EUnetHTA Joint Action 3 WP4

Relative effectiveness assessment of pharmaceutical technologies

ELIVALDOGENE AUTOTEMCEL (ELI-CEL) FOR TREATMENT OF CEREBRAL ADRENOLEUKODYSTROPHY (CALD).

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Project Plan

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V0.2	**06/01/2021**	Input from Dedicated Reviewers has been processed
V0.3	**24/05/2021**	Input from the scoping meeting with (p)MAH, patient organisations and CHMP opinion has been processed
V1.0	**25/05/2021**	Final Project Plan

Disclaimer

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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, 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. 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

ALDP	Adrenoleukodystrophy protein
allo-HSCT	Allogeneic haematopoietic stem cell transplant
CALD	Cerebral adrenoleukodystrophy
cDNA	Complementary DNA
CHMP	Committee for Medicinal Products for Human Use
CSR	Clinical Study Reports
DOI	Declaration of Interest
DR	Dedicated Reviewers
DP	Drug Product
Eli-cel	Elivaldogene autotemcel
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EUnetHTA	European Network of Health Technology Assessment
GVHD	Graft versus host disease
HLA	Human leukocyte antigen
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HTAi	Health Technology Assessment international
HSC	Haematopoietic stem cell
LVV	Lentiviral vector
MFD	Major functional disabilities
MRI	Magnetic resonance imaging
NFS	Neurologic Function Score
PICO	Population, intervention, control, outcome
pMAH	Prospective Marketing Authorisation Holder
PTJA	Pharmaceutical Joint Assessment
REA	Relative Effectiveness Assessment
VLCFA	very long chain fatty acid
WP4	Work Package 4

1 INTRODUCTION

On 11/09/2020, EUnetHTA and the prospective Marketing Authorisation Holder (pMAH) of Elivaldogene autotemcel (eli-cel) *(bluebird bio)* agreed that EUnetHTA will perform a joint relative effectiveness assessment of elivaldogene autotemcel (eli-cel) for treatment of cerebral adrenoleukodystrophy (CALD). 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.

1.1 Pathophysiology

X-linked adrenoleukodystrophy (ALD) is a rare genetic disease that affects the nervous system and the adrenal glands [1]. This disease is a result of mutations in the ABCD1 gene and concomitant loss of function of its product, adrenoleukodystrophy protein (ALDP), leading to accumulation of very-long-chain fatty acids (VLCFA) [1, 2]. People with this disease often have progressive loss of the lipid covering (myelin) that surrounds the nerves in the brain and spinal cord [1].

While all boys with ALD are born asymptomatic, most will develop adrenal insufficiency in early childhood. Approximately 40% of boys with ALD will develop CALD, typically between 3 and 12 years of age [3]. This is the most severe form of ALD and is devastating for affected boys and their families, as patients may progress rapidly. The early stages of CALD are clinically asymptomatic but brain abnormalities can already be detected by MRI. When progressing, patients are eventually left profoundly disabled: blind, incontinent, and unable to move, hear, speak, or respond. They require tube feeding and are totally depending on caregivers [1]. This condition has been described as an "apparent vegetative state" [1, 4]. If not treated with allogeneic haematopoietic stem cell transplantation (allo-HSCT), nearly half of patients with CALD die within 5 years of symptom onset [4, 5].

1.2 Current treatment options

There is currently no treatment approved for CALD anywhere in the world and there are no official guidelines for the treatment of CALD in Europe, although allo-HSCT has been shown to have a beneficial effect on clinical indices of disease and long-term survival. Allo-HSCT involves administering chemotherapy to clear space in the bone marrow (known as conditioning), then replenishing with healthy hematopoietic stem cells from a donor. Allo-HSCT is thought to enable migration of donor-derived cells into the brain, which include donor-derived macrophages and/or microglial cells that express functional ALDP and function normally, thereby stopping further demyelination [5-7].

Various therapies are used as supportive care in European countries, but evidence for effectiveness is lacking. An oral dietary therapy (Lorenzo’s oil) made of oil mixture was used and investigated as supportive care, but several open-label trials have shown that it fails to slow or prevent CALD progression [8].

1.3 Elivaldogene autotemcel (eli-cel; Skysona)

Eli-cel (also known as Lenti-D Drug Product, Skysona) is classified as an advanced therapy medicinal product; in particular, a gene therapy medicinal product (EMA/989166/2011) in the EU. Skysona received positive CHMP opinion on May 20 for the treatment of early cerebral adrenoleukodystrophy in patients less than 18 years of age, with an ABCD1 genetic mutation, and for whom a human leukocyte antigen (HLA)-matched sibling haematopoietic stem cell (HSC) donor is not available [9].

