizumab groups with respect to cardiac disorders (RR 0.84, 95% CI 0.57 to 1.23), neoplasms (RR 0.99, 95% CI 0.61 to 1.61), and nervous system disorders (RR 1.14, 95% CI 0.68 to 1.93). Investigators reported more gastrointestinal disorders (RR 1.76, 95% CI 0.99 to 3.14), infections (RR 1.42, 95% CI 0.93 to 2.17), injuries and procedural complications (RR 1.27, 95% CI 0.78 to 2.06), and surgical or medical procedures (RR 1.41, 95% CI 0.88 to 2.27) in the bevacizumab groups than in the ranibizumab groups at one year.

Table 14: Adverse Events

Serious ocular adverse event	**Bevacizumab**		**Ranibizumab**		**RR [95% CI]**
	Number with event	**Total parti-cipants**	**Number With event**	**Total parti-cipants**	**Bevacizumab vs ranibizumab**
Endophthalmitis and pseudo-endophthalmitis	5 (< 1%)	1052	3 (< 1%)	1059	1.68 [0.40 to 7.00]
Retinal detachment	3 (< 1%)	832]	0	838	7.05 [0.36 to 136.28
Retinal pigment epithelial tear	4 (< 1%)	1102	3 (< 1%)	1134	1.37 [0.31 to 6.12]
Traumatic cataract	1 (< 1%)	1128	2 (< 1%)	1152	0.51 [0.05 to 5.62]
Severe uveitis	4 (< 1%)	882	1 (< 1%)	913	4.14 [0.46 to 36.97]
Non-ocular adverse event	**Bevacizumab**		**Ranibizumab**		**RR [95% CI]**
	Number with event	**Total parti-cipants**	**Number With event**	**Total parti-cipants**	**Bevacizumab vs ranibizumab**
At least 1 serious adverse event	298 (18%)	1663	265 (16%)	1702	1.15 [0.99 to 1.34]
Death	30 (2%)	1663	28 (2%)	1702	1.10 [0.66 to 1.83]
Myocardial infarction	8 (< 1%)	1502	16 (1%)	1536	0.51 [0.22 to 1.19]
Stroke or cerebral infarction	7 (< 1%)	1502	11 (< 1%)	1536	0.65 [0.25 to 1.67]
Transient ischemic attack	6 (< 1%)	1348	4 (< 1%)	1373	1.53 [0.43 to 5.40]
Venous thrombotic event	8 (< 1%)	1348	4 (< 1%)	1373	2.04 [0.61 to 6.75]
Cardiac disorders	46 (3%)	1663	56 (3%)	1702	0.84 [0.57 to 1.23]
Gastrointestinal disorders	31 (2%)	1663	18 (1%)	1702	1.76 [0.99 to 3.14]
Infections	50 (3%)	1663	36 (2%)	1702	1.42 [0.93 to 2.17]
Injury and procedural complications	36 (2%)	1663	29 (2%)	1702	1.27 [0.78 to 2.06]
Neoplasms (benign, malignant, unspecified)	32 (2%)	1663	33 (2%)	1702	0.99 [0.61 to 1.61]
Nervous system disorders	29 (2%)	1663	26 (2%)	1702	1.14 [0.68 to 1.93]
Surgical or medical procedure	40 (2%)	1663	29 (2%)	1702	1.41 [0.88 to 2.27]

At two years, data for ocular and systemic adverse events were available for two studies. Less than 1% of participants were reported to have had endophthalmitis, retinal detachment, retinal pigment epithelial tear, traumatic cataract, or uveitis (Table 15). As a result of the small numbers of events, risk estimates for these adverse events are imprecise. In the bevacizumab groups, 36% of participants

had at least one serious adverse event compared with 30% in the ranibizumab groups (RR 1.20, 95% CI 1.05 to 1.37). Mortality from any cause was 6% and 5% in the bevacizumab and ranibizumab groups, respectively (RR 1.12, 95% CI 0.76 to 1.65).

In all, 2% or fewer participants experienced myocardial infarction, stroke or cerebral infarction, a venous thrombotic event, or a transient ischemic attack (Table 15). As with one-year outcomes, investigators reported more gastrointestinal disorders (RR 2.74, 95% CI 1.49 to 5.02), infections (RR 1.37, 95% CI 0.96 to 1.95), and injuries and procedural complications (RR 1.33, 95% CI 0.86 to 2.05) in the bevacizumab groups than in the ranibizumab groups, and reported more cardiac disorders in the bevacizumab groups than in the ranibizumab groups at two years (RR 1.25, 95% CI 0.92 to 1.71). Rates were comparable between bevacizumab and ranibizumab groups with respect to neoplasms (RR 0.98, 95% CI 0.63 to 1.53), nervous system disorders (RR 1.06, 95% CI 0.70 to 1.60), and surgical or medical procedures (RR 0.91, 95% CI 0.44 to 1.84). The certainty of evidence for ocular and systemic adverse events at two years as moderate.

Table 15: Adverse Events

Ocular adverse event (CATT trial)[a]	**Bevacizumab n = 586**	**Ranibizumab n = 599**	**RR [95% CI] Bevacizumab vs ranibizumab**
Endophthalmitis	7 (1%)	4 (< 1%)	1.79 [0.53 to 6.08]
Ocular adverse event (IVAN trial)[b]	**Bevacizumab n = 296**	**Ranibizumab n = 314**	**RR [95% CI] Bevacizumab vs ranibizumab**
Traumatic cataract	1 (< 1%)	1 (< 1%)	1.06 [0.07 to 16.88]
Severe uveitis	1 (< 1%)	0	3.18 [0.13 to 77.80]
Retinal detachment	0	1 (< 1%)	0.35 [0.01 to 8.64]
Retinal pigment epithelial tear	1 (< 1%)	3 (< 1%)	0.35 [0.04 to 3.38]
Non-ocular adverse event[c]	**Bevacizumab n = 882**	**Ranibizumab n = 913**	**RR [95% CI] Bevacizumab vs ranibizumab**
At least 1 serious adverse event	314 (36%)	271 (30%)	1.20 [1.05 to 1.37]
Death	51 (6%)	47 (5%)	1.12 [0.76 to 1.65]
Myocardial infarction	11 (1%)	13 (1%)	0.88 [0.39 to 1.94]
Stroke or cerebral infarction	11 (1%)	14 (2%)	0.81 [0.37 to 1.78]
Venous thrombotic event	14 (2%)	6 (< 1%)	2.42 [0.93 to 6.26]
Transient ischemic attack	1 (< 1%)	1 (< 1%)	1.04 [0.06 to 16.52]
Cardiac disorders	81 (9%)	67 (7%)	1.25 [0.92 to 1.71]
Gastrointestinal disorders	37 (4%)	14 (2%)	2.74 [1.49 to 5.02]
Infections	66 (7%)	50 (5%)	1.37 [0.96 to 1.95]

Injury and procedural complications	45 (5%)	35 (4%)	1.33 [0.86 to 2.05]
Neoplasms (benign, malignant, unspecified)	36 (4%)	38 (4%)	0.98 [0.63 to 1.53]
Nervous system disorders	44 (5%)	43 (5%)	1.06 [0.70 to 1.60]
Surgical or medical procedure	14 (5%)	16 (5%)	0.91 [0.44 to 1.84]

RR: risk ratio.
[a]Adverse events for endophthalmitis not reported in IVAN 2013; data for CATT 2011 only.
[b]Adverse events for traumatic cataract, uveitis, retinal detachment, retinal pigment epithelial tear, transient ischemic attack, and surgical or medical procedure not reported in CATT 2011; data for IVAN 2013 study only.
[c]Adverse events experienced by 1185 participants in CATT 2011 and by 610 participants in IVAN 2013.

Overall, the authors concluded that the safety profile of anti-VEGFs, as reported in the included studies, was acceptable. Based on the performed review the authors conclude that ranibizumab and bevacizumab have comparable safety in treated eyes.

Table 16: Summary of findings 2: Summary of findings: bevacizumab versus ranibizumab

Bevacizumab versus ranibizumab for neovascular age-related macular degeneration

Participant or population: people with neovascular age-related macular degeneration

Settings: clinical centers

Intervention: intravitreal injections of bevacizumab

Comparison: intravitreal injections of ranibizumab

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk Ranibizumab	Corresponding risk Bevacizumab				
Serious systemic adverse events at 1 year[b]	**156 per 1000** with at least 1 serious systemic adverse event	**179 per 1000** (154 to 209)	**RR 1.15** (0.99 to 1.34)	3365 (6)	⊕⊕⊕⊖ **Moderate[a]**	
Serious ocular adverse events at 1 year	**< 5 per 1000**	**< 5 per 1000**	Range of **RR 0.51** (0.05 to 5.62) to **7.05** (0.36 to 136.28)	Range 1670 to 2280 (2 to 3)	⊕⊕⊕⊖ **Moderate[a]**	Studies reported different ocular adverse events. One study reported only that there was no difference between treatment arms

*The basis for the **assumed risk** is estimated by the proportion with the event in the ranibizumab group. The **corresponding risk** (and its 95% CI) is based on assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; MD: mean difference; RR: risk ratio.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence.
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Quality of life and adverse event outcomes downgraded to moderate quality as not all eligible trials reported these outcomes, and numbers of some adverse events were small (< 1%).
[b]A Cochrane review on systemic safety of bevacizumab versus ranibizumab includes more complete data for this finding (Moja 2014). Please refer to Moja 2014 for the most complete information on systemic safety for bevacizumab versus ranibizumab.

Of note: One publication, also included in the review by Solomon et al 2019, reported the following:

Rates of death, myocardial infarction, and stroke were similar for patients receiving either bevacizumab or ranibizumab (P>0.20). The proportion of patients with serious systemic adverse

events (primarily hospitalisations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern.

Thulliez et al 2018: Overview of Systematic Reviews and Meta-analyses on Systemic Adverse Events Associated With Intravitreal Anti–Vascular Endothelial Growth Factor Medication Use

This overview evaluates systemic adverse events associated with intravitreal anti-VEGF treatments in patients with neovascular age-related macular degeneration (AMD), diabetic macular oedema (DME), or retinal vein occlusion. The authors included 21 systematic reviews published between January 1, 2011, and June 30, 2016.

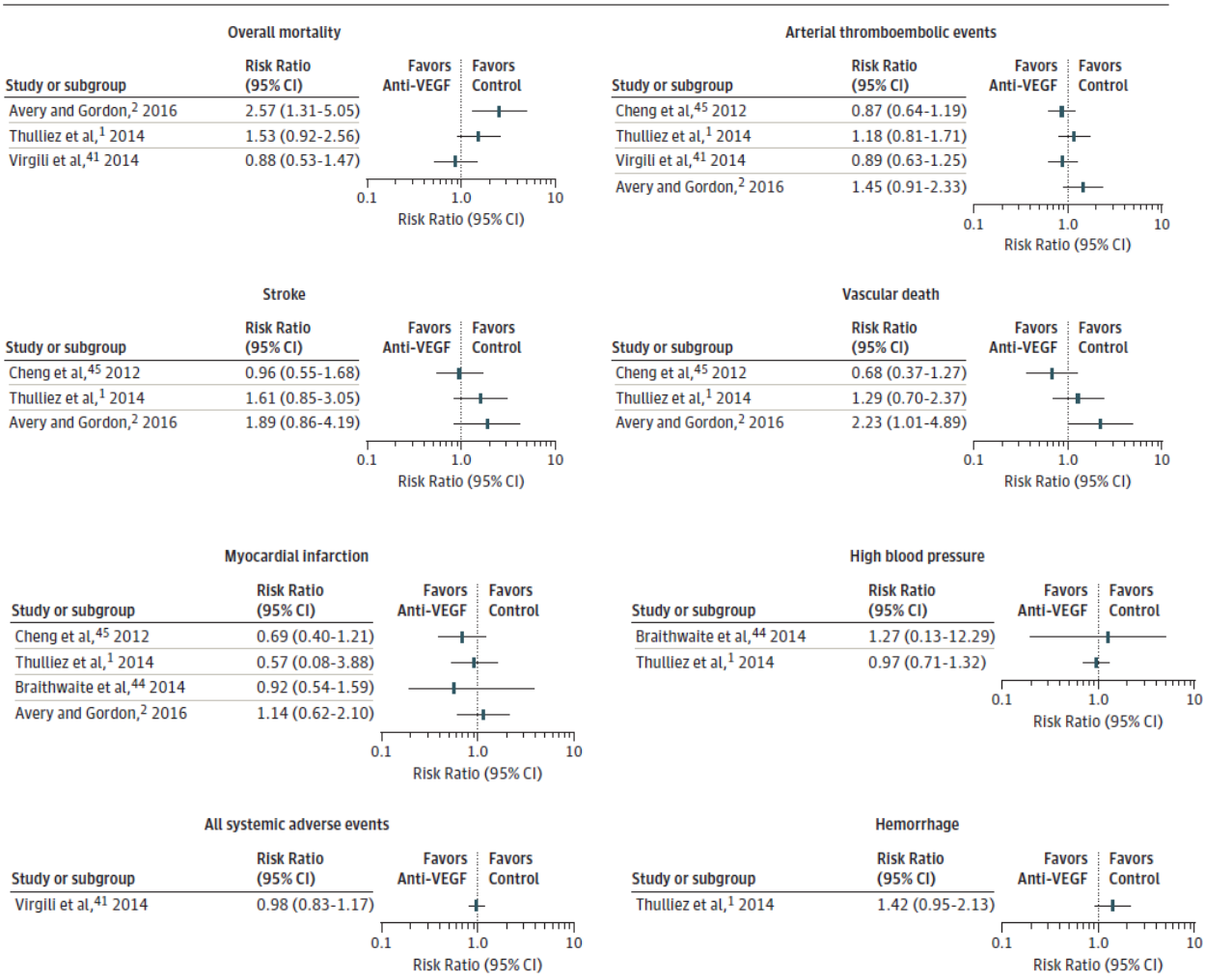
Ten reviews studied patients with AMD. They included 2 to 12 RCTs each, and overlapping comparisons were observed for 7 reviews. Six reviews studied patients with DME, including 4 to 18 RCTs each, and overlapping comparisons for 4 reviews. Two reviews focussed on Retinal Vein Occlusion and another three reviews included patients with all 3 diseases.

Several meta-analyses compared the **systemic safety of pooled anti-VEGF treatments with control drugs** for various diseases. With the exception of one review (performed by Avery and Gordon in DME patients 2016; full text was not provided by the applicant), which reported an increased risk of death and vascular death in patients with DME, no other systemic AEs were increased (Figure 13). The meta-analysis by Avery and Gordon specifically aimed to assess systemic AEs with the highest levels of exposure by including only trials that evaluated 2 years of monthly anti-VEGF treatments (aflibercept and ranibizumab compared with control regimens). However, the number of events was very low, and a sensitivity analysis with 1 vascular death moved into the sham/laser (control) study arm was sufficient to change the results from statistically significant to non-significant.

Thulliez et al further stated that vascular deaths were not adjudicated in half of the included studies, which could also introduce bias in risk estimates. In the absence of increased risk of myocardial infarction and hemorrhagic events, the most probable explanation for the increase in vascular deaths in patients with DME may be a higher risk of ischemic stroke. Yet evidence from trials in patients with cancer showed that antiangiogenic treatments were more likely to increase the risk of myocardial infarction than the risk of stroke and that no clear relationship with the dose of bevacizumab existed. This risk could also be associated with arterial hypertension, yet no increased risk of anti–VEGF vs control regimens was apparent in the included meta-analyses. Therefore, the possible increase of stroke risk and vascular death is not fully understood. Thulliez et al further mentioned that confounding factors may explain part of the risk, such as age and/or other cardiovascular risk factors, among high-risk populations such as patients with diabetes. Another hypothesis could be that interactions exist between anti-VEGF treatments and antidiabetic treatments or between anti-VEGF treatment and the diseases itself, but more research is needed. Finally, enrollment criteria in many of the trials tended to bias the results toward a lower incidence of those adverse events because patients with cardiovascular diseases were often excluded. One may also note that the risk of these events among patients with cancer who had high exposure to systemic bevacizumab is relatively low (<4%). Therefore, in the hypothesis of an exposure-risk relationship, intra ocular anti-VEGF trials were most probably underpowered to accurately detect differences in risk among various anti-VEGF medications, even if they exist. In addition, underreporting of systemic AEs in trials, either during follow-up or after the last intravitreal injection, could have led to the underestimation of systemic AE risks in systematic reviews and meta-analyses.

Therefore, post marketing studies, ideally prospective and on large databases, may provide useful information regarding safety issues.

Figure 13: Anti-VEGF medications compared with control for systematic adverse events



This figure includes studies that compared anti-vascular endothelial growth factors (anti-VEGF) medications to controls (including any drug other than an anti-VEGF medication, laser procedures, sham procedures, and no treatment) and measured systematic adverse events. Anti-VEGF medications used in each review are as per the Table and Figure 2.

Bevacizumab was compared with ranibizumab only in patients with AMD. The included reviews largely agree that VEGF treatment were not associated with an increased risk of systemic AEs, particularly cardiovascular adverse events. However, compared with ranibizumab, bevacizumab was associated with an increased risk of venous thrombotic events in 1 review (relative risk [RR], 3.45; 95% CI, 1.25-9.54) with 4 other reviews finding lower point-estimates (range of RR findings, 2.32 to 2.78) but with wide and non-significant confidence intervals (Figure 14). However, because of a very low number of events, confidence intervals were large for venous thrombotic events: from 0.96 to 5.60 in the most recent meta-analysis. This reduced the authors' confidence in these results.

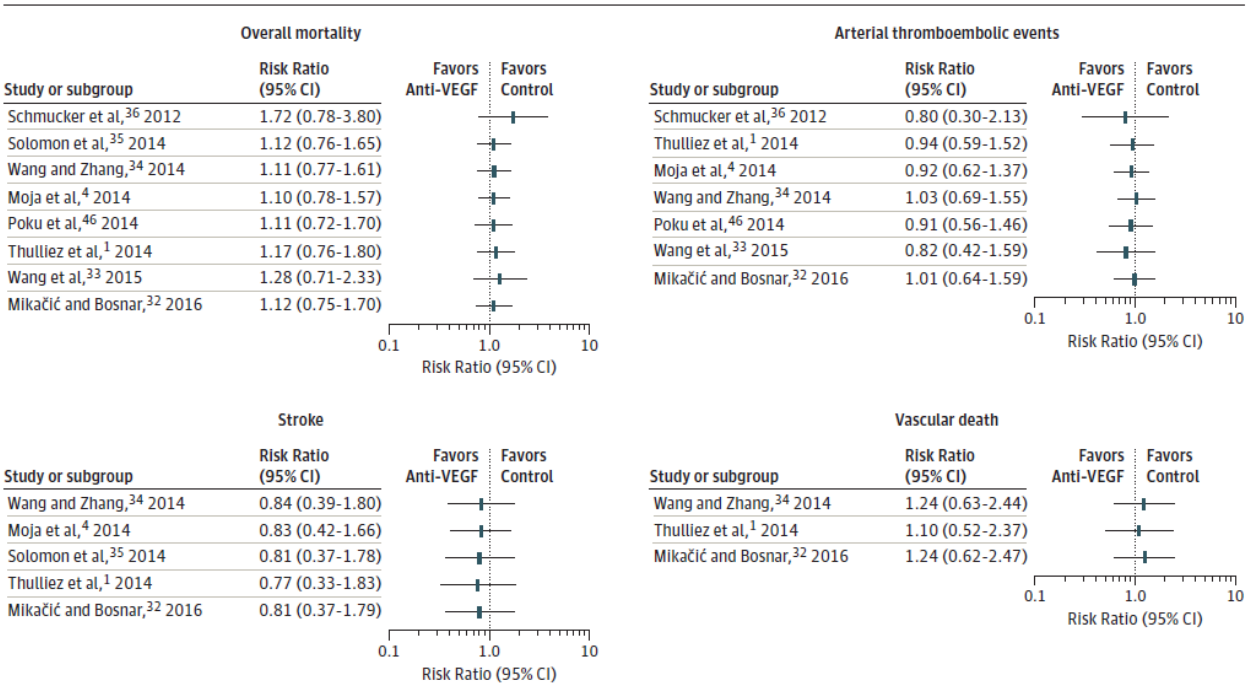
Bevacizumab also increased the relative risk of systemic AEs by 20% to 35% in 3 reviews (Figure 14) but not in the most recent and most exhaustive Cochrane Review about safety of anti-VEGF products, which included additional unpublished data (RR, 1.08; 95% CI, 0.90-1.31) (Moja 2014). This review also examined the influence of unpublished evidence on systemic AEs and showed that the inclusion of

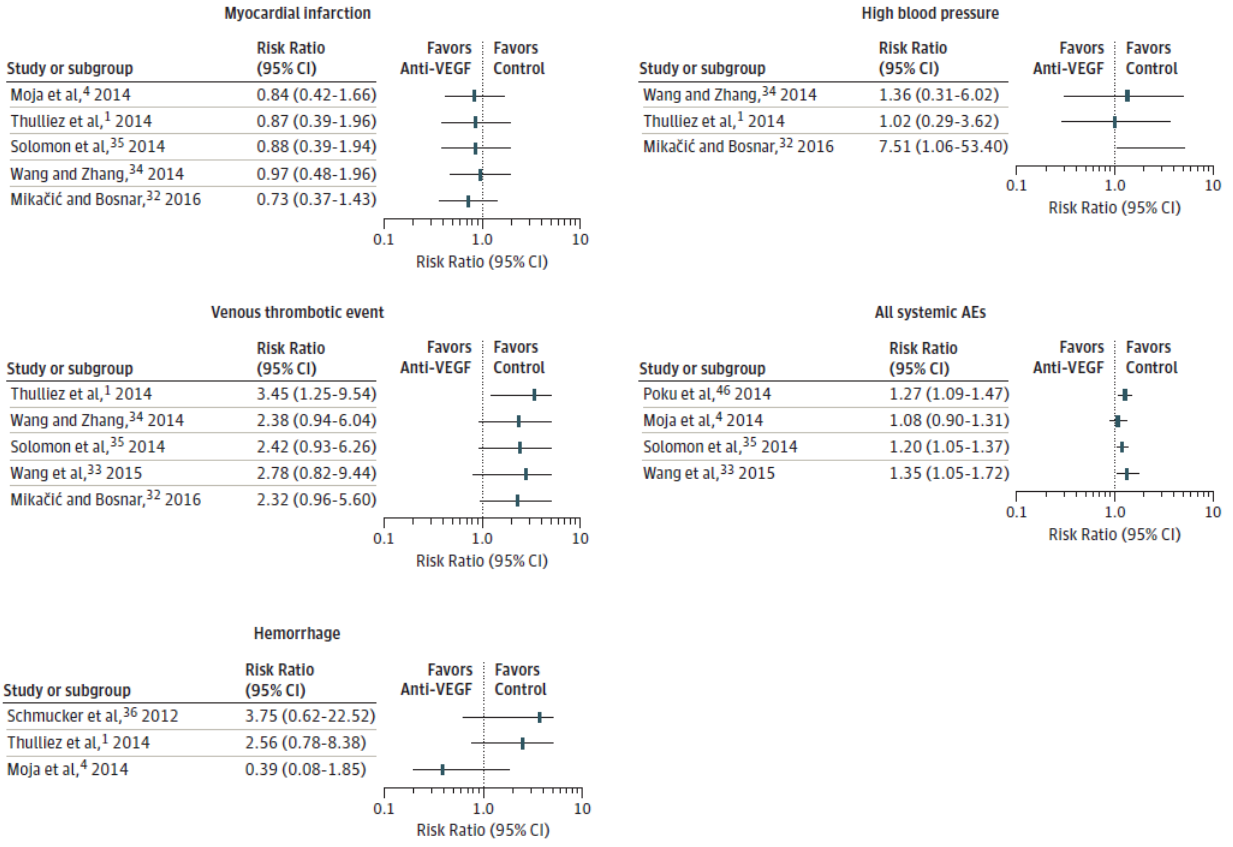
unpublished evidence reduced the risk of systemic AEs in patients treated with bevacizumab vs those treated with ranibizumab, eliminating the statistical significance that had been observed in an analysis that excluded the unpublished evidence. No such differences in systemic risks were reported when comparing aflibercept with ranibizumab or when comparing monthly regimens with as-needed regimens.

Results for high blood pressure and non-ocular haemorrhage were heterogeneous. The authors further observed that, compared with control treatments, ranibizumab may be associated with an increase in the risk of non-ocular hemorrhage in patients with age-related macular degeneration. The results for haemorrhage are overall comparable between ranibizumab and bevacizumab this finding might also be applicable to bevacizumab

Bevacizumab increased the risk of gastrointestinal disorders in 2 out of 3 reviews, but did not increase other risks, such as transient ischemic attack, infections, cardiac disorders, nervous system disorders, or neoplasms.

Figure 14: Bevacizumab compared with ranibizumab for the systematic adverse events in patients with age-related macular degeneration





The figure includes studies that compared bevacizumab with ranibizumab and measured systematic adverse events. Anti-vascular endothelial growth factors (anti-VEGF) medications used in each review are as per the Table and Figure 2.

Limitations identified by the authors:

One potential limitation of our review is that we only included reviews that reported 95% CIs for SAEs. This was the most common factor accounting for ineligibility, and it therefore strongly contributed to the volume of evidence we were subsequently able to evaluate. Another limitation was the fact that we did not re-extract data from original research. However, this was outside the scope of our review, which aimed to describe available evidence from already published systematic reviews. A deeper analysis of all included trials would have allowed us to present conclusions by considering prediction intervals. These reflect the variation of treatment effect over various settings, even if some limitations have been described. In addition, we could not analyse the risks related to the duration of various treatments because this was not reported by included meta-analyses. Finally, we could not analyze if adverse events were related to various drug doses used in clinical trials.

None of the included meta-analyses used adjusted statistical thresholds to control for spurious findings. Fifteen of the 21 reviews (71%) reported sensitivity analyses, but only 13 reviews (62%) prespecified these analyses in their methods, and only 10 (48%) specifically used sensitivity analyses to test the robustness of their results. Of these 10, 4 reported significant changes in their results.

