EU-RISK MANAGEMENT PLAN FOR TABELECLEUCEL

Risk Management Plan (RMP) version to be assessed as part of this application:

RMP Version number	1.0
Data lock point for this RMP	05 November 2021 • The pivotal study ATA129-EBV-302 and the expanded access programmes (ATA129-EAP-901 and ATA129-SPU) were ongoing at the time of the data lock point • Studies EBV-CTL-201, 11-130, and 95-024 were completed by the time of the data lock point
Date of final sign off	04 October 2022
Rationale for submitting an updated RMP	Not applicable
Summary of significant changes in this RMP	Initial submission
Other RMP versions under evaluation	Not applicable
Details of the currently approved RMP	Not applicable
Qualified Person for Pharmacovigilance (QPPV)	Steen Ottosen
QPPV oversight declaration	The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

Term or Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AID	acquired immunodeficiency
ATG	antithymocyte globulin
BLCL	B-lymphoblastoid cell line
BMT	bone marrow transplant
CAR	chimeric antigen receptor
CB	cord blood
CMV	cytomegalovirus
CRS	cytokine release syndrome
CT	chemotherapy
CTCAE	common terminology criteria for adverse events
CTL	cytotoxic T lymphocyte
CTLp	cytotoxic T-lymphocyte precursor
EAP	expanded access programme
EBV	Epstein-Barr virus
EBV^+	EBV positive
EBV^+ PTLD	Epstein-Barr virus-positive posttransplant lymphoproliferative disease
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GvHD	graft-versus-host disease
HBV	hepatitis B virus
HCT	haematopoietic cell transplant
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLT	High-level term
ICANS	immune effector cell-associated neurotoxicity syndrome
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IL	interleukin
IRR	infusion-related reaction
LPD	lymphoproliferative disorders
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
PASS	postauthorisation safety study

Term or Abbreviation	Definition
PBRER	periodic benefit risk assessment report
PID	primary immunodeficiency
PL	package leaflet
PT	preferred term
PTLD	posttransplant lymphoproliferative disease
RMP	risk management plan
R/R	relapsed and/or refractory
SmPC	summary of product characteristics
SMQ	standardized MedDRA query
SOC	system organ class
SOT	solid organ transplant
SPU	single patient use
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TFR	tumour flare reaction
US	United States

PART I. PRODUCT(S) OVERVIEW

Table 1. Product Overview

Active substance(s) (INN or common name)	Tabelecleucel
Pharmacotherapeutic group(s) (ATC Code)	Not yet assigned
Marketing Authorisation Applicant	Atara Biotherapeutics, Ireland
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Ebvallo
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class Tabelecleucel is an allogeneic Epstein-Barr virus (EBV)-specific T-cell immunotherapy.
	Summary of mode of action Tabelecleucel is an allogeneic EBV-specific T-cell immunotherapy which targets and eliminates EBV^+ cells in a HLA-restricted manner. Tabelecleucel is produced from T cells harvested from human donors. Each tabelecleucel lot within the product inventory is tested for specificity of lysis of EBV^+ targets, T-cell HLA restriction of specific lysis, and verification of low alloreactivity. A tabelecleucel lot is selected for each patient from the existing product inventory based on an appropriate HLA restriction.
	Important information about tabelecleucel's composition Each vial contains 1 mL deliverable volume of tabelecleucel at a concentration of 2.8 - 7.3 × 10^7 viable T cells/mL dispersion for injection. Excipients include dimethyl sulfoxide, human serum albumin, and phosphate buffered saline.
Hyperlink to the Product Information	Module 1.3.1 Summary of Product Characteristics, Labeling and Package Leaflet
Indication(s) in the EEA	Current: Tabelecleucel is indicated 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.
	Proposed: Not applicable

Table 1. Product Overview

Dosage in the EEA	Current: The recommended dose of tabelecleucel contains 2×10^6 viable T cells per kg of the patient's body weight. Tabelecleucel is administered as an intravenous injection over 5 to10 minutes. Tabelecleucel is administered over multiple 35-day cycles, during which patients receive tabelecleucel on days 1, 8, and 15, followed by observation through day 35. Response is assessed at approximately day 28.
	Proposed: Not applicable
Pharmaceutical form(s) and strength(s)	Current: Dispersion for injection Each vial contains 1 mL deliverable volume of tabelecleucel at a concentration of 2.8 - 7.3 $\times 10^7$ viable cells/mL.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: ATC, Anatomical Therapeutic Chemical Classification System; EBV, Epstein-Barr virus; EBV^+, EBV-associated; EBV^+ PTLD, Epstein-Barr virus positive posttransplant lymphoproliferative disease; EEA, European Economic Area; EU, European Union; HLA, human leukocyte antigen; INN, International Nonproprietary Name; RMP, risk management plan.

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population(s)

Epstein-Barr virus-positive posttransplant lymphoproliferative disease (EBV$^+$ PTLD) is an ultra-rare disease, and a very small number of patients with EBV$^+$ PTLD relapse or are refractory to a previous treatment. It is estimated that ~290 European Union (EU) patients annually are impacted by EBV$^+$ PTLD that is relapsed and/or refractory (R/R) to rituximab.

Proposed Indication

Tabelecleucel is indicated as monotherapy for treatment of adult and paediatric patients 2 years of age and older with relapsed or refractory EBV$^+$ PTLD who have received at least one prior therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate.

Incidence

Incidence of EBV$^+$ PTLD following HCT

The overall annual incidence of PTLD following haematopoietic cell transplant (HCT) is approximately 1.1 – 1.7% [Dierickx 2013; Garcia-Cadenas 2019]. Nearly all PTLD cases that develop after HCT are EBV$^+$ [Garcia-Cadenas 2019; Socié 2020; Styczynski 2013; Uhlin 2014]. Thus, the overall incidence of EBV$^+$ PTLD following HCT is approximately 1.1 – 1.7%.

In the HCT setting, the majority of PTLD cases occur within 1 year after transplant, with median time to diagnosis of about 2-4 months [Dierickx 2018]. Since there is no approved treatment for PTLD, many clinicians use rituximab, a monoclonal anti-CD20 antibody indicated to treat non-Hodgkin's lymphoma, as initial treatment for PTLD [Dierickx 2018; Jagadeesh 2019; Rituximab 2020]. However, approximately 50% of patients with PTLD following HCT fail initial treatment with rituximab [Garcia-Cadenas 2019]. Based on the reported number of allogeneic bone marrow transplants in 28 countries of the EU (EU28) [EDQM 2020], the overall incidence of EBV$^+$ PTLD following HCT, and the proportion of patients failing initial therapy, the estimated total number of EBV$^+$ PTLD patients following HCT R/R to rituximab was 90-140 in the EU28 for the year 2019.

Incidence of EBV$^+$ PTLD following SOT

In the solid organ transplant (SOT) setting, chronic immunosuppression confers lifelong risk for PTLD, which can occur up to 30 years posttransplant [Jagadeesh 2020; Trappe 2017]. The incidence is largely dependent on the type of transplanted organ, the type and degree of immunosuppression, and patient characteristics [Al-Mansour 2013].

To estimate the annual incidence of PTLD following SOT, given the time to PTLD diagnosis and varying rates of PTLD over time, the construction of a dynamic model that incorporates all of the following variables is required: the number of EU transplants since 2000 (Global Observatory on Donation and Transplantation [GODT]), the annual rate of PTLD over time by organ type, and survival rate over time for transplant patients [Graham 2020a; Graham 2020b]. Based on the above factors, it is estimated that about 750-900 new PTLD cases occurred in the EU28 in 2019.

About fifty percent of cases of PTLD following SOT are EBV$^+$ [Jagadeesh 2020; Trappe 2017]. Among all cases of PTLD following SOT, around a third of patients eventually relapse or become refractory to initial treatment with rituximab or rituximab plus chemotherapy (CT) [Jagadeesh 2020; Trappe 2017]. In the EU, the total number of patients with EBV$^+$ PTLD following SOT who fail initial treatment with rituximab plus CT is about 125-150 in 2019.

Incidence of R/R EBV$^+$ PTLD following HCT or SOT

EBV$^+$ PTLD after failure of rituximab affects ~90 to 140 patients following HCT annually in the EU and ~125 to 150 patients following SOT in the EU.

Prevalence

Specific data on the prevalence of EBV$^+$ PTLD in the EU is not available. The prevalence of EBV$^+$ PTLD is expected to approximate the incidence of the disease since the survival of these patients is approximately 1 to 4 months after first-line treatment failure.

Demographics of the Population in the Proposed Indication and Risk Factors for the Disease:

Demographics (Age, Gender, Racial and/or Ethnic Origin)

Limited data exist on demographics in this population. Regarding ethnic origin, most patients report race/ethnicity as White; other demographic criteria are summarised below:

- PTLD Following SOT: In the PTLD-1 trial of treatment-naïve adult subjects (N = 70) with PTLD following SOT, the median age was 53.3 years (range 16 – 74 years), with 30% of subjects ≥ 60 years; and 67% of the subjects were male [Trappe 2012]. These demographic patterns remained in the long-term analysis of PTLD-1 study with final 152 subjects total: median age 56.4 years (range 18 – 82 years); 76% males [Trappe 2017].
- PTLD Following HCT: In a recent retrospective analysis of claims database in the US, the majority of patients with PTLD following HCT were between 45 and 64 years of age with a median age of 54.0 years, and 56.5% were male [Watson 2020]. This combined database included US Medicare and a commercial MarketScan databases with 5091 patients with HCT overall, of which 92 patients with PTLD following HCT.
- Atara studies in the tabelecleucel development programme included subjects with a broad range of characteristics and enrolled subjects of all ages [Refer to Module SIII].

Risk Factors

The risk factors common to the development of PTLD following SOT or HCT include the degree of T-cell immunosuppression and the EBV serologic status of the recipient, time posttransplant, recipient age, and ethnicity [Al-Mansour 2013]. Patient baseline characteristics such as advanced age, especially above 50 years, and history of splenectomy also pose significant risk for PTLD development [Al-Mansour 2013]. Additional risk factors for PTLD following HCT are degree of HLA mismatch, T-cell depletion of the bone marrow, and use of antithymocyte globulin (ATG) or anti-CD3-monocloinal antibody for prophylaxis treatment of acute graft-versus-host disease (GvHD) [Curtis 1999]. Major risk factors for early PTLD after SOT are well-established and include primary EBV infection in the SOT recipient, burden of immunosuppression, and EBV DNA load [Al-Mansour 2013]. As a patient accumulates risk factors, the risk of developing PTLD also increases. In one study, individuals with one risk factor had a 0.4% risk of developing PTLD, while individuals with 2, 3, 4, and 5 risk factors had an increased risk of 3%, 10.4%, 26.5%, and 40%, respectively [Al Hamed 2020].

Risk Factors Common to Development of PTLD Following SOT or HCT

- Age: Individuals aged < 10 and > 60 years are at increased risk of PTLD following SOT [Al-Mansour 2013]. A retrospective study that included 92 patients with PTLD after HCT showed that most patients who developed PTLD within the first year after transplant were younger than 65 years (93.2%): 8.7% were younger than 18 years and the mean age was 46.8 years [Barlev 2018; Watson 2020].

- Ethnicity: Higher incidence of PTLD has been reported in White transplant patients compared with Black transplant patients, irrespective of recipient EBV serostatus. White patients have been shown consistently to be at higher risk for PTLD [Dharnidharka 2001; Dharnidharka 2002; Nee 2011].
- Degree of immunosuppression: Long-term immunosuppression is the most recognised risk factor for late PTLD [San-Juan 2014].

Additional Risk Factors for Development of PTLD Following SOT

- EBV seronegativity and donor to recipient EBV seromismatch: Since most adults are EBV seropositive, donor organs sourced from these adults carry latent EBV that is transmitted along with passenger lymphoid tissue to transplant recipients. Patients who are EBV seronegative (not yet exposed to EBV) include some children and 8-15% of adult population, both groups are susceptible to primary EBV infection posttransplant under immunosuppressive regimen (to prevent organ rejection) and, thus, increasing the risk of PTLD due to oncogenic nature of EBV[Dharnidharka 2018].

Additional Risk Factors for Development of PTLD Following HCT

- T-cell depletion: Because of increased number of allogeneic HCTs performed from HLA-mismatched or unrelated donors, T-cell depletion strategies are also increasingly used as a conditioning regimen. Such strategies include in vivo depletion of T cells using ATG and ex vivo depletion by elutriation/density gradient centrifugation. The aim of these strategies is to reduce the risk of graft rejection and to reduce the risk of severe GvHD. T-cell depletion also removes EBV-specific cytotoxic T lymphocytes (EBV-CTLs); this procedure compromises T-cell-mediated immunity, thereby increasing the risk of EBV reactivation and development of PTLD. Furthermore, the degree of T-cell depletion is associated with risk of PTLD: High dose ATG, defined as a total dose of thymoglobulin > 2.5 mg/kg or ATG-F > 5.0 mg/kg, was associated with a 2.3-fold higher risk of PTLD than low dose ATG, suggesting that ATG increases the risk of PTLD in a dose-dependent manner [Fujimoto 2020].
- HLA mismatch. Styczynski et al demonstrated that the overall incidence of PTLD for a matched related donor was 1.16%, compared with 2.86% for a mismatched related donor, 3.97% for a matched unrelated donor, and 11.24% for a mismatched unrelated donor [Styczynski 2013]. Interestingly, use of cord blood (CB) for the transplant is associated with a 1.5- to 2.0-fold increased risk of PTLD when compared with an HLA-mismatched or unrelated donor. According to the previous reports on the incidence of PTLD among CB recipients, the incidence of PTLD after CB transplantation is around 2.0-4.5% [Fujimoto 2020].
- Other identified risk factors for PTLD following HCT include occurrence of acute or chronic GvHD and undergoing a second HCT [Kamble 2020] [Nee 2011].

The Main Existing Treatment Options

A significant unmet medical need exists for patients with EBV$^+$ PTLD following either HCT or SOT, especially given the lack of approved therapies and rapid decline with high mortality (often within 1 or 4 months, respectively) observed in those who do not respond to or relapse after initial treatment [Dharnidharka 2021; Sanz 2021; Socié 2020; Zimmermann 2019]. In the absence of approved drugs, guidelines for the management of PTLD have been developed, as summarised in Table 2. These

guidelines include recommendations for the use of EBV-specific CTLs for treatment of EBV^+ PTLD, although no such products are currently authorised.

The de facto international standard of care for first-line therapy of PTLD is rituximab, either as monotherapy in both HCT and SOT or as combination therapy with CT agents, eg, R-CHOP, in SOT. Rituximab is a monoclonal anti-CD20 antibody that has become a standard of care in patients with polymorphic PTLD, or monomorphic diffuse large B-cell lymphoma-like PTLD, who are unresponsive to initial reduction in immunosuppression [Shah 2021]. The international phase 2 PTLD-1 trial demonstrated the safety and efficacy of 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 CT (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 2017]. Responses to first-line therapy, however, are not durable in all cases. In the SOT setting, up to one-third of patients fail initial treatment [Trappe 2017]. Rituximab failure, either relapse or failure to respond, is typically followed by multiagent CT. Although some patients benefit from CT (R-CHOP/CHOP), 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]. In the HCT setting, approximately 50% of PTLD cases fail initial treatment [Garcia-Cadenas 2019]. Treatment options for paediatric patients with PTLD follow the same treatment algorithms as adults with generally similar outcomes [Mynarek 2013].

As a result of the limited treatment options for patients who fail initial therapy, disease progression is usually rapid with poor outcomes. In a recent retrospective cohort study of 18 patients who had EBV^+ PTLD following HCT, the median survival of patients of rituximab-refractory disease was 1.7 months [Socié 2020]. In patients with EBV^+ PTLD following SOT who failed rituximab plus CT or did not receive a CT regimen, the median survival was approximately 3 months [Zimmermann 2019]. Analysis of an expanded multinational population in 2021 confirmed these findings and underscored the continued high unmet need: patients with PTLD following HCT who failed rituximab had a median overall survival (OS) of 0.7 months (81 patients) [Sanz 2021]; patients with PTLD following SOT who failed CT after initial rituximab had a median OS of 4.1 months (86 patients) [Dharnidharka 2021].

Table 2. Summary of Guidelines for the Treatment of PTLD Following HCT or SOT

Treatment	Line of treatment	BSH [Shah 2021] (PTLD-SOT)	NCCN[a] [Zelenetz 2019] (PTLD following HCT and SOT)	AST IDCOP [Allen 2019] (PTLD following SOT)	ECIL-6 [Styczynski 2016] (PTLD following HCT)
RIS	1st (typically + RTX)	New diagnosis (systemic) monomorphic B-cell PTLD	Initial therapy in early lesions and, if possible, in monomorphic (B-cell type) PTLD.	Lowest tolerated level of RIS as initial therapy for nearly all early and late B-cell PTLD in patients who do not have rapidly progressive disease[b].	Rarely successful as the sole intervention in PTLD following HCT. It should be combined with RTX administration, if possible
RTX alone	1st or 2nd	RTX after failed RIS in (systemic) monomorphic B-cell PTLD-SOT.	After lack of response to RIS in non-destructive lesions / monomorphic (B-cell type) PTLD. Initial treatment in monomorphic (B-cell type) alone and/or RIS. Initial treatment in polymorphic[c] PTLD alone plus RIS, if possible. • systemic: RTX alone • localised: rituximab alone or RTX + surgery or RTX + radiation	In patients with CD20 positive PTLD with progressive disease after RIS.	RTX monotherapy is the treatment of choice for EBV-PTLD following HCT
RTX + CT or CT alone	1st or 2nd	RTX + CT (sequential) after failed RIS in (systemic) monomorphic B-cell PTLD-SOT.	RTX + CT (concurrent or sequential)[d] after lack of response to RTX in monomorphic (B-cell type) and polymorphic[c] PTLD. RTX + CT (concurrent or sequential)[d] as initial treatment in monomorphic (B-cell type) and polymorphic[c] PTLD in combination with RIS, if possible. Follow-up, second line therapy in polymorphic[c] PTLD alone plus RIS, if possible. • localised: CT	RTX-CT in patients with CD20 positive PTLD who have progressive disease after RTX and can tolerate therapy. For CNS PTLD, chemotherapy regimens used to treat primary CNS lymphoma in immunocompetent patients is recommended if tolerated. CT alone in CD20 negative B-cell PTLD, T-cell PTLD, and Hodgkin and Burkitt lymphoma.	1st line RTX ± CT is a potential option for CNS disease. CT after HCT is otherwise not recommended as 1st-line therapy CT ± RTX is a potential 2nd line option after failure of other methods.

Table 2. Summary of Guidelines for the Treatment of PTLD Following HCT or SOT

Treatment	Line of treatment	BSH [Shah 2021] (PTLD-SOT)	NCCN[a] [Zelenetz 2019] (PTLD following HCT and SOT)	AST IDCOP [Allen 2019] (PTLD following SOT)	ECIL-6 [Styczynski 2016] (PTLD following HCT)
CTL	1st or 2nd	Treatment of PTLD with EBV-specific CTLs should be considered where available with R/R EBV $^{+}$ PTLD (1C).	Listed as a 2nd line option in patients with partial response, persistent disease, or progressive disease after first-line RTX-containing treatment After partial response, persistent or progressive disease: EBV-specific cytotoxic T-cell immunity (if EBV driven)	Listed as an alternative in allogeneic HCT recipients, but in the SOT setting experience is more limited.	1st-line: EBV-specific CTL, if available. 2nd-line ECIL's preferred approach is EBV-specific CTL or DLI

Abbreviations: AST IDCOP, American Society of Transplantation Infectious Diseases Community of Practice; BSH, British Society for Haematology; CD20, cluster of differentiation 20 (B-lymphocyte antigen); CNS, central nervous system; CT, chemotherapy; CTL, cytotoxic T-cell therapy; DLI, donor lymphocyte infusion; EBV, Epstein-Barr virus; ECIL-6, Sixth European Conference on Infections in Leukaemia; HCT, haematopoietic cell transplant; NCCN, National Comprehensive Cancer Network; PTLD, posttransplant lymphoproliferative disease; RIS, reduction in immunosuppression; RTX, Rituximab; R/R, refractory and/or relapsed; SOT, solid organ transplant

[a] Updated NCCN guidelines are available for: B-cell lymphomas. Version 3.2021. 16 March 2021.
[b] Not validated for some pathologic subtypes such as Burkitt and Hodgkin lymphoma.
[c] Systemic polymorphic PTLD (B-cell type; see NCCN guidelines for recommendations for localised polymorphic PTLD or T-cell type PTLD).
[d] Concurrent therapy: RTX + CT at the same time; sequential: RTX for 4 weeks, then depending on restaging results, RTX every 3 weeks for another 4 cycles or CT.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

Nearly all PTLD cases following HCT are EBV$^+$ [Al-Mansour 2013; Allen 2013; Dierickx 2018; Styczynski 2016]. Most cases occur early, within 2-12 months [Jain 2005; Naik 2019; Styczynski 2016] of transplantation because of the temporary administration of immunosuppressive therapy [Dierickx 2018] and prior to patients' endogenous immune reconstitution. An analysis of a large United States (US) claims database and a retrospective chart study including data from US and EU found that the median time from HCT to PTLD diagnosis is 90 days [Barlev 2018; Sanz 2021; Socié 2020]. Only 4% of PTLD cases occur later than 12 months after HCT, and cases occurring more than 5 years after HCT are very rare [Styczynski 2016].

In PTLD following SOT, ~50% of cases are found to be EBV$^+$ [Al-Mansour 2013; Dharnidharka 2018; Dierickx 2018], with 2 peaks in incidences as follows:

- Early-onset PTLD diagnoses peak in the first 2 years after SOT and are more frequently EBV$^+$.
- Late-onset PTLD diagnoses peak 5-10 years after SOT and are more frequently EBV$^-$ [Al-Mansour 2013; Allen 2013; Dierickx 2018; Jagadeesh 2019; Jain 2005].

