28 June 2018
EMA/485563/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kymriah

International non-proprietary name: tisagenlecleucel

Procedure No. EMEA/H/C/004090/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Administrative information

Name of the medicinal product:	Kymriah
Applicant:	Novartis Europharm Limited Vista Building Elm Park, Merrion Road Dublin 4 Ireland
Active substance:	tisagenlecleucel
International Non-proprietary Name/Common Name:	tisagenlecleucel
Pharmaco-therapeutic group (ATC Code):	other antineoplastic agents (Not yet assigned)
Therapeutic indications:	Indicated for the treatment of: • Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (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.
Pharmaceutical form:	dispersion for infusion
Strength:	$1.2 \times 10^6 - 6 \times 10^8$ cells
Route of administration:	intravenous use
Packaging:	bag (ethylene vinyl acetate)
Package size:	1-3 bags

Table of contents

List of abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ADR	Adverse drug reaction
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under curve
AUC0-28d	AUC from time zero to Day 28, in peripheral blood (% or copies/µg DNA x days)
AUC0-84d	AUC from time zero to Day 84, in peripheral blood (% or copies/µg DNA x days)
BOR	Best overall response
BSA	Bovine serum albumin
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CF	Cell factory
CHMP	Committee for Medicinal Products for human Use
CHOP	Children's Hospital of Philadelphia
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
Cmax	Maximum (peak) expansion observed in peripheral blood drug concentration after administration of tisagenlecleucel (% or copies/µg genomic DNA)
CNS	Central nervous system
CNS3	Central nervous system involvement
CPP	Critical process parameter
CPV	Continuous process verification
CQA	Critical quality attribute
CR	Complete remission
Cri	Complete remission with incomplete blood count recovery
CRS	Cytokine release syndrome
CSR	Clinical study report
DLBCL	Diffuse large B cell lymphoma
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DOR	Duration of remission
EFS	Event-free survival
EMA	European Medicines Agency
EQ VAS	EuroQol visual analogue scale
EU	European Union
FAS	Full analysis set
FAST	Flow through antibody-based selection of T cells
FBS	Foetal bovine serum
FDA	Food and Drug Administration
FH IZI	Fraunhofer Institut für Zelltherapie und Immunologie
GVHD	Graft-versus-host-disease
HD	Healthy donor
HEK	Human embryonic kidney
HLH	Hemophagocytic lymphohistiocytosis
HRQoL	Health related quality of life
HSA (hABs)	Human serum albumin
HSCT	Hematopoietic stem cell transplantation
ICU	Intensive care unit
IFNγ	Interferon-gamma

IL6	Interleukine-6
IPM	In-process monitoring
IRC	Independent review committee
KPP	Key process parameter
LD	Lymphodepleting/lymphodepletion
LOD	Limit of detection
LOQ	Limit of qualification
MAS	Macrophage activation syndrome
mCAR19	Mouse CAR 19
MCB	Master cell bank
MHC	Major histocompatibility complex
MOI	Multiplicity of infection
MP	Novartis Morris Plains facility
MRD	Minimal residual disease
NE	Non-estimable
NHL	Non-Hodgkin's lymphoma
nKPP	Non-key process parameter
NOR	Normal operating range
NR	No response
OOS	Out of specification
ORR	Overall response rate
OS	Overall survival
OXB	Oxford BioMedica
pALL	Paediatric acute lymphoblastic leukaemia
PAR	Proven acceptable range
PCR	Polymerase chain reaction
PD	Progressive disease
PedsQL	Paediatric quality of life inventory
Penn	University of Pennsylvania
PET	Positron emission tomography
PFS	Progression-free survival
PIP	Paediatric investigation plan
PK	Pharmacokinetics
PR	Partial response
PRIME	Priority Medicines
PT	Preferred term
QoL	Quality of life
qPCR	Quantitative polymerase chain reaction
R-CHOP	Rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone
RCL	Replication-competent lentivirus
R-DHAP	Rituximab-dexamethasone, high dose cytarabine, and cisplatin
R-GDP	Rituximab-gemcitabine, dexamethasone, cisplatin
R-ICE	Rituximab-ifosfamide, carboplatin, etoposide
r/r	Relapsed or refractory
RFS	Relapsed-free survival
SAE	Serious adverse event
SCE	Summary of clinical efficacy
SCP	Summary of clinical pharmacology
SCS	Summary of clinical safety
SCT	Stem cell transplantation
SD	Stable disease
SIN	Self-inactivating
SpKi	Specific killing
T1/2	Half-life
Tlast	Time of last measured concentration
TLS	Tumour lysis syndrome

Tmax	The time to reach the maximum (peak) expansion observed in peripheral blood drug concentration after administration of tisagenlecleucel
TTR	Time-to-response
UCL	Upper control limit
ULN	Upper limit of normal
US	United-States
VLP	Virus-like particles
WBC	White blood cells
WCB	Working cell bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Limited submitted on 2 November 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Kymriah, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

Kymriah was designated as an orphan medicinal product EU/3/14/1266 on 29 April 2014 in the following condition: Treatment of B-lymphoblastic leukaemia/lymphoma, and EU/3/16/1745 on 14 October 2016 in the following condition: Treatment of diffuse large B-cell lymphoma.

Kymriah was granted eligibility to PRIME on 23 June 2016 in the following indication: Treatment of paediatric patients with relapsed or refractory B cell acute lymphoblastic leukaemia.

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

- Despite significant advances in treatment, approximately 15% to 20% of patients with ALL will suffer relapsed disease, the most common cause of treatment failure. Available treatments in paediatric patients with relapsed/refractory ALL after at least 2 prior therapeutic regimens show overall remission rate in 20% of patients. The unmet medical need in relapsed or refractory (r/r) paediatric ALL patients was agreed.
- The applicant has presented evidence from Study CCTL019B2202 showing initial high remission rates (82%) in paediatric r/r B-cell ALL patients at 28 Day assessment, accompanied with MRD negativity, with individual data from several patients showing duration of the responses over 4 months.
- Although preliminary, these results are further supported by a similar study conducted in the US and compare favourably with historical controls. In conclusion, the evidence presented support the product's potential to significantly address the unmet medical need in paediatric patients with relapsed or refractory ALL.
- Although the product is at an advanced stage of development, it is considered that there are benefits of supporting the development in preparation for an accelerated assessment (e.g. on long-term follow-up, manufacturing aspects).

The applicant applied for the following indication:

Kymriah is indicated for the treatment of:

- Paediatric and young adult patients aged 3 to 25 years with relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL).
- Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are ineligible for autologous stem cell transplant.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Kymriah as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:

ema.europa.eu/Find medicine/Human medicines/European public assessment reports

The legal basis for this application refers to:

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

The application submission is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0270/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0270/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products for the acute lymphoblastic leukaemia indication.

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

New active Substance status

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

PRIME support

Upon granting of eligibility to PRIME, the Rapporteur was appointed by the CHMP.

A kick-off meeting was subsequently organised with EMA, Rapporteur, assessors team and experts from relevant scientific committees. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures: comparability between manufacturing sites and processes, risk minimisation plan, including plans for registry to collect long term safety data, regulatory strategy and paediatric investigation plan.

Scientific advice and Protocol assistance

The applicant received Scientific Advice/Protocol Assistance from the CHMP on 25 April 2014 (EMEA/H/SA/2738/1/2014/ADT/II and EMEA/H/SA/2738/2/2014/PED/ADT/II), 28 April 2016 (EMEA/H/SAH/061/1/2016/ADT/II and EMEA/H/SA/2738/4/2016/PA/ADT/III), 20 July 2017 (EMEA/H/SA/2738/5/2017/PA/ADT/PR/I) and 14 September 2017 (EMEA/H/SA/2738/6/2017/PA/ADT/PR/II). The Scientific Advice/Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

CAT Rapporteur: Rune Kjeken CAT Co-Rapporteur: Christiane Niederlaender

CHMP Coordinator (Rapporteur): Bjorg Bolstad CHMP Coordinator (Co-Rapporteur): Greg Markey

The application was received by the EMA on	2 November 2017
Accelerated Assessment procedure was agreed-upon by CAT and CHMP on	31 October 2017 and 9 November 2017
The procedure started on	23 November 2017
The CAT agreed to consult the national competent authorities on the environmental risk assessment of the GMO as the ATMP is a gene therapy medicinal product. The consultation procedure started on	29 November 2017
The Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	15 February 2018
The Co-Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	13 February 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	26 February 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 March 2018
The CAT agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	16 March 2018
The applicant submitted the responses to the CAT consolidated List of Questions on	24 April 2018
The following GMP inspection was requested by the CHMP and its outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
− A GMP inspection at Novartis Pharmaceuticals Corporation, 220 E	19 March 2018

Hanover Avenue, Morris Plains, New Jersey (NJ) 07950, United States (USA), responsible for manufacture of the active substance and finished product, between 5-8 March 2018. The outcome of the inspection carried out was issued on	
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CAT and CHMP members on	11 May 2018
The consultation procedure related to the evaluation of the environmental risk assessment of the GMO closed on	16 May 2018
The CAT agreed on a list of outstanding issues in writing a to be sent to the applicant on	29 May 2018
The Procedure reverted to a standard timetable as agreed-upon by CHMP on:	31 May 2018
The applicant submitted the responses to the CAT List of Outstanding Issues on	7 June 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CAT and CHMP members on	12 June 2018
A SAG was convened to address questions raised by the CAT and CHMP on The CAT and CHMP considered the views of the SAG as presented in the minutes of this meeting	18 June 2018
The outstanding issues were addressed by the applicant during an oral explanation before the CAT during the meeting on	20 June 2018
The CAT, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Kymriah on	22 June 2018
The CAT adopted a report on the similarity of Kymriah with Xaluprine, Blincyto, Iclusig and Besponsa (Appendix 1) on	22 June 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Kymriah on	28 June 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Acute lymphoblastic leukaemia (ALL)

Treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.

Diffuse large B cell lymphoma (DLBCL)

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

2.1.2. Epidemiology and risk factors, screening tools/prevention

Acute lymphoblastic leukaemia (ALL)

The majority of ALL malignancies are of B-cell origin, and although ALL can occur at any age, it has a bimodal incidence. It is more commonly seen in children with approximately 60% of the cases occurring in patients aged younger than 20 years, with a peak incidence between 2 to 5 years and with the incidence rising again after the age of 60 years. ALL is a rare disease. The incidence rate of paediatric ALL is 3.5/100000 in the United States (US) and 2.9/100000 in the European Union (EU). About 3000 children in the US and 5000 children in the EU are diagnosed with ALL. Most cases of ALL occur due to an unknown reason. There are a number of known genetic risk factors including Down syndrome, Bloom syndrome, Li-Faumeni syndrome, Fanconi anaemia and constitutional mismatch repair deficiency. Environment risk factors may include radiation exposure and prior chemotherapy.

Diffuse large B cell lymphoma (DLBCL)

DLBCL is the most common type of NHL, accounting for 30–40% of all cases. DLBCL accounts for approximately 31% of all NHLs in Western countries and 37% of B-cell tumours worldwide. The median age at presentation is 70 years old; however, it can occur at any age, with a slightly higher incidence in men. The incidence rate of DLBCL was 3.44/100000 in the European Union (EU) in 2014 [1]. The probability of having DLBCL increases with age, from 0.13% and 0.09% before the age of 29 to 1.77% and 1.4% after the age of 70 in men and women, respectively [2]. For the vast majority of patients, the aetiology of DLBCL is unknown. Factors thought to potentially confer increased risk include immunosuppression (including AIDS, and iatrogenic aetiologies in the setting of transplantation or autoimmune diseases), ultraviolet radiation, pesticides, hair dyes, and diet. A subset of diffuse large B cell lymphoma, including immunoblastic and primary CNS disease is highly associated with the EBV virus, although unlike certain indolent histologies, the concept of antigen-driven lymphomagenesis is less developed in DLBCL.

B-cell malignancies represent a heterogeneous group of lympho-hematopoietic malignancies including acute lymphoblastic leukaemia, Hodgkin's lymphoma and most non-Hodgkin's lymphomas (NHL). NHLs

are classified according to the current WHO classification into immature lymphoid neoplasms, mature B-cell neoplasms, T-cell and NK-cell neoplasms, and post-transplant lymphoproliferative disorders [3]. Mature B-cell lymphomas are further clinically classified into indolent lymphomas and aggressive lymphomas.

2.1.3. Biologic features Aetiology and pathogenesis

Acute lymphoblastic leukaemia

Most cases occur due to an unknown reason. Genetic risk factors may include Down syndrome. Environment risk factors may include significant radiation exposure or prior chemotherapy. The underlying mechanism involves multiple genetic mutations that results in rapid cell division. The excessive immature lymphocytes in the bone marrow interfere with the production of new red blood cells, white blood cells and platelets.

Diffuse large B cell lymphoma (DLBCL)

DLBCL is a heterogeneous disease with several subtypes identified, each subtype having different clinical presentations and prognosis. These subtypes can be differentiated based on the location of tumour, cell of origin and molecular profiling (e.g. germinal B-cell center (GBC)-like, activated B-cell (ABC)-like, primary mediastinal large B-cell lymphoma) [4]; [5]. However, the majority of DLBCL cases do not conform to any of these subtypes, and are classified as DLBCL, not otherwise specified (DLBCL, NOS). The WHO classification system describes many subtypes based on location of the tumour, the presence of other cells (such as T cells) within the tumour and whether the patient has other illnesses related to DLBCL.

The causes of diffuse large B-cell lymphoma are not well understood. For the vast majority of patients, the aetiology of DLBCL is unknown, although, immunosuppression (including iatrogenic aetiologies) and the exposure to significant radiation or certain chemicals (pesticides, hair dyes) have been associated with a potentially increased risk. Usually DLBCL arises from normal mature B-cells at different stages of differentiation, although it can also represent a malignant transformation of other types of lymphoma or leukaemia. Multiple molecular pathways of B-cell proliferation and differentiation may result in the activation of oncogenes (i.e. BCL2, BCL6, and MYC) and the inactivation of tumour suppressor genes (i.e. p53 and INK4), as well as other important transcription factors such as OCT-1 and OCT-2. Cell surface protein CD19 is a member of the immunoglobulin superfamily and a component of a cell surface signal transduction complex that regulates signal transduction through the B - cell receptor (Ledbetter et al 1988, Stamenkovic and Seed 1988, Fearon and Carroll 2000). CD19 is a promising target antigen for B-cell malignancies, as the protein is expressed by B-cells and their ([6]; [7]; [8])precursors, but not pluripotent hematopoietic stem cells [9], and it is expressed in most B-cell neoplasms [10]. It is not present on most normal tissues, other than normal B-cells [11], which makes CD19 a relatively safe target.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Acute lymphoblastic leukaemia

Symptoms may include feeling tired, pale skin colour, fever, easy bleeding or bruising, enlarged lymph nodes and bone pain.

