EUnetHTA Joint Action 3 WP4

**Relative effectiveness assessment of pharmaceutical technologies**

# VENETOCLAX IN COMBINATION WITH A HYPOMETHYLATING AGENT FOR THE TREATMENT OF ADULT PATIENTS WITH NEWLY-DIAGNOSED ACUTE MYELOID LEUKAEMIA (AML) WHO ARE INELIGIBLE FOR INTENSIVE CHEMOTHERAPY.

**Project ID: PTJA16**
Project Plan

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# DOCUMENT HISTORY AND CONTRIBUTORS

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| **V0.1** | **09/10/2020** | First draft |
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| **V0.3** | **26/04/2021** | Input from the F2F meeting with (p)MAH, patient organisations and CHMP opinion has been processed |
| **V1.0** | **28/04/2021** | Final Project Plan |

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For further information on the work distribution and further contributors, please see section 4.1

### Conflict of interest

All authors, co-authors, dedicated reviewers, 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. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AML | Acute myeloid leukemia |
| CHMP | Committee for Medicinal Products for Human Use |
| CR | Complete remisson |
| CRi | Complete remisson with incomplete haematological recovery |
| CSR | Clinical Study Reports |
| DOI | Declaration of Interest |
| DR | Dedicated Reviewers |
| EFS | Event Free Survival |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| EUnetHTA | European Network of Health Technology Assessment |
| HTA | Health Technology Assessment |
| HTAi | Health Technology Assessment international |
| JAZMP | Agency for Medicinal Products and Medical Devices of the Republic of Slovenia |
| LDAC | Low-dose cytarabine |
| MDS | Myelodysplastic syndrome |
| NIPHNO | The Norwegian Institute of Public Health |
| NOMA | Norwegian Medicines Agency |
| PICO | Population, intervention, control, outcome |
| pMAH | Prospective Marketing Authorisation Holder |
| PTJA | Pharmaceutical Joint Assessment |
| REA | Relative Effectiveness Assessment |
| RoB | Risk of Bias |
| WP4 | Work Package 4 |
| ZIN | Zorginstituut Nederland |

# 1 INTRODUCTION

On 20/07/2020, EUnetHTA and the prospective Marketing Authorisation Holder (pMAH) of venetoclax *(AbbVie)* agreed that EUnetHTA will perform a joint relative effectiveness assessment of venetoclax. Venetoclax is indicated in combination with a hypomethylating agent for the treatment of adult patients with newly-diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy. 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.

# 2 RESEARCH QUESTION AND SCOPE

The aim of this project is to compare the clinical effectiveness and safety of venetoclax in the target patient populations with relevant comparators. The target patient populations 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 venetoclax.

**Table 2.1 Assessment scope: relevant PICO(s) identified for the planned assessment.**

| Description | Assessment scope |
|---|---|
| | PICO 1 |
| **Population** | Adult patients with newly- diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.[a] [b]<br><br>ICD-10: C92.0<br>MeSH-terms: Leukemia, Myeloid, Acute<br>Tree Number(s): C04.557.337.539.275<br>MeSH Unique ID: D015470 |
| **Intervention** | Venetoclax (400 mg orally once daily [QD]) in combination with hypomethylating agents (HMAs; azacitidine or decitabine)[c]<br><br>Synonyms for venetoclax: Venclexta, Venclyxto, GDC-0199, ABT-199, RG-7601 |
| **Comparison** | • Azacitidine<br>• Decitabine<br>• Low-dose cytarabin<br>• Glasdegib in combination with LDAC<br>• Best Supportive Care (national differences exists, may include: hydroxyurea, 6-mercaptopurine, 6-thyoguanine, low dose melphalan, transfusion support, anti-infective therapies etc.)[d]<br><br>Available MeSH for comparators:<br><br>Azacitidine<br>Unique ID: D001374<br>Tree Numbers:<br>D02.145.150<br>D03.383.742.680.245.217<br>D13.570.685.245.217<br>D13.570.800.286.300<br><br>Decitabine<br>Unique ID: D000077209 |

[a] The relevant population will be accordance with the products final marketing authorisation and the indication maybe adjusted during the EMA procedure.

[b] Several subgroups analyses may be considered (de novo and secondary AML including MDS, mutational status, cytogentic risk etc).

[c] Venetoclax will be assessed in accordance with its final marketing authorisation using the dosing and combination defined in the SPC.