Important Comorbidities

Fever and lymphadenopathy are the most common symptoms, although some PTLDs develop with nonspecific symptoms such as prolonged fever, night sweats, general malaise, and weight loss, and others are found incidentally. By contrast, some PTLDs show common symptoms of malignant lymphoma such as lymphadenopathy, swelling of tonsils or adenoids, and hepatosplenomegaly. As it progresses, PTLD can involve any organ, including bone marrow, liver, spleen, lung, gastrointestinal tract, and kidney, even the central nervous system in some cases. Thus, PTLD may present with organ-specific symptoms such as abdominal pain, gastrointestinal bleeding, or dyspnoea. PTLD after HCT often progresses rapidly, and an advanced stage of PTLD is more common in patients after HCT than in those after SOT [Fujimoto 2020].

Module SII. Nonclinical Part of the Safety Specification

Tabelecleucel is an ex vivo expanded T-cell immunotherapy that has an equivalent mechanism of action (MOA) to endogenous circulating cytotoxic T lymphocytes (CTLs) (targeting EBV antigens through the native T-cell receptor [TCR]). Tabelecleucel is not genetically modified. As such, tabelecleucel represents a T-cell immunotherapy that shares components of the natural immune response without any component of supraphysiologic signaling.

The nonclinical experience with tabelecleucel supports its specificity and efficacy and demonstrates HLA and EBV-antigen specific homing to and accumulation in EBV$^+$ tumours (2.4 Nonclinical Overview). No effects have been observed with tabelecleucel beyond those predicted by the natural pharmacology of T cells.

Based on the species-specific nature of tabelecleucel and the limited applicability of non-human toxicology models, single dose toxicity studies were not conducted as these studies would yield no additional information to aid in the understanding of the potential toxicity of tabelecleucel. Additionally, pharmacology studies in preclinical models demonstrated that no overt signs of toxicity (loss of activity, weight loss, ruffled hair, ascites, palpable tumours or alloreactivity) were observed with single doses of tabelecleucel in murine xenograft models of EBV-induced B-cell lymphoproliferation [Doubrovin 2007; Koehne 2003; Lacerda 1996; Lacerda 1997]. Similarly, repeat dose toxicity studies were not conducted as these studies would yield no additional information to aid in the understanding of the potential toxicity of tabelecleucel in humans.

Carcinogenicity/Tumorigenicity

The manufacture of tabelecleucel involves stimulation and sensitisation of donor T cells (obtained from EBV-seropositive unrelated donors) cocultured with donor-autologous EBV-transformed B cells (referred to as EBV B-lymphoblastoid cell lines [BLCLs]) in the presence of cytokines, thereby stimulating expansion of EBV-specific T cells. The EBV-BLCLs are irradiated prior to addition to tabelecleucel cultures. As such, the manufacture includes exposure of tabelecleucel drug product intermediate to EBV antigens though not to intact EBV virus. As is established, EBV has transformative potential and can be oncogenic [Yin 2019]; therefore, the elimination of transformative potential of the virus and/or viral transformed cells to the final product was assessed.

Four nonclinical studies assessed the tumorigenicity potential associated with potential transfer of EBV from tabelecleucel (EBV-CTLs) and reagents (such as EBV-BLCL cell lines) to tabelecleucel recipients. In summary, results from these studies demonstrated no transformation associated with potential transfer of EBV from tabelecleucel or BLCL reagent (RPT-129-1002); and demonstrated clearance of EBV and BLCL reagent during the manufacturing process (TRPT-PS-033, TRPT-PD-004, and TRPT-PS-014). These nonclinical data show no/low risk for carcinogenicity/tumorigenicity. Consistent with the nonclinical findings, no evidence of secondary malignancies attributable to tabelecleucel has been observed in patients in clinical studies or expanded access programmes (EAPs) as of the most recent data lock point.

Report Number	Study Title	Study Type
RPT-129-1002	Evaluation of transmission and transformation potential of EBV infection from B95.8 BLCL or EBV-CTL to cord blood cells and autologous T-cell depleted peripheral blood cells	Toxicology/Tumorigenicity
TRPT-PS-033	EBV clearance in ATA129	Toxicology/Safety (EBV clearance)
TRPT-PD-004	Residual EBV clearance during the cGMP culture process of ATA129	Toxicology/Safety (EBV clearance)
TRPT-PS-014	Kinetics of BLCL clearance	Toxicology/Safety (Irradiated BLCL clearance)

Abbreviations: EBV, Epstein-Barr virus; BLCL, EBV B-lymphoblastoid cell lines; cGMP, current good manufacturing practices; CTL, cytotoxic T lymphocytes

Study RPT-129-1002 (EBV Transformation Potential to Cord Blood Cells and Autologous T-Cell Depleted Peripheral Blood Mononuclear Cells)

Transformation associated with potential transfer of EBV B95.8 to CB cells was assessed by using a coculture assay CCI BLCL reagent and EBV-CTLs (tabelecleucel) used within the same test were of the same donor origin. After 4 to 6 weeks of culture, cluster formation and cell appearance were recorded.

These data demonstrate the lack of transformation associated with potential transfer of EBV from tabelecleucel or reagents to CB mononuclear cells.

A similar model was used to determine in vitro transformation associated with potential transfer of EBV infection from B95.8 EBV transformed cell line (BLCL) or EBV-CTLs to autologous T-cell-depleted peripheral blood mononuclear cells.

These studies showed no evidence of transformation associated with potential transfer of EBV as a component of reagents and products generated with acyclovir treated BLCL reagent.

Studies TRPT-PS-033, TRPT-PD-004 (Clearance of EBV Virus in Tabelecleucel T-Cell Product)

The tabelecleucel manufacturing process comprises a series of stimulations of EBV-CTLs with BLCL. The B95.8 laboratory strain of wildtype EBV reagent used for BLCL transformations is derived from a good manufacturing practice master cell bank and tested in compliance with regulatory guidance. Studies were conducted to determine the residual infectious levels of EBV in tabelecleucel products at different manufacturing steps (CCI [redacted]) on harvest day.

These studies indicate clearance of infectious EBV virus (to below the quantifiable limits from wash process to cryo-formulation) in tabelecleucel prior to patient administration and therefore do not raise concerns in relation to transmission of transformative EBV.

Study TRPT-PS-014 (Clearance of Irradiated BLCL in Drug Product)

Studies were conducted to establish the kinetics of irradiated BLCL clearance during manufacturing of tabelecleucel. Data showed clearance of irradiated BLCLs from tabelecleucel cultures. The estimated frequency of irradiated BLCL (CD19 positive) cells was CCI [redacted] The time to reach BLCL clearance decreased as the number of re-stimulation cycles increased. These findings demonstrate clearance of irradiated BLCL in tabelecleucel drug product.

Genotoxicity

As stated in the ICH S6(R1) *Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals*, the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals. As tabelecleucel is a non-genetically engineered cell product, it is not expected to interact directly with DNA or other chromosomal material.

Reproductive/Developmental Toxicity

Due to the species-specific nature of the pharmacology of tabelecleucel, Atara did not perform nonclinical reproductive/developmental toxicity studies to support its clinical development. Per ICH S6(R1) and ICH S9, the need for reproductive/developmental toxicity studies is dependent upon the product, clinical indication, and intended patient population.

Tabelecleucel is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised on potential risks for the foetus and potential risks to the breastfed child. However, pregnancy is an unlikely event in this population due to the underlying disease and previous and concomitant therapies.

Discussion and Conclusion

Nonclinical toxicology studies conducted with tabelecleucel were limited to tumorigenicity and EBV and BLCL clearance studies; the outcome of these studies is summarised as follows:

- Tumorigenicity testing revealed lack of transformation associated with potential transfer of EBV to CB cells or autologous T-cell-depleted peripheral blood mononuclear cells from tabelecleucel (EBV-CTLs) or reagents (such as BLCL reagent) using coculture systems.
- Clearance of infectious EBV virus (to below the quantifiable limits from wash process to cryo-formulation) from tabelecleucel product.
- Clearance of irradiated BLCLs from tabelecleucel product.

Tabelecleucel is an ex vivo expanded T-cell product that is not genetically modified and has an equivalent MOA to endogenous circulating CTLs. As such, tabelecleucel represents a T-cell product that shares components of the natural immune response. Based on the species-specific nature of tabelecleucel and

limited applicability of non-human toxicology models, further toxicology studies would yield little additional information to aid in the understanding of the potential toxicology of tabelecleucel.

Module SIII. Clinical Trial Exposure

The clinical development programme to evaluate the efficacy and safety of tabelecleucel monotherapy includes clinical studies and EAPs:

- Pivotal phase 3 clinical study:
  - ATA129-EBV-302: Multicentre, single-arm, open-label study for treatment of EBV$^+$ PTLD following HCT after failure of rituximab or following SOT after failure of rituximab and/or rituximab plus CT (ALLELE).
- Supportive clinical studies:
  - EBV-CTL-201: Multicenter, single-arm, open-label, phase 2 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.
  - 11-130: Single-centre, single-arm, open-label, phase 2 study for treatment of EBV$^+$ PTLD and other EBV-associated lymphoproliferative diseases or malignancies.
  - 95-024: Single-centre, single-arm, open-label, phase 1/2 study for treatment of EBV$^+$ PTLD and other EBV-associated lymphoproliferative diseases or malignancies.
- Expanded access programmes (also known as compassionate use or single patient use [SPU]):
  - ATA129-EAP-901: Multicenter, expanded access protocol for treatment of EBV-associated viremia or malignancies for whom there are no appropriate alternative therapies and who are not eligible to enrol in any other Atara clinical studies.
  - ATA129-SPU: Single patient use (SPU) programme for the treatment of EBV$^+$ diseases and malignancies for whom there are no appropriate alternative therapies, and who are not eligible to enrol in any other Atara clinical development studies or EAP protocols.

The cumulative exposure data is presented in 3 sets of tables as of the data lock point: (1) data from the pivotal study along with the supportive clinical studies (Table 3 to Table 5), (2) data from both EAPs (Table 6 to Table 8). And (3) data from the 6 studies combined (pivotal study, supportive clinical studies, and EAPs; Table 9 to Table 11). While the proposed indication is limited to the treatment of EBV$^+$ PTLD, tabelecleucel has been investigated by the applicant in other EBV$^+$ diseases. The cumulative exposure data in this document includes data from subjects in EBV$^+$ PTLD and non-PTLD cohorts that have been treated with tabelecleucel, including EBV$^+$ PTLD, EBV$^+$ lymphoproliferative diseases in the setting of primary immunodeficiency lymphoproliferative disorders (EBV$^+$ PID LPD) or acquired immunodeficiency (EBV$^+$ AID LPD), EBV$^+$ viremia, EBV$^+$ sarcoma including leiomyosarcoma, EBV$^+$ lymphoma, EBV$^+$ natural killer (NK)/T-cell lymphoma, EBV$^+$ hemophagocytic lymphohistiocytosis (HLH), chronic active EBV (CAEBV), EBV$^+$ nasopharyngeal carcinoma (EBV$^+$ NPC), and other solid tumours (refer to 2.7.4 Summary Clinical Safety Section 1.2.3 and Section 1.2.4.1). The following cohorts are described in the cumulative exposure tables:

- C-PTLD: all subjects with EBV$^+$ PTLD following either SOT or HCT, including:
  - C-HCT: all subjects with EBV$^+$ PTLD following HCT (R/R to rituximab)
  - C-SOT: all subjects with EBV$^+$ PTLD following SOT, including:
    - C-SOT-R+C: subjects with EBV$^+$ PTLD (R/R to rituximab and CT)
    - C-SOT-R: subjects with EBV$^+$ PTLD following SOT (R/R to rituximab)

Note: Two SOT patients from ATA129-SPU who did not receive prior rituximab (CD20-negative) and were CT inappropriate were included in the C-SOT and C-PTLD.

- C-Non-PTLD: all subjects with EBV^+ disease other than EBV^+ PTLD, including: EBV^+ PID LPD, EBV^+ AID LPD, EBV^+ viremia, EBV^+ sarcoma including leiomyosarcoma, EBV^+ lymphoma, EBV^+ NK/T-cell lymphoma, EBV^+ HLH, CAEBV, EBV^+ nasopharyngeal carcinoma, and other EBV^+ solid tumour
- C-Overall: all subjects with EBV^+ diseases, including C-PTLD and C-Non-PTLD

Cumulative Exposure for Clinical Studies

Table 3. Cumulative Exposure for Clinical Studies: Studies ATA129-EBV-302, EBV-CTL-201, 11-130, and 95-024

Duration of Exposure	Subjects (n)	Subject-years[a]
C-Overall (N = 202)		
≤ 5 weeks	70	2.5
> 5 to 10 weeks	43	5.9
> 10 to 15 weeks	35	8.3
> 15 weeks	54	38.5
Total person-time	55.2	
C-PTLD (N = 110)		
≤ 5 weeks	37	1.3
> 5 to 10 weeks	26	3.6
> 10 to 15 weeks	22	5.3
> 15 weeks	25	13.6
Total person-time for indication	23.8	
C-HCT (N = 59)		
≤ 5 weeks	22	0.8
> 5 to 10 weeks	12	1.6
> 10 to 15 weeks	13	3.1
> 15 weeks	12	6.2
Total person-time for indication	11.7	
C-SOT (N = 51)		
≤ 5 weeks	15	0.5
> 5 to 10 weeks	14	2.0
> 10 to 15 weeks	9	2.2
> 15 weeks	13	7.4
Total person-time for indication	12.1	
C-SOT-R+C (N = 31)		
≤ 5 weeks	12	0.4
> 5 to 10 weeks	5	0.7

Table 3. Cumulative Exposure for Clinical Studies: Studies ATA129-EBV-302, EBV-CTL-201, 11-130, and 95-024

Duration of Exposure	Subjects (n)	Subject-years[a]
> 10 to 15 weeks	6	1.4
> 15 weeks	8	5.3
Total person-time for indication	7.9	
C-SOT-R (N = 20)		
≤ 5 weeks	3	0.08
> 5 to 10 weeks	9	1.3
> 10 to 15 weeks	3	0.8
> 15 weeks	5	2.1
Total person-time for indication	4.2	
C-Non-PTLD (N = 92)		
≤ 5 weeks	33	1.1
> 5 to 10 weeks	17	2.2
> 10 to 15 weeks	13	3.0
> 15 weeks	29	24.9
Total person-time for indication	31.4	

Abbreviations: C-HCT, HCT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT, SOT EBV$^+$ PTLD cohort, including C-SOT-R, C-SOT-R+C, and C-SOT-Other; C-SOT-R, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT-R+C, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab and chemotherapy) cohort; C-PTLD, EBV$^+$ PTLD cohort, including C-HCT and C-SOT (ie, C-SOT-R, C-SOT-R+C, and C-SOT-Other); C-Non-PTLD, Subjects with EBV$^+$ disease other than those in C-PTLD; C-Overall, Subjects with EBV$^+$ diseases, including those in C-PTLD and C-Non-PTLD.

[a] Subject-years of exposure is the duration from first dose to last exposure date in years across all subjects.

One subject received tabelecleucel in both 11-130 and 95-024. This subject was considered as 2 separate subjects in this analysis.

Source: ATA129 RMP Table 1.1.1-01

Table 4. Cumulative Exposure for Clinical Studies by Age Group and Gender: Studies ATA129-EBV-302, EBV-CTL-201, 11-130, and 95-024

	Subjects-N		Subject-years[a]	
Age Group	**M**	**F**	**M**	**F**
C-Overall				
Infants and toddlers (< 2 years)	1	0	0.2	0
Children (2 to < 12 years)	10	14	5.8	5.5
Adolescents (12 to < 18 years)	8	12	1.7	3.1
Adults (18 to < 65 years)	72	49	14.6	15.0
Elderly people				
65 to < 75 years	12	17	3.1	4.7
75 to < 85 years	3	4	0.8	0.5
≥ 85 years	0	0	0	0

Table 4. Cumulative Exposure for Clinical Studies by Age Group and Gender: Studies ATA129-EBV-302, EBV-CTL-201, 11-130, and 95-024

	Subjects-N		Subject-years[a]	
Age Group	**M**	**F**	**M**	**F**
Total	106	96	26.3	28.9
C-PTLD				
Infants and toddlers (< 2 years)	0	0	0	0
Children (2 to < 12 years)	6	8	1.8	2.3
Adolescents (12 to < 18 years)	4	8	0.6	1.6
Adults (18 to < 65 years)	36	28	6.5	5.7
Elderly people				
65 to < 75 years	8	9	1.6	3.0
75 to < 85 years	2	1	0.7	0.04
≥ 85 years	0	0	0	0
Total	56	54	11.3	12.5
C-HCT				
Infants and toddlers (< 2 years)	0	0	0	0
Children (2 to < 12 years)	3	5	0.7	0.8
Adolescents (12 to < 18 years)	2	2	0.3	1.0
Adults (18 to < 65 years)	23	14	3.5	2.2
Elderly people				
65 to < 75 years	4	6	1.0	2.4
75 to < 85 years	0	0	0	0
≥ 85 years	0	0	0	0
Total	32	27	5.5	6.2
C-SOT				
Infants and toddlers (< 2 years)	0	0	0	0
Children (2 to < 12 years)	3	3	1.2	1.5
Adolescents (12 to < 18 years)	2	6	0.3	0.7
Adults (18 to < 65 years)	13	14	3.0	3.5
Elderly people				
65 to < 75 years	4	3	0.6	0.6
75 to < 85 years	2	1	0.7	0.04
≥ 85 years	0	0	0	0
Total	24	27	5.9	6.3
C-SOT-R+C				
Infants and toddlers (< 2 years)	0	0	0	0
Children (2 to < 12 years)	1	3	0.7	1.5
Adolescents (12 to < 18 years)	2	3	0.3	0.3

Table 4. Cumulative Exposure for Clinical Studies by Age Group and Gender: Studies ATA129-EBV-302, EBV-CTL-201, 11-130, and 95-024

	Subjects-N		Subject-years[a]	
Age Group	**M**	**F**	**M**	**F**
Adults (18 to < 65 years)	6	11	1.3	3.1
Elderly people				
65 to < 75 years	2	2	0.1	0.6
75 to < 85 years	0	1	0	0.04
≥ 85 years	0	0	0	0
Total	11	20	2.5	5.4
C-SOT-R				
Infants and toddlers (< 2 years)	0	0	0	0
Children (2 to < 12 years)	2	0	0.5	0
Adolescents (12 to < 18 years)	0	3	0	0.4
Adults (18 to < 65 years)	7	3	1.7	0.4
Elderly people				
65 to < 75 years	2	1	0.5	0.04
75 to < 85 years	2	0	0.7	0
≥ 85 years	0	0	0	0
Total	13	7	3.4	0.9
C-Non-PTLD				
Infants and toddlers (< 2 years)	1	0	0.2	0
Children (2 to < 12 years)	4	6	4.0	3.3
Adolescents (12 to < 18 years)	4	4	1.1	1.5
Adults (18 to < 65 years)	36	21	8.1	9.4
Elderly people				
65 to < 75 years	4	8	1.4	1.8
75 to < 85 years	1	3	0.2	0.4
≥ 85 years	0	0	0	0
Total	50	42	15.0	16.4

Abbreviations: C-HCT, HCT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT, SOT EBV$^+$ PTLD cohort, including C-SOT-R, C-SOT-R+C, and C-SOT-Other; C-SOT-R, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT-R+C, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab and chemotherapy) cohort; C-PTLD, EBV$^+$ PTLD cohort, including C-HCT and C-SOT (ie, C-SOT-R, C-SOT-R+C, and C-SOT-Other); C-Non-PTLD, Subjects with EBV$^+$ disease other than those in C-PTLD; C-Overall, Subjects with EBV$^+$ diseases, including those in C-PTLD and C-Non-PTLD.

[a] Subject-years of exposure is the duration from first dose to last exposure date in years across all subjects. One subject received tabelecleucel in both 11-130 and 95-024. This subject was considered as 2 separate subjects in this analysis.

Source: ATA129 RMP Table 1.1.2-01

Table 5. Cumulative Exposure for Clinical Studies by Ethnic Origin: Studies ATA129-EBV-302, EBV-CTL-201, 11-130, and 95-024

Ethnic Origin	Subjects-N	Subject-years[a]
C-Overall		
White	135	37.0
Black or African American	15	8.3
Native Hawaiian or Other Pacific Islander	2	0.9
Asian	29	5.7
Other	10	1.7
Unknown	7	1.0
Missing	4	0.5
Total	202	55.2
C-PTLD		
White	84	18.1
Black or African American	6	1.8
Native Hawaiian or Other Pacific Islander	2	0.9
Asian	7	1.3
Other	4	0.9
Unknown	4	0.5
Missing	3	0.2
Total	110	23.8
C-HCT		
White	43	8.3
Black or African American	4	1.7
Native Hawaiian or Other Pacific Islander	0	0
Asian	5	0.9
Other	1	0.2
Unknown	4	0.5
Missing	2	0.1
Total	59	11.7
C-SOT		
White	41	9.8
Black or African American	2	0.1
Native Hawaiian or Other Pacific Islander	2	0.9
Asian	2	0.4
Other	3	0.7
Unknown	0	0
Missing	1	0.1
Total	51	12.1

Table 5. Cumulative Exposure for Clinical Studies by Ethnic Origin: Studies ATA129-EBV-302, EBV-CTL-201, 11-130, and 95-024

Ethnic Origin	Subjects-N	Subject-years[a]
C-SOT-R+C		
White	27	6.7
Black or African American	1	0.003
Native Hawaiian or Other Pacific Islander	2	0.9
Asian	1	0.2
Other	0	0
Unknown	0	0
Missing	0	0
Total	31	7.9
C-SOT-R		
White	14	3.1
Black or African American	1	0.1
Native Hawaiian or Other Pacific Islander	0	0
Asian	1	0.1
Other	3	0.7
Unknown	0	0
Missing	1	0.1
Total	20	4.2
C-Non-PTLD		
White	51	18.9
Black or African American	9	6.5
Native Hawaiian or Other Pacific Islander	0	0
Asian	22	4.4
Other	6	0.8
Unknown	3	0.5
Missing	1	0.3
Total	92	31.4

Abbreviations: C-HCT, HCT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT, SOT EBV$^+$ PTLD cohort, including C-SOT-R, C-SOT-R+C, and C-SOT-Other; C-SOT-R, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT-R+C, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab and chemotherapy) cohort; C-PTLD, EBV$^+$ PTLD cohort, including C-HCT and C-SOT (ie, C-SOT-R, C-SOT-R+C, and C-SOT-Other); C-Non-PTLD, Subjects with EBV$^+$ disease other than those in C-PTLD; C-Overall, Subjects with EBV$^+$ diseases, including those in C-PTLD and C-Non-PTLD.