Diagnosis is typically based on blood tests and bone marrow examination. Some clinicians continue to use the French-American-British (FAB) system to classify ALL by the histological appearance of tumour

cells. In 2008, WHO introduced a system of classification based on cytogenetic and molecular diagnostic tests to help determine prognosis and the most appropriate treatment for each specific case of ALL.

If untreated, ALL progresses rapidly and is typically fatal within weeks or months. With current management strategies that include risk-directed therapies, survival for children has increased from under 10% in the 1960s to over 80% in the present day. Survival rates remain lower for babies (about 50%) and adults (about 35%).

Diffuse large B cell lymphoma (DLBCL)

The clinical manifestations of DLBCL are variable and depend on the site of disease involvement. Rapidly growing tumours may present as masses, causing symptoms when they infiltrate tissues or organs. Pain may occur due to rapid or invasive tumour growth, and is often the first sign of this illness, sometimes associated with "B-symptoms" of fever, drenching night sweats, and weight loss. Generalized pruritus may also be present. The diagnosis of DLBCL should be carried out in a reference haematopathology laboratory with expertise in morphological interpretation and the facilities to carry out the full range of phenotypic and molecular investigations. A surgical excision biopsy remains the optimal method of diagnosis. A morphological diagnosis of DLBCL should be confirmed in all cases by immunophenotypic investigations, either immunohistochemistry (IHC) or flow cytometry or a combination of both techniques.

DLBCL shows an aggressive behaviour and in untreated patients the median survival is less than one year. About half of the patients respond to current treatment with an overall 5-year survival of about 60%.

2.1.5. Management

Acute lymphoblastic leukaemia

For r/r ALL treatment options include high-dose chemotherapy with subsequent allogeneic stem cell transplantation (SCT), standard chemo-immunotherapy, targeted treatment with small molecule pathway inhibitors, or supportive care with non-curative palliative goals. Allogeneic SCT is the only potentially curative option for r/r pALL, but outcomes are suboptimal. Among r/r pALL patients who received allogeneic SCT in third or later remission, received allogeneic SCT with active disease or received allogeneic SCT after relapse from previous allogeneic SCT, the 1-year overall survival (OS) rates are in 25 to 55% range and 5-year OS rates are generally in 20 to 45% range.

For Ph+ patients, dasatinib (Sprycel) was approved in 2006 for the treatment of adult patients with resistance or intolerance to prior therapy. Ponatinib (Iclusig) was approved in 2013 for the treatment of adult patients with Ph+ ALL who are resistant to/ intolerant of dasatinib. Blincyto (blinatumomab), a bispecific anti-CD3/CD19 monoclonal antibody, has been approved for the treatment of adults with Ph- relapsed or refractory B-precursor ALL.

Despite the current treatment modalities, maintaining a remission in relapsed patients is difficult, the patients are being hospitalized for a long periods of time with a poor QoL, and the prognosis of patients with r/r disease still remains poor.

Diffuse large B cell lymphoma (DLBCL)

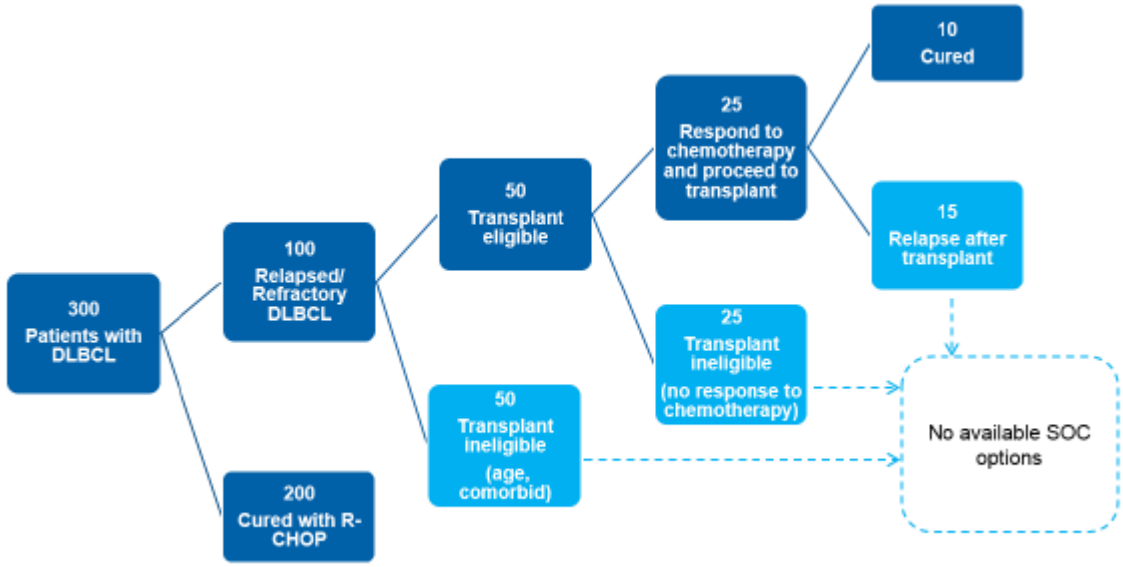
The front-line standard of care for patients with DLBCL includes a combination of CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone) with rituximab (R -CHOP). The addition of rituximab, which is a monoclonal antibody directed against CD20, to first-line chemotherapy has

improved the outcome of patients with DLBCL resulting in a survival rate of about 75% at 6 years [12]. However, 30-50% of the patients do not have long-term benefit from first-line therapy (approximately 30% relapse and 20% have refractory disease) [13].

For patients who are deemed eligible for high dose chemotherapy and autologous stem cell transplant (HD-ASCT) based on adequate performance status (defined by age and absence of major organ dysfunctions), clinical treatment guidelines for r/r DLBCL patients recommend salvage therapy with platinum-based chemotherapy regimens (i.e. R-DHAP, R-ICE, R-GDP) followed by HD-ASCT. However, about half of patients r/r to first-line therapy are not eligible for ASCT because of advanced age and/or comorbidities. Furthermore, among patients suitable for HD-ASCT, only about half will have a response to salvage therapy that is sufficient to be able to proceed to HD-ASCT [14], [15]. In addition, of those proceeding to HD-ASCT, 60% of patients will relapse after transplant. Clinical studies, palliative chemotherapy, and in rare cases a second HD-ASCT or allogeneic stem cell transplant (AlloSCT) are some of the options available for these patients [16].

Options for patients with DLBCL are presented in the following diagram:

Figure 1 Role of ASCT in r/r DLBCL



DLBCL=diffuse large B-cell lymphoma; SOC=standard of care

Overall, prognosis in patients who are refractory or who have relapsed is poor. There is, therefore, an unmet medical need.

About the product

Tisagenlecleucel was applied for the treatment of:

- Paediatric and young adult patients aged 3 to 25 years with relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL).
- Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are ineligible for autologous stem cell transplant.

In response to the comments made by CAT on the List of Questions (16/03/2018), the applicant submitted in its responses of 25/04/2018 a revised SmPC with the broader indication with regard the

paediatric population (see discussion on clinical efficacy).Following the assessment the indication was agreed as for the treatment of:

- Paediatric and young adult patients up to 25 years of age with B cell acute lymphoblastic leukaemia (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.

Tisagenlecleucel is an autologous, immunocellular cancer therapy which involves reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19 expressing cells. The CAR is comprised of a murine single chain antibody fragment which recognises CD19 and is fused to intracellular signalling domains from 4 1BB (CD137) and CD3 zeta. The CD3 zeta component is critical for initiating T cell activation and antitumour activity, while 4 1BB enhances the expansion and persistence of tisagenlecleucel. Upon binding to CD19 expressing cells, the CAR transmits a signal promoting T cell expansion and persistence of tisagenlecleucel (SmPC, section 5.1).

The recommended dosage in paediatric and young adult B cell ALL patients are as follows:

- For patients 50 kg and below: 0.2 to 5.0 x 10^6 CAR positive viable T cells/kg body weight.
- For patients above 50 kg: 0.1 to 2.5 x 10^8 CAR positive viable T cells (non weight based).

The recommended dosage in adult DLBCL patients is 0.6 to 6.0 x 10^8 CAR positive viable T cells (non weight based) (SmPC, section 4.2).

Type of Application and aspects on development

The CHMP and CAT agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the following:

For paediatric and young adult patients aged 3 to 25 years of age with relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL), it can be agreed that the apparent improved overall survival constitutes a major interest from the point of view of public health in a disease with a poor prognosis with current therapies.

In addition, in adult patients with relapsed or refractory diffuse DLBCL who are ineligible for autologous stem cell transplant, the apparent improved overall response rate would constitute a major interest from the point of view of public health in a disease with an extremely poor prognosis with current therapies.

For both indications the use of targeted cell therapy is considered to be a major therapeutic innovation.

However, during assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, since major objections had been identified, which precluded an accelerated assessment.

2.2. Quality aspects

2.2.1. Introduction

Kymriah (INN: tisagenlecleucel, product code CTL019) is a gene therapy product which contains autologous genetically modified T cells. The product is manufactured from the patient's own T cells, which are transduced with a lentiviral vector that encodes a chimeric antigen receptor (CAR) directed against human CD19. This allows these T cells to specifically target and destroy CD19-positive B cells in an antigen dependent, but major histocompatibility complex (MHC) independent manner.

The finished product is presented as dispersion for infusion. The quantitative information regarding CAR-positive viable T cells/mL and total cells in the product is presented in the labelling for each patient-specific batch. The concentration is dependent on indication and patient body weight.

For treatment of B-cell acute lymphoblastic leukaemia (ALL):

Body weight ≤50 kg: 1-3 bags contain a total of 0.2 to 5 x 10^6 CAR-positive viable T cells/kg body weight.

Body weight >50 kg: 1-3 bags contain a total of 0.1 to 2.5 x 10^8 CAR-positive viable T cells.

For treatment of diffuse large B-cell lymphoma (DLBCL):

1-3 bags contain a total of 0.6 to 6 x 10^8 CAR-positive viable T cells.

Other ingredients are: glucose, sodium chloride, human albumin solution, dextran 40 for injection, dimethylsulfoxide (DMSO), sodium gluconate, sodium acetate, potassium chloride, magnesium chloride, sodium-N-acetyltryptophanate, sodium caprylate, aluminium and water for injections.

The finished product is supplied in ethylene vinyl acetate (EVA) infusion bag(s) with polyvinyl chloride (PVC) tubing and a luer spike interconnector closed by a luer-lock cap containing either 10–30 mL (50 mL bags) or 30–50 mL (250 mL bags) cell dispersion.

2.2.2. Active Substance

The section on the active substance is separated into two parts; part 1 for the gene therapy viral vector and part 2 for the transduced cells.

General Information (viral vector)

The CTL019 (murine) HIV-1 vector is a replication-defective, recombinant third-generation self-inactivating (SIN) lentiviral vector derived from the HIV-1 lentiviral genome. It encodes a CAR against human CD19 expressed under the control of the human elongation factor 1α (EF-1α) promoter, see Figure 2.

The CAR transgene is comprised of an extracellular murine single chain antibody fragment (anti-CD19scFv) linked via a human CD8 hinge and transmembrane region to an intracellular signalling chain consisting of human 4-1BB and CD3ζ.

The majority (approximately 85%) of the native HIV-1 sequence has been removed to produce a replication-defective lentiviral vector system. The vector system is comprised of four plasmid constructs;

- pRKHVmuEC19: the transfer plasmid, containing the CTL019 vector genome,
- pRKHSYNGP: the HIV-1 Gag/Pol packaging plasmid
- pRKHG: the envelope packaging plasmid
- pRKHREV: the Rev packaging plasmid

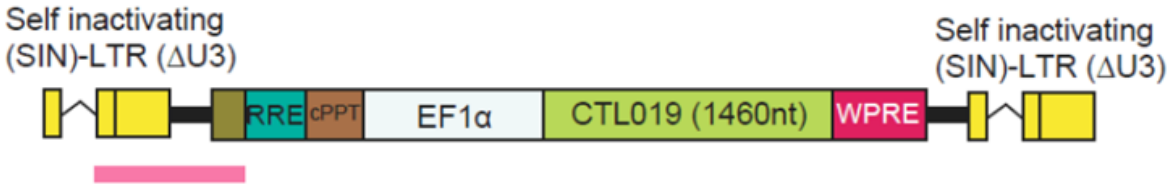


Figure 2 Genetic structure of the integrated vector

Biological activity of the vector is controlled for batch release by measuring the transduction efficiency corresponding to a measurement of the infectivity of the vector. The result is expressed in transducing units (TU) per mL. In addition, transgene expression is characterized for each vector batch.

Manufacture, process controls and characterisation (viral vector)

The CTL019 vector is manufactured under contract by Oxford BioMedica, Oxford, UK (OXB) using an upstream process (consisting of thawing of the working cell bank (WCB), expansion of the production cell bank, plasmid transfection, induction and harvest), followed by a downstream purification process (consisting of filtration, chromatography and nuclease treatment steps) to yield the 'vector substance' (purified bulk vector). The vector substance undergoes sterile filtration, concentration and filling to obtain the vector product.

Overall, a sufficient level of detail for the manufacturing process has been provided, including cell density, culture conditions, media description and in-process controls (IPCs).

The purification process is also described satisfactorily. Process intermediates are identified and hold times and conditions are given. All buffer preparations and storage are described.

Data presented, including process characterisation, validation and batch release data, demonstrate consistency in production of the vector substance and vector product and as such, the presented approach is considered acceptable.

Control of materials (viral vector)

The raw materials are in general sufficiently documented with certificates of analysis and specifications with acceptance criteria provided in the dossier. Raw materials of biological origin used during manufacture of the viral vector are sufficiently documented with certificates of suitability. Porcine trypsin and the recombinant alternative are sufficiently documented regarding viral safety and are in accordance with TSE guidelines.

Generation of the starting plasmids is fully described, including full listing of all genetic elements. Manufacture of the plasmid is based on a bacterial cell banking system and plasmids are extensively release tested. The origin and preparation of the cell banks has been set out in sufficient detail. The Applicant includes a discussion on the tumorigenic risk of the cell line. The assessment of low tumorigenicity risk of the vector cell substrate is acceptable.

