EUnetHTA Joint Action 3 2016-2020

# ENASIDENIB FOR THE TREATMENT OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY ACUTE MYELOID LEUKAEMIA (AML) WITH AN ISOCITRATE DEHYDROGENASE 2 (IDH2) MUTATION

*PROJECT ID:* ***PTJA05***

## Project description and planning


NOMA, Norway

AEMPS, Spain

AETSA, Spain


**Template Version 2, November 2018**

## VERSION LOG

| Version number | Date | Modification | Reason for the modification |
|---|---|---|---|
| V0.1 | 11/12/2018 | 1st version draft | |
| V0.2 | 11/01/2019 | 2nd version draft | Input from Dedicated Reviewers incorporated |
| V0.3 | 29/01/2019 | 3rd version draft | Input from scoping F2F meeting with manufacturer and input from patient organisations incorporated |
| V1.0 | 07/02/2020 | Final version of the project plan | Final after company withdrawal from EMA marketing authorisation application |

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse events |
| AEMPS | Spanish Agency of Medicines and Medical Devices |
| AETSA | Andalusian Unit for Health Technology Assessment |
| AIFA | Agenzia Italiana del Farmaco |
| Allo-SCT | Allegenic stam cell transplantation |
| BSC | Best supportive care |
| CHMP | Committee for medicinal products for human use |
| CR | Complete remission |
| CSR | Clinical study report |
| CUR | Current use of technology |
| DFS | Disease- free survival |
| DOICU | Declaration of Interest and Confidentiality Undertaking |
| DPA | Directorate for Pharmaceutical Affairs |
| EFF | Relative effectiveness domain |
| EFS | Event-free survival |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| EUnetHTA | European Network of Health Technology Assessment |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HAS | Haute Autorité de santé |
| HIS | Healthcare Improvement Scotland |
| HMA | Hypomethylating agents |
| HRQL | Health-related quality of life |
| ICD | International Classification of diseases |
| IDH2 | Isocitrate dehydrogenase 2 |
| IDH2X | Isocitrate dehydrogenase 2 mutation unknown |
| IRR | Incidence of relapse or refractory disease |
| LDAC | Low dose azecitadine citarabine |
| MAH | Marketing Authorisation Holder |
| MAIC | Matched adjusted indirect comparison |
| MeSH | Medical Subject Headings |
| NCCN | National Comprehensive Cancer Network |
| NOMA | Norwegian Medicines Agency |
| ORR | Objective response rate |
| OS | Overall survival |
| PFS | Progression-free survival |
| PICO | Population, Intervention, Comparator and Outcomes |
| pMAH | prospective Marketing Authorisation Holder |
| R/R AML | Refractory/relapsed acute myeloid leukaemia |
| RFS | Relapse-free survival |
| SAF | Safety assessment domain |
| SmPC | Summary of product characteristics |
| SNHTA | Swiss Network for Health Technology Assessment |
| STC | Simulated treatment comparison |
| TEC | Technology domain |
| ZIN | Zorginstituut Nederland |

# 1 INTRODUCTION

On 05/10/2018, EUnetHTA and the prospective Marketing Authorisation Holder (pMAH) of enasidenib (Celgene) agreed that EUnetHTA will perform a joint relative effectiveness assessment of enasidenib for the treatment of adult patients with relapsed or refractory acute myeloid leukaemia (AML) with an isocitrate dehydrogenase 2 (IDH2) mutation.

On 6 Dec 2019, Celgene officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for enasidenib. Since no CHMP opinion will be granted at this stage, EUnetHTA closed this Joint Assessment on 12 Dec 2019.

This document is the final Project Plan for the applied indication for enasidenib, with details on the scope and methods for the anticipated assessment. Should Celgene reapply to EUnetHTA in the future, the need for an updated Project Plan will have to be assessed. For further information regarding the withdrawal, please visit the EMA website.