We found that systemic AEs of intravitreal anti-VEGF were heterogeneously reported: 10 meta-analyses in patients with AMD reported 19 SAEs, while 6 meta-analyses in patients with DME only reported 7 SAEs. One potential explanation is that the frequent off-label use of bevacizumab resulting from its low costs may have led to an inflation of safety analyses, especially in patients with AMD.

Further, we observed a substantial number of overlapping meta-analyses in patients with AMD and patients with DME.

Virgili et al 2018: Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis (Review)

A total of twenty-four studies included 6007 participants with DMO and moderate vision loss. Data were collected from three studies on aflibercept (975 eyes), eight studies on bevacizumab (515 eyes), and 14 studies on ranibizumab (1518 eyes).

The authors focussed on three safety outcomes: all severe systemic adverse events (SSAEs), all-cause death and arterial thromboembolic events.

The previous version of this review found moderate-certainty evidence of good safety of antiangiogenic drugs versus control. This update used data at the longest available follow-up (one or two years) and found that aflibercept, ranibizumab and bevacizumab do not differ regarding systemic serious adverse events (SSAEs) (moderate- or high-certainty evidence). However, risk of bias was variable, loop inconsistency could be found and estimates were not precise enough on relative safety regarding less frequent events such as arterial thromboembolic events or death (low- or very low-certainty evidence).

In the recent review, the authors found no signals of differences in overall safety between the three antiangiogenic drugs that are currently available to treat DMO, but the estimates are imprecise for cardiovascular events and death.

Safety at the longest available follow-up

A network meta-analysis confirms that aflibercept, bevacizumab and ranibizumab do not increase the risk of all SSAEs compared to laser photocoagulation or sham at one year. The authors considered this evidence of high-certainty. Of notice, SSAEs are a generic indicator of harm, mostly including hospitalisation or death for any cause and unrelated to antiangiogenic effect.

Regarding 'Antiplatelet Trialists Collaboration arterial thromboembolic events' and all-cause death, no statistically significant difference was found between any anti-VEGF drug and control, but the certainty of the evidence was generally low due to imprecision (large 95% CIs).

Table 17: Summary of findings 3: Ranibizumab versus bevacizumab for diabetic macular oedema

Ranibizumab versus bevacizumab for diabetic macular oedema					
Patient or population: people with diabetic macular oedema **Settings:** ophthalmology clinics **Interventions:** bevacizumab, ranibizumab					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI), mixed evidence****	**Certainty of the evidence (GRADE)**	**Reason for downgrading certainty of evidence**
	Assumed risk	**Corresponding risk**			
	Bevacizumab	**Ranibizumab**			

All serious systemic adverse events at 1 to 2 years	**240 per 1000**	**250 per 1000** (202 to 307)	**RR 1.04** (0.84 to 1.28)	⊕⊕⊕ moderate	Unclear risk of bias (−1)
Arterial thromboembolic events at 1 to 2 years	**60 per 1000**	**70 per 1000** (26 to 189)	**RR 1.17** (0.43 to 3.13)	⊕ very low	Unclear risk of bias (−1) Imprecise estimate (−2)
Death at 1 to 2 years	**40 per 1000**	**29 per 1000** (9 to 95)	**RR 0.73** (0.22 to 2.37)	⊕ very low	High risk of bias (−2) Imprecise estimate (−2)

The **assumed risk** in the bevacizumab group was estimated as the row sum of the events divided by the row sum of the participants (eyes) for dichotomous variables, and as the (unweighted) median change of visual acuity or central retina thickness.

The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

** The risk ratio was estimated from mixed (direct and indirect) comparisons.
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High-certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate-certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-certainty: we are very uncertain about the estimate.

Figure 15: All direct and mixed comparisons: serious systemic adverse events at the longest available follow-up (1 or 2 years)

Figure 9. All direct and mixed comparisons: serious systemic adverse events at the longest available follow-up (1 or 2 years)

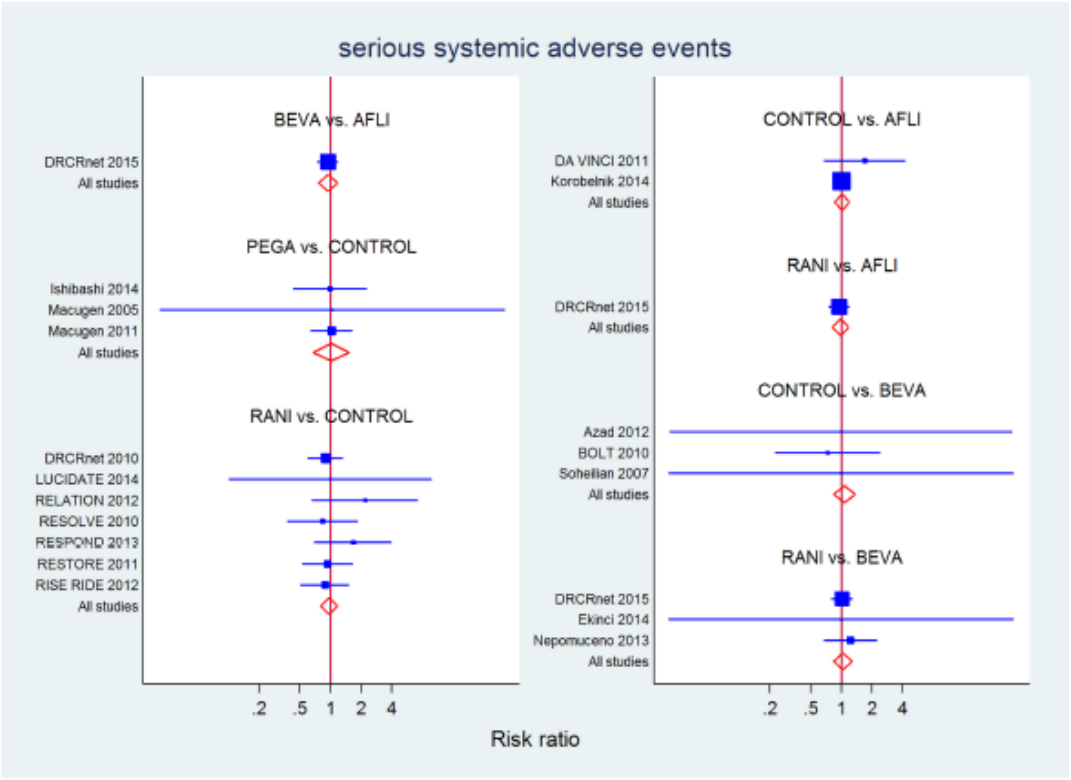


Figure 16: All direct and mixed comparisons: arterlal thromboembolic events at the longest available follow-up (1 or 2 years)

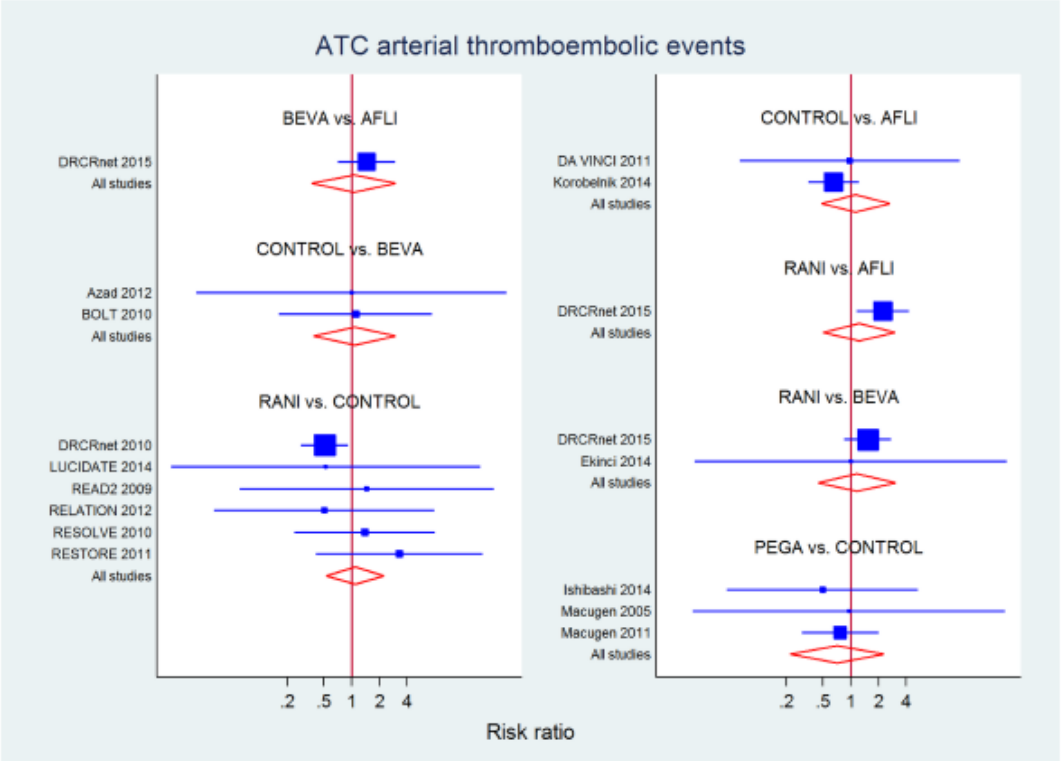
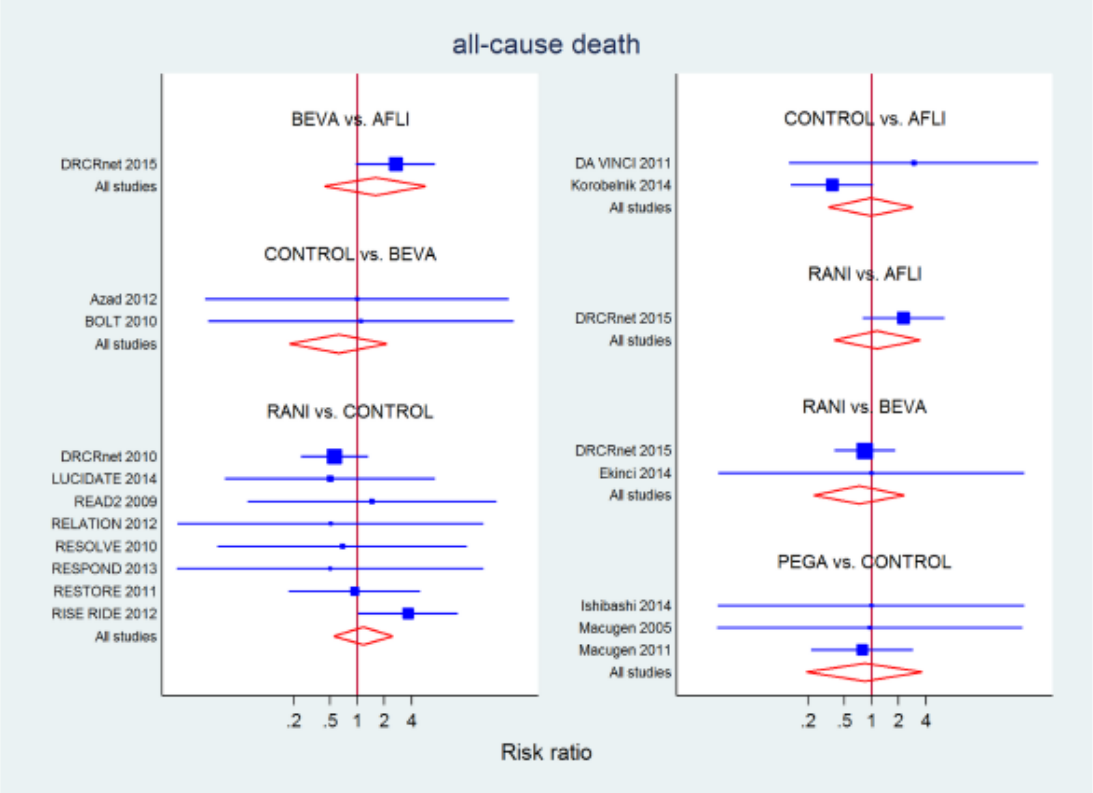


Figure 17: All direct and mixed comparisons: all-cause death at the longest available follow-up (1 or 2 years)



Two-year data were available and reported in only four RCTs in this review. Though no analysis suggested a difference among drugs for any safety outcome, only estimates for SSAEs (18 studies, 4229 eyes) reached sufficient precision to exclude very large differences among drugs. Overall, no difference was detected in mixed evidence estimates for any drug compared to laser or sham. Moreover, RR 95% CI width excluded differences of 20% to 30% or more between aflibercept, bevacizumab and ranibizumab, while estimates for pegaptanib were less precise. No overall (P = 0.86) or loop-specific inconsistency was detected.

Fifteen studies (3718 eyes) contributed to this analysis on 'Antiplatelet Trialists Collaboration arterial thromboembolic events'. No difference was detected in mixed evidence estimates for any drug compared to laser or sham or between drugs, but estimates were very imprecise. No overall inconsistency was detected (P = 0.19), but direct evidence from DRCRnet 2015 showed increased risk for ranibizumab compared to aflibercept (RR 2.26, 95% CI 1.15 to 4.23) which was larger and inconsistent with indirect evidence (P = 0.002), resulting in mixed evidence showing no difference (RR 1.25, 95% CI 0.50 to 3.05).

Seventeen studies (4455 eyes) contributed to the analysis of 'all cause mortality'. No difference was detected for direct, indirect and mixed evidence estimates for any drug compared to laser or sham or between drugs, but estimates were imprecise.

Mean risk of bias was unclear for bevacizumab versus ranibizumab for SSAEs. Regarding ATC arterial thromboembolic events and all-cause death, risk of bias was unclear or high for bevacizumab versus ranibizumab.

Adverse events included in the SmPC

At D181, the applicant submitted an updated version of the SmPC. No discussion has been provided. The following AEs are listed in section 4.8. of the SmPC:

Summary of the safety profile

The majority of adverse reactions reported following administration of bevacizumab are related to the intravitreal injection procedure.

The most frequently reported ocular adverse reactions following injection of bevacizumab are expected to be related to the intravitreal injection and may include: eye pain, ocular hyperaemia, increased intraocular pressure, vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, increased lacrimation, blepharitis, dry eye and eye pruritus.

Tabulated list of adverse reactions

From observational clinical studies, the following adverse reactions may be related to the intravitreal use of bevacizumab.

The adverse reactions are listed by system organ class and frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and infestations

Very common: Nasopharyngitis

Unknown: Endophthalmitis

Blood and lymphatic system disorders

Common: Anaemia

Immune system disorders

Common: Hypersensitivity

Psychiatric disorders

Common: Anxiety

Nervous system disorders

Very common: Headache

Eye disorders

Very common: Vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperaemia, eye pruritus.

Common: Retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of the retinal pigment epithelium, retinal pigment epithelium tear, visual acuity reduced, vitreous haemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, cataract, cataract subcapsular, posterior capsule opacification, punctuate keratitis,

corneal abrasion, anterior chamber flare, vision blurred, injection site haemorrhage, eye haemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eyelid oedema, eyelid pain, conjunctival hyperaemia.

Uncommon: Blindness, endophthalmitis, hypopyon, hyphaema, keratopathy, iris adhesion, corneal deposits, corneal oedema, corneal striae, injection site pain, injection site irritation, abnormal sensation in eye, eyelid irritation.

Respiratory, thoracic and mediastinal disorders

Common: Cough

Gastrointestinal disorders

Common: Nausea

Skin and subcutaneous tissue disorders

Common: Allergic reactions (rash, urticaria, pruritus, erythema)

Musculoskeletal and connective tissue disorders

Very common: Arthralgia

Investigations

Very common: Intraocular pressure increased

In addition, several ocular adverse events are included in section 4.4. of the SmPC:

Intravitreal injection-related reactions
Intravitreous injections have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see section 4.8). Proper aseptic injection techniques must always be used when administering Ipique. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above-mentioned events without delay.

Intraocular pressure increases
In adults transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of bevacizumab. Sustained IOP increases have also been identified (see section 4.8). Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately.

Patients should be informed of the symptoms of these potential adverse reactions and instructed to inform their physician if they develop signs such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in their vision, or increased sensitivity to light (see section 4.8).

Retinal pigment epithelial tear
Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD and potentially also other forms of CNV, include a large and/or high pigment epithelial retinal detachment. When initiating bevacizumab therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.

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

Immunogenicity
As this is a therapeutic protein, there is a potential for immunogenicity with Ipique (see section 4.8). Patients should be instructed to report any signs or symptoms of intraocular inflammation, e.g. pain, photophobia, or redness, which may be a clinical sign attributable to hypersensitivity.

Systemic effects
There are no data indicating a systemic effect of bevacizumab after intravitreal injection.

2.7.2.1 Serious adverse events, deaths, other significant events

The applicant presented only literature references for the assessment of the safety profile of Ipique. Serious adverse events and deaths are therefore discussed as part of the respective publications in the previous section but a short overview is presented here:

Solomon et al 2019: AMD patients:

Overall the rate of serious adverse events is comparable between ranibizumab (1 year: 16%; 2 years: 30%) and bevacizumab (1 year 18%; 2 years: 36%).

The incidence rate of death is comparable between both treatments at one year (2% each) and two years (bevacizumab 6%, ranibizumab 5%).

Thulliez et al 2018: AMD and DME patients

Only one review of patients with DME reported an increased risk of death and vascular death in the comparison of pooled anti-VEGF treatments (aflibercept and ranibizumab) with control treatments. The respective publication aimed to assess systemic AEs with the highest levels of exposure. However, the number of events was very low (exact numbers not provided), and a sensitivity analysis with 1 vascular death moved into the sham/laser (control) study arm was sufficient to change the results from statistically significant to non-significant.

Thulliez et al stated that vascular deaths were not adjudicated in half of the included studies.

The reviews that compared bevacizumab with ranibizumab in AMD patients (no comparison in DME patients presented) largely agree that VEGF treatment were not associated with an increased risk of systemic AEs, particularly cardiovascular adverse events. However, compared with ranibizumab, bevacizumab was associated with an increased risk of venous thrombotic events in 1 review (relative risk [RR], 3.45; 95% CI, 1.25-9.54) with 4 other reviews finding lower point-estimates (range of RR findings, 2.32 to 2.78) but with wide and non-significant confidence intervals.

Virgili et al 2018: DME patients

The authors reported serious systemic adverse events, all-cause death and arterial thromboembolic events and found no significant differences between bevacizumab and ranibizumab regarding these aspects. The authors also stated that the estimates are imprecise and the risk of bias was unclear.

2.7.3 Laboratory findings

No specific information or discussion was provided.

2.7.4 Safety in special populations

Hepatic impaired patients

No specific information or discussion was provided in the dossier. The applicant provided the following information in section 4.2. of the SmPC:

> *Hepatic impairment*
> No special considerations are needed in this population.

Renal impaired patients

No specific information or discussion was provided in the dossier. The applicant provided the following information in in section 4.2. of the SmPC:

> *Renal impairment*
> Dose adjustment is not needed in patients with renal impairment (see section 5.2).

Paediatric population

No specific information or discussion was provided in the dossier. The applicant provided the following information in section 4.2. of the SmPC:

> *Paediatric population*
> The safety and efficacy of Ipique in children and adolescents below 18 years of age have not been established.

Elderly population

No specific information or discussion was provided in the dossier. The applicant provided the following information in the SmPC:

> *Elderly*
> No dose adjustment is required in the elderly.

It is unclear whether differences between age groups exist.

2.7.5 Immunological events

No specific information or discussion was provided in the dossier. The applicant provided the following information in section 4.4. of the initial SmPC:

> *Immunogenicity*
>
> There is a potential for immunogenicity with Ipique. An increased risk for developing hypersensitivity cannot be excluded. Patients should also be instructed to report if an intraocular inflammation increases in severity, which may be a clinical sign attributable to intraocular antibody formation.

This representation was considered inadequate. Upon request, the applicant provided a risk evaluation, and proposed risk mitigation activities in order to address the immunogenicity concern. Moreover, information on Avastin, Eylea and Lucentis, has been included to support their approach. The applicant concluded that bevacizumab has a low risk of immunogenicity in the intended indication.

Bevacizumab has been shown to be immunogenic when used systemically for the treatment of cancers. Of note, the excipients of Ipique have not been associated with modulating immunogenicity or activation of the innate immune system.

The applicant provided the assessment of IVT immunogenicity of other intravitreal medicinal products in non-clinical and/or clinical studies:

- Aflibercept (Eylea) for intravitreal injection. Immunogenicity non-clinical data was provided (Monkeys) and showed immunogenicity response
- Ranibizumab (Lucentis) for intravitreal injection: Immunoreactivity was detected in a clinical study, those patients with antibodies against ranibizumab were followed. A decrease in visual acuity was observed during the second year of treatment but no clear correlation was found.
- Bevacizumab for intravenous injection. About 2% of patients treated systemically with high doses of bevacizumab intravenously produce antibodies. Patients treated with intravitreal bevacizumab receive 1000 times less on a yearly basis than cancer patients. Cancer patients are however immune suppressed by the disease and the concomitant treatment with anti-cancer drugs.

The applicant has provided a summary of the events related to immune reactivity which have been reported with intravitreal bevacizumab in the literature references.

- Tachyphylaxis has only been reported in case studies or retrospective studies of relatively small groups of patients. There is no consensus in the literature whether tachyphylaxis in the form of loss of efficacy occurs and how frequent it is.
- The occurrence of sterile endophtalmitis as a possible marker of immunogenicity of intravitreal has been better documented. The incidence seems to be <1%.

At D181, the following wording for section 4.4. of the SmPC was proposed:

> Immunogenicity
>
> As this is a therapeutic protein, there is a potential for immunogenicity with Ipique (see section 4.8). Patients should be instructed to report any signs or symptoms of intraocular inflammation, e.g. pain, photophobia, or redness, which may be a clinical sign attributable to hypersensitivity.

2.7.6 Safety related to drug-drug interactions and other interactions

No specific information or discussion was provided in the dossier. The applicant provided the following information in the SmPC:

> **Interaction with other medicinal products and other forms of interaction**
>
> No formal interaction studies have been performed.

2.7.7 Discontinuation due to adverse events

No specific information or discussion of discontinuations was provided by the applicant in the initial dossier. Upon request the applicant provided discontinuation rates for four studies not included in the initially presented reviews.

Table 18: Discontinuation rates

Study	Number of patients/eyes	Discontinuation rate	Reasons for discontinuation
Westborg et al. 2018	932 AMD patients	50.9% at one year	Low VA at baseline Serious comorbidities Treatment at university hospital
Gillies et al 2015	1043 patients	53% at 5 years	20% doctor's decision 20% patient's decision 20% discomfort/referral to other physician 20% death or serious comorbidity
Lad et al. 2014	459.237 AMD patients	57% at 1 year 71% at 2 years	Not known. Authors suggest lack of experience of ophthalmologists about proper use of bevacizumab
Curtis et al. 2012	284.380 AMD patients	53.6% at 1 year 61.7% at 18 months	Costs Discomfort and inconvenience of treatment Perceived lack of benefit Safety concerns mainly possible systemic adverse effects

2.7.8 Post marketing experience

Upon request, the applicant provided a discussion on post marketing data of Avastin. Although Avastin is not indicated for intravitreal use, the SmPC of Avastin contains statements about the safety of intravitreal use. As part of good pharmacovigilance practice, the marketing authorisation holder has collected safety information about the off-label use of Avastin. Detailed pharmacovigilance data are not publicly available, however, the total number of individual cases reported for eye disorders is 1835 (All ages, Eudravigilance database 16 February 2021). Of these 1835 reports, the age was not specified in 453 cases. In the age groups 18-64, 65-85 and >85 yrs, 503, 733 and 146 cases were reported respectively.

This safety information, together with safety information of several clinical studies (until 2012 as per Var/H/II/0044) is reflected under sections 4.4 and 4.8 of the Avastin SmPC.

The last change made to the Avastin SmPC with regards intravitreal use dates from 2012 (with variation II/0044) from this date on, apparently there has been no reason from a safety perspective to update the SmPC with regards the use of bevacizumab (Avastin) in ophthalmologic indications.

From the SmPC of Avastin the following side effects may occur after injection into the eye:

- Infection or inflammation of the eye globe
- Redness of the eye, small particles or spots in your vision (floaters), eye pain,
- Seeing flashes of light with floaters, progressing to a loss of some of your vision,
- Increased eye pressure,
- Bleeding in the eye.

The Avastin SmPC also highlights systemic effects following intravitreal use of bevacizumab. A reduction of circulating VEGF concentration has been demonstrated following intravitreal anti- VEGF therapy. Systemic adverse reactions including non-ocular haemorrhages and arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors.

2.7.9 Discussion on clinical safety

In order to be able to extrapolate the safety profile of bevacizumab in AMD patients established in the literature to Ipique, it should have been demonstrated that the product used in the relevant studies is sufficiently representative of Ipique, which has not been established. Please refer also to the discussions concerning the required bridge to Avastin in the sections above.

From a safety perspective, some aspects have to be highlighted especially. During the quality assessment impurities, glycosylation levels, and sub-visible particles have been identified, which slightly differ from the comparator bevacizumab, EU-Avastin. The clinical relevance of these differences is unclear. This is especially of concern for an intravitreal administration as intended for Ipique where particles could play a role for immunogenic/inflammatory reactions. Although the applicant provided a "risk assessment", this lacked quantitative aspects and relied on the assumption that either Avastin and Ipique don't have differences or that such differences do not present increased risks. Such assumptions are too uncertain and the potential risks too high to be accepted without appropriate evidence. The only discussion on the differences between Avastin and Ipique was the mention that Ipique specifications for the level of particulate matter are defined on the basis of the USP monograph for ophthalmic solutions whereas Avastin, used OFF-label, likely followed less stringent principles. The argumentation is insufficient, and it is also observed that the intended use is intravitreal rather than ophthalmic (applied on the surface of the eye). Clinical data from intravitreal administration with Ipique is required to address potential differences in safety aspects specific to the intended indication.