The Applicant has presented sufficient information on the qualification of the current Master Cell Bank (MCB) and Working Cell Bank (WCB), including a comprehensive adventitious agent testing programme in accordance with ICH Q5A (R1), covering relevant human, porcine and bovine viruses. The Applicant is in the process of converting the current WCB 1390.01 into a new MCB as stocks are running low. A suitable testing profile for the additional characterisation of this cell bank has been provided.

Process validation (viral vector)

The Applicant has presented a brief overview of the risk assessment approach and process characterisation studies that were undertaken. The results are presented in the form of overview tables summarising the characterisation range, Normal Operating Ranges (NORs), Proven Acceptable Ranges (PARs), criticality designation, as well as a brief justification. In general, the process characterisation is considered acceptable. The Applicant has demonstrated that the NORs largely operate within clinically proven limits and the PARs are generally justified.

The Applicant has set out the process validation for both vector substance manufacturing sites and the two vector filling sites. Different lots of raw materials were used for the different campaigns.

Validation data for the vector substance lots consisted of KPP and CPP data, incubation, holding and process times and IPC, In-Process Monitoring (IPM) and some characterisation results. Data show that the process is well controlled and can be consistently carried out at both sites.

Aseptic process validation is performed at the filling sites.

Vector substance shipping qualification is sufficiently documented.

Manufacturing process development (viral vector)

The changes introduced to the plasmid by OXB are all designed to increase the safety of the vector and are as such endorsed and generally considered conservative. A comparability exercise on healthy donor T cells was conducted versus an earlier version of the plasmid and an overview has been provided. Importantly, the OXB vector has undergone clinical qualification. Sufficient comparability is shown.

Two comparability exercises were conducted, one for the introduction of the second vector substance manufacturing site and one for the introduction of the second vector product manufacturing site.

For the manufacture of the vector product a complete side-by-side evaluation of any difference in the facility and equipment is presented together with and evaluation of the potential impact. Differences observed are minor and considered acceptable.

Characterisation (viral vector)

Studies to confirm the structure and characteristics are brief. The most important features such as the viral infectious titre and the integrity of the RNA insert as well as control of impurities have however been sufficiently investigated.

The vector proteome analysis and identification were performed.

The particle number was determined.

Biological activity has been satisfactorily analysed, including analysis of CAR expressing cells.

Investigation into the multiplicity of infection (MOI) and transduction efficiency have been performed.

The investigation of impurities focuses on process related impurities. For product related impurities, replication competent lentivirus (RCL) has been investigated, with satisfactory information presented.

Process related impurities are identified and are generally considered adequately characterised.

Specification, analytical procedures, reference standards, batch analysis, and container closure (viral vector)

The specifications for the vector substance and vector product include identity, quantity, biological activity, purity and impurities, bacterial endotoxins, bioburden, sterility and adventitious agents' tests.

The presented panel of specifications for the vector substance and vector product is in general considered acceptable. RCL testing is performed in line with Ph. Eur. 5.14. The validation of the applied methods are adequately performed and documented in the dossier.

Analytical procedures (viral vector)

The analytical methods have been described and validation summaries and validation reports were presented for all analytical assays.

Reference standard (viral vector)

The Applicant has included a list of all reference materials including commercially available standards and positive controls that are included in assay kits. This list includes the origin of the reference preparation and acceptance criteria.

Details regarding reference standard specification and qualification were provided for the viral vector reference standard. This includes a description of the manufacture of the standard as well as characterisation in respect of the assays to be used. A stability testing programme is also provided and is acceptable.

Batch analysis (viral vector)

Batch analytical data for all vector substance and product batches are provided. This includes vector substance and vector product batches which were used in clinical trials, stability studies, process validation, comparability studies, and for specification setting. Representative certificates of analysis are provided.

Container closure (viral vector)

The primary packaging for the vector product consists of clear type I glass vials with a grey fluorocarbon layer coated chlorinated bromobutyl rubber stopper. The rubber stopper is sealed with an aluminium flip tear-up seal.

The Applicant has provided a description of the container closure systems for the vector substance and vector product. Both comply with Ph. Eur. requirements where applicable. Specifications and acceptance criteria are provided.

Stability (viral vector)

The Applicant has requested a shelf-life for the vector substance of 12 months at -60°C to -90°C and has provided primary and supportive real-time stability data to support this. The proposed shelf-life for the vector substance is acceptable.

A shelf-life of 36 months at -60°C to -90°C is requested for the vector product. Primary real-time and supportive stability data were provided to support the proposed shelf life. Based on the data provided, the proposed shelf-life for the vector product is acceptable.

Active substance part 2 (transduced cells CTL019)

General information (transduced cells CTL019)

The CAR-19 protein is comprised of a murine single chain antibody fragment (anti-CD19scFv), a CD8 hinge and transmembrane region, a 4-1BB (CD137) and a CD3ζ signalling domain (See **Figure 3**).

CTL019 targets cells expressing CD19. CD19 is expressed on B cells from early development until differentiation into plasma cells but is not present on pluripotent blood stem cells.

The generation of a robust and sustained anti-tumour immune response requires triggering of cytokine production, cytotoxicity, and T cell proliferation. Chimeric receptors bearing CD3ζ (CD3-zeta) signalling modules are sufficient to trigger T cell activation and proliferation but are not sufficient to drive robust *in vivo* expansion and persistence of chimeric antigen receptor T cells (CAR T cells). Addition of the intracellular transduction domain of CD137 (4-1BB), enhances T cell activation compared to lymphocytes expressing equivalent receptors lacking 4-1BB. In preclinical models, inclusion of the CD137 (4-1BB) signalling domain significantly increased antitumor activity at low effector: target ratios, and *in vivo* persistence of chimeric antigen receptors as compared with inclusion of the CD3ζ signalling domain alone.

CTL019, like other CAR T cells, can work through multiple mechanisms of action. In response to CD19 expressing cells, CTL019 can proliferate, secrete cytokines, efficiently kill cells expressing the CD19 antigen, and persist long term *in vivo*.

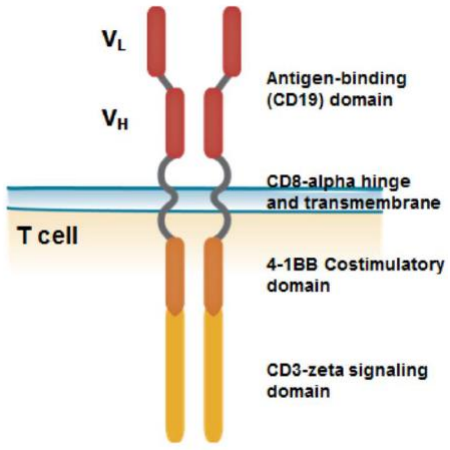


Figure 3 Structure of the CTL019 CAR

Manufacture, process controls and characterisation (transduced cells CTL019)

Description of the manufacturing process and process controls (transduced cells CTL019)

CTL019 will be manufactured according to current good manufacturing practices at the Novartis Pharmaceuticals Corporation, 220 East Hanover Avenue, Morris Plains (MP) facility in US and at the Fraunhofer Institut für Zelltherapie und Immunologie (FH IZI) in Perlickstraße 1, 04103 Leipzig, in Germany. Novartis Pharma GmbH in Roonstraße 21-25, DE-90429 Nürnberg in Germany is responsible for batch certification.

The manufacture of CTL019 starts with the acceptance and thawing of the leukapheresis material and ends with the cryopreservation of the CAR-positive T-cell containing product. Washed leukapheresis cells are enriched and are then transduced with the vector. After static incubation, the cells are eventually expanded in a bioreactor. At the end of the culture period the cells are washed and cryopreserved. The microbial control strategy has been adequately described.

The Applicant has explained the steps in sufficient detail and has provided CPPs and KPPs in a tabular format for each step. Flow diagrams setting out in process controls are provided. Compositions of cell culture media and solutions are provided and processing times are defined.

The batch definition and numbering system has been suitably explained.

Control of materials (transduced cells CTL019)

The control of the vector is described in detail in part 1 above.

Materials that are chemically defined and materials of animal, human or recombinant origin

The Applicant has given a general overview of the principles of material control for the manufacture of CTL019. Materials used for the leukapheresis material that are chemically defined and materials of biological origin as well as their specifications are listed and certificates of analysis provided. The components are either compendial or tested according to the Applicant's internal specifications. Product contact consumables and compositions of the cell culture media are also listed. A material qualification and control program is in place and standard operating procedures are used to assess both suppliers and materials. Suppliers are assessed for quality criteria including adherence to cGMP regulations. At a minimum, an identity test and a check for compliance of the vendor certificate of analysis are conducted on all components in accordance with Ph. Eur. 5.2.12 and ICH Q7.

Leukapheresis material

The collection and initial processing of the leukapheresis material is adequately described. Infectious disease testing of the donor will be performed as part of the patient leukapheresis eligibility process according to Annex IV of Directive 2002/98/EC and any local additional testing requirements for tissues and cell donors. The processing of cells for further manufacturing is performed in line with Directive 2004/23/EC.

A full list of apheresis sites used during clinical development in both the pALL and the DLBCL study has been provided. The process for selection approval and implementation as well as oversight of new apheresis sites has been described. Sites are required to be licensed under 2004/23/EC as well as

having JACIE accreditation and implemented ISBT-128 labelling standards. Implementation of a new apheresis site requires an assessment by the Applicant.

Batch analysis data from the collected batches for pALL and DLBCL are presented and demonstrate the variability of the starting material in terms of cellular composition.

A thorough characterisation of the key attributes of leukapheresis material has been undertaken and adequate specifications have been set.

Description of packaging and cryopreservation of the patient leukapheresis material and a brief overview of the stability studies has been provided. This consisted of a study to determine stability for storage before cryopreservation, as well as a real-time storage conditions study, i.e. after cryopreservation.

Process validation (CTL019)

The Applicant has provided an overview of the process validation approach. This included a summary of the process characterisation that formed the basis of the setting of process parameters, in addition to PARs and NORs. The Applicant has undertaken a process risk assessment to identify high-risk parameters followed by a process capability analysis of clinical batches manufactured so far to designate high-risk parameters as key or critical. Lastly, PARs and NORs were set based on previous manufacturing experience.

The Applicant produced several process validation batches covering both manufacturing sites and both patient and healthy donor material. Batches were deliberately chosen to display a variety of starting material compositions, in particular varying B-cell content. The approach taken for the starting material selection and the number of batches used are endorsed.

The Applicant has provided data on processing times for individual culturing steps, results for CPPs and IPCs, information on yield and Population Doubling Levels (cPDLs). Based on the data provided, the process appears overall consistent.

Aseptic process validation was conducted at both MP and FH IZI. Results were satisfactory. Adequate results from shipping validation studies have also been provided.

The Applicant has presented a continuous process verification (CPV) plan that outlines monitoring activities planned for the future. The explanation of the CPV approach has been provided and is acceptable.

Manufacturing process development (CTL019)

The Applicant has given an overview of the process development for CTL019, covering several process versions. The most significant changes are associated with the various options introduced for starting material processing and a transfer of the process from the initial manufacturing site to MP.

Overall, quality data indicate that the changes had no major impact on product composition and comparability. The Applicant has demonstrated the comparability of the product manufactured at MP and FH IZI sufficiently on the basis of in-process controls, release testing results and additional characterisation.

Characterisation (CTL019)

The Applicant has used a range of analytical methodologies to analyse the cell composition of the product, CAR expression and functionality.

The overall cell populations present in CTL019 are sufficiently characterised, and consist mainly of T cells with a minimum percentage of T cells being required. Occasionally some NK cells are detected but the eventual presence of NK cells in the finished product is considered sufficiently justified. All other cell populations are below the limit of detection. The proportion of CAR positive viable cells in the population is variable. An acceptable specification limit has been set. The quantitative information regarding CAR-positive viable T cells/mL and total cells in the product is presented in the batch-specific documentation accompanying Kymriah.

T-cell subsets were also adequately described, starting with the CD4:CD8 ratio, and including naïve T cells, central memory and memory effector cells. Immunosenescence was also investigated satisfactorily.

The Applicant has performed deep single cell phenotyping to obtain more in depth data on the proteome and activation status of the cells. Results complement the information obtained regarding activation status of the cells.

Overall, the Applicant has obtained a good picture of relevant characteristics of the finished product in terms of cellular composition and effector function.

On a molecular level, an integration site analysis has been performed. A verification that the constructs are of full length is provided.

The Applicant has generally discussed the relevant cell-based impurities sufficiently and has also included some discussion on the controls required where applicable. Overall, the rationale and control mechanisms are accepted.

Residual B cells are consistently below the level of detection by flow cytometry and the Applicant discussed the theoretical risk associated with CAR transduced B cells, which is considered low.

Generation of a RCL following infusion of the T cells transduced by the lentiviral vector remains a theoretical possibility, albeit with a low probability since multiple recombination events would be necessary to generate a RCL. For all CTL019 batches manufactured during clinical development, the release testing results for RCL were below the limit of quantification (LOQ) which confirms that no homologous recombination has occurred with VSV-G to generate VSV-G pseudotyped RCL.

A list of potential cell culture related impurities is given. The justification provided for the satisfactory removal of these is overall accepted.

Specification, analytical procedures, reference standards, batch analysis, and container closure (CTL019)

As the manufacture of CTL019 is a continuous process, the relevant data are discussed in the finished product section.

Stability (CTL019)

As the manufacture of CTL019 is a continuous process, the relevant data are discussed in the finished product section.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The concentration of CAR-positive viable T cells is dependent on indication and patient body weight. The cellular composition and the final cell number vary between individual patient batches. In addition to T cells, NK cells may be present. The quantitative information regarding CAR-positive viable T cells/mL and total cells in the product is presented in the batch-specific documentation accompanying Kymriah.

For treatment of B-cell acute lymphoblastic leukaemia (ALL):

Body weight ≤50 kg: 1-3 bags contain a total of 0.2 to 5.0 x 10^6 CAR-positive viable T cells/kg body weight.

Body weight >50 kg: 1-3 bags contain a total of 0.1 to 2.5 x 10^8 CAR-positive viable T cells.

For treatment of diffuse large B-cell lymphoma (DLBCL):

1-3 bags contain a total of 0.6 to 6 x 10^8 CAR-positive viable T cells.

Other ingredients are: glucose, sodium chloride, human albumin solution, dextran 40 for injection, dimethylsulfoxide (DMSO), sodium gluconate, sodium acetate, potassium chloride, magnesium chloride, sodium-N-acetyltryptophanate, sodium caprylate, aluminium and water for injections.

