16 October 2021
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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/P46/012

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Introduction

On the 16 March 2021, the MAH submitted the final study results from a completed phase IIIB paediatric clinical study for Kymriah (tisagenlecleucel; ATC code: L01XX71) in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

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

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

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

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the Phase IIIb study CCTL019B2001X (hereafter referred to as study B2001X) in paediatric and young adult patients with relapsed/refractory (r/r) acute lymphoblastic leukaemia (ALL) treated with tisagenlecleucel is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

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

Kymriah comprises cell dispersion for infusion, where 1-3 infusion bags contain a total of $1.2x10^6$ to $6x10^8$ CAR-positive viable T-cells. The concentration of CAR-positive viable T-cells is dependent on patient body weight for treatment of patients with B-cell ALL. The cellular composition and the final cell number varies between individual patient batches.

The approved dose range for paediatric and young adult patients with B-cell ALL is 0.2 to $5x10^6$ 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.

No change in formulation was made for the paediatric population in study B2001X.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study CCTL019B2001X (B2001X; Protocol version 4.0 dated 06.08.2019). The Final Report is dated 5th March 2021.

Study B2001X is a phase IIIb open-label, multicentre, single arm study designed to further evaluate the safety and efficacy of tisagenlecleucel in paediatric and young adult patients with r/r B-cell ALL after the closure of enrolment to the pivotal study CCTL019B2202 (hereafter referred to as B2202). The inclusion of certain patients not studied during study B2202 was also allowed, e.g., < 3-year-olds or patients with prior blinatumomab exposure.

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

- Paediatric and young adult patients up to and including 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse.
- Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

The evidence of efficacy in paediatric and young adult patients with 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. In addition, the final results from the complete data set of study B2205J, which was reviewed during a previous Article 46 procedure (Procedure No. EMA/H/C/004090/P46/011), have provided supportive evidence for the efficacy of tisagenlecleucel in the approved ALL indication (Procedure No. EMEA/H/C/004090/II/0030). Study B2205J was a phase II, open-label, multicentre, single arm study that was designed to 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.

The final results of study B2001X are now submitted in accordance with Article 46 of Regulation (EC) No 1901/2006, which requires that any MAH-sponsored study involving use in a paediatric population of a medicinal product covered by a MA, whether or not it is conducted in compliance with an agreed PIP, should be submitted to the competent authority within six months of completion of the concerned study.

2.3.2. Clinical study

Study B2001X

Methods

Objectives and outcome/endpoints

The primary objective of study B2001X was to evaluate the safety of tisagenlecleucel treatment as measured by adverse events (AEs) and laboratory abnormalities.

Secondary objectives included various efficacy, exposure-responses to cytokine release syndrome (CRS) grades, clinical cellular kinetic, and immunogenicity endpoints. These included, but were not limited to: response using MRD assessments before infusion and Day 28 ± 4 days and before haematopoietic stem cell transplantation (HSCT) by local assessment, i.e. flow cytometry with or without qPCR.

Study objectives and related endpoints are shown in Table 1.

Table 1: *Objectives and related endpoints in study B2001X*

Objective	Endpoint
Primary	
Evaluate the safety of CTL019 therapy	Type, frequency and severity of adverse events (AEs) and laboratory abnormalities
Secondary	
Evaluate the efficacy of CTL019 therapy as measured by complete remission (CR) rate, which includes CR and CR with incomplete blood count recovery (CRi).	Percentage of patients who achieve CR or CRi during the 6 months after CTL019 infusion.
Evaluate the percentage of patients who achieve CR or CRi at Month 6 without stem cell transplantation (SCT) between CTL019 infusion and Month 6 response assessment.	Percentage of patients who achieve CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment
Evaluate the percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment.	Percentage of patients who achieve CR or CRi and then proceed to SCT while in remission prior to Month 6 response assessment In addition, all patients that proceed to SCT after CTL019 infusion will be described
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 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 CTL019 infusion to the earliest of death, relapse or treatment failure
Evaluate the overall survival (OS)	OS, i.e. the time from date of CTL019 infusion to the date of death due to any reason
Evaluate the response at Day 28 ± 4 days	Proportion of patients attaining CR or CRi at Day 28 ± 4 days post CTL019 infusion
Evaluate the impact of baseline tumor burden on response	Descriptive summary of response at Day 28 ± 4 days post CTL019 infusion as a function of baseline tumor burden (tumor load) (i.e. by the subgroup baseline bone marrow tumor burden).
Evaluate the quality of response using MRD assessments before treatment and at Day 28 ± 4 days after treatment and before SCT by local assessment (flow cytometry +/- quantitative polymerase chain reaction (q-PCR))	Descriptive summary of MRD qualitative result (positive/negative) before treatment and at Day 28 ± 4 days after treatment and before HSCT by local assessment (flow cytometry or qPCR).
Describe the prevalence and incidence of immunogenicity of antibodies against CTL019	Prevalence and incidence of immunogenicity and anti-CTL019 assay titers
Characterize the *in vivo* cellular kinetic profile (expansion, persistence, trafficking) of CTL019 cells in the blood	Maximum concentration (C_{max}), time to peak concentration (T_{max}), area under the curve (AUC) and other relevant kinetic parameters of CTL019 in the blood Persistence of CTL019 in the blood
Evaluate the relationship between exposure to CTL019 with CRS grades	Relationship of C_{max} and $AUC_{0\text{-}28d}$ of CTL019 in the blood with CRS grade

Study design

Study B2001X had the following sequential phases for all patients: screening including leukapheresis, enrolment and pre-treatment (cell product preparation, bridging- and lymphodepleting [LD] chemotherapy), treatment and follow-up, which included a single tisagenlecleucel infusion and follow-up until month 12. After 12 months post-infusion, the patients were transitioned into the long-term follow-up (LTFU) study A2205B for lentiviral vector safety and efficacy follow-up that was run under a separate protocol in accordance with health authority guidelines for patients treated with gene therapies (Figure 1). The main purpose of the study was to assess the safety of tisagenlecleucel for up to 12 months post-infusion.

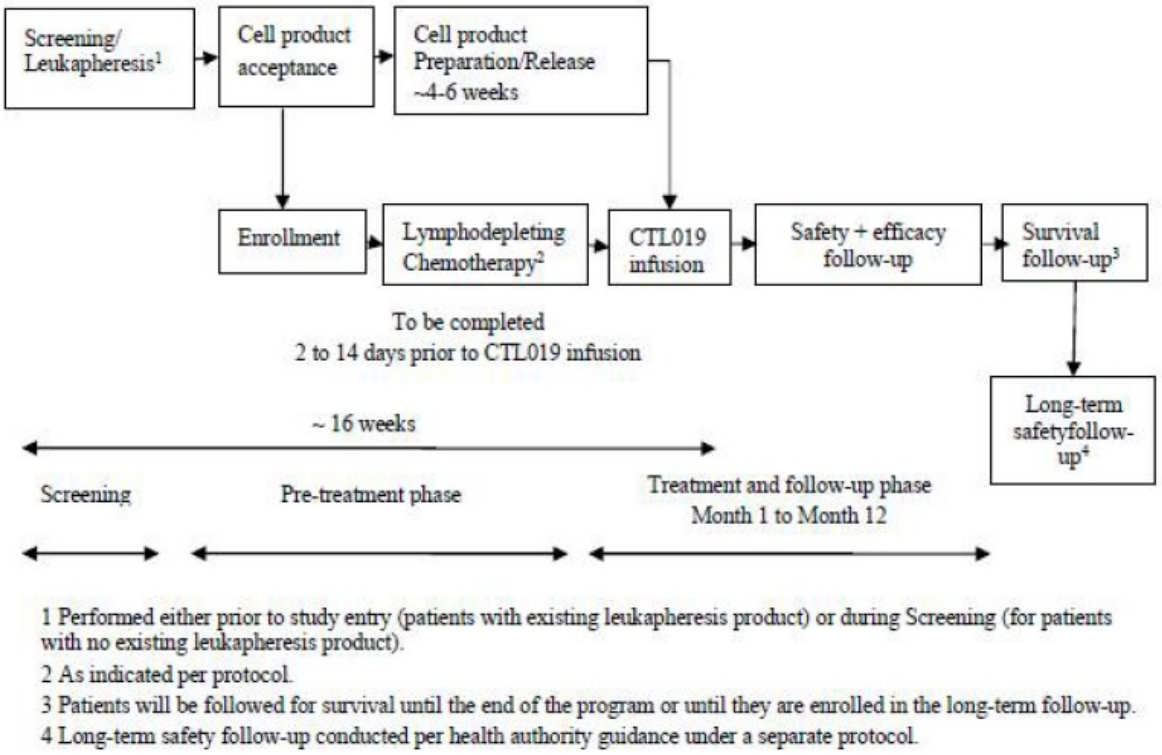


Figure 1: *CTL019 in r/r B-cell pediatric/young adult ALL*

Study population

The target population for enrolment in this study consisted of pediatric and young adult patients with B-cell ALL < 26 years of age at screening who were primary refractory, chemo-refractory, relapsed after allogeneic SCT, or who were otherwise ineligible for allogeneic SCT.

Assessor's comment:

Only the paediatric study population (<18 years of age) will be the focus of this assessment in accordance with the requirements laid down in Article 46 of Regulation No 1901/2006.

Inclusion criteria:

1. Relapsed or refractory B-cell ALL in pediatric or young adult patients:

a. Second or greater bone marrow relapse, or

b. Any bone marrow relapse after allogeneic SCT and must have been ≥ 4 months from SCT at the time of tisagenlecleucel infusion with leukapheresis for tisagenlecleucel manufacturing performed at least 12 weeks after allogeneic SCT, 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 leukemia, or

d. Patients with Philadelphia chromosome positive (Ph+) ALL were eligible if they were intolerant to or had failed 2 prior lines of tyrosine kinase inhibitor (TKI) therapy, or if TKI therapy was contraindicated, or

e. Ineligible for allogeneic SCT because of comorbid disease, other contraindications to allogeneic SCT conditioning regimen, lack of suitable donor, prior SCT, declined allogeneic SCT as a therapeutic option

after documented discussion about the role of SCT with a bone marrow transplantation physician who was not a member of the study team.

2. For relapsed patients, CD19 tumor expression demonstrated in bone marrow or peripheral blood by flow cytometry within 3 months of study entry. For relapsed or refractory patients previously treated with blinatumomab, CD19 tumor expression must have been demonstrated (via flow cytometry) at Screening.

3. Adequate renal, hepatic pulmonary and cardiac organ functions.

4. Life expectancy > 12 weeks.

5. Age < 26 years at the time of Screening.

6. Karnofsky (age ≥ 16 years) or Lansky (age < 16 years) performance status ≥ 50 at Screening.

7. Patients previously treated with blinatumomab who had detectable leukemia and documented CD19+ expression (via flow cytometry) and confirmed absence of CD19- leukemic blasts at Screening could be included. In that case, at least a 1-week washout period had to be applied from last dose of blinatumomab to start of leukapheresis. Patients previously treated with blinatumomab and no detectable MRD (i.e. MRD negative demonstrated by leukemic blasts < 0.01%) were excluded.

Note: blinatumomab must not have been administered as a bridging therapy prior to tisagenlecleucel infusion while the patient is awaiting manufacture of tisagenlecleucel.

8. Signed written informed consent forms (ICFs) and assent forms if applicable must have been obtained prior to any study procedures.

9. Must have met the institutional criteria to undergo leukapheresis or have had an acceptable, stored leukapheresis product.

10. Once all other eligibility criteria were confirmed, must have had a leukapheresis product of non-mobilized cells received and accepted by the manufacturing site. Note: Leukapheresis product were not shipped to or assessed for acceptance by the manufacturing site until documented confirmation of all other eligibility criteria was received.

11. Patients with active central nervous system (CNS) leukemia involvement defined as CNS-3 by cerebrospinal fluid (CSF) findings only were eligible but had their tisagenlecleucel infusion delayed until CNS disease was reduced to CNS-1 or CNS-2 by CSF findings. Patients with other forms of active CNS-3 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 CNS-3 leukemic involvement (non-CSF involvement) were eligible if there was documented evidence of disease stabilization for at least 3 months prior to tisagenlecleucel infusion. Patients must have had no 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 previous 3 months.

Exclusion criteria:

Patients meeting any of the following criteria were excluded from the study:

1. Isolated extra-medullary disease relapse.

2. 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 were not excluded.

3. Patients with Burkitt's lymphoma/leukemia (i.e. patients with mature B-cell ALL, leukemia with B-cell surface immunoglobulin (sIg) positive and kappa or lambda restricted positivity ALL, with French-American-British Classification System for Hematologic Disease L3 morphology and/or a MYC translocation).

4. Prior malignancy, except carcinoma *in situ* of the skin or cervix treated with curative intent and with no evidence of active disease.

5. Prior treatment with any gene therapy product.

6. Prior treatment with any anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy, except for patients pre-treated with blinatumomab who fulfill inclusion criterion no.7.

7. Presence of active replication of hepatitis B or hepatitis C. Serology had to be repeated if the interval between testing at Screening and tisagenlecleucel infusion exceeded 8 weeks.

8. HIV positivity as indicated by serology. Serology had to be repeated if the interval between testing at Screening and tisagenlecleucel infusion exceeded 8 weeks.

9. Presence of grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD).

10. Uncontrolled acute life-threatening infection at Screening.

11. Previous or concurrent malignancy with the following exceptions:

a. Adequately treated basal cell or squamous cell carcinoma (adequate wound healing is required prior to study entry).

b. *In situ* carcinoma of the cervix or breast, treated curatively and without evidence of recurrence for at least 3 years prior to the study.

c. A primary malignancy which had been completely resected and in CR for ≥ 5 years.

12. Intolerance to the excipients of the tisagenlecleucel product (i.e. dimethyl sulfoxide).

13. Cardiac or cardiac repolarization abnormality, including any of the following:

- History of myocardial infarction, angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to starting study treatment.
- Clinically significant cardiac arrhythmias (e.g. ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular (AV) block (e.g. bifascicular block, Mobitz type II and third degree AV block).
- LVEF < 45% as determined by ECHO or magnetic resonance angiography (MRA) or multiple uptake gated acquisition (MUGA).
- New York Heart Association (NYHA) functional class III or IV.

14. Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies.

15. Patient had an investigational medicinal product within the last 30 days prior to Screening.

16. 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, mycophenolate, rapamycin, thalidomide, or immunosuppressive antibodies such as anti-CD20 (rituximab), anti-tumor necrosis factor (anti-TNF), anti-IL-6 or anti-IL-6 receptor, systemic steroids).

d. **Chemotherapy:**

- TKIs and hydroxyurea had to be stopped > 72 hours prior to tisagenlecleucel infusion.
- The following drugs had to be stopped > 1 week prior to tisagenlecleucel infusion and should not have been administered concomitantly or following lymphodepleting chemotherapy: vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate < 25 mg/m^2, cytosine arabinoside < 100 mg/m^2/day, asparaginase (non-pegylated).
- 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 lymphodepleting chemotherapy drugs.
- 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**

- Non-CNS site of radiation had to be completed > 2 weeks prior to tisagenlecleucel infusion.
- 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 could 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 was to be contacted, consultation with a pharmacology expert was to be considered, and measurement of residual drug levels was to be considered, if feasible, prior to tisagenlecleucel infusion.

17. Pregnant or nursing (lactating) women.

NOTE: Women of child-bearing potential must have had a negative serum pregnancy test performed within 24 hours before leukapheresis, lymphodepletion and prior to tisagenlecleucel infusion.

18 & 19. Women of child-bearing potential defined as all women physiologically capable of becoming pregnant, and sexually active males, unless they agreed to using highly effective methods of contraception from enrollment and for at least 12 months after the tisagenlecleucel infusion and until CAR T-cells were no longer present by q-PCR on 2 consecutive tests. q-PCR test results were available upon request. In addition, male participants must not have donated sperm for the time period specified

above. NOTE: If local regulations deviated from the contraception methods listed in the protocol to prevent pregnancy, local regulations applied and were to be described in the ICF.

In addition to exclusion criteria, live vaccines were not to be used in tisagenlecleucel recipients for at least 6 weeks prior to the start of LD chemotherapy, during tisagenlecleucel treatment, and until immune recovery following treatment with tisagenlecleucel.

Treatments

Leukapheresis: Leukapheresis was performed as per study protocol or per local institutional guidelines. The manufacturing facility evaluated the patient's leukapheresis product for acceptance. Final enrollment was defined as the point at which the patient met all clinical inclusion/exclusion criteria, and the patient's leukapheresis product was accepted for manufacturing.

Lymphodepletion (LD): If patients had a white blood cell (WBC) count ≤ 1,000 cells/μL within 1 week prior to tisagenlecleucel infusion, LD regimen was not required. LD chemotherapy was to start 1 week prior to tisagenlecleucel infusion, which meant that tisagenlecleucel was infused 2 to 14 days after LD depending on the LD regimen used. LD could be repeated in case tisagenlecleucel was delayed by more than 4 weeks. The preferred regimen was as follows:

- Fludarabine (30 mg/m^2 i.v. daily for 4 days), and

Cyclophosphamide (500 mg/m^2 i.v. daily for 2 days starting with the first dose of fludarabine)

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

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

No other regimen was allowed for LD. Female patients of childbearing potential were to have a negative pregnancy test (urine or serum) within 24 hours prior to the start of LD therapy or within 5 days prior to tisagenlecleucel infusion.

Tisagenlecleucel infusion: Tisagenlecleucel was released to the study site provided all required safety and quality release specifications were met.

Once tisagenlecleucel transduced viable T-cells were thawed and at room temperature (20°C to 25°C), they were to be infused within 30 minutes to maintain maximum product viability, including any interruption during the infusion.

Based on the patient's weight reported at the time of leukapheresis/Screening (note: for patients with a historical leukapheresis product, the patient's weight reported at the time of Screening was used), one of the 2 following allowable dose ranges was prepared:

- For pediatric and young adult patients with r/r ALL whose weight was ≤ 50 kg, the targeted dose was 0.2 to 5.0 × 10^6 autologous CAR-positive viable T-cells per kg body weight.
- For pediatric and young adult patients with r/r ALL whose weight was > 50 kg, the targeted dose was 0.1 to 2.5 × 10^8 autologous CAR-positive viable T-cells.

