EUnetHTA Joint Action 3 WP4

Relative effectiveness assessment of pharmaceutical technologies

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

Project ID: PTJA17

Assessment Report

Version 2.0, 9 September 2021

Template version 2.2, April 2020

This Assessment was started as part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014- 2020). Even though EUnetHTA JA3 has formally ended in May 2021, the authors of this assessment continued their commitment to finalize this assessment under the agreed methodology of EUnetHTA Joint Action 3

DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description
V0.1	**28/06/2021**	First draft
V0.2	**30/07/2021**	Input from dedicated reviewers has been processed
V0.3	**16/08/2021**	Input from medical editor and manufacturer(s) has been processed
V1.0	**16/08/2021**	Final assessment report
V2.0	**09/09/2021**	The following corrections were made: • Table 0.2 "Evidence table" and Table 4.13 "Evidence table". For the outcome "Discontinuations due to treatment-related AEs" the reported number of events (%) for TPES-103 population 23/27 (85.2) is corrected to 0/27 (0). • Table 4.12. "Adverse events". For the outcome "Total adverse events grade ≥3 related to therapy" the reported number of events (%) is corrected: NR to 18 (30.5) for TP-103 population and 7 (11.9) to 7 (25.9) for TPES-103 population. • Table 4.12. "Adverse events". For the outcome "Total serious adverse events related to therapy" the reported number of events (%) is corrected: 4 (14.8) to 12 (20.3) for TP-103 population and 12 (20.3) to 4 (14.8) for TPES-103 population.

Disclaimer

The content of this Assessment Report represents a consolidated view based on the consensus within the Authoring Team; it cannot be considered to reflect the views of the European Network for Health Technology Assessment (EUnetHTA), EUnetHTA's participating institutions, the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

Assessment team

Author(s)	Zorginstituut Nederland [ZIN], the Netherlands
Co-Author(s)	Gesundheit Österreich GmbH [GÖG], Austria Agency for Health Technology Assessment and Tariff System [AOTMiT], Poland
Dedicated Reviewer(s)	Swiss Network for HTA [SNHTA], Switzerland Ministry of Health of the Republic of Croatia [MIZ], Croatia

Further contributors

External experts	
Johannes Berger, *PhD*	Answered specific questions from the Authoring Team during this assessment
Manufacturer(s) [v0.2]	
bluebird bio B.V.	Preparation of the Submission Dossier Factual accuracy check
Medical editor [v0.2]	
Nextgenology Ltd (Nextgenediting)	Medical editing of v0.2
Patient(s) / patient organisation(s) / citizens	
ELA Deutschland e.V., Germany ELA-España European Leukodystrophy Association, Spain AIALD ONLUS, Italy Parent of a deceased child with CALD, the Netherlands	Completion of the open call for patient input Participated in an interview
Project Management	
Zorginstituut Nederland (ZIN), Netherlands	Coordination between involved parties throughout the assessment

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).

Copyright:

How to cite this assessment

Please cite this assessment as follows:

EUnetHTA PTJA17. Authoring Team. Elivaldogene autotemcel (eli-cel) for the treatment of cerebral adrenoleukodystrophy (CALD). Joint Assessment. Diemen (The Netherlands): EUnetHTA; 2021. [date of citation]. 73 pages. Report No.: PTJA17. Available from: https //www.eunethta.eu

Contact the EUnetHTA Secretariat EUnetHTA@zinl.nl with enquiries about this assessment.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

Tables

Figures

LIST OF ABBREVIATIONS

AE	Adverse event
ALD	Adrenoleukodystrophy
ALDP	Adrenoleukodystrophy protein
Allo-HSCT	Allogeneic haematopoietic stem cell transplant
ARR	Absolute risk reduction
ATC	Anatomical Therapeutic Chemical [Classification System]
ATMP	Advanced therapy medicinal product
BSC	Best supportive care
BL	Baseline
CALD	Cerebral adrenoleukodystrophy
CCALD	Childhood cerebral adrenoleukodystrophy
cDNA	Complementary DNA
CI	Confidence interval
CSR	Clinical study report
DOI	Declaration of interest
DOUC-01	Umbilical cord blood-derived oligodendrocyte-like cells
EBMT	European Society for Blood and Marrow Transplant
ECA	EUnetHTA confidentiality arrangement
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EUnetHTA	European Network of Health Technology Assessment
GdE	Gadolinium enhancement
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GVHD	Graft-versus-host disease
HLA	Human leukocyte antigen
HR	Hazard ratio
HRQOL	Health-related quality of life
HSCT	Haematopoietic stem cell transplant
HTAi	Health Technology Assessment international
ICD	International classification of diseases
ITT	Intention-to-treat
LVV	Lentiviral vector
pMAH	Prospective marketing authorisation holder
MAH	Marketing authorisation holder
MD	Mean difference
MeSH	Medical subject headings
MFD	Major functional disabilities
MGTA-456	Produced from a single cord blood unit using an aryl hydrocarbon receptor antagonist in a 15-day expansion culture of $CD34^+$ cells
MIN-102	Leriglitazone
MRI	Magnetic resonance imaging
MSD	Matched sibling donors
NA	Not applicable
NFS	Neurologic Function Score
NMSD	Non-matched sibling donor

NR	Not reported
OR	Odds ratio
OS	Overall survival
PedsQL	Paediatric Quality of Life Inventory
PP	Per protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
REA	Relative effectiveness assessment
RR	Relative risk
SAE	Serious adverse event
SD	Standard deviation
SMD	Standardised mean difference
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
TP	Transplanted population
TPE	Eligible transplant population
TPES	Strictly eligible transplant population
TRM	Transplant-related mortality
VLCFA	Very long chain fatty acid
WP4	Work package 4

EXECUTIVE SUMMARY OF THE ASSESSMENT OF ELI-CEL

Introduction

Cerebral adrenoleukodystrophy (CALD) is a rare, X-linked metabolic disorder caused by mutations in the *ABCD1* gene. *ABCD1* encodes adrenoleukodystrophy protein (ALDP), which is involved in the peroxisomal degradation of very long-chain fatty acids (VLCFAs). In the absence of functional ALDP, VLCFAs accumulate in the blood plasma and tissues, particularly those of the adrenal glands and white substance of the brain and spinal cord [1]. CALD is a severe neurodegenerative disease that predominately affects young boys, and it is characterised by rapidly progressive inflammatory cerebral demyelination. If untreated, affected individuals suffer from progressive, irreversible loss of neurological function and usually death within a decade of diagnosis.

There is currently only one approved treatment for CALD – elivaldogene autotemcel (authorised in the EU for the treatment of children under 18 years of age with early CALD), and there are no official management guidelines for CALD in Europe. There is, however, expert consensus that allogeneic haematopoietic stem cell transplantation (allo-HSCT) is the only disease-modifying treatment available for CALD, despite a significant mortality risk associated with the procedure. However, allo-HSCT is only possible if a human leukocyte antigen (HLA)-matched donor or cord blood is available and the procedure is performed at the early stage of the disease (no or minor symptoms of cerebral demyelinating disease, generally defined as a Neurologic Function Score (NFS) 0 or 1 and Loes score ≤9). HLA-matched siblings should be prioritised as donors, since graft selection should minimise complications of graft failure and graft-versus-host disease (GVHD). A HLA-matched unrelated donor is an acceptable option if an appropriate HLA-matched sibling donor is not available. HLA-mismatched unrelated donor transplantation is associated with a high risk of GVHD [2]. Unfortunately, according to the European Society for Blood and Marrow Transplant (EBMT) registry, >70% of transplants for CALD involve unrelated donors, whereas 84% had no matched sibling donor [3].

Elivaldogene autotemcel, also known as eli-cel, Lenti-D Drug Product (DP), or Skysona®, is a one-time autologous *ex vivo* gene therapy. Elivaldogene autotemcel is a genetically modified autologous $CD34^+$ cell-enriched population that contains hematopoietic stem cells (HSCs) transduced with a lentiviral vector (LVV) encoding *ABCD1* complementary deoxyribonucleic acid (cDNA) for human ALDP protein suspended in cryopreservation solution. The final product comprises one or more infusion bags containing a dispersion of 2-30 × 10^6 cells/mL suspended in cryopreservative. Each infusion bag contains approximately 20 mL of drug product. Prior to eli-cel treatment, the patient receives myeloablative conditioning – chemotherapy to clear space in the bone marrow – after which the transduced stem cells are infused to repopulate the bone marrow.

Eli-cel is indicated for the treatment of early cerebral adrenoleukodystrophy in patients <18 years of age, with an *ABCD1* mutation, and for whom an HLA-matched sibling haematopoietic stem cell (HSC) donor is not available.

Objective and scope

The aim of this EUnetHTA Joint Relative Effectiveness Assessment is to compare the clinical effectiveness and safety of Skysona® (elivaldogene autotemcel, eli-cel) in the target patient populations with relevant comparators. The target patient populations and relevant comparators (based on the requirements of EUnetHTA Partners) are defined in the project scope in Table 0.1.

The assessment was based on the Submission Dossier submitted by the Marketing Authorisation Holder (MAH) bluebird bio B.V.

The scope of the assessment (Table 0.1) does not differ from the scope described in the project plan, except moving engraftment failure from clinical effectiveness to safety in the outcomes.

Table 0.1. Scope of the assessment

Description	Assessment scope
	PICO
Population	Treatment of early cerebral adrenoleukodystrophy in patients <18 years of age, with an *ABCD1* mutation, and for whom an HLA-matched sibling haematopoietic stem cell (HSC) donor is not available
Intervention	Elivaldogene autotemcel (Skysona®; eli-cel)
Comparison	Allogeneic haematopoietic stem cell transplant (allo-HSCT) from a donor, excluding an HLA-matched sibling donor Best supportive care[a]
Outcomes	**Clinical effectiveness** • Overall survival* • Major functional disability (MFD)[b]-free survival* • Severity of gross neurological dysfunction (change in Neurologic Function Score (NFS)) [4]* • Health-related quality of life (HRQoL; reported by patient or their carer)[c] • HRQoL of parents/carers* • Change in brain lesions (Loes magnetic resonance imaging score) [5] • Proportion of subjects undergoing subsequent allo-HSCT* • Time to subsequent allo-HSCT • Resolution of gadolinium enhancement positivity
	Safety • Treatment-related adverse events (AEs) grade 3-5* • Discontinuations due to treatment-related AEs • AEs of special interest (incidence of acute or chronic graft-vs-host disease (GVHD), engraftment failure)* • Other AE*
Study design	Not defined

[a] 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.
[b] MFD includes 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.

Methods

The MAH run systematic searches in PubMed and EMBASE. In addition, the MAH searched their registries to identify relevant studies and searched three trial registries (*ClinicalTrials.gov, ICTRP Search Portal, EU CTR*). The authoring team verified the completeness and adequateness of the information retrieval process and additionally searched the same three trial registries.

Information was extracted from the Submission Dossier and verified against the clinical study reports (CSRs) or other original documentation provided in the Submission Dossier. The study design, methods, populations, endpoints (patient relevance, validity, and operationalisation), and results provided in the Submission Dossier were evaluated and relevant analyses identified. The methodologies of meta-analyses, sensitivity analyses, and subgroup analyses (if presented in the Submission Dossier) were evaluated.

Risk of bias was assessed where possible. Aspects related to the (un-)certainty of the evidence were evaluated and presented by partial use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method following the EUnetHTA framework [6, 7]. In the evidence table (Table 0.2), all relevant information regarding (un-)certainty of evidence was flagged for each outcome to provide a transparent and systematic assessment. The assessment was performed context-independently and without overall conclusions on quality or certainty of evidence.

Patient involvement was requested via an open call published on the EUnetHTA website at the start of this Joint Assessment. General questions were asked to elicit patients' views on living with the disease, important outcomes to be considered in this assessment, and expectations about eli-cel. In addition, a

parent of a deceased child suffering from CALD was interviewed to provide insights into the impact of CALD on patients' quality of life and the current standard-of-care.

Results

Five studies conducted by the MAH were included: two observational data collection studies (one retrospective (ALD-101) and one partly prospective (ALD-103)); two interventional single-arm studies (ALD-102 and ALD-104); and one observational long-term follow-up study (LTF-304).

ALD-101 included a patient cohort treated with allo-HSCT (n=65) and an untreated patient cohort (n=72), and ALD-103 (only) included a patient cohort treated with allo-HSCT (n=59). Both studies have been completed. ALD-102 and ALD-104 included patients for treatment with eli-cel. Both are ongoing, with study enrolment complete in ALD-102 (n=32) and 20 patients enrolled in ALD-104 as of the latest data cut-off. LTF-304 has enrolled/will enrol patients from parent studies ALD-102 and ALD-104 when they have completed 24-months of follow-up for long-term (13 years) assessment. To date, a majority of ALD-102 patients but no ALD-104 patients have been included in LTF-304.

ALD-101 was a preparatory study and informed the design of the following eli-cel trials (ALD-102, ALD-104, and LTF-304), which were single-arm trials because a randomised controlled trial was not deemed feasible. The MAH therefore designed ALD 103 to be consistent with ALD-102 so that the derived data could be used as an external comparator for outcomes after treatment with eli-cel in ALD-102.

The median age at CALD diagnosis was between six and eight years in the five studies, with a broad range of ages included in each study. Inclusion criteria for ALD-102 and ALD-104 were consistent with the proposed label indication and the target population of this assessment, including early disease (Loes score ≥0.5 to ≤9.0; NFS ≤1) and early signs of cerebral inflammation as defined by contrast (gadolinium) enhancement (GdE^+) at baseline. Baseline characteristics were, however, not fully reported for patients in ALD-104, in which enrolment is ongoing.

The ALD-101 study population in consisted of: (1) untreated subjects who were diagnosed in or after 1990 and (2) subjects who had undergone allo-HSCT from an HLA-matched sibling donor (MSD) or non-matched sibling donor (NMSD) in or after 2001, when allo-HSCT became the standard-of-care for CALD. Inclusion criteria regarding disease status were less stringent, and patients with more severe disease were included at baseline. Only one out of 72 subjects in the untreated cohort and 27 out of 65 subjects in the allo-HSCT cohort strictly matched the ALD-102 inclusion criteria (NFS ≤1, Loes score 0.5 to ≤9, and GdE^+), so constituted the "strictly eligible transplant population" (TPES). Of the 27, five had an MSD, 21 an NMSD, and one was unknown. The study was not used in the clinical effectiveness and safety comparisons due to issues with external validity. In ALD-103, no specific eligibility criteria were used to select only early CALD subjects; 27 out of 59 subjects strictly matched the ALD-102 population, again constituting the TPES population. Of these, ten had an MSD and 17 an NMSD.

Most of the outcomes deemed relevant for this assessment (see Table 0.1) were covered within the five studies. However, whereas outcome data for ALD-101, ALD-102 and ALD-103 is available, the vast majority of outcome data from ALD-104 is not available to date and no or incomplete results (covering only ALD-102 patients) are available from LTF-304.

Twenty-six studies additionally included in the Submission Dossier on the comparator intervention were excluded because they did not fully report baseline characteristics of disease status (24 studies) or because they did not include separate analyses for patients fulfilling all TPES criteria (two studies).

Therefore, this assessment was mainly based on results from the transplant population (TP) in ALD-102 (and, where possible, ALD-104 and LTF-304) for eli-cel and ALD-103 (preferentially the TPES NMSD subpopulation) for allo-HSCT. Results for the TPES MSD population are reported to support the comparison between eli-cel and allo-HSCT in a conservative manner, since MSD allo-HSCT is currently the best available therapy and analysed numbers for allo-HSCT from an NMSD were small. The main results (see Table 0.2) on clinical effectiveness and safety for eli-cel and allo-HSCT from the most recent cut-off dates can be summarised naively as follows, as no adjusted indirect comparison was available:

- The Kaplan-Meier estimate for overall survival rate at 48 months was 96.6% (95%CI: 77.9 to 99.5; n=32; ALD-102) for eli-cel, higher than that for NMSD allo-HSCT (75.5%, 95%CI: 39.7 to 91.8;

n=17, ALD-103 TPES) and NMSD allo-HSCT (74.1%, 95%CI: 28.9 to 93.0; n=10, ALD-103 TPES);

- The MFD-free survival rate at 24 months was 90.0% (95%CI 73.5 to 97.9; n=30; ALD 102) for eli-cel, higher than for NMSD allo-HSCT (66.7%, 95%CI: 29.9 to 92.5; n=9; TPES ALD-103) but comparable to MSD allo-HSCT (88.9%, 95%CI: 51.8 to 99.7; n=9; TPES ALD-103);
- 96.4% (95%CI: 81.7 to 99.9; n=28; ALD-102) of patients receiving eli-cel had a stable NFS at 24 months, comparable to 100% (95%CI: 73.5 to 100.0; n=12; TPES ALD-103) for allo-HSCT from any donor. 77.8% (95%CI: 57.7 to 91.4; n=27; ALD-102) of patients receiving eli-cel had a stable Loes score at 24 months, lower than the 92.3% (95%CI: 64.0 to 99.8; n=13; TPES ALD-103) observed for allo-HSCT from any donor type. Similarly, 85.2% (95%CI: 66.3 to 95.8; n=27; ALD-102) of patients receiving eli-cel were GdE^- at 24 months compared to 100% (95%CI: NR; n=13; TPES ALD-103) for allo-HSCT from any donor type;
- Of the 27 patients enrolled in LTF-304, 26 (96.3%) remained alive and MFD-free after a median follow-up of 58.6 months (range 23.4-82.7);
- Neutrophil and platelet engraftment were successful at month 24 in all evaluable patients treated with eli-cel in ALD-102 and ALD-104. Platelet engraftment was also seen in all evaluable patients treated with NMSD allo-HSCT in ALD-103. The proportion of NMSD allo-HSCT patients with neutrophil engraftment was lower in ALD-103; seven out of twelve evaluable patients had primary or secondary neutrophil engraftment failure (58.3%; 95%CI: 27.7 to 84.8);
- None of the 32 patients treated with eli-cel experienced acute or chronic GVHD in ALD-102, while seven out of 14 (50.0%; 95%CI: 23.0 to 77.0) evaluable TPES patients in ALD-103 receiving an NMSD allo-HSCT developed GVHD;
- Two out of 32 eli-cel patients in ALD-102 (6.3%; 95%CI: 0.8 to 20.8) required subsequent allo-HSCT compared to six out of 17 (35.3%; 95%CI: 14.2 to 61.7) evaluable TPES patients in ALD-103 receiving an NMSD allo-HSCT;
- Five out of 51 patients (9.8%) in TP-102/104 experienced AEs potentially related to eli-cel therapy, of whom three (5.9%) experienced serious AEs (SAEs): BK-mediated viral cystitis (TP ALD-102) and two cases of pancytopenia (TP-103). In ALD-103 study grade ≥3 SAEs related to allo-HSC infusion were reported for 12 (20.3%) TP and four (14.8%) TPES patients. None of the reported AEs led to discontinuation of the studies;
- No treatment-related mortality with eli-cel has been reported. In ALD-103, eight (13.6%) of 59 patients died from treatment-related causes within one year of allo-HSCT. All deaths occurred in patients who lacked an MSD (one-year transplant-related mortality (TRM), 22.2%). In the TPES (NMSD) population, TRM frequency was lower and was observed in one patient (9.1%);
- Treatment with eli-cel carries a theoretical risk of insertional oncogenesis (e.g., myelodysplasia, leukaemia, lymphoma), but no insertional oncogenesis events were reported. Clonal expansion resulting in clonal predominance without clinical evidence of malignancy was detected in some patients treated with eli-cel;
- No additional AEs related to eli-cel were reported in LTF-304 up to the cut-off date for the interim analysis.

Patients were involved through answers from three patient organisations who completed the questionnaire in the open call and a one-hour web-based interview with a mother of a deceased child who suffered from CALD. Answers from patient organisations and the mother were consistent with each other: both indicated that CALD is a terrible disease that has a huge impact on the QoL of patients and their families. They indicated that early diagnosis is crucial to benefit from treatment, but that treatments that can improve the course of the disease and provide QoL to affected patients are still lacking. Current treatments were described as stressful and complicated, with finding a matching donor before the disease is too far advanced challenging. Gene therapy for CALD is considered a hope for affected patients because it avoids waiting for a compatible donor and GVHD.

Discussion

The evidence on the estimates of effects of eli-cel have severe limitations:

- Eli-cel was studied in open-label, single-arm trials and effects of eli-cel were indirectly compared with allo-HSCT studied in mixed retrospective and prospective data collection studies. The risk of bias for all studies was considered critical, e.g., the study design could not rule out confounding and there was a large amount of missing data. Several additional issues were flagged in the risk of bias and partial GRADE assessments, including applicability concern regarding the study population (indirectness), small numbers, interim analyses, overlapping CIs (imprecision), no pre-planned propensity score analyses, and conflicts of interest;
- Results were based on available data, and no intention-to-treat analyses were performed. The EPAR [8] states that sensitivity analyses were performed for MFD-free survival, where in TP-102 non-evaluable patients were considered as having a negative outcome and in TPES-103 missing data were imputed as a success for the selected primary and secondary efficacy endpoints. The sensitivity analysis using the most conservative imputation approach did not change the conclusions of the main analysis for these parameters performed on non-missing observations. Nevertheless, the effect estimates were sensitive and prone to bias with increasing rates of missing data and should be interpreted cautiously [8]. The EMA informed the Authoring Team that sensitivity analyses were also performed for other outcomes but similarly they did not change the conclusions drawn from the main analysis;
- Different myeloablative conditioning treatments were used in the studies. In ALD-102, busulfan with cyclophosphamide was used, whereas the conditioning regimen in ALD-104 consists of busulfan with fludarabine as the lymphodepletion agent. It should be noted that the best choice of conditioning treatment is still unknown for this indication;
- Data on change in HRQoL (a critical outcome) could only be collected from two patients in ALD-103, so a comparison with ALD-102 was not feasible. Data on time to subsequent allo-HSCT were not reported;
- To date, eli-cel studies are still ongoing and the results are based on interim analyses. Longer term follow-up data are needed. These data are expected from ALD-102 (according to submission dossier study completion was expected in May 2021), ALD-104 (expected completion February 2024), and LTF-304 (expected completion May 2037). The post-authorisation efficacy/safety study REG-502 will follow eli-cel treated patients for up to 15 years after treatment.

Despite the limitations outlined above, the EMA accepted the comparison for the following reasons: the rarity of the disease, the severity and fast progression of the disease, the limited treatment options, the inability of transplants to be blinded, and the potential impact of time required to identify a donor match on cerebral disease progression. However, further data on long-term effectiveness and safety are needed and requested [8].

Apart from discussion of the available clinical data, it is important to highlight potential issues with the implementation of eli-cel treatment. As stated in the Submission Dossier, manufacturing of eli-cel is centralised at one site for European patients (Minaris Regenerative Medicine (previously known as Apceth Biopharma), Munich, Germany). Treatment can be given only at specialised care centres. Significant distances between the manufacturing site and treatment centres may influence the rate of successfully infused patients (and have an impact on costs, especially as specific storage conditions are required for eli-cel). Future studies must gather data on reasons for non-infusion of the product that may be clinical (e.g., unsuccessful conditioning), practical (e.g., various problems during manufacturing or transport), or both.