[a] Subject-years of exposure is the duration from first dose to last exposure date in years across all subjects.

One subject received tabelecleucel in both 11-130 and 95-024. This subject was considered as 2 separate subjects in this analysis.

Source: ATA129 RMP Table 1.1.3-01

Cumulative Exposure for Expanded Access Programmes

Table 6. Cumulative Exposure for Expanded Access Programmes: ATA129-EAP-901 and ATA129-SPU

Duration of Exposure	ATA129-EAP-901		ATA129-SPU	
	Patients-N	Patient-years[a]	Patients-N	Patient-years[a]
C-Overall (901, n = 43; SPU, n = 95)				
≤ 5 weeks	12	0.5	54	1.8
> 5 to 10 weeks	6	0.8	13	1.9
> 10 to 15 weeks	15	3.5	16	3.9
> 15 weeks	10	8.9	12	7.4
Total person-time	13.8		14.9	
C-PTLD (901, n = 19; SPU, n = 54)				
≤ 5 weeks	6	0.3	27	0.9
> 5 to 10 weeks	2	0.3	8	1.2
> 10 to 15 weeks	8	1.8	12	3.0
> 15 weeks	3	2.0	7	3.4
Total person-time for indication	4.3		8.5	
C-HCT (901, n = 10; SPU, n = 20)				
≤ 5 weeks	3	0.1	14	0.4
> 5 to 10 weeks	1	0.1	1	0.1
> 10 to 15 weeks	6	1.4	4	1.0
> 15 weeks	0	0	1	0.4
Total person-time for indication	1.6		1.9	
C-SOT (901, n = 9; SPU, n = 34)				
≤ 5 weeks	3	0.2	13	0.5
> 5 to 10 weeks	1	0.1	7	1.1
> 10 to 15 weeks	2	0.4	8	2.0
> 15 weeks	3	2.0	6	3.1
Total person-time for indication	2.7		6.6	
C-SOT-R+C (901, n = 7; SPU, n = 17)				
≤ 5 weeks	3	0.2	5	0.2
> 5 to 10 weeks	1	0.1	4	0.7
> 10 to 15 weeks	2	0.4	3	0.7
> 15 weeks	1	0.5	5	2.0
Total person-time for indication	1.2		3.6	
C-SOT-R (901, n = 2; SPU, n = 15)				
≤ 5 weeks	0	0	7	0.2
> 5 to 10 weeks	0	0	2	0.3
> 10 to 15 weeks	0	0	5	1.3

Table 6. Cumulative Exposure for Expanded Access Programmes: ATA129-EAP-901 and ATA129-SPU

> 15 weeks	2	1.5	1	1.1
Total person-time for indication	1.5		2.9	
C-Non-PTLD (901, n = 24; SPU, n = 41)				
≤ 5 weeks	6	0.2	27	0.9
> 5 to 10 weeks	4	0.6	5	0.7
> 10 to 15 weeks	7	1.7	4	0.9
> 15 weeks	7	6.9	5	3.9
Total person-time for indication	9.5		6.4	

Abbreviations: C-HCT, HCT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT, SOT EBV$^+$ PTLD cohort, including C-SOT-R, C-SOT-R+C, and C-SOT-Other; C-SOT-R, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT-R+C, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab and chemotherapy) cohort; C-PTLD, EBV$^+$ PTLD cohort, including C-HCT and C-SOT (ie, C-SOT-R, C-SOT-R+C, and C-SOT-Other); C-Non-PTLD, Subjects with EBV$^+$ disease other than those in C-PTLD; C-Overall, Subjects with EBV$^+$ diseases, including those in C-PTLD and C-Non-PTLD.

[a] Patient-years of exposure is the duration from first dose to last exposure date in years across all patients.

Source: ATA129 RMP Table 1.1.1-02 and Table 1.1.1-03

Table 7. Cumulative Exposure for Expanded Access Programmes by Age Group and Gender: ATA129-EAP-901 and ATA129-SPU

	ATA129-EAP-901				**ATA129-SPU**			
	Patients-N		**Patient-years[a]**		**Patients-N**		**Patient-years[a]**	
Age Group	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
C-Overall								
Infants and toddlers (< 2 years)	1	0	0.3	0	0	1	0	0.1
Children (2 to < 12 years)	4	5	3.0	2.3	10	8	0.9	2.6
Adolescents (12 to < 18 years)	3	1	0.7	0.1	4	4	1.1	0.4
Adults (18 to < 65 years)	13	9	2.2	3.7	29	30	2.2	6.8
Elderly people								
65 to < 75 years	3	3	0.4	0.7	6	0	0.7	0
75 to < 85 years	1	0	0.3	0	2	1	0.2	0.04
≥ 85 years	0	0	0	0	0	0	0	0
Total	25	18	6.9	6.9	51	44	5.0	9.9
C-PTLD								
Infants and toddlers (< 2 years)	0	0	0	0	0	0	0	0

Table 7. Cumulative Exposure for Expanded Access Programmes by Age Group and Gender: ATA129-EAP-901 and ATA129-SPU

	ATA129-EAP-901				ATA129-SPU			
	Patients-N		Patient-years[a]		Patients-N		Patient-years[a]	
Age Group	M	F	M	F	M	F	M	F
Children (2 to < 12 years)	0	2	0	0.1	3	5	0.5	2.1
Adolescents (12 to < 18 years)	1	0	0.3	0	1	3	0.2	0.4
Adults (18 to < 65 years)	8	5	1.4	2.0	15	21	1.5	3.4
Elderly people								
65 to < 75 years	1	1	0.02	0.2	4	0	0.4	0
75 to < 85 years	1	0	0.3	0	1	1	0.003	0.04
≥ 85 years	0	0	0	0	0	0	0	0
Total	11	8	2.0	2.3	24	30	2.6	5.9
C-HCT								
Infants and toddlers (< 2 years)	0	0	0	0	0	0	0	0
Children (2 to < 12 years)	0	0	0	0	2	2	0.4	0.4
Adolescents (12 to < 18 years)	1	0	0.3	0	0	2	0	0.08
Adults (18 to < 65 years)	6	1	0.9	0.2	6	6	0.7	0.3
Elderly people								
65 to < 75 years	1	0	0.02	0	1	0	0.04	0
75 to < 85 years	1	0	0.3	0	1	0	0.003	0
≥ 85 years	0	0	0	0	0	0	0	0
Total	9	1	1.4	0.2	10	10	1.1	0.8
C-SOT								
Infants and toddlers (< 2 years)	0	0	0	0	0	0	0	0
Children (2 to < 12 years)	0	2	0	0.1	1	3	0.2	1.7
Adolescents (12 to < 18 years)	0	0	0	0	1	1	0.2	0.3
Adults (18 to < 65 years)	2	4	0.6	1.8	9	15	0.8	3.1
Elderly people								
65 to < 75 years	0	1	0	0.2	3	0	0.4	0

Table 7. Cumulative Exposure for Expanded Access Programmes by Age Group and Gender: ATA129-EAP-901 and ATA129-SPU

	ATA129-EAP-901				ATA129-SPU			
	Patients-N		Patient-years[a]		Patients-N		Patient-years[a]	
Age Group	M	F	M	F	M	F	M	F
75 to < 85 years	0	0	0	0	0	1	0	0.04
≥ 85 years	0	0	0	0	0	0	0	0
Total	2	7	0.6	2.1	14	20	1.5	5.1
C-SOT-R+C								
Infants and toddlers (< 2 years)	0	0	0	0	0	0	0	0
Children (2 to < 12 years)	0	2	0	0.1	1	1	0.2	0.4
Adolescents (12 to < 18 years)	0	0	0	0	0	1	0	0.3
Adults (18 to < 65 years)	1	3	0.09	0.8	6	7	0.6	1.9
Elderly people								
65 to < 75 years	0	1	0	0.2	1	0	0.2	0
75 to < 85 years	0	0	0	0	0	0	0	0
≥ 85 years	0	0	0	0	0	0	0	0
Total	1	6	0.09	1.1	8	9	1.0	2.6
C-SOT-R								
Infants and toddlers (< 2 years)	0	0	0	0	0	0	0	0
Children (2 to < 12 years)	0	0	0	0	0	2	0	1.3
Adolescents (12 to < 18 years)	0	0	0	0	1	0	0.2	0
Adults (18 to < 65 years)	1	1	0.5	1.0	3	7	0.2	1.1
Elderly people								
65 to < 75 years	0	0	0	0	1	0	0.04	0
75 to < 85 years	0	0	0	0	0	1	0	0.04
≥ 85 years	0	0	0	0	0	0	0	0
Total	1	1	0.5	1.0	5	10	0.4	2.5
C-Non-PTLD								
Infants and toddlers (< 2 years)	1	0	0.3	0	0	1	0	0.1
Children (2 to < 12 years)	4	3	3.0	2.1	7	3	0.3	0.5

Table 7. Cumulative Exposure for Expanded Access Programmes by Age Group and Gender: ATA129-EAP-901 and ATA129-SPU

	ATA129-EAP-901				ATA129-SPU			
	Patients-N		Patient-years[a]		Patients-N		Patient-years[a]	
Age Group	M	F	M	F	M	F	M	F
Adolescents (12 to < 18 years)	2	1	0.4	0.1	3	1	1.0	0.04
Adults (18 to < 65 years)	5	4	0.8	1.8	14	9	0.7	3.4
Elderly people								
65 to < 75 years	2	2	0.4	0.5	2	0	0.3	0
75 to < 85 years	0	0	0	0	1	0	0.2	0
≥ 85 years	0	0	0	0	0	0	0	0
Total	14	10	4.9	4.6	27	14	2.4	4.0

Abbreviations: C-HCT, HCT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT, SOT EBV$^+$ PTLD cohort, including C-SOT-R, C-SOT-R+C, and C-SOT-Other; C-SOT-R, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT-R+C, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab and chemotherapy) cohort; C-PTLD, EBV$^+$ PTLD cohort, including C-HCT and C-SOT (ie, C-SOT-R, C-SOT-R+C, and C-SOT-Other); C-Non-PTLD, Subjects with EBV$^+$ disease other than those in C-PTLD; C-Overall, Subjects with EBV$^+$ diseases, including those in C-PTLD and C-Non-PTLD.

[a] Patient-years of exposure is the duration from first dose to last exposure date in years across all patients.

Source: RMP Table 1.1.2-02 and Table 1.1.2-03

Table 8. Cumulative Exposure for Expanded Access Programmes by Ethnic Origin: ATA129-EAP-901 and ATA129-SPU

	ATA129-EAP-901		ATA129-SPU	
Ethnic Origin	Patients-N	Patient-years[a]	Patients-N	Patient-years[a]
C-Overall				
White	23	6.8	60	9.9
Black or African American	4	0.2	5	0.6
Native Hawaiian or Other Pacific Islander	1	0.04	1	0.04
Asian	5	1.8	3	0.5
Other	9	4.7	11	1.6
Unknown	N/A	N/A	15	2.3
Missing	1	0.2	N/A	N/A
Total	43	13.8	95	14.9
C-PTLD				
White	10	3.2	43	6.3

Table 8. Cumulative Exposure for Expanded Access Programmes by Ethnic Origin: ATA129-EAP-901 and ATA129-SPU

	ATA129-EAP-901		ATA129-SPU	
Ethnic Origin	**Patients-N**	**Patient-years[a]**	**Patients-N**	**Patient-years[a]**
Black or African American	3	0.2	3	0.5
Native Hawaiian or Other Pacific Islander	0	0	0	0
Asian	3	0.4	0	0
Other	3	0.5	4	1.2
Unknown	N/A	N/A	4	0.5
Missing	0	0	N/A	N/A
Total	19	4.3	54	8.5
C-HCT				
White	4	0.7	14	1.3
Black or African American	1	0.04	1	0.1
Native Hawaiian or Other Pacific Islander	0	0	0	0
Asian	3	0.4	0	0
Other	2	0.4	2	0.1
Unknown	N/A	N/A	3	0.5
Missing	0	0	N/A	N/A
Total	10	1.6	20	1.9
C-SOT				
White	6	2.5	29	5.0
Black or African American	2	0.1	2	0.5
Native Hawaiian or Other Pacific Islander	0	0	0	0
Asian	0	0	0	0
Other	1	0.1	2	1.1
Unknown	N/A	N/A	1	0.1
Missing	0	0	N/A	N/A
Total	9	2.7	34	6.6
C-SOT-R+C				
White	4	1.0	13	3.0
Black or African American	2	0.1	2	0.5

Table 8. Cumulative Exposure for Expanded Access Programmes by Ethnic Origin: ATA129-EAP-901 and ATA129-SPU

	ATA129-EAP-901		ATA129-SPU	
Ethnic Origin	**Patients-N**	**Patient-years[a]**	**Patients-N**	**Patient-years[a]**
Native Hawaiian or Other Pacific Islander	0	0	0	0
Asian	0	0	0	0
Other	1	0.1	1	0.02
Unknown	N/A	N/A	1	0.1
Missing	0	0	N/A	N/A
Total	7	1.2	17	3.6
C-SOT-R				
White	2	1.5	14	1.8
Black or African American	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Asian	0	0	0	0
Other	0	0	1	1.1
Unknown	N/A	N/A	0	0
Missing	0	0	N/A	N/A
Total	2	1.5	15	2.9
C-Non-PTLD				
White	13	3.6	17	3.6
Black or African American	1	0.04	2	0.1
Native Hawaiian or Other Pacific Islander	1	0.04	1	0.04

Table 8. Cumulative Exposure for Expanded Access Programmes by Ethnic Origin: ATA129-EAP-901 and ATA129-SPU

	ATA129-EAP-901		ATA129-SPU	
Ethnic Origin	**Patients-N**	**Patient-years[a]**	**Patients-N**	**Patient-years[a]**
Asian	2	1.4	3	0.5
Other	6	4.2	7	0.4
Unknown	N/A	N/A	11	1.8
Missing	1	0.2	N/A	N/A
Total	24	9.5	41	6.4

Abbreviations: C-HCT, HCT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT, SOT EBV$^+$ PTLD cohort, including C-SOT-R, C-SOT-R+C, and C-SOT-Other; C-SOT-R, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT-R+C, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab and chemotherapy) cohort; C-PTLD, EBV$^+$ PTLD cohort, including C-HCT and C-SOT (ie, C-SOT-R, C-SOT-R+C, and C-SOT-Other); C-Non-PTLD, Subjects with EBV$^+$ disease other than those in C-PTLD; C-Overall, Subjects with EBV$^+$ diseases, including those in C-PTLD and C-Non-PTLD.

[a] Patient-years of exposure is the duration from first dose to last exposure date in years across all patients.

Source: RMP Table 1.1.3-02 and Table 1.1.3-03

Cumulative Exposure for the 6-study Pool

Table 9. Cumulative Exposure for Clinical Studies and Expanded Access Programmes: ATA129-EBV-302, EBV-CTL-201, 11-130, 95-024, ATA129-EAP-901, and ATA129-SPU

Duration of Exposure	**Subjects-N**	**Subject-years[a]**
C-Overall (n = 340)		
≤ 5 weeks	136	4.8
> 5 to 10 weeks	62	8.6
> 10 to 15 weeks	66	15.8
> 15 weeks	76	54.7
Total person-time	83.9	
C-PTLD (n =183)		
≤ 5 weeks	70	2.5
> 5 to 10 weeks	36	5.1
> 10 to 15 weeks	42	10.1
> 15 weeks	35	19.0
Total person-time for indication	36.7	
C-HCT (n = 89)		
≤ 5 weeks	39	1.3
> 5 to 10 weeks	14	1.9
> 10 to 15 weeks	23	5.4
> 15 weeks	13	6.5
Total person-time for indication	15.2	

Table 9. Cumulative Exposure for Clinical Studies and Expanded Access Programmes: ATA129-EBV-302, EBV-CTL-201, 11-130, 95-024, ATA129-EAP-901, and ATA129-SPU

Duration of Exposure	Subjects-N	Subject-years[a]
C-SOT (n = 94)		
≤ 5 weeks	31	1.2
> 5 to 10 weeks	22	3.2
> 10 to 15 weeks	19	4.6
> 15 weeks	22	12.4
Total person-time for indication	21.5	
C-SOT-R+C (n = 55)		
≤ 5 weeks	20	0.8
> 5 to 10 weeks	10	1.5
> 10 to 15 weeks	11	2.6
> 15 weeks	14	7.7
Total person-time for indication	12.7	
C-SOT-R (n = 37)		
≤ 5 weeks	10	0.3
> 5 to 10 weeks	11	1.6
> 10 to 15 weeks	8	2.1
> 15 weeks	8	4.7
Total person-time for indication	8.6	
C-Non-PTLD (n = 157)		
≤ 5 weeks	66	2.3
> 5 to 10 weeks	26	3.5
> 10 to 15 weeks	24	5.7
> 15 weeks	41	35.8
Total person-time for indication	47.2	

Abbreviations: C-HCT, HCT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT, SOT EBV$^+$ PTLD cohort, including C-SOT-R, C-SOT-R+C, and C-SOT-Other; C-SOT-R, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT-R+C, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab and chemotherapy) cohort; C-PTLD, EBV$^+$ PTLD cohort, including C-HCT and C-SOT (ie, C-SOT-R, C-SOT-R+C, and C-SOT-Other); C-Non-PTLD, Subjects with EBV$^+$ disease other than those in C-PTLD; C-Overall, Subjects with EBV$^+$ diseases, including those in C-PTLD and C-Non-PTLD.

[a] Subject-years of exposure is the duration from first dose to last exposure date in years across all subjects.

One subject received tabelecleucel in both 11-130 and 95-024. This subject was considered as 2 separate subjects in this analysis.

Source: ATA129 RMP Table 1.1.1-04

**Table 10. Cumulative Exposure for Clinical Studies and Expanded Access Programmes by Age Group and Gender:
ATA129 EBV-302, EBV-CTL-201, 11-130, 95-024, ATA129-EAP-901, and ATA129-SPU**

	Subjects-N		Subject-years[a]	
Age group	**M**	**F**	**M**	**F**
C-Overall				
Infants and toddlers (< 2 years)	2	1	0.6	0.1
Children (2 to < 12 years)	24	27	9.6	10.4
Adolescents (12 to < 18 years)	15	17	3.5	3.7
Adults (18 to < 65 years)	114	88	19.0	25.6
Elderly people				
65 to < 75 years	21	20	4.2	5.5
75 to < 85 years	6	5	1.3	0.5
≥ 85 years	0	0	0	0
Total	182	158	38.2	45.7
C-PTLD				
Infants and toddlers (< 2 years)	0	0	0	0
Children (2 to < 12 years)	9	15	2.4	4.5
Adolescents (12 to < 18 years)	6	11	1.0	2.0
Adults (18 to < 65 years)	59	54	9.5	11.1
Elderly people				
65 to < 75 years	13	10	2.1	3.1
75 to < 85 years	4	2	0.9	0.08
≥ 85 years	0	0	0	0
Total	91	92	15.9	20.8
C-HCT				
Infants and toddlers (< 2 years)	0	0	0	0
Children (2 to < 12 years)	5	7	1.0	1.2
Adolescents (12 to < 18 years)	3	4	0.5	1.0
Adults (18 to < 65 years)	35	21	5.1	2.7
Elderly people				
65 to < 75 years	6	6	1.1	2.4
75 to < 85 years	2	0	0.3	0
≥ 85 years	0	0	0	0
Total	51	38	8.0	7.2
C-SOT				
Infants and toddlers (< 2 years)	0	0	0	0
Children (2 to < 12 years)	4	8	1.3	3.3
Adolescents (12 to < 18 years)	3	7	0.5	0.9

**Table 10. Cumulative Exposure for Clinical Studies and Expanded Access Programmes by Age Group and Gender:
ATA129 EBV-302, EBV-CTL-201, 11-130, 95-024, ATA129-EAP-901, and ATA129-SPU**

	Subjects-N		Subject-years[a]	
Age group	**M**	**F**	**M**	**F**
Adults (18 to < 65 years)	24	33	4.4	8.4
Elderly people				
65 to < 75 years	7	4	1.0	0.8
75 to < 85 years	2	2	0.7	0.08
≥ 85 years	0	0	0	0
Total	40	54	7.9	13.5
C-SOT-R+C				
Infants and toddlers (< 2 years)	0	0	0	0
Children (2 to < 12 years)	2	6	0.9	2.0
Adolescents (12 to < 18 years)	2	4	0.3	0.6
Adults (18 to < 65 years)	13	21	2.0	5.8
Elderly people				
65 to < 75 years	3	3	0.4	0.8
75 to < 85 years	0	1	0	0.04
≥ 85 years	0	0	0	0
Total	20	35	3.5	9.1
C-SOT-R				
Infants and toddlers (< 2 years)	0	0	0	0
Children (2 to < 12 years)	2	2	0.5	1.3
Adolescents (12 to < 18 years)	1	3	0.2	0.4
Adults (18 to < 65 years)	11	11	2.4	2.6
Elderly people				
65 to < 75 years	3	1	0.5	0.04
75 to < 85 years	2	1	0.7	0.04
≥ 85 years	0	0	0	0
Total	19	18	4.2	4.4
C-Non-PTLD				
Infants and toddlers (< 2 years)	2	1	0.6	0.1
Children (2 to < 12 years)	15	12	7.3	5.9
Adolescents (12 to < 18 years)	9	6	2.5	1.7
Adults (18 to < 65 years)	55	34	9.6	14.5
Elderly people				
65 to < 75 years	8	10	2.1	2.3
75 to < 85 years	2	3	0.3	0.4

**Table 10. Cumulative Exposure for Clinical Studies and Expanded Access Programmes by Age Group and Gender:
ATA129 EBV-302, EBV-CTL-201, 11-130, 95-024, ATA129-EAP-901, and ATA129-SPU**

	Subjects-N		Subject-years[a]	
Age group	**M**	**F**	**M**	**F**
≥ 85 years	0	0	0	0
Total	91	66	22.3	24.9

Abbreviations: C-HCT, HCT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT, SOT EBV$^+$ PTLD cohort, including C-SOT-R, C-SOT-R+C, and C-SOT-Other; C-SOT-R, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT-R+C, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab and chemotherapy) cohort; C-PTLD, EBV$^+$ PTLD cohort, including C-HCT and C-SOT (ie, C-SOT-R, C-SOT-R+C, and C-SOT-Other); C-Non-PTLD, Subjects with EBV$^+$ disease other than those in C-PTLD; C-Overall, Subjects with EBV$^+$ diseases, including those in C-PTLD and C-Non-PTLD.

