EUnetHTA Joint Action 3 2016-2020

PRETOMANID FGK IS INDICATED IN COMBINATION WITH BEDAQUILINE AND LINEZOLID, IN ADULTS, FOR THE TREATMENT OF PULMONARY EXTENSIVELY DRUG RESISTANT (XDR), OR TREATMENT-INTOLERANT OR NONRESPONSIVE MULTIDRUG-RESISTANT (MDR) TUBERCULOSIS (TB).

PROJECT ID: PTJA14

PROJECT DESCRIPTION AND PLANNING

HAS, France

MIZ, Croatia

Template Version 2, December 2018

VERSION LOG

Version number	Date	Modification	Reason for the modification
V0.1	05/02/2020	First draft of the project plan	N/A
V0.2	18/02/2020	Second draft of the project plan	Comments from dedicated reviewers included
V0.3	25/02/2020	Third draft of the project plan	Modification of the PP after pre-scoping e-meeting
V0.4	30/03/2020	Fourth draft of the project plan	Modification of information about indication, external expert, patient organisation and indirect comparison
V1.0	02/04/2020	Final version of the project plan	N/A

CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AAZ	Agency for Quality and Accreditation in Health Care and Social Welfare – now Ministry of Health, Croatia
ACTUME	Association Contre la Tuberculose et les Maladies Endémiques
AE	Adverse event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
CHMP	Committee for Medicinal Products for Human Use
CSR	Clinical Study Report
EPAR	European Public Assessment Report
EUnetHTA	European Network for Health Technology Assessment
HAS	Haute Autorité de Santé
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
IPData	Individual Patient Data
pMAH	Prospective Marketing Authorisation Holder
MAIC	Matching-adjusted indirect comparison
MDR	Multidrug-resistant
MIZ	Ministry of Health of the Republic of Croatia
NMA	Network meta-analysis
PICO	Population Intervention Comparison Outcomes
SNHTA	Swiss Network for Health Technology Assessment
STC	Simulated treatment comparison
TB	Tuberculosis
UU	University of Utrecht
WHO	World Health Organization
XDR	Extensively drug resistant
ZIN	Zorginstituut Nederland

1 INTRODUCTION

On 22-11-2019, EUnetHTA and the prospective Marketing Authorisation Holder (pMAH) of pretomanid (Mylan) agreed that EUnetHTA will perform a joint relative effectiveness assessment of pretomanid. The full indication granted by the CHMP on the 26th of March 2020 is: "Pretomanid FGK is indicated in combination with bedaquiline and linezolid, in adults, for the treatment of pulmonary extensively drug resistant (XDR)[1], or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB)[2]. Consideration should be given to official guidance on the appropriate use of antibacterial agents". 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.

[1] Extensively drug-resistant TB (XDR-TB): defined tuberculosis with resistance to any fluoroquinolone, and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.

[2] Multidrug resistant TB (MDR-TB): defined as tuberculosis with resistance to at least both isoniazid and rifampicin.

2 RESEARCH QUESTION AND SCOPE

The aim of this project is to compare the clinical effectiveness and safety of pretomanid 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 pretomanid.

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

<table>
<tr><th>Description</th><th>Assessment scope</th></tr>
<tr><td>Population</td><td>Adult patients with pulmonary extensively drug resistant (XDR), or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB).</td></tr>
<tr><td>Intervention</td><td>Pretomanid is indicated in combination with bedaquiline and linezolid.

Posology:
The recommended dosage for pretomanid is 200 mg orally (1 tablet of 200 mg), daily, for 26 weeks.

Pretomanid should be administered only in combination with bedaquiline (400 mg once daily for 2 weeks followed by 200 mg 3 times per week [with at least 48 hours between doses] orally for a total of 26 weeks) and linezolid (1200 mg daily orally for up to 26 weeks).</td></tr>
<tr><td>Comparison</td><td>• Treatments authorised in MDR-TB in association with other tuberculosis medicines:
– Bedaquiline
– Delamanid
– Para-amino salicylic acid
• Other treatments not authorized in MDR-TB but recommended for use by WHO (see. Table below). It should be considered that the certainty on the effect of these products is moderate or very low according to WHO.