Conclusion

There was only limited evidence to compare eli-cel and allo-HSCT in the population of patients without an MSD (the population of interest). Analysis was based on a naive comparison only; no adjusted indirect comparison was possible. Results from interim analyses suggested that overall survival rate and the MFD-free survival rate were higher for eli-cel than allo-HSCT for patients with an NMSD. No data were available on NFS, Loes score, and GdE status for the TPES NMSD population. Stable NFS rates were comparable between eli-cel and allo-HSCT from any donor type, while stable Loes score and GdE^- rates were lower for eli-cel than allo-HSCT from any donor type. Comparison of HRQoL was not feasible as a too low number of patients contributed to this outcome.

No treatment-related mortality with eli-cel was reported up to the cut-off date for the interim analysis, whereas in the TPES NMSD allo-HSCT population, one out of 17 patients died. Most AEs associated with eli-cel administration were consistent with those associated with mobilisation and myeloablative conditioning performed for allo-HSCT and resolved with standard measures. None of patients treated with eli-cel experienced graft failure or graft rejection, while 58% patients in the TPES NMSD allo-HSCT population did. The risk of insertional oncogenesis with eli-cel should be monitored; while not been reported thus far, clonal expansion resulting in clonal predominance without clinical evidence of malignancy was detected in some patients treated with eli-cel.

The risk of bias for all eli-cel studies was considered critical. Longer-term data on the effectiveness of eli-cel are awaited and needed.

Table 0.2. Evidence table*

Outcome	Design	Factors that may affect certainty of evidence					Eli-cel		Allo-HSCT		Comparison
		Risk of Bias[c]	Indirectness	Inconsistency	Imprecision	Other	Study; number of patients	n events/n evaluable patients (%; 95%CI)	Study; number of patients	n events/n evaluable patients (%; 95%CI)	Effect estimate (95%CI); P-value
OS at month 24	⅄	C	▲	★	★✶	COI	TP-102; N=32	31/32 (96.6; 77.9 to 99.5)	TPES-103 NMSD; N=17	n=14/17 (86.3; 54.7 to 96.5)	HR: 0.118 (0.012 to 1.152); P=0.0285[d]
MFD-free survival at month 24[a]								n=27/30 (90.0; 73.5 to 97.9)		n=6/9 (66.7; 29.9 to 92.5)	HR: 0.178 (0.044 to 0.73); P=0.0068[d]
Stable NFS at month 24	⅄	C	▲+	★	★✶	COI	TP-102; N=32	n=27/28 (96.4; 81.7 to 99.9)	TPES-103[e]; N=27	n=12/12 (100.0; 73.5 to 100.0)	NC
Stable LOES score at month 24								n=21/27 (77.8; 57.7 to 91.4)		n=12/13 (92.3; 64.0 to 99.8)	NC
GdE$^-$ at month 24								n=23/27 (85.2; 66.3 to 95.8)		n=13/13 (100; 75.3 to 100.0)	NC
Change in PedsQL by month 24	⅄	C	▲+	★	★	COI	TP-102; n/N=23/32	-4.66 points (range -44.6 to 31.5)	TP-103[e]; n=2/59	11.67 points (range 16.0 to 17.4)	NC
Neutrophil engraftment failure (primary or secondary) by month 24	⅄	C	▲	★	★✶	COI	TP-102/TP-104, N=51	n=0/27 (0; 0 to 12.8)	TPES-103 NMSD; N=17	n=7/12 (58.3; 27.7 to 84.8)	NC
Platelet engraftment							TP-102/TP-104, N=51	n=47/47 (100.0; 92.5 to 100.0		n=12/12 (100.0; 73.5 to 100.0)	NC
Acute or chronic graft versus host disease by month 24	⅄	C	▲	★	★	COI	TP-102; N=32	n=0/32 (0; 0.0 to 10.9)	TPES-103 NMSD; N=17	n=7/14 (50.0; 23.0 to 77.0)	NC
Subsequent allo-HSCT	⅄	C	▲	★	★✶	COI	TP-102; N=32	n=2/32 (6.3; 0.8 to 20.8)	TPES-103 NMSD; N=17	n=6/17 (35.3; 14.2 to 61.7)	NC

Outcome	Design	Factors that may affect certainty of evidence					Eli-cel		Allo-HSCT		Comparison
		Risk of Bias[c]	Indirectness	Inconsistency	Imprecision	Other	Study; number of patients	n events/n evaluable patients (%; 95%CI)	Study; number of patients	n events/n evaluable patients (%; 95%CI)	Effect estimate (95%CI); P-value
Adverse events (AEs) grade ≥3	⅄	C	▲+	★	★	COI	TP-102/TP-104, N=51	Total: 48/51 (94.1) Related to eli-cel: 3 (5.9)	TPES-103[e]; N=27[b]	Total: 25/27 (92.6) Related to allo-HSCT: 7/27 (25.9)	NC
									TP[e]; N=59[b]	Total: 55/59 (93.2) Related to allo-HSCT: 18/59 (30.5)	NC
Discontinuations due to treatment-related AEs	⅄	C	▲	★	★	COI	TP-102/TP-104, N=51	n=0/51 (0)	TPES-103[e]; N=27[b]	n=0/27 (0)	NC

* Following partial use of GRADE recommendations by EUnetHTA [6, 7].
[a] No MFD, alive, not withdrawn or lost to FU, no rescue eli-cel, no allo-HSCT.
[b] First allo-HSCT period.
[c] See risk of bias assessment in Section 4.6.
[d] Derived from Kaplan-Meier analysis. Hazard ratio (95%CI) based on Cox regression model, and p-value based on log-rank test.
[e] Results were not reported per donor type.
⅄ Open-label, multi-centre, single arm trial versus retrospective and prospective, data collection study.
▲ Eli-cel was indirectly compared to allo-HSCT.
+ Partially not focused population (patients with MSD).
* Only one comparison.
★ Small numbers and interim analysis data. No pre-planned propensity score analyses.
* Overlapping confidence intervals.
Note: The TP of ALD-103 is identical to the ITT population and includes 59 patients who received allo-HSCT. The TPES is defined to strictly align with ALD-102 eligibility criteria: TPES subjects are TP patients who at baseline had NFS ≤1, Loes score ≥ 0.5 and ≤ 9, and GdE+.
Abbreviations: allo-HSCT=allogeneic haematopoietic allogenic stem cell transplant; C=critical; COI=conflict of interest; eli-cel=elivaldogene autotemcel; HR=hazard ratio; NA=not applicable; NC=not computable; PedsQL=Paediatric Quality of Life Inventory; TP=transplant population; TPE=ALD-102-eligible transplant population; TPES=strictly ALD-102-eligible transplant population; TPG=GdE+ transplant population.

1 BACKGROUND

1.1 Overview of the disease or health condition

Cerebral adrenoleukodystrophy (CALD) is a rare, X-linked metabolic disorder caused by mutations in the *ABCD1* gene. *ABCD1* encodes adrenoleukodystrophy protein (ALDP), which is involved in the peroxisomal degradation of very long-chain fatty acids (VLCFAs). In the absence of functional ALDP, VLCFAs accumulate in the blood plasma and tissues, particularly those of the adrenal glands and white substance of the brain and spinal cord [1]. CALD is a severe neurodegenerative disease that predominately affects young boys, and it is characterised by rapidly progressive inflammatory cerebral demyelination. If untreated, affected individuals suffer from progressive, irreversible loss of neurological function and death, usually within a decade of diagnosis.

1.1.1 Clinical presentation, natural history, and prognosis

CALD usually manifests early in childhood between the ages of three and 12 years, with a peak incidence between six and eight years of age. However, it can also occur in adolescence and adulthood with similar symptoms and clinical presentations [1]. Disease stage is usually quantified using the Loes score and the Neurologic Function Score (NFS). The Loes score is a 34-point scale used to quantify the extent of brain lesions in CALD, which are visible as pathological hyperintense regions in the white substance; higher scores indicate greater lesion extent [5]. The clinical symptoms of CALD can be graded using the NFS, a 25-point score that evaluates the severity of gross neurological dysfunction by scoring 15 symptoms across multiple domains (hearing and communication, vision, feeding, locomotion, incontinence, and seizures; higher scores indicate greater dysfunction) [4]. The early stages of CALD are clinically asymptomatic, but brain abnormalities can be detected by MRI. The initial neurological symptoms are typically cognitive and behavioural problems and decline in school performance in early- to mid-childhood (median age seven years), which may be misdiagnosed as attention deficit hyperactivity disorder or other more common developmental issues [1, 9].

The clinical course of untreated CALD begins with mild cognitive and motor deficits followed by a rapidly progressive and devastating inflammatory phase, leading to irreversible brain damage and severe physical and cognitive disability. Patients are eventually left profoundly disabled: blind, incontinent, and unable to move, speak, or respond. They require tube feeding and full-time nursing care. Death from CALD is almost always inevitable without treatment [1, 10].

1.1.2 Prevalence and incidence

There are only limited epidemiological data on the incidence and prevalence of CALD in Europe, mainly studies reporting the incidence, prevalence, and proportion of CALD patients in the population of ALD patients. No major differences in incidence rates of ALD or CALD have been reported between different countries around the world [11, 12].

The estimated incidence of ALD at birth ranges from 1.6 per 100,000 inhabitants in Norway [13] to 1 in 21,000 newborn males in the USA [11] and 1 in 17,000 male and female newborns in France [14]. The point prevalence of X-linked ALD in Norway on July 1, 2011, was 0.8 per 100,000 inhabitants [13].

The estimated incidence of CALD is based on the proportion of males with ALD who are expected to develop CALD; up to 40% of boys with ALD will progress to CALD between the ages of three and 18 years (onset before the age of three is rare) [15]. Considering 4.2 million live births in the EU, approximately 2.1 million male live births (based on sex ratio of 1.06 males:females) are expected per year [16, 17]. Of these, approximately 103 males would have ALD, leading to approximately 40 patients in Europe who develop CALD each year [11, 15].

1.1.3 Burden of the disease

CALD is associated with six MFDs [18] that develop as the disease progresses and result in:

- loss of communication;
- cortical blindness;
- dependence on tube feeding;

- wheelchair dependence;
- loss of voluntary movement;
- total incontinence.

The devastating nature of CALD means that it has a severe and rapidly progressive impact on HRQoL if not treated. Although very few studies on HRQoL in patients with untreated CALD are present in the literature, the disease clearly has a severe impact on the patient, caregivers, and family through having to experience a healthy boy deteriorating both physically and cognitively. Estimated utility weights[1] associated with childhood CALD in the UK were 0.682, 0.599, 0.11, and 0.031 for ALD-DRS1, ALD-DRS2, ALD-DRS3, and ALD-DRS4 respectively (a higher ALD-DRS score meaning greater disability) [19]. Also, children with CALD experience significant problems with social isolation, and patients with progressive disease require assistance 24 hours a day, which is a huge burden for both the patient and their family [20].

1.2 Current clinical practice

There is currently only one approved treatment for CALD – elivaldogene autotemcel (authorised in the EU for the treatment of children under 18 years of age with early CALD), and there are no official management guidelines for CALD in Europe. However, three consensus publications have been published on the management of ALD/CALD in boys [1, 21, 22]:

Engelen et al. [1] concluded that allogeneic haematopoietic stem cell transplantation (allo-HSCT) remains the only disease-modifying treatment available for CALD patients, despite the procedure carrying a significant mortality risk. However, allo-HSCT is only possible if an HLA-matched donor or cord blood is available and the procedure is performed at the early stage of the disease (no or minor symptoms of cerebral demyelinating disease, generally defined as NFS 0 or 1 and Loes score ≤9). Regelmann et al. [22] suggested that allo-HSCT does not prevent progression of adrenal insufficiency, probably because VLCFAs have already irreversibly accumulated in the adrenal cortex by the time of transplant.

Allo-HSCT involves administering chemotherapy to clear space in the bone marrow (through a procedure known as conditioning) and then replenishing the bone marrow with healthy haematopoietic stem cells from a donor. Allo-HSCT is thought to enable migration of donor-derived cells to the brain, including donor-derived macrophages and/or microglial cells that express functional ALDP and function normally, thereby stopping further demyelination [2, 23, 24].

Miller [2] suggested prioritising HLA-matched sibling donors over other unrelated donors, because carefuly graft selection should minimise complications of graft failure and graft-versus-host disease (GVHD). When an appropriate HLA-matched sibling donor is not available, an HLA-matched unrelated donor is an acceptable next-best option, since an HLA-mismatched unrelated donor transplant is associated with a high risk of GVHD [2]. Unfortunately, according to the European Society for Blood and Marrow Transplant (EBMT) registry, >70% of transplants for CALD involve unrelated donors, whereas 84% had no matched sibling donor [3].

Regelmann et al. [22] also highlighted that it is unknown whether gene therapy for CALD would prevent the progression of adrenal insufficiency, but it is thought to be unlikely. Engelen et al. 2012 suggested that, in the future, genetically corrected autologous HSCs cells might become an alternative to autologous HCT [1].

Mallack et al. [21] provided expert consensus guidelines focusing on the MRI surveillance of boys with ALD during childhood but did not present guidance on treatment.

[1] Bessey et al. 19. Bessey A, Chilcott JB, Leaviss J, Sutton A. Economic impact of screening for X-linked Adrenoleukodystrophy within a new born blood spot screening programme. Orphanet J Rare Dis. 2018;13(1):179. stated that the calculation reflected overall quality-adjusted life years, but the presentation seemed to show utility weights, so they are presented this way in report.

Other therapies recommended by Engelen et al. [1] include endocrine replacement therapy in cases with adreno-cortical insufficiency. Furthermore, it should be noted that several therapies are used as supportive care in European countries, e.g., a low-fat dietary regimen and Lorenzo's oil. Several other treatments are also being investigated including lovastatin, DOUC-01, MGTA-456, rivogenlecleucel, sobetirome, MIN-102, vorinostat, mesenchymal stem cells, rituximab, and HemoCard, but evidence for their efficacy is lacking ([1] and Submission Dossier).

1.3 Features of the intervention

The features of the intervention are shown in Table 1.1. Administration and dosing of the technology are summarised in Table 1.2.

1.3.1 Elivaldogene autotemcel

Elivaldogene autotemcel, also known as eli-cel, Lenti-D Drug Product (DP), or Skysona®, is a one-time autologous *ex vivo* gene therapy. Elivaldogene autotemcel is a genetically modified autologous $CD34^+$ cell-enriched population that contains hematopoietic stem cells (HSCs) transduced with a lentiviral vector (LVV) encoding the *ABCD1* complementary deoxyribonucleic acid (cDNA) for human adrenoleukodystrophy protein (ALDP) suspended in cryopreservation solution. The finished product is composed of one or more infusion bags containing a dispersion of 2-30 × 10^6 cells/mL suspended in cryopreservative solution. Each infusion bag contains approximately 20 mL of drug product.

Eli-cel is indicated for the treatment of males <18 years of age with an *ABCD1* mutation and early cerebral adrenoleukodystrophy for whom an HLA-matched sibling HSC donor is not available. Eli-cel is expected to offer a durable, life-long treatment effect through stable integration of functional *ABCD1* cDNA into long-term repopulating HSCs.

Figure 1.1. outlines a gene therapy workflow.

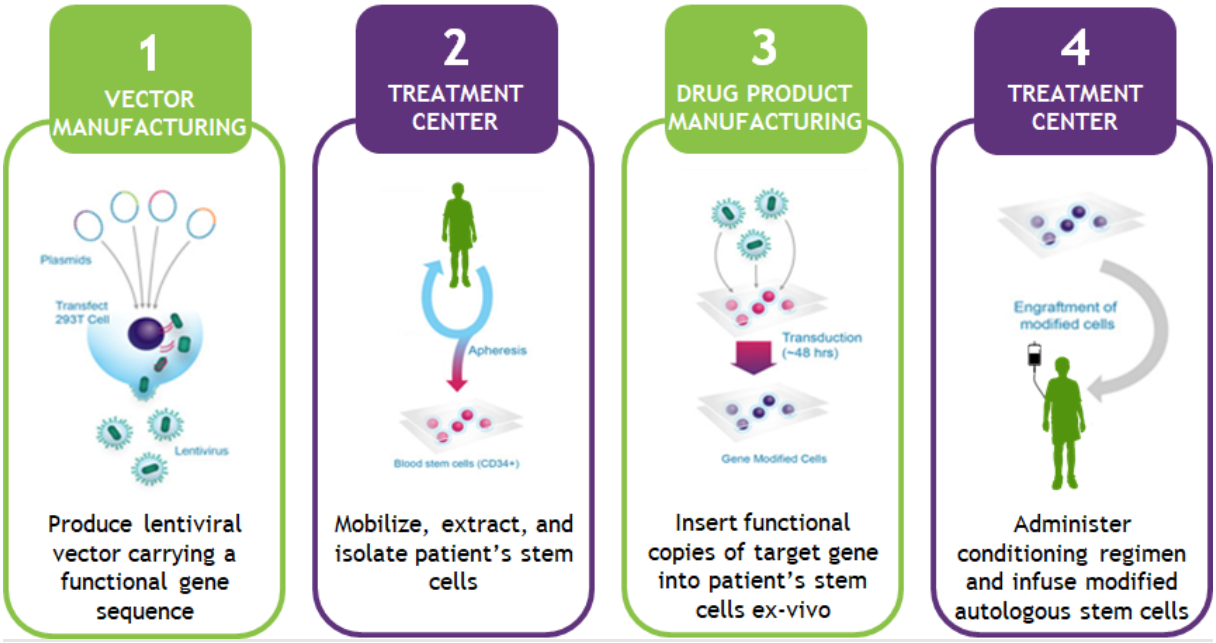

Figure 1.1. Patient and product journey in the commercial setting

Detailed information relating to the investments, tools, and requirements needed to introduce and use eli-cel is presented in Chapters 5 and 6 of the Submission Dossier.

Table 1.1. Features of the intervention

Non-proprietary name	Elivaldogene autotemcel
Proprietary name	Skysona®
Registered EMA indication	Skysona® is indicated for the treatment of early cerebral adrenoleukodystrophy in patients <18 years of age, with an *ABCD1* mutation, and for whom an HLA-matched sibling HSC donor is not available.
Prospective marketing authorisation holder	bluebird bio B.V.
Contraindications	Hypersensitivity to the active substance(s) or to Cryostor CS5. Contraindications to the mobilisation agents and the conditioning agents must be considered.
Drug class	Gene therapy.
Active substance(s)	Elivaldogene autotemcel is a genetically modified autologous $CD34^+$ cell-enriched population that contains HSCs transduced with a lentiviral vector (LVV) encoding *ABCD1* cDNA for human ALDP at a strength of 2-30 × 10^6 cells/mL.
Pharmaceutical formulation(s)	Dispersion for infusion. One or more infusion bags containing a dispersion of 2-30 × 10^6 cells/mL suspended in cryopreservative solution. Each infusion bag contains approximately 20 mL for dispersion to infusion.
ATC code	Not yet assigned.
In vitro diagnostics required	Not applicable.
Monitoring required	Prolonged cytopenias Blood counts should be monitored after Skysona® infusion, and patients should be evaluated for signs and symptoms of bleeding and infection. Risk of insertional oncogenesis Patients should be monitored at least annually for myelodysplasia, leukaemia, or lymphoma (including with a complete blood count) for 15 years after treatment with Skysona®. If myelodysplasia, leukaemia, or lymphoma is detected in a patient who received Skysona®, blood samples should be collected for integration site analysis.
Orphan Designation	Yes
ATMP	Yes

Source: Eli-cel Summary of Product Characteristics (SmPC).
Abbreviations: ALDP=adrenoleukodystrophy protein; ATC=Anatomical Therapeutic Chemical; cDNA=complementary deoxyribonucleic acid; HSC=haematopoietic stem cell; LVV=lentiviral vector.

Table 1.2. Administration and dosing of the technology

	Elivaldogene autotemcel
Method of administration	Eli-cel is an *ex vivo* gene therapy administered intravenously by infusion. Eli-cel is manufactured from the patient's own previously harvested stem cells. After enrichment for $CD34^+$ cells, the cells undergo *ex vivo* transduction with the Lenti-D LVV. Prior to eli-cel treatment, the patient receives myeloablative conditioning (chemotherapy to clear space in the bone marrow), after which the transduced stem cells, i.e., eli-cel, are infused to repopulate the bone marrow. • Expose the sterile port on the infusion bag by tearing off the protective wrap covering the port. • Access the medicinal product infusion bag and infuse as per the administration site's standard procedures for administration of cell therapy products. Do not use an in-line blood filter or an infusion pump. • Infuse Skysona® as soon as possible and store for no more than four hours at room temperature (20ºC – 25ºC) after thawing. • Administer each infusion bag of Skysona® via intravenous infusion over a period of less than 60 minutes. • Flush all Skysona® remaining in the infusion bag and any associated tubing with at least 50 mL of sodium chloride 9 mg/mL (0.9%) solution for injection to ensure as many cells as possible are infused into the patient. Skysona® must be administered in a qualified treatment centre by a physician(s) with experience in HSC transplantation and in the treatment of patients with neurological disorders.
Doses	The minimum recommended dose of eli-cel is 5.0×10^6 $CD34^+$ cells/kg. In clinical studies, doses up to 38.2×10^6 $CD34^+$ cells/kg have been administered.
Dosing frequency	Eli-cel is a one-time treatment.
Standard length of a course of treatment	Eli-cel is a one-time treatment administered on a single day. However, patients are hospitalised from the beginning of myeloablative conditioning until they achieve neutrophil engraftment or are clinically stable. In clinical study ALD-102, patients spent a median of 29.0 days (range 15–54) in hospital from conditioning through to neutrophil engraftment.
Standard interval between courses of treatments	Not applicable. Eli-cel is a one-time treatment.
Standard number of repeat courses of treatments	Not applicable. Eli-cel is a one-time treatment.*
Dose adjustments	The minimum target number of $CD34^+$ cells to be collected is 12×10^6 $CD34^+$ cells/kg. If the minimum dose of Skysona® 5×10^6 $CD34^+$ cells/kg is not met after initial medicinal product manufacturing, the patient may undergo one or more additional cycles of mobilisation and apheresis separated by at least 14 days to obtain more cells for additional manufacture. A back-up collection of $CD34^+$ stem cells of $\geq 1.5 \times 10^6$ $CD34^+$ cells/kg is required. These cells must be collected from the patient and be cryopreserved prior to initiating conditioning and infusion with Skysona®. The back-up collection may be needed for rescue treatment if there is: 1) compromise of Skysona® after initiation of conditioning and before Skysona® infusion, 2) primary engraftment failure, or 3) loss of engraftment after infusion with Skysona®.

Source: Eli-cel Summary of Product Characteristics (SmPC), Submission Dossier.

