28 May 2020
EMA/61202/2020
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Kymriah

tisagenlecleucel

Procedure no: EMEA/H/C/004090/P46/011

Note

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

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1. Introduction

On 20 November 2019, the MAH submitted the final study results from a completed paediatric study for Kymriah, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

These data are also submitted as part of a post-authorisation measure (PAM) for this study.

A short critical expert overview summarizing the results in the final CSR has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study B2205J is a supportive stand-alone study.

The MAH has recently submitted a type II group of variations currently under review in a parallel procedure (Procedure No. EMEA/H/C/004090/II/0013/G) that includes updated interim results from this study as well as the pivotal phase II study B2202. Both of these multicentre studies enrolled comparable patient populations with B-cell acute lymphoblastic leukaemia (ALL) and had similar study designs. The MAH has in the requested group of variations proposed updates and amendments to the Summary of Product Characteristics (SmPC; section 4.4, 4.8, 5.1, and 5.2) the Package Leaflet and the Risk Management Plan (RMP) related to the current approved ALL indication.

2.2. Information on the pharmaceutical formulation used in the study

Kymriah cells dispersion for infusion, where 1-3 infusion bags contain a total of $1.2x10^6$ to $6x10^8$ genetically modified anti CD19 chimeric antigen receptor (CAR) positive viable autologous T cells (tisagenlecleucel). 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 $5x10^6$ CAR positive viable T cells/kg body weight for subjects ≤50 kg and 0.1 to $2.5x10^8$ CAR positive viable T cells (non-weight based) for patients >50 kg.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study CCTL019B2205 (B2205J; Protocol no.03)

Study B2205J (ENSIGN) is a phase II, single arm, open-label multi-center study designed to demonstrate or support the efficacy and safety of tisagenlecleucel in paediatric and young adult patients with B-cell ALL who have relapsed or are refractory to prior therapies.

Kymriah (tisagenlecleucel) was approved in the EU via the centralized procedure (Procedure No. EMEA/H/C/004090) on 23-Aug-2018. Kymriah 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 in paediatric and young adult patients with relapsed or refractory (r/r) B-cell ALL was at the time of initial marketing authorization (MA) primarily based on data from the pivotal study B2202, which is a phase II open-label, multicentre, single arm study. Results from the first interim analysis (IA1) of study B2205J provided supportive evidence for the efficacy of tisagenlecleucel (see Table 1).

Table 1. Listing of the clinical studies B2205J and B2202 currently under review

Study ID	No. of study centres/countries	Design	Study Posology	Subjects enrolled /infused	Gender M/F Mean Age	Diagnosis Incl. criteria	Primary Endpoint
CCTL019 -**B2205J** Efficacy and Safety	9/US	Phase II, single arm, open-label, multi-center	Tisagenlecleucel; single infusion; target total dose 0.2-5.0×10^6 viable CAR T-cells/kg body weight (for patients ≤50 kg) and of 0.1-2.5 ×10^8 viable CAR T-cells (for patients >50 kg)	75/64	30/34 12.4 (3-25) years	Paediatric patients with r/r B-cell ALL and B-cell lymphoblastic lymphoma	IRC assessed ORR (CR+CRi) during 6 months after infusion
CCTL019 -**B2202** IA 2018 Efficacy and Safety	25/11	Phase II, single arm, open-label, multi-center	Tisagenlecleucel; single infusion; target dose 0.2-5.0×10^6 viable CAR T-cells/kg body weight (for patients ≤50 kg) and/or 0.1-2.5 ×10^8 cells (for patients >50 kg)	97/79	45/34 12.0 (3-24) years	Paediatric and young adult patients with r/r B-cell ALL	IRC assessed ORR (CR+CRi) during 3 months after infusion of tisagenlecleucel from *all* manuf. sites

Results from study B2205J have been reported previously in two interim clinical study reports (CSRs). The first interim CSR (data cut-off [DCO] date: 01-Feb-2016; final CSR: 24-Nov-2016) was submitted to EMA as part of the initial MA application for tisagenlecleucel on 02-Nov-2017. The second interim CSR (DCO: 06-Oct-2017; final CSR: 01-Nov-2018) served to fulfil the paediatric investigation plan (PIP) Study 2 of PIP EMEA-001654-PIP01-M03, and compliance was confirmed on 01-March-2019 based on this CSR.

The final results from the complete data set of this study are now submitted according to Article 46 of Regulation (EC) No 1901/2006, which requires that any MAH-sponsored study involving use in the paediatric population of a medicinal product covered by a MA should be submitted to the competent authority within six months of completion of the concerned study.

2.3.2. Clinical study

Study B2205J

Methods

Objective(s) and Outcomes/endpoints

The primary objective was to evaluate the efficacy of tisagenlecleucel therapy as measured by overall remission rate (ORR), which includes complete response (CR) and CR with incomplete blood count recovery (CRi) as determined by Independent Review Committee (IRC) assessment within 6 months after tisagenlecleucel administration for patients with B-cell ALL.

The secondary efficacy objectives included the following:

Table 2. Secondary objectives and related endpoints in study B2205J

Objective	Endpoint
Evaluate the percentage of subjects who achieve CR or CRi at Month 6 without SCT between tisagenlecleucel infusion and Month 6 response assessment	• Percentage of subjects who achieve CR or CRi at Month 6 without SCT between tisagenlecleucel infusion and Month 6 response assessment
Evaluate the percentage of subjects who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment	• Percentage of subjects who achieve CR or CRi and then proceed to SCT while in remission prior to Month 6 response assessment • In addition, all subjects that proceed to SCT after tisagenlecleucel infusion will be listed
Evaluate the duration of remission (DOR)	• DOR, i.e. the time from achievement of CR or CRi, whichever occurs first, to relapse or death due to ALL • Site of involvement of subsequent relapse will be summarized
Evaluate the quality of response by assessing the percentage of subjects who achieve a BOR of CR or CRi with a minimal residual disease (MRD) negative bone marrow6 months after tisagenlecleucel infusion and at Day 28 by central analysis	• Percentage of subjects with BOR of CR or CRi with MRD negative bone marrow 6 months after tisagenlecleucel infusion, among all subjects who are infused • MRD status before treatment, at Day 28 +/- 4 days after treatment will also be described
Evaluate the relapse-free survival (RFS)	• RFS, i.e. the time from achievement of CR or CRi whichever occurs first to relapse or death due to any cause during CR or CRi
Evaluate the event-free survival (EFS)	• EFS, i.e. the time from date of tisagenlecleucel infusion to the earliest of death, relapse or treatment failure
Evaluate the overall survival (OS)	• OS, i.e. the time from date of tisagenlecleucel infusion to the date of death due to any reason
Evaluate the response at Day 28 +/- 4 days	• Proportion of subjects attaining CR or CRi at Day 28 +/- 4 days post tisagenlecleucel infusion
Evaluate the impact of baseline tumor burden on response	• Response as a function of baseline tumor burden (tumor load) (MRD, extramedullary disease, etc)
Evaluate the safety of tisagenlecleucel therapy	• Type, frequency and severity of adverse events and laboratory abnormalities

The pre-specified primary efficacy endpoint ORR was defined as the proportion of patients with a best overall disease response of CR or CRi. The best overall disease response was the best disease response recorded from tisagenlecleucel infusion until start of new anticancer therapy (including SCT).

For the best overall disease response to be categorized as CR or CRi, ,remission status was required to be maintained for at least 4 weeks (28 days) without clinical evidence of relapse.

Study design/Treatments

Study B2205J had several sequential periods for all subjects as follows: screening, enrolment, and pre-treatment (cell product preparation, bridging- and lymphodepleting (LD) chemotherapy), treatment and primary follow-up (which included one single dose of tisagenlecleucel infusion and follow-up until

month 60). Subjects who discontinued from primary follow–up (i.e. patients with relapse after remission, treatment failure, stem cell transplantation (SCT) while in remission, or who withdrawn) prior to month 60 entered a secondary follow-up and from primary or secondary follow-up, patient entered long-term survival and safety follow-up (see Figure 1 below).

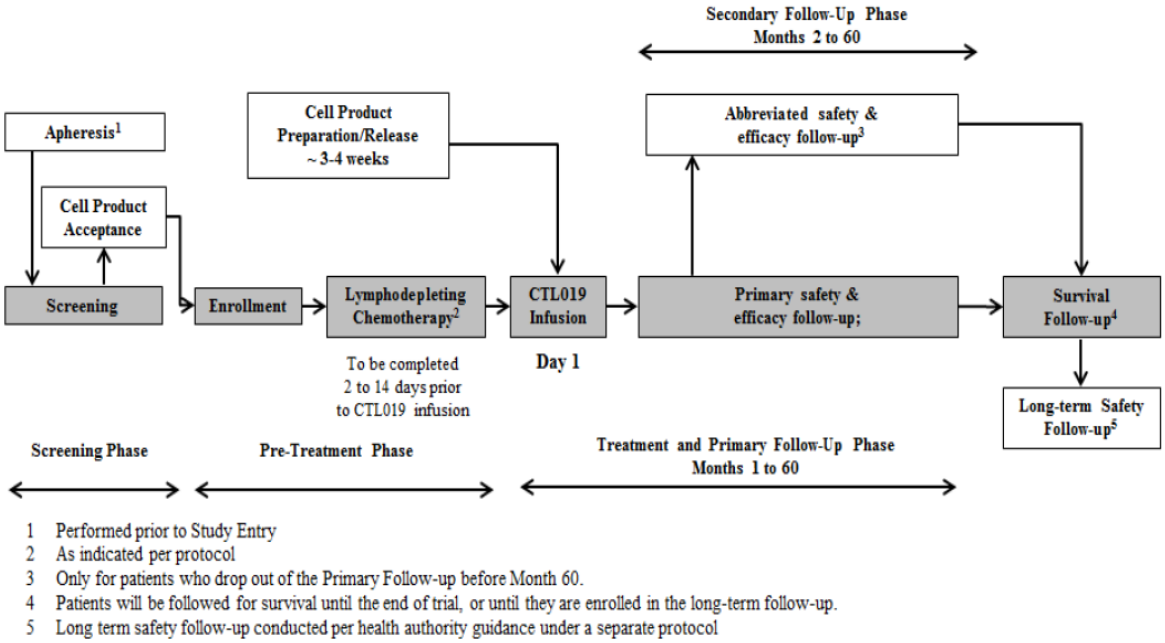

Figure 1. Study design of B2205J

Leukapheresis: Leukapheresis was performed as per study protocol or per local institutional guidelines.

Bridging chemotherapy: Bridging chemotherapy was allowed per investigator choice.

Lymphodepletion (LD): Prior to tisagenlecleucel infusion, a LD chemotherapy cycle was planned. Cyclophosphamide-based regimens were the agents of choice and the LD regimen consisted of:

- Fludarabine (30 mg/m^2 iv daily for 4 doses) and cyclophosphamide (500 mg/m^2 iv daily for 2 doses starting with the first dose of fludarabine)

If the patient had a previous grade 4 hemorrhagic cystitis with cyclophosphamide, or the patient demonstrated a chemorefractory state to a cyclophosphamide-containing regimen administered shortly before LD chemotherapy, then the following was used:

- Cytarabine (500 mg/m^2 iv daily for 2 days) and etoposide (150 mg/m^2 iv daily for 3 days starting with the first dose of cytarabine)

If patients had a white blood cell (WBC) count ≤ 1,000 cells/µL within one week prior to tisagenlecleucel infusion, LD chemotherapy was not required.

Tisagenlecleucel infusion: Investigational treatment consisted of a single iv infusion with a target dose range of 2.0 to 5.0×10^6 tisagenlecleucel cells (i.e. CAR-positive viable T-cells) per kg body weight (for patients ≤ 50 kg) or of 1.0 to 2.5×10^8 tisagenlecleucel cells (for patients >50 kg).

The following cell dose ranges were allowed if all other safety release criteria were met:

- Patients ≤ 50 kg: 0.2 to 5.0×10^6 CAR-positive viable T-cells per kg body weight
- Patients >50 kg: 0.1 to 2.5×10^8 CAR-positive viable T-cells

The tisagenlecleucel dose was administered via a single iv infusion.

The total duration of the study is 5 years. After tisagenlecleucel infusion, efficacy is assessed monthly for the first 6 months, then quarterly up to 2 years and semi-annually afterwards up to 5 years, or until the patient relapse. In addition, semiannual and annual evaluations are to be performed for up to 15 years in the long-term follow up on all patients under a separate destination protocol (study A2205) as recommended by health authority guidance for patients treated with gene therapies.

Table 3. ORR classification at a given evaluation time in ALL patients

Response category	Definition
Complete remission(CR)	All the following criteria were met: **Bone marrow** • < 5% blasts **Peripheral blood** • Neutrophils > 1.0 x 10^9/L, and • Platelets > 100 x 10^9/L, and • Circulating blasts < 1% **Extramedullary disease** • No clinical evidence of extramedullary disease (by physical exam and central nervous system (CNS) symptom assessment), and • If additional assessments (e.g. CSF assessment by lumbar puncture (LP), CNS imaging, biopsy, etc.) were performed, results must show remission status **Transfusion independency** • No platelet and/or neutrophil transfusions less than or equal to 7 days before peripheral blood sample for disease assessment
Complete remission with incomplete blood count recovery (CRi)	All criteria for CR as defined above were met, except that the following existed: • Neutrophils ≤ 1.0 x 10^9/L, and/or • Platelets ≤ 100 x 10^9/L, and/or • Platelet and/or neutrophil transfusions less than or equal to 7 days before peripheral blood sample for disease assessment
No response	Failure to attain the criteria needed for any response categories or relapse
Relapsed Disease	Only in patients with a CR or CRi and who had: • Reappearance of blasts in the blood (≥ 1%), or • Reappearance of blasts in bone marrow (≥ 5%), or • (Re-)appearance of any extramedullary disease after CR or CRi

Study population

Paediatric and young adult subjects (age 3 years at the time of screening to age 21 years at the time of initial diagnosis) with B-cell ALL and lymphoblastic lymphoma who were primary refractory, chemo-refractory, relapsed after allogeneic SCT, or were otherwise ineligible for allogeneic SCT were enrolled in the study.

