EUnetHTA Joint Action 3 2016-2020

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

Project ID: ***PTJA09***

Project description and planning

FIMEA, Finland

AEMPS, Spain

AETSA, Spain

Template Version 2, December 2018

Version Log

Version number	Date	Modification	Reason for the modification
V1	02/07/19	First draft of the project plan	-
V2	12/08/19	Second draft of the project plan	Input from Dedicated Reviewers and patient survey incorporated
V3	28/11/19	Third draft of the project plan	Input from pre-scoping e-meeting, scoping F2F-meeting & SLR methods incorporated
Final version	18/12/2019	Final version of the project plan	Final, after positive CHMP opinion release

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List of abbreviations

AE	Adverse Event
AEMPS	Spanish Agency of Medicine and Sanitary Products
AETSA	Andalusian Unit for Health Technology Assessment
AMD	Age-related macular degeneration
AOTMiT	Agency for Health Technology Assessment and Tariff System
BCVA	Best-Corrected Visual Acuity
CHMP	Committee for Medicinal Products for Human Use
CRD	Centre for Reviews and Dissemination
CSR	Clinical Study Report
DOICU	Declaration of Interest and Confidentiality Undertaking
DR	Dedicated Reviewer
EPAR	European Public Assessment Report
EUnetHTA	European Network for Health Technology Assessment
F2F	Face-to-Face
FIMEA	Finnish Medicines Agency
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HAS	French National Authority for Health
HVB	Association of Austrian Social Insurance Institutions
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
MAH	Marketing Authorisation Holder
NMA	Network Meta-Analysis
PICO	Population, Intervention, Comparator and Outcomes
pMAH	Prospective Marketing Authorisation Holder
RCT	Randomised Controlled Trial
RER	Regione Emilia-Romagna
SAE	Serious adverse event
SR	Systematic Review
SLR	Systematic Literature Review
q12w	Every 12 weeks
QoL	Quality of Life
VEGF	Vascular Endothelial Growth Factor
VEGF-A	Vascular Endothelial Growth Factor A

1 Introduction

On 28-02-2019, EUnetHTA and the prospective Marketing Authorisation Holder (pMAH) of brolucizumab (*Novartis)* agreed that EUnetHTA will perform a joint relative effectiveness assessment of brolucizumab for the treatment of adults with neovascular (wet) age-related macular degeneration (AMD). Once finalised this assessment is made publicly available and can be used by European HTA bodies for their national processes supporting reimbursement and pricing decisions.

AMD is a chronic eye disease, which is a leading cause of severe vision loss and legal blindness in people over the age of 65 in developed countries. There are two types of AMD: the non-neovascular (atrophic) or dry form and the neovascular (exudative) or wet form. Dry AMD is the more frequent of the two (85%-90% of all cases), while neovascular (wet) AMD is less common (10%-15% of all cases). However, the neovascular AMD accounted for approximately 90% of the severe vision loss from AMD prior to the introduction of anti-VEGF treatments. (1-3)

Two authorized anti-VEGF treatment options for neovascular AMD are currently available in Europe: aflibercept (Eylea®) and ranibizumab (Lucentis®). Also a third anti-VEGF product, bevacizumab (Avastin®) is used for AMD in several European countries. Bevacizumab does not have an approved indication for AMD. Bevacizumab and ranibizumab have similar effects for maintaining and improving visual acuity (4). Also their safety profiles are almost similar (4, 5). The use of bevacizumab is supported by comparative data showing a similar benefit/risk profile to approved therapies and by economic analyses.

Brolucizumab is a humanized single-chain Fv antibody fragment inhibitor of vascular endothelial growth factor A (VEGF-A) with a molecular weight of ~26 kDa. By formulating at concentrations of 120 mg/mL, a 50 µL injection of brolucizumab is expected to provide a molar dose approximately 11-fold higher than aflibercept 2 mg and 22-fold higher than ranibizumab 0.5 mg. Thus, brolucizumab is expected to have potential for long-lasting efficacy while reducing the frequency and burden of treatment and monitoring visits.

2 Research question and scope

The aim of this project is to compare the clinical effectiveness and safety of brolucizumab in the target patient population with relevant comparators. The target patient population and relevant comparators (based on the requirements of the EUnetHTA partners) are defined in the project scope below.

The following table provides the scope identified for the assessment of brolucizumab.