* To date, no engraftment failure or GVHD has been observed in the trial patient pool (ALD-102 and ALD-104).

Abbreviations: LVV=lentiviral vector.

1.3.2 Comparators

Allo-HSCT, excluding those with an HLA-matched sibling donor and best supportive care for patients that have no access to allo-HSCT, represent the comparator of interest for this assessment.

According to the management guidelines for ALD/CALD, allo-HSCT is currently the only disease-modifying treatment available for CALD patients [1, 22]

Best supportive care includes any treatment for symptom relief and may include treatments that aim to delay/stop disease progression. Various therapies are used as supportive care in European countries, e.g., Lorenzo's oil, dietary treatments, or post-HSCT immunosuppressive treatments; however, evidence of efficacy is lacking [1].

2 OBJECTIVE AND SCOPE

The aim of this EUnetHTA Joint Relative Effectiveness Assessment is to compare the clinical effectiveness and safety of Skysona® (elivaldogene autotemcel, eli-cel) in the target patient populations with relevant comparators. The target patient populations and relevant comparators (based on the requirements of EUnetHTA Partners) are defined in the project scope below (Table 2.1).

The assessment was based on the Submission Dossier submitted by the MAH bluebird bio B.V

The scope of the assessment (Table 2.1) does not differ from the scope described in the project plan, except moving engraftment failure from Clinical Effectiveness to Safety in the Outcomes.

Table 2.1. Scope of the assessment

Description	Assessment scope
	PICO
Population	Treatment of early cerebral adrenoleukodystrophy in patients <18 years of age, with an *ABCD1* mutation, and for whom an HLA-matched sibling HSC donor is not available
Intervention	Elivaldogene autotemcel (Skysona®; eli-cel)
Comparison	Allogeneic haematopoietic stem cell transplant (allo-HSCT) from a donor, excluding an HLA-matched sibling donor Best supportive care[a]
Outcomes	**Clinical effectiveness** • Overall survival* • Major functional disability (MFD)[b]-free survival* • Severity of gross neurological dysfunction (change in Neurologic Function Score (NFS)) [4]* • Health-related quality of life (HRQoL; reported by patient or their carer)[c] • HRQoL of parents/carers* • Change in brain lesions (Loes magnetic resonance imaging score) [5] • Proportion of subjects undergoing subsequent allo-HSCT* • Time to subsequent allo-HSCT • Resolution of gadolinium enhancement positivity
	Safety • Treatment-related adverse events (AEs) grade 3-5* • Discontinuations due to treatment-related AEs • AEs of special interest (incidence of acute or chronic GVHD, engraftment failure)* • Other AE*
Study design	Not defined

[a] 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.
[b] MFD includes 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

This assessment is based on the data and analyses included in the Submission Dossier prepared by the MAH. During the assessment, the completeness of data and analyses in the Submission Dossier was verified. Furthermore, the methods for data analysis and synthesis applied by the MAH were checked against the requirements of the Submission Dossier and applicable EUnetHTA Guidelines and assessed with respect to scientific validity.

3.1 Information retrieval

The Authoring Team reviewed the evidence base for the drug under assessment provided by the MAH. Search strategies were checked for appropriateness, and the results of information retrieval included in the MAH's Submission Dossier were checked for completeness against a search of study registries and against the studies included in the regulatory assessment report. Most of flaws identified in the pMAH's search strategy by the information specialist were resolved during checking, so no supplemental searches were performed. The full details of the search strategy were not reported, so it was impossible to verify the use of MeSH and Emtree terms. However, the use of the correct range of search terms and the ultra-rare nature of the disease minimised the chance of missing relevant studies. A summary of the MAH search strategy and study selection is shown in Table 3.1.

Table 3.1. Summary of information retrieval and study selection

Elements	Details
List of studies submitted by MAH	Beam et al. 2007 [25] Beckmann et al. 2018 [26] Bladowska et al. 2015 [27] Fernandes et al. 2018 [28] Göttingen 1985, 2003 [29, 30] Jardim et al. 2010 [31] Kato et al. 2019 [32] Kühl et al. 2018 [33] Mahmood et al. 2007 [10] McKinney et al. 2016 [34] McKinney et al. 2013 [35] Miller et al. 2016 [36] Miller et al. 2011 [37] Moser et al. 2005 [38] Orchard et al. 2019 [39] Peters et al. 2004 [40] Pierpont et al. 2017 [41] Pierpont et al. 2018 [42] Pierpont et al. 2020 [43] Polgreen et al. 2011 [44] Saute et al. 2016 [45] Shapiro et al. 2000 [46] Suzuki et al. 2001 [47] Tokimasa et al. 2008 [48] Tran et al. 2017 [49] van den Broek et al. 2018 [50]
Databases and trial registries searched	Databases: PubMed, Medline, EmBase. Trial registries: ClinicalTrials.gov, ICTRP Search Portal, EU CTR, "eli-cel clinical development programme"
Search date	First run: 14 November 2019; Updates: 5 January 2021; Period covered: 1 January 1999 – 5 January 2021

Search terms	Covering:
	• Population:
	  ○ Adrenoleukodystrophy
	  ○ X-linked adrenoleukodystrophy
	  ○ Cerebral adrenoleukodystrophy
	• Treatments:
	  ○ Hematopoietic stem cell transplantation

Elements	Details
	○ Bone marrow transplantation ○ Immunosuppressive agent ○ Lorenzo oil ○ Erucic acid ○ Diet therapy • Outcomes: ○ Severity ○ Efficacy ○ Effectiveness ○ Survival ○ Functional disability ○ Clinical disability ○ Neurological functional score ○ Loes score ○ Loes pattern ○ Gadolinium ○ Enhancement ○ Resolution ○ Re-transplant ○ Retransplant ○ Safety ○ Mortality ○ Adverse events ○ Infections ○ GVHD ○ Graft-versus-host disease ○ Graft failure ○ Nonengraftment ○ Transplant-related mortality ○ HRQoL ○ Health-related quality of life ○ Quality of life ○ QoL ○ EQ-5D ○ SF-36 ○ SF-12 ○ Neuro-QoL ○ PROMIS ○ McGill
Inclusion criteria	**Population:** • Patients younger than 18 years of age, having elevated VLCFA values, a Loes score between 0.5 and 9 (inclusive), gadolinium enhancement on MRI of demyelinating lesions (evidence of active CALD), an NFS of ≤1, and no MSD available. **Intervention(s):** • Elivaldogene autotemcel gene therapy. **Comparator(s):** • Allo-HSCT excluding MSD • BSC (Lorenzo's oil, dietary treatment, anti-inflammatory treatment). **Outcomes:** ***Clinical efficacy:*** • Overall survival (mortality) • Major functional disability-free survival • Loes Score and Loes pattern • Change in neurologic function scale • Gadolinium enhancement ***HRQoL:*** • Short and long-term • EQ-5D • SF-12 • SF-36 • Neuro-QoL

Elements	Details
	• McGill QoL • PROMIS QoL ***Safety:*** • Adverse events (incl. discontinuation and treatment-related AEs) • Neutrophil recovery • Platelet recovery • Acute/chronic GVHD • Graft failure • Graft rejection • Transplant-related mortality • Subsequent allo-HSCT (incl. time to subsequent allo-HSCT) **Settings (if applicable):** • Short and long-term follow-up • Publications from 1 January 1999 up to the date of the search **Study design:** • Randomised controlled trials • Single-arm interventional studies • Observational studies **Language restrictions:** • English, German, French, Italian, Spanish, or a Scandinavian language for full text publications • English language limit for abstracts **Other search limits or restrictions applied:** • Published in full text
Exclusion criteria	**Population:** • ALD patients without cerebral involvement • Adult CALD patients **Intervention(s):** NR **Comparator(s):** • Treatments not used for CALD • Treatments currently in clinical development **Outcomes:** NR **Settings (if applicable):** • Earlier than 1999 **Study design:** • Case studies • Systematic reviews **Language restrictions:** • Full text in another language than those listed **Other search limits or restrictions applied:** • Non-published material; • Conference abstracts
Date restrictions	See above “Search date” element
Other search limits or restrictions	None.

Abbreviations: AEs=adverse event; ALD=adrenoleukodystrophy; BSC=best supportive care; CALD=cerebral adrenoleukodystrophy; GVHD=graft-versus-host disease; HRQoL=health-related quality of life; HSCT= haematopoietic stem cell transplantation; ICTRP=international clinical trials registry portal; MAH=marketing authorisation holder; MSD=matched sibling donor; NFS=Neurologic Function Score; NR=not reported; VLCFA=very long-chain fatty acids.

The study pool of the assessment was compiled based on the following information:

Sources of the company in the Submission Dossier:

- Study list of the MAH on elivaldogene autotemcel gene therapy (status: 5th January 2021);
- Bibliographical databases (last search on 5th January 2021);
- Trials registries: ClinicalTrials.gov, ICTRP Search Portal, EU CTR (last search on 25 March 2021) and search via "eli-cel clinical development programme"[2], no date given.

Check of the completeness of the study pool:

- Trials registries (last search on 25th March 2021).

The check identified no additional relevant study.

3.2 Data extraction

Information used for the assessment of clinical effectiveness and safety was extracted from the Submission Dossier and verified against the clinical study reports (CSRs) or other original documentation provided in the Submission Dossier.

3.3 Risk of bias assessment

No risk of bias tools are available for single-arm trials. The MAH provided a risk of bias assessment based on the quality appraisal checklist for observational studies by Berger et al. [51]; this checklist assesses the relevance and credibility of each study based on questions in the following domains: design, data, analysis, reporting, interpretation, and conflicts of interest. The assessment provided by the MAH was checked by two assessors. The findings were then translated into the following seven domains to judge risk of bias:

- Bias due to confounders;
- Bias in selection of participants into the study;
- Bias in classification of interventions;
- Bias due to deviations from intended interventions;
- Bias due to missing data;
- Bias in measurement of outcomes;
- Bias in selection of the reported result.

The assessment was only performed for each study and was not specified separately for each patient-relevant outcome, which is a deviation from the project plan.

3.4 Results and analyses of the included studies

The information in the Submission Dossier on the study design, study methods, populations, endpoints (patient relevance, validity, and operationalisation), and study results were evaluated. The results of this evaluation were used to identify relevant analyses and were considered for the conclusions of the assessment report.

3.4.1 Meta-analysis

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, were evaluated.

3.4.2 Sensitivity analysis

To evaluate the robustness of results, it was planned to evaluate sensitivity analyses with regard to methodological factors presented in the Submission Dossier and the corresponding methods applied.

[2] The eli-cel clinical development programme is an internal company database containing several single-arm trials.

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.

Note: The EMA requested sensitivity analyses to assess the impact of missing data, since analyses were based on available (non-missing) observations, and this was not according to the intention-to-treat (ITT) principle. The authors refer to these sensitivity analyses mentioned in the EPAR [8]. However, since these sensitivity analyses were not presented in the Submission Dossier nor shown in the EPAR, the authors could not assess these sensitivity analyses.

3.4.3 Subgroup analysis and other effect modifiers

During the assessment, the subgroup analyses examining potential effect modifiers presented in the Submission Dossier and the corresponding methods applied were evaluated.

3.4.4 Certainty of the evidence

Issues related to the (un-)certainty of the evidence were evaluated and presented for each outcome across all studies (i.e., the body of evidence for an outcome) by partial use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) domains and evidence table [7]. The domains include:

- study limitations (risk of bias);
- inconsistency of results;
- indirectness of evidence;
- imprecision;
- publication bias.

In the evidence table, all relevant information per domain was flagged for each outcome to provide a transparent and systematic assessment. The assessment was context-independent and without overall conclusions on the quality or certainty of evidence. The evidence was not downgraded nor upgraded and no overall judgement of the certainty of the evidence was provided per outcome or across outcomes. No balancing of favourable and unfavourable effects was performed. Also, outcomes were not ranked in terms of importance or otherwise. Surrogate outcomes were presented as measured.

This assessment was performed following the “Partial Use of GRADE in EUnetHTA Framework” (2020) by the EUnetHTA Task Group for Common Phrases and GRADE [6].

3.5 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 are ideally placed to collect and present patients’ and caregivers’ views and experiences by engaging with a wide range of patients and their carers. The open call used by EUnetHTA asked 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 questionnaire as developed by the HTAi was adapted to the EUnetHTA context. 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 or in the language of the Authoring Team (i.e., Dutch, German, or Polish). In all parts of the open call, the term ‘patient’ referred to anyone living with, or who has lived with, the condition for which the new medicine is indicated. Since this is a rare disease in patients under 18 years of age, parents and/or caregivers were also invited to respond to the open call.

In addition, a parent of a deceased child suffering from CALD was interviewed to gain insights into the impact of CALD on patients’ quality of life and the current standard of care.

The key questions and a summary of the answers are presented in Appendix 2. The information gathered from the open call and patient interview was used to inform the scope of this assessment and in particular the considered outcomes. In the PICO in Table 2.1, the outcomes related to issues particularly emphasised by patient organisations are indicated with an asterisk (*). The majority of

outcomes were mentioned indirectly by the patient organisations and interview, ensuring clinical relevancy of the outcomes used in this assessment.

4 RESULTS

4.1 Information retrieval

An Information Specialist (IS) checked that the pMAH's search strategies of bibliographic databases and study registries based on the PICOs were correct. The IS also checked the list of studies and the study pool. A full assessment of the correctness of the searches was not possible due to the way in which they were presented: there was no clear indication of the use of PubMed MeSH and Embase Emtree dictionaries. Nevertheless, the MAH's search strategy used the correct range of search terms for free-text searching, so there was no reason to conduct supplementary searches. PRISMA flow charts are in Subsection 5.1. of the Submission Dossier.

4.2 Studies included in the assessment

The studies listed in Table 4.1 were included in the assessment.

Table 4.1. Study pool – list of relevant studies used for the assessment

Study reference/ID	Study category		
	Study for marketing authorization of the technology under assessment (yes/no)	Sponsored or third-party study[a]	Available documentation
ALD-101	Yes	Sponsored	Full text publication [18] Core Submission Dossier Clinical Study Report [52]
ALD-102 (STARBEAM) [NCT01896102; EudraCT entry: 2011-001953-10]	Yes	Sponsored	Core Submission Dossier Interim Clinical Study Report [53-55]
ALD-103 [NCT02204904]	Yes	Sponsored	Core Submission Dossier Clinical Study Report [56]
ALD-104 [NCT03852498]	Yes	Sponsored	Core Submission Dossier Interim Clinical Study Report [55, 57, 58]
LTF-304[b] [NCT02698579]	Yes	Sponsored	Core Submission Dossier Interim Clinical Study Report [55, 59, 60]

[a] Study sponsored by the MAH or in which the MAH participated financially in some other way.
[b] LTF-304 is the long-term follow-up observational study for patients who completed ALD-102 or ALD-104.

4.3 Excluded studies

Table 4.2 lists the studies that were included in the Submission Dossier provided by the MAH but were excluded for further consideration in this assessment.

Table 4.2. Excluded studies

Study reference/ID	Reason for non-consideration of the study
Beam et al. 2007 [25]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Beckmann et al. 2018 [26]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Bladowska et al. 2015 [27]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Fernandes et al. 2018 [28]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Göttingen 1985, 2003 [29, 30]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Jardim et al. 2010 [31]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Kato et al. 2019 [32]	No separate analysis for patients fulfilling all TPES criteria available
Kühl et al. 2018 [33]	No separate analysis for patients fulfilling all TPES criteria available
Mahmood et al. 2007 [10]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
McKinney et al. 2016 [34]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
McKinney et al. 2013 [35]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Miller et al. 2016 [36]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Miller et al. 2011 [37]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Moser et al. 2005 [38]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Orchard et al. 2019 [39]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Peters et al. 2004 [40]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Pierpont et al. 2017 [41]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Pierpont et al. 2018 [42]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Pierpont et al. 2020 [43]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Polgreen et al. 2011 [44]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Saute et al. 2016 [45]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Shapiro et al. 2000 [46]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Suzuki et al. 2001 [47]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Tokimasa et al. 2008 [48]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
Tran et al. 2017 [49]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported
van den Broek et al. 2018 [50]	BL characteristics of disease status (Loes, NFS, GdE) not fully reported

Source: Submission Dossier.
Abbreviations: BL=baseline; GdE=gadolinium enhancement; NFS=Neurologic Function Score; TPES strictly ALD-102 eligible transplant population.

4.4 Characteristics of the included studies

The eli-cel clinical development programme comprised five studies: two observational data collection studies (one retrospective, ALD-101 [18, 52], and one partly prospective, ALD-103 [56]); two interventional single-arm studies (ALD-102 [53] and ALD-104 [57]); and one observational long-term follow-up study (LTF-304 [59]).

ALD-101 included a patient cohort treated with allo-HSCT (n=65) and an untreated patient cohort (n=72), and ALD-103 (only) included a patient cohort treated with allo-HSCT (n=59). Both studies have been completed. ALD-102 and ALD-104 included patients for treatment with eli-cel. Both are ongoing, with study enrolment complete in ALD-102 (n=32) and 20 patients enrolled in ALD-104 as of the latest data cut-off. LTF-304 has enrolled/will enrol patients from parent studies ALD-102 and ALD-104 when they have completed 24-months of follow-up for long-term (13 years) assessment. To date, most ALD-102 patients but no ALD-104 have been included in LTF-304.

ALD-101 was a preparatory study and informed the design of the following eli-cel trials (ALD-102, ALD-104, and LTF-304), which were single-arm trials because a randomised controlled trial was not deemed

feasible. ALD 103 was therefore designed to be consistent with ALD-102 by the MAH so that the derived data could be used as external comparator for outcomes after treatment with eli-cel in ALD-102 (see Submission Dossier).

A detailed description of the study characteristics is presented in in Table 4.3 and Table 4.4. Information was taken from the submission file, from publications (where available), and from CSRs.

ALD-101 [18] was a multicentre study (five study centres) including boys aged one to 15 years with CALD (see Table 4.3), who were included when diagnosed in or after 1990 (the untreated cohort) and, for the allo-HSCT cohort, when treated in or after 2001. The objective of the study was to characterise the natural history of childhood CALD and to investigate the influence of allo-HSCT on affected subjects. Most subjects in the allo-HSCT cohort were diagnosed after 2000 (HSCT 1997-2004, n=31 (four subjects before 2000); HSCT 2005-2010, n=34), whereas untreated cohort subjects were mostly diagnosed in the 1990s prior to frequent standard monitoring of Loes scores and NFS. Thus, only one subject in the untreated cohort fulfilled the criteria for the "strictly ALD-102 eligible transplant population" (TPES; GdE^{+}, NFS ≤1, and Loes score between 0.5 and 9 (inclusive) documented at baseline). In the allo-HSCT cohort, 27 subjects met the TPES criteria. The population was also divided into subgroups with a matched sibling donor (MSD) and with no matched sibling donor (NMSD).

ALD-103 was a prospective and retrospective multicentre study (nine countries) aiming to evaluate outcomes in males <18 years of age undergoing allo-HSCT for the treatment of CALD. Retrospective subjects were <18 years of age at the time of treatment; prospective subjects were <18 years of age at the time of consent. Similar to the ALD-101 population, ALD-103 was analysed with a view to eligibility for ALD-102. Certain safety and efficacy endpoints were summarised in subgroups by donor type as in ALD-101.

ALD-102 and ALD-104 are ongoing multicentre studies, so several data cut-offs were provided by the MAH (see Table 4.3). As per the last data cut-off, 27 patients from ALD-102 were enrolled into the follow-up-study LTF-304 (one of whom discontinued). Both studies include similar outcomes but differ with respect to the type of myeloablative conditioning used which, according to the MAH, reflects a general change in clinical practice.

