EUnetHTA Joint Action 3 2016-2020

Ustekinumab for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic, or have medical contraindications to such therapies.

Project ID: ***PTJA07***

Project description and planning

MIZ, Croatia

TLV, Sweden

AOTMiT, Poland

Template Version 2, December 2018

Version Log

Version number	Date	Modification	Reason for the modification
V1	22/02/19	First draft of project plan	
V2	11/03/19	Second draft of project plan	Comments from reviewers and Scoping document from MAH
V3	15/03/19	Third draft of the project plan	Discussion between authors and reviewers
V4	09/04/19	Fourth draft of the project plan	Additional information received during F2F meeting
Final version	26/07/2019	Fifth draft of the project plan	Final, after positive CHMP opinion released

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List of abbreviations

AE	Adverse Event
CHMP	Committee for Medicinal Products for Human Use
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
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
IBDQ	Inflammatory Bowel Disease Questionnaire
NMA	Network Meta-Analysis
PICO	Patient, Intervention, Comparator and Outcome
pMAH	prospective Marketing Authorisation Holder
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SF remission	Steroid-Free remission
UC	Ulcerative Colitis

1 Introduction

On 17/09/2018, EUnetHTA and the prospective Marketing Authorisation Holder (pMAH) of ustekinumab (*Janssen Pharmaceutical N.V.)* agreed that EUnetHTA will perform a joint relative effectiveness assessment of ustekinumab for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic, or have medical contraindications to such therapies. Once finalised this assessment is made publicly available and can be used by European HTA bodies for their national/regional HTA processes, e.g. supporting reimbursement, pricing decisions and clinical guideline development.

2 Research question and scope

The aim of this project is to compare the clinical effectiveness and safety of ustekinumab in the target patient population with relevant comparators. The choice of comparators is based on the target patient population and the relevant comparators recommended in this target group of the EUnetHTA partners, specified in the project scope below.

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

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

Description	Assessment scope
PICO 1	
Population	Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to conventional therapy and to at least one biologic therapy or have medical contraindications to such therapies.
Intervention	Ustekinumab
Comparison	Adalimumab, infliximab, golimumab, vedolizumab, tofacitinib
Outcomes	**Efficacy**: • Clinical response after induction • Clinical response after one year • Clinical remission after induction • Clinical remission after one year • Inflammatory Bowel Disease Questionnaire (IBDQ) response • Generic HRQoL • Steroid-free (SF) remission • Mucosal healing (endoscopic healing) after induction • Mucosal healing (endoscopic healing) after one year • Surgery required • Hospitalization **Safety**: • Overall adverse events (AEs) • Serious AEs • Discontinuations due to AEs • Severe AEs • Fatal AEs • Infections • Severe infection
PICO 2	
Population	Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to conventional therapy or have medical contraindications to such therapy.
Intervention	Ustekinumab
Comparison	Adalimumab, infliximab, golimumab, vedolizumab, tofacitinib
Outcomes	**Efficacy**: • Clinical response after induction

	• Clinical response after one year • Clinical remission after induction • Clinical remission after one year • Inflammatory Bowel Disease Questionnaire (IBDQ) response • Generic HRQoL • Steroid-free (SF) remission • Mucosal healing (endoscopic healing) after induction • Mucosal healing (endoscopic healing) after one year • Surgery required • Hospitalization **Safety**: • Overall adverse events (AEs) • Serious AEs • Discontinuations due to AEs • Severe AEs • Fatal AEs • Infections • Severe infection

3 Methods

The EUnetHTA Guidelines, available at http://www.eunethta.eu/eunethta-guidelines, will be consulted throughout the assessment process [1-10].

3.1 Inclusion criteria

During the assessment the inclusion criteria applied by the pMAH will be checked to evaluate if they capture the PICO defined for the assessment. In addition, the following criteria are considered relevant for study inclusion:

- Only English language studies will be included in this assessment as this is the language in common for the countries involved in this assessment and most often the language used in the relevant publications and reports to be assessed.