Main inclusion criteria

1. Relapsed or refractory paediatric B-cell ALL and lymphoblastic lymphoma:

a. 2nd or greater bone marrow (BM) relapse OR

b. Any BM relapse after allogeneic SCT and was > 6 months from SCT at the time of tisagenlecleucel infusion OR

c. Primary refractory as defined by not achieving a CR after 2 cycles of a standard chemotherapy regimen or chemo-refractory as defined by not achieving a CR after 1 cycle of standard chemotherapy for relapsed leukaemia OR

d. Patients with Philadelphia chromosome positive (Ph+) ALL were eligible if they were intolerant to or had failed two prior lines of tyrosine kinase inhibitor (TKI) therapy, or if TKI therapy was contraindicated OR

e. Ineligible for allogeneic SCT because of: co-morbid disease, other contraindications to allogeneic SCT conditioning regimen, lack of suitable donor, prior SCT, declined allogeneic SCT as a therapeutic option after documented discussion, including expected outcomes, about the role of SCT with a BM transplantation physician not part of the study team

2. Age 3 at the time of screening to age 21 at the time of initial diagnosis.

3. For relapsed patients, CD19 tumour expression demonstrated in bone marrow or peripheral blood by flow cytometry within 3 months of study entry

4. Adequate renal, hepatic, and pulmonary functions

5. Bone marrow with ≥ 5% lymphoblasts by morphologic assessment at screening

6. Life expectancy > 12 weeks

7. Karnofsky (age ≥16 years) or Lansky (age <16 years) performance status ≥50 at screening

8. Once all other eligibility criteria are confirmed, must have a leukapheresis product of nonmobilized cells received and accepted by the manufacturing site. Note: Leukapheresis product will not be shipped to or assessed for acceptance by the manufacturing site until documented confirmation of all other eligibility criteria is received 1

9. Patients with active central nervous system (CNS) leukaemia involvement defined as CNS3 by CSF findings only were eligible but would have their tisagenlecleucel infusion delayed until CNS disease was reduced to CNS1 or CNS2 by CSF findings. Patients with other forms of active CNS3 leukemic involvement such as CNS parenchymal or ocular disease, cranial nerve involvement or significant leptomeningeal disease were not eligible. However, such patients with other forms of CNS3 leukemic involvement (non-CSF involvement) were eligible if there were documented evidence of disease stabilization for at least 3 months prior to tisagenlecleucel infusion. Patients should not have any acute/ongoing neurologic toxicity > Grade 1 with the exception of a history of controlled seizures or fixed neurologic deficits that had been stable/improving over the past 3 months.

Main exclusion criteria

1. Isolated extra-medullary disease relapse

2. Reduced cardiac function

3. Patients with concomitant genetic syndromes associated with bone marrow failure states: such as patients with Fanconi anemia, Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome. Patients with Down Syndrome will not be excluded.

4. Patients with Burkitts lymphoma/leukemia (i.e. patients with mature B-cell ALL, leukemia with B-cell [sIg positive and kappa or lambda restricted positivity] ALL, with French-American-British (FAB) L3 morphology and /or a MYC translocation)
5. Prior malignancy, except carcinoma in situ of the skin or cervix treated with curative intent and with no evidence of active disease.
6. Treatment with any prior gene therapy product, or had prior treatment with any anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy6. Active or latent hepatitis B or active hepatitis C (test within 8 weeks of screening), or any uncontrolled infection at screening
7. Human Immunodeficiency Virus (HIV) positive test within 8 weeks of screening
8. Presence of Grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD)
9. Patient had participated in an investigational research study using an investigational agent within the last 30 days prior to screening
10. The following medications were excluded:
    a. **Steroids**: Therapeutic systemic doses of steroids had to be stopped >72 hours prior to tisagenlecleucel infusion. However, the following physiological replacement doses of steroids were allowed: <12 mg/m^2/day hydrocortisone or equivalent
    b. **Allogeneic cellular therapy**: Any donor lymphocyte infusions had to be completed >6 weeks prior to tisagenlecleucel infusion
    c. **GVHD therapies**: Any systemic drug used for GVHD had to be stopped >4 weeks prior to tisagenlecleucel infusion to confirm that GVHD recurrence was not observed (e.g. calcineurin inhibitors, methotrexate or other chemotherapy drugs, mycophenolyate, rapamycin, thalidomide, or immunosuppressive antibodies such as anti-CD20 (rituximab), anti-tumour necrosis factor [anti-TNF], anti-interleukin 6 [anti-IL6] or anti-interleukin 6 receptor [anti-IL6R], systemic steroids)
    d. **Chemotherapy**:
        i. Tyrosine kinase inhibitors and hydroxyurea had to be stopped >72 hours prior to tisagenlecleucel infusion
        ii. The following drugs had to be stopped >1 week prior to tisagenlecleucel infusion and should not be administered concomitantly or following LD chemotherapy: vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate <25 mg/m^2, cytosine arabinoside <100 mg/m^2/day, asparaginase (non-pegylated)
        iii. The following drugs had to be stopped >2 weeks prior to tisagenlecleucel infusion: salvage chemotherapy (e.g. clofarabine, cytosine arabinoside >100 mg/m^2, anthracyclines, cyclophosphamide, methotrexate ≥ 25 mg/m^2), excluding the required LD chemotherapy drugs
        iv. Pegylated-asparaginase had to be stopped >4 weeks prior to tisagenlecleucel infusion
    e. **CNS disease prophylaxis**: CNS prophylaxis treatment had to be stopped >1 week prior to tisagenlecleucel infusion (e.g. intrathecal methotrexate)
    f. Radiotherapy

i. Non-CNS site of radiation had to be completed >2 weeks prior to tisagenlecleucel infusion

ii. CNS directed radiation had to be completed >8 weeks prior to tisagenlecleucel infusion

g. **Anti T-cell antibodies**: Administration of any T cell lytic or toxic antibody (e.g. alemtuzumab) within 8 weeks prior to tisagenlecleucel was prohibited since residual lytic levels may destroy the infused tisagenlecleucel cells and/or prevent their in vivo expansion. If such an agent had been administered within 8 weeks prior to tisagenlecleucel, the Sponsor had to be contacted, consultation with an pharmacology expert was considered, and measuring residual drug levels was considered, if feasible, prior to tisagenlecleucel infusion.

11. Women of child-bearing potential (defined as all women physiologically capable of becoming pregnant) and all male participants, unless they are using highly effective methods of contraception for a period of 1 year after the tisagenlecleucel infusion. Women who are not of reproductive potential (defined as either <11 years of age, Tanner Stage 1, post-menopausal for at least 24 consecutive months (i.e. have had no menses) or have undergone hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy) were eligible without requiring the use of contraception. In case of use of oral contraception, women must be stable on the same pill for a minimum of 3 months before taking study treatment.
12. Pregnant or nursing (lactating) women. NOTE: female study participants of reproductive potential must have had a negative serum or urine pregnancy test performed within 48 hours before infusion.

Statistical Methods

Analysis sets

The *Enrolled set* comprised all patients who were enrolled in the study. Enrolment date was defined as the point at which the patient met all inclusion/exclusion criteria, and the patients' leukapheresis product was received and accepted by the manufacturing facility.

The *Full analysis set (FAS)* comprised of all patients who received infusion of tisagenlecleucel.

The *Efficacy Analysis Set (EAS)* consisted of a subset of patients in the FAS who were treated with tisagenlecleucel at least 6 months prior to the last subject last visit (LSLV). In the final report, EAS was identical to the FAS.

The *Safety set* comprised of all patients who received infusion of tisagenlecleucel.

The *Per-protocol set (PPS)* consisted of a subset patients in the FAS who were compliant with major requirements of the clinical study protocol.

The *Pharmacokinetic analysis set (PAS)* consisted of a subset of patients in the FAS who had at least one sample providing evaluable PK data.

Hypothesis and primary efficacy analysis

The primary efficacy analysis was performed by testing whether the ORR was greater than 20% at overall one-sided 2.5% level of significance:

H_0: $p \leq 0.2$ vs. H_a: $p > 0.2$.

This was tested by comparing the lower bound of two-sided exact Clopper-Pearson confidence intervals for ORR in the EAS to 20%.

Interim analysis

An interim analysis and a final analysis was planned for the primary endpoing (ORR), and an α-spending function according to Lan-DeMets (O'Brien-Fleming) was used to control the Type I error for the primary endpoint (ORR) at a one-sided level of significance of 2.5%. The bound for declaring success at the interim/final analysis was determine based on the actual number of patients (29/45), and the corresponding confidence interval calculated. If the calculated confidence interval for ORR exceeded 20% the study was to be declared a success.

Planned Analysis	Two-sided CI	ORR needed to exceed 20%
Interim N=29	98.95%	13/29 = 45%
Final N=45	95.33%	16/45 = 35%

Statistical methods for secondary endpoints

No formal hypothesis testing was planned or carried out for secondary endpoints. For secondary endpoints involving disease assessments the IRC assessment (done during treatment and primary follow-up phase only) was considered primary.

Percentage of patients who achieved CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment, and Percentage of patients who achieved CR or CRi and then proceed to SCT while in remission before Month 6 response assessment, were presented with .two-sided exact 95% Clopper-Pearson confidence intervals.

For time-to-event analyses (DOR, RFS, EFS and OS), the survival function was estimated using the Kaplan-Meier (product-limit) method. Median survival and KM-estimates at specific time points with 95% confidence intervals were presented.

Duration of remission (DOR) was defined as the duration from the date when the response criteria of CR or CRi was first met to the date of relapse or death due to underlying cancer.

Relapse free survival (RFS) was measured by the time from achievement of CR or CRi whatever occured first to relapse or death due to any cause during CR or CRi.

Event free survival was the time from date of first CTL019 infusion to the earliest of: Death from any cause after remission, Relapse or Treatment failure. Treatment failure was defined as no response in the study and discontinuation from the study due to any of the following reasons: Death Adverse event, Lack of efficacy, New anticancer therapy.

For DOR,RFS and EFS Patients were censored at the last disease assessment prior or on the date of: ongoing no event, lost to follow-up, withdrew consent, New anti-cancer therapy, adequate assessment no longer available, event after at least two missing scheduled disease assessments. Sensitivity analyses not censoring for SCT were performed.

Overall survival was defined as the time from date of first CTL019 infusion to the date of death due to any reason. Patients not known to have died were censored at latest date known to be alive. No censoring for SCT was done.

Missing Data

Patients with unknown clinical response were treated as non-responders, or by censoring for the time to event endpoints as described above.

Subgroup Analyses

Subgroup analyses were considered exploratory and only ORR by age subgroups was presented.

(Statistical methods of analysis)

Assessor's comment

Standard methods have been applied for testing of hypotheses and estimation of primary and secondary endpoints. The censoring rules applied to the time-to-event endpoints are the same as in the B2202 pivotal study. Overall the statistical methods are endorsed.

Sample size

The sample size calculation was primarily based on the hypothesis testing for ALL patients. Based on the null hypothesis of ORR $\leq$ 20% and alternative hypothesis of ORR >20%, 45 ALL patients in the FAS was calculated to provide 93% power to demonstrate statistical significance using a 2-look Lan-Demets group sequential design with O'Brien-Fleming type boundary at one-sided cumulative 0.025 level of significance, if the underlying ORR is 45%.

Results

Recruitment/ Number analysed

Study B2205J enrolled and treated paediatric and young adult patients with r/r B-cell ALL and lymphoblastic lymphoma at 9 investigative centres in the US. Study initiation date was 14-Aug-2014 (first subject first visit) and study completion date was 24-May-2019 (last subject last visit).

A total of 85 paediatric and young adult patients with r/r B-cell ALL and lymphoblastic lymphoma were screened, 75 were enrolled in the study and 64 patients were infused with tisagenlecleucel. Ten screened patients could not be enrolled (nine subjects did not satisfy all clinical inclusion criteria or met exclusion, and one was not enrolled due to physician decision). Among the enrolled patients, 14.7% (11/75) discontinued after enrolment and prior to tisagenlecleucel infusion (8.0% [6 patients] died and 6.7% [5 patients] discontinued due to product related issues. The median times from screening and enrolment to tisagenlecleucel infusion were 54.5 days (range: 33 to 182) and 37.5 (range: 22 to 118), respectively.

Table 4. Overall patient disposition (Enrolled set)

Disposition Reason	All subjects N = 75 n (%)
Enrolled in the study	75 (100)
Discontinued prior to tisagenlecleucel infusion	11 (14.7)
Death	6 (8.0)
Tisagenlecleucel product related issues	5 (6.7)
Tisagenlecleucel infused	64 (85.3)
Study follow-up completed	4 (5.3)
Discontinued study follow-up	60 (80.0)
Study terminated by sponsor	24 (32.0)
Lack of Efficacy	18 (24.0)
Death	12 (16.0)
Physician Decision	3 (4.0)
Subject/guardian decision	2 (2.7)
New therapy for study indication	1 (1.3)
Enrolled into long-term follow up protocol[1]	31 (41.3)

- Enrolled set = All subjects who meet all inclusion/exclusion criteria, and whose apheresis product is received and accepted by the manufacturing facility

- Study follow-up includes both primary and secondary follow-up. Subjects may move from primary to secondary follow-up due to treatment failure, relapse, pursuing SCT or other reasons.

[1]Includes all subjects transited to the long term follow up study

All patients (n = 64) who received tisagenlecleucel infusion completed 6 months follow up and were included in the efficacy analysis set (EAS), including 84.4% (54/64) patients <18 years of age.

There were no major protocol deviations leading to exclusion from PPS. Of the 64 subjects, 12 subjects (18.8%) were excluded from the PPS not due to protocol deviation but due to an infused dose below the minimum target dose: less than $2x10^6$ tisagenlecleucel transduced viable T cells/kg for subjects ≤ 50 kg (n = 4) and less than $1x10^8$ transduced cells for subjects > 50 kg (n = 8). Minor protocol deviations were reported in 12 subjects who received tisagenlecleucel infusion and one additional patient who did not receive tisagenlecleucel. The minor protocol deviations are not considered to have had a significant impact on the assessment of the final study results.

Baseline data

The demographics and baseline disease characteristics for all patients who were enrolled and received tisagenlecleucel infusion in study B2205J are presented in Table 5, Table 6 and Table 7 below:

Table 5. Demographic summary (EAS/FAS)

Demographic variable Statistics	All subjects N = 64
Age (years)	
n	64
Mean (SD)	12.4 (5.16)
Median	12.5
Min-Max	3 - 25
Age category (years) - n (%)	
less than 10	20 (31.3)
more than or equal to 10 to less than 18	34 (53.1)
more than or equal to 18	10 (15.6)
Sex - n (%)	
Female	34 (53.1)
Male	30 (46.9)
Race - n (%)	
White	52 (81.3)
Asian	5 (7.8)
Other	7 (10.9)
Ethnicity - n (%)	
Hispanic or Latino	25 (39.1)
Other	39 (60.9)
Weight for tisagenlecleucel manufacturing (kg)	
n	64
Mean (SD)	43.7 (20.10)
Median	42.4
Min-Max	16.2 - 93.4
Karnofsky/Lansky performance status - n (%)	
100	18 (28.1)
90	28 (43.8)
80	13 (20.3)
70	2 (3.1)
60	1 (1.6)
50	2 (3.1)
less than 50	0

SD = Standard deviation

Table 6. Primary disease history and prior antineoplastic therapies (EAS/FAS)

Disease history	All subjects N = 64
Diagnosis of disease - n (%)	
ALL B-CELL	64 (100)
Age at initial diagnosis (years)	
n	64
Mean (SD)	8.6 (5.28)
Median	8.0
Min-Max	1 - 19
Age at initial diagnosis category (years) - n (%)	
less than 10	36 (56.3)
greater than or equal to 10	28 (43.8)
Prior Hematopoietic Stem Cell Transplant (SCT) - n (%)	
0	36 (56.3)
1	26 (40.6)
2	2 (3.1)
Disease status - n (%)	
Primary refractory	7 (10.9)
Relapsed disease	57 (89.1)
Number of previous lines of therapies	
n	64
Mean (SD)	2.9 (1.45)
Median	3.0
Min-Max	1 - 9
Time since initial diagnosis to first relapse (months) [1]	
n	56
Mean (SD)	33.6 (23.75)
Median	27.6
Min-Max	1.0 - 108.0
Time since initial diagnosis to first relapse category (months) - n (%)[1]	
less than 18	16 (28.1)
18 to 36	18 (31.6)
greater than 36	22 (38.6)
Not applicable	1 (1.8)
Time since most recent relapse to tisagenlecleucel infusion (months) [1]	
n	57
Mean (SD)	3.1 (1.65)
Median	2.6
Min-Max	1.3 - 9.8

Primary refractory: Never had a morphologic complete remission (CR) prior to the study
Relapsed disease: Had at least one relapse prior to the study.
[1]Calculated for relapsed disease subjects only.