At the oral explanation, the applicant reiterated the claim that a clinical comparative bridging study was unfeasible, mentioning that an (unethical) placebo arm would have been needed and that the sample size would have been excessive. It is observed that the applicant did not justify adequately the supposed need for a placebo arm, nor detailed a convincing power calculation in support of the need for an excessively large sample size. The claim is therefore unfounded and, in any case, not accepted by the CHMP. In any event, it is the applicant's responsibility to properly and sufficiently demonstrate the safety of its medicinal product. The fact that the applicant only contemplated the conduct of a certain study design to demonstrate safety and later claimed it to be unfeasible cannot be accepted as evidence to the safety of the medicinal product.

Data from literature is presented to establish the basis for a marketing authorisation based on well-established use in the indication: treatment of neovascular (wet) age-related macular degeneration (AMD). Initially, the applicant had also applied for the treatment of visual impairment due to diabetic macular oedema (DME). During the procedure, in response to major concerns of the CHMP on the insufficiency of the data supporting DME, the indication was withdrawn. The safety data for DME are however considered supportive to establish the safety profile of bevacizumab in patients with AMD.

During the procedure, the applicant added the indication treatment of macular oedema secondary to retinal vein occlusion (RVO). The addition of the RVO indication was not accepted. The data were considered given their potential to be informative on the AMD indication, despite the fact that the assessment performed revealed that they would have been clearly insufficient for an RVO indication. In any event, the overarching lack of adequate bridge between Ipique and the bevacizumab used to generate the data present in the literature (see below) also apply to this indication.

The applicant initially presented a list of 11 publications without any further presentation of the joint results or discussion of the safety profile, also the clinical overview and summary documents in the dossier were very short and uncritical. The documents only included a very brief summary of the safety conclusion for each of the three main references: Solomon et al 2019, Virgili et al 2018 and Thulliez et al 2018. The other references were not discussed at all. In the initially presented literature, patients with AMD or DME are only included in five of the presented reviews: Solomon et al (2019, 2016 and

2014), Virgili et al 2018 and Thulliez 2018. The three reviews by Solomon et al (2019, 2016 and 2014) include redundant data and are therefore regarded as one dataset. Six of the initial eleven listed publications are focussed on indications for which the applicant did not apply. While additional data might be helpful to form a more comprehensive view of the safety profile, some indications seem too far off from the target indication, to yield informative data. Further, some of the presented reviews stated that the quality of the evidence is rather low or even very low. The presented literature is mainly based on Cochrane reviews, which are generally regarded as critical reviews of high quality. However based on the Cochrane inclusion criteria applied to the selected literature only controlled clinical trials are included. Further, the Cochrane authors excluded a variety of publications that did not fit to the exact review topic. Especially for safety also other published articles in the intended indications or others would have been informative. For the submitted literature no sufficient description of the literature search or selection process has been provided. This is however, immanent for this application in order to derive and assess a comprehensive safety profile. Although the applicant submitted a new search upon request and updated the search again at D181, the representation and the selection criteria were still not adequately documented. Consequently, uncertainties remain concerning the totality of data and are considered in the B/R balance.

Concerning safety, the reported data are very limited. The provided literature mainly focussed on efficacy and only reported a few serious safety events (serious ocular events and serious systemic events). Non serious safety events are hardly reported in these reviews, but might be relevant in clinical practice. Upon request, the applicant presented a brief overview of how safety events have been monitored in the trials included in the main reviews, which seems acceptable. Initially no discontinuation rates have been presented. Upon repeated request the applicant provided discontinuation rates from four studies that were not included in the main reviews. The presented discontinuation rates are rather high (>50% in the first year of treatment) and the included reasons indicate discontinuations due to lack of effect or adverse events. A respective discussion and data from the other trials is requested.

In the indication applied for, bevacizumab has only been used off label. Since off-label use should generally be reported, the applicant was asked to provide post-marketing data for the administered products, if available. The applicant provided data from a variation procedure in order to include respective data for intravitreal use of Avastin to the SmPC. The respective data are in line with the reported AEs and respective inclusion in the SmPC of Ipique is requested.

The bevacizumab in Ipique has recently been approved as biosimilar to Avastin. To support the marketing authorisation, a clinical trial comparing to Avastin has been performed, however, with intravenous administration in an oncological indication. Even though comparable safety has been shown in the intravenous administration in an oncological indication, this is of little support to characterise the ocular safety.

The applicant did not provide an overview or discussion of **adverse events**. The following publications are regarded as the main data source for the target indication AMD: Solomon et al (2019, 2016, 2014) included only reviews on AMD patients, and Thulliez et al 2018 included patients with AMD, DME and Retinal Vein Occlusion. The review by Virgili et al 2018 focussed on DME patients and is considered informative for the safety profile in AMD patients.

The review by *Solomon et al* included clinical trials comparing bevacizumab and ranibizumab in a non-inferiority setting and several trials comparing each with control treatments. Overall the authors provided a good overview of the available data concerning safety of the treatment with bevacizumab and ranibizumab in patients with AMD. However, the detailed reporting of safety is limited. Safety events were not reported for all trials and if some were reported they focussed on serious ocular and systemic events. Therefore, the safety profile cannot be considered as completely described.

Nevertheless, overall, the number of adverse events was low and the reported adverse events were overall comparable between ranibizumab and bevacizumab. Some concerns arise for both anti-VEGF treatments concerning endophthalmitis, which is appropriately reflected in the SmPC of Ipique. Some differences have been reported with an increased risk for bevacizumab but the reported numbers were small and the results seem to differ between trials.

Virgili et al focussed on three safety outcomes: all severe systemic adverse events (SSAEs), all-cause death and arterial thromboembolic events. Data was mainly available for one year or maximum two years. The authors found no significant differences in overall safety (defined by the three included aspects) between bevacizumab and ranibizumab in DME patients. However, the authors also stated that the estimates are imprecise and the risk of bias was unclear. Since the authors focussed only on three main serious safety outcomes and no other adverse events were reported, the presented review does not present a comprehensive safety profile for patients with DME but is nevertheless supportive in order to establish a safety profile for patients with AMD.

The review by *Thulliez et al* is well documented and provides a critical discussion of their finding. They also mentioned that adverse events are mostly underreported in the included reviews and that data from RCTs are often overlapping. They further noted some methodological shortcomings, which might have a negative impact on the robustness of the reported data. Besides these limitations identified by the authors concerning the included reviews and meta-analyses, the publication by Thulliez et al itself is only partly informative for the safety profile of bevacizumab since the authors only focussed on systemic adverse events. These are an important aspect for the assessment of the safety profile of bevacizumab but still a comprehensive overview is missing.

The conclusions of the authors are mainly focussed on the comparison between control and anti-VEGF treatments in general. For patients with DME, the authors identified in the analyses of pooled anti-VEGF treatments vs control drugs an increased risk of death and vascular death. Although this finding was made with ranibizumab and aflibercept in DME patients and no data seems to be available for bevacizumab, a similar risk seems likely, based on the comparison between ranibizumab and bevacizumab in AMD patients which showed no difference between both treatments concerning death and vascular death.

Thulliez et al further provided comparisons between anti-VEGF treatments. Although the included reviews largely agree that anti-VEGF treatments were not associated with an increased risk of systemic AEs compared to control treatment, some differences between bevacizumab and ranibizumab have been observed:

- Bevacizumab was associated with an increased risk of venous thrombotic events in one review, which was supported by trends in 4 other reviews. However, the very low number of events and large confidence intervals reported in Thulliez et al 2018, hinder further conclusions. Respective wording has to be included in the SmPC.
- Bevacizumab also increased the relative risk of systemic AEs by 20% to 35% in 3 reviews. This was, however, not observed in one more recent review, which included additional unpublished data. The same review, however, also examined the influence of unpublished evidence on systemic AEs and showed that the inclusion of unpublished evidence reduced the risk of systemic AEs in patients treated with bevacizumab vs those treated with ranibizumab, eliminating the statistical significance that had been observed in an analysis that excluded the unpublished evidence. Since no further information was given concerning the additionally included unpublished data, several sources of bias cannot be excluded. Based on the provided data an increased relative risk of systemic AEs for bevacizumab cannot be ruled out.

- In the comparison ranibizumab vs control in AMD patients, an increased risk of non-ocular haemorrhage has been found for ranibizumab. Given that in the comparison between bevacizumab and ranibizumab, heterogeneous results for non-ocular haemorrhage were found, an increased risk for bevacizumab cannot be ruled out. The risk is adequately reflected in the SmPC.
- The increased risk of gastrointestinal disorders found in 2 out of 3 reviews for bevacizumab seems however manageable and was reflected in the proposed SmPC.
- One publication, which was not specifically mentioned by the applicant but included in the Solomon 2019 review, reported a higher proportion of patients with serious systemic adverse events (primarily hospitalisations) with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66). The review by Solomon et al reported overall comparable rates of serious adverse events between ranibizumab and bevacizumab. But for both treatments the rates increased by 14 and 18% respectively between the first and the second year. Also the incidence rate of death is comparable between both treatments at one year (2% each) but increased at two years (bevacizumab 6%, ranibizumab 5%). Although the incidence rates are comparable between treatments, the increase between the first year of treatment and the second year for both death and serious adverse events is of concern. Unfortunately, the majority of trials were only performed over one year and only very sparse data is available beyond one year. This uncertainty remains but it is acknowledged that a similar observation was made with ranibizumab.

The overall reported AEs suggest comparable safety profiles between bevacizumab and ranibizumab. Several AEs (e.g. ocular serious adverse effects, events related to immunogenicity or arterial hypertension) reported with different anti-VEGF have been observed.

Overall, the proposed SmPC of Ipique is in line with Lucentis (ranibizumab). Based on largely comparable safety profiles, this could be in general acceptable. However, in the literature presented for the clinical pharmacology assessment of Ipique, it has been seen that bevacizumab reaches systemic serum concentrations of 1.58 nM, which is higher than the estimated inhibitory concentration (IC50) for VEGF factors (IC50 = 0.668 nM) suggesting that bevacizumab might have the potential for systemic side effects. Therefore, respective AEs in relation to systemic exposure should be included in the SmPC. Several other SmPC amendments are requested in order to adapt it to the data available for bevacizumab.

Upon request, the applicant provided a risk evaluation of intravitreal immunogenicity and proposed risk mitigation activities. Moreover, supportive information on Avastin, Eylea and Lucentis has been included. Even if it is expected that bevacizumab has a low risk of immunogenicity in the intended indication, the data provided does not allow to draw any conclusion. Additionally, the potential impact of quality differences between Ipique and Avastin has not been sufficiently established yet. Respective comparability data has to be presented. Further, in order to properly reflect the immunoreactivity risk in the product information and RMP, further information is needed related to the product expected to be marketed (intravitreal bevacizumab as Ipique).

Further, no information is available concerning laboratory findings or drug-drug interactions. Since relevant systemic levels are reached with intravitreal administration, interactions with other systemic products cannot be excluded. The lack of data is adequately reflected in the SmPC.

Exposure to bevacizumab of a woman of childbearing potential seems to be unlikely given the indication. However, already licensed products of the same therapeutic class (Lucentis and Eylea) should not be used during pregnancy unless there is a clear benefit. As highlighted in the non-clinical assessment, bevacizumab has been shown to be embryotoxic and teratogenic when administered to

rabbits. Although the applicant agreed on updating the SmPC in line with contraindications and respective wording in line with the SmPC of Avastin, this has not been applied to the current SmPC and is again requested.

The original dossier included only a 4ml vial for Ipique. The intended injection volume is however much smaller with only 0.05 ml. Therefore, overdosing or misuse, including administration to several patients, could not be ruled out. The applicant proposed to develop a pre-filled syringe (PFS) within 14-16 months. However, no detailed data has been provided (please also refer to the discussion of Quality aspects). The SmPC states that: "The vial is for single use only and the precautions in section 6.6. should be followed for the preparation of Ipique. After injection any unused product must be discarded." This warning is strongly encouraged and generally considered as adequate until the PFS is developed (please also refer to the discussion of Quality aspects).

Additional expert consultation

N/A

Assessment of paediatric data on clinical safety

N/A

2.7.10 Conclusions on clinical safety

The initially presented literature was not sufficient to establish a comprehensive safety profile of bevacizumab in AMD. Several limitations concerning the choice of the presented literature and the safety reporting in the respective publications have been identified and respective updates were requested. Upon repeated requests the quality and quantity of the available information increased during the last rounds of assessment and can be regarded as sufficient to establish a safety profile of bevacizumab in AMD patients. Nevertheless it cannot be considered as comprehensive due to the remaining uncertainties introduced by the lacking documentation of the performed literature search.

The limited safety reports indicate overall comparable safety between bevacizumab and ranibizumab based on the reported aspects. However, for some aspects the reports differ between trials and reviews but these differences could be adequately represented in the SmPC. These include a potentially increased risk of venous thrombotic events, increased relative risk of (serious) systemic AEs or immunogenicity events and increased risk of non-ocular haemorrhage with bevacizumab. For example, it is unknown whether the observed increase in impurities and subvisible particles would lead to increased immunogenicity or inflammatory reactions in the eye, which are considered as serious adverse events.

In addition to establishing a safety profile for bevacizumab from the literature, similarity between Ipique and the bevacizumab described in the literature has to be established. No clinical data in the intended indication is available. As discussed above, several differences between EU-Avastin and Ipique were identified during the quality assessment of unclear clinical relevance for the intended route of administration and claimed indication.

In the absence of evidence in intravitreal use establishing similarity of Ipique and the bevacizumab referred to in the literature, and in view of the differences highlighted in the quality assessment, the abovementioned safety results cannot be extrapolated to Ipique in AMD. The need for evidence establishing similarity between medicinal products is of particular importance for biological medicinal

products where minor differences in their active substances may result in significant differences in safety and immunogenicity.

2.8. Risk Management Plan

Given the negative concerns identified and the negative risk-benefit, an RMP could not have been agreed.

2.9. Pharmacovigilance

2.9.1. 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.

2.9.2. Periodic Safety Update Reports submission requirements

Not applicable.

2.10. Product information

2.10.1. User consultation

The applicant will submit the results of a user consultation with target patient groups on a package leaflet – still not provided by the applicant - that 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* prior to placing the product on the market.

3. Benefit-Risk Balance

3.1. Therapeutic context

The target indication – the only one requested at the time of opinion (for other indications explored during the procedure, see above) is '*treatment of neovascular (wet) age-related macular degeneration (AMD)'*. AMD is a degenerative disease of the central portion of the retina (the macula) that results primarily in loss of central vision. Wet AMD is characterised by growth of abnormal vessels into the subretinal space, usually from the choroidal circulation and less frequently from the retinal circulation. These abnormal blood vessels (choroidal neovascularization) leak, leading to collections of subretinal fluid and/or blood beneath the retina. Wet AMD is characterised by rapid distortion and loss of central vision over a period of days to weeks. The contralateral eye is at high risk of developing neovascularisation. The aim of therapy is to slow down the progression of AMD and central vision loss.

3.1.1. Disease or condition

AMD is a progressive blinding disease with no cure at present. Intravitreous injection of a vascular endothelial growth factor (VEGF) inhibitor is the gold standard of therapy. Photodynamic therapy (PDT) is another option and often used in combination with anti-VEGF agents. Supplementation with zinc and antioxidant vitamins as well as visual aids are suggested.

3.1.2. Available therapies and unmet medical need

Aflibercept (Eylea), ranibizumab (Lucentis) and brolucizumab (Beovu) are approved in AMD. All three products are available across the European Union.

3.1.3. Main clinical studies

There are no studies of Ipique in the target indication. Literature concerning studies conducted with the available bevacizumab (assumed to be mostly EU- and US-sourced Avastin) have been submitted. In particular, one Cochrane meta-analysis for AMD is the basis for the assessment of efficacy of bevacizumab: Solomon et al 2019; *Anti-vascular endothelial growth factor for neovascular age-related macular degeneration*. The review compared efficacy of bevacizumab to other (approved) anti-VEGF agents, other standard of care, sham or no treatment, using the standard methodological procedures expected by Cochrane. Only RCTs were included, most of the studies were masked.

The Cochrane review focussed mainly on efficacy and only reported some serious safety aspects. In order to further support the claim of benign safety the applicant provided one additional review by Thulliez et al. 2018; *Overview of Systematic Reviews and Meta-analyses on Systemic Adverse Events Associated With Intravitreal Anti–Vascular Endothelial Growth Factor Medication Use*. The initially submitted review for the indication of diabetic macular oedema (DME) (*Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis*.) is considered supportive for the establishing of the safety profile of bevacizumab in AMD patients.

A comprehensive and well documented literature search has not been provided by the applicant.

3.2. Favourable effects

From the literature, it can be concluded that intravitreous injection of bevacizumab has beneficial effects on best corrected visual acuity in eyes with neovascular age-related macular degeneration.

Visual acuity outcomes after bevacizumab and ranibizumab were similar when the same RCTs compared the same regimens with respect to gain of 15 or more letters (15 letters corresponds to 3 lines) of visual acuity (RR 0.95, 95% CI 0.81 to 1.12; high-certainty evidence) and loss of fewer than 15 letters of visual acuity (RR 1.00, 95% CI 0.98 to 1.02; high-certainty evidence); results showed similar mean improvement in visual acuity (mean difference [MD] -0.5 letters, 95% CI -1.5 to 0.5; high-certainty evidence) after one year of follow-up. Other secondary endpoints such as prevention of blindness (visual acuity better than 20/200), maintenance of visual acuity, mean change in visual acuity, visual function, morphological outcomes and quality of life also showed comparable results.

Two year results were consistent with one-year outcomes in terms of the effect estimate and confidence intervals

When comparing three anti VEGF treatments (pegaptanib, ranibizumab, or bevacizumab) with control, more participants who received intravitreous injection of any of the three anti-VEGF agents had gained 15 letters or more of visual acuity (risk ratio [RR] 4.19, 95% CI 2.32 to 7.55), had lost fewer than 15

letters of visual acuity (RR 1.40, 95% CI 1.27 to 1.55), and showed mean improvement in visual acuity after one year of follow-up. Participants treated with anti-VEGF agents showed improvement in morphologic outcomes compared with participants not treated with anti-VEGF agents.

3.3. Uncertainties and limitations about favourable effects

Ipique has never been tested in the target indication.

No comprehensive literature search has been conducted and the search strategy and selection of submitted information is not fully transparent.

Based on the provided literature, the source of the used product is unclear for some of the submitted studies.

The characteristics demonstrated for the bevacizumab used in the literature cannot be used to conclude on the existence and extent of benefits of Ipique in the claimed indication, due to the possible effects of known and unknown differences.

In addition, there are uncertainties on the robustness of the conclusion of non-inferiority to other established treatments. For the most relevant studies submitted (CATT 2015, IVAN 2012, LUCAS 2015, DRCR net 20015) a non-inferiority limit of 5 letters was considered, which was wider than the one regulatorily accepted and/or the analyses were primarily performed on the basis of the intention-to-treat principle. These non-conservative conditions may increase the risk of falsely concluding on non-inferiority between bevacizumab and ranibizumab or aflibercept.

Some differences in the outcomes of the largest studies were observed. The CATT study demonstrated a head-to-head equivalent effect on visual acuity at 1 year when bevacizumab and ranibizumab were compared. Monthly administration showed better results than as-needed regimen. However, the results of IVAN study were considered as inconclusive when a similar comparison was established. Otherwise, LUCAS 2015 exploring a "treat and extend" scheme found bevacizumab non-inferior to ranibizumab. Further justification of the recommended dosing schedule would have been necessary.

3.4. Unfavourable effects

The most frequently reported ocular AEs were uveitis, vitreous haemorrhage, and ocular inflammation. Endophthalmitis, retinal detachment, epithelial tear, traumatic cataract, or uveitis were also reported although in general with incidences around 1% or even lower.

In Solomon et al 2019, after one year overall the reported safety events are comparable between bevacizumab and ranibizumab. Investigators reported more gastrointestinal disorders (RR 1.76, 95% CI 0.99 to 3.14), infections (RR 1.42, 95% CI 0.93 to 2.17), injuries and procedural complications (RR 1.27, 95% CI 0.78 to 2.06), and surgical or medical procedures (RR 1.41, 95% CI 0.88 to 2.27) in the bevacizumab groups than in the ranibizumab groups. After one year of treatment a rate of serious adverse events of 16% was reported for ranibizumab and 18% for bevacizumab. An incidence rate of 2% for death has been reported after one year for both treatments.

The same review reported that after two years in both groups less than 1% of participants were reported to have had endophthalmitis, retinal detachment, retinal pigment epithelial tear, traumatic cataract, or uveitis. In the bevacizumab groups, 36% of participants had at least one serious adverse event compared with 30% in the ranibizumab groups (RR 1.20, 95% CI 1.05 to 1.37). Mortality from any cause was 6% and 5% in the bevacizumab and ranibizumab groups, respectively (RR 1.12, 95% CI 0.76 to 1.65). As with one-year outcomes, investigators reported more gastrointestinal disorders (RR 2.74, 95% CI 1.49 to 5.02), infections (RR 1.37, 95% CI 0.96 to 1.95), and injuries and

procedural complications (RR 1.33, 95% CI 0.86 to 2.05) in the bevacizumab groups than in the ranibizumab groups, and reported more cardiac disorders in the bevacizumab groups than in the ranibizumab groups at two years (RR 1.25, 95% CI 0.92 to 1.71)

In Thulliez et al 2018, Bevacizumab was associated with an increased risk of venous thrombotic events in one review, which was supported by trends in 4 other reviews. Bevacizumab also increased the relative risk of systemic AEs by 20% to 35% in 3 reviews.

In one study (CATT Research Group, 2011) the proportion of AMD patients with serious systemic adverse events (primarily hospitalisations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66).

In the literature presented for the clinical pharmacology assessment, bevacizumab reaches systemic serum concentrations of 1.58 nM, which is higher than the estimated inhibitory concentration (IC50) for VEGF antagonists (IC50 = 0.668 nM).

3.5. Uncertainties and limitations about unfavourable effects

The characteristics demonstrated for the bevacizumab used in the literature cannot be used to conclude on the risks of Ipique in the claimed indication, due to the possible effects of known (e.g. subvisible particles, different levels of glycosylation, different distribution of glycophorms, higher level of the HHL fragment) and unknown differences.

Furthermore, there are uncertainties regarding the safety of the originator bevacizumab in AMD based on differently reported safety outcomes in the main literature references, missing data on exposure or dosing intervals and the limited reporting of safety in general in the provided literature.

The immunogenic potential of intravitreal administered bevacizumab is not clear. No clinical data has been submitted by the applicant and the respective sections in the proposed SmPC are based on Lucentis (ranibizumab). Data from ranibizumab might not be specific enough since Ipique is a significantly larger molecule than Lucentis (ranibizumab), including a Fc fragment which may make it more immunogenic. Although immunogenicity events seem rare with bevacizumab and other ocular products (Eylea, Lucentis), the risk of immunogenicity events with Ipique is unclear. There is no demonstration that Ipique does not increase the risk of inflammatory or immunogenicity reactions compared to the bevacizumab from literature.

Further, no information is available concerning laboratory findings, differences between age groups or drug-drug interactions. Due to the fact that the ocular conditions claimed in the indication worsen with age, respective information is required. Further, since relevant systemic levels are reached with intravitreal administration, interactions with other systemic products cannot be excluded. Respective interactions could also increase with age, since different concomitant medications could increase.

3.6. Effects Table

Given the nature and the extent of uncertainty, and the impossibility to express credible confidence intervals, an effects table is not produced.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The outcome measures used in the provided literature are accepted in regulatory practice and can be assumed to have clinical value.

The observed adverse events are of relevance and, lacking the possibility to precisely quantify their incidence with Ipique, they are of severe concern.

Unfavourable effects that are not known in the published literature for bevacizumab in AMD and might arise with the use of Ipique. Their importance cannot be quantified.

3.7.2. Balance of benefits and risks

The scientific literature submitted in support of the claimed indication of Ipique, entailing intravitreal administration, was obtained using Avastin. No evidence was submitted comparing Ipique and Avastin in intravitreal use.

In absence of a comparative bridge between Ipique and Avastin when the products are administered intravitreally, it is not possible to conclude on whether, in the claimed indication, the known and unknown differences between Ipique and Avastin have a significant impact in terms of efficacy and safety. Consequently, it has not been demonstrated that the scientific literature obtained with Avastin administered intravitreally can be extrapolated to Ipique. As a result, the safety and efficacy of Ipique have not been properly or sufficiently demonstrated.

In conclusion, the benefit/risk balance of Ipique is negative.

3.8. Conclusions

The overall benefit/risk balance of Ipique is negative.

Divergent position(s) are appended to this report.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy for Ipique in the proposed indication, the CHMP considers by majority that

The safety and efficacy of the above-mentioned medicinal product is not sufficiently demonstrated, and therefore recommends the refusal of the granting of the marketing authorisation for the above-mentioned medicinal product. The CHMP considers that:

Whereas

- The application is submitted under Article 10a of Directive 2001/83/EC (so-called 'well-established use' application). In this context, pre-clinical and clinical studies can be replaced by appropriate scientific literature if it can be demonstrated that the active substances of a medicinal product in the claimed therapeutic indication have been in well-established medicinal use within the Union for at least ten years, with recognised efficacy and an acceptable level of safety. In order to extrapolate the results in the scientific literature to the applied medicinal product, the applicant

shall demonstrate that their product is similar to the product(s) referred to in the scientific literature submitted.

- In the absence of an appropriate clinical comparison in the intended indication and route of administration to demonstrate that Ipique and the medicinal product referred to in the literature are similar, the data from the literature cannot be extrapolated to Ipique in the claimed indication. As a result, the safety and efficacy of Ipique have not been properly or sufficiently demonstrated.

the CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004,

the safety and efficacy of the above-mentioned medicinal product is not properly or sufficiently demonstrated.

Therefore, the CHMP has recommended the refusal of the granting of the marketing authorisation for Ipique.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan, and post-authorisation measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Divergent position(s)

Divergent position(s) to the majority recommendation are appended to this report.

5. Re-examination of the CHMP opinion

5.1. Assessment of the applicant's responses to the grounds for refusal

5.2. Introduction

The applicant Rotterdam Biologics (ROBIO) submitted the detailed grounds for the request of re-examination in several documents. All such documents have been assessed to reach the conclusions outlined below.