Patients were infused with the maximum cell dose within the recommended ranges that can be individually manufactured. Products falling below the minimum values in the above allowable cell dose ranges were evaluated for provision to the patient under exceptional circumstances after approval by Health Authorities for infusion.

The tisagenlecleucel dose was administered via a single intravenous (IV) infusion.

Statistical Methods

Sample size

There were no formal sample size calculations performed for this study. Based on the estimated availability of eligible patients who could provide an acceptable leukapheresis product of non-mobilized cells to the manufacturing site, manufacturing capacity of tisagenlecluecel product, and an anticipated recruitment duration will be ~ 2 years, it was anticipated to enrol approximately 80 patients.

Analysis sets

The *Screened Set* comprised all patients who have signed the informed consent/assent and were screened in the study.

The *Enrolled set* (ENS) 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 *Safety set* (SAF) comprised of all patients who received infusion of tisagenlecleucel.

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

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

Primary analysis

The primary variable was overall TEAEs (including SAEs and laboratory abnormalities observed after tisagenlecleucel infusion) in the Safety set (SAF, equivalent to FAS), for which no statistical hypothesis testing was planned or performed.

Statistical methods for secondary endpoints

For secondary endpoints response was determined by the investigator. The FAS was used as the efficacy analysis set.

Estimates of:

- The proportion of patients who achieved complete remission (which included CR or CRi during the 6 months after tisagenlecleucel infusion),
- Percentage of patients who achieved CR or CRi and then proceed to SCT while in remission before Month 6 response assessment, and
- Percentage of patients who achieved CR or CRi and then proceed to HSCT while in remission before Month 6 response assessment, and
- Response at Day 28 ± 4 days*, were all summarised with two-sided exact 95% Clopper-Pearson confidence intervals.

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 whichever occurred first to relapse or death due to any cause during CR or CRi.

Event free survival (EFS) was the time from date of first tisagenlecleucel 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 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.

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 HSCT were performed. As HSCT was considered an important treatment option in responding patients, it was deemed appropriate to consider the date of HSCT as the censoring date, instead of censoring at the last tumour assessment date. A sensitivity analysis was to be performed in which the date of relapse or death (if due to the underlying cancer) after HSCT was used for the calculation of DOR. In case of treatment failure, the event date was set to Study Day 1. In addition, a sensitivity analysis of EFS was performed by considering time of discontinuation from the study as the event time for treatment failure, instead of setting to Study Day 1.

Overall survival (OS) was defined as the time from date of first tisagenlecleucel 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, ORR by age subgroups (< 12y, ≥12y to <18y, ≥ 18y) tumour burden at baseline were presented.

Interim analysis

No formal interim analysis was planned or performed; safety was reviewed periodically.

Assessor's comment

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

Results

Recruitment/ Number analysed

Study B2001X enrolled and treated paediatric and young adult patients with r/r B-cell ALL at 11 investigative centers in 9 countries (Austria, Belgium, Canada, Germany, Spain, France, Italy, Japan, and Norway). Study initiation date was 24-Apr-2017 (first patient first visit) and study completion date was 13-Oct-2020 (last patient last visit).

A total of 81 patients were screened, 77 (95.1%) of whom satisfied all eligibility criteria; of these, 74 patients (91.4%) were enrolled in the study and 3 (3.7%) were not enrolled (1 patient died, 1 was not enrolled due to physician decision and 1 was a screen failure).

Table 2: *Overview of paediatric disposition during Study B2001X*

Disposition Primary reason	Pediatrics Nonadolescents: < 12 y N (%)	Pediatrics Adolescents: 12 y to < 18 y N (%)	Overall study population N=74 n (%)
Enrolled in study			74 (100)
Discontinued prior to tisagenlecleucel infusion			5 (6.8)
Death			4 (5.4)
Technical problems			1 (1.4)
Tisagenlecleucel infused[1]			69 (93.2)
Entered treatment and primary follow-up phase[1]	42 (100)	10 (100)	69 (100)
Completed both treatment and study follow-up	20 (47.6)	5 (50.0)	33 (47.8)
Discontinued treatment and follow-up phase	22 (52.4)	5 (50.0)	36 (52.2)
Progressive disease	7 (16.7)	5 (50.0)	18 (26.1)
Lack of efficacy	5 (11.9)	0	6 (8.7)
Death	4 (9.5)	0	5 (7.2)
Physician decision	2 (4.8)	0	2 (2.9)
Subject/guardian decision	2 (4.8)	0	2 (2.9)
Protocol deviation	1 (2.4)	0	1 (1.4)
New therapy for study indication	1 (2.4)	0	1 (1.4)
Lost to follow-up	0	0	1 (1.4)

Enrolled set=all patients who met all inclusion/exclusion criteria, and whose leukapheresis product was received and accepted by the manufacturing facility.
[1] FAS

Of the 74 patients who constituted the Enrolled set, 69 (93.2%; 52 pediatrics) were infused and received tisagenlecleucel and thereby constituted the FAS (Table 2). The remaining 5 patients (6.8%) discontinued after enrolment and prior to tisagenlecleucel infusion due to the following reasons: There were 4 patients (5.4%) who died while waiting for infusion and 1 patient (1.4%) had their investigational product not released from manufacturing, i.e. product could not be manufactured. Among the 69 patients who received tisagenlecleucel infusion in the FAS, 33 (47.8%) completed both their treatment and primary follow-up phase of whom 36.2% (25/69) were pediatric patients. Reasons for discontinuing tisagenlecleucel infusion and the primary follow-up- phase are detailed in Table 2.

Patients < 12 years of age

A total of 42 patients were < 12 years of age in the FAS; 20 patients (47.6%) completed the primary follow-up phase and 22 patients (52.4%) discontinued. The most frequent reason for discontinuation was progressive disease (16.7%; 7/42), followed by lack of efficacy (11.9%; 5/42), death (9.5%; 4/42), physician's decision and patient/guardian decision (4.8%; 2/42 of each). The remaining 2 patients discontinued due to new therapy for study indication and protocol deviation. The majority of patients (83.3%; 35/42) < 12 years of age were enrolled into the LTFU study A2205B.

Patients ≥ 12 to < 18 years of age

A total of 10 patients were ≥ 12 and < 18 years of age in the FAS; 5 patients (50%) completed the primary follow-up phase and 5 patients (50%) discontinued (all due to progression of the underlying disease). Over half of patients (60%; 6/10) ≥ 12 and < 18 years of age were enrolled into the LTFU study A2205B.

Protocol deviations

Protocol deviations are presented for the FAS by deviation category in Table 3.

There were no major protocol deviations.

Table 3: *Protocol deviations (FAS)*

Category	All subjects N=69 n (%)
Any protocol deviation	28 (40.6)
Treatment deviation	15 (21.7)
Any exclusion criteria deviation	9 13.0)
Any inclusion criteria deviation	7 (10.1)
Other deviation	3 (4.3)
Prohibited concomitant medication	3 (4.3)

Percentages are based on the number of subjects in the FAS (N).

Treatment deviations mainly consisted of total window between signature of ICF and tisagenlecleucel infusion exceeded 16 weeks (8 patients, 11.6%); and cardiac evaluation was not repeated prior to tisagenlecleucel infusion (6 patients, 8.7%). In addition, influenza testing was not performed, or no confirmation of symptoms was performed prior to infusion for 1 patient (1.4%), and 1 patient (1.4%) had an uncontrolled active infection prior to tisagenlecleucel infusion.

Exclusion criteria deviations consisted of patient had active or latent hepatitis B per exclusion criteria at study entry (4 patients, 5.8%); use of non-study chemotherapy within excluded time frame prior to tisagenlecleucel infusion (3 patients, 4.3%); patient had active CNS involvement by malignancy, defined as CNS-3 per NCCN guidelines per exclusion criteria at study entry (2 patients, 2.9%); and use of steroid medication within excluded time frame prior to tisagenlecleucel infusion (1 patient, 1.4%). Inclusion criteria deviations consisted of ALT results not meeting the inclusion criteria (2 patients, 2.9%), written informed consent not obtained (2 patients, 2.9%) AST results not meeting the inclusion criteria (1 patient, 1.4%), age at initial diagnosis not met (1 patient, 1.4%), and incorrect version of informed consent obtained (1 patient, 1.4%).

Baseline data

The number of participants included in each data analysis set are shown in**Table 4** Table 4.

Table 4: *Analysis sets (screened set)*

Analysis set	All subjects N=81 n (%)
Screened set	81
Enrolled set (ENS)	74 (100)
Full analysis set (FAS)	69 (93.2)
Safety set (SAF)	69 (93.2)
Cellular kinetic analysis set (CKAS)	69 (93.2)
Per-protocol set (PPS)	61 (82.4)

Percentages are based on the number of subjects in the ENS.

Patient disposition:

An overview of patient disposition is shown in Table 5

Table 5: Subject demographics and other baseline characteristics (FAS)

Demographic variable Statistics	All subjects N=69
Age (years)	
n	69
Mean (SD)	11.3 (6.72)
Age category 2 - n (%)	
Infants and toddlers, ≥ 28 days to <2 years	1 (1.4)
Children, ≥ 2 to <12 years	41 (59.4)
Adolescents, ≥ 12 to <18 years	10 (14.5)
Adults, ≥ 18 to ≤ 65 years†	17 (24.6)
Sex - n (%)	
Female	28 (40.6)
Male	41 (59.4)
Race - n (%)	
White	52 (75.4)
Black or African American	2 (2.9)
Asian	4 (5.8)
American Indian or Alaska Native	1 (1.4)
Unknown	3 (4.3)
Other	7 (10.1)
Weight for CTL019 manufacturing (kg)	
n	69
Mean (SD)	38.4 (23.49)
Weight for CTL019 manufacturing category (kg) - n (%)	
< 50	49 (71.0)
≥ 50	20 (29.0)

SD=standard deviation

† The upper age limit at Screening was amended to < 26 years of age in accordance with Protocol Amendment 3. Prior to this amendment, one patient > 26 years of age (i.e. aged 33 years) was enrolled and treated on the study following the issue of an Urgent Safety Measure by Novartis.

Percentages are based on the number of subjects in the FAS (N).

Patients < 12 years of age

A total of 42 patients were < 12 years of age in the FAS; the median age was 7 years. The majority of patients were White (71.4%; 30/42); 9.5% (4/42) were Asian, and 2.4% (1 patient of each) was Black or African/American and American Indian or Alaska Native. Three patients (7.1%) were of other race and the remaining 3 patients (7.1%) were of unknown race. There was a similar proportion of male

and female patients (52.4% [22/42] vs. 47.6% [20/42]). The median weight of patients (considered for the tisagenlecleucel manufacturing) was 23.2 kg. Nearly all patients (97.6%; 41/42) were ≤ 50 kg except for one patient who was > 50 kg. This subgroup included one 10-month old female infant.

Patients ≥ 12 to < 18 years of age

A total of 10 patients were ≥ 12 and < 18 years of age in the FAS; the median age was 13.5 years. The majority of patients were White (60.0%; 6/10); 1 patient was Black or African/American and the remaining 3 patients (30.0%) were of other race. The majority of patients were male (80.0%; 8/10). The median weight of patients (considered for the tisagenlecleucel manufacturing) was 38.8 kg. Most patients (70.0%; 7/10) were ≤ 50 kg; the remaining 3 patients (30.0%) were > 50 kg.

Patients ≥ 18 years of age

A total of 17 patients were ≥ 18 years of age in the FAS; the median age was 20.0 years. The majority of patients were White (94.1%; 16/17); 1 patient was of other race. The majority of patients were male (64.7%; 11/17). The median weight of patients (considered for the tisagenlecleucel manufacturing) was 62.2 kg. Nearly all patients (94.1%; 16/17) were > 50 kg except for one patient who was ≤ 50 kg.

The upper age limit at Screening was amended to < 26 years of age in accordance with Protocol Amendment 3. Prior to this amendment, one patient > 26 years of age (i.e. aged 33 years) was enrolled and treated on the study following the issue of an Urgent Safety Measure by Novartis.

Baseline ALL characteristics

Baseline ALL disease characteristics are presented for the FAS in Table 6.

Table 6: *Baseline acute lymphoblastic leukemia (ALL) disease characteristics (Full analysis set)*

Characteristic	All subjects N=69
CD19 status [1] - n (%)	
Positive	60 (87.0)
Not done	1 (1.4)
Unknown	8 (11.6)
Morphologic blast count in bone marrow (%) [2]	
n	66
Mean (SD)	56.7 (33.48)
CNS status classification - n (%)	
CNS-1	52 (75.4)
CNS-2	5 (7.2)
CNS-3	2 (2.9)
Indeterminate	6 (8.7)
Missing	4 (5.8)
Extramedullary disease presentation at physical exam - n (%)	
Yes	9 (13.0)
No	60 (87.0)

CNS=central nervous system; SD=standard deviation
CNS-1: No lymphoblasts in the cerebral spinal fluid (CSF) regardless of white blood cell (WBC) count;
CNS-2: WBC less than 5/µL in CSF with presence of lymphoblasts;
CNS-3: WBC of 5/µL or greater with presence of lymphoblasts.
[1] CD19 status is from the bone marrow result, or from blood result if bone marrow is not available.

[2] Morphologic blasts count in bone marrow is from bone marrow aspirate.
Percentages are based on the number of subjects in the FAS (N).

Patients < 12 years of age

The majority of patients < 12 years of age in the FAS (n=42) had a positive CD19 status (88.1%; 37/42); CD19 status was unknown in 5 patients (11.9%). The mean morphologic blast count was 59.5% for bone marrow. Most patients had a CNS-1 (78.6%; 33/42), 7.1% (3/42) had CNS-2, 2.4% (1/42) had CNS-3, 4.8% (2/42) had indeterminate CNS status, and 7.1% (3/42) had missing CNS status. The majority of patients had no extra-medullary disease (EMD) presentation at physical examination (88.1%; 37/42).

Patients ≥ 12 to < 18 years of age

The majority of patients ≥ 12 and < 18 years of age in the FAS (n=10) had a positive CD19 status (90.0%; 9/10); CD19 status was unknown in 1 patient (10.0%). The mean morphologic blast count was 50.3% for bone marrow. Most patients had a CNS-1 (80.0%; 8/10), 1 patient (10.0%) had CNS-3, and 1 patient (10.0%) had an indeterminate CNS status. The majority of patients had no EMD at physical examination (70.0%; 7/10).

Patients ≥ 18 years of age

The majority of patients ≥ 18 years of age in the FAS (n=17) had a positive CD19 status (82.4%; 14/17); CD19 status was unknown in 2 patients (11.8%) and was not done for the remaining patient. The mean morphologic blast count was 53.8% for bone marrow. Most patients had a CNS-1 (64.7%; 11/17), 11.8% (2/17) had CNS-2, 17.6% (3/17) had indeterminate CNS status, and 1 patient had missing CNS status. The majority of patients had no EMD at physical examination (94.1%; 16/17).

Assessor's comment:

CD19 status for the paediatric population was similar to that of the adult population. The majority of the paediatric population had CNS-1 and no EMD at physical examination.

Primary disease history and prior antineoplastic therapies

Primary disease history and prior antineoplastic therapies are presented for the FAS in

Table 7.

All patients in the FAS had B-cell ALL. The median age at initial diagnosis was 4.0 years, most patients (66.7%) were < 10 years of age at the initial diagnosis. All patients had relapsed disease except for one patient who had refractory disease.

Table 7: *Primary disease history and prior antineoplastic therapies (FAS)*

Disease history	All subjects N=69
Diagnosis of disease - n (%)	
ALL B-cell	69 (100.0)
Age at initial diagnosis (years)	
n	69
Mean (SD)	7.2 (5.79)
Age at initial diagnosis category (years) - n (%)	
<10	46 (66.7)
≥ 10	23 (33.3)
Disease status - n (%)	
Refractory	1 (1.4)
Relapsed disease	68 (98.6)

SD=standard deviation
Refractory: Never had a morphologic complete remission (CR) prior to the study;
Relapsed disease: Had at least one relapse prior to the study.
Percentages are based on the number of subjects in the FAS (N).

Patients < 12 years of age

The median age at initial diagnosis for patients < 12 years of age in the FAS (n=42) was 3.0 years; all patients were < 10 years of age at the initial diagnosis. All patients had relapsed disease except for one patient who had refractory disease.

Patients ≥ 12 to < 18 years of age

The median age at initial diagnosis for patients ≥ 12 and < 18 years of age in the FAS (n=10) was 10.5 years; most patients (70.0%; 7/10) were ≥ 10 years at the initial diagnosis (i.e. a number of years prior to Screening). All patients had relapsed disease.

Patients ≥ 18 years of age

The median age at initial diagnosis for patients ≥ 18 years of age in the FAS (n=17) was 17.0 years; most patients (94.1%; 16/17) were ≥ 10 years at the initial diagnosis (i.e. a number of years prior to Screening). All patients had relapsed disease.

Prior anti-neoplastic therapy

All patients had received prior antineoplastic therapy. The number of prior lines of therapy are shown in Table 8.

Table 8: *Primary disease history and prior antineoplastic therapies (FAS)*

Disease history	All subjects N=69
Number of previous complete remissions	
n	69
Mean (SD)	1.6 (1.07)
Median	1.0
Min-Max	0.0-6.0
Number of previous lines of therapies	
n	69
Mean (SD)	2.7 (1.36)
Median	2.0
Min-Max	1.0-8.0
Time since initial diagnosis to first relapse/progression (months) [1]	
n	66
Mean (SD)	33.6 (24.56)
Median	29.8
Min-Max	4.4-156.0
Time since initial diagnosis to first relapse/progression category (months) [1] - n (%)	
<18	16 (23.2)
18 to 36	25 (36.2)
>36	25 (36.2)

The majority of patients (81.2%) discontinued prior antineoplastic medications due to completion of the prescribed regimen; 8.7% discontinued due to disease progression. The best hematological response at last treatment was CR (36.2%), CRi (1.4%), PR (7.2%), treatment failure (20.3%), unknown (15.9%), or not applicable (18.8%).