List of medicines recommended for use in longer MDR-TB regimens (cf. 2019 WHO consolidated guidelines on DR tuberculosis treatment for further details on the composition of the recommended regimens)

<table>
<tr><td>Group A</td><td>Levofloxacin OR moxifloxacin
Bedaquiline
Linezolid</td></tr>
<tr><td>Group B</td><td>Clofazimine
Cycloserine OR terizidone</td></tr>
<tr><td>Group C</td><td>Ethambutol
Delamanid
Pyrazinamide
Imipenem-cilastin OR meropenem
Amikacin (OR streptomycin)
Ethionamide OR prothionamide
para-aminosalicylic acid</td></tr>
</table>
</td></tr>
<tr><td>Outcomes</td><td>• Proportion of subjects with sputum culture (± smear microscopy) conversion to negative status and time to culture conversion (± smear microscopy) to negative status
• Cure (according to WHO definition* or other clinically relevant definition)
• Treatment failure including bacteriological/clinical failure and relapse (according to WHO definition* or other clinically relevant definition)
• Treatment completed (according to WHO definition* or other clinically relevant definition)
• Treatment success (includes cure and treatment completed)
• Mortality
• Health-related QoL
• Safety, including serious adverse events (AEs) and treatment-related AEs

*WHO. Companion handbook to the 2011 WHO guidelines for the programmatic management of drug-resistant tuberculosis. 2014. http://www.who.int/tb/publications/pmdt_companionhandbook/en/
Additional outcomes not captured in the PICO may be described in the assessment report as submitted by MAH.</td></tr>
</table>

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 applied by the pMAH will be checked to evaluate if they capture the PICO defined for the assessment.

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 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, as appropriate, 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 own searches and analyses by the authors of the assessment. 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. Analyses that are not pre-specified in the study protocols (i.e. post hoc analysis) will not be presented in the assessment report.

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 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

Direct comparative evidence remains the most reliable source of evidence to assess relative effectiveness. In case the pMAH considers that indirect comparative data should be submitted, this should be thoroughly justified in the submission dossier. Whenever the comparison versus one or several comparators is not considered feasible, the pMAH should justify absence of comparative data in the submission dossier, taking into account the different possible combination regimens and the data available for each one. As stated in EunetHTA guideline [10], the preferred option for indirect comparison is network meta-analysis (NMA). If NMAs are performed, the NMA methods should be described in sufficient detail, and any deviations from protocol defined methods should be justified. In case a NMA is not feasible, the authoring team does not advocate for a specific method (other types of indirect comparison should be explored, notably population-adjusted indirect comparison such as MAIC or STC). The MAH is invited to justify the choice of the method(s) used in the submission dossier and to detail as much as possible its methodology (in particular regarding effect modifiers and prognostic variables). The methods applied, and if applicable, the justification in the event of deviations from the required

approaches will be evaluated [10]. If imputations are used, the imputation methods need to be clearly described in the dossier (ideally in a pre-defined protocol). It should also be clarified where IPData and where aggregate information on study arms are used. The quality of evidence derived from non-population-adjusted indirect comparisons is considered very low. Although submission of such data is possible, the authoring team does not advise the pMAH to do so. The indirect comparisons relevant for the research questions (see Section 2) will be presented and examined in the assessment report.

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.

Relevant European and national patient and consumer 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.

The open call for patient input was online from 20 January – 23 March 2020. After this deadline, no patient organisations completed the survey.

In addition, an interview with a patient organisation was conducted to gain input regarding the impact of tuberculosis on patients' quality of life as well as the current standard of care. This interview was conducted with a patient representative from the patient organisation ACTUME.