5.3. Grounds for refusal – adopted in the initial opinion of the CHMP

The CHMP concluded that safety and efficacy of the above-mentioned medicinal product is not sufficiently demonstrated and therefore recommended the refusal of the granting of the marketing authorisation for the above-mentioned medicinal product. The CHMP considered that:

"*Whereas*

- *The application is submitted under Article 10a of Directive 2001/83/EC (so-called 'well-established use' application). In this context, pre-clinical and clinical studies can be replaced by appropriate scientific literature if it can be demonstrated that the active substances of a medicinal product in the claimed therapeutic indication have been in well-established medicinal use within the Union for at least ten years, with recognised efficacy and an acceptable level of safety. In order to extrapolate the results in the scientific literature to the applied medicinal product, the applicant shall demonstrate that their product is similar to the product(s) referred to in the scientific*

literature submitted.

- *In the absence of an appropriate clinical comparison in the intended indication and route of administration to demonstrate that Ipique and the medicinal product referred to in the literature are similar, the data from the literature cannot be extrapolated to Ipique in the claimed indication. As a result, the safety and efficacy of Ipique have not been properly or sufficiently demonstrated.*

the CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the safety and efficacy of the above-mentioned medicinal product is not properly or sufficiently demonstrated".

5.3.1. Grounds for re-examination from applicant:

Text from applicant:

The applicant holds the view that the recommendation cannot be upheld for two main reasons:

(i) Directive 2001/83/EC ("the Directive") has not been applied correctly and

(ii) the recommendation lacks scientific rationale

The applicant further points at inconsistent reasoning by the CHMP with regards the request for clinical data with Ipique to enable 'bridging' [CHMP view].

It is kindly noted that safety information about intravitreal use with biosimilars of Avastin (sections 4.4 and 4.8 of the SmPCs of Avastin) is identical to the information in the Avastin SmPC. This does not sit well with CHMP's request for clinical data because the CHMP/EC here allow direct to the safety information, irrespective of the known and unknown differences between Avastin and the biosimilars of Avastin.

Having said that, as per the main principle on which ICH S6 is based: The potential for adverse events of biopharmaceuticals is due to exaggerated pharmacology, implicating that when similar pharmacology has been demonstrated, as has been done for bevacizumab in IPIQUE and bevacizumab in Avastin, a similar efficacy and safety profile must be assumed.

With regards the **first reason**:

The WEU legislation in the Directive stipulates that all safety and efficacy information should be based on published data. The intention of the WEU regulations is to prevent unnecessary clinical trial by replacing trial data with data from the literature. To request a clinical trial as a condition for allowing the use of published data does not make sense. In addition, by collecting data on safety and efficacy by a clinical trial, there is no need for using published data and claim WEU.

The only paragraph in the Annex I of the Directive which may hint to the need for bridging:

"d) The non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences."

It means a judgement, not a clinical trial, in the overviews is needed if data are used concerning a product different from IPIQUE. However, the active substance of IPIQUE is a biosimilar of Avastin and has the same composition as Avastin and cannot be considered to be a different product.

The applicant therefore urges CHMP reconsidering of their interpretation of the stipulations about WEU in the Directive. As it is the intention of the bibliographical application procedure allowing products already on the market or already used as a medicinal product to stay there, even if they come to fall under the scope of the pharmaceutical legislation. This was relevant in 1965 when the first Directive (65/65/EEC) became applicable to the proprietary medicinal products, in 1975 when other pharmaceuticals came to fall under the legislation, 1980s when radiopharmaceuticals, immunological medicinal products, plasma derived products and homeopathic medicines started to be regulated and 2004 when 10 new member states acceded to the EU with their well-established medicinal products.

Another possible use of the bibliographical application is to function as an alternative to a generic/biosimilar application: instead of demonstrating bioequivalence to a reference medicinal product, a full dossier can be compiled from the scientific literature. This is probably the reason why CHMP considers the bibliographical application of IPIQUE as an abridged procedure like a generic/biosimilar application. From a legal point of view this is not correct.

The application for IPIQUE is completely different. It is not a generic/biosimilar application, and it is not an alternative procedure for a generic/biosimilar procedure. The outcome of a generic/biosimilar procedure is always a copy of the marketing authorisation and in the case of IPIQUE this is not the case. The indications for IPIQUE are for use in ophthalmological indications and the active substance bevacizumab has never been authorised in this indication. The application for IPIQUE is therefore the first application for a marketing authorisation for bevacizumab in the ophthalmological indication. This means that there is no dossier available to bridge the active substance of IPIQUE to.

As there is no reference medicinal product and no product dossier for bevacizumab in ophthalmology, extrapolation from a reference product to the new medicinal product is not possible like in the case of generic, hybrid or biosimilar applications. In fact, no dossier about bevacizumab in ophthalmology exists in the EU competent authorities. It does therefore not make sense to bridge the first application to an available dossier.

The clinical trial suggested by the CHMP bridging the efficacy and safety of IPIQUE to the well-established medicinal use of Avastin in the eye lacks rationale as there is no dossier for Avastin in the eye. Moreover, there is no reason to suspect the presence of differences between IPIQUE and Avastin: it is obvious from the marketing authorisation of the bevacizumab as biosimilar of Avastin that both contain bevacizumab with similar efficacy and safety in oncology indications. It is scientifically impossible for biological medicinal products that such differences exist in another indication.

Finally, if relevant differences in efficacy and safety of Avastin used for the bibliographical data would exist, these differences would be so small that a gigantic clinical trial would be required to actually detect them.

With regards the **second reason**:

The applicant holds the view that (ii) the recommendation lacks scientific rationale.

The analysis of possible risks of IPIQUE specific adverse events shows that these risks are negligible and therefore there is no scientific rationale for any specific risk assessment. The differences between IPIQUE and Avastin are extremely small and clinical trials are not sensitive to pick up these small differences. The active substance of IPIQUE is a biosimilar of Avastin approved by the EMA. Since 2006 > 70 biosimilar have been accepted in the EU and although data exist for millions of treatment years not a single biosimilar specific adverse event has been reported.

The adverse event associated with intravitreal Avastin treatment in AMD are rare: based on large observational studies the incidence of specific local reaction is < 0.04% and systemic side effects <.0.01%. The number of subjects needed per arm to have a statistical power of 0.8 and an alpha of

0.05 and find a doubling of local adverse events: 117,660 patients. For the systemic side effects for a population with 10% comorbidity: 784,789 patients per arm needed. The great majority of local side effects of intravitreal injections are the result of the injection procedure. Also, the patient population with AMD is >75 years old and shows a high level of ocular and cardiovascular co-morbidities. A placebo group will be essential to enable valid conclusions about the specificity of the IPIQUE adverse events. However, leaving patients untreated with a condition which leads to blindness, is ethically unacceptable.

5.3.2. Assessment of applicant's submitted documentation supporting the Grounds for Re-examination

The applicant summarised in the document entitled '*ema-responses-grounds'*, that the applicant has the following grounds for re-examination:

1. The pharmacology of bevacizumab after systemic and after intravitreal administration, as elaborated in the response to Other Concern 18 of the D180 LoOI.
2. The clinical safety of Ipique and the identification of negligible residual risk as has been addressed by the applicant in the response to Major Objection 16 of the LoOI.
3. The appropriateness of the legal basis of the application, as addressed by the applicant in the response to Major Objection 15 of the LoOI.

- for assessment of Other Concern 18 of the D180 LoOI, please see section 5.3.5.
- for the assessment of the response to Major Objection 16 of the LoOI which covers clinical safety of Ipique the residual risk analysis, and the appropriateness of the legal basis, please see section 5.3.3.
- for the assessment of response to Major Objection 15 of the LoOI with regard to literature, please see section 5.3.4.
- for overall conclusion regarding assessment of the applicant's grounds for re-examination, please see section 5.3.8.

All submitted documentation, as grounds for re-examination, has been considered in formulating the below assessment.

5.3.3. Assessment of the response to Major Objection 16 of the LoOI, which covers the need for clinical bridging data IVT, risk analysis, considerations relating to the legal basis and related issues arising from applicant's submitted documentation

The applicant's submitted response to MO 16 is included in the documentation submitted for the grounds for re-examination documents and also in previous responses.

From the aforementioned six documents submitted as grounds for re-examination on this topic, the applicant's arguments were overlapping and dispersed throughout the different documents, therefore, the principle issues have been collated, examined and are addressed below together.

The applicant has questioned the need for data to bridge Ipique product IVT use to Avastin in the context of well-established use for neovascular age related macular degeneration (nAMD) arguing:

- that "*Bridging the body of evidence for the intravitreal use of bevacizumab and the current product has been adequately established via the approved biosimilar of), to which the product IPIQUE is identical";*
- that "*clinical trials included in the MAA for the product included PK studies and one large clinical phase 3 study, in Stage IIIB/IV Nonsquamous Non-Small Cell Lung Cancer (NSCLC), comparing (with Avastin. Similar PK and similar efficacy, safety and immunogenicity was observed*";
- that the applicant also had conducted a residual risk assessment for IVT use of Ipique, and submitted expanded literature information on well-established use of Avastin which were not adequately discussed by CHMP in the initial assessment;
- that a comparative trial of Ipique with Avastin administered IVT in an ophthalmic setting is not feasible, ethical, or sensitive and the request lacks scientific rationale;
- that the biosimilar regulatory framework assumes interchangeability of approved biosimilars with the reference product and that requesting additional clinical data to rule out potential differences in relation to the method of administration would undermine the biosimilar regulatory framework;
- the applicant further argues that the Directive 2001/83/EC has not been applied correctly by CHMP, that CHMP has considered this as an abridged application;
- that the legal basis of well-established use under which the application is submitted precludes consideration of differences due to factors such as e.g. the manufacturing process, impurities, and micro-heterogeneity of products, because well-established use concerns safety and efficacy of active substance;
- that reference in the SmPC of EU Avastin Biosimilars to safety data collected with Avastin supposedly implies that CHMP has allowed safety conclusions from evidence generated with Avastin to apply to biosimilars regardless of differences;
- that comparison with the Avastin used to generate the data in the literature is impossible because the current version of Avastin might be different from that one;
- that "a direct comparison of IPIQUE with Avastin as suggested is in the opinion of the applicant not warranted from a regulatory perspective under the current legal basis nor can be considered necessary because the body of evidence *is* the submitted literature. Under this legal basis, only data that enable bridging to the body of evidence (i.e. literature) demonstrating safety and efficacy of IPIQUE, is presented and considered necessary".

All submitted documentation, as grounds for re-examination, has been considered by the CHMP in formulating the below assessment.

5.3.3.1. Scientific evaluation of the need for clinical bridging data in intravitreal use in nAMD in the current case

The responses of the applicant have been considered in detail. The foremost scientific question considered is:

if, taking into account the approval of EU approved biosimilar , which is stated as identical to Ipique by the applicant, as biosimilar of Avastin, and the concerned EU approved biosimilarclinical studies, including the study in NSCLC, these submitted data are sufficient to make the bridge between Ipique and the submitted literature on Avastin IVT use.

It is not agreed that the submitted comparative data generated for EU approved biosimilar (i.e. quality comparison and comparative IV trial in an oncology setting) is sufficient for the bridging of that

product (and by extension Ipique) to Avastin in local ophthalmic IVT use for nAMD (in order to characterise the safety and efficacy of Ipique based on the use of Avastin IVT reported in the scientific literature). This is because, similarly to published regulatory guidance relevant to comparability between biological medicinal products (EMEA/CHMP/BMWP/42832/2005 Rev1 discussed below), the studied therapeutic indication in oncology is not relevant for the nAMD indications (as for others indications including all those requiring intravitreal administration) in terms of efficacy or safety, i.e. is not sensitive for differences in all relevant aspects of efficacy and safety and immunogenicity. Sensitivity refers to conducting a study in a population at risk of events of interest, one that has fewer factors that cause major inter-individual or time-dependent variation and where administered doses are likely to show a rising doses response effect.

The oncology setting is highly unlikely to be a sensitive model for the nAMD indication for a number of reasons as follows:

5.3.3.1.1. Immunogenicity/Immunoreactivity/Patient Characteristics

As stated in Weiss 2014, (the science of extrapolation), extrapolation of immunogenicity is only possible from high- to low-risk patient populations and clinical settings (e.g., from SC to IV route of administration or from immunocompetent to immunocompromised patients).

Considering characteristics of the NSCLC trial, in the oncology population, there are high levels of immunosuppression, high morbidity, toxic background anti-cancer therapies, all factors which may increase rates of non-allergic ADRs, potentially decrease rates of immune reactions and thus decrease sensitivity.

5.3.3.1.2. Dose and PK

The Epoetin regulatory guidance EMA/CHMP/BMWP/301636/2008 Corr., a relevant guidance in the present context, states - with respect to PK and dosing – that "*Similar clinical efficacy between the similar and the reference product should be demonstrated in adequately powered, randomised, parallel group clinical trials. Since pharmacokinetics and dose requirements usually differ for IV and SC use, similar efficacy between the test and the reference product should be ensured for both routes of administration* […]". The same principle applies in this case, whereby high doses of Avastin are administered IV in oncology (15mg/kg) in contrast to doses of Avastin 1.25mg in 0.05 MicroMl administered IVT in nAMD.

Notwithstanding the lower dose with intravitreal administration and even though only small amounts of bevacizumab are released from the eye into the systemic circulation compared with the amount released after the high dosages used in oncology, mean serum concentrations of these drugs after intravitreal administration remained above their IC50 values for VEGF-A ≥ 7 days post dose. These exposure levels were sufficient to suppress circulating VEGF in vivo. Bevacizumab evinces "flip-flop" pharmacokinetics IVT, in which the drug dissipates slowly from the globe but is then rapidly metabolised in the systemic circulation. FcRn plays an important role in eliminating intravitreally administered full-length IgGs across the blood-retina barrier into the systemic blood system.

Furthermore, the pharmacodynamic effect size of clinical irrelevance (equivalence margin for comparability primary endpoint) is approximately 35 microns for central subfield thickness (CST) in the nAMD indication. It is not clear how equivalence margins in oncology translate into measures of relevance to this indication.

5.3.3.1.3. Consideration of impact of quality attributes in the ophthalmic IVT context

Regarding quality attributes of Ipique, that were identified following a quality comparability exercise comparing Avastin with Ipique, the following comments are made:

The distribution of the glycoforms differs between Ipique and Avastin whereby Ipique contains higher percentages of certain glycoforms (afucosylated, galactosylated and mannosylated glycans). Thus, it is not agreed that the glycosylation pattern of Ipique and Avastin are similar in the context of the intravitreal indication where these differences may be clinically relevant. The claim that Ipique does not contain any non-human glycans is noted. However, the absence of non-human glycans does not obviate the need to consider the potential impact of the glycosylation differences observed. For example, apart from the issue of non-human carbohydrate residues, it is hypothesised that differences in glycosylation patterns can also induce neoepitopes resulting in changes to the immunogenicity of therapeutic proteins (Kuriakose 2016 Immunogenicity of Biotherapeutics: Causes and Association with Posttranslational Modifications). Ipique also contains higher levels of a HHL fragment, light chain fragments and low molecular weight species when evaluated by nrCE-SDS. Neoepitopes due to fragmentation are also a potential factor contributing to the risk of immunogenicity of biopharmaceuticals (Doevendans et. Schellekens 2019). The lack of clinical impact of these fragmentation differences for the intravitreal route of administration are not sufficiently established by the applicant.

The applicant states (in their comments to the Final CHMP AR) that a comparison of Ipique against the Avastin batches used to generate the data in the supportive literature is not possible and, as such, it cannot be verified if the above referenced differences in quality profile are relevant. Cross reference is made to section 5.3.3.6. for further discussion of regulatory considerations pertaining to well-established use submissions. The relevance of the applied-for product (Ipique) to the applicant's submitted literature which aims to establish safety and efficacy (in this case Avastin in nAMD) needs to be shown at the product level. If the submitted data is not considered to be relevant, then it is unclear how it is intended to establish a bridge at the quality level between Ipique and the Avastin used in the literature.

In the response to the grounds for refusal, the applicant also states that the safety risk arising from subvisible particles present in the drug product is mitigated due to the fact that Ipique complies with the USP monograph for ophthalmic solutions. This is not understood. The drug product specifications for subvisible particles comply with the limits described in Ph. Eur. 2.9.19. However, in general, a more stringent limit should be considered for a state-of-the-art product for intravitreal application. Nonetheless, the proposed specifications for control of subvisible particles were accepted on the basis that data would be presented demonstrating a reduction of subvisible particles by the 5 micron filter needle used for extraction of the product from the vial. This data was requested in an outstanding quality question which has not been addressed. No comparative data is provided comparing subvisible particle levels in Ipique vs. Avastin. Hence, the claim that the specifications for Ipique should result in lower levels of subvisible particles than are present in Avastin has not been substantiated.

5.3.3.1.4. Regarding extrapolation scientifically overall

On balance, given the potential lower sensitivity of the oncology population to issues of interest, (such as immunogenicity or inflammatory reactions), higher rate of adverse events overall in the oncology setting, different dosing and PK, the data and argumentation provided by the applicant is not sufficient to bridge Ipique IVT to Avastin IVT and therefore extrapolate in terms of safety, efficacy and safety (including immunogenicity) in the IVT setting of Ipique IVT.

5.3.3.2. Sensitivity of clinical trials

The applicant argues that clinical studies are insensitive to detect differences between products. This is not agreed by the CHMP. Clinical studies can be sensitive to detect small differences in efficacy in the range of the non-inferior margins used of 3-4 letters. The margins used for PD primary endpoint of Central Subfield Thickness is 35 Microns for comparability purposes. The CHMP considers these margins are also eminently achievable in clinical studies.

5.3.3.3. Risk assessment provided by the applicant

The applicant provides a risk assessment covering adverse reactions relating to intravitreal injection, safety of Avastin IVT and Ipique product specific differences, positing that most safety issues are very rare, related to injection trauma, and that the impact of Ipique product specific differences are speculative and negligible. See Table 19 below submitted with the applicant's response to MO16.

The CHMP does not agree with the applicant's conclusions that the impact of Ipique product specific differences is speculative and that the risks are negligible. This is reasoned because for potential product differences and possible relationship to safety issues and immunogenicity, or efficacy and PK, the applicant acknowledges the differences between Ipique and Avastin in Table 2 (see Table 19) of the submitted risk assessment that for post translational modifications *"These analyses show small differences in glycosylation between IPIQUE and Avastin, and that potentially, these differences may influence biological activity, PK and immunogenicity"* and contends that the IV oncology study is sufficient to address these issues.

The CHMP disagrees with this because without a sensitive study in an ophthalmic setting IVT, the impact of these differences cannot be assessed by extrapolation from data from a study in an oncology setting.

The applicant cites the traumatic impact of intravitreal injections which is acknowledged, however not all listed reactions could be considered to be product independent. In the case of sustained IOP following Anti-VEGF injection for example which may affect 10% of patients , the mechanism is uncertain and may stem from issues such as including microparticle obstruction of the trabecular meshwork or inflammation; thus product specific issues can not be excluded.

- Regarding the safety of Avastin IVT from published literature. The study (Ramos 2020) cited by the applicant is noted as a retrospective claims-based study measuring patient-initiated encounters post injection with 1.1% of injections associated with such complications adjudicated by the study team as not related to diseases progression. It is also noted that authors acknowledge the limitations of the study and potential for under reporting. In additional the complication rate was 12.5% *of patients*. Real world studies in general are relatively less sensitive measures of safety reporting that clinical trials settings. The data on Avastin can inform on nature and potential expected rates of potential serious adverse events with Avastin in a comparative setting. Further reflections on a possible study design to address the uncertainties are below. Please see also below the further consideration of the literature review and MO15 response.

Applicant's Risk Assessment's Table 2 Physical-chemical differences between Ipique and Avastin:

Table 19: Physical-chemical differences between Ipique and Avastin

		Risk analysis	Risk assessment
Primary structure			
	Difference in glycation	Glycation occurs in most therapeutic proteins and has no biological effects	
	Marginal differences in N and C terminal modifications	N and C terminal modification occur in all monoclonal antibodies and also occurs naturally	
Secondary/tertiary structure			
	Increased level of free thiols in Ipique	Level of free thiols has no biological consequences	
Post translational modifications			
	Batch age dependent differences in charge variants	These analyses show small differences in glycosylation between Ipique and Avastin. Potentially, these differences may influence biological activity, PK and immunogenicity.	No differences between proposed biosimilar, the bevacizumab in Ipique and Avastin were found in vitro in the clinical PK and NSCLC study.
	Ipique higher level of galactose		
	Ipique higher level of sialic acid		
	Ipique higher percentage of afucosylation, galactosylation, mannosylation and sialyation		
Purity and degradation pathways			
	Lower level high molecular species in IPQUE and higher level of monomers	High molecular weight species especially aggregates are the most important risk factors for immunogenicity. So Ipique has a lower risk of immunogenicity than Avastin.	No differences in immunogenicity between proposed biosimilar and Avastin were identified in the clinical PK and NSCLC study
	In forced degradation studies, no differences noted by mechanical, pH or light stress. After oxidative stress some differences in degradation products by CE-SDS analysis.	The forced degradation studies confirm the similarity of the overall impurity profiles of Ipique and Avastin.	No differences in immunogenicity between proposed biosimilar and Avastin were identified in the clinical PK and NSCLC study

Applicant's Risk Assessment's Tables 3 (RCT's comparing intravitreal bevacizumab versus ranibizumab in AMD with certainty of evidence from moderate to high), 4 (Adverse event as reported in RCT's bevacizumab versus ranibizumab), 5 (Safety assessment of intravitreal Avastin in AMD in meta-analyses and systematic reviews) of applicant's risk assessment have been reviewed and considered: these are acknowledged but considered as literature on safety/efficacy of Avastin IVT and not on the main question of whether data generated with Avastin IVT can be used to conclude on Ipique.

As regard to the applicant points raised on the level of knowledge of immunogenic aspects of protein, the CHMP noted the following elements

The immunogenicity of chimeric and humanised antibodies is summarised in a number of review articles. It is noted that in clinical studies a strong correlation has been found between immunogenicity and the presence of aggregates. Schellekens 2010 (The Immunogenicity of Therapeutic Proteins).

- a broad range of immunogenic aggregate sizes can overcome tolerance, (Lundahl 2021 Aggregation of protein therapeutics enhances their immunogenicity: causes and mitigation strategies);

- Post-translation modifications such as glycosylation all influence the immunogenicity of protein products. (Dingman 2019 Immunogenicity of Protein Pharmaceuticals). It is hypothesised that PTMs induce neoepitopes that can generate novel antibody specificities probably triggering autoimmunity. Given the multiplicity of possible PTMs, any variation in a recombinant proteins PTM profile relative to the natural product might be of concern and should be evaluated. (Kuriakose 2016 Immunogenicity of Biotherapeutics: Causes and Association with Posttranslational Modifications). Immune response cascade against preparations of protein therapeutics that may contain very low levels of aggregates;

- Various studies have demonstrated the effects of the Fc N-glycosylation on safety, Fc effector functions, and pharmacokinetics, both dependent and independent of neonatal Fc receptor (FcRn) pathway although investigating the biological and functional relevance of glycosylation is a major challenge. (Wada 2011 Influence of N-glycosylation on effector functions);

- Neoepitopes due to fragmentation are also a potential factor contributing to the risk of immunogenicity of biopharmaceuticals, Immunogenicity of Innovative and Biosmilar monoclonal antibodies– Antibodies (Doevendans et. Schellekens 2019).

5.3.3.4. Feasibility and design of clinical bridging study in IVT setting for nAMD

As a preliminary remark and notwithstanding the following discussion on feasibility, it is noted that claims on feasibility of studies can not substitute the requirement for the applicant to establish the efficacy and safety of the applied medicinal product.

The applicant's arguments for not conducting a comparative clinical study based on lack of feasibility or for ethical reasons are not accepted by the CHMP. The applicant's proposed single arm safety study in 200 subjects post authorisation is not considered adequate to provide the required information by reason of timing and design.

Per applicant's response to MO 16:

"The rapporteur has demanded a proposal for a comparative clinical trial comparing Avastin with IPIQUE to assess potential additional adverse events specific for IPIQUE. The incidence of such adverse events, if they occur, will be extremely low and will need even more patients to be statistically powered to find differences. The current estimate is that at least 20,000 patients will be needed per arm."

From Annex I of the applicant's response to MO 16:

"And although the bevacizumab in IPIQUE has recently been accepted as a biosimilar of Avastin, the rapporteur persists in requesting an additional comparative clinical trial of IPIQUE versus Avastin in AMD with safety as primary endpoint. The trial is intended to identify possible IPIQUE specific adverse effect. To reach 80% reliability such a trial would need 20.000 treatment naïve patients per arm and an inclusion of a placebo injected group to validate the sensitivity of the study population for adverse events."

The CHMP considers that the conduct of a comparative clinical trial of Ipique versus Avastin in AMD with safety as a primary endpoint and the precision assumed by the applicant would raise doubts on its feasibility. However, the request in MO16 "to show comparability of intravitreal safety and immunogenicity in a clinical study conducted in the indication most sensitive to detect potential differences" should be understood in the context of providing "comparative evidence of the clinical performance between IPIQUE and Avastin when administered in the eye".

An equivalence clinical trial evaluating the efficacy and safety of Ipique IVT vs. Avastin IVT could provide an acceptable bridge. It is also noted by the CHMP that no concern on feasibility of such study has been substantiated.

As per the CHMP scientific advice given to the applicant, *"In terms of clinical data the recommended option is that this is provided by establishing clinical comparability (equivalence in PK, efficacy and sufficient similarity in safety) in a sensitive model of an approved oncology indication".* This is acknowledged and agreed that this has been carried out as a first step through the reference to study in NSCLC and EU approved biosimilar as Ipique. The CHMP scientific advice continues however: *"For a clear demonstration of efficacy and safety in the intended indications the Applicant is advised to further include another clinical study investigating efficacy, safety and immunogenicity of the product applied for as compared to an anti-VEGF approved for ocular use in one of the settings of either nAMD or DME. Another option, though seen highly risky from a scientific perspective, might be to supplement the initial biosimilarity demonstration at the clinical level against Avastin with data derived from a thorough literature review on the efficacy and safety of the well-established use of Avastin, together with safety and immunogenicity data of the Applicant's own product IPIQUE collected after intravitreal administration in either sought indication, i.e. in nAMD and/or in DME."*

In line with the CHMP scientific advice, an equivalence clinical trial in nAMD to investigate the safety and immunogenicity of the product applied for compared to an anti-VEGF, or in this case Avastin IVT, would be relevant in establishing the bridge between the applied product and the scientific literature on Avastin IVT . Efficacy would be investigated using a sensitive endpoint and timing (on the rising part of the efficacy curve) for example Central Subfield Thickness (CST) measured at Week 4. Longer-term data on CST and BCVA would be available to assess the peak effect and maintenance. A placebo arm is not required in such a study.