# 2 RESEARCH QUESTION AND SCOPE

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

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

| **Description** | **Assessment scope** | |
|---|---|---|
| | **PICO1** | **PICO2** |
| **Population** | • Enasidenib for the treatment of adult patients (≥18) with relapsed/ refractory acute myeloid leukemia and mIDH2+ mutation<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<br>Enasidenib is expected to be prescribed in IDH2+ patients only. Limited evidence on efficacy of chemotherapy in the mIDH2+ population is expected, therefore two different patient populations are suggested. Please see PICO 2 in table below.<br>Population 1: Adults (≥18) with R/R AML with IDH2 mutation positive (mIDH2+ population) for both intervention and comparators. | • Enasidenib for the treatment of adult patients (≥18) with relapsed/ refractory acute myeloid leukemia and mIDH2+ mutation<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<br>Enasidenib is expected to be prescribed in IDH2+ patients only. Limited evidence on efficacy of chemotherapy in the mIDH2+ population is expected, therefore two different patient populations are suggested.<br>Population 2 only for comparators: Adults (≥18) with R/R AML mIDH2 status unknown (IDH2X population). For intervention it would be adults (≥18) with R/R AML with IDH2 mutation positive (mIDH2+ population) [3]. |
| **Intervention** | Enasidenib as monotherapy. Orally taken tablets on every day of 28 day cycles until disease progression or unacceptable toxicities.<br>MeSH Unique ID: C000605269 | |
| **Comparison** | The following comparators have been selected based on European treatment guidelines (Döhner, 2017; NCCN, 2018) [1, 2] and national guidelines (France, Italy and Switzerland)<br>Intensive (salvage) therapy, Intensive chemotherapy:<br>Standard dose cytarabine The standard dose of cytarabine is 100-200 mg / m2 / day as a continuous intravenous infusion over 7 days. In high doses of 2-3 g / m2, cytarabine is given intravenously for 1-3 hours at 12-hour intervals and for 2-6 days.<br>HMA: *azacitidine and decitabine*<br>Low dose cytarabine (LDAC)<br>Best supportive care (BSC)<br>Unique MeSH ID cytarabine D003561<br>Unique MeSH ID azacitidine D001374<br>Unique MeSH ID decitabine C014347 | |
| **Outcomes** | Efficacy:<br>Overall survival (OS)<br>Event-free survival (EFS) | |

| | |
|---|---|
| | Relapse-free survival (RFS)<br>Progression-free survival (PFS)<br>Disease- free survival (DFS)<br>Incidence of relapse or refractory disease<br>Complete remission (CR)<br>Objective response rate (ORR)<br>Health-related quality of life (HRQL) – generic and disease specific HRQL<br>Safety:<br>AEs (adverse events)<br>serious AEs (SAE)<br>Discontinuation due to AE<br>Death as SAE<br>AEs of special interest<br>Dose and time dependencies of harms and patient groups that are most likely to be harmed will be covered under this issue. discontinuations due to adverse events, and key individual adverse events)<br>Note! Additional outcomes may be considered based on data presented in the submission or CSR. These data are currently not available for the authors. |

# 3 METHODS

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

## *3.1 Inclusion/exclusion criteria*

During the assessment the inclusion/exclusion 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:

- For both PICO patients in the comparator arm should be unfit for allo-SCT

## *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) which are presented in section 2 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 [4]. The search strategies for published literature should be described and justified by Manufacturer following EUnetHTA guideline “Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness”, as applicable.

Internal validity should be assessed using the Cochrane Risk of bias tool. 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 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 should follow the criteria described in the two EUnetHTA guidelines on the internal validity of randomised controlled trials [5] and non-randomised studies on interventions [6]. 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. The outcome of this evaluation will be reported. In case the risk-of-bias assessment provided by the pMAH in the submission dossier is considered inadequate by the authors, they will use their corrected assessment to inform the description of certainty of results.

### 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

#### 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. Relevant subgroup analyses should be presented in the submission file especially for the most important outcomes. 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 [7]. The indirect comparisons relevant for the research questions (see Section 2) will be presented and examined in the assessment report.

Due to the nature of the main clinical study (single arm) a proper statistical method for indirect treatment comparison should be applied for evidence synthesis. NICE guidelines for STA or MAIC [8] are recommended if any of these approaches are taken by MAH. The use of real world evidence (RWE) can be considered but published clinical trials are preferred. The use of RWE should also follow NICE guidelines [9].