Table 4.3. Characteristics of the studies included – single-arm and observational studies

Study reference/ID	Estimated completion date	Study type	Intervention[b] (number of included patients)	Patient population	Primary endpoint; patient-relevant secondary endpoints[a]
Single arm studies, Eli-cel					
ALD-102 (STARBEAM); NCT01896102	May 2021* 1st data cut-off (interim CSR): 17.01.2020 2nd data cut-off: 23.10.2020 3rd data cut-off: 2.11.2020 (in LTF-304, see below)	Interventional single-arm, open-label, multi-site	Eli-cel (N = 32) (enrolment complete, 20/28/30 patients reached 24-month-follow-up or discontinued as of 1st/2nd/3rd cut-off date) • Total number of study discontinuations: 3d/3/4e patients as of 1st/2nd/3rd cut-off date	Males aged <18 years with active CALD as defined by elevated VLCFA values and active CNS disease established by central radiographic review of brain MRI demonstrating a Loes score of ≥0.5 and ≤9 and gadolinium enhancement on MRI of demyelinating lesions, with an NFS ≤1	**Primary**: **MFD**: MFD-FS at month 24 **AEs of special interest**: Proportion of subjects who experience either acute (≥ grade 2) or chronic GVHD by month 24 **Secondary**: **OS** **MFD**: MFD-FS over time **Neurological function**: NFS change from baseline **Subsequent allo-HSCT**: Proportion of subjects who underwent a subsequent HSC infusion by month 24 **GdE resolution**: Proportion of subjects with resolution of GdE^+; Time to sustained resolution of GdE^+ **Tr-AE grade 3-5**: Proportion of subjects with transplant-related mortality through 100 and 365 days post-drug product infusion **AEs of special interest**: Proportion of subjects with neutrophil engraftment (NE) by 42 days after drug product infusion; proportion of subjects with platelet engraftment (PE) by month 24; proportion of subjects with loss of engraftment after drug product infusion by month 24 **Other AEs**: Proportion of subjects with and severity of clinical ≥ grade 3 adverse events (AEs), all drug product-related AEs, all serious adverse events (SAEs), ≥ grade 3 infections by month 24 **Other AEs**: Incidence of vector-derived replication-competent lentivirus (RCL) at month 24 Incidence of insertional mutagenesis leading to clonal dominance or leukaemia by month 24 **Exploratory**: **Brain lesions**: Loes Score: change in Loes score from baseline; Proportion of subjects who maintained a Loes score ≤ 9 or did not increase their Loes score by ≥ 6 points from baseline **HRQoL**: Pediatric Quality of Life Inventory (PedsQL) score

Study reference/ID	Estimated completion date	Study type	Intervention[b] (number of included patients)	Patient population	Primary endpoint; patient-relevant secondary endpoints[a]
ALD-104; NCT03852498	February 2024 1st data cut-off (interim CSR): 21.02.2020 2nd data cut-off: 9.10.2020	Interventional single-arm, open-label, multi-site	Eli-cel (N = 13/20[h] as of 1st/2nd cut-off date) Total number of study treatment discontinuations: 0/1[g] patients as of 1st/2nd cut-off date	Males aged <18 years with active CALD as defined by elevated VLCFA values and active CNS disease established by central radiographic review of brain MRA demonstrating a Loes score of ≥0.5 and ≤9 and gadolinium enhancement on MRI of demyelinating lesions, with and NFS of ≤1	**Primary**: **MFD**: MFD-FS at month 24 **AE of special interest**: Proportion of subjects experiencing neutrophil engraftment after drug product infusion (42 days after drug product infusion) **Secondary**: **OS** **MFD**: MFD-FS over time **Neurological function**: NFS change from baseline **Subsequent allo-HSCT**: Proportion of subjects undergoing a subsequent HSC infusion by month 24 **GdE resolution**: Proportion of GdE- subjects **Tr-AE grade 3-5**: Proportion of subjects experiencing transplant-related mortality through 100 and 365 days after drug product infusion **AEs of special interest**: The proportion of subjects who experience either acute (≥ grade II) or chronic GVHD at month 24; the proportion of subjects with platelet engraftment by month 24; the proportion of subjects with loss of neutrophil engraftment post-drug product infusion by month 24 **Other AEs**: Proportion of subjects with clinical ≥ grade 3 AEs, all investigational medicinal product-related AEs, all SAEs, ≥ grade 3 infections by month 24 **Exploratory**: **Brain lesions**: Loes Score: value and change in Loes score from baseline to month 24; change in Loes pattern from baseline to month 24 **HRQoL**: PedsQL score
LTF-304c; NCT02698579	May 2037 1st data cut-off (interim CSR): 31.01.2020 2nd data cut-off (only	Observational case-only, long-term follow-up	Eli-cel (N = TBD; enrolment not complete, 21/27 as of 1st/2nd cut-off date) Total number of study discontinuations: 1[f]/1 patients as of 1st/2nd cut-off date	Patients who received eli-cel drug product in a parent study (ALD-102 or ALD-104)	**Primary**: **MFD**: MFD-FS at month 24 **AEs of special interest:** Proportion of subjects who experience GVHD **Subsequent allo-HSCT**: Proportion of subjects who undergo a subsequent stem cell transplantation (i.e., second HSC infusion)

Study reference/ID	Estimated completion date	Study type	Intervention[b] (number of included patients)	Patient population	Primary endpoint; patient-relevant secondary endpoints[a]
	patients from parent study ALD 102): 02.11.2020				**AEs of special interest**: Serious or non-serious immune-related AEs and new or worsening haematological or neurological disorders or malignancies **Tr-AE grade 3-5**: All drug product-related AEs **Other AE**: All SAEs (regardless of relatedness to drug product) **Secondary**: **OS** **Neurologic function**: NFS change from baseline **GdE resolution**: Change in GdE status from last MRI performed in parent study **Exploratory**: **Brain lesions**: Loes score: change from baseline (defined in parent study); Loes pattern: change from baseline (defined in parent study); proportion of subjects who maintain a Loes score ≤9 or do not increase their score by 6 points or more **Neurological function:** Proportion of subjects who maintain an NFS ≤4 and do not increase their score by >3 points **HRQoL**: PedsQL score
Observational studies, Allo-HSCT					
ALD-101 (Raymond et al.)	Complete (data were collected between 16 April 2011 and 27 March 2012)	Retrospective, non-interventional data collection study, multicentre (5 study centres in France and USA)	Untreated cohort (N=72) fulfilling TPES criteria[j] (n=1) Allo-HSCT Cohort (N=65) fulfilling TPES criteria[j] (n=27[k]) • MSD (n=5) • NMSD (n=21[l]) • Unknown – matched sibling donor (n=1)	Boys diagnosed with CALD (either by pathognomonic VLCFA concentrations or documented pathogenic mutation in *ABCD1*) between the ages of three and 15 years (four subjects were younger)[i], and an ALD Loes MRI score of ≥0.5 and ≤14.5). Patients were included in the study when diagnosed in or after 1990 (untreated cohort) or when treated in or after 2001* (allo-HSCT cohort; depending on the time the study centre commenced use of intravenous (IV) busulfan). They had to have follow-up for at least	**Primary*:*** **MFD**: presence of MFDs at the time of diagnosis and at the follow-up time points (up to 259 months) **Secondary:** **OS** at 2 and 5 years **MFD-FS**: 2-year MFD-free survival **Neurological function**: NFS at the time of diagnosis and at the follow-up time points (defined as a score from 0 (normal functioning) to 25) **Safety*:*** **Tr-AEs**: infections, use of concomitant medication, 100-day and 1-year mortality post-HSCT **AEs of special interest**: graft failure (time to engraftment failure after first allo-HSCT); acute and chronic GVHD

Study reference/ID	Estimated completion date	Study type	Intervention[b] (number of included patients)	Patient population	Primary endpoint; patient-relevant secondary endpoints[a]
				two years after diagnosis or until death (untreated cohort) or follow-up data available for at least two years or until death following transplant (Allo-HSCT Cohort).	**Other AEs**: SAE **<u>Historical data</u>*:*** **Brain lesions**: Loes MRI score (GdE^+, GdE^-, or NA) to assess the extent of demyelination as evaluated by MRI (ranging from 0 (no abnormalities) to 34)
ALD-103 (NCT02204904)	Complete – study was early terminated due to sponsor decision[m] (data were collected between 10 April 2015 and 06 December 2019)	Prospective and partially retrospective data collection study, multicentre (Canada, USA, Germany, UK, Netherlands, France, Italy, Spain, Argentina)	Allo-HSCT cohort (N=59) fulfilling TPES criteria[j] (n=27) • MSD (n=10) • NMSD (n=17)	Males aged <18 years with confirmed diagnosis of CALD as defined by an abnormal VLCFA profile and cerebral lesion on brain MRI and either scheduled for allo-HSCT evaluation or received an allo-HSCT infusion.	**<u>Efficacy</u>*:*** Outcomes were planned to be measured at 1-48 months after allo-HSCT, unless otherwise stated: **OS** **MFD-FS:** Incidence of MFD (defined as any of the following: loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement) **Change in brain lesions:** change from baseline in Loes score **Neurological function**: change from baseline in NFS **GdE resolution**: frequency and timing of resolution of gadolinium enhancement on MRI, if applicable **<u>Safety:</u>** **Tr-AEs grade 3-5**: Frequency and severity of common CTCAE ≥grade 3 AEs; CTCAE ≥grade 3 infections; all SAEs **AEs of special interest**: Incidence of transplant-related mortality (TRM) (100-365 days) Incidence of engraftment failure or allograft rejection Incidence and timing of neutrophil and platelet engraftment Incidence of primary donor-derived chimerism of ≥50% (by 100 days) Proportion of subjects who experience either ≥grade II acute GVHD or chronic GVHD Incidence of ≥grade II acute GVHD Incidence of chronic GVHD **Other AEs**: Number of emergency room visits Number and duration of intensive care unit stays Number and duration of inpatient hospitalisation

Study reference/ID	Estimated completion date	Study type	Intervention[b] (number of included patients)	Patient population	Primary endpoint; patient-relevant secondary endpoints[a]
					Exploratory*:* **HRQoL:** PedsQL and UMNQL **Intelligence quotient (IQ)**

* According to submission dossier study completion was expected in May 2021.
[a] Primary outcomes contain information without consideration of its relevance for this assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this assessment.
[b] No separate column for comparator because study pool includes only single arm studies.
[c] LTF-304 is the long-term follow-up observational study for patients who completed ALD-102 or ALD-104.
[d] Two discontinued to receive allo-HSCT, one died.
[e] Refused further follow-up (when already enrolled in LTF-304).
[f] Refused further follow-up; see footnote e.
[g] Did not receive eli-cel treatment, reason unclear.
[h] Enrolment obviously ongoing.
[i] Exemptions were granted to four subjects who were <3 years of age at CCALD diagnosis (one untreated [age two years] and three allo-HSCT-treated [ages 1 to 2 years]) and for two allo-HSCT subjects who were treated before 2001 (1997 and 2000).
[j] Subjects who had early disease (NFS ≤1 and Loes 0.5 to ≤9 at baseline) and were GdE^{+}.
[k] All types of donor, including one subject with an unknown-match sibling-donor and one subject with an unknown-match unrelated-donor.
[l] After exclusion of five subjects with matched sibling donor and one with unknown-match sibling donor.
[m] Having met the objective of collecting contemporaneous observational data on allo-HSCT for the treatment of CALD, the Sponsor terminated Study ALD-103 with 06 December 2019 as the last day for protocol-defined study visits and subject assessments.
Abbreviations: AE=adverse event; CALD=cerebral adrenoleukodystrophy; CNS=central nervous system; CSR=clinical study report; CTCAE=Terminology Criteria for Adverse Events; $GdE^{+/-}$ =gadolinium enhancement positive/negative; GVHD=graft versus host disease; HSC=haematopoietic stem cells; MFD-FS=major functional disability-free survival; MRA=magnetic resonance angiography; MRI=magnetic resonance imaging; MSD=matched sibling donor; N=number of included patients; n=relevant subpopulation; NFS=Neurologic Function Score; NMSD=non-matched sibling donor; OS=overall survival; PedsQL= Pediatric Quality of Life Inventory score; UMNQL= University of Minneapolis Quality of Life Inventory; SAE=serious adverse event; TBD=to be determined; TPES=strictly ALD-102 eligible transplant population; Tr=treatment-related; VLCFA=very long chain fatty acid; vs.=versus.

Table 4.4. Characterisation of the interventions and comparators: single-arm and observational studies

Study reference / ID	Intervention	Additional information
Single arm studies, eli-cel		
ALD-102 (STARBEAM); NCT01896102	Eli-cel (elivaldogene autotemcel) single-dose intravenous infusion of 20-80 ml dispersion containing 2-30 × 10^6 cells/mL with a minimum dose of 5 × 10^6 cells/kg of body weight.	Treatments prior to eli-cel administration: Patients received HSC mobilising treatment consisting of 4-5 doses of G-CSF (lenograstim or filgrastim, starting dose 10 µg/kg) and an optional 1-4 doses of plerixafor (240 µg/kg), depending on peripheral blood $CD34^+$ count. Apheresis of $CD34^+$ cells was then performed per standard clinical site practice. • Myeloablative and lymphodepleting conditioning was performed on an in-patient basis using first busulfan IV followed by cyclophosphamide IV.[a]
ALD-104; NCT03852498	Eli-cel (elivaldogene autotemcel) single-dose intravenous infusion of a minimum dose of 5 × 10^6 cells/kg of body weight.	Treatments prior to eli-cel administration: Patients received HSC mobilising treatment consisting of four doses of G-CSF (lenograstim or filgrastim, starting dose 10 µg/kg) and an optional 1-3 doses of plerixafor (240 µg/kg), depending on peripheral blood $CD34^+$ count. Apheresis of $CD34^+$ cells was then performed per standard clinical site practice. Myeloablative and lymphodepleting conditioning was performed on an in-patient basis using first busulfan IV followed by fludarabine IV.[a]
LTF-304[b]; NCT02698579	No intervention[b] (No study intervention; for received treatments see ALD-102 and ALD-104).	This study includes patients who have completed ALD-102 or ALD-104 and have thus received the respective above-described treatments.
Observational studies, allo-HSCT		
ALD-101	No intervention[c] (no study intervention; received treatments are described under "additional information").	Untreated cohort: Receipt of at least one concomitant medication intended for the treatment of CCALD was documented in 69 (96%) subjects. The most common (>10% of subjects) treatments: Lorenzo's oil (60 subjects; 83%), corticosteroids (not otherwise specified) (16 subjects; 22%), thalidomide (12 subjects; 17%), β-interferon (11 subjects; 15%), and Trental® (pentoxifylline) (eight subjects; 11%). All other treatments were administered in <10% of subjects. Allo-HSCT: • Concomitant medication: intended for the treatment of CCALD and/or adrenal insufficiency, reported in 44 (68%) of allo-HSCT subjects. The most common treatments: hydrocortisone (17 subjects; 26%), Florinef® (fludrocortisone), and N-acetylcysteine (Mucomyst) (16 subjects each; 25%), Lorenzo's oil (14 subjects; 22%), and corticosteroids (not otherwise specified) (12 subjects; 19%). All other treatments were administered in one subject. • Conditioning: 82% - myeloablative conditioning regime, 19% - reduced intensity conditioning. Most common: busulfan (51/65; 78%), cyclophosphamide (32/65; 49%), anti-thymocyte globulin (22/65; 34%), and alemtuzumab (17/65; 26%). Other conditioning agents were given in < 25% of subjects. The median number of $CD34^+$ cells transplanted was 0.93 × 10^6/kg with a range of 0.1 to 18.7 × 10^6/kg, and the median number of total nucleated cells was 7.00 × 10^7/kg, with a range of 0.8 to 147 × 10^7/kg.
ALD-103	No intervention[c] (no study intervention; received treatments are described under "additional information").	• Concomitant medication: hydrocortisone (54/59; 91.5%). • Conditioning: o TP - most common: busulfan (57/59 subjects; 96.6%), cyclophosphamide (28/59; 47.5%), fludarabine (38/59; 64.4), anti-thymocyte globulin (28/59; 47.5%), and alemtuzumab (14/59; 23.7%). o Conditioning by regimen: busulfan/cyclophosphamide (21, 35.6%), busulfan/ fludarabine (30, 50.8%). o TPES - most common: busulfan (27/27 subjects; 100%), cyclophosphamide (10/27; 37,0%), fludarabine (20/27;

	74.1), anti-thymocyte globulin (12/27; 44.4%), and alemtuzumab (5/27; 18.5%). ○ Conditioning by regimen: busulfan/cyclophosphamide (7, 25.9%), busulfan/ fludarabine (17, 63.0%). • Treatment was a single IV administration of allogeneic cells. • The median number of $CD34^+$ cells transplanted: ○ TP (n=58): 3.300×10^6/kg with a range of 0.02 to 189.00×10^6/kg. ○ TPES (n=27): 3.560×10^6/kg with a range of 0.25 to 189.00×10^6/kg.

[a] For details on dosing and administration of conditioning treatment, see interim CSR.
[b] LTF-304 is the long-term follow-up observational study for patients who completed ALD-102 or ALD-104.
[c] ALD-101 and 103 are observational studies.
Abbreviations: ABCD1=ATP-binding cassette subfamily D member 1; ALDP=adrenoleukodystrophy protein; cDNA=complementary deoxyribonucleic acid; G-CSF=granulocyte-colony stimulating factor; HSCs=haematopoietic stem cells; IV=intravenous; kg=kilogram; LVV=lentiviral vector; mL=millilitre; µg= microgram; vs.=versus, TP=transplant population, TPES=strictly ALD-102 eligible transplant population.

Table 4.5 shows the planned and the mean and median duration of follow-up observation from time of treatment or time of diagnosis (for the ALD-101 untreated cohort).

Table 4.5. Information on the course of the studies (including planned duration of follow-up): single-arm and observational studies

Study reference / ID Outcome category	Planned follow-up	Eli-cel	Untreated cohort	Allo-HSCT
ALD-102 (STARBEAM); NCT01896102 (2nd data cut-off, 23.10.2020)	**24 months**	**N = 32**		–
Duration of follow-up from day of eli-cel infusion to day of last contact in study [months]				
Median [Min; Max]	–	24.07 (13.4; 25.3)		–
Mean (SD)	–	23.21 (2.580)		–
ALD-104; NCT03852498 (2nd data cut-off, 9.10.2020)	**24 months**	**N = 19[e]**		–
Duration of follow-up from day of eli-cel infusion to day of last contact in study [months]				
Median [Min; Max]	–	8.64 [0.1, 16.8]		–
Mean (SD)	–	8.49 (5.996)		–
LTF-304; NCT02698579 (2nd data cut-off, 2.11.2020)	**180 months[f]**	**N = 27**		–
Duration of follow-up after drug product infusion [months]				
Median [Min; Max]	–	58.61 [23.4, 82.7]		–
Mean (SD)	–	51.45 (18.560)		–
ALD-101	**NA[c]**	–	**N = 72**	**N = 65**
Duration of follow-up from confirmed CCALD diagnosis [months][a]				
Median [Min; Max]	–	–	52.2 (0.2, 259.2)	54.1 (4.8, 125.3)
Mean (SD)	–	–	81.8 (72.36)	57.4 (34.98)
Duration of follow-up from first allo-HSCT [months][b]				
Median [Min; Max]	–	–	–	45.8 (0.4, 117.7)
Mean (SD)	–	–	–	48.9 (33.51)
ALD-103	**48 ± 1 months**	–	-	**N = 59**
Duration of follow-up from first allo-HSCT [months][b]				
Median [Min; Max]	–	–	–	23.0 (0.9; 49.5)
Mean (SD)	–	–	–	–

[a] Measured from confirmed CCALD to last evaluation date/date of death.
[b] Measured from first allo-HSCT to last evaluation date/date of death.
[c] Main criteria for inclusion in the untreated cohort included follow-up for at least two years after diagnosis or until death if sooner. Main criteria for inclusion in the allo-HSCT cohort included follow-up for at least two years following allo-HSCT or until death if sooner.
[e] Excludes one patient who did not receive eli-cel treatment (see Table 4.3).
[f] Including the 24 months in the parent studies ALD-102 and ALD-104.
Abbreviations: Max=maximum; min=minimum; N=number of analysed patients; NA=not applicable; SD=standard deviation; vs.=versus.

Table 4.6 shows the characteristics of the patients in the included studies.

In the allo-HSCT cohort from the ALD-101 study, only 13 (20%) subjects had an HLA-matched related donor. The majority of subjects (46; 71%) had unrelated donors. Thirty-two subjects (49%) had unrelated HLA-mismatched donors and for 13 (20%) the donor was HLA-matched (for one patient the data was missing). In the ALD-103 TPES population, out of 27 patients, 17 (63%) were subjects without matched sibling donors.

Table 4.6. Baseline characteristics of study populations: eli-cel clinical development programme

Parameter / statistic	ALD-102	ALD-104	LTF-304	ALD-101		ALD-103	
	N = 32	N = 19	N = 27	Untreated (N = 72)	HSCT (N = 65)	All N = 59	TPES n=27
Median age at ALD diagnosis, years (min, max)	NR	NR	NR	7.0 (0, 15)	7.0 (0, 13)	NR	NR
Median age at CALD diagnosis, years (min, max)	6.0 (3, 13)	7.0 (2, 13)	NR	8.0 (2, 15)	8.0 (1, 13)	7.0 (0, 14)	7.0 (0, 11)
Median age at start of treatment, years (min, max)	6.0 (4, 14)	7.0 (5,13)	NR	NA	8.3 (2, 18)	8.0 (2, 14)	8.0 (5, 11)
Median age at start parent study, years	NA	NA	6.0 (3, 13)	NA	NA	NA	NA
Median time from earliest onset of symptoms to CALD diagnosis (months, min.-max.)	NR	NR	NR	5.4 (-134.0, 142.4)[a]	4.8 (-70.3, 149.6)	NR	NR
Race, n (%)							
White	15 (46.9)	13 (68.4)	NR	51 (70.8)	42 (64.6)	51 (86.4)	25 (92.6)
Black or African American	1 (3.1)	1 (5.3)	NR	6 (8.3)	2 (3.1)	2 (3.4)	0
Asian	1 (3.1)	0	NR	5 (6.9)	2 (3.1)	1 (1.7)	0
Other	5 (15.6)	0	NR	1 (1.4)	2 (3.1)	3 (5.1)	2 (7.4)
Native Hawaiian or Other Pacific Islander	0	0	NR	1 (1.4)	0	0	0
Unknown/not reported	10 (31.3)	5 (26.3)	NR	8 (11.1)	17 (26.2)	2 (3.4)	0
Ethnicity, n (%)							
Hispanic	12 (37.5)	-	-	-	-	12 (20.3)	7 (25.9)
Non-Hispanic	17 (53.1)	-	-	-	-	32 (54.2)	11 (40.7)
Not reported	3 (9.4)	-	-	-	-	15 (25.4)	9 (33.3)
Clinical presentation, n (%)							
Signs and symptoms	31 (96.9)	NR	NR	42 (58.3)	38 (58.5)	NR	NR
Family history	19 (59.4)	9 (47.4)	NR	26 (36.1)	28 (43.1)	31 (52.5)	16 (59.3)
Adrenal insufficiency	27 (84.4)	16 (84.2)	NR	33 (45.8)	41 (63.1)	44 (74.6)	20 (74.1)
GdE^+ (%)	32 (100)	NR	NR	15 (20.8)[b]	45 (69.2)	39 (66.1)	27 (100.0)
Baseline Loes score							
Mean	2.31 (1, 9)	2.0 (1.0, 7.5)	NR	NR	NR	4.25 (0, 18.5)[c]	3.0 (1, 9)[d]
≤9	32 (100)	NR	NR	39 (54.2)	40 (61.5)	NR	NR
>9	0 (0)	NR	NR	25 (34.7)	18 (27.7)	NR	NR
Missing	0	NR	NR	8 (11.1)	7 (10.8)	NR	NR
Baseline NFS							

Parameter / statistic	ALD-102	ALD-104	LTF-304	ALD-101		ALD-103	
	N = 32	N = 19	N = 27	Untreated (N = 72)	HSCT (N = 65)	All N = 59	TPES n=27
≤1	32	18 (94.7)	NR	24 (33.3)	42 (64.6)	50 (84.8)	27 (100.0)
>1	0	1 (5.3)	NR	27 (37.5)	14 (21.5)	5 (8,5)	0
Missing	0	0	NR	21 (29.2)	9 (13.8)	4 (6.8)	0
MFDs at baseline							
0	NR	NR	NR	38 (74.5)	54 (98.2)	NR	NR
1	NR	NR	NR	8 (15.7)	1 (1.8)	NR	NR
≥2	NR	NR	NR	5 (9.8)	0	NR	NR
Type of donor							
Unrelated	NA	NA	NA	NA	46 (70.8)	42 (71.2)	17 (63.0)
Sibling	NA	NA	NA	NA	17 (26.2)	11 (18.6)	10 (37.0)
Parent	NA	NA	NA	NA	2 (3.1)	5 (8.5)	0
Other related	NA	NA	NA	NA	-	1 (1.7)	0
Donor HLA match							
HLA matched related	NA	NA	NA	NA	13 (20.0)	11 (18.6)[e]	10 (37.0)[e]
HLA mismatched related	NA	NA	NA	NA	5 (7.7)	48 (81.4)[f]	17 (63.0)[f]
HLA matched unrelated	NA	NA	NA	NA	13 (20.0)		
HLA mismatched unrelated	NA	NA	NA	NA	32 (49.2)		
Missing	NA	NA	NA	NA	2 (3.1)	-	

[a] Data available for 62 subjects.
[b] GdE^+ at baseline; GdE^+ at any time during the observation period w as 21 patients.
[c] For 56 out of 59 subjects.
[d] Median (min, max).
[e] MSD – matched sibling donor.
[f] NMSD – subjects w ithout matched sibling donor.
Abbreviations: ALD=adrenoleukodystrophy; CALD=cerebral adrenoleukodystrophy; GdE=gadolinium enhancement; HSCT=haematopoietic stem cell transplant; MFD=major functional disabilities; NFS=Neurologic Function Score; NR=not reported; NA=not applicable; TPES=strictly ALD-102 eligible transplant population.