Compatibility of CTL019 with the excipients stock solutions has been established during clinical development and is supported by the stability studies.

The formulation development has been described.

Pharmaceutical development studies were conducted to evaluate robustness and suitability of the chosen formulation for CTL019. The results support the selection of the current formulation.

The inclusion of DMSO in the final formulation has been justified.

The Applicant has discussed safety aspects of the excipients in the excipient stock solutions for infusion in paediatric patients, and concluded that they are unlikely to present a safety concern with the exception of DMSO and dextran 40. The amounts of these excipients used in patients can however be accepted. A warning on the known possibility of an anaphylactic reaction to dextran 40 and of the possible adverse effects of DMSO has been included in the product information.

The finished product is supplied in EVA infusion bag(s) with PVC tubing and a luer spike interconnector closed by a luer-lock cap.

Following a risk assessment of the manufacturing process to identify the highest risk factors for extractables and leachables, a leachable study was performed on the bags. This study identified the selected bags as the most suitable. The level of leachables identified with these bags was satisfactorily justified as safe, and toxicologic assessments are provided.

The results of the container closure integrity study are acceptable.

Manufacture of the product and process controls

Please refer to the active substance section. All manufacturing steps until release of the product have been described in the active substance part of the dossier as part of the continuous manufacturing process.

Product specification, analytical procedures, batch analysis

The specifications for the finished product were based on the analysis of the batches that were infused. The panel of specifications include tests for appearance, identity, purity, impurities, quantity, biological activity and microbial safety.

The manufacturing process for CTL019 is a continuous process with no holding step; beginning with thawing of the leukapheresis starting material and ending with finished product formulation. The presented approach for the release testing is endorsed.

Potency is measured as to ensure appropriate CAR expression and cytokine secretion upon T cell activation.The proposed specifications are considered appropriate. However, the Applicant should re-evaluate the release tests and their acceptance criteria based on post approval data.

Analytical procedures

A description of the analytical procedures used for specification testing is provided. The analytical assays were in general validated satisfactorily. A number of the validations are in respect of assays that represent derogations from Ph. Eur. assays. These have been validated against Ph. Eur. requirements.

Batch analysis

Batch analytical data for all batches manufactures at MP and FH IZI were presented. All provided stability for released batches are within specification.

Reference standards

An overview of the use of reference standards in the manufacture and analysis of CTL019 has been provided.

No reference standard is routinely used for the control of CTL019. It is acknowledged that it would be unethical to retain a patient-specific batch of product for the purpose of standardization.

Stability of the product

Stability data, summaries, and conclusions are presented to support a shelf-life of 9 months for CTL019 stored in infusion bags at ≤ -120°C in vapour phase liquid nitrogen, and 30 minutes in-use shelf-life after thawing at room temperature 20-25°C.

Stability data has been provided covering the long term storage condition as well as the in-use shelf-life after thawing.

All provided stability data for released finished product batches are within specification.

Post approval change management protocol(s)

A post approval change management protocol (PACMP) has been provided in relation to the production cell bank for the viral vector. The PACMP is considered acceptable.

Adventitious agents

The Applicant has given a satisfactory overview of the adventitious agent control strategy together with an overview of all materials of biological origin. Control of all raw and starting materials has been demonstrated satisfactorily.

A number of materials of biological origin are used throughout the CTL019 manufacturing process. Due to the nature of the product, viral clearance studies are not considered feasible.

Adequate information on TSE has been presented and the risk of inadvertent transmission of TSE agents from the manufacturing process to patients is considered low.

A testing strategy for adventitious or endogenous viruses adopted throughout process manufacture is implemented. In summary, raw materials of biological origin for CTL019 vector manufacture (including cell banks) are sufficiently described.

Infectious disease testing of the donors will be performed as part of the patient leukapheresis eligibility process according to Annex IV of Dir. 2002/98/EC and any local additional testing requirements for tissues and cell donors.

GMO

CTL019 contains autologous genetically modified T cells. The product is manufactured from the patient's own T cells, which are transduced with a lentiviral vector that encodes a chimeric antigen receptor (CAR). Safety features of the virus are described above and an environmental risk assessment in accordance with Directive 2001/18/EC has been presented with respect to the risk of release of GMO into the environment. This assessment is discussed in more detail in the non-clinical part.

2.2.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

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

During the procedure a major objection was raised in relation to lack of appropriate documentation to demonstrate GMP compliance for the manufacturing/batch release sites. In response the Applicant provided satisfactory documentation for all three sites and consequently the major objection was resolved.

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

2.2.5. Recommendations for future quality development

In the context of the obligation of MAHs to take due account of technical and scientific progress, the CAT recommends several points for investigation including completing the characterisation and testing of the viral vector, the leukapheresis starting material and the finished product.

The CHMP endorses the CAT assessment regarding the recommendations for future quality development as described above.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical toxicology studies were not conducted in compliance with Good Laboratory Practice (GLP), because there was no independent Quality Assurance (QA) audit of integral study parts and raw data storage was not applied in compliance with GLP regulations. The absence of GLP compliance is acceptable since standard single or repeat-dose toxicity studies could not be performed due to lack of a relevant animal model.

2.3.2. Pharmacology

Primary pharmacodynamic studies

- ***In vitro***

Selection of eukaryotic promotor for tisagenlecleucel [17]

Experiments were performed to optimize tisagenlecleucel. Four eukaryotic promoters - elongation factor 1-alpha (EF-1α), cytomegalovirus (CMV), ubiquitin C (UbiC) and phosphoglycerokinase (PGK) - were evaluated for gene expression stability and level in CD4+ and CD8+ T cells. T cells were transduced with lentiviruses expressing green fluorescent protein (GFP) under control of each of the four promoters in the tisagenlecleucel self-inactivating virus (SIN) backbone at a low multiplicity of infection (MOI, 0.2) (i.e. the amount of functional viral particles per cell) so that only one gene copy was integrated in a cell. Flow cytometry was used to detect GFP expression.

In this study, EF-1α driven GFP expression was higher than for any other promoter in both CD4+ and CD8+ T cells, and was stable for the 17 day duration of the experiment. Based on these results, EF-1α was selected as the promoter for expression of the transgene in tisagenlecleucel.

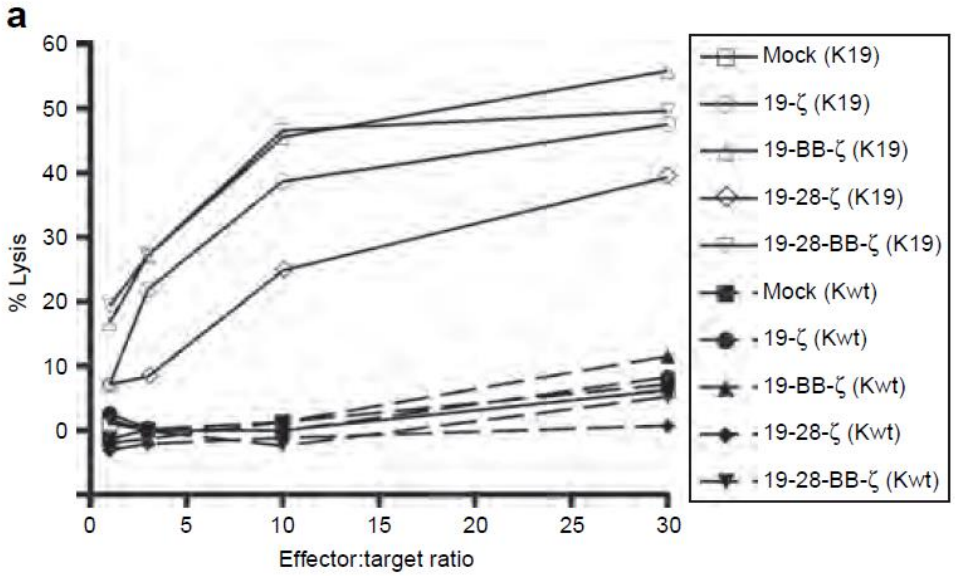
Selection of costimulatory domain for tisagenlecleucel [17]

Various αCD19 CARs were generated and tested for CD19-specific T cell function. The scFv (FMC63) recognizing CD19 was originally derived from a mouse hybridoma and has been characterized for its specificity to CD19 in several preclinical CAR T cell systems. In addition to tisagenlecleucel (αCD19-BB-ζ, which contains the 4-1BB costimulatory domain from CD137), other αCD19 CARs were evaluated in parallel including αCD19-ζ (no costimulatory domain), αCD19-28-ζ (contains the CD28 costimulatory domain) and αCD19-28-BB-ζ (contains both the CD28 and 4-1BB costimulatory domains) to characterize the influence of the costimulatory domain on T effector cell function. To evaluate the

cytolytic function of CAR+ T cells, K562-wt and K562-CD19 cells lines were used as targets in a chromium release T cell killing assay. K562 is a myelogenous leukaemia cell line.

T cells transduced with various αCD19 CARs, including αCD19-BB-ζ, killed K562 cells expressing CD19 (K19) at low effector: target ratios (10:1, 30-50% killing) in a chromium release assay (Figure 8).

Figure 4: Antigen-specific killing of CD19+ tumour cells by CD19-specific CAR+ T cells



CAR+ T cell cytolytic activity against primary B-ALL tumour cells [17]

Primary pre-B ALL cells were obtained from normally discarded cells obtained from individuals undergoing therapeutic apheresis for acute pre-B ALL. αCD19-BB-ζ [tisagenlecleucel] effector cells were capable of killing primary human pre-B acute lymphoblastic leukemic (ALL) cells expressing physiological levels of CD19 in a chromium release assay. Additionally, a full-length TCRζ domain was required for killing as αCD19 CAR with a truncated TCR ζ domain (Δζ) did not lyse targets.

Cytokine production of CAR+ T cells after stimulation with tumour cells [17]

Supernatant cytokine production from CAR+ CD4+ and CD8+ T cells was quantified by a flow cytometry-based cytometric bead array in response to K562-wt and K562-CD19 as antigen presenting cells. For all CARs, Interleukin-2 (IL-2) and interferon gamma (IFN-γ) production from CD4+ T cells was comparable to TCR/CD28 receptor stimulation. IL-2 production was greater for αCD19-28-ζ and αCD19-BB-ζ [tisagenlecleucel] compared to αCD19-ζ transduced T cells. IFN-γ release from CD8+ T cells was similar for αCD19-BB-ζ and αCD19-ζ, while αCD19-28-ζ was significantly higher. Interleukin-4 (IL-4) and Interleukin-10 (IL-10), type 2 cytokines, were produced by all CAR+ CD4+ T cells. Tisagenlecleucel had decreased production compared to the other CAR constructs.

Proliferation and survival of CAR+ T cells without CD19 re-stimulation [17]

In vitro proliferation of CAR transduced T cells was tested in the absence of CD19 re-stimulation. CD4+ and CD8+ T cells were engineered with the indicated CAR and expanded in the absences of K562-CD19 stimulator cells.T cells expressing tisagenlecleucel had increased proliferative capacity, as measured by

population doublings, and survival, as measured by cell volume on day 8, during *in vitro* expansion compared to the other groups, independently of receptor ligation with the surrogate CD19 antigen.

- ***In vivo***

Determination of CART-19 specific tumour effects and dose optimization (CART-19 preclinical animal studies)

Initial *in vivo* studies with first generation CAR (αCD19-ζ) were performed in mice. Mice were given T cells. The CAR construct αCD19-ζ showed target-dependent anti-tumour activity, as measured by a reduction in CD19+ ALL blasts in the peripheral blood. The reduction required an intact CD3ζ domain. Mock transduced T cells had minimal to no activity, supporting the lack of a general allogeneic T cell response to the tumour.

A follow up study was carried out to determine the dose dependent effect of the αCD19-ζ constructs. Peripheral blood CD19+ B ALL blast cell counts were measured at weekly intervals in mice (>4 mice/group) that were injected with the indicated numbers of αCD19-ζ CAR+ T cells or mock-transduced T cells.

Results showed that the blast count in the $5x10^6$ CAR+ T cell group was significantly lower than the count in the Mock and no T cell groups (ANOVA on the log-transformed blast counts, P test p=0.008). Lower doses still had an anti-tumour effect which was proportional to the dose administered.

Further, leukaemia-free survival over time was studied in animals receiving no T cells, mock-transduced T cells, or αCD19 -ζ CAR+ T cells ($5x10^6$). Animals were assessed for leukaemia at weekly intervals. The group receiving αCD19-ζ cells showed an increased median survival (log-rank test, p<0.001) compared to animals receiving mock-transduced or no T cells. Five animals were included in each group.

Determination of threshold of efficacy for CART-19 cells (CART-19 preclinical animal studies)

Based on prior experiments, two cell doses were used for the αCD19-ζ CART-19 cells (2×10^6 and 5×10^6), and for comparison, a dose of 2×10^6 of the αCD19-BB-ζ CART-19 cells was included. Mock transduced cells (20×10^6) and a no T cell group were included as controls for graft versus leukaemia effects and for B-ALL viability, respectively.

Results showed that the threshold of efficacy was around 2×10^6 for the αCD19-ζ cells in this model. Both constructs were effective, and the bipartite αCD19-BB-ζ cells seemed to have a slight improvement in anti-tumour activity compared to αCD19-ζ at 2×10^6 cells/dose, but these results are not conclusive from this study. In addition, the mock transduced cells were given at a 4-fold higher dose than the αCD19-ζ cells.

A follow-up study with the same model was conducted to evaluate all the CART-19 constructs at the threshold dose of 2×10^6 to compare the efficacy of the various signalling chains.

All of the CARs showed potent anti-leukemic activity when $2x10^6$ CAR+ T cells were injected two weeks after establishing leukaemia in the mice. The treatment effect was significant for the αCD19-ζ CAR (p<0.05) and for CARs that expressed costimulatory domains (p<0.01).

Engraftment of CD4 and CD8 T cells was determined by Trucount analysis. There were no significant increase (p>0.14) in engraftment between the mock and CART-19 transduced cells, supporting the absence of uncontrolled cell proliferation of CART-19 cells in this model.

In vivo comparison of persistence, anti-B-ALL activity and effect on survival (CART-19 preclinical animal studies)

In this series of investigations, the *in vivo* efficacy of T cells expressing the αCD19-ζ, αCD19- 28-ζ and αCD19-BB-ζ CARs was compared by injecting 10 million bulk T cells (adjusted to 50% CAR+ T cells in order to follow the fate of CAR+ vs. CAR- cells) three weeks after establishment of leukaemia in NOD/Shi-scid IL-2Rγ null (NOG) mice. In order to best track the transduced cells *in vivo*, CART-19 T cells were engineered to express GFP as well as the CAR.