## *3.4 Patient input*

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 Deutsche Leukämie- & Lymphom-Hilfe; Association of Cancer Patients in Finland'.

# 4 PROJECT ORGANISATION

## *4.1 Participants*

*Table 4-1: Project participants*

| | Agency | Role in the project | Country | Distribution of work |
|---|---|---|---|---|
| Assessment team | | | | |
| 1. | Norwegian Medicines Agency [NOMA] | Author | Norway | •Develop first draft and final version of EUnetHTA project plan with co-authors<br>•Relative effectiveness and safety assessment (EFF and SAF domains).<br>•Perform GRADE assessment<br>•Adapt documents according to reviewers comments together with co-authors<br>•Answer comments expert and manufacturer together with co-authors<br>•Prepare the final assessment including a final summary of the assessment |
| 2. | Spanish Agency of Medicines and Medical Devices [AEMPS]<br>Andalusian Unit for Health Technology Assessment<br>[AETSA] | Co-Author | Spain | •Develop first draft and final version of EUnetHTA project plan with Author<br>•Responsible for supporting the authors in all project phases<br>•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.<br>•Check all steps |
| 3. | Norwegian Medicines Agency [NOMA] | Information specialist | | 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. | Norwegian Medicines Agency [NOMA] | Statistical specialist | Norway | Expert review of statistical analyses presented in submission dossier, statistical support for authors |
| 5. | Haute Autorité de santé [HAS] | Dedicated Reviewer | France | |
| 6. | Agenzia Italiana del Farmaco [AIFA] | Dedicated Reviewer | Italy | |
| 7. | Swiss Network for Health Technology Assessment [SNHTA] | Dedicated Reviewer | Switzerland | |

| | | | | |
|---|---|---|---|---|
| 8. | Healthcare Improvement Scotland [HIS] | Dedicated Reviewer | Scotland | |
| 9. | Directorate for Pharmaceutical Affairs [DPA] | Dedicated Reviewer | Malta | |
| Contributors | | | | |
| 10. | Erasmus MC | Healthcare professional | Netherlands | Answered specific questions the team had during the scoping phase. |
| 11. | Deutsche Leukämie- & Lymphom-Hilfe; Association of Cancer Patients in Finland' | Patient organisation | Germany, Finland | The input of patients was received when developing the project plan. And will be incorporated in a sensible manner during assessment phase |
| 12. | Zorginstituut Nederland [ZIN] | Project Manager | Netherlands | Coordination between involved parties throughout the assessment period.<br>For questions please contact EUnetHTA Secretariat: EUnetHTA@zinl.nl |

## *4.2 Project stakeholders*

*Table 4-2: Project stakeholders*

| **Organisation** | **Role in the project** |
|---|---|
| Celgene | Manufacturer [MAH];<br>Completing the submission dossier;<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** |
|---|---|---|
| Expression of interest of manufacturer | 05/10/2018 | |
| Establish assessment team, identify external experts and patients | 05/10/2018 | 05/10/2018 |
| **Scoping phase** | | |
| Scoping and development of draft Project Plan incl. preliminary PICOs from Member States | 09/11/2018 | 23/11/2018 |
| Pre-scoping e-meeting with the assessment team | 04/01/2018 | |
| Scoping F2F meeting with manufacturer(s) | 22/01/2018 | |
| Review of draft Project Plan with dedicated reviewers | 13/12/2018 | 20/12/2018 |
| Amendment of draft Project Plan & final Project Plan available | 20/12/2018 | 07/02/2020 |
| Completion and submission of Submission file template by manufacturer | 07/08/2019 | |
| Withdrawal from marketing authorisation application | **06/12/2019** | |

## *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

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10. European Network For Health Technology Assessment (EuNetHTA). *HTA Core Model for Rapid Relative Effectiveness Assessments*. 2015 November 2015 14.03.2018]; Available from: https://www.eunethta.eu/wp-content/uploads/2018/06/HTACoreModel_ForRapidREAs4.2-3.pdf.