Table 7. Disease characteristics (EAS/FAS)

Characteristic	All subjects N = 64
MRD in bone marrow by flow cytometry (%)	
n	60
Mean (SD)	45.368 (33.7927)
Median	51.010
Min-Max	0.00 - 98.98
Morphologic blast count in bone marrow (%)[1]	
n	64
Mean (SD)	60.59 (30.141)
Median	68.50
Min-Max	8.0 - 98.0
CNS status classification - n (%)	
CNS-1	56 (87.5)
CNS-2	7 (10.9)
CNS-3	1 (1.6)
Extramedullary disease presentation at physical exam - n (%)	
Yes	5 (7.8)
No	59 (92.2)

Baseline = The most current assessment on or prior to the date of enrollment.
[1]Morphologic blasts count in bone marrow is the max from biopsy or aspirate if both are available.
- The most current assessment on or prior to the date of enrollment is summarized.

Clinical pharmacology

Biopharmaceutics

Updated data on humoral and cellular immunogenicity will be provided later in a separate report.

Assessor`s comment

The applicant has not described in detail which data/analysis the report on biopharmaceutics will contain. The submitted package with this Article 46 procedure does not include updated dose-exposure-response analysis. It is presumed this will be submitted later (**OC**).

Cellular kinetics and pharmacokinetic data

Methods – analysis of data submitted

Updated results (i.e. updated cellular kinetics) are presented for study B2205J with study completion date: 24-May-2019 (last subject last visit).

Results

All tisagenlecleucel infused subjects were included in the kinetic analysis for the derivation of cellular kinetic parameters (n = 64). Transgene levels were determined in peripheral blood via quantitative polymerase chain reaction (qPCR) with a lower limit of quantification of 10 copies/200 ng of DNA that approximates to 50 copies/µg of genomic DNA. Cellular kinetic parameters of tisagenlecleucel were derived from qPCR data, and summarized. Concentration-time profiles of tisagenlecleucel as measured by qPCR by response category are displayed in Figure 2 (D28) and Figure 3.

CR/CRi subjects showed a trend for greater maximal expansion (Cmax) and durability of persistence (AUC0-28d and AUC0-84d) relative to a limited number of NR subjects.

- The median time to reach Cmax (Tmax) for tisagenlecleucel transgene was approximately 10 days in the CR/CRi subjects and 20 days in the NR subjects.
- The transgene levels in pheripehral blood was higher in CR/CRi patients than in NR.
- Tisagenlecleucel was measurable in peripheral blood up to 921 days in CR/CRi subjects.
- In CR/CRi subjects the transgene levels in bone marrow were present at the first post-infusion time point (at Day 28), followed by a decline in levels over time. A wide range of transgene levels measured across all CR/CRi subjects showing the trafficking of tisagenlecleucel to the bone marrow space while transgene was not measureable in the NR subjects at collections beyond Day 28.
- Biomarker studies further supported the on-target effects of tisagenlecleucel including B-cell aplasia. As measured by the average level of peripheral blood CD19-positive B-cells, tisagenlecleucel effectively eradicated CD19 positive B-cells in CR/CRi subjects. The KM estimated probability that a subject will remain with B-cell aplasia was 67.6% (95% CI: 52.0%, 79.1%) at Month 6, and 53.9% (95% CI: 37.6%, 67.7%) at Month 12 and at Month 30.

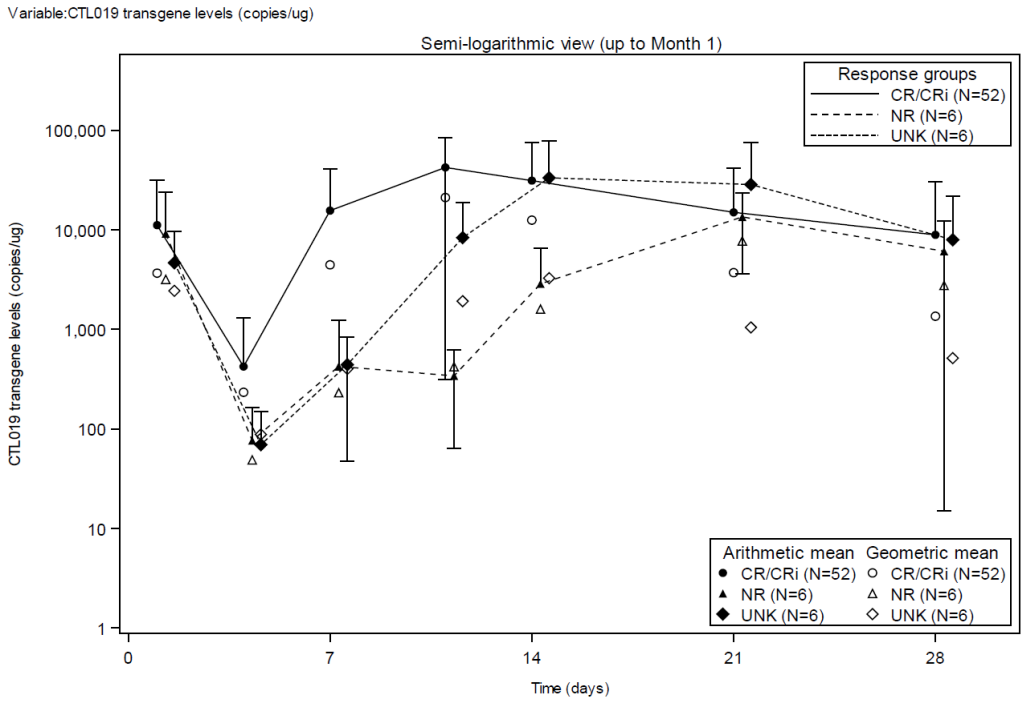

Figure 2. Geometric mean and arithmetic mean (SD) concentration-time profiles for tisagenlecleucel transgene levels by qPCR in peripheral blood by Day 28 disease response by independent review committee (IRC)assessment (Pharmacokinetic analysis set).

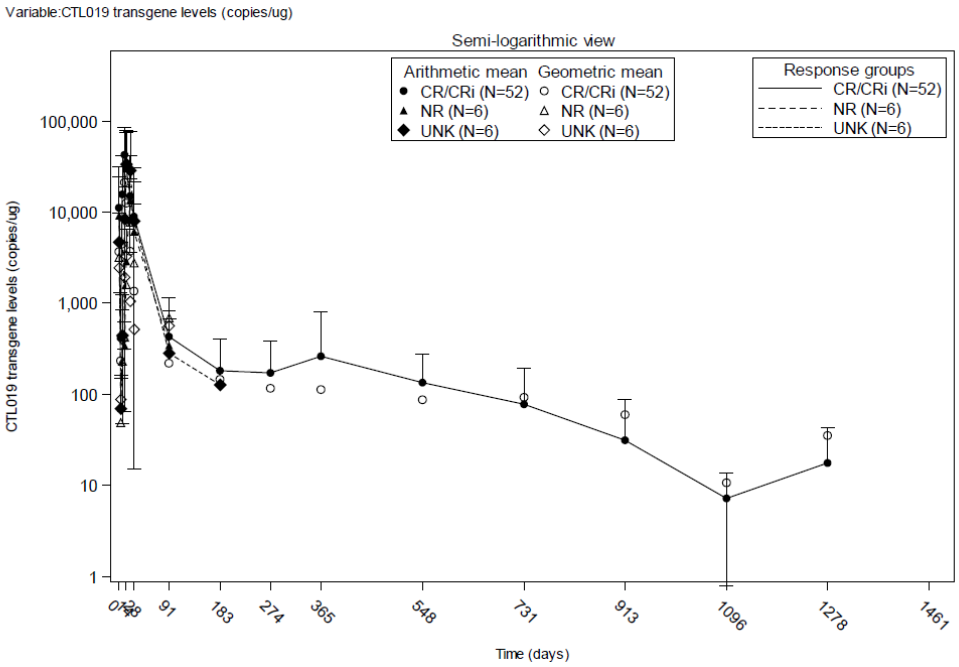

Figure 3. Geometric mean and arithmetic mean (SD) concentration-time profiles for tisagenlecleucel transgene levels by qPCR in peripheral blood by disease response by independent review committee (IRC)assessment (Pharmacokinetic analysis set).

Assessor`s comment:

The cellular kinetics profile appears consistent with that of the two prior interim studies, although direct comparisons have not been submitted. The dose- and exposure-efficacy relationships have not been reinvestigated based on the updated data from study B2205J.

For the variation EMEA/H/C/4090/II/013/G (currently ongoing) the applicant submitted updated analysis of the exposure-response relationship. In that analysis, in contrast to previous analyses, the updated data reveal an apparent exposure-response relationship, with DOR being considerably longer in DLBCL patients with exposure above the median exposure, most notably for Cmax, but also for AUC0-28d. In ALL patients, there was still no apparent relationship between weight-adjusted dose and DOR in patients ≤50 kg. In patients >50 kg, DOR was notably shorter in patients who received a dose lower than the median dose (1.75 x 108 CAR-positive viable T cells). However, due to the small number of patients in this analysis, the results should be interpreted with caution. The MAH's plans to further assess the dose and the exposure-response relationships as more data become available was supported.

The applicant is asked to clarify their approach for assessing the clinical relevance of the trend for difference in exposure-response between responders and non-responders as more data come available. Specifically, the following point should be addressed for updated exposure-response analysis and any implications of new results for the dosing rationale should be discussed (**OC**).

- exposure categorized into quartiles

- additional analyses to re-evaluate the relationship between exposure parameters (preferably considering all potentially important exposure parameters, including AUC0-28d, AUC0-84d and Cmax, unless otherwise justified) and PFS, EFS (i.e. as in the initial MAA submission) as well as DOR.

- tumor burden and the actual dose administered to the individual patients.

Efficacy results

Results from the IA1 with DCO of 01-Feb-2016 and a median follow-up of 11.5 months was submitted to EMA as part of the initial MAA. The main efficacy results from the IA1 is summarised in Table 8 below:

Table 8. Summary of efficacy results from study B2205J (IA1)

	Study B2205J
Efficacy parameter	**N=29**
ORR [1]	
ORR (CR + CRi), n (%)	20 (69.0)
(95% CI)	(43.6, 88.1)
p-value	<0.0001 [5]
CR, n (%)	18 (62.1)
CRi, n (%)	2 (6.9)
NR [2], n (%)	7 (24.1)
Unknown, n (%)	2 (6.9) [3]
ORR with MRD-negative bone marrow	
n (%)	18 (62.1)
(95% CI)	(42.3, 79.3)
DOR	
Events/Responders (%)	8/20 (40.0)
Median follow-up (months)	6.4
Median (months) (95% CI)	Not reached
% Event-free probability estimates at Month 6 (95% CI) [4]	66.4 (39.3, 83.6)
EFS	
Events/Total (%)	17/29 (58.6)
Median follow-up (months)	5.7
Median (months) (95% CI)	6.9 (1.5, NE)
% Event-free probability estimates at Month 6 (95% CI) [4]	55.0 (35.3, 70.9)
OS	
Events/Total (%)	10/29 (34.5)
Median follow-up (months)	7.3
Median (months) (95% CI)	Not reached
% Survival probability estimates at Month 6 (95% CI) [4]	75.7 (55.7, 87.6)

The final analysis includes updated efficacy data based on 75 patients who were enrolled, including 64 who received tisagenlecleucel infusion and completed 6 month follow up. The median follow-up time for the 64 patients treated with tisagenlecleucel defined as median duration from first infusion until LSLV was 31.74 months (range: 17.6-56.0).

Table 9. Summary of final efficacy results from study B2205J (EAS/FAS)

Efficacy parameter	Study B2205J		
	< 10 years N=20	≥ 10 to 18 N=34	All subjects N=64
Primary endpoint			
ORR [1], N	**20 (EAS)**	**34 (EAS)**	**64 (EAS)**
ORR (CR + CRi), n (%)	14 (70.0)	25 (73.5)	45 (70.3)
(95% CI); p-value [2]	(45.7, 88.1), NA	(55.6, 87.1), NA	(52.9, 82.4); <0.0001
CR, n (%)	13 (65.0)	20 (58.8)	38 (59.4)
CRi, n (%)	1 (5.0)	5 (14.7)	7 (10.9)
NR [3], n (%)	4 (20.0)	5 (14.7)	13 (20.3)
Unknown, n (%)	2 (10.0)	4 (11.8)	6 (9.4)
Secondary endpoints			
ORR with minimal residual disease - negative bone marrow, N	**20 (EAS)**	**34 (EAS)**	**64 (EAS)**
n (%)	14 (70.0)	24 (70.6)	43 (67.2)
(95% CI)	(45.7, 88.1)	(52.5, 84.9)	(54.3, 78.4)
DOR, N	**34 (EAS)**	**34 (EAS)**	**64 (EAS)**
Events/Responders (%)	6/14 (42.9)	4/25 (16.0)	13/45 (28.9)
Median (months) (95% CI)	13.6 (4.7, NE)	NE (14.8, NE)	NE (13.6, NE)
% Event-free probability estimates (95% CI) [4]:			
Month 6	58.4 (26.2, 80.6)	96.0 (74.8, 99.4)	79.5 (62.9, 89.3)
Month 12	58.4 (26.2, 80.6)	85.3 (60.7, 95.1)	70.5 (52.8, 82.6)
Month 24	48.7 (18.8, 73.4)	77.6 (49.2, 91.3)	62.8 (43.9, 76.9)
Event-free survival, N	**NA**	**NA**	**64 (FAS)**
Events/Total (%)			28/64 (43.8)
Median (months) (95% CI)			15.6 (6.4, NE)
% Event-free probability estimates (95% CI) [4]:			
Month 6			67.0 (53.5, 77.4)
Month 12			53.6 (39.3, 66.0)
Month 24			47.8 (33.0, 61.1)
Overall survival, N	**NA**	**NA**	**64 (FAS)**
Events/Total (%)			30/64 (46.9)
Median time from infusion to LSLV (months)			15.13
Median (months) (95% CI)			29.9 (15.1, 42.4)
% Event-probability estimates (95% CI) [4]:			
Month 6			84.4 (72.9, 91.3)
Month 12			65.4 (52.4, 75.7)
Month 24			54.7 (39.8, 67.4)

[1] ORR was a primary endpoint; responses were assessed by IRC; and BOR lasting for at least 28 days during 6 months after infusion

[2] No formal significance testing was conducted as the endpoint was met at the first interim analysis. Nominal p-value is presented.