In general, to characterise the ADR pattern over time, the cohort of exposed subjects should be large enough to observe also less frequently occurring events. To detect a common AE (appearing in ≥1% of patients) with sufficient precision, at least 300 subjects needs to be treated. From a safety view, the applicant is advised to ensure that 12-months safety data are made available from well over 300 subjects. It is noted that in the CATT study (Martin et al, Ophthalmology 2012; 119: 1388–1398) one or more serious systemic adverse events occurred in 255 patients (21.5%), with 53 (17.6%) in the ranibizumab-monthly group, 64 (22.4%) in the bevacizumab-monthly group. Serious adverse events in the Ocular SOC were reported between rates of 5.6 to 7% per group. (CATT research group 2011 Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration (nih.gov))

Conduct of a masked, randomised comparative trial is preferred as it is considered that such a study will provide estimates of treatment differences in efficacy, safety and immunogenicity that are less

susceptible to bias than those derived from comparison of data from an observational, single-arm study with external (historic) data.

5.3.3.5. Additional points raised by the applicant

The applicant argues that safety information about intravitreal use with biosimilars of Avastin (sections 4.4 and 4.8 of the SmPCs of biosimilars of Avastin) is identical to the information in the Avastin SmPC, thereby implying that CHMP considered Avastin bevacizumab information directly applicable to bevacizumab biosimilars. The applicant states that "*it is kindly noted that safety information about intravitreal use with biosimilars of Avastin (sections 4.4 and 4.8 of the SmPCs of Avastin) is identical to the information in the Avastin SmPC. This does not sit well with CHMP's request for clinical data because the CHMP/EC here allow direct to the safety information, irrespective of the known and unknown differences between Avastin and the biosimilars of Avastin*".

The CHMP does not agree with this conclusion. There is no implicit recognition of similarity between the products across different unauthorised indications. Depending on the sensitivity of the indication and route of administration, the extent of evidence needed in order to be able to rely on the safety information about intravitreal use with Avastin may vary. The Avastin SmPC 4.4 states that

"Intravitreal use: Avastin is not formulated for intravitreal use.

Eye disorders: Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intravitreal use of Avastin compounded from vials approved for intravenous administration in cancer patients. These reactions included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these reactions have resulted in various degrees of visual loss, including permanent blindness.

Systemic effects following intravitreal use: A reduction of circulating VEGF concentration has been demonstrated following intravitreal anti-VEGF therapy. Systemic adverse reactions including non-ocular haemorrhages and arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors"

The applicant claims that, based on ICH S6 guideline, the potential for adverse events of biopharmaceuticals is due to exaggerated pharmacology, and that when similar pharmacology has been demonstrated, a similar efficacy and safety profile must be assumed. This is disagreed by the CHMP; it is noted that ICH S6 guideline also provides that concerns may arise from the presence of impurities or contaminants, or unpredicted cross tissue reactivity or immunogenicity.

5.3.3.6. Regulatory considerations

The applicant has questioned the need to bridge IVT Ipique use *at product level* to the scientific literature on Avastin IVT in the context of a well-established use application.

Under the submitted legal basis Article 10a of Directive 2001/83/EC, of well-established use, relevance of the applied-for product (Ipique) to the product(s) used in the submitted literature, which aims to establish safety and efficacy (in this case Avastin in nAMD) of the applied product based on the submitted litterature needs to be shown at the product level. This is of particular importance for biological medicinal products where differences in quality attributes may translate in clinical differences in terms of safety and/or efficacy. Comparative studies to demonstrate the above may be relevant in the context of a well-established use application.

In this regard, Directive 2001/83/EC, Annex 1, part II. 1 well established medicinal use, d, states "*The non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences*". (emphasis added).

The above is also echoed in Volume 2A of Chapter 1 of the Notice to Applicants which clarifies in section 5.4 that "*In certain cases, studies may be provided only to support the relevance of the literature (used to demonstrate safety and efficacy of the active substance(s)), to the product intended for marketing*".

It is acknowledged that the applicant has submitted such an explanation in favour of the relevance (clinical comparability) of Ipique IVT to Avastin IVT from the submitted literature, (further considered below scientifically) arguing in principle that:

"*in light of the legal basis it is specifically noted that the potential differences the CHMP has highlighted concern potential minor differences due to factors such as e.g. the manufacturing process, impurities and micro-heterogeneity of products. These potential differences are however inherently exempted from within the definition of an Article 10a of Directive 2001/83/EC that specifically states that the well-established use of the actual active substances of a medicinal product needs to be demonstrated."*

However, it is for CHMP to assess the data submitted and form an opinion, as to whether the relevance of the literature has been satisfactorily demonstrated by the applicant for the applied medicinal product . As highlighted above, this demonstration is essential in order to conclude whether the safety and efficacy in the applied indication can be relied upon the submitted literature.

It is considered that in assessing the well-established use and the relevance of the literature to the applied-for product, the applicant is required to consider any differences with the literature product, e.g. strength, form, but also its intrinsic characteristics and to demonstrate there is no significant differences in term of safety or efficacy of the said product, taking into account also the claimed indication and route of administration.

It is emphasised that comparative clinical studies are not prohibited in the context of a well-established use application in order to support demonstration of the relevance of the literature data to the applied-for product.

In light of above, the CHMP maintains that it is necessary to bridge IVT Ipique use *at product level* to the scientific literature on Avastin IVT, and that the applicant did not establish this bridge.

In view of the given the (biological) nature,, the products and intended IVT use/indication and the potential clinical impact on efficacy and safety (including immunogenicity), comparative clinical data is required before a conclusion can be drawn on the similarity between the two products, allowing the reliance on the submitted literature.

5.3.3.7. Principles for comparability and extrapolation

The applicant argues for extrapolation of safety and efficacy data from the IV oncology setting to the IVT setting based on:

"existing precedential principal decisions are applicable to the possible extrapolation between routes of administration. Requesting additional substantiation goes against several principal decisions,"

the " *safety information, together with safety information of several clinical studies is reflected under sections 4.4 and 4.8 of the Avastin SmPC and all current approved biosimilars indicated for the oncology indications include the references in 4.4 and 4.8 on ophthalmological use*",

"*previous decision making on extrapolation between routes of administration in biosimilars*" and publications by CHMP members.

As for any marketing authorisation applications, the applicant needs to establish the safety and efficacy of the applied medicinal product. In the context of a well-established use application, it is needed to demonstrate the relevance of the literature to the applied-for product. In this regard, it bears noting that the aforementioned directive (Annex I, part II.4) states that "*In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications*" (emphasis added).

It is acknowledged that the applicant refers to the approval of an EU approved biosimilar of Avastin, that Ipique is stated by the applicant as identical to, for which clinical trials included in the MAA for that product included PK studies and the clinical phase 3 study, (study, in Stage IIIB/IV Non-squamous Non-Small Cell Lung Cancer (NSCLC)), comparing the EU approved biosimilar with Avastin administered IV where similar PK and similar efficacy, safety and immunogenicity were observed in an oncology setting and that based on these findings extrapolation to all other approved Avastin oncology indications of the reference product was considered acceptable.

Thus, if the comparative data (i.e comparative IV oncology trial) from the approved biosimilar application were to be considered sufficient for bridging of that product to Avastin in local ophthalmic IVT use, which it is not, then the requirement of establishing the relevance of the Avastin literature use to Ipique would have been addressed.

The applicant argues that extrapolation of safety and efficacy across routes and formulations for similar biological products is possible and that there are clear precedents. The CHMP does not agree that extrapolation can be *a priori* for all medicinal biological products but must be assessed on a case-by-case based on the characteristics of the medicinal product at stake and the data provided by the applicant.

The CHMP noted that the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, EMEA/CHMP/BMWP/42832/2005 Rev1, chapter 6 on extrapolation (the https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf), states that

"When biosimilar comparability has been demonstrated in one indication, extrapolation of clinical data to other indications of the reference product could be acceptable, but needs to be scientifically justified. In case it is unclear whether the safety and efficacy confirmed in one indication would be relevant for another indication, additional data will be required." Furthermore it is stated that *"Additional data are required in certain situations, such as*

1. *the active substance of the reference product interacts with several receptors that may have a different impact in the tested and non-tested therapeutic indications*
2. *the active substance itself has more than one active site and the sites may have a different impact in different therapeutic indications*
3. *the studied therapeutic indication is not relevant for the others in terms of efficacy or safety, i.e. is not sensitive for differences in all relevant aspects of efficacy and safety.*

Immunogenicity is related to multiple factors including the route of administration, dosing regimen, patient-related factors and disease-related factors (e.g. co-medication, type of disease, immune status). Thus, immunogenicity could differ among indications. Extrapolation of immunogenicity from the studied indication/route of administration to other uses of the reference product should be justified".

The scientific principles above stand true whenever extrapolation of clinical data to other (non-studied) indications is being considered, regardless of the legal basis under which the application was submitted.

In addition, further **regulatory precedents** in the context of comparability exists, where data on safety and efficacy from one route of administration of a biological product cannot be extrapolated to the other route, and where data are required for both routes of administration. According to the Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins (Revision) EMA/CHMP/BMWP/301636/2008 Corr.* ,https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-non-clinical-clinical-development-similar-biological-medicinal-products-containing_en-2.pdf;

"Since pharmacokinetics and dose requirements usually differ for IV and SC use, similar efficacy between the test and the reference product should be ensured for both routes of administration. This could be achieved by performing separate clinical trials for both routes or by performing one clinical trial for one route and providing adequate bridging data for the other route (see below)." Comparative immunogenicity between products is also required for the most immunogenic population.

Thus, contrary the applicant's claim, it can not scientifically be stated that extrapolation of safety and efficacy data across routes and formulations for biological products is automatic between biological medicinal products ; on the contrary it needs to be determined after an individual assessment based on the characteristics of the applied medicinal product.

5.3.3.8. Overall Conclusion following assessment of the response to Major Objection 16 of the LoOI which covers clinical safety of Ipique, the residual risk analysis, considerations relating to the legal basis, and the need for bridging data IVT

Given above reasons, the requirement for bridging of IVT Ipique to Avastin IVT is required, and the relevance of the published literature on Avastin IVT to Ipique remains to be shown.

5.3.4. Re-examination review of MO15 regarding Literature review

The issues raised by the MO15 in the day 180 list of outstanding issues were as follows:

a. The applicant has not explained their strategy for study search in sufficient detail and the selection of submitted studies can still not be followed properly. The submitted publications are not critically discussed and no updated overviews have been provided in Module 2. It is thus still unclear whether the referred-to studies indeed represent the overall published data and the coherence of results cannot be finally assessed.

   i. A detailed scientific bibliography for each of the claimed indications to address the clinical characteristics of bevacizumab is again requested. A qualitative synthesis needs to be established and a systematic approach needs to be applied, so that selection bias can be excluded. Search criteria, selection criteria and the respective selection process shall been outlined (e.g. via a PRISMA flow diagram).

ii. The potential for publication bias and the availability of 'grey literature' as potentially relevant data source should be addressed for each search.

iii. Besides RCTs, controlled trials comparing different doses or regimens as well as single arm studies could be relevant insofar as they might inform recommendations regarding posology, optimal treatment timing and duration as well as target population definition. These aspects need to be discussed based on the provided publications (see also **OC 23 b** on dose regimens).

iv. All available literature should be graded and discussed according to their quality and relevance for this application.

v. The clinical overviews and summaries (pharmacology, efficacy and safety) need to be updated according to requirements outlined in the Notice to Applicants Volume 2 B and need to address the target indications.

vi. In addition, coherence of scientific assessments should be argued based on a comprehensive literature search for each target indication.

The applicant is asked to elaborate on their systematic review once more, taking the abovementioned into account. Further guidance on what is expected for a comprehensive literature overview is outlined in the assessment of the response to former MO 114.

5.3.4.1. Applicants MO15 response submitted for day 180, and resubmitted for grounds for re-examination.

The applicant has decided to only claim the indication neovascular age related macular degeneration and to not further pursue the indications DME and RVO. Consequently, the (sub)questions a and b phrased as part of MO15 and pertaining to DME and RVO have not been addressed. The sub-questions c, parts i t/m vi are addressed below in answer:

The use of intravitreal bevacizumab in neovascular macular degeneration in the EEA started in 2006 about one year ahead of the introduction of Lucentis and Macugen in 2007. Eylea (aflibercept), a VEGF-trap biologic compound, followed in 2013. Not surprisingly, even when (late stage) clinical studies in oncologic indications were ongoing, bevacizumab was implicated in ocular indications, including neovascular (wet) age-related degeneration (AMD) [Refer to response to OC19]. Already in 2002 it was mentioned that the role of bevacizumab in the treatment of angio-proliferative retinal disorders was being actively investigated [Ferrara 2002]. By 2020, a wealth of studies (including many randomized controlled trials) about the intravitreal use of bevacizumab in age-related macular degeneration had been published. From 2005 until today the use of (off-label) bevacizumab in AMD has been an important and widely used treatment modality, although other (licensed) anti-VEGF inhibitors became available. In many European countries, bevacizumab is regarded first choice medicinal treatment of AMD, [NICE, EURETINA, Dutch Society of Ophthalmologists]. Hence, we can safely assume that the off-label use of intravitreal bevacizumab in AMD is widespread and that the bibliography about its' safety and efficacy is extensive; cumulating in a Cochrane review [Solomon 2019] comparing the anti-VEGF compounds bevacizumab, ranibizumab and pegaptanib, essentially concluding that further clinical efficacy studies are not required. However, the authors also advice to incorporate research evaluating variable dosing regimens of anti-VEGF agents and study effects of long-term use, beyond 2-years.

In a recent paper by Corazza et al. 2021 studied the long-term outcomes of intravitreal anti- VEGF therapies in AMD in a monocentric cohort study. In this study, a total of 865 eyes in 780 patients treated with an anti-VEGF treat-and-extend regimen over a long-term follow-up (up to 5 years).

Follow-up data were recorded for 37.6%, 25.1% and 15.0% of the cohort at years 3, 4 and 5 respectively. Patients treated with bevacizumab received fewer yearly injections than those treated with ranibizumab. However, no significant difference in the number of injections per year was detected in other comparisons between groups. Baseline characteristics between treatment groups were similar and treatment was provided based upon NICE guidance (see below).

Table 20

Indication	• Wet AMD
Clinical and imaging features	• Best-corrected visual acuity between 6/12 and 6/96 • Evidence of disease activity • Absence of permanent structural damage to the central fovea • Lesion size ≤ 12 disc areas

Whilst the data showed no significant difference in mean BCVA between the three groups, a slight reduction in visual function was observed, especially after the third year of treatment. This study confirms the conclusion of a study by Maguire et al. (2016) where outcomes patients were monitored for 3 years after release from the CATT study (2 years). Outcome measures were BVCA and morphologic retinal features 5 years after initiation of treatment with either bevacizumab or ranibizumab. Vision gains during the first 2 years of the trial were not maintained at 5 years. However, 50% of eyes had VA 20/40 or better, confirming anti- VEGF therapy as a major long- term therapeutic advance for neovascular AMD. In line with the expectations as set out in article 10(a) the applicant has demonstrated that the scientific interest for intravitreal bevacizumab has been overwhelming and its' use in medical practice (AMD) has been established (for more than 10 years with the community) and is laid down in European treatment consensus documents.

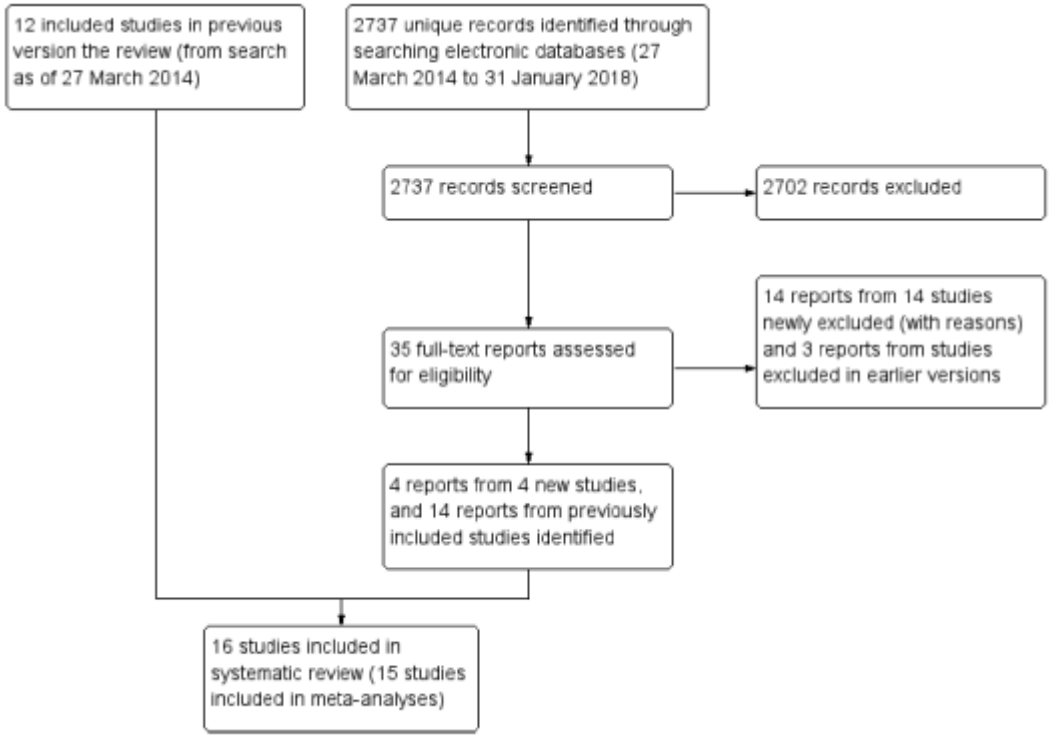
Considering the vast number of publications and considering that for other full applications under article 8(3) usually about 2-10 phase III or pivotal studies are submitted to substantiate the claimed indications, the applicant has relied on a key Cochrane review by Solomon et al. (2019) on the premise that the scientific community generally recognizes Cochrane reviews as the gold standard of systematic review. Furthermore, for the purpose of this this marketing authorisation procedure, the applicant has validated the Cochrane review (see hereunder). Solomon et al. (2019), have performed a systematic meta-analysis of the efficacy of bevacizumab (and safety, although studies were not powered to study safety) in comparator studies. With the applied dosing regimen starting with three monthly injections (1.25 mg, 50 µL) after which the frequency of injections is based on clinical improvement and at the discretion of the treating ophthalmologist (pro re nata – PRN), the effect-size of bevacizumab in AMD in maintaining visual acuity (proportion of patients losing fewer than 15 letters) has been unequivocally shown consistent between studies. In addition, the studies show that ranibizumab and bevacizumab improved visual acuity in some eyes that received these agents and were equally effective.

The applicant acknowledges that comparative studies between bevacizumab and aflibercept have not been included. Sarwar et al. (216) concluded that no trials were found that compared aflibercept versus bevacizumab into the eye. For their review 'Anti-vascular endothelial growth factor for neovascular age-related macular degeneration', Solomon et al., assessed and weighed literature for inclusion: two review authors independently evaluated the titles and abstracts obtained through electronic searches in main databases such as PubMed and others*. Also available 'grey literature' has been adequately addressed: the records were classified as "definitely relevant," "possibly relevant (or

'grey literature')," or "definitely not relevant"; a third review author resolved discrepancies. Full-text reports were obtained for all records assessed as "definitely relevant" or "possibly relevant." Two review authors independently assessed the full-text reports and classified each study as "include," "exclude," "awaiting classification," or "ongoing"; a third review author resolved discrepancies. For trials identified by handsearching of conference abstracts, a second review author verified eligibility based on the stated criteria. If necessary, study authors were contacted to clarify any details necessary for a complete assessment of relevance of the study. The latter would never have been possible for the applicant. The studies that were excluded after review of the full-text report were documented and the reasons for exclusion were noted. With this methodology the authors have minimized the risk for not including a study that would be relevant. The authors furthermore assessed selective outcome reporting for each study by comparing outcomes specified in a protocol, research plan, or clinical trial registry with reported results. When protocols, research plans, or clinical trial registry records were not available, the selective outcome reporting was assessed based on outcomes specified in the methods section of the study reports and on data collected as specified in the study design.

With regard to the mentioning of the search protocol used and the requested PRISMA flow diagram, reference is made to the flow diagram as used for Solomon et al. which is shown herewith.

Figure 18: Study flow diagram



It is noted that the dosing regimen was consistent between studies; starting with three monthly injections after which the frequency of injections of bevacizumab is based on clinical improvement and at the discretion of the treating ophthalmologist. A review by Li et al. (Cochrane 2020) focussing on treatment regimens of anti-VEGF concluded that, at one-year, monthly regimens are probably more effective than PRN regimens using seven or eight injections in the first year, but the difference is small and clinically insignificant. Hence, the proposed posology of Ipique is in line with the treatment regimens used in the clinical studies, being appropriate as confirmed by Li et al., and moreover is the

dosing scheme as is laid down in European treatment-guidance documents. In addition, long-term efficacy is similar between the anti-VEGF inhibitors, and a gradual deterioration of visual function (BCVA) over time has been observed for all anti-VEGF inhibitors. In their systematic review with the purpose of validating the Cochrane review by Solomon, the applicant has not identified papers with clinical trial data or case series of sufficient quality, which were not discussed in at least one of the meta-analyses validating these meta-analyses as unbiased and complete. In the additional literature identified with data with possible relevance for the efficacy of intravitreal bevacizumab in macular neovascularisation not a single paper was found with data contradicting the general conclusions of the metaanalyses, concluding that the coherence of the scientific assessments can be considered as

extremely high. Pending the current round assessment and oral explanation the applicant commits to submit a fully updated CTD, including updated summaries and all references prior to D210.

5.3.4.2. Assessment of response to MO15 at re-examination

The conclusion from the previous assessment at D195 of this M015 response was that:

"However, due to the lack of proper explanation of the Applicant's approach to scientific literature collection for this submission, there is still remaining uncertainty whether the totality of data has been considered for the AMD indication and this is considered a shortcoming for the bibliographic application. The lack of proper documentation adds uncertainty to the conclusions on efficacy in this procedure, and this is reflected in the benefit/risk discussion. Uncertainties about applicability of literature data generated with a product from outside the EU for IPIQUE is reflected in the remaining clinical MO on the scientific bridge between Avastin and IPIQUE."

The d195 conclusion was that the:

"Issue was not further pursued, remaining uncertainties are considered in the B/R".

It is not directly explained by the applicant why the applicant has re-submitted the response to MO15 as part of the grounds for re-examination, given the grounds for refusal hinged on the demonstration for the relevance of the submitted literature to Ipique. It is noted that in the *ema-re-examination-grounds*, MO15 is referenced with regard to the appropriateness of the legal basis- however, this is covered by MO16. It is noted in the document submitted as grounds for re-examination entitled "*ema-responses-reexamination-chmparcommented*" where the applicant has commented upon the final CHMP assessment report, that the applicant has made a number of comments concerning the literature review;

> Commented [SH(92] on the grounds for refusal that "*According to the WEU legislation, safety and efficacy should be demonstrated by literature data".*
>
> Commented [SH(77]: on the discussion on clinical safety *"The search was comprehensive, the selection criteria were clear, a quality assessment of the papers were included, including of the papers which were not included in the analysis.*
>
> Commented [DE(62]:conclusion on clinical efficacy *"See previous comments about completeness of the bibliographic data submitted by the applicant. Largely ignored by CHMP"*
>
> Commented [SH(57]: on methods *"Obviously, the rapporteur only selects these two studies herself, because we have submitted a complete review of the literature"*

The extent of literature submitted in the dossier has been reassessed including the document entitled "Systematic review of the literature on the safety of intravitreal bevacizumab for the treatment of Age-related Macular Degeneration (AMD)" provided in the d180 responses, which details the search process

and was referred to in the applicant's response to MO15. Also reviewed was the response to the MO15, the document in CTD 5.2 entitled "Tabular Listing of All Clinical Studies". All full text article listed both documents and available in CTD 5.4 were retrieved in full and reviewed (14 systematic reviews and 5 case series). The applicant states that the final selection of full-text articles Table 1 and 2 of this document were submitted. However, the following articles of observational studies were not obviously available in the clinical dossier (Bhavsar 2015, Cambell 2012a, Cambell2021b, Casparis 2014, Englander 2013, Cheung 2012, Etminan 2015, Rayess 2016, Schlenker 2015, Vanderbreek).

The clinical articles submitted were also considered in this assessment.

Additionally a document was available and entitled as "Lit-reference-list". This contains not a reference list, but a selection of abstracts from pubmed; There is no accompanying explanation in the document of how/why these articles were selected or where they are critically discussed within the dossier and synthesised for reference to the product profile/product information e.g. why did this include an article on coefficient of repeatability in BCVA in patients with nAMD wherein there is no mention on bevacizumab. (Aslam T 2014). The document merely states:

"Abstracts of clinical studies in age and diabetes associated macular neovascularisation with intravitreal bevacizumab in the EU".

Observational studies provided from published literature concerning infectious endophthalmitis with Bevacizumab

Borkar 2018;

> *retrospective cohort study in one large practice US over 5.5 years to examine endophthalmitis rates after bilateral anti-VEGF injections in 5890 patients.* Endophthalmitis rates were 0.035% per injections bevacizumab (1/3700) injections. Patient rates were not calculable for individual anti-VEGF. Cases of post-injection inflammation that were treated with topical steroids alone were not included. Missing data for coding was possible. Some limitations; retrospective non-randomised study design. Data from single institute.