All CAR+ T cells exhibited significant anti-leukemic efficacy. Differences were observed in the engraftment and persistence of the CAR cells bearing different costimulatory domains. Four weeks following T cell injection, the total T cell counts were highest in mice after injection with αCD19-BB-ζ CAR+ T cells, and the T cells comprised of CD4+ and CD8+ CAR+ T cells.

After injection into leukemic animals, the proportion of αCD19-BB-ζ CAR+ T cells was higher than αCD19-ζ CARs+ T cells and the αCD19-28-ζ CAR+ T cells ($p<0.01$). The enhanced engraftment and/or persistence of the αCD19-BB-ζ CAR+ CD4 and CD8 T cells was also observed in animals that were not injected with ALL cells ($p<0.05$).

αCD19-BB-ζ expressing T cells showed a significant enhancement in anti-leukemic efficacy compared with T cells expressing either the αCD19-ζ or αCD19-28-ζ receptors. Median leukaemia free survival was increased by 7 weeks ($p=0.009$). Based upon an approximate doubling time of 2.7 days for pre-B ALL cells (derived by fitting the leukemic blast counts in untreated animals to an exponential growth model), this 7-week delay in onset of leukaemia corresponds to a reduction in leukaemia burden of $>10^5$–fold following T cell injection when compared with the burden present in animals receiving either the αCD19-ζ or αCD19-28-ζ modified T cells.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been conducted (see non-clinical discussion).

Safety pharmacology programme

No safety pharmacology studies have been conducted (see non-clinical discussion).

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been conducted (see non-clinical discussion).

2.3.3. Pharmacokinetics

One non-clinical bio distribution study has been performed to investigate the pharmacokinetic properties of tisagenlecleucel. NOG mice (4 animals/group) were engrafted with human acute B-ALL (Study Day 0), followed three weeks (21 days) later by CAR+ T cells at doses of 1×10^6, 5×10^6 or 20×10^6 cells. The test article used in this study was a 1:1 mixture of two different CD19-directed CARs, αCD19-ζ CAR (LTG118 Lentigen vector which expresses the scFv αCD19-CD3-ζ chimeric immunoreceptor) and αCD19-BB-ζ CAR (i.e. tisagenlecleucel; LTG119 vector which expresses the scFv αCD19-CD3-ζ-4-1-BBL chimeric immunoreceptor). There were 2.4 copies of LTG118 and 1.7 copies of

LTG119 relative to glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and the vector 119/vector 118 ratio was 0.7.

Scheduled sacrifices took place on Study Day 42 and 56 (21 and 35 days after administration of the T cells). At subsequent time points, animals were sacrificed when they appeared to be moribund, with any remaining animals being sacrificed on approximately Study Day 217. At 21 and 35 days after the administration of the mixture of the T cells, the T cells were detected in the spleen, lung and kidney in all animals that were administered 20 x 10^6 cells except for kidney sample from one animal (35 days post-dose; LTG118 and LTG119). In the bone marrow valid results could not be obtained at 21 days post dose; however, T cells could be detected in all animals at 35 days post-dose. At the lower dose levels of 5 x 10^6 and 1 x 10^6 cells T cells were detected in only a few animals except for the lung at a dose of 5 x 10^6 cells where T cells were detected in the majority of animals. On Study Day 217, T cells could be detected in the spleen, kidney and bone marrow of one animal that was administered a dose of 5 x 10^6 cells.

At both 21 and 35 days post T cell dose, the median number of copies of vector/500 ng DNA was approximately 3-20x higher in the lung compared to the spleen, kidney and bone marrow. The number of copies was similar in the spleen, kidney and bone marrow samples. On Study Day 217, the number of copies of T cells with LTG119 vector in the one animal that was administered a dose of 5 x 10^6 cells were higher in the bone marrow than in the spleen with the number of copies being lowest in the kidney. The number of copies of T cells with the LTG118 vector was higher in the spleen than in the bone marrow, with no valid result being obtained in the kidney sample.

There was a good correlation between the number of copies of the LTG118 and LTG119 vectors in the spleen and kidney on Study Days 42 and 56. The correlation was less evident in the lung and bone marrow.

2.3.4. Toxicology

Single dose toxicity

No standard single-dose toxicity studies have been conducted (see non-clinical discussion).

Repeat dose toxicity

No standard repeat-dose toxicity studies have been conducted (see non-clinical discussion).

Genotoxicity

Lentivirus integration site analysis characterization of tisagenlecleucel using lentivirus insertion site analysis (Report 1620234, non-GLP)

Lentivirus insertion site analysis (LISA) was conducted on tisagenlecleucel manufacturing samples from 6 paediatric ALL (CCTL019B2202), 6 DLBCL (CCTL019C2201) patients and 2 healthy volunteers [18].

In general the integration pattern seen with the tisagenlecleucel vector resembles well known patterns for lentiviral integration. In all the analysed tisagenlecleucel products a high degree of polyclonality was observed and there was no evidence for preferential integration near genes of concern, or

preferential outgrowth of cells harbouring integration sites of concern during the cell culture in the manufacturing process.

Lentivirus integration site analysis characterization of tisagenlecleucel using shearing-extension primer tag selection and ligation-mediated PCR (Report 1620234a, non-GLP)

The same DNA samples used in the lentivirus insertion site analysis (LISA) were also processed by sonication and shearing-extension primer tag selection (S-EPTS) followed by ligation-mediated PCR (LM-PCR) [19].

The general integration pattern was consistent with lentiviral infection, all analysed tisagenlecleucel products showed high degree of polyclonality and no evidence for preferential integration near genes of concern or preferential outgrowth of cells harbouring such integration sites during the manufacturing process.

Carcinogenicity

No carcinogenicity studies have been conducted (see non-clinical discussion).

Reproduction toxicity

No reproductive toxicity studies have been conducted (see non-clinical discussion).

Toxicokinetic data

Local tolerance

No local tolerance studies were conducted (see non-clinical discussion).

Other toxicity studies

Impurities and excipients

Dynabeads

Tisagenlecleucel product is engineered using magnetic anti-CD3/CD28-coated beads (Dynabeads) for T cell enrichment and activation. The potential for acute toxicity from Dynabeads M-450 Sheep Anti-Mouse IgG ST (SAM-Beads) administered once intravenously to male and female rats was assessed [20]. Rats administered 9.6 x 10^4 beads/kg were killed 14 days posttreatment. Rats administered 8.3 x 10^8 beads/kg were killed either 14 or 42 days posttreatment. Saline containing 0.5% PPF served as the control article. Treatment groups were statistically compared with respect to clinical chemistry, haematology parameters, and body weight data. No significant group differences were detected (α = 0.01) with respect to any statistically analyzed data. The majority of the SAM-Beads were found in the lung, liver, and spleen and were slightly more numerous among animals who were killed at 14 days. There was also a trend toward an increased incidence and/or distribution of phagocytized beads in the bone marrow of animals killed 42 days posttreatment when compared with the 14-day killed animals. A few extracellular beads were present in the lymph nodes, kidneys, and sternal bone marrow. Under the conditions of this study, intravenous administration of Dynabeads M-450 Sheep Anti-Mouse IgG ST

did not result in any adverse test-article-related macroscopic, clinical pathologic, or histopathologic changes.

In rats, Dynabead-labelled pancreatic islets transplanted into the liver through the portal vein could be visualized weekly by MRI *in vivo* and did not noticeably change in either their shape or their size and remained in the same positions during the entire monitored period of 2 months [21].

The worst-case exposure of paediatric patients to residual Dynabeads after infusion of the tisagenlecleucel product (activated viable T cells) can be assessed as follows:

- specification for beads: ≤ 50 beads per 3 x 10^6 cells
- maximum number of viable cells (transduced and non-transduced) per single dose of tisagenlecleucel product for paediatric use: 5 x 10^9 total cells (in 50 mL)
- maximum number of beads per single dose of tisagenlecleucel product: 5 x 10^9 cells x 50 beads / 3 x 10^6 cells = 83'333 beads
- for 3-6 year old children with 18.6 kg average body weight (EPA, 2008): 83'333 beads / 18.6 kg = 4480 beads/kg (or for a child with 50 kg body weight: 83'333 beads / 50 kg = 1667 beads/kg).

The maximum number of residual Dynabeads in tisagenlecleucel product for injection to children (4480 beads/kg) is more than 20-fold lower than the low dose in rats (96'000 beads/kg), where no beads were detected in any tissue, and thus is considered not to represent an undue safety risk to the patient.

Benzyl alcohol

Patients administered Kymriah is estimated to be exposed to a maximum level of 21 µg benzyl alcohol (BZA) per dose/day (equivalent to 1.5 µg/kg body weight for a 2-year old child with 13.8 kg body weight). BZA is a natural constituent of a number of plants and is used as a flavouring substance in some foods and beverages.

An estimated maximum exposure level of 21 µg BZA per dose/day (equivalent to 1.5 µg/kg body weight for a 2-year old child with 13.8 kg body weight) administered intravenously is considered to pose a low toxicological risk to children ≥2 years based on the below considerations:

- it is approx. 10-fold and 12-fold below the single IV exposure levels of 0.0146 and 0.0186 mg/kg body weight that were without any adverse effects in preterm and term infants, respectively
- it is approx. 730-fold below the lowest IV exposure level of 1.1 mg/kg body weight/day for at least 2 days that was not associated with hypertension, seizures, vomiting, or clinical or laboratory indications of liver or kidney toxicity in preterm infants
- it is 18000-fold below the highest IV exposure level of 27 mg/kg body weight/day for 8 days that was not associated with kernicterus or intraventricular haemorrhage in preterm infants
- it is approx. 21300-fold below the lowest IV exposure level of 32 mg/kg body weight/day for 7 days at which potential clinical symptoms of benzyl alcohol poisoning were present in a preterm infant but could not be distinguished from clinical manifestations of asphyxia and underlying hyaline membrane disease

- it is 66000-fold below the lowest IV exposure level of 99 mg/kg body weight/day for 2 to 28 days that was associated with the "gasping syndrome" in premature infants in the early 1980s
- hepatic metabolism and renal clearance mechanisms, which are considered most relevant to minimize risk of benzyl alcohol toxicity and "gasping syndrome" in paediatric populations, are considered mature in children ≥2 years of age
- according to the "EMA QA on benzyl alcohol used as an excipient in medicinal products for human use" (2017), benzyl alcohol should not be used in neonates, buy may be used for children aged older than 4 weeks with caution.

Hypersensitivity reactions to drug formulations containing BZA have been reported in adults: such reactions occurring in the paediatric population cannot be ruled out.

2-Ethylhexanol (2-EH)

2-EH is well absorbed from the gastrointestinal tract following oral administration and rapidly eliminated. After oral gavage of 50 or 500 mg EH/kg to female rats, the absorption rate was about 80%, independent of the administered dose. The main metabolic pathway is via 2-ethylhexanoic acid, followed by conjugation with glucuronic acid.

An estimated maximum exposure level of 15 µg 2-ethylhexanol per dose/day (equivalent to approx. 1.1 µg/kg body weight for a 2-year old child with 13.8 kg body weight) administered intravenously is significantly below the above mentioned oral ADI level, and thus considered not to represent an undue safety risk to children ≥2 years, in particular since tisagenlecleucel will be administered with a very low frequency, i.e. maximum 2-3 administrations per lifetime.

Dextran 40

Dextran is a high molecular-weight polymer of α-D-glucose, which contains long linear chains of saccharide units with occasional short (one or two unit) branches. Anaphylactic reactions to Dextran-40 occur in approximately 1-5 cases per 10,000 patients treated with Dextran-40. This warning is also included in the LMD (dextran 40) prescribing information.

DMSO

DMSO total quantity present in the final product is within the current practice in transplantation, i.e. no more than 1g/kg body weight.

Other studies

In vivo safety assessment of tisagenlecleucel in mice (pcs-racgt-10-pre-clinical report-FRA1, non-GLP)

Two Lentigen vectors, LTG118 and LTG119, were used in this murine leukaemia xenograft model. An overview of the study details and major findings are presented in Table 5.

Table 1: Overview of the human B-ALL NOD/SCID-γc $^{-/-}$ murine leukaemia xenograft study

Species (Strain) Cells (cell line, donor type) Study No	Method of administration (Vehicle / Formulation)	Duration (days) after B-ALL inj.* and after T cell inj.**	Cell doses	Gender and No. per group	Major findings
NOD.Cg-Prkdc^{scid} IL2rg^{tm1Wjl}/SzJ mice (NOG) mice [pcs-racgt-10--pre-clinical safety report-FRA1]	Single i.v. injection of cell suspensions	*42, 56 and 217 and **21, 35 and 196	20E+6, 5E+6, 1E+6 CTL019* (Gr 1 to 3) cells or mock transduced T cells (Gr 4 to 6) on day 21 after 1E+6 B-ALL cells; 1E+6 B-ALL alone (Gr 7); 20E+6 CTL019* alone (Gr 8) *: CTL019: 1:1 ratio of αCD19-ζ and αCD19-BB-ζ transduced T cells	16(M, F)/group 4/control	αCD19-BB- ζ and αCD19- ζ T cells showed similar patterns of bio-distribution αCD19-BB-ζ T cells exhibited preferential survival No uncontrolled T cell proliferation High dose (20E+06) resulted in GVHD No treatment-associated toxicity upon necropsy

In vitro expansion profile studies of CART-19 transduced T cells (multiple studies, non-GLP)

Table 2: *In vitro* toxicity studies

Cell source, cell line Study No	Test system, study design	Concentrations	Major findings
PBL from 1 HD [pcs-rsir08-009--pre-clinical-study-report]	Expansion profile of CART-19 transduced primary human T cells	MOI for αCD19-BB-ζ and αCD19-ζ of 4, 10, 20, or 40 Both equally (50:50) distributed on d0 and d1 of culture	No uncontrolled T cell proliferation was observed; MOI of 4 to 20 TU/cell resulted in similar growth, 40TU/cell less efficacious; αCD19-BB-ζ transfected T cells grew for 38d; αCD19-ζ grew for 28d; CD8 T cells mostly contribute to proliferation whereas CD4 T cells start to cease after 14d; CD8 T cells start to cease after 21d; TG expression: >20%
PBL from 1 CLL [pcs-rsir09-003--pre-clinical-study-report]	Expansion profile of CART-19 transduced primary human T cells	MOI for αCD19-BB-ζ of 25; equally (50:50) distributed on d0 and d1 of culture	No uncontrolled T cell proliferation was observed; αCD19-BB-ζ transfected T cells grew and started to die between d21 and 28; control cells between d18 and d21; TG expression: >70%
PBL from 1 HCL and 1 HD [pcs-rsir09-004--pre-clinical-study-report]	Expansion profile of CART-19 transduced primary human T cells	MOI for αCD19-BB-ζ of 10, 20; equally (50:50) distributed on d0 and d1 of culture	No uncontrolled T cell proliferation was observed; αCD19-BB-ζ transfected T cells grew and started to die between d18 and 20; no difference to control cells; TG expression: >20%

HD: Healthy Donor; HCL: Hairy Cell Leukaemia; CLL: Chronic Lymphocytic Leukaemia; TG: Transgene

Tissue cross-reactivity (Novartis study 1470028)

A murine CD19 chimeric antigen receptor (CAR) single variable fragment (scFv) (NVPLYS631) equal to the one transduced into tisagenlecleucel cells was used for cross-reactivity testing in a human

membrane surface protein array. This protein array covers approximately 3550 full human membrane proteins, which are expressed on HEK293 cells.