The mode of action of eli-cel is production of functional ALDP by the patient's own hematopoietic stem cells that have been transduced ex vivo with Lenti-D Lentivirus Vector (LVV) containing a functioning copy of the ABCD1 gene that enables the local degradation of VLCFAs for addressing the underlying genetic cause of the disease.

Following engraftment in the bone marrow, the transduced stem cells differentiate into various cell types, including monocytes that are supposed to migrate to the brain, where they further differentiate into effector cells, including cerebral microglia. These microglia produce functional ALDP in the brain, enabling transport of VLCFAs into cellular peroxisomes for degradation and thus arresting cerebral disease progression. Following successful engraftment with genetically modified cells, the expression

of ALDP is expected to be life-long. Eli-cel is an orphan designated product (EU/3/12/1003, received June 2012), and a request to retain the Orphan Medicinal Product (OMP) status as a commercial product has been submitted through an Orphan Maintenance report for the assessment by Committee of Orphan Medicinal Products (COMP).

2 RESEARCH QUESTION AND SCOPE

The aim of this project is to compare the clinical effectiveness and safety of eli-cel 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 eli-cel.

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

Description	Assessment scope
Population	Treatment of early cerebral adrenoleukodystrophy in patients less than 18 years of age, with an ABCD1 genetic mutation, and for whom a human leukocyte antigen (HLA)-matched sibling haematopoietic stem cell (HSC) donor is not available
Intervention	Elivaldogene autotemcel (Skysona®)[a]
Comparison	• Allogeneic haematopoietic stem cell transplant (allo-HSCT) from a donor excluding HLA-matched sibling • Best supportive care[b]
Outcomes	<u>Efficacy</u> • Overall survival* • Major functional disabilities (MFD) [c] - free survival* • Severity of gross neurologic dysfunction (Change in Neurologic Function Score (NFS))[10]* • Health-related quality of life (HRQoL; reported by patient or their carer)* • HRQoL of parents/carers* • Change in brain lesions (Loes magnetic resonance imaging score) [11] • Engraftment failure* • Proportion of subjects who undergo subsequent allo-HSCT* • Time to subsequent allo-HSCT • Resolution of gadolinium enhancement positivity <u>Safety</u> • Treatment-related adverse events (AE) grade 3-5* • Discontinuations due to treatment-related adverse events • AE of special interest (incidence of acute or chronic graft versus host disease (GVHD))* • Other AE*

[a] Also known as Lenti-D Drug Product (DP), a single-administration gene therapy medicinal product. The active substance (elivaldogene autotemcel) is a genetically modified autologous CD34+ cell-enriched population that contains hematopoietic stem cells (HSCs) transduced with lentiviral vector (LVV) encoding ABCD1 complementary DNA (cDNA) for human adrenoleukodystrophy protein (ALDP), suspended in cryopreservation solution. The finished product is composed of one or more infusion bags, which contain a dispersion of 2-30 × 10^6 cells/mL suspended in cryopreservative solution. Each infusion bag contains approximately 20 mL of drug product.
[b] Includes any treatment for symptom relief. May also include treatments that aim to slow/halt disease progression but have not shown effectiveness in clinical trials.
[c] MFD include loss of communication, cortical blindness, dependence on tube feeding, wheelchair dependence, no voluntary movement, and total incontinence
* Outcomes directly/indirectly mentioned by patient organisations in their contributions or during an interview with a parent of a deceased child suffering from CALD.

3 METHODS

The EUnetHTA Guidelines, available at https://eunethta.eu/methodology-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. Due to the limited amount of studies expected in this field, no restrictions on study design should be applied.

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 [12]. 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.

Internal validity should be assessed using the latest 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.

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 (if provided) should follow the criteria described in the two EUnetHTA guidelines on the internal validity of randomised controlled trials [13] and non-randomised studies on interventions[1] [14]. For single-arm trials no risk of bias tool is available, but quality appraisal checklists are available that should be used [15-17]. 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 [18].

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

[1] The guideline (2015) recommends to use A Cochrane Risk of Bias Assessment Tool - Non-Randomized Studies of Interventions (ACROBAT-NRSI). However in the meantime a new risk of bias tool has been developed, which is Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I). Therefore, ROBINS-I should be used instead of the ACROBAT-NRSI tool.

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 [18]. The indirect comparisons relevant for the research questions (see Section 2) will be presented and examined in the Assessment Report.

For single-arm studies a proper statistical method for indirect treatment comparison should be applied for evidence synthesis. NICE guidelines for Simulated Treatment Comparisons or Matching-adjusted Indirect Comparisons [19] are recommended if any of these approaches are taken by MAH.

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.

The open call of eli-cel was online from 19th of October until 15th of December 2020. Three patient organisations completed the survey, namely ELA Deutschland e.V. (Germany), ELA-España European Leukodystrophy Association (Spain) and AIALD ONLUS (Italy). The information gathered from the open call was used to inform the scope of this assessment.