All patients had received prior antineoplastic therapy. Of the 52 paediatric patients there were 21.2% (11/52) with prior exposure to blinatumomab and 9.6% (5/52) with prior inotuzumab therapy. This trend was consistent with the overall study population, e.g. 21.7% (15/69) with prior blinatumomab exposure; 10.1% (7/69) with prior inotuzumab exposure.

A total of 6 patients (8.7%) had prior antineoplastic surgery (4 patients, 5.8% had a biopsy and 2 patients, 2.9% had other procedure). Overall, 42.0% of patients had prior radiotherapy, at the last radiotherapy mostly in the body (26.1%) as conditioning for SCT (31.9%). All patients had prior antineoplastic medications, mostly as an induction treatment (37.7%) followed by conditioning for SCT (27.5%), salvage (18.8%), maintenance (13.0%), or consolidation (2.9%).

Furthermore, a number of participants had received prior HSCT (Table 9). The allogenic donor was most frequently unrelated (fully matched (38.1%)) or sibling (fully matched (26.2%)) or unrelated (any mismatch (23.8%)). The MRD status was negative prior to HSCT for the majority of patients (61.9%).

Table 9: *Prior anti-neoplastic therapy – HSCT (FAS)**

Characteristic	**All subjects**

	N=69
Number of prior HSCT:	
0	27 (39.1%)
1	38 (55.1%)
2	4 (5.8%)
Specifications of last HSCT:	
Time since last HSCT tisagenlecleucel infusion (months)	
n	42
Mean (SD)	20.5 (17.28)
Median	15.5
Min-Max	4-89
Graft type – n (%):	
Cord blood	7 (16.7)
Bone Marrow	21 (50.0)
Peripheral blood	13 (31.0)
Unknown	1 (2.4)

*Table by assessor from data in Table 14.1-6.1

Exposure to study treatment

Regarding the tisagenlecleucel dose, the majority of patients (85.5%) had a dose within the target range, 11.6% (8/69) had a dose below the target range, and 2.9% (2/69) had a dose above the target range. Similar values were obtained for patients ≤ 50 kg and > 50 kg. The mean weight-adjusted transduced cell dose infused was 2.2 × 10^6 cells/kg overall; 2.2 × 10^6 cells/kg for patients ≤ 50 kg and 2.1 × 10^6 cells/kg for patients > 50 kg. The mean weight-adjusted total cell dose infused was 10.8 × 10^6 cells/kg; 12.3 × 10^6 cells/kg for patients ≤ 50 kg and 7.0 × 10^6 cells/kg for patients > 50 kg.

Weight adjusted dose is based on weight used for manufacturing. The target dose range is 0.2 to 5 x 10^6 CAR-positive cells/kg for patients ≤ 50 kg, and 0.1 to 2.5 x 10^8 tisagenlecleucel for patients >50 kg. Percentages are based on the number of subjects in the SAF (N).

Patients < 12 years of age

Regarding the tisagenlecleucel dose, the majority of patients < 12 years of age in the SAF (90.5%; 38/42) had a dose within the target range, 7.1% (3/42) had a dose below the target range, and 1 patients (2.4%) had a dose above the target range. The mean weight-adjusted transduced cell dose infused was 2.3 × 10^6 cells/kg overall; 2.3 × 10^6 cells/kg for patients ≤ 50 kg and 1.8 × 10^6 cells/kg for patients > 50 kg. The mean weight-adjusted total cell dose infused was 13.2 × 10^6 cells/kg; 13.4 × 10^6 for patients ≤ 50 kg and 3.0 × 10^6 cells/kg for patients > 50 kg.

Patients ≥ 12 to < 18 years of age

The majority of patients ≥ 12 and < 18 years of age in the SAF (80.0%; 8/10) had a dose within the target range, and 20.0% (2/10) had a dose below the target range. The mean weight-adjusted transduced cell dose infused was 1.7 × 10^6 cells/kg overall; 1.9 × 10^6 cells/kg for patients ≤ 50 kg and 1.4 × 10^6 cells/kg for patients > 50 kg. The mean weight-adjusted total cell dose infused was 7.7 × 10^6 cells/kg; 7.5 × 10^6 patients ≤ 50 kg and 8.2 × 10^6 cells/kg for patients > 50 kg.

Patients ≥ 18 years of age

The majority of patients ≥ 18 years of age in the SAF (76.5%; 13/17) had a dose within the target range, 17.6% (3/17) had a dose below the target range and 1 patient (5.9%) had a dose above the target range. The mean weight-adjusted transduced cell dose infused was 2.2×10^6 cells/kg overall; 0.1×10^6 cells/kg for patients ≤ 50 kg and 2.3×10^6 cells/kg for patients > 50 kg. The mean weight-adjusted total cell dose infused was 6.6×10^6 cells/kg; 0.1×10^6 patients ≤ 50 kg and 7.0×10^6 cells/kg for patients > 50 kg.

One patient aged 33 years received a split dose of tisagenlecleucel due to Urgent Safety Measure. The patient was administered the split dose safely over 2 days: 0.5×10^8 cells (partial infusion) on 15-Aug-2018 and 0.8×10^8 cells (full infusion) on 16-Aug-2018, resulting in a total dose of 1.3×10^8 cells. The mean weight-adjusted total cell dose for this patient was 2.6×10^6 cells/kg and the mean tisagenlecleucel dose was 2.2×10^6 cells/kg, which was within the target dose range.

Assessor's comment

The clinical study report (CSR) does not clearly identify whether any delays were reported for tisagenlecleucel production and in relation to leukapheresis and time to infusion. Information on the time interval between screening and enrolment, and the time from enrolment to infusion for study B2001X was omitted from the CSR.

The majority of participants (55.1%) had received one HSCT prior to tisagenlecleucel treatment, in common with the proportion reported for study B2202, where 53.2% of the infused participants had undergone one prior HSCT.

In contrast to study B2202, study B2001X allowed for the inclusion of participants who were previously treated with blinatumomab when CD19 tumour expression was demonstrated (via flow cytometry) at screening. Of the 52 paediatric patients enrolled, 21.2% (11/52) had previously been exposed to blinatumomab. This proportion was consistent with the overall study population where 21.7% (15/69) had prior blinatumomab exposure. Currently the product information states that "there is limited experience with Kymriah in patients exposed to prior CD19-directed therapy". Data on enrolled patients who were previously treated with blinatumomab in study B2001X indicates revision of section 4.4 of the SmPC is appropriate.

Efficacy results

Efficacy was assessed as a secondary endpoint in this study.

The median duration of study follow-up defined as the time from Kymriah infusion to the date of completion or discontinuation from follow-up prior to the data cut-off date in the SAF was 11.6 months (range: 0.2-13.1). The majority of patients (42.0%; 29/69) were followed up for 6 to < 12 months, whereas 29.0% (20/69) of each were followed up for either < 6 months or ≥ 12 months.

Overall response assessments are presented for the FAS (Table 10). The median follow-up time for ORR was 11.7 months (without censoring HSCT) with a maximum follow-up time of 24.4 months.

Overall, efficacy results were consistent in pediatrics (i.e. non-adolescents and adolescents) vs. the overall study population with respect to ORR, DOR, and EFS, during study B2001X.

Table 10: *Overview of paediatric efficacy results during study B2001X (FAS)*

Secondary endpoint	Pediatrics		Overall study population
	Nonadolescents: < 12 y	Adolescents: 12 y to < 18 y	
	N=42	N=10	N=69
BOR[1], N	42	10	69
ORR (CR + CRi)[1], n (%)	35 (83.3)	9 (90.0)	57 (82.6)
(95% CI)	(68.6, 93.0)	(55.5, 99.7)	(71.6, 90.7)
CR, n (%)	28 (66.7)	6 (60.0)	39 (56.5)
CRi, n (%)	7 (16.7)	3 (30.0)	18 (26.1)
NR, n (%)	0	1 (10.0)	3 (4.3)
Unknown, n (%)	7 (16.7)[2]	0	9 (13.0)
Achieved CR/CRi without HSCT[3], n/N (%)	Not analyzed		41/69 (59.4)
(95% CI)			(46.9, 71.1)
Achieved CR/CRi with HSCT[4], n/N (%)			1/69 (1.4)
(95% CI)			(0.0, 7.8)
DOR[5], N	35	9	57
Events/responders (%)	6/35 (17.1)	5/9 (55.6)	15/57 (26.3)
Median follow-up (mo after patient first met BOR of CR or CRi, i.e. confirmed response)	8.8	9.1	8.9
% Event-free probability estimates (95% CI)[6]:			
Month 3	90.9 (74.3, 97.0)	88.9 (43.3, 98.4)	90.8 (79.2, 96.1)
Month 6	87.4 (69.7, 95.1)	77.8 (36.5, 93.9)	82.7 (69.3, 90.6)
Month 9	83.4 (64.3, 92.8)	66.7 (28.2, 87.8)	76.0 (61.5, 85.7)
RFS[5], N	Not analyzed		57
Events/responders (%)			15/57 (26.3)
Median follow-up (mo after patient first met BOR of CR or CRi, i.e. confirmed response)			8.9
% Event-free probability estimates (95% CI)[6]:			
Month 3			90.8 (79.2, 96.1)
Month 6			82.7 (69.3, 90.6)
Month 9			76.0 (61.5, 85.7)
EFS[5], N	42	10	69
Events/responders (%)	9/42 (21.4)	6/10 (60.0)	20/69 (29.0)
Median follow-up (mo)	8.4	9.6	9.0
% Event-free probability estimates (95% CI)[6]:			
Month 3	89.9 (75.2, 96.1)	100.0 (100.0, 100.0)	90.5 (80.0, 95.6)
Month 6	80.6 (63.2, 90.3)	70.0 (32.9, 89.2)	75.9 (62.6, 85.1)
Month 9	76.9 (58.6, 87.9)	70.0 (32.9, 89.2)	71.8 (58.0, 81.8)
Month 12	76.9 (58.6, 87.9)	46.7 (15.0, 73.7)	67.3 (52.8, 78.2)
OS[5], N	Not analyzed		69
Events/responders (%)			9/69 (13.0)
Median follow-up (mo)			11.7
% Event-probability estimates (95% CI)[6]:			
Month 3			94.0 (84.8, 97.7)
Month 6			94.0 (84.8, 97.7)
Month 9			89.8 (78.5, 95.4)
Month 12			87.7 (75.6, 94.0)
Achieved CR/CRi at Day 28 ± 4 d, n/N (%)	Not analyzed		59/69 (85.5)
(95% CI)			(75.0, 92.8)
High baseline bone marrow tumor burden	Not analyzed		
Achieved CR/CRi at Day 28 ± 4 d, n/N (%)			31/40 (77.5)
(95% CI)			(61.5, 89.2)
CR, n (%)			6 (15.0)
CRi, n (%)			25 (62.5)
Unknown, n (%)			9 (22.5)

Secondary endpoint	Pediatrics		Overall study population
	Nonadolescents: < 12 y	Adolescents: 12 y to < 18 y	
	N=42	N=10	N=69
Low baselinge bone marrow tumor burden	Not analyzed		
Achieved CR/CRi at Day 28 ± 4 d, n/N (%) (95% CI)			25/26 (96.2) (80.4, 99.9)
CR, n (%)			11 (42.3)
CRi, n (%)			14 (53.8)
NR, n (%)			1 (3.8)
Bone marrow MRD status by flow cytometry, N Enrollment/before chemotherapy, n (%)	Not analyzed		69
Negative			0
Positive			51 (73.9)
Unknown			4 (5.8)
Not done			1 (1.4)
Missing			13 (18.8)
Negative results only, n (%); (95% CI)[7]:			
Day 28			44 (63.8); (51.3, 75.0)
Month 3			34 (49.3); (37.0, 61.6)
Month 6			30 (43.5); (31.6, 56.0)
Month 9			14 (20.3); (11.6, 31.7)
Month 12			14 (20.3); (11.6, 31.7)
Bone marrow MRD status by qPCR, N Enrollment/before chemotherapy, n (%)	Not analyzed		69
Negative			1 (1.4)
Positive			32 (46.4)
Unknown			4 (5.8)
Missing			32 (46.4)
Negative results only, n (%); (95% CI)[7]:	Not analyzed		
Day 28			31 (44.9); (32.9, 57.4)
Month 3			25 (36.2); (25.0, 48.7)
Month 6			20 (29.0); (18.7, 41.2)
Month 9			7 (10.1); (4.2, 19.8)
Month 12			10 (14.5); (7.2, 25.0)

[1] BOR and ORR (confirmed response) during 6 months after infusion.
[2] In the youngest paediatric patient, one post-tisagenlecleucel infusion assessment was reported, i.e. CR. As there is no additional assessment, BOR is unknown for the infant/toddler.
[3] Clinical response (without confirmation) at Month 6 without HSCT after infusion and before Month 6 response assessment.
[4] Clinical response (without confirmation) with HSCT during remission and before Month 6 response assessment.
[5] Censoring HSCT.
[6] % Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified timepoint.
[7] Exact Clopper-Pearson CI.

Data for patients >18 years was not included in Table 10. This information is provided below for completeness.

ORR for Patients ≥ 18 years of age

The ORR (BOR as CR or CRi, confirmed response) reported during the 6 months after tisagenlecleucel administration for patients ≥ 18 years of age in the FAS (n=17) was 76.5% (95% CI: 50.1, 93.2). The BOR (confirmed response) was CR for 29.4% (5/17), CRi for 47.1% (8/17), no response for 2 patients (11.8%), and unknown for 2 patients (11.8%).

DOR in Patients ≥ 18 years of age

A total of 13 patients ≥ 18 years of age had a BOR of CR or CRi (confirmed response) in the FAS. Overall, 30.8% (4/13) who achieved a BOR of CR or CRi reported relapse or death due to underlying cancer. The estimated DOR probability was 100.0% (95% CI: 100.0, 100.0) 28 days after patients first met BOR of CR or CRi (confirmed response), 92.3% (95% CI: 56.6, 98.9) 3 months after patients first met BOR of CR or CRi (confirmed response), 75.5% (95% CI: 41.6, 91.4) 6 months after patients first met BOR of CR or CRi (confirmed response), and 66.1% (95% CI: 32.5, 85.8) 9 months after patients first met BOR of CR or CRi (confirmed response).

EFS in patients >18 years of age

Among the patients ≥ 18 years of age who had EFS data in the FAS (n=17), 29.4% (5/17) had an event of relapse. The estimated EFS probability was 100.0% (95% CI: 100.0, 100.0) at Day 28, 85.1% (95% CI: 52.3, 96.1) at Month 3, 68.8% (95% CI: 36.4, 87.1) at Month 6, and 60.2% (95% CI: 28.8, 81.3) at month 9 and month 12.

Patients with low baseline tumor burden

A total of 26 patients had low bone marrow tumor burden at Baseline in the FAS. The ORR reported during the 6 months after tisagenlecleucel administration was 88.5% (95% CI: 69.8, 97.6). The BOR (confirmed response) was CR for 61.5% (16/26), CRi for 26.9% (7/26), no response for 1 patient (3.8%) and unknown for 2 patients (7.7%).

Patients with high baseline tumor burden

A total of 40 patients had high bone marrow tumor burden at Baseline in the FAS. The ORR reported during the 6 months after tisagenlecleucel administration was 77.5% (95% CI: 61.5, 89.2). The BOR (confirmed response) was CR for 52.5% (21/40), CRi for 25.0% (10/40), no response for 2 patients (5.0%), and unknown for 7 patients (17.5%).

Clinical Response

Among the 69 patients who received tisagenlecleucel, 41 patients (59.4%; 95% CI: 46.9, 71.1) achieved CR or CRi at month 6 without HSCT between the tisagenlecleucel infusion and the month 6 response assessment. One patient (1.4%; 1/69) achieved CR or CRi and then proceeded to HSCT while in remission before the month 6 response assessment in the FAS.

A Kaplan-Meier plot for OS (without censoring HSCT) is shown in Figure 2.

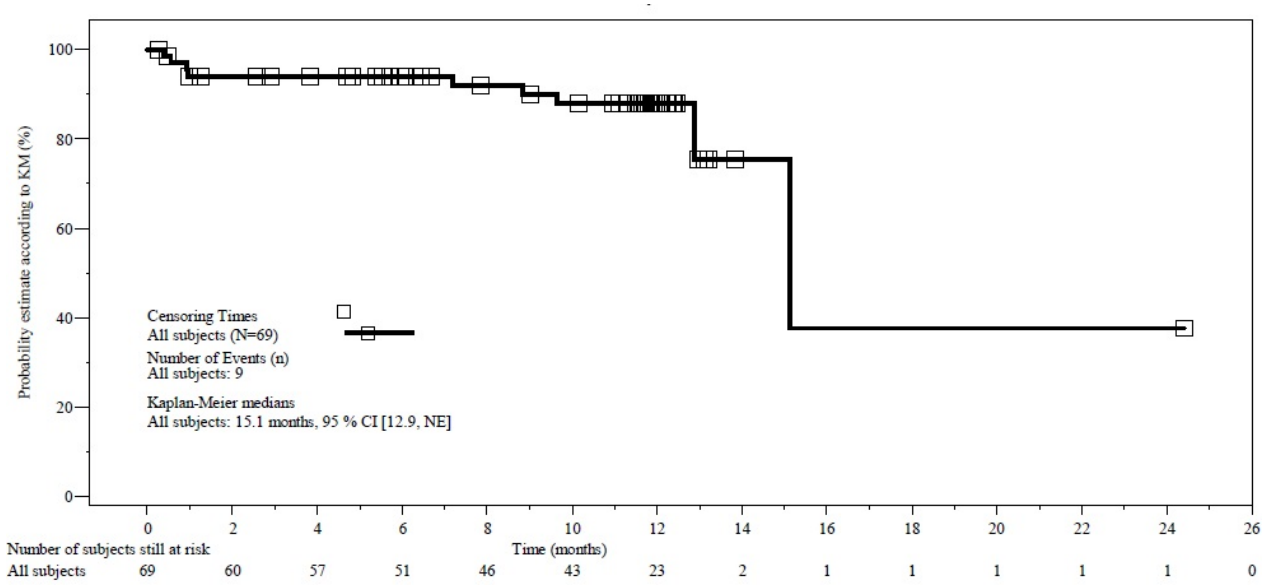


Figure 2: *Kaplan-Meier plot of OS (without censoring HSCT) (FAS).*

Assessor's comments:

Data for the paediatric population (< 18 years) were provided for ORR, DOR and EFS. All other parameters related to efficacy were only provided for the overall population such as RFS, OS and findings related to tumour burden which limits assessment according to age.

