Amsterdam, 15 September 2022
EMA/800781/2022
Committee for Advanced Therapies (CAT)

Assessment report

Kymriah

International non-proprietary name: tisagenlecleucel

Procedure No. EMEA/H/C/004090/P46/017

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Steps taken for the assessment	
Description	**Date**
Start of procedure	25 Apr 2022
CAT Rapporteur Assessment Report	30 May 2022
CAT conclusion	17 Jun 2022
CHMP adoption of conclusion	23 Jun 2022
Submission of responses	08Aug 2022
Re-start of procedure	11 Aug 2022
CAT Rapporteur Assessment Report	23 Aug 2022
CAT conclusion	09 Sep 2022
CHMP adoption of conclusion	15 Sep 2022

Table of contents

1. Introduction

On 15th March 2022, the MAH submitted a phase II paediatric clinical study for Kymriah (tisagenlecleucel; ATC code: L01XX71), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The study was terminated early on 19 October 2021 by the MAH due to slow recruitment of patients. These data are also submitted as part of the post-authorisation measure. A short critical expert overview has also been provided.

This phase II clinical study is not part of any paediatric investigational plan (PIP).

2. Scientific discussion

Information on the development program

The MAH stated that the Phase II study CCTL019BUS03 (hereafter referred to as study BUS03) in paediatric and adolescent young adult patients with ALL previously treated with tisagenlecleucel who experienced loss of B-cell aplasia, and subsequently re-administred tisagenlecleucel is a stand-alone study.

Information on the pharmaceutical formulation used in the study

Kymriah is an immunocellular therapy containing tisagenlecleucel, autologous T cells genetically modified ex vivo using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR).

Kymriah comprises cell dispersion for infusion, where 1-3 infusion bags contain a total of 1.2x106 to 6x108 CAR-positive viable T-cells. The concentration of CAR-positive viable T-cells is dependent on patient body weight for treatment of patients with B-cell ALL. The cellular composition and the final cell number varies between individual patient batches.

The approved dose range for paediatric and young adult patients with B-cell ALL is 0.2 to 5x106 CAR-positive viable T-cells/kg body weight for subjects ≤50 kg and 0.1 to 2.5x108 CAR-positive viable T-cells (non-weight based) for patients >50 kg.

No change in formulation was made for the paediatric population in study BUS03.

Clinical aspects

Introduction

The MAH submitted a final report for:

- Study **CCTL019BUS03** *(i.e* **BUS03**)

Study BUS03 is a phase II, open-label, multi-center trial to determine the efficacy and safety of tisagenlecleucel re-infusion in Paediatric and Adolescent Young Adult (AYA) patients with acute lymphoblastic leukemia (ALL) who were previously treated with tisagenlecleucel and experiencing loss of B-cell aplasia.

Kymriah (INN: tisagenlecleucel, product code CTL019) was approved in the EU via the centralised procedure (Procedure No. EMEA/H/C/004090) on 23-Aug-2018 and is indicated for the treatment of:

- Paediatric and young adult patients up to and including 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse.

- Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

The evidence of efficacy and safety of tisagenlecleucel re-infusion was not evaluated at the time of initial marketing authorisation (MA).

The current submission provides a summary of the findings obtained from Study BUS03. The study was terminated early on 19-Oct-2021 by the Sponsor due to slow recruitment of patients. According to the MAH, no safety reasons were involved in the decision to terminate the study prematurely. At the time of the study termination, there were five patients enrolled, including four paediatric patients (aged < 18 years) and one young adult patient (aged ≥ 18 years).

The low sample size provided insufficient data to perform the planned statistical analyses; therefore, the primary and secondary efficacy analyses were not conducted. Available study data were presented in listings.

The final study report is submitted in accordance with Article 46 of Regulation (EC) No 1901/2006, which requires that any MAH-sponsored study involving use in a paediatric population of a medicinal product covered by a MA, whether it is conducted in compliance with an agreed PIP, should be submitted to the competent authority within six months of completion of the concerned study.

Clinical study BUS03

A phase II, open label, multi-center trial to determine the efficacy and safety of tisagenlecleucel re-infusion in Pediatric and Adolescent Young Adult (AYA) patients with acute lymphoblastic leukemia (ALL) experiencing loss of B-cell aplasia.

Methods

Objectives and outcome/endpoints

The primary objective of the study was to evaluate the incidence of B-cell aplasia within 12 months after re-infusion of tisagenlecleucel. Efficacy in this setting will be defined as establishing B cell aplasia and/or presence of tisagenlecleucel cells (by qPCR). As per the study protocol, B-cell aplasia was defined as peripheral blood absolute B lymphocyte count < 50/µL, as measured by flow cytometry.

Loss of B-cell aplasia (i.e., B-cell recovery) was defined per protocol as:

- absolute B-lymphocytes count ≥ 50 µL in peripheral blood for 2 consecutive measurements 1 week apart, OR

- B lymphocytes ≥ 10% of total lymphocytes in peripheral blood, OR

- Peripheral blood absolute B lymphocyte count ≥ 200/µL (one measurement, no repeat is required)

Secondary objectives included efficacy of re-infusion of tisagenlecleucel for loss of B-cell aplasia as measured by overall remission rate (ORR) with MRD (minimal residual disease) negativity by investigator 12 months after re-infusion. ORR included CR and CRi (CR with incomplete blood count recovery). MRD was assessed in bone marrow as part of the ORR evaluation. Bone marrow aspirate or biopsy was to be performed during screening and at Day 28, and was optional (i.e., to be performed as clinically indicated) at Month 3, 6 and 12.