[d] Heuser M et al. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. Annals of oncology: official journal of the European Society for Medical Oncology. 2020.

Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-47.

| | |
|---|---|
| | Tree Numbers:<br>D02.145.150.500<br>D03.383.742.680.245.217.500<br>D13.570.685.245.217.500<br>D13.570.800.286.300.500<br><br>Low-dose cytarabine<br>Unique ID: D003561<br>Tree Numbers:<br>D03.383.742.680.245.453<br>D13.570.065.300<br>D13.570.685.245.453<br><br>Synonyms for glasdegib: PF-04449913 |
| **Outcomes** | <u>Effectiveness:</u><br>• Overall survival<br>• Health-related quality of life<br>• Complete remission (CR)<br>• Composite CR: CR plus CR with incomplete haematological recovery (CR + CRi)<br>• Event-free survival (EFS)<br>• Transfusion independency<br><br><u>Safety:</u><br>• Serious adverse events (AEs)<br>• Grade ≥3 AEs, including treatment related AE's<br>• Fatal AEs, including treatment related fatal AE's<br>• Overall AEs<br>• Treatment discontinuations and dose reductions due to AEs |
| **Study type** | <u>Effectiveness</u><br><br>• Randomised controlled trials (RCT)<br><br><u>Safety:</u><br><br><u>If suitable evidence syntheses (SRs/HTA reports) are available:</u><br>• Evidence syntheses (SRs/HTA reports); and<br>• Primary studies (as described in next bullet) published after the last search date of the latest SR/HTA document.<br><br><u>If suitable evidence syntheses (SRs/HTA reports) are NOT available:</u><br><br>• Randomised controlled trials;<br>• Non-randomised controlled trials;<br>• Observational studies; |

# 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. In addition, the following criteria are considered relevant for study inclusion:

- Inclusion of non-randomised controlled clinical trials (additional inclusion criterion 1)
- Inclusion of observational studies (additional inclusion criterion 2)

## *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 (venetoclax) 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.

### 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 (if provided) 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.

The methods and outcome of the risk-of-bias assessment if presented in the Submission Dossier will be evaluated 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***

If indirect comparisons are included in the Submission Dossier, the methods applied, including the justification for the methods applied will be evaluated [10]. 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.

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.

An open call for patient input was published on the EUnetHTA website on the 21st September 2020. The questions were based on the HTA international (HTAi) questionnaire template that was adapted for this project and covered the following topics:

- The impact of AML on patients' quality of life;
- Impact of AML on carers/unpaid care-givers;
- Experiences with currently available treatment options;
- Expectations/requirements for a new medicine for AML.

Eight patient organisations provided input in response to the Open Call for Patient Input published on 21st of September 2020: Association of Cancer Patients in Finland; MOHA, Hungary; Blodkreftforeningen, Norway;Hrvatska udruga leukemija i limfomi (HULL), Croatia; LYLE - Patient organization for lymphoma, leukemia and MDS, Denmark; Diagnoza leukemie, Czech Republic;Leukaemia Care, United Kingdom; Deutsche Leukämie- & Lymphom-Hilfe, Germany.

The information gathered from the open call was used to inform the scope of this assessment.

# 4 PROJECT ORGANISATION

## *4.1 Participants*

**Table 2.1 Project participants**

| Role in the project | Agency | Country | Distribution of work |
|---|---|---|---|
| **Assessment Team** | | | |
| Author | The Norwegian Medicines Agency (NOMA) | Norway | Develop first draft and final version of EUnetHTA project plan with co-author.<br>Methods section: Analysis of included studies.<br>Review of statistical analyses presented in submission dossier.<br>Results section: relative effectiveness assessment (EFF domains).<br>Prepare draft for DR and adapt documents according to reviewers comments together with co-authors.<br>Answer comments of expert and manufacturer together with co-authors.<br>Prepare the final assessment including a final summary of the assessment. |
| Co-Author | Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP) | Slovenia | Develop first draft and final version of EUnetHTA project plan with authors.<br>Prepare CUR and TEC Domains.<br>Safety assessment (SAF domain).<br>Patient Involvement.<br>Support authors in Summary and Discussion sections.<br>Support authors to adapt the JA according to reviewers comments.<br>Support author in answering comments of expert and manufacturer. |
| Information specialist | NIPHNO | Norway | 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.<br>GRADE and RoB assessment. |
| Statistical specialist | The Norwegian Medicines Agency (NOMA) | Norway | Expert review of statistical analyses presented in Submission Dossier, statistical support for authors. |
| Dedicated Reviewer | Spanish Agency of Medicine and Sanitary Products (AEMPS) | Spain | Review draft project plan and first draft of assessment report. |
| Dedicated Reviewer | HTA Department of State Expert Centre of MoH, Ukraine | Ukraine | Review draft project plan and first draft of assessment report. |
| Dedicated Reviewer | State Medicines Control Agency of Lithuania (SMCA) | Lithuania | Review draft project plan and first draft of assessment report. |
| **Contributors** | | | |
| External expert | Expert recruitment ongoing | | Review of the scope of the assessment and the draft Assessment Report. In addition, answer specific question during the assessment. |
| Patient organisations | Association of Cancer Patients | Finland | Complete the EUnetHTA open call in order to inform the scope of the assessment. |