[a] Subject-years of exposure is the duration from first dose to last exposure date in years across all subjects.

One subject received tabelecleucel in both 11-130 and 95-024. This subject was considered as 2 separate subjects in this analysis.

Source: ATA129 RMP Table 1.1.2-04

**Table 11. Cumulative Exposure for Clinical Studies and Expanded Access Programmes by Ethnic Origin:
ATA129 EBV-302, EBV-CTL-201, 11-130, 95-024, ATA129-EAP-901, and ATA129-SPU**

Ethnic origin	**Subjects-N**	**Subject-years[a]**
C-Overall		
White	218	53.7
Black or African American	24	9.2
Native Hawaiian or Other Pacific Islander	4	1.0
Asian	37	8.0
Other	30	8.0
Unknown	22	3.3
Missing	5	0.7
Total	340	83.9
C-PTLD		
White	137	27.6
Black or African American	12	2.5
Native Hawaiian or Other Pacific Islander	2	0.9
Asian	10	1.7
Other	11	2.6
Unknown	8	1.0
Missing	3	0.2
Total	183	36.7
C-HCT		
White	61	10.3

**Table 11. Cumulative Exposure for Clinical Studies and Expanded Access Programmes by Ethnic Origin:
ATA129 EBV-302, EBV-CTL-201, 11-130, 95-024, ATA129-EAP-901, and ATA129-SPU**

Ethnic origin	Subjects-N	Subject-years[a]
Black or African American	6	1.8
Native Hawaiian or Other Pacific Islander	0	0
Asian	8	1.4
Other	5	0.7
Unknown	7	0.9
Missing	2	0.1
Total	89	15.2
C-SOT		
White	76	17.3
Black or African American	6	0.7
Native Hawaiian or Other Pacific Islander	2	0.9
Asian	2	0.4
Other	6	2.0
Unknown	1	0.1
Missing	1	0.1
Total	94	21.5
C-SOT-R+C		
White	44	10.7
Black or African American	5	0.6
Native Hawaiian or Other Pacific Islander	2	0.9
Asian	1	0.2
Other	2	0.1
Unknown	1	0.1
Missing	0	0
Total	55	12.7
C-SOT-R		
White	30	6.4
Black or African American	1	0.1
Native Hawaiian or Other Pacific Islander	0	0
Asian	1	0.1
Other	4	1.8
Unknown	0	0
Missing	1	0.1
Total	37	8.6
C-Non-PTLD		

**Table 11. Cumulative Exposure for Clinical Studies and Expanded Access Programmes by Ethnic Origin:
ATA129 EBV-302, EBV-CTL-201, 11-130, 95-024, ATA129-EAP-901, and ATA129-SPU**

Ethnic origin	Subjects-N	Subject-years[a]
White	81	26.2
Black or African American	12	6.6
Native Hawaiian or Other Pacific Islander	2	0.1
Asian	27	6.3
Other	19	5.3
Unknown	14	2.3
Missing	2	0.5
Total	157	47.2

Abbreviations: C-HCT, HCT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT, SOT EBV$^+$ PTLD cohort, including C-SOT-R, C-SOT-R+C, and C-SOT-Other; C-SOT-R, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab) cohort; C-SOT-R+C, SOT EBV$^+$ PTLD (relapsed/refractory to rituximab and chemotherapy) cohort; C-PTLD, EBV$^+$ PTLD cohort, including C-HCT and C-SOT (ie, C-SOT-R, C-SOT-R+C, and C-SOT-Other); C-Non-PTLD, Subjects with EBV$^+$ disease other than those in C-PTLD; C-Overall, Subjects with EBV$^+$ diseases, including those in C-PTLD and C-Non-PTLD.

[a] Subject-years of exposure is the duration from first dose to last exposure date in years across all subjects.

One subject received tabelecleucel in both 11-130 and 95-024. This subject was considered as 2 separate subjects in this analysis.

Source: ATA129 RMP Table 1.1.3-04

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 12. Pivotal Study ATA129-EBV-302 Protocol Amendment 4 Eligibility Criteria

ELIGIBILITY Criterion *(Study ATA129-EBV-302, Protocol Amendment 4, 15 October 2020)*	**Reason for Exclusion**	**Is the Criteria Considered Missing information?**	**Rationale for Being Considered (or not Considered) as Missing Information**
Exclusion Criterion 1. Burkitt lymphoma, classical Hodgkin lymphoma, or any T-cell lymphoma	Subjects with these malignancies were excluded because the expectation for these malignancies to respond to tabelecleucel was low based on the previous clinical experience.	No	There is no expected difference in the safety profile for subjects with Burkitt lymphoma, classical Hodgkin lymphoma, or any T-cell lymphoma compared to the population enrolled in Study ATA129-EBV-302.

Table 12. Pivotal Study ATA129-EBV-302 Protocol Amendment 4 Eligibility Criteria

ELIGIBILITY Criterion *(Study ATA129-EBV-302, Protocol Amendment 4, 15 October 2020)*	**Reason for Exclusion**	**Is the Criteria Considered Missing information?**	**Rationale for Being Considered (or not Considered) as Missing Information**
Exclusion Criterion 2. Daily steroids of > 0.5 mg/kg prednisone or glucocorticoid equivalent, ongoing methotrexate, or extracorporeal photopheresis	Use of immunosuppressive agents can potentially reduce tabelecleucel efficacy.	No	There is no expected difference in the safety profile of subjects receiving these immunosuppressive agents concomitantly with tabelecleucel compared to the population enrolled in Study ATA129-EBV-302.
Exclusion Criterion 3. Untreated CNS PTLD or CNS PTLD for which the subject is actively receiving CNS-directed chemotherapy (systemic or intrathecal) or radiotherapy at enrollment. NOTE: Subjects with previously treated CNS PTLD may enrol if CNS-directed therapy is complete.	CNS involvement of PTLD has been shown to be associated with poor prognosis; therefore, subjects with untreated CNS PTLD were not enrolled in the pivotal study. Subjects actively receiving treatment for CNS PTLD were not enrolled in the pivotal study to avoid confounding the tabelecleucel study results.	No	There is no expected difference in the safety profile of these subjects compared to the population enrolled in Study ATA129-EBV-302. The treatment of these subjects is based on physician risk-benefit analysis.
Exclusion Criterion 4. Suspected or confirmed grade ≥ 2 GvHD per the CIBMTR consensus grading system at enrollment	Given the potential overlapping safety profile of tabelecleucel and suspected GvHD, these subjects were excluded to avoid confounding the tabelecleucel study results.	No	There is no expected difference in the safety profile for these subjects compared to the population enrolled. The treatment of subjects with preexisting GvHD is based on physician risk-benefit analysis.
Exclusion Criterion 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 enrollment	These subjects were excluded to avoid confounding the tabelecleucel study results with those from other therapies.	No	There is no expected difference in the safety profile for these subjects compared to the population enrolled. The treatment of these subjects is based on physician risk-benefit analysis.
Exclusion Criterion 6. For HCT cohort only: Active adenovirus viremia	Subjects with EBV^+ PTLD following HCT with ongoing uncontrolled infection requiring systemic therapy were excluded from the study to avoid confounding tabelecleucel efficacy with the effect of concomitant immunosuppressive antiviral treatment.	No	There is no expected difference in the safety profile for these subjects compared to the population enrolled. The treatment of these subjects is based on physician risk-benefit analysis.

Table 12. Pivotal Study ATA129-EBV-302 Protocol Amendment 4 Eligibility Criteria

ELIGIBILITY Criterion *(Study ATA129-EBV-302, Protocol Amendment 4, 15 October 2020)*	**Reason for Exclusion**	**Is the Criteria Considered Missing information?**	**Rationale for Being Considered (or not Considered) as Missing Information**
Exclusion Criterion 7. Need for vasopressor or ventilatory support	Subjects with need for this support were excluded to limit to a population with reasonable performance status who are able to complete the study procedures per protocol.	No	There is no expected difference in the safety profile for these subjects compared to the population enrolled in Study ATA129-EBV-302. The treatment of these subjects is based on physician risk-benefit analysis.
Exclusion Criterion 8. ATG or similar anti-T-cell antibody therapy ≤ 4 weeks prior to enrollment	Subjects treated with these antibody therapies were excluded to avoid confounding the tabelecleucel study results.	No	There is no expected difference in the safety profile for these subjects compared to the population enrolled. The treatment of these subjects is based on physician risk-benefit analysis.
Exclusion Criterion 9. Treatment with EBV-CTLs or chimeric antigen receptor T cells directed against B cells within 8 weeks of enrollment (SOT or HCT cohorts); or unselected DLI within 8 weeks of enrollment (HCT cohort only)	Subjects treated with these cell therapies were excluded to avoid confounding the tabelecleucel study results.	No	There is no expected difference in the safety profile for these subjects compared to the population enrolled. The treatment of these subjects is based on physician risk-benefit analysis.
Exclusion Criterion 10. Female who is 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	Per ICH guidelines, pregnant women should normally be excluded from clinical trials with new investigational product. Tabelecleucel has not been tested in pregnant women or breastfeeding women in any clinical study or expanded access programme.	Yes	No data in pregnancy or breastfeeding is currently available and use in pregnancy and lactation was therefore added as missing information. Pregnancy is an unlikely event in this population due to underlying disease and associated treatments In addition, tabelecleucel is not recommended for women who are pregnant, or for women of childbearing potential not using contraception.

Table 12. Pivotal Study ATA129-EBV-302 Protocol Amendment 4 Eligibility Criteria

ELIGIBILITY Criterion *(Study ATA129-EBV-302, Protocol Amendment 4, 15 October 2020)*	**Reason for Exclusion**	**Is the Criteria Considered Missing information?**	**Rationale for Being Considered (or not Considered) as Missing Information**
INCLUSION CRITERIA			
Inclusion Criterion 7. ECOG performance status ≤ 3 for subjects aged ≥ 16 years; Lansky score ≥ 20 for subjects < 16 years	Subjects with ECOG score > 3 or Lansky score < 20 were excluded to limit to a population with reasonable performance status who are able to complete the study procedures per protocol.	No	There is no expected difference in the safety profile for these subjects compared to the population enrolled in Study ATA129-EBV-302. The treatment of these subjects is based on physician risk-benefit analysis.
Inclusion Criterion 9a and 9b. 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, is permissible if the subject has not had grade ≥ 2 bleeding in the prior 4 weeks (where grading of the bleeding is determined per the National Cancer Institute's CTCAE, version 5.0)	The subjects with poor bone marrow function were excluded to avoid confounding the tabelecleucel study results.	No	There is no expected difference in the safety profile for these subjects compared to the population enrolled in Study ATA129-EBV-302. The treatment of these subjects is based on physician risk-benefit analysis.
Inclusion Criterion 9c. Adequate organ function c. ALT and AST, and TBILI each < 5 × upper limit of normal; however, ALT, AST, and TBILI each ≤ 10 × upper limit of normal is acceptable if the elevation is considered by the investigator to be due to EBV and/or PTLD	The subjects with overt liver function insufficiency (based on higher cutoffs for liver enzymes) were excluded to avoid confounding the tabelecleucel study results.	No	No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of tabelecleucel. Liver toxicity with the use of tabelecleucel is not anticipated, as it is cell therapy and not likely to be cleared through the liver.

Table 12. Pivotal Study ATA129-EBV-302 Protocol Amendment 4 Eligibility Criteria

ELIGIBILITY Criterion *(Study ATA129-EBV-302, Protocol Amendment 4, 15 October 2020)*	**Reason for Exclusion**	**Is the Criteria Considered Missing information?**	**Rationale for Being Considered (or not Considered) as Missing Information**
involvement of the liver as long as there is 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).			

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATG, antithymocyte globulin; CIBMTR, Centre for International Blood and Marrow Transplant Research; CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; CTL, cytotoxic T lymphocytes; DLI donor lymphocyte infusion; ECOG, Eastern Cooperative Oncology Group; EBV, Epstein-Barr virus; GvHD, graft-versus-host disease; HCT, haematopoietic cell transplant; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; MOA, mechanism of action; PTLD, posttransplant lymphoproliferative disease; SOT, solid organ transplant; TBILI, total bilirubin

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, or adverse reactions with a long latency.

SIV.3. Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programmes

Table 13. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	**Exposure**
Pregnant women	There are no data for tabelecleucel use during pregnancy or lactation. Tabelecleucel is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised on potential risks for the foetus and potential risks to the breastfed child. However, pregnancy is an unlikely event in this population due to underlying disease and previous and concomitant therapies.
Breastfeeding women	
Patients with relevant comorbidities:	
• Patients with hepatic impairment	150 out of 202 (74.3%) subjects were identified with hepatic impairment in 4 clinical trials and the cumulative duration of exposure was 44.3 person-years.[a]

Table 13. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	The safety profile of hepatic impaired and not impaired in clinical studies was comparable. Based on tabelecleucel's MOA and commonly reported AEs, as well as no hepatic excretion mechanism, there is no expected difference in the safety profile.
• Patients with renal impairment	103 out of 202 (51.0%) patients were identified with renal impairment in 4 clinical trials and the cumulative duration of exposure was 29.5 person-years.[b] The safety profile of renal impaired and not impaired in clinical studies was comparable. Based on tabelecleucel's MOA and commonly reported AEs, as well as no renal excretion mechanism, there is no expected difference in the safety profile.
• Patients with cardiovascular impairment	65 out of 202 (32.2%) patients were identified with cardiovascular impairment in 4 clinical trials and the cumulative duration of exposure in 14.8 person-years.[c] The safety profile of cardiovascular impaired and not impaired in clinical studies was comparable. Based on tabelecleucel's MOA and commonly reported AEs, there is no expected difference in the safety profile.
• Immunocompromised patients	All EBV^+ PTLD patients in the tabelecleucel clinical development programme (N = 183) can be considered as immunocompromised due to the nature of the condition and immunosuppressive treatments administered to these patients.
• Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable.
Population with relevant different ethnic origin	Subjects of all races were included in the clinical development programme.
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Other	Not applicable.

Abbreviations: AE, adverse event; EBV^+ PTLD, Epstein-Barr virus-positive posttransplant lymphoproliferative disease; MOA, mechanism of action

[a] Hepatic impaired in clinical studies: includes grade 1 or higher aspartate aminotransferase (AST) or alanine transaminase (ALT) or total bilirubin (TB) or alkaline phosphatase (ALP) at baseline or liver related medical history including liver transplant

[b] Renal impaired in clinical studies: includes grade 1 or higher creatinine at baseline or renal related medical history including renal transplant

[c] Cardiovascular impaired in clinical studies: includes cardiac medical history including heart transplant or concomitant medication indicating cardiovascular disease

Source: RMP Tables 2.1.1-01 to 02, Tables 2.1.2-01 to 05, Tables 2.1.3-01 to 05, Tables 2.1.4-01 to 04, Tables 2.2.2-01 to 05, Tables 2.2.3-01 to 05, and Tables 2.2.4-01 to 04.

Module SV. Postauthorisation Experience

SV.1. Postauthorisation Exposure

Tabelecleucel is currently not approved for marketing in any country. Therefore, no postauthorisation experience is available.

SV.1.1. Method Used to Calculate Exposure

Not applicable.

SV.1.2. Exposure

Not applicable.

Module SVI. Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Not applicable. There is low potential for misuse as the product will be kept at treatment centres and administered by healthcare professionals. In addition, potential for misuse is unlikely based on the nature of the product and its MOA.

Specific Risks of Advanced Therapy Medicinal Products

Specific risks associated with tabelecleucel as an advanced therapy medicinal product have not been identified.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: Tumour flare reaction (TFR)

Risk-benefit impact: Tumour flare reaction (TFR) is an established adverse drug reaction (ADR) associated with the use of tabelecleucel. Tumour flare reaction occurred at a low frequency with 1 of 103 subjects (1.0%)[1] reporting TFR in Studies ATA129-EBV-302 and EBV-CTL-201. No treatment-emergent serious adverse event (TESAE) of TFR was reported in the other clinical studies (11-130 and 95-024; N = 99) and 3 patients reported TESAEs of TFRs in the EAPs (ATA129-EAP-901 and ATA129-SPU; N = 138). All 4 events were considered at least possibly related by the investigator (in clinical studies) or treating physician (in EAPs); 1 was grade 4, 2 were grade 3, and

[1] Frequency was determined from clinical studies ATA129-EBV-302 and EBV-CTL-201 which systematically collected treatment-emergent adverse events (TEAEs) including serious and nonserious. The other clinical studies (11-130 and 95-024) and EAPs collected TESAEs.

1 was grade 2. Depending on the anatomic tumour location, there is a potential for severe complications. As TFR can be life-threatening, it is considered an important identified risk.

Important Identified Risk: Graft-versus-host disease (GvHD)

Risk-benefit impact: Graft-versus-host disease (including in gastrointestinal tract and in liver, and rash maculo-papular [skin GvHD]) is an ADR associated with the use of tabelecleucel. Graft-versus-host disease occurred at a low frequency with 5 of 103 subjects (4.9%)[1] reporting GvHD in Studies ATA129-EBV-302 and EBV-CTL-201. An additional 9 subjects reported GvHD in the other clinical studies and EAPs (N = 99 and N = 138, respectively). The majority of the events were considered unrelated by the investigator (in clinical studies) or treating physician (in EAPs) and 8 were grade ≥ 3.

Although the GvHD cases were confounded by other risk factors such as transplant history and decrease of immunosuppressants for PTLD as per standard of care, the contribution of tabelecleucel to risk of developing GvHD cannot be excluded based on the MOA of an allogeneic therapy. As GvHD can be life-threatening or cause chronic comorbidities, it is considered an important identified risk.

Important Potential Risk: Solid organ transplant (SOT) rejection

Risk-benefit impact: The evidence of SOT rejection after administration of tabelecleucel in patients with previous allogeneic donor-derived SOT is limited, as the small number of reported cases of SOT rejection after administration of tabelecleucel had other risk factors including decrease of immunosuppressants as standard of care or a medical history of previous episodes of SOT rejection. SOT rejection occurred at a low frequency with 1 of 40 (2.5%)[1] subjects with EBV^+ PTLD following SOT reporting SOT rejection in Studies ATA129-EBV-302 and EBV-CTL-201, which was nonserious, grade 1, and considered unrelated by the investigator. None of the subjects with EBV^+ PTLD following SOT reported a TESAE of SOT rejection in the other clinical studies (11-130, and 95-024; N = 11). Three patients reported grade 1 or 2 TESAEs of SOT rejection in the EAPs (ATA129-EBV-901 and ATA129-SPU; N = 43); 1 event was considered possibly related by the treating physician. As SOT rejection can be life-threatening or cause chronic comorbidities, it is considered an important potential risk.

Important Potential Risk: Bone marrow transplant (BMT) rejection

Risk-benefit impact: There is a theoretical risk of tabelecleucel-mediated cytotoxic damage in patients who have had HCT. None of the subjects who were treated with tabelecleucel for EBV^+ PTLD following HCT reported an event of BMT rejection in the clinical studies (ATA129-EBV-302, EBV-CTL-201, 11-130, and 95-024; N = 59)[1] or in the EAPs (ATA129-EBV-901 and ATA129-SPU; N = 30)[1]. As BMT rejection can be life-threatening or cause chronic comorbidities, it is considered an important potential risk.

Important Potential Risk: Cytokine release syndrome (CRS)

Risk-benefit impact: Cytokine release syndrome (CRS) has been observed with antibody therapies and non-protein-based cancer therapies but has shown particularly high incidence rate and pronounced morbidity in chimeric antigen receptor (CAR)-T cellular immune therapy [Shimabukuro-Vornhagen 2018]. However, CRS occurred at a low frequency after administration of tabelecleucel with none of the subjects reporting any event in the clinical studies (ATA129-EBV-302 and EBV-CTL-201 [N = 103], 11-130 and 95-024 [N = 99])[1]. Two patients reported grade 1 events; 1 event was considered possibly related by the treating physician in the EAPs (ATA129-EBV-901 and ATA129-SPU; N = 138). These reported cases of CRS had confounding factors suggesting that tabelecleucel is not associated with CRS. Cytokine release syndrome is considered an important potential risk due to its potential for severe outcomes if left untreated.

Important Potential Risk: Immune effector cell-associated neurotoxicity syndrome (ICANS)

Risk-benefit impact: 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 development programme (clinical studies: ATA129-EBV-302 and EBV-CTL-201 [N = 103] and 11-130 and 95-024 [N = 99], and EAPs: ATA129-EBV-901 and ATA129-SPU [N = 138]), 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 Studies ATA129-EBV-302 and EBV-CTL-201. Immune effector cell-associated neurotoxicity syndrome is considered an important potential risk due to its potential for severe outcomes.