4 Project organisation

4.1 Participants

Table 4-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	Haute Autorité de Santé [HAS]	Author	France	Author will draft the report and in particular the following sections: Research question and scope; Methods; Results (efficacy); Discussion and Conclusion. Author will review and comment the sections drafted by the co-author. All important milestones will be discussed in advance with the co-author.
2.	Ministry of Health of the Republic of Croatia [MIZ] (former Agency for Quality and Accreditation in Health Care and Social Welfare [AAZ])	Co-Author	Croatia	Co-author will draft the following sections of the report: Background and Results (safety). Co-author will review and comment on all parts of the report.
3.	Haute Autorité de Santé [HAS]	Information specialist	France	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
4.	Haute Autorité de Santé [HAS]	Statistical specialist	France	Expert review of statistical analyses presented in submission dossier, statistical support for authors
5.	HTA Department SEC Ministry of Health (MoH) Ukraine	Dedicated Reviewer	Ukraine	Performing a thorough review of the content-related aspects of the first draft of the project plan based on the checklist by using the comments form (relevant EUnetHTA guidelines, SOPs etc. Responding to author´s and co-author´s questions/requests (in a timely manner).
6.	University of Utrecht [UU]	Dedicated Reviewer	Netherlands	
7.	Agencia Española de Medicamentos y Productos Sanitarios [AEMPS]	Dedicated Reviewer	Spain	
8.	Swiss Network for Health Technology Assessment [SNHTA]	Dedicated Reviewer	Switzerland	

Contributors				
9.	Radboud University	External expert	The Netherlands	Answer specific questions during the assessment phase
10.	ACTUME	Patient organisation		Answer specific question in the context of an interview in order to provide input regarding the impact of tuberculosis on patients' quality of life as well as the current standard of care.
11.	TBD	Medical Editor		Performing medical editing of the second draft of the assessment report
12.	Zorginstituut Nederland [ZIN]	Project Manager	The Netherlands	Coordination between involved parties throughout the assessment period

4.2 Project stakeholders

Table 4-2: Project stakeholders

Organisation	**Role in the project**
Mylan	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	**31-10-2019**	**26-08-2020**
Letter of Intent received	22-11-2019	
Scoping phase	**13-01-2020**	**28-05-2020**
Scoping PICO and development of first draft Project Plan	13-01-2020	05-02-2020
PICO survey – request relevant PICO from Member States	21-01-2020	30-01-2020
Adapt draft Project Plan based on PICO survey	13-01-2020	05-02-2020
Open call for patient input	20-01-2020	23-03-2020
Review of first draft Project Plan	06-02-2020	12-02-2020
Development of second draft Project Plan & answers to DR comments	13-02-2020	17-02-2020
Receive scoping F2F meeting documents from pMAH	10-02-2020	
Pre-scoping e-meeting with the assessment team	24-02-2020	
Share discussion topics for Scoping F2F Meeting	26-02-2020	
Scoping F2F meeting with manufacturer	04-03-2020	
Share action points from F2F meeting with manufacturer	11-03-2020	
(pre-)Assessment phase	**21-04-2020**	**06-05-2020**
Receive Submission Dossier from pMAH	21-04-2020	
Check formal completeness of Submission Dossier	22-04-2020	01-05-2020
Receive missing items and comments on the requests from the formal completeness check from pMAH	06-05-2020	
CHMP opinion	26-03-2020	
Finalize Project Plan	30-03-2020	
Assessment phase	**30-04-2020**	**15-07-2020**
Writing first draft Joint Assessment	30-04-2020	01-06-2020
Review by DRs (and if applicable include experts)	02-06-2020	11-06-2020
Writing second draft Joint Assessment	12-06-2020	29-06-2020
Medical Editing	29-06-2020	03-07-2020
Fact Check by pMAH (parallel with medical editing)	29-06-2020	03-07-2020
Final Assessment + response Fact Check	03-07-2020	13-07-2020
Expected EPAR	15-06-2020	
Publication final version of rapid assessment	14-07-2020	15-07-2020

** Given the expected Market Authorisation transfer of pretomanid to Mylan, PTJA14 timelines are not in parallel to the EMA regulatory timelines.*

4.4 Conflict of interest management

Conflicts of interest will be handled according to the EUnetHTA Conflict of Interest Policy. All authors, co-authors, dedicated reviewers, observers, external experts (health care professionals, patients or patient representatives) involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form, which was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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.

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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.