With the exception of CD19 none of the proteins presented in this assay were identified by the murine CD19 CAR scFv. No clinical effects related to cross-reactivity to non-CD19 targets were reported thus far.

Immunohistochemistry, in situ hybridization and RTPCR analysis on human and cynomolgus monkey CNS tissues (Novartis studies 1420055 and 1420059)

Immunohistochemistry was performed with commercially available rabbit monoclonal antibodies on cerebrum and cerebellum and did not detect CD19 protein expression in either species. This finding was confirmed by in situ hybridization which failed to show CD19 mRNA in the brain.

Anti-CD19 human-scFv (from tisagenlecleucel) rabbit-Fc and anti-CD19 murine-scFv rabbit-Fc chimeric tool reagents were also developed. While these tool reagents detected CD19 on human cell lines (K562 cells expressing CD19) and normal human tissue (tonsils and spleen), they did not produce a specific reaction in human brain tissue.

In addition, RTPCR analysis of the expression of 5 human and 3 cynomolgus CD19 splice variants in respective brain tissues was negative.

2.3.5. Ecotoxicity/environmental risk assessment

The environmental risk assessment was performed in accordance with Annex II to Directive 2001/18/EC on the deliberate release into environment of genetically modified organisms (GMOs) and following the precautionary principle using the methodology set down in Commission Decisions 2002/812/EC and 2002/623/EC and EMA guidelines on environmental risk assessments for medicinal products consisting of, or containing GMOs (EMEA/CHMP/BWP/473191/2006) and on scientific requirements for the environmental risk assessment of gene therapy medicinal products (EMEA/CHMP/GTWP/125491/2006).

In accordance with Article 6 of Regulation (EC) No 726/2004, national competent authorities established under Directive 2001/18/EC have been consulted.

Potential hazards

- Presence of RCL in the drug product and transmission to contact persons e.g. during application, after shedding, or via donation of blood, organs, tissues or cells for transplantation, bears the risk of infection of human beings, other than the patient, with a new replication competent lentivirus (HIV lentivirus). Theoretically, vector mobilization may occur by generation of RCL during manufacturing of the vector or of the GMO. The magnitude of this theoretical potential adverse effect for the environment is considered to be high, since a new replication competent lentivirus could be released to and spread within human populations.

- Formation of RCL in patients may occur by vector mobilization as the consequence of complementation between proviral and host sequences after administration of tisagenlecleucel to the patient bearing the risk of transmission of a new lentivirus to contact persons after shedding or via donation of blood, organs, tissues or cells for transplantation. This hypothetical homologous recombination between the retroviral vector in its proviral form with an endogenous retrovirus could either be in the shape of a completely new type of lentivirus, or, in the case of a patient who is HIV+ from before, the generation of new HIV viruses. The magnitude of this theoretical potential adverse

effect for the environment is considered to be high, since a new replication competent lentivirus could be released to and spread within human populations.

- Presence of residual non-replicative infectious lentiviral vectors in the drug product and transmission to contact persons, either during application, after shedding or via donation of blood, organs, tissues or cells for transplantation. The magnitude of this theoretical potential adverse effect for the environment is considered to be low, since only few contact persons would be affected without the risk of spreading to human populations. Furthermore, adverse effects to any person exposed are unlikely due to the (benign) nature of the vector.

- Transmission of genetically modified T-cells, e.g. by accidental infusion of the drug product or via donation of blood, organs, tissues or cells for transplantation. The magnitude of this theoretical potential adverse effect for the environment is considered to be negligible, since the (allogeneic) genetically modified cells are expected to be rapidly cleared by the host immune system.

Evaluation of likelihood

- Likelihood of presence of RCLs in the final product and subsequent transmission of RCRs to thirds: The deleted elements in the design of the vector system minimize vector recombination probability and thus the possibility of generation of RCL. In addition, the final product is washed with multiple steps in the manufacturing process and therefore the viral vectors that potentially could have been present in Kymriah will have been reduced by a factor of 5000. Therefore, it is highly unlikely that measurable functional vector particle would be present in Kymriah.
- Likelihood of formation of RCL in patients: CTL019 lentiviral vector is a 3rd generation self-inactivating vector designed to minimize the likelihood of RCL emergence, as packaging plasmids are provided in trans and split on to 3 different plasmids. Plasmid sequences have been optimized to have minimal homology with the parental HIV, in order to minimize the chance of homologous recombination. Therefore, formation of RCL in patients is considered highly unlikely. Horizontal gene transfer of CTL019 lentiviral vector sequences could only happen upon generation of RCL in a significant number of patients, post-administration of Kymriah, and their being shed into the environment. This would require co-infection of CAR+ T cells together with retroviruses with sufficient sequence homologies for recombination to occur, which is highly improbable since the risk of RCL formation has been reduced to the minimum.
- Likelihood of transmission of replication-incompetent vectors. Since the CTL019 lentiviral vector is replication deficient, only one round on infection can occur, and for a potential adverse effect to happen, significant numbers of free lentiviral particles would have to be released directly into the environment. Such a scenario is highly unlikely as no free vector is present in the end-product, due to the multiple washing steps.
- Likelihood of transmission of genetically modified T-cells by accidental administration to thirds or after bleeding: The risk for the environment in general and for transmission to third parties associated with the genetically modified T cells is low, as the risk of accidental administration is minimized by the safety measures during application, and the lack of survival capability of T-cells in the environment. If transmitted to third parties through direct contact e.g. during application, the (allogeneic) genetically modified cells are expected to be recognized by the immune system and cleared rapidly. Thus, the likelihood of hazard by transmission of genetically modified T-cells is deemed as negligible.

Since the likelihood of all hazards identified is evaluated to be negligible, also the overall risk for the environment is considered to be negligible, provided that the safety measures described are applied.

However, a number of measures are implemented to prevent any potentially remaining minimal risks.

First of all, tisagenlecleucel will only be supplied to hospitals and associated centres that are appropriately qualified and only if the healthcare professionals involved in the treatment of a patient have completed the educational programme. The standard measures for universal blood product and routine cleaning procedures using adequate disinfectant is deemed as appropriate, also for the case of spillage of the drug product. Furthermore, since cancer patients are generally excluded from donation of blood, organs, tissues or cells for transplantation, also patients treated with Kymriah will be excluded from donations.

Altogether, the strategies to prevent theoretical minimal risks for the environment are deemed as appropriate for the intended use of Kymriah.

2.3.6. Discussion on the non-clinical aspects

Referenced literature in the application indicated that 4-1BB favours the outgrowth of younger, central memory T cells responses, whereas CD28 drives toward more effector memory T cell responses with an exhausted phenotype. Further, central memory T cells are believed to have higher proliferative potential and can mediate better anti-tumour immunity through the generation and maintenance of a pool of memory cells, whereas effector memory T cells are more short-lived with limited proliferative capacity. Exhausted T cells are neither able to proliferate nor mediate effector functions. Immunophenotypic sub-typing of the CAR+ T cells have been performed with other CAR-T DLBCL treatments [22]. Similar phenotyping of tisagenlecleucel CAR+ T cells has not been provided in the non-clinical dossier. Even though such information is valuable, the lack of these data is considered acceptable taken into consideration the knowledge about the CAR+ T cell properties gathered through clinical experience.

Milone et al [17] discuss findings with other constructs indicating that CARs containing either 4-1BB or CD28 endomains were equivalently active at controlling large tumours, and that the combination of CD28 and 4-1BB cytosolic domains resulted in the best persistence of CAR+ T cells in the tumour bearing mice and that 4-1BB endodomains tended to keep CAR+ T cells in a central memory state. The authors suggested that the optimal signals required by CARs may be dependent on the particular tumour being targeted and/or the nature of the particular single-chain variable fragment antibody. Thus, leaving the CD28 domain out of the tisagenlecleucel construct seems to be based on limited data from primary tumours, and some of these data actually indicate that the tripartite construct is more effective than the bipartite construct. Tisagenlecleucel is a so-called second (2G) CAR containing only one signalling domain. Subsequent to the 2G CAR constructs a third generation (3G) of CARs has appeared. These CARs contain multiple costimulatory domains, such as the tripartite construct tested here. Clinical trials with 3G cars with both CD28 and 4-1BB are currently ongoing [23].

The *in vitro* and *in vivo* non-clinical studies were performed using tumour cells from patients with ALL, and not from patients with diffuse large B-cell lymphoma (DLBCL). The lack of non-clinical pharmacology studies with DLBCL cells is acceptable based on the clinical experience with this indication.

Concerning the use of different vectors, the pharmacology studies were conducted with cells transduced with lentiviral vector made at the University of Pennsylvania, or at a further facility in the US, whereas clinical studies were done with cells transduced with vector made by Oxford Biomedica in

the UK. The two manufacturing sites used different plasmids to generate the lentiviral vectors used. The commercial supply is intended from a site in Germany at the Fraunhofer Institute, in Leipzig. In 2015, the applicant sought CHMP advice on comparative *in vivo* pharmacology studies to support this change. The CHMP advised that such studies were inappropriate as they do not have the capacity to generate results that could be interpreted in the context of a comparability exercise. The absence of comparative *in vivo* preclinical experiments to support the use of the clinical product in Europe is thus agreed.

The lack of single-dose toxicity studies is acceptable, since tisagenlecleucel is a patient specific product, which is not appropriate to administer to immune competent animals. The lack of repeat-dose toxicity studies is acceptable based on the fact that tisagenlecleucel will be administered as a single IV infusion, and since tisagenlecleucel is a patient specific product which is not appropriate to administer to immune competent animals.

Genotoxicity assays and carcinogenicity studies in rodents are not appropriate to assess the risk of insertional mutagenesis for genetically modified cell therapy products. No alternative adequate animal models are available (SmPC, section 5.3).

The risk of inadvertent germline transmission of the CD19 CAR construct has not been addressed; however, the Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors, EMEA/273974/2005 indicates that the risk of germline transmission associated with the administration of genetically modified human cells is considered to be low and, as animal testing of human cells may be difficult or not meaningful, non-clinical germline transmission studies of human genetically modified cells are not recommended.

In vitro expansion studies with CAR positive T cells (Kymriah) from healthy donors and patients showed no evidence for transformation and/or immortalisation of T cells. *In vivo* studies in immunocompromised mice did not show signs of abnormal cell growth or signs of clonal cell expansion for up to 7 months, which represents the longest meaningful observation period for immunocompromised mouse models. A genomic insertion site analysis of the lentiviral vector was performed on Kymriah products from 14 individual donors (12 patients and 2 healthy volunteers). There was no evidence for preferential integration near genes of concern or preferential outgrowth of cells harbouring integration sites of concern (SmPC, section 5.3).

This medicinal product contains 2.43 mg sodium per mL. This medicinal product contains 24.3 to 121.5 mg sodium per dose, equivalent to 0.01 to 0.06% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This is to be taken into consideration for patients on a controlled sodium diet. This medicinal product contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially "potassium free" (SmpC, section 4.4).

This medicinal product contains 10 mg dextran 40 and 82.5 mg dimethyl sulfoxide (DMSO) per mL. Each of these excipients are known to possibly cause anaphylactic reaction following parenteral administration. Patients not previously exposed to dextran should be observed closely during the first minutes of the infusion period (SmpC, section 4.4).

It is concluded that there is a negligible risk for the environment associated with the clinical use of Kymriah. Replication-competent lentivirus (RCL) may be generated during the tisagenlecleucel manufacturing or subsequently after introduction of vector transduced viable T-cells into the patient. Generation of replication competent lentivirus has been categorized as potential risk (see Risk Management Plan).

Insertion of lentiviral vector sequences throughout the genome has the potential to dysregulate local host cell gene expression with a theoretical risk of insertional oncogenesis resulting from disruption of normal function of genes that control cell growth and potential risk of development of secondary malignancies. New or secondary malignancies (including vector insertion site oligo/monoclonality) have been categorized as potential risk (see Risk Management Plan).

Kymriah contains genetically-modified human blood cells. Local biosafety guidelines should be followed for unused medicinal product or waste material. All material that has been in contact with Kymriah (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local biosafety guidelines(SmpC, section 6.6).

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

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical documentation submitted was considered adequate. The relevant information has been included in the SmPC (sections 4.4, 5.1, 5.3, 6.6) and in the RMP.

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

2.4. Clinical aspects

2.4.1. Introduction

GCP

The applicant claimed that the clinical trials were performed in accordance with GCP.