Methodologically similar studies were also provided for infectious endophthalmitis rates-(Clay-bavinger 2019 US, Bhavsar 2015 US, Gregori 2015 US, Casparis 2014 Switzerland, Englander 2013 US, Cheung 2012 US, Rayness 2016 US, Vanderbreek 2015 US).

It is agreed that from the literature, the rates of infectious endophthalmitis appear low 0-0.074% in association with IVT bevacizumab.

Regarding submitted observational studies for systemic safety

Cambell 2021b

> This was a population based nested case-control study in 91,278 patients with retinal disease diagnoses identifying those who had stroke, myocardial infarction and congestive heart failure cases, comparing them to controls from the same population. After adjustment for potential confounders, participants who had ischaemic stroke, acute myocardial infarction, congestive heart failure, or venous thromboembolism were not more likely than control participants to have been exposed to either bevacizumab (adjusted odds ratios of 0.95 (95% confidence interval 0.68 to 1.34) for ischaemic stroke, 1.04 (0.77 to 1.39) for acute myocardial infarction, 0.81 (0.49 to 1.34) for venous thromboembolism, and 1.21 (0.91 to 1.62) for congestive heart failure.
>
> Some limitations noted: retrospective claims database study, intravitreal injection and bevacizumab exposure were not directly linked requiring assumptions, not captured episodes which happened outside hospital, or emergency department, not captured or deaths

attributable to outcomes. Possible issue with including prevalent MI cases as opposed to incident cases resulting in residual confounding.

Etminan 2015

This was a population based retrospective cohort study (N= 8,208) of bevacizumab users compared to nonusers derived from an earlier time period, and a nested case-control study for first myocardial infarction (MI) amongst an inception cohort of intravitreal users only (N=3,443 in AMD). The rate of first MI among bevacizumab users was 11/1000 person-years. The adjusted rate ratio (RR) for MI was 0.74 (0.46-1.20) for the propensity score-adjusted analysis. Some limitations; not captured deaths as a result of MI, not controlled for smoking, no non exposed comparison to bevacizumab in case control study.

Schlenker 2015

This was a before-and-after study examining thromboembolic events during the period after a first intravitreal VEGF inhibitor injection compared to a 3-year look-back period prior to this date. The age-adjusted RR for thromboembolic events for bevacizumab and ranibizumab were 1.83 (95% CI: 1.61–2.09) and 1.61 (95% CI: 1.39–1.87), respectively. This study only examined the risk of thromboembolic events from a single injection. According to Etaminan, the within-subject design might have controlled for some fixed confounders (such as sex), but time-dependent confounders such as history of cardiovascular disease, which may alter over time, might have affected the results.

Maloney 2021

This was a retrospective claims database study examining systemic reactions.

Post-injection 180-day event rates per 100 patients for MI, CVD, major bleeding, and all-cause hospitalisation were similar for bevacizumab (0.64, 0.59, 0.34, and 10.41, respectively), ranibizumab (0.62, 0.53, 0.40, and 9.44, respectively), and aflibercept (0.63, 0.60, 0.20, and 9.88, respectively). Included 69,007 bevacizumab patients. Patients with a history of MI, CVD, and renal disease had predictably higher rates of systemic SAE in the months after anti-VEGF treatment initiation compared with the rest of the treated population. uncontrolled non-randomised study design which cannot adjust for potential confounders.

Other submitted studies (Biagi 2014, Cambell 2012a were less informative methodologically). Safety data from systematic reviews was also assessed below.

Regarding submitted systematic reviews.

Solomon 2019 Cochrane review of anti-VEGF in nAMD

Efficacy; bevacizumab vs ranibizumab: gain of 15 letters or more at 1 year 3144 participants RR 0.95 (0.81-1.12). Analysable data for the primary outcome of this review for 3144 (86%) of 3657 participants.

Serious systemic events at 1year Ranibizumab 156/1000, Bevacizumab 154-209/1000 RR 1.15 (0.99-1.34)

Serious ocular ADRs at 1 yr; Studies reported different ocular adverse events. As a result of the small numbers of events, risk estimates for these adverse events were considered imprecise.

In CATT 2011, GEFAL 2013, IVAN 2013, and LUCAS 2015, less than 1% of participants had serious ocular adverse events

It is noted that sources searched included FDA but not EMA, and the applicant identified the limitations in the safety reporting for many of the included trials.

Six trials reported that 18% of participants in the bevacizumab groups versus 16% in the ranibizumab groups experienced at least one serious adverse event (RR 1.15, 95% CI 0.99 to 1.34) (BRAMD 2016; CATT 2011; GEFAL 2013; IVAN 2013; LUCAS 2015; MANTA 2013).

consistent with traditional, clinical reviews, (Ip 2008; Mitchell 2011; Schmucker 2010; Schmucker 2012).

The authors conclude that at one-year and two-year follow-up, visual acuity outcomes were comparable for bevacizumab and ranibizumab, clinically and statistically, although confidence intervals for some outcomes reported by individual studies indicated some uncertainty regarding true effects.

Researchers reported a small number of [serious] ocular adverse events for both bevacizumab and ranibizumab groups (< 1%) across all trials.

At both one-year and two-year follow- up, fewer participants in the ranibizumab groups experienced any serious systemic adverse events compared with those in the bevacizumab groups.

Under implications for research the authors note the lingering concerns about ocular and systemic toxicity.

Note the assessor attempted to reconcile the safety reporting with event rates observed in the EMA Lucentis EPAR to validate the Bevacizumab -Ranibizumab data:

From the EPAR pivotal study for ranibizumab (0.5mg) serious adverse events were in the order of 6% for ocular and 20% for non-ocular SAE

From Solomon 2019,

ranibizumab serious ADRs at 1 year were reflected as 0.5% ocular SAEs and 15.6%, for non ocular bevacizumab serious ADRs at 1 year were reflected as 0.5% Ocular SAEs was 15-20% non-ocular

From the EPAR Ranibizumab intraocular inflammation by 1 year was 15 % and IOP increase >30mmHG was 8%.

Thus equivalent granularity of ADR rates does not seem to be available for safety reporting in the Cochrane meta-analysis concerning Bevacizumab-Ranibizumab for ocular SAEs.

To further validate the ADRs reporting rate data from Solomon, the CATT publication was reviewed.

Ranibizumab and Bevacizumab for Treatment of Neovascular Age-Related Macular Degeneration: 2-Year Results (nih.gov)

Incidence of systemic SAEs for Lucentis does not appear to be lower in this trial than reported in the Lucentis EPAR at 1 year although direct comparison are difficult because of timing and potential difference in definitions.

Lucentis EPAR: rates of APTC during 2years in the order of 4.6% for Lucentis 0.5mg.

CATT; At 2 years, 32 (5.3%) of 599 patients assigned to ranibizumab and 36 (6.1%) of 586 assigned to bevacizumab had died p=0.62).

The proportion of patients with arteriothrombotic events was similar in the ranibizumab-treated patients (4.7%) and the bevacizumab-treated patients (5.0%; p=0.89).

Venous thrombotic events occurred in 3 (0.5%) of ranibizumab-treated patients and 10 (1.7%) bevacizumab-treated patients (p=0.054).

CAT; One or more serious systemic adverse events occurred in 190 (31.7%) of ranibizumab-treated patients and 234 (39.9%) of bevacizumab-treated patients (p=0.004).

After adjustment for demographic features and coexisting illnesses at baseline, the risk ratio for all systemic serious adverse events within two years for bevacizumab was 1.30 (CI: [1.07, 1.57]; p=0.009). Patients treated as needed had higher rates than patients treated monthly (risk ratio1.20; CI: [0.98, 1.47]; p=0.08).

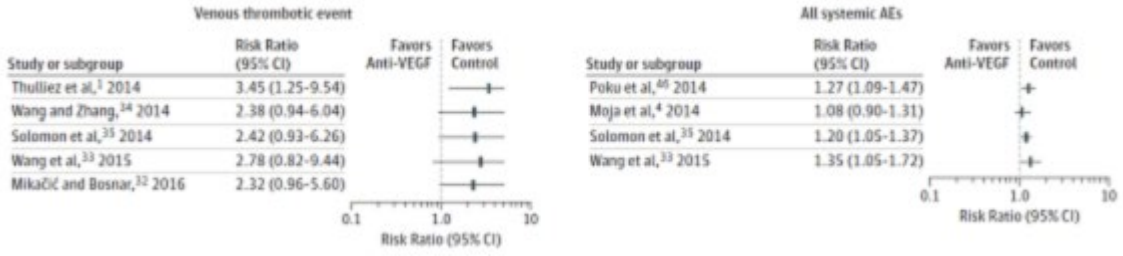
Thulliez 2018 overview of systematic review and meta-analyses of systemic ADRS with IVT anti-VEGF

According to the authors: Bevacizumab was compared with ranibizumab only in patients with AMD. Compared with ranibizumab, bevacizumab was associated with an increased risk of venous thrombotic events in 1 review (relative risk [RR], 3.45; 95% CI, 1.25-9.54)1 with 4 other reviews finding lower point-estimates (range of RR findings, 2.32 to 2.78) but with wide and nonsignificant confidence intervals. Bevacizumab also increased the relative risk of SAEs by 20% to 35% in 3 reviews but not in the most recent and most exhaustive Cochrane Review, (Moya 2014) which included unpublished data (RR, 1.08; 95% CI, 0.90-1.31). Results for high blood pressure and nonocular hemorrhage were heterogeneous. Bevacizumab increased the risk of gastrointestinal disorders in 2 out of 3 reviews but did not increase other risks, such as transient ischemic attack, infections, cardiac disorders, nervous system disorders, or neoplasms.

It is noted that no patient level data were synthesised, only trials with 95%CI for SAEs were included. Missing for example Cochrane reviews by; Zhu, and by Smith. The handling of overlapping included RCTs is not fully clear in the methodology. There is no submitted discussion on Figure 19 comparing Bevacizumab with ranibizumab which shows clear consistency on increased venous thrombo embolism and all SAES. It is noted that the *favours Anti-VEGF* and *favours control* do not correspond to the figure heading although for example the RR for Moja 2014 indicates that *favours Anti-VEGF* is bevacizumab and *favours control* is ranibizumab.

Figure 19

Figure 4. Bevacizumab Compared With Ranibizumab for the Systematic Adverse Events in Patients with Age-Related Macular Degeneration



Virgili 2014 Cochrane review anti-VEGF DMO

Pooled anti VEGF for safety for ATC events; excluded a moderate to large increased risk with anti-VEGF treatments compared to control (RR 0.98, 95% CI 0.83 to 1.17). Did not show a

significant difference regarding serious systemic adverse events (15 studies, 441 events in 2985 participants, RR 0.98, 95% CI 0.83 to 1.17), arterial thromboembolic events (14 studies, 129 events in 3034. participants, RR 0.89, 95% CI 0.63 to 1.25) and overall mortality (63 events in 3562 participants, RR 0.88, 95% CI 0.52 to 1.47). The authors judged the quality of the evidence on adverse effects as moderate due to partial reporting of safety data and the exclusion of participants with previous cardiovascular events in some studies.

Zhu 2016 Cochrane review anti-VEGF pathologic myopia;

Of the included six studies, two studies reported no adverse events in either group and two industry-sponsored studies reported both systemic and ocular adverse events. In the control group, there were no systemic or ocular adverse events reported in 149 participants. Fifteen people reported systemic serious adverse events among 359 people treated with anti-VEGF agents (15/359, 4.2%). Five people reported ocular adverse events among 359 people treated with anti-VEGF agents (5/359, 1.4%). The number of adverse events was low, and the estimate of RR was uncertain regarding systemic serious adverse events (4 RCTs, 15 events in 508 people, RR 4.50, 95% CI 0.60 to 33.99, very low-certainty evidence) and serious ocular adverse events (4 RCTs, 5 events in 508 people, RR 1.82, 95% CI 0.23 to 14.71, very low-certainty evidence). There were no reports of mortality or cases of endophthalmitis or retinal detachment.

Micacic 2016 IVT bevacizumab and CVS risk in AMD Systematic review and Metanalysis of RCT and Observational studies

Authors conclude "Intravitreal bevacizumab (IVTB) is used to treat age-related macular degeneration (ARMD), although its use is off-label and its cardiovascular safety has not been unequivocally established. Published data on IVTB in AMRD provide only a low level of evidence on its cardiovascular safety and do not support any finite conclusions."

Moja 2014 systemic safety bevacizumab and ranibizumab in AMD

Data from nine studies (3665 participants), including six published (2745 participants) and three unpublished (920 participants) RCTs,

At the maximum follow-up (one or two years), the estimated risk ratio (RR) of death with bevacizumab compared with ranibizumab was 1.10 (95% confidence interval (CI) 0.78 to 1.57, P value = 0.59; eight studies, 3338 participants; moderate quality evidence).

Based on the event rates in the studies, this gives a risk of death with ranibizumab of 3.4% and with bevacizumab of 3.7% (95% CI 2.7% to 5.3%).

For All Systemic SAEs, the estimated relative risk was RR 1.11; 95% CI 0.90 to 1.37, P value = 0.33) in participants assigned to bevacizumab versus ranibizumab nine studies, 3665 participants; low quality evidence). Based on the event rates in the studies, this gives a risk of SSAEs of 22.2% with ranibizumab and with bevacizumab of 24% (95% CI 20% to 29.1%).

The authors conclude current evidence is imprecise and might vary across levels of patient risks, but overall suggests that if a difference exists, it is likely to be small.

It is noted to be a significant overlap of studies with Solomon 2019.

Table 21

Bevacizumab compared with ranibizumab for neovascular age-related macular degeneration						
Patient or population: patients with neovascular age-related macular degeneration Intervention: bevacizumab Comparison: ranibizumab						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Ranibizumab	**Bevacizumab**				
All serious systemic adverse events Follow-up: 1 to 2 years	222 per 1000	240 per 1000 (200 to 291)	RR 1.08 (0.90 to 1.31)	3665 (9)	⊕⊕◯◯ **low** 1,2,3,4	
Infection	37 per 1000	50 per 1000 (36 to 69)	RR 1.34 (0.97 to 1.86)	3190 (6)	⊕⊕⊕◯ **moderate** 1,2,3	
Arterial thromboembolic event	35 per 1000	32 per 1000 (21 to 47)	RR 0.92 (0.62 to 1.37)	3190 (6)	⊕⊕⊕◯ **moderate** 1,2,3	
Myocardial infarction	14 per 1000	12 per 1000 (6 to 23)	RR 0.84 (0.42 to 1.66)	3190 (6)	⊕⊕⊕◯ **moderate** 1,2,3	
Stroke	11 per 1000	9 per 1000 (5 to 19)	RR 0.83 (0.42 to 1.66)	3190 (6)	⊕⊕⊕◯ **moderate** 1,2,3	
Gastrointestinal disorders MedDRA class	16 per 1000	29 per 1000 (16 to 50)	RR 1.82 (1.04 to 3.19)	3190 (6)	⊕⊕⊕◯ **moderate** 1,4,5	

Poku 2014 IVT bevacizumab safety systematic review

Eighty-nine studies of bevacizumab monotherapy in patients with diverse ophthalmic conditions were included. ▪ A majority of relevant existing studies were characterised by small sample sizes, unclear diagnostic criteria and reporting of safety outcomes.

The relationship between the incidence of adverse events and variables such as injection techniques, pre-existing risk factors (eg, immunosuppression, cross-contamination) and quality of bevacizumab could not be explored due to limited data.

The most robust data for safety are from the CATT and IVAN trials which were large trials that reported longer term data. The results of these trials when meta-analysed revealed a statistically significantly higher rate of 1 or more serious systematic AE (RR 1.27; 95% CI 1.09 to 1.47) in the IVB group.

Authors state that it is also important to note that AEs were more common in those patients who received discontinuous rather than patients on continuous treatment, that is, those with lower exposure to the drug experienced higher AE rates. An explanation for this observation is the possible role of immunological processes in drug interactions

Vander reis 2012 systematic review of ADRs of IVT anti-VEGF treatments.

This paper presented tabulated data estimates on ocular and systemic ADR frequencies from both safety and efficacy studies on ADRs for bevacizumab.

The following studies provided data which was either overlapping, or superseded or pooled with other anti-VEGF treatments and thus not particularly informative for a specific drug product in the current context:

Schmuker 2011, Micieli 2010; Smith 2011 Cochrane, Low 2019 systematic review and metanalysis-2018 for NAMD, DMO and RVO, Nguyen 2018 anti VEGF AMD metanalysis of RCTS, Braithwaite Cochrane review of anti-VEGF secondary to CRVO.

In addition, the submitted (CTD) clinical summary of safety, clinical summary of efficacy, the clinical summary of clinical pharmacology, the clinical overview and the proposed SPC for Ipique were reviewed in the light of the literature.

Re-examination assessment regarding selection criteria for literature search:

According to the applicant, the final search and selection of articles was based on relevance according to the inclusion criteria which are assumed to be the below (Table 22).

Table 22

Population	Adult patients with wet age-related macular degeneration
Intervention	Bevacizumab per intravitreal injection
Comparator	No comparator, photodynamic therapy, pegatinib, placebo, ranibizumab, or aflibercept
Outcomes	Ophthalmic-related safety outcomes: intraocular inflammation, endophthalmitis, uveitis, retinal detachment
	Cardio-thromboembolic safety outcomes: myocardial infarction, ischemic stroke, hemorrhagic stroke, bleeding, transient ischemic attack, venous thromboembolism, arterial-thromboembolic events, hypertension
Study Designs	Systematic reviews with meta-analysis and observational studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined, did not asses safety outcomes as a primary outcome, were duplicate publications, case series with < 2000 injections or < 100 patients, they were published prior to 2007, they were not written in English, or reported on studies not performed in the EU, North America or Australia.

Critical Appraisal of Individual Studies

Systematic reviews reports were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.
The included observational studies were critically appraised using the modified Downs and Black checklist. A review of the strengths and limitations of each included study are described narratively in the tables.

Search results

The first searches based on the search terms: intravitreal bevacizumab, safety, adverse events, clinical trials, case series and age-associated macula degeneration.

Considering the applicant's MO15 response, and the above, this is not considered a reproductible literature search string /strategy. Neither is it possible to assess how subjectively the criteria were applied or how relevance was assessed. It is not clear why the literature search was restricted to the above chosen study types, and ADRs.

The applicant justified the approach taken in the MO15 response stating that:

"the applicant has relied on a key Cochrane review by Solomon et al. (2019) on the premise that the scientific community generally recognizes Cochrane reviews as the gold standard of systematic review" and that

"In their systematic review with the purpose of validating the Cochrane review by Solomon, the applicant has not identified papers with clinical trial data or case series of sufficient quality, which were not discussed in at least one of the meta-analyses validating these metaanalyses as unbiased and complete. …. not a single paper was found with data contradicting the general conclusions of the metaanalyses",

Apart from the statements by the applicant, no information/evidence on the validation of the search strategy was submitted. However, the applicant added a number of references relevant to efficacy (eg Li et al Cochrane 2020, Maguire et al 2016) to their MO15 response. It is agreed that Cochrane systematic reviews are recognised for quality. However, it is questioned that the literature list is comprehensive.

A limited literature review conducted by the assessor identified some literature articles potentially relevant for the safety and efficacy discussion as follows; Kwon 2018; The association between myocardial infarction and intravitreal bevacizumab injection. Weinstein 2020; Intravitreal bevacizumab treatment for neovascular age-related macular degeneration and thromboembolic events. Jaffe 2018; Macular Morphology and Visual Acuity in Year Five of the Comparison of Age-related Macular Degeneration Treatments Trials. Daniel 2020; Incidence and Progression of Nongeographic Atrophy in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) Clinical Trial. George 2014; The methodological quality of systematic reviews comparing intravitreal bevacizumab and alternates for neovascular age related macular degeneration: A systematic review of reviews. Chin-yee 2016; A systematic review of as needed versus treat and extend ranibizumab or bevacizumab treatment regimens for neovascular age-related macular degeneration.

Some articles have been submitted in the dossier but not deeply discussed in the clinical summary or literature review or MO15 responses, or with regard to the proposed SPC. *Hanhart 2018; Mortality associated with bevacizumab intravitreal injections in age-related macular degeneration patients after acute myocardial infarct: a retrospective population-based survival analysis. Maguire 2016:Five-Year Outcomes with Anti-Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration: The Comparison of Age-Related Macular Degeneration Treatments Trials. Amarakoon 2019; Bevacizumab in age-related macular degeneration: a randomized controlled trial on the effect of on-demand therapy every 4 or 8 weeks.*

For example, re Maguire, additional discussions on the mean change of vision at 5 years vs baseline, and the likely selectivity of good responders at 5 years was not discussed.

Regarding safety

There is no in-depth discussion of possible estimates on frequency of ADRs or the impact of missing studies/articles in the Systemic Review Document, the Clinical Summary of Safety, or Clinical Overview giving a comprehensive and critical synthesis of information, and how the information can be justified for the draft SmPC. No *in-depth* analysis or discussion of ATC events, or gastrointestinal safety was provided by the applicant. It is noted that for example gastro-intestinal ADRs is listed as *nausea* in the draft SmPC Ipique section 4.8, and that the proposed SPC section on special warnings 4.4 currently states. "*There are no data indicating a systemic effect of bevacizumab after intravitreal injection."* This statement is questioned considering available literature see Thulliez 2018 re VTE, and the existence of an anti-VEGF class warning in section 4.8 Lucentis EU product information re arterial thromboembolic events, the American academy of ophthalmology 2015; "There was a higher rate of serious systemic events (e.g., arteriothrombotic events, venous thrombosis, or gastrointestinal disorders, such as

haemorrhage) among patients treated with bevacizumab compared with ranibizumab (24% vs. 19%, P=0.04) and this statistically significant difference was persistent at 2 years of follow-up. Solomon 2019 notes that "*There are lingering concerns about ocular and systemic safety issues", and "At both one-year and two-year follow- up, fewer participants in the ranibizumab groups appear to have experienced any serious systemic adverse events compared with those in the bevacizumab groups."*

It is noted that the proposed SmPC for Ipique section 4.8 *Tabulated list of adverse reactions* is identical (except 1 possible error regarding endophthalmitis included twice (once as unknown frequency and once as uncommon)) for the included ADRs as for Lucentis. This is despite the fact that the Ipique states that data come from observational studies and for Lucentis SmPC 4.8 that data come from administration of Lucentis in clinical trials. The applicant's submitted clinical overview CTD 2.5 and 2.7, and the systematic review of literature document, there is no in depth adequate critical discussion or justification of what has been proposed for the Ipique SmPC in terms of safety. Whilst Bevacizumab clinical trials lack granularity for non-serious ADRs, the articles submitted in the dossier could provide relevant information e.g. Van der reis 2012.

Regarding posology

The proposed Ipique SmPC includes loading dose, PRN and treat and extend; and is largely identical to Lucentis. The clinical overview only indicates that dosage is 1.25mg, and the dose should at least 4 weeks apart. The optimum posology is not discussed in depth or justified in the light of literature. For example from the Comparison of Age-related Macular Degeneration Treatment Trials (CATT) which evaluated the relative efficacy of ranibizumab and bevacizumab to determine whether an as-needed (pro-re-nata, PRN) regimen would compromise long-term visual acuity, as compared with a monthly regimen, twelve-month data reported that between PRN bevacizumab compared to monthly bevacizumab was inconclusive (did not meet non-inferiority). Furthermore, in CATT, there were increased ADRs with bevacizumab with discontinuous use.

Literature has suggested that employing a PRN approach in a real-life setting often produces unsatisfactory results, mainly during the maintenance phase. Patients typically experience a gradual deterioration of visual function after the initial visual acuity gain obtained during the loading phase (3 monthly injections) (Holz 2015 Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration). It is appreciated that the applicant has provided a reference to the Cochrane review LI et al 2020 in the response to MO15.

Cochrane review of pooled anti-VEGF concluded monthly regimens are probably more effective than PRN regimens using seven or eight injections in the first year, but considered the difference was small and clinically insignificant, and that endophthalmitis is probably more common with monthly injections. CD012208.pdf (nih.gov) updated 2019. However, there is no discussion by the applicant about heterogeneity and the pooling approach and the cautions described in regard to PRN dosing of bevacizumab in the American Academy of Ophthalmology preferred practice guidance.

In terms of grey literature, the applicant justifies the benefit risk of bevacizumab IVT in nAMD with reference to the practice guidances by different ophthalmology learned societies including the American Academy of Ophthalmology (AAO). It is noted however, that the applicant has not included or discussed a reference to the statement from the AAO July 2021 that:

"*it is inappropriate for plans to recommend or mandate use of these [Avastin] biosimilars for intravitreal injection without a prior clinical trial in eye disease and testing for retinal toxicity"*

The applicant makes reference in the re-examination submission to post-marketing data associated with another product Lumiere, which was referenced by the applicant also in the response package to the day 120 list of questions. The applicant claims that Lumiere is a comparable product, derived from a comparable process and derived from the same Master Cell Bank.

In the absence of a formal assessment of similarity, and given the insufficient data provided by the applicant in support of it, it is not possible to further consider these data, given potential uncertainties regarding differences between products.

The Lumiere data are summarised for reference:

2 PSURS for the Lumiere product for the following periods and products were submitted.

PSUR no 4- 7 Nov 2019 – 4 Jun 2020: estimated 3,192 patients (based on 3 doses /patient): no ADR reports.

PSUR no 1- 05/06/2018 – 06/11/2018: estimated 589 patients, (based on 3 doses /patient), 2 reports of adverse events were received, one of which was serious. Both events were listed.

In addition, an open label uncontrolled study in 21 patients was mentioned, for which a publication was submitted by the applicant also in the response package to the day 120 list of questions. The observed cumulative rate (total) of AEs was 79 reports of AEs per 100 intravitreal applications. The majority of cases (57 reports: 72.2%) were AEs listed (expected) in the Investigator's Brochure for LUMIERE.

In any case, the data generated with Lumiere are qualitatively (i.e. due to the lack of appropriate study design and comparator) not suited to neither (1) establish a bridge with Avastin nor(2) support efficacy and safety of Lumiere itself .

