13 October 2022
EMA/858618/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ebvallo

International non-proprietary name: tabelecleucel

Procedure No. EMEA/H/C/004577/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ABL	Advanced Bioscience Laboratories
APC	antigen presenting cell
BLCL	B lymphoblastoid cell line
BOR	best overall response
BPyV	bovine polyoma virus
CAPA	corrective and preventive action
CBR	clinical benefit rate
CI	confidence interval
CIK	cytokine induced killer
CMV	cytomegalovirus
CoA	certificate of analysis
CPP	critical process parameter
CQAs	critical quality attributes
CR	complete response
CRS	cytokine release syndrome
CSR	clinical study report
CTL	Cytotoxic T cell
CTLp	CTL precursor
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DOR	duration of response
DPI	drug product inventory
DRR	durable response rate
EAP	expanded access programme
EAS	evaluable analysis set
EBV	Epstein-Barr virus
EBV+	Epstein Barr virus positive or -associated
EBV CTL	Epstein Barr virus cytotoxic T lymphocyte
EBV CTLp	EBV specific cytotoxic T cell precursor
EBV+ LPD	EBV+ lymphoproliferative disease/disorder
EBV+ PTLD	EBV+ posttransplant lymphoproliferative disease
EMA	European Medicines Agency

EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
fePTP	fold expansion PTP method
GvHD	graft versus host disease
HBV	hepatitis B virus
HCT	allogeneic haematopoietic cell transplant
HLA	human leukocyte antigen
HAS	human serum albumin
IDM	infectious disease marker
IES	IORA evaluable set
IORA	independent oncologic response adjudication
IPC	in-process control
IPT	in-process test
ISE	integrated summary of efficacy
ISS	integrated summary of safety
IV	intravenous(ly)
KM	Kaplan Meier
LIVCA	limit of *in vitro* cell age
LLOQ	lower limit of quantitation
MNC	mononuclear cell
MSKCC	Memorial Sloan Kettering Cancer Center
NAT	nucleic acid testing
NCK	non-critical key process parameter
NE	not evaluable (in the context of best overall response); not estimable (in the context of overall survival or duration of response)
NK	natural killer
OOS	out of specification
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PBS	phosphate buffered saline
PD	progressive disease
PDCO	Paediatric Committee

PHAb	phytohemagglutinin blast
PPQ	process performance qualification
PR	partial response
PTLD	posttransplant lymphoproliferative disease
PTP	post-thaw proliferation
PV	process versions
R CHOP	combination chemotherapy regimen including rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride (doxorubicin hydrochloride), vincristine sulfate (Oncovin), and prednisone
RMP	risk management plan
R/R	relapsed and/or refractory
SAE	serious adverse event
SAL	sterility assurance level
SAP	statistical analysis plan
SD	stable disease
SOT	solid organ transplant
SPU	single patient use
TCID50	50% tissue culture infectious dose
TEAE	treatment-emergent adverse event
TESAE	treatment emergent serious adverse event
TOST	two one-sided test
TTBR	time to best response
TTR	time to response
TU	transducing unit

Cohort Abbreviations	**Definition**
C-PTLD	Tabelecleucel EBV+ PTLD
C-SOT	Tabelecleucel SOT EBV+ PTLD
C SOT R	Tabelecleucel SOT EBV+ PTLD (R/R Rituximab)
C SOT R+C	Tabelecleucel SOT EBV+ PTLD (R/R Rituximab and Chemotherapy)
C HCT	Tabelecleucel HCT EBV+ PTLD (R/R Rituximab)

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Atara Biotherapeutics Ireland Limited submitted on 5 November 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Ebvallo, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

Ebvallo, was designated as an orphan medicinal product EU/3/16/1627 on 21 March 2016. Ebvallo was designated as an orphan medicinal product in the following indication: treatment of post-transplant lymphoproliferative disorder.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Ebvallo as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/ebvallo.

The applicant applied for the following indication: treatment of patients with Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have received at least one prior therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is considered inappropriate.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that tabelecleucel was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0490/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-002025-PIP04-19 was not yet completed as some measures were deferred.

The PDCO issued an opinion on compliance for the PIP EMEA-002025-PIP04-19.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's requests for consideration

1.5.1. Marketing authorisation under exceptional circumstances

The applicant requested consideration of its application for a marketing authorisation under exceptional circumstances in accordance with Article 14(8) of the above-mentioned Regulation.

1.5.2. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.3. New active substance status

The applicant requested the active substance tabelecleucel contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5.4. Scientific recommendation on classification

The applicant Atara Biotherapeutics Ireland Limited submitted on 7 April 2016 an application for Scientific recommendation on Classification to the European Medicines Agency (EMA) for Ebvallo, which was designated as an Advanced Therapy Medicinal (EMA/CAT/327742/2016) on 30 May 2016.

1.6. PRIME

Ebvallo was granted eligibility to PRIME on 13 October 2016 in the following indication: treatment of patients with Epstein-Barr Virus-associated Post Transplant Lymphoproliferative Disorder in the allogeneic haematopoietic cell transplantation setting.

Eligibility to PRIME was granted at the time in view of the following:

There are unmet therapeutic needs for patients with an Epstein-Barr virus (EBV)-associated/-related post-transplantation lymphoproliferative disease (PTLD); less than half of the patients survive for more than 3 years onset of PTLD, anti-CD20 and cytotoxic therapy incur a high treatment burden, and in a portion of patients, PTLD becomes refractory to anti-CD20 therapy.
The HLA-matched, allogeneic EBV-specific cytotoxic T lymphocytes (ATA129) represent a novel mechanism of action and has the potential to address the unmet therapeutic needs, including when in anti-CD20 therapy refractory PTLD.
In clinical experiments, a complete response has been reported in about half of the patients with an anti-CD20 therapy refractory PTLD using ATA129 as single agent.

Upon granting of eligibility to PRIME, Egbert Flory was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 9 October 2019. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

- The comparability between the different generations of the product that have been used throughout the clinical development programme.
- The manufacturing controls, release criteria, and the stability plan for the product.
- The plan for donor HLA selection and matching with patients to be treated.
- The need for non-clinical *in vivo* studies in addition to any *in vitro* data that can be generated.

- Determine the number of patient and endpoints to be used in the pivotal trial.
- Engagement with established registries for long-term follow up of patients to be treated with the product.
- The requirements for maintenance of the orphan designation through demonstration of significant benefit compared to available treatments.
- The paediatric plan proposal.

1.7. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
15 December 2016	EMEA/H/SAH/072/1/2016/SME/ADT/III	Olli Tenhunen and Dr Hans Ovelgönne
13 December 2018	EMEA/H/SA/3977/1/FU/1/2018/PA/SME/ADT/PR/III	Hans Ovelgönne and Jan Mueller-Berghaus
17 September 2020	EMEA/H/SA/3977/1/FU/2/2020/PA/ADT/PR/I	Jens Reinhardt and Rune Kjeken

The protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

Quality

- Manufacturing process related GMP compliance aspects, strategy for comparability assessment for product versions generated via different manufacturing processes, manufacturing process validation plans, approach for manufacture of reagents, viral risk assessment and control strategy
- Potency assay, batch release testing for drug product, donor eligibility / collection and testing criteria and testing programme for infectious disease markers of leukapheresis starting material, stability testing and shelf-life

Non-Clinical

- Sufficiency of a non-clinical programme based on primary pharmacodynamic studies only

Clinical

- Adequacy of the clinical development plans to support an MA
- Acceptability of pivotal clinical trial design elements, including single arm trial design, choice of endpoints and associated statistical analysis aspects to support benefit-risk assessment
- Cell selection algorithms for HLA-matching

1.8. Steps taken for the assessment of the product

The CAT Rapporteur and Co-Rapporteur appointed by the CHMP were:

CAT Rapporteur: Egbert Flory CAT Co-Rapporteur: Romaldas Mačiulaitis

The application was received by the EMA on	5 November 2021
Accelerated Assessment procedure was agreed-upon by CAT and CHMP	16 September 2021

on	
The procedure started on	25 November 2021
The CAT Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	14 February 2022
The CAT Co-Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	14 February 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	1 March 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CAT during the meeting on	10 March 2022
The CAT agreed on the consolidated List of Questions to be sent to the applicant and to revert to a standard timetable during the meeting on	18 March 2022
The applicant submitted the responses to the CAT consolidated List of Questions on	1 July 2022
The following GMP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
GMP inspections at 6 manufacturing/testing sites in the US between 16 March-13 May 2022. The final outcome of the inspections carried out was issued on 08 September 2022.	8 September 2022
The CAT Rapporteur circulated the Joint Assessment Report on the responses to the List of Questions to all CAT and CHMP members on	17 August 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	1 September 2022
The CAT agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	9 September 2022
The applicant submitted the responses to the CAT List of Outstanding Issues on	15 September 2022
The CAT Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CAT and CHMP members on	27 September 2022
The CAT, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ebvallo on	7 October 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ebvallo on	13 October 2022
Furthermore, the CAT and CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product on	13 October 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Ebvallo is indicated for the treatment of patients with Epstein-Barr Virus positive post-transplant lymphoproliferative disease (EBV^+ PTLD) who have received at least one prior therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is considered inappropriate.

2.1.2. Epidemiology and risk factors

EBV+ PTLD is a rare and aggressive haematological malignancy that can occur after solid organ transplant (SOT) or haematopoietic cell transplant (HCT) due to immunosuppression that is induced to prevent graft rejection. The estimated annual incidence of EBV+ PTLD in the EU is approximately 125 to 150 patients in the SOT setting and approximately 90 to 140 patients in the HCT setting.

Several risk factors have been shown to increase the risk of PTLD; these include infection, degree and duration of immunosuppression, age and race of recipient, type of allograft, and genetic factors.

2.1.3. Biologic features

EBV is a DNA virus of the gamma herpes family. More than 90% of the worldwide population are EBV positive. In healthy individuals, EBV-specific CD8+ and CD4+ T-cell responses against viral antigens exert immunologic control over long-term infection. B lymphocytes are an important reservoir for EBV. The virus can insert its genome into the B cells and can induce uncontrolled B cell proliferation. Once the primary infection resolves, the virus persists in resting B cells. In case of immunosuppression after solid organ transplantation or haematopoietic stem cell transplantation a consequence is the inhibition of anti- EBV-specific CD3 T cells. In this setting, the EBV-infected B cells may proliferate uncontrolled. This proliferation might be especially strong when patients are EBV negative and acquire an infection when immunosuppressed.

2.1.4. Clinical presentation and prognosis

Post-transplant lymphoproliferative disorders (PTLD) are lymphoid and/or plasmacytic proliferations that occur in the setting of solid organ or allogeneic haematopoietic cell transplantation as a result of immunosuppression. They are among the most serious and potentially fatal complications of transplantation. The majority is related to the presence of Epstein-Barr virus (EBV).

Lymphadenopathy is often absent, and symptoms are usually due to interference with the function of involved organs. Classic B symptoms such as pyrexia, sweats, and weight loss can occur. Clinical features of PTLD are often non-specific, while extranodal involvement is common, including gastrointestinal tract (GIT), lungs, skin, bone marrow (BM), and central nervous system (CNS). Rarely, BM involvement can be the only disease site. PTLD typically has a more rapid onset in HSCT patients, with median time of 4–6 months after transplant.

Most PTLD cases are B cell (5–10% T/NK cell or Hodgkin lymphoma), while approximately one-third are EBV-negative. World Health Organization (WHO) diagnostic categories are: early lesions, polymorphic, and monomorphic PTLD; although in practice, a clear separation is not always possible.

2.1.5. Management

First-line treatment:

- Reduction of immunosuppression is the first step in the therapy of PTLD. It aims to achieve control of PTLD by the body's own immune system, but without compromising the function of the transplanted organ. With few exceptions, however, the rapid initiation of further therapeutic measures is essential.
- Rituximab, a monoclonal anti-CD20 antibody is used off-label in patients with polymorphic PTLD, or monomorphic diffuse large B-cell lymphoma-like PTLD.
- Epstein-Barr virus-specific cytotoxic T-cell therapy.

Second-line therapy:

second-line therapy options include cellular therapy (DLI or CTLs) or chemotherapy±rituximab (CHOP/R-CHOP). In patients after allogeneic haematopoietic stem cell transplantation, unselected DLI from an EBV-positive donor are employed to restore broad T-cell reactivity, including EBV-specific responses; unselected DLI, however, can be associated with severe GvHD. However, the use of DLI for EBV-PTLD is not recommended in any line of therapy in the most recent National Comprehensive Cancer Network non-Hodgkin lymphoma treatment guidelines [NCCN NHL Guidelines, 3.2016]

The international phase 2 PTLD-1 trial established sequential therapy of 4 cycles of weekly intravenous (IV) rituximab at standard dose (375 mg/m^2) followed by 4 cycles of standard dose CHOP-21 chemotherapy (50 mg/m^2 doxorubicin; 750 mg/m^2 cyclophosphamide, 1.4 mg/m^2 vincristine, 50 mg/m^2 prednisolone) every 21 days alongside mandatory granulocyte colony-stimulating factor (G-CSF) [Trappe 2012] Although some patients benefit from chemotherapy, it is associated with a high treatment-related mortality [Trappe 2017] and both short and long-term adverse effects [Children's Oncology Group 2018; Watson 2019].

Treatment options for paediatric patients with PTLD follow the same treatment algorithms as adults with generally similar outcomes.

The treatment goal is resolution of all signs and symptoms of PTLD, including a negative viral load. Response to rituximab therapy can be identified by a decrease in EBV DNA-aemia of at least 1 log10 in the first week of treatment.

Responses to first-line therapy are not durable in most cases. In the HCT setting, approximately 50% of cases fail initial treatment. In patients who fail initial therapy, disease progression is usually rapid with poor outcomes. In SOT patients who failed rituximab plus chemotherapy or cannot receive a chemotherapy regimen, the median survival was approximately 3 months. In a recent retrospective cohort study of 18 HCT subjects, the median survival from diagnosis of rituximab-refractory disease was 1.7 months. Analysis of an expanded multinational population in 2021 confirmed these findings: Patients with PTLD following HCT who failed rituximab has a median OS of 0.7 months (81 patients); patients with PTLD following SOT who failed chemotherapy after initial rituximab had a median OS of 4.1 months (86 patients).

2.2. About the product

Ebvallo is an allogeneic T cell immunotherapy composed of EBV antigen-specific cytotoxic T cells (EBV-CTLs). Ebvallo acts with an equivalent mechanism of action to that demonstrated by endogenous circulating EBV-CTLs and specifically targets and eliminates cells expressing EBV antigens. Ebvallo is generated from high resolution human leukocyte antigen (HLA)-typed EBV+ donor-derived T cells that are stimulated with EBV-infected antigen presenting cells, resulting in expansion of the T cells. The

cells are characterised and cryopreserved for future use as an allogeneic T cell immunotherapy. Ebvallo exhibits EBV-directed *in vitro* cytotoxic activity restricted by defined HLA alleles. To produce Ebvallo, the EBV-specific T cell reservoir in peripheral blood mononuclear cells from EBV+ donors is expanded and differentiated into an enriched oligoclonal population of EBV-specific effector memory T cells by multiple ex-vivo cycles of stimulation with a lethally irradiated autologous EBV-transformed B lymphoblastoid cell line (BLCL).

As a verification of potency and specificity, Ebvallo is required to have a detected class I (CD8) HLA restriction of EBV-specific cytotoxicity, which enables Ebvallo to detect and eliminate EBV+ cells.

2.3. Type of application and aspects on development

The CHMP and CAT agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on reported beneficial effects in the pivotal study, including potential prolongation of survival in patients treated with Ebvallo.

The advantage compared to available treatments was based on results available from historical controls obtained from the literature.

However, during assessment the CAT and CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as after the initial evaluation of this application a number of significant uncertainties related to the safety profile of the product and a detailed plan on how to address these were identified. In addition evidence of GMP compliance was also required at that stage for a number of manufacturing sites for the product.

The applicant requested consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of the above-mentioned Regulation based on:

The rarity of the disease
The challenges in recruiting EBV+ PTLD patients in clinical trials
The significant unmet need in EBV+ PTLD patients following either HCT or SOT who do not respond to or relapse after initial therapy given the lack of approved therapies and rapid decline with high mortality after initial treatment.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as dispersion for injection containing $2.8 \times 10^7 – 7.3 \times 10^7$ cells/mL of tabelecleucel as active substance.

Other ingredients are: dimethyl sulfoxide (DMSO), human serum albumin (HSA), phosphate buffered saline (PBS).

The product is available in cyclo-olefin copolymer stoppered vials with a thermoplastic elastomer closure containing 1.2 mL (2 mL vial) to ensure a minimum of 1 mL deliverable volume. Vials are packaged in a carton. The total number of vials in each carton (between 1 vial and 6 vials) corresponds to the dosing requirement for each individual patient.

2.4.2. Active substance

2.4.2.1. General Information

Tabelecleucel is an allogeneic T cell immunotherapy product composed of Epstein-Barr Virus (EBV) antigen-specific cytotoxic T cells (EBV-CTLs) stimulated, expanded and enriched *ex vivo* using EBV reagent and B lymphoblastoid cell line (BLCL) antigen presenting cells (BLCL APC). The finished product is derived from peripheral blood mononuclear cells (PBMCs) from a single donor using BLCL APC generated from the same donor. Each finished product batch has a human leukocyte antigen (HLA) restriction to be used for selection for individual patients. Several finished product batches with different HLA restrictions build up a product batch inventory.

The active substance (International non-proprietary name: tabelecleucel) is EBV - specific cytotoxic T lymphocytes, which are CD3+ T cells that specifically lyse target cells presenting EBV antigens in complex with a HLA to which the EBV-CTL is restricted.

The structural and physicochemical properties have adequately been described. Since tabelecleucel is a cell-based product most physicochemical characteristics relevant for e.g. recombinant proteins are not applicable. The mechanism of action has been described as relying on the cytotoxicity of tabelecleucel toward malignant EBV-infected cells of the patient. Sufficient information was provided.

2.4.2.2. Manufacture, process controls and characterisation

Manufacturers

The sites responsible for manufacturing and testing of the PBMC intermediate, active substance and finished product have been outlined in the dossier. The active substance is manufactured at Charles River Laboratories, Inc., Memphis, USA.

During the procedure a major objection was raised due to the absence of EU GMP certificates for several of the manufacturing and testing sites. Following completion of the relevant EU GMP inspections and submission of the requested GMP certificates this major objection has been satisfactorily resolved.

Description of manufacturing process and process controls

The manufacturing of tabelecleucel is comprised of five process stages: 1) Preparation of purified PBMC intermediate; 2) Transformation of the B-cell component of the autologous PBMC intermediate with EBV reagent (preparation of BLCL reagent); 3) Expansion and irradiation of BLCL cells (preparation of BLCL APC reagent); 4) Stimulation and expansion of EBV-specific T-cells by co-culture with BLCL APC, followed by harvest, wash and formulation in cryopreservation solution; 5) After active substance in-process control (IPC) testing, final fill and finish is performed followed by cryopreservation to yield the finished product.

No distinct active substance that is stored and tested is defined in the tabelecleucel manufacturing process as the process is continuous from PBMC intermediate through finished product. The active substance manufacturing process description includes the manufacture of PBMC intermediate from leukapheresis collection starting material through EBV-CTL formulated bulk active substance.

The active substance manufacturing process encompasses two segments: a core active substance (and finished product) process stream and a reagents process stream. The reagent process stream serves to produce the BLCL APCs that are used for selective stimulation and expansion of the desired final cytotoxic T cells. Further information related to the BLCL reagents is provided in the control of materials section.

A detailed overview of the manufacture and control of the PBMC intermediate has been provided. The leukapheresis starting material is collected at qualified sites and shipped to Charles River Laboratories, Inc. for subsequent manufacture of PBMC intermediate. This intermediate is used for the manufacture of the active substance.

The manufacturing process has been adequately described, including the associated critical process parameters (CPPs), non-critical key process parameter (NCKs), IPCs and in-process tests (IPTs). The associated acceptance range and target values for each CPP and NCK have been listed.

Cell concentration and viability is continuously measured during the cell culture. Samples for mycoplasma and adventitious viruses are used for finished product release.

The applicant sufficiently described the manufacture of finished product including the PBMC intermediate.

Control of materials

For all non-compendial materials specifications, including tests and acceptance criteria, have been set. The source (supplier/vendor) for each raw material has been presented.

The composition of formulated media, buffers and solutions has been detailed by the applicant, and their use in the manufacturing process steps has been specified.

BLCL APC reagent

The BLCL APC reagent is an EBV transformed B cell line used to stimulate autologous PBMCs. BLCLs and PBMCs are derived from the same leukapheresis donation. The BLCL APC reagent is obtained from the BLCL reagent by expansion in cell culture.

The manufacture of the BLCL APC reagent from the BLCL reagent has been adequately described. Throughout the expansion process cell concentration and viability is measured.

BLCL reagent

The manufacturing process of the BLCL reagent has been sufficiently described, and suitable IPCs have been established. PBMCs are infected with the EBV reagent followed by expansion of the culture for a defined time period. Finally, formulation and filling of the harvest is carried out.

For the release of BLCL reagent the control of relevant quality attributes such as identity, purity, strength and safety (sterility, endotoxin, and mycoplasma testing) has been established. Acceptable justification of specification for the BLCL reagent was provided. Based on the currently available stability data a shelf life has been established for the BLCL reagent.

EBV

The EBV producer cell line, derived from a primate B cell line transformed with EBV, master cell bank (MCB) is used directly to seed cell culture for the production of EBV reagent. A description on source, history and generation of MCB has been provided.

Testing of the MCB and limit of *in vitro* cell age (LIVCA) cells for adventitious and endogenous viruses is in line with ICH Q5A and Ph. Eur. 5.2.3 and is deemed sufficient. No viruses have been found in either the MCB or LIVCA cells.

The EBV reagent manufacturing process was described. Manufacture is controlled by appropriate IPCs.

The EBV reagent is tested on the harvest for adventitious viruses. The testing is in line with Ph.Eur. 2.6.16 requirements and is deemed sufficient.

The EBV reagent specification includes tests for identity, purity, potency, sterility, endotoxin and mycoplasma.

The testing performance for adventitious and endogenous viruses has been described, and data on assay qualification are provided.

The proposed shelf-life for the EBV reagent is acceptable.

Leukapheresis, donor testing

Testing of the allogeneic donors follows EU Directives for blood and cells/tissues, i.e. Directive 2002/98/EC and its implementing Directive 2004/33/EC as well as Directive 2004/23/EC and its implementing Directive 2006/17/EC.

IDM testing was and will be performed exclusively with CE-labelled IVDs in laboratories in the EU.

The infectious disease marker panel is appropriate. All tested markers must be negative with exception for CMV. PBMCs from CMV positive donors (IgG, IgM, NAT) may be used for tabelecleucel manufacture. The finished product will be labelled with the donor's CMV status. In addition, appropriate questions for minimising the risk for human TSE are also implemented.

Future changes may occur related to the introduction of batches (with different HLA genotypes and HLA restrictions) manufactured from new donors in a new country and/or different region with significantly different pattern of infection disease. In this perspective, a variation will be submitted for evaluation of the revised adventitious agent risk assessment and consequent update of the viral safety testing programme.

Information on the shipping process of the donor samples for IDM testing to the EU testing laboratory have been provided giving sufficient assurance on the appropriateness of the shipping conditions.

Control of critical steps and intermediates

Active substance

The applicant classified process parameters either into critical or non-critical. A complete list of process parameters as occurring during manufacture was included. Acceptable ranges have been defined for all parameters and IPCs. A summary of the validation parameters and validation results was provided for the IPC analytical methods.

PBMC intermediate

For the PBMC intermediate critical and non-critical process parameters have been presented together with IPCs.

The PBMC specification includes appearance, sterility, viable cell concentration, viability, endotoxin, HLA type. Appropriate justification for each attribute was provided.

The quality of the PBMC intermediate is sufficiently controlled. All batches shown are within specification.

Long-term stability of the PBMC intermediate will be assessed for the duration of the study. The currently available real-time stability data support the established shelf life. The stability data for all batches tested are within specification.

Certificate of analysis (CoA) of vials confirming sterility has been provided. The same container closure system is used for the storage of BLCL reagent.

Process validation and/or evaluation

For manufacturing process validation the applicant applied a consecutive validation approach, starting with the validation of PBMC manufacture. This section specifically covers the validation of the PBMC manufacture. Validation of the active substance/finished product manufacture is discussed in the finished product section.

PBMC PPQ lots were manufactured and all fulfilled the release criteria. Critical and key process parameters were fulfilled for each batch. The validation of PBMC manufacture is considered sufficient.

The PBMC aseptic validation is considered sufficient.

Shipping of leukaphereses has been sufficiently validated.

PBMC shipment was sufficiently validated.

Manufacturing process development

Active substance process characterisation

Manufacturing process version PV1 and the associated batch release test methods have been developed and performed at the original manufacturer over the course of approximately twenty years. The manufacturing process was transferred for the late-stage clinical development and commercialisation. As the manufacturing process was transferred, the process was scaled-up and improved with a process version PV2 and then process version PV3.

Within PV3, the further process versions are defined based on manufacturing site and use of different EBV reagent versions.

The approach to demonstrate comparability of product manufactured by PV1, PV2, PV3 is further discussed in the finished product section.

EBV reagent comparability

Analytical comparability of EBV reagent supplies manufactured at different locations was assessed. All EBV reagents were manufactured using the same cell line.

A statistical rationale is provided for the comparability margins.

Characterisation

Various characterisation studies have been performed on multiple batches produced by PV2 and PV3 manufacturing processes.

Characterisation studies confirm that tabelecleucel is predominantly a TCRα/β+CD45RO+CCR7- effector memory T cell (CD3+) population comprised of CD8+ cells, and to a lesser degree CD4+ cells, that have demonstrated cytotoxicity to Epstein-Barr virus (EBV)-antigen presenting targets. Tabelecleucel is comprised of an enriched EBV-specific effector T cell population that is cytotoxic toward autologous EBV antigen-positive target cells as well as toward allogeneic EBV antigen-positive target cells matched to at least one HLA restriction of tabelecleucel (restricting allele).

Impurities

Impurities have not been characterised at the active substance level. The theoretical and actual impurities observed in tabelecleucel are discussed below although they were addressed in the finished product part of the dossier.

A list of all process- and product-related impurities was presented.

The irradiation dose ensures that no replication competent BLCLs are introduced into the finished product. The ability of residual EBV to infect PBMCs or cord blood cells has been addressed in the non-clinical part of the dossier.

The washing steps efficiently removed medium components The levels of monocytes, granulocytes, B cells, and NK cells were shown to be low.

2.4.2.3. Specification

No distinct active substance that is stored and tested is defined in the tabelecleucel manufacturing process since the process is continuous. Therefore, specification, analytical procedures, batch analyses, reference standards, and container closure system information is provided only in the finished product section.

2.4.2.4. Stability

As the active substance is immediately processed to finished product without a hold step, no active substance stability data has been submitted, which is acceptable.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and Pharmaceutical Development

Each vial of tabelecleucel contains a target concentration of 5 x 10^7 viable T cells/mL (acceptable range 2.8 × 10^7 – 7.3 × 10^7 cells/mL) with DMSO and HSA in a buffered saline solution. The excipients used in the final formulation are commonly used for cell therapy product formulations. After thawing, tabelecleucel needs to be diluted with commercially available multiple electrolytes solution for injection (pH 7.4) before injection by healthcare professionals.

There is no overage in the tabelecleucel formulation. Vials are overfilled to 1.2 mL to ensure that there is a sufficient withdrawable dose of 1.0 mL in each vial.

The compatibility of the excipients with the CTLs has been demonstrated through formulation development studies. The information presented describes the compatibility of excipients with CTLs across a range of concentrations and hold times.

The proposed commercial formulation has been used for all process versions and throughout clinical development.

Manufacturing process development

CQAs were identified through a risk-based approach, taking into account impact and uncertainty. A list of attributes belonging to categories general (e.g. appearance, pH), safety, strength, potency, purity and identity were assessed by the applicant and defined as either CQA, potential CQA, or non-CQA. The presented approach is considered acceptable. It was further outlined by the applicant how each attribute is controlled during manufacture and release.