Important Potential Risk: Infusion-related reactions (IRR)

Risk-benefit impact: Based on its biological nature and mode of administration, tabelecleucel has a theoretical risk of causing infusion-related reactions (IRRs). None of the subjects reported IRR in Studies ATA129-EBV-302 and EBV-CTL-201[1]. Four subjects reported TESAEs of IRR in the other clinical studies and EAPs (N = 99 and N = 138, respectively). Two of the events were considered at least possibly related by the investigator (in clinical studies) or treating physician (in EAPs) and all were grade ≤ 2 with most cases presenting with low grade fever and confounded by other risk factors. As IRR can be life-threatening or cause chronic comorbidities it is considered an important potential risk.

Important Potential Risk: Immunogenicity

Risk-benefit impact: Anti-HLA antibodies can reduce the efficacy of tabelecleucel and can cause safety events such as SOT rejection and hypersensitivity that may require medical intervention. There were no cases of lack of efficacy reported in the clinical development programme[1] as described in the decrease in cell viability due to inappropriate handling of the product below and a limited number of SOT rejection as well as hypersensitivity events. No AEs of immunogenicity were specific to development of anti-HLA antibodies, and therefore, no definitive conclusions regarding the association of HLA antibody positivity with immunogenicity adverse events can be drawn. Immunogenicity is considered an important potential risk due to their potential for severe outcomes.

Important Potential Risk: Transmission of infectious agents (including cytomegalovirus [CMV])

Risk-benefit impact: Tabelecleucel is obtained from human donor blood cells. Donors are screened and must test negative for relevant communicable disease agents and diseases, including hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). Although tabelecleucel lots are tested for sterility, mycoplasma, and adventitious agents, a risk of transmission of infectious agents exists. No cases of transmission of infectious agents have been reported after tabelecleucel administration in the clinical development programme[1].

Some tabelecleucel lots are manufactured from donors who are cytomegalovirus (CMV) positive. All lots are tested to ensure no detection of adventitious agents, including CMV. During clinical development, tabelecleucel lots derived from CMV-positive donors were administered to CMV-negative patients when an appropriate lot derived from a CMV-seronegative donor was unavailable; in this subpopulation no seroconversions were observed. Due to the theoretical potential of transmission of infectious agents, transmission of infectious agents (including CMV) is considered an important potential risk.

Important Potential Risk: Decrease in cell viability due to inappropriate handling of the product

Risk-benefit impact: No medication error or lack of efficacy that may have resulted from a decrease in cell viability due to inappropriate handling of tabelecleucel have been reported in the clinical development programme[1]. Because of the seriousness of the treated pathology, decrease in cell viability due to inappropriate handling of the product is considered an important potential risk.

Missing Information: Use in paediatric population

Risk-benefit impact: A total of 340 subjects have been treated with tabelecleucel, 254 (74.7%) were ≥ 18 years of age and 86 (25.3%) were < 18 years of age, as of the data lock point. Among the paediatric group, 3 (0.9%) were < 2, 20 (5.9%) were ≥ 2 to < 6, 31 (9.1%) were ≥ 6 to < 12, and 32 (9.4%) were ≥ 12 to < 18 years of age. Based on the rare disease indication further safety data collection in the postmarketing setting is required.

Missing Information: Use in elderly population

Risk-benefit impact: A total of 340 subjects have been treated with tabelecleucel, 288 (84.7%) were < 65 years of age and 52 (15.3%) were ≥ 65 years of age, as of the data lock point. Among the elderly group, 41 (12.1%) were ≥ 65 to < 75, 11 (3.2%) were ≥ 75 to < 85, and 0 were ≥ 85 years of age. Based on the rare disease indication, further safety data collection in the postmarketing setting is required.

Missing Information: Use in pregnancy and lactation

Risk-benefit impact: No information is available with tabelecleucel use in pregnant women as pregnant and breastfeeding women were excluded from the clinical development programme. No animal reproductive and developmental toxicity studies have been conducted with tabelecleucel. It is not known if tabelecleucel has the potential to be transferred to the foetus or can cause foetal harm when administered to a pregnant woman. It is unknown whether tabelecleucel is excreted in human milk or transferred to the breastfeeding child. Based on the rare disease indication further safety data collection in the postmarketing setting is required.

Missing Information: Long-term safety information

Risk-benefit impact: In Study ATA129-EBV-302, systematic safety data collection occurred through 2 years after first dose for events considered by the investigator to be at least possibly related. All subjects have a minimum of systematic safety data collection for 18 months and up to 23 months after last dose. Additional long-term safety data collection is required in the postmarketing setting to confirm the long-term safety profile in an ultra-rare indication.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Tumour Flare Reaction (TFR)

Potential Mechanisms: Immunologic treatments may induce the infiltration of immune cells and inflammation of the tumour, which results in increased tumour size by objective measures. Alternately, the growth of pre-existing lesions or the appearance of new lesions can occur after administration of

immunotherapy, as the process of immune activation may potentially be delayed. The tumour may grow transiently during the period of immune activation and before an effective antitumour response occurs.

In the past decade, TFR was considered as a new side effect associated with immunomodulatory agents and as a condition of chronic lymphocytic leukaemia. Tumour flare reaction is also observed in solid tumours treated with immune checkpoint inhibitors. Several cases of flare reaction with hormonotherapy and haematologic malignancies and manifestations of TFR possibly mimicking disease progression have been reported. Tumour flare reaction is also observed in solid tumours treated with immune checkpoint inhibitors, though TFR is less common in solid tumours [Taleb 2019].

Evidence Source(s) and Strength of Evidence: Tumour flare reaction was identified in the tabelecleucel clinical development programme as ADR based on a plausible MOA and aggregate review of all TFR events, which include a case with positive rechallenge. Therefore, and due to the potential to be life-threatening TFR is considered an important identified risk.

Characterisation of the Risk: The clinical database was searched for Medical Dictionary for Regulatory Activities (MedDRA) PT: tumour flare (refer to Table 19 for a list of PTs). Treatment-emergent adverse events or TESAEs were defined as any AE or SAE that started on or after the first dose of tabelecleucel through 30 days, inclusive, after the last dose of tabelecleucel. The severity of each AE was determined using a severity grading system, which could have been either the common terminology criteria for adverse events (CTCAE) or categorical descriptions (mild, moderate, severe, life-threatening, or death) and summarised by worst grade (Table 20).

In Studies ATA129-EBV-302 and EBV-CTL-201, 1 of 103 subjects (1.0%)[1] reported TFR: 0 with EBV$^+$ PTLD and 1 with non-PTLD. The event was serious, grade 3, and considered related by the investigator. The outcome of TFR in this subject was reported as recovered by the time of the data lock point.

In the other 2 clinical studies (11-130 and 95-024; N = 99), no TESAE of TFR was reported.

In the 2 EAPs (ATA129-EAP-901 and ATA129-SPU; N = 138), 3 patients reported TESAEs of TFR. Of the 3 events, 1 was grade 4, 1 was grade 3, and 1 was grade 2, and all were considered possibly related by the treating physician. Of the 3 patients with TFR, 2 were not recovered and 1 was recovered by the time of the data lock point.

All 4 cases occurred shortly after first dose. One grade 3 TFR case described in a subject with PPD had a positive rechallenge following the second dose. The highest severity was the grade 4 TFR case with right PPD occurred in the context of PPD , events of grade 4 respiratory failure, grade 5 septic shock, as well as a positive test for clostridium difficile toxin A/B, both events (respiratory failure and septic shock) were assessed as unrelated by the treating physician to tabelecleucel.

Risk Factors and Risk Groups: The patients at risk of severe TFR are those with high tumour burden prior to treatment [Chanan-Khan 2011; Taleb 2019]. Depending on the anatomic location of the tumour or lymphadenopathy, complications may arise from mass effect including compression and/or obstruction of adjacent anatomic structures.

Preventability: Monitoring for signs and symptoms and potential pretreatment for high-risk patients are included in the product information as routine risk minimisation measures. Appropriate monitoring, early detection, anti-inflammatory therapy, and supportive treatments as needed per institutional standards may modulate the severity [Taleb 2019].

Impact on the Risk-benefit Balance of the Product: Tumour flare reaction occurred at a low subject incidence rate of 1.0% in Studies ATA129-EBV-302 and EBV-CTL-201.

Depending on the anatomic tumour location, there is a potential for severe complications. Tabelecleucel is a medicinal product subject to restricted medical prescription and is administered in a clinical setting under strict supervision of experienced healthcare professionals. PTLD patients are managed under the care of trained physicians who have experience in treating these complicated diseases and in evaluating the risks associated with TFR. Tumour flare reaction is a manageable event, treated by supportive care as appropriate. Even though rare severe cases of TFR are described in the literature with other agents, symptoms described with other agents were usually mild and responded to anti-inflammatory therapy [Taleb 2019].

Therefore, routine risk minimisation measures described in the product information are considered sufficient to manage this risk. It is expected that further data collection in the postmarketing setting via routine pharmacovigilance activities will confirm that this risk is sufficiently managed through routine risk minimisation measures.

Tabelecleucel provides meaningful benefit to an advanced oncology population with limited treatment options and a rapidly compromised prognosis in the absence of treatment. Based on available data, the risk-benefit balance for tabelecleucel is considered and expected to remain favourable.

Public Health Impact: The public health impact is expected to be low.

Important Identified Risk: Graft-versus-host disease (GvHD)

Potential Mechanisms: Tabelecleucel is an allogeneic EBV-specific T-cell immunotherapy which targets and eliminates EBV expressing cells in an HLA-restricted manner. Tabelecleucel is partially HLA matched and has a theoretical risk of alloreactivity. The potential risk of tabelecleucel-mediated cytotoxic damage that could theoretically occur in host tissues may be due to non-EBV alloreactivity and antigenic mimicry, may occur in any treated subject (with or without transplant history), and may be clinically indistinguishable from donor-mediated GvHD. Since tabelecleucel has a restricted T-cell repertoire [Benoun 2021], and therefore, the ability to target host extra-tumoural tissues is reduced, the risk of GvHD is mitigated.

Evidence Source(s) and Strength of Evidence: Graft-versus-host disease was identified in the tabelecleucel clinical development programme as an ADR based on a plausible MOA. A causal relationship between tabelecleucel and GvHD cannot be excluded. Each tabelecleucel lot within the product inventory is tested for specificity of lysis of EBV^+ targets, T-cell HLA restriction of specific lysis, and verification of low alloreactivity. The tabelecleucel lot is selected for each patient from the existing product inventory based on an appropriate HLA restriction.

As GvHD can be life-threatening or cause chronic comorbidities, it is considered an important identified risk.

Characterisation of the Risk: The clinical database was searched as follows: MedDRA PTs were searched for the terms “graft” and “host” and “versus”; in addition, the investigator in the clinical studies or treating physician in the EAPs classified the event as GvHD, which was considered an adverse event of special interest (refer to Table 19 for a list of PTs). Treatment-emergent adverse events or TESAEs were defined as any AE or SAE that started on or after the first dose of tabelecleucel through 30 days, inclusive, after the last dose of tabelecleucel. The severity of each AE was determined using a severity grading system, which could have been either the CTCAE or categorical descriptions (mild, moderate, severe, life-threatening, or death) and summarised by worst grade (Table 20).

In Studies ATA129-EBV-302 and EBV-CTL-201, 5 of 103 subjects (4.9%)[1] reported GvHD: 4 with EBV^+ PTLD and 1 with non-PTLD. Of the 5 subjects, 2 reported 3 serious events (1 with 2 grade 4 events considered possibly related by the investigator, and the other with a grade 2 event considered unrelated by the investigator) and 3 reported nonserious events (1 with a grade 3 event [rash maculo-papular] considered possibly related and 2 with grade 1 events considered unrelated by the investigator). Of the

5 subjects with GvHD, 1 was not recovered (with the 2 serious grade 4 events) and 4 were recovered by the time of the data lock point.

In the other 2 clinical studies (11-130 and 95-024; N = 99), 3 subjects with EBV^+ PTLD reported 3 events of GvHD. Two events were serious, 1 grade 4 considered unlikely related by the investigator and 1 grade 3 considered unrelated by the investigator, and 1 was nonserious (grade 3 and considered unlikely related by the investigator). Of the 3 subjects with GvHD, all were recovered by the time of the data lock point.

In the EAPs (ATA129-EAP-901 and ATA129-SPU; N = 138), 6 patients reported GvHD, 4 with 5 serious events (1 grade 5 considered unrelated, 2 grade 4 considered unlikely related by the treating physician, 1 grade 3 considered unrelated by the treating physician, and 1 grade 1 considered related by the treating physician) and 2 with nonserious events (1 grade 2 and 1 grade 1, both considered unrelated). Of the 6 patients with GvHD, 1 was fatal, 3 were not recovered, and 2 were recovered by the time of the data lock point.

Risk Factors and Risk Groups: No risk factors have been identified leading to increased risk of developing GvHD after tabelecleucel administration.

Preventability: The discontinuation of immunosuppressive therapies for the treatment of PTLD may trigger the occurrence of GvHD. Monitoring for signs and symptoms are included in the product information as routine risk minimisation measures and early treatment is indicated as clinically appropriate per institutional standards.

Impact on the Risk-benefit Balance of the Product: Graft-versus-host disease occurred at a subject incidence rate of 4.9% in Studies ATA129-EBV-302 and EBV-CTL-201. The incidence rate of GvHD in the tabelecleucel clinical development programme was lower than the background incidence rate of acute GvHD which is estimated to be approximately 30-50% of patients after allogeneic HCT [Malard 2020]. All GvHD cases were confounded by transplant history, medical history of previous episodes of GvHD, or reduction in immunosuppressive treatment prior to the events due to standard of care. A few cases were not histologically confirmed, including 2 out of the 3 cases assessed as treatment-related by the sites, and the diagnosis of GvHD was hypothetical.

Tabelecleucel is a medicinal product subject to restricted medical prescription and is administered in a clinical setting under strict supervision of experienced healthcare professionals. As part of their posttransplant clinical management and high risk for GvHD post-HCT, PTLD patients are closely monitored by experienced healthcare professionals and early detection and treatment of GvHD per institutional standards would be expected.

Therefore, routine risk minimisation measures described in the product information are considered sufficient to manage this risk. It is expected that further data collection in the postmarketing setting via routine pharmacovigilance activities will confirm that this risk is sufficiently managed through routine risk minimisation measures.

Tabelecleucel provides meaningful benefit to an advanced oncology population with limited treatment options and rapidly compromised prognosis in the absence of treatment.

Based on available data, the risk-benefit balance for tabelecleucel is considered and expected to remain favourable.

Public Health Impact: The public health impact is expected to be low.

Important Potential Risk: Solid organ transplant (SOT) rejection

Potential Mechanisms: Tabelecleucel is an allogeneic EBV-specific T-cell immunotherapy which targets and eliminates EBV expressing cells in an HLA-restricted manner. Tabelecleucel is partially HLA matched and has a theoretical risk of SOT rejection based on humoral or cell-mediated immune reactions. The potential risk of tabelecleucel-mediated graft rejection may be due to non-EBV alloreactivity and antigenic mimicry and may be clinically indistinguishable from other mechanisms of SOT-mediated rejection.

For patients with SOT, administration of tabelecleucel sharing HLA alleles with the transplanted organ but not shared with the patient`s immune system poses the risk of generation of cross-reactive anti-HLA antibodies that could mediate SOT rejection. This risk is considered a potential risk. There were no reports of anti-HLA antibody-mediated rejection among the reported cases of SOT rejection in the tabelecleucel clinical development programme (including the 4 clinical studies and 2 EAPs).

Evidence Source(s) and Strength of Evidence: The evidence of SOT rejection after administration of tabelecleucel in patients with previous allogeneic donor-derived SOT is limited, as the small number of reported cases of SOT rejection after administration of tabelecleucel had other risk factors including decrease of immunosuppressants as standard of care or a medical history of previous episodes of SOT rejection. As SOT rejection can be life-threatening or cause chronic comorbidities, it is considered an important potential risk.

Characterisation of the Risk: The clinical database was searched as follows: MedDRA HLTs were searched for the term “transplant rejection” or MedDRA PTs were searched for the terms “engraft” within the SOT cohort (refer to Table 19 for a list of PTs). Treatment-emergent adverse events or TESAEs were defined as any AE or SAE that started on or after the first dose of tabelecleucel through 30 days, inclusive, after the last dose of tabelecleucel. The severity of each AE was determined using a severity grading system, which could have been either the CTCAE or categorical descriptions (mild, moderate, severe, life-threatening, or death) and summarised by worst grade (Table 20).

In Studies ATA129-EBV-302 and EBV-CTL-201, 1 of 40 (2.5%)[1] subjects with EBV$^+$ PTLD following SOT reported SOT rejection (the event was nonserious, grade 1, and considered unrelated by the investigator). This subject had a medical history of PPD and PPD rejection prior to the first dose of tabelecleucel. The subject recovered by the time of the data lock point.

In the other clinical studies (11-130 and 95-024; N = 11), none of the subjects with EBV$^+$ PTLD following SOT reported a TESAE of SOT rejection.

In the EAPs (ATA129-EAP-901 and ATA129-SPU; N = 43), 3 of the patients with EBV$^+$ PTLD following SOT reported TESAEs of SOT rejection. Two of the events were grade 2 and considered unrelated by the treating physician and 1 was grade 1 and considered possibly related by the treating physician. The patient had another episode of transplant rejection a few months after the end of tabelecleucel treatment that was reported as unrelated to the product; both episodes were similar in presentation, and both were histologically confirmed as cellular rejection. Of the 3 patients with SOT rejection, 1 was not recovered and 2 were recovered by the time of the data lock point. [Van Herck 2017]

Risk Factors and Risk Groups: No risk factors have been identified leading to increased risk of developing SOT rejection after tabelecleucel administration.

Preventability: The discontinuation of immunosuppressive therapies for the treatment of PTLD may trigger the occurrence of SOT rejection. Monitoring for signs and symptoms are included in the product information as risk routine minimisation measures and early treatment is indicated as clinically appropriate per institutional standards.

Impact on the Risk-benefit Balance of the Product: Overall, the incidence rate in the clinical development programme was lower than the allogeneic donor-derived SOT-mediated rejection rate reported in literature:

- Heart Transplant: Overall, the incidence of SOT rejection events in Studies ATA129-EBV-302 and EBV-CTL-201 (1 of 8 subjects with heart transplants) was not higher than the rates of corresponding SOT rejections reported in literature. According to the registry of the International Society of Heart and Lung Transplantation, approximately 20% to 40% of heart transplant recipients will experience at least 1 episode of acute cellular rejection in the first postoperative year [Stehlik 2012].
- Lung and Liver Transplant: Similarly, patients with lung and liver transplant have a high risk of transplant rejection. The registry data from the International Society for Heart and Lung Transplantation show that about a third of patients will have at least one episode of treated rejection in the first year after transplantation [Yusen 2016]. Survival following lung transplantation remains worse compared with other SOT types, with a median survival of 6 years [Parulekar 2019]. Survival is limited by the development of chronic rejection that occurred in 45% of patients within 5 years posttransplant [Van Herck 2017]. Acute allograft rejection remains a common complication of liver transplantation, with an incidence ranging from 20% to 40% [Dogan 2018].

The strength of evidence for SOT rejection after tabelecleucel administration seems limited, however, further data will be collected in the postmarketing setting.

Tabelecleucel is a medicinal product subject to restricted medical prescription and is administered in a clinical setting under strict supervision of experienced healthcare professionals. As part of their posttransplant clinical management of PTLD, patients are closely monitored by experienced healthcare professionals and early detection and treatment of SOT rejection per institutional standards would be expected. Therefore, routine risk minimisation measures described in the product information are considered sufficient to manage this risk. It is expected that further data collection in the postmarketing setting via routine pharmacovigilance activities will confirm that this risk is sufficiently managed through routine risk minimisation measures.

Tabelecleucel provides meaningful benefit to an advanced oncology population with limited treatment options and rapidly compromised prognosis in the absence of treatment. Based on available data, the risk-benefit balance for tabelecleucel is considered and expected to remain favourable.

Public Health Impact: The public health impact is expected to be low.

Important Potential Risk: Bone marrow transplant (BMT) rejection

Potential Mechanisms: Tabelecleucel is an allogeneic EBV-specific T-cell immunotherapy which targets and eliminates EBV expressing cells in an HLA-restricted manner. Tabelecleucel is partially HLA matched and has a theoretical risk of BMT rejection based on humoral or cell-mediated immune reactions. The potential risk of tabelecleucel-mediated graft rejection may be due to non-EBV alloreactivity and antigenic mimicry, which may be clinically indistinguishable from other mechanisms of BMT rejection [Hows 1991].

Evidence Source(s) and Strength of Evidence: There is no evidence of BMT rejection after administration of tabelecleucel in patients with previous allogeneic donor-derived HCT, as no cases have been reported in the clinical development programme. In addition, a severely diminished host immune system after HCT would limit the potential for immune reactions [Kroger 2006; van der Maas 2019]. As BMT rejection can be life-threatening or cause chronic comorbidities, it is considered an important potential risk.

Characterisation of the Risk: The clinical database was searched as follows: MedDRA HLTs were searched for the term "transplant rejection" or MedDRA PTs were searched for the terms "engraft" within the HCT cohort (refer to Table 19 for a list of PTs). Treatment-emergent adverse events or TESAEs were defined as any AE or SAE that started on or after the first dose of tabelecleucel through 30 days, inclusive, after the last dose of tabelecleucel. The severity of each AE was determined using a severity grading system, which could have been either the CTCAE or categorical descriptions (mild, moderate, severe, life-threatening, or death) and summarised by worst grade (Table 20).

In Studies ATA129-EBV-302 and EBV-CTL-201, none of 28[1] subjects with EBV^+ PTLD following HCT reported BMT rejection.

In the other clinical studies (11-130 and 95-024; N = 31) and EAPs (ATA129-EAP-901 and ATA129-SPU; N = 30), none of the subjects with EBV^+ PTLD following HCT reported BMT rejection.

Risk Factors and Risk Groups: No risk factors have been identified leading to increased risk of developing HCT graft after tabelecleucel administration.