The age group of patients between 12-18 years and >18 years appears to show a lower estimated event-free probability in terms of EFS at 12 months compared to those <12 years. Values for 12-18 years (46.7%, [95% CI: 15.0 – 73.7] n=10) and >18 years (60.2% [95% CI: 28.8, 81.3] n=17) compared to those <12 (76.9% [95% CI: 58.6, 87.9], n=42). However, the sample size for the two age groups >12 years is small with wide confidence intervals and should therefore be interpreted with caution.

The estimated event-free probability for DOR was similarly lower in the group 12 -<18 years at 9 months (66.7% [95% CI: 28.2, 87.8] n=10) and those >18 (66.1% [95% CI: 32.5, 85.8] n=17) compared to those <12 years (83.4% [95% CI: 64.3, 92.8] n=42). Again, the sample sizes are smaller for those 12 -<18 and >18 years.

In the overall study population, patients with low and high tumour burden at baseline achieved a BOR at 28 days post-infusion of 96.2% (95% CI: 80.4, 99.9; n=26) and 77.5% (95% CI: 61.5, 89.2; n= 40) respectively (Table 10). The data was presented for the overall population, and it was not possible to determine any differences for the lower age groups (<18 years).

Cellular kinetics

Tisagenlecleucel transgene levels in peripheral blood were determined by qPCR. The cellular kinetic parameters were estimated from the individual concentration versus time profiles using a non-compartmental approach within the modelling program Phoenix® (Pharsight, Mountain View, CA).

Data observed in this study are consistent with the cellular kinetics and exposure results previously observed and reported in paediatric and young adult patients with r/r B-cell ALL in Study B2202.

Cellular kinetics and exposure parameters (AUCs, C_{max}, T_{max}) from the study were summarized by response on Day 28 ± 4 days and by CRS grade.

For patients with CR/CRi response (without confirmation) at Day 28 ± 4 days, the geometric mean (geometric CV) $AUC_{0\text{-}28d}$ was 352000 copies/µg x day (171.8%) and $AUC_{0\text{-}84d}$ was 526000 copies/µg × day (182.0%). Geometric mean (geometric CV) C_{max} was 34400 copies/µg (222.7%) and median T_{max} for the tisagenlecleucel transgene was 9.9 days, which is consistent with that observed among responding pediatric patients with r/r B-cell ALL in previous studies. For the only patient with NR (without confirmation) at Day 28 ± 4 days, PK parameters were not evaluated.

Transgenes were detected by qPCR in peripheral blood up to 379 days, i.e. maximum T_{last}, among patients with CR/CRi response (without confirmation) at Day 28 ± 4 days.

In general, patients presenting CRS showed a trend towards higher maximal expansion (C_{max}) and exposure ($AUC_{0\text{-}28d}$ and $AUC_{0\text{-}84d}$) relative to those without CRS.

- For patients with maximum grade-1/2 CRS, the geometric mean (geometric CV) C_{max} was 31200 copies/µg (199.3%); maximum grade-3 CRS, 66600 copies/µg (299.9%); and maximum grade-4 CRS, 87900 copies/µg (84.9%).
- For patients with maximum grade-1/2 CRS, the geometric mean (geometric CV) AUC0-28d was 37400 copies/µg × day (72.6%); maximum grade-3 CRS, 64300 copies/µg × day (272.8%); and maximum grade-4 CRS, 890000 copies/µg × day (119.1%).
- For patients with maximum grade-1/2 CRS, the geometric mean (geometric CV) AUC0-84d was 536000 copies/µg × day (65.2%); maximum grade-3 CRS, 1720000 copies/µg × day (174.8%); and maximum grade-4 CRS, 1430000 copies/µg × day (125.1%).

Safety

The study included 52 children (<18 years old) and 17 young adults. Safety data from the total population and from children separate is presented. The assessment for this procedure, focused on safety in the paediatric population (52 subjects) including 1 infant/toddler, 41 children, and 10 adolescent patients.

Most safety endpoints are analyzed for this study's paediatrics as divided into patients younger than 12 years (hereafter referred to as non-adolescents) and ≥ 12-years-old (hereafter referred to as adolescents). As the number of infants and toddlers was limited, this classification was combined with the children thereby forming the non-adolescent grouping.

Safety results are based on completed treatment and follow-up of 42 non-adolescents and 10 adolescents.

All paediatrics had an initial diagnosis of B-cell ALL. At baseline, more than two-thirds had leukemia CNS-1 classification (33 non-adolescents, 78.6%; 8 adolescents, 80.0%) and less than one-third had extra-medullary involvement (5 non-adolescents, 11.9%; 3 adolescents, 30.0%).

All paediatrics had received prior antineoplastic therapy. Of these 52, there were 11 paediatrics with prior exposure to blinatumomab and 5 paediatrics with prior inotuzumab therapy.

The mean duration of follow-up of patients in the safety set was 8.7 months (range: 0.2 to 13.1); 42.0% of patients were followed up for 6 to < 12 months, 29.0% were followed up for < 6 months and 29.0% were followed up for ≥ 12 months.

Adverse events

An overview of paediatric adverse events is shown in Table 11 and

Table 11: *Overview of paediatric AEs as frequency and maximum severity during study B2001X (Safety set)*

	Pediatrics		Overall study population N=69
	Nonadolescents: < 12 y N=42	Adolescents: 12 y to < 18 y N=10	
Primary endpoint	**n (%)**	**n (%)**	**n (%)**
AEs (all grades)	42 (100)	10 (100)	69 (100)
Grade 3	14 (33.3)	3 (30.0)	26 (37.7)
Grade 4	21 (50.0)	7 (70.0)	33 (47.8)
Causally related	Not analyzed		64 (92.8)
SAEs (all grades)	Not analyzed		50 (72.5)
Grade 3	Not analyzed		24 (34.8)
Grade 4	Not analyzed		19 (27.5)
Causally related	Not analyzed		37 (53.6)
Fatal AE	Section 6.2.2		4 (5.8)[1]
Casually related	Not analyzed		1 (1.4)
AEs requiring medication or therapy (all grade)	Not analyzed		69 (100)
Grade 3	Not analyzed		27 (39.1)
Grade 4	Not analyzed		21 (30.4)

[1]The child with an AE of fatal outcome post-tisagenlecleucel infusion and missing start date is described in Section 6.2.2. The young adult with SAE not reported with fatal outcome post-tisagenlecleucel infusion is described in [Study B2001X-Table 12-5, Section 12.2.1]. All remaining deaths are described in Section 6.2.2.
A patient with multiple severity grades is counted only once under the maximum toxicity grade.

AE is any AE with time of onset any time post-tisagenlecleucel infusion.

Table 12: *Common AEs by frequency and maximum severity (at least 10% overall) with onset post-tisanglecleucel infusion, including paediatrics, during Study B2001X (Safety set)*

	Pediatrics								
	Nonadolescents: < 12 y N=42			Adolescents: 12 y to < 18 y N=10			Overall study population N=69		
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Number of patients with at least one event	**42 (100)**	**14 (33.3)**	**21 (50.0)**	**10 (100)**	**3 (30.0)**	**7 (70.0)**	**69 (100)**	**26 (37.7)**	**33 (47.8)**
Cytokine release syndrome	30 (71.4)	6 (14.3)	9 (21.4)	7 (70.0)	1 (10.0)	2 (20.0)	47 (68.1)	9 (13.0)	13 (18.8)
Pyrexia	22 (52.4)	3 (7.1)	0	2 (20.0)	0	0	33 (47.8)	5 (7.2)	0
Hypogammaglobulinaemia	16 (38.1)	2 (4.8)	0	3 (30.0)	0	0	21 (30.4)	2 (2.9)	0
Diarrhoea	10 (23.8)	1 (2.4)	0	4 (40.0)	1 (10.0)	0	17 (24.6)	2 (2.9)	0
Headache	14 (33.3)	1 (2.4)	0	1 (10.0)	0	0	16 (23.2)	1 (1.4)	0
Nausea	9 (21.4)	1 (2.4)	0	4 (40.0)	0	0	16 (23.2)	1 (1.4)	0
Hypokalaemia	12 (28.6)	7 (16.7)	0	0	0	0	15 (21.7)	7 (10.1)	0
Anaemia	11 (26.2)	6 (14.3)	0	1 (10.0)	1 (10.0)	0	14 (20.3)	7 (10.1)	0
Cough	11 (26.2)	0	0	1 (10.0)	0	0	14 (20.3)	0	0
White blood cell count decreased	11 (26.2)	3 (7.1)	6 (14.3)	2 (20.0)	0	1 (10.0)	14 (20.3)	4 (5.8)	7 (10.1)
Vomiting	11 (26.2)	0	0	2 (20.0)	0	0	13 (18.8)	0	0
Neutrophil count decreased	8 (19.0)	1 (2.4)	6 (14.3)	2 (20.0)	0	2 (20.0)	11 (15.9)	2 (2.9)	8 (11.6)
Hypophosphataemia	7 (16.7)	2 (4.8)	0	1 (10.0)	0	0	10 (14.5)	2 (2.9)	0
Neutropenia	7 (16.7)	2 (4.8)	4 (9.5)	2 (20.0)	0	2 (20.0)	10 (14.5)	2 (2.9)	6 (8.7)
Platelet count decreased	7 (16.7)	1 (2.4)	4 (9.5)	1 (10.0)	0	1 (10.0)	10 (14.5)	2 (2.9)	5 (7.2)
Rash	8 (19.0)	1 (2.4)	0	0	0	0	10 (14.5)	1 (1.4)	0
Arthralgia	4 (9.5)	0	0	2 (20.0)	2 (20.0)	0	9 (13.0)	2 (2.9)	0
Nasopharyngitis	5 (11.9)	0	0	3 (30.0)	0	0	9 (13.0)	0	0
Tachycardia	4 (9.5)	0	0	3 (30.0)	0	0	9 (13.0)	0	0
Abdominal pain	6 (14.3)	0	0	0	0	0	8 (11.6)	0	0
Aspartate aminotransferase increased	5 (11.9)	2 (4.8)	1 (2.4)	1 (10.0)	0	0	8 (11.6)	2 (2.9)	1 (1.4)
Decreased appetite	5 (11.9)	0	0	3 (30.0)	1 (10.0)	0	8 (11.6)	1 (1.4)	0
Epistaxis	6 (14.3)	0	0	1 (10.0)	0	0	8 (11.6)	0	0
Hypertension	6 (14.3)	1 (2.4)	0	2 (20.0)	2 (20.0)	0	8 (11.6)	3 (4.3)	0
Hypoalbuminaemia	4 (9.5)	0	0	3 (30.0)	1 (10.0)	0	8 (11.6)	1 (1.4)	0
Hypocalcaemia	4 (9.5)	2 (4.8)	2 (4.8)	2 (20.0)	0	0	8 (11.6)	2 (2.9)	2 (2.9)
Hypoxia	5 (11.9)	3 (7.1)	1 (2.4)	1 (10.0)	1 (10.0)	0	8 (11.6)	4 (5.8)	1 (1.4)
Pruritus	6 (14.3)	0	0	1 (10.0)	0	0	8 (11.6)	0	0
Alanine aminotransferase increased	4 (9.5)	2 (4.8)	1 (2.4)	1 (10.0)	0	0	7 (10.1)	2 (2.9)	1 (1.4)
Constipation	5 (11.9)	0	0	0	0	0	7 (10.1)	0	0
Fatigue	4 (9.5)	0	0	0	0	0	7 (10.1)	0	0
Hypomagnesaemia	3 (7.1)	0	0	1 (10.0)	0	0	7 (10.1)	0	0
Pain in extremity	5 (11.9)	0	0	1 (10.0)	0	0	7 (10.1)	0	0
Upper respiratory tract infection	7 (16.7)	0	0	0	0	0	7 (10.1)	0	0

Time of onset is any time post-tisagenlecleucel infusion.
PTs are sorted in descending frequency of all grades column, as reported in the overall study population column.
A patient with multiple occurrences of an AE is counted only once under the maximum grade in the AE category.
A patient with multiple events is counted only once in the total row.
Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 and Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 were used.

Non-adolescents

The most frequent AEs by primary SOC in patients < 12 years of age at any time post infusion were immune system disorders (34 patients, 81.0%); followed by general disorders and administration site conditions (27 patients, 64.3%); infections and infestations (27 patients, 64.3%); gastrointestinal disorders (26 patients, 61.9%); investigations (24 patients, 57.1%); metabolism and nutrition disorders (21 patients, 50.0%); blood and lymphatic system disorders (21 patients, 50.0%); and nervous system disorders (21 patients, 50.0%).

The most frequent AEs by PT in non-adolescents with onset any time post-tisagenlecleucel infusion were (in decreasing order of frequency for events with an incidence of > 20%):

- CRS (30 patients, 71.4%)
- Pyrexia (22 patients, 52.4%)

- Hypogammaglobulinemia (16 patients, 38.1%)
- Headache (14 patients, 33.3%)
- Hypokalemia (12 patients, 28.6%)
- Anemia, WBC count decreased, vomiting, and cough (11 patients/each, 26.2%)
- Diarrhea (10 patients, 23.8%)
- Nausea (9 patients, 21.4%)

All remaining PTs in non-adolescents presented with an overall incidence of ≤ 20.0%.

Within first 8 weeks after infusion all patients (100%) in the non-adolescent group had AEs, 28.6% (12 patients) had grade 3 events and 45.2% (19 patients) had grade 4 events. The most frequent AEs by PT within 8 weeks post CTL019 infusion in patients < 12 years of age were CRS (30 patients, 71.4%); followed by pyrexia (17 patients, 40.5%); hypogammaglobulinemia (12 patients, 28.6%); hypokalaemia (12 patients, 28.6%); headache, anaemia, WBC count decreased, and diarrhoea, each of which occurred in 10 patients (23.8%); and vomiting and neutrophil count decreased (8 patients, 19.0%). Nausea, vomiting, and cough were less frequent within the 8 weeks after infusion vs. any time post-infusion.

The most frequent grade 3 AE was hypokalaemia, and most frequent grade 4 AE was CRS.

Adolescents

The most frequent AEs by primary SOC any time post CTL019 infusion in patients ≥ 12 and <18 years of age were immune system disorders (8 patients, 80.0%); blood and lymphatic system disorders (7 patients, 70.0%); general disorders and administration site conditions (7 patients, 70.0%); infections and infestations (7 patients, 70.0%); gastrointestinal disorders (7 patients, 70.0%); metabolism and nutrition disorders (6 patients, 60.0%); investigations (5 patients, 50.0%); and musculoskeletal and connective tissue disorders (5 patients, 50.0%).

The most frequent AEs by PT in adolescents with onset any time post-tisagenlecleucel infusion were (in decreasing order of frequency for events with an incidence of > 20%):

- CRS (7 patients, 70.0%)
- Diarrhea, nausea (4 patients/each, 40.0%)
- Hypogammaglobulinemia, nasopharyngitis, tachycardia, decreased appetite, and hypoalbuminemia (3 patients/each, 30.0%)

All remaining PTs, hemophagocytic lymphohistiocytosis, febrile neutropenia, neutropenia, pyrexia, herpes zoster, sepsis, lymphocyte count decreased, neutrophil count decreased, WBC count decreased, vomiting, hyperglycaemia, hypocalcaemia, oropharyngeal pain, hypertension and arthralgia, each of which occurred in 2 patients (20.0%).

Within 8 weeks after infusion, all patients in the adolescent group (100%) had AEs, 10.0% (one patient) had grade 3 events and 60.0% (6 patients) had grade 4 events. The most frequent AEs by PT within 8 weeks post CTL019 infusion in patients ≥ 12 and < 18 years of age were CRS (7 patients, 70.0%), tachycardia (3 patients, 30.0%), diarrhoea (3 patients, 30.0%), hypogammaglobulinemia (3 patients, 30.0%), decreased appetite (3 patients, 30.0%), and hypoalbuminemia (3 patients, 30.0%). Nausea; vomiting; hemophagocytic lymphohistiocytosis; neutrophil count decreased; hyperglycaemia; hypocalcaemia; hypertension; neutropenia; and febrile neutropenia, each of which occurred in 2

patients (20.0%). Nausea and nasopharyngitis were less frequent within the 8 weeks after infusion vs. thereafter, albeit the numbers of patients were limited.

The most frequent grade-3 AEs was arthralgia, febrile neutropenia, and hypertension (2 patients/each, 20.0%). The most frequent grade-4 AEs were CRS, neutrophil count decreased, and neutropenia (2 patients/each, 20.0%).

In the overall study population, there were 64 patients (92.8%) with AEs suspected to be related to tisagenlecleucel as assessed by the Investigator with onset any time post-tisagenlecleucel infusion. Of these 64, 21 patients (30.4%) presented maximum grade 3 and 25 patients (36.2%) presented maximum grade 4. The most frequent of this type of event was CRS.

Assessor's comments

The number of children included in study B2001X (52 subjects) is small and only the most common AEs would be detected. Due to the limited number of adolescents (10 subjects) and imbalance in the number of patients within each subpopulation, it is difficult to assess any difference in AE profile between non-adolescent and adolescent group.

The most important AEs like CRS, pyrexia, haematological AEs and hypogammaglobulinemia are frequently observed in the current study as earlier reported in study B2202, which is the basis for frequency data referred in the current product information.

Grade 3 AEs were reported in 33.3% in the non-adolescent group and in 30.0% in the adolescent group, grade 4 AEs were reported in 50.0% and in 70.0% in the respective groups. In non-adolescents, the most frequent grade 3 AE was hypokalaemia (16.7%), and most frequent grade 4 AE was CRS (21.4%). In adolescents the most frequent grade 3 AEs was arthralgia (20.0%), febrile neutropenia (20%), and hypertension (20%), the most frequent grade 4 AEs were CRS (20.0%), neutrophil count decreased (20%), and neutropenia (20.0%).