Comparability studies

Please refer also to the active substance section for details on the different processes. The applicant has conducted comprehensive analytical comparability studies to assess:

1. Comparability of the product manufactured with the commercial process to product manufactured with the PV3 processes used in the pivotal clinical trial.

2. Comparability of the product manufactured with PV1 to clinically used product.

The current comparability strategy lacks process version 2 (PV2) product batches. Only a few batches of PV2 were used in the clinical development. Since these were not used in the pivotal study it can be agreed that the impact of not assessing comparability between PV1 and PV2 has minimal impact on the interpretation of efficacy. It is expected that no further PV2 batches will be used in the future.

The assignment of quality attributes into two tiers representing critical ones or characterisation attributes/attributes not associated with quantitative potency, safety, purity is acceptable.

The statistical testing for equivalence is endorsed and general considerations presented by the applicant on the overlap of distributions are in principle supported.

Comparability of PV1 material to clinically used PV3 material

The applicant provided evidence that the batches used for comparability purposes are representative of all PV1 batches.

Altogether, clinical data derived from PV1 batches can be considered suitable for supporting clinical data obtained from the pivotal study.

Comparability of commercial material to clinically used PV3 material

All quality attributes were comparable although a statistically significant difference was observed for some attributes. It can be agreed that these differences are not of practical importance. Comparability of commercial material to the clinically used material is considered to be shown.

Container closure

The primary container closure system consists of the 2 mL vial and a cap. The vial comprises a cyclo-olefin copolymer vial body with a pre-sealed thermoplastic elastomer stopper. The filled and re-sealed vial is fitted with a single-use cap assuring a tamper evident closure.

The Vial/Stopper system consist of the bottom ring, vial body, stopper and top ring.

The supplier of the container closure system is indicated. Specifications of the primary packaging components are provided, as well as schematic drawings. A certificate of conformity has been provided.

The container closure system is sterilised by gamma irradiation. A sterility assurance level (SAL) of 10-6 is achieved according to presented certificate of conformity.

2.4.3.2. Manufacture of the product and process controls

Manufacturers

For details of the sites responsible for manufacturing, testing and release of the finished product have been outlined in the dossier. Batch release is performed at Fisher Clinical Services GmbH, Weil am Rhein, Germany.

Exemption from EU batch release testing

The applicant applied for an exemption from finished product batch release testing in the EU. An exemption from the requirement for EU release testing is considered justified in view of the limited amount of material available.

Manufacturing process and process controls

The manufacturing process is a continuous process without a defined active substance hold step. The applicant has described in the active substance section the manufacture up to the level of bulk active substance ahead of formulation and filling. This is acceptable.

The finished product manufacturing process consists of filling, inspection, labelling and cryopreservation.

Process characterisation and validation

Validation of the freezing process was executed. All vials derived from the validation batches passed the specification. Validation is considered acceptable. Aseptic processing is requalified regularly.

Shipper thermal operational qualification was done via (i) temperature simulations and (ii) real shipments. In summary, shipping validation is considered appropriate.

For process validation multiple PPQ batches were manufactured at the commercial manufacturing site. All process parameters and IPCs were fulfilled for each batch. The filling process was successful for all batches as verified by fill volume check.

To qualify labelling, packaging and handling primary vial integrity was tested. Transport from liquid nitrogen to shipper was also successfully validated.

In conclusion, the overall manufacturing process (refer also to the active substance section) is considered adequately validated.

2.4.3.3. Product specification

The finished product specification is provided. Quality categories and associated attributes include general (appearance, pH, osmolality), strength (fill volume, viable cell concentration), purity (viability), identity (immunophenotype, HLA type, HLA restriction), potency (T cell proliferation by fold expansion assay, EBV specificity by ^{51}Cr release assay), safety (alloreactivity, EBV impurity, particulates, sterility, endotoxin, mycoplasma, and *in vitro* adventitious viruses). The presented specification is considered appropriate to control the quality of the finished product.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical methods

Verification of the methods according to Ph.Eur. was sufficiently performed.

Non-compendial methods have been appropriately validated.

Batch analyses

Batch release data have been provided for the batches currently available for commercial distribution. All batches met the release specification criteria.

Reference materials

No unique reference standards exist for calculating quantitative results. This is acknowledged considering the donor-specificity of each product batch.

2.4.3.4. Stability of the product

A shelf-life of 4 years when stored in the vapour phase of liquid nitrogen at ≤ -150°C is proposed by the applicant. Based on the presented stability data this shelf-life is justified.

The stability studies are carried out in accordance with current guidelines. Stability studies are performed at the long-term storage condition and accelerated storage condition. Long-term stability data of commercial batches and clinical batches are provided. Also, stress stability studies and in-use stability studies were performed.

All batches in the long-term stability programme were manufactured at the proposed commercial manufacturing site using the intended commercial formulation and container closure.

Evaluation of test attributes including appearance, viable cell concentration, viability, T-cell proliferation potential, sterility, particulates and pH confirms that the finished product remains within the acceptance criteria during long term storage. No significant trend in any attribute has been observed at the long-term storage condition and all batches have met all stability protocol acceptance criteria.

An in-use stability study was conducted. The applicant's conclusion that the finished product is stable at room temperature for a cumulative total of 3 hours from start of the thaw is acceptable.

Photostability studies were not included in the stability programme, based on the proposed storage condition (stored in vapor phase cryogenic nitrogen at ≤ -150°C, preventing exposure to light). This is considered acceptable. The SmPC includes a statement that the product should be protected from light when stored at room temperature after thawing.

A commitment is made to continue the ongoing long-term stability studies and accelerated studies for the finished product. In addition, one finished product batch per year will be placed on stability. This commitment is considered acceptable.

In conclusion, based on the presented stability data, the proposed shelf-life of 4 years when stored in the vapour phase of liquid nitrogen at ≤ -150°C is considered acceptable.

2.4.3.5. Post approval protocol

In module 3.2.R the applicant has provided information on the drug product inventory (DPI). The DPI is comprised of individual finished product batches of tabelecleucel of diverse HLA genotypes and confirmed HLA restrictions. The applicant states that finished product batches with replacement and/or incrementally different HLA genotypes and HLA restrictions manufactured and released per procedures described in the approved marketing application will be added into the inventory post-approval. A protocol for such additions has also been included in 3.2.R (this is however not formally a post approval change management protocol). In view of the need to make new batches available without delay, the applicant considers prior approval unfeasible and proposes notifications on an annual basis.

In principle it is acceptable that batches with different HLA genotypes and HLA restrictions manufactured from new donors will be added post-approval without prior assessment for each batch. The applicant has demonstrated that consistent finished product quality is achieved with donors displaying different HLA alleles. Manufacturing of batches derived from a variety of different donors is controlled by critical and key process parameters, in-process controls, and specifications, thereby

resulting in consistent finished product quality. In case an HLA-associated factor would negatively impact on finished product quality the existing manufacturing controls and release testing would prevent release and use in patients.

In conclusion, the inclusion of new batches in the DPI without prior assessment is acceptable. However, the applicant is recommended to present batch data for the newly included batches for review on an annual basis (Recommendation 3).

2.4.3.6. Adventitious agents

The final product consists of living cells, therefore, virus inactivation steps cannot be implemented in the tabelecleucel manufacturing process. The overall TSE and virus safety strategy thus relies on the careful selection, control, testing of raw materials and inactivation procedures applied to them, testing of the PBMC donors as well as testing of tabelecleucel intermediates such as EBV reagent and its production cell bank and of the finished product testing.

Several human and animal-derived materials, besides the human donor PBMCs, are included in the manufacturing process of tabelecleucel. HSA is also used as excipient. The HSA is an approved product in the EU and reference to a plasma master file (PMF) is provided. For all human-derived materials, implementation of a full traceability system from the donor to the tabelecleucel finished product and vice versa is implemented.

The EBV reagent used for generation of BLCL APCs is produced from a cell line which permanently produces infectious EBV. Genealogy of the cell line including information on which animal and human raw materials were used in its development have been sufficiently described. The MCB used for production of the commercial EBV reagent as well as an end-of-production cell bank were generated and tested for adventitious viruses according to ICH Q5A and Ph. Eur. 5.2.3 requirements. No viruses have been found in either cell bank, therefore, the use of the MCB in the manufacture of the EBV reagent is acceptable.

Data have been submitted to demonstrate adequate capability of tabelecleucel manufacturing process steps to remove EBV.

In conclusion, information has been provided to give sufficient reassurance in relation to viral/TSE safety.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure a major objection was raised due to the absence of EU GMP certificates for several of the manufacturing and testing sites. Following completion of the relevant EU GMP inspections and submission of the requested GMP certificates this major objection has been satisfactorily resolved.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the benefit/risk ratio of the product, which include control of the EBV reagent, control of a material of human origin used in the manufacturing process, and reporting of data for new batches added to the DPI. These points are put forward and agreed as recommendations for future quality development (see below).

To manage the inclusion of new batches in the DPI during the post-authorisation lifecycle of the product it has been agreed that the applicant will present batch data for the newly included batches for review on an annual basis (see Recommendation 3).

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

The CHMP endorses the CAT assessment regarding the conclusions on the chemical, pharmaceutical and biological aspects as described above.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends some points for investigation.

The CHMP endorses the CAT assessment regarding the recommendation(s) for future quality development as described above.

2.5. Non-clinical aspects

2.5.1. Introduction

Tabelecleucel is an allogeneic Epstein-Barr virus (EBV)-specific T-cell immunotherapy which targets and eliminates EBV-positive cells in a human leukocyte antigen (HLA)-restricted manner. The Ebvallo manufacturing process uses human- and animal-derived materials. Ebvallo is tested for specificity of lysis of EBV+ targets, T-cell HLA restriction of specific lysis, and verification of low alloreactivity. Ebvallo is selected for each patient from the existing product inventory based on an appropriate HLA restriction.

2.5.2. Pharmacology

The pharmacological action of tabelecleucel has been extensively reported in literature [Doubrovina 2012; Lacerda 1996; O'Reilly 2016]. Tabelecleucel cytolytic function is accomplished by the formation of an immune-stimulatory synapse, comprised of a tripartite interaction between the T cell receptor (TCR) of a given tabelecleucel T cell clone, and an EBV-epitope in complex with an HLA molecule on the target cell. The specific HLA molecule expressed on the target cell that "presents" the EBV epitope to the TCR is also referred to as the restricting HLA allele. Similarly, the epitope, or EBV antigen peptide sequence presented by the specific HLA molecule, is referred to as a restricting epitope. Stimulation of the TCR through this tripartite synapse results in a degranulation event by the T cell delivering perforin and granzymes to the target cell and resulting in enzymatic degradation and apoptosis of the target. Expression of FAS ligand on tabelecleucel also facilitates ligand mediated apoptosis of the target cell through activation of an extrinsic apoptotic cascade following co-localisation between tabelecleucel and target cells mediated through the same TCR interactions [Russell 2002].

2.5.2.1. Primary pharmacodynamic studies

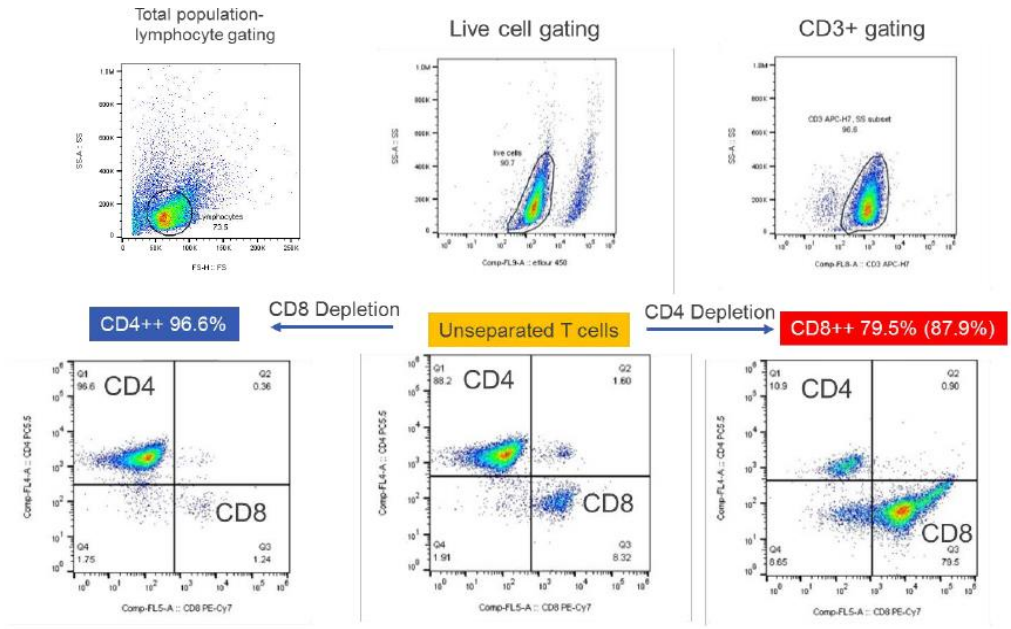
Study Number: PHRM-RPT-129-1005

Study Title: Evaluation of the contribution of CD4 and CD8 component parts to the EBV-specific cytotoxicity of ATA129

The goal of the study was to elucidate whether isolated CD4+ or CD8+ fractions of an ATA129 lot contribute to the overall cytotoxic activity of the product. In process ATA129 product was received on Day 27 of ongoing culture and was separated into CD4 and CD8 enriched fractions.

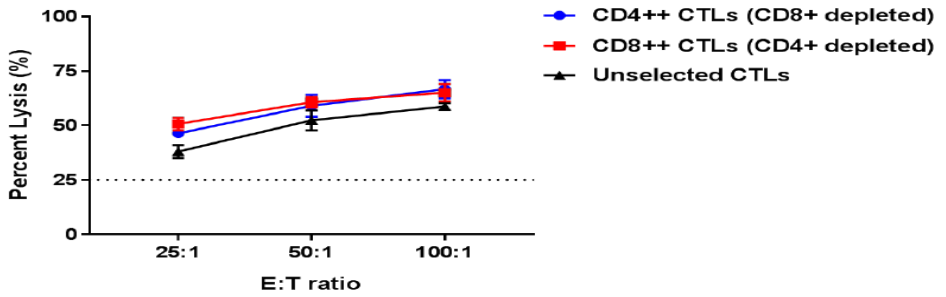
Expression of CD4 and CD8 on CD3+ live cells on unseparated ATA129 was found to be 8.3% CD8+ and 88.2% CD4+ (Expression of CD4 and CD8 on CD3+ live cells on untouched CD4+ was found to be 1.24% CD8+ and 96.6%% CD4+, equating to an approximate 90% efficiency in CD8 depletion. Expression of CD4 and CD8 on CD3+ live cells on untouched CD8+ was found to be 79.5% CD8+ and 10.9% CD4+), equating to an approximate 90% efficiency in CD4 depletion (**Figure 1**).

Figure 1. Gating strategy and resulting populations following depletion of CD8 (blue box, left) or CD4 (red box, right) T Cells from the unseparated (yellow box, centre) population. The total population percentage of all CD4 depletion is also shown (value in red box in parentheses).



Cytotoxicity was performed on autologous chromium-labelled EBV B-lymphocyte cell lines (EBV BLCL, the raw material to stimulate EBV-specific CTLs) on Day 27 (**Figure 2**).

Figure 2. Cytotoxicity values obtained using autologous BLCLs as the target at the E:T ratios listed. The dotted line at 25% represents the specification for cytotoxicity of manufactured ATA 129-Study PHRM-RPT-129-1005



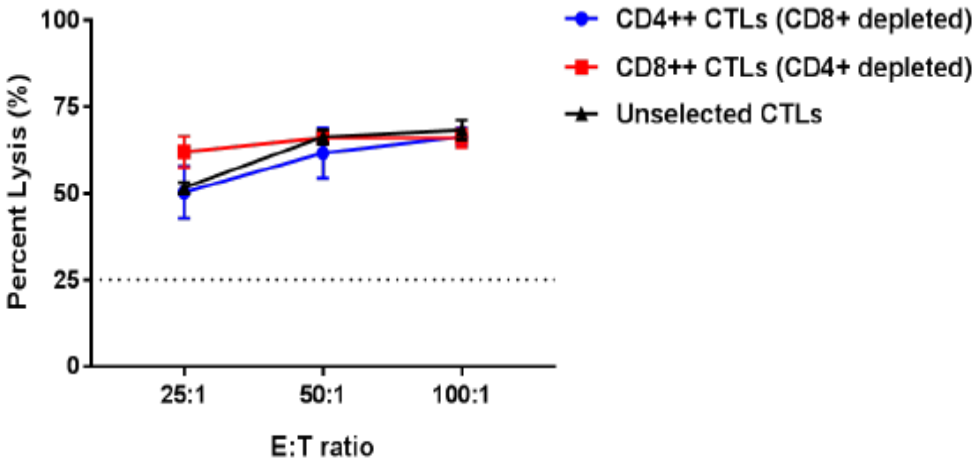
	CD4+			CD8+			Unselected		
E:T ratio	100 to 1	50 to 1	25 to 1	100 to 1	50 to 1	25 to 1	100 to 1	50 to 1	25 to 1
% Lysis	67%	59%	46%	65%	60%	51%	58%	52%	38%

Study Number: PHRM-RPT-129-1006

Study Title: Evaluation of the contribution of CD4 and CD8 component parts to the EBV – specific cytotoxicity of ATA129

In process ATA129 product was received on **Day 23** of ongoing culture and was separated into CD4 and CD8 enriched fractions. Cytotoxicity was performed on autologous chromium-labeled BLCLs on Day 24 (**Figure 3**).

Figure 3. Cytotoxicity values obtained using autologous BLCLs as the target at the E:T ratios listed. The dotted line at 25% represents the specification for cytotoxicity of manufactured ATA 129-Study: PHRM-RPT-129-1006



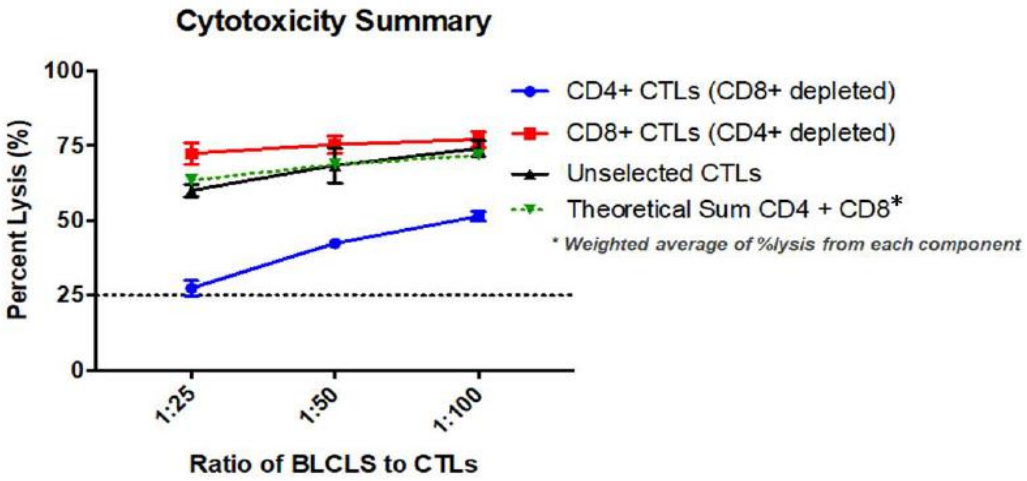
% Lysis = ((ER-ΔSR)/(ΔMR-ΔSR))*100	CD4+			CD8+			Unselected		
E:T ratio	100 to 1	50 to 1	25 to 1	100 to 1	50 to 1	25 to 1	100 to 1	50 to 1	25 to 1
Average (Δ) % Lysis	66%	62%	50%	66%	66%	62%	69%	66%	51%

Study Number: RPT-129-1004

Study Title: Evaluation of the contribution of CD4 and CD8 component parts to the EBV – specific cytotoxicity of ATA129

In process ATA129 product was received on **Day 35** of ongoing culture and was separated into CD4 and CD8 enriched fractions. Cytotoxicity was performed on autologous chromium-labeled BLCLs on Day 37 (**Figure 4**).

Figure 4. Cytotoxicity values obtained using autologous BLCLs as the target at the E:T ratios listed. The dotted line at 25% represents the specification for cytotoxicity of manufactured ATA 129-Study PHRM-RPT-129-1004



	CD4+			CD8+			CD4+/CD8+			Theoretical Sum CD4+/CD8+		
E:T Ratio	100 to 1	50 to 1	25 to 1	100 to 1	50 to 1	25 to 1	100 to 1	50 to 1	25 to 1	100 to 1	50 to 1	25 to 1
% Lysis	51%	42%	27%	77%	75%	72%	74%	68%	60%	72%	69%	63%

***In vivo* experiments**

Human Epstein-Barr Virus (EBV)-Specific Cytotoxic T Lymphocytes Home Preferentially to and Induce Selective Regressions of Autologous EBV-induced B Cell Lymphoproliferation in Xenografted C.B-17 SCID/SCID Mice [Lacerda 1996]

Mutant C.B-17 mice homozygous for the autosomal recessive mutation (SCID mice) are severely deficient in B and T cells. Because SCID mice are unable to generate functional lymphocytes, engraftment and growth of human lymphocytes and several human tumours are possible. Human lymphocytes have been shown to remain functional in SCID mice after adoptive transfer. Inoculation of SCID mice with EBV+ BLCL results in development of EBV-induced immunoblastic B cell lymphomas with characteristics similar to EBV-PTLD arising in immunocompromised hosts [Rowe 1991]. Furthermore, SCID mice were used to evaluate the anti-lymphoma activity of different human effector cell populations [Schmidt-Wolf 1991]. The primary goal of this study was to assess in-vivo homing and EBV specificity and efficacy of tabelecleucel in the presence or absence of IL-2.

In the experiments described below, SCID mice were treated intraperitoneally (IP) with rabbit anti-asialo GM1 antiserum on days 1, 4, 8, and every 5 to 7 days thereafter, to deplete endogenous NK cell function. Mice were inoculated with EBV+ BLCL on day 1 followed by administration of tabelecleucel to mice in each treatment group.

SCID mice inoculated IP with autologous (donor 1) but not with HLA-mismatched (donor 2) EBV+ BLCL had significantly improved survival relative to untreated mice after IP inoculation of tabelecleucel ($p < 0.001$). Of these animals inoculated with autologous EBV+ BLCL and then treated with tabelecleucel, 2 of 5 survived long-term without ever developing lymphomas. Thereafter, the authors investigated whether the IV infusion of tabelecleucel would also mediate a therapeutic effect. The IV inoculation of 107 EBV-specific CTL resulted in improved survival of SCID mice ($n = 5$) ($p < 0.001$) relative to untreated animals ($n = 10$)

The authors investigated whether tabelecleucel might require IL-2 support for prolonged *in vivo* survival in the IP and SC EBV+ SCID mouse model. Both tabelecleucel and tabelecleucel-plus-IL-2-treated mice survived significantly longer than untreated animals ($p < 0.001$ and $p = 0.02$, respectively) or animals treated with IL-2 alone ($p = 0.004$ and $p < 0.004$, respectively). Three of the 5 mice treated with both IL-2 and tabelecleucel ultimately died of lymphoma, but onset was delayed compared to all other groups. Furthermore, SCID mice bearing large SC EBV+ tumours (~80 mm2) and treated IV with tabelecleucel or tabelecleucel-plus-IL-2 at a dose of 107 cells achieved complete tumour regression. Two of 5 mice in each group had complete tumour regression and survived > 5 months after tabelecleucel treatment.

Preferential homing of PKH26 fluorescent-labelled tabelecleucel to autologous EBV+ tumours was observed as early as 24 hours after IV adoptive transfer; homing to HLA-mismatched EBV+ tumours was not observed (data not shown). Immunophenotypic analyses also demonstrated preferential infiltration of T cells into the autologous EBV+ tumour in SCID mice bearing both the autologous or genotypically related haplotype-sharing EBV+ tumours. The human T cells infiltrating EBV+ tumours were CD3+ and predominantly CD8+CD4-.

2.5.2.2. Secondary pharmacodynamic studies

There is no known measurable off-target or on-target off-tumour pharmacodynamics of tabelecleucel in either clinical investigations or non-clinical models. Based on clinical study results with tabelecleucel and nonclinical studies completed to date, no unexpected effects on the pharmacodynamics were observed which could have warranted additional investigation through secondary pharmacodynamic studies.

2.5.2.3. Safety pharmacology programme

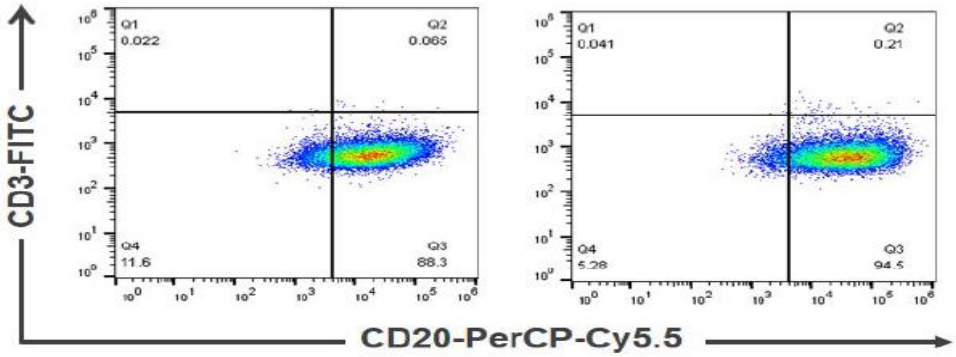
Safety pharmacology studies were not conducted due to the species-specific nature of tabelecleucel and the limited applicability of non-human toxicology models.

2.5.2.4. Pharmacodynamic drug interactions

Considering that Rituximab is an anti-CD20 used as a front-line treatment for B-cell malignancies, potential drug-drug interaction could interfere with EBV-CTLs (referred to as ATA 129 PV2A in this study) if CD20 is expressed on the CTLs cell therapy product.

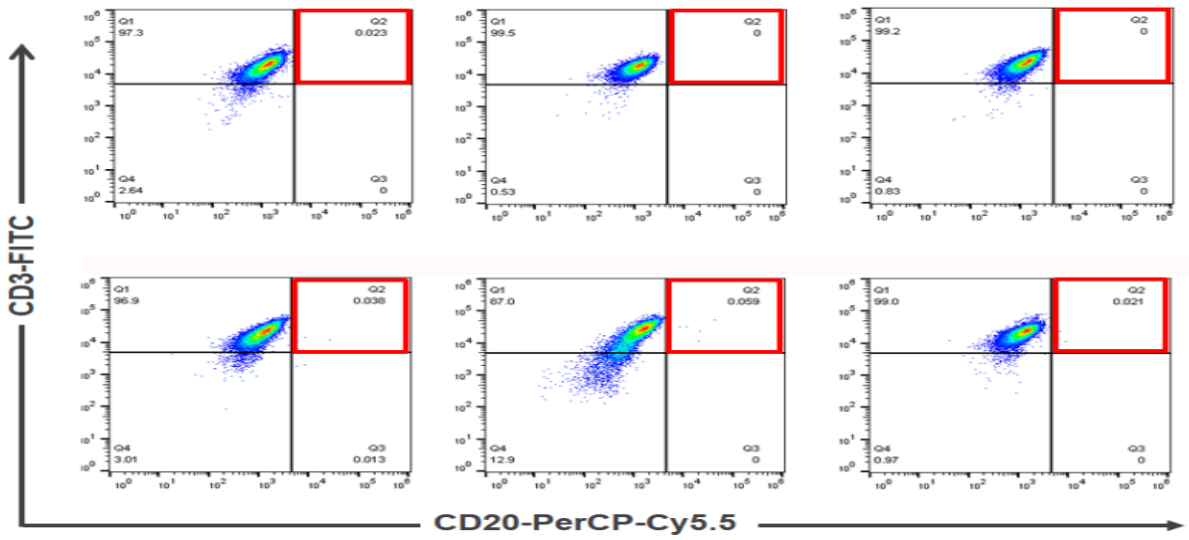
Flow cytometric evaluation showed that CD20 was highly expressed on BLCL (88-4%-94.5%; n=2) Conversely, BLCL did not express CD3 marker (0.02%-0.04%; n=2) (**Figure 5**).