3.2 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(s). 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 [7]. 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 (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform and EU Clinical Trials Register) and against the studies included in the regulatory assessment report. If there are major flaws in the search conducted by the manufacturer, further supplementary searches in PubMed or screening of reference lists of relevant systematic reviews will be conducted to check for possible incompleteness of the study pool. The search date, complete search strategies and the results of these searches will be reported in the assessment.

If the evidence provided in the submission dossier is incomplete it will not be supplemented by evidence from own searches nor will the authors of the assessment perform additional analyses. The incompleteness and its consequences for the conclusions of the report will be described in the assessment report.

3.3 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.

3.3.1 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.

3.3.2 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 [8] and non-randomised studies on interventions [9]. 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.*

3.3.3 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.

3.3.4 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 [10].

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 evaluation of 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 [10]. The indirect comparisons relevant for the research questions (see Section 2) will be presented and examined in the assessment report.

If an NMA is performed only data from RCTs should be included. Results should be presented separately for after induction and after 1 year of treatment. The selection of outcomes included in the indirect comparison should be justified by the company.

3.4 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 had 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. Two patient organisations completed the survey, namely Pacienti IBD z.s. (Czech Republic) and European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA).

The information gathered from the open call was used to inform the scope of this assessment, in particular the outcomes to be considered. In addition, the information will be used to support the assessment of health technology, specifically to provide a summary text related to impact of condition; experience with currently available pharmaceuticals; experiences with, and expectations of the drug under assessment.

4 Project organisation

4.1 Participants

Table 4-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	Ministry of Health of the Republic of Croatia [MIZ Croatia]	Author	Croatia	• Develop the final version of EUnetHTA project plan with co-authors • Review the NMA • Relative effectiveness and safety assessment • Send “draft versions” to reviewers, compile feedback from reviewers and perform changes according to reviewers comments • Prepare the final assessment including a final summary of the assessment
2.	Agencja Oceny Technologii Medycznych i Taryfikacji, Agency for Health Technology Assessment and Tariff System [AOTMiT]	Co-Author	Poland	• Develop the first draft and the final version of EUnetHTA project plan with first author. • Carry out the assessment: TEC Domain and CUR Domain. • Support EFF, and SAF Domains, Summary, Method and Discussion sections
3.	Tandvårds- och läkemedelsförmånsverket [TLV]	Co-Author	Sweden	• Develop the first draft and the final version of EUnetHTA project plan with first author. • Support EFF, and SAF Domains, Summary, Method and Discussion sections
4.	Agencja Oceny Technologii Medycznych i Taryfikacji, Agency for Health Technology Assessment and Tariff System [AOTMiT]	Information specialist	Poland	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
5.	Schweizer Netzwerk für HTA [SNHTA]	Statistical specialist	Switzerland	Expert review of statistical analyses presented in submission dossier, statistical support for authors
6.	Università Cattolica del Sacro Cuore [UCSC Gemelli]	Dedicated Reviewer	Italy	
7.	Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet [NIPN]	Dedicated Reviewer	Hungary	
8.	Schweizer Netzwerk für HTA [SNHTA]	Dedicated Reviewer	Switzerland	Assist in assessing the NMA methodology

9.	Servicio de Evaluación y Planificación del Servicio Canario de la Salud [SESCS] and Fundación Canaria de Investigación Sanitaria [FUNCANIS]	Dedicated Reviewer	Spain	
10.	Националният център по обществено здраве и анализи [NCPHA]	Observer	Bulgaria	
Contributors				
11.	Dr. V. Pittet	External expert	Switzerland	Answer specific question during the assessment.
12.	Pacienti IBD z.s European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA)	Patient Organisations		Complete the EUnetHTA open call in order to inform the scope of the assessment. When relevant, information will also be used in the assessment report.
13.	Compuscript	Medical Editor		Responsible for the medical editing of the report
14.	Zorginstituut Nederland [ZIN]	Project Manager	Netherlands [NL]	Coordination between involved parties throughout the assessment period