[3] Includes relapse from response without maintenance for at least 28 days.

[4] Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. % Event-free probability estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of Kaplan-Meier estimates.

A total of 13 of the 45 patients (28.9%) who achieved a BOR of CR or CRi reported relapse per IRC review prior to LSLV. The median DOR was not reached. The estimated relapse-free rate among responders was 79.5% (95% CI: 62.9, 89.3) at month 6, 70.5% (95% CI: 52.8, 82.6) at month 12, and 62.8% (95% CI: 43.9, 76.9) at month 24 after onset of remission per IRC review for the EAS/FAS.

There was 100% concordance between the IRC assessment and local assessment of BOR and ORR within 6 months post -tisagenlecleucel infusion in the enrolled set (Table 10).

Table 10. BOR and ORR within 6 months post tisagenlecleucel (Enrolled Set)

	Local assessment N=75		IRC assessment N=75	
	n (%)	95% CI	n (%)	95% CI
Best overall response (BOR)				
CR	38 (50.7)		38 (50.7)	
CRi	7 (9.3)		7 (9.3)	
No response	13 (17.3)		13 (17.3)	
Unknown (UNK)	17 (22.7)		17 (22.7)	
Overall Remission Rate (ORR: CR+CRi)	45 (60.0)	(48.0,71.1)	45 (60.0)	(48.0,71.1)

The robustness of the primary analysis of ORR (per IRC assessment) was confirmed by the results of a series of predefined sensitivity analyses (Table 11). The ORR ranged from 59.2% to 73.1% in different analysis sets, with the lower bounds of all 95% CIs above 20% for all analysis.

Table 11. ORR by IRC assessment - Sensitivity analyses

	All subjects	
	n/N (%)	95% CI
ORR (CR+CRi)		
EAS (Primary analysis)	45/64 (70.3)	(57.6,81.1)
PPS	38/52 (73.1)	(59.0,84.4)
Enrolled set	45/75 (60.0)	(48.0,71.1)
EAS plus subjects who satisfy all clinical eligibility and discontinued prior to tisagenlecleucel infusion	45/76 (59.2)	(47.3,70.4)

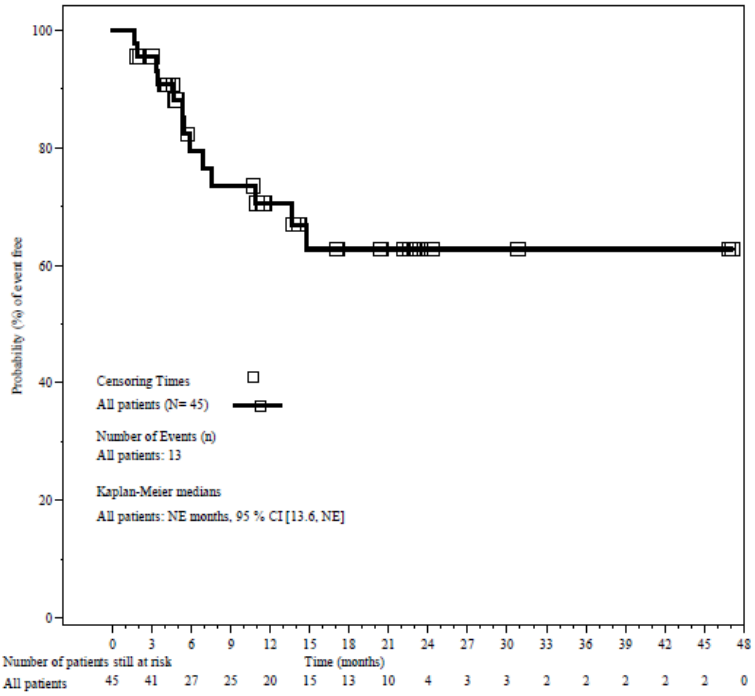

Figure 4. KM plot of DOR censoring HSCT by IRC assessment (EAS/FAS)

Only subjects who achieved CR or CRi are included. Time is relative to onset of remission, 1 month = 30.4375 days.
Source: Figure 14.2-6.1.

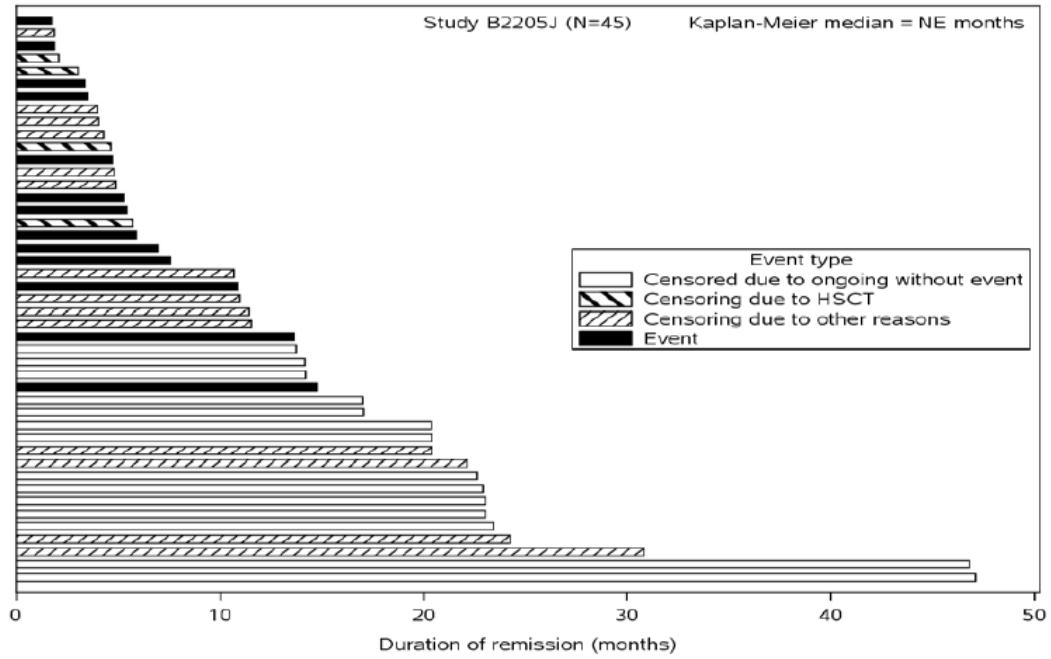

Figure 5. Swimmer-plot for DOR censoring HSCT by IRC assessment (EAS/FAS)

Only subjects who achieved CR or CRi are included. Time is relative to first tisagenlecleucel infusion date, 1 month = 30.4375 days.

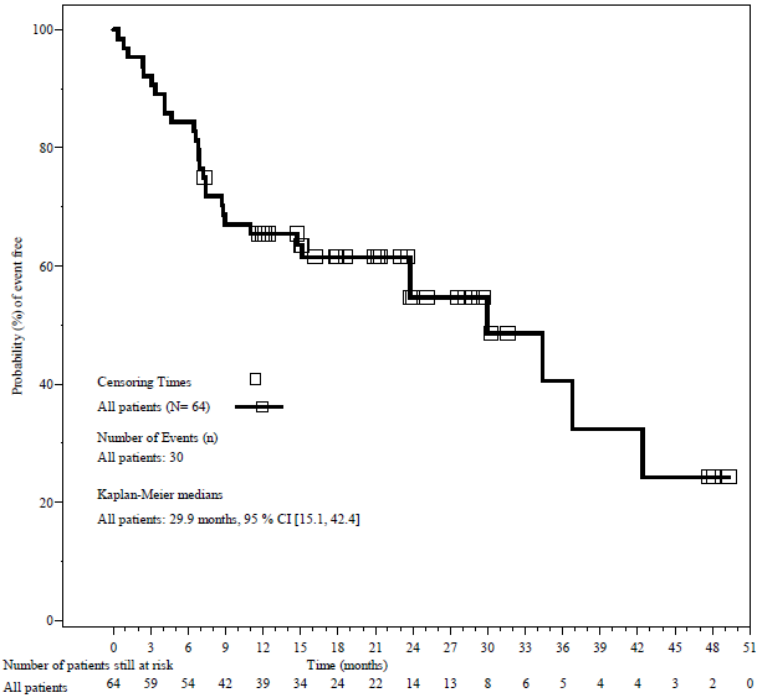

Figure 6. KM plot of overall survival in all infused patients (EAS/FAS)

Time is relative to first tisagenlecleucel infusion date, 1 month=30.4375 days. Source: Figure 14.2-9.1.

Table 12. Overall survival from enrolment (Enrolled set)

	All patients N=75
Events/Total (%)	36/75 (48.0)
Maximum follow-up (months)	50.2
Median follow-up (months)	13.60
Percentiles (95% CI) [1]	
25th	7.8 (3.7, 9.7)
50th	25.9 (10.2, 37.7)
75th	43.2 (35.6, NE)
% Event-free probability estimates (95% CI) [2]	
Month 3	88.7 (78.6, 94.2)
Month 6	78.7 (67.1, 86.5)
Month 9	68.6 (56.3, 78.1)
Month 12	59.9 (47.4, 70.3)
Month 15	59.9 (47.4, 70.3)
Month 18	56.5 (43.9, 67.3)
Month 21	56.5 (43.9, 67.3)
Month 24	56.5 (43.9, 67.3)

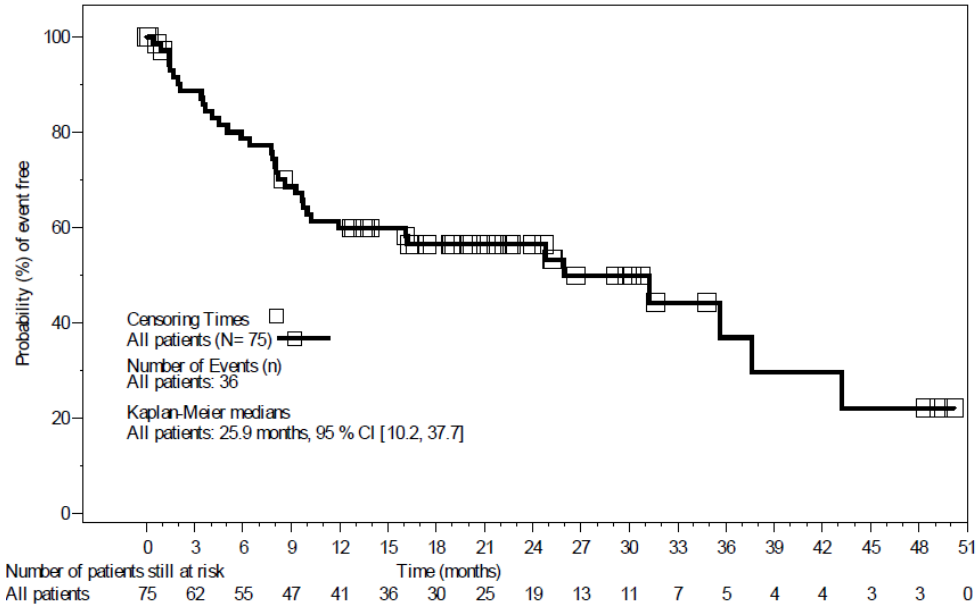

Figure 7. KM plot of overall survival in all enrolled patients (Enrolled set)

Clinical response with and without SCT at Month 6

Among the 64 patients who were infused at least 6 months prior to LSLV, 34 patients (53.1%; 95% CI: 40.2, 65.7) achieved CR or CRi at month 6 without SCT between tisagenlecleucel infusion and the month 6 response assessment. In addition, five patients (7.8%; 95% CI: 2.6, 17.3) achieved CR or CRi and then proceeded to SCT while in remission before month 6 response assessment in the EAS.

Safety results

The amendment submitted applies to the published clinical study report (CSR) entitled "A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric subjects with relapsed and refractory B-cell acute lymphoblastic leukemia" dated 12-Nov-2019.

The purpose of this amendment is to correct results (text) reported for the overall survival (OS). The changes are in the following sections:

☐ Section 11.2.6 (Overall survival)

☐ Section 13 (Discussion and overall conclusions)

Changes in safety results are summerised below.

At the time of approval, a preliminary report of the current study (B2205J) was submitted as a supportive study, Phase II, patients enrolled: N=35, patients infused: N=29.

The safety assessment in pediatric patients with B-cell ALL was based on data presented by pooling safety data from study B2205J with safety data from the pivotal study B2202 (Phase II study, patients enrolled: N=92, patients infused: N =75).

The study B2205J was completed 24-may-2019 and the following safety data is presented based on data observed in 64 subjects followed for a median of 31.74 months.

Adverse events

The AEs remained consistent with that reported in the previous two interim CSRs (Clinical Study Reports) and with similar incidence rates with more subjects (N = 64 vs N = 58 and N = 29). Majority of the AEs were reported within 8 weeks. Similarly, AEs suspected to be related to tisagenlecleucel cell product by PT occurred at a higher frequency during the first 8 weeks after the infusion.