Additional secondary objectives were evaluation of overall survival (OS), event free survival (EFS) and safety evaluation. Cellular immunogenicity was an exploratory objective. Study objectives and related endpoints are shown in Table 1.

Table 1. Study objectives and related endpoints in study CCTL019BUS03

Objectives:

Objectives	Endpoints
Primary objective	**Primary endpoint‡‡**
• Evaluate the incidence of B-cell aplasia after re-infusion of tisagenlecleucel.	• Proportion of patients who established B-cell aplasia within 12 months of re-infusion, as measured by circulating B lymphocytes (< 50/µL) and the presence of tisagenlecleucel cells by quantitative polymerase chain reaction (qPCR) in the peripheral blood.
Secondary objectives	**Secondary endpoints‡‡**
• Evaluate the efficacy of reinfusion of tisagenlecleucel for loss of B cell aplasia as measured by overall remission rate (ORR) 12 months after tisagenlecleucel re-infusion, which includes complete recovery (CR) and CR with incomplete blood count recovery (CRi) as determined by investigator assessment. • Evaluate event free survival (EFS). • Evaluate overall survival (OS). • Evaluate the safety of tisagenlecleucel re-infusion therapy.	• Proportion of patients with ORR (= CR + CRi) per Investigator assessment in patients during 12 months post-re-infusion. • EFS, i.e. the time from date of tisagenlecleucel re-infusion to the earliest of relapse, treatment failure, or death. • OS, i.e. the time from date of tisagenlecleucel re-infusion to the date of death due to any reason. • Safety parameters including adverse events (AEs) and laboratory abnormalities.
Exploratory objective	**Exploratory endpoint‡‡**
• Describe the prevalence and incidence of cellular immunogenicity against tisagenlecleucel.	• Prevalence and incidence of cellular immunogenicity.

‡‡ Due to data analysis limitations as a result of early closure of the study, data for these endpoints were listed only.

Study design

The study was planned to have the following sequential phases for all patients: Screening, Pre-Treatment (Lymphodepleting Chemotherapy), Treatment and Follow-up. The total duration of the study was planned to 12 months. After tisagenlecleucel re-infusion, efficacy would be assessed at month 1, 3, 6, 9 and 12. Safety would be assessed throughout the study. The end of the study was planned to be when all patients complete a month 12 visit unless discontinuing prior. However, the study was closed early by the MAH due to slow enrolment of patients.

Patients who receive commercial tisagenlecleucel should be followed for up to 15 years post-infusion. Patients can be followed under the Center for International Blood and Marrow Transplant Research (CIBMTR) cellular therapy registry if consented for participation.

Study participants

Table 2. Key inclusion and exclusion criteria

Study population	It was planned that approximately 54 patients up to and including 25 years of age would be enrolled in this study to compensate for dropouts and allow for 49 evaluable patients. However, only 5 patients were enrolled as the study was terminated early due to a low rate of enrolment.
Key inclusion criteria	The target population consisted of pediatric and adolescent young adult patients up to and including 25 years of age with B-cell ALL who had been previously infused once with tisagenlecleucel and had a loss of B-cell aplasia (defined as peripheral blood absolute B lymphocyte count ≥ 50/µL OR peripheral blood B lymphocyte ≥ 10% of the total lymphocytes), and who had an additional dose of unexpired, commercial tisagenlecleucel available and prescribed by a physician in the course of medical practice. Patients were required to have adequate hematological values, pulmonary functions, liver functions, and renal functions, as defined in the protocol, as well as Karnofsky (age ≥ 16 years) or Lansky (age < 16 years) performance status ≥ 50.
Key exclusion criteria	Patients who had received any prior gene therapies or adoptive T-cell therapies other than tisagenlecleucel were excluded, as well as patients who had received systemic chemotherapy or radiotherapy within 2 weeks prior to enrolment or tyrosine kinase inhibitors within 1 week prior to enrolment. Patients who were human immunodeficiency virus positive or had active or latent hepatitis B or C were also not eligible for inclusion. Patients with clinically significant acute infections and cardiac disorders, as defined by the protocol, and those with previous or concurrent malignancies except for curatively treated non-melanoma skin cancers, in situ carcinoma, and cancers in complete remission for at least 3 years, were also excluded.

Treatments

Lymphodepletion (LD):

If patients have a White Blood Cell (WBC) count ≤ 1,000 cells/µL within one week prior to tisagenlecleucel infusion, lymphodepleting chemotherapy is NOT required. The availability of tisagenlecleucel must be confirmed prior to starting the lymphodepleting regimen. Tisagenlecleucel should be infused 2 to 14 days after lymphodepletion depending on the lymphodepleting regimen. If there is a delay of more than 4 weeks between completing lymphodepleting chemotherapy and the infusion and the WBC count is >1,000cells/µL, the patient should be re-treated with lymphodepleting chemotherapy prior to receiving tisagenlecleucel. The preferred regimen for paediatric participants is as follows:

- Cytarabine 500 mg/m2 i.v. daily for 2 days and
- Etoposide 150 mg/m2 i.v. daily for 3 days starting with the first dose of cytarabine

All paediatric patients received lymphodepleting chemotherapy with cyclophosphamide and fludarabine prior to tisagenlecleucel re-infusion.

Tisagenlecleucel infusion:

The doses available for re-infusion were previously manufactured for each individual patient as commercial product and the physician could request an additional dose for commercial release at any time, prior to product expiration and subject to availability.

The tisagenlecleucel dose was administered via a single intravenous (IV) infusion. The recommended dose range for this trial was consistent with the approved dose range:

- 0.2 to 5.0×10^6 CAR positive viable T cells / kg for patients < 50 kg or
- 0.1 to 2.5×10^8 CAR-positive viable T cells for patients > 50 kg.