4.5 Outcomes included

Table 4.7 shows for which outcomes to be included in the assessment data were available in the included studies.

Table 4.7. Matrix of outcomes in the included studies

Study reference/ID	Outcomes										
	Mortality (OS)	MFD-FS	NFS	Loes score	GdE	Hr-QoL (PedsQL)	Subsequent allo-HSCT	Tr-AE G3-5	Discontinuations due to Tr-AE	AE of special interest	Other AE
ALD-102 (STARBEAM) NCT01896102	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
ALD-104 NCT03852498	no	no	no	no	no	no	no	yes	no	no	yes
LTF-304	no	no	yes	yes	yes	yes	yes	yes	yes	yes	yes
ALD-101	yes	yes	yes	yes	yes	no	yes[c]	yes/no[b]	no	yes/no[a]	yes
ALD-103	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

[a] AE of special interest (incidence of acute or chronic graft versus host disease (GVHD), engraftment failure) reported in allo-HSCT cohort.
[b] Reported only for GVHD.
[c] NA for untreated cohort.
Abbreviations: AE=adverse event; G3-5=grade 3-5; GdE=gadolinium enhancement; Hr-QoL=health-related quality of life; HSCT=haematologic stem cell transplant; MFD-FS=major functional disability-free survival; NFS=Neurologic Function Score; OS=overall survival; PedsQL= Pediatric Quality of Life Inventory score; TrAE=treatment-related adverse event.

4.6 Risk of bias

The assessment of risk of bias per domain for studies ALD-102 and ALD-103 is shown in Table 4.8. The overall risk of bias for these studies was judged critical.

Study ALD-101 was a retrospective study, collecting data in 2011-2012 from medical files. The untreated cohort were to be diagnosed in or after 1990, whereas for allo-HSCT-treated subjects, they should have undergone allo-HSCT in or after 2001, when allo-HSCT became the standard of care for CALD. Only those data that were available in the medical files could be collected. The overall risk of bias was judged critical. The risk of bias for this study was not judged per domain, as this study was not used for the comparison of clinical effectiveness and safety. For more details, see Section 4.7.

For studies ALD-104 and LTF-304, no risk of bias assessment per domain was performed by the MAH, as no full report was available (enrolment still ongoing). The design of ALD-104 is similar to ALD-102, so the risk of bias is expected to be similar. Due to the open-label design, bias due to confounding cannot be ruled out. For this assessment only, limited safety data could be derived from the study (maximum follow-up 16.8 months). LTF-304 is the follow-up study of ALD-102 and ALD-104 and includes subjects who completed the follow-up period in ALD-102 or ALD-104. So far, all patients who completed study ALD-102 have been enrolled into LTF-304, and the available data for these patients are included in this assessment.

Table 4.8. Risk of bias in non-randomised studies*

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
ALD-102	C[a]	S[b]	L	L	S[d]	L	L
ALD-103	C[a]	S[b]	S[c]	S[c]	S[d]	S[e]	L

Source: Submission dossier. bluebird bio, Inc. interim clinical study report ALD-102 and ALD-103. EPAR.
*Adapted from the risk of bias in non-randomised studies of interventions (ROBINS-I) assessment tool.
Abbreviations: C=critical risk; L=low risk; M=moderate risk; NI=no information; S=serious risk.
[a] The study design could not rule out risk of bias due to confounding.
[b] There were four sites recruiting for both studies, and two of them recruited for ALD-103 while ALD-102 recruitment was active. Difference in exclusion criteria between studies.
[c] This was an observational study; no treatment selection was dictated by the protocol. Transplant protocols and conditioning regimens in CALD varied between study sites.
[d] The extent of missing data was not reported. Effect estimates came from interim analyses. Analyses were based on missing data, no ITT analysis was performed. The EPAR states that sensitivity analyses were performed for MFD-free survival, where in TP-102 non-evaluable subjects were considered as having a negative outcome, while in TPES-103 missing data were imputed as a success for the selected primary and secondary efficacy endpoints. The sensitivity analysis using the most conservative imputation approach did not change the conclusions of the main analysis for these parameters performed on non-missing observations. However, it was seen that the effect estimates were sensitive and prone to bias with increasing amounts of missing data and should be interpreted cautiously [8].
[e] Partial prospective/retrospective and retrospective cohorts; the retrospective visit data were collected according to schedule whenever possible. If data were missing for a retrospective visit, this was not considered a protocol deviation. Procedures performed were according to institutional treatment protocols (i.e., common medical practice) and the accepted management of CALD.

4.7 External validity

The external validity of the eli-cel studies (ALD-102 and ALD-104) and allo-HSCT studies (ALD-101 and ALD-103) is reported below.

4.7.1 Population

The study populations of ALD-102 and ALD-104 were according to the proposed label indication and the target population in this assessment. The population included paediatric CALD patients (<18 years of age) with early disease (Loes score ≥0.5 to ≤9.0; NFS ≤1) and early signs of cerebral inflammation as defined by contrast enhancement (GdE^+) at baseline. These criteria are important, since early disease at commencement of treatment is considered the main criterion for a favourable outcome. When treated too late, the CALD inflammatory process continues, leading to irreversible neurological damage. Since only 30-40% of boys carrying *ABCD1* mutations will get the severe childhood CALD variant and an early sign of cerebral inflammation is contrast enhancement (GdE^+), boys with a genetic diagnosis are regularly monitored with brain MRI scans and neurological examinations to capture the earliest signs of conversion from ALD to CALD (See Section 1).

Study ALD-101 was a retrospective study that collected data in 2011-2012 from medical files. The study population consisted of: (1) untreated subjects who were diagnosed in or after 1990; and (2) subjects who had undergone allo-HSCT from an HLA-matched or non-matched sibling in or after 2001, when allo-HSCT became the standard-of-care for CALD. Inclusion criteria regarding disease status were less stringent, only requiring a Loes score >0 and <15, so the study also included patients with more severe disease at baseline related to lower chances of successful treatment. There were no inclusion/exclusion criteria related to NFS or contrast enhancement status. In total, one of 72 subjects in the untreated cohort and 27 of 65 subjects in the allo-HSCT cohort strictly matched the ALD-102 population (TPES population: NFS ≤1, Loes score 0.5 to ≤9, and GdE^+).

In the mixed (prospective and retrospective) study ALD-103, there were also no specific eligibility criteria to select only early CALD subjects. In total, 27 out of 59 subjects strictly matched the ALD-102 population (TPES population: NFS ≤1, Loes score 0.5 to ≤9, and GdE^+). There were 26 subjects in the prospective-only cohort, seven in the retrospective-only cohort, and 26 subjects in the mixed prospective/retrospective cohort.

4.7.2 Intervention

The intervention was according to the proposed PICO, namely administration of eli-cel in ALD-102 and ALD-104. It should be noted, however, that different myeloablative conditioning regimens were used in ALD-102 and ALD-104. In ALD-102, busulfan with cyclophosphamide was used, whereas busulfan with fludarabine was used as the lymphodepletion agent in ALD-104.

4.7.3 Comparison

According to the PICO, the comparator should be allo-HSCT from a donor excluding HLA-matched siblings and/or best supportive care.

In ALD-101, only one subject that strictly matched the ALD-102 inclusion criteria was untreated, so the comparison with best supportive care was not meaningful. The other 27 subjects who strictly matched the ALD-102 criteria received allo-HSCT from an NMSD (n=21) or an MSD (n=5); for one subject, the donor was unknown. Different conditioning therapies were used in these subjects: 82% had a myeloablative conditioning regimen and 19% had reduced-intensity conditioning. The most commonly administered conditioning agents for allo-HSCT were busulfan (51 subjects; 78%), cyclophosphamide (32 subjects; 49%), anti-thymocyte globulin (22 subjects; 34%), and alemtuzumab (17 subjects; 26%). Other conditioning agents were given in <25% of subjects.

Of the 27 subjects included in ALD-103 who strictly matched the ALD-102 eligibility criteria, 17 and 10 subjects received allo-HSCT from an NMSD and MSD, respectively. The conditioning regimen in the NMSD population comprised busulfan/fludarabine (23/48, 47.9%) or busulfan/cyclophosphamide (18/48, 37.5%). In addition, some subjects received other conditioning agents such as anti-thymocyte globulin (58.3%) and/or alemtuzumab (22.9%).

4.7.4 Outcomes

The outcomes included in all studies were of clinical relevance; however, longer follow-up is needed to draw conclusions on clinical effectiveness and safety. Most outcomes included in the PICO were reported; see Table 4.7 matrix of outcomes for the included studies.

ALD-102 and ALD-104 are still ongoing. For ALD-102, interim analyses for all outcomes are available as of cut-off date of 23 October 2020 (according to submission dossier study completion was expected in May 2021). For ALD-104, limited data could be derived (safety data only) due to the trial currently ongoing with a follow-up of maximum 16.8 months (expected completion February 2024). Patients enrolled in both ALD-102 and ALD-104 will enrol in a long-term follow-up study (LTF-304) once the follow-up period of the respective initial studies has been completed (expected completion May 2037).

ALD-101 and ALD-103 are completed studies. Since these were (partly) retrospective studies, only those data that were available in the medical files could be collected.

4.8 Results on clinical effectiveness and safety

The results on clinical effectiveness and safety of the indirect comparison of eli-cel with allo-HSCT in the treatment of early CALD in patients <18 years of age, with an *ABCD1* mutation, and for whom an HLA-matched sibling HSC donor was not available are summarised below.

For eli-cel, results from ALD-102 and, where possible, ALD-104 and LTF-304 are reported. For allo-HSCT, results from ALD-103 study are preferentially reported for the TPES NMSD population, since this was the best comparator according to the PICO. Furthermore, results for the TPES MSD population are reported to support a conservative comparison between eli-cel and allo-HSCT, since MSD allo-HSCT is currently the best available therapy and analysed numbers for allo-HSCT from an NMSD are small. For outcomes where results were not specified per donor type, the results for the ALD-103 TPES and TP populations (including MSD and NMSD) are reported. Study ALD-101 was not used in the comparison of clinical effectiveness and safety due to issues with external validity (see Section 4.7). Results of study ALD-101 can be found in the Submission Dossier and EPAR [8].

The outcomes, as described in the PICO, are categorised by survival (overall survival and MFD-free survival), disease parameters (NFS; Loes-score; GdE status), QoL, and AEs (including engraftment failure and GVHD).

4.8.1 Survival

MFD-free survival and overall survival for ALD-102 (TP) and ALD-103 (TPES NMSD), including Kaplan-Meier estimates, are shown in Table 4.9 and Figure 4.1 and Figure 4.2. The median MFD-free and overall survival were not evaluable in any study population.

As of 23 October 2020, after a median follow-up of 24.1 months (range 13.4 to 25.3), 32 patients had been treated with eli-cel in ALD-102, of whom 31 were still alive (96.6%; 95%CI: 77.9 to 99.5; Kaplan-Meier (KM) analysis). Fourteen out of 17 (86.3%; 95%CI: 54.7 to 96.5; KM analysis) patients who received allo-HSCT from an NMSD and 8/10 (88.9%; 95%CI: 43.3 to 98.4; KM analysis) who had an MSD were alive in the ALD-103 TPES population.

Twenty-seven of 30 evaluable patients receiving eli-cel (90.0%; 95%CI 73.5 to 97.9) were MFD-free at month 24. A further two patients had been treated but were not evaluable as they had not reached 24 months of follow-up. MFD-free survival at month 24 in the eli-cel population was higher than in the TPES population treated with NMSD allo-HSCT (n=6/9, 66.7%; 95% CI: 29.9 to 92.5) but comparable to that seen in the TPES treated with allo-HSCT from an MSD.

Overall survival and MFD-free survival remained stable up to month 48 for eli-cel, while there was a decrease for allo-HSCT, mostly due to death and failure in immune-compatibility as indicated by the number of second allo-HSCTs (5/17, 29.4%).

Table 4.9. Summary of MFD-free and overall survival (dichotomous): indirect comparison of eli-cel versus allo-HSCT in ALD-102 (data cut-off 23 October 2020) and ALD-103 TPES MSD/NMSD populations

Study reference/ID	Eli-cel	Allo-HSCT	
	TP-102	TPES-103	
		NMSD	MSD
N	**32**	**17**	**10**
Overall survival rate by month 24 (Kaplan-Meier analysis)			
% 95% CI	96.6 77.9 to 99.5	86.3 54.7 to 96.5	88.9 43.3 to 98.4
Overall survival rate at month 48 (Kaplan-Meier analysis)			
% 95% CI	96.6 77.9 to 99.5	75.5 39.7 to 91.8	74.1 28.9 to 93.0
Death, n (%)	1 (3.1)	3 (17.6)	2 (20.0)
MFD-free survival at month 24			
Evaluable subjects n (%) 95% CI	30[a] 27 (90.0) 73.5 to 97.9	9[b] 6 (66.7) 29.9 to 92.5	9[b] 8 (88.9) 51.8 to 99.7
Initial failure of MFD-free survival by month 24			
Death, n (%) MFD, n (%) Second allo-HSCT, n (%)	0 1 (3.3) 2 (6.3)	0 0 3 (33.3)	1 (11.1) 0 0
MFD-free survival rate at month 24 (Kaplan-Meier analysis)			
% 95%CI	90.6 73.7 to 96.6	70.6 43.1 to 86.6	88.9 43.3 to 98.4
MFD-free survival rate at month 48 (Kaplan-Meier analysis)			
% 95%CI	90.6 73.7 to 96.9	58.8 27.5 to 80.4	74.1 28.9 to 93.0
Events			
Death, n (%) MFD, n (%) Second allo-HSCT, n (%)	0 1 (3.1) 2 (6.3)	1 (5.9) 0 5 (29.4)	2 (20.0) 0 0

Source: bluebird bio, Inc. TLFs ALD Inter-Study D120 MAA. bluebird bio, Inc. interim clinical study report ALD-103.
Abbreviations: allo-HSCT=allogeneic hematopoietic stem cell transplantation; CI=confidence interval; n=number of patients with (at least one) event; N=number of patients in population; NMSD=no matched sibling donor subgroup; TP=transplant population; TPES=strictly ALD-102 eligible transplant population.
Note: Estimates of MFD-free survival were obtained using the Kaplan-Meier method, where events included deaths, MFDs, and rescue cell administration or second allo-HSCT. Sensitivity analyses can be found in the EPAR [8]. Estimates of overall survival rates were obtained using the Kaplan-Meier method, where the event is death from all causes.
[a] ALD-102 evaluable subjects are defined as subjects who have been followed for 24 months (i.e., relative day of data cut ≥730) or have completed the month 24 visit or discontinued from the study but would have been followed for 24 months if still on the study (i.e., relative day of data cut ≥730) at the time of the data cut. Twenty patients completed month 24, three discontinued (MFD and allo-HSCT), nine patients had most recent visits ranging from month 9 to month 21.
[b] A subject is month 24 evaluable if he satisfies any of the following: completed the month 24 visit in the first allo-HSCT period within the protocol-defined visit window; was followed for at least 730 days; or discontinued study for reasons other than study termination or was lost to follow-up and would have been followed for at least 730 days at data cut if still in study.
[c] Deaths and MFDs are considered events.

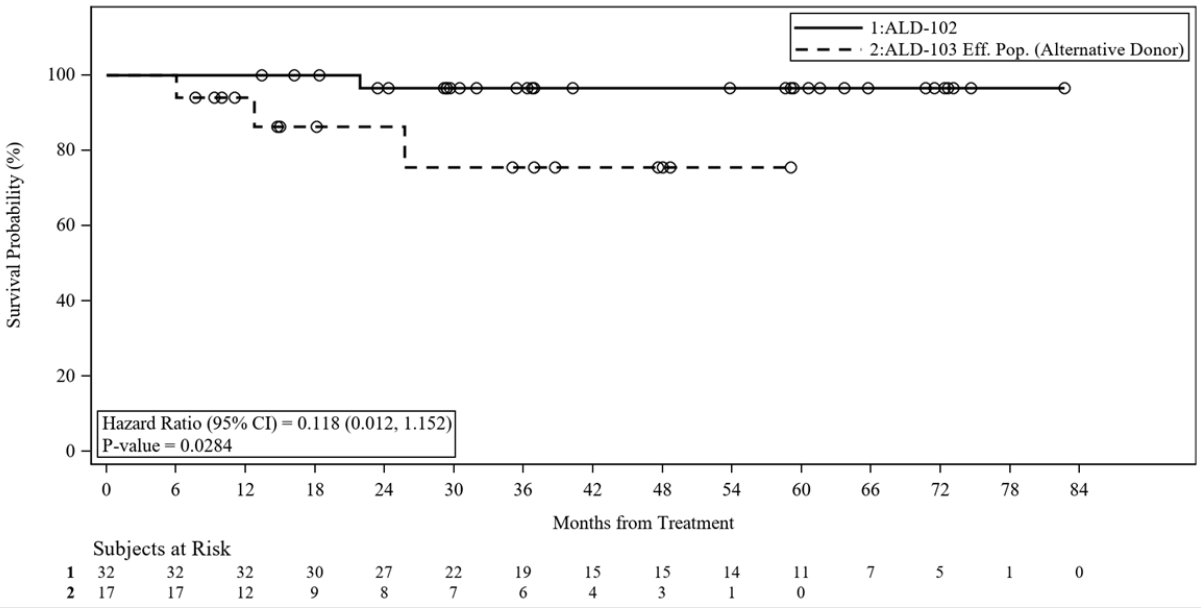

Figure 4.1. Overall survival in ALD-102 and ALD-103 TPES-population NMSD

Source: bluebird bio, Inc. TLFs ALD Inter-Study D120 MAA.
Estimates of overall survival rates were obtained using the Kaplan-Meier method, where the event was death from all causes. 'o' represents censoring. The hazard ratio (95%CI) is based on a Cox regression model, and the p-value is based on the log-rank test.

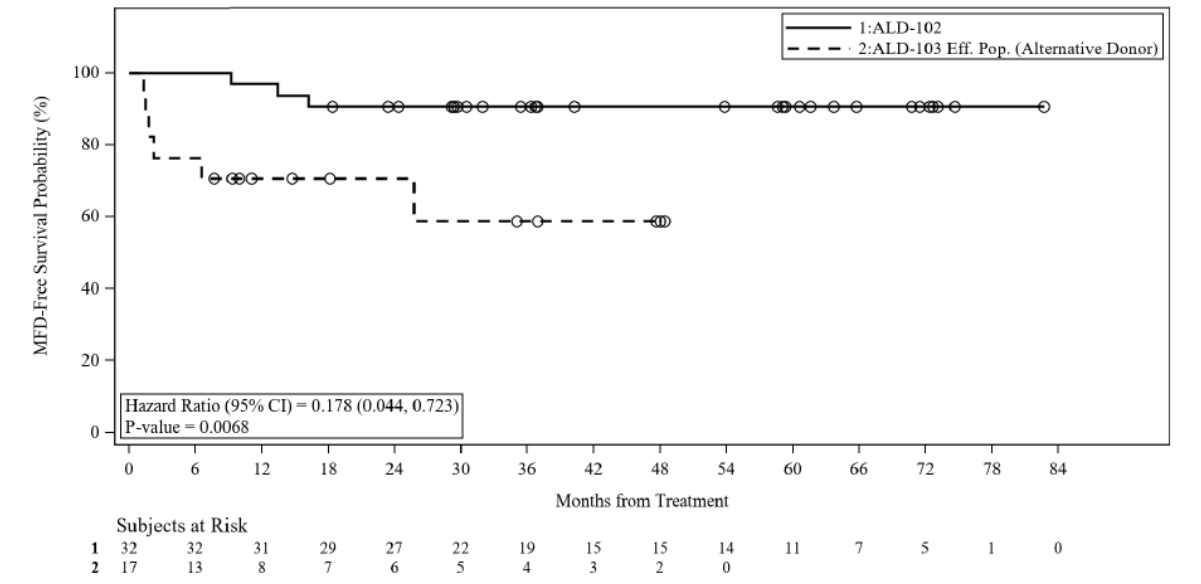

Figure 4.2. MFD-free survival in ALD-102 and in ALD-103 TPES NMSD

Source: bluebird bio Inc. TLFs ALD Inter-Study D120 MAA.
Estimates of MFD-free survival time were obtained using the Kaplan-Meier method, where events included deaths, MFDs, and rescue cell administration or second allo-HSCT. 'o' represents censoring. The hazard ratio (95%CI) is based on a Cox regression model, and the p-value is based on the log-rank test.

As of 2 November 2020, after a median follow-up of 58.6 months (range 23.4-82.7), 26 out of 27 patients (96.3%) who enrolled in the LTF-304 study remained alive and MFD-free after a median follow-up of 58.6 months (range 31.9 to 70.7). One patient refused further follow-up.

4.8.2 Disease parameters

NFS, Loes score, and gadolinium enhancement status for ALD-102 (TP) and ALD-103 (TPES and TP) are shown in Table 4.10.

As of 23 October 2020, in ALD-102, 27 of 28 evaluable patients (96.4%; 95%CI: 81.7 to 99.9) who had been treated with eli-cel had a stable NFS score at month 24, which was comparable to the NFS in the ALD-103 TPES population (12/12 were stable; 100%; 95%CI: 73.5 to 100.0).

The proportion of subjects with a stable Loes score at month 24 was lower in eli-cel study ALD-102 (21/27 were stable; 77.8%; 95%CI: 57.7 to 91.4), compared to 12 of 13 evaluable subjects (92.3%; 95%CI: 64.0 to 99.8) treated with allo-HSCT in the ALD-103 TPES population.

Also, fewer patients in ALD-102 were GdE^- at month 24 (23/27, 85.2%; 95%CI: 66.3 to 95.8), versus 13 out of 13 evaluable patients (100%, 95%CI: 75.3 to 100.0) in the ALD-103 TPES population.