Table 2-1: Assessment scope: relevant PICO(s) identified for the planned assessment

Description	Assessment scope
Population	Adults with neovascular (wet) age-related macular degeneration (AMD)
Intervention	Brolucizumab as an intravitreal injection in a dosage strength of 6 mg/0.05 mL
Comparison	• Aflibercept (Eylea®) 2 mg/0,05 mL • Ranibizumab (Lucentis®) 0,5 mg/0,05 mL • Bevacizumab (Avastin®) 1,25 mg/0,05 mL[1]
Efficacy-related outcomes	Best-corrected visual acuity (BCVA) (treated eye)[2] Treatment frequency of brolucizumab in loading/maintenance phase (e.g. proportion of patients maintained on q12w dosing through week 48) [2] Anatomical parameters of disease activity: • Central subfield thickness • Choroidal neovascularization area • Subretinal fluid • Intraretinal fluid / intraretinal cyst • Sub-retinal pigment epithelium fluid • Neurosensory retinal thickness Vision-related QoL[2] Health-related QoL
Safety-related outcomes	Adverse effects of treatment[2] • Any AEs (adverse events) • Serious AEs (SAE) • Grade ≥3 AEs • Death as SAE • AE of special interest (e.g. ocular/non-ocular AEs) Rates of discontinuation[2]: • All cause • Due to AE Percentage of patients who discontinued the treatment by reason for discontinuation

[1] At the time of publication (December 2019), bevacizumab did not have an EU Marketing Authorisation for the indication under assessment. Bevacizumab is included as a comparator due to its identified importance in the EUnetHTA PICO survey, however its inclusion in the Joint Assessment should not be understood or quoted as a recommendation for its unlicensed use.
[2] Outcomes are related to issues particularly emphasised by patient organisations (please see patient involvement in section 3.5)

3 Methods

The EUnetHTA Guidelines, available at http://www.eunethta.eu/eunethta-guidelines, will be consulted throughout the assessment process.

3.1 Inclusion criteria

During the assessment the inclusion criteria of studies applied by the pMAH will be checked to evaluate if they capture the population, intervention, comparators and outcomes (PICO) defined for the assessment (Table 2-1). Efficacy evaluation will be based on clinical trials (primarily randomized clinical trials [RCTs]). Additionally, observational studies may also be considered for safety evaluation purposes. In addition, systematic reviews (SRs) of RCTs and network meta-analyses (NMAs) will be considered for efficacy and safety regarding the comparators. Only studies published in English will be included.

3.2 Off-label comparator bevacizumab

During the scoping meeting in October 2019 the pMAH indicated that no information about the off-label comparator bevacizumab will be included in their Submission Dossier. Since bevacizumab was identified as an important off-label comparator option for AMD in several European countries in the PICO survey, the authoring team decided to perform a systematic literature review with support of the EUnetHTA Senior Scientific Officer. See details below.

3.3 Information retrieval

The assessment will be based on a submission dossier submitted by the pMAH. To allow for a meaningful assessment, the submission dossier has to be complete with regard to the available evidence relevant for the research question. This requires the systematic identification of all published and unpublished studies relevant to the assessment according to the research question and scope defined in Section 2 (6). The assessment will investigate whether these requirements are met and thus whether the evidence base for the assessment is complete.

Quality of evidence should be assessed in the submission using GRADE (Grading of Recommendations, Assessment, Development and Evaluation). The assessment will investigate whether these requirements are met and thus whether the evidence base for the assessment is complete.

The cut-off date for the pMAH's list of sponsored studies and the searches should be a maximum of three months before submission (of the submission dossier). This cut-off date will also be relevant for the assessment. There will be no updates of searches beyond this cut-off by the authors of the assessment.

During the assessment, the evidence base with regard to the drug under assessment provided by the pMAH will be reviewed. Search strategies will be checked for appropriateness and the results of information retrieval included in the pMAH's submission dossier will be checked for completeness against a search in study registries (e.g. ClinicalTrials.gov, WHO International Clinical Trials Registry Platform and EU Clinical Trials Register) and against the studies included in the regulatory assessment report.

Major flaws in the search conducted by the manufacturer, that probably would have major consequences for the completeness of the evidence base, will be commented on in the assessment report. If the submission dossier does not cover all the relevant details of assessment scope defined in PICO (Table 2-1), the authors may perform additional searches for evidence.

3.3.1 Information retrieval for bevacizumab

An exhaustive search of the literature will be performed to identify studies with the pre-defined eligibility criteria detailed below.