Sample size

Sample size was based on an exact test for single proportion to test the null hypothesis H0: p≤0.10, where p is the percent of patients who establish B cell aplasia during 12 months. Assuming the true rate was p>= 0.25, and a one sided alpha level of 2.5% it was calculated that 49 evaluable patients would be required to reach at least 80% power. Accounting for a drop-out rate of 10%, a total of approximately 54 patients were planned to be enrolled into the study.

Randomisation and blinding (masking)

N/A (single arm open-label study)

Statistical Methods

Analysis populations

The Screened Set comprises all patients who have signed informed consent/assent and been screened in the study.

The Enrolled Set (ENS) comprises all patients who are enrolled in the study. Enrollment is defined as the point at which the patient meets all inclusion/exclusion criteria and the patients' additional non-expired dose of tisagenlecleucel has been confirmed available.

The Full Analysis Set (FAS) consists of all patients who have received re-infusion of tisagenlecleucel.

The Safety Set is identical to the FAS.

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS (at interim and final analysis respectively) who are compliant with major requirements of the clinical study protocol (CSP). Major protocol deviations, determined prior to primary analysis, leading to exclusion from the PPS include; No diagnosis of ALL at baseline, Prior therapy does not match with CSP requirements in terms of number and types of previous therapy regimens, Missing or incomplete documentation of disease.

The primary analysis was to be performed using the FAS after all patients had completed the 12-month follow-up period or discontinued earlier. The Safety Set was to be used for all the safety analysis.

Primary endpoint

The primary endpoint for this study was defined as the proportion of patients who restore B-cell aplasia (as defined in Section 2.6) within 12 months following re-infusion with tisagenlecleucel as measured by circulating B-lymphocytes (<50/µL) in PB. For the primary analysis, percent of patients who establish B cell aplasia during 12 months was to be presented together with an exact 95% Clopper-Pearson confidence interval. The null hypothesis was to be rejected if the lower limit of the 95% confidence interval was greater than 0.10, demonstrating improvement after of reinfusion. Patients in the study who were of unknown clinical response was to be treated as non-responders. Other missing data were to be noted as missing on appropriate tables/listings. No sensitivity analyses or supportive analyses were planned.

Analysis of secondary endpoints

Investigators assessment was to be used in the main analysis of secondary endpoints that involve disease assessment.

Overall Remission rate (ORR), as determined by investigators assessment during the 12 months after CTL019 administration, was defined as percentage of patients who maintain ORR (= CR + CRi) with MRD negativity per Investigator assessment in pALL patients during 12 months post-reinfusion. The ORR in the FAS was to be summarized and 95% confidence interval reported.

Event free survival (EFS), was defined as the time from date of first CTL019 infusion to the earliest of the following: Death from any cause after remission, Relapse, Treatment failure: Defined as no response in the study and discontinuation from the study due to any of the following reasons: Death, Adverse event (including abnormal laboratory values or abnormal test procedure results), Lack of efficacy or progressive disease, New anticancer therapy. In the main analysis of EFS, patients who proceed to SCT after CTL019 infusion was to be censored at the time of SCT. In addition, a sensitivity analysis of EFS was to be performed without censoring SCT. EFS was to be assessed in all patients in the FAS. The distribution function of EFS was to be estimated using the Kaplan-Meier method, and the median EFS along with 95% confidence intervals presented, if appropriate.

Overall survival (OS), was defined as the time from date of CTL019 infusion to the date of death due to any reason. In case a patient was alive at the date of last contact on or before data cutoff, OS was to be censored at the date of last contact. No censoring was to be done in case of SCT, and patients were to be followed-up for survival also in case of SCT.

Subgroup analyses

Subgroup analyses were planned to only summarise data within each subgroup due to the small planned sample size, and to be performed on the primary endpoint based on the patient's baseline status: Age [<10 years, ≥10 years to <18 years, ≥18 years], Gender [Male, Female], Race [White, Asian, Other], Patients with a loss of B-cell Aplasia within 9 months of 1st infusion AND are MRD(+) at time of enrolment, Patients with a loss of B cell aplasia following first infusion by time period [very early (<3 months), early (>3 to <6 months), late (>6 months)].

Interim analyses

No formal interim analysis was to be performed for this study. As required, interim analyses would be performed every six months annually for publication purpose.

Assessor's comment

The MAH terminated the study early due a very low rate of enrolment, when only 5 out of a planned 54 patients were enrolled. None of the planned statistical analyses were performed, and study data were listed only for the primary objective using the Full Analysis Set. It is agreed that the low sample size provides insufficient data to perform the planned statistical analyses.

Results

Participant flow

A total of seven paediatric and adolescent young adult patients were screened, of whom five (4 paediatrics and 1 young adult) were enrolled while two (1 paediatric and 1 young adult) were screen failures. No patient had completed the 12-month study at the time of study closure. One paediatric patient was withdrawn from the study on Day 53 due to physician's decision, as the patient was proceeding to transplant, and one paediatric patient was withdrawn from the study on Day 74 due to

an unsatisfactory therapeutic effect. All other patients (i.e., 2 paediatrics and 1 young adult) completed early due to premature study termination by the MAH.

Post re-infusion treatment

Two paediatric patients underwent hematopoietic stem-cell transplantations post tisagenlecleucel re-infusion; one non-adolescent patient had a bone marrow allogenic transplant, and one adolescent patient had a peripheral blood allogenic transplant.

Two paediatric patients (both adolescent) received antineoplastic therapy post tisagenlecleucel re-infusion; of those, one patient received investigational treatment of humanised CART-19 cells at another institution.