Re-examination conclusions re MO15

The re-examination assessment of MO15 with respect to the following issues:

i. A detailed scientific bibliography for each of the claimed indications to address the clinical characteristics of bevacizumab is again requested. A qualitative synthesis needs to be established and a systematic approach needs to be applied, so that selection bias can be excluded. Search criteria, selection criteria and the respective selection process shall been outlined (e.g. via a PRISMA flow diagram).

ii. The potential for publication bias and the availability of 'grey literature' as potentially relevant data source should be addressed for each search.

iii. Besides RCTs, controlled trials comparing different doses or regimens as well as single arm studies could be relevant insofar as they might inform recommendations regarding posology, optimal treatment timing and duration as well as target population definition. These aspects need to be discussed based on the provided publications (see also **OC 23 b** on dose regimens).

iv. All available literature should be graded and discussed according to their quality and relevance for this application.

v. The clinical overviews and summaries (pharmacology, efficacy and safety) need to be updated according to requirements outlined in the Notice to Applicants Volume 2 B and need to address the target indications.

vi. In addition, coherence of scientific assessments should be argued based on a comprehensive literature search for each target indication.

Overall conclusions at re-examination for MO 15 resubmitted response:

The utility of the literature provided, in terms of overall broadly establishing safety and efficacy of Avastin IVT is supportive but not comprehensive. A comprehensive synthesis of information has not been critically compiled in order to provide complete product information to patients and prescribers.

Regarding the grounds for re-examination, the reassessment of the response to MO15 and extent of the literature review has not materially addressed the fundamental issue outlined in the grounds for refusal. That is, in the absence of an appropriate clinical comparison in the intended indication and route of administration to demonstrate that Ipique and the medicinal product referred to in the literature are similar, the data from the literature cannot be extrapolated to Ipique in the claimed indication regarding demonstration of the relevance of the literature to the applied for product.

5.3.5. Assessment of response to OC18 – Former OC 122 at re-examination

It is unclear how the established inhibition of tumour angiogenesis could be translated in a beneficial effect for AMD or DME. The role of VEGF-inhibition in approved oncology indications should be contextualised to the aspired ophthalmological indications, if possible. The applicant should furthermore provide an adequate literature review on pharmacodynamics of bevacizumab (focus intraocular use) for this well-established use application and follow recommendations on literature reviews outlined in other questions, e.g. the former MO 114. In addition, details of the literature search for pharmacodynamic interactions should be outlined. Statements on potential genetic differences in PD response should be made that are supported by clinical data and a respective discussion.

5.3.5.1. Applicants Response

Introduction

The applicant is seeking approval for the use of bevacizumab for the treatment of neovascular AMD and not for the oncology indications. Today, the European Commission has approved an EU approved biosimilar and it is kindly noted that Ipique is identical to EU biosimilar of Avastin – development. Because the use of bevacizumab in oncology indications is authorised, the applicant relies on the mode of action and pharmacodynamics of bevacizumab in these indications as has been summarised in the Avastin and EU approved biosimilar. The applicant strongly holds the position that a full elaboration on the pharmacodynamics of bevacizumab in oncology is not required within the Ipique marketing authorisation application. Nevertheless, a summary contextualizing the role of VEGF in neovascularisation in tumours and in the macular, as well as the pharmacodynamics of bevacizumab after intravenous (oncology) and intravitreal administration (AMD) has been provided in this response.

Literature about preclinical and clinical pharmacology of intravitreal bevacizumab, is scarce as demonstrated by a systematic review of relevant databases. Still, the role of VEGF in AMD as well as the effect of neutralizing VEGF in-vivo and in-vitro have been demonstrated and the available clinical literature seems overall of good quality and supportive of the safety and efficacy of Ipique in AMD, implying a similar efficacy as other anti-VEGF antibodies (ranibizumab and aflibercept) and confirming a clinical pharmacodynamic effect in terms of clinical endpoints. The clinical evidence confirms the (limited) primary pharmacology data in AMD.

Mode of action of bevacizumab in oncological indications

Bevacizumab binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.

Pharmacodynamic effects

Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast, pancreas, and prostate. Metastatic disease progression was inhibited, and microvascular permeability was reduced.

Background of bevacizumab development

The human VEGF-A gene is organised in 8 exons separated by 7 introns resulting in the generation of at least 7 isoforms of VEGF-A xxx, where xxx is the number of amino acids encoded. The various isoforms contain between 121 and 206 amino acids, where VEGF-A165 is the predominant member, followed by VEGF-A121 [Ferrara et al. 2003, Ferrara 2010].

It is widely recognised that VEGF is a key mediator of neovascularisation associated with tumours. Today, the role and properties of VEGF and the inhibition thereof in cancerous growth is considered text-book knowledge. Angiogenesis, the creation of new blood vessels from existing ones, is essential in cancer to supply cancerous growth. Moreover, the development and the progression of the tumour and its metastases are the result of an efficient vascular response. Cancer cells release and activate different angiogenic growth factors and their receptors in the tumour microenvironment to promote the angiogenic process. The most important pro-angiogenic factor is VEGF because of its mitogen activity on vascular endothelium. VEGF expression by tumour cells is upregulated by multiple stimuli together with oncogenes and mutation of tumour suppressors.

Anti-VEGF antibodies such as bevacizumab obstruct the binding of circulating vascular endothelial growth factor to its receptors and thereby prevents neovascularisation. Bevacizumab (Avastin) is licensed for several oncological indications.

Similarly, angiogenesis in the eye and the role of VEGF in that process is well understood. Neovascularisation in the eye is associated with various disorders and is often causing severe loss of vision and eventually blindness. Among these disorders, age-related macular degeneration (AMD) is the most prevalent.

Vascular endothelial growth factors (VEGFs) play an important role in the pathogenesis of neovascularisation processes of macular and in tumours. Evidently, VEGF-A is the main regulator of pathologic angiogenesis in the eye. The rationale for neutralisation of VEGF-A in disease of neovascularisation of the macular is demonstrated through animal data (e.g., Adamis 1996) and human data. An increased level of VEGF in aqueous humor as measured in patients undergoing intraocular surgery, was observed in patients with neovascular eye disease such as neovascular glaucoma [Tripathi 1998]; diabetic retinopathy, neovascularisation of the iris and ischemic occlusion of the central vein [Aiello 1994]; and proliferative diabetic retinopathy [Adamis 1994]. Importantly, Hata et al. (2017) measured VEGF in 21 treatment naïve human AMD eyes. Aqueous humor samples were collected prior to initial anti-VEGF injection, VEGF levels of 89.8 ± 45.0 pg/ml were measured in neovascular AMD eyes.

On that premise, Genentech Inc. (California, USA) developed the anti-VEGF antibodies bevacizumab and ranibizumab for treatment of respectively cancers and neovascularisation disorders of the eye. The lead compound for both these therapeutics was a murine anti-human-VEGF-A165 antibody (code MuMab A.4.6.1 - Information about the generation and characterisation of this murine antibody is presented in the box below).

Generation and biological characterisation of an anti-human-VEGFA165 murine MAbs (muMAbs)

An anti-VEGF-A165 antibody was developed on the notion that the most abundant product of the VEGF gene is VEGF165.

For immunisation recombinant human VEGF165 [Leung et al. 1989] was conjugated with keyhole limpet hemocyanin (KLH). BALB/c mice were hyperimmunised intraperitioneally with 10 micrograms of KLH/VEGF165 conjugate resuspended in MPL/TDM adjuvant. Spleen cells were fused with mouse myeloma [Köhler and Milstein 1975]. Hybridomas were screened and anti-human-VEGF-A165 muMAbs were cloned.

Four anti-VEGF antibodies (IgG1 type) were selected, of which Mab A.4.6.1 binds to the receptor binding domain sequence in VEGF-A and neutralises three isoforms of VEGF-A: 121, 165 and 189. Furthermore, it showed very potent neutralising activities in the ACE proliferation assay as well as in the in vivo assays: angiogenesis in chicken chorioallantoic membrane, and vascular permeability assay in male guinea pig [Kim 1992].

MuMab A.4.6.1, was tested in a non-human primate model for neovascularisation of the human retina. This cynomolgus monkey model permits the direct visualisation of retinal ischemia associated ocular neovascularisation and closely resembles human central vein occlusion. Laser retinal vein occlusion was used to produce retinal ischemia in 16 eyes of 8 animals. Eyes were randomised to treatment every other day with intravitreal injection of either muMab A.4.6.1 or a control monoclonal of the same isotype. Serial iris fluorescein angiograms were assessed using a standardised grading system and retinal VEGF and placental growth factor expression were assessed by Northern blotting. Zero of eight eyes receiving neutralising anti-VEGF antibodies developed iris neovascularisation (P=0.03). Furthermore, intravitreal injection did not impair the ability of the ischemic retina to increase VEGF messenger RNA expression [Adamis 1996]. As discussed above, VEGF is also a key mediator of neovascularisation associated with tumours. VEGF-A expression by tumour cells is upregulated by multiple stimuli together with oncogenes and mutation of tumour suppressors [Maria 2007]. MuMab A.4.6.1 has been shown to potently suppress angiogenesis and growth in a variety of human tumour cell lines transplanted into nude mice by neutralising VEGF-A [Presta 1997].

Subsequently, the murine antibody was humanised by transferring the six CDRs from muMab A.4.6.1 to a human framework (IgG1). Seven framework residues in the humanised variable light (VL) domain were changed from human to murine to achieve binding of VEGF equivalent to muMab A.4.6.1.

First, humanised Fab fragments were constructed using the pEMX1 vector containing a DNA fragment encoding consensus human κ subgroup I light chain (VLκ-CL) and a consensus human subgroup III heavy chain (VHIII-CH1) and an alkaline phosphatase promotor. The six CDRs were changed to the murine A.4.6.1 sequence; the residues included in each CDR were from the sequence-based CDR definitions [Kabat 1991]. The fab fragment expressed in *E.coli* therefore consisted of a complete human framework with the six complete murine CDR sequences. A series of optimisations was performed resulting in Fab-1 to Fab-12, the last variant, Fab-12 had a similar binding activity the donor Mab, muMab A.4.6.1.

This Fab-12 variant is both the basis of Lucentis as well as Avastin. It was adapted for improved monovalent phage display and designated Y0192 [Muller 1998a]. Y0192 served as starting point for affinity maturation by phage display which yielded Y0317, a Fab fragment with a reported improved affinity and potency compared to Fab-12. Y0317 contained six mutations compared to Fab-12 [Chen 1999]. Y0317, or ranibizumab is the active substance of Lucentis® which is licensed for the treatment of neovascular AMD, visual impairment due to DME, proliferative diabetic retinopathy, choroidal neovascularisation, and branch RVO or central RVO.

The humanised IgG1-12 (of which the Fab fragment is Fab-12) is later developed as bevacizumab (Avastin®) [Chen 1999].

Bevacizumab and ranibizumab are directed against the same epitope A.4.6.1 and, as their pedigree shows, the molecules are highly related. Early studies claim a strongly improved binding of

ranibizumab (Y0317) compared to bevacizumab (IgG-12). However, these data were derived by comparing Y0317 (ranibizumab) to Fab-12 instead of IgG-12 (bevacizumab). In later studies comparing ranibizumab and bevacizumab directly, these differences proved to be minor. In a study from 1997, the KD of bevacizumab for VEGF-A165 was 58 pM, markedly lower than that reported previously for Fab-12 [Chen 1999, Presta 1997] and within twofold of the binding affinity of

ranibizumab [Papadopoulos 2012].

Considering:

i. the apparent similar binding KD (within twofold) of ranibizumab and bevacizumab towards the same epitope of VEGF
ii. the molar ratio of clinical dose of bevacizumab and ranibizumab (bevacizumab : ranibizumab 0.84)
iii. that ranibizumab and bevacizumab have the same specificity and share CDRs from the same donor molecule

It has been demonstrated that the activity of ranibizumab and bevacizumab is solely attributable to binding of Fab to VEGF, hence it is not surprising that there is not a difference in clinical effects between bevacizumab and ranibizumab in treatment of neovascular AMD. VEGF-A is overexpressed in the macular in nAMD and tumour tissues and has the same (patho)physiological role independent of the location of expression (e.g., eye or tumour). Furthermore, VEGF-A is neutralised by anti-VEGF inhibitors such as Y0317 (ranibizumab) and IgG1-12 (bevacizumab). Both antibodies target the same epitope of VEGF-A165. Therefore, the clinical safety and efficacy obtained in disorders as a result of neovascularisation of the macular are, as would be expected, similar.

Applying the same reasoning and considering that Ipique is biosimilar to Avastin, the pharmacology, safety and efficacy of Ipique demonstrated in NSCLC can be extrapolated to nAMD.

However, the applicant acknowledges the specific safety aspects related to intravitreal injection and has consequently chosen to follow the WEU route for MA thereby relying on the vast amount of evidence about the safe and efficacious use of bevacizumab in the treatment of neovascular AMD.

Mode of action / pharmacology of bevacizumab in neovascular AMD contextualised

VEGF is secreted by several cell types in the retina, such as vascular endothelial cells, retinal pigment epithelium, pericytes, retinal neurons, and astrocytes, indicating that VEGF plays important functions in ocular homeostasis. In particular, VEGF is a critical factor for the homeostasis and plasticity of both blood vessels and neurons [Amadio 2015]. Its' synthesis is upregulated by hypoxia, nitric oxide, growth factors (basic fibroblastic growth factor, epidermal growth factor, insulin-like growth factor, keratinocyte growth factor and platelet-derived growth factor), inflammatory mediators (IL-1, IL-6, IL-10, TNF-β and prostaglandin E2) and mechanical forces such as sheer and stretch [Stewart 2014].

It is widely recognised that VEGF, of which VEGF-A165 is the most abundant isoform, is a key mediator of neovascularisation in tumours and macular. VEGF expression is upregulated in tumours [e.g., Dvorak HF, 1991, Shweiki D, 1992 not included], and in patients with neovascular eye disease such as neovascular glaucoma [Tripathi 1998]; diabetic retinopathy, neovascularisation of the iris and ischemic occlusion of the central vein [Aiello 1994]; and proliferative diabetic retinopathy [Adamis 1994] and importantly in AMD [Hata 2016]. Notably, in the Avastin EPAR, reference is made to a study in the retina of cynomolgus monkeys by Shima et al. (1996). This study describes the comparison of the relative levels of alternatively spliced VEGF mRNAs and the localisation of VEGF mRNA in ischemic and nonischemic retinas of cynomolgus monkeys. In conclusion, the elevation of simVEGF121 and VEGF 165 in ischemic retinas is consistent with a role for diffusible, retina-derived angiogenic factors in the development of ocular neovascularisation. [Shima, 1998].

VEGF-A is proven to have the same (patho)physiological role independent of the location of expression (e.g., eye or tumour). Inhibition of vascular growth can be achieved through neutralisation of (circulating) vascular endothelial growth factor thereby obstructing binding to its receptors. Consequently, the approach to target VEGF in AMD and tumours is considered relevant and the mode of action (MoA) of bevacizumab in neovascular AMD is similar to the MoA in oncology. Anti-VEGF inhibitors such as bevacizumab and ranibizumab have been shown to effectively bind to VEGF in tumour and eye respectively.

The pharmacology of bevacizumab in oncology indications was primarily investigated in murine xenograft models using the parent murine antibody A.4.6.1 (muMab A.4.6.1) of ranibizumab and bevacizumab. MuMab A.4.6.1 has been shown to potently suppress angiogenesis and growth in a variety of human tumours transplanted into nude mice [Presta 1997]. Furthermore, bevacizumab

nd A4.6.1 were compared for their ability to inhibit bovine capillary endothelial cell proliferation in response to VEGF [Presta et al 1997]. The pharmacological activities of bevacizumab were evaluated in a number of in vitro assays using recombinant human VEGF. The two MAbs were essentially equivalent, both in potency and efficacy. The ED50s were, respectively, 50 ± 5 and 48 ± 8 ng/ml. 90 % inhibition was achieved at 500 ng/ml for both antibodies. Bevacizumab and A4.6.1 are pharmacologically equivalent when tested with human cells, human tissues or human VEGF isoforms [Kim 1992, Presta 1997].

The same parenteral murine antibody has shown efficacy in a non-human primate model for neovascularisation of the human retina showing prevention of neovascularisation [Adamis 1996]. From these study results is it derived that bevacizumab conclusively prevents neovascularisation in the eye and neovascularisation solid tumours: the compound targets human vascular endothelial growth factor A (VEGF-A) independent of the location of VEGF-A. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which contribute to the progression of the neovascular form of AMD. By binding to the VEGF-A isoforms (VEGF110, VEGF121 and VEGF165), bevacizumab prevents binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2 and thereby inhibits endothelial cell proliferation and neovascularisation.

Primary pharmacology

The intraocular pharmacodynamics relies on in vitro data, on very limited animal data and importantly on studies in humans demonstrating safety and efficacy (comparable to that of Lucentis). The efficacy and safety of bevacizumab in neovascular AMD is well established and it is kindly noted that the vast amount of clinical efficacy data about the use of bevacizumab in AMD is considered to prevail over non-clinical in-vitro and in-vivo pharmacology data. Clinical pharmacodynamic studies in which biomarkers such as VEGF is measured are very limited.

In-vitro pharmacodynamics

The in-vitro data consist of (comparative) cell-based potency assays and extensive binding studies as have been shared with the initial submission and were re-iterated in the responses to the List of Questions. Binding assays and potency assays that have been performed are listed in Table 23.

Table 23: In-vitro assays

- Binding to VEGF 165 by ELISA and SPR
- Binding to VEGF A variants 121, 189 and 206 by ELISA
- Absence of binding to VEGF B, C and D variants and PIGF by BLI
- Potency by antiproliferation bioassay using HUVECs

- Potency by VEGF blocker reporter bioassay
- Potency by PathHunter® KDR/KDR dimerisation bioassay
- Absence of CDC and ADCC
- Binding to C1q by ELISA
- Binding to FcγRI, FcγRIIa and FcγRIIb, by SPR
- Binding to FcγRIIIa V Variant by AlphaLISA and SPR
- Binding to FcγRIIIa F Variant by AlphaLISA and SPR
- Binding to macrophage mannose receptor by BLI
- Binding to FcRn by ELISA and SPR

Bevacizumab binds with high affinity to the VEGF-A isoforms. The binding is strong (in the nanomolar region - (*K* D = 58–1100 pM), dissociates slowly and it is likely that once the bevacizumab-VEGF complex is formed, it is very stable [Papadopoulos 2012, Presta 1997].

Bevacizumab dose-dependently inhibited VEGF-induced proliferation in human umbilical vein endothelial cell (HUVEC), which are cells that express the VEGF-receptors, with IC50 values of about 60 ng/mL [Comparability reports and establishment of reference standards, Liu 2019(b), Jiang et al., Avastin public assessment report, and others].

This is around the clinical systematic Cmax after intravitreal injection. Consequently, no significant systemic VEGF-inhibiting activity is expected in humans.

Migration and invasion of endothelial cells are essential in vitro angiogenesis. Whether bevacizumab inhibits this process was tested in a wound-healing assay and in a Transwell invasion assay. Bevacizumab inhibits HUVEC migration in a wound healing assay by 66%. When tested in a Transwell invasion assay whereby the ability of HUVECs to pass through a Matrigel and Transwell membrane barrier was tested, bevacizumab inhibits invasion by about 60% in this assay [Liu 2019(b)]. In addition, in-vitro tube formation (in Matrigel) was inhibited by about 60% [Liu 2019(b) and Jiang 2020]. Furthermore, bevacizumab was found to inhibit choroid-retina endothelial (RF/6A) and 3-D cultured HUVEC cells [Hu 2014].

In-vivo pharmacodynamics

MuMab A.4.6.1, the parenteral murine anti-human antibody of bevacizumab was tested in a nonhuman primate model for neovascularisation of the human retina. This cynomolgus monkey model permits the direct visualisation of retinal ischemia associated ocular neovascularisation and closely resembles human central vein occlusion. Laser retinal vein occlusion was used to produce retinal ischemia in 16 eyes of 8 animals. Eyes were randomised to treatment every other day with intravitreal injection of either muMab A.4.6.1 or a control monoclonal of the same isotype. Serial iris fluorescein angiograms were assessed using a standardised grading system and retinal VEGF and placental growth factor expression were assessed by Northern blotting. Zero of eight eyes receiving neutralizing anti-VEGF antibodies developed iris neovascularisation (P=0.03).

Furthermore, intravitreal injection did not impair the ability of the ischemic retina to increase VEGF messenger RNA expression [Adamis 1996].

Each bevacizumab molecule potentially binds two different VEGF dimers, each of which can be captured by two different bevacizumab molecules.

In their assessment (D150 JAR / D180 LoOI) the rapporteurs summarised: "*Evidence for the in vivo activity of bevacizumab as submitted by the Applicant is limited to a couple of non-clinical studies in several species like pigs, monkeys, mice and rabbits, which demonstrated effects mainly in models of choroidal or corneal neovascularisation or uveitis (Lassota et al, 2010; Goody et al, 2011; Hollanders et al, 2015; Avisar et al, 2010; Ayyildiz et al, 2015). In a rapid search in PubMed some additional publications of non-clinical in vivo pharmacology studies of intravitreal or topical bevacizumab in choroid neovascularisation models in the mouse (Bock et al, 2007), rat (Lu et al, 2009, Sahan et al, 2020), or monkey (Lichtlen et al, 2010; Olvera-Montaño et al, 2019) could be identified, some comparing the activity of bevacizumab with other anti-VEGF drugs. There is, however, some evidence that rodent and rabbit CNV (choroid neovascularisation) models are not appropriate for intravitreal bevacizumab activity assessment (Lu et al, 2009; Yu et al, 2008) probably due to differences in retinal anatomy and the narrow species specificity of anti-VEGF antibodies. Hence, the in vivo pharmacologic effects of bevacizumab may best be studied reliably in primate models.*"

Indicating that both Lichtlen et al. and Olvera-Montaño et al (respectively 2010 and 2019) have published studies demonstrating a CNV lesion reduction (clinical endpoint) after intravitreal bevacizumab in respectively a cynomolgus and rhesus laser-induced CNV monkey model.

Bevacizumab was used as a (positive) control in both studies. Considering the extensive clinical experience with intravitreal bevacizumab in macular degeneration, also investigating secondary endpoints such as CNV membrane growth and leakage, the monkey studies as well as the rodent and rabbit studies have been superseded by the clinical data.

Nevertheless an additional literature search has been performed, see box below.

A review about the pharmacodynamics of intravitreal bevacizumab has been authored by Michael

W. Stewart (Pharmacokinetics, pharmacodynamics and pre-clinical characteristics of ophthalmic drugs that bind VEGF. Expert Review of Clinical Pharmacology, 2014). Medline/PubMed searches

using the keywords aflibercept, bevacizumab, pegaptanib and ranibizumab were performed to identify manuscripts. Additional manuscripts were identified from the reference list of these articles. The review of Stewart covers literature published between 1998 and 2013. Based on this review, the applicant has performed two additional searches for literature published from 2012 on, using the following arguments (Search 1): vivo AND pharmacodynamic AND intravitreal AND bevacizumab in PubMed between 2012-2021; and (Search 2): vivo AND pharmacodynamics AND intraocular AND bevacizumab. Double hits were removed, and the list is presented in Annex 1 of this response. All literature in the list has been assessed (39 publications) and the relevant literature was selected (14 publications). Most of the literature pertains to the development of new antiangiogenic compounds or existing anti-VEGF in new formulations for e.g., sustained release. Bevacizumab was used as a positive control in these studies.

It was demonstrated that bevacizumab is delivered at the site of the retina after intravitreal injection in a CNV model of mice [De Cogan 2017].

Bevacizumab binds exclusively to diffusible VEGF, but the resultant clinical response is complex and disease dependent. VEGF levels are elevated in neovascular AMD, and these stimulate blood vessel development. Intervention with intravitreal bevacizumab blocks VEGF from binding to its receptors.

Bevacizumab decreases programmed retinal cell death (apoptosis) and increases proliferation (gliosis) and reactivity in juvenile rabbit eyes. After both single and repeated injections of bevacizumab into adult rabbit eyes, ERGs and histological analyses were normal up to 4 weeks later. However, bevacizumab disrupts photoreceptor mitochondria and apoptotic protein (bax, caspase-3, caspase-9) expression and causes mild dose-related apoptosis. Single injections of bevacizumab do not cause

structural changes, gliosis or apoptosis in the porcine retina, but VEGF transcription is downregulated in the retina (by 60%) and retinal pigment epithelium (by 35%). Early injection of bevacizumab prevents VEGF-induced disc edema, vascular hyperemia and tortuosity and retinal and iris neovascularisation, but late injection leads to capillary closure. After injections of bevacizumab into streptozotocin-induced rats, concentrations of VEGF decreased for 1 month and CD34 decreased for 2 months, suggesting that VEGF suppression occurred quickly but the effects on endothelial cell proliferation were delayed. In rats with endotoxin-induced uveitis, intravitreal bevacizumab increases the concentrations of MCP-1, RANTES and IFN-γ, therefore suggesting that bevacizumab should be used with caution in patients with uveitis [Stewart 2014]. An inhibitory effect of bevacizumab on blood vessel formation and thus reduction of vascular density was demonstrated in chicken embryos by about 58% [Liu 2019(a), Liu 2019(b)]. In a rabbit CNV model constructed by laser photocoagulation an intravitreal injection of bevacizumab reduced the leakage area of CNV by 30% [Mu 2018]. In mouse model with streptozotocin-induced diabetes, a preoperative intravitreal injection of bevacizumab reduced the VEGF-A levels but not the galectin-1 levels [Kanda 2015]. Furthermore, bevacizumab demonstrates to attenuate the increase in retinal vascular leakage and diabetes-induced blood retinal barrier breakdown in the diabetic (streptozotocin) mice [Abu El-Asrar 2015].

Clinical pharmacodynamics

Intravitreal bevacizumab has been demonstrated to be safe and efficacious in the treatment of neovascular AMD.