In addition, an interview with a parent of a deceased child suffering from CALD was conducted to gain input regarding the impact of CALD on patients' quality of life as well as the current standard of care.

4 PROJECT ORGANISATION

4.1 Participants

Table 2. Project participants

Role in the project	Agency	Country	Distribution of work
Assessment Team			
Author	Zorginstituut Nederland (ZIN)	Netherlands	Author will draft the report and in particular the following sections: Results (Risk of bias; External validity, Results on clinical effectiveness and safety); Patient Involvement; Discussion. Author will review and comment on all parts of the report. All important milestones will be discussed in advance with the co-authors.
Co-Author	Agency for Health Technology Assessment and Tariff System (AOTMiT)	Poland	Co-Author will draft the following sections of the report: Background; Methods (Information retrieval; Characteristics of included studies); Patient Involvement; Discussion Co-Author will review and comment on all parts of the report.
Co-Author	Gesundheit Österreich GmbH(GÖG)	Austria	Co-Author will draft the following sections of the report: Methods (Data extraction, results and analyses of included studies) Results (Studies included in this assessment; Characteristics of included studies; Outcomes included); Patient involvement; Discussion. Co-Author will review and comment on all parts of the report.
Information specialist	Agency for Health Technology Assessment and Tariff System (AOTMiT)	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
Statistical specialist	EUnetHTA Statistical Speciliast Network (TBC)		Expert review of statistical analyses presented in Submission Dossier, statistical support for authors
Dedicated Reviewer (information specialist)	Swiss Network for HTA (SNHTA)	Switzerland	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
Dedicated Reviewer	Ministry of Health of the Republic of Croatia (MIZ)	Croatia	

Role in the project	Agency	Country	Distribution of work
Contributors			
External expert	Medical University of Vienna	Austria	Review of the scope of the assessment and the draft Assessment Report. In addition, answer specific question during the assessment.
Patient organisations	ELA Deutschland e.V. ELA-España European Leukodystrophy Association AIALD ONLUS	Germany Spain Italy	Completed the EUnetHTA open call in order to inform the scope of the assessment.
	Vereniging Volwassenen, Kinderen en Stofwisselingszieketen (VKS)	Netherlands	Patient representative answered specific questions in the context of an interview in order to provide input regarding the impact of CALD on patients' quality of life as well as the current standard of care.
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. Project stakeholders

Organisation	Role in the project
Bluebird bio	Manufacturer [pMAH]; Completing the Submission Dossier; Fact Check of the draft Assessment Report

4.3 Milestones and deliverables

Table 4. Milestones and deliverables

Milestones/Deliverables	Start date	End date
Project duration	**11-09-2020**	**09-06-2021**
Letter of Intent received	11-09-2020	
Scoping phase	**09-11-2020**	**25-03-2021**
Scoping PICO and development of first draft Project Plan	09-11-2020	04-12-2020
PICO survey – request relevant PICO from Member States	17-11-2020	26-11-2020
Adapt draft Project Plan based on PICO survey	09-11-2020	04-12-2020
Open call for patient input	19-10-2020	15-12-2020
Review of first draft Project Plan	07-12-2020	11-12-2020
Development of second draft Project Plan & answers to DR comments	14-12-2020	06-01-2021
Receive scoping Scoping meeting documents from pMAH	09-11-2020	
Pre-scoping e-meeting with the assessment team	08-01-2021	
Share discussion topics for Scoping Meeting	12-01-2021	
Scoping Meeting with manufacturer	19-01-2021	
Share action points from Scoping Meeting with manufacturer	26-01-2021	
(pre-)Assessment phase	**10-02-2021**	**25-03-2021**
Receive Submission Dossier from pMAH	09-03-2021	
Check formal completeness of Submission Dossier	10-03-2021	19-03-2021
Receive missing items and comments on the requests from the formal completeness check from pMAH	26-03-2021	
Start writing Assessment (background, methods)	03-05-2021	20-05-2021
CHMP opinion	*20-05-2021*	
Finalize Project Plan	24-05-2021	
Optional: Grace period to revise Submission Dossier by pMAH (based on CHMP opinion)	21-05-2021	
Assessment phase	**20-05-2021**	**18-08-2021**
Writing first draft Joint Assessment	20-05-2021	28-06-2021
Review by DRs (and if applicable include experts)	29-06-2021	08-07-2021
Writing second draft Joint Assessment	09-07-2021	30-07-2021
Medical Editing	02-08-2021	06-08-2021
Fact Check by pMAH (parallel with medical editing)	02-08-2021	06-08-2021
Final Assessment + response Fact Check	16-08-2021	
Expected EPAR	*09-08-2021*	
Publication final version of rapid assessment	17-08-2021	18-08-2021

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