Figure 5. Representative dot plots for CD3 and CD20 expression on BLCL (n=2)



CD3 was highly expressed on all ATA 129 vials (96.4%±4.8%; n=6). Moreover, flow cytometric examination of CD20 receptor expression revealed that the CD3+ cell population did not express significant levels of this marker (0.03%±0.03%; n=6).

Figure 6. Representative dot plots for CD3 and CD20 expression on ATA 129 PV2A (n=6) (The red rectangle depicts CD20 expression on CD3+ cells)



2.5.3. Pharmacokinetics

Conventional studies on pharmacokinetics, absorption, distribution, metabolism, and elimination are not applicable for tabelecleucel as described in the CHMP's 2006 Guideline on human cell based medicinal products (EMEA/CHMP/410869/2006). In order to address the persistence and/or the fate of the infused cells the applicant referred to published literature ([Doubrovin 2007] and [Koehne 2003]), describing in detail the *in vivo* imaging experiments conducted in tumour-bearing mice with radiolabelled tabelecleucel. It was shown that tabelecleucel was able to migrate to and infiltrate sc BLCL tumours within 1 day. Further infiltration was observed on days 8 and 28 [Doubrovin 2007]. Migration and infiltration occurred into fully HLA-matched tumours and was absent from mismatched tumours. Similarly, infiltration/absence of infiltration occurred in EBV+/EBV- BLCL [Koehne 2007].

2.5.4. Toxicology

2.5.4.1. Single and repeat dose toxicity

Single and repeat dose toxicity studies were not conducted as due to the species-specific nature of tabelecleucel these studies would yield no additional information to aid in the understanding of its potential toxicity in humans.

2.5.4.2. Genotoxicity

As tabelecleucel is a non-genetically engineered cell product, it is not expected to interact directly with DNA or other chromosomal material. In accordance with ICH S6(R1), genotoxicity studies with tabelecleucel were not conducted.

2.5.4.3. Carcinogenicity

Tabelecleucel has not demonstrated, and is not anticipated to have, carcinogenic potential and as stated in ICH S6(R1), standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals.

The applicant conducted study RPT-129-1002 to investigate potential EBV transmission and tumorigenic effect. This study utilised a co-culture assay using and EBV-specific cytotoxic T lymphocytes lines (EBV-CTL) or EBV BLCL with cord blood mononuclear cells (MCBC). B-cell transformation and the presence of EBV did not occur in any instance when EBV BLCL or EBV CTL were cocultured with the cord blood samples.

A similar coculture assay was conducted with T cell depleted normal PBMC, used as targets for infection. Data showed that, in no instance, B cell transformation or the presence of EBV was detected in the T cell depleted PBMC cultured with the EBV-specific CTLs. However, B cell transformation and the presence of EBV was detected in 3/10 samples in which autologous irradiated EBV BLCL. Such growth was only detected when the EBV BLCL were cultured in the absence of either acyclovir or ganciclovir.

Comparative analyses of BLCL and EBY-specific CTL derived from 5 individuals cocultured both with the T cell depleted mononuclear cells and with the cord blood cells was also conducted. Again, in no instance was EBV detected in the cord blood samples. EBV was detected in one of the 5 samples of T cell depleted PBMC cocultured with autologous BLCL in the absence of acyclovir or ganciclovir.

These results suggest that coculture of EBV BLCL and EBV-specific CTLs with T cell depleted PBMC in the presence of cyclosporin may be more sensitive for detecting EBV. Again, in no instance, however, was transmissible EBV detected in the CTLs in the presence or absence of acyclovir or ganciclovir. The comparative studies suggest that co-culture of cell products with T cell depleted PBMC in the presence of cyclosporin may, in fact, be more sensitive than coculture with cord blood samples.

Taken together, this data showed the lack of transmission and uncontrolled proliferation of infectious EBV to MCBC and autologous T cell depleted PBMC.

2.5.4.4. Reproductive and developmental toxicity

Due to the highly species-specific nature of the pharmacology associated with tabelecleucel, nonclinical reproductive/developmental toxicity studies were not submitted with this application.

2.5.4.5. Local tolerance

As tabelecleucel is administered intravenously, no local tolerance studies were submitted.

2.5.5. Ecotoxicity/environmental risk assessment

Tabelecleucel is a cell based therapeutic product that is not genetically modified. In accordance with the EMA guidance 'Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms (GMOs)', EMEA/CHMP/BWP/473191/2006 – Corr., tabelecleucel is not expected to pose a risk to the environment and therefore an environmental risk assessment was not performed.

2.5.6. Discussion on the non-clinical aspects

Ebvallo consists of a mixture of EBV-specific CD4 and CD8 T cells generated by *ex vivo* stimulation with EBV-infected BLCLs. Ebvallo's mechanism of action is cytotoxicity toward malignant EBV-infected B cells in PTLD patients. Three independent *in vitro* primary PD studies with identical designs confirmed that Ebvallo is cytotoxic toward autologous BLCLs. Besides CD8+ T cells the CD4+ T cells also displayed cytotoxic potential. Study PHRM-RPT-129-1005 demonstrated identical cytotoxicity of both CD4 and CD8, while slightly higher and considerably higher CD8 cytotoxicity was shown in studies PHRM-RPT-129-1006 and RPT-129-1004, respectively. In conclusion, the *in vitro* studies confirmed that besides CD8+ T cells also the CD4 T cells contribute to the mode of action of Ebvallo.

The *in vivo* experiments demonstrated a pronounced therapeutic effect/increased survival of SCID mice suffering from intraperitoneal EBV-induced lymphoblastic B cell lymphomas (EBV-BLCL) that were treated with autologous (with respect to EBV-BLCL) tabelecleucel. This effect was also seen in sc or ip tumours treated with tabelecleucel. Therapeutic effect was observed in the presence or in the absence of IL-2. In a further experiment the migration to and infiltration of tumours was shown in SCID mice. Most of the tumour-infiltrating T cells were CD8+, less were CD4+. Stronger infiltration was found in the autologous tabelecleucel/EBV-BLCL setting, less in the HLA-matched situation. Altogether, the experiments demonstrate *in vivo*-proof of-principle.

The only measurable effect of Ebvallo relies on its mechanism of action, i.e. lysis of EBV-infected B cells. Secondary PD studies are therefore not considered necessary.

Flow cytometric examination of CD20 receptor expression revealed that the CD3+ T cell population did not express significant levels of this marker. These data demonstrate that tabelecleucel does not express CD20 and is not considered to be of high risk for CD20 targeting by Rituximab therapy in patients with EBV+PTLD. Pharmacodynamic drug interactions relying on residual Rituximab are thus unlikely.

The applicant conducted experiments to evaluate the risk of B cell infection either by CTLs or the EBV-infected BLCL stimulator cells. B cells present in allogeneic mononuclear cord blood cells or in autologous T cell depleted PBMC were used as targets for infection. In two cases PBMC could be productively infected with BLCLs. This could be prohibited in the presence of acyclovir that is used in routine manufacture of BLCLs. There were no instances in which CTLs could infect B cells present in cord blood or PBMC. These results provide reassurance regarding the potential of tabelecleucel for EBV transmission and infection.

Due to the nature of the product, *in vitro* assays and studies in *ex vivo* models or *in vivo* models cannot accurately assess and predict the toxicological characteristics of this product in humans. Hence,

conventional toxicology, carcinogenicity, genotoxicity, mutagenicity and reproductive toxicology studies have not been performed with tabelecleucel.

Studies conducted in immunodeficient animal models for EBV+ PTLD revealed no overt signs of toxicity (e.g. loss of activity or weight loss) associated with a single dose of tabelecleucel.

No ecotoxicity/environmental risk assessment was conducted. The active substance consists of non-genetically modified T cells and thus is not expected to pose a risk to the environment.

The CHMP endorse the CAT discussion on the non-clinical aspects as described above.

2.5.7. Conclusion on the non-clinical aspects

From a non-clinical point of view Ebvallo (tabelecleucel) has been adequately characterised and is recommended for marketing authorisation.

The CHMP endorse the CAT conclusions on the non-clinical aspects as described above.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Study/Program Information[a,b]	Phase	Study Design and Populations	Enrolment Information Product and Dosing
ATA129-EBV-302 Start date: 27 June 2018 Status: ongoing Regions: NA, Europe, APAC	3	Multicentre, single-arm, open-label study for treatment of EBV$^+$ PTLD following SOT or HCT after failure of rituximab or rituximab plus chemotherapy (ALLELE)	Planned enrolment: 66 No. enrolled/treated: 39/39 No. treated who had EBV$^+$ PTLD: 39 Tabelecleucel Dose: 2 × 10^6 cells/kg IV on day 1, day 8, and day 15 of a 35-day cycle, and up to 2 different HLA restrictions (SOT subjects) or up to 4 different HLA restrictions (HCT subjects)

EBV-CTL-201 Start date: 28 June 2016 Status: completed, 08 September 2020 Region: US only	2	Multicentre, single-arm, open-label expanded access study for treatment of EBV-associated viremia or malignancies for whom there are no appropriate alternative therapies; the design, data collection, and monitoring were consistent with standard clinical trial procedures	No. enrolled/treated: 66/60 No. treated who had EBV$^+$ PTLD: 25 Tabelecleucel Dose: 1.6 - 2 × 10^6 cells/kg IV on day 1, day 8, and day 15 of a 35-day cycle, and up to 4 different HLA restrictions
11-130 Start date: 20 December 2011 Status: completed, 01 March 2018 Region: US only	2	Single-centre, open-label study for treatment of EBV$^+$ PTLD and other EBV-associated lymphoproliferative diseases or malignancies	No. enrolled/treated: 87/85 No. treated who had EBV$^+$ PTLD: 35 Tabelecleucel Dose: 2 × 10^6 cells/kg IV once weekly for 3 doses, with an option for multiple cycles
95-024 Start date: 24 March 1995 Status: completed, 21 May 2018 Region: US only	1/2	Single-centre, open-label study for treatment of EBV$^+$ PTLD and other EBV-associated lymphoproliferative diseases or malignancies	No. enrolled/treated[c]: 25/14 No. treated who had EBV$^+$ PTLD: 7 Tabelecleucel Dose: 1 - 2 × 10^6 cells/kg IV once weekly for 3 doses, with an option for multiple cycles

Abbreviations: APAC, Asia Pacific; CTL, cytotoxic T lymphocyte; EA, Expanded Access; EBV, Epstein-Barr virus; FAS, full analysis set; HLA, human leukocyte antigen; HCT, haematopoietic cell transplantation; IV, intravenous(ly); NA, North America; NPC, nasopharyngeal carcinoma; PTLD, posttransplant lymphoproliferative disease; LPD, lymphoproliferative disease; ROW, rest of world; SOT, solid organ transplant; US, United States.

[a] Study information definitions: Start date is the date that first subject was included in the study; Status: ongoing or completed with the date of last subject last visit (for ATA129-RS002 completed is the date of database lock).

[b] For the ongoing Studies ATA129-EBV-302, ATA129-EAP-901, and ATA129-SPU, the dataset included available data for all cohorts as of 07 May 2021 for Study ATA129-EBV-302 and 02 July 2021 for the EAPs (ATA129-EAP-901 and ATA129-SPU). For Studies EBV-CTL-201, 11-130, and 95-024, the final datasets were used.

[c] In Study 95-024, a total of 58 subjects received treatment: 14 received tabelecleucel, 11 received nonrepresentative lots, and 33 received transplant donor-derived or autologous EBV-CTLs

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

As this is a cell-based medicinal product, no PK analyses were performed by the applicant. No clinical PK (or PD) studies were performed. Residual amounts of rituximab might interfere with tabelecleucel treatment by binding to CD20. However, as described in the non-clinical section of this report, CD20 is not expressed on tabelecleucel, and PK or PD interactions are therefore unlikely.

2.6.2.2. Pharmacodynamics

Mechanism of action

Tabelecleucel consists of T cells that specifically target and eliminate cells expressing EBV antigens. Tabelecleucel is claimed as being capable to lyse cells presenting EBV antigens in complex with a human leukocyte antigen (HLA) to which the EBV-CTLs are restricted. This includes EBV-transformed B

lymphocytes responsible for EBV+ PTLD.

Primary and Secondary pharmacology

Studies 11-130 and 95-024

Studies 11-130 and 95-024 were combined and analysed as a single study due to their small sample size and similarity in design (open-label single-arm, single-centre studies). The objective of both studies was to explore the relationship of EBV Cytotoxic T-Lymphocyte Precursor (CTLp) with the efficacy and safety endpoints investigated (These studies are further detailed in the Clinical Efficacy section of this report).

According to the investigation plan of study 11-130 the EBV CTLp data per patient were collected at baseline (pre infusion) and up to 13 days post infusion. In study 95-024 the EBV-specific CTLp were measured immediately before, 1, and 7 days following the first and third infusion of cells in each cycle, at days 14 and 21 following the last infusion of each cycle and at 1, and 4 months following completion of additional cycle of cells. The criteria for including patients in the CTLp analysis were application of "at least 1 representative dose of the tabelecleucel cell therapy product".

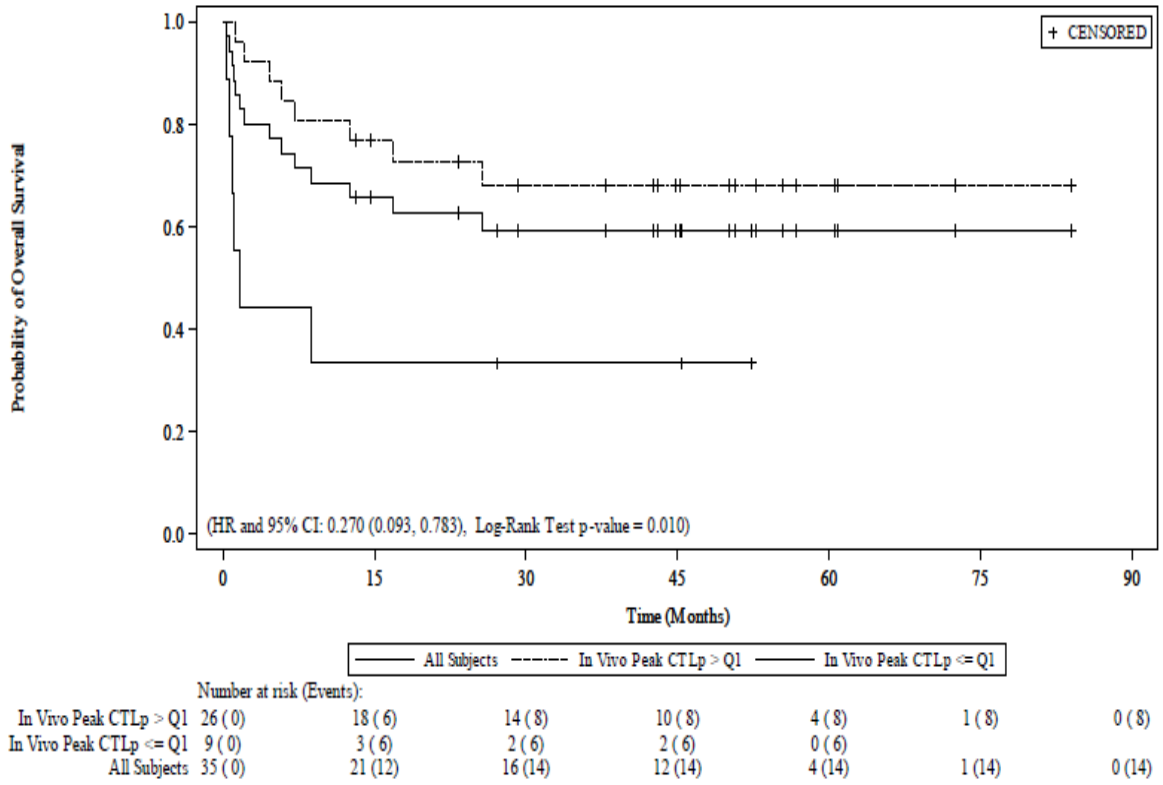
Disease response (**Table 1**) and overall survival (OS,**Figure 7**) parameters were examined by peak EBV-CTLp subgroups (≤Q1 as low or > Q1 high).

Table 1. Summary of EBV Cytotoxic T-Lymphocyte Results by Responder Status Subjects with EBV+ PTLD (Biomarker Analysis Set, Studies 11-130 and 95-024)

In Vivo Peak CTLp (CTLp/mL blood)	Responder (N = 24)	Nonresponder (N = 11)
Mean	104.41	86.90
SD	196.753	275.731
Median	34.05	0.10
Q1, Q3	15.57, 70.11	0.01, 5.50
Min, Max	0.01, 731.9	0.01, 918.0

Abbreviations: EBV, Epstein-Barr virus; CTLp, cytotoxic T-lymphocyte precursor; Max, maximum; Min, Minimum; Q, quartile; SD, standard deviation.
Biomarker analysis set is defined as all subjects with EBV+ PTLD who received at least 1 dose of tabelecleucel and had in vivo peak CTLp (CTLp/mL blood) data.
A subject is considered as responder if the best overall response is either CR or PR. Therefore, non-responder subjects are assessed if best overall response is either SD, PD, or NE.

Figure 7. Overall survival by *in vivo* peak cytotoxic T-Lymphocyte Precursor (CTL_p p/mL blood) Biomarker stratum (≤Q1, > Q1), (Biomarker Analysis Set, Studies 11-130 and 95-024)



Abbreviations: CTLp, cytotoxic T-lymphocyte precursor; HR, hazard ratio; Q, quartile.
Biomarker analysis set is defined as all subjects with EBV+ PTLD who received at least 1 dose of tabelecleucel and had in vivo peak CTLp (cells/mL blood) data.
HR was calculated for the upper three quartiles (> Q1) when compared to first quartile (≤ Q1) as a reference group. P-value results for the comparison of overall survival curves were generated based on the Log-Rank test at the 0.05 significance level.

Study ATA129-EBV-302:

Biomarkers EBV-CTLp, cytokines (IL-1β, IL-2, IL-6, TNF-α), plasma EBV DNA, and anti-HLA antibody were assessed to explore a possible relationship to efficacy and safety endpoints.

Patients in this study received an intravenous infusion of a fixed dose of 2×10^6 cells/kg on days 1, 8, and 15 of each 35-day cycle. Therefore, it is not possible to assess a possible dose response relationship.

39 EBV+ PTLD patients were included in Study ATA129-EBV-302 (25 C-SOT; 12 C-SOT-R; 13 C-SOT-R+C; 14 C-HCT). The criteria for including patients in the CTLp analysis were application of "at least 1 dose of the tabelecleucel cell therapy product" and "evaluable baseline and at least 1 post-baseline measurement" was fulfilled by only 26 patients in the study ATA129-EBV-302.

EBV-CTLp:

Responders showed a higher "Peak Fold Change" for EBV CTLp from baseline (data not shown).

The applicant also provided data from a publication [Prockop 2020]. IFN- γ+ EBV-specific T cells of third-party donor origin were detectable by differences to the host by short tandem repeats (STR). Third-party EBV-CTLs were detectable in patients in the range of 16 days to 32 days and in one patient up to 23.7 months after infusion. The cited literature proposed an activation of endogenous

T cell responses potentially stimulated by cross-presentation of antigens from EBV-associated lymphomas targeted by the third-party EBV-CTLs.

The persistence of infusion product was assessed for five patients using a genetic assay that uses single tandem repeats (STR) from 8 loci to differentiate between the patient PBMCs and infusion product. This detection method does not have broad utility because it can only work when there is enough mismatch at the STR loci to be able to differentiate donor cells from patient cells. This was performed on IFN-gamma^{+} cells post peptide stimulation and limited to the material available. Third-party EBV-CTLs were detected 32 days after initial infusion and 16 days after third infusion in cycle 1, and in one solid organ transplant recipient, at 23.7 months after infusion.

Cytokines:

Plasma was collected prior to infusion of tabelecleucel, then again at safety follow-up. Therefore, long time effects of Ebvallo are recorded. Acute post infusion reactions were not found.

In general, the four evaluated cytokines (IL-1β, IL-2, IL-6, and TNF-α) showed no change to baseline in studies EBV-CTL-201 and ATA129-EBV-302. One patient had elevated IL-6 in study ATA129-EBV-302 that could be related to Ebvallo treatment, but several other factors unrelated to the treatment could also have contributed to the increase in IL-6.

Serum Epstein-Barr Virus DNA:

The PCR-based measurement of the virus load is suitable for monitoring disease progression. The baseline EBV copies/mL ranged from 195 (LLOD) to 1920000 (ULOD). During treatment, the value raised and fell for the patients.

In order to better assess whether the treatment has an influence on the individual virus load, "post-baseline fold change" was plotted. When "Lowest Post-baseline" and "Lowest Fold Change" of Epstein-Barr virus DNA in serum was plotted against responders and non-responders a statistically significant correlation with clinical response was observed. Responders showed lower post-baseline levels of serum Epstein-Barr Virus DNA (data not shown).

Anti-HLA Antibodies:

The anti-HLA antibody dataset was limited to subjects who were tested negative for anti-HLA antibodies prior to the first infusion of tabelecleucel. As all patients came into contact with foreign HLA due to organ transplantation or stem cell transplantation only 7 subjects were tested.

Of the 7 subjects, a single subject in C-SOT subsequently developed a positive anti-HLA antibody result.

2.6.3. Discussion on clinical pharmacology

Biomarker studies were conducted aiming to enumerate the EBV CTLp associated with Ebvallo treatment. However, as the EBV CTLp assay cannot distinguish between endogenous EBV-reactive CTLp and those infused by Ebvallo it cannot provide an accurate estimation for the latter.

A joint analysis of studies 11-130 and 95-024 showed that responders had higher CTLp peaks than non-responders. Similarly, study ATA129-EBV-302 demonstrated a correlation of post-infusion levels of EBV-CTLp with clinical efficacy. Consequently, it is agreed that the EBV-CTLp biomarker may be used to predict the outcome of a patient. However, it cannot be determined whether the biomarker changes seen were in response to treatment or a result of endogenous T cells. Median fold EBV CTLp change from baseline were sometimes below one. This suggests that the EBV CTLp cell number is lower than before the treatment. In addition, not all patients included in these analyses were assessed

at every time point. Data from [Prockop 2020] suggest that in some cases when there is sufficient differentiation in the STR loci between donor and patient cells it is possible to distinguish between the two. However, as such an analysis was limited to only 5 patients, the overall value of the biomarker studies submitted is considered limited.

A statistically significant correlation between EBV DNA levels with clinical response was observed. Responders showed lower post-baseline levels of serum Epstein-Barr Virus DNA. However, as with EBV CTLp, it is not clear whether an endogenous anti EBV immune response is responsible for this effect.

The anti-HLA antibody dataset was limited to only 7 subjects from whom only one developed a positive anti-HLA antibody result. Valid conclusions related to anti-drug antibody (ADA) induction are therefore not possible.

The applicant did not submit secondary PD studies which is considered acceptable due to the nature of the product. Certain concomitant or recently administered medicinal products including chemotherapy (systemic or intrathecal), anti-T-cell antibody-based therapies, extracorporeal photopheresis or brentuximab vedotin could potentially impact the efficacy of Ebvallo. Ebvallo should therefore only be administered after an adequate washout period of such agents.

As tabelecleucel has not been evaluated in patients receiving corticosteroid doses greater than 1 mg/kg per day of prednisone or equivalent, it is recommended not to exceed such doses in patients receiving Ebvallo treatment.

Finally, as *in vitro* characterisation data demonstrated the absence of CD20 expression on tabelecleucel, it is not expected that anti-CD20 antibody treatments will affect tabelecleucel activity.

2.6.4. Conclusions on clinical pharmacology

Limited clinical pharmacology data are available which is to be expected as the nature of the product poses significant challenges to fully characterise its pharmacological properties. Necessary warnings to minimise any potential risks from the administration of tabelecleucel with commonly used concomitant medication in this clinical setting are included in the SmPC. There are no clinical pharmacology objections for the approval of Ebvallo.

The CHMP endorse the CAT assessment regarding the conclusions on the Clinical pharmacology as described above.

2.6.5. Clinical efficacy

2.6.5.1. Dose response studies

No dedicated dose response studies were submitted for Ebvallo. The rationale for the recommended dosing schedule is presented in this section.

Rationale for dose 2x10^6 viable T cells/kg

The tabelecleucel dose administered in Study ATA129-EBV-302 and the supportive study EBV-CTL-201 was 2 × 10^6 viable T cells/kg in treatment cycles of 3 weekly IV infusions (days 1, 8, and 15) followed by an observation period of up to 3 weeks.

In the study 95-024 patients were divided into two groups. The group 1 with subjects with high risk of GvHD were treated with 1 x 10^6 cells/kg tabelecleucel. Two additional dose levels of EBV-CTLs (2 × 10^6 and 5 × 10^6 cells/kg) were planned for subjects in group 2 (low risk of GvHD). As doses of only 1 × 10^6 cells/kg could be consistently generated in a timely fashion from the transplant donors, the protocol-specified dose escalation was not completed. With the median of the average number of cells

received per dose of tabelecleucel was 1.06 × 10^6 cells/kg and a median of 7.0 doses of tabelecleucel an ORR of the 15 subjects with EBV+ PTLD was 63.6%. Of note, majority of subjects in this study were paediatric patients. The median (min, max) age was 11.5 years (5, 70); 8 subjects were < 16 years and 10 subjects were < 18 years.

In study 11-130 subjects in group 1 were to receive a cycle of 3 weekly IV infusions of tabelecleucel at a dose of 2 × 10^6 cells/kg of recipient body weight. After the third dose, subjects were observed for approximately 3 weeks. Clinical benefit was demonstrated in the group of 35 patient with EBV+PTLD. In the C-HCT, 17 of the 25 subjects had a best overall response of either CR (13 subjects) or PR (4 subjects), giving an ORR of 68.0%. In the C-SOT, 5 of the 10 subjects had a best response of either CR (2 subjects) or PR (3 subjects), giving an ORR of 50.0%. Regarding demographics, subjects in the C-PTLD had median age of 28.3 years in the C-HCT cohort and 22.0 years in the SOT PTLD cohort. Nine patients of the whole C-PTLD cohort were <18 years.

Importantly, the dose selection was made taking to the account the threshold of 10^5 alloreactive cytotoxic T lymphocyte precursor/kg (potentially coadministered), since the risk of GvHD below this threshold is low [Kernan 1986].

Rationale for Dosing on Days 1, 8, and 15

The approach of dosing on Days 1, 8, and 15 allows for clinical evaluation and ruling out of hyperacute alloreactive manifestations prior to subsequent dosing and has previously been shown to be safe, without acute toxicities or instances of graft-versus-host disease (GvHD) [O'Reilly 2015]. Weekly dosing over 3 weeks allows for minimisation of alloreactivity events based on the presence of low levels of cytotoxic T lymphocytes precursors that have potential to induce GvHD observed at higher doses [Doubrovina 2012].

Rationale for a 35-Day Cycle

The dosing schedule of 35 days used in pivotal study ATA129-EBV-302 was informed by early clinical experience, including Studies 95-024 and 11-130 and takes into account optimal timing for response assessments as well as logistics related to selection of an appropriate tabelecleucel lot and shipping to site. For efficacy, median time to response was 1.1 month. Safety events of concern (such as GvHD, for which the concern was initially based on extrapolation from experience with donor lymphocyte infusion) are more likely to occur prior to Day 30 [Frey 2008]. The 35-day cycle consists of a weekly dosing regimen over the first 3 weeks (Days 1, 8, and 15, as described above). The remainder of time in the 35-day cycle allows for time to determine a response, to select the appropriate lot for the next dose based on response, and for the site to procure the first dose for the next cycle.