Table 4.10. Summary of NFS, LOES score, and GdE status: indirect comparisons of eli-cel versus allo-HSCT in ALD-102 (data cut-off 23 October 2020) and ALD-103 TPES/TP population

Study reference/ID	Eli-cel	Allo-HSCT	
	TP-102	TPES-103	TP-103
N	**32**	**27**	**59**
NFS at month 24			
Evaluable subjects 0, n(%) 1, n(%) >1 to ≤4, n(%) >4, n(%)	28 24 (85.7) 2 (7.1) 1 (3.6) 1 (3.6)	12 11 (91.7) 1 (8.3) 0 0	26 17 (65.4) 6 (23.1) 2 (7.7) 1 (3.8)
NFS change from baseline to month 24[a]			
Decreased, n(%) No change, n(%) Increased ≤3, n(%) Increased >3, n(%)	0 24 (85.7) 3 (10.7) 1 (3.6)	0 11 (91.7) 1 (8.3) 0	1 (3.8) 17 (65.4) 6 (23.1) 2 (7.7)
Stable NFS at month 24[b]			
Evaluable subjects n (%) 95% CI	28 27 (96.4) 81.7 to 99.9	12 12 (100.0) 73.5 to 100.0	26 24 (92.3) 74.9 to 99.1
Loes score at month 24[c]			
Evaluable subjects Median Min, max	27 5.00 2.00 to 11.00	13 2.00 0.0 to 15.0	26 2.00 0.0 to 17.0
Loes score change from baseline to month 24[c]			
Decreased, n(%) No change, n(%) Increased ≤6, n(%) Increased >6, n(%)	0 5 (18.5) 14 (51.9) 8 (29.6)	4 (30.8) 1 (7.7) 7 (53.8) 1 (7.7)	6 (23.1) 7 (26.9) 11 (42.3) 2 (7.7)
Stable Loes score at month 24[d]			
Evaluable subjects n (%) 95% CI	27 21 (77.8) 57.7 to 91.4	13 12 (92.3) 64.0 to 99.8	26 21 (80.8) 60.6 to 93.4
Subjects who were GdE$^-$ at month 24[e]			
Evaluable subjects n (%) 95%CI	27 23 (85.2) 66.3 to 95.8	13 13 (100) 75.3 to 100.0	24 24 (100.0) 85.8 to 100.0

Source: bluebird bio, Inc. TLFs ALD-102 D120 MA. bluebird bio, Inc. interim clinical study report ALD-103.
Abbreviations: CI=confidence interval; GdE=Gadolinium enhancement. NFS=neurologic function score; NR=not reported; TP=transplant population; TPES=strictly ALD-102 eligible transplant population.
[a] The analysis is based on subjects who have available baseline and month 24 assessments.
[b] Stable NFS at month 24 is defined as maintaining a NFS ≤4 without an increase of >3 points from baseline.
[c] The analysis is based on subjects who have completed the month 24 visit or would have reached the month 24 visit if still in the study at the time of data cut.
[d] Stable Loes score at month 24 is defined as either maintaining a Loes score ≤9 or not increasing a Loes score by ≥6 points from baseline.
[e] Evaluable subjects are subjects who have completed the month 24 Visit GdE assessment.

As of the 2nd November 2020, the following results from LTF-304 were available:

- 16/19 evaluable patients (84.2%; 95% CI 60.4 to 96.6) had a stable Loes score relative to their last assessment, meaning they maintained a Loes score ≤9 or had not increased their Loes score by ≥6 points from baseline;
- 23/27 patients (85.2%) who enrolled in the study had no change in NFS between ALD-102 baseline and their last assessment. Four patients (14.8%) had an increase in NFS of ≤3 between ALD-102 baseline and last follow-up visit. Data were available for 26 patients at month 24, 20 at month 36, 14 at month 48, 14 at month 60, and 7 at year 6;

- 16 out of 19 evaluable patients beyond months 24 (84.2%, 95% CI 60.4 to 96.6) were GdE negative at their last assessment. Data were available for 26 patients at month 24, 19 at month 36, 14 at month 48, and 13 at month 60.

4.8.3 Quality of life

In ALD-102, the median PedsQL total scale score at baseline (n=29) was 88.04 (range 39.1 to 100.0). As of 23rd October 2020, this score decreased from baseline to month 24 by a median of 4.66 points (range -44.6–31.5) in 23 evaluable patients; for a full summary, see Submission Dossier, p. 82.

In ALD-103, the median PedsQL total scale score at baseline (n=10) was 86.53 (range 37.0 to 100.0). Serial values up to month 24 were only available for two patients, for whom the PedsQL total scale score increased by a median of 11.67 points (range 16.0 to 17.4).

4.8.4 Adverse events

Neutrophil and platelet engraftment (failure), incidence of GVHD, and subsequent allo-HSCT for ALD-102 (TP), pooled ALD-102/104 (TP), and ALD-103 (TPES NMSD) are shown in Table 4.11.

As of 23rd October 2020, all evaluable subjects treated with eli-cel in ALD-102 had successful neutrophil and platelet engraftment at month 24. The median time to neutrophil and platelet engraftment was 13.0 (range 11.0 to 41.0) and 32.0 (range 16.0 to 60.0) days, respectively. This was similar to the 19 subjects treated with eli-cel in ALD-104, with a median time to neutrophil and platelet recovery of 13.0 (range 12.0 to 31.0) and 29.0 (14.0 to 108.0) days, respectively. Platelet engraftment was also seen in all evaluable subjects treated with allo-HSCT from an NMSD in ALD-103 (median time 23.5, range 18 to 61). The proportion of subjects with neutrophil engraftment was lower in ALD-103 NMSD; seven out of 12 evaluable subjects had primary or secondary neutrophil engraftment failure (58.3%; 95%CI: 27.7 to 84.8). In ALD-102, two subjects had a serious reaction of pancytopenia following neutrophil engraftment approximately two months after eli-cel infusion. These reactions were considered as possibly related to eli-cel. Both patients had delayed hematopoietic reconstitution requiring prolonged support including G-CSF (n=2), platelet infusion (n=2), eltrombopag (n=2, ongoing as of February 2020), packed red blood cell transfusions (n=2), and intravenous immunoglobulin (n=1). One patient had intercurrent parvovirus infection. Both events were ongoing at least 18 months after eli-cel infusion.

None of the 32 patients treated with eli-cel experienced acute or chronic GVHD, while seven out of 14 evaluable subjects (50.0%; 95%CI: 23.0 to 77.0) from ALD-103 TPES who received an allo-HSCT from an NMSD developed GVHD.

Subsequent allo-HSCT treatment occurred in two out of 32 subjects in ALD-102 (6.3%; 95%CI: 0.8 to 20.8), whereas six out of 17 evaluable patients (35.3; 95%CI: 14.2 to 61.7) treated with allo-HSCT from a NMSD in ALD-103 TPES required subsequent allo-HSCT.

Table 4.11. Summary of engraftment (failure), GVHD, and subsequent allo-HSCT results: indirect comparisons of eli-cel versus allo-HSCT in ALD-102/104 (data cut-off 23rd October 2020) and ALD-103 TPES NMSD population

Study reference/ID	Eli-cel		Allo-HSCT
	TP-102	TP-102/TP-104	TPES-103 NMSD
N	**32**	**51**	**17**
Neutrophil engraftment by relative day 43			
Evaluable subjects[a] n (%) 95%CI	32 32 (100.0) 89.1 to 100.0	49 49 (100.0) 92.7 to 100.0	17 13 (76.5) 50.1 to 93.2
Secondary neutrophil engraftment failure by month 24			
Evaluable subjects[b,c] n (%) 95%CI	27 0 (0) 0.0 to 12.8	27 0 (0) 0.0 to 12.8	8 3 (37.5) 8.5 to 75.5
Neutrophil engraftment failure (primary or secondary) by month 24			
Evaluable subjects[c] n (%) 95%CI	27 0 0.0 to 12.8	27 0 0 to 12.8	12 7 (58.3) 27.7 to 84.8
Platelet engraftment			
Evaluable subjects n (%) 95%CI	32 32 (100.0) 89.1 to 100.0	47 47 (100.0) 92.5 to 100.0	12 12 (100.0) 73.5 to 100.0
Acute graft versus host disease (≥ grade II) by month 24			
Evaluable subjects n (%) 95%CI	32 0 (0) 0.0 to 10.9	NR	13 4 (30.8) 9.1 to 61.4
Chronic graft versus host disease by month 24			
Evaluable subjects n (%) 95%CI	32 0 (0) 0.0 to 10.9	NR	12 5 (41.7) 15.2 to 72.3
Acute or chronic graft versus host disease by month 24			
Evaluable subjects n (%) 95%CI	32 0 (0) 0.0 to 10.9	NR	14 7 (50.0) 23.0 to 77.0
Subsequent allo-HSCT[d]			
Evaluable subjects n (%) 95%CI	32 2 (6.3) 0.8 to 20.8	NR	17 6 (35.3) 14.2 to 61.7

Source: bluebird bio, Inc. TLFs ALD Inter-Study D120 MAA.
[a] Evaluable subjects included those who had NE or had been followed to at least relative day 43.
[b] Evaluable subjects included those who achieved NE and either had secondary engraftment failure or had been followed for at least 24 months if no events.
[c] Results are available for 27 patients enrolled in LTF-304 from ALD-102; this is not the fully trial population, as the LTF-304 trial is still enrolling.
[d] Evaluable subjects were defined as those who have had subsequent allo-HSCT or rescue cell administration by month 24 (relative day 730 or completed month 24 visit) or last follow-up, respectively, or have been followed to at least relative day 730 or until last follow-up, respectively, if no subsequent allo-HSCT yet. Relative day 1 is the day of eli-cel infusion for TP-102 and TP-304 and the day of the 1st allo-HSCT infusion in TPES-103 (NMSD).
[e] Time to subsequent allo-HSCT was not reported as part of the endpoints in the eli-cel clinical development program, so timepoint of study withdrawal was taken as a proxy.
Abbreviations: allo-HSCT=allogeneic haematopoietic stem cell transplantation; CI=confidence interval; MSD=matched sibling donor; n=number of patients with (at least one) event; N=number of patients in population; NMSD=not a matched sibling donor; TP=transplant population; TPES=strictly ALD-102-eligible transplant population.

While there is a theoretical risk of insertional oncogenesis (e.g., myelodysplasia, leukaemia, lymphoma) after eli-cel treatment, no events were noted. The EPAR stated that clonal expansion resulting in clonal predominance without clinical evidence of malignancy was detected in two patients treated with eli-cel. Therefore, patients should be monitored at least annually for myelodysplasia, leukaemia, or lymphoma (including a complete blood count) for 15 years after treatment with eli-cel. If myelodysplasia, leukaemia,

or lymphoma is detected in a patient who received eli-cel, blood samples should be collected for integration site analysis.

4.8.5 Overall adverse events

As of 23 October 2020, none of the reported AEs (excluding deaths) led to discontinuation of the studies. Most AEs related to eli-cel administration were consistent with those associated with mobilisation and myeloablative conditioning performed for HSCT and resolved with standard measures.

Serious adverse events (SAEs) were less frequent in the eli-cel (TP-102/104: 58.8%) than the allo-HSCT group (TP-103:7 2.9% and TPES-103: 63.0%). SAEs occurring in >5% of patients and reported more frequently in the eli-cel (ALD-102/104) vs. allo-HSCT (TP-103) group were: febrile neutropenia (23.5% vs. 6.8%), pyrexia (19.6% vs. 5.1%), and seizures (5.9% vs. 3.4%). SAEs occurring in >5% of patients and reported less frequently in the eli-cel (ALD-102/104) vs. allo-HSCT (TP-103) group were: device-related infection (3.9% vs. 6.8%), BK virus infection (0% vs. 5.1%), bacteraemia (0% vs. 5.1%), staphylococcal infection (0% vs. 5.1%), and neurological decompensation (2.0% vs. 10.2%).

Five of 51 patients (9.8%) in TP-102/104 experienced AEs that were potentially related to eli-cel, of which three (5.9%) were SAEs: BK-mediated viral cystitis (TP-102) and two cases of pancytopenia (TP-104). In ALD-103 study grade ≥3 SAEs related to allo-HSC infusion were experienced by 12 (20.3%) TP and four (14.8%) TPES patients.

No treatment-related mortality with eli-cel was reported. In ALD-103, eight (13.6%) patients died from treatment-related causes within one year of allo-HSCT. All treatment-related deaths resulted from allo-HSCT transplantation and occurred in patients who lacked an MSD (NMSD: n=48, one-year transplant-related mortality (TRM) 22.2%). The TPES was noted to have lower incidence of TRM and lower overall incidence of death than the TP. In the TPES (NMSD) population, TRM was observed in one patient (9.1%). The MAH estimated that eli-cel reduces the risk of death by 88.2% compared to the TPES-103 (NMSD) population[3]. No deaths or new AEs related to eli-cel were reported in LTF-304 up to the cut-off date for the interim analysis.

No deaths or new AEs related to eli-cel were reported in LTF-304 up to the cut-off date for the interim analysis.

Table 4.12 outlines the AEs observed in the eli-cel clinical development programme and allo-HSCT cohort. Detailed information on the AEs per standard-of-care are provided in Appendix 4.

A summary of the evidence is provided in Table 4.13.

[3] Hazard ratio 0.118 (95%CI: 0.012, 1.152). The hazard ratio of TP-102 vs. other analysis populations is based on a Cox regression model.

Table 4.12. Adverse events: overview of indirect comparisons of eli-cel versus allo-HSCT in ALD-102/104 (data cut-off 23rd October 2020), LTF-304 (data cut-off 2nd November 2020) and ALD-103 TPE and TPES NMSD populations

Intervention	Eli-cel				Allo-HSCT		
Study reference/ID	TP-102	TP-104	TP-102/ TP-104	LTF-304	TP-103	TPES-103	TPES-103 NMSD
Adverse events[a]	N=32	N=19	N=51	N=27	N=59	N=27	N=17
Total adverse events, n (%)	32 (100)	18 (90.0)	50 (98.0)	27 (100.0)	55 (93.2)[b]	25 (92.6)[b]	NR
Total adverse events related to therapy, n (%)	3 (9.4)[c]	2 (10.5)[c]	5 (9.8)[c]	3 (11.1)[c]	NR[d]	NR[d]	NR
Total serious adverse events n (%)	21 (65.6)	9 (47.4)	30 (58.8)	17 (63.0)	43 (72.9)	17 (63.0)	NR
Total serious adverse events related to therapy, n (%)	1 (3.1)	2 (10.5)	3 (5.9)	1 (3.7)[e]	12 (20.3) [f]	4 (14.8)[f]	NR
Total adverse events grade ≥3	30 (93.8)	18 (90.0)	48 (94.7)	26 (96.3)	55 (93.2)	25 (92.6)	NR
Total adverse events grade ≥3 related to therapy	1 (3.1)	2 (10.5)	3 (5.9)	1 (3.7)[e]	18 (30.5)	7 (25.9)	NR
Treatment-related mortality[g]	0 (0)	0 (0)	0 (0)	0 (0)	8 (13.6)	1 (5.0)[h]	1 (9.1)
Total deaths n (%)	1 (3.1)	0 (0)	1 (2.0)	0 (0)	15 (25.4)	3 (11.1)	3 (17.6)
Discontinuation due to AE (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Source: bluebird bio, Inc. TLFs ALD Inter-Study D120 MAA, bluebird bio, Inc. LTF-304 D120 MAA.
[a] At least 1 AE.
[b] All AEs recorded in study ALD-103 were, by definition, grade 3 or higher treatment-emergent AEs (TEAEs), defined as AEs occurring at or after the initiation of allo-HSC infusion.
[c] AEs related to eli-cel.
[d] Overall AEs related to allo-HSCT was not reported; data are shown for subjects with at least 1 grade ≥ 3 TEAE related to allo-HSC infusion and subjects with TEAEs attributed to allo-HSC infusion, conditioning, or immunosuppression secondary to drugs for post-transplant management.
[e] SAEs reported in LTF-304 are the same as the SAEs reported in ALD-102.
[f] Number of patients with at least 1 grade ≥3 SAE related to allo-HSC infusion.
[g] For ALD-103, treatment-related mortality was synonymous with transplant-related mortality within 365 days after allo-HSC infusion.
[h] Evaluable subjects n=20.
Abbreviations: AE=adverse event, NMSD=not a matched sibling donor, NR=not reported, TP=transplant population, TPES= strictly ALD-102 eligible transplant population.

Table 4.13. Evidence table*

Outcome	Design	Factors that may affect certainty of evidence					Eli-cel		Allo-HSCT		Comparison
		Risk of Bias[c]	Indirectness	Inconsistency	Imprecision	Other	Study; number of patients	n events/n evaluable patients (%; 95%CI)	Study; number of patients	n events/n evaluable patients (%; 95%CI)	Effect estimate (95%CI); P-value
OS at month 24	⅄	C	▲	★	★✶	COI	TP-102; N=32	31/32 (96.6; 77.9 to 99.5)	TPES-103 NMSD; N=17	n=14/17 (86.3; 54.7 to 96.5)	HR: 0.118 (0.012 to 1.152); P=0.0285[d]
MFD-free survival at month 24[a]								n=27/30 (90.0; 73.5 to 97.9)		n=6/9 (66.7; 29.9 to 92.5)	HR: 0.178 (0.044 to 0.73); P=0.0068[d]
Stable NFS at month 24	⅄	C	▲+	★	★✶	COI	TP-102; N=32	n=27/28 (96.4; 81.7 to 99.9)	TPES-103[e]; N=27	n=12/12 (100.0; 73.5 to 100.0)	NC
Stable LOES score at month 24								n=21/27 (77.8; 57.7 to 91.4)		n=12/13 (92.3; 64.0 to 99.8)	NC
GdE$^-$ at month 24								n=23/27 (85.2; 66.3 to 95.8)		n=13/13 (100; 75.3 to 100.0)	NC
Change in PedsQL by month 24	⅄	C	▲+	★	★	COI	TP-102; n/N=23/32	-4.66 points (range -44.6 to 31.5)	TP-103[e]; n=2/59	11.67 points (range 16.0 to 17.4)	NC
Neutrophil engraftment failure (primary or secondary) by month 24	⅄	C	▲	★	★✶	COI	TP-102/TP-104, N=51	n=0/27 (0; 0 to 12.8)	TPES-103 NMSD; N=17	n=7/12 (58.3; 27.7 to 84.8)	NC
Platelet engraftment							TP-102/TP-104, N=51	n=47/47 (100.0; 92.5 to 100.0		n=12/12 (100.0; 73.5 to 100.0)	NC
Acute or chronic graft versus host disease by month 24	⅄	C	▲	★	★	COI	TP-102; N=32	n=0/32 (0; 0.0 to 10.9)	TPES-103 NMSD; N=17	n=7/14 (50.0; 23.0 to 77.0)	NC
Subsequent allo-HSCT	⅄	C	▲	★	★✶	COI	TP-102; N=32	n=2/32 (6.3; 0.8 to 20.8)	TPES-103 NMSD; N=17	n=6/17 (35.3; 14.2 to 61.7)	NC

Outcome	Design	Factors that may affect certainty of evidence					Eli-cel		Allo-HSCT		Comparison
		Risk of Bias[c]	Indirectness	Inconsistency	Imprecision	Other	Study; number of patients	n events/n evaluable patients (%; 95%CI)	Study; number of patients	n events/n evaluable patients (%; 95%CI)	Effect estimate (95%CI); P-value
Adverse events (AEs) grade ≥3	⅄	C	▲+	★	★	COI	TP-102/TP-104, N=51	Total: 48/51 (94.1) Related to eli-cel: 3 (5.9)	TPES-103[e]; N=27[b]	Total: 25/27 (92.6) Related to allo-HSCT: 7/27 (25.9)	NC
									TP[e]; N=59[b]	Total: 55/59 (93.2) Related to allo-HSCT: 18/59 (30.5)	NC
Discontinuations due to treatment-related AEs	⅄	C	▲	★	★	COI	TP-102/TP-104, N=51	n=0/51 (0)	TPES-103[e]; N=27[b]	n=0/27 (0)	NC

* Following partial use of GRADE recommendations by EUnetHTA [6, 7].
[a.] No MFD, alive, not withdrawn or lost to FU, no rescue eli-cel, no allo-HSCT.
[b.] First allo-HSCT period.
[c.] See risk of bias assessment in Section 4.6.
[d.] Derived from Kaplan-Meier analysis. Hazard ratio (95%CI) based on Cox regression model, and p-value based on log-rank test.
[e.] Results were not reported per donor type.
⅄ Open-label, multi-centre, single arm trial versus retrospective and prospective, data collection study.
▲ Eli-cel was indirectly compared to allo-HSCT.
+ Partially not focused population (patients with MSD).
* Only one comparison.
★ Small numbers and interim analysis data. No pre-planned propensity score analyses.
* Overlapping confidence intervals.
Note: The TP of ALD-103 is identical to the ITT population and includes 59 patients who received allo-HSCT. The TPES is defined to strictly align with ALD-102 eligibility criteria: TPES subjects are TP patients who at baseline had NFS ≤1, Loes score ≥ 0.5 and ≤ 9, and GdE+.
Abbreviations: allo-HSCT=allogeneic haematopoietic allogenic stem cell transplant; C=critical; COI=conflict of interest; eli-cel=elivaldogene autotemcel; HR=hazard ratio; NA=not applicable; NC=not computable; PedsQL=Paediatric Quality of Life Inventory; TP=transplant population; TPE=ALD-102-eligible transplant population; TPES=strictly ALD-102-eligible transplant population; TPG=GdE+ transplant population.

5 PATIENT INVOLVEMENT

Groups and individuals who produce HTAs recognise that patients and those who support them have unique knowledge about what it is like to live with a specific disease or medical condition. Patients can help to understand unique perspectives by presenting patients' and carers/caregivers' views and experiences. Patients can describe the advantages and disadvantages of health interventions based on patients' experiences and values of a new intervention [61].

The open call for patient involvement in this assessment was online on the EUnetHTA website from 19th October to 15th December 2020. Three patient organisations completed the survey, namely ELA Deutschland e.V. (Germany), ELA-España European Leukodystrophy Association (Spain), and AIALD ONLUS (Italy).

In addition, on the 12th February 2021, the mother of a deceased child who suffered from CALD was interviewed for an hour online to gain input regarding the impact of CALD on patients' QoL and the current standard-of-care. The child, a boy, was born in 1988 after a difficult pregnancy. First symptoms occurred at age six. Over the following two years he visited many doctors (psychologists, psychiatrists, paediatricians) before the diagnosis CALD was established by a paediatric neurologist when he was almost eight years old. He was prescribed hydrocortisone, to which he responded well. He underwent an experimental therapy with immunoglobulins, but this had no effect on the disease. He did not receive stem cell transplantation. He died in 1999, at age 10.

5.1 Main results

Answers from patient organisations and the mother were consistent with each other. Both indicated that CALD is a terrible disease with a huge impact on the QoL of both patients and their families. They indicated that early diagnosis is crucial to benefit from treatment. They noted that there is still a lack of treatments that improve the course of the disease and QoL of affected patients. Current treatments were described as stressful and complicated, and the challenge in finding a matching donor before the disease became too far advanced was highlighted. Gene therapy for CALD represents a hope for affected patients because it avoids waiting for a compatible donor and GVHD.

The summary of the most important answers related to different questions on the impact of condition; experience with currently available medicines; expectations of the medicines being assessed; and additional information which the patient (or patient's carer/patient organisation) believed would be helpful to the HTA researchers are provided in Table A1.

6 DISCUSSION

This assessment compared eli-cel with allo-HSCT for the treatment of early CALD in patients under 18 years of age, with an *ABCD1* mutation, and for whom an HLA-matched sibling HSC donor was not available.

The available evidence was limited, i.e., only indirect comparisons of eli-cel with allo-HSCT for the treatment of early CALD. Any effectiveness evidence that could be used for comparative analysis of best supportive care, which consists of various treatments for symptom relief, was lacking. Nevertheless, according to consensus guidelines for ALD/CALD, management with allo-HSCT is currently the only disease-modifying treatment available for CALD patients. The available evidence on the comparison of eli-cel versus allo-HSCT is summarised below.