The mean duration of follow-up of patients in the safety set was 8.7 months (range: 0.2 to 13.1); 42.0% of patients were followed up for 6 to < 12 months, 29.0% were followed up for < 6 months and 29.0% were followed up for ≥ 12 months. As experienced in earlier studies, most AEs were reported first 8 weeks following infusion, indicating the observation time in the current study is sufficient for an overall picture of the safety profile in this patient group.

In general, the AEs reported in the current study are comparable to what have been observed in Study B2202 including 79 children and adolescents. The data from the adolescent group in the current study is however too small for assessing the safety profile adequately. The MAH does not propose any updates of the safety part of the product information based on data from the current study.

Paediatric patients are now included in several studies (i.e., B2001X, B2202, and B2205J), and the MAH should submit a Type-II variation to reflect the pooled safety data from these studies in section 4.4 and 4.8 of the product information.

Death and Serious AEs

Deaths

There were 9 deaths post-tisagenlecleucel infusion in the whole study population, 4 were non-adolescents and 2 were adolescents.

Three children died within ≤ 30 days of CTL019 infusion:

- Patient (5 years of age at Screening) died on 30-Oct-2018 (Day 12) due to study indication with concurrent SAE of hepatosplenomegaly.
- Patient (3 years of age at Screening) died on 17-Sep-2018 (Day 28) due to sepsis with concurrent SAE of multiorgan dysfunction syndrome.
- Patient (5 years of age at Screening) died on 17-Apr-2019 (Day 17) due to study indication with concurrent SAEs of TLS and CRS.

One more child and two adolescents died > 30 days post CTL019 infusion:

- Patient (9 years of age at Screening) died on 22-Mar-2018 (Day 269) due to study indication with concurrent SAE of infection (reported as infection of unknown origin). It should be noted that there was no start date for the concurrent SAE of infection; therefore, it could not be allocated to a specific study period.
- Patient (14 years of age at Screening) died on 11-Mar-2019 (Day 294) due to study indication.
- Patient (14 years of age at Screening) died on 05-Jan-2019 (Day 460) due to study indication.

In addition, eight patients in the paediatric group died before any CTL019 infusion had started.

Of these 6 paediatrics, 1 death was assessed as causally related to study drug by the Investigator:

Patient– Death (**Cytokine release syndrome, Tumour lysis syndrome**), SAE (Allergic transfusion reaction, Cytokine release syndrome [2 occurrences], Tumour lysis syndrome)

Patient details: 5 years, male, Asian

The patient was diagnosed with ALL in Aug-2016; the most recent relapse/progression was on 09-Oct-2018. No prior antineoplastic therapy was reported.

Event description:

On 01-Apr-2019, the patient received the CTL019 infusion (Day 1).

On 02-Apr-2019 (Day 2), during the Post-Infusion Period, the patient had a body temperature between 38 ºC and 39 ºC, and was diagnosed with a non-serious grade 1 AE of CRS. He was subsequently transferred to the ICU. On the same day, the patient's ferritin level was 1981.8 ng/mL (normal range: 0 to 279.9 ng/mL), and CRP was 2.4 mg/dL (normal range: 0 to 2 mg/dL). The event of CRS was treated with meropenem, teicoplanin, voriconazole, piperacillin/tazobactam and paracetamol.

On 08-Apr-2019 (Day 8), the patient's body temperature increased to 41 ºC, and he was tachycardic and hypertensive; and the non-serious event of CRS was upgraded to a grade 3 SAE. On the same day the patient's CRP was 5.6 mg/dL, and ferritin was 1749.7 ng/mL. The event was further treated with tocilizumab, and methylprednisolone.

On 13-Apr-2019 (Day 13), the patient was diagnosed with a grade 4 SAE of tumour lysis syndrome, which was treated with rasburicase and paracetamol.

On 14-Apr-2019 (Day 14), the SAE of CRS progressed to grade 4, and was further treated with micafungin and phenylephrine. On the same day, a chest x-ray showed a decrease in the radiolucency of the right lung and exacerbation of pulmonary oedema. The patient underwent endotracheal intubation for CRS-related hypoxia. On 16-Apr-2019 (Day 16), the patient exhibited decreased kidney function and urine output, and hence underwent dialysis for CRS-related acute kidney injury.

The patient died on 17-Apr-2019 (Day 17) due to CRS and tumour lysis syndrome secondary to ALL. No autopsy was performed.

The Investigator suspected a relationship between the investigational treatment and the events CRS and tumor lysis syndrome, the reason cited being that the events occurred after the CTL019 infusion.

Serious Adverse Events

The most frequent SAEs that occurred at any time post CTL019 infusion by PT were CRS (28 patients, 40.6%), followed by pyrexia (11 patients, 15.9%); and recurrent ALL, herpes zoster, and sepsis, each of which occurred in 3 patients (4.3%). All remaining individual SAEs occurred in no more than 2 patients (2.9%).

The most frequent SAEs suspected to be related to CTL019 by PT were CRS (28 patients, 40.6%) and pyrexia (8 patients, 11.6%). All remaining individual SAEs suspected to be related to CTL019 occurred in no more than 2 patients (2.9%).

The most frequent SAEs within 8 weeks post CTL019 infusion by PT were CRS (28 patients, 40.6%) and pyrexia (7 patients, 10.1%), while remaining individual SAEs occurred in no more than 2 patients (2.9%).

The most frequent SAEs suspected to be related to CTL019 within 8 weeks post infusion by PT were CRS (28 patients, 40.6%) and pyrexia (5 patients, 7.2%). All remaining individual SAEs suspected to be related to CTL019 occurred in no more than 2 patients (2.9%).

Assessor's comments

Among the 6 deaths occurring post-infusion in children, one death (5 years old) associated with Cytokine release syndrome and Tumour lysis syndrome was assessed as causally related to study drug by the Investigator. The case was treated according to the CRS management algorithm.

No specific pattern of AEs contributing to fatal outcome can be identified based on the current study.

The MAH does not propose any updates of the product information based on data from the study B2001X.

Cytokine-release syndrome (CRS)

CRS was reported in 71.1% (37) of pediatrics, maximum grade 3 and 4 was observed in 34.6% (18 pediatrics). The corresponding numbers in the non-adolescent group were 71.4% (30 subjects) and 35.7% (15 subjects) grade 3 and 4, and in the adolescents group 70.0% (7 subjects) and 30.0% (3 subjects) grade 3 and 4.

Median duration of CRS was 7 days

- 42.2% of patients with CRS were admitted to the ICU (19 out of 45) for the treatment of CRS.
- Median duration of the ICU stay was 8 days

Systemic anti-cytokine therapy was administered to 42.2% of patients with CRS resulting in CRS improvement or resolution. Further, tocilizumab was administered to 37.8% of patients and by quantity: 1 dose (20.0%), 2 doses (11.1%), 3 doses (2.2%), and 4 doses (4.4%). Siltuximab was administered to 4.4% of patients and corticosteroids to 8.9% of patients.

Serious neurological adverse reactions

There were few AEs of confusional state, encephalopathy, seizures, delirium, and tremor in paediatric patients, all of which occurred within 8 weeks post-infusion. Seizure presented in 5 non-adolescents (11.9%), tremor in 3 non-adolescents (7.1%) and 1 adolescent (10.0%), confusional state and

delirium presented in 2 non-adolescents (4.8%, each), and encephalopathy presented in 1 non-adolescent (2.4%).

For patients by maximum severity grade, grade-3/4 events presented only as grade-3 seizure (2 non-adolescents, 4.8%), grade-3 confusional state or grade-3 encephalopathy (1 non-adolescent/each, 2.4%).

Infections

Non-adolescents: Overall, events of infections and infestations SOC with onset any time post-tisagenlecleucel infusion presented in 27 non-adolescents (64.3%), with 8 patients (19.0%) having maximum grade-3 events and 1 patient (2.4%) having maximum grade-4 event. The most frequent of each category by frequency: URTI (non-adolescents: 7 patients, 16.7%); and by maximum severity: pneumonia (grade 3: 3 patients, 7.1%), and sepsis (grade 4: 1 patient, 2.4%).

Adolescents: Overall, events of this SOC with onset any time post-infusion presented in 7 adolescents (70.0%), with 4 patients (40.0%) having maximum grade-3 events and 1 patient (10.0%) having maximum grade-4 event. The most frequent of each category by frequency: nasopharyngitis (adolescents: 3 patients, 30.0%); and by maximum severity: atypical pneumonia, bacterial infection, device-related infection, herpes zoster, sepsis, or systemic infection (grade 3: 1 patient/each, 10.0%); and sepsis (grade 4: 1 patient, 10.0%).

The majority of AEs occurred within 8 weeks after infusion, i.e. no further substantial increase in reporting rate when onset was any time post-infusion, for both non-adolescents and adolescents.

Tumor lysis syndrome

The 1 case (1.4%) presenting grade-4 tumor lysis syndrome within 8 weeks after infusion had fatal outcome and is described above.

Prolonged depletion of normal B-cells/agammaglobulinemia

The PT of hypogammaglobulinemia with onset any time post-tisagenlecleucel infusion presented in 16 non-adolescents (38.1%), with 2 patients (4.8%) having maximum grade-3 events and no patient having maximum grade-4 event.

The PT of hypogammaglobulinemia with onset any time post-infusion presented in 3 adolescents (30.0%) with no patient presenting a grade 3/4 event.

The majority of AEs occurred within 8 weeks after infusion, i.e., no further substantial increase in reporting rate when onset was any time post-infusion, for both non-adolescents and adolescents.

Haematological disorders including cytopenias

There were few AEs of febrile neutropenia, anaemia, WBC decreased, and platelet count decreased in paediatric patients. All within 8 weeks post-infusion, febrile neutropenia (2 non-adolescents, 4.8%; 2 adolescents, 20.0%), anaemia and WBC decreased (10 non-adolescents/each, 23.8%; 1 adolescent/each, 10.0%), or platelet count decreased (6 non-adolescents, 14.3%; 1 adolescent, 10.0%).

For patients by maximum severity grade, grade-3/4 events presented only as grade-3 febrile neutropenia (2 non-adolescents, 4.8%, 2 adolescents, 20.0%), grade-3 anaemia (5 non-adolescents, 11.9%; 1 adolescent, 10.0%), grade-3 WBC decreased (3 non-adolescents, 7.1%), grade-3 platelet count decreased (2 non-adolescents, 4.8%), grade-4 WBC decreased (5 non-adolescents, 11.9%; 1 adolescent, 10.0%), or grade-4 platelet count decreased (2 non-adolescents, 4.8%; 1 adolescent, 10.0%).

When onset was anytime post-infusion, there was onset of 1 event each in an additional patient: in non-adolescents, febrile neutropenia, grade-3 anaemia, grade-4 WBC decreased, and platelet count decreased; and in adolescents, WBC decreased.

Clinical laboratory abnormalities

Data are presented for the whole study population and no specific safety issues have been highlighted for the paediatric population.

MAH conclusion on safety

Treatment is associated with significant toxicity in the initial 8 weeks post-tisagenlecleucel infusion, especially in patients with high disease burden; however, AEs can be managed with the application of specific protocol-mandated algorithms/guidelines at centres with appropriate training in tisagenlecleucel safety management.

- The majority of patients develop CRS. Key elements of this protocol-mandated algorithm include an improved CRS grading scale and the administration of anti-cytokine therapy. Cytokine release syndrome is limited to the first 8 weeks post-infusion.
- Neurological events are transient, can be associated with CRS, and typically occur within the initial 30 days post-tisagenlecleucel infusion.
- Other AEs are well characterized and are manageable with supportive care.
- Patients with pre-existing and prolonged neutropenia post-tisagenlecleucel infusion may be at increased risk for severe or fatal infections.

Of the 9 post-infusion deaths during study B2001X, 4 were non-adolescents and 2 were adolescents. Of these 6 paediatrics, 5 were due to study indication. The remaining case (1.4%), i.e., AE with fatal outcome, that was not attributed to the underlying disease (primary reason for death outcome was multi organ failure syndrome) was in a child.

Immunogenicity

Humoral immunogenicity assessments were performed for the measurement of antibodies binding to murine CAR19 (for simplicity named here anti-mCAR19 antibodies) in human serum. Cellular immunogenicity measures the presence of CAR19-specific CD4+ and CD8+ T-cells against tisagenlecleucel.

Humoral Immunogenicity

The humoral immunogenicity assessment included evaluation of pre-existing (pre-treatment) and post-treatment anti-tisagenlecleucel antibodies to examine the incidence of immunogenicity with treatment, as a secondary endpoint. A validated assay was used to determine presence of anti-mouse CAR19 (m-CAR19) antibodies in serum of patients who received tisagenlecleucel treatment. Antibodies binding to tisagenlecleucel (anti-mCAR19) in human serum were measured using a flow cytometry method. Anti-mCAR19 antibodies in human serum samples were captured by Jurkat cells transfected to express murine CAR19. Untransfected cells were used as reference. The method measures bound IgG/M on viable cells. Subjects were counted as positive if they had one or more positive sample post Baseline, otherwise negative if they had at least one negative sample post Baseline and otherwise unknown.

Humoral immunogenicity interpretation data are presented overall for the SAF in Table 13. The majority of patients were humoral-immunogenicity reactive at Baseline (89.9%; 62/69), while 94.2% (65/69) were positive at any time point post-infusion. Humoral immunogenicity data summarized by Day 28 response and time point showed that pre-existing anti-mCAR19 antibodies were detected in similar proportion of patients as those who achieved a BOR of CR/Cri, which is consistent with that previously observed in pediatric r/r ALL patients in study B2202.

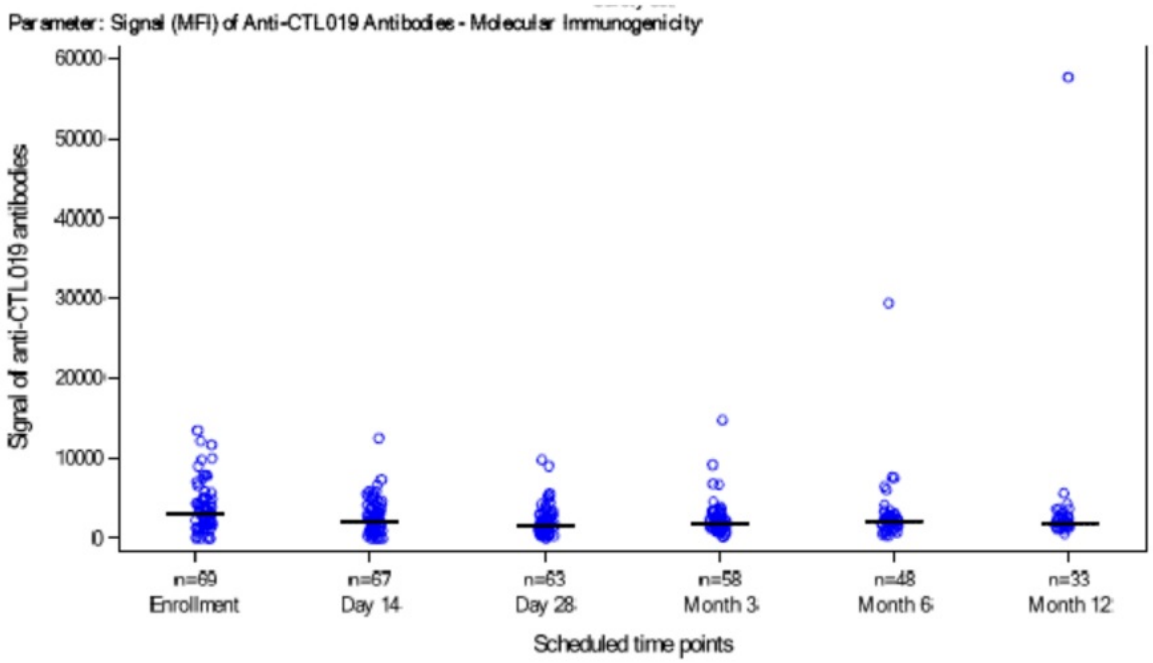
Table 13: *Humoral immunogenicity interpretation by time point, overall (Safety set)*

Time point		All subjects N=69
Baseline	Positive	62 (89.9)
	Negative	7 (10.1)
Day 14	Positive	53 (76.8)
	Negative	14 (20.3)
	Missing	2 (2.9)
Day 28	Positive	50 (72.5)
	Negative	13 (18.8)
	Missing	6 (8.7)
Month 3	Positive	53 (76.8)
	Negative	5 (7.2)
	Missing	11 (15.9)
Month 6	Positive	44 (63.8)
	Negative	4 (5.8)
	Missing	21 (30.4)
Month 12	Positive	32 (46.4)
	Negative	1 (1.4)
	Missing	36 (52.2)
At any time post-baseline *	Positive	65 (94.2)
	Negative	2 (2.9)
	Missing	2 (2.9)

* Summary at any time post-baseline also includes unscheduled assessments. Subjects are counted as positive if they have one or more positive samples post-baseline, otherwise negative if they have at least one negative sample post baseline and otherwise unknown.

Percentages are based on the number of subjects in the SAF (N).

A strip plot of anti-mCAR19 antibodies by time points is shown in Figure 3. Median mean fluorescent intensity signals were observed to be similar at different time points, (i.e. enrollment, Day 14, Day 28, Month 3, Month 6, and Month 12).



Values below 0 were imputed as 0.

Figure 3: *Strip plot of anti-tisagenlecleucel antibodies by time point – Safety set*

Assessor's comments:

Humoral immunogenicity data is only provided for the safety population as a whole. It is therefore not possible to distinguish data from the different age groups in the paediatric population. Although the majority of participants had pre-existing antibody responses, the frequency of antibody responses in the study population was reduced over time and it is not clear from Table 13 if there were differences according to age, for example if all patients <18 years were seropositive, and whether any of those seronegative at baseline did seroconvert. In addition, no indication is provided as to whether any of the antibody responses may be neutralizing. Thus, the MAH is recommended to discuss this data when the Bioanalysis reports are submitted (Q4 2021).