Recruitment

The study was initiated on 19-Oct-2020 (First Patient First Visit) and completed on 19-Oct-2021 (Last Patient Last Visit). All study patients were recruited at four study sites in the US.

The study was terminated early on 19-Oct-2021 by the MAH due to slow recruitment of patients.

Assessor's comment

The MAH has not provided detailed reasons for the slow recruitment of patients to study **BUS03**, e.g. to which degree feasibility issues was related to low number of patients eligible for retreatment with Kymriah, lack of available doses of Kymriah, or if other measures could have facilitated recruitment and, thus, prevented the premature closure of the study. A more detailed explanation was provided by the MAH with regards to feasibility, including information on the actual number of patients in clinical practice receiving a second dose of Kymriah (See Request for Supplementary Information).

Protocol deviations

No protocol deviations were registered during the study.

Baseline data

All patients enrolled in this study had previously been infused once with tisagenlecleucel for the treatment of ALL and received a re-infusion of tisagenlecleucel. Patients were reintroduced to tisagenlecleucel at a mean of 120.8 days (range 77-220 days) following the initial infusion.

Of the four paediatric patients enrolled, two were children (hereafter referred to as non-adolescents), aged 3 years and 8 years; and two were adolescents, aged 14 years and 15 years. Most paediatric patients included in this study were male (3 patients; 2 non-adolescents and 1 adolescent), and all paediatric patients were white.

Disease (ALL) characteristics

The age at initial diagnosis of ALL was 2 years for the two non-adolescent patients and ranged from 11 to 15 years for the two adolescent patients.

All patients had tumour samples that were positive for presence of CD19 disease prior to study entry, except for one patient (the 8-year-old), who had a cerebral spinal fluid sample that tested negative for presence of CD19 disease and was assessed as minimal residual disease (MRD) negative. None of the paediatric patients at study entry had extra-medullary involvement or elevated lactate dehydrogenase at baseline.

Prior treatment

All paediatric patients received antineoplastic therapies prior to their first tisagenlecleucel infusion, except for one non-adolescent patient. All patients received LD chemotherapy with both cyclophosphamide and fludarabine prior to re-infusion of tisagenlecleucel. None of the paediatric patients received any other antineoplastic therapies prior to re-infusion.

Number analysed

At the time of the study termination, there were five patients enrolled, including four paediatric patients (aged < 18 years) and 1 young adult patient (aged ≥ 18 years). The low sample size provided insufficient data to perform the planned statistical analyses. Therefore, the primary and secondary efficacy analyses were not conducted.

Clinical pharmacology results

Peripheral blood pharmacokinetic (PK) concentrations for tisagenlecleucel were quantified by qPCR using the Murine CART-19 qPCR Assay (A_WI-01188, see bioanalytical report). PK sampling were planned at four timepoints following reinfusion (Table 3). Thirteen observations from five patients were analysed. Three patients (8y, 14y, 15y) displayed an increase in tisagenlecleucel PK concentration from Day 1 to Day 28. No quantifiable PK data were available for the 19-year old on Day 1, or for the 3-year old at any time point. The 8-year old and 19-year old had a decrease in tisagenlecleucel PK concentration from Day 28 to their last assessment whereas the 15-year old patient had an increase in PK concentration from Day 28 to her last assessment. Results are presented in Table 3. No patient received prior or concomitant tocilizumab medication.

Table 3. Overview of administered re-infusion tisagenlecleucel dose and observed kinetics (copies/µg DNA) as measured by qPCR (Table assembled by assessor, based on study synopsis and CSR Listing 14.2-1)

Patient	**Tisagenlecleucel exposure**		**Peripheral blood PK concentration (copies/µg DNA)[b, c]**			
	Re-infusion dose[d]	*Time of initial infusion*	*Day 1*	*Day 28*	*Month 3*	*Month 12/EOS*
3y, male	3×10^6 /kg	Day -77	NQ	NQ	NA	NA
8y, male	4.4×10^6 /kg	Day -141	4.2	68.3	NA	33.4
14y, male	3.07×10^6 /kg	Day -82	99.6	248.0	NA	NA
15y, female	2.69×10^6 /kg	Day -84	36.0	200.0	515.5	NA
19y, male	4.59×10^6 units[d]	Day -220	NQ	62.3	11.3	NA

a The dose is given as number of CAR positive viable T-cells count per kg. The study inclusion criteria specified that patients should have an additional dose of unexpired, commercial tisagenlecleucel available.
b NQ = No quantifiable PK results. NA=not applicable; PK sampling was not performed.
c Below the limit of quantitation (BLQ) value is < 50 copies/µg DNA.
d It should be noted this calculation reflects the total cells infused on a per kilogram basis as 4.59×10^6. The CAR positive cells infused equals 1.38×10^6 per kg.

Assessor's comment:

The study terminated early with less than 10% (5/54) of the planned study population enrolled. Four patients were <18 years and are considered in this P46 procedure. For completeness, results from all enrolled patients are reported.

Patients were reintroduced to tisagenlecleucel at a mean of 120.8 days (range 82-220 days) following the initial infusion. The administered doses were within the approved dose range for B-cell ALL. (According to the CSR, the dose administered to the 19-year-old with BW 118 kg were $53.2x10^7$ cells.) Validated, previously submitted bioanalytical assays for qPCR (RPT-01324 and RPT-10016) were used (EPAR, EMEA/H/C/004090/P46/012.1) and bioanalytical methods have not been further evaluated in the present assessment report.