Preventability: Appropriate monitoring of BMT rejection signs and symptoms and early treatment is indicated as clinically appropriate per institutional standards.

Impact on the Risk-benefit Balance of the Product: No cases of BMT rejection were reported in Studies ATA129-EBV-302 and EBV-CTL-201 and strength of evidence seems extremely limited; however, further data will be collected in the postmarketing setting.

Tabelecleucel is a medicinal product subject to restricted medical prescription and is administered in a clinical setting under strict supervision of experienced healthcare professionals. As part of their posttransplant clinical management of PTLD, patients are closely monitored by experienced healthcare professionals and early detection and treatment of BMT rejection per institutional standards would be expected. Therefore, routine risk minimisation measures described in the product information are considered sufficient to manage this risk. It is expected that further data collection in the postmarketing setting via routine pharmacovigilance activities will confirm that this risk is sufficiently managed through routine risk minimisation measures.

Tabelecleucel provides meaningful benefit to an advanced oncology population with limited treatment options and rapidly compromised prognosis in the absence of treatment. Based on available data, the risk-benefit balance for tabelecleucel is considered and expected to remain favourable.

Public Health Impact: The public health impact is expected to be low.

Important Potential Risk: Cytokine release syndrome (CRS)

Potential Mechanisms: Infusion of T-cell therapy may activate bystander immune cells and non-immune cells resulting in supraphysiologic release of cytokines leading to a systemic inflammatory response. Cytokine release syndrome has been seen in antibody therapies and non-protein-based cancer therapies but has shown particularly high incidence rate and pronounced morbidity in CAR-T cellular immune therapy [Shimabukuro-Vornhagen 2018].

Cytokine release syndrome is a well-established risk for CAR-T therapies, which generally manifests within 7-14 days of drug administration, and has a clear association with their MOA [Lee 2019; Maude

2018; Neelapu 2017; Schuster 2019]. Lymphodepletion typically precedes CAR-T administration to allow for expansion of the CAR-T cells, the resulting peak in CAR-T expansion is associated with the cytokine burst [Hay 2017]. Following administration of tabelecleucel no cytokine bursts have been associated with EBV-CTLp expansion (2.7.2 Summary of Clinical Pharmacology Section 2.2 and 5.3.4.2 ATA129-EBV-302 Biomarker Report Section 4.2.2). Tabelecleucel is an activated T-cell which once administered is expected to target and specifically kill EBV+ target cells [Benoun 2021]. Once target cells are gone tabelecleucel is expected to be exhausted and not persist long-term [Prockop 2020]. Therefore, based upon the activated phenotype of tabelecleucel and no observations of cytokine increases associated with EBV-CTLp peak expansion, the risk of CRS following tab-cel administration is low.

Tabelecleucel is an ex vivo expanded T-cell product that is not genetically modified and has an equivalent MOA to endogenous circulating CTLs.

Evidence Source(s) and Strength of Evidence: There was no case of CRS reported in any of the 4 clinical studies. Two patients with confounding factors (ie, PPD) reported grade 1 CRS case each in the EAPs. This low incidence rate and severity of CRS with tabelecleucel suggests that tabelecleucel is not associated with CRS, since in contrast the rates observed with CAR-T-cell therapies is higher: a systematic review and meta-analysis across 9 clinical studies of CAR-T therapies in B-cell malignancies reported pooled CRS rates of 59.3% (95% CI 30.5%, 88.1%) [Chattaraj 2022] and among 4 CAR-T therapies, grade ≥ 3 events were reported at rates of 4-77% [Sengsayadeth 2022]. Cytokine release syndrome is considered an important potential risk due to its potential for severe outcomes if left untreated.

To study the potential risk of CRS in association with tabelecleucel, cytokines commonly associated with CRS were analysed in 45 subjects with EBV$^+$ PTLD and other EBV$^+$ diseases enrolled in clinical studies (ATA129-EBV-302 and EBV-CTL-201) who had evaluable data (2.7.2 Summary of Clinical Pharmacology Section 2.2). Samples from these subjects were collected and a panel of 4 analytes (ie, interleukin [IL]-1β, IL-2, IL-6, and tumour necrosis factor-α) encompassing inflammatory, immune-modulating, and immune effector-related molecules were measured at various time points prior to and after infusion of tabelecleucel. The evaluation of plasma cytokine levels revealed very little modulation from baseline in these studies, supporting no causal relationship of tabelecleucel with CRS.

Characterisation of the Risk: The clinical database was searched as follows: MedDRA PTs were searched for the term “cytokine”; in addition, the investigator in the clinical studies or treating physician in the EAPs classified the event as CRS, which was considered an adverse event of special interest (refer to Table 19 for a list of PTs). Treatment-emergent adverse events or TESAEs were defined as any AE or SAE that started on or after the first dose of tabelecleucel through 30 days, inclusive, after the last dose of tabelecleucel. The severity of each AE was determined using a severity grading system, which could have been either the CTCAE or categorical descriptions (mild, moderate, severe, life-threatening, or death) and summarised by worst grade (Table 20).

In Studies ATA129-EBV-302 and EBV-CTL-201[1], none of 103 subjects reported CRS.

In the other 2 clinical studies (11-130 and 95-024; N = 99), no TESAE of CRS was reported.

In the EAPs (ATA129-EAP-901 and ATA129-SPU; N = 138), 2 patients reported CRS; both events were grade 1 with 1 serious and considered possibly related by the treating physician and the other nonserious and considered unrelated by the treating physician. Of the 2 patients with CRS, 1 was not recovered and 1 was recovered by the time of the data lock point. The nonserious grade 1 CRS event occurred after first dose of tabelecleucel in context of PPD . The patient developed a concomitant event of encephalopathy that was fatal. For this case, the CRS and encephalopathy events were not considered treatment-related. The encephalopathy was due to progression of the PPD . The second serious grade 1 event of CRS reported as possibly related by the investigator occurred after 16 doses of tabelecleucel in the context of PPD

PPD and rechallenge was negative after patient received 11 additional doses. In both cases, PPD were strong confounding factors, and the time of occurrence was atypical for CRS in the related case.

Risk Factors and Risk Groups: No risk factors have been identified leading to increased risk of developing CRS after tabelecleucel administration.

Preventability: Monitoring for signs and symptoms are included in the product information as routine risk minimisation measures and early treatment is indicated as clinically appropriate per institutional standards.

Impact on the Risk-benefit Balance of the Product: There was no case of CRS reported in the clinical studies, CRS was reported at a low frequency rate with 2 cases in the EAPs, and the strength of evidence for CRS after tabelecleucel administration seems very limited, however, further data will be collected in the postmarketing setting.

Tabelecleucel is a medicinal product subject to restricted medical prescription and is administered in a clinical setting under strict supervision of experienced healthcare professionals. As part of their posttransplant clinical management of PTLD, patients are closely monitored by experienced healthcare professionals and early detection and treatment of CRS per institutional standards would be expected. Therefore, routine risk minimisation measures described in the product information are considered sufficient to manage this risk. It is expected that further data collection in the postmarketing setting via routine pharmacovigilance activities will confirm that this risk is sufficiently managed through routine risk minimisation measures.

Tabelecleucel provides meaningful benefit to an advanced oncology population with limited treatment options and rapidly compromised prognosis in the absence of treatment. Based on available data, the risk-benefit balance for tabelecleucel is considered and expected to remain favourable.

Public Health Impact: The public health impact is expected to be low.

Important Potential Risk: Immune effector cell-associated neurotoxicity syndrome (ICANS)

Potential Mechanisms: Immune effector cell-associated neurotoxicity syndrome is a common toxicity that can occur following CAR-T cell therapy and anti-CD19 immunotherapies [Lee 2019]. The proposed MOA for developing ICANS suggests roles for endothelial activation and disruption of the blood-brain barrier [Gust 2017]. One mechanism that may increase the risk of ICANS development following anti-CD19 targeting immunotherapies is due to the presence of CD19 on mural brain cells which support the vasculature of the brain and play a role in maintaining blood-brain barrier integrity [Parker 2020]. These $CD19^{+}$ brain cells represent an on-target off-tumour effect for anti-CD19 immunotherapies and likely play a role in the development of ICANS in patients treated with these therapies.

As tabelecleucel is an EBV-specific T-cell therapy, this MOA in decreasing the integrity of the blood-brain barrier is unlikely; furthermore, these cells are not expected to present antigens recognised by tabelecleucel.

While it remains a theoretical possibility that in patients with systemic inflammation who may already have impaired blood-brain barrier integrity, activated T cells may cross the blood-brain barrier; however, no evidence of neurotoxicity has been observed in patients treated with virus-specific, expanded T cells [Simmons 2019]. Due to this theoretical possibility, but no reported event of ICANS in the clinical development programme, as of the data lock point, and with the low incidence and severity of related events from broader search criteria, the risk of ICANS following tabelecleucel administration is considered low.

Evidence Source(s) and Strength of Evidence: As of the data lock point, there have been no reports of the PT: ICANS in the clinical development programme. Applying a broader search criterion, only 1

grade ≥ 3 event of grade 3 confusional state considered related by the investigator was reported in Studies ATA129-EBV-302 and EBV-CTL-201. The majority of events within the broader search criteria were assessed as not related and occurred in the context of confounding factors. This low incidence rate and severity of possible ICANS associated neurological toxicities with tabelecleucel suggests that tabelecleucel is not associated with ICANS, since in contrast the rates observed with CAR-T-cell therapies is higher: a systematic review and meta-analysis across 9 clinical studies of CAR-T therapies in B-cell malignancies reported pooled ICANS rates of 15.4% (95% CI 4.6%, 26.3%) [Chattaraj 2022] and among 4 CAR-T therapies, grade ≥ 3 events were reported at rates of 12-40% [Sengsayadeth 2022]. ICANS is considered an important potential risk due to its potential for severe outcomes if left untreated.

Characterisation of the Risk: The clinical database was searched for the standardised MedDRA query (SMQ): noninfectious encephalopathy_delirium (narrow or broad). Treatment-emergent adverse events or TESAEs were defined as any AE or SAE that started on or after the first dose of tabelecleucel through 30 days, inclusive, after the last dose of tabelecleucel. The severity of each AE was determined using a severity grading system, which could have been either the CTCAE or categorical descriptions (mild, moderate, severe, life-threatening, or death) and summarised by worst grade (Table 20).

There have been no reports of the PT: ICANS in the clinical development programme (4 clinical studies: ATA129-EBV-302, EBV-CTL-201, 11-130, 95-024, and 2 EAPs: ATA129-EBV-901 and ATA129-SPU), as of the data lock point. The search strategy was broadened to capture potentially associated neurological events. Adverse drug reactions observed with this broader search strategy included muscular weakness, depressed level of consciousness, somnolence, confusional state, delirium, and disorientation.

In Studies ATA129-EBV-302 and EBV-CTL-201, 26 of 103 subjects (25.2%)[1] experienced these TEAEs from the noninfectious encephalopathy_delirium SMQ (16 with EBV^+ PTLD and 10 with non-PTLD) with 3 subjects (2.9%) experiencing treatment-related TEAEs. The treatment-related events included: 1 grade 3 confusional state with an outcome of not recovered and grade 2 delirium, and depressed level of consciousness, disorientation, muscular weakness, and somnolence reported in 1 subject each with 3 outcomes of not recovered and 2 recovered. Of the 26 subjects experiencing these neurological TEAEs, 9 had grade ≥ 3 events: 1 had grade 4 depressed level of consciousness, and 8 had grade 3 events: encephalopathy (3 subjects), muscular weakness (3 subjects), delirium (2 subjects), seizure (1 subject), somnolence (2 subjects), confusional state (1 subject), dysphagia (1 subject), agitation (1 subject), hypersomnia (1 subject). Of the 26 subjects experiencing these neurological TEAEs, outcomes were not recovered for 13, recovering for 2, and recovered for 16 by the time of the data lock point. The neurological events occurring in 23 of 26 subjects were assessed as not related by the investigator and occurred in the context of an advanced oncology population with multiple comorbidities and/or disease progression.

In the 4 clinical studies (ATA129-EBV-302, EBV-CTL-201, 11-130, and 95-024; N = 202), 16 subjects experienced these TESAEs from the noninfectious encephalopathy_delirium SMQ (7 with EBV^+ PTLD and 9 with non-PTLD) with 2 subjects experiencing treatment-related events: a grade 3 mental status changes and a grade 2 depressed level of consciousness (described above). Of the 16 subjects experiencing these neurological TESAEs, 12 had grade ≥ 3 events: 4 had grade 4 events: 3 with depressed level of consciousness (1 described above), and 1 with encephalopathy; and 8 had grade 3 events: 2 with confusional state, 2 with mental state changes, 1 with seizure (described above), 1 with delirium (described above), 1 with muscular weakness, and 1 with dysphagia. Of the 16 subjects reporting these neurological TESAEs, the outcomes were not recovered for 6, recovering for 1, recovered for 2, and 2 had an unknown or missing outcome by the time of the data lock point. The neurological events occurring in 14 of 16 subjects were assessed as not related by the investigator and occurred in the context of an advanced oncology population with multiple comorbidities and/or disease progression.

In the EAPs (ATA129-EAP-901 and ATA129-SPU; N = 138), 7 patients experienced these TESAEs from the noninfectious encephalopathy_delirium SMQ (4 with EBV+ PTLD and 3 with non-PTLD) and no patient had a treatment-related event (one patient had a TESAE of grade 4 seizure that was initially reported as possibly related but was updated to unrelated to tabelecleucel by the treating physician on 23 November 2021, a few days after the data lock point). . Of the 7 patients experiencing these TESAEs, 6 had grade ≥ 3 events: 2 had grade 5 encephalopathy; and 1 had grade 4 seizure; and 3 had grade 3 events: encephalopathy (2 patients) and confusional state (1 patient). Of the 7 patients experiencing these TESAEs, the outcomes were fatal for 2, recovering for 1, and recovered for 4 by the time of the data lock point. All events occurred in the context of an advanced oncology population with multiple comorbidities and/or disease progression.

Across the clinical development programme, the reported cases of encephalopathy were confounded with either disease progression PPD and/or other contributing factors such as PPD disease, concomitant medications, or infections as noted by the investigator or treating physician and were assessed as not related to tabelecleucel.

Risk Factors and Risk Groups: No risk factors have been identified leading to an increased risk of developing ICANS after tabelecleucel administration.

Preventability: Monitoring for signs and symptoms are included in the product information as routine risk minimisation measures and early treatment is indicated as clinically appropriate per institutional standards.

Impact on the Risk-benefit Balance of the Product: As of the data lock point, there have been no reports of the PT: ICANS in the clinical development programme. Applying a broader search criterion, only 1 grade 3 event of confusional state considered related by the investigator was reported in Studies ATA129-EBV-302 and EBV-CTL-201. Thus, the strength of evidence is extremely limited; however, further data will be collected in the postmarketing setting.

Tabelecleucel is a medicinal product subject to restricted medical prescription and is administered in a clinical setting under strict supervision of experienced healthcare professionals. As part of their posttransplant clinical management of PTLD, patients are closely monitored by experienced healthcare professionals and early detection and treatment of ICANS per institutional standards would be expected. Therefore, routine risk minimisation measures described in the product information are considered sufficient to manage this risk. It is expected that further data collection in the postmarketing setting via routine pharmacovigilance activities will confirm that this risk is sufficiently managed through routine risk minimisation measures.

Tabelecleucel provides meaningful benefit to an advanced oncology population with limited treatment options and rapidly compromised prognosis in the absence of treatment. Based on available data, the risk-benefit balance for tabelecleucel is considered and expected to remain favourable.

Public Health Impact: The public health impact is expected to be low.

Important Potential Risk: Infusion-related reaction (IRR)

Potential Mechanisms: Due to its biological nature and mode of administration, tabelecleucel has a theoretical risk of infusion-related reactions. Per published literature IRRs can occur with various biological agents due to possible allergic reactions to foreign protein administered intravenously [Cruz 2010; Rosello 2017].

Evidence Source(s) and Strength of Evidence: Evidence for relationship of IRR with tabelecleucel is limited. As IRR can be life-threatening or cause chronic comorbidities, it is considered an important potential risk.

Characterisation of the Risk: The clinical database was searched as follows: MedDRA PTs were searched for the terms "infusion" and "related", and the event(s) occurred within 24 hours after the infusion; in addition, the investigator in the clinical studies or treating physician in the EAPs classified the event as IRR, which was considered an adverse event of special interest (refer to Table 19 for a list of PTs). Treatment-emergent adverse events or TESAEs were defined as any AE or SAE that started on or after the first dose of tabelecleucel through 30 days, inclusive, after the last dose of tabelecleucel. The severity of each AE was determined using a severity grading system, which could have been either the CTCAE or categorical descriptions (mild, moderate, severe, life-threatening, or death) and summarised by worst grade (Table 20).

In Studies ATA129-EBV-302 and EBV-CTL-201[1], none of the 103 subjects reported IRR.

In the other 2 clinical studies (11-130 and 95-024; N = 99), 3 subjects reported TEASEs of IRR: 2 grade 2 events (PT: pyrexia) with 1 considered possibly related by the investigator and 1 considered unlikely related by the investigator, and 1 grade 1 event (PT: noncardiac chest pain) considered unlikely related by the investigator. Of the 3 subjects with IRR, 1 was recovering and 2 were recovered by the time of the data lock point.

In the EAPs (ATA129-EAP-901 and ATA129-SPU; N = 138), 1 patient reported a TESAE of IRR (pyrexia) that was grade 1 and considered possibly related by the treating physician. The patient recovered from the event by the time of the data lock point. These events were associated with concomitant disease or had negative rechallenge following tabelecleucel re-administration.

Risk Factors and Risk Groups: No risk factors have been identified leading to increased risk of developing IRR after tabelecleucel administration.

Preventability: Monitoring for signs and symptoms are included in the product information as routine risk minimisation measures and early treatment is indicated as clinically appropriate per institutional standards.

Impact on the Risk-benefit Balance of the Product:

No cases of IRR were reported in Studies ATA129-EBV-302 and EBV-CTL-201 and the other cases were confounded but there is a theoretical risk based on the biological nature and mode of administration of tabelecleucel for which further data will be collected in the postmarketing setting.

Tabelecleucel is a medicinal product subjected to restricted medical prescription and is administered in a clinical setting under strict supervision of experienced healthcare professionals.

As part of their posttransplant clinical management, PTLD patients are closely monitored by experienced healthcare professionals and early detection, and treatment of IRR per institutional standards would be expected.

Routine risk minimisation measures described in the product information are considered sufficient to manage this risk. It is expected that further data collection in the postmarketing setting via routine pharmacovigilance activities will confirm that this risk is sufficiently managed through routine risk minimisation measures.

Tabelecleucel provides meaningful benefit to an advanced oncology population with limited treatment options and a rapidly compromised prognosis in the absence of treatment.

Based on available data, the risk-benefit balance for tabelecleucel is considered and expected to remain favourable.

Public Health Impact: The public health impact is expected to be low.

Important Potential Risk: Immunogenicity

Potential Mechanisms: Therapeutic proteins are recognised by the human immune system. This recognition is often followed by an immune response to therapeutic proteins. This potentially harmful immune response is complex and, in addition to antibody formation, involves T-cell activation and innate immune responses. The consequences of an immune reaction to a therapeutic protein range from transient appearance of antibodies without any clinical significance to severe life-threatening conditions. Potential clinical consequences of an unwanted immune response include loss of efficacy of the therapeutic protein and serious acute immune effects such as anaphylaxis [EMA CHMP 2017].

Tabelecleucel is an allogeneic EBV-specific T-cell immunotherapy which targets and eliminates EBV expressing cells in an HLA-restricted manner. Tabelecleucel is partially HLA matched and has a theoretical risk of immunogenicity based on humoral or cell-mediated immune reactions.

Evidence Source(s) and Strength of Evidence: HLA antibodies can potentially reduce the efficacy of tabelecleucel and can cause clinical manifestations of immunogenicity such as anaphylaxis and SOT rejection that may require medical intervention. No immunogenicity adverse events were specific to development of anti-HLA antibodies therefore, no definitive conclusions regarding the association of HLA antibody positivity with immunogenicity adverse events can be drawn, and hence, immunogenicity is an important potential risk.

Characterisation of the Risk: Immunogenicity was characterised by evaluation of anti-HLA antibody antibodies and cases of SOT rejection. In addition, the clinical database was searched for SMQ: hypersensitivity (narrow) or SMQ: lack of efficacy (narrow). Treatment-emergent adverse events or TESAEs were defined as any AE or SAE that started on or after the first dose of tabelecleucel through 30 days, inclusive, after the last dose of tabelecleucel. The severity of each AE was determined using a severity grading system, which could have been either the CTCAE or categorical descriptions (mild, moderate, severe, life-threatening, or death) and summarised by worst grade (Table 20).

In Study ATA129-EBV-302, anti-HLA antibody data was examined to determine if tabelecleucel may invoke a humoral immune response toward one or more allogeneic HLA after infusion. Only 7 (5 with EBV^+ PTLD following SOT and 2 in with EBV^+ PTLD following HCT) of the 35 subjects with anti-HLA antibody data had negative tests before treatment and then were subsequently evaluated with at least one postinfusion test (5.3.5.4 ATA129-EBV-302 Biomarker Report Section 4.3.3.2). Of these 7 subjects, 1 developed anti-HLA antibodies after treatment. There was no indication of a clinical manifestation (hypersensitivity, SOT rejection, or lack of efficacy) due to anti-HLA antibodies from the adverse events reported for this single subject.

There were no cases of lack of efficacy reported in the clinical development programme as described in the decrease in cell viability due to inappropriate handling of the product below.