Cellular immunogenicity results

Activation of T-cells in PBMC collected from patients in response to mCAR19-derived peptides was used to assess the cellular immunogenicity against tisagenlecleucel. T-cell activation was measured by the percentage of interferon gamma (IFNγ)-positive cells detected by intracellular staining and subsequent flow cytometric analysis. Net responses (in %) were calculated for two non-overlapping mCAR19 peptide pools (i.e. Pool 1 and Pool 2), which together span the full mCAR19 protein sequence. Cellular immunogenicity assessment included the percentage of CD4+ and CD8+ T-cells specific to mCART peptides and were measured pre-dose (Enrollment) and up to 12 months post-tisagenlecleucel dose. Cellular responses were consistent over time for all patients with mean values < 0.5% at any time point, demonstrating that cellular immunogenicity does not fluctuate over time.

Assessor's comment:

Strip plots in the CSR were shown for CD4+ and CD8+ T-cells for each pool separately. Although both pools together span the entire mCAR19 protein sequence, further information of the difference between these pools would have been useful since there was slightly greater spread in responses for

pool 2 for CD3+CD4+ cells. This should be discussed in the Bioanalysis report due to be submitted Q4 2021.

2.3.3. Discussion on clinical aspects

The complete data set of the clinical study B2001X submitted and reviewed under this Article 46 procedure is not part of a PIP but includes participants <26 years (and one participant aged 33 years). A total of 52 participants in the FAS population were <18 years (75%). Study treatment and follow-up was completed for 47.6% (20/42) of the patients <12 years of age and for 50% (5/10) of those 12-<18 years of age. The main reasons for discontinuation was progressive disease and lack of efficacy in patients <12 years.

Efficacy:

Study B2001X enrolled comparable patient populations with r/r B-cell ALL and had a similar study design as the pivotal study B2202 and the key supportive study B2205J. However, the main purpose for the conductance of this study was to further evaluate the safety of tisagenlecleucel for up to one year post-infusion. Assessment of efficacy was therefore only defined as secondary endpoints in this study and the follow-up was rather limited. Data for the efficacy endpoints ORR, DOR and EFS have been provided for the paediatric population (<12 years and 12-<18 years). However, the remaining efficacy parameters for other relevant secondary endpoints were only provided based on the overall population which limits the assessment in this group.

In line with the definition of ORR in study B2205J, ORR was measured within 6 months after tisagenlecleucel administration in study B2001X, but within 3 months in the pivotal study B2202. The ORR reported in the final analysis of study B2001X in the FAS of 69 patients was 82.6% (57/69; 95% CI: 71.6, 90.7). Among the responding patients, 56.5% (39/69) achieved a CR, while 26.1% (18/69) obtained a CRi. The findings relating to ORR for the paediatric age groups in study B2001X were similar to that of the overall population and to the efficacy results reported earlier for study B2202, but slightly higher than observed in study B2205J. The proportion of infused patients who achieved a best response of CR was similar in the three clinical studies (62% in B2202 and 59.4% in B2205J), while a slightly lower proportion in study B2205J obtained a best response of CRi (i.e. 10.9% vs. 26.1% in B2001X and 20.3% in B2202). The proportion of patients who achieved CR or CRi and then proceeded to HSCT while in remission within the first 6 months post-infusion was lower (1.4%) in study B2001X than in the two other clinical studies (i.e. 8% in both B2202 and B2205J).

The median DOR for the overall population was not reached in any of the three clinical studies. The median follow-up in study B2001X from onset of response was 8.9 months. In line with the results from the latest interim analysis reported for study B2202, the median EFS and OS was not reached at the data cut-off (DCO) for the final analysis of study B2001X. Nevertheless, the estimated event-free probability for the overall population was comparable to that reported in the two other clinical studies at month 6 (76% vs. 71% in B2202 and 67% in B2205J) and slightly higher at month 12 (67% vs. 56% in B2202 and 54% in B2205J). Moreover, the estimated probability of survival from infusion in the infused patient population was similar to the two other clinical studies at month 6 (94% vs. 89% in B2202 and 84% in B2205J), but somewhat higher at month 12 (88% vs. 76% in B2202 and 65% in B2205J).

The age group of patients between 12-18 and >18 years in study B2001X appears to show a lower estimated event-free probability in terms of DOR and EFS at 9 and 12 months respectively, compared to those <12 years. However, the sample size for the two age groups >12 years is small with wide confidence intervals and should therefore be interpreted with caution. Data for the age group 18-<25 years was not tabulated. The MAH has provided upon request data according to each age subgroup as

well as for the overall study population (i.e. <12 years; 12-<18 years, >18 years, Overall) for the clinical studies conducted in r/r ALL patients (i.e. B2001X, B2202, and B2205J). They concluded in their assessment of this data that there is no need to revise the current product information for the paediatric population for the approved ALL indication. However, in contrast to the clinical studies B2202 and B2205J, study B2001X permitted inclusion of individuals below 3 years of age, and individuals that who had experienced prior anti-CD19-directed therapy (i.e., blinatomumab). Three participants below the age of three years were enrolled in study B2001X rendering the following statement in section 4.2 of the SmPC as factually incorrect "*Paediatric population; B-cell ALL: No formal studies have been performed in paediatric patients below the age of three years*". Since B2001X is a formal clinical study, the wording will need to be amended to reflect the current experience with Kymriah in this paediatric patient group to "*There is limited experience with Kymriah in paediatric patients below the age of 3 years*". Furthermore, this will need to be reconsidered when data from the required PAMs to the MA concerning r/r ALL patients have been completed.

The MAH has provided data regarding the median time for tisagenlecleucel production which was omitted from the main text of the CSR. The current SmPC section 4.2, states that manufacture and release of Kymriah usually takes about 3-4 weeks. However, the time interval from enrolment to tisagenlecleucel infusion in study B2001X was found to be variable with a median of 64 days and maximum time of 219 days.

In contrast to the pivotal study B2202 and study B2205J, patients in study B2001X who were previously treated with blinatumomab when CD19 tumor expression was demonstrated (via flow cytometry) at screening were eligible for participation. The MAH has provided data from the 15 patients enrolled in study B2001X who were previously treated with blinatumomab prior to study entry, based on analysis from a DCO of 04-Nov-2019 whilst the DCO for the last patient last visit for study B2001X was 13-Oct-2020. There was a consistent trend in most parameters towards sub-optimal outcomes in patients that received prior blinatumomab compared to those patients who had not previously been treated with blinatumomab. On the other hand, duration of response appeared similar in patients previously treated with blinatomumab. However, these findings should be interpreted with caution due the small cohort size, the broad confidence intervals, and because such patients may have had more advanced/aggressive disease. Nevertheless, the current statement in the SmPC section 4.4 "*There is limited experience with Kymriah in patients exposed to prior CD19-directed therapy*" should be expanded to include the following statement "*While some activity of tisagenlecleucel has been observed, data are currently too limited to make an adequate assessment of the benefit-risk profile in these patients.*" Furthermore, revision of this statement should be reconsidered when additional data becomes available from the agreed non-interventional PAES B2401.

In general, the efficacy results from the final analysis of study B2001X (FAS) are considered to support the data underlying the approved indication for Kymriah in r/r ALL patients.

Cellular kinetics:

Characterisation of the cellular kinetics was a secondary endpoint in the B2001x study. Overall, the observed cellular kinetics was comparable to previous results from studies B2202 and B2205J.

Increasing C_{max}, AUC0-28d and AUC0-84d were associated with higher grade CRS, which is in line with previous findings in B2202 and B2205J trials.

Safety

Evaluation of the safety of CTL019 therapy was the primary endpoint of study B2001X, in which a total of 52 paediatric patients <18 years of age was included; 42 non-adolescents (<12 years of age) and 10 adolescents (12-<18 years of age).

The mean duration of follow-up of patients in the safety set was 8.7 months (range: 0.2 to 13.1); 42.0% of patients were followed up for 6 to < 12 months, 29.0% were followed up for < 6 months and 29.0% were followed up for ≥ 12 months. As experienced in earlier studies, most AEs were reported first 8 weeks following infusion, indicating the observation time in the current study is sufficient for an overall picture of common AEs in this patient group.

Due to the limited number of adolescents (10 subjects) and imbalance in the number of patients within each subpopulation, it is difficult to assess any difference in AE profile between non-adolescent and adolescent group, and the data from the adolescent group is too small for assessing the safety profile adequately.

In general, the AEs reported in the current study are comparable to what have been observed in earlier studies in ALL patients (Study B2202, and study B2205J). The most important AEs like CRS, pyrexia, haematological AEs and hypogammaglobulinemia were frequently observed in the current study in line with what has earlier been reported in study B2202, which is the reference to ADR frequency data in the current product information. Grade 3 AEs were reported in 33.3% in non-adolescent group and in 30.0% in the adolescent group, grade 4 AEs were reported in 50.0% and in 70.0% in the respective groups in study B2001X.

The majority of patients reported CRS limited to the first 8 weeks post-infusion. The reactions were adequately managed with treatment according to the management algorithm. However, CRS was a contributing factor in fatal outcome in a 5-year-old child.

Neurological events were observed. The MAH has provided an overview of time to onset, duration, management and relationship to possible concomitant CRS.

Most frequent infections were URTIs and nasopharyngitis, while pneumonia was the most commonly occurring severe infection. Most infections were seen first 8 weeks post-infusion.

The review of fatal cases did not identify a definitive pattern as most patients had underlying contributing comorbidities and complications associated with relapsed or refractory B-cell ALL. Of interest is the one case (a 5-year-old) reporting CRS and tumour lysis syndrome (TLS), the one case (9 year old) reporting CRS, Febrile neutropenia, Hyponatraemia, Infection and the one case (3 years old) reporting Seizure, Central nervous system infection, Pneumonia and Multiple organ dysfunction syndrome. Only the case with CRS and TLS were suspected related to the study drug by the investigator.

Overall, it can be concluded that the pattern of AEs reported in study B2001X are comparable to AEs reported in children with ALL in earlier clinical studies. The data from the adolescent group in the current study is however too small for assessing the safety profile adequately.

The MAH does not propose any updates of the safety and efficacy parts of the product information based on data from the current study. However, paediatric patients are now included in several studies (i.e., B2001X, B2202, and B2205J), while the product information refers to safety data from the pivotal study B2202 only and efficacy data are reported from the two clinical studies B2202 and B2205J. Regarding safety, the MAH should submit a type II variation to reflect pooled data for the three clinical studies B2001X, B2205J and B2202 in the SmPC section 4.4 and 4.8 concerning the paediatric and young adult ALL population.

3. Request for Supplementary Information

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

1. The MAH is requested to provide information on the time interval from screening to enrolment (defined as the point at which the patient met all clinical inclusion/exclusion criteria and their leukapheresis product was accepted for manufacturing), and from enrolment to infusion with tisagenlecleucel.
2. Neurological events were observed. However, time to onset, duration and how they were treated is not described. The MAH is requested to provide an overview of time to onset, duration, management and relationship to possible concomitant CRS.
3. The MAH should review the data of the 15 patients enrolled in study B2001X who were previously treated with blinatumomab and discuss whether section 4.4. of the SmPC should be updated accordingly
4. The MAH should review all available data concerning safety and efficacy in paediatric patients with r/r ALL and provide a summary assessment, which shows that there is currently no need for revision of the product information regarding the approved ALL indication.

The timetable is a 30 day response timetable with clock stop.

4. MAH responses to Request for supplementary information

Question 1

The MAH is requested to provide information on the time interval from screening to enrolment (defined as the point at which the patient met all clinical inclusion/exclusion criteria and their leukapheresis product was accepted for manufacturing), and from enrolment to infusion with tisagenlecleucel.

Summary of the MAH's response

The time interval from screening to enrolment and from enrolment to tisagenlecleucel infusion for patients enrolled in study B2001X is presented in Table 14.

Table 14: *Time since screening and enrolment to CTL019 infusion (Safety set)*

	All Patients N=69
Time since screening to enrollment (days)	
n	69
Mean	16.7
SD	17.43
Median	10.0
Minimum	1.0
Maximum	93.0
Time since enrollment to CTL019 infusion (days)	
n	69
Mean	71.2
SD	36.68
Median	64.0
Minimum	7.0
Maximum	219.0

Source: [t1_ema_b2001x:Table 1]

Of note, the time interval from screening to enrolment in study B2001X (median:10.0 days) encompassed the provision of cryopreserved apheresis material by the study site, and the subsequent acceptance for manufacturing by Novartis; this might have included a number of apheresis attempts for some patients. The time interval from study enrolment to tisagenlecleucel infusion (median: 64 days) was similarly variable, since it encompassed a number of Novartis- and study site-based activities, including the scheduling of manufacturing and the manufacturing period itself, and the delivery of the final manufactured product back to the study site. Once the final product was received by the study site, the study subject underwent additional protocol-mandated activities, such as disease restaging and lymphodepletion therapy, prior to tisagenlecleucel infusion.

Assessment of the MAH's response

The requested data has been provided. It is acknowledged that this could be due to multiple apheresis attempts before cells were considered suitable for manufacturing. The time interval from enrolment to tisagenlecleucel infusion was similarly variable with a median of 64 days and maximum time of 219 days.

According to the CSR, tisagenlecleucel was released to the study, provided all required safety and quality release specifications were met. It is therefore anticipated that all tisagenlecleucel infusions fell within the required specifications. However, it is not clear whether for some participants, the product did not fall within the required specifications, and that apheresis and subsequent manufacturing had to be repeated. However, this will not be pursued further in this procedure since it will be addressed in one of the PAMs that the MAH has committed to conduct as part of the MA (agreed Annex II condition).

Issue clarified and will not be pursued further in this procedure.

Question 2

Neurological events were observed. However, time to onset, duration and how they were treated is not described. The MAH is requested to provide an overview of time to onset, duration, management and relationship to possible concomitant CRS.

Summary of the MAH's response

A total of 22 events of serious neurological adverse reactions (SNARs), including both nonserious and serious AEs, were reported in 18 patients (26.1%) post-tisagenlecleucel infusion (Table 15). In 17 (24.6%) patients these SNARs occurred within the initial 8 weeks post-tisagenlecleucel infusion with Grade 3 and Grade 4 SNARs occurring in 6 (8.7%) and 1 (1.4%) patients, respectively. There were no fatal SNARs. The most frequent MedDRA PTs reported (≥ 5%) were seizure (6 patients; 8.7%) and tremor (4; 5.8%).

Time to onset

The median time to onset of the first SNAR was 9.0 days (range: 2 to 121).

Table 15: *Serious neurological adverse reactions (SNARs) episodes post tisanglecleucel infusion, overall and by age group (Safety set)*

	Age < 12 years N=42	Age 12 - < 18 years N=10	Age ≥18 years N=17	All patients N=69
Serious neurological adverse reactions (SNARs) - n (%)				
No	30 (71.4)	9 (90.0)	12 (70.6)	51 (73.9)
Yes	12 (28.6)	1 (10.0)	5 29.4)	18 (26.1)
Total number of episodes of SNARs[1]	15	1	6	22
Maximum SNARs grade – n (%)				
Grade 1	3 (7.1)	0	2 (11.8)	5 (7.2)
Grade 2	5 (11.9)	1 (10.0)	0	6 (8.7)
Grade 3	4 (9.5)	1 (70	2 (11.8)	6 (8.7)
Grade 4	0	0	1 (5.9)	1 (1.4)
Fatal – n (%)	0	0	0	0
Among patients with SNARs[2]				
Time to onset of SNARs(days)				
n	12	1	5	18
Mean (SD)	11.9 (10.47)	20.0	32.8 (49.40)	18.2 (27.13)
Median	8.0	20.01	12.0	9.0
Min - Max	2 - 37	20 - 20	7 - 121	2 - 121
Time to grade 3 or 4 SNARs (days)				
n	4	0	3	7
Mean (SD)	20.0 (22.20)		10.3 (2.08)	15.9 (16.57)
Median	10.5		11.0	11.0
Min - Max	6 - 53		8 - 12	6 - 53
Among all the episodes of SNARs				
Resolved - n (%)	11 (73.3)	1 (100.0)	5 (83.3)	17 (77.3)
Median (95% CI) of time to resolution (days)[3]	2 (1, 40)	2 (NE, NE)	8 (3, NE)	5 (1, 19)
% Resolved probability estimates (95% CI)[4]				
Day 7	60.0 (37.2, 83.5)	100.0 (NE, NE)	33.3 (8.6, 80.5)	55.6 (36.2, 76.8)
Day 14	60.0 (37.2, 83.5)	100.0 (NE, NE)	66.7 (32.4, 95.4)	66.7 (46.4, 85.6)
Day 28	70.0 (45.1, 91.1)	100.0 (NE, NE)	66.7 (32.4, 95.4)	72.2 (51.9, 89.4)
Day 91	80.0 (54.3, 96.3)	100.0 (NE, NE)	100.0 (NE, NE)	85.2 (64.6, 97.0)

1: One episode of serious neurological adverse reactions is from concatenation of multiple overlapping records under the risk name ' Serious neurological adverse reactions'
2: All percentages presented below are based on the number of subjects with SNARs in the safety set. Only the first SNARs episode is summarized for each subject.
3: Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
4: % resolved probability is obtained from the Kaplan-Meier survival estimates.
Sources: [t4_ema_b2001x], [t5_ema_b2001x]

Duration

The majority of events of SNARs (17 out of 22; 77.3%) were resolved as of the data cut-off date. The Kaplan-Meier estimated probability of SNARs having completely resolved was 55.6% (95% CI [36.2, 76.8]) at Day 7 and 72.2% [51.9, 89.4] from Day 28 onwards.

Management

The majority of the tisagenlecleucel-related SNARs were treated by concomitant medication

Relation to episodes of CRS

Of the 22 total events of SNARs reported, 3 (13.6%) occurred in patients who did not develop CRS at any time point during the study. One event of SNARs (4.5%) occurred prior to the onset of CRS and during CRS. Ten events occurred after the onset of CRS, six of which (27.3%) resolved prior to resolution of CRS and four (18.2%) after resolution of CRS. Eight events (36.4%) occurred after CRS had already resolved.