Death, other serious or clinically significant adverse events post tisagenlecleucel

Infusion (safety set, final study report)

	All subjects N=64
Number of subjects with at least 1 AE	64 (100)
Suspected to be study drug related	62 (96.9)
Death within 30 days post tisagenlecleucel infusion	2 (3.1)
Death > 30 days post tisagenlecleucel infusion	28 (43.8)
Subjects with serious or other significant events	
Any time post tisagenlecleucel infusion	
SAE	52 (81.3)
Suspected to be study drug related	46 (71.9)
Grade 3/4 AE	59 (92.2)
Suspected to be study drug related	52 (81.3)
Within 8 weeks post tisagenlecleucel infusion	
SAE	46 (71.9)
Suspected to be study drug related	44 (68.8)
Grade 3/4 AE	54 (84.4)
Suspected to be study drug related	49 (76.6)
AE of special interest (AESI) based on identified risks	59 (92.2)
Grade 3/4 AE	39 (60.9)
Suspected to be study drug related	58 (90.6)
>8 weeks post tisagenlecleucel infusion	N=56
SAE	24 (42.9)
Suspected to be study drug related	8 (14.3)
Grade 3/4 AE	31 (55.4)
Suspected to be study drug related	14 (25.0)

	All subjects N=64

Frequency by SOC (System Organ Class)

All subjects in safety set reported at least 1 AE. Post-tisagenlecleucel transduced cell infusion, the most frequently reported AEs by system organ class (SOC) (in ≥ 40% subjects) regardless of the study drug relationship were: immune system disorders in 58 subjects (90.6%), investigations in 56 subjects (87.5%), blood and lymphatic system disorders in 48 subjects (75.0%), infections and infestations in 46 subjects (71.9%), gastrointestinal disorders in 43 subjects (67.2%), metabolism and nutrition disorders in 43 subjects (67.2%), general disorders and administration site conditions in 42 subjects (65.6%), respiratory thoracic and mediastinal disorders in 38 subjects (59.4%), nervous system disorders in 35 subjects (54.7%), and skin and subcutaneous tissue disorders in 30 subjects (46.9%)

Frequency by PT (Preferred Term)

The AEs by preferred term (PT) reported in ≥ 35% subjects were: CRS in 50 subjects (78.1%), WBC count decreased in 35 subjects (54.7%), hypogammaglobulinemia in 32 subjects (50.0%), neutrophil count decreased in 28 subjects (43.8%), anemia in 27 subjects (42.2%), vomiting in 27 subjects (42.2%), nausea and pyrexia in 25 subjects each (39.1%), diarrhea, febrile neutropenia, headache in 24 subjects each (37.5%). Based on the analysis of hematology lab results, 64.1% subjects had neutropenia not resolved by Day 28, 40.6% had grade 3 or 4 low platelets count (regardless of blood transfusion), 57.8% had WBC decreased, 6.3% had low hemoglobin and 51.6% subjects had low lymphocytes not resolved by Day 28

Severity

Out of 64 subjects, AEs of 47 subjects were with maximum grade 4; and AEs of 12 subjects were with maximum grade 3. The most commonly reported grade 3 AEs by PT regardless of the study drug relationship were febrile neutropenia (35.9%), anemia (29.7%), decreased appetite (18.8%), alanine aminotransferase increased (21.9%), WBC count decreased (18.8%), CRS (12.5%), aspartate aminotransferase increased (12.5%), hypokalemia (12.5%), hypophosphatemia (10.9%), hypotension (10.9%), and lymphocyte count decreased (10.9%).

The most commonly reported grade 4 AEs by PT regardless of the study drug relationship were also similar and were as follows: neutrophil count decreased (32.8%), WBC count decreased (28.1%), platelet count decreased (18.8%), CRS (17.2%), hypotension (12.5%), and neutropenia (12.5%).

Seriousness

The most frequently reported SAEs were: CRS, febrile neutropenia, hypotension, and pyrexia which was consistent with that reported in the previous two interim CSRs (Data cut-off 27-Nov-2016 and 06-Oct-2017, respectively). Seven additional subjects reported SAEs since the second interim CSR. Fifty-two subjects (81.3%) reported at least 1 SAE irrespective of study drug relationship. The most frequently reported SAEs were consistent with those reported in the previous two interim CSRs (N = 58 and N = 29): CRS in 41 subjects (64.1% vs 67.2% and 69.0%), febrile neutropenia in 23 subjects (35.9% vs 32.8% and 34.5%), and hypotension in 7 subjects (10.9% vs 12.1% and 13.8%) and pyrexia in 7 subjects each (10.9% vs 10.3% and 6.9%).

Forty-six subjects (71.9%) reported at least 1 SAE suspected to be related to tisagenlecleucel infused product. The most frequently reported SAEs suspected to be related to tisagenlecleucel cell product were: CRS (64.1%), and febrile neutropenia (31.3%)

Deaths

Overall, 30 subjects (46.9%) died at any time after tisagenlecleucel infusion. Eleven deaths were reported since the second interim CSR.

No new deaths were reported within 30 days of tisagenlecleucel infusion since the second interim CSR.

Twenty-eight subjects (43.8%) died > 30 days post-infusion, out of which 24 (37.5%) subjects died due to ALL disease progression and 1 subject each (1.6%) died due to complications of transplant surgery, glioblastoma multiforme, seizure and sepsis.

Table 12-3 Adverse events post tisagenlecleucel infusion, regardless of study drug relationship, by preferred term and maximum CTC grade- more than 5% in all grades (Safety set)

	All subjects N = 64		
Preferred term	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Number of subjects with at least one AE	64 (100)	12 (18.8)	47 (73.4)
Cytokine release syndrome	50 (78.1)	8 (12.5)	11 (17.2)
White blood cell count decreased	35 (54.7)	12 (18.8)	18 (28.1)
Hypogammaglobulinaemia	32 (50.0)	5 (7.8)	0
Neutrophil count decreased	28 (43.8)	4 (6.3)	21 (32.8)
Anaemia	27 (42.2)	19 (29.7)	1 (1.6)
Vomiting	27 (42.2)	3 (4.7)	0
Nausea	25 (39.1)	5 (7.8)	0
Pyrexia	25 (39.1)	6 (9.4)	1 (1.6)
Diarrhoea	24 (37.5)	2 (3.1)	0
Febrile neutropenia	24 (37.5)	23 (35.9)	1 (1.6)
Headache	24 (37.5)	2 (3.1)	0
Decreased appetite	22 (34.4)	12 (18.8)	0
Alanine aminotransferase increased	21 (32.8)	14 (21.9)	0
Aspartate aminotransferase increased	20 (31.3)	8 (12.5)	4 (6.3)
Platelet count decreased	20 (31.3)	3 (4.7)	12 (18.8)
Hypokalaemia	19 (29.7)	8 (12.5)	1 (1.6)
Hypotension	16 (25.0)	7 (10.9)	8 (12.5)
Lymphocyte count decreased	16 (25.0)	7 (10.9)	5 (7.8)
Fatigue	15 (23.4)	1 (1.6)	0
Tachycardia	15 (23.4)	2 (3.1)	0
Cough	14 (21.9)	0	0
Hypertension	12 (18.8)	1 (1.6)	0
Abdominal pain	11 (17.2)	1 (1.6)	0
Neutropenia	11 (17.2)	3 (4.7)	8 (12.5)
Pain in extremity	11 (17.2)	0	0
Chills	10 (15.6)	0	0
Epistaxis	10 (15.6)	4 (6.3)	1 (1.6)
Hypophosphataemia	10 (15.6)	7 (10.9)	1 (1.6)
Hypoxia	10 (15.6)	4 (6.3)	3 (4.7)
Thrombocytopenia	10 (15.6)	3 (4.7)	6 (9.4)
Acute kidney injury	9 (14.1)	4 (6.3)	3 (4.7)
Blood creatinine increased	9 (14.1)	2 (3.1)	0

Preferred term	All subjects N = 64 All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
International normalised ratio increased	9 (14.1)	1 (1.6)	0
Prothrombin time prolonged	9 (14.1)	1 (1.6)	0
Upper respiratory tract infection	9 (14.1)	1 (1.6)	0
Blood bilirubin increased	8 (12.5)	3 (4.7)	0
Hyperphosphataemia	8 (12.5)	0	0
Pleural effusion	8 (12.5)	2 (3.1)	0
Rash	8 (12.5)	0	0
Anxiety	7 (10.9)	1 (1.6)	0
Constipation	7 (10.9)	0	0
Pulmonary oedema	7 (10.9)	4 (6.3)	2 (3.1)
Confusional state	6 (9.4)	0	0
Dizziness	6 (9.4)	0	0
Oropharyngeal pain	6 (9.4)	0	0
Rhinorrhoea	6 (9.4)	0	0
Sinus tachycardia	6 (9.4)	0	0
Activated partial thromboplastin time prolonged	5 (7.8)	0	0
Arthralgia	5 (7.8)	1 (1.6)	0
Clostridium difficile infection	5 (7.8)	1 (1.6)	0
Dry skin	5 (7.8)	0	0
Erythema	5 (7.8)	0	0
Gastroenteritis	5 (7.8)	1 (1.6)	0
Haematuria	5 (7.8)	2 (3.1)	1 (1.6)
Hypoalbuminaemia	5 (7.8)	1 (1.6)	0
Myalgia	5 (7.8)	0	0
Nasal congestion	5 (7.8)	0	0
Procedural pain	5 (7.8)	1 (1.6)	0
Rash maculo-papular	5 (7.8)	1 (1.6)	0
Rhinovirus infection	5 (7.8)	0	0
Tachypnoea	5 (7.8)	1 (1.6)	0
Urinary tract infection	5 (7.8)	2 (3.1)	0
Blood fibrinogen decreased	4 (6.3)	2 (3.1)	1 (1.6)
Blood immunoglobulin m decreased	4 (6.3)	0	0
Catheter site pain	4 (6.3)	0	0
Clostridium difficile colitis	4 (6.3)	1 (1.6)	0
Dehydration	4 (6.3)	3 (4.7)	0
Delirium	4 (6.3)	0	0
Disseminated intravascular coagulation	4 (6.3)	2 (3.1)	0
Encephalopathy	4 (6.3)	2 (3.1)	0
Hyperhidrosis	4 (6.3)	0	0
Hypernatraemia	4 (6.3)	0	1 (1.6)

Preferred term	All subjects N = 64 All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Influenza	4 (6.3)	0	0
Infusion related reaction	4 (6.3)	0	0
Lymphopenia	4 (6.3)	1 (1.6)	1 (1.6)
Malaise	4 (6.3)	0	0
Otitis media	4 (6.3)	1 (1.6)	0
Pain	4 (6.3)	2 (3.1)	0
Periorbital oedema	4 (6.3)	0	0
Petechiae	4 (6.3)	0	0
Pneumonia	4 (6.3)	1 (1.6)	0
Pruritus	4 (6.3)	0	0
Rhinitis allergic	4 (6.3)	0	0
Seizure	4 (6.3)	2 (3.1)	0
Sinusitis	4 (6.3)	0	0
Vision blurred	4 (6.3)	0	0
Weight decreased	4 (6.3)	0	0

- A subject with multiple occurrences of an AE is counted only once in the AE category at the maximum toxicity grade.
- Preferred terms are presented in descending frequency of all grades column, as reported in the All subjects column.
- MedDRA version 22.0 and CTCAE version 4.03 have been used for the reporting of adverse events.
Source: Table 14.3.1-1.1

Adverse events of special interest

The majority of these AESI occurred within 8 weeks of tisagenlecleucel infusion.

With more subjects and longer follow-up compared to the previous two interim CSRs (N = 58 and N = 29, respectively), most AESIs appear similar in incidence including CRS.

Fifty-eight (90.6%) subjects had at least 1 AESI suspected to be related to tisagenlecleucel cell product (10 additional subjects since the second interim CSR. The most frequently reported AESI suspected to be related to tisagenlecleucel cell product was CRS (78.1%) similar to that reported in the second interim CSR. The most frequent AESIs reported in subjects < 18 years of age were similar to the overall population.

Table 12-8 Adverse events of special interest (AESI) within 8 weeks post tisagenlecleucel infusion based on identified risks, regardless of study drug relationship, by group term and maximum CTC grade (Safety set)

	All subjects N = 64		
Group term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Number of subjects with at least one event	59 (92.2)	18 (28.1)	21 (32.8)
Cytokine Release Syndrome	50 (78.1)	8 (12.5)	11 (17.2)
Hematopoietic cytopenias not resolved by Day 28	27 (42.2)	10 (15.6)	12 (18.8)
Infections	26 (40.6)	6 (9.4)	1 (1.6)
Prolonged depletion of normal B cells or Agammaglobulinemia	27 (42.2)	4 (6.3)	0
Serious neurological adverse reactions	19 (29.7)	4 (6.3)	0
Tumour Lysis Syndrome	1 (1.6)	1 (1.6)	0

- A subject with multiple adverse events within a primary system organ class is counted only once in the total row.
- A subject with multiple occurrences of an AE is counted only once in the AE category at the maximum toxicity grade.
- Preferred terms are presented within group term in descending frequency of all grades column, as reported in the All subjects column.
- MedDRA version 22.0 and CTCAE version 4.03 have been used for the reporting of adverse events.

Source: Table 14.3.1-1.6

AESIs after 8 weeks to 1 year and after 1 year post tisagenlecleucel infusion:

Thirty five subjects (62.5%) had at least 1 AESI after 8 weeks to 1 year post tisagenlecleucel infusion. The most frequent AESI by group term was infections (58.9%). No incidence of CRS was observed in study subjects beyond 8 weeks of tisagenlecleucel infusion.

Cytokine release syndrome

The median time to onset of CRS was 4.5 days (range: 1 to 20 days). The median time to onset of CRS in subjects with CR/CRi was 4.0 days. Eight subjects reported CRS of grade 3 and 11 subjects reported CRS of grade 4. All the CRS events were suspected to be related to tisagenlecleucel cell product. Thirteen subjects (26.0%) received concomitant medication or non-drug therapy such as systemic anti-cytokine therapy, 12 subjects received tocilizumab, 9 subjects received corticosteroids, and 5 subjects were treated with other anticytokine therapy (Etanercept) and 12 subjects required high dose vasopressors. Out of these 50 subjects, the outcome was reported as recovered/resolved in all except 1 subject. In Subject the event was reported as not resolved. The subject died while the event was ongoing. Among 50 subjects with CRS, none of the events were fatal.

	All subjects N=64
Systemic anti-cytokine therapy given - n (%)	13 (26.0)
Tocilizumab	12 (24.0)
1 dose	5 (10.0)
2 doses	4 (8.0)
3 doses	3 (6.0)
4 doses	0
>4 doses	0
Siltuximab	0
Corticosteroids	9 (18.0)
Other	5 (10.0)

Hematopoietic cytopenias not resolved by Day 28

Table 12-10 Clinical impact of Hematopoietic cytopenias not resolved by Day 28 (Safety set)

		All subjects N = 58			
		By Month 3[2]		By Month 6[2]	
Parameter	Day 28[1] n (%)	Subjects at risk	% Resolved probability	Subjects at risk	% Resolved probability
WBC	37 (57.8)	7	72.3	1	96.0
Hemoglobin	4 (6.3)	0	NE	0	NE
Platelets	26 (40.6)	2	86.7	1	86.7
Neutrophils	41 (64.1)	9	68.2	3	89.4
Lymphocytes	33 (51.6)	10	55.6	3	86.7

- Based on laboratory results regardless of blood transfusion.
- NE = Not estimable.
[1]Number of subjects with last value on or prior to Day 28 indicating Grade 3 or 4 cytopenia
[2]Resolution of cytopenia is defined as achieving lab results of grade 2 or below. % resolved probability is among subjects with cytopenia at Day 28, obtained from the KM survival estimates

Infections

Within 8 weeks of tisagenlecleucel infusion, infections were reported in 26 subjects (40.6%). Grade 3 infections were reported in 6 subjects (9.4%) and grade 4 infections were reported in 1 subject (1.6%) (Table 12-8). Four subjects had Clostridium difficile colitis (no additional subject since the second interim CSR with 1 subject with grade 3 infection, 4 subjects had Clostridium difficile infection (2 additional subjects since the second interim CSR with no grade 3 or 4 infection, and 3 subjects had rhinovirus infection (no additional subjects since the second interim CSR, with no grade 3 or 4

infections. Overall, other infections were reported in 2 subjects each or 1 subject each of which 6 events were grade 3 or 4 (1 each of gastroenteritis, pneumonia, Staphylococcal infection, catheter site infection, septic embolus and urinary tract infection enterococcal).