Population	Adults with neovascular (wet) age-related macular degeneration (AMD)
Intervention	Bevacizumab
Comparators	Any of the pharmaceuticals currently used in clinical practice
Outcomes	Clinical outcomes (efficacy and safety)
Design	Systematic reviews (SRs) of randomised controlled trials (RCTs) and network meta-analyses (NMAs)

At a first step, the following bibliographic databases will be searched for: MEDLINE, Embase, Cochrane Database of Systematic Reviews and Centre for Reviews and Dissemination (CRD). The searches will not include language or publication year restrictions. The aim of these searches is to find comprehensive, high-quality and up-to-date SRs/NMAs.

Two researchers will independently screen studies retrieved through the literature search against the pre-defined inclusion and exclusion criteria. After the exclusion of articles considered not relevant by title and abstract, the full-text reports will be reviewed independently by two researchers for all the records that will be considered potentially relevant in order to classify each record as “included or excluded”. The reasons for exclusion by full text report will be described. Any discrepancies in each step will be resolved by discussion. In a second step, a systematic search in MEDLINE and Embase will be conducted for primary studies (RCTs) for the period not covered by the selected SRs or NMAs.

3.4 Data analysis and synthesis

The assessment will be based on the data and analyses included in the submission dossier prepared by the pMAH. During the assessment, the completeness of data and analyses in the submission dossier will be verified. Furthermore, the methods for data analysis and synthesis applied by the pMAH will be checked against the requirements of the submission dossier and applicable EUnetHTA Guidelines and assessed with regard to scientific validity. The results of this assessment and the results of the included studies, as appropriate, will be presented in the assessment report according to the research questions defined in Section 2.

3.4.1 Data extraction

Information used for the assessment of benefits and harms will be extracted from the submission dossier and verified against the Clinical Study Reports (CSR) or other original documentation provided in the submission dossier.

3.4.2 Assessment of risk of bias

The assessment of risk of bias should follow the criteria described in the two EUnetHTA guidelines on the internal validity of randomised controlled trials (7) and non-randomised studies on interventions (8). A validated tool to assess the methodological quality of SRs and NMAs will be used. The risk of bias of the results of each included study should be described separately for each patient-relevant outcome. For this purpose, risk of bias should be assessed at the study level as well as at the outcome level.

If the outcome-specific risk of bias is classified as high for an outcome, this should not lead to exclusion of the corresponding data. Rather, the risk-of-bias classification should inform the discussion on heterogeneous study results and the determination of certainty of results.

During the assessment, the methods and outcome of the risk-of-bias assessment presented in the submission dossier will be evaluated. Risk-of-bias will be assessed by the authors only for outcomes (and studies) that are included based on the research question(s) (PICO). The result of the risk-of-bias assessment will be presented in the assessment report.

3.4.3 Description of design and results of individual studies

During the assessment, the information in the submission dossier on the study design, study methods, populations, endpoints (patient relevance, validity, and operationalization) and study results will be evaluated. The results of this evaluation will be presented, used for identification of relevant analyses and considered for the conclusions of the assessment report.

3.4.3.1 Data synthesis for bevacizumab

A descriptive analysis of the available literature on the off-label use of bevacizumab for adults with neovascular (wet) age-related macular degeneration (AMD) will be included in the assessment report. Relevant studies identified in the systematic search for SR and primary articles will not be extracted to conduct an NMA.

3.4.4 Synthesis of study results

Meta-analyses

If several studies are available for the same PICO, they should be quantitatively pooled in a meta-analysis if they are sufficiently comparable from a clinical (e.g. patient groups) and methodological (e.g. study design) point of view (9).

During the assessment, the methods applied for the meta-analyses presented in the submission dossier, and, if applicable, the justification for deviations from the procedures described above will be evaluated. The meta-analyses relevant for the research questions (see Section 2) will be presented in the assessment report.

Sensitivity analyses

To evaluate the robustness of results, sensitivity analyses with regard to methodological factors presented in the submission dossier and the corresponding methods applied will be evaluated. These methodological factors arise from decisions made within the framework of the retrieval and assessment of information, for example, the specification of cut-offs for the time point of data collection or the choice of effect measure. The sensitivity analysis should in particular consider the classification of the risk of bias of study results. The result of the sensitivity analysis can affect the assessment of the certainty of results.

Subgroup analyses and other effect modifiers

During the assessment, the subgroup analyses examining potential effect modifiers presented in the submission dossier and the corresponding methods applied will be evaluated. The evaluation also includes the justification for the choice of cut-offs if quantitative characteristics were categorized. If potential effect modifiers are identified, the conclusions inferred from the effects observed in the complete patient group can possibly be formulated more precisely.