Rationale for switching to other HLA product

If a subject does not respond, an HLA restriction switch (switch to tabelecleucel with a different HLA restriction) is recommended. Selection of an alternative tabelecleucel product using a different HLA restriction enables killing of the malignant cell via a different EBV target peptide-HLA complex. Durable responses were observed in the Phase 1/2 trials with switch therapy.

Based on results from Studies 95-024 and 11-130, up to 4 HLA restrictions were originally proposed for subjects with relapsed and/or refractory Epstein-Barr virus positive posttransplant lymphoproliferative disease (R/R EBV^+ PTLD) in the pivotal study ATA129-EBV-302. The protocol was amended to limit the number of HLA restrictions to 2 for the SOT cohort, considering that subjects with EBV^+ PTLD following SOT-R may yet benefit from salvage chemotherapy and based on a recommendation from the FDA. To remain consistent between HCT and SOT cohorts, objective response rate is based on response assessments performed at up to 2 restrictions for all cohorts in this global study.

Regarding responses assessed after 2 restrictions, for those subjects who responded to treatment, one subject who received 4 different HLA restrictions had a response in Study 11-130 after the 4th restriction; to date, 2 subjects received 3 different HLA restrictions in Study ATA129-EBV-302, of which 1 subject achieved clinical benefit (defined as complete response, partial response, or stable disease) after the 3rd restriction. For both C-SOT-R+C and C-HCT, the target indications, salvage chemotherapy is less likely to be a feasible option, and there is potential for clinical benefit with a restriction switch of tabelecleucel if needed. Therefore, up to 4 restrictions are allowed in both indications.

2.6.5.2. Main study

ATA129-EBV-302: Multicenter, Open-Label, Phase 3 Study of Tabelecleucel for Solid Organ or Allogeneic Haematopoietic Cell Transplant Subjects with Epstein-Barr Virus-Associated Post-Transplant Lymphoproliferative Disease after Failure of Rituximab or Rituximab and Chemotherapy (ALLELE Study).

Methods

The phase 3 tabelecleucel clinical development programme, initiated in 2018, initially comprised 2 studies, ATA129-EBV-301 in subjects with EBV+ PTLD following allogeneic HCT and ATA129-EBV-302 in subjects with EBV+ PTLD following SOT. These 2 studies were merged under ATA129-EBV-302 (Protocol Amendment 3, 31 May 2019) due to the ultra-low incidence of relapsed/refractory EBV+ PTLD and to mitigate against the risk of sites terminating participation in the studies due to slow enrolment.

Study Participants

Inclusion criteria

1. Prior SOT of kidney, liver, heart, lung, pancreas, small bowel, or any combination of these (SOT cohort); or prior allogeneic HCT (HCT cohort)
2. A diagnosis of locally-assessed, biopsy-proven EBV+ PTLD
3. Availability of appropriate partially HLA-matched and restricted tabelecleucel confirmed by the sponsor.
4. Measurable 18F-deoxyglucose-avid (Deauville score ≥ 3) systemic disease using Lugano classification response criteria [Cheson 2014] by positron emission tomography (PET)-diagnostic computed tomography (CT), except when contraindicated or mandated by local practice, then magnetic resonance imaging (MRI) may be used. For subjects with treated CNS disease, a head diagnostic CT and/or brain/spinal MRI as clinically appropriate was required to follow CNS disease response per Lugano classification response criteria.
5. Treatment failure of rituximab or interchangeable commercially available biosimilar monotherapy (SOT subgroup A or HCT cohort) or rituximab plus any concurrent or sequentially administered chemotherapy regimen (SOT subgroup B) for treatment of PTLD. Treatment failure was defined based on rituximab response as follows:

    a. Radiographic disease progression per Lugano classification following a minimum cumulative dose of 1125 mg/m2 rituximab (typically, 3 weekly doses of 375 mg/m2), or

    b. Failure to achieve a CR or PR, defined by Lugano radiographic criteria, after a minimum cumulative dose of 1500 mg/m2 rituximab (typically, 4 weekly doses of 375 mg/m2), or

    c. Relapse/progression of PTLD after a response to rituximab (SOT subgroup A or HCT cohort) or rituximab plus chemotherapy (SOT subgroup B), defined as radiographic and/or biopsy evidence of relapse/progression consistent with PTLD; if the underlying disease for which the subject underwent allogeneic HCT (HCT cohort) was lymphoma, biopsy confirmation of

relapsed EBV+ PTLD was required

6. Males and females of any age
7. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 3 for subjects aged16 years; Lansky score ≥ 20 for subjects < 16 years
8. For HCT cohort only: If allogeneic HCT was performed as treatment for an acute lymphoid or myeloid malignancy, the underlying primary disease for which the subject underwent transplant must have been in morphologic remission
9. Adequate organ function

    a. Absolute neutrophil count ≥ 1000/μL (SOT cohort) or ≥ 500/μL (HCT cohort), with or without cytokine support

    b. Platelet count ≥ 50,000/μL, with or without transfusion or cytokine support. For HCT cohort, platelet count < 50,000/μL but ≥ 20,000/μL, with or without transfusion support, was permissible if the subject had not had grade ⩾ 2 bleeding in the prior 4 weeks (where grading of the bleeding was determined per the National Cancer Institute's Common Terminology Criteria for Adverse Events [NCI-CTCAE], version 5.0)

    c. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and total bilirubin (TBILI) each < 5 × upper limit of normal; however, ALT, AST, and TBILI each ≤ 10 × upper limit of normal was acceptable if the elevation was considered by the investigator to be due to EBV and/or PTLD involvement of the liver as long as there was no known evidence of significant liver dysfunction (eg, elevated prothrombin time due to liver dysfunction, signs/symptoms of liver dysfunction such as asterixis, or similar).

10. Subject or subject's representative was willing and able to provide written informed consent.

Exclusion criteria

1. Burkitt lymphoma, classical Hodgkin lymphoma, or any T-cell lymphoma
2. Daily steroids of > 0.5 mg/kg prednisone or glucocorticoid equivalent, ongoing methotrexate, or extracorporeal photopheresis
3. Untreated CNS PTLD or CNS PTLD for which the subject was actively receiving CNS-directed chemotherapy (systemic or intrathecal) or radiotherapy at enrolment.
4. Suspected or confirmed grade ≥ 2 GvHD per the Centre for International Blood and Marrow Transplant Research consensus grading system at enrolment
5. Ongoing or recent use of a checkpoint inhibitor agent (eg, ipilimumab, pembrolizumab, nivolumab) within 3 drug half-lives from the most recent dose to enrolment
6. For HCT cohort only: active adenovirus viremia
7. Need for vasopressor or ventilatory support
8. Anti-thymocyte globulin or similar anti-T-cell antibody therapy ≤ 4 weeks prior to enrolment
9. Treatment with EBV-CTLs or chimeric antigen receptor T cells directed against B cells within 8 weeks of enrolment (SOT or HCT cohorts) or unselected donor lymphocyte infusion within 8 weeks of enrolment (HCT cohort only)
10. Female who was breastfeeding or pregnant, or female of childbearing potential, or male with a female partner of childbearing potential unwilling to use a highly effective method of contraception
11. Inability to comply with study-related procedures

Treatments

Subjects were administered tabelecleucel via slow IV push over 5 to 10 minutes at doses of 2×10^6 cells/kg of actual body weight at screening by the investigator or designated trained personnel. There

was no dose adjustment for obesity or for weight changes after baseline. Each cycle lasted 5 weeks (35 days) and consisted of 3 doses of tabelecleucel, which were administered on day 1 (up to + 4 days relative to day 1 of the prior cycle), day 8 (± 2 days relative to day 1 of the current cycle), and day 15 (± 2 days relative to day 1 of the current cycle), followed by an observation period. Treatment with tabelecleucel continued until maximal response, unacceptable toxicity, initiation of non-protocol therapy, or failure of up to 2 tabelecleucel with different HLA restrictions (SOT subjects) or up to 4 tabelecleucel with different HLA restrictions (HCT subjects), if available.

Maximal response was reached when the subject received 3 consecutive PR assessments, or 2 consecutive CR assessments as assessed by the investigator using Lugano classification response criteria with LYRIC modification. In instances where the subject's PTLD rapidly progressed during the first cycle, the subject had documented radiographic or clinical progressive disease (PD) any time after the third tabelecleucel dose (cycle 1 day 15), and the medical monitor had been consulted and approved, restriction switch (i.e., treatment with tabelecleucel with a different HLA restriction) could be initiated before the 35 days of cycle 1 was complete. The first dose of tabelecleucel after the restriction switch would constitute cycle 2 day 1.

Objectives

The primary objective of the main study was to determine the clinical benefit of tabelecleucel

- in subjects with EBV+ PTLD following SOT after failure of rituximab (subgroup A) or

- in subjects with EBV+ PTLD following SOT after failure rituximab + chemotherapy (subgroup B) or

- in subjects with EBV+ PTLD following allogeneic HCT after failure of rituximab, as measured by the objective response rate (ORR).

The secondary objectives of this study were as follows:

• To evaluate duration of response (DOR) in the SOT and HCT cohorts separately

• To evaluate ORR and DOR in the SOT and HCT cohorts combined

• To evaluate rates of CR and PR

• To evaluate time to response (TTR) and time to best response (TBR)

• To evaluate OS

• To evaluate graft status (SOT subjects only)

• To characterise the safety profile of tabelecleucel in this subject population

Outcomes/endpoints

The primary efficacy endpoint of the study is ORR (CR or PR) determined separately in each cohort (SOT and HCT) following administration of tabelecleucel with up to 2 different HLA restrictions. The primary efficacy analyses of disease assessment-related endpoints were based on the disease assessments by IORA (independent oncologic response adjudication).

Secondary efficacy endpoints were:

DOR in SOT and HCT cohorts separately

ORR and DOR in SOT and HCT cohorts combined

Rate of CR and PR

TTR and TTBR

OS

The safety endpoint was as follows:

• Rates of allograft loss/rejection episodes (for SOT cohort only): loss is defined as allograft removal, resumption of renal replacement therapy (kidney), initiation of a ventricular assist device (heart), need for mechanical ventilation or extracorporeal membrane oxygenation (lung), re-transplant (any), or placement on a SOT list (any); rejection episodes were defined according to appropriate criteria for the particular organ transplant.

Sample size

For each cohort, the estimated ORR for treatment with tabelecleucel was ≥ 48%, and the null ORR was assumed to be 20%. Based on a 1-sided exact binomial test at the alpha = 0.025 level of significance, a sample size of 29 subjects provided 90% power to detect a true ORR of at least 48%. Four additional subjects were to be enrolled, as needed, to achieve 29 evaluable subjects, for a total sample size of up to 33 subjects per cohort. For the SOT cohort, the enrolment was to take all comers, i.e., there was no limitation on the number of subjects to be enrolled within each of the 2 subgroups.

Randomisation and Blinding (masking)

This is an open-label, non-randomised, single-arm study.

Statistical methods

Analysis sets

The Full Analysis Set (FAS) was defined as all subjects who have received at least 1 dose of tabelecleucel. The Safety Analysis Set was identical to the FAS. All efficacy and safety analyses were planned to be based on the FAS unless otherwise specified.

The All-Enrolled Analysis Set was defined as subjects whose study eligibility was confirmed and who were enrolled into the study. The All-Enrolled Analysis Set was planned to be used for sensitivity analysis of ORR, if different from the FAS.

The Evaluable Analysis Set (EAS) was defined post-hoc and comprises all subjects who received at least 1 dose of tabelecleucel and had at least 1 evaluable postbaseline disease assessment per IORA, or discontinued study or received non-protocol anti-PTLD therapy.

Cohorts

This study had 2 cohorts: the C-SOT and C-HCT. The C-SOT included SOT subjects who had failed rituximab alone (subgroup A) or rituximab and chemotherapy (subgroup B) for the treatment of PTLD. The C-HCT included HCT subjects who had failed rituximab for the treatment of PTLD.

The primary analysis and hypothesis testing were planned to be conducted for the C-SOT and C-HCT, respectively.

In addition, analyses based on the SOT and HCT cohorts combined were planned to be performed and considered as secondary and for SOT subgroups A and B separately as exploratory analyses.

Hypothesis and/or Estimation

Objective response rate based on IORA-adjudicated disease assessment in the FAS was planned as the primary analysis for ORR.

If a new PTLD treatment, other than specified in the protocol, was initiated, response data after the initiation date was planned to be censored for the purpose of the efficacy analysis.

Interim analyses

In total, 3 efficacy analyses were planned for the SOT cohort, with 2 interim analyses (at N = 15 and 21 subjects) and 1 final analysis. At the first interim analysis (N = 15), a futility analysis was also planned to be performed. An O'Brien Fleming spending function was planned to be used for the interim analyses with 1-sided alpha being 0.0009, 0.0047 and 0.0234 at the 2 interim analyses and the final analysis, respectively. If the timing of the interim analysis deviates from the schedule, the alpha level was planned to be kept the same as pre-specified. For the futility analysis at N = 15 subjects, the conditional power approach was planned to be used.

More specifically, if the conditional power under the average of observed data and alternative hypothesis is less than 10%, the futility boundary was planned to be met. At the interim analyses, it was planned that the totality of data may also be considered in addition to the statistical boundary for formal decision-making.

While no formal interim analysis was planned for the HCT cohort, at the time of an interim analysis for the SOT cohort, the data for the HCT cohort was also planned to be analysed.

Results

Participant flow

Prior to study enrolment, 107 subjects signed consent to allow inventory match, 77 of these subjects had matched tabelecleucel product, and 55 subjects were screened.

Study disposition is summarised in **Table 2** for the FAS.

Table 2. Patient disposition for study ATA129-EBV-302 (data cut-off 7 May 2021)

	C-SOT			C-HCT	Overall Total
	C-SOT-R	C-SOT-R+C	Total		
Number of subjects screened					55
Subjects enrolled	12	13	25	14	39
Subjects treated - N	12	13	25	14	39
Study disposition – n (n/N × 100%)					
Completed	0	0	0	1 (7.1)	1 (2.6)
Ongoing	5 (41.7)	5 (38.5)	10 (40.0)	7 (50.0)	17 (43.6)

	C-SOT			C-HCT	Overall Total
	C-SOT-R	C-SOT-R+C	Total		
Discontinued	7 (58.3)	8 (61.5)	15 (60.0)	6 (42.9)	21 (53.8)
Death	3 (25.0)	5 (38.5)	8 (32.0)	3 (21.4)	11 (28.2)
Lost to follow-up	0	2 (15.4)	2 (8.0)	0	2 (5.1)
Other	2 (16.7)	0	2 (8.0)	3 (21.4)	5 (12.8)
Withdrawal by subject	2 (16.7)	1 (7.7)	3 (12.0)	0	3 (7.7)

Abbreviations: C-HCT, subjects with EBV+ PTLD following HCT; C-SOT, subjects with EBV+ PTLD following SOT; C-SOT-R, subjects with EBV+ PTLD following SOT and relapsed/refractory to rituximab; C-SOT-R+C, subjects with EBV+ PTLD following SOT and relapsed/refractory to rituximab plus chemotherapy; HCT, hematopoietic cell transplant; SOT, solid organ transplant
N represents the number of subjects in the full analysis set. n represents the number of subjects in each category. Subjects with AE preferred term disease progression leading to study treatment discontinuation were considered as discontinuing study treatment due to disease progression.

Recruitment

Study initiated: 26 June 2018 (date of main informed consent)

Data cut-off date 05 November 2021 (study is ongoing)

Conduct of the study

The original protocol was dated 31 July 2016 and was amended 4 times.

In protocol amendment 3, EBV+ PTLD following allogeneic HCT after failure of rituximab from Study ATA129-EBV-301 were added as an additional cohort (HCT cohort) in this study, to adapt to slower-than-expected enrolment due to the ultra-low incidence of relapsed/refractory EBV+ PTLD and to mitigate against the risk of sites terminating participation in the studies due to slow enrolment.

In the FU Protocol Assistance (EMEA/H/SA/3977/1/FU/1/2018/PA/SME/ADT/PR/III) CHMP agreed with a merge of studies ATA129-EBV-301 and ATA129-EBV-302 in case the benefit / risk assessment and the efficacy and safety analyses of the two studies / cohorts were to be evaluated independently.

Protocol violations were sporadic and were not considered to impact on the validity of the efficacy results.

Baseline data

Demographics and baseline characteristics are summarised in **Table 3**.

Table 3. Demographics and baseline characteristics of patients in study ATA129-EBV-302, data cut-off 05 November 2021 (FAS)

	Ebvallo SOT EBV+ PTLD[a,b]			Ebvallo HCT EBV+ PTLD[a]	Overall Total[a]
	After rituximab (N = 13)	After rituximab and chemotherapy (N = 16)	Total (N = 29)	After rituximab (N = 14)	(N = 43)
Age					
Median years (min, max)	55.2 (6.1, 75.7)	39.2 (16.7, 81.5)	44.4 (6.1, 81.5)	51.9 (3.2, 73.2)	48.5 (3.2, 81.5)
Male, n (%)	9 (69.2)	7 (43.8)	16 (55.2)	8 (57.1)	24 (55.8)
ECOG score (age ≥ 16)[c]					
patients in the age group	11	16	27	13	40
ECOG < 2	9 (81.8)	9 (56.3)	18 (66.7)	10 (76.9)	28 (70.0)
ECOG ≥ 2	2 (18.2)	6 (37.5)	8 (29.6)	3 (23.1)	11 (27.5)
Missing	0	1 (6.3)	1 (3.7)	0	1 (2.5)
Lansky score (age < 16)[c]					
patients in the age group	2	0	2	1	3
Lansky < 60	1 (50.0)	0	1 (50.0)	0	1 (33.3)
Lansky ≥ 60	1 (50.0)	0	1 (50.0)	1 (100)	2 (66.7)
Elevated LDH (age ≥ 16), n (%)	7 (63.6)	12 (75.0)	19 (70.4)	11 (84.6)	30 (75.0)
PTLD-adapted prognostic index[d] (age ≥ 16), n (%)					
Low risk	1 (9.1)	1 (6.3)	2 (7.4)	1 (7.7)	3 (7.5)
Intermediate risk	7 (63.6)	6 (37.5)	13 (48.1)	6 (46.2)	19 (47.5)
High risk	3 (27.3)	8 (50.0)	11 (40.7)	6 (46.2)	17 (42.5)
Unknown	0	1 (6.3)	1 (3.7)	0	1 (2.5)
PTLD morphology/histology, n (%)					
DLBCL	9 (69.2)	10 (62.5)	19 (65.5)	10 (71.4)	29 (67.4)
Other[e]	4 (30.8)	4 (25.0)	8 (27.6)	3 (21.4)	11 (25.6)
Plasmablastic lymphoma	0	2 (12.5)	2 (6.9)	1 (7.1)	3 (7.0)
Extranodal disease	11 (84.6)	13 (81.3)	24 (82.8)	9 (64.3)	33 (76.7)
Prior therapies					
Median number of prior systemic therapies (min, max)	1.0 (1, 1)	2.0 (1, 5)	1.0 (1, 5)	1.0 (1, 4)	1.0 (1, 5)
Rituximab monotherapy, n (%)	13 (100)	10 (62.2)	23 (79.3)	14 (100)	37 (86.0)
Rituximab monotherapy as first line, n (%)	13 (100)	9 (56.3)	22 (75.9)	14 (100)	36 (83.7)
Chemotherapy-containing regimen[f], n (%)	0	16 (100)	16 (55.2)	3 (21.4)	19 (44.2)

DLBCL = diffuse large B-cell lymphoma; EBV+ PTLD = Epstein-Barr virus positive post-transplant lymphoproliferative disease; ECOG = Eastern Cooperative Oncology Group; HCT = hematopoietic cell transplant; LDH = lactate dehydrogenase; max = maximum; min = minimum; SOT = solid organ transplant

[a] Patients received at least one dose of Ebvallo.

[b] SOT types included kidney, heart, liver, lung, pancreas, bowel and multiviscera.

[c] Percentages for ECOG and Lansky scores were based on the number of patients in the corresponding age group.

[d] Disease risk for PTLD patients was assessed at baseline using the PTLD-adapted prognostic index (based on age, ECOG score and serum LDH level).

[e] Morphologies not clearly DLBCL or plasmablastic lymphoma were categorized as Other and were consistent with PTLD.

[f] Chemotherapy regimens could have also been combined with rituximab or other immunotherapy agents.

- **Numbers analysed**

A total of 43 subjects have been enrolled in Study ATA129-EBV-302 (14 subjects C-HCT, 29 subjects C-SOT [13 C-SOT-R, 16 C-SOT-R+C]), of those, 4 subjects (1 subject C-SOT-R and 3 subjects C-SOT-R+C) were enrolled after the cut-off date used in the initial MAA submission (07 May 2021).

The number of subjects in the All-Enrolled Analysis Set (N = 43) was the same as in the FAS, therefore sensitivity analysis for ORR was not conducted using the All Enrolled Analysis Set.

- **Outcomes and estimation**

Primary Efficacy Endpoint

The primary efficacy endpoint results are summarised in **Table 4**, using two different cut-off dates.

Table 4. Summary of efficacy results for study ATA129-EBV-302 per IORA in C-HCT and C-SOT-R+C (two data cut-off: 07 May 2021 and 05 November 2021) (FAS)

Per IORA	07May2021 DCO		05NOV2021 DCO	
	C-HCT (N = 14)	C-SOT-R+C (N = 13)	C-HCT (N = 14)	C-SOT-R+C (N = 16)
ORR[a]				
Best Overall Response, n (%)				
CR	5 (35.7)	4 (30.8)	6 (42.9)	5 (31.3)
PR	2 (14.3)	3 (23.1)	1 (7.1)	4 (25.0)
Responders – n (%)				
Yes	7 (50.0)	7 (53.8)	7 (50.0)	9 (56.3)
95% CI	23.0, 77.0	25.1, 80.8	23.0, 77.0	29.9, 80.2

IORA: independent oncologic response adjudication; ORR: objective response rate, DCO: Data cut-off; HCT: haematopoietic cell transplant; SOT: solid organ transplant; R: rituximab; C: chemotherapy; CR: complete response; PR: partial response

Secondary and Other Key Efficacy Endpoints

The secondary efficacy endpoint results are summarised in **Table 5**, using two different cut-off dates. Kaplan Meier curves for responders vs non-responders for the C-HCT and C-COT-R+C cohorts are shown in **Figure 8** and **Figure 9** respectively.

Table 5. Summary of efficacy results for study ATA129-EBV-302 per IORA in C-HCT and C-SOT-R+C (two data cut-off: 07 May 2021 and 05 November 2021) (FAS)

Per IORA	07May2021 DCO		05NOV2021 DCO	
	C-HCT (N = 14)	C-SOT-R+C (N = 13)	C-HCT (N = 14)	C-SOT-R+C (N = 16)
DOR estimate for responders only (KM) (months), median (95% CI)	NE	NE (0.8, NE)	23.0 (15.9, NE)	15.2 (0.8, 15.2)
Follow-up time after achieving first response (months), median (min, max)	10.2 (1.3, 23.3)	6.8 (0.8, 9.3)	15.9 (1.3, 23.3)	2.3 (0.8, 15.2)
DRR[b] – n (%)				
> 6 months	5 (35.7)	4 (30.8)	6 (42.9)	4 (25.0)
95% CI	12.8, 64.9	9.1, 61.4	17.7, 71.1	7.3, 52.4
OS				
OS Estimate (KM) (months), median (95% CI)	NE (5.7, NE)	16.4 (1.8, NE)	NE (5.7, NE)	16.4 (3.5, NE)
Follow-up time (months), median (min, max)	10.6 (2.0, 31.4)	9.5 (0.4, 20.3)	14.1 (2.0, 35.4)	5.5 (0.4, 25.3)
OS rate at 12 months (95% CI) (KM)	66.8 (32.4, 86.6)	61.5 (30.8, 81.8)	70.1 (38.5, 87.6)	64.3 (33.8, 83.5)

IORA: independent oncologic response adjudication; ORR: objective response rate, DCO: Data cut-off; HCT: haematopoietic cell transplant; SOT: solid organ transplant; R: rituximab; C: chemotherapy; DOR: duration of response; DRR: durable response ratel; OS: overall survival; KM: Kaplan Meier

Figure 8. Kaplan-Meier plot of overall survival: responder vs Non-responder per IORA for study ATA129-EBV-302 per IORA, data cut-off:5 November 2021, (C-HCT, FAS)

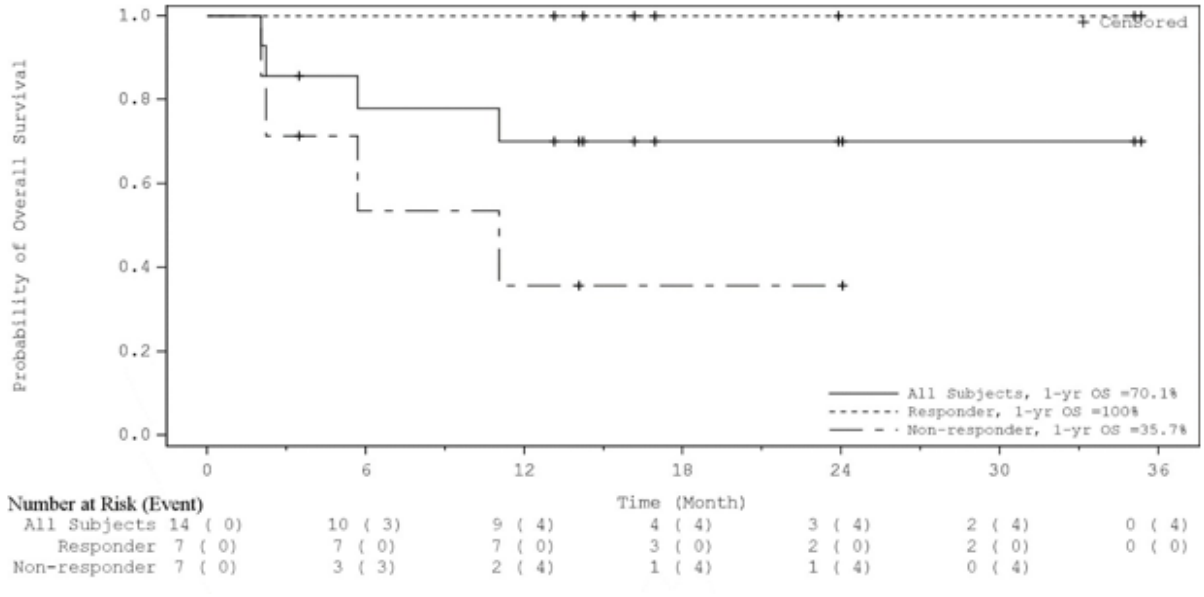
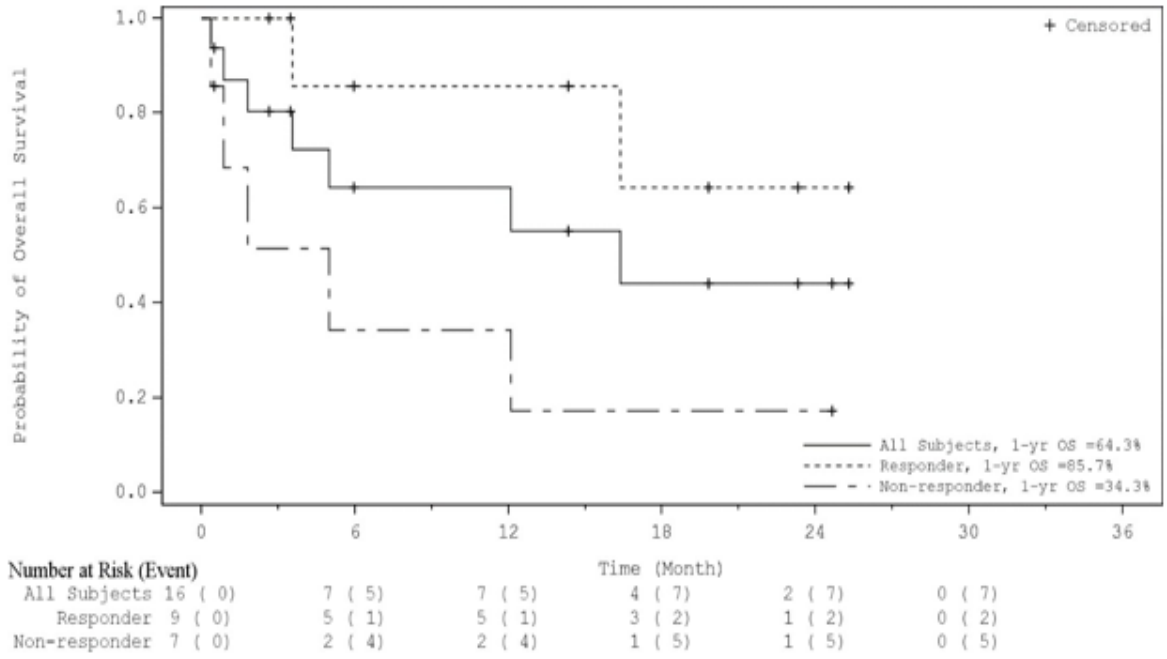


Figure 9. Kaplan-Meier plot of overall survival: responder vs Non-responder per IORA for study ATA129-EBV-302 per IORA, data cut-off:5 November 2021, (C-SOT-R+C, FAS)



Durable response rate

Analyses of subjects who achieved complete response (CR) and durable CR were conducted on the full analysis set (FAS) in Study ATA129-EBV-302 using data from the 05 November 2021 data cut-off, per IORA assessment.