Infections suspected to be related to tisagenlecleucel cell product were reported in 7 subjects (10.9%) and were as follows: staphylococcal infection, acute sinusitis, catheter site cellulitis, enterococcal infection, herpes simplex, influenza, orchitis, and urinary tract infection enterococcal.

The outcome was reported as fatal in 2 subjects with grade 4 infection. Subject experienced septic embolus on Day 25 and died the same day due to embolic stroke and Subject experienced respiratory tract infection on Day 1038 and died on Day 1047

Prolonged depletion of normal B cells or Agammaglobulinemia

AESI agammaglobulinemia was reported in 27 subjects (42.2%) within 8 weeks post-tisagenlecleucel infusion. Of these 27 subjects, AESI agammaglobuminemia was suspected to be tisagenlecleucel-related in 25 subjects with 4 subjects having grade 3 AESI agammaglobuminemia. No grade 4 AESI agammaglobuminemia were reported. Prophylaxis for Agammaglobulinemia was recommended as per local guidelines. Of note, many subjects had IVIg replacement initiated prior to the subject developing grade 3 agammaglobulinemia.

Neurological events

The SMQ (broad) "noninfectious encephalopathy/delirium" was used to identify and define the frequency of SNAR (serious neurological adverse reactions) grouped AEs. This query included the PT of "Autoimmune encephalopathy", "CAR T-cell-related encephalopathy syndrome", "Delirium" and "Tremor".

Nineteen subjects (29.7%) all of which had CRS had transient neuropsychiatric events within 8 weeks of tisagenlecleucel infusion (no additional subjects since the second interim CSR [Study B2205J second interim CSR]. Six subjects had confusional state, all with a maximal CTCAE grade less than 3. Four subjects experienced delirium and encephalopathy, 3 subjects experienced seizures. Other events were reported in 1 or 2 subjects.

Neurological events suspected to be related to tisagenlecleucel cell product were reported in 13 subjects (20.3%). Grade 3 neurological events suspected to be related to tisagenlecleucel cell product were encephalopathy, seizure, and dysphagia in 1 subject each (1.6%).

The outcome was reported as recovered or resolved in all subjects except six (due to confusion, in 3 patients, disturbance in attention, dysarthria and tremor one patient each).

Tumor lysis syndrome

One AESI of tumor lysis syndrome was reported within 8 weeks of tisagenlecleucel infusion. Subject reported grade 3 tumor lysis syndrome and it was suspected to be related to tisagenlecleucel cell product from Day 6 to Day 9. The outcome was reported as recovered or resolved.

Aggravation of graft-versus-host disease (GVHD), cerebral edema, and hematological disorders (including aplastic anemia and bone marrow failure)

The majority of these AESI occurred within 8 weeks of tisagenlecleucel infusion. Forty-seven subjects (73.4%) had hematological disorders, WBC decreased in 30 subjects, anemia in 27 subjects, neutrophil count decreased in 25 subjects, febrile neutropenia in 22 subjects, platelet count decreased in 19 subjects, lymphocyte count decreased in 14 subjects, neutropenia in 8 subjects, thrombocytopenia in 8 subjects, lymphopenia in 3 subjects, and hemoglobin decreased and pancytopenia in 1 subject each. Aggravation of GVHD and cerebral edema was reported in 1 subject each (1.6%). Grade 3 or 4 hematological disorders were reported in 45 subjects.

Conclusion on safety by the MAH:

In this final CSR for Study B2205J, there were no unexpected safety findings in the pediatric subjects with relapsed or refractory B-cell ALL identified. The safety profile corresponds to that observed in the other studies of tisagenlecleucel in this indication, and as reported in prior Interim CSRs for Study B2205J, the final CSR for Study B2101J as well as in the Interim CSRs for pivotal Study B2202 and previously discussed in the context of the Kymriah Marketing Application, and continues to be consistent with the known safety profile for tisagenlecleucel. The benefit risk assessment remains unchanged and positive.

Based on the results of Study B2205J, the Marketing Authorization Holder does not propose any changes to the pediatric information of the current Kymriah Core Data Sheet or the Kymriah European Summary of Product Characteristics.

2.3.3. Discussion on clinical aspects

Final efficacy results compared to the IA1 results reported at the time of initial MA

The MAH has submitted comprehensive overviews of the demographics and baseline disease characteristics of both the enrolled patient population (N=75) as well as the EAS/FAS population (N=65) in study B2205J. Overall, the baseline data between the enrolled and infused sets appear to be similar. Still, the submitted data reveal that a higher proportion from the two older age groups (82%; 9/11) and male patients (91%; 10/11) are those who drop out after enrolment in study B2205J before receiving the study treatment. Thus, among the patients who received tisagenlecleucel a slightly higher proportion of 53% were female patients. In contrast, male patients constituted a majority (57%) of the infused patients in the pivotal study B2202. In total, 41% of the infused patients in study B2205J underwent a prior hematopoietic SCT (HSCT), whereas 3% had two prior HSCTs. The median number of previous therapies patients had received was 3 (range: 1-9); the majority (89%) had relapsed disease, and the minimum bone marrow blast count was 8%. The demographics, baseline disease status and disease history of the population appear to be representative for the current approved indication of patients with r/r B-cell ALL.

Among the 64 patients who received tisagenlecleucel, 57 patients (89%) received bridging therapy while waiting for the infusion. In addition, 94% (60/64) of the patients who received tisagenlecleucel received LD chemotherapy after enrolment and prior to infusion in order to facilitate engraftment and homeostatic expansion of tisagenlecleucel. The proportions of patients reported to have been receiving bridging- and LD therapies and the type of chemotherapy combinations the infused patients received in study B2205J appear to be similar to study B2202.

The primary endpoint of best ORR within 6 months based on IRC assessment in the EAS of 29 patients from the IA1 (DCO: 01-Feb-2016) was 69.0% (20/29; 95% CI: 43.6%, 88.1%). Among the responding patients, 62.1% (18/29) achieved a CR, while 6.9% (2/29) obtained a CRi.

The ORR reported in the final analysis in the FAS of 64 patients was 70.3% (45/64; 95% CI: 52.9, 82.4). Among the responding patients, 59.4% (38/64) achieved a CR, while 10.9% (7/64) obtained a CRi. The ORR for the enrolled set in the final analysis was 60.0% (45/75: 95% CI 48.0, 71.1). Among all the enrolled patients, 38 patients (50.7%; 38/75) achieved a best response of CR, and 7 patients (9.3%; 7/75) obtained a best response of CRi.

With respect to the secondary endpoints, all patients in the final analysis who achieved a BOR of CR or CRi except for two patient, also achieved bone marrow MRD negative remission (43/64; 67.2%; 95% CI: 54.3, 78.4). The total proportion was slightly higher than reported in the first interim analysis. The median DOR was not reached. Median follow up from onset of response was 10.97 months (range: 4.7, 47.1). Among the responding patients, 31.1% (14/45) were still in remission at the DCO of the final analysis. In total, 28.9% (13/45) of the patients who achieved a BOR of CR or CRi reported relapse prior to LSLV.

The median EFS in the final analysis increased compared to the interim analyses, i.e. median EFS was 15.6 months (95% CI: 6.4, NE). The estimated event-free probability was 67.0% (53.5, 77.4) at month 6, 53.6% (39.3, 66.0) at month 12 and 47.8% (95% CI: 33.0, 61.1) at month 24. This could be expected with a longer median follow-up of 31.74 months (range: 17.6-56.0).

The median OS in the infused patients was 29.9 months (95% CI: 15.1, 42.4) in the final analysis with a median follow-up time of 15.13 months (range: 4.1, 49.3). The median OS in the enrolled patient population was 25.9 months (95% CI: 10.2, 37.7) with a median follow of 13.60 months (range: 3.7, 50.2). The estimated probability of survival from infusion was 84.4% (95% CI: 72.9, 91.3) at month 6, 65.4% (95% CI: 52.4, 75.7) at month 12 and 54.7% (95% CI: 39.8, 67.4) at month 24 in the infused patient population. In the enrolled patient population, the estimated probability from enrolment was 78.7% (95% CI: 67.1, 86.5) at month 6, 59.9% (95% CI: 47.4, 70.3) at month 12 and 56.5% (95% CI: 43.9, 67.3) at month 24.

At the time of the final OS analysis, 34 patients were censored of whom 19 patients where alive at the DCO, whereas 15 patients were reported as "lost to-follow up". According to the MAH, 14 of these patients discontinued the study at about 24 months follow-up and switched to the long-term follow-up study A2205B. Another patient discontinued "when the subject reached 18 years of age and did not have IRB approved adult informed consent form (ICF)". The OS curve, especially beyond 24 months including the estimated median OS should therefore be interpreted with caution. The MAH has clarified in the response to the request for further information, the rationale for censoring for OS follow up in the final analysis for the 14 patients who switched to the long–term follow-up study A2205B and have provided individual patient data at the time of transition for these 14 patients. However, no updated OS analyses including these patients have been submitted. The MAH's approach to define patients that transitioned to study A2205B as "lost–to-follow-up" and therefore censoring them in the final OS analysis in study B2205J is not supported. Several of these patients have been censored for OS a considerably long time prior the last DCO of 24-May 2019. Updated OS analyses for study B2205J with the latest possible survival status for the 14 patients transitioned to the follow-up study should therefore be provided and included in the recommended update of section 5.1 of the SmPC.

In total, 5 of the 64 patients who achieved CR or CRi proceeded to SCT while in remission before the 6 months response assessment. According to additional data provided, a total of 9 patients among the 64 infused patients proceeded to HSCT during the study. The proportion of patient proceeding to HSCT constitutes only 14% (9/64) of the total FAS population. The exclusion or censoring of patients proceeding to HSCT was explored in requested sensitivity analyses for OS. The analyses revealed no impact on the event free probability estimates at different time points or on the median OS compared to the OS FAS.

Overall, it is agreed that the efficacy results from the final analysis are consistent with the IA1 results reported at the time of initial MA. In addition, the final data included almost the double of patients with r/r B-cell ALL than the IA1 and contained more mature data from the target patient population.

Efficacy results from supportive study B2205J compared to the pivotal study B2202

Study B2205J enrolled comparable patient populations with r/r B-cell ALL and had similar study design as study B2202. The main difference between the two studies was the definition of the primary efficacy endpoint ORR, which was measured within 6 months after tisagenlecleucel administration in study BB2205J compared to 3 months in study B2202. Furthermore, a University of Pennsylvania manufacturing process was used for the manufacturing of tisagenlecleucel for the first 29 batches included in the IA1, whereas a Novartis manufacturing process was used thereafter for the manufacturing of CAR T-cells to the rest of the patients enrolled in study B2205J. Thus, the IA1 results are based solely on tisagenlecleucel products produced by using the Pennsylvannia manufacturing process whereas the final analysis is based on patients receiving tisagenlecleucel from the Novartis manufacturing process as well.

Overall, the updated efficacy results from the final analysis of study B2205J is consistent with the efficacy data reported in an updated interim analysis of the pivotal study B2202 with the DCO of 13-Apr-2018, which are currently under assessment in a type II group of variations (Procedure No. EMEA/H/C/004090/II/0013/G).

Nevertheless, the best ORR within 6 months in study B2205J is lower than the ORR reported within 3 months in study B2202 in both all the enrolled patients (60% vs 67%) as well as in the infused patient population (69% vs 82%). The proportion of enrolled patients who achieved a best response of CR was the same (51%) in the two studies, and a slightly lower proportion in study B2205J obtained a best response of CRi (9.3% vs 16.5%). The median DOR was not reached in any of the two studies. In contrast to the interim analysis for the pivotal study B2202 was the median EFS reached at the latest DCO of the final analysis (15.6 months; 95% CI: 6.4, NE) of study B2205J. The estimated event-free probability was comparable at month 6 (67% vs 71%), month 12 (54% vs 56%) and month 24 (48% vs. 53%) between study B2205J and B2202.

The median OS was only reached in the final analysis of study B2205J, both in the infused patients (29.9 months; 95% CI: 15.1, 42.4) as well as in the enrolled patient population (25.9 months; 95% CI: 10.2, 37.7). The estimated probability of survival from enrolment in the enrolled patient population was comparable at month 6 (79% vs. 78%), lower at month 12 (60% vs. 70%), but the same at month 24 (57%) in study B2205J compared to study B2202. The proportion of patients who achieved CR or CRi and then proceeded to SCT while in remission before month 6 was identical (8%) between the two studies.

In conclusion, the efficacy results from the complete data set of study B2205J are considered to confirm the data underlying the approved indication of Kymriah in r/r ALL patients. Study B2205J had similar study design and enrolled comparable patient populations with r/r B-cell ALL as the pivotal study B2202. In addition, the efficacy results from the final analysis are consistent with the IA1 results reported at the time of initial MA, the final data included almost the double of patients with r/r B-cell ALL compared to the IA1 and contained more mature data from the target patient population. Since the complete data set of study B2205J along with updated data from study B2202 provide a more robust foundation for the approved ALL indication, the MAH is strongly recommended to present the final study results of study B2205J in section 5.1 of the SmPC during a variation application following the conclusion of this procedure.

Safety data from the supportive study B2205J and compared to the pivotal study B2202

AEs reported in this final analyses of study C2205J (N = 64) are consistent with the safety profile of tisagenlecleucel previously reported in interim CSRs (N = 58 and N = 29).

The majority of the subjects who developed CRS that was manageable with supportive measures; in some cases CRS events required hospitalization and administration of anti-cytokine therapy (24% received one or more doses of tocilizumab). No deaths were attributable to CRS.

The last updated SmPC section 4.8 uses frequency data based on **the pivotal study B2202 (paediatric and young adult B-cell ALL)**:

The most common non-haematological adverse reactions were cytokine release syndrome (77%), infections (72%), hypogammaglobulinaemia (53%), pyrexia (42%) and decreased appetite (38%).

The most common haematological adverse reactions were decreased white blood cells (100%), decreased haemoglobin (100%), decreased neutrophils (100%), decreased lymphocytes (100%) and decreased platelets (97%).