Expansion was observed for three of five patients during the first four weeks; concentrations at D28 ranged from 68.3 to 248.0 copies/µg DNA. The expansion continued at month 3 for one patient (515.5 copies/µg DNA). Only one patient provided data at month 12 (*i.e.* EOS, end of study). No PK parameters could be derived based on NCA. No information on observed cellular kinetics following the initial infusion of tisagenlecleucel was provided by the Applicant. The initial expansion appears modest compared to that observed for paediatric and young adult responders in study **B2202** (B-cell ALL), however the limited data prevents any confident comparison.

No conclusions on cellular kinetics following re-infusion of tisagenlecleucel in paediatric and young adults with B-cell ALL can be drawn from the very limited data available. To the assessor's knowledge re-infusion data is not available from other studies.

Efficacy results

The low sample size provided insufficient data to perform the planned statistical analyses; therefore, the primary and secondary efficacy analyses were not conducted. Available study data were presented in listings and are descriptive only.

Primary endpoint

Loss of B-cell aplasia within 12 months after re-infusion

Incidence of B-cell aplasia was to be assessed on Day 1 (prior to re-infusion) and at Day 28, Month 3, and Month 12. All paediatric patients experienced B-cell aplasia on the day of re-infusion, (i.e., on Day 1), following lymphodepleting chemotherapy, but prior to re-infusion of tisagenlecleucel. All paediatric patients later experienced loss of B-cell aplasia (i.e., B-cell recovery) at the available post-baseline time point(s) prior to the early termination of the study. Results for the paediatric patients is shown in Table 4 below:

Table 4. B-cell aplasia and B-cell recovery data by patient and time point

Age/Sex	Study day*	Absolute B-lymphocyte count (cells/µL)	Total lymphocytes (cells/µL)	B-cell aplasia
3/Male	1	1	53	Yes
	34	285	1092	No
8/Male	1	0	26	Yes
	24	8	563	Yes
	53	150	745	No
14/Male	1	1	104	Yes
	35	54	660	No
15/Female	1	0	34	Yes
	29	98	1906	No
	84	240	907	No

Source: [Study BUS03-Listing 14.2.6-1], [Study BUS03-Listing 14.2.6-9]

* Study day is relative to the first day of tisagenlecleucel re-infusion (Day 1)

The young adult (19-year-old) had B-cell aplasia on day 1, and experienced B-cell recovery at day 78.

Secondary endpoints

Overall remission rate (ORR) after re-infusion

Overall remission rate includes CR and CRi with MRD negativity, as determined by investigator assessment, and was to be assessed at Day 28, and at month 3, 6, and 12. All paediatric patients had a best response of CR or CRi around Day 28 (i.e., between Day 24 and Day 34). See Table 5 below:

Table 5 Overall disease response (ORR)

Age/Sex	Study day*	Best response reported	Bone marrow assessment
3/Male	34	CR	Yes
	67	CR	Yes
8/Male	24	CRi	Yes
14/Male	32	CR	Yes
	91	CRi	No
	182	CR	No
	274	CRi	No
15/Female	29	CR	Yes
	84	CRi	No
	177	CRi	No
	211	CRi	No

The young adult (a 19-year-old) had best response CR at day 28. CR was lost at next evaluation.

Minimal residual disease (MRD) in bone marrow

Bone marrow aspirate was performed for all paediatric patients both prior to study entry and during the study. The specimen quality was adequate for three of the four paediatric patients (1 non-adolescent and 2 adolescents), allowing for MRD assessments by flow cytometry

Of the three paediatric patients with adequate specimen quality, two patients (both adolescent) had positive phenotype results and one patient (non-adolescent) had negative phenotype results at all available time points prior to early termination of study. All three paediatric patients with adequate specimen quality had negative overall MRD status around Day 28 (i.e., between Day 24 and Day 32).

Bone marrow biopsy was performed for three of the four paediatric patients (1 non-adolescent and 2 adolescents) both prior to study entry and during the study. Of those, two patients (both adolescent) had low cell count while one patient (non-adolescent) had a normal cell count at all available time points prior to early termination of study.

Assessor's comment

It is acknowledged that the low sample size provided insufficient data to perform the planned statistical analyses. The MAH's possibility to make a comprehensive discussion of the descriptive efficacy results from the five enrolled patients is obviously hampered. Although the study BUS03 did not manage to clarify potential benefits and risks for the paediatric ALL patients in a re-infusion setting, the issue is still of clinical relevance and important questions are left unanswered.

Safety results

Study **BUS03** was terminated early due to slow recruitment of patients; no safety reasons were involved in the decision to terminate the study prematurely. At the time of the study termination, there were five patients enrolled, including four paediatric patients (<18 years) and one young adult patient (≥18 years). Of the four paediatric patients enrolled, two were children (non-adolescents), aged 3 years and 8 years; and two were adolescents, aged 14 years and 15 years. The young adult patient was a 19-year old.

Safety was assessed by monitoring the frequency, duration and severity of AEs, performing physical examinations, measuring changes in vital signs, body weight and performance status (Karnofsky/ Lansky), and evaluating changes in haematology and biochemistry results. AEs (with the exception of cytokine release syndrome) were assessed and graded according to CTCAE v4.03 and coded with MedDRA v24.1.

Patients treated with tisagenlecleucel should be monitored for specific toxicities for 15 years post-infusion, irrespective of their response to tisagenlecleucel.

Adverse events

Most paediatric patients (3 patients; 1 non-adolescent and 2 adolescents) experienced ≥ 1 AE during the study. The majority of the AEs were CTCAE Grade 1/2, non-serious, and not suspected to be related to the study drug.