In the C-PTLD, **12 of 43 subjects** (27.9%) in the FAS had achieved CR per IORA assessment, among **whom 9 (75.0%) had durable CR (with a duration of > 6 months).** Four of the 9 subjects (44.4%) had subsequent progression of disease. Subjects who achieved CR are discussed further below.

The Kaplan-Meier (KM) estimate of **median (95% CI) duration of CR was 23.0 months** (6.8, not estimable [NE]), with a median (min, max) follow-up time in response of 14.5 months (0.03, 23.3).

- In the C-HCT, the KM estimate of median (95% CI) duration of CR was 23.0 months (15.9, NE) with a median (min, max) follow-up time in response of 18.8 months (0.03, 23.3).

- In the C-SOT-R+C, the KM estimate of median (95% CI) duration of CR was 14.1 months (6.8, NE) with a median (min, max) follow-up time in response of 7.1 months (1.6, 14.9).

- In the C-SOT-R, the single subject who achieved CR was censored at data cut-off after a follow-up time of 19.8 months.

Four subjects in the C-HCT, 4 subjects in the C-SOT-R+C, and 1 subject in the C-SOT-R had durable CR. **Three subjects had non-durable CR** (all subjects censored at the time of data cut-off, with 2 subjects in the C-HCT and 1 subject in the C-SOT-R+C:

- One subject first achieved CR at the end of cycle 5 per IORA, however treatment was discontinued due to investigator assessment of PD at the same time. The subject later ended the study with overall survival of 13.1 months (censored).

- One subject achieved 4 consecutive PRs starting at cycle 1 followed by 2 consecutive CRs per IORA. The subject ended treatment per dosing algorithm, remains on study, and has been in follow-up for 14.2 months at data cut-off

- One subject received 2 cycles of tabelecleucel, achieved CR at the end of cycle 1 and cycle 2 per IORA, and ended treatment per the dosing algorithm. The subject remains on study and has been in follow-up for 2.6 months at data cut-off.

TTR (time to response)

- In the C-HCT, the median (min, max) TTR was 1.0 month (1.0, 4.7).
- In the C-SOT-R+C, the median (min, max) TTR was 1.1 months (0.7, 4.1).

TTP (time to progression)

- In the C-HCT, 6 of 14 subjects (42.9%) progressed, and the median (min, max) follow-up time was 4.7 months (0.03, 24.2). The KM estimate of median TTP was 20.4 months (95% CI: 1.0, NE).

- In the C-SOT-R+C, 10 of 16 subjects (62.5%) progressed, and the median (min, max) follow-up time was 2.2 months (0.03, 18.9). The KM estimate of median TTP was 2.8 months (95% CI: 0.9, 18.4).

- **Ancillary analyses**

Observational real-world data were collected (Study RS002) to create a control arm for the single arm study 302. The data were collected retrospectively in the time span of over 20 years. The objective of this analysis was to compare OS in patients treated with tabelecleucel in the study 302 (27 subjects, 14 HCT and 13 SOT setting, data cut-off 07 May 2021) with the control arm of subjects who received standard of care next line treatment for EBV+ PTLD (36 HCT and 48 SOT setting). A comparison of the demographics, baseline characteristics, disease risk factors and time related variables are summarised in **Table 6**, **Table 7** and **Table 8**.

Table 6. Demographic and baseline characteristics of populations from studies RS002 and ATA129-EBV-302data cut-off:07 May 2021

Characteristic	Study RS002 (N = 84)	Study 302 (N = 27)
Age at index date[a] (years)		
Median (Q_1, Q_3)	44.1 (26.4, 58.6)	42.4 (21.9, 65.1)
Min, Max	3.1, 73.6	3.2, 81.5
Female, n (%)	27 (32.1)	13 (48.1)
Extranodal sites of PTLD, n (%)	56 (66.7)	19 (70.4)
Early PTLD onset[b], n (%)	44 (52.4)	11 (40.7)
Response to initial rituximab treatment, n (%)		
Responders (CR + PR)	24 (28.6)	8 (29.6)
Non-responders (SD + PD)	60 (71.4)	19 (70.4)
Number of prior therapies, n (%)		
1	55 (65.5)	15 (55.6)
≥ 2	29 (34.5)	12 (44.4)

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; PTLD, posttransplant lymphoproliferative disease; Q, quartile; SD, stable disease

[a] Defined as the date of the first dose of tabelecleucel for subjects in Study 302 and the start of the next-line of systemic therapy for subjects in Study RS002

[b] Defined according to the time from transplant to PTLD diagnosis: early onset (late onset) was defined as ≤ 100 (> 100) days for HCT subjects and ≤ 2 (> 2) years for SOT subjects

Table 7. Disease risk factors of populations from studies RS002 and ATA129-EBV-302

Risk Factor	Study RS002 (N = 84)	Study 302 (N = 27)
Age, n (%)		
< 60 years (low risk)	65 (77.4)	16 (59.3)
≥ 60 years (high risk)	19 (22.6)	11 (40.7)
ECOG / Karnofsky (Lansky) score, n (%)		
< 2 / ≥ 70 (low risk)	15 (17.9)	18 (66.7)
≥ 2 / < 70 (high risk)	25 (29.8)	9 (33.3)
Missing	44 (52.4)	0 (0.0)
Serum LDH, n (%)		
Normal (< 250 U/L) (low risk)	12 (14.3)	5 (18.5)
Elevated (≥ 250 U/L) (high risk)	50 (59.5)	21 (77.8)
Missing	22 (26.2)	1 (3.7)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PTLD, posttransplant lymphoproliferative disease

Table 8. Time related variables of populations from studies RS002 and ATA129-EBV-302

Time Related Variable	Study RS002 (N = 84)	Study 302 (N = 27)
Transplant to PTLD diagnosis, months		
Median (Q_1, Q_3)	6.5 (3.0, 79.2)	6.7 (3.7, 63.7)
Min, Max	0.9, 334.5	0.6, 167.5
PTLD diagnosis to R/R date, months		
Median (Q_1, Q_3)	3.1 (0.8, 8.2)	1.6 (0.8, 3.4)
Min, Max	0.0[a], 87.5	0.0[a], 189.6
PTLD diagnosis to index date[b], months		
Median (Q_1, Q_3)	3.6 (1.1, 9.6)	3.4 (1.8, 13.0)
Min, Max	0.0, 90.0	0.7, 190.5

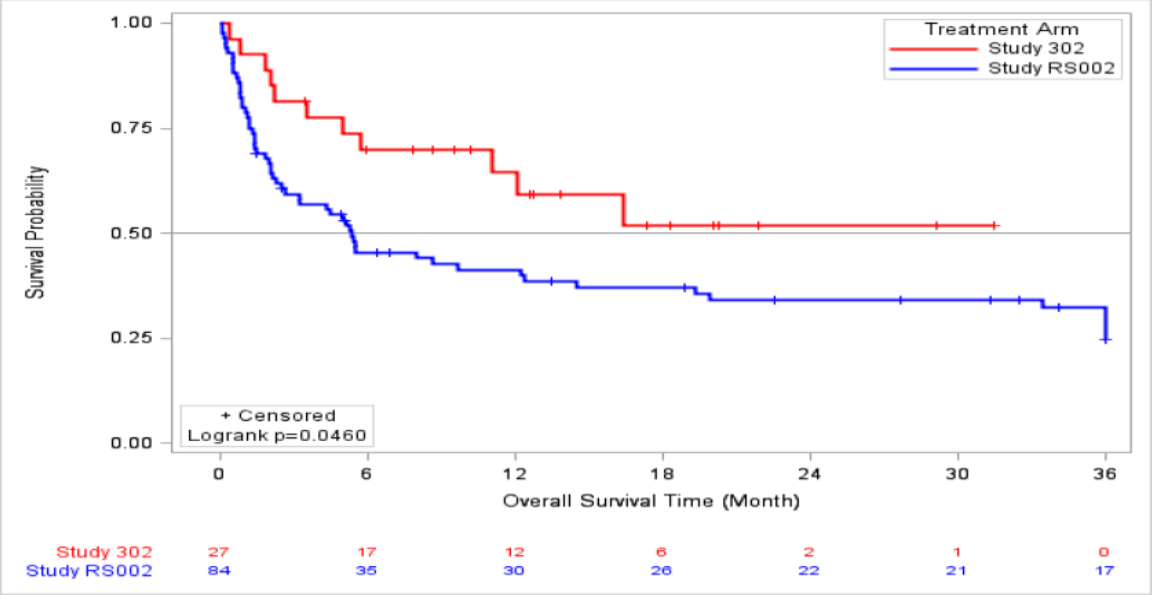
Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; PTLD, posttransplant lymphoproliferative disease; Q, quartile; R/R, relapse/refractory; SD, stable disease

[a] A prior initiation of rituximab in the HCT setting before PTLD diagnosis by biopsy

[b] Defined as first dose of tabelecleucel for subjects in Study 302 and the start of the next line of systemic therapy for subjects in Study RS002

The index date (randomisation point) was defined as the start date of the next line of systemic therapy in Study RS002, aligning with the first dose of tabelecleucel in Study 302. Kaplan-Meier curve in **Figure 10**, represents unadjusted results. OS differences were shown suggesting better survival in patients treated with tabelecleucel as compared to the external historical control, with hazard ratio of 0.52.

Figure 10. Kaplan-Meier survival estimates between treatment arm and the external control arm (unadjusted)



The point estimate remained positive when weighting approaches were used to account for observed differences in patient characteristics, adjusted hazard ratio of 0.40.

For the HCT setting, the median OS was not estimable vs. 2.0 months (treatment vs. control); and for the SOT setting, the median OS was 16.4 vs. 9.7 months (treatment vs. control).

In order to have a contemporary sample, the applicant performed an analysis of subjects diagnosed with PTLD between 2010 and 2018.

The 30 patients from Study ATA129-EBV-302 (data cut-off: 05 November 2021) included 14 patients post HCT (46.7%) and 16 patients (53.3%) post-SOT-R+C. The 55 patients from Study ATA129-RS002 include 27 (49.1%) with EBV+ PTLD following HCT and R/R to rituximab and 28 (50.9%) with EBV+ PTLD following SOT and R/R to rituximab plus chemotherapy.

In this analysis of patients treated between 2010 and 2018 in Study ATA129-RS002, tabelecleucel demonstrated an OS benefit compared to SOC with an unadjusted HR of 0.46 and an adjusted HR of approximately 0.34 for both targeted cohorts.

Summary of main efficacy results

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 9. Summary of efficacy for trial ATA129-EBV-302

Title: Multicenter, Open-Label, Phase 3 Study of Tabelecleucel for Solid Organ or Allogeneic Hematopoietic Cell Transplant Subjects with Epstein Barr Virus-Associated Posttransplant Lymphoproliferative Disease after Failure of Rituximab or Rituximab and Chemotherapy (ALLELE Study)	
Study identifier	Clinicaltrials.gov number: NCT03394365
	multicentre, open label, phase 3 trial

Title: Multicenter, Open-Label, Phase 3 Study of Tabelecleucel for Solid Organ or Allogeneic Hematopoietic Cell Transplant Subjects with Epstein Barr Virus-Associated Posttransplant Lymphoproliferative Disease after Failure of Rituximab or Rituximab and Chemotherapy (ALLELE Study)		
Study identifier	Clinicaltrials.gov number: NCT03394365	
Design	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Ongoing not applicable not applicable
Hypothesis	The null hypothesis was ORR $\leqslant$ 20% for each of the SOT and HCT cohorts. For each cohort, if the lower limit of the 95% CI of the ORR based on the FAS was > 20%, the null hypothesis was rejected for the corresponding cohort. The analyses were also conducted for the SOT and HCT cohorts combined as secondary and for SOT subgroups A and B separately as exploratory analyses.	
Treatments groups	**SOT cohort**, consisting of SOT subjects with EBV+ PTLD who had failed rituximab alone or rituximab + chemotherapy for the treatment of PTLD	Tabelecleucel at a dose of 2 × 10^6 cells/kg by IV infusion on day 1, day 8, and day 15, followed by observation through day 35. Treatment continued until maximal response, unacceptable toxicity, initiation of non-protocol therapy, or failure of tabelecleucel with up to 2 different HLA restrictions
	HCT cohort, consisting of HCT subjects with EBV+ PTLD who had failed rituximab for the treatment of PTLD	Tabelecleucel at a dose of 2 × 10^6 cells/kg by IV infusion on day 1, day 8, and day 15, followed by observation through day 35. Treatment continued until maximal response, unacceptable toxicity, initiation of non-protocol therapy, or failure of tabelecleucel with up to 4 different HLA restrictions (HCT subjects)
	SOT subgroup A: SOT cohort, consisting of SOT subjects with EBV+ PTLD who had failed rituximab alone for the treatment of PTLD	Tabelecleucel at a dose of 2 × 10^6 cells/kg by IV infusion on day 1, day 8, and day 15, followed by observation through day 35. Treatment continued until maximal response, unacceptable toxicity, initiation of non-protocol therapy, or failure of tabelecleucel with up to 2 different HLA restrictions (SOT subjects)
	SOT subgroup B: SOT subjects who had failed both rituximab and chemotherapy for the treatment of PTLD	Tabelecleucel at a dose of 2 × 10^6 cells/kg by IV infusion on day 1, day 8, and day 15, followed by observation through day 35. Treatment continued until maximal response, unacceptable toxicity, initiation of non-protocol therapy, or failure of tabelecleucel with up to 2 different HLA restrictions (SOT subjects)

Title: Multicenter, Open-Label, Phase 3 Study of Tabelecleucel for Solid Organ or Allogeneic Hematopoietic Cell Transplant Subjects with Epstein Barr Virus-Associated Posttransplant Lymphoproliferative Disease after Failure of Rituximab or Rituximab and Chemotherapy (ALLELE Study)			
Study identifier	Clinicaltrials.gov number: NCT03394365		
Endpoints and definitions	Primary endpoint	ORR	Overall response rate (CR or PR) obtained following administration of tabelecleucel with up to 2 different HLA restrictions in the SOT or HCT cohort.
	Secondary endpoint	DOR	Duration of response in SOT and HCT cohorts separately
	Secondary endpoint	ORR, DOR	ORR and DOR in SOT and HCT cohorts combined
	Secondary endpoint	CR, PR	Rate of CR (complete remission) and PR (partial remission)
	Secondary endpoint	TTR and TTBR	Time to response, time to best response
	Secondary endpoint	OS	Overall survival
Data cut-off	5.11.2021		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	FAS (all subjects enrolled and treated with at least one dose)			
Descriptive statistics and estimate variability	Treatment group	SOT cohort	HCT cohort	overall cohort (SOT + HCT)
	Number of subjects	n=29	n=14	n=43
	ORR N (%)	15 (51.7)	7 (50.0)	22 (51.2)
	exact 95% confidence interval	32.5, 70.6	23.0, 77.0	35.5, 66.7

Effect estimate per comparison	Primary endpoint ORR in SOT cohort	Comparison groups	SOT cohort
		ORR (N%)	15 (51.7)
		exact 95% confidence interval	32.5, 70.6
		Nominal P-value (H0: ORR $\leqslant$ 20%)	0.0001
	Primary endpoint ORR in HCT cohort	Comparison groups	HCT cohort
		ORR (N%)	7 (50.0)
		exact 95% confidence interval	23.0, 77.0
		Nominal P-value (H0: ORR $\leqslant$ 20%)	0.0116
	Primary endpoint ORR in pooled SOT and HCT cohort	Comparison groups	overall cohort (SOT + HCT)
		ORR (N%)	22 (51.2)
		exact 95% confidence interval	35.5, 66.7
		Nominal P-value (H0: ORR $\leqslant$ 20%)	< 0.0001

Title: Multicenter, Open-Label, Phase 3 Study of Tabelecleucel for Solid Organ or Allogeneic Hematopoietic Cell Transplant Subjects with Epstein Barr Virus-Associated Posttransplant Lymphoproliferative Disease after Failure of Rituximab or Rituximab and Chemotherapy (ALLELE Study)				
Study identifier	Clinicaltrials.gov number: NCT03394365			
Notes	p-values are nominal and may not necessarily indicate statistical significance with strong control of type-I-error analyses of HCT cohort are post-hoc			
Analysis description	**Secondary analysis**			
Analysis population and time point description	FAS (all subjects enrolled and treated with at least one dose)			
Descriptive statistics and estimate variability	Treatment group	SOT cohort	HCT cohort	overall cohort (SOT + HCT)
	Number of subjects	n=29	n=14	n=43
	CR N (%)	6 (20.7)	6 (42.9)	12 (27.9)
	exact 95% confidence interval	8.0, 39.7	17.7, 71.1	15.3, 43.7
	PR N (%)	9 (31.0)	1 (7.1)	10 (23.3)
	exact 95% confidence interval	15.3, 50.8	0.2, 33.9	11.8, 38.6

2.6.5.3. Clinical studies in special populations

Paediatric population:

As of the 5 November 2021, 6 and 20 paediatric subjects were treated in the main and supportive studies, respectively. The age breakdown of those patients as well as the paediatric patients treated with tabelecleucel in the expanded access programmes are summarised in **Table 10**.

Table 10. Paediatric subjects in C-PTLD treated with tabelecleucel across all clinical trials and expanded access programmes data cut-off: 05 November 2021

	Study	Total Number of Subjects, N	Total Paediatric Subjects, n (n/N)	Age (years) ≥ 2 to < 6, n (n/N)	Age (years) ≥ 6 to < 12, n (n/N)	Age (years) ≥ 12 to < 18, n (n/N)
Clinical Studies	95-024	7	5 (71.4)	0	4 (57.1)	1 (14.3)
	11-130	35	9 (25.7)	1 (2.9)	2 (5.7)	6 (17.1)
	EBV-CTL-201	25	6 (24.0)	1 (4.0)	4 (16.0)	1 (4.0)
	ATA129-EBV-302	43	6 (14.0)	1 (2.3)	1 (2.3)	4 (9.3)
Expanded Access Programs	ATA129-EAP-901	19	3 (15.8)	1 (5.3)	1 (5.3)	1 (5.3)
	ATA129-SPU	54	12 (22.2)	4 (7.4)	4 (7.4)	4 (7.4)
All Studies/Programs		183	41 (22.4)	8 (4.4)	16 (8.7)	17 (9.3)

There were no subjects < 2 years of age in the C-PTLD across clinical studies and EAPs.

Objective response rates in studies and expanded access programmes are summarised in **Table 11** and **Table 12** respectively.

Table 11. Summary of ORR in paediatric patients in C-PTLD across all clinical studies

Per IORA	Age < 18 Years		Age ≥ 18 Years	
	Total (11-130, 95-024 and EBV-CTL-201) (N = 20)	ATA129-EBV-302 (N = 6)	Total (11-130, 95-024 and EBV-CTL-201) (N = 47)	ATA129-EBV-302 (N = 37)
Best overall response–n (%)				
CR	3 (15.0)	2 (33.3)	10 (21.3)	10 (27.0)
PR	5 (25.0)	2 (33.3)	10 (21.3)	8 (21.6)
SD	3 (15.0)	0	6 (12.8)	5 (13.5)
PD	3 (15.0)	2 (33.3)	11 (23.4)	7 (18.9)
NE	6 (30.0)	0	10 (21.3)	7 (18.9)
Responders–n (%)				
Yes	8 (40.0)	4 (66.7)	20 (42.6)	18 (48.6)
95% CI	19.1, 63.9	22.3, 95.7	28.3, 57.8	31.9, 65.6

Table 12. Summary of ORR in paediatric patients in C-PTLD across all expanded access programmes

Per Investigator	Age < 18 Years		Age ≥ 18 Years	
	ATA129-EAP-901 (N=3)	ATA129-SPU (N=12)	ATA129-EAP-901 (N=16)	ATA129-SPU (N=42)
Best overall response–n (%)				
CR	0	5 (41.7)	8 (50.0)	11 (26.2)
PR	3 (100)	4 (33.3)	2 (12.5)	6 (14.3)
SD	0	0	2 (12.5)	5 (11.9)
PD	0	3 (25.0)	3 (18.8)	13 (31.0)
NE	0	0	1 (6.3)	7 (16.7)
Responders–n (%)				
Yes	3 (100)	9 (75.0)	10 (62.5)	17 (40.5)
95% CI	29.2, 100	42.8, 94.5	35.4, 84.8	25.6, 56.7

Elderly patients:

A summary of the elderly patients included in the tabelecleucel clinical trials is summarised in **Table 13**.

Table 13. Elderly subjects in C-PTLD treated with tabelecleucel across all clinical studies

Study	Total Number of Subjects, N	Age (years) < 65, n (n/N)	Age (years) ≥ 65 to < 75, n (n/N)	Age (years) ≥ 75 to < 85, n (n/N)	Age (years) ≥ 85, n (n/N)
95-024	7	7 (100)	0	0	0
11-130	35	29 (82.9)	5 (14.3)	1 (2.9)	0
EBV-CTL-201	25	23 (92.0)	2 (8.0)	0	0
ATA129-EBV-302	43	31 (72.1)	10 (23.3)	2 (4.7)	0
All Clinical Studies	110	90 (81.8)	17 (15.5)	3 (2.7)	0

Objective response rates in studies are summarised in **Table 14**.

Table 14. Summary of ORR in elderly patients (<65 and ≥65 years) in C-PTLD across all clinical studies

Per IORA	Age < 65 Years		Age ≥ 65 Years[a, b]	
	Total (11-130, 95-024 and EBV-CTL-201) (N = 59)	ATA129-EBV-302 (N = 31)	Total (11-130, 95-024 and EBV-CTL-201) (N = 8)	ATA129-EBV-302 (N = 12)
Best overall response–n (%)				
CR	12 (20.3)	10 (32.3)	1 (12.5)	2 (16.7)
PR	12 (20.3)	7 (22.6)	3 (37.5)	3 (25.0)
SD	9 (15.3)	4 (12.9)	0	1 (8.3)
PD	11 (18.6)	5 (16.1)	3 (37.5)	4 (33.3)
NE	15 (25.4)	5 (16.1)	1 (12.5)	2 (16.7)

Per IORA	Age < 65 Years		Age ≥ 65 Years[a, b]	
	Total (11-130, 95-024 and EBV-CTL-201) (N = 59)	ATA129-EBV-302 (N = 31)	Total (11-130, 95-024 and EBV-CTL-201) (N = 8)	ATA129-EBV-302 (N = 12)
Responders–n (%)				
Yes	24 (40.7)	17 (54.8)	4 (50.0)	5 (41.7)
95% CI	28.1, 54.3	36.0, 72.7	15.7, 84.3	15.2, 72.3

Abbreviations: CI, confidence interval; CR, complete response; FAS, full analysis set; IORA, Independent oncologic response adjudication; PD, progressive disease; PR, partial response; SD, stable disease.

FAS includes subjects who received tabelecleucel from only representative lots. For Study ATA129-EBV-302, subjects also had ≥ 1 non-NE postbaseline disease assessment per IORA, or discontinued study or received non-protocol anti-PTLD therapy.

95% CI was calculated based on binomial exact method.

A subject is considered as a responder if the best overall response is either CR or PR.

[a] The best overall response per IORA for the 17 subjects in the ≥ 65 to < 75 years age group was CR for 2 subjects, PR for 6 subjects, SD for 1 subject, PD for 6 subjects, and NE for 2 subjects.

[b] The best overall response per IORA for the 3 subjects in the ≥ 75 to < 85 years age group was CR for 1 subject, PD for 1 subject, and NE for 1 subject.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

A combined analysis including all patients across all clinical studies (**Table 15**) was conducted for Overall Survival in the C-HCT (**Figure 11**)(and C-SOT-R+C (**Figure 12**)) cohorts.

Table 15. Tabelecleucel integrated analysis of efficacy analysis sets and cohorts (for ongoing ATA129-EBV-302, data cut-off: 07 May 2021)

Analysis Set and Cohort	11-130 N	95-024 N	201 N	Total (201, 11-130, 95-024) N	302 N
Full Analysis Set					
C-PTLD	35	7	25	67	39 (38[a])
C-HCT	25	6	14	45	14
C-SOT	10	1	11	22	25 (24)
C-SOT-R+C	8	1	6	15	13
C-SOT-R	2	0	5	7	12 (11)
IORA Evaluable Set					
C-PTLD	28	6	24	58	39 (38[a])
C-HCT	19	5	13	37	14
C-SOT	9	1	11	21	25 (24)
C-SOT-R+C	7	1	6	14	13
C-SOT-R	2	0	5	7	12 (11)

Abbreviations: C-HCT, haematopoietic cell transplant cohort; C-PTLD, posttransplant lymphoproliferative disease cohort; C-SOT, solid organ transplant cohort; C-SOT-R, solid organ transplant post-rituximab failure cohort; C-SOT-R+C, solid organ transplant post-rituximab and chemotherapy failure cohort; IORA, independent oncologic response adjudication

[a] Number of subjects included in analysis of response-related endpoints. FAS and IES are pending one patient from the C-SOT-R in the ongoing Study ATA129-EBV-302 that has not yet reached the first timepoint for radiographic assessment.