4.2 Project stakeholders

Table 4-2: Project stakeholders

Organisation	**Role in the project**
Janssen Pharmaceutical N.V.	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	**17-09-2018**	**22-10-2019**
Letter of Intent received	17-09-2018	
Scoping phase	**08-02-2019**	**25-07-2019**
PICO survey – request relevant PICO from Member States	01-02-2019	15-02-2019
Open call for patient input	13-02-2019	05-04-2019
Review of first draft Project Plan	22-02-2019	01-03-2019
Development of second draft Project Plan & answers to DR comments	04-03-2019	11-03-2019
Scoping F2F meeting with manufacturer	22-03-2019	
Pre-assessment phase	**01-07-2019**	**25-07-2019**
Receive Submission Dossier from pMAH	01-07-2019	
Check formal completeness of Submission Dossier	01-07-2019	11-07-2019
Receive missing items and comments on the requests from the formal completeness check from pMAH	16-07-2019	
Start writing Assessment (background, methods)	01-07-2019	25-07-2019
CHMP opinion	25-07-2019	
Assessment phase	**25-07-2019**	**22-10-2019**
Writing first draft Joint Assessment	25-07-2019	29-08-2019
Review by DRs	29-08-2019	09-09-2019
Writing second draft Joint Assessment	09-09-2019	04-10-2019
Medical Editing	07-10-2019	11-10-2019
Fact Check by pMAH (parallel with medical editing)	07-10-2019	11-10-2019
Final Assessment + response Fact Check	21-10-2019	
Publication final version of rapid assessment	22-10-2019	

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.

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. European Network For Health Technology Assessment (EuNetHTA). Comparators & Comparisons: Criteria for the choice of the most appropriate comparator(s) [online]. November 2015 [Access: 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/03/Criteria_WP7-SG3-GL-choice_of_comparator_amend2015.pdf.

2. European Network For Health Technology Assessment (EuNetHTA). Endpoints used for Relative Effectiveness Assessment: Clinical Endpoints [online]. November 2015 [Access: 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/02/WP7-SG3-GL-clin_endpoints_amend2015.pdf.

3. European Network For Health Technology Assessment (EuNetHTA). Endpoints used in Relative Effectiveness Assessment: Surrogate Endpoints [online]. November 2015 [Access: 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/03/surrogate_endpoints.pdf.

4. European Network For Health Technology Assessment (EuNetHTA). Endpoints used for Relative Effectiveness Assessment: Composite endpoints [online]. November 2015 [Access: 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/03/composite_endpoints.pdf.

5. European Network For Health Technology Assessment (EuNetHTA). Endpoints used for Relative Effectiveness Assessment: Health related quality of life and utility measures [online]. November 2015 [Access: 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/01/Endpoints-used-for-Relative-Effectiveness-Assessment-Health-related-quality-of-life-and-utility-measures_Amended-JA1-Guideline_Final-Nov-2015.pdf.

6. European Network For Health Technology Assessment (EuNetHTA). Endpoints used in Relative Effectiveness Assessment: Safety [online]. November 2015 [Access: 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/03/WP7-SG3-GL-safety_amend2015.pdf.

7. European Network For Health Technology Assessment (EuNetHTA). Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness [online]. December 2017 [Access : 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/01/Guideline_Information_Retrieval_V1-2_2017.pdf.

8. European Network For Health Technology Assessment (EuNetHTA). Levels of Evidence - Internal validity of randomised controlled trials [online]. November 2015 [Access : 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/01/16_WP7-SG3-GL-int_val_RCTs_amend2015.pdf.

9. European Network For Health Technology Assessment (EuNetHTA). Internal validity of non-randomised studies (NRS) on interventions [online]. July 2015 [Access : 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-non-randomised-studies-NRS-on-interventions_Guideline_Final-Jul-2015.pdf.

10. European Network For Health Technology Assessment (EuNetHTA). Comparators & Comparisons: Direct and indirect comparisons [online]. November 2015 [Access: 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/03/Direct_comparators_comparisons.pdf.