Grade 3/4 AEs were reported in two paediatric patients (2 adolescents) and included decreased appetite, neutrophil count decreased, anaemia, nausea, stomatitis, polyomavirus viremia, platelet count decreased, and hypokalaemia. All Grade 3/4 AEs were assessed as non-serious and none were suspected to be related to the study drug, except the non-serious AE of neutrophil count decreased, which was suspected to be related to tisagenlecleucel and resolved without treatment medication/ therapy given to the patient.

Details from the two patients which experienced Grade 3 and 4 AEs are given below.

Grade 3 and Grade 4 adverse events

☐ 14-year old patient had:

- Grade 3 stomatitis, decreased appetite and nausea from Day 57 that resolved on Day 80; these events were unrelated to tisagenlecleucel.
- Grade 4 platelet count decreased from Day 58 that resolved on Day 84; this event was unrelated to tisagenlecleucel but was assessed as related to leukapheresis.
- Grade 3 hypokalaemia from Day 60 that resolved on Day 62; this event was unrelated to tisagenlecleucel.
- Grade 3 anaemia from Day 64 that resolved on Day 91; this event was unrelated to tisagenlecleucel.
- Grade 3 polyomavirus viremia from Day 79 that had not resolved at the time of study closure; this event was unrelated to tisagenlecleucel.

☐ 15-year old (female) patient had:

- Grade 3 neutrophil count decreased from Day 4 to Day 11 that worsened to Grade 4 on Day 11 and then resolved on Day 18; both events were assessed as related to tisagenlecleucel.
- Grade 4 neutrophil count decreased from Day 84 that had not resolved at time of study closure; this event was unrelated to tisagenlecleucel.
- Grade 3 decreased appetite on Day 162 that had not resolved at time of study closure; this event was unrelated to tisagenlecleucel.

Deaths and other serious or clinically relevant adverse events

No patients died during the study.

Serious adverse events

Three patients experienced a total of 4 SAEs during the study; 2 were assessed as related to tisagenlecleucel:

☐ 8-year old patient had Grade 1 paresthesia and Grade 2 headache on Day 4 that resolved the following day; both events were assessed as related to tisagenlecleucel. This patient was in general ward for 1 day due to an AE.

☐ 15-year old (female) patient had grade 1 cytokine release syndrome (CRS) on Day 155 that resolved on Day 163; the event occurred after the patient received investigational treatment of humanized CAR-T cells at another institution, and was assessed as unrelated to tisagenlecleucel. This patient was in general ward for 8 days due to an AE.

☐ 19-year old patient had Grade 2 pyrexia on Day 21 that resolved on Day 23; the event was assessed as unrelated to tisagenlecleucel. This patient was in intensive care unit (ICU) for 28 days for LD chemotherapy and tisagenlecleucel re-infusion; and emergency room for 1 day and general ward for 2 days due to an AE.

No AEs led to study discontinuation.

No AEs of special interest were reported during the course of the study, except the above-mentioned case of cytokine release syndrome.

Clinical chemistry / hematology

Laboratory data and vital signs

No definite trends were observed with regard to laboratory data. All patients had some abnormal laboratory parameters at screening and during the study; however, most laboratory abnormalities were not assessed as AEs. Those that were assessed as Grade 3 or 4 AEs or SAEs are described above.

Vital signs data were generally unremarkable.

Assessor's comments

Four (4) paediatric patients (3, 8, 14, and 15 years old, respectively) and one young adult (19-year old) participated in this study which was early terminated due to slow recruitment and not due to safety reasons.

Most AEs were of Grade 1 or 2 i.e. of mild to moderate intensity, however, the MAH does not describe what kind of adverse events, and how many these were.

Two patients (14-year old, and 15-year old) experienced a total of eight Grade 3 AEs and three Grade 4 AEs; none were assessed as related to tisagenlecleucel, except for one Grade 3 and one Grade 4 event of neutrophil count decreased in one patient (15-year old female), both of which had resolved prior to study closure. This latter patient later developed neutrophil count decreased again, which was not assessed as related to tisagenlecleucel by the investigator. However, for CAR T therapy, it is found that prolonged or recurrent cytopenias have been increasingly reported at varying rates. No further details are given in this case.

Three patients (8-year old, 15-year old and 19-year old) experienced a total of 4 SAEs during the study. The 8-year old had paresthesia and headache on Day 4 that resolved the following day; both events were assessed as related to tisagenlecleucel. The 15-year old had cytokine release syndrome (CRS), and the 19-year old had pyrexia; both events were assessed as unrelated to tisagenlecleucel. No other patient experienced CRS during the study. The three patients who experienced SAEs were all hospitalized during the study due to AEs.

No AEs of special interest were reported during the course of the study, except the above-mentioned case of cytokine release syndrome, which started after the patient was given a novel, investigational treatment of humanized CART-19 cells at another institution and was not considered as related to the study drug.

No patient discontinued due to an AE and no patient died during the study. According to the MAH, there was no impact to patient safety due to COVID-19 during the conduct of this trial.

Although no definite safety conclusions can be drawn from this study due to very limited data with four enrolled paediatric patients only in addition to one young adult, no new safety signals were detected.

Summary of COVID-19 impact

The COVID-19 pandemic, caused by SARS-CoV-2, was first identified by the World Health Organization in Dec-2019 and was declared as a pandemic on 11-Mar-2020. Prior to Mar-2020, the study had not yet opened to enrolment or enrolled any patients. In Mar-2020, following Novartis guidance, the clinical trial team for this study was informed to continue opening the study as there were no major operational issues.