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

- Tabular overview of clinical studies

Table 3: Tabular listing of clinical studies with tisagenlecleucel

Study ID	No. of study centres/countries	Design	Study Posology	Subjs by arm entered /compl.	Gender M/F Mean Age	Diagnosis Incl. criteria	Primary Endpoint
CCTL019-**B2202** IA 2017 Efficacy and Safety	25/11	Phase II, single arm, open-label, multicenter	Tisagenlecleucel; single infusion; target dose 0.2-5.0×10^6 CTL019 cells/kg bw (for pts ≤ 50 kg) and/or 0.1-2.5×10^8 cells (for pts >50 kg)	92/75	43/32 12.0 (3-23) years	Paediatric and young adult patients with r/r B-cell ALL	IRC assessed ORR (CR+CRi) during 3 months after infusion of tisagenlecleucel from *all* manuf. sites
CCTL019-**B2205J** IA Efficacy and Safety	9/US	Phase II, single arm, open-label, multicenter	Tisagenlecleucel; single infusion; target total dose 0.2-5.0×10^6 CTL019 cells/kg bw (for patients ≤	35/29	11/18 12.6 (3-25) years	Paediatric patients with r/r B-cell ALL and B-cell lymphoblastic lymphoma	IRC assessed ORR (CR+CRi) during 6 months after infusion

			50 kg) and of 0.1-2.5×10^8 CTL019 cells (for patients >50 kg)				
CTL019-**B2101J** IA 2017 Efficacy and Safety	1/US	Phase I/IIA single arm, open-label	Tisagenlecleucel; multiple infusion; target total dose 1.5x10^7-5x10^9 CTL019 cells, i.e. 0.3×10^6-1.0×10^8 cells/kg bw; Day 0 (10%), Day 1-4 (30%), and Day 14 or later (up to 60%)	73/62	34/28 12.2 (1-27) years	Paediatric and young adult patients with CD19+ B-cell malignancies	Safety, feasibility of administering, and persistence of tisagenlecleucel
CCTL019-**C2201** Efficacy and Safety	27/10	Phase II, single arm, open label, multicenter	Tisagenlecleucel; single infusion; target dose 1.0-5.0x10^8 CTL019 cells	147/99	63/36 54.0 (22-76) years	Adult patients with r/r DLBCL	ORR by IRC

2.4.2. Pharmacokinetics

All cellular kinetic parameters indicative of expansion (Cmax) and persistence (AUC, Tlast) were derived from the clinical phase II pivotal and supportive studies B2202, B2205J, B2101J (ALL indication) and C2201 (DLBCL indication). Cellular kinetics were determined from peripheral blood and bone marrow samples analysed by qPCR (i.e. number of copies of CAR per µg of DNA), and flow cytometry (i.e. % CTL019 expressing CD3+ cells). The impact of intrinsic and extrinsic factors on cellular kinetics were assessed using NCA (both indications) and population modelling (ALL). Tisagenlecleucel cellular kinetics was presented for the individual studies and for pooled data (SPC pool) generated from studies with similar study designs (B2202 and B2205J).

Absorption

Tisagenlecleucel is administered as an IV infusion

Following infusion of Kymriah into paediatric and young adult r/r B-cell ALL and r/r DLBCL patients, Kymriah typically exhibited an initial rapid expansion followed by a slower bi-exponential decline (SmPC section 5.2).

ALL indication

Tisagenlecleucel cellular kinetics were characterised after IV infusion of CAR-positive viable T cells in three studies.

Table 4 Summary of peripheral blood cellular kinetic parameters for tisagenlecleucel by qPCR, by Day 28 response (across studies and SCP Pool) (Pharmacokinetic analysis set)

		Study B2202		Study B2205J		Study B2101J		SCP Pool	
Parameter	Statistics	CR/CRi N=60	NR N=6	CR/CRi N=20	NR N=5	CR/CRi N=53	NR N=3	CR/CRi N=80	NR N=11
AUC0-28d (copies/µg genomic DNA×days)	n	59	5	19	3	53	3	78	8
	Geo-mean	315000	301000	260000	116000	318000	105000	300000	210000
	Geo-CV%	185.9	116.8	226.4	54.5	182.3	1168.1	193.4	111.7
AUC0-84d (copies/µg genomic DNA×days)	n	49	2	17	1	44	0	66	3
	Geo-mean	495000	1010000	384000	270000	442000	-	463000	652000
	Geo-CV%	218.1	113.7	273.5	-	144.0	-	228.9	131.0
Cmax (copies/µg)	n	60	6	19	4	53	3	79	10
	Geo-mean	36100	20900	24000	17700	42900	17200	32700	19500
	Geo-CV%	154.3	187.3	187.3	53.5	162.1	779.4	163.4	123.7
Tmax (days)	n	60	6	19	4	53	3	79	10
	Median	9.84	19.9	7.81	20.0	11.0	13.0	9.83	20.0
	[Min; Max]	[5.70; 27.8]	[12.6; 62.7]	[0.0111; 15.0]	[0.0278; 22.8]	[2.00; 31.0]	[8.00; 16.0]	[0.0111; 27.8]	[0.0278; 62.7]
T1/2 (days)	n	47	2	18	1	41	2	65	3
	Geo-mean	23.1	3.64	18.6	1.48	20.0	2.31	21.7	2.70
	Geo-CV%	199.0	238.2	198.0	-	329.7	30.3	196.8	154.4
Clast (copies/µg)	n	60	6	20	5	33	1	80	11
	Geo-mean	281	1450	263	1750	241	26.4	277	1580
	Geo-CV%	249.4	341.4	156.6	264.3	415.4	-	221.4	269.1
Tlast (days)	n	60	6	20	5	33	1	80	11
	Median	168	48.5	190	26.9	251	23.0	170	28.8
	[Min; Max]	[19.8; 617]	[13.9; 376]	[17.8; 380]	[20.9; 28.8]	[18.0; 784]	[23.0; 23.0]	[17.8; 617]	[13.9; 376]

N/A: Not applicable

DLBCL indication

The clinical pharmacology of tisagenlecleucel was investigated in the pivotal study C2201 (Table 9). The cell product for seven of the 99 patients in the PAS was manufactured at the EU manufacturing facility (Cohort A).

Table 5. Summary of peripheral blood cellular kinetic parameters for tisagenlecleucel by qPCR by indication

		B2202 pedALL		A2201 CLL			B2102J CLL			C2201 DLBCL	
Parameter	Statistics	CR/CRi N=60	NR N=6	CR/CRi N=6	PR N=3	PRi/NR/PD N=19	CR/CRi N=3	PR N=3	NR/PD N=8	CR/PR N=31	SD/PD/UKN N=50
AUC0-28d (copies/ug×days)	n	59	5	6	3	15	3	3	5	29	36
	Geo-mean	315000	301000	165000	98300	5420	175000	1110000	13000	69300	70700
	Geo-CV%	185.9	116.8	391.3	365.7	4291.0	3176.8	21.0	442.4	161.3	282.0
AUC0-84d (copies/ug×days)	n	49	2	5	3	7	2	3	4	28	17
	Geo-mean	495000	1010000	361000	187000	12900	1640000	1600000	35600	106000	122000
	Geo-CV%	218.1	113.7	486.9	571.3	29591.8	90.4	10.0	179.8	146.2	146.1
Cmax (copies/ug)	n	60	6	6	3	17	2	3	6	31	45
	Geo-mean	36100	20900	17700	9790	659	101000	87500	1020	6470	5050
	Geo-CV%	154.3	187.3	381.3	148.7	1898.9	696.5	38.0	724.5	244.4	376.5
	[Min; Max]	[2090,316000]	[2570,57700]	[1800; 132000]	[2950, 24000]	[47.6, 161000]	[25100; 410000]	[63200, 130000]	[65.4, 13900]	[382, 69900]	[146, 111000]
Tmax (days)	n	60	6	6	3	17	2	3	6	31	45
	Median	9.84	19.9	14.0	15.0	15.0	18.0	17.0	13.0	9.83	8.96
	[Min; Max]	[5.70; 27.8]	[12.6; 62.7]	[13.0,22.0]	[0.999,22.0]	[0.999, 29.0]	[4.00; 32.0]	[16.0, 22.0]	[2.00, 32.0]	[5.78, 16.8]	[3.04, 27.7]
Tlast (days)	n	60	6	6	3	17				29	36
	Median	168	48.5	256	176	28.0		N.D.		180	59.9
	[Min; Max]	[19.8; 617]	[13.9; 376]	[56.0,364]	[79.0,253]	[0.999,172]				[56.9, 367]	[21.9, 264]

pedALL: pediatric acute lymphoblastic leukemia; CLL: chronic lymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma
CR: complete response; CRi: Complete remission with incomplete hematologic recovery
PR: partial response; NR: non-responder; PD: progressive disease; UKN: unknown; N.D. = Not derived

Distribution

In paediatric and young adult B-cell ALL patients, tisagenlecleucel has been shown to be present in the blood and bone marrow beyond 2 years (study B2101J). The blood to bone marrow partitioning of tisagenlecleucel in bone marrow was 47.2% of that present in blood at day 28 while at months 3 and 6 it distributes at 68.3% and 69%, respectively (Studies B2202 and B2205J). Tisagenlecleucel also traffics and persists in cerebrospinal fluid in paediatric and young adult B-cell ALL patients (Study B2101J) for up to 1 year (SmPC, section 5.2).

In adult DLBCL patients (Study C2201), tisagenlecleucel has been detected for up to 2 years in peripheral blood and up to month 9 in bone marrow for complete responder patients. The blood to bone marrow partitioning in bone marrow was nearly 70% of that present in blood at day 28 and 50% at month 3 in both responder and non-responder patients (SmPC, section 5.2).

Elimination

The elimination profile of Kymriah includes a bi exponential decline in peripheral blood and bone marrow (SmPC, section 5.2).

Dose proportionality and time dependencies

There is no apparent relationship between dose and AUC0 28d or Cmax (SmPC, section 5.2).

Special populations

Age

Table 6 Summary of peripheral blood cellular kinetic parameters for CTL019, by qPCR by age group (B2202 and B2205J) Pharmacokinetic analysis set

Parameter	Statistics	<10 years N=31	>=10 years to <18 years N=31	>=18 years N=13
AUC0-28d (copies/ug*days)	n	28	30	12
	Mean (SD)	602000 (627000)	613000 (535000)	546000 (859000)
	CV%	104.1	87.2	157.3
	Geo-mean	291000	422000	250000
	Geo-CV%	244.7	126.6	200.1
	Median	427000	460000	238000
	[Min; Max]	[33300; 2070000]	[19900; 2170000]	[33500; 3110000]
AUC0-84d (copies/ug*days)	n	22	24	10
	Mean (SD)	1150000 (1500000)	922000 (999000)	1450000 (2740000)
	CV%	129.8	108.4	188.9
	Geo-mean	483000	587000	479000
	Geo-CV%	293.4	143.9	281.4
	Median	841000	597000	379000
	[Min; Max]	[41600; 6270000]	[24100; 4730000]	[82500; 9020000]
Cmax (copies/ug)	n	30	30	12
	Mean (SD)	56000 (63900)	61100 (36100)	49000 (46700)
	CV%	114.1	59.1	95.2
	Geo-mean	28200	48000	31400
	Geo-CV%	220.4	103.0	137.9
	Median	37600	52700	40400
	[Min; Max]	[2570; 316000]	[2090; 146000]	[7490; 165000]

n: number of patients with non-missing values.
CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Table 7 Summary of peripheral blood cellular kinetic parameters for CTL019 by qPCR, by age group Pharmacokinetic analysis set

Parameter	Statistics	Age < 40 years N=14	40 years <= Age < 65 years N=62	Age >= 65 years N=23	All Patients N=99
AUC0-28d (copies/ug*days)	n	14	44	18	76
	Mean (SD)	232000 (346000)	166000 (260000)	77800 (114000)	157000 (255000)
	CV%	149.6	156.6	146.2	162.3
	Geo-mean	106000	75100	38200	68200
	Geo-CV%	192.1	207.3	188.0	210.2
	Median	74300	67800	42100	63800
	[Min; Max]	[11600; 1120000]	[6090; 1490000]	[4500; 441000]	[4500; 1490000]
AUC0-84d (copies/ug*days)	n	8	33	8	49
	Mean (SD)	374000 (537000)	187000 (216000)	186000 (264000)	217000 (297000)
	CV%	143.6	115.8	141.8	136.8
	Geo-mean	208000	106000	110000	119000
	Geo-CV%	143.6	160.6	127.3	154.2
	Median	193000	114000	90200	114000
	[Min; Max]	[73500; 1670000]	[11300; 888000]	[35600; 830000]	[11300; 1670000]
AUC0-Tmax (copies/ug*days)	n	12	49	22	83
	Mean (SD)	61700 (88100)	45700 (68100)	24300 (37700)	42400 (65300)
	CV%	142.9	149.0	154.7	154.3
	Geo-mean	27800	19800	12600	18400
	Geo-CV%	259.4	229.6	154.2	215.2
	Median	30800	22600	11100	17700
	[Min; Max]	[1320; 313000]	[1110; 317000]	[2190; 160000]	[1110; 317000]

- n: number of patients with non-missing values.
- CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Gender

In Study B2202, 43% female and 57% male patients and in Study C2201 39% female and 61% male patients received Kymriah (SmPC, section 5.2).

Race/ethnicity

Table 8 Summary of statistical analysis of race effect on cellular kinetic parameters for tisagenlecleucel by qPCR- SCP Pool (Pharmacokinetic analysis set)

					Treatment comparison 90% CI		
Parameter (unit)	Treatment	n[1]	Adjusted geo-mean	Comparison(s)	Geo-mean ratio	Lower	Upper
AUC0-28d	White	55	264000				
(copies/µg DNA×days)	Asian	5	299000	Asian/White	1.13	0.473	2.72
	Other	10	791000	Other/White	3.00	1.57	5.71
Cmax	White	59	29500				
(copies/µg genomic DNA)	Asian	5	34500	Asian/White	1.17	0.519	2.65
	Other	10	68200	Other/White	2.32	1.27	4.21

Model is a linear mixed effects model of the log-transformed cellular kinetic parameters. Included in the model was ethnicity as a fixed effect
The results were back transformed to get adjusted geometric mean, geometric mean ratio, and 90% CI.
n[1] = number of observations used for the analysis.

Body weight
In DLBCL patients, across the weight ranges (38.4 to 186.7 kg), the scatter plots of qPCR cellular kinetic parameters versus weight revealed no apparent relationship between cellular kinetic parameters with weight (SmPC, section 5.2).

Pharmacokinetic interaction studies

No PK drug interaction studies have been conducted with tisagenlecleucel.