The following hypersensitivity data presentation is based on an SMQ search. No life-threatening potentially anaphylactic reactions were observed. In Studies ATA129-EBV-302 and EBV-CTL-201, 23 of 103 (22.3%)[1] subjects reported hypersensitivity with 3 reporting grade ≥ 3 events: rash erythematous (grade 4, serious, considered possibly related to tabelecleucel by the investigator, and the subject recovered), tongue oedema (grade 3, nonserious, considered unrelated, in context of contrast administration for imaging investigation, and the subject was not recovered by the data lock point), and rash maculo-papular (grade 3, nonserious, considered an acute GvHD event and possibly related, and the subject recovered). There was 1 other serious event of rash not otherwise specified, which occurred in the subject reporting the rash erythematous which was grade 2, considered possibly related by the investigator, and the subject recovered by the time of the data lock point. In the other 2 clinical studies (11-130 and 95-024; N = 99), 1 subject reported a hypersensitivity TESAE of grade 2 periorbital oedema that was considered unrelated to tabelecleucel by the investigator, and the subject recovered from 1 event and was not recovered from the other by the time of the data lock point.

In the EAPs (ATA129-EAP-901 and ATA129-SPU; N = 138), 3 patients reported hypersensitivity TESAEs; none were considered related to tabelecleucel treatment: 1 grade 3 rash maculo-papular, 1 grade 2 rash, and 1 grade 2 infusion-related reaction. Of these 3 patients, all were recovered by the time of the data lock point.

SOT rejection events were reported in 1 of 40 (2.5%)[1] subjects with EBV^+ PTLD following SOT in Studies ATA129-EBV-302 and EBV-CTL-201 as described in the SOT rejection above.

Risk Factors and Risk Groups: No risk factors have been identified leading to increased risk of developing immunogenicity after tabelecleucel administration, however, patient- and disease-related factors may influence the development of an immune response and it would be expected that in the immunocompromised PTLD population, an immune response might be less likely to occur.

Preventability: Appropriate monitoring of signs and symptoms of hypersensitivity are included in the product information as routine risk minimisation measures. Monitoring signs and symptoms of the clinical consequences of immunogenicity including events of lack of efficacy, or SOT rejection and early treatment is indicated as clinically appropriate as per institutional standards.

Impact on the Risk-benefit Balance of the Product: No events of potential clinical manifestation of immunogenicity including lack of efficacy or severe events of hypersensitivity or SOT rejection were reported with the use of tabelecleucel in the clinical development programme.

Tabelecleucel is a medicinal product subject to restricted medical prescription and is administered in a clinical setting under strict supervision of experienced healthcare professionals. As part of their posttransplant clinical management of PTLD, patients are closely monitored by experienced healthcare professionals and early detection and treatment of clinical manifestations of immunogenicity per institutional standards would be expected. Therefore, routine risk minimisation measures described in the product information are considered sufficient to manage this risk. It is expected that further data collection in the postmarketing setting via routine pharmacovigilance activities will confirm that this risk is sufficiently managed through routine risk minimisation measures.

Tabelecleucel provides meaningful benefit to an advanced oncology population with limited treatment options and rapidly compromised prognosis in the absence of treatment. Based on available data, the risk-benefit balance for tabelecleucel is considered and expected to remain favourable.

Public Health Impact: The public health impact is expected to be low.

Important Potential Risk: Transmission of infectious agents (including cytomegalovirus [CMV])

Potential Mechanisms: Tabelecleucel is obtained from human donor blood cells and is manufactured using human- and animal-derived materials.

Evidence Source(s) and Strength of Evidence: The risk associated with tabelecleucel is considered very low. Strict precautions to prevent transmission of infectious agents and to ensure microbial safety of tabelecleucel are in place in compliance with principles of good manufacturing practices and regulatory guidelines.

Characterisation of the Risk: The clinical database was searched as follows: MedDRA PTs were searched for the term “transmission”; in addition, the investigator in the clinical studies or treating physician in the EAPs classified the event as transmission of infectious agents (including CMV), which was considered an adverse event of special interest (refer to Table 19 for a list of PTs). Treatment-emergent adverse events or TESAEs were defined as any AE or SAE that started on or after the first dose of tabelecleucel through 30 days, inclusive, after the last dose of tabelecleucel. The severity of each AE was determined using a severity grading system, which could have been either the CTCAE or categorical descriptions (mild, moderate, severe, life-threatening, or death) and summarised by worst grade (Table 20).

No cases of transmission of infectious agents have been reported after tabelecleucel administration in the clinical development programme[1] as of the data lock point. In CMV-negative subjects who received tabelecleucel from a CMV-positive donor, no CMV seroconversions have been observed.

Risk Factors and Risk Groups: No risk factors have been identified leading to increased risk of transmission of infectious agents after tabelecleucel administration.

Preventability: To minimise this risk, potential donors are screened and must test negative for relevant communicable disease agents and diseases, including HBV, HCV, and HIV to be donor-eligible. All tabelecleucel lots are tested to ensure no detection of adventitious agents, including CMV. The outcome of CMV testing will be communicated to prescribers.

Monitoring for signs and symptoms are included in the product information as routine risk minimisation measures and early treatment is indicated as clinically appropriate per institutional standards.

Impact on the Risk-benefit Balance of the Product: No cases of transmission of infectious agents (including CMV) were reported in Studies ATA129-EBV-302 and EBV-CTL-201 and strength of evidence seems limited; however, further data will be collected in the postmarketing setting.

Tabelecleucel is a medicinal product subject to restricted medical prescription and is administered in a clinical setting under strict supervision of experienced healthcare professionals. As part of their posttransplant clinical management of PTLD, patients are closely monitored by experienced healthcare professionals and early detection and treatment of infections per institutional standards would be expected. Therefore, routine risk minimisation measures described in the product information are considered sufficient to manage this risk. It is expected that further data collection in the postmarketing setting via routine pharmacovigilance activities will confirm that this risk is sufficiently managed through routine risk minimisation measures.

Tabelecleucel provides meaningful benefit to an advanced oncology population with limited treatment options and rapidly compromised prognosis in the absence of treatment. Based on available data, the risk-benefit balance for tabelecleucel is considered and expected to remain favourable.

Public Health Impact: The public health impact is expected to be low.

Important Potential Risk: Decrease in cell viability due to inappropriate handling of the product

Potential Mechanisms: Tabelecleucel must be prepared and administered per specifications or there is a potential risk of decrease in viability of the product. The preparation and administration specifications address the factors that may affect cell viability including thaw rate, temperature (applies in both the frozen state and thawed state), time (applies in both the frozen state and thawed state), dilution level, diluent, gauge of needle to draw from vial, and gauge of intravenous catheter to administer.

Evidence Source(s) and Strength of Evidence: Based on potential inconsistencies that may arise due to product handling, decrease in cell viability due to inappropriate handling of the product is considered an important potential risk.

Characterisation of the Risk: The clinical database was searched for SMQ: medication error (narrow and broad) or SMQ: lack of efficacy (SMQ narrow). Treatment-emergent adverse events or TESAEs were defined as any AE or SAE that started on or after the first dose of tabelecleucel through 30 days, inclusive, after the last dose of tabelecleucel. The severity of each AE was determined using a severity grading system, which could have been either the CTCAE or categorical descriptions (mild, moderate, severe, life-threatening, or death) and summarised by worst grade (Table 20).

In Studies ATA129-EBV-302 and EBV-CTL-201, 1 of 103 subjects (1.0%)[1] with EBV^+ PTLD reported multiple-drug resistance which was flagged as lack of efficacy; however, this case was not related to a

decrease in cell viability due to inappropriate handling of the product, and therefore, the case was excluded from this analysis.

In the other 2 clinical studies (11-130 and 95-024; N = 99) and EAPs (ATA129-EAP-901 and ATA129-SPU; N = 138), no serious event resulting from a decrease in cell viability due to inappropriate handling of the product was reported.

Risk Factors and Risk Groups: No risk groups or risk factors have been identified.

Preventability: Adherence to routine risk minimisation measures in the product information, which includes the Healthcare Professional tear-off mitigate this risk.

Impact on the Risk-benefit Balance of the Product: There are no safety-related issues expected as potential consequences to this risk and lack of efficacy events are being closely monitored. Therefore, routine risk minimisation measures described in the product information are considered sufficient to manage this risk. It is expected that further data collection in the postmarketing setting via routine pharmacovigilance activities will confirm that this risk is sufficiently managed through routine risk minimisation measures.

Public Health Impact: The public health impact is expected to be low.

SVII.3.2. Presentation of the Missing Information

Missing information: Use in paediatric population (Population between birth to < 18 years of age)

Evidence source: A total of 340 subjects have been treated with tabelecleucel, 254 (74.7%) were ≥ 18 years of age and 86 (25.3%) were < 18 years of age, as of the data lock point. Among the paediatric group, 3 (0.9%) were < 2, 20 (5.9%) were ≥ 2 to < 6, 31 (9.1%) were ≥ 6 to < 12, and 32 (9.4%) were ≥ 12 to < 18 years of age. The available safety data in the paediatric population did not show differences in the safety profile compared to the adult safety data. Based on the ultra-rare disease indication, further safety data collection in the postmarketing setting is required.

Population in need of further characterisation: There is a need to further define risks in the paediatric population to confirm the safety profile in this population, which was established based on a limited dataset as is expected in this ultra-rare disease indication. No additional risks or consequences are expected in this population based on the MOA and clinical safety data in 86 paediatric patients collected in the clinical development programme as of the data lock point.

Missing information: Use in elderly population (Population ≥ 65 years of age)

Evidence source: A total of 340 subjects have been treated with tabelecleucel, 288 (84.7%) were < 65 years of age and 52 (15.3%) were ≥ 65 years of age, as of the data lock point. Among the elderly group, 41 (12.1%) were ≥ 65 to < 75, 11 (3.2%) were ≥ 75 to < 85, and 0 were ≥ 85 years of age. The available safety data in the elderly did not show differences in the safety profile compared to the adult safety data. Based on the ultra-rare disease indication, further safety data collection in the postmarketing setting is required.

Population in need of further characterisation: There is a need to further define risks in the elderly population to confirm the safety profile in this population, which was established based on a limited dataset as is expected in this ultra-rare disease indication. No additional risks or consequences are expected in this population based on the MOA and clinical safety data in 52 elderly patients collected in the clinical development programme as of the data lock point.

Missing information: Use in pregnancy and lactation

Evidence source: No information is available for tabelecleucel use in pregnant women as pregnant and breastfeeding women were excluded from the clinical studies. No animal reproductive and developmental

toxicity studies have been conducted with tabelecleucel. It is not known if tabelecleucel has the potential to be transferred to the foetus or can cause foetal harm when administered to a pregnant woman.

It is unknown whether tabelecleucel is excreted in human milk or transferred to the breastfeeding child.

Population in need of further characterisation: There is a need to further define risks during pregnancy and lactation to better characterise the safety profile in this patient population; however, based on the proposed indication of an advanced oncology population with at least one prior therapy the occurrence of pregnancy is expected to be rare.

Missing information: Long-term safety

Evidence source: In Study ATA129-EBV-302, systematic safety data collection occurred through 2 years after first dose for events considered by the investigator to be at least possibly related. All subjects have a minimum of systematic safety data collection for 18 months and up to 23 months after last dose. No related events were reported beyond 2 months after last dose. Long-term reporting of at least possibly related AEs is required at any time per protocol.

Population in need of further characterisation: Additional long-term safety data collection is required in the postmarketing setting to confirm the long-term safety profile in an ulta-rare indication. No additional long-term risks or consequences are expected since tabelecleucel is not genetically modified and consequently, the risk of cell transformation or malignancy is not expected. Additionally based on the partially matched allogenicity nature of tabelecleucel, no engraftment is expected. Tabelecleucel is an activated T cell which once administered is expected to target and specifically kill EBV^+ target cells [Benoun 2021]. Once target cells are eliminated tabelecleucel is expected to be exhausted and not persist long-term.

Module SVIII. Summary of the Safety Concerns

Table 14. Summary of 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

Table 14. Summary of Safety Concerns

	Use in elderly population
	Use in pregnancy and lactation
	Long-term safety

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific ADR Follow-up Questionnaires for CRS and medication errors that may impact the cell viability of tabelecleucel:

Specific ADR follow-up forms applicable to tabelecleucel are used as part of the routine pharmacovigilance activities to document and follow-up any case of CRS and any case of medication error that occurs during the steps of prescription, preparation, and/or administration of the product which may have an impact on the cell viability (see Annex 4 – Specific Adverse Drug Reaction Follow-up Forms).

Other Forms of Routine Pharmacovigilance Activities:

None.

III.2. Additional Pharmacovigilance Activities

The study protocol is provided in Annex 3 – Protocols For Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan.

ATA129-PTLD-801

Title: 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.

Rationale and Study Objectives: Considering the limited safety data in paediatric and elderly population and the need for long-term safety monitoring for the identified and potential risks, this postauthorisation safety study (PASS) is designed to collect additional safety and effectiveness data in the real-world setting in Europe.

- 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 tabelecleucel in patients treated for EBV^+ PTLD following HCT or SOT in a real-world setting
    - To describe the patient population treated with tabelecleucel for EBV^+ PTLD following HCT or SOT in a real-world setting
    - To describe tabelecleucel treatment patterns, including dosing and schedule in patients treated for EBV^+ PTLD following HCT or SOT in a real-world setting

Study Design: Observational, multicentre, multinational, PASS with the primary objective of further characterising the safety and secondary objectives including real-world effectiveness of tabelecleucel in patients with EBV^+ PTLD following HCT or SOT.

Study Population: Patients treated with tabelecleucel for EBV^+ PTLD following HCT or SOT in the real-world setting in Europe, with targeted enrollment of paediatric (aged < 18 years) and elderly (aged ≥ 65 years) patients

Milestones:

Protocol submission: within 3 months of marketing authorisation

Registration in the EU PASS register: prior to start of study

Annual reports: to be submitted with annual reassessments

Final study report submission: not applicable

III.3. Summary Table of Additional Pharmacovigilance Activities

Table 15. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation: Not applicable				
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 fulfilled by annual reports for ATA129-PTLD-801 (PASS)	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 tabelecleucel in patients treated	TFR; GvHD; SOT rejection; BMT rejection; CRS; ICANS; IRR; immunogenicity; transmission of infectious agents (including CMV); decreased cell viability due to inappropriate handling of the product; use in paediatric population elderly population, and pregnancy and	Protocol submission Annual reports Final report submission	Within 3 months of marketing authorisation To be submitted with annual reassessments Not applicable

	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	lactation; and long-term safety		
Category 3 - Required additional pharmacovigilance activities: Not applicable.				

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 authorization holder; PASS, postauthorisation safety study; PBRER, periodic benefit risk assessment report; SOT, solid organ transplant; TFR, tumour flare reaction

PART IV. PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

The study protocol is provided in Annex 5 – Protocols for Proposed and Ongoing Studies in Part IV.

ATA129-EBV-302

Title: 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 (ALLELE Study)

Study Objectives:

- Primary objective: To determine the clinical benefit of tabelecleucel in subjects with EBV^+ PTLD following (1) SOT and after failure of rituximab (Subgroup A) and rituximab plus CT (Subgroup B) or (2) allogeneic HCT after failure of rituximab, as measured by the objective response rate
- Secondary objectives:
    - To evaluate duration of response in the SOT and HCT cohorts separately
    - To evaluate objective response rate and duration of response in the SOT and HCT cohorts combined
    - To evaluate rates of complete response and partial response
    - To evaluate time to response and time to best response
    - To evaluate overall survival
    - To evaluate graft status (SOT subjects only)
    - To characterise the safety profile of tabelecleucel in this subject population

Study Design: Multicenter, open-label, single-arm phase 3 study to assess the efficacy and safety of tabelecleucel for the treatment of EBV^+ PTLD in the setting of (a) SOT after failure of rituximab or rituximab plus CT, or (b) HCT after failure of rituximab

Study Population: Males and females of any age with EBV^+ PTLD following SOT and after failure of rituximab or rituximab plus CT and allogeneic HCT after failure of rituximab

Milestones:

Protocol submission (first global submission): 04 August 2016, study is ongoing

Registration in the EU PASS register: not applicable (currently reported in EU Clinical Trials Register)

Start of data collection (date of main informed consent): 26 June 2018

End of data collection (estimated): June 2027

Study progress reports: to be submitted with annual re-assessment

Interim report(s): submitted with marketing authorisation application (November 2021); updated data submitted with responses to questions (2022 Q3)

Final study report submission (estimated): December 2027

Table 16. Planned and Ongoing Postauthorisation Efficacy Studies Which Are Conditions of the Marketing Authorisation or Which Are Specific Obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorisation: Not applicable.				
Efficacy studies which are Specific Obligations in the context of a marketing authorisation under exceptional circumstances:				
ATA129-EBV-302 Ongoing	Primary objective: to determine the clinical benefit of tabelecleucel in subjects with EBV$^+$ PTLD following SOT and after failure of rituximab and rituximab plus chemotherapy or following allogeneic HCT after failure of rituximab, as measured by the objective response rate. Secondary objectives: to evaluate response, overall survival, and graft status in organ transplant subjects; and to characterise the safety profile of tabelecleucel in subjects with EBV$^+$ PTLD	Long-term efficacy: response data in the complete study population and survival over 8 years	Study progress reports Final report submission	With annual re-assessment December 2027

Abbreviations: EBV$^+$ PTLD, Epstein-Barr virus-positive posttransplant lymphoproliferative disease; HCT, haematopoietic cell transplant; SOT, solid organ transplant

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1. Routine Risk Minimisation Measures

Table 17. Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Tumour flare reaction	Routine risk communication: SmPC: Sections 4.4 and 4.8 Package Leaflet: Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC: Section 4.4 Package Leaflet: Sections 2 and 4 Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription and use intended for physicians experienced in the treatment of cancer.
Graft-versus-host disease	Routine risk communication: SmPC: Sections 4.4 and 4.8 Package Leaflet: Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC: Section 4.4 Package Leaflet: Sections 2 and 4 Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription and use intended for physicians experienced in the treatment of cancer.
Important potential risks	
Solid organ transplant rejection	Routine risk communication: SmPC: Section 4.4 Package Leaflet: Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC: Section 4.4 Package Leaflet: Section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription and use intended for physicians experienced in the treatment of cancer.

Table 17. Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Bone marrow transplant rejection	Routine risk communication: SmPC: Section 4.4 Package Leaflet: Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC: Section 4.4 Package Leaflet: Section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription and use intended for physicians experienced in the treatment of cancer.
Cytokine release syndrome	Routine risk communication: SmPC: Section 4.4 Package Leaflet: Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC: Section 4.4 Package Leaflet: Section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription and use intended for physicians experienced in the treatment of cancer.
Immune effector cell-associated neurotoxicity syndrome	Routine risk communication: SmPC: Section 4.4 Package Leaflet: Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC: Section 4.4 Package Leaflet: Section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription and use intended for physicians experienced in the treatment of cancer.
Infusion-related reactions	Routine risk communication: SmPC: Section 4.4 Package Leaflet: Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 Package Leaflet: Section 2 Other routine risk minimisation measures beyond the Product Information:

Table 17. Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
	Legal status: Medicinal product subject to restricted medical prescription and use intended for physicians experienced in the treatment of cancer.
Immunogenicity	Routine risk communication: SmPC: Section 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not required Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription and use intended for physicians experienced in the treatment of cancer.
Transmission of infectious agents (including cytomegalovirus)	Routine risk communication: SmPC: Section 4.4 Package Leaflet: Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC: Section 4.4 Package Leaflet: Section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription and use intended for physicians experienced in the treatment of cancer.
Decrease in cell viability due to inappropriate handling of the product	Routine risk communication: SmPC: Sections 6.3, 6.4, and 6.6 Package Leaflet: Healthcare Professional tear-off Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC: Sections 6.3, 6.4, and 6.6 Package Leaflet: Healthcare Professional tear-off Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription and use intended for physicians experienced in the treatment of cancer.
Missing information	
Use in paediatric population	Routine risk communication: SmPC: Sections 4.2, 4.8, and 5.1 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not required Other routine risk minimisation measures beyond the Product Information:

Table 17. Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
	Legal status: Medicinal product subject to restricted medical prescription and use intended for physicians experienced in the treatment of cancer.
Use in elderly population	Routine risk communication: SmPC: Sections 4.2, 4.4, and 5.1 Package Leaflet: Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not required Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription and use intended for physicians experienced in the treatment of cancer.
Use in pregnancy and lactation	Routine risk communication: SmPC: Section 4.6 Package Leaflet: Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC: Section 4.6 Package Leaflet: Section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription and use intended for physicians experienced in the treatment of cancer.
Long-term safety	Not applicable

In order to assess the effectiveness of the proposed routine risk minimisation measure to mitigate the risk of decrease in cell viability in case of inappropriate handling of the product, the following outcome indicators will be checked on a periodic basis in the Periodic Benefit Risk Evaluation Report (PBRER):

- Monitoring the reporting frequency of:
  - Cases of medication errors in the prescribing, preparation, and administration steps
  - Cases of lack of efficacy of the product for which a medication error has been reported
- Identification and analysis of the root causes leading to the medication error.

The success criteria will be the absence of recurrence of specific types of medication errors.

V.2. Additional Risk Minimisation Measures

The routine risk minimisation activities described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of Risk Minimisation Measures

Table 18. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

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

Table 18. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	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

Table 18. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR EBVALLO (TABELECLEUCEL)

This is a summary of the risk management plan (RMP) for Ebvallo. The RMP details important risks of Ebvallo, and how these risks can be minimised, and how more information will be obtained about Ebvallo's risks and uncertainties (missing information).

Ebvallo's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Ebvallo should be used.

This summary of the RMP for Ebvallo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ebvallo's RMP.

I. The Medicine and What It Is Used For

Ebvallo is authorised for the treatment of adult and pediatric 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 (see SmPC for the full indication).

Ebvallo contains tabelecleucel as the active substance and it is given by intravenous injection.