Overall, there were no major changes in the conduct of the study due to COVID-19. There was no impact on patient recruitment. Onsite monitoring was performed at a reduced frequency due to COVID-19 but monitoring plan reflected this frequency and contained provisions for remote

monitoring. There was no impact to patient safety due to COVID-19 during the conduct of this trial. No patients tested positive for COVID-19 during their participation in the trial. One patient (young adult) had documented COVID-19 infection in their medical history, several months prior to enrolment into the trial. Patients attended trial visits as planned. There were no protocol deviations related to COVID-19.

Discussion on clinical aspects

Study CCTL019BUS03 (Study BUS03), a Phase 2, open-label study, was set up to determine the efficacy and safety of tisagenlecleucel re-infusion in paediatric and AYA patients with ALL experiencing loss of B-cell aplasia (i.e. B-cell recovery). The results of study BSU03, which is not part of a PIP, are now submitted and reviewed under this Article 46 procedure. The study was closed early by the Sponsor due to very slow enrolment of patients, which meant that only five patients were enrolled as opposed to 54 patients as originally planned. At the time of study closure, four male patients who were 3, 8, 14 and 19 years of age, and one female patient who was 15 years of age had been enrolled. Therefore, no statistical analysis of the study endpoints was possible; efficacy, safety and PK data were listed only. No comprehensive discussion of the study results is feasible given the very limited and descriptive data provided.

It is acknowledged that the low sample size provided insufficient data to perform the planned statistical analyses. The MAH's possibility to make a comprehensive discussion of the descriptive efficacy and safety results from the five enrolled patients is obviously hampered. Although the study BUS03 did not manage to clarify potential benefits and risks for the paediatric patients in a re-infusion setting, the issue is still of clinical relevance and important questions are left unanswered. The MAH was requested to further elaborate on reasons for slow recruitment in study BUS03, including information on the actual number of patients in clinical practice receiving a second dose of Kymriah which was adequately answered.

Efficacy

Study BUS03's primary objective was to evaluate the incidence of B-cell aplasia after re-infusion of tisagenlecleucel in paediatric patients with ALL experiencing loss of B-cell aplasia (i.e. B-cell recovery). The primary endpoint was defined as proportion of patients who establish B-cell aplasia within 12 months of re-infusion, as measured by circulating B lymphocytes (< 50/µL) and presence of CTL019 cells by qPCR in the peripheral blood.

All four (4) paediatric patients experienced B-cell aplasia on the day of re-infusion, (i.e., on Day 1), following lymphodepleting chemotherapy, but prior to re-infusion of tisagenlecleucel. All four patients later experienced loss of B-cell aplasia (i.e., B-cell recovery) prior to early termination of the study.

All paediatric patients had a best response of ORR (CR + Cri) around Day 28 (i.e., between Day 24 and Day 34) and prior to early termination of the study.

No conclusions can be drawn regarding efficacy of re-infusion of tisagenlecleucel in paediatric patients with ALL based on the limited and descriptive data provided.

Cellular kinetics

Modest expansion was observed for three paediatric patients during the first four weeks, and expansion continued at month 3 for one of the patients. Only one paediatric patient provided data at month 12 (*i.e.* EOS, end of study). No conclusions on cellular kinetics following re-infusion of tisagenlecleucel in paediatric patients with ALL can be drawn based on the very limited available data.

Safety

Most AEs were of Grade 1 or 2 i.e. of mild to moderate intensity, however, the MAH does not describe what kind of adverse events these are, and how many.

Two patients (14-year old, and 15-year old) experienced a total of eight Grade 3 AEs and three Grade 4 AEs; none were assessed as related to tisagenlecleucel, except for one Grade 3 and one Grade 4 event of neutrophil count decreased in one patient (15-year old female), both of which had resolved prior to study closure. This latter patient later developed neutrophil count decreased again, which event was not assessed as related by the investigator. However, for CAR T therapy, it is found that prolonged or recurrent cytopenias have been increasingly reported at varying rates. No further details are given in this case.

Three patients (8-year old, 15-year old and 19-year old) experienced a total of 4 SAEs during the study. The 8-year old had paresthesia and headache on Day 4 that resolved the following day; both events were assessed as related to tisagenlecleucel. The 15-year old had CRS, and the 19-year old had pyrexia; both events were assessed as unrelated to tisagenlecleucel.

No AEs of special interest were reported during the course of the study, except the above-mentioned case of cytokine release syndrome, which was not considered as related to the study drug.

No patient discontinued due to an AE. No patient died during the study. According to the MAH, there was no impact to patient safety due to COVID-19 during the conduct of this trial.

Although no definite safety conclusions can be drawn from this study due to very limited data with 4 enrolled paediatric patients only in addition to one young adult, no new safety signals were detected.

No updates on the product information based on data from the study BUS03 has been proposed. However, the MAH was asked to discuss whether the limited data on efficacy and safety for tisagenlecleucel re-infusion in general ought to be reflected in the SmPC section 4.2. The requested discussion has been provided and accepted by the Rapporteur.

3. Rapporteur's overall conclusion and recommendation

In accordance with Article 46 of Regulation (EC) No 1901/2006, the MAH has submitted the final study results from the complete data set of study BUS03, a Phase 2, open-label study, set up to determine the efficacy and safety of tisagenlecleucel re-infusion in paediatric and AYA patients with ALL experiencing loss of B-cell aplasia (i.e. B-cell recovery). The study was closed early by the MAH due to slow enrolment of patients, which meant that only five patients (i.e. four paediatric patients and one young adult) were enrolled. Therefore, no analyses of cellular kinetics, efficacy and safety following re-infusion of tisagenlecleucel in paediatric patients with ALL were conducted. Thus, no comprehensive discussion and conclusion of the results is feasible given the limited available data.

No new safety signals were detected.