Tocilizumab, inhibitor of interleukin-6, was administered for the management of cytokine release syndrome (CRS). In the SCP Pool, 35 patients (33.7%) received tocilizumab for the management of CRS. The onset of CRS often coincides with the initial expansion of tisagenlecleucel followed by a peak in cytokines such as IL-6. In this population, the CR/CRi patients treated with tocilizumab to manage CRS, had approximately 333% and 220% higher $AUC_{0\text{-}28d}$ and C_{max}, respectively, compared with CR/CRi patients that did not receive tocilizumab. Tocilizumab is most commonly administered to patients with grade 3/4 CRS and these patients also tend to have greater expansion and higher C_{max} and $AUC_{0\text{-}28d}$. Tisagenlecleucel $AUC_{0\text{-}28d}$ and C_{max} determined from qPCR data in study B2202, were 358% and 216% higher in CR/CRi patients treated with tocilizumab compared with patients that did not receive tocilizumab; and in study B2205J, approximately 236% and 196% higher, respectively, than patients that did not receive tocilizumab. Per the CRS treatment algorithm, patients with CRS that did not respond to tocilizumab received corticosteroids for limited dosage and duration and weaned rapidly. CR/CRi patients that received corticosteroids had 68% higher $AUC_{0\text{-}28d}$ compared with CR/CRi patients that did not receive corticosteroids. In this paediatric ALL study, high tumour burden at baseline resulted in higher expansion, and as a result, these patients experienced CRS and thus received tocilizumab for CRS management, depending on the severity.

For the r/r DLBCL-indication, the impact of anti-cytokine medication, tocilizumab, on the cellular kinetics of tisagenlecleucel was investigated in study C2201. Transgene continues to expand and persist following tocilizumab administration. The C_{max} and $AUC_{0\text{-}28d}$ of transgene were 286% and 219% higher, respectively, in patients that received tocilizumab for CRS management compared to patients that did not receive tocilizumab. Patients with grade 3/4 CRS generally have higher expansion of transgene compared to patients with grade 1/2 CRS or no CRS.

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

No formal clinical pharmacology studies were performed for tisagenlecleucel. All clinical pharmacology related endpoints and analyses are derived from Study C2201 (DLBCL) or studies B2202, B2205J and B2101J (ALL indication).

Mechanism of action

No specific mechanism of action studies have been conducted.

Primary and Secondary pharmacology

Antibodies binding to murine CAR19 in human serum were measured using a validated flow cytometry method, and levels were reported by median fluorescence intensity (MFI). T cell activation was measured by the percentage of interferon gamma (IFNγ) positive cells detected by intracellular staining and subsequent flow cytometric analysis. A positive treatment-induced immunogenicity response was determined by change from baseline value to the post-treatment value. In the SCP pool (ALL indication), the majority of patients (84.6 %; n=88) tested positive for pre-dose anti-mCAR19 antibodies (i.e. pre-existing immunogenicity). Treatment induced-immunogenicity was detected in 34.6 % of patients. Several analyses supported that observed ADA amounts did not impact cellular kinetics. A concentration time profile of tisagenlecleucel transgene by occurrence (or lack) of treatment-induced immunogenicity, showed consistent exposure between the two groups. Cellular kinetic parameters summarised by ADA positive or negative, showed that C_{max}, $AUC_{0\text{-}28d}$, T_{max}, and $T_{1/2}$ are comparable between the categories and within the observed kinetic variability observed in this population overall.

Methods used to analyse humoral and cellular immunogenicity in the r/r DLBCL population, were the same as were used in the pALL population. The majority of patients (main cohort patients according to the CSR; 91.4%) tested positive for pre-dose ADAs (i.e., pre-existing immunogenicity) and 5% of the patients had treatment-induced anti-mCAR19 antibodies. Pre-existing antibodies were not associated with any impact on clinical response nor had an impact on the *in vivo* initial expansion and persistence (C_{max} and $AUC_{0\text{-}28d}$) of tisagenlecleucel. The levels of pre-existing immunogenicity seen in DLBCL patients are consistent with observations in healthy donor samples evaluated during the assay validation. A strip plot of ADAs by time points showed that the assay signal was consistent across time points for individual patients. Treatment-induced or boosted anti-mCAR19 antibodies were observed in five patients in the Pharmacokinetic analysis set, while the majority of patients tested negative. The geometric mean C_{max} and $AUC_{0\text{-}28d}$ estimates were observed to be 70% and 152% higher in patients with treatment-induced or boosted anti-tisagenlecleucel antibodies post-tisagenlecleucel infusion.

The impact of several extrinsic factors on tisagenlecleucel cellular kinetics was evaluated. Both the pediatric ALL and r/r DLBCL patients received a multitude of therapies prior to receiving tisagenlecleucel. The purpose of these analyses was to evaluate their impact on cellular kinetics. Results of the analyses indicated that the number of lines of prior therapy, prior SCT (stem cell transplantation), and treatment with lymphodepleting (LD) regimens did not seem to impact the cellular kinetics of tisagenlecleucel (data not shown).

Relapsed/refractory DLBCL patients enrolled in study C2201 may have received rituximab, an anti-CD20 monoclonal antibody, as part of prior treatment regimens. Thirty-three patients received antineoplastic therapy post-tisagenlecleucel infusion (mainly nivolumab and rituximab (10.1% each) in Study C2201. Rituximab has a long half-life (~22 days), and is known to cause B-cell depletion [24], and tisagenlecleucel has previously been shown to cause long term B cell aplasia. High levels of rituximab were measurable at Day 21 following tisagenlecleucel infusion. Data were limited in PR and SD patients due to fewer patients in these responses categories. During the study after tisagenlecleucel infusion, only two patients showed CD19+ B cell levels returning to normal range (or slightly above normal range), as of the data cut-off date. B cell levels immediately prior to tisagenlecleucel infusion were summarised by absence or presence of detectable levels of rituximab. Patients with detectable rituximab prior to tisagenlecleucel did not have measurable B cell levels. In contrast, some patients without measurable rituximab levels (at baseline) had detectable B cells.

- *ALL indication*

Dose response analyses

The relationship between tisagenlecleucel dose and response (efficacy and safety) was explored using individual study data and SCP Pool. All patients in the SCP Pool (n=104) were included in the dose response analyses. Efficacy endpoints evaluated for dose response analysis included Day 28 response, DOR and EFS. The safety endpoints evaluated were CRS grade, time to resolution of hematopoietic cytopenias and neurological events.

The logistic regression dose response for patients >50 kg showed an increasing trend in probability of response for doses between 0.1 x 10^8 to 1.0×10^8 total CAR-positive viable T cells while the probability of response plateaus for doses higher than 1.0×10^8 CAR-positive viable T cells. Similarly, for patients ≤ 50 kg, the dose-response curve showed a moderate increasing trend in probability of response between 0.2 x 10^6 and 1.5×10^6 CAR-positive viable T cells per kg, after which the probability of response plateaus. Additionally, responses were observed across the dose range studied with both weight-adjusted and total doses.

In Study B2202, 52 patients were ≤ 50 kg and 23 patients were >50 kg; in Study B2205J, 17 patients were ≤ 50 kg and 12 patients were >50 kg. Based on results of logistic regression analysis, a doubling in total dose is associated with an odds ratio of 1.56 (95% CI: 1.000, 2.424) on average. Weight group (>50 kg and ≤ 50 kg) did not have a significant impact on the model. A consistent result was obtained in logistic regression analysis for Day 28 response and body weight adjusted tisagenlecleucel CAR - positive viable cell dose.

Analyses of Day 28 response by dose quartile were performed for the SCP Pool (for patients >50 kg and patients ≤ 50 kg) (Table 13 and Table 14).

Table 9. Day 28 disease response by IRC assessment by quartile of total CAR positive viable cell dose for patients > 50 kg only (SCP Pool) (FAS)

	CTL019 dose ≤ Q1(1.0) N=9 n (%) (95% CI)	Q1(1.0) <CTL019 dose≤ Q2(1.9) N=10 n (%) (95% CI)	Q2(1.9) <CTL019 dose≤ Q3(2.4) N=8 n (%) (95% CI)	Q3(2.4) <CTL019 dose N=8 n (%) (95% CI)	All patients N=35 n (%) (95% CI)
Day 28 ± 4 days disease response					
CR	1 (11.1)	4 (40.0)	3 (37.5)	3 (37.5)	11 (31.4)
CRi	5 (55.6)	3 (30.0)	3 (37.5)	3 (37.5)	14 (40.0)
No response	2 (22.2)	2 (20.0)	1 (12.5)	1 (12.5)	6 (17.1)
Unknown (UNK)	1 (11.1)	1 (10.0)	1 (12.5)	1 (12.5)	4 (11.4)
Achieved CR or CRi at Day 28 ± 4 days	6 (66.7) (29.9, 92.5)	7 (70.0) (34.8, 93.3)	6 (75.0) (34.9, 96.8)	6 (75.0) (34.9, 96.8)	25 (71.4) (53.7, 85.4)

CR=Complete remission; CRi=Complete remission with incomplete blood count recovery, CI: Confidence interval; IRC=Independent review committee

The 95% CIs are exact Clopper-Pearson CIs.

Doses are expressed $\times 10^8$ cells

Table 10. Day 28 disease response by IRC assessment by quartile of weight adjusted CAR-positive viable cell dose for patients less than or equal to 50 kg only (SCP Pool) (FAS)

	Weight-adjusted CTL019 dose ≤Q1(2.9) N=18 n (%) (95% CI)	Q1(2.9) < Weight-adjusted CTL019 dose≤ Q2(3.5) N=17 n (%) (95% CI)	Q2(3.5) < Weight-adjusted CTL019 dose≤ Q3(4.7) N=17 n (%) (95% CI)	Q3(4.7) < Weight-adjusted CTL019 dose N=17 n (%) (95% CI)	All patients N=69 n (%) (95% CI)
Day 28 ± 4 days disease response					
CR	6 (33.3)	4 (23.5)	4 (23.5)	3 (17.6)	17 (24.6)
CRi	7 (38.9)	9 (52.9)	11 (64.7)	11 (64.7)	38 (55.1)
No response	3 (16.7)	1 (5.9)	0	1 (5.9)	5 (7.2)
Unknown (UNK)	2 (11.1)	3 (17.6)	2 (11.8)	2 (11.8)	9 (13.0)
Achieved CR or CRi at Day 28 ± 4 days	13 (72.2) (46.5, 90.3)	13 (76.5) (50.1, 93.2)	15 (88.2) (63.6, 98.5)	14 (82.4) (56.6, 96.2)	55 (79.7) (68.3, 88.4)

CR=Complete remission; CRi=Complete remission with incomplete blood count recovery, CI: confidence interval, The 95% CIs are exact Clopper-Pearson Cis, Doses are expressed $\times 10^6$ cells/kg.

In Study B2202, the median CAR-positive viable T cell dose administered was 1.0×10^8 cells and the median weight adjusted dose was 3.0×10^6 cells/kg. The median CAR-positive viable T cell dose for the pooled analyses was 1.9×10^8 for patients > 50 kg and median weight adjusted CAR-positive viable T cells per kg was 3.5×10^6 for patients ≤ 50 kg.

The KM analysis of DOR for patients ≤ 50 kg indicated a similar DOR in patients treated with doses greater than or less than the median weight adjusted cell dose in the SCP Pool. The KM analysis of DOR for patients > 50 kg indicated separation between curves of less than and more than median total dose after Month four. However, there were only nine events out of the 28 patients included in this analysis with the rest of the patients censored so it may be premature to make definitive conclusions. The median DOR in patients with ≤ median dose was 8.6 months while it was not reached in patients with > median dose. In the SCP pool, based on the Cox regression model of DOR by log of weight adjusted dose, the hazard ratio for a doubling in dose was 0.77 (95% CI: 0.54, 1.08).

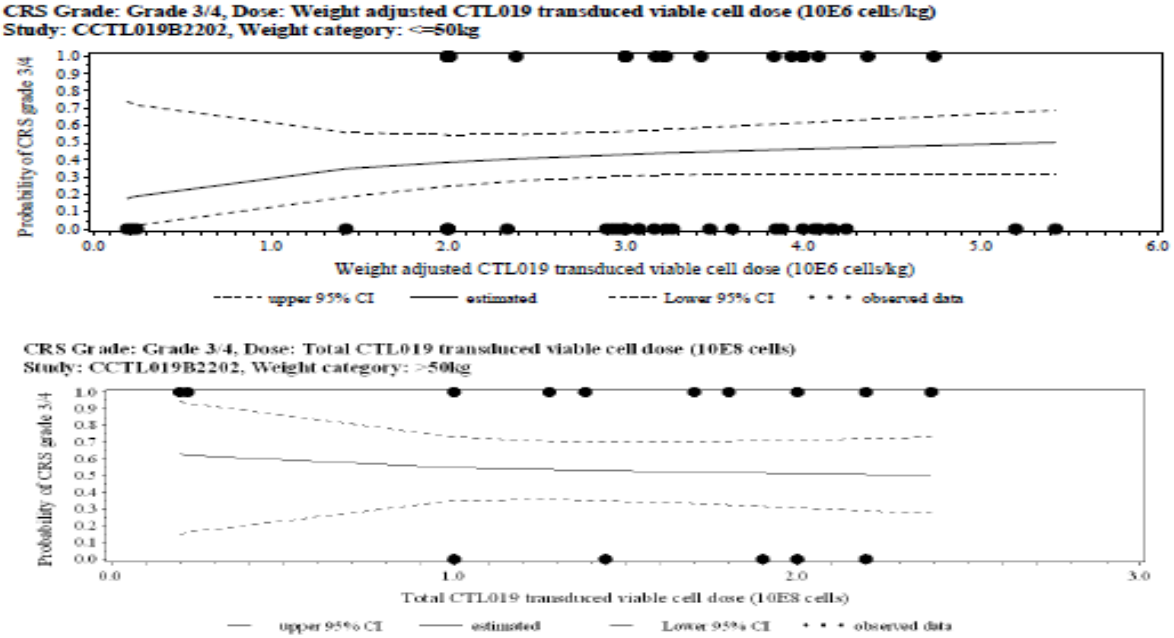
In study B2101J, the dose-DOR analysis, indicated a separation between curves for patients that received doses greater than the median dose and patients that received doses less than the median dose for both weight categories (>50 kg and ≤ 50 kg). Additionally, in Study B2101J the Cox regression model of DOR by log of weight adjusted dose, the hazard ratio for a doubling in dose was 1.20 (95% CI: 0.67, 2.12).

The impact of dose on EFS was analysed by plotting the weight -adjusted dose by EFS category (EFS event ≥ 3 months, EFS event <3 months, EFS censor <3 months, treatment failure, and other). The results of dose and EFS category analysis showed that there is no apparent effect of dose on EFS categories analysed although many of the categories had a small sample size (data not shown).

The impact of body weight (≤ 50 kg and >50 kg) on EFS was analysed using KM plot. The result of K-M analysis indicated that there is no clinically meaningful separation in the two curves. The median time for EFS in the patients of body weight >50 kg was 9.8 months, whereas the median EFS time in the patients ≤ 50 kg was not reached.

Dose-safety analysis

Logistic regression analysis was