Bevacizumab exerts inhibitory effects on angiogenesis and has stabilizing actions on vessel permeability through the blocking of VEGF165, 121 and 110. Demonstration of clinical efficacy of intravitreal bevacizumab has been demonstrated in neovascular age-related degeneration, hence proof of concept has been provided with these studies, mostly by comparing its' efficacy to ranibizumab. In a number of these studies CNV membrane growth and leakage was explored as a (secondary) outcome measure with fluorescein angiography and to a lesser extent with ocular coherence tomography (OCT) as an exploratory analysis. Both fluorescein angiography and OCT are recognised as adequate tools for investigation CNV membrane growth and leakage. In addition, thickness of the CNV was measured. In other studies [e.g. Shetty 2008, Macky 2012] retinal function prior and after intravitreal bevacizumab using electrophysiological tests: bevacizumab did not appear toxic to the retina or the optic nerves at a dose of 1.25 mg.

In a study by Hata et al. (2017) VEGF was measured in 21 treatment naïve human AMD eyes. Aqueous humor samples were collected prior to initial anti-VEGF injection, VEGF levels of 89.8 ± 45.0 pg/ml were measured in neovascular AMD eyes. The effect of bevacizumab on the VEGF levels was not investigated in this study.

Tanaka et al. (2021) measured the changes in the complement activation products (C3a and C4a) and cytokines (including VEGF in the aqueous humor of eyes with drusen-associated nAMD during bevacizumab therapy). The VEGF level decreased significantly (from about 38 pg/mL at baseline to about 8 pg/mL two months after treatment) indicating the effect of intravitreal bevacizumab. C3a level increased at 2 months after the initial bevacizumab injections. The tendency of C3a to increase and for VEGF to decrease at 2 months was similar across CNV size. The correlations between the C3a and VEGF levels differed at baseline and 2 months. The activation of the complement system after anti-VEGF therapy did not change the clinical outcome of the eyes with CNV for 1 year and no significant differences were observed between the elevation of C3a after bevacizumab treatment and the logMAR changes, achievement of dry maculas, and the number of injections for 12 months after treatment were observed.

Pharmacodynamic drug interactions

Although combination therapies with triamcinolone, verteporfin and corticosteroids have been explored, currently intravitreal bevacizumab is used as monotherapy in the treatment of macular neovascularisation in AMD, DME and RVO. Considering the mode of action of bevacizumab and the absence of an effect on the cell metabolism, any interaction is unlikely. This is confirmed in the SmPC of Avastin which states the absence of any interaction with concomitant anticancer therapies.

Systemic exposure

Please refer to the applicants' safety-assessment about the systemic exposure.

Potential genetic differences in PD response

Genetic differences might impact PD response of intravitreal bevacizumab. In particular one study by Gourgouli (2020) is considered relevant.

A total of 170 patients with dry AMD and 52 neovascular AMD patients were genotyped for the following single nucleotide polymorphisms (SNPs): rs1061170/Y402H in CFH gene, rs10490924/A69S in ARMS2 gene, rs9332739/E318D and rs547154/IVS10 in C2 gene, and rs4151667/L9H and rs2072633/IVS17 in CFB gene. Treatment response was evaluated by comparing visual acuity and optical coherence tomography between baseline and at the end of the

treatment. The CFH/Y402H variant was associated with the response to antioxidants in dry AMD patients. Carriers of one or two CFH risk alleles displayed a lower chance of responding compared to those with no risk allele. No association of antioxidants' response and ARMS2/A69S genotype was identified. The analysis of the C2 and CFB genetic variants (protective SNPs) revealed that antioxidant supplementation was much more effective in protective SNP carriers. In neovascular AMD patients, the analysis indicated that Y402H homozygous patients were less likely to respond to anti-VEGF therapy compared to heterozygous. Regarding the ARMS2/A69S genotype, carriers of the risk variant experienced significantly worse treatment outcome compared to wild-type patients [Gourgouli 2020].

5.3.5.2. Assessment of the response

This Other Concern with the same response from the applicant was already considered resolved before adoption of the initial opinion of the CHMP, in the Day 195 Joint Assessment Report of the responses to the list of outstanding issues.

5.3.6. Report from the Ad Hoc advisory group (AHEG)

The Experts considered the principles of the grounds for refusal. The issues are covered in their views below.

1. **discuss whether for extrapolation of efficacy and safety, the comparability of the biological medicinal products Ipique IVT vs Avastin can be established considering that source data derive from different indications and administration routes. Discussion should consider mechanism of action (binding affinity to all VEGF isoforms present in the eye, PK/PD data, anatomical characteristics, etc of Ipique and Avastin and other relevant factors such as background oncology treatments, population characteristics, relative doses and routes.**

   The specific following sub-questions address elements to further elaborate the overall discussion:

i. discuss whether IVT and IV relative immunogenicity in general (as well as related treatment failure and risk of hypersensitivity reactions) can be assumed with certainty to be the same taking into account immune privilege of the eye, breakdown of blood ocular barrier and treatment-related factors.

The experts expressed the view that there is a modest level of uncertainty regarding the existence of differences in the immunogenicity between Avastin and Ipique.

ii. Discuss the potential for intraocular inflammation or other local adverse reactions

a) with IVT anti-VEGFs products in general (immunogenicity, toxicity associated with impurities or possible off-target activity), and

b) the potential implications and uncertainties specifically for Ipique when administered IVT (see annexes including Summary of product differences);

The Experts observed that safety should not be assumed but demonstrated. Given the experience with other products used intravitreally, it was mentioned by the Experts that differences in the toxicity – for example associated with impurities – could exist and could potentially be source of significant problems in clinical practice.

In support of this view, Experts mentioned that several treatment guidelines and Ophthalmology societies have expressed the view that biosimilars of Avastin should not be used intravitreally without a prior clinical trial in eye disease and testing for retinal toxicity. There was divergence on this point (see iii below).

iii. provide views if any further data, such as a clinical trial are needed pre-authorisation to determine comparable efficacy and safety of Ipique with Avastin IVT, given that Ipique has not been administered IVT in a clinical trial setting although has been shown to be biosimilar to Avastin in the oncological setting and if yes, the nature of such data;

The Experts observed that the approval of a product that was never administered in the eye would raise relevant safety concerns. They also noted that clinical trials in the target indication are feasible and are indeed conducted. Experts expressed the view that a trial enrolling around 300 patients, primarily targeting a safety objective, would be both necessary and feasible. The presence of a placebo arm was not deemed necessary by the Experts.

There was however divergence on this point where other experts considered that no additional data of safety and efficacy of Ipique were needed, and that there are very limited safety issues with Avastin IVT based on Italian experience as long as sterile 'fractionation' of multi-dose vials or preferably single dose intravitreal preparations can be ensured.

iv. Provide views on the risk analysis on administration of IVT Ipique vs Avastin conducted by the applicant (See applicant risk assessment from the grounds for re-examination section c)

As expressed above, the risk analysis is based on assumptions but cannot give certainty of sufficient safety.

Of note, both the efficacy and the safety of Avastin IVT were well recognised.

5.3.7. Oral explanation

The applicant presented at an oral explanation the grounds for re-examination.

Information or argumentation presented by the applicant included the following information on slides 13-17 of the applicant's presentation:

- Although bevacizumab biosimilars, including EU approved biosimilar , are increasingly used for intravitreal treatment no specific safety issues have been reported.
- No safety issues reported in publication of (small) case studies of intravitreal bevaciumab.
- Screen shots of health authority information from IT, NL and FR-Iile de France about off-label use of Avastin biosimilar use in the respective territories.

The applicant's statements on biosimilar safety in IVT off label use are not sufficient to establish the safety profile of the applied product. Details which were not clear include the level of exposure IVT, the regions, which Avastin Biosimilar was used IVT, and which publications were referred to. Further to clarification questions, the applicant confirmed that there were no publications on the EU approved biosimilar IVT and that the published case series with other biosimilars had not been submitted. The applicant clarified that some of these data referred to Lumiere product (which the applicant considered as a comparable product to Ipique) from Argentina. Note that the Lumiere comparability exercise and the clinical data relating to this product was reviewed and discussed in the assessment of the response to MO 15 (extent of the literature) and found not to be relevant to the grounds for re-examination.

Similarly, the applicant's claim of health authority recognition of off-label use of the EU approved biosimilar IVT, which currently authorised in oncology indications only, or in 1 case of multiple Avastin biosimilars IVT is noted, however this does not bring evidence on safety and/or efficacy of Ipique and does not substitute the need of establishing these criteria.

The applicant mentioned potential availability concerns to justify the need of Ipique as an argument to support re-examination (slide 21 of the applicant's position). This argument in establishing the safety and efficacy of Ipique.

In addition, it is noted that the cost considerations put forward by the applicant do not enter the benefit-risk consideration and are outside of the remits of the regulator.

Overall, the arguments presented by the applicant did not address the concerns raised by the CHMP with regard to the safety and efficacy of Ipique.

The applicant further reiterated that a comparative study to show safety and/or efficacy is not appropriate in the context of this application. This is disagreed with as already fully discussed in the sections on regulatory considerations and on study design under the assessment of MO16 responses. The quote from the rapporteur report in slide 8 should be read with the entire section in the assessment report above on an appropriate study design to demonstrate comparability. It is also reiterated that applicant's claim on feasibility of a study does not substitute the requirement to establish efficacy and safety of the applied medicinal product. Other arguments made by the applicant through the applicant's presentation, or upon questioning by CHMP members (covering issues including immunoreactivity bridging, sensitivity of clinical study, sterile endophthalmitis, need for placebo) were also considered throughout the re-examination assessment and the responses of the applicant were not found to be persuasive with regard to obviating the need for an ophthalmic equivalence trial of Ipique IVT as outlined above in the section on study designs. It was also clarified by the applicant that the applicant intends to market a single use vial for IVT, however this formulation is not yet developed.

5.3.8. Overall conclusion regarding the grounds for re-examination

The applicant acknowledged that the product Ipique was never tested in a clinical ophthalmic study. Given above assessments, the requirement for bridging data of IVT Ipique to Avastin IVT in a sensitive study is maintained and the relevance of the published literature on Avastin IVT to Ipique remains to be shown. The re-submitted responses of OC18, MO15 and MO16, and other documentation submitted with the grounds for re-examination do not change this conclusion. Thus, the grounds for refusal are upheld.

6. Updated benefit-risk balance

6.1. Therapeutic Context

The target indication – the only one requested at the time of opinion (for other indications explored during the procedure, see above) is '*treatment of neovascular (wet) age-related macular degeneration (AMD)'*. AMD is a degenerative disease of the central portion of the retina (the macula) that results primarily in loss of central vision. Wet AMD is characterised by growth of abnormal vessels into the subretinal space, usually from the choroidal circulation and less frequently from the retinal circulation. These abnormal blood vessels (choroidal neovascularisation) leak, leading to collections of subretinal fluid and/or blood beneath the retina. Wet AMD is characterised by rapid distortion and loss of central vision over a period of days to weeks. The contralateral eye is at high risk of developing neovascularisation. The aim of therapy is to slow down the progression of AMD and central vision loss.

6.1.1. Disease or condition

AMD is a progressive blinding disease with no cure at present. Intravitreous injection of a vascular endothelial growth factor (VEGF) inhibitor is the gold standard of therapy. Photodynamic therapy (PDT) is another option and often used in combination with anti-VEGF agents. Supplementation with zinc and antioxidant vitamins as well as visual aids are suggested.

6.1.2. Available therapies and unmet medical need

Aflibercept (Eylea), ranibizumab (Lucentis) and brolucizumab (Beovu) are approved in AMD. All three products are available across the European Union.

6.1.3. Main clinical studies

There are no studies of Ipique in the target indication. Literature concerning studies conducted with the available bevacizumab (assumed to be mostly EU- and US-sourced Avastin) have been submitted. In particular, one Cochrane meta-analysis for AMD is the basis for the assessment of efficacy of bevacizumab: Solomon et al 2019; *Anti-vascular endothelial growth factor for neovascular age-related macular degeneration*. The review compared efficacy of bevacizumab to other (approved) anti-VEGF agents, other standard of care, sham or no treatment, using the standard methodological procedures expected by Cochrane. Only RCTs were included, most of the studies were masked.

The Cochrane review focussed mainly on efficacy and only reported some serious safety aspects. In order to further support the claim of benign safety the applicant provided one additional review by

Thulliez et al. 2018; *Overview of Systematic Reviews and Meta-analyses on Systemic Adverse Events Associated With Intravitreal Anti–Vascular Endothelial Growth Factor Medication Use*. The initially submitted review for the indication of diabetic macular oedema (DME) (*Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis*.) is considered supportive for the establishing of the safety profile of bevacizumab in AMD patients.

A comprehensive and well documented literature search has not been provided by the applicant, nor critically discussed in terms of proposals for the Ipique SmPC regarding section 4.2 and 5.1.

6.2. Favourable effects

From the literature, it can be concluded that intravitreous injection of bevacizumab has beneficial effects on best corrected visual acuity in eyes with neovascular age-related macular degeneration.

Visual acuity outcomes after bevacizumab and ranibizumab were similar when the same RCTs compared the same regimens with respect to gain of 15 or more letters (15 letters corresponds to 3 lines) of visual acuity (RR 0.95, 95% CI 0.81 to 1.12; high-certainty evidence) and loss of fewer than 15 letters of visual acuity (RR 1.00, 95% CI 0.98 to 1.02; high-certainty evidence); results showed similar mean improvement in visual acuity (mean difference [MD] -0.5 letters, 95% CI -1.5 to 0.5; high-certainty evidence) after one year of follow-up. Other secondary endpoints such as prevention of blindness (visual acuity better than 20/200), maintenance of visual acuity, mean change in visual acuity, visual function, morphological outcomes and quality of life also showed comparable results.

Two-year results were consistent with one-year outcomes in terms of the effect estimate and confidence intervals

When comparing three anti VEGF treatments (pegaptanib, ranibizumab, or bevacizumab) with control, more participants who received intravitreous injection of any of the three anti-VEGF agents had gained 15 letters or more of visual acuity (risk ratio [RR] 4.19, 95% CI 2.32 to 7.55), had lost fewer than 15 letters of visual acuity (RR 1.40, 95% CI 1.27 to 1.55), and showed mean improvement in visual acuity after one year of follow-up. Participants treated with anti-VEGF agents showed improvement in morphologic outcomes compared with participants not treated with anti-VEGF agents.

6.3. Uncertainties and limitations about favourable effects

Ipique has never been tested in the target indication.

No comprehensive literature search has been conducted and the search strategy and selection of submitted information is not fully transparent.

Based on the provided literature, the source of the used product is unclear for some of the submitted studies.

Data from the clinical study (, in Stage IIIB/IV Non-squamous Non-Small Cell Lung Cancer (NSCLC)), comparing proposed biosimilar with Avastin administered IV) is not sensitive to allow extrapolation of efficacy of Ipique to the non-studied indication of nAMD when administered IVT given significantly different dose and PK (flip flop/ vitreous reservoir) with IVT use than in IV use. Therefore, uncertainties remain with regard to the efficacy of Ipique IVT in nAMD.

The characteristics demonstrated for the bevacizumab used IVT in the literature cannot be used to conclude on the existence and extent of benefits of Ipique in the claimed indication, due to the possible effects of known and unknown differences.

In addition, there are uncertainties on the robustness of the conclusion of non-inferiority to other established treatments. For the most relevant studies submitted (CATT 2015, IVAN 2012, LUCAS 2015, DRCR net 20015) a non-inferiority limit of 5 letters was considered, which was wider than the one regulatorily accepted and/or the analyses were primarily performed on the basis of the intention-to-treat principle. These non-conservative conditions may increase the risk of falsely concluding on non-inferiority between bevacizumab and ranibizumab or aflibercept.

Some differences in the outcomes of the largest studies were observed. The CATT study demonstrated a head-to-head equivalent effect on visual acuity at 1 year when bevacizumab and ranibizumab were compared. Monthly administration showed better results than as-needed regimen. However, the results of IVAN study were considered as inconclusive when a similar comparison was established. Otherwise, LUCAS 2015 exploring a "treat and extend" scheme found bevacizumab non-inferior to ranibizumab. Further discussion of the optimum and recommended dosing schedule would have been necessary.

6.4. Unfavourable effects

The most frequently reported ocular AEs were uveitis, vitreous haemorrhage, and ocular inflammation. Endophthalmitis, retinal detachment, epithelial tear, traumatic cataract, or uveitis were also reported although in general with incidences around 1% or even lower.

In Solomon et al 2019, after one year overall the reported safety events are comparable between bevacizumab and ranibizumab. Investigators reported more gastrointestinal disorders (RR 1.76, 95% CI 0.99 to 3.14), infections (RR 1.42, 95% CI 0.93 to 2.17), injuries and procedural complications (RR 1.27, 95% CI 0.78 to 2.06), and surgical or medical procedures (RR 1.41, 95% CI 0.88 to 2.27) in the bevacizumab groups than in the ranibizumab groups. After one year of treatment a rate of serious adverse events of 16% was reported for ranibizumab and 18% for bevacizumab. An incidence rate of 2% for death has been reported after one year for both treatments.

The same review reported that after two years in both groups less than 1% of participants were reported to have had endophthalmitis, retinal detachment, retinal pigment epithelial tear, traumatic cataract, or uveitis. In the bevacizumab groups, 36% of participants had at least one serious adverse event compared with 30% in the ranibizumab groups (RR 1.20, 95% CI 1.05 to 1.37). Mortality from any cause was 6% and 5% in the bevacizumab and ranibizumab groups, respectively (RR 1.12, 95% CI 0.76 to 1.65). As with one-year outcomes, investigators reported more gastrointestinal disorders (RR 2.74, 95% CI 1.49 to 5.02), infections (RR 1.37, 95% CI 0.96 to 1.95), and injuries and procedural complications (RR 1.33, 95% CI 0.86 to 2.05) in the bevacizumab groups than in the ranibizumab groups, and reported more cardiac disorders in the bevacizumab groups than in the ranibizumab groups at two years (RR 1.25, 95% CI 0.92 to 1.71).

In Thulliez et al 2018, Bevacizumab was associated with an increased risk of venous thrombotic events in one review, which was supported by trends in 4 other reviews. Bevacizumab also increased the relative risk of systemic AEs by 20% to 35% in 3 reviews.

In one study (CATT Research Group, 2011) the proportion of AMD patients with serious systemic adverse events (primarily hospitalisations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66).

In the literature presented for the clinical pharmacology assessment, bevacizumab reaches systemic serum concentrations of 1.58 nM, which is higher than the estimated inhibitory concentration (IC50) for VEGF antagonists (IC50 = 0.668 nM).

Sterile intra-ocular inflammation (SII) is associated with intravitreal anti-VEGF injections, this can manifest with a broad range of clinical features ranging from subclinical anterior chamber inflammation to significant inflammation mimicking endophthalmitis. Bevacizumab has been shown to have an incidence of sterile [uveitis/endophthalmitis] inflammation between 0.09% and 1.1% according to several retrospective studies. Retrospective and prospective data suggest that the rates of SII from bevacizumab are significantly higher than those of ranibizumab or aflibercept although not all papers have found this.

6.5. Uncertainties and limitations about unfavourable effects

No comprehensive literature search has been conducted and the search strategy and selection of submitted information is not fully transparent. The provided literature was not fully and critically discussed by the applicant in terms of proposed wording for section 4.4 and 4.8 for the Ipique SmPC.

The characteristics demonstrated for the bevacizumab used in the literature cannot be used to conclude on the risks of Ipique in the claimed indication, due to the possible effects of known (e.g. different levels of glycosylation, higher level of the HHL fragment) and unknown differences between Avastin and Ipique. Any impact of specific quality attributes has not been ascertained in a clinical *ophthalmic* setting.

Furthermore, there are uncertainties regarding the safety of the originator bevacizumab in AMD based on differently reported safety outcomes in the main literature references, missing data on exposure or dosing intervals and the limited reporting of safety in general in the provided literature.

The immunogenic potential of intravitreal administered bevacizumab is not clear. No clinical data on IVT use with Ipique has been submitted by the applicant and the respective sections in the proposed SmPC are based on Lucentis (ranibizumab). Data from ranibizumab might not be specific enough since Ipique is a significantly larger molecule than Lucentis (ranibizumab), including a Fc fragment which may make it more immunogenic. Although immunogenicity events seem rare with bevacizumab and other ocular products (Eylea, Lucentis), the risk of immunogenicity events with Ipique is unclear. There is no demonstration that Ipique does not increase the risk of inflammatory or immunogenicity reactions compared to the bevacizumab from literature.

Further, no information is available concerning laboratory findings, differences between age groups or drug-drug interactions. Due to the fact that the ocular conditions claimed in the indication worsen with age, respective information is required. Further, since relevant systemic levels are reached with intravitreal administration, interactions with other systemic products cannot be excluded. Respective interactions could also increase with age, since different concomitant medications could increase.

Data from the clinical study (, in Stage IIIB/IV Non-squamous Non-Small Cell Lung Cancer (NSCLC)), comparing a proposed biosimilar with Avastin administered IV in Combination with Carboplatin and Paclitaxel), is not sensitive to allow extrapolation of safety or immunogenicity data of Ipique to the non-studied indication of nAMD when administered IVT given the unique ophthalmic ADRs, the need to assess immunogenicity in an AMD population without immunosuppressive medication and different PK in IVT. In addition, the immune privilege of the eye is not absolute following bevacizumab IVT and the relative immune reactivity of the IVT and IV routes cannot be assumed to be the same. Therefore, uncertainties remain with regard to the immunogenicity of Ipique when administered intravitreally.

Regarding the conclusions of the applicant's risk analysis of IVT Ipique in the absence of an IVT bridging study preauthorisation ("that the impact of Ipique product specific differences are speculative and the risks negligible"), it is considered that the risks are uncertain without testing in a more sensitive disease model administered IVT.

6.6. Effects Table

Given the nature and the extent of uncertainty, and the impossibility to express credible confidence intervals, an Effects table is not produced.

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

The outcome measures used in the provided literature are accepted in regulatory practice and can be assumed to have clinical value.

The observed adverse events are of relevance and lacking the possibility to precisely quantify their incidence with Ipique, they are of severe concern.

Unfavourable effects that are not known in the published literature for bevacizumab in AMD and might arise with the use of Ipique. Their importance cannot be quantified.

6.7.2. Balance of benefits and risks

The scientific literature submitted in support of the claimed indication of Ipique, entailing intravitreal administration, was obtained using Avastin. No evidence was submitted comparing Ipique and Avastin in intravitreal use.

In absence of a comparative bridge between Ipique and Avastin when the products are administered intravitreally, it is not possible to conclude on whether, in the claimed indication, the known and unknown differences between Ipique and Avastin have a significant impact in terms of efficacy and safety. Consequently, it has not been demonstrated that the scientific literature obtained with Avastin administered intravitreally can be extrapolated to Ipique. As a result, the safety and efficacy of Ipique have not been properly or sufficiently demonstrated.

In conclusion, the benefit/risk balance of Ipique is negative.

6.7.3. Conclusions

The overall benefit/risk balance of Ipique is negative.

6.8. Conclusions and recommendation following re-examination

The grounds for refusal have not been solved.

Whereas

- The application is submitted under Article 10a of Directive 2001/83/EC (so-called 'well-established use' application). In this context, pre-clinical and clinical studies can be replaced by appropriate scientific literature if it can be demonstrated that the active substances of a medicinal product in the claimed therapeutic indication have been in well-established medicinal use within the Union for at least ten years, with recognised efficacy and an acceptable level of safety. In order to extrapolate the results in the scientific literature to the applied medicinal product, the applicant shall demonstrate that their product is similar (relevant) to the product(s) referred to in the scientific literature submitted

- In the absence of an appropriate and sensitive clinical comparison in the intended indication (wet AMD) and route of administration (IVT) to demonstrate that Ipique and the medicinal product referred to in the literature are similar (and relevant), the data from the literature cannot be extrapolated (bridged) to Ipique in the claimed indication. As a result, the safety and efficacy of Ipique have not been properly or sufficiently demonstrated.

the CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the safety and efficacy of the above-mentioned medicinal product are not properly or sufficiently demonstrated.

Therefore, the CHMP has recommended the refusal of the granting of the marketing authorisation for Ipique.

Due to the aforementioned concerns, a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan, and post-authorisation measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

7. Appendices

7.1. Divergent position(s) to the majority recommendation

The undersigned members of the CHMP did not agree with the CHMP's negative opinion recommending the refusal of the granting of the marketing authorisation of Ipique indicated for treatment of neovascular (wet) age-related macular degeneration (AMD).

The reason for divergent opinion was the following:

Ipique pertains to the active substance bevacizumab for which a marketing authorisation is applied in the context of a well-established use application (Article 10a of Directive 2001/83/EC) for the treatment of neovascular (wet) age-related macular degeneration (AMD).

Well-established use refers to use of the active substance in the claimed indication for more than 10 years, but does not concern dosing, formulation and route of administration for which literature data should be submitted by the applicant for support.

Data to substantiate the extensive clinical use of bevacizumab in AMD within the EU with regard to the time, quantitative aspects of use, scientific interest and coherence of data has been submitted and is deemed adequate to support a systematic and documented use in the Union for at least 10 years. In addition, the efficacy and acceptable safety profile of bevacizumab in AMD is supported by Cochrane reviews, i.e. Solomon et al 2019 and Virgili et al 2017, and additional data is provided by a systematic review by Thulliez et al 2018. The safety profile is further substantiated by literature data where the safety of intravitreal use of bevacizumab was compared to ranibizumab. The safety of other anti-VEGF treatments (i.e. aflibercept (Eylea) and VEGF-trap (Macugen)) was presented as well. No major safety issues emerged, also not in relation to immunogenicity. In addition, the use of bevacizumab in AMD is recommended in several therapeutic guidelines (e.g. the European Society of Retina Specialists (EURETINA), NICE, the UK Royal College of Ophthalmologists, the Dutch Ophthalmology Society) and it is included in the WHO Essential Medicines List for the applied indication. I-pique has been shown to be biosimilar to Avastin based on all relevant tests and as such it is considered that the applicant provided sufficient justification to bridge the data described in the submitted literature to Ipique.

Therefore, it is considered that the applicant has demonstrated that Ipique fulfils the criteria of well-established use in AMD, that the benefit/risk balance is positive and that the marketing authorisation application for Ipique is approvable.

Armando Genazzani, IT

Edward Laane, EE

Elita Poplavska, LV

Johann Lodewijk Hillege, NL

Kristina Dunder, SE

Margareta Bego, HR

Outi Mäki-Ikola, FI

Sinan B. Sarac, DK