Figure 11. Kaplan-Meier plot of overall survival by response per IORA for studies 11-130, 95-024, EBV-CTL201 combined (C-HCT, FAS)

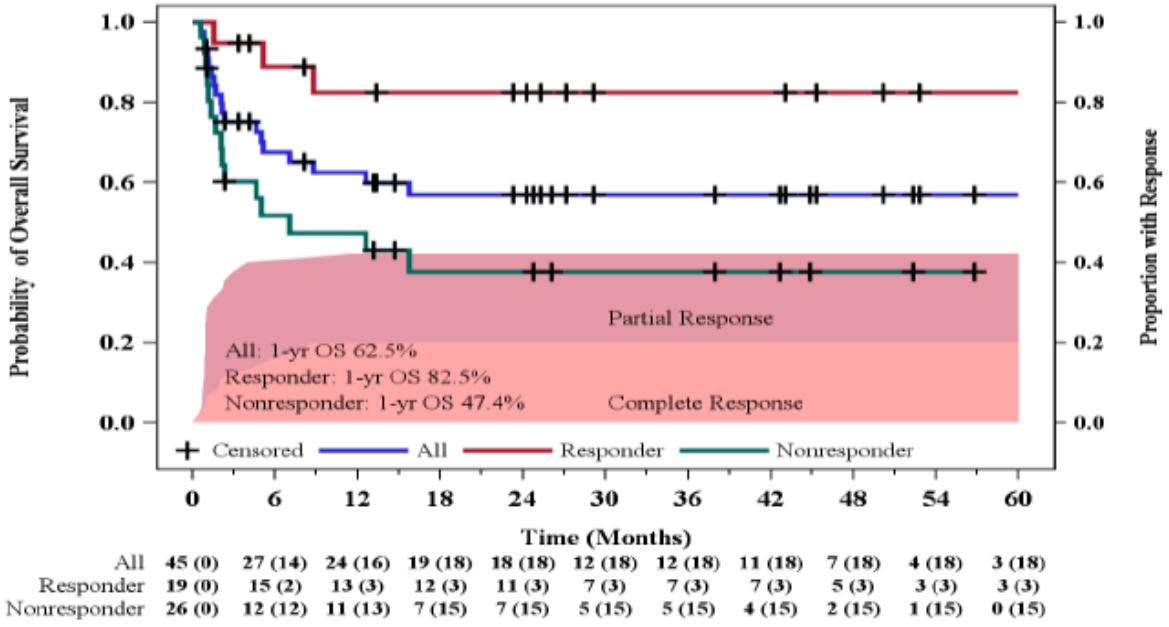
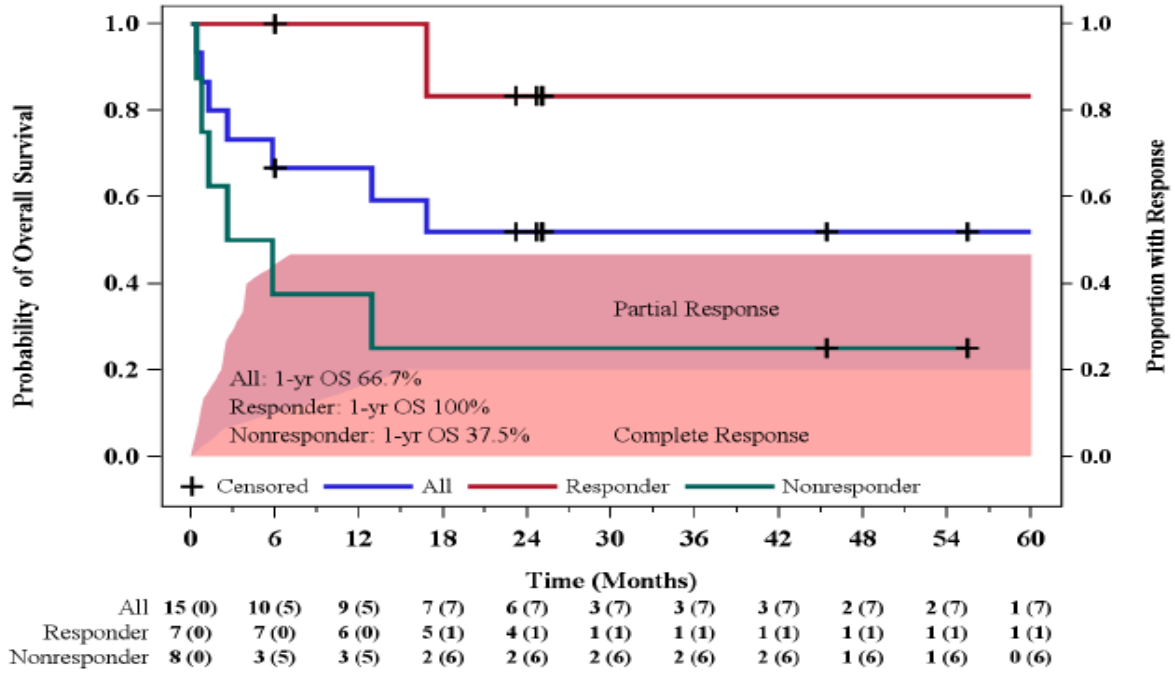


Figure 12. Kaplan-Meier plot of overall survival by response per IORA for studies 11-130, 95-024, EBV-CTL201 combined (C-SOT-R+C, FAS)



Supportive studies

The following supportive studies were performed in the process of development of tabelecleucel:

Study 95-024, an investigator-initiated proof-of-concept phase 1/2, open-label, single-site study conducted at MSKCC to evaluate the toxicities and therapeutic potential of adoptive immunotherapy with EBV-CTLs for the treatment of EBV-associated LPDs or other EBV-associated diseases.

Study 11-130, a non-randomised, single institution (MSKCC), phase 2, single-arm study, designed to evaluate the therapeutic activity of tabelecleucel in subjects with an EBV lymphoma, an EBV+ LPD, or other EBV-associated disease.

EBV-CTL-201, a multi-centre, single-arm, open-label expanded access study, a bridge to the pivotal phase 3 studies ATA129-EBV-302 and ATA129-EBV-301.

Patients have also been treated with tabelecleucel in the following expanded access programmes (EAP):

ATA129-EAP-901, an EAP in patients with EBV+ diseases, who are not eligible for treatment in other Atara clinical development studies.

Individual Patient Expanded Access (ATA129-SPU) for individual patients with EBV+ diseases, including EBV+ PTLD, who cannot be enrolled in Atara clinical studies or other EAP protocols (no prespecified efficacy assessments, only clinical assessment of response)

Compared to the pivotal study, supportive studies have several important differences regarding patient selection, treatment and response assessment:

Subjects in the supportive clinical studies and EAPs were assigned to the groups (C-HCT, C-SOT) retrospectively. Critically ill patients and untreated central nervous system disease were allowed in the supportive studies and EAPs, but not in Study ATA129-EBV-302. Whereas in the 95-024 study subjects received doses of either 1 or 2 × 10^6 cells/kg (depending on cohort and product availability), the dose administered in all other clinical studies and EAPs was 2 × 10^6 cells/kg. Importantly, for supportive studies, IORA data are reported only in integrated analysis, since IORA analyses were performed post hoc.

Main results:

In study 95-024, 15 patients were treated with tabelecleucel due to EBV+ PTLD (11 following HCT and 4 following SOT). The majority of patients had high risk disease. For the C-HCT, the ORR was 63.6% and the 1-year OS rate was 54.5%. For the C-SOT, the ORR was 50.0%, and the 1-year OS rate was 75.0%.

In study 11-130, 35 subjects had EBV+ PTLD (25 following HCT and 10 following SOT for the C-HCT, the ORR was 68.0% and the 1-year OS rate was 68.0%. For the C-SOT, the ORR was 50.0% and the 1-year OS rate was 60.0%.

Results of both studies demonstrated clinical benefit compared with historical data for rituximab-refractory EBV+PTLD.

Patients after HCT reached higher response rates than those in the SOT cohorts. Especially the rate of complete remissions was significantly higher in the HCT group in both studies.

However, there were several limitations in these early phase single-site studies, such as the small sample size, inconsistency in dosing, response assessment only by investigator and low frequency and inconsistency in duration of follow-up.

In the multicentre study EBV-CTL-201, 26 subjects had EBV+ PTLD (14 following HCT and 12 following SOT); For the C-HCT, the ORR was 50.0% and the 1-year OS rate was 61.5%. For the C-SOT, the ORR was 83.3% and the 1-year OS rate was 81.5%. Thus, ORR and OS rate were higher in the C-SOT group. Importantly, the results in the C-HCT cohort (e.g. DOR) must be interpreted in context with very short follow-up period of 2.8 months of this cohort (vs 22.5 months in the C-SOT group). In contrast to the main study, maximum of 4 different tabelecleucel cell product lots were allowed for all PTLD patients.

In the ATA129-EAP-901 a total of 46 patients were enrolled, 18 of which had EBV+ PTLD (10 C-HCT, 8 C-SOT and received tabelecleucel from only representative lots as of the data cut-off date (02 July 2021). The ORR was 72.2% for in the C-PTLD (n = 18), 70.0% in the C-HCT (n = 10), 75.0% in the C-SOT (n = 8).

In the ATA-129-SPU 48 patients with EBV+ PTLD (19 following HCT and 29 following SOT) were enrolled, as of the data cut-off date (02 July 2021). For the C-PTLD, the ORR was 43.8%, for the C-HCT, the ORR was 26.3% and for the C-SOT, the ORR was 55.2%.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The phase 3 tabelecleucel clinical development programme initially comprised 2 studies, ATA129-EBV-301 in subjects with EBV+ PTLD following allogeneic HCT and ATA129-EBV-302 in subjects with EBV+ PTLD following SOT. These 2 studies were merged under ATA129-EBV-302 due to the ultra-low incidence of relapsed/refractory EBV+ PTLD and to mitigate against the risk of sites terminating

participation in the studies due to slow enrolment. ATA129-EBV-302 is a multi-centre, phase 3, single arm, open label study and is the pivotal study in support of this application.

The single-arm, open label design is considered acceptable, taking into account the claimed indication of an ultra-rare condition and the lack of an appropriate comparator.

The patient population in the pivotal study included patients with relapsed/refractory EBV+ PTLD after rituximab for HCT cohort /rituximab with or without chemotherapy for SOT cohort and were treated with tabelecleucel monotherapy. To reflect this, the indication for Ebvallo was modified following a request from the CHMP, as monotherapy for treatment of adult and paediatric patients 2 years of age and older with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have received at least one prior therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate.

Patients with more severe GvHD as well as patients with active CNS lymphoma requiring treatment were excluded from the trial and response failure following a minimum cumulative dose for rituximab was defined in the inclusion criteria.

The median age of patients included in the study age was 48.5 years. The majority of subjects (86.0%) were adults ≥ 18 years of age; 3 subjects were < 17 years and 6 subjects were < 18 years. The small number of paediatric patients is a limitation of the study but more data in this population are expected through the pivotal study which is continuing to recruit patients but also the planned post-authorisation study to describe the safety and effectiveness of tabelecleucel in patients with Epstein-Barr Virus-Positive Posttransplant Lymphoproliferative Disease in a Real-world setting in Europe which will specifically target enrolment of paediatric (aged<18 years) as well as elderly patients (aged≥ 65 years).

The primary objective of the study was to determine the clinical benefit of tabelecleucel in subjects with EBV+ PTLD following SOT after failure of rituximab or rituximab plus chemotherapy or allogeneic HCT after failure of rituximab, as measured by the objective response rate (ORR). The primary efficacy endpoint of the study is ORR (CR+PR) determined separately in both cohorts (SOT and HCT). The primary efficacy analyses of disease assessment-related endpoints were based on the disease assessments by IORA (independent oncologic response adjudication), which is endorsed. Secondary endpoints include evaluation of overall survival, duration of response, time to response, ORR determined separately in SOT and HCT cohort and evaluation of safety profile of tabelecleucel. Overall, the endpoints are considered clinically relevant and appropriate.

The study aimed to show that ORR is greater than 20% in the SOT cohort at the one-sided significance level of 0.025. The one-sided level of 0.025 is acceptable, however, there was no prospective multiplicity control for the HCT cohort, meaning that results in this cohort are descriptive and should be interpreted with care. Interim analyses were planned for the SOT cohort. The merit of these analyses is not fully clear, given the small sample sizes. The boundaries for significance were not updated with the observed information fraction (O'Brien-Fleming type spending function planned). The applicant explained that in total there were 4 analyses of the data. The first interim analysis was conducted with 20 patients in the SOT cohort and was not significant. The second analysis with 24 patients in the SOT cohort reached statistical significance at the nominal level of 0.0074. The analysis was then updated two times to incorporate 'overrunning' data, after statistical significance had been reached at the second interim analysis. The timing of neither of the interim analyses is in line with the prespecified time points for analysis, as these were planned with n=15, n=21 and n=33 subjects in the SOT cohort. These differences in planned and observed sample sizes at the interim analyses are not fully understood in light of the small sample size and presumably very close monitoring of the data. Potential upward bias associated with the timing of the interim analyses in this open-label, single arm study cannot be fully excluded, however, point estimates are rather similar across the 4 analyses.

Considering the therapeutic circumstances, an ad-hoc interpretation of results despite statistical uncertainties appears reasonable.

The recommended dose for tabelecleucel is $2x10^6$ viable cells/kg administered over multiple 35-day cycles on days 1, 8, and 15 and response assessment at day 28, followed by observation through day 35. The number of treatment cycles with tabelecleucel is determined by the response to treatment. If a complete or partial response is not obtained, patients may be switched to an Ebvallo lot with a different HLA restriction. This dosing regimen was selected based upon efficacy and safety results in the initial supportive studies 95-024 and 11-130. The dose selection was made taking to the account the threshold of 10^5 alloreactive cytotoxic T lymphocyte precursor/kg since the risk of GvHD below this threshold is low and the optimal timing for response assessments as well as logistics related to selection of an appropriate tabelecleucel lot and shipping to site. Overall, the recommended dosing for tabelecleucel of 2×10^6 cells/kg is acceptable.

Three supportive studies and data from two expanded access programs were also submitted. All supportive studies have a single arm, open-label design. The applicant also submitted a non-interventional retrospective review study analysing patients diagnosed between 2000 and 2018 who received a next-line of systemic therapy (HCT/post rituximab or SOT/post rituximab-chemotherapy) and provided a comparative analysis with the single-arm pivotal study. These data are considered supportive, considering well-known limitations of retrospective studies compared to RCT.

Overall, the clinical development strategy has been discussed via Scientific Advice and complies with the provided recommendations.

Efficacy data and additional analyses

ATA129-EBV-302 is an ongoing study, initiated on 26 June 2018. At the cut-off date of the latest interim analysis (data cut-off date 05 November 2021) 43 patients had been enrolled. The SOT cohort (29 patients) consisted of SOT patients who had failed rituximab monotherapy (13 patients) and SOT patients who had failed rituximab plus chemotherapy (SOT-R+C, 16 patients), the latter being the pivotal population for the SOT population. All enrolled subjects had received at least one dose of tabelecleucel and were included in the full analysis set (FAS).

In the C-HCT cohort, ORR was 50%; 6 subjects achieved CR and 1 subject achieved PR. In the C-SOT-R+C, ORR was 56%, 5 achieved CR and 4 PR. In the C-HCT, the KM estimate of median DOR was 23.0 months (95% CI: 15.9, NE), and the median (min, max) follow-up time was 15.9 months (1.3, 23.3). In the C-SOT-R+C, the KM estimate of the median DOR was 15.2 months (95% CI: 0.8, 15.2), and the median (min, max) follow-up time was 2.3 months (0.8, 15.2). In the C-HCT, the DRR was 42.9%, in the C-SOT-R+C, the DRR was 25.0%.

In the C-HCT, 4 of 14 subjects (28.6%) died, and the median (min, max) follow-up time was 14.1 months (2.0, 35.4). The KM estimated 1-year OS rate was 70.1% and the KM estimate of median OS was NE. In the C-SOT-R+C, 7 of 16 subjects (43.8%) died, and the median (min, max) OS follow-up time was 5.5 months (0.4, 25.3). The KM estimated 1-year OS rate was 64.3% and the KM estimate of median OS was 16.4 months. The KM estimated 1-year OS rate for responders was higher than that for non-responders.

Analyses of subjects who achieved complete response (CR) and durable CR were also conducted on the full analysis set (FAS) in Study ATA129-EBV-302 using data from the 05 November 2021 data cut-off, per IORA.

In the C-PTLD, 12 of 43 subjects (27.9%) in the FAS had achieved CR per IORA assessment, among whom 9 (75.0%) had durable CR (with a duration of > 6 months) which is considered

clinically meaningful. Four of the 9 subjects (44.4%) had subsequent progression of disease. The Kaplan-Meier (KM) estimate of median (95% CI) duration of CR was 23.0 months (6.8, not estimable [NE]), with a median (min, max) follow-up time in response of 14.5 months (0.03, 23.3).

For both C-SOT-R+C and C-HCT, the target indications, salvage chemotherapy is less likely to be a feasible option, and there is potential for clinical benefit with a restriction switch of tabelecleucel if needed. This is supported by efficacy and safety results for Study ATA129-EBV-302 using the FAS in which 17 subjects received a restriction switch, among whom 7 (1 in the C-SOT-R, 3 in the C-SOT-R+C, and 3 in the C-HCT) achieved clinical benefit (CR, PR or SD). Subjects from all cohorts experienced clinical benefit. No relevant safety concerns were observed in the subjects who received a restriction switch compared to those who did not. Importantly, no subjects in either group experienced the identified or potential risks of tumour flare reaction, infusion-related reactions, cytokine release syndrome, bone marrow transplant rejection, or transmission of infectious agents including CMV. Overall, the provided data indicate a positive effect for the HLA-restriction switch in all cohorts, even considering the relatively small sample size. Up to 4 different human leukocyte antigen (HLA) restrictions in the solid organ transplant (SOT) population similar to the haematopoietic cell transplant (HCT) population are allowed.

Special populations

As of the 5 November 2021, 6 and 20 paediatric subjects were treated in the main and supportive studies, respectively. The ORR per IORA was 66% and 40%, respectively. Cumulatively 41 paediatric subjects were treated with tabelecleucel across all clinical studies and EAPs. There were no subjects < 2 years. 8 subjects were ≥2 to < 6, 16 patients were ≥ 6 to < 12 and 17 patients were ≥12 to < 18 age of years. Although the responses seem to be similar, the small sample sizes (especially in age subgroup <6 years), do not allow definite conclusion. Due to the lack of data in patients < 2 years tabelecleucel use is limited to paediatric patients 2 years of age and older.

For subjects ≥ 65 years of age in the C-PTLD, 41.7% (95% CI: 15.2, 72.3) in the main study and 50.0% (95% CI: 15.7, 84.3) in the supportive studies were responders per IORA. The efficacy analysis by the age subgroups was not possible, due to very small sample sizes. In the main study, efficacy of tabelecleucel was slightly lower in the population ≥ 65 years compared to < 65 years of age (54% vs 41%). The interpretation of these results is limited by the sample size, since only 5 elderly patients were treated in the main study. The comparison in supportive studies showed favourable results for elderly population (40% vs 50%), however, the sample size was also very small with 4 subjects ≥ 65 years of age. Additional information for both the elderly and the paediatric populations are expected to be collected through the ongoing recruitment of the pivotal study and the planned post-authorisation study to describe the safety and effectiveness of tabelecleucel in patients with Epstein-Barr Virus-Positive Posttransplant Lymphoproliferative Disease in a Real-world setting.

The safety and efficacy of tabelecleucel have not been studied in patients with severe renal or hepatic impairment. However, based on the tabelecleucel mechanism of action, the influence of renal or hepatic impairment on the pharmacokinetics of tabelecleucel is considered unlikely.

Supportive studies

Based on the original application, a total of 106 patients with relapsed/refractory EBV+PTLD received at least 1 dose of tabelecleucel within the framework of the four studies and 66 patients were treated with tabelecleucel within expanded access programs. Compared to the pivotal study, supportive studies have several important differences: Subjects in the supportive clinical studies and EAPs were assigned to the groups (C-HCT, C-SOT) retrospectively. Critically ill patients and untreated central nervous system disease were allowed in the supportive studies and EAPs, but not in Study ATA129-EBV-302. Whereas in the 95-024 study subjects received doses of either 1 or 2 × 10^6 cells/kg

(depending on cohort and product availability), the dose administered in all other clinical studies and EAPs was 2 × 10^6 cells/kg. Importantly, for supportive studies, IORA analyses were performed post hoc.

The ORR in the main study ATA129-EBV-302 (05 November 2021 data cut-off) is comparable with the cumulative ORR of the three supportive studies (50% C-HCT, 56% -SOT-R+C vs. 48%). The ORR results for the EAP programs were different, 72.2% in the ATA129-EAP-901 vs. 43.8% in the SPU (based on 07 July 2021 data cut-off). The EAP programs have several limitations, e.g. simplified data collection, reduced requirements for assessments, which may influence the comparison of these results with the efficacy data from clinical trials. However, the efficacy results from all clinical studies and SAP are favourable, compared to historical data for patients with r/r EBV+ PTLD.

The OS data from supportive studies are also consistent with the pivotal study results. The KM estimated 6-month and 1-year OS rates were 70.9% and 65.9%. In the cumulative analysis of supportive trials, the OS of responders was significantly higher, compared to non-responders. These findings are also in line with the results of the pivotal study.

Using historical controls, the applicant also performed an external comparison to the pivotal study (study RS002). Results of this study were updated restricting the external control group to patients with an index diagnosis date between 2010-2018. The 30 patients from Study ATA129-EBV-302 included 14 patients post HCT (46.7%) and 16 patients (53.3%) post-SOT-R+C (based on 05 November 2021 data cut-off). These were propensity score matched to 55 patients from Study ATA129-RS002, including 27 (49.1%) with EBV+ PTLD following HCT and R/R to rituximab and 28 (50.9%) with EBV+ PTLD following SOT and R/R to rituximab plus chemotherapy. In this analysis tabelecleucel continues to demonstrate significant OS benefit compared to SOC with an unadjusted HR of 0.46 and an adjusted HR of approximately 0.34 compared to the historical cohort. Despite the inherent limitation in such comparisons these results are considered supportive for contextualisation of efficacy results from the main study.

Additional efficacy data needed in the context of a MA under exceptional circumstances

Due to the ultra-rare incidence of EBV+ PTLD, the limited number of patients included in the pivotal trial and the under-representation of elderly and paediatric patients in the study is considered acceptable. Additional efficacy data, with an emphasis on the elderly and paediatric patients will be collected through the planned post-authorisation observational study which will describe the effectiveness of tabelecleucel in patients treated for EBV+ PTLD following HCT or SOT in a real-world setting. Additional data are also expected through the ongoing pivotal study ATA129-EBV-302 for which the final study report is expected in December 2027. Finally, the applicant will submit yearly updates on any new information concerning the safety and efficacy of Ebvallo.

2.6.7. Conclusions on the clinical efficacy

Tabelecleucel demonstrated clinically significant responses in both post SOT and post HCT EBV^+ PTLD cohorts. Approximately half of subjects in both C-HCT and C-SOT-R+C cohorts achieved partial or complete remission. Durable responses, lasting > 6 months were also observed in a number of responders. The efficacy results from supportive studies are consistent with the pivotal study results.

Despite the limitations, of the interim analysis and the small sample size, in the therapeutic setting of r/r EBV+ PTLD, where there are no therapeutic alternatives and patients have a dismal prognosis, these results are considered clinically meaningful.

The CAT considers the following measures necessary to address the missing efficacy data in the context of a MA under exceptional circumstances:

- Provision of the final results of the ongoing pivotal study ATA129-EBV-302 to provide further data on the clinical benefit of tabelecleucel in subjects with EBV+ PTLD following SOT after rituximab plus chemotherapy failure or allogeneic HCT after failure of rituximab

- A post-authorisation safety study (PASS) to describe the safety and effectiveness of tabelecleucel in patients with EBV+ PTLD following HCT or SOT in a real-world setting

- In order to ensure adequate monitoring of safety and efficacy of Ebvallo in the treatment of patients with EBV+ PTLD, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Ebvallo.

The CHMP endorses the CAT conclusion on clinical efficacy as described above.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

The evaluation of safety is based on data for all subjects in the pivotal study (ATA129-EBV-302) and an integrated summary of safety (ISS) for subjects with EBV-driven diseases including the supportive clinical studies and all subjects in the Expanded Access Programs (EAPs). In the ISS, data were pooled across all clinical studies for all disease cohorts (EBV+ PTLD and non-PTLD combined), all EBV+ PTLD cohorts, and all non-PTLD disease cohorts.

While the pivotal study is limited to the proposed indication of EBV+ PTLD, the supportive clinical studies and the Expanded Access Programs also contain patients with other EBV driven diseases.

The ISS included 340 patients, of which 202 were recruited in clinical studies and 138 exposed to tabelecleucel through EAPs. This included 52 elderly patients (36 from clinical studies and 16 in EAPs), and 86 paediatric and adolescent patients (45 from clinical studies and 41 in EAPs).

The median dose of tabelecleucel in the ISS was 2.00×10^6 cells/kg (range: 0.8-3.3) The median number of cycles was 2.0 (range: 1-14) over a median of 1.7 months (range: 0.03-52.5) of treatment.

In the C-PTLD population (N = 183) across all clinical studies and EAPs, the median dose of tabelecleucel was 2.00×10^6 cells/kg (range: 0.8-2.4). The median number of cycles was 2.0 (range: 1-9) over a median of 1.8 months (range: 0.03-18.5) of treatment.

The demographic characteristics were similar across the studies. About half subjects were females (46.5%). Most subjects were White/Caucasian (64.1%), not Hispanic/Latino (56.5%) with a mean age of 37.8 years (range of 1-84 years, the majority of subjects (80.0%) were ≥ 16 years of age), about 15% were elderly (≥ 65 years). In general, all age groups were represented across EBV^+ PTLD and non-PTLD populations except for the children < 2 years of age who were only represented in the non-PTLD population.

All data presented in this section, are with the data cut-off of 5th November 2021 unless otherwise specified.

2.6.8.2. Adverse events

Treatment-emergent AEs (TEAEs) include any AE that occurred after first dose of tabelecleucel through 30 days after the last dose of tabelecleucel or any related AE started on or after the first dose of tabelecleucel. TEAEs leading to study treatment discontinuation was collected only in Studies EBV-CTL-201 and ATA129-EBV-302 and all EAPs. Studies 11-130 and 95-024 collected only SAE, therefore

TESAE Summary outputs include all four Studies, while TEAE Summary outputs report Studies 201 and 302 only. TEAEs are summarised in **Table 16** and TEAEs related to study treatment in **Table 17**.

Table 16. Overall summary of subject incidence of treatment emergent adverse events (TEAEs), EBV+ and overall populations, Full Analysis Set.

	EBV+ PTLD (N=68) n (%)	AID LPD (N=7) n (%)	PID LPD (N=5) n (%)	Viremia (N=5) n (%)	LMS (N=4) n (%)	Lymphoma (N=8) n (%)	NPC (N=5) n (%)	Other Solid Tumor (N=1) n (%)	Non-PTLD Total (N=35) n (%)	Overall Total (N=103) n (%)
Subjects reporting any TEAEs	65 (95.6)	7 (100)	5 (100)	5 (100)	4 (100)	8 (100)	4 (80.0)	1 (100)	34 (97.1)	99 (96.1)
Worst grade >=3	49 (72.1)	6 (85.7)	4 (80.0)	2 (40.0)	2 (50.0)	4 (50.0)	2 (40.0)	0	20 (57.1)	69 (67.0)
Serious	40 (58.8)	4 (57.1)	3 (60.0)	2 (40.0)	2 (50.0)	3 (37.5)	2 (40.0)	0	16 (45.7)	56 (54.4)
Fatal	10 (14.7)	1 (14.3)	1 (20.0)	0	1 (25.0)	1 (12.5)	1 (20.0)	0	5 (14.3)	15 (14.6)
Leading to study treatment discontinuation	16 (23.5)	2 (28.6)	1 (20.0)	0	0	1 (12.5)	1 (20.0)	1 (100)	6 (17.1)	22 (21.4)
Leading to study discontinuation	7 (10.3)	0	2 (40.0)	0	0	3 (37.5)	0	0	5 (14.3)	12 (11.7)

EBV: Epstein-Barr virus; PTLD: post-transplant lymphoproliferative disease; AID: acquired immunodeficiency; PID: primary immunodeficiency; LPD: lymphoproliferative disease; LMS: leiomyosarcoma; NPC: nasopharyngeal carcinoma

Table 17. Overall summary of subject incidence of treatment emergent adverse events (TEAEs) related to study treatment, EBV+ and overall populations, Full Analysis Set

	EBV+ PTLD (N=68) n (%)	AID LPD (N=7) n (%)	PID LPD (N=5) n (%)	Viremia (N=5) n (%)	LMS (N=4) n (%)	Lymphoma (N=8) n (%)	NPC (N=5) n (%)	Other Solid Tumor (N=1) n (%)	Non-PTLD Total (N=35) n (%)	Overall Total (N=103) n (%)
Subjects reporting any TEAEs related to study treatment	25 (36.8)	4 (57.1)	4 (80.0)	1 (20.0)	3 (75.0)	2 (25.0)	2 (40.0)	0	16 (45.7)	41 (39.8)
Worst grade >=3	12 (17.6)	3 (42.9)	1 (20.0)	0	0	1 (12.5)	0	0	5 (14.3)	17 (16.5)
Serious	7 (10.3)	2 (28.6)	2 (40.0)	0	0	0	0	0	4 (11.4)	11 (10.7)
Fatal	0	0	0	0	0	0	0	0	0	0
Leading to study treatment discontinuation	0	1 (14.3)	0	0	0	0	0	0	1 (2.9)	1 (1.0)
Leading to study discontinuation	1 (1.5)	0	1 (20.0)	0	0	0	0	0	1 (2.9)	2 (1.9)

EBV: Epstein-Barr virus; PTLD: post-transplant lymphoproliferative disease; AID: acquired immunodeficiency; PID: primary immunodeficiency; LPD: lymphoproliferative disease; LMS: leiomyosarcoma; NPC: nasopharyngeal carcinoma

Nearly all subjects in Studies ATA129-EBV-302 and EBV-CTL-201 experienced TEAEs: (96.1%). Most frequently reported TEAEs by PT were disease progression, pyrexia, and diarrhoea, followed by fatigue, cough, nausea, and vomiting. TEAEs had a maximum severity of grade 3 for 37 (35.9%) subjects, grade 4 for 17 (16.5%) subjects, and grade 5 for 15 (14.6%) subjects. Treatment-emergent adverse event with a maximum severity of grade 4 that occurred in > 1 subject were neutrophil count decreased (reported for 5 subjects [4.9%]), white blood cell count decreased and sepsis (reported for 4 subjects [3.9%] each), lymphocyte count decreased (reported for 2 subjects [1.9%]). Treatment-emergent adverse events with a maximum severity of grade 5 that occurred in > 1 subject included disease progression (8 subjects [7.8%]) and multiple organ dysfunction syndrome (reported in 2 subjects [1.9%]).