Indirect comparisons

If indirect comparisons are included in the submission dossier, the methods applied, and if applicable, the justification in the event of deviations from the required approaches will be evaluated (9). The indirect comparisons relevant for the research questions (see Section 2) will be presented and examined in the assessment report.

3.5 Patient involvement

At the start of this Joint Assessment an open call for patient input was published on the EUnetHTA website. This open call specifically asked patient organisations to answer the questions, as they have the position to collect and present patient's and care-givers' views and experiences by engaging with a wide range of patients and their careers.

The open call used by EUnetHTA asks general questions to elicit patients' views on living with the disease, important outcomes to be considered in this assessment and expectations about the drug under assessment. The questions are based on the HTAi questionnaire template. For more information on the development of the HTAi questionnaire template please see their website.

European and national patient organisations were asked to provide an organisational perspective on the questions in English. In all parts of the open call, the term 'patient' refers to anyone living with, or who has lived with, the condition for which the new medicine is indicated. Seven patient organisations completed the survey, namely Asociación Acción Visión España (Spain), Društvo MDSS Kranj (Slovenia), Fighting Blindness (Ireland), Macula Retina (Spain), Retina Bulgaria (Bulgaria), Retina International (Ireland) and Retina Suisse (Swiss Confederation).

The information gathered from the open call was used to inform the scope of this assessment, in particular the outcomes to be considered. In the PICO table (Table 2-1), the outcomes that are related to issues particularly emphasised by patient organisations are marked by a superscript "2".

4 Project organisation

4.1 Participants

Table 4-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	Finnish Medicines Agency [FIMEA]	Author	Finland	• Develop first draft and final version of EUnetHTA project plan with co-authors • Relative effectiveness and safety assessment (EFF and SAF domains). • Perform GRADE assessment • Adapt documents according to reviewers comments together with co-authors • Answer comments of expert and manufacturer together with co-authors • Prepare the final assessment including a final summary of the assessment
2.	Spanish Agency of Medicine and Sanitary Products [AEMPS] Andalusian Unit for Health Technology Assessment [AETSA]	Co-Author	Spain	• Develop first draft and final version of EUnetHTA project plan with Author • Responsible for supporting the authors in all project phases • Carry out the assessment: answer assessment elements of CUR and TEC Domains; support authors in EFF and SAF Domains. Support authors in Summary, Method and Discussion sections. • Check all steps
3.	Andalusian Unit for Health Technology Assessment [AETSA]	Information specialist	Spain	• Review of information retrieval, conduct of searches required for checking completeness of information retrieval in submission dossier; reporting information retrieval check in the assessment report • Perform the searches for the SLR on the off-label use of bevacizumab
4.	Finnish Medicines Agency [FIMEA]	Statistical specialist	Finland	Expert review of statistical analyses presented in submission dossier, statistical support for authors
5.	French National Authority for Health [HAS]	Dedicated Reviewer	France	
6.	Agency for Health Technology Assessment and Tariff System [AOTMiT]	Dedicated Reviewer	Poland	

7.	Regione Emilia-Romagna [RER]	Dedicated Reviewer	Italy	
8.	Association of Austrian Social Insurance Institutions [HVB]	Dedicated Reviewer	Austria	
9.	HTA department/EC Ukraine	Observer	Ukraine	
Contributors				
10.	João Barbosa Breda	External expert	Portugal	On a Q&A basis: answer specific questions related to physiopathology/natural disease history/current management.
11.	Asociación Acción Visión España (Spain) Društvo MDSS Kranj (Slovenia) Fighting Blindness (Ireland) Macula Retina (Spain) Retina Bulgaria (Bulgaria) Retina International (Ireland) Retina Suisse (Swiss Confederation)	Patient organisations	-	Complete the EUnetHTA open call in order to inform the scope of the assessment.
12.	TBD	Medical Editor		Responsible for the medical editing of the report
13.	Zorginstituut Nederland [ZIN]	Project Manager	Netherlands	Coordination between involved parties throughout the assessment period
14.	Giovanni Tafuri [ZIN]	Senior Scientific Officer	Netherlands	Provide support in the systematic literature review on the off-label use of bevacizumab.