As re-infusion of tisagenlecleucel is of clinical relevance and important questions are left unanswered, the MAH was requested to elaborate on reasons for slow recruitment. In addition, the MAH was asked to discuss whether an update of the SmPC is warranted. These requests are considered adequately addressed by the MAH.

☒**Fulfilled**

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The MAH has not provided detailed reasons for the slow recruitment of patients to study BUS03, e.g to which degree feasibility issues was related to low number of patients eligible for retreatment with Kymriah, lack of available doses of Kymriah, or if other measures could have facilitated recruitment and, thus, prevented the premature closure of the study. A more detailed explanation should be provided with regards to feasibility, including information on the actual number of patients in clinical practice receiving a second dose of Kymriah.
2. Independently of the results from study BUS03, the applicant is asked to discuss whether the limited data on efficacy and safety for tisagenlecleucel re-infusion in general ought to be reflected in the SmPC section 4.2.

MAH responses to Request for supplementary information

Question 1

The MAH has not provided detailed reasons for the slow recruitment of patients to study BUS03, e.g to which degree feasibility issues was related to low number of patients eligible for retreatment with Kymriah, lack of available doses of Kymriah, or if other measures could have facilitated recruitment and, thus, prevented the premature closure of the study. A more detailed explanation should be provided with regards to feasibility, including information on the actual number of patients in clinical practice receiving a second dose of Kymriah.

Summary of MAH answer

CCTL019BUS03 trial was designed and conducted in the United States (USA) only. Results were reported in the European Union in line with the article 46 requirements, but no European sites participated in the trial.

The slow recruitment of patients to study CTL019BUS03 could be explained by the existing alternative set up to get access to additional Kymriah dose outside of this clinical trial as well as the limited additional dose requests.

Also, in the USA, physicians are able to access additional commercial doses of Kymriah outside of the clinical trial at no cost. This is possible prior to the product 9-month expiry date via a request for additional available commercial product. Hence patients are not required to participate in the CCTL019BUS03 clinical trial to receive these additional doses, contributing to the difficulty in enrollment. Therefore, the inclusion criteria that required doses to be requested within the in-specification 9-month expiry date was a limiting factor to enrollment as the requests for additional cells for reinfusion can also be done via the commercial process. The additional burden of meeting Inclusion/Exclusion criteria for the trial could also explain the limited patient participation in CCTL019BUS03 trial.

Additionally, the rate of additional Kymriah dose request evolved over time and may have been overestimated at time of protocol concept development. CCTL019BUS03 trial was designed with a 1-year enrollment period. During the enrollment period (October 2020 to October 2021), there were 37

commercially released additional doses for reinfusion in paediatric ALL in the USA. Thirteen doses went to sites that opened the trial for enrollment and 5 of these 13 doses went to patients meeting inclusion/exclusion criteria for the trial that also enrolled into the trial. It is noted that 7 doses went to sites planning to participate in the trial, that had not yet opened, but it is not known if those patients would have met CCTL019BUS03 inclusion/exclusion criteria. The remainder of the additional doses requested were released commercially, to sites not participating in the trial. The low number of requests, particularly at participating sites, supports Novartis's assertion that it was no longer feasible to reach the enrollment goal of 54 patients within a reasonable time period.

Rapporteur Assessment

The MAH has provided a summary of reasons for slow recruitment of patients to study BUS03. According to the MAH, the main reasons are the limited additional dose requests, as well as the existing alternative for physicians in the US to get access to these additional Kymriah doses outside of this clinical trial.

During the enrollment period (October 2020 to October 2021), there were 37 commercially released additional doses for reinfusion in paediatric ALL in the USA. However, only 5 of these doses went to participants enrolled to the trial. Twenty-four (24) doses went to sites not participating in the trial (17 doses) or sites that had not yet opened the trial (7 doses).

The low number of requests, even at sites enrolling participants, is a plausible explanation to the slow recruitment during the enrollment period of one year. It is acknowleged that at the time of protocol development the feasibility of patient recruitment was unknown, and in hindsight, the goal of accruing 54 patients may have been somewhat optimistic.

Conclusion

Issue resolved

Question 2

Independently of the results from study BUS03, the applicant is asked to discuss whether the limited data on efficacy and safety for tisagenlecleucel re-infusion in general ought to be reflected in the SmPC section 4.2.

Summary of MAH answer

There is limited data on efficacy and safety for tisagenlecleucel re-infusion. CCTL019BUS03 was early terminated due to low enrollment and no conclusions on reinfusion could be elaborated from this clinical trial. In commercial practice, reinfusion is at the discretion of the physician in consultation with the patient and family. Novartis is able to provide additional cells if available, when requested, with clear guidelines regarding whether this can be released commercially prior to the 9-month expiry date or requires additional Health Authority review and approval. Very limited efficacy and/or safety data is available from these reinfusions for patients enrolled in the CIBMTR registry and reported to Novartis in the context of CCTL019B2401 study, but currently no data on B cell aplasia vs recovery is captured, neither is the indication for reinfusion. Many of these patients move to HSCT shortly after reinfusion, hence any efficacy or safety data may be more related to the subsequent allogeneic HSCT and/or other anti-neoplastic therapy.
Considering the very limited data on reinfusion available, the low proportion of additional dose(s) requests for patients treated in the post-marketing setting, also that Kymriah is approved as a single dose treatment and Novartis does not intent to promote off label use, no SmPC update is proposed.

Rapporteur Assessment

The MAH's discussion regarding limited safety and efficacy data for tisagenlecleucel re-infusion is acknowledged. Not updating the SmPC section 4.2 based on the limited new information available is agreed.

Conclusion

Issue resolved.