Grade 3 and 4 adverse reactions were reported in 89% of patients. The most common Grade 3 and 4 non-haematological adverse reaction was cytokine release syndrome (48%).

The most common Grade 3 and 4 haematological laboratory abnormalities were white blood cells decreased (97%), lymphocytes decreased (96%), neutrophils decreased (95%), platelets decreased (77%) and haemoglobin decreased (48%).

Grade 3 and 4 adverse reactions were more often observed within the initial 8 weeks post-infusion (82% of patients) compared to after 8 weeks post-infusion (51% of patients).

The frequency data (AEs all grades) seen in the **final study report of the supportive study B2205J** are much the same or lower: cytokine release syndrome 78.1%, infections (within first 8 weeks) 40.6%, hypogammaglobulinaemia 50.0%, pyrexia 39.1%, decreased appetite 34.4%. The frequencies of haematological adverse reactions seems lower in study B2205J than found in the pivotal study B2202: white blood cell decreased 54.7%, anaemia 42.2%, neutrophil count decrease 43.8%, lymphocyte count decreased 25.0%, platelet count decrease 25.0%.

The frequency data given in the SmPC is referred to study B2202 specifically and for most adverse events, except the haematological events, are pretty much the same. The frequency table categorising AEs in very common, common etc will be the same.

It can be agreed that no further updates of the PI concerning SmPC section 4.4 and 4.8 is needed based on data in the final study report.

3. Rapporteur's updated overall conclusion and recommendation

In accordance with Article 46 of Regulation (EC) No 1901/2006, the MAH submitted the final study results from the complete data set of study B2205J. The study is a phase II, single arm, open-label multi-center study designed to demonstrate or support the efficacy and safety of tisagenlecleucel in paediatric and young adult patients with r/r B-cell ALL. The evidence of efficacy for the approved ALL indication was primarily based on data from the pivotal study B2202 at the time of initial MA. Results from the IA1 of study B2205J with data from 29 patients was concluded at that time to be immature and therefore only provided supportive evidence for the efficacy of tisagenlecleucel.

The cellular kinetics profile reported in the final study report of study B2205J appears consistent with that of the two prior interim studies, although direct comparisons have not been submitted. The dose- and exposure-efficacy relationships have not been reinvestigated based on the updated data from study B2205J. Based on prior analysis, there is a trend for difference in exposure-response between responders and non-responders, however the clinical relevance of this for the dosing rationale is not yet clear. The MAH's plans to further assess the dose and the exposure-response relationships as more data become available is supported. Some clarification is requested to understand their approach.

The final study results from the complete data set of study B2205J are considered to support the data underlying the approved indication of Kymriah in r/r ALL patients. It is therefore agreed that the data from this study do not change, but rather confirm the favourable benefit-risk conclusion of Kymriah in the currently approved ALL indication. Study B2205J had similar study design and enrolled comparable patient populations with r/r B-cell ALL as the pivotal study B2202. In addition, the efficacy results from the final analysis are consistent with the IA1 results reported at the time of initial MA, the final data included almost the double of patients with r/r B-cell ALL compared to the IA1 and contained more mature data from the target patient population. Since the complete data set of study B2205J along with updated data from study B2202 provide a more robust foundation for the approved ALL indication, the MAH should present the final study results of study B2205J in section 5.1 of the SmPC during a variation application following the conclusion of this procedure.

The last updated SmPC section 4.8 uses frequency data based on the pivotal study B2202 (paediatric and young adult B-cell ALL). The frequency data (AEs all grades) seen in the final study report of the supportive study B2205J are much the same or lower: cytokine release syndrome 78.1%, infections (within first 8 weeks) 40.6%, hypogammaglobulinaemia 50.0%, pyrexia 39.1%, decreased appetite 34.4%. The frequencies of haematological adverse reactions seems lower in study B2205J than found in the pivotal study B2202: white blood cell decreased 54.7%, anaemia 42.2%, neutrophile count decrease 43.8%, lymphocyte count decreased 25.0%, platelet count decrease 25.0%.

The frequency data given in the SmPC refers to study B2202 specifically and for most adverse events, except the haematological events, are pretty much the same. The frequency table categorising AEs in very common, common etc will however be the same. It can be agreed that no further updates of the PI concerning SmPC section 4.4 and 4.8 is needed based on data in the final study report.

The procedure is concluded and there is no request for more information. However, the final variation application to update the SmPC with the complete data set of study B2205J is awaited.

The overall benefit-risk balance of Kymriah remains positive 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.

☒ Fulfilled:

The procedure is concluded and there is no request for more information.

However, the MAH should commit to submit an application for a variation to update section 5.1 of the SmPC with the complete data set of the paediatric B-cell ALL study B2205J.

4. Additional clarification requested

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

1. A biopharmaceutics report on humoral and cellular immunogenicity will be submitted later. Please clarify when the report will be submitted and what the report will contain, specifically whether updated exposure response analysis will be conducted.
2. Please clarify the approach for assessing the clinical relevance of the trend for difference in exposure-response between responders and non-responders as more data come available. Specifically, the following point should be addressed for updated exposure-response analysis and any implications of new results for the dosing rationale should be discussed:
    a. exposure categorized into quartiles
    b. additional analyses to re-evaluate the relationship between exposure parameters (preferably considering all potentially important exposure parameters, including AUC0-28d, AUC0-84d and Cmax, unless otherwise justified) and PFS, EFS (i.e. as in the initial MAA submission) as well as DOR.
    c. tumor burden and the actual dose administered to the individual patients.
3. Please provide an overview of the demographics, baseline disease status and disease history for all the enrolled patients (N=75), including those who did not receive the study drug, as these comprises the intention-to-treat (ITT) population.
4. Please provide data describing the proportion of patients who received bridging- and lymphodepleting therapies and further specify which therapy combinations were selected for the patient population in the FAS.
5. The rationale for censoring the 14 patients for OS follow up in the final analysis who switched to the long –term follow-up study is not understood. Please justify why relevant follow-up data for these 14 patients were not included, or provide updated analyses including these patients.
6. The impact HSCT had on the OS results is not known since no sensitivity analysis of OS excluding patients receiving HSCT post-randomisation was provided. The MAH should provide sensitivity analysis exploring the impact of HSCT on the OS results.
7. The updated efficacy data from study B2205J should be reflected in section 5.1 of the SmPC. Please make a proposal for inclusion of study results from the final analysis of study B2205J in section 5.1 of the current SmPC.

The timetable is a 30 day response timetable without clock stop.

5. MAH responses to Request for supplementary information

Clinical pharmacology

Question 1
A biopharmaceutics report on humoral and cellular immunogenicity will be submitted later. Please clarify when the report will be submitted and what the report will contain, specifically whether updated exposure response analysis will be conducted.

Summary of the MAH's response

The biopharmaceutics report will be based on data from the two single-arm, multicenter clinical studies in pediatric and young adult r/r B-cell ALL patients, Study B2205J and pivotal Study CCTL019B2202 (hereafter referred to as B2202) pooled, to provide larger number of patients in the analysis sets and thus to increase statistical power of the biopharmaceutics evaluations and correlative analyses. The report will be submitted with the final CSR for Study B2202 (estimated in 2022, the study completion depends on last patient last visit date) and will contain analyses of product characteristics as well as correlations between cellular kinetics, dose efficacy and safety endpoints. For updated exposure response analysis, please see response to Question 2.

Assessment of the MAH's response

The MAH has provided the estimated submission date and a brief overview of the content of the biopharmaceutical analysis, please refer also to question 2.

Issue resolved.

Question 2
Please clarify the approach for assessing the clinical relevance of the trend for difference in exposure-response between responders and non-responders as more data come available. Specifically, the following point should be addressed for updated exposure-response analysis and any implications of new results for the dosing rationale should be discussed:

a) exposure categorized into quartiles

b) additional analyses to re-evaluate the relationship between exposure parameters (preferably considering all potentially important exposure parameters, including AUC0-28d, AUC0-84d and Cmax, unless otherwise justified) and PFS, EFS (i.e. as in the initial MAA submission) as well as DOR.

c) tumor burden and the actual dose administered to the individual patients.

Summary of the MAH's response

Cellular kinetic concentrations and parameters have been summarized by response category in the B2205J final CSR (dated 12-Nov-2019), showing consistent trends with responders having higher exposure than non-responders but with overlapping distributions. The Kymriah SmPC reflects the cellular kinetics data in paediatric and young adult B cell ALL patients based on a pool of studies B2202 and B2205J. These data have been recently updated (SmPC dated 03- Mar-2020) in the context of procedure EMEA/H/C/004090/II/0013/G based on data cut-off dates of 13-Apr-2018 for Study B2202 and 06-Oct-2017 for Study B2205J (second interim CSR). The procedure also contained Module 2.7.2 "Addendum to Summary of Clinical Pharmacology Studies in Pediatric and Young Adult Relapsed/Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL)" based on the respective data

cut-off dates of Studies B2202 and B2205J. Five additional patients were infused in Study B2205J between the 06-Oct-2017 data cut-off date for the second interim CSR and the 24-May-2019 cut-off date for the final CSR. Based on the totality of current data, Novartis considers that pharmacological conclusions remain unchanged.

Quartile based exposure analyses as well as efficacy analyses on DOR using pooled data from Studies B2205J and B2202 will be updated at the conclusion of Study B2202 and will be included in an additional report. Dose-response and dose-safety analysis will also be updated. Sensitivity analyses will be run to investigate the impact of baseline tumor burden considering the caveat that tumor burden may have changed between the time of collection and the time of infusion due to bridging and/or lymphodepleting chemotherapy.

Assessment of the MAH's response

The plan for updated exposure-response analysis has been clarified as requested and an additional report with the requested analysis will be submitted upon the conclusion of Study B2202. Regarding the sensitivity analysis on impact of tumor burden; if data is available on tumor burden at the time of administration for all/some of the patients, these should be included in the analysis.

Issue resolved.

Efficacy

Question 3

Please provide an overview of the demographics, baseline disease status and disease history for all the enrolled patients (N=75), including those who did not receive the study drug, as these comprises the intention-to-treat (ITT) population.

Summary of the MAH's response

Demographics, baseline disease status for the enrolled set are displayed at the [B2205J final CSR - Tables 14.1-4.1] and [B2205J final CSR – Table 14.1-4.4]. The MAH also provided an additional table, i.e. Table 2-1 that depicts the primary disease history and prior antineoplastic therapies for the enrolled set.

Assessment of the MAH's response

The MAH has submitted the requested data on the demographics and baseline disease characteristics for the enrolled set, including information on primary disease history and prior antineoplastic therapies. A summary of demographics and baseline disease history for all patients who were enrolled (the enrolled set) and those who received tisagenlecleucel infusion (the infused set) in study B2205J are presented in Table 13 below.

Table 13. Baseline data across the enrolled and infused sets in study B2205J

	Enrolled N=75 n (%)	Infused N=64 n (%)
Diagnosis of disease - n (%)		
B-Cell ALL	75 (100)	64 (100)
Age (years)		
Mean (standard deviation)	12.8 (5.26)	12.4 (5.16)
Median (minimum – maximum)	13.0 (3 – 25)	12.5 (3 – 25)
Age category (years) - n (%)		

	Enrolled N=75 n (%)	Infused N=64 n (%)
<10 years	22 (29.3)	20 (31.3)
≥10 years and <18 years	39 (52.0)	34 (53.1)
≥18 years	14 (18.7)	10 (15.6)
Sex - n (%)		
Male	40 (53.3)	30 (46.9)
Female	35 (46.7)	34 (53.1)
Disease status (%)		
Primary refractory[1]	8 (10.7)	7 (10.9)
Relapsed disease[2]	67 (89.3)	57 (89.1)
Number of previous complete remissions		
Mean (standard deviation)	1.9 (1.35)	1.9 (1.32)
Median (minimum – maximum)	2.0 (0 – 7)	2.0 (0 – 7)
Number of previous lines of therapies		
Mean (standard deviation)	3.0 (1.51)	2.9 (1.45)
Median (minimum – maximum)	3.0 (1 – 9)	3.0 (1 – 9)
Prior stem-cell transplantation - n (%)		
0	43 (57.3)	36 (56.3)
1	30 (40.0)	26 (40.6)
2	2 (2.7)	2 (3.1)

[1]Primary refractory: Never had a morphologic complete remission (CR) prior to the study;
[2]Relapsed disease: Had at least one relapse prior to the study

Overall, the baseline data between the enrolled and infused sets appear to be quite similar. However, the submitted data reveal that a higher proportion from the two older age groups (82%; 9/11) and male patients (91%; 10/11) are those who drop out after enrolment in study B2205J before receiving the study treatment. Thus, among the patients who received tisagenlecleucel a slightly higher proportion of 53% were female patients. In comparison constituted the male patients with 57% the majority of the infused patients in the pivotal study B2202. Furthermore, the patients enrolled in study B2205J compared to the pivotal study B2202 were slightly older with the majority of the patients in the ≥10 to <18 years of age group (52 vs. 41%). In addition, a higher proportion of the enrolled patients had not underwent a prior HSCT compared to those enrolled in study B2202 (57% vs. 40%). The median numbers of previous therapies patients had received were identical between the two studies, i.e. 3 (range: 1-9), and a similar proportion of approximately 90% of all the enrolled patients had relapsed disease. Thus, despite some differences as outlined above, the demographics, baseline disease status and disease history of the included patient population in study B2205J appear to be representative for the current approved indication of patients with r/r B-cell ALL.

Issue clarified.

Question 4

Please provide data describing the proportion of patients who received bridging- and lymphodepleting therapies and further specify which therapy combinations were selected for the patient population in the FAS.

Summary of the MAH's response

Historically, lymphodepleting (LD) agents before adoptive T-cell therapy were selected based on clinical experience from single agent and combination chemotherapies and include the alkylating agent cyclophosphamide and the family of nucleoside analogues, encompassing the pyrimidine nucleoside cytarabine and the purine nucleosides cladribine, pentostatin and fludarabine that demonstrate potent cytotoxic activity (Lowe, 2018). In the early paediatric ALL studies of tisagenlecleucel, the use of LD chemotherapy prior to infusion was recommended but left at the discretion of the investigator, and the regimen of choice was dependent on the patient's underlying disease and prior therapies. Thirteen out of the first 16 patients infused with tisagenlecleucel received a LD conditioning regimen prior to adoptive transfer of T cells. Six patients received a LD-conditioning regimen consisting of cyclophosphamide and fludarabine, five patients received cyclophosphamide and etoposide, one patient received etoposide and cytarabine and one patient received cyclophosphamide alone. Based on this experience, cyclophosphamide and fludarabine was chosen as the regimen of choice. However, for patients with prior history of Grade 4 haemorrhagic cystitis with cyclophosphamide, or if the patient demonstrated a chemo refractory state to a cyclophosphamide-containing regimen administered shortly before LD chemotherapy, cytarabine and etoposide was recommended. Both cytarabine and etoposide are part of the treatment guidelines to treat patients with ALL and have myelosupressive effects, including lymphodepletion (NCCN Guidelines, Cytarabine and Etoposide prescribing information).