4.2 Project stakeholders

Table 4-2: Project stakeholders

Organisation	Role in the project
Novartis	Manufacturer [MAH]; Completing the submission dossier; Fact check of the draft assessment report

4.3 Milestones and deliverables

Table 4-3: Milestones and deliverables

Milestones/Deliverables	Start date	End date
Project duration	**28-02-2019**	**12-03-2020**
Letter of Intent received	28-02-2019	
Scoping phase	**20-05-2019**	**12-12-2019**
Scoping PICO and development of first draft Project Plan	20-05-2019	03-07-2019
PICO survey – request relevant PICO from Member States	28-05-2019	17-06-2019
Adapt draft Project Plan based on PICO survey	20-06-2019	03-07-2019
Open call for patient input	20-05-2019	15-07-2019
Review of first draft Project Plan	04-07-2019	12-07-2019
Development of second draft Project Plan & answers to DR comments	16-07-2019	12-08-2019
Receive scoping F2F meeting documents from pMAH	10-09-2019	
Pre-scoping e-meeting with the assessment team	26-09-2019	
Share discussion topics for Scoping F2F Meeting	04-10-2019	
Scoping F2F meeting with manufacturer	15-10-2019	
Share action points from F2F meeting with manufacturer	18-10-2019	
(pre-)Assessment phase	**12-11-2019**	**12-12-2019**
Receive Submission Dossier from pMAH	11-11-2019	
Check formal completeness of Submission Dossier	12-11-2019	22-11-2019
Receive missing items and comments on the requests from the formal completeness check from pMAH	30-11-2019	
Start writing Assessment (background, methods)	22-11-2019	12-12-2019
CHMP opinion (expected date)	12-12-2019	
Finalize Project Plan	13-12-2019	
Optional: Grace period to revise Submission Dossier by pMAH (based on CHMP opinion)	TBD	
Assessment phase	**12-12-2019**	**12-03-2020**
Writing first draft Joint Assessment	12-12-2019	28-01-2020
Review by DRs (and if applicable include experts)	29-01-2020	07-02-2020
Writing second draft Joint Assessment	10-02-2020	21-02-2020
Medical Editing	24-02-2020	28-02-2020
Fact Check by pMAH (parallel with medical editing)	24-02-2020	28-02-2020
Final Assessment + response Fact Check	10-03-2020	
Expected EPAR	06-03-2020	
Publication final version of rapid assessment	11-03-2020	12-03-2020

4.4 Conflict of interest management

Conflicts of interest will be handled according to the EUnetHTA Conflict of Interest Policy. All individuals participating in this project will sign the standardised “Declaration of Interest and Confidentiality Undertaking” (DOICU) statement. In addition, due to an update in the confidentiality policy (December 2019), all participants will sign the project specific Confidentiality Agreement replacing the CU part of the DOICU.

Authors, co-authors and dedicated reviewers who declare a conflict of interest will be excluded from parts of or the whole work on this specific topic. However, they may still be included in other assessments.

For external experts and patients, conflict of interest declarations are collected with regard to the topic. External experts or patients who declare conflict of interest will be excluded from parts of or the whole work on this specific topic. However, they may still be included in other assessments.

5 References

1. Ferris FL, 3rd. Senile macular degeneration: review of epidemiologic features. American journal of epidemiology. 1983;118(2):132-51.

2. Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javitt JC, et al. Racial differences in the cause-specific prevalence of blindness in east Baltimore. The New England journal of medicine. 1991;325(20):1412-7.

3. Wong TY, Chakravarthy U, Klein R, Mitchell P, Zlateva G, Buggage R, et al. The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. Ophthalmology. 2008;115(1):116-26.

4. Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. The Cochrane database of systematic reviews. 2014(8):Cd005139.

5. Moja L, Lucenteforte E, Kwag KH, Bertele V, Campomori A, Chakravarthy U, et al. Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. The Cochrane database of systematic reviews. 2014(9):Cd011230.

6. European Network For Health Technology Assessment (EuNetHTA). Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness 2017 [updated Dezember 2017. Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Guideline_Information_Retrieval_V1-2_2017.pdf.

7. European Network For Health Technology Assessment (EuNetHTA). Levels of Evidence - Internal validity of randomised controlled trials 2015 [updated November 2015. Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/16_WP7-SG3-GL-int_val_RCTs_amend2015.pdf.

8. European Network For Health Technology Assessment (EuNetHTA). Internal validity of non-randomised studies (NRS) on interventions 2015 [updated Juli 2015. Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-non-randomised-studies-NRS-on-interventions_Guideline_Final-Jul-2015.pdf.

9. European Network For Health Technology Assessment (EuNetHTA). Comparators & Comparisons: Direct and indirect comparisons 2015 [updated November 2015. Available from: https://www.eunethta.eu/wp-content/uploads/2018/03/Direct_comparators_comparisons.pdf.