The assessment was based on studies from the eli-cel programme and consisted of five studies:

- Two completed observational data collection studies investigating disease progression/outcomes and the effectiveness and safety of allo-HSCT: ALD-101 [52] and ALD-103 [56];
- Two ongoing interventional single-arm studies investigating the effectiveness and safety of the eli-cel-treatment: ALD-102 (according to submission dossier study completion was expected in May 2021) and ALD-104 (expected completion in February 2024);
- One observational long-term follow-up study that enrolled patients from parent studies ALD-102 and ALD-104 after completion of the 24-month follow-up period: LTF-304 (expected completion in May 2037) [59].

Most of the outcomes deemed relevant for this assessment were covered within these five studies. However, whereas outcome data for ALD-101, ALD-102 and ALD-103 is available, the vast majority of outcome data from ALD-104 is not available to date and no or incomplete results (covering only ALD-102 patients) are available for outcomes from LTF-304.The MAH additionally conducted a systematic literature search for studies investigating the comparator intervention. They identified 26 studies, but these were not included in this assessment because all but two failed to not list baseline characteristics in sufficient detail. Also, the two remaining studies had to be excluded because they did not perform separate analyses for patients who were strictly eligible to the ALD-102 population (see Section 4.3).

Therefore, this assessment is mainly based on results from TP ALD-102 (and where possible ALD-104 and LTF-304) for eli-cel and ALD-103 (preferably the TPES NMSD subpopulation) for allo-HSCT. Furthermore, results for the TPES MSD population are reported to support a conservative comparison between eli-cel and allo-HSCT, since this is currently the best available therapy and analysed numbers for allo-HSCT from an NMSD are small. The main results on clinical effectiveness and safety for eli-cel and allo-HSCT from the most recent cut-off dates can be summarised naively as follows, as no adjusted indirect comparison was available:

- The Kaplan-Meier estimate for overall survival rate at 48 months was 96.6% (95%CI: 77.9 to 99.5; n=32; ALD-102) for eli-cel, higher than that for NMSD allo-HSCT (75.5%, 95%CI: 39.7 to 91.8; n=17, ALD-103 TPES) and NMSD allo-HSCT (74.1%, 95%CI: 28.9 to 93.0; n=10, ALD-103 TPES);
- The MFD-free survival rate at 24 months was 90.0% (95%CI 73.5 to 97.9; n=30; ALD-102) for eli-cel, higher than for NMSD allo-HSCT (66.7%, 95%CI: 29.9 to 92.5; n=9; TPES ALD-103) but comparable to MSD allo-HSCT (88.9%, 95%CI: 51.8 to 99.7; n=9; TPES ALD-103);
- 96.4% (95%CI: 81.7 to 99.9; n=28; ALD-102) of patients receiving eli-cel had a stable NFS at 24 months, comparable to 100% (95%CI: 73.5 to 100.0; n=12; TPES ALD-103) for allo-HSCT from any donor. 77.8% (95%CI: 57.7 to 91.4; n=27; ALD-102) of patients receiving eli-cel had a stable Loes score at 24 months, lower than the 92.3% (95%CI: 64.0 to 99.8; n=13; TPES ALD-103) observed for allo-HSCT from any donor type. Similarly, 85.2% (95%CI: 66.3 to 95.8; n=27; ALD-102) of patients receiving eli-cel were GdE^- at 24 months compared to 100% (95%CI: NR; n=13; TPES-ALD-103) for allo-HSCT from any donor type;

- Of the 27 patients enrolled in LTF-304, 26 (96.3%) remained alive and MFD-free after a median follow-up of 58.6 months (range 23.4-82.7);
- Neutrophil and platelet engraftment were successful at month 24 in all evaluable patients treated with eli-cel in ALD-102 and ALD-104. Platelet engraftment was also seen in all evaluable patients treated with NMSD allo-HSCT in ALD-103. The proportion of NMSD allo-HSCT patients with neutrophil engraftment was lower in ALD-103; seven out of twelve evaluable patients had primary or secondary neutrophil engraftment failure (58.3%; 95%CI: 27.7 to 84.8);
- None of the 32 patients treated with eli-cel experienced acute or chronic GVHD in ALD-102, while seven out of 14 (50.0%; 95%CI: 23.0 to 77.0) evaluable TPES patients in ALD-103 receiving an NMSD allo-HSCT developed GVHD;
- Two out of 32 eli-cel patients in ALD-102 (6.3%; 95%CI: 0.8 to 20.8) required subsequent allo-HSCT compared to six out of 17 (35.3%; 95%CI: 14.2 to 61.7) evaluable TPES patients in ALD-103 receiving an NMSD allo-HSCT;
- Five out of 51 patients (9.8%) in TP-102/104 experienced AEs potentially related to eli-cel therapy, of whom three (5.9%) experienced serious AEs (SAEs): BK-mediated viral cystitis (TP ALD-102) and two cases of pancytopenia (TP-103). In ALD-103 study grade ≥3 SAEs related to allo-HSC infusion were reported for 12 (20.3%) TP and four (14.8%) TPES patients. None of the reported AEs led to discontinuation of the studies;
- No treatment-related mortality with eli-cel has been reported. In ALD-103, eight (13.6%) of 59 patients died from treatment-related causes within one year of allo-HSCT. All deaths occurred in patients who lacked an MSD (one-year transplant-related mortality (TRM), 22.2%). In the TPES (NMSD) population, TRM frequency was lower and was observed in one patient (9.1%);
- Treatment with eli-cel carries a theoretical risk of insertional oncogenesis (e.g., myelodysplasia, leukaemia, lymphoma), but no insertional oncogenesis events were reported. Clonal expansion resulting in clonal predominance without clinical evidence of malignancy was detected in some patients treated with eli-cel;
- No additional AEs related to eli-cel were reported in LTF-304 up to the cut-off date for the interim analysis.

The evidence on the estimates of effects of eli-cel have severe limitations:

- Eli-cel was studied in open-label, single-arm trials and effects of eli-cel were indirectly compared with allo-HSCT studied in mixed retrospective and prospective data collection studies. The risk of bias for all studies was considered critical, e.g., the study design could not rule out confounding and there was a large amount of missing data. Several additional issues were flagged in the risk of bias and partial GRADE assessments including applicability concern regarding study population (indirectness), small numbers, interim analyses, overlapping CIs (imprecision), no pre-planned propensity score analyses, and conflicts of interest;
- Results were based on available data, and no intention-to-treat analyses were performed. The EPAR [8] states that sensitivity analyses were performed for MFD-free survival, where in TP-102 non-evaluable patients were considered as having a negative outcome and in TPES-103 missing data were imputed as a success for the selected primary and secondary efficacy endpoints. The sensitivity analysis using the most conservative imputation approach did not change the conclusions of the main analysis for these parameters performed on non-missing observations. Nevertheless, the effect estimates were sensitive and prone to bias with increasing rates of missing data and should be interpreted cautiously [8]. The EMA informed the Authoring Team that sensitivity analyses were also performed for other outcomes but similarly they did not change the conclusions drawn from the main analysis;
- Different myeloablative conditioning treatments were used in the studies. In ALD-102, busulfan with cyclophosphamide was used, whereas the conditioning regimen in ALD-104 consists of busulfan with fludarabine as the lymphodepletion agent. It should be noted that the best choice of conditioning treatment is still unknown for this indication;

- Data on change in HRQoL (a critical outcome) could only be collected from two patients in ALD-103, so a comparison with ALD-102 was not feasible. Data on time to subsequent allo-HSCT were not reported;
- To date, eli-cel studies are still ongoing and the results are based on interim analyses. Longer term follow-up data are needed. These data are expected from ALD-102 (according to submission dossier study completion was expected in May 2021), ALD-104 (expected completion February 2024), and LTF-304 (expected completion May 2037). The post-authorisation efficacy/safety study REG-502 will follow eli-cel treated patients for up to 15 years after treatment.

Despite the limitations outlined above, the EMA accepted the comparison for the following reasons: the rarity of the disease, the severity and fast progression of the disease, the limited treatment options, the inability of transplants to be blinded, and the potential impact of time required to identify a donor match on cerebral disease progression. However, further data on long-term effectiveness and safety are needed and requested [8].

Due to the limitations of the body of the evidence provided, the Authoring Team have proposed recommendations for further research, which can be found in Table A2 of Appendix 3.

Apart from discussion of the available clinical data, it is important to highlight potential issues with the implementation of eli-cel treatment. As stated in the Submission Dossier, manufacturing of eli-cel is centralised at one site for European patients [Minaris Regenerative Medicine (previously known as Apceth Biopharma), Munich, Germany]. Treatment can be given only at specialised care centres. Significant distances between the manufacturing site and treatment centres may influence the rate of successfully infused patients (and has impact on costs, especially as specific storage conditions are required). Future studies must gather data on reasons for non-infusion of the product that may be clinical (e.g., unsuccessful conditioning), practical (e.g., various problems during manufacturing or transport), or both.

7 CONCLUSION

There was only limited evidence to compare eli-cel and allo-HSCT in the population of patients without an MSD (the population of interest). Analysis was based on a naive comparison only; no adjusted indirect comparison was possible. Results from interim analyses suggested that overall survival rate and the MFD-free survival rate were higher for eli-cel than allo-HSCT for patients with an NMSD. No data were available on NFS, Loes score, and GdE status for the TPES NMSD population. Stable NFS rates were comparable between eli-cel and allo-HSCT from any donor type, while stable Loes score and GdE^- rates were lower for eli-cel than allo-HSCT from any donor type. Comparison of HRQoL was not feasible as a too low number of patients contributed to this outcome.

No treatment-related mortality with eli-cel was reported up to the cut-off date for the interim analysis, whereas in the TPES NMSD allo-HSCT population, one out of 17 patients died. Most AEs associated with eli-cel administration were consistent with those associated with mobilisation and myeloablative conditioning performed for allo-HSCT and resolved with standard measures. None of patients treated with eli-cel experienced graft failure or graft rejection, while 58% patients in the TPES NMSD allo-HSCT population did. The risk of insertional oncogenesis with eli-cel should be monitored; while not been reported thus far, clonal expansion resulting in clonal predominance without clinical evidence of malignancy was detected in some patients treated with eli-cel.

The risk of bias for all eli-cel studies was considered critical. Longer-term data on the effectiveness of eli-cel are awaited and needed.

8 REFERENCES

1. Engelen M, Kemp S, de Visser M, van Geel BM, Wanders RJ, Aubourg P, et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. Orphanet J Rare Dis. 2012;7:51.
2. Miller W. Stem cell-transplantation therapy for adrenoleukodystrophy: current perspectives. Neurorestoratology. 2017;5(1):5-19.
3. bluebird bio Inc. EBMT Registry CALD allo-HSCT 2015-2020. Data on file. 2021.
4. Moser H, Loes D, Melhem E, Raymond G, Bezman L, Cox CS, et al. X-Linked adrenoleukodystrophy: overview and prognosis as a function of age and brain magnetic resonance imaging abnormality. A study involving 372 patients. Neuropediatrics. 2000;31(05):227-39.
5. Loes DJ, Hite S, Moser H, Stillman AE, Shapiro E, Lockman L, et al. Adrenoleukodystrophy: a scoring method for brain MR observations. AJNR Am J Neuroradiol. 1994;15(9):1761-6.
6. EUnetHTA. Partial use of GRADE and common phrases 2020 [Available from: https://www.eunethta.eu/grade/.
7. The GRADE Working Group. GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations 2013 [Available from: https://gdt.gradepro.org/app/handbook/handbook.html.
8. European Medicines Agency. Skysona® EPAR 2021 [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/skysona.
9. Engelen M, Salzman R, Kemp S. Facts on ALD 2018 [Available from: https://adrenoleukodystrophy.info/clinical-diagnosis/facts-on-ald.
10. Mahmood A, Raymond GV, Dubey P, Peters C, Moser HW. Survival analysis of haematopoietic cell transplantation for childhood cerebral X-linked adrenoleukodystrophy: a comparison study. The Lancet Neurology. 2007;6(8):687-92.
11. Bezman L, Moser HW. Incidence of X-linked adrenoleukodystrophy and the relative frequency of its phenotypes. Am J Med Genet. 1998;76(5):415-9.
12. Wiesinger C, Eichler FS, Berger J. The genetic landscape of X-linked adrenoleukodystrophy: inheritance, mutations, modifier genes, and diagnosis. Appl Clin Genet. 2015;8:109-21.
13. Horn MA, Retterstol L, Abdelnoor M, Skjeldal OH, Tallaksen CM. Adrenoleukodystrophy in Norway: high rate of de novo mutations and age-dependent penetrance. Pediatr Neurol. 2013;48(3):212-9.
14. Aubourg P, editor X-linked adrenoleukodystrophy. Annales d'endocrinologie; 2007.
15. Moser HW, Mahmood A, Raymond GV. X-linked adrenoleukodystrophy. Nature Clinical Practice Neurology. 2007;3(3):140-51.
16. Eurostat. Fertility statistics 2019. Data extracted March 2021 2021 [Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Fertility_statistics.
17. The Word Bank. Sex ratio at birth (male births per female births) - European Union 2019 2021 [Available from: https://data.worldbank.org/indicator/SP.POP.BRTH.MF?locations=EU.
18. Raymond GV, Aubourg P, Paker A, Escolar M, Fischer A, Blanche S, et al. Survival and Functional Outcomes in Boys with Cerebral Adrenoleukodystrophy with and without Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2019;25(3):538-48.
19. Bessey A, Chilcott JB, Leaviss J, Sutton A. Economic impact of screening for X-linked Adrenoleukodystrophy within a newborn blood spot screening programme. Orphanet J Rare Dis. 2018;13(1):179.
20. AIALD Onlus Associazione Italiana Adrenoleucodistrofia. Health Technology Assessment on drug for CALD answered by the associations of patients. 2020.
21. Mallack EJ, Turk BR, Yan H, Price C, Demetres M, Moser AB, et al. MRI surveillance of boys with X-linked adrenoleukodystrophy identified by newborn screening: Meta-analysis and consensus guidelines. J Inherit Metab Dis. 2021;44(3):728-39.
22. Regelmann MO, Kamboj MK, Miller BS, Nakamoto JM, Sarafoglou K, Shah S, et al. Adrenoleukodystrophy: Guidance for Adrenal Surveillance in Males Identified by Newborn Screen. J Clin Endocrinol Metab. 2018;103(11):4324-31.
23. Hobbs JR, Hugh-Jones K, Barrett AJ, Byrom N, Chambers D, Henry K, et al. Reversal of clinical features of Hurler's disease and biochemical improvement after treatment by bone-marrow transplantation. Lancet. 1981;2(8249):709-12.
24. Pridjian G, Humbert J, Willis J, Shapira E. Presymptomatic late-infantile metachromatic leukodystrophy treated with bone marrow transplantation. J Pediatr. 1994;125(5 Pt 1):755-8.

25. Beam D, Poe MD, Provenzale JM, Szabolcs P, Martin PL, Prasad V, et al. Outcomes of unrelated umbilical cord blood transplantation for X-linked adrenoleukodystrophy. Biol Blood Marrow Transplant. 2007;13(6):665-74.
26. Beckmann NB, Miller WP, Dietrich MS, Orchard PJ. Quality of life among boys with adrenoleukodystrophy following hematopoietic stem cell transplant. Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence. 2018;24(7):986-98.
27. Bladowska J, Kulej D, Biel A, Zimny A, Kalwak K, Owoc-Lempach J, et al. The Role of MR Imaging in the Assessment of Clinical Outcomes in Children with X-Linked Adrenoleukodystrophy after Allogeneic Haematopoietic Stem Cell Transplantation. Pol J Radiol. 2015;80:181-90.
28. Fernandes JF, Bonfim C, Kerbauy FR, Rodrigues M, Esteves I, Silva NH, et al. Haploidentical bone marrow transplantation with post transplant cyclophosphamide for patients with X-linked adrenoleukodystrophy: a suitable choice in an urgent situation. Bone marrow transplantation. 2018;53(4):392-9.
29. Baumann M, Korenke GC, Weddige-Diedrichs A, Wilichowski E, Hunneman DH, Wilken B, et al. Haematopoietic stem cell transplantation in 12 patients with cerebral X-linked adrenoleukodystrophy. European journal of pediatrics. 2003;162(1):6-14.
30. Wilken B, Dechent P, Brockmann K, Finsterbusch J, Baumann M, Ebell W, et al. Quantitative proton magnetic resonance spectroscopy of children with adrenoleukodystrophy before and after hematopoietic stem cell transplantation. Neuropediatrics. 2003;34(5):237-46.
31. Jardim LB, da Silva AC, Blank D, Villanueva MM, Renck L, Costa ML, et al. X-linked adrenoleukodystrophy: clinical course and minimal incidence in South Brazil. Brain & development. 2010;32(3):180-90.
32. Kato K, Maemura R, Wakamatsu M, Yamamori A, Hamada M, Kataoka S, et al. Allogeneic stem cell transplantation with reduced intensity conditioning for patients with adrenoleukodystrophy. Mol Genet Metab Rep. 2019;18:1-6.
33. Kuhl JS, Kupper J, Baque H, Ebell W, Gartner J, Korenke C, et al. Potential Risks to Stable Long-term Outcome of Allogeneic Hematopoietic Stem Cell Transplantation for Children With Cerebral X-linked Adrenoleukodystrophy. JAMA Netw Open. 2018;1(3):e180769.
34. McKinney AM, Benson J, Nascene DR, Eisengart J, Salmela MB, Loes DJ, et al. Childhood Cerebral Adrenoleukodystrophy: MR Perfusion Measurements and Their Use in Predicting Clinical Outcome after Hematopoietic Stem Cell Transplantation. AJNR Am J Neuroradiol. 2016;37(9):1713-20.
35. McKinney AM, Nascene D, Miller WP, Eisengart J, Loes D, Benson M, et al. Childhood cerebral X-linked adrenoleukodystrophy: diffusion tensor imaging measurements for prediction of clinical outcome after hematopoietic stem cell transplantation. AJNR Am J Neuroradiol. 2013;34(3):641-9.
36. Miller WP, Mantovani LF, Muzic J, Rykken JB, Gawande RS, Lund TC, et al. Intensity of MRI Gadolinium Enhancement in Cerebral Adrenoleukodystrophy: A Biomarker for Inflammation and Predictor of Outcome following Transplantation in Higher Risk Patients. AJNR Am J Neuroradiol. 2016;37(2):367-72.
37. Miller WP, Rothman SM, Nascene D, Kivisto T, DeFor TE, Ziegler RS, et al. Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report. Blood. 2011;118(7):1971-8.
38. Moser HW, Raymond GV, Lu SE, Muenz LR, Moser AB, Xu J, et al. Follow-up of 89 asymptomatic patients with adrenoleukodystrophy treated with Lorenzo's oil. Archives of neurology. 2005;62(7):1073-80.
39. Orchard PJ, Nascene DR, Miller WP, Gupta A, Kenney-Jung D, Lund TC. Successful donor engraftment and repair of the blood-brain barrier in cerebral adrenoleukodystrophy. Blood. 2019;133(12):1378-81.
40. Peters C, Charnas LR, Tan Y, Ziegler RS, Shapiro EG, DeFor T, et al. Cerebral X-linked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999. Blood. 2004;104(3):881-8.
41. Pierpont EI, Eisengart JB, Shanley R, Nascene D, Raymond GV, Shapiro EG, et al. Neurocognitive Trajectory of Boys Who Received a Hematopoietic Stem Cell Transplant at an Early Stage of Childhood Cerebral Adrenoleukodystrophy. JAMA neurology. 2017;74(6):710-7.

42. Pierpont EI, McCoy E, King KE, Ziegler RS, Shanley R, Nascene D, et al. Post-transplant adaptive function in childhood cerebral adrenoleukodystrophy. Annals of clinical and translational neurology. 2018;5(3):252-61.
43. Pierpont EI, Nascene DR, Shanley R, Kenney-Jung DL, Ziegler RS, Miller WP, et al. Neurocognitive benchmarks following transplant for emerging cerebral adrenoleukodystrophy. Neurology. 2020;95(5):e591-e600.
44. Polgreen LE, Chahla S, Miller W, Rothman S, Tolar J, Kivisto T, et al. Early diagnosis of cerebral X-linked adrenoleukodystrophy in boys with Addison's disease improves survival and neurological outcomes. European journal of pediatrics. 2011;170(8):1049-54.
45. Saute JA, Souza CF, Poswar FO, Donis KC, Campos LG, Deyl AV, et al. Neurological outcomes after hematopoietic stem cell transplantation for cerebral X-linked adrenoleukodystrophy, late onset metachromatic leukodystrophy and Hurler syndrome. Arquivos de neuro-psiquiatria. 2016;74(12):953-66.
46. Shapiro E, Krivit W, Lockman L, Jambaque I, Peters C, Cowan M, et al. Long-term effect of bone-marrow transplantation for childhood-onset cerebral X-linked adrenoleukodystrophy. Lancet. 2000;356(9231):713-8.
47. Suzuki Y, Imamura A, Shimozawa N, Kondo N. The clinical course of childhood and adolescent adrenoleukodystrophy before and after Lorenzo's oil. Brain & development. 2001;23(1):30-3.
48. Tokimasa S, Ohta H, Takizawa S, Kusuki S, Hashii Y, Sakai N, et al. Umbilical cord-blood transplantations from unrelated donors in patients with inherited metabolic diseases: Single-institute experience. Pediatric transplantation. 2008;12(6):672-6.
49. Tran C, Patel J, Stacy H, Mamak EG, Faghfoury H, Raiman J, et al. Long-term outcome of patients with X-linked adrenoleukodystrophy: A retrospective cohort study. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society. 2017;21(4):600-9.
50. van den Broek BTA, Page K, Paviglianiti A, Hol J, Allewelt H, Volt F, et al. Early and late outcomes after cord blood transplantation for pediatric patients with inherited leukodystrophies. Blood advances. 2018;2(1):49-60.
51. Berger ML, Martin BC, Husereau D, Worley K, Allen JD, Yang W, et al. A questionnaire to assess the relevance and credibility of observational studies to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health. 2014;17(2):143-56.
52. bluebird bio Inc. Clinical Study Report ALD-101. Data on file. 2015.
53. bluebird bio Inc. Interim clinical study report ALD-102. Data on file. 2020.
54. bluebird bio Inc. TLFs ALD-102 D120 MAA. Data on file. 2021.
55. bluebird bio Inc. TLFs Interstudy D120 MAA. Data on file. 2021.
56. bluebird bio Inc. Clinical Study Report ALD-103. Data on file2020.
57. bluebird bio Inc. Interim clinical study report ALD-104. Data on file. 2020.
58. bluebird bio Inc. TLFs ALD-104 D120 MAA Data on file 2021.
59. bluebird bio Inc. Interim clinical study report LTF-304. Data on file. 2020.
60. bluebird bio Inc. TLFs LTF-304 D120 MAA. Data on file. 2021.
61. Health Technology Assessment Interntional. Values and Quality Standards for Patient Involvement in HTA 2014 [Available from: https://transfer.htai.org/wp-content/uploads/2018/02/PCISG-Info-ValuesandStandards-30-Jun14.pdf.