Overall, it appears that the onset of events of SNARs typically occurred either during the course of CRS or after the resolution of CRS. However, SNARs starting prior to the onset of CRS and SNARs not in conjunction with CRS were also observed (Table 16).

Table 16: Onset of serious neurological events post CTL019 infusion and relationship with CRS (Safety *set)*

	All patients N=69
Number of patients with serious neurological adverse event - n (%)	18 (26.1)
Number of serious neurological adverse event [1]	22
Event prior to CRS (a)	0
Event prior to and during CRS (b)	1 (4.5)
Event during CRS only (c)	6 (27.3)
Event during CRS and after resolution of CRS (d)	4 (18.2)
Event after resolution of CRS only (e)	8 (36.4)
Event without CRS (f)	3 (13.6)

[1] One event of serious neurological adverse reactions is from concatenation of multiple overlapping episodes under the risk name 'Serious neurological adverse reactions'. Percentages of events are among total number of events.
a: The serious neurological adverse reaction ended and later a CRS episode occurred
b: the serious neurological adverse reaction started prior to the start of a CRS episode and the AESI was continued during the CRS episode
c: the serious neurological adverse reaction started and ended during the CRS episode
d: the serious neurological adverse reaction started during the CRS episode and continued after the CRS episode ended
e: the serious neurological adverse reaction started and ended after the CRS episode ended
f: the serious neurological adverse reaction occurred and the patient had no CRS episode
Source: [t7_ema_b2001x]

Assessment of the MAH's response

The data provided is based on study B2001X, including 69 patients, of which 42 are <12 years of age, 10 are 12 - <18 years of age and 17 are ≥18 years of age.

Time to onset

Time to onset in all patients was median 9 days (range 2 to 121), but median time to onset varied from 8 days in the group <12 years to 20 days in the group 12-<18 years.

Duration

At time of data cut-off 77.3% of serious neurological AE were resolved. The duration has been given by probability estimates. It is estimated that 55.6% (36.2-76.8) are resolved by day 7 post-infusion, 66.7% (46.4-85.6) are resolved by day 14, 72.2% (51.9-89.4) by day 28 and 85.2% (64.6-97.0) by day 91. This means that among ca 75% of patients the serious neurological AEs did not last beyond four weeks.

Management

The majority of the tisagenlecleucel-related SNARs were treated by concomitant medication, no further description.

Serious neurological AEs in relation to episodes of CRS

Neurological AEs were seen both during the CRS episode (27.3%), during and after resolution of CRS (18.2%) and after resolution of CRS (36.4%). Even in 13.6% neurological events were seen without episodes of CRS. The numbers are small in each category and no specific trend can be concluded.

Data currently given in section 4.4 concerning median time to onset and median time to resolution is based on study B2202. It can be agreed that new data from study B2001X are more or less similar to what was reported for study B2202. However, the duration of neurological AEs seems to be longer in study B2001X than in study B2202 (median time to resolution 8 days). It would be preferred that data in SmPC reflects the overall experience in paediatric B-cell ALL based on data from all studies (B2001X, B2205J and B2205).

In conclusion

The MAH should submit a Type-II variation to reflect pooled data on neurological AEs in paediatric B-cell ALL studies in SmPC section 4.4, see also Q 4.

Question 3

The MAH should review the data of the 15 patients enrolled in study B2001X who were previously treated with blinatumomab and discuss whether section 4.4. of the SmPC should be updated accordingly.

Summary of the MAH's response

The inclusion of certain patients not studied during study B2202 was allowed in study B2001X. This is the case for patients with prior blinatumomab exposure. Fifteen patients with prior blinatumomab exposure were enrolled in study B2001X. Outcomes for these patients were previously presented (Krueger et al 2020). Out of a total of 67 patients included in the FAS who at the DCO for the interim publication analysis completed 3 months of follow up or prematurely discontinued study B2001X, 15 patients had received blinatumomab prior to tisagenlecleucel infusion. The efficacy of tisagenlecleucel in this population is summarized in Table 17 below.

Table 17: *Efficacy Summary (Krueger et al. 2020)*

	All Patients N=65 (OS, N=67)	Prior blinatumomab n=15	No Prior blinatumomab n=50
CR+CRi ≤3 months ,n(%)	55[a] (85)	10 (67)	45 (90)
(95% CI)	(74-92)	(38-88)	(78-97)
MRD (-) in CR/CRi patients, %	96	100	95
DOR, % (95% CI)			
Month 6	83 (69-91)	88 (39-98)	82 (66-91)
Month 9	74 (57-85)	70 (23-92)	75 (57-86)
Relapse in patients with CR/CRi at any time, n	14	2	12
CD19 status at relapse, n (-)/n (+)	9/5	2/0	7/5

[a] 3 patients with no CR/CRi, 5 early progression, 2 deaths precluding disease evaluation

Although outcomes in patients with prior blinatumomab tend to be numerically lower than those for the overall population, these results should be interpreted with caution due to a number of reasons, including small cohort size, short follow-up (median follow-up from infusion to DCO: 9.6 months [range, 0.2-16.5 months] in Krueger et al 2020), and potential confounding factors. For example, patients with prior blinatumomab had more previous lines of treatment than the overall population (median of 3 versus 2, respectively), and more patients in the prior blinatumomab cohort had previous allogeneic stem cell transplantation than those in the overall population (87% versus 61%, respectively) (Krueger et al 2020). In addition, patients might have simply required treatment with blinatumomab as a means to control aggressive disease (such as chemotherapy-refractory ALL), which can be associated with worse outcomes. Due to these limitations and consequent unfeasibility to clearly interpret these limited data, Novartis is of the opinion that an update of the SmPC is not warranted. Notably, currently the product information states that "there is limited experience with Kymriah in patients exposed to prior CD19-directed therapy", this statement remains accurate and appropriate.

Assessment of the MAH's response

The Krueger et al. reference (https://ascopubs.org/doi/10.1200/JCO.2020.38.15_suppl.10518) is an abstract published in May 2020, that does not appear to have been included in the dossier. The efficacy summary provided in Krueger et al. 2020 for study B2001X is based on data from a DCO of 04-Nov-2019; whilst the DCO for the last patient last visit for study B2001X was 13-Oct-2020. The data presented in Krueger et al. 2020 therefore do not correspond to the complete and final data analysis of study B2001X.

The data for overall survival (OS) at 12 months was presented in the abstract but not listed in Table 2-4. The median OS at 12 months for all patients (n=67) was 83% (95% CI: 69-72), whereas for patients who had received prior blinatumomab (n=15) the median OS was 53% (95% CI:19-78) and 91% (95% CI: 74-97) for patients with no prior blinatumomab exposure (n=50). There was therefore a consistent trend in the majority of parameters towards sub-optimal outcomes in patients that had received prior blinatumomab. While it is agreed that the cohort size is small, the confidence intervals are broad and such patients may have had more advanced/aggressive disease where the results should be interpreted with caution, duration of response was similar between the groups. The wording of the SmPC section 4.4 should be modified to reflect the current experience by adding the following "*while some activity of tisanglecleucel has been observed, data are currently too limited to make an adequate assessment of the benefit-risk profile in these patients" to the current statement*.

Furthermore, revision of this statement should be reconsidered when additional data becomes available from one of the agreed PAES which is ongoing (i.e., the non-interventional study B2401).

Issue not resolved but will not be pursued further in this procedure. However, the required changes to the SmPC should be implemented at the time the required type II variation is submitted.

Question 4

The MAH should review all available data concerning safety and efficacy in paediatric patients with r/r ALL and provide a summary assessment, which shows that there is currently no need for revision of the product information regarding the approved ALL indication.

Summary of MAH's response

Safety data

Overall, the AE profile by SOC and PT of the respective three age groups and the overall study population was similar across all three studies (Table 18 and Table 19).

Table 18: *Summary of Grade 3 or 4 CRS events by age: Studies B2001X, B2205J, and B2202*

	B2001X		B2205J		B2202	
Cytokine Release Syndrome	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Age < 12 years	6 (14.3)	9 (21.4)	3 (10.7)	4 (14.3)	4 (10.0)	10 (25.0)
Age 12 to 18 years	1 (10.0)	2 (20.0)	5 (19.2)	4 (15.4)	9 (36.0)	7 (28.0)
Age ≥ 18 years	2 (11.8)	2 (11.8)	0	3 (30.0)	4 (28.6)	4 (28.6)

Sources: [t3_ema_b2001x], [Table RSI_Jun21_2.2a], [Table RSI_Jun21_2.2b]

Table 19: *Summary of AESIs by age: Studies B2001X, B2205J, and B2202 (Safety set)*

	Study B2001X				Study B2205J				Study B2202			
	All patients	< 12 years	12 - < 18 years	≥ 18 years	All patients	< 12 years	12 - < 18 years	≥ 18 years	All patients	< 12 years	12 - < 18 years	≥ 18 years
	N = 69	n = 42	n = 10	n = 17	N = 64	n = 28	n = 26	n = 10	N = 40	n = 40	n = 25	n = 14
	%	%	%	%	%	%	%	%	%	%	%	%
Number of subjects with at least one AESI	95.7	97.6	100.0	88.2	98.4	100	96.2	100	98.7	97.5	100	100
Cytokine release syndrome	68.1	71.4	70.0	58.8	78.1	78.6	76.9	80.0	77.2	70.0	84.0	85.7
Hematopoietic cytopenias not resolved by Day 28[1]	55.1	54.8	70.0	47.1	42.2	39.3	42.3	50.0	69.6	75.0	68.0	57.1
Infections	65.2	64.3	70.0	64.7	71.9	78.6	65.4	70.0	73.4	70.0	68.0	92.9
Prolonged depletion of normal B cells or agammaglobulinemia	40.6	42.9	40.0	35.3	51.6	53.6	57.7	30.0	54.4	50.0	60.0	57.1
Serious neurological adverse reactions[2]	26.1	28.6	10.0	29.4	32.8	28.6	42.3	20.0	44.3	45.0	48.0	35.7
Tumor lysis syndrome	1.4	2.4	0	0	3.1	3.6	3.8	0	6.3	0	16.0	7.1

1: In Study B2001X and B2202, the AESI category is "Hematopoietic disorders including cytopenias".
2: In Study B2205J, the AESI category is "Neurological events".
Sources: [t2_ema_b2001x], [t3_ema_b2001x] [Table RSI_Jun21_2.2a], [Table RSI_Jun21_2.2b], [Study B2205J-Table 14.3.1-1.6], [Study B2202- Table 14.3.1-1.6]

Overall safety conclusion

Key efficacy and safety results across 212 patients (171 pediatric patients) from three studies in r/r ALL did not indicate clinically meaningful differences between the respective age groups across the studies, or when comparing the age groups to the overall study population within each individual studies. For safety, the results are similar between the three age groups in each individual study, with no trend observed.

Summary of efficacy data

In order to provide a comprehensive overview of the efficacy of tisagenlecleucel in pediatric patients with r/r ALL, data from three studies in pediatric r/r ALL are provided in this response. Novartis has conducted additional age-wise analysis to supplement already reported clinical study data. The age subgroups are < 12 years (non-adolescents); 12 - < 18 years (adolescents), ≥ 18 years.

Overall response rate

The ORR (CR+CRi) was consistently high in all three age groups across the studies. The ORR was similar among the three studies: ranging between 70.3% and 82.6% (Table 20). Response rates were similar across all age subgroups in all three studies. Although the > 18 years subgroup response rate was numerically lower in all three studies, due to the low sample size and wide confidence intervals, it is difficult to draw any conclusions about potential efficacy differences based on age.

Table 20: *BOR and ORR within 3 or 6 months post tisanglecleucel infusion per IRC assessment by age: Studies B2001X, B2205J, and B2202 (FAS)*

	Overall	Age group		
		< 12 years	12 to < 18 years	≥ 18 years
Study B2001X[1]				
BOR (n/N, %)				
CR (n/N, %)	39/69 (56.5)	28/42 (66.7)	6/10 (60.0)	5/17 (29.4)
CRi (n/N, %)	18/69 (26.1)	7/42 (16.7)	3/10 (30.0)	8/17 (47.1)
No response (n/N, %)	3/69 (4.3)	0	1/10 (10.0)	2/17 (11.8)
Unknown (n/N, %)	9/69 (13.0)	7/42 (16.7)	0	2/17 (11.8)
ORR [95% CI]	57/69 (82.6) [71.6, 90.7]	35/42 (83.3) [68.6, 93.0]	9/10 (90.0) [55.5, 99.7]	13/17 (76.5) [50.1, 93.2]
Study B2205J[1]				
BOR (n/N, %)				
CR (n/N, %)	38/64 (59.4)	18/28 (64.3)	15/26 (57.7)	5/10 (50.0)
CRi (n/N, %)	7/64 (10.9)	1/28 (3.6)	5/26 (19.2)	1/10 (10.0)
No response (n/N, %)	13/64 (20.3)	6/28 (21.4)	3/26 (11.5)	4/10 (40.0)
Unknown (n/N, %)	6/64 (9.4)	3/28 (10.7)	3/26 (11.5)	0/10 (0)
ORR [95% CI]	45/64 (70.3) [57.6, 81.1]	19/28 (67.9) [47.6, 84.1]	20/26 (76.9) [56.4, 91.0]	6/10 (60.0) [26.2, 87.8]
Study B2202[2]				
BOR (n/N, %) at 3 months				
CR (n/N, %)	49/79 (62.0)	23/40 (57.5)	18/25 (72.0)	8/14 (57.1)
CRi (n/N, %)	16/79 (20.3)	9/40 (22.5)	4/25 (16.0)	3/14 (21.4)
No response (n/N, %)	7/79 (8.9)	3/40 (7.5)	2/25 (8.0)	2/14 (14.3)
Unknown (n/N, %)	7/79 (8.9)	5/40 (12.5)	1/25 (4.0)	1/14 (7.1)
ORR [95% CI]	65/79 (82.3) [72.1, 90.0]	32/40 (80.0) [64.4, 90.9]	22/25 (88.0) [68.8, 97.5]	11/14 (78.6) [49.2, 95.3]

ORR: CR+CRi
1 BOR/ORR during the first 6 months
2 BOR/ORR during the first 3 months
Note: BOR requires remission status to be maintained for at least 28 days without clinical evidence of relapse.
Sources: Table 14.2-1-1 of respective studies, [Table 14.2-1-3 of B2201X], [Table RSI_Jun21_1.1.a], [Table RSI_Jun21_1.1.b]

In Studies B2202 and B2205J, nearly all patients who achieved BOR of CR or CRi also achieved bone marrow MRD negative remission: 43/45 in study B2205J and 64/65 in study B2202. In Study B2001X, bone marrow MRD evaluation was missing for a larger proportion of patients as compared to the other two trials. However, available data show that most of responding patients did achieve bone marrow MRD negative remission. MRD evaluations were performed by local assessment in Study B2001X, while it was performed by central evaluations in Studies B2202 and B2205J.

Duration of remission

Median duration of remission was not reached in Studies B2202 and B2205J (Study B2202- Section 11.1.3.11, and Study B2205J-Section 11.2.3). For B2001X, median estimate was 14.4 months, however it should be considered with caution as majority of patients were censored before 12 months.

Comparing DOR between the pediatric age subgroups, there was no noticeable trend differentiating patients < 12 years old vs. 12 to < 18 years old. The improvement in DOR for patients < 12 years old observed in study B2001X was not observed in studies B2205J and B2202 (Table 21).

When comparing patients > 18 years old to the pediatric population, it is seen that the > 18 years subgroup had numerically lower DOR at 9 months in all three studies. However, due to the low sample size and wide confidence intervals, it is difficult to draw any conclusions about potential efficacy differences for patients > 18 years old.

Table 21: *DOR censoring HSCT per IRC assessment by age: Studies B2001X, B2205J, and B2202 (FAS)*

	Overall	Age group		
		< 12 years	12 to < 18 years	≥ 18 years
Study B2001X				
Median (months) (95% CI)	14.4 (NE, NE)	NE (11.1, NE)	14.4 (2.4, NE)	NE (3.3, NE)
Responders n/N (%)	15/57 (26.3)	6/35 (17.1)	5/9 (55.6)	4/13 (30.8)
% Event-free probability estimates (95% CI)				
3 months	90.8 (79.2, 96.1)	90.9 (74.3, 97.0)	88.9 (43.3, 98.4)	92.3 (56.6, 98.9)
6 months	82.7 (69.3, 90.6)	87.4 (69.7, 95.1)	77.8 (36.5, 93.9)	75.5 (41.6, 91.4)
9 months	76.0 (61.5, 85.7)	83.4 (64.3, 92.8)	66.7 (28.2, 87.8)	66.1 (32.5, 85.8)
Study B2205J				
Median (months) (95% CI)	NE (13.6, NE)	NE (5.4, NE)	NE (14.8, NE)	10.9 (1.9, NE)
Responders (n/N (%))	13/45 (28.9)	8/19 (42.1)	2/20 (10.0)	3/6 (50.0)
% Event-free probability estimates (95% CI)				
3 months	95.6 (83.4, 98.9)	100 (100, 100)	95.0 (69.5, 99.3)	83.3 (27.3, 97.5)
6 months	79.5 (62.9, 89.3)	71.0 (43.3, 86.9)	95.0 (69.5, 99.3)	62.5 (14.2, 89.3)
9 months	73.6 (56.2, 84.9)	58.1 (31.2, 77.6)	95.0 (69.5, 99.3)	62.5 (14.2, 89.3)
12 months	70.5 (52.8, 82.6)	58.1 (31.2, 77.6)	95.0 (69.5, 99.3)	31.3 (1.3, 73.4)
18 months	62.8 (43.9, 76.9)	51.6 (25.8, 72.4)	83.1 (43.0, 96.0)	31.3 (1.3, 73.4)
Study B2202				
Median (months) (95% CI)	NE (20.0, NE)	NE (7.5, NE)	NE (8.0, NE)	NE (8.6, NE)
Responders n/N (%)	19/65 (29.2)	10/32 (31.3)	6/22 (27.3)	3/11 (27.3)
% Event-free probability estimates (95% CI)				
3 months	93.4 (83.4, 97.5)	89.9 (71.8, 96.6)	95.0 (69.5, 99.3)	100 (100, 100)
6 months	80.3 (67.2, 88.6)	71.0 (50.2, 84.4)	84.1 (58.3, 94.6)	100 (100, 100)
9 months	66.3 (51.8, 77.4)	67.1 (46.1, 81.4)	67.3 (41.1, 83.8)	62.5 (22.9, 86.1)
12 months	66.3 (51.8, 77.4)	67.1 (46.1, 81.4)	67.3 (41.1, 83.8)	62.5 (22.9, 86.1)
18 months	66.3 (51.8, 77.4)	67.1 (46.1, 81.4)	67.3 (41.1, 83.8)	62.5 (22.9, 86.1)

Sources: [Study B2001X-Table 14.2-3.1], [Study B2001X-Table 14.2-3.3], [Study B2205J-Table 14.2-6.1], [Study B2202-Table 14.2-6.1], [Table RSI_Jun21_1.3.a], [Table RSI_Jun21_1.3.b]

Event-free survival

A similar proportion of pediatric patients across the three studies experienced treatment failure, relapse, or death due to any cause after remission. These values were similar to those of the overall population in the individual studies. (Table 22).