Treatment-related TEAEs (based on investigator assessment) for Studies ATA129-EBV-302 and EBV-CTL-201 were reported for 39.8% of subjects. Treatment-related TEAEs with the highest subject number by PT were pyrexia, fatigue, hypotension and nausea followed by neutrophil count decreased and diarrhoea. 16.5% of subjects had grade ≥ 3 TEAEs. No fatal treatment-related TEAEs were reported. One subject (1.0%) had a treatment-related TEAE that led to study discontinuation.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

In study ATA129-EBV-302, treatment-emergent serious adverse events were reported for 60.5% of subjects. Reported TESAEs by PT are summarised in **Table 18**.

Table 18. Treatment emergent serious adverse event (TESAEs) by preferred term, Study ATA129-EBV-302

	Tab-cel SOT EBV+ PTLD			Tab-cel HCT EBV+ PTLD	Overall Total
Preferred Term	R/R Rituximab (N=13) n (%)	R/R Rituximab + Chemo (N=16) n (%)	Total (N=29) n (%)	R/R Rituximab (N=14) n (%)	(N=43) n (%)
Subjects reporting any TESAEs	7 (53.8)	8 (50.0)	15 (51.7)	8 (57.1)	23 (53.5)
Disease progression	1 (7.7)	3 (18.8)	4 (13.8)	4 (28.6)	8 (18.6)
Sepsis	2 (15.4)	0	2 (6.9)	3 (21.4)	5 (11.6)
Acute kidney injury	1 (7.7)	2 (12.5)	3 (10.3)	0	3 (7.0)
Pneumonia	1 (7.7)	0	1 (3.4)	2 (14.3)	3 (7.0)
Respiratory failure	2 (15.4)	1 (6.3)	3 (10.3)	0	3 (7.0)
Vomiting	1 (7.7)	2 (12.5)	3 (10.3)	0	3 (7.0)
Atrial flutter	1 (7.7)	1 (6.3)	2 (6.9)	0	2 (4.7)
Dehydration	0	1 (6.3)	1 (3.4)	1 (7.1)	2 (4.7)
Delirium	1 (7.7)	1 (6.3)	2 (6.9)	0	2 (4.7)
Fatigue	1 (7.7)	0	1 (3.4)	1 (7.1)	2 (4.7)
Febrile neutropenia	1 (7.7)	0	1 (3.4)	1 (7.1)	2 (4.7)
Hypoxia	1 (7.7)	0	1 (3.4)	1 (7.1)	2 (4.7)
Influenza	0	1 (6.3)	1 (3.4)	1 (7.1)	2 (4.7)
Nausea	1 (7.7)	1 (6.3)	2 (6.9)	0	2 (4.7)
Pyrexia	1 (7.7)	1 (6.3)	2 (6.9)	0	2 (4.7)

In the ISS population, 57.9% of subjects were reported as having any TESAEs. The most frequently reported SOCs for those patients were Infections and Infestations (27.4%), General disorders and administration site conditions (24.1%), Respiratory, thoracic and mediastinal disorders (13.2%) and Gastrointestinal disorders (10.9%). The most frequently reported PTs were disease progression (10.9%), pneumonia (10.3%), pyrexia (7.6%), sepsis (4.7%), febrile neutropenia (4.1%), respiratory failure (4.1%), death (3.8%), acute kidney injury (2.9%), and device related infection (2.9%).

Related serious adverse events

ATA129-EBV-302

A total of 4 subjects (9.3%) had a TESAE that was considered by the investigator as related to treatment. The treatment-related TESAE with the highest subject incidence by PT was pyrexia (reported for 2 subjects [4.7%]); all other treatment-related TESAEs, such as diarrhoea, hypotension, hypoxia, rash, rash erythematous and tachycardia, were reported in only 1 subject for each PT.

In the ISS, 35 subjects (10.3%) had a TESAE that was considered by the investigator as related to treatment. The treatment-related TESAEs with the highest subject incidence by PT were pyrexia, reported for 5 subjects [1.5%]); tumour flare in 4 subjects [1.2%] and hypoxia in 3 subjects [0.9%]. Febrile nreutropenia, lymphocyte count decreased, neutrophil count decreased, pneumonitis were all reported in 2 subjects each [0.6%]; all other treatment-related TESAEs, were reported in only 1 subject for each PT.

Deaths

In the pivotal study ATA129-EBV-302, a total of 18 subjects (41.9%) died; 5 subjects (11.6%) had a fatal TESAE, and 13 subjects (30.2%) died due to other causes. By PT, fatal TESAEs included disease progression (3 subjects [7.7%]), multiple organ dysfunction syndrome (1 subject [2.6%]), and respiratory failure (1 subject [2.6%]). None of the fatal TESAEs were considered by the investigator as related to treatment.

Across all 4 clinical studies and Expanded Access Programs, 71 fatal TESAEs were reported (20.0%). The most frequent fatal TESAEs were disease progression and death, in all cohorts, followed by pneumonia and pneumonia adenoviral. None of the fatal TESAEs were considered related to treatment except one subject in the Expanded Access Programme (C-HCT cohort) had 2 grade 5 TESAEs (Enterococcal infection and Citrobacter bacteraemia) that were considered possibly related to tabelecleucel by the investigator.

Adverse Events of Special Interest (AESI)

In the clinical programme, a number of AEs were identified as AESIs of tabelecleucel based on its mechanism of action, biological nature, and mode of administration. These were infusion-related reaction IRR, transmission of infectious diseases agents including cytomegalovirus CMV), cytokine release syndrome CRS, and graft versus host disease GvHD.

Infusion-related reactions (IRR)

Due to its biological nature and mode of administration, tabelecleucel has a theoretical risk of infusion-related reactions (IRR). Infusion-related reactions has been considered as an adverse event of special interest for the tabelecleucel clinical development programme. There were 4 subjects who experienced events that were considered as IRR by the investigators or treating physician in the clinical studies across the clinical development programme (3 in the clinical studies and one in the EAP). The overall subject incidence was 1.2% across all 4 clinical studies (N = 202) and 0.7% in EAPs (N = 138).

Overall, events from 1 subject from clinical study 11-130 and 1 subject from the EAP ATA129-SPU were reported as possibly related by the investigator/treating physician. Although, these events were reported as possibly related by the investigator, the relationship between tabelecleucel and IRR could not be confirmed.

Transmission of infectious agents, including cytomegalovirus

The applicant states that no transmissions of infectious agents, including transmission of cytomegalovirus, were reported. One subject (with prior HCT) was discontinued from treatment and

subsequently died due to a TESAEs of Enterococcal infection and Citrobacter bacteraemia that were considered by the investigator as possibly related to tabelecleucel.

Cytokine release syndrome (CRS)

Systemic levels of 4 key cytokines (interleukin-1beta [IL 1β], IL 2, IL 6, and TNFα) were evaluated from subjects treated with tabelecleucel.

No event of treatment-emergent CRS was reported in any subjects in the clinical studies. Two grade 1 events of CRS were reported in 2 of 138 subjects in the EAPs; both subjects had non-PTLD EBV+ lymphoma. One case was a nonserious CRS event that occurred after the first dose of tabelecleucel in the context of confounding events. The subject developed a concomitant event of encephalopathy that was fatal. Neither event was considered treatment related; the encephalopathy was due to progression of the patient's disease. The second case was a serious event of CRS event reported as possibly related by the investigator that occurred after multiple doses of tabelecleucel in context of confounding events. In both cases, confounding factors were present, and in the second case, the time of occurrence was atypical.

To study the potential risk of CRS in association with tabelecleucel, cytokines commonly associated with CRS were analysed in subjects with EBV+ PTLD and other EBV-driven diseases enrolled in clinical studies. The applicant states that in pharmacology studies, the evaluation of plasma cytokine levels revealed very little modulation from baseline indicating that tabelecleucel as a T cell therapy does not depend on systemic cytokine release to evoke clinical benefit and does not promote the risks known to occur with increases in cytokines, further supporting the benefit-risk profile of tabelecleucel.

Neurologic treatment-emergent adverse events

In addition to CRS, neurologic events were assessed in the context of the possible similarity between tabelecleucel and other T-cell therapies such as chimeric antigen receptor T-cell drugs.

38.8% of subjects in the ISS experienced at least 1 neurologic TEAE, 14.6% experienced neurologic TEAEs with a maximum severity of grade ≥ 3, and 1 (1.0%) subject died as a result of a neurologic TEAE, which was not considered related to treatment by the investigator.

Treatment-related neurologic TEAEs were reported for 5.8% of subjects; of these, 1 (1.0%) subject had at least 1 treatment-related TEAE with a maximum severity of grade ≥ 3.

Overall subject incidences of treatment-related neurologic TEAEs by PT category were low, with the most common being dizziness and headache (reported in 2 subjects, 1.9% in each PT).

Graft-versus-host disease

The subject incidence of GvHD (acute and chronic, serious and nonserious, and treatment-emergent or not)was approximately 5% 14 of 340 subjects, 8 of 202 in clinical studies, and 6 of 138 in the EAPs. Graft-versus-host disease events were reported as not related to tabelecleucel by the investigator in 11 of 14 subjects and had a maximum severity grade of 5 in 1 subject.

The incidence of TEAEs of GvHD in Studies ATA129-EBV-302 and EBV-CTL-201, which collected all events (serious and nonserious), was 4.9% (5/103 subjects). Of these, 2 subjects in Study EBV-CTL-201 reported treatment-emergent GvHD events that were assessed as possibly related to tabelecleucel by the investigator. Both subjects had a medical history of allogeneic HCT and were confounded (in one case by concomitant use of clindamycin and in the other by recent medical history of GvHD). Two (40%) patients had Grade 1, 1 patient (20%) had Grade 2, 1 patient (20%) had Grade 3, and 1 (20%) patient had Grade 4 events. No fatal events were reported. Four (80%) patients recovered from GvHD. The median time to onset was 42 days (range: 8 to 44 days). The median duration was 35 days (range: 7 to 133 days).

Graft-versus-host disease events occurred almost exclusively in subjects with history of transplantation: (HCT = 12 and SOT = 1). There was no confirmed case of GvHD in subjects without transplant history. The only reported case of GvHD in a subject without transplant history was reported as a grade 1 skin GvHD (rash) that occurred in a patient with a complicated history of chronic autoimmune skin disease that was ongoing at time of event; the event was assessed as related by the investigator, however, no biopsy was performed to confirm the suspected skin GvHD event; the event resolved within 4 days and additional doses of tabelecleucel were administered with no subsequent aggravation or relapse observed.

Tumour flare reaction

Tumour flare reaction (TFR) is considered an identified risk with an established causal relationship to tabelecleucel. Overall, 4 of 340 subjects (1.2%) reported at least 1 TFR; all but 1 of the events reported in these subjects were serious and all were considered related to treatment.

2.6.8.4. Laboratory findings

Most frequently shifts in grade form baseline for laboratory parameters observed in clinical studies are summarised in **Table 19**.

Table 19. Shifts in grade from baseline for laboratory parameters in >10% of subjects overall or in any EBV^{+}PTLD cohorts in clinical studies (Full analysis set, data cut-off 7 May 2021)

Laboratory Parameter Shift by Grade	C-SOT			C-HCT (N = 59) n (%)	C-PTLD (N = 106) n (%)	Overall Total (N = 198) n (%)
	C-SOT-R N = 19 n (%)	C-SOT-R+C N = 28 n (%)	Total N = 47 n (%)			
Aspartate aminotransferase (U/L) increased						
Grade 0 to 1	3 (15.8)	4 (14.3)	7 (14.9)	8 (13.6)	15 (14.2)	31 (15.7)
Alkaline phosphatase (U/L) increased						
Grade 0 to 1	2 (10.5)	4 (14.3)	6 (12.8)	7 (11.9)	13 (12.3)	26 (13.1)
Alanine aminotransferase (U/L) increased						
Grade 0 to 1	2 (10.5)	5 (17.9)	7 (14.9)	8 (13.6)	15 (14.2)	25 (12.6)
Platelets (10^9/L) decreased						
Grade 0 to 1	1 (5.3)	5 (17.9)	6 (12.8)	8 (13.6)	14 (13.2)	23 (11.6)
Grade 1 to 3	2 (10.5)	1 (3.6)	3 (6.4)	3 (5.1)	6 (5.7)	8 (4.0)
Leukocytes (10^9/L) decreased						
Grade 0 to 1	1 (5.3)	3 (10.7)	4 (8.5)	4 (6.8)	8 (7.5)	13 (6.6)
Grade 0 to 2	1 (5.3)	2 (7.1)	3 (6.4)	12 (20.3)	15 (14.2)	23 (11.6)
Grade 2 to 3	0	3 (10.7)	3 (6.4)	2 (3.4)	5 (4.7)	8 (4.0)
Hemoglobin (mmol/L) decreased						
Grade 1 to 2	4 (21.1)	3 (10.7)	7 (14.9)	5 (8.5)	12 (11.3)	26 (13.1)
Grade 2 to 3	0	3 (10.7)	3 (6.4)	13 (22.0)	16 (15.1)	30 (15.2)
Lymphocytes (10^9/L) decreased						
Grade 1 to 2	2 (10.5)	1 (3.6)	3 (6.4)	1 (1.7)	4 (3.8)	12 (6.1)
Grade 2 to 3	3 (15.8)	2 (7.1)	5 (10.6)	7 (11.9)	12 (11.3)	20 (10.1)
Grade 3 to 4	0	1 (3.6)	1 (2.1)	10 (16.9)	11 (10.4)	15 (7.6)

Laboratory Parameter Shift by Grade	C-SOT			C-HCT (N = 59) n (%)	C-PTLD (N = 106) n (%)	Overall Total (N = 198) n (%)
	C-SOT-R N = 19 n (%)	C-SOT-R+C N = 28 n (%)	Total N = 47 n (%)			
Neutrophils (10^9/L) decreased						
Grade 0 to 2	2 (10.5)	4 (14.3)	6 (12.8)	10 (16.9)	16 (15.1)	24 (12.1)
Grade 0 to 3	0	1 (3.6)	1 (2.1)	7 (11.9)	8 (7.5)	16 (8.1)
Bilirubin (umol/L) increased						
Grade 0 to 1	1 (5.3)	0	1 (2.1)	6 (10.2)	7 (6.6)	10 (5.1)
Creatinine (umol/L) increased						
Grade 0 to 1	0	3 (10.7)	3 (6.4)	5 (8.5)	8 (7.5)	17 (8.6)

Source: 5.3.5.3 ISS Table 3.2.1-1.1.1a-Table 3.2.1-1.1.1f
Abbreviations: EBV, Epstein-Barr virus; HCT, hematopoietic cell transplant; PTLD, posttransplant lymphoproliferative disease

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Table 20. Summary of subject incidence of treatment-emergent serious adverse events by elderly age subgroups in clinical studies and EAP (Full Analysis Set, data cut-off 05 November 2021)

MedDRA Term	Age < 65 years (N = 288) n (%)	Age ≥ 65 to < 75 years (N = 41) N (%)	Age ≥ 75 to < 85 years (N = 11) N (%)	Age ≥ 85 years (N = 0) N (%)
TESAEs - Total	168 (58.3)	23 (56.1)	6 (54.5)	NA
Fatal	61 (21.2)	7 (17.1)	2 (18.2)	NA
Hospitalization/prolonged hospitalization	122 (42.4)	19 (46.3)	4 (36.4)	NA
Life-threatening	51 (17.7)	8 (19.5)	3 (27.3)	NA
Disability/incapacity	2 (0.7)	1 (2.4)	1 (9.1)	NA
Other (medically significant)	59 (20.5)	6 (14.6)	0	NA
Leading to study treatment discontinuation	23 (8.0)	4 (9.8)	1 (9.1)	NA
Psychiatric disorders[a]	7 (2.4)	5 (12.2)	1 (9.1)	NA
Nervous system disorders[a]	20 (6.9)	2 (4.9)	1 (9.1)	NA
Accidents and injuries[b]	1 (0.3)	0	0	NA
Cardiac disorders[a]	14 (4.9)	2 (4.9)	0	NA
Vascular disorders[a]	11 (3.8)	4 (9.8)	0	NA
Cerebrovascular disorders[b]	5 (1.7)	0	0	NA
▪ Infections and infestations[a]	76 (26.4)	15 (36.6)	2 (18.2)	NA
▪ Anticholinergic syndrome[c]	0	0	0	NA
▪ Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[d]	2 (0.7)	0	0	NA

Abbreviations: EAP, expanded access programme; ECOG, Eastern Oncology Cooperative Group; NA, not applicable; TESAE, treatment-emergent serious adverse event

a Cardiac disorders, infections and infestations, nervous system disorders, psychiatric disorders, and

vascular disorders, if any, were identified by system organ class searching.

b Accidents and injuries and cerebrovascular disorders were identified by searching with standardised MedDRA queries (SMQs) 'accidents and injuries' and 'central nervous system hemorrhages and cerebrovascular conditions', respectively.

c Anticholinergic syndrome was searched by preferred term.

d Fractures were searched by preferred terms that included 'fracture'. Results are the sum of the incidence of the following preferred terms: ankle fracture, femur fracture, lower limb fracture, spinal compression fracture.

Blackout was searched by preferred term 'loss of consciousness', and postural hypotension was searched by preferred term 'orthostatic hypotension'. Dizziness, ataxia, fall, and syncope were searched with corresponding preferred terms.

Some PTs were reported only in specific age groups: confusional state, hypoxia and sepsis (3 subjects) in subjects ≥ 65 years, and device related infection, multiple organ dysfunction syndrome and otitis media (3 subjects) in the age group < 16 years.

2.6.8.7. Immunological events

Anti-Human Leukocyte Antigen (anti-HLA) Antibodies

Plasma samples were collected from some subjects enrolled in Study ATA129-EBV-302, and a subset of anti-HLA antibody testing was performed following the testing strategy commonly used in conjunction with SOT and at various local laboratories which regularly perform such testing. Only 7 subjects were evaluable for anti-HLA antibody immunogenicity assessment in Study ATA129-EBV-302 and a single C SOT subject was found to be anti-HLA positive post-infusion.

Marrow or organ rejection

No events of marrow rejection were reported in the tabelecleucel clinical studies and EAPs. The subject incidence of TEAEs of SOT rejection events was 2.0% (1/51 SOT subjects) in the clinical studies and 7.0% (3/43 SOT subjects) in the EAPs, with an overall incidence of 4.3% (4/94 total SOT subjects). The events were reported as not related to tabelecleucel by the investigator except for 1 SPU subject who had a grade 1 TESAE. Three of 4 events were serious and there was no event reported with severity grade > 2. All 4 events (1 event per subject) had confounding factors, such as history of transplant rejection episodes or reduced dosing of immunosuppressive treatments prior to the event. The 4 events occurred in lung, liver and heart SOT subjects who are known to have higher baseline risk of rejection than in kidney transplant and the incidence rate of 4.3% overall was lower than the lowest transplant rejection rate reported in literature which is for kidney transplants patients. Based on available data, no relationship between marrow or organ rejection and tabelecleucel has been established.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Based on clinical experience with tabelecleucel, low doses of corticosteroids, ciclosporin, tacrolimus, sirolimus, and other immunosuppressive therapies have no impact on the safe use of tabelecleucel. However, tabelecleucel has not been evaluated in patients receiving corticosteroid doses greater than 1 mg/kg per day of prednisone or equivalent.

2.6.8.9. Discontinuation due to adverse events

TESAEs leading to study treatment discontinuation was collected only in Studies EBV-CTL-201 and ATA129-EBV-302 and all EAPs and are summarised in **Table 21**.

The most common TESAE leading to treatment discontinuation was disease progression. None of these TESAEs were considered related to study treatment.

While one non-PTLD subject in study EBV-CTL-201 had a treatment-related TESAE of depressed level of consciousness that led to treatment discontinuation (the subject subsequently recovered from the event), all other reported TESAEs leading to treatment discontinuation, were not considered related to treatment.

Table 21. Treatment-emergent serious adverse events (TESAEs) leading to study treatment discontinuation

	Original Data[a]		Updated Data[b]	
	Clinical studies 201 and 302 (N = 99) n (%)	EAPs 901 and SPU (N = 130) n (%)	Clinical studies 201 and 302 (N = 103) n (%)	EAPs 901 and SPU (N = 138) n (%)
Subjects reporting any TESAEs leading to study treatment discontinuation	11 (11.1)	15 (11.5)	12 (11.7)	16 (11.6)
Disease progression	8 (8.1)	6 (4.6)	8 (7.8)	6 (4.3)

Abbreviations: EAP, expanded access programme; SPU, single patient use; TESAE, treatment-emergent serious adverse event

a 07 May 2021 cut-off for ATA129-EBV-302 and 02 July 2021 for EAPs

b 05 November 2021 cut-off

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Patient exposure

The safety profile of tabelecleucel has been established from cumulative data collected over a period of more than 20 years involving 340 subjects across several indications in the clinical studies and EAPs.

The evaluation of safety is based on data for all subjects in the pivotal study (ATA129-EBV-302) and an integrated summary of safety (ISS) for subjects with EBV-driven diseases including the supportive clinical studies and all subjects in the Expanded Access Programs (EAPs). In the ISS, data were pooled across all clinical studies for all disease cohorts (EBV+ PTLD and non-PTLD combined), all EBV+ PTLD cohorts, and all non-PTLD disease cohorts.

Adverse events

Treatment-emergent AEs are summarised from Studies ATA129-EBV-302 and EBV-CTL-201 only as non-serious TEAEs were not collected in Studies 11-130 and 95-024 or the 2 EAPs.

Nearly all subjects experienced TEAEs: (96.1%). Most frequently reported TEAEs by PT were disease progression, pyrexia, and diarrhoea, followed by fatigue, cough, nausea, vomiting, anaemia, decreased appetite, hyponatraemia, neutrophil count decreased and white blood cell decreased. TEAEs had a maximum severity of grade 3 for 37 (35.9%) subjects, grade 4 for 17 (16.5%) subjects, and grade 5 for 15 (14.6%) subjects.

Treatment-related TEAEs (based on investigator assessment) for Studies ATA129-EBV-302 and EBV-CTL-201 were reported for 39.8% of subjects. Treatment-related TEAEs with the highest subject number by PT were pyrexia, fatigue and hypotension, nausea, neutrophil count decreased, and diarrhoea. 16.5% of subjects had grade ≥ 3 TEAEs. No fatal Treatment-related TEAEs were reported.

All of the most frequently reported TEAEs are included in section 4.8 of the SmPC.

Serious Adverse Events

In study ATA129-EBV-302, treatment-emergent serious adverse events were reported for 53.5% of subjects. The most frequently reported TESAEs by PT (> 5% of subjects) were disease progression (18.6%), sepsis (11.6 %), acute kidney injury, pneumonia, respiratory failure, and vomiting (7.0% in each PT); and atrial flutter, dehydration, delirium, fatigue, febrile neutropenia, hypoxia, influenza, nausea, and pyrexia (4.7% in each PT).

A total of 4 subjects (9.3%) had a TESAE that was considered by the investigator as related to treatment. The treatment-related TESAE with the highest subject incidence by PT was pyrexia (reported for 2 subjects [4.7%]); all other treatment-related TESAEs, such as diarrhoea, hypotension, hypoxia, rash, rash erythematous and tachycardia, were reported in only 1 subject for each PT. All of these events are included in Section 4.8 of the SmPC.

Across all EBV-driven diseases evaluated in the 4 clinical studies, 55.0% of subjects had at least 1 TESAE, 50.0% of subjects had at least 1 TESAE with a maximum severity of grade ≥ 3; 17.8% of subjects died due to a TESAE. None of the fatal TESAEs were considered related to treatment. Most treatment-related TESAEs were reported by 1 subject in each PT.

Deaths

None of the fatal TESAEs were considered related to treatment except one subject in the Expanded Access Programme (C-HCT cohort) who had 2 grade 5 TESAEs (Enterococcal infection and Citrobacter bacteraemia) that were considered possibly related to tabelecleucel by the investigator.

Adverse Events of Special Interest (AESI)

In the clinical programme, a number of AEs were identified as AESIs of tabelecleucel based on its mechanism of action, biological nature, and mode of administration. These were infusion-related reaction (IRR), transmission of infectious agents including cytomegalovirus (CMV), cytokine release syndrome (CRS), and graft-versus-host disease (GvHD).

For infusion-related reactions, 3 (1.2%) subjects in the clinical studies (N = 202) and 1 (0.7%) subject in the EAPs (N = 138) experienced infusion-related reactions, such as pyrexia and non-cardiac chest pain, have been reported. Patients should be monitored for at least 1 hour after treatment for signs and symptoms of infusion-related reactions. SmPC section 4.8 also includes pyrexia and chest pain (including non-cardiac chest pain), which are signs and symptoms of IRR.

As tabelecleucel is obtained from human donor blood cells, donors are screened and have tested negative for relevant communicable disease agents and diseases, including HBV, HCV and HIV. Although tabelecleucel lots are tested for sterility, mycoplasma and adventitious agents, a risk of transmission of infectious agents exists. One subject (with prior HCT) was discontinued from treatment and subsequently died due to a TESAEs of Enterococcal infection and Citrobacter bacteraemia that

were considered by the investigator as possibly related to tabelecleucel. As causality with tabelecleucel use cannot be excluded in this case, transmission of infectious agents has been included as an important potential risk in the RMP.

For cytokine release syndrome no event of CRS was reported in any subject in the clinical studies (N = 202). Two events of grade 1 CRS were reported in the EAPs (N = 138) in two subjects with non-PTLD EBV+ lymphoma. Patients should be monitored for signs and symptoms of CRS, such as pyrexia, chills, hypotension and hypoxia. Diagnosis of CRS requires excluding alternate causes of systemic inflammatory response, including infection. CRS should be managed at the physician's discretion, based on the patient's clinical presentation.

Treatment-related neurologic TEAEs were reported for 5.8% of subjects; and only one subject had at least 1 treatment-related TEAE with a maximum severity of grade ≥ 3.

Overall subject incidences of treatment-related neurologic TEAEs by PT category were low, with the most common being dizziness and headache (each reported in 2 subjects). Both of these events are included in section 4.8 of the SmPC.

Immune effector cell-associated neurotoxicity syndrome (ICANS) has been observed with particularly high incidence rate and pronounced morbidity in CAR-T cellular immune therapy and anti-CD19 immunotherapies [Lee 2019; Sheth 2021]. There have been no reports of the preferred term (PT): ICANS in the clinical studies and EAPs as of the data lock point. With a broadened search strategy, only 1 grade ≥ 3 event of grade 3 confusional state considered related by the investigator was reported in the clinical studies. Due to its potential severe outcomes ICANS is considered an important potential risk due to its potential for severe outcomes.