APPENDIX 1: GUIDELINES FOR DIAGNOSIS AND MANAGEMENT

There is currently no approved treatment for CALD in any country, and there are no official management guidelines for CALD in Europe. However, three consensus publications have been published on the management of ALD/CALD in boys.

APPENDIX 2: PATIENT INVOLVEMENT

Table A1. Summary of answers from patient's parent and patient organisation

Question	Patient's parent view (The Netherlands)	Patient organisations view (Germany, Spain and Italy)
Key messages		• **Early diagnosis** is crucial. Without that, there is no efficacy of treatments. • Create **shared guidelines** • A new treatment may help to promote **newborn screening** • **Lack of treatments that improve the course of the disease** and give **quality of life** to the affected patients • **Challenging to find matching donor before the disease is too far advanced**. Otherwise the transplant will not have the desired results-. Gene therapy for CALD is the hope for affected patients because it avoids waiting for a compatible donor and graft-versus-host disease. • **Treatments.** Today families have to pause their lives for even two years to follow the children in the complicated management of the transplant, it can therefore mean an **improvement in the quality of life with advantages in the health and social fields** but also in the economic impact on families and the Health System. • **Ease the stress of affected families**. Create an integrated health and social care system, so that the needs of the whole family are accomplished.
How does cerebral adrenoleukodystrophy (CALD) affect patients' quality of life?	When he was 6 years old he suddenly could no longer cope with the lessons at school, *for example with learning words - a week later he had forgotten it again. That got worse, a few months later he could only read single words. He could not zip his jacket, tie shoelaces. He had to redo 3rd grade. He became incontinent and could not walk far, after a 500m walk he had to go to the toilet (poop). He got the feeling that he couldn't do things*. He had to see many doctors (psychologists, psychiatrists, paediatrics), it took 2 years before the diagnosis CALD was established. His IQ dropped, he had to go to a special school. He went there for 1,5 years and had to leave because his condition got worse, at some point he could no longer speak properly. *That was very tough, because he had to let go of the known people he also loved very much.* He could not do much anymore. He had to eat through a probe. He got spasms and could only lie from that moment on. Family tried to comfort him as much as possible. The decision was made to not stretch life, because of low quality of life.	CALD affects boys. The usual age of development of the disease occurs in children under 10 years of age. The quality of life of patients with cerebral ALD is progressively reduced in relation to the evolution of the symptoms. It is a neurodegenerative disease so all abilities- or skills are lost (walking, speaking, swallowing, sphincter control, suffer from a lot of spasticity which causes a lot of pain, which is difficult to control, scoliosis which causes breathing problems...) and those affected need the help of a third person, or main caregiver for all tasks of daily life. Normally one of the parents has to stop working to take care of the affected person, in 99% of cases the mother does it). It is a disease that causes a 100% disability, so there is a need to adapt the home environment with special equipment. Your loved one lose their abilities so it has a great emotional and psychological charge. It affects the entire family environment, loss of purchasing power, etc.

		Children experience in most cases significant problems of social isolation, due to delays in taking charge, difficulties of peers to relate to them, their own disabilities and fears, and also overprotective attitudes of the family. Caregivers often engaged in H24 care, due to sleep deprivation, stress from loads, living in a state of perennial emergency, are subjected to a daily load of unbearable inhuman fatigue and have to deal with hernias, cardiovascular, gastrointestinal, psychological disorders and immunodeficiencies. We also point out that when it comes to meeting the medical needs of those affected by ALD, there is not always a good relationship between doctor and patient/parents and often patients are followed in centres far from home
How does cerebral adrenoleukodystrophy (CALD) affect carers/unpaid care-givers?	The search for a diagnosis was very difficult. GP and school felt that she (the mother) was *unnecessary concerned. There was absolutely no understanding from the outside world.* Psychologist thought he should do a compulsory 2-month admission, during which the mother was not allowed to see him. *I got furious because I felt something else was going on. He was almost 8 when diagnosed. On the one hand, terrible because you receive a death sentence, but also a warm bath because your feelings and worries were recognized.* The mother worked part-time, *I wanted to quit my job, but everyone advised against that. Once he got to the phase he only could lie in bed, I stayed home from work - I called in sick because I couldn't handle it anymore. … The impact of this (his death) is huge in a family. You should also not underestimate what it does for brothers and sisters. …They lost their brother, with super sad parents who cannot find each other. Friends don't understand, …. no one recognizes what it is to lose a brother.* The marriage broke.	Parents have to watch helplessly as their previously inconspicuous and healthy children lose all their physical functions. Additionally you have to provide full time care for your children. This also means high income losses, as in almost no case the professional activity can be fully continued. It means a lot of mental and physical strain, and they suffer from depression and frustration of not being able to do anything to change the situation. Also, they feel guilt because it is a genetically transmitted disease. Due to the disease, the patient and the family caring for them are socially isolated and can no longer go about their normal activities.
How well are patients less than 18 years of age managing cerebral adrenoleukodystrophy (CALD) with currently available therapies? (Currently available therapies may include any	After diagnosis the paediatric neurologist prescribed him hydrocortisone; *then he brightened up completely. We quickly noticed that it made him feel much better.* There was no eligible donor for stem cell transplantation within the family. Finding a donor outside the family was discussed, but was decided not to do. The reason for this was that stem cell transplantation would have effects after six months, while the IQ is dropping and the quality of life was considered then very low. *This reasoning was found to be very bad to the outside world. But how can you accept an IQ of 40 for a child who has always been so active. In retrospect I am glad that it could not continue, for him for his quality of life, because I heard how difficult that process was.* An experimental treatment with immunoglobulin was started. *For around three months we had to go to the hospital every 3 weeks. That was very intense. Also very intense for him.* It did not have any effect on the	If the disease is recognized presymptomatically, the only way to stop the disease at the moment is a stem cell transplant, but this can only occur in extremely selected cases. In addition to the timely diagnosis, this requires a well-fitting donor. Stem cell transplantation can greatly improve the progression. However, this is not a curative treatment. Damages to the central nervous system already occurred cannot be corrected, nor was the disease stopped in all cases. In cases where the cerebral form has been successfully stopped, patients survive and can lead an almost normal life. However, in the further course they develop the neurodegenerative form of the disease and continue to suffer from adrenomyeloneuropathy. Stem cell transplantation has the disadvantage of possible complications. Some patients have lost their lives to infections. Others suffer from permanent GvHd or for example have lost sight as a result of Gvhd.

form of medical intervention such as medicines, rehabilitation, counselling, hospital interventions etc. If no specific therapy is available, that should be stated.)	disease. As far as the mother can remember, no other medication was used by her child. She knows about 2 other children who did undergo stem cell transplantation. *The last one was done about 4 years ago and that is still a very difficult process. Still a lot of medication to keep it normal, the child is sick a lot, a lot of flu. I know of another boy who was transplanted when we heard that our son sick was, it seemed to work. He had a normal puberty, but he is now starting to get complaints again. So with the transplantation you will not get rid of it, but it will come back again in a different way.*	Children who have already developed symptoms and who do not have a donor can only be supported by symptomatic or palliative treatment. Since it is a metabolic disease, dietary treatment is an important aid to the reduction of VLCFA levels, which are believed to be "toxic" at high levels for tissue cells (central and peripheral nervous system). There are other attempts at healing, for example with Lorenzo's oil, but they have no proven success. In particular, for spasticity (feeling of stiff legs) it is possible to use baclofen, eperisone or - in some cases - diazepam. In addition, should spasticity become particularly disabling, more invasive approaches such as botulinum toxin infiltration or implantation of a baclofen intrathecal infusion pump can be considered. To reduce the feeling of fatigue and more generally the disability of walking is indicated a therapeutic attempt with 4-aminopyridine, in the absence of cardiological contraindications. For urination urgency it is possible to use oxybutynin or equivalent, for constipation macrogol or other mass-forming laxatives, for potency disorders tadalafil or equivalent or alprostadil for more severe cases. For sensitivity disorders (tingling, pain or burning sensation especially in the legs) it is possible to use drugs such as gabapentin and pregabalin, while valproic acid can be used as mood stabilizer. Finally, physiotherapy and more generally aerobic physical activity is essential, to be practiced regularly and after medical evaluation to determine, among other things, whether additional doses of cortone acetate or equivalent are necessary before exercise in order to prevent acute adrenal attacks.
What are the expectations of/requirements for a new medicine for patients less than 18 years of age with cerebral adrenoleukodystrophy (CALD)?	*If gene therapy will work out, it seems great to me*. She stresses that starting early with treatment is very important. *I'm under no illusion that the gene therapy can fix what's broken, but it might just stop the progression of the disease. …* *I have also spoken to people at the patient association, where it was monitored enormously if they knew that the disease is found in the family that they would immediately do SCT when complaints arise. If you could do gene therapy immediately at that time, it would hopefully work much better.*	The most waited therapy for patients with CALD under 18 years of age is certainly the gene therapy that would allow a faster intervention, not requiring the search for a donor and would lead to fewer side effects due to possible rejection and particularly strong immunosuppression therapy. Expectations of a new therapy are that the progressions stops and children survive. Also, the therapy should prevent patients from the neurodegenerative form of the disease. Prevent disabilities and offer to these patients a normal health status and a normal life, should be considered at any rate not a cost but an investment, without remarking the uncountable value of a saved life.
Any additional information	*I think the quality of life is so important for these children. If you see change a child in two years into a plant, that is really awful. If you can change that progression, it may still not be completely great - e.g. assisted living and sheltered workshop, but then you will have a liveable life. There, children can become very happy. … Perhaps you should indeed take that into account, that you should also be able to live from the moment the*	An untreated child has a life expectancy of between 5 and 8 years after diagnosis. The quality of life of those affected is very bad. A child treated with this new treatment is like he has never been affected. As patient association we constantly interface with parents who receive a late diagnosis for their children, after having made huge rounds

	progression is stopped. With bone marrow transplantation, for example, you also have a lot of concern afterwards, due to the side effects of the transplant, or the progression continues at a later time.	(pilgrimages), having consulted various specialists, only to be told that it is too late to intervene. From that moment on, the difficulties become unbearable, the family goes through continuous changes in the health status of their family member, continuous expenses, and great isolation. Today most of the early diagnoses are posed only thanks to innocent victims, brothers, cousins who perish opening long tunnels of pain in the history of the families. These victims bring than to extensive investigations which could prevent to have other affected relatives.

APPENDIX 3: EVIDENCE GAPS

Table A2. Recommendations for research

Additional evidence generation needs	
Research question 1: What is the comparative clinical effectiveness and safety of eli-cel for CALD?	
Evidence	Indirect comparison of single arm trial with an external comparator. The external comparator is a mixed retrospective/prospective data collection study. Short follow-up, small sample size, large amount of missing data, interim analysis, partly retrospective data collection, no pre-planned propensity score analysis.
Population	Patients with early CALD with and without an HLA-matched sibling donor.
Intervention	Eli-cel treatment with different conditioning regimens.
Comparator	Allo-HSCT treatment with different conditioning regimens.
Outcome(s)	Overall survival, MFD-free survival, change in neurological function (NFS-score), Loes score, Gadolinium contrast enhancement, engraftment failure, graft versus host disease, adverse events (including long-term risk of oncogenesis, such as myelodysplasia, leukaemia, or lymphoma).
Time stamp	25 June 2021
Study design	Long term follow-up data from ongoing studies. Post marketing surveillance on safety. Registries for eli-cel treatment and allo-HSCT (including MSD and NMSD).
Ongoing studies	ALD-102 – according to submission dossier study completion was expected in May 2021. ClinicalTrials.Gov entry: NCT01896102; EudraCT entry: 2011-001953-10 ALD-104 - expected completion in February 2024. ClinicalTrials.Gov entry: NCT03852498; EudraCT entry: 2018-001145-14 Long term follow-up study of ALD-102/ALD-104 LTF-304 – expected completion in May 2037. ClinicalTrials.Gov entry: NCT02698579; EudraCT entry: 2015-002805-13 Post-authorisation efficacy/safety study REG-502 will follow eli-cel treated patients for up to 15 years post treatment.

APPENDIX 4: SAFETY OUTCOMES – ADVERSE EVENTS BY SYSTEM ORGAN CLASS

Table A3. Frequency and severity of all grades adverse events by system organ class, which occurred in ≥10% patients

System organ/ class/adverse events	All grades		
	ALD-102 n = 32	ALD-103 n = 59	ALD-104 n = 13
Infections and infestations			
Device-related infection	4 (12.5)	5 (8.5)	NR
Viral upper respiratory infection	NR	NR	2 (15.4)
Blood and lymphatic system disorders			
Pancytopenia	NR	NR	2 (10.5)
Thrombocytopenia	31 (96.9)	15 (25.4)	17 (89.5)
Neutropenia	30 (93.8)	7 (11.9)	10 (52.6)
Febrile neutropenia	25 (78.1)	27 (45.8)	13 (68.8)
Leukopenia	11 (34.4)	4 (6.8)	NR
Anaemia	27 (84.4)	18 (30.5)	14 (73.7)
General disorders and administration site conditions			
Pyrexia	12 (37.5)	7 (11.9)	4 (21.1)
Catheter site pain	8 (25.0)	NR	8 (61.5)
Fatigue	2 (6.3)	NR	2 (10.5)
Nervous system disorders			
Headache	3 (9.4)	3 (5.1)	5 (26.3)
Neurological decompensation	1 (3.1)	6 (10.2)	NR
Seizure	4 (12.5)	3 (5.1)	NR
Renal and urinary disorders			
Dysuria	2 (6.3)	NR	2 (10.5)
Cystitis noninfective	NR	NR	2 (15.4)
Gastrointestinal disorders			
Nausea	30 (93.8)	11 (18.6)	12 (92.3)
Stomatitis	26 (81.3)	30 (50.8)	16 (84.2)
Vomiting	10 (31.3)	4 (6.8)	5 (26.3)
Abdominal pain	10 (31.3)	5 (8.5)	4 (21.1)
Diarrhoea	10 (31.3)	4 (6.8)	2 (10.5)
Nausea	6 (18.8)	NR	6 (31.6)
Constipation	2 (6.3)	NR	5 (26.3)
Skin and subcutaneous tissue disorders			
Alopecia	23 (71.9)	NR	13 (68.4)
Pruritus	2 (6.3)	NR	3 (15.8)
Rash	2 (6.3)	NR	2 (10.5)
Skin hyperpigmentation	3 (9.4)	NR	3 (15.8)
Dry skin	1 (3.1)	NR	2 (10.5)
Metabolism and nutrition disorders			
Decreased appetite	11 (34.4)	24 (40.7)	6 (31.6)
Hypokalaemia	10 (31.3)	10 (16.9)	3 (15.8)
Hypophosphatemia	5 (15.6)	NR	3 (15.8)
Fluid retention	4 (12.5)	NR	NR
Injury, poisoning and procedural complications			
Anaphylactic transfusion reaction	NR	NR	2 (10.5)
Investigations			
Alanine aminotransferase increased	4 (12.5)	NR	3 (15.8)
Aspartate aminotransferase increased	2 (6.3)	NR	2 (10.5)

Respiratory, thoracic and mediastinal disorders			
Cough	5 (15.6)	NR	1 (5.3)
Epistaxis	4 (12.5)	3 (5.1)	6 (31.6)
Vascular disorders			
Hypertension	2 (6.3)	28 (47.5)	2 (10.5)
Hepatobiliary disorders			
Tachycardia	1 (3.1)	NR	2 (10.5)
Psychiatric disorders			
Agitation	NR	4 (6.8)	3 (15.8)
Eye disorders			
Dry eye	NR	NR	2 (10.5)
Vision blurred	NR	NR	2 (10.5)
Visual acuity reduced	1 (3.1)	NR	2 (10.5)

Source: Submission Dossier.

Table A4. Frequency of serious adverse events by system organ class

System organ/ class/adverse events	Serious adverse events		
	ALD-102 n = 32	**ALD-103** n = 59	**ALD-104** n = 19
Endocrine disorders			
Adrenal insufficiency	2 (6.3)	1 (1.7)	NR
Infections and infestations			
Pneumonia	NR	1 (1.7)	NR
Adenovirus infection	NR	1 (1.7)	NR
Sepsis	NR	2 (3.4)	NR
Human herpesvirus 6 infection	NR	2 (3.4)	NR
Pseudomonal bacteraemia	NR	NR	1 (5.3)
Device-related infection	2 (6.3)	4 (6.8)	NR
Gastroenteritis	1 (3.1)	1 (1.7)	NR
Influenza	1 (3.1)	NR	NR
Otis media	1 (3.1)	NR	NR
Sinusitis	1 (3.1)	1 (1.7)	NR
Viral infection	1 (3.1)	1 (1.7)	NR
BK virus infection	NR	3 (5.1)	NR
Bacteraemia	NR	3 (5.1)	NR
Staphylococcal infection	NR	3 (5.1)	NR
Clostridium difficile Infection	NR	2 (3.4)	NR
Epstein-Barr viraemia	NR	2 (3.4)	NR
Lung infection	NR	2 (3.4)	NR
Septic infection	NR	2 (3.4)	NR
Atypical pneumonia	NR	1 (1.7)	NR
Bronchiolitis	NR	1 (1.7)	NR
Coxsackie viral infection	NR	1 (1.7)	NR
Cytomegalovirus infection	NR	1 (1.7)	NR
Cytomegalovirus viraemia	NR	1 (1.7)	NR
Enterococcal bacteraemia	NR	1 (1.7)	NR
Gastroenteritis adenovirus	NR	1 (1.7)	NR
Kidney infection	NR	1 (1.7)	NR
Parvovirus infection	NR	1 (1.7)	NR
Pneumonia viral	NR	1 (1.7)	NR
Tooth abscess	NR	1 (1.7)	NR
Upper respiratory infection	NR	1 (1.7)	NR
Viral upper respiratory infection	NR	NR	NR
Streptococcal bacteraemia	NR	NR	1 (5.3)
Blood and lymphatic system disorders			
Anaemia haemolytic autoimmune	0 (0)	1 (1.7)	NR

Pancytopenia	0 (0)	0 (0)	2 (10.5)
Thrombocytopenia	NR	4 (6.8)	NR
Neutropenia	NR	2 (3.4)	NR
Febrile neutropenia	8 (25.0)	4 (6.8)	4 (21.1)
Leukopenia	NR	2 (3.4)	NR
Anaemia	NR	2 (3.4)	NR
Bone marrow failure	NR	2 (3.4)	NR
Haemolytic anaemia	NR	2 (3.4)	NR
Cytopenia	NR	1 (1.7)	NR
General disorders and administration site conditions			
Pyrexia	7 (21.9)	3 (5.1)	3 (15.8)
Disease progression	NR	2 (3.4)	NR
Device-related infection	NR	1 (1.7)	NR
Multiple organ dysfunction syndrome	NR	1 (1.7)	NR
Fatigue	1 (3.1)	NR	NR
Nervous system disorders			
Dyskinesia	1 (3.1)	NR	NR
Neurological decompensation	1 (3.1)	6 (10.2)	NR
Seizure	3 (9.4)	2 (3.4)	NR
Aphasia	NR	2 (3.4)	NR
Encephalopathy	NR	1 (1.7)	NR
Intracranial pressure Increased	NR	1 (1.7)	NR
Visual field defect	NR	1 (1.7)	NR
Transverse myelitis	NR	NR	1 (5.3)
Renal and urinary disorders			
Acute kidney injury	1 (3.1)	2 (3.4)	NR
Cystitis viral	1 (3.1)	NR	NR
Chronic kidney disease	NR	1 (1.7)	NR
Dysuria	NR	1 (1.7)	NR
Urinary tract obstruction	NR	1 (1.7)	NR
Gastrointestinal disorders			
Stomatitis	1 (3.1)	NR	1 (5.3)
Vomiting	1 (3.1)	1 (1.7)	NR
Abdominal pain	1 (3.1)	1 (1.7)	NR
Diarrhoea	NR	2 (3.4)	NR
Constipation	NR	NR	1 (7.7)
Gastritis	NR	1 (1.7)	NR
Haematemesis	NR	1 (1.7)	NR
Intestinal obstruction	NR	1 (1.7)	NR
Hepatobiliary disorders			
Acute hepatic failure	1 (3.1)	NR	NR
Metabolism and nutrition disorders			
Decreased appetite	1 (3.1)	1 (1.7)	NR
Dehydration	NR	1 (1.7)	NR
Malnutrition	NR	1 (1.7)	NR
Feeding intolerance	NR	1 (1.7)	NR
Injury, poisoning and procedural complications			
Procedural complications	1 (3.1)	NR	NR
Head injury	1 (3.1)	NR	NR
Spinal fracture	1 (3.1)	NR	NR
Engraft failure	NR	2 (3.4)	NR

Anaphylactic transfusion reaction	NR	NR	1 (5.3)
Transplant failure	NR	1 (1.7)	NR
Investigations			
Clostridium test positive	NR	1 (1.7)	NR
Transaminase increased	NR	NR	1 (5.3)
Weight decreased	NR	1 (1.7)	NR
Respiratory, thoracic and mediastinal disorders			
Respiratory distress	1 (3.1)	NR	NR
Haemothorax	NR	2 (3.4)	NR
Respiratory failure	NR	2 (3.4)	NR
Hypoxia	NR	1 (1.7)	NR
Pleural effusion	NR	1 (1.7)	NR
Pulmonary haemorrhage	NR	1 (1.7)	NR
Vascular disorders			
Hypertension	NR	2 (3.4)	NR
Cerebral infarction	NR	1 (1.7)	NR
Deep vein thrombosis	NR	1 (1.7)	NR
Haematochezia	NR	1 (1.7)	NR
Hypotension	NR	1 (1.7)	NR
Thrombosis	NR	1 (1.7)	NR
Veno-occlusive disease	NR	1 (1.7)	NR
Cardiac disorders			
Cardio-respiratory arrest	1 (3.1)	NR	NR
Hepatobiliary disorders			
Acute hepatic failure	1 (3.1)	NR	NR
Acute myocardial infarction	NR	1 (1.7)	NR
Cardiac arrest	NR	1 (1.7)	NR
Coronary artery disease	NR	1 (1.7)	NR
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis	1 (3.1)	NR	NR
Immune system disorders			
Anaphylactic reaction	NR	2 (3.4)	NR
Immunosuppression	NR	1 (1.7)	NR
Transplant rejection	NR	1 (1.7)	NR
Ear and labyrinth disorders			
Hypoacusis	NR	2 (3.4)	NR
Auditory disorder	NR	1 (1.7)	NR
Psychiatric disorders			
Aversion	NR	NR	1 (5.3)
Depression	1 (3.1)	NR	NR
Agitation	NR	1 (1.7)	NR

Source: Submission Dossier.