Comparing between the pediatric age subgroups there was no noticeable trend differentiating patients < 12 years old vs. 12 to < 18 years old when comparing EFS. The improvement in EFS for patients < 12 years old observed in study B2001X was not observed in studies B2205J and B2202.

When comparing patients > 18 years old to pediatric population, it was seen that the > 18 years subgroup had numerically lower EFS at 12 months in all three studies. However, due to the low sample size and wide confidence intervals, it is difficult to draw any conclusions about potential efficacy differences for patients > 18 years old.

Table 22: *EFS censoring HSCT per IRC assessment by age: Studies B2001X, B2205J, and B2202 (FAS)*

	Overall	Age group		
		< 12 years	12 to < 18 years	≥ 18 years
Study B2001X				
Median (months) (95% CI)	15.1 (12.0, NE)	NE (12.0, NE)	10.2 (3.2, NE)	NE (4.2, NE)
n/N (%)	20/69 (29.0)	9/42 (21.4)	6/10 (60.0)	5/17 (29.4)
% Event-free probability estimates (95% CI)				
3 months	90.5 (80.0, 95.6)	89.9 (75.2, 96.1)	100 (100, 100)	85.1 (52.3, 96.1)
6 months	75.9 (62.6, 85.1)	80.6 (63.2, 90.3)	70.0 (32.9, 89.2)	68.8 (36.4, 87.1)
9 months	71.8 (58.0, 81.8)	76.9 (58.6, 87.9)	70.0 (32.9, 89.2)	60.2 (28.8, 81.3)
12 months	67.3 (52.8, 78.2)	76.9 (58.6, 87.9)	46.7 (15.0, 73.7)	60.2 (28.8, 81.3)
Study B2205J				
Median (months) (95% CI)	15.6 (6.4, NE)	7.9 (4.3, NE)	NE (15.6, NE)	4.9 (0.0, NE)
n/N (%)	28/64 (43.8)	15/28 (53.6)	6/26 (23.1)	7/10 (70.0)
% Event-free probability estimates (95% CI)				
3 months	72.7 (59.7, 82.1)	73.9 (52.8, 86.6)	80.2 (58.8, 91.3)	50.0 (18.4, 75.3)
6 months	67.0 (53.5, 77.4)	62.0 (40.7, 77.5)	80.2 (58.8, 91.3)	50.0 (18.4, 75.3)
9 months	56.0 (41.7, 68.1)	42.9 (22.8, 61.6)	80.2 (58.8, 91.3)	37.5 (9.9, 65.9)
12 months	53.6 (39.3, 66.0)	42.9 (22.8, 61.6)	80.2 (58.8, 91.3)	18.8 (1.2, 52.9)
18 months	47.8 (33.0, 61.1)	38.1 (19.0, 57.2)	70.2 (41.1, 86.9)	18.8 (1.2, 52.9)
Study B2202				
Median (months) (95% CI)	NE (9.2, NE)	20.9 (6.0, NE)	NE (8.6, NE)	11.6 (2.8, NE)
n/N (%)	31/79 (39.2)	16/40 (40.0)	9/25 (36.0)	6/14 (42.9)
% Event-free probability estimates (95% CI)				
3 months	83.3 (72.9, 89.9)	82.0 (65.9, 91.0)	88.0 (67.3, 96.0)	78.6 (47.2, 92.5)
6 months	71.2 (59.2, 80.3)	66.7 (48.4, 79.7)	73.8 (50.5, 87.4)	78.6 (47.2, 92.5)
9 months	62.8 (50.1, 73.2)	56.7 (38.2, 71.5)	64.0 (40.4, 80.3)	78.6 (47.2, 92.5)
12 months	55.9 (43.0, 67.0)	56.7 (38.2, 71.5)	59.1 (35.7, 76.4)	49.1 (19.0, 73.7)
18 months	55.9 (43.0, 67.0)	56.7 (38.2, 71.5)	59.1 (35.7, 76.4)	49.1 (19.0, 73.7)

Sources: [Study B2001X-Table 14.2-5.1], [Study B2001X-Table 14.2-5.4], [Study B2205J-Table 14.2-8.1], [Study B2202-Table 14.2-8.1], [Table RSI_Jun21_1.4.a], [Table RSI_Jun21_1.4.b]

Overall survival

Survival rate was similar in the pediatric age groups in all three studies, and consistent with the overall population (Table 23).

Comparing between the pediatric age subgroups there is no noticeable trend differentiating patients < 12 years old vs. 12 to < 18 years old when comparing OS.

When comparing patients > 18 years old to the rest of the population, it is seen that the > 18 years subgroup had numerically worse survival at 12 months in all three studies. However, due to the low sample size and wide confidence intervals, it is difficult to draw any conclusions about potential efficacy differences for patients > 18 years old.

Table 23: *OS by age: Studies B2001X, B2205J, and B2202 (FAS)*

	Overall	Age group		
		< 12 years	12 to < 18 years	≥ 18 years
Study B2001X				
Median (months) (95% CI)	15.1 (12.9, NE)	NE (NE, NE)	15.1 (9.7, NE)	12.9 (NE, NE)
n/N (%)	9/69 (13.0)	4/42(9.5)	2/10 (20.0)	3/17 (17.6)
% Event-free probability estimates (95% CI)				
3 months	94.0 (84.8, 97.7)	92.6 (78.7, 97.5)	100.0 (100.0,100.0)	93.8 (63.2, 99.1)
6 months	94.0 (84.8, 97.7)	92.6 (78.7, 97.5)	100.0 (100.0,100.0)	93.8 (63.2, 99.1)
9 months	90.0 (78.9, 95.4)	89.3 (73.6, 95.9)	100.0 (100.0,100.0)	85.2 (51.9, 96.2)
12 months	88.0 (76.2, 94.1)	89.3 (73.6, 95.9)	87.5 (38.7, 98.1)	85.2 (51.9, 96.2)
Study B2205J				
Median (months) (95% CI)	29.9 (15.1, 42.4)	29.9 (9.0, 36.8)	NE (15.1, NE)	7.4 (1.2, NE)
n/N (%)	30/64 (46.9)	16/28 (57.1)	8/26 (30.8)	6/10 (60.0)
% Event-free probability estimates (95% CI)				
3 months	92.2 (82.2, 96.7)	96.4 (77.2, 99.5)	92.3 (72.6, 98.0)	80.0 (40.9, 94.6)
6 months	84.4 (72.9, 91.3)	89.3 (70.4, 96.4)	84.6 (64.0, 93.9)	70.0 (32.9, 89.2)
9 months	67.0 (54.0, 77.1)	67.9 (47.3, 81.8)	76.9 (55.7, 88.9)	36.0 (9.0, 64.8)
12 months	65.4 (52.4, 75.7)	64.3 (43.8, 78.9)	76.9 (55.7, 88.9)	36.0 (9.0, 64.8)
18 months	61.6 (48.2, 72.4)	60.7 (40.4, 76.0)	71.8 (49.4, 85.6)	36.0 (9.0, 64.8)
Study B2202				
Median (months) (95% CI)	NE (28.2, NE)	NE (17.9, NE)	NE (28.2, NE)	NE (10.2, NE)
n/N (%)	25/79 (31.6)	14/40 (35.0)	5/25 (20.0)	6/14 (42.9)
% Event-free probability estimates (95% CI)				
3 months	92.4 (83.9, 96.5)	92.5 (78.5, 97.5)	96.0 (74.8, 99.4)	85.7 (53.9, 96.2)
6 months	88.6 (79.2, 93.9)	87.4 (72.4, 94.6)	92.0 (71.6, 97.9)	85.7 (53.9, 96.2)
9 months	84.6 (74.4, 90.9)	82.1 (66.1, 91.1)	88.0 (67.3, 96.0)	85.7 (53.9, 96.2)
12 months	76.4 (65.2, 84.5)	74.2 (57.3, 85.2)	88.0 (67.3, 96.0)	62.3 (31.7, 82.4)
18 months	70.3 (58.4, 79.4)	65.1 (47.4, 78.2)	88.0 (67.3, 96.0)	53.4 (23.9, 76.0)

Sources: [Study B2001X-Table 14.2-6.1], [Study B2205J-Table 14.2-9.1], [Study B2202-Table 14.2-9.1], [Table RSI_Jun21_1.4a], [Table RSI_Jun21_1.4b], [t21_ema_b2001x]

Overall efficacy conclusions

Key efficacy and safety results across 212 patients (171 pediatric patients) from three studies in r/r ALL did not indicate clinically meaningful differences between the respective age groups across the studies, or when comparing the age groups to the overall study population within each individual studies. For efficacy, there was no clear trend observed based on age within the pediatric population (patients < 18 years old). Although a trend towards reduced efficacy in the patients over 18 years old was observed in all three studies, this should be interpreted with caution due to the low sample size and the fact that confidence intervals were overlapping. Historically it has been observed that

adolescents and young adults have worse prognosis with ALL, which may be due to the difference in the disease biology or host factors. This difference in underlying disease characteristics could explain the trend in efficacy outcomes, however given the lack of statistical significance, no conclusion can be made.

In view of these results, Novartis is not of the opinion that there is a need to update the current data presented in the product information for the pediatric population in the approved ALL indication.

Assessment of MAH's response

Safety data

The MAH has presented safety data in ALL patients separately for the three studies (Study B2001X, B2205J and B2202). The MAH states that "Overall the AE profile by SOC and PT of the respective three age groups and the overall study population was similar across all three studies.", and concludes that "In view of these results, Novartis is not of the opinion that there is a need to update the current data presented in the product information for the paediatric population in the approved ALL indication."

In the current SmPC section 4.8 it is stated that for the B-cell ALL population "The adverse reactions described in this section were characterised in 79 patients infused with Kymriah in the multi-centre, pivotal clinical study B2202." Also, the data given in SmPC section 4.4 concerning time to onset and duration of AEs in the paediatric ALL population is based on study B2202 (see Q 2).

According to SmPC guidelines, section 4.8 *"Safety data from several studies should be pooled to increase the precision of adverse reaction rates as appropriate without introducing bias (e.g. major difference in population characteristics or exposure to the product)."*

The complete information on AEs in the paediatric and young adult ALL population in section 4.4 and 4.8 should be revised by referring to "studies in paediatric and young adult B-cell ALL patients,", e.g. frequencies, time to onset and duration based on the pooled data from all three studies B2001X, B2205J and B2202.

In conclusion on safety data

The MAH should submit a type II variation to reflect pooled data for the three studies B2001X, B2205J and B2202 in SmPC section 4.4 and 4.8 concerning the paediatric and young adult ALL population.

Efficacy data

Summary data has been provided according to age group for the three clinical studies as requested.

It is agreed that the efficacy findings are in general similar between the different studies. However, event-free survival appears more sustained in children < 12 years in study B2001X at 12 months compared to the same age group in the two clinical studies B2202 and B2205J. Similarly, DOR at 9 months was greater for children <12 years in study B2001X compared to the same age group in the B2202 and B2205J studies. The observations of lower efficacy in patients >18 years is acknowledged, however, the focus of the evaluation for this procedure are patients <18 years of age.

According to the SmPC guideline, 'the results of all pharmacodynamic (clinically relevant) or efficacy studies conducted in children should be presented'. Furthermore, it states that 'the information should be updated when new relevant information becomes available' and 'the results should also be presented by age or relevant subsets.' The MAH has, upon request, now provided information

according to age from an additional clinical study. However, including this data may be delayed until further information is available for the paediatric population as discussed below.

Study B2001X included participants <3 years of age, in addition to those that had received prior blinatumomab. Such participants were excluded from study B2202. As a result, there were no data on the benefit-risk profile in the youngest ALL patients less than 3 years of age at the time of the initial MA of Kymriah and the SmPC therefore currently states under special populations regarding the B-cell ALL indication that "*no formal studies have been carried out in paediatric patients below the age of three years*". In the B2001X study, three participants were <3 years of age at screening where the youngest was a 10-month-old female. Since B2001X is a formal study, the SmPC should be revised to state: "*There is limited experience with Kymriah in paediatric patients below the age of 3 years."*

Since children with r/r ALL less than 3 years old were excluded from the pivotal study B2202, the MAH agreed to conduct a post-authorisation efficacy study (PAES) to fulfil one of the required PAMs to the MA (ANX 006; Category 1) in order to characterize the efficacy and safety of Kymriah in ALL patients below the age of 3 years. This data will be derived from paediatric r/r ALL patients treated with tisagenlecleucel participating in the non-interventional registry study B2401. The final study results from this study are expected in December 2023. The SmPC should therefore be updated when the agreed PAES B2401 in ANX 006 is fulfilled.

Issue clarified. However, Section 4.2 of the SmPC should reflect the current experience with Kymriah in children below 3 years of age, since B2001X is a formal study. This should be implemented at the time the requested type II variation is submitted. Furthermore, the SmPC should be updated as and when more information on the efficacy of tisagenlecleucel in paediatric patients with r/r ALL becomes available based on completion of the respective required PAMs to the MA concerning r/r ALL patients.

5. MS comments on the CAT Rapporteur's Preliminary responses assessment report

Comments to the CAT Rapporteur's preliminary responses assessment report dated 23-Sep-2021 were received from one member state.

The recommendation to update section 4.4 and 4.8 of the SmPC with the pooled safety data was supported.

Regarding data in paediatric patients less than 3 years of age, the current statement in section 4.2 of the SmPC "*No formal studies have been performed in paediatric patients below 3 years of age"* is no longer considered correct since B2001X is a formal study, and 3 patients less than 3 years were included in this study. Consideration should therefore be given as to whether this is acceptable or whether data on these patients should be requested to amend the statement to reflect the current experience.

Regarding data in blinatumomab-experienced patients, the uncertainties were acknowledged, however, the available data could also be considered reassuring since patients pre-exposed to blinatumomab could still respond to tisagenlecleucel. Further, although efficacy appears to be lower in patients pre-exposed to blinatumomab, which may be driven by a somewhat lower response rate (DoR is the same), this might be due to differences in disease characteristics but could also be a chance finding given the very low sample size.

Therefore, the Member State proposes to expand the statement on prior treatment with anti-CD19-directed therapy in section 4.4 of the current SmPC and indicate that *While activity of tisanglecleucel has been observed, data are currently too limited to make an adequate assessment of the benefit-risk profile in these patients*.

6. Overall conclusion and recommendation

In accordance with Article 46 of Regulation (EC) No 1901/2006, the MAH has submitted the final study results from the complete data set of study B2001X. The study is a phase IIIb open-label, multicentre, single-arm study designed to further evaluate the safety and efficacy of tisagenlecleucel in paediatric and young adult patients with r/r B-cell ALL after the closure of enrolment to the pivotal study B2202. 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. In addition, the final results from the complete data set of study B2205J have provided supportive evidence for the efficacy of tisagenlecleucel in r/r B-cell ALL patients.

The efficacy results from the final analysis of study B2001X are considered to support the results from the two clinical studies B2202 and B2205J, underlying the approved indication of Kymriah in r/r ALL patients.

Overall, it can be concluded that the pattern of AEs reported in study B2001X is comparable to AEs reported in children with ALL in earlier studies. The data from the adolescent group in the current study is however too small for assessing the safety profile adequately. The MAH does not propose any updates of the safety or efficacy parts of the product information based on data from the current study. However, paediatric patients are now included in several studies (i.e. B2001X, B2202, and B2205J), while the product information refers to safety data from the pivotal study B2202 only and efficacy data from the two clinical studies B2202 and B2205J. The MAH should therefore submit a Type-II variation to reflect the pooled safety data in paediatric patients with r/r ALL from the three clinical studies B2001X, B2202, and B2205J in the SmPC section 4.4 and 4.8.

The data provided according to age subgroups and for the overall population on efficacy in paediatric and young adult patients with r/r ALL has been provided. However, the following revisions to sections 4.2 and 4.4 of the SmPC regarding efficacy should be implemented:

SmPC section 4.2 "*Paediatric population: B-cell ALL: No formal studies have been performed in paediatric patients below the age of three years*".

Should be modified to:

SmPC section 4.2 "*Paediatric population: B-cell ALL "'There is limited experience with Kymriah in paediatric patients below the age of 3 years*".

SmPC section 4.4 "*There is limited experience with Kymriah in patients exposed to prior CD19-directed therapy*"

should be expanded to:

SmPC section 4.4 "*There is limited experience with Kymriah in patients exposed to prior CD19-directed therapy. While activity of tisanglecleucel has been observed, data are currently too limited to make an adequate assessment of the benefit-risk profile in these patients"*

Both of these statements will need to be reconsidered as information in the paediatric population becomes available when the required PAMs to the MA concerning r/r ALL patients have been completed.

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:**

☐ **Not fulfilled:**

The procedure is concluded. However, the MAH should submit an application for a variation to update section 4.4. and 4.8 of the SmPC with the pooled safety data in paediatric and young adult patients with r/r B-cell ALL from the three clinical studies B2001X, B2202, and B2205J. At this time, the requested changes to the SmPC sections 4.2 and 4.4 regarding current experience with Kymriah in patients below the age of 3 years and those previously exposed to blinatomumab should be made.