| Role in the project | Agency | Country | Distribution of work |
|---|---|---|---|
| | MOHA<br><br>Blodkreftforeningen<br><br>Hrvatska udruga leukemija i limfomi (HULL); LYLE<br><br>Patient organization for lymphoma, leukemia and MDS<br><br>Diagnoza leukemie<br><br>Leukaemia Care<br><br>Deutsche Leukämie- & Lymphom-Hilfe | Hungary<br><br>Norway<br><br>Croatia<br><br>Denmark<br><br>Czech Republic<br>United Kingdom<br>Germany | |
| Medical Editor | *TBD* | *TBD* | Responsible for the medical editing of the report |
| Project Manager | Zorginstituut Nederland (ZIN) | Netherlands | Coordination between involved parties throughout the assessment period |

## *4.2 Project stakeholders*

**Table 3.2. Project stakeholders**

| Organisation | Role in the project |
|---|---|
| AbbVie | Manufacturer [MAH];<br><br>Completing the Submission Dossier;<br><br>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** | **20-07-2020** | **07-07-2021** |
| Letter of Intent received | 20-07-2020 | |
| **Scoping phase** | **14-09-2020** | **28-01-2021** |
| Scoping PICO and development of first draft Project Plan | 14-09-2020 | 09-10-2020 |
| PICO survey – request relevant PICO from Member States | 23-09-2020 | 01-10-2020 |
| Adapt draft Project Plan based on PICO survey | 14-09-2020 | 09-10-2020 |
| Open call for patient input | 14-09-2020 | 30-10-2020 |
| Review of first draft Project Plan | 12-10-2020 | 16-10-2020 |
| Development of second draft Project Plan & answers to DR comments | 19-10-2020 | 23-10-2020 |
| Receive Scoping F2F meeting documents from pMAH | 04-10-2020 | |
| Pre-scoping e-meeting with the Assessment Team | 20-10-2020 | |
| Share discussion topics for Scoping F2F Meeting | 28-10-2020 | |
| Scoping F2F meeting with manufacturer | 04-11-2020 | |
| Share action points from F2F meeting with manufacturer | 09-11-2020 | |
| **(pre-)Assessment phase** | **08-12-2020** | **22-04-2021** |
| Receive Submission Dossier from pMAH | 08-12-2020 | |
| Check formal completeness of Submission Dossier | 09-12-2020 | 18-12-2020 |
| Receive missing items and comments on the requests from the formal completeness check from pMAH | 08-01-2021 | |
| Start writing Assessment (background, methods) | 08-03-2021 | 22-04-2021 |
| *CHMP opinion* | *22-04-2021* | |
| Finalize Project Plan | 28-04-2021 | |
| Optional: Grace period to revise Submission Dossier by pMAH (based on CHMP opinion) | TBD | |
| **Assessment phase** | **08-04-2021** | **07-07-2021** |
| Writing first draft Joint Assessment | 08-04-2021 | 10-05-2021 |
| Review by DRs (and if applicable include experts) | 11-05-2021 | 20-05-2021 |
| Writing second draft Joint Assessment | 21-05-2021 | 04-06-2021 |
| Medical Editing | 07-06-2021 | 11-06-2021 |
| Fact Check by pMAH (parallel with medical editing) | 07-06-2021 | 11-06-2021 |
| Final Assessment + response Fact Check | 21-06-2021 | |
| *Expected EPAR* | *01-07-2021* | |
| Publication final version of rapid assessment | 06-07-2021 | 07-07-2021 |

# 5 REFERENCES

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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.
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