In study B2205J, four infused patients did not receive LD chemotherapy as per protocol criteria, since WBC were ≤1000 within one week prior to tisagenlecleucel infusion. One patient received a regimen of both cytarabine and etoposide as LD regimen. All remaining patients received the combination of cyclophosphamide and fludarabine, including one patient who received both regimens, first LD chemotherapy consisting of cyclophosphamide and fludarabine (from D-14 to D-11). However, the patient still had an elevated blast count observed in the peripheral blood and an alternate regimen of LD chemotherapy was given with cytarabine and etoposide (150 mg/m2) from D-7 to D-5. All other patients received fludarabine in combination with cyclophosphamide as LD regimen.

Concerning bridging therapy, the use of any additional chemotherapy prior to the LD chemotherapy was at the discretion of the investigator and dependent on the patient's disease burden. Table 14 below lists the proportion of patients in the FAS who received both bridging- and LD therapies prior to tisagenlecleucel infusion. An overview of the breakdown of concomitant antineoplastic therapy before LD therapy by ATC class and preferred term, by whether patient received study infusion has been submitted. In total, 83% in the FAS received both bridging- and LD chemotherapies. Patient level data for these patients on concomitant antineoplastic therapy prior to start of infusion were provided.

Table 14. Percentage of patients who received both bridging- and LD therapies (EAS/FAS)

	All patients N=64 n/N (%)
Received bridging therapies	57/ 64 (89.1)
Received lymphodepleting therapies	60/ 64 (93.8)
Received both bridging- and lymphodepleting therapies	53/ 64 (82.8)

Assessment of the MAH's response

The MAH explain how the selection of an appropriate LD chemotherapy regimen has evolved during conductance of the early paediatric ALL studies of tisagenlecleucel. The use of LD chemotherapy prior to infusion was recommended in these studies, but the regimen of choice was left at the discretion of the investigator, and was dependent on the patient's underlying disease and prior therapies. Based on experiences from these studies, cyclophosphamide in combination with fludarabine have been chosen as the preferred LD regimen.

Among the 64 patients who received tisagenlecleucel, 57 patients (89%) received bridging therapy while waiting for the infusion. This is the same proportion as has been reported in the pivotal study B2202 (87%; 69/79). The most common concomitant antineoplastic medications used before LD therapy in study B2205J were methotrexate (70%), vincristine (53%), cytarabine (42%), etoposide (36%), and mercaptopurine (34%), either used alone or in combination. Similarly, in study B2202 were methotrexate (66%), cytarabine (65%), vincristine (57%), etoposide and mercaptopurine (34% of each), and dexamethasone (33%) the most common bridging therapies used by the infused patients.

In total, 94% (60/64) of the patients who received tisagenlecleucel received LD chemotherapy after enrolment and prior to infusion in order to facilitate engraftment and homeostatic expansion of tisagenlecleucel. This proportion is similar to that reported in study B2202 (96%; 76/79). The most common LD therapies were fludarabine (30 mg/m^2 iv daily for 4 doses) and cyclophosphamide (500 mg/m^2 iv daily for 2 doses starting with the first dose of fludarabine) each used in 92% of the infused patients as recommended by the protocol. The protocol defined alternative LD therapies of cytarabine (500 mg/m^2 iv daily for 2 days) and etoposide (150 mg/m^2 iv daily for 3 days starting with the first dose of cytarabine, e.g. for patients who had previous grade 4 haemorrhagic cystitis with cyclophosphamide) were each used in only 2 patients, i.e. 3% of the infused patients. In total, 6% (4/64) of the infused patients did not receive any LD chemotherapy as they had WBC ≤1000 within one week prior to infusion. The most common LD therapies used in study B2202 were also fludarabine and cyclophosphamide, each used in 95% of the infused patients. The alternative LD therapies of cytarabine and etoposide were infrequently used, each in only one patient. Three patients in this study did not receive any LD therapy.

In summary, the proportions of patients reported to have been receiving bridging- and LD therapies and the type of chemotherapy combinations the infused patients received appear to be similar in the two paediatric B-cell ALL studies B2205J and B2202.

Issue resolved.

Question 5

The rationale for censoring the 14 patients for OS follow up in the final analysis who switched to the long–term follow-up study is not understood. Please justify why relevant follow-up data for these 14 patients were not included, or provide updated analyses including these patients.

Summary of the MAH's response

This report concerns study B2205J and therefore includes information only from the B2205J database with a DCO of 24-May-2019 and locked on 18-Jul-2019. At the time of study closure, patients in primary follow-up had the option to transition to the long-term follow up study A2205B and were censored for events at the time of their last contact date. Considering that survival status was updated every 3 months, those patients whose last contact date was at least 105 days (i.e., 3 months plus 2

weeks, assuming 1 month = 30.4375 days) earlier than the analysis DCO of 24-May-2019 were categorized as lost to follow-up.

There were 14 patients in this category and their follow-up data after the transition was not included in the OS analysis in the B2205J final analysis. For the 14 patients censored as lost to follow-up and transitioned to A2205B, relevant follow-up data (including an updated OS analysis for all infused patients in study B2205J) will be submitted exceptionally if requested as part of the upcoming annual report for the A2205B study, which will be appended to the next PSUR (PSUR4 with a reporting interval 13-Feb-2020 to 12-Aug-2020). Individual patient data at the time of transition to study A2205B has been provided.

Novartis acknowledges the Agency's comment about the relevance of the appropriate follow-up data for these 14 patients and the impact on the interpretation of the overall survival curve. Note that in the B2205J final CSR it is stated that the OS curve beyond 24 months should be interpreted with caution (including the estimated median OS), since it was at about 24 follow-up that the 14 subjects discontinued the trial in order to switch to the long-term follow-up study. This meant a low number of subjects at risk, and less reliable survival estimates.

Assessment of the MAH's response

The MAH has clarified the rationale for censoring for OS follow up in the final analysis for the 14 patients who switched to the long–term follow-up study A2205B and have provided individual patient data at the time of transition for these 14 patients. However, no updated OS analyses including these patients have been submitted. The MAH's approach to define patients that transitioned to study A2205B as "lost–to-follow-up" and therefore censoring them in the final OS analysis in study B2205J is not supported. In total, 13 of the 14 patients had confirmed an overall response of CR or CRi at the latest assessment before transition to the long-term follow up study. According to the reported individual patient level data, 8 of these patients have been censored for OS in study B2205J as far back as from 2015-2018, meaning a considerably long time before the last DCO of 24-May 2019. Several of these patients, i.e. 6 patients, were censored approximately one year or less after infusion with tisagenlecleucel.

In the final OS analysis of study B2205J, there are only 14 patients "at risk" at 24 months follow-up among the total 64 infused patients and 30 reported deaths (See Fig 6). It is noted that there is frequent censoring in the OS KM curve during 12-24 months and few reported deaths in the same time interval. If only a few of the 14 patients who transitioned to the follow-up study and were decided by the MAH to be censored for OS actually died before the last DCO, this would impact the OS curve.

Standard requirements in a setting with a rather high proportion of "lost to follow-up" for OS, would be to submit a conservative sensitivity analysis and discuss the impact of a scenario where censoring is linked to an unfavourable clinical outcome.

An updated OS analysis for study B2205J (including both the ITT, i.e. the enrolled patient population, and the FAS population) with the latest possible survival status for the 14 patients transitioned to the follow-up study should be provided and included in an updated version of section 5.1 of the SmPC.

Issue not pursued further in this procedure.

Question 6

The impact HSCT had on the OS results is not known since no sensitivity analysis of OS excluding patients receiving HSCT post-randomisation was provided. The MAH should provide sensitivity analysis exploring the impact of HSCT on the OS results.

Summary of the MAH's response

Sensitivity analysis exploring the impact of HSCT on the OS results are shown in the table below. There is no difference in overall survival if patients that received HSCT post infusion are excluded or censored at the time of HSCT.

Table 15. Overall survival (OS) (FAS)

	FAS	FAS excluding patient receiving HSCT	FAS censoring for HSCT
Events/Total (%)	30/64 (46.9)	26/55 (47.3)	26/64 (40.6)
Maximum follow-up (months)	49.3	49.3	49.3
Median follow-up (months)	15.13	14.8	12.1
Percentiles (95% CI) [1]			
25th	7.3 (4.1, 14.8)	6.9 (4.1, 11.0)	7.2 (4.7, 14.8)
50th	29.9 (15.1, 42.4)	29.9 (11.0, NE)	29.9 (14.8, NE)
75th	42.4 (34.4, NE)	NE (36.8, NE)	NE (36.8, NE)
% Event-free probability estimates (95% CI) [2]			
Month 3	92.2 (82.2, 96.7)	90.9 (79.5, 96.1)	92.0 (81.9, 96.6)
Month 6	84.4 (72.9, 91.3)	83.6 (70.9, 91.1)	85.3 (73.6, 92.1)
Month 9	67.0 (54.0, 77.1)	65.3 (51.1, 76.3)	67.2 (53.4, 77.7)
Month 12	65.4 (52.4, 75.7)	63.4 (49.2, 74.6)	65.3 (51.4, 76.1)
Month 15	63.6 (50.4, 74.1)	61.1 (46.8, 72.7)	62.9 (48.8, 74.2)
Month 18	61.6 (48.2, 72.4)	58.7 (44.1, 70.7)	60.4 (46.0, 72.1)
Month 21	61.6 (48.2, 72.4)	58.7 (44.1, 70.7)	60.4 (46.0, 72.1)
Month 24	54.7 (39.8, 67.4)	54.2 (38.2, 67.7)	55.8 (39.6, 69.2)
Month 27	54.7 (39.8, 67.4)	54.2 (38.2, 67.7)	55.8 (39.6, 69.2)
Month 30	48.6 (31.2, 64.0)	47.4 (28.8, 63.9)	48.8 (29.8, 65.4)

- FAS = All subjects who received an infusion of tisagenlecleucel
[1]Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
[2]% Event-free probability estimate is the estimated probability that a subject will remain event-free up to the specified time point.
% Event-free probability estimates are obtained from the KM survival estimates; Greenwood formula is used for CIs of KM estimates.

Assessment of the MAH's response

Based on the new data provided, 9 of the 64 infused patients proceeded to HSCT during the study, i.e. number of patients in FAS OS compared to number of patients in FAS OS excluding patients receiving HSCT. According to the final CSR report, only 4 patients were censored due to HSCT in the DOR analysis, whereas 6 patients were censored due to HSCT in the EFS analysis.

No individual patient data for patients proceeding to HSCT has been provided and the dates of censoring for OS are not known. Patients may have progressed or been censored for other primary reasons than HSCT in the DOR and EFS analysis, for instance due to "New cancer therapy other than HCST", and later proceeded to HSCT and therefore censored in the OS analysis. The proportion of

patient proceeding to HSCT constitutes only 14% (9/64) of the total FAS population and the exclusion or censoring of these patients in the analyses seems to have no impact on event-free probability estimates at different time points or on the median OS.

Issue resolved.

Question 7

The updated efficacy data from study B2205J should be reflected in section 5.1 of the SmPC. Please make a proposal for inclusion of study results from the final analysis of study B2205J in section 5.1 of the current SmPC.

Summary of the MAH's response

In the original marketing authorization application of Kymriah, Novartis suggested inclusion of study B2205J data as supportive information. During review of the MAA, it was agreed with EMA that the presentation of efficacy and safety data in the SmPC should focus on the pivotal study B2202 and data related to supportive study B2205J were removed. The SmPC was recently updated (03-Mar-2020) with safety and efficacy data from study B2202 including longer follow-up of patients compared to the original SmPC. The final results of study B2205J do not provide new information in respect to efficacy/ safety of tisagenlecleucel in the paediatric population and the benefit risk profile remains positive, so no update to the SmPC is warranted.

Assessment of the MAH's response

It is acknowledged that the presentation of the efficacy and safety data of study B2205J was agreed to be removed from the SmPC during the review of the MAA. At the time of the initial MA, data from only 29 patients was available from this study and it was therefore concluded during the review that the data from study B2205J were immature and could only be considered as supportive to the data of the pivotal study B2202. However, the submitted efficacy results from the final analysis of study B2205J are considered sufficiently mature and further support the data underlying the approved indication of Kymriah for patients with r/r B-cell ALL.

As already discussed in the assessment report above, a University of Pennsylvania manufacturing process was used for the manufacturing of tisagenlecleucel for the first 29 batches included in the IA1, whereas a Novartis manufacturing process was used thereafter for the manufacturing of CAR T-cells to the rest of the patients enrolled in study B2205J. The results of the IA1 were therefore solely based on tisagenlecleucel products produced by using the University of Pennsylvannia manufacturing process, whereas the final analysis was based on patients receiving tisagenlecleucel from the Novartis manufacturing process as well. In relation to the assessment of the manufacturing process development for tisagenlecleucel, covering several process versions, the CAT/CHMP have concluded that the quality data for the most significant changes associated with the various options introduced for starting material processing and transfer of the process from the initial manufacturing site to MP, did not indicate that the changes had any major impact on product composition and comparability.

It is agreed that the final study results of study B2205J do not change, but rather confirm the favourable benefit-risk conclusion of Kymriah in the currently approved ALL indication. Study B2205J was designed to either demonstrate or support the efficacy and safety of tisagenlecleucel in paediatric and young adult patients with B-cell ALL who had relapsed or were refractory to prior therapies. Although it was planned to include patients with relapsed or refractory paediatric B-cell ALL and lymphoblastic lymphoma in study B2205J were only patients with ALL enrolled. Thus, study B2205J had similar study design and enrolled comparable patient populations with r/r B-cell ALL as the pivotal

study B2202. Two different manufacturing processes were used in study B2205J, but the differences in these processes have earlier been concluded by the CAT/CHMP to not have had any major impact on product quality and comparability. In addition, the efficacy results from the final analysis are consistent with the IA1 reported at the time of initial MA, the final data included almost the double of patients with r/r B-cell ALL compared to the IA1 and contained more mature data from the target patient population. On these grounds, the MAH is strongly recommended to update section 5.1 of the SmPC with the final results from the complete data set of study B2205J.

The procedure is concluded and there is no request for more information. However, the MAH should commit to submit an application for a variation to update section 5.1 of the SmPC with the complete data set of the paediatric B-cell ALL study B2205J.

6. MS comments on the CAT Rapporteur's Updated assessment report

None.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Kymriah Active substance: tisagenlecleucel

Study title	Study number	Date of completion	Date of submission of final study report
A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric subjects with relapsed and refractory B-cell acute lymphoblastic leukemia (ENSIGN)	CCTL019B2205J	24-May-2019 (last subject last visit)	