The number of subjects who reported treatment-emergent events of GvHD was 14 of 340 subjects in the clinical studies and EAPs; 8 of 202) in clinical studies and 6 of 138) in the EAPs. Overall, the incidence of GvHD in the tabelecleucel clinical development programme was much lower than the background incidence of donor mediated GvHD reported in literature.

GvHD has been reported in 5 (4.9%) patients in the two clinical studies (ATA129-EBV-302 and EBV-CTL-201; N=103) in which serious and non-serious AEs were recorded after treatment with tabelecleucel. In the overall clinical development programme, GvHD events occurred almost exclusively in subjects with history of transplantation: there was a single case of GvHD in a subject without transplant history that was reported as a grade 1 skin GvHD (rash) that occurred in a patient with a complicated history of chronic autoimmune skin disease that was ongoing at time of event; the event was assessed as related by the investigator, however, no biopsy was performed to confirm the suspected skin GvHD event; the event resolved within 4 days and additional doses of tabelecleucel were administered with no subsequent aggravation or relapse observed.

It is not possible to ascertain whether reported events are related to the decrease or discontinuation of immunosuppressive therapies for the treatment of PTLD rather than to a direct action of tabelecleucel. The benefit of treatment with tabelecleucel versus the risk of possible GvHD should be considered before initiating treatment. Patients should be monitored for signs and symptoms of GvHD, such as skin rash, abnormal liver enzymes in the blood, jaundice, nausea, vomiting, diarrhoea and bloody stools. To further characterise this risk, GvHD has been classified as an important identified risk and additional data on this risk will be collected through the planned study described in the RMP.

TFR is an identified risk with an established causal relationship to tabelecleucel occurring generally within the first few days after receiving treatment. TFR presents as an acute inflammatory reaction involving tumour sites which may include a sudden and painful increase in the tumour size or enlargement of disease-involved lymph nodes. TFR may mimic progression of disease.

Patients with high tumour burden prior to treatment are at risk of severe TFR. Depending on the location of the tumour or lymphadenopathy, complications (e.g. respiratory distress and cognitive disorders) may arise from mass effect, including compression/obstruction of adjacent anatomic structures. Analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) or localised radiotherapy could be considered prior to tabelecleucel use administration for those patients in whom the location of the tumour could potentially lead to complications. Patients should be closely monitored for signs and symptoms of TFR, especially during the first cycle.

All of these risks will be further characterised by the planned post-authorisation Safety Study (PASS) to describe the safety and effectiveness of tabelecleucel in patients with Epstein-Barr Virus-positive PTLD in a Real-world Setting in Europe.

Laboratory findings

None of the subjects in the Study ATA129-EBV-302 had laboratory abnormalities that were reported as TESAEs. In general, the majority of shifts in laboratory parameters could be explained by other risk factors, including the underlying disease and concomitant medications.

Even though no specific safety signal was identified by the laboratory results, due to the relative high incidence of laboratory abnormalities reported, the following have been added in section 4.8 of the SmPC: white blood cell count decreased, lymphocyte count decreased, platelet count decreased, aspartate aminotransferase increased and alanine aminotransferase increased.

Safety in special populations

Overall, approximately 52% to 58% of subjects in each age subgroup experienced TESAEs. Disease progression, pneumonia and pyrexia were by far the most common events, without considerable differences between the age groups. Based on available data, the elderly population (≥ 65 years of age) may be at increased risk of serious adverse events leading to hospitalisation/prolonged hospitalisation, psychiatric disorders, vascular disorders, and infections and infestations. Ebvallo should be used with caution in elderly patients.

There are no data for tabelecleucel use during pregnancy or lactation and paediatric data are limited especially for young children. Additional information on these populations will be collected through the planned-observational PASS.

Immunological events

No events of marrow rejection were reported in the tabelecleucel clinical studies and EAPs. There is a potential risk of bone marrow transplant rejection based on humoral or cell-mediated immune reactions.

A small number of solid organ transplant rejection was reported in the clinical studies and EAPs. Treatment with tabelecleucel may increase the risk of rejection in solid organ transplant recipients. This could be related to the decrease or discontinuation of immunosuppressive therapies for the treatment of PTLD rather than to a direct action of tabelecleucel. The benefit of treatment with tabelecleucel versus the risk of possible solid organ transplant rejection should be considered prior to the start of treatment. Patients should be monitored for signs and symptoms of solid organ transplant rejection.

Only 7 subjects were evaluable for anti-HLA antibody immunogenicity assessment in Study ATA129-EBV-302 and a single C-SOT subject was found to be anti-HLA positive post-infusion. The applicant presented a detailed evaluation plan for immunogenicity which will be assessed during the annual re-assessment of the product.

Safety related to drug-drug interactions and other interactions

No interaction studies have been performed.

In clinical studies, patients received ciclosporin, tacrolimus, sirolimus and other immunosuppressive therapies at the lowest dose considered clinically safe and appropriate. For patients receiving chronic corticosteroid therapy, the dose of these drugs should be reduced as much as is clinically safe and appropriate; as tabelecleucel has not been evaluated in patients receiving corticosteroid doses greater than 1 mg/kg per day of prednisone or equivalent it is recommended not to exceed such doses.

Overdose is not expected since tabelecleucel is formulated as an IV injection to be administered in healthcare settings.

Discontinuation due to adverse events

Most reported TESAEs leading to study treatment discontinuation was related to disease progression. No signals were identified from the other TESAE leading to treatment discontinuation.

Additional safety data needed in the context of a MA under exceptional circumstances

Taking into account the totality of the available data, the CAT was of the view that the data set on the clinical safety of Ebvallo under normal conditions of use could not be considered comprehensive due to the small size of the clinical trials and the lack of a comparator in those studies.

The CAT acknowledged that the rarity of the disease, the challenges in recruiting patients in clinical trials for a condition with a very short life expectancy and ethical considerations prevent the conduct of bigger and longer duration-controlled trials. The CAT was therefore of the view that a marketing authorisation under exceptional circumstances should be granted, subject to the specific obligation of conducting a post-authorisation safety study to describe the safety and effectiveness of tabelecleucel in patients with EBV+ PTLD following HCT or SOT in a real-world setting in particular with regards to the important identified and potential risks associated with tabelecleucel use. The applicant will also provide yearly updates on any new information concerning the safety and efficacy of Ebvallo.

2.6.10. Conclusions on the clinical safety

Clinical safety data has been analysed from the data of one pivotal study, 3 supportive clinical studies and 2 expanded access programs, totalling 340 subjects exposed to tabelecleucel in a number of indications. All studies were uncontrolled. Considering the fact that the claimed indication for Ebvallo, Epstein-Barr Virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) is an ultra-rare disease, the relatively small subject number and heterogeneous populations included in the clinical development programme and the uncontrolled nature of the studies are considered acceptable. The most frequently reported treatment emergent adverse events were disease progression, pyrexia and pneumonia. The most frequently reported treatment-related emergent serious adverse was pyrexia. Considering the prognosis of the disease the reported safety profile is considered manageable with the proposed routine risk minimisation measures and will be further characterised through a dedicated post-authorisation safety study.

The CAT considers the following measures necessary to address the missing safety data in the context of a MA under exceptional circumstances:

- A post-authorisation safety study (PASS) to describe the safety of tabelecleucel in patients with EBV+ PTLD following HCT or SOT in a real-world setting

- In order to ensure adequate monitoring of safety and efficacy of Ebvallo in the treatment of patients with EBV+ PTLD, the MAH shall provide yearly updates on any new information

concerning the safety and efficacy of Ebvallo.

The CHMP endorses the CAT conclusion on clinical safety as described above.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	Tumour flare reaction
	Graft-versus-host disease
Important potential risks	Solid organ transplant rejection
	Bone marrow transplant rejection
	Cytokine release syndrome
	Immune effector cell-associated neurotoxicity syndrome
	Infusion-related reaction
	Immunogenicity
	Transmission of infectious agents (including cytomegalovirus)
	Decrease in cell viability due to inappropriate handling of the product
Missing information	Use in paediatric population
	Use in elderly population

2.7.2. Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context a marketing authorisation under exceptional circumstances:				
Yearly updates on any new information concerning the safety and efficacy of tabelecleucel	In order to ensure adequate monitoring of the safety and efficacy of tabelecleucel in the treatment of patients with EBV$^+$ PTLD, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of tabelecleucel	Any new information concerning the safety and efficacy of tabelecleucel	Annual reports	To be submitted with annual reassessments
ATA129-PTLD-801 (PASS) Planned	Primary objective: To describe the safety of tabelecleucel in patients with EBV$^+$ PTLD following HCT or SOT in a real-world setting Secondary objectives: To describe the effectiveness of	TFR; GvHD; SOT rejection; BMT rejection; CRS; ICANS; IRR; immunogenicity; transmission of infectious agents	Protocol submission Annual reports	Within 3 months of marketing authorisation To be submitted with annual reassessments Not applicable

	tabelecleucel in patients treated with tabelecleucel for EBV+ PTLD in a real-world setting; to describe the patient population treated with tabelecleucel for EBV+ PTLD in a real-world setting; and to describe tabelecleucel treatment patterns, including dosing and schedule in patients treated with tabelecleucel for EBV+ PTLD in a real-world setting	(including CMV); decreased cell viability due to inappropriate handling of the product; use in paediatric population elderly population, and pregnancy and lactation; and long-term safety	Final report submission	

Abbreviations: BMT, bone marrow transplant; CMV, cytomegalovirus; CRS, cytokine release syndrome; DLP: data lock point; EBV+ PTLD, Epstein-Barr virus-positive posttransplant lymphoproliferative disease; EU, European Union; GvHD, graft-versus-host disease; HCT, haematopoietic cell transplant; ICANS, immune effector cell-associated neurotoxicity syndrome; IRR, infusion-related reaction; MAH, marketing authorisation holder; PASS, postauthorisation safety study; PBRER, periodic benefit risk assessment report; SOT, solid organ transplant; TFR, tumour flare reaction

2.7.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Tumour flare reaction	Routine risk minimisation measures: SmPC: Sections 4.4 and 4.8 Package Leaflet: Sections 2 and 4 Additional risk minimisation measures: Not required	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not required Additional pharmacovigilance activities: Category 2: ATA129-PTLD-801
Graft-versus-host disease	Routine risk minimisation measures: SmPC: Sections 4.4 and 4.8 Package Leaflet: Sections 2 and 4 Additional risk minimisation measures: Not required	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not required Additional pharmacovigilance activities: Category 2: ATA129-PTLD-801
Important potential risks		
Solid organ transplant rejection	Routine risk minimisation measures: SmPC: Section 4.4 Package Leaflet: Section 2 Additional risk minimisation measures: Not required	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not required Additional pharmacovigilance activities: Category 2: ATA129-PTLD-801
Bone marrow transplant rejection	Routine risk minimisation measures: SmPC: Section 4.4 Package Leaflet: Section 2 Additional risk minimisation measures: Not required	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not required Additional pharmacovigilance activities: Category 2: ATA129-PTLD-801
Cytokine release syndrome	Routine risk minimisation measures: SmPC: Section 4.4 Package Leaflet: Section 2 Additional risk minimisation measures: Not required	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: CRS Questionnaire Additional pharmacovigilance activities: Category 2: ATA129-PTLD-801
Immune effector cell-associated neurotoxicity syndrome	Routine risk minimisation measures: SmPC: Section 4.4 Package Leaflet: Section 2 Additional risk minimisation measures: Not required	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not required Additional pharmacovigilance activities: Category 2: ATA129-PTLD-801
Infusion-related reactions	Routine risk minimisation measures: SmPC: Section 4.4 Package Leaflet: Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not required

	Additional risk minimisation measures: Not required	Additional pharmacovigilance activities: Category 2: ATA129-PTLD-801
Immunogenicity	Routine risk minimisation measures: SmPC: Section 4.8 Additional risk minimisation measures: Not required	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not required Additional pharmacovigilance activities: Category 2: ATA129-PTLD-801
Transmission of infectious agents (including cytomegalovirus)	Routine risk minimisation measures: SmPC: Section 4.4 Package Leaflet: Section 2 Additional risk minimisation measures: Not required	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not required Additional pharmacovigilance activities: Category 2: ATA129-PTLD-801
Decrease in cell viability due to inappropriate handling of the product	Routine risk minimisation measures: SmPC: Sections 6.3, 6.4, and 6.6 Package Leaflet: Healthcare Professional tear-off Additional risk minimisation measures: Not required	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Medication Error Questionnaire Additional pharmacovigilance activities: Category 2: ATA129-PTLD-801
Missing information		
Use in paediatric population	Routine risk minimisation measures: SmPC: Sections 4.2, 4.8, and 5.1 Additional risk minimisation measures: Not required	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not required Additional pharmacovigilance activities: Category 2: ATA129-PTLD-801
Use in elderly population	Routine risk minimisation measures: SmPC: Sections 4.2, 4.4, and 5.1 Package Leaflet: Section 2 Additional risk minimisation measures: Not required	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not required Additional pharmacovigilance activities: Category 2: ATA129-PTLD-801
Use in pregnancy and lactation	Routine risk minimisation measures: SmPC: Section 4.6 Package Leaflet: Section 2 Additional risk minimisation measures: Not required	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not required Additional pharmacovigilance activities: Category 2: ATA129-PTLD-801
Long-term safety	Not applicable	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not required Additional pharmacovigilance activities: Category 2: ATA129-PTLD-801

2.7.4. Conclusion

The CAT considers that the risk management plan version 1.0 is acceptable.

The CHMP endorses the CAT conclusion on the RMP as described above.

2.7.5. Pharmacovigilance system

The CHMP and CAT considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.6. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The new EURD list entry will therefore use the EBD determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.* However, as the consultation was conducted with a preliminary version of the leaflet, it is recommended to carry out a focused test after marketing authorisation with the adopted package leaflet. The reduced testing will cover 2 rounds of testing with 5 participants each round. The readability guideline and the comments included in the QRD checklist should be taken on board.

2.8.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

For the translation exemption, the Group accepted the use of EN only for the primary (vial) and all secondary packaging (cartons, lot information sheet and package leaflet), with the exemption of Germany and Belgium that requested the package leaflet to be provided outside of the pack in the national language so that it can be provided to the patient. Germany and Belgium accept the use of EN only for all the other labelling components. The Group requested, however, that the company explore the possibility of providing the package leaflet, inside the lid of the cryoshipper, in the national language (in all instances) if at all possible. If this is not possible then the requirements of Germany and Belgium, as a minimum, should be met.

The QRD Group accepted the request for omission of the invented name on the immediate vial label, with the condition that if a global tradename is accepted, it should be included on the label.

The Group agreed to the omission of the expiry date on the immediate label until a final shelf life is agreed, and that this should be reflected as a condition to the marketing authorisation upon approval of the product. Once a final shelf-life is established it should be presented on the immediate packaging label. Furthermore, the group agreed that the format of the EXP should not be MM/YYYY as this is the EN abbreviation but should be presented as a numerical format. The Group also considered that it would be helpful to include an explanation in the product information on the meaning of the MFD abbreviation, and on how to calculate the expiry date on the basis of the manufacturing date; it was highlighted however, that the expiry date should not appear in the product information.

The Group agreed that in order to avoid the loss of already manufactured product, an exemption could be granted for those batches already manufactured to use nominal strength of 5 x 10^7 viable T cells per mL. However, once the assessment is completed, and the batches printed at risk consumed, the correct expression of strength should be printed on the primary vial.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

For the translation exemption, the QRD group accepted the use of EN only for the primary (vial) and all secondary packaging (cartons, lot information sheet and package leaflet), with the exemption of Germany and Belgium that requested the package leaflet to be provided outside of the pack in the national language so that it can be provided to the patient. Germany and Belgium accept the use of EN only for all the other labelling components.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

2.8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ebvallo (tabelecleucel) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It has a PASS imposed either at the time of authorisation or afterwards; [REG Art 9(4)(cb), Art 10a(1)(a), DIR Art 21a(b), Art 22a(1)(a)];
- It is approved under exceptional circumstances [REG Art 14(8), DIR Art (22)]

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

EBV+ PTLD is a rare and life-threatening haematological malignancy that can occur after solid organ transplant (SOT) or haematopoietic cell transplant (HCT) due to immunosuppression. The aim of new treatments is to reach complete remission and prolong overall-survival and thereby reduce treatment related morbidity of patients with EBV^+ PTLD.

The target indication applied for by the applicant was for the treatment of patients with Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV^+ PTLD) who have received at least one prior therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless

chemotherapy is inappropriate. Following a request from the CHMP, and to better reflect the intended target population this was modified to monotherapy treatment of adult and paediatric patients 2 years of age and older with relapsed or refractory EBV$^+$ PTLD.

3.1.2. Available therapies and unmet medical need

The standard of care for first-line therapy of EBV$^+$ PTLD is rituximab, either as monotherapy in HCT or mostly as a combination therapy with chemotherapy agents (e.g. R-CHOP) in SOT. Patients whose disease is relapsed/refractory after treatment with first-line therapy have limited treatment options and rapid decline with high mortality, often within 1 or 4 months, respectively (Dharnidharka 2021; Sanz-Caballer 2021). In a retrospective cohort study of 18 patients with EBV+ PTLD post HCT, the median survival of patients with rituximab-refractory disease was 1.7 months (Socié 2020). In patients with EBV+ PTLD following SOT who failed rituximab plus chemotherapy or did not receive a chemotherapy regimen, the median survival was 3 months (Zimmermann 2019).

3.1.3. Main clinical studies

An ongoing multicentre, phase 3, single arm, open label study ATA129-EBV-302 was submitted as pivotal study for MAA of Ebvallo (tabelecleucel) for the target indication.

Patients with relapsed/refractory EBV$^+$PTLD after rituximab for HCT cohort /rituximab with or without chemotherapy for SOT cohort are included in this pivotal study.

At the cut-off date of the latest interim analysis (data cut-off date 05 November 2021) 43 patients had been enrolled. The SOT cohort (29 patients) consisted of SOT patients who had failed rituximab monotherapy (13 patients) and SOT patients who had failed rituximab plus chemotherapy (SOT-R+C, 16 patients). The HCT cohort (14 patients) consisted of HCT patients who had failed rituximab.

3.2. Favourable effects

At the time of the latest interim analysis, overall response rate (CR+PR) per IORA was 50% in C-HCT and 56.3% in C-SOT-R+C cohort after a median of 1.1 months, demonstrating clinical efficacy in the population of relapsed/refractory EBV+ PTLD. The median follow-up was longer in the HCT cohort (15.9 months) vs. 2.3 months in the SOT-R+C cohort.

The median DOR in the C-HCT and C-SOT-R+C cohort was 23 and 15.2 months, respectively.

42.9% of patients in the HCT and 25% in the SOT-R+C cohort experienced durable response, lasting > 6 months.

The K-M estimated overall survival of the HCT and SOT-R+C population at 1-year was 70.1 and 64.3%, respectively.

The ORR in the main study ATA129-EBV-302 is comparable with the cumulative ORR of the three supportive studies (50% (HCT), 56.3% (SOT-R+C) vs. 48%).

The OS data from supportive studies are also consistent with the pivotal study results. The KM estimated 6-month and 1-year OS rates were 70.9% and 65.9%.

3.3. Uncertainties and limitations about favourable effect

There are a number of methodological limitations in the pivotal study, including limited size for both C-HCT (N = 14) and C-SOT (N=29) cohorts, lack of type I error in the HCT cohort and timing of analyses

which was not in line with the prespecified interim or final analyses. Reported results therefore might be influenced by bias, especially selection bias. However, due to the rare incidence of the condition these limitations were considered acceptable by the CHMP.

Conclusions on responses in paediatric and elderly subjects are limited by very small sample sizes in these subgroups. Additional data in these populations will be collected through the ongoing pivotal study and the planned post authorisation study in a real-world setting.

Interpretation of data from supportive studies is limited by several factors, e.g. small sample size, retrospective assignment to the groups (C-HCT, C-SOT), inconsistency in dosing, response assessment only by investigator, low frequency and inconsistency in duration of follow-up.

3.4. Unfavourable effects

According to integrated analyses of pool safety data of studies ATA129-EBV-302 and EBV-CTL-201, (96.1%) patients had TEAEs. Most frequently reported TEAEs by PT were disease progression, pyrexia, and diarrhoea, followed by fatigue, cough, nausea, and vomiting. Across all 4 clinical studies 55.0% of subjects had at least 1 TESAE. Treatment-related TESAEs were reported for 8.9% of subjects. The most frequently reported TESAEs by PT were disease progression (10.9%), pneumonia and pyrexia (9.4%), death (6.4%), febrile neutropenia (5.4%), sepsis (4.5%), acute kidney injury (4.0%), device related infection (3.5%), hypoxia (3.5%). None of the fatal TESAEs were considered related to treatment in the clinical studies. The most frequent fatal TESAEs were disease progression in all cohorts.

The AESIs assessed in the tabelecleucel clinical programme include infusion-related reaction (IRR), transmission of infectious agents including cytomegalovirus (CMV), cytokine release syndrome (CRS), and graft-versus-host disease (GvHD). These AESIs constitute 4 of the 6 predetermined risks for tabelecleucel based on its mechanism of action, biological nature, and mode of administration. Additional important potential safety concerns identified by the CHMP during the evaluation include tumour flare, neurological events / ICANS, immunogenicity, BMT / SOT rejection and decrease in cell viability due to inappropriate handling of the product.

3.5. Uncertainties and limitations about unfavourable effects

The overall safety population comprised 340 patients but this includes a large number of patients outside the claimed indication. In view of the rarity of the disease, the heterogeneous population included in the safety analysis is considered acceptable.

Adverse events for some (but not all) of the important potential risks which were identified for tabelecleucel were observed in the clinical studies or in the expanded access programmes. Due to the small size of the studies, it is not possible to determine with high precision the incidence of those events in association with tabelecleucel. These risks will be further characterised by the planned PASS to describe the safety of tabelecleucel in patients with EBV+ PTLD following HCT or SOT in a real-world setting.

3.6. Effects Table

Table 22. Effects table for Ebvallo for the treatment relapsed or refractory EBV+ PTLD who have received at least one prior therapy (data cut-off: 5 November 2021)

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
Favourable Effects					
ORR (C-SOT-R+C)	CR or PR by IORA	% (95%CI)	56.3 (29.9, 80.2)	Small single arm trial Potential bias due to deviation from pre-specified analysis	ATA129-EBV-302
ORR (C-HCT)			50.0 (23.0, 77.0)	No type-I-error control, results are descriptive	
DOR (C-SOT-R+C)	Median (min, max)	months	2.3 (0.8,15)	4 patients with DOR> 6 months	
DOR (C-HCT)			15.9 (1.3,23.3)	6 patients with DOR> 6 months	
Unfavourable Effects					
IRR		%	1.5% CS 0.7% EAPs	Small safety database, difficult to estimate precise incidence of risks	ISS
CRS		%	0% CS 1.5% EAPs		
GvHD		%	4.5% CS 5.1% EAPs		
Tumour flare		%	0.5% CS 2.2% EAPs		
SOT rejection		%	0.5% CS 2.2% EAPs		
ICANS		%	0.0% CS 0.7% EAP		

Abbreviations: EBV+: Epstein Barr virus positive or -associated; PTLD: post-transplant lymphoproliferative disease; ORR: objective response rate; SOT: Solid organ transplant; C-SOT R+C: SOT EBV+ PTLD (Relapsed/refractory Rituximab and Chemotherapy); HCT: allogeneic haematopoietic cell transplant; C-HCT: HCT EBV+ PTLD (Relapsed/refractory Rituximab); CR: complete response; PR: partial response; IORA: independent oncologic response adjudication; IRR: Infusion-related-reaction; CS: Clinical Study; EAP: expanded access programme; CRS: cytokine release syndrome; GvHD: graft versus host disease; ICANS: Immune effector cell-associated neurotoxicity syndrome, ISS: integrated summary of safety

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Tabelecleucel demonstrated clinically significant responses in both proposed indications. Approximately half of treated subjects in both C-HCT and C-SOT-R+C cohorts achieved partial or complete remission. Durable responses, lasting > 6 months were also observed in a number of responders.

In the therapeutic setting of r/r EBV+ PTLD, where there are no therapeutic alternatives, these results are considered relevant and demonstrate clinical efficacy.

In the safety profile frequently reported adverse events were disease progression, pyrexia and pneumonia, followed by fatigue, cough, nausea, and vomiting. The most frequent TESAEs and fatal

TESAEs were disease progression in all cohorts and were not considered related to tabelecleucel treatment. A small number of events for a number of identified and potential risks for tabelecleucel, including CRS, IRR, TFR, GvHD and SOT rejection were also observed.

3.7.2. Balance of benefits and risks

Overall, the efficacy of tabelecleucel in relapsed or refractory EBV+ PTLD patients after rituximab (HCT) / rituximab + chemotherapy (SOT) is considered promising and clinically meaningful in a setting with no standard of care therapy and a dismal prognosis. The important safety concerns which were observed during the clinical development programme of tabelecleucel are expected to be managed adequately by routine risk minimisation measures and warnings in the SmPC. Further characterisation of these risks will be carried on with ongoing and planned studies described in the RMP.

3.7.3. Additional considerations on the benefit-risk balance

Marketing authorisation under exceptional circumstances

As comprehensive data on the product are not available, a marketing authorisation under exceptional circumstances was requested by the applicant in the initial submission.

The CAT considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use. In the context of a serious orphan disease, such as relapsed/refractory EBV+ PTLD which has a very low prevalence/incidence and patients have a short life expectancy it is acceptable to derive the evidence within a single arm trial with a limited follow-up period.

Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate.

The CHMP endorses the CAT conclusion on marketing authorisation under exceptional circumstances as described above.

3.8. Conclusions

The overall benefit/risk balance of Ebvallo is positive, subject to the conditions stated in section 'Recommendations'.

The CHMP endorse the CAT conclusion on Benefit Risk balance as described above.

4. Recommendations

Outcome

Based on the CAT review of data on quality, safety and efficacy, the CAT considers by consensus that the benefit- risk balance of Ebvallo is favourable in the following indication:

as monotherapy for treatment of adult and paediatric patients 2 years of age and older with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV^+ PTLD) who have received at least one prior therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate.

Based on the draft opinion adopted by the CAT and the review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit- risk balance of Ebvallo in the above indication is

favourable and therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Specific obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	**Due date**
In order to ensure adequate monitoring of safety and efficacy of tabelecleucel in the treatment of patients with EBV+ PTLD, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of tabelecleucel.	Annually (with annual re-assessment)
Non-interventional post-authorisation safety study (PASS): An Observational, Post-authorisation Safety Study to Describe the Safety and Effectiveness of Tabelecleucel in Patients with Epstein-Barr Virus-Positive Posttransplant Lymphoproliferative Disease in Real-world Setting in Europe.	Protocol submission: Within 3 months of marketing authorisation Study progress reports: Annually (with annual

Description	Due date
	re-assessment)
In order to further characterise the long-term efficacy and safety of tabelecleucel in patients with EBV$^+$ PTLD, the MAH shall provide the final results of the ongoing study ATA129-EBV-302: A Multicentre, Open-Label, Phase 3 Study of Tabelecleucel for Solid Organ or Allogeneic Haematopoietic Cell Transplant Subjects with Epstein-Barr Virus-Associated Post-Transplant Lymphoproliferative Disease after Failure of Rituximab or Rituximab and Chemotherapy.	Interim reports: With annual re-assessment Final CSR: December 2027

The CHMP endorses the CAT conclusion on the specific obligations to complete post-authorisation measures for the marketing authorisation under exceptional circumstances as described above.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully partly reflect the advice received from the PRAC.

The CHMP endorse the CAT conclusion on the conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

New active substance status

Based on the review of available data on the active substance, the CAT considers that tabelecleucel is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

The CHMP endorses the CAT conclusion on the new active substance claim.

Paediatric data

Furthermore, the CAT reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0490/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

The CHMP endorses the CAT conclusion on the paediatric data.