Further information about the evaluation of Ebvallo's benefits can be found in Ebvallo's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Ebvallo, together with measures to minimise such risks and the proposed studies for learning more about Ebvallo's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can include the following:

- Specific information, such as warnings, precautions, and advice on correct use, in the SmPC and PL addressed to healthcare professionals and patients.
- Important advice on the medicine's packaging.
- Ebvallo should be administered under the supervision of a physician experienced in the treatment of cancer.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

Important risks of Ebvallo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ebvallo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
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
	Use in pregnancy and lactation
	Long-term safety

II.B. Summary of Important Risks

Important identified risk: Tumour flare reaction (TFR)	
Evidence for linking the risk to the medicine	Tumour flare reaction (TFR) was identified in the clinical development programme as an adverse drug reaction based on a plausible mechanism of action and aggregate review of all TFR events, which include a case with positive rechallenge.
Risk factors and risk groups	The patients at risk of severe TFR are those with high tumour burden prior to treatment.[a,b] Depending on the anatomic location of the tumour or lymphadenopathy, complications may arise from mass effect including compression and/or obstruction of adjacent anatomic structures.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Sections 4.4 and 4.8 Package Leaflet: Sections 2 and 4. Additional risk minimiation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: ATA129-PTLD-801 See Section II.C of this summary for an overview of the postauthorisation development plan.
Important identified risk: Graft-versus-host Disease (GvHD)	
Evidence for linking the risk to the medicine	Graft-versus-host disease (GvHD) was identified in the tabelecleucel clinical development programme as an adverse drug reaction based on a plausible mechanism of action. A causal relationship between tabelecleucel and GvHD cannot be excluded. As GvHD can be life-threatening or cause chronic comorbidities, it is considered an important identified risk.
Risk factors and risk groups	No risk factors have been identified leading to increased risk of developing GvHD after tabelecleucel administration.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Sections 4.4 and 4.8 Package Leaflet: Sections 2 and 4 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: ATA129-PTLD-801 See Section II.C of this summary for an overview of the postauthorisation development plan.
Important potential risk: Solid Organ Transplant (SOT) Rejection	
Evidence for linking the risk to the medicine	The evidence of SOT rejection after administration of tabelecleucel in patients with previous allogeneic donor-derived

	SOT is limited, as the small number of reported cases of SOT rejection after administration of tabelecleucel had other risk factors including decrease of immunosuppressants as standard of care or a medical history of previous episodes of SOT rejection. As SOT rejection can be life-threatening or cause chronic comorbidities, it is considered an important potential risk.
Risk factors and risk groups	No risk factors have been identified leading to increased risk of developing SOT rejection after tabelecleucel administration.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.4 Package Leaflet: Section 2 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: ATA129-PTLD-801 See Section II.C of this summary for an overview of the postauthorisation development plan.
Important potential risk: Bone marrow transplant (BMT) rejection	
Evidence for linking the risk to the medicine	There is no evidence of BMT rejection after administration of tabelecleucel in patients with previous allogeneic donor-derived HCT, as no cases have been reported in the clinical development programme. In addition, a diminished host immune system after HCT would unlikely facilitate immune reactions. As BMT rejection can be life-threatening or cause chronic comorbidities, it is considered an important potential risk.
Risk factors and risk groups	No risk factors have been identified leading to increased risk of developing HCT graft after tabelecleucel administration.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.4 Package Leaflet: Section 2 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: ATA129-PTLD-801 See Section II.C of this summary for an overview of the postauthorisation development plan.

Important potential risk: Cytokine release syndrome (CRS)	
Evidence for linking the risk to the medicine	There was no case of CRS reported in any of the 4 clinical studies and 2 patients reported grade 1 CRS cases in the EAPs with confounding factors (ie, PPD) suggesting that tabelecleucel is not associated with CRS. CRS is considered an important potential risk due to its potential for severe outcomes if left untreated.
Risk factors and risk groups	No risk factors have been identified leading to increased risk of developing CRS after tabelecleucel administration.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.4 Package Leaflet: Section 2 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: ATA129-PTLD-801 See Section II.C of this summary for an overview of the postauthorisation development plan.
Important potential risk: Immune effector cell-associated neurotoxicity syndrome (ICANS)	
Evidence for linking the risk to the medicine	There have been no reports of the PT: ICANS in the clinical development programme. Applying a broader search criterion, only 1 grade 3 event of confusional state that was considered related by the investigator was reported in Studies ATA129-EBV-302 and EBV-CTL-201. The majority of events were assessed as not related and occurred in the context of confounding factors, suggesting that tabelecleucel is not associated with ICANS. ICANS is considered an important potential risk due to its potential for severe outcomes if left untreated.
Risk factors and risk groups	No risk factors have been identified leading to increased risk of developing ICANS after tabelecleucel administration.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.4 Package Leaflet: Section 2 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: ATA129-PTLD-801 See Section II.C of this summary for an overview of the postauthorisation development plan.

Important potential risk: Infusion-related reaction (IRR)	
Evidence for linking the risk to the medicine	Evidence for relationship of IRR with tabelecleucel is limited. As IRR can be life-threatening or cause chronic comorbidities, it is considered an important potential risk.
Risk factors and risk groups	No risk factors have been identified leading to increased risk of developing IRR after tabelecleucel administration.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.4 Package Leaflet: Section 2 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: ATA129-PTLD-801 See Section II.C of this summary for an overview of the postauthorisation development plan.
Important potential risk: Immunogenicity	
Evidence for linking the risk to the medicine	HLA antibodies can potentially reduce the efficacy of tabelecleucel and can cause clinical manifestations of immunogenicity such as anaphylaxis and SOT rejection that may require medical intervention. No immunogenicity adverse events were specific to development of anti-HLA antibodies therefore, no definitive conclusions regarding the association of HLA antibody positivity with immunogenicity adverse events can be drawn, and hence, immunogenicity is an important potential risk.
Risk factors and risk groups	No risk factors have been identified leading to increased risk of developing immunogenicity after tabelecleucel administration, however, patient- and disease-related factors may influence the development of an immune response and it would be expected that in the immunocompromised PTLD population, an immune response might be less likely to occur.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.8 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: ATA129-PTLD-801 See Section II.C of this summary for an overview of the postauthorisation development plan.

Important potential risk: Transmission of infectious agents (including cytomegalovirus)	
Evidence for linking the risk to the medicine	The risk associated with tabelecleucel is considered very low. Strict precautions to prevent transmission of infectious agents and to ensure microbial safety of tabelecleucel are in place in compliance with principles of good manufacturing practices and regulatory guidelines.
Risk factors and risk groups	No risk factors have been identified leading to increased risk of transmission of infectious agents after tabelecleucel administration.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.4 Package Leaflet: Section 2 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: ATA129-PTLD-801 See Section II.C of this summary for an overview of the postauthorisation development plan.
Important potential risk: Decrease in cell viability due to inappropriate handling of the product	
Evidence for linking the risk to the medicine	Based on potential inconsistencies that may arise due to product handling, decrease in cell viability due to inappropriate handling of the product is considered an important potential risk.
Risk factors and risk groups	No risk factors have been identified leading to increased risk of decrease in cell viability due to inappropriate handling of the product after tabelecleucel administration.
Risk minimisation measures	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
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: ATA129-PTLD-801 See Section II.C of this summary for an overview of the postauthorisation development plan.
Missing Information: Use in paediatric population	
Risk minimisation measures	Routine risk minimisation measures: SmPC: Sections 4.2, 4.8, and 5.1 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: ATA129-PTLD-801

Missing Information: Use in elderly population	
Risk minimisation measures	Routine risk minimisation measures: SmPC: Sections 4.2, 4.4, and 5.1 Package Leaflet: Section 2 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: ATA129-PTLD-801
Missing Information: Use in pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.6 Package Leaflet: Section 2 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: ATA129-PTLD-801
Missing Information: Long-term safety	
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: ATA129 PTLD 801

Abbreviations: SmPC, summary of product characteristics

[a] Chanan-Khan A, et al. (2011) Cancer 117(10):2127-2135. doi:10.1002/cncr.25748

[b] Taleb BA (2019) Anticancer Drugs 30(9):953-958. doi:10.1097/CAD.0000000000000814

II.C. Postauthorisation Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorisation

The following studies are specific obligations in the context of a marketing authorisation under exceptional circumstances:

Study short name: ATA129-PTLD-801

Purpose of the study:

- 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 tabelecleucel in patients treated for EBV^+ PTLD following HCT or SOT 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 for EBV^+ PTLD in a real-world setting

Study short name: ATA129-EBV-302

Purpose of the study:

- Primary objective: To determine the clinical benefit of tabelecleucel in subjects with EBV^+ PTLD following (1) SOT and after failure of rituximab (Subgroup A) and rituximab plus chemotherapy (Subgroup B) or (2) allogeneic HCT after failure of rituximab, as measured by the objective response rate
- Secondary objectives:
    - To evaluate duration of response in the SOT and HCT cohorts separately
    - To evaluate objective response rate and duration of response in the SOT and HCT cohorts combined
    - To evaluate rates of complete response and partial response
    - To evaluate time to response and time to best response
    - To evaluate overall survival
    - To evaluate graft status (SOT subjects only)
    - To characterise the safety profile of tabelecleucel in this subject population

II.C.2. Other Studies in Postauthorisation Development Plan

There are no studies required for Ebvallo.

PART VII. ANNEXES

Annex 4 – Specific Adverse Drug Reaction Follow-up Forms

Annex 6 – Details of Proposed Additional Risk Minimisation Activities (if Applicable)

Annex 4 – Specific Adverse Drug Reaction Follow-up Forms

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ADVERSE DRUG REACTION COLLECTION FORM IN CASE OF CYTOKINE RELEASE SYNDROME – EBVALLO

File number: |__|__|__|__|__| - |__|__|__|__|__| *(for department use only - make no entry in this space)*

Patient Identification
Last name (First 3 letters): |__|__|__| First name (First letter): |__| Sex: ☐ F ☐ M
Date of birth: ___/___/_____ or Age: ___Unit: ___ Height: ____ Unit: ___ Weight: ___ Unit: ___

Reporter information
☐ Healthcare Professional: ☐ Physician, specialty: _____ ☐ Pharmacist ☐ Other: _____
☐ Patient ☐ Other: _____

Did the patient have a **history of Cytokine Release Syndrome** (CRS)? ☐ No ☐ Yes, specify (dates, symptoms, other suspected drug(s)…):
_____
_____

Other **past medical history if any** *(specify if possible starting dates)*
_____
_____
_____
_____

Surgical history
Type of transplant: ☐ HCT ☐ SOT Date of transplant: ___/___/_____
Post-transplant complications: ☐ No ☐ Yes, specify: _____
Other: _____

Suspected drug involved
Trade Name: EBVALLO® Dose received: _____x 10^6 cells/mL Indication: _____ Route: _____
BATCH NUMBER (mandatory): _____ Associated quality complaint: ☐ Yes ☐ No
Date of first dose: ___/___/_____ Date of last date dose: ___/___/_____ that corresponds to: Cycle____ ☐ D1 ☐ D8 ☐ D15

Did the patient receive prophylactic medication prior to the administration (corticosteroids, antipyretics, etc.)?
☐ Yes, specify: _____ ☐ No
Are there any concomitant treatments that can induce CRS? ☐ Yes, specify: _____ ☐ No

Other concomitant treatments if any (including self-medication products)

Trade Name	Indication	Dosage/Form	Suspect (tick box)	Start Date	End date
_____	_____	_____	☐	___/___/____	___/___/____
_____	_____	_____	☐	___/___/____	___/___/____
_____	_____	_____	☐	___/___/____	___/___/____

ADVERSE REACTION(S)
Symptoms (Provide relevant detail information on symptoms)

☐ Fever* _____
Onset Date ___/___/____ Outcome: _____ Date of outcome: ___/___/____

☐ Hypotension* _____
Onset Date ___/___/_____ Outcome: _____ Date of outcome ___/___/____

☐ Hypoxia* _____
Onset Date ___/___/____ Outcome: _____ Date of outcome: ___/___/____

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ADVERSE DRUG REACTION COLLECTION FORM IN CASE OF CYTOKINE RELEASE SYNDROME – EBVALLO

☐ Organ toxicity** (such as hepatic, cardiac, neuro toxicities.) Please indicate which organ/symptom, if any, and the outcome below

Event/Symptom: _____
Onset Date ___/___/___ Grade _____ Outcome: _____ Date of outcome: ___/___/___

Event/Symptom: _____
Onset Date ___/___/___ Grade _____ Outcome: _____Date of outcome: ___/___/___

Event/Symptom _____
Onset Date ___/___/___ Grade _____Outcome: _____Date of outcome: ___/___/___

*CRS grade (Refer to ASTCT CRS Consensus Grading Table at the end of the form) ☐ Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4
** Organ toxicity to be graded with CTCAE v.5.0

Potential differential diagnoses: ☐ Infection ☐ Sepsis ☐ HLH ☐ Allergic reaction ☐ Other: _____

Please complete the table below if there are other symptoms/adverse reaction(s) (e.g., Myalgia, Headache, nausea)

Adverse reaction(s)	Onset date	End date (if applicable)	Ongoing
☐ Related to CRS	___/___/___	___/___/___	☐ Yes ☐ No
☐ Related to CRS	___/___/___	___/___/___	☐ Yes ☐ No
☐ Related to CRS	___/___/___	___/___/___	☐ Yes ☐ No

Please provide the subject's vital signs at onset of the event:

- Body temperature: _____ Unit: ____
- Respiration rate: _____ Unit: ____
- Blood pressure: _____ Unit: ____
- Heart rate: _____ Unit: ____
- Oxygen saturation: _____ Unit: ____

If available, please attach copies of the **laboratory test results for inflammatory markers**: IL-1, IL-6, IFN- γ and IFN-α.

Please describe the adverse reaction(s) and provide the results of any additional examinations ordered following the adverse event (attach photocopies of hospital report or lab data if possible)

_____
_____
_____
_____
_____
_____
_____
_____

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ADVERSE DRUG REACTION COLLECTION FORM IN CASE OF CYTOKINE RELEASE SYNDROME – EBVALLO

Action taken

☐ Withdrawn ☐ Dose reduced ☐ Dose delayed and reduced ☐ Infusion interrupted ☐ Dose delayed ☐ Not applicable
☐ No change ☐ Unknown

	No	Yes	
Did the adverse event lead to corrective treatment?	☐	☐	If yes, which treatment? _____
Did the event abate after interruption of the treatment?	☐	☐	
Were there any further infusions?	☐	☐	If yes, date: ____/____/_____ and dose: ____
If yes, did the event reoccur?	☐	☐	If yes, date the event reappeared: ____/____/_____

Criteria for Seriousness

The adverse event led to:	No	Yes		No	Yes
Death	☐	☐	Persistent or significant disability/incapacity	☐	☐
Life threatening	☐	☐	Congenital anomaly/birth defect	☐	☐
Inpatient Hospitalisation or prolongation of existing Hospitalisation	☐	☐	Medically significant	☐	☐
			Other (specify): _____		

Outcome

Recovered/resolved	☐	Recovery date: ____/____/_____
Recovering/resolving	☐	
Not recovered/not resolved	☐	
Recovered/resolved with sequelae	☐	Specify sequelae: _____
Fatal	☐	Date of death: ____/____/_____
Unknown	☐	

If the outcome was fatal, please specify the cause of death.

_____
_____
_____

Comments by the reporter

_____
_____
_____

If you are not the prescriber, please provide their contact details:_____

Has this case been notified to the Competent Authorities? ☐ No ☐ Yes

Last name, first name, address, qualification and/or stamp [ii]	Date: _____ Signature:

Thank you for filling out this Pharmacovigilance form
Email the completed form to: drugsafety@atarabio.com

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ADVERSE DRUG REACTION COLLECTION FORM IN CASE OF CYTOKINE RELEASE SYNDROME – EBVALLO		

[i] **ASTCT CRS Consensus Grading**

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
Hypotension[b]	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
Hypoxia	None	Requiring low-flow nasal cannula[c] or blow-by	Requiring high-flow nasal cannula[c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

Abbreviations: BiPAP: bilevel positive airway pressure; CPAP: continuous airway pressure; CRS: cytokine release syndrome

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

[a] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
[b] **CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause**. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
[c] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low-flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.
[1] Lee DW (2019) ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells.

[ii] The data collected about you will be subject to data processing in accordance with the provisions of the General Data Protection Regulation (GDPR) of April 27, 2016. All information and personal data that you share with us via this form will be protected and will remain confidential in accordance with our company policy and the regulation in force. The information you provide will be used for safety monitoring and may be shared with health authorities, the processing of your personal data being necessary for compliance with a legal obligation to which our company is subject. Please note that this personal data will be deleted or anonymized 50 years after marketing authorization withdrawal of our products. You have a right of access, rectification and restriction of processing of your personal data. You can exercise these rights by contacting us drugsafety@atarabio.com *(local GDPR contact to be completed)*. You have the right to lodge a complaint with the national supervisory authority in charge of protection of personal data *(name to be added)*.

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ADVERSE DRUG REACTION COLLECTION FORM IN CASE OF INAPPROPRIATE HANDLING OF EBVALLO LEADING TO A DECREASE IN CELL VIABILITY

File number: |__|__|__|__|__| - |__|__|__|__|__| *(for department use only - make no entry in this space)*

Patient identification
Last name (First 3 letters): |__|__|__| First name (First letter): |__| Sex: ☐ F ☐ M
Date of birth: ___/___/_____ or Age: ___Unit: ___ Height: ____ Unit: ___ Weight: ___ Unit: ___

Reporter information
☐ Healthcare Professional: ☐ Physician, specialty: _____ ☐ Pharmacist ☐ Other: _____
☐ Patient ☐ Other: _____

Relevant medical history if any *(specify if possible starting dates)*
_____
_____
_____

Surgical history
Type of transplant: ☐ HCT ☐ SOT Date of transplant: ___/___/_____
Post-transplant complications: ☐ No ☐ Yes, specify: _____
Other: _____

Suspected drug involved
Trade Name: EBVALLO® Dose received: _____ x 10^6 cells/mL Indication: _____ Route: _____
BATCH NUMBER (**mandatory**): _____ Associated quality complaint: ☐ Yes ☐ No
Date of first dose: ___/___/_____ Date of last date dose: ___/___/_____ that corresponds to: Cycle____ ☐ D1 ☐ D8 ☐ D15

Date of the **Medication Error**: ___/___/_____
What was the nature of the Medication Error(s)? (tick box and complete):

	No	Yes	
Reception	☐	☐	If yes, explain: _____
Storage	☐	☐	If yes, explain: _____
Preparation of materials	☐	☐	If yes, explain: _____
Thawing	☐	☐	If yes, explain: _____
Dilution	☐	☐	If yes, explain: _____
Dose preparation	☐	☐	If yes, explain: _____
Administration	☐	☐	If yes, explain: _____

Other: _____
Cause of the medication error: _____

Concomitant treatments if any (including self-medication products)

Trade Name	Indication	Dosage/Form	Suspect (tick box)	Start Date	End date
_____	_____	_____	☐	___/___/___	___/___/___
_____	_____	_____	☐	___/___/___	___/___/___
_____	_____	_____	☐	___/___/___	___/___/___

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ADVERSE DRUG REACTION COLLECTION FORM IN CASE OF INAPPROPRIATE HANDLING OF EBVALLO LEADING TO A DECREASE IN CELL VIABILITY

ADVERSE REACTION(S) related to decrease in cell viability due to inappropriate handling of the product

Adverse reaction(s)	Onset date	End date (if applicable)	Ongoing?
	___/___/____	___/___/____	☐ Yes ☐ No
	___/___/____	___/___/____	☐ Yes ☐ No
	___/___/____	___/___/____	☐ Yes ☐ No

Please describe the adverse reaction(s) (eg, lack of efficacy), and provide the results of any additional examinations ordered following the event (attach photocopies of hospital report or lab data if possible)

_____
_____
_____
_____
_____
_____
_____

Action Taken
☐ Withdrawn ☐ Infusion interrupted ☐ Dose delayed ☐ Not applicable ☐ No change ☐ Unknown

	No	Yes	
Were there any further injections of EBVALLO?	☐	☐	If yes, date: ____/____/_____ and dose: ____
(Check only one) If yes, was the patient switched to a different batch (or lot)? **OR** Was the same batch re-administered?	☐ ☐		Batch Number:_____

Criteria for Seriousness

The adverse event led to:	No	Yes		No	Yes
Death	☐	☐	Persistent or significant disability/incapacity	☐	☐
Life threatening	☐	☐	Medically significant	☐	☐
Inpatient Hospitalisation or prolongation of existing Hospitalisation	☐	☐	Other (specify): _____		

Outcome

Recovered/resolved	☐	Recovery date: ____/____/_____
Recovering/resolving	☐	
Not recovered/not resolved	☐	
Recovered/resolved with sequelae	☐	Specify: _____
Fatal	☐	Date of death: ____/____/_____
Unknown	☐	

Particular comments on suspected cause(s) in reporter's opinion

_____
_____
_____
_____
_____
_____
_____

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ADVERSE DRUG REACTION COLLECTION FORM IN CASE OF INAPPROPRIATE HANDLING OF EBVALLO LEADING TO A DECREASE IN CELL VIABILITY

If you are not the prescriber, please provide their contact details:_____

Has this case been notified to the Competent Authorities? ☐ No ☐ Yes

Last name, first name, address, qualification and/or stamp [i]	Date: _____ Signature:

Thank you for filling out this Pharmacovigilance form
Email the completed form to: drugsafety@atarabio.com

[i] The data collected about you will be subject to data processing in accordance with the provisions of the General Data Protection Regulation (GDPR) of April 27, 2016. All information and personal data that you share with us via this form will be protected and will remain confidential in accordance with our company policy and the regulation in force. The information you provide will be used for safety monitoring and may be shared with health authorities, the processing of your personal data being necessary for compliance with a legal obligation to which our company is subject. Please note that this personal data will be deleted or anonymized 50 years after marketing authorization withdrawal of our products. You have a right of access, rectification and restriction of processing of your personal data. You can exercise these rights by contacting us at drugsafety@atarabio.com *(local GDPR contact to be completed)*. You have the right to lodge a complaint with the national supervisory authority in charge of protection of personal data *(name to be added)*.

Annex 6 – Details of Proposed Additional Risk Minimisation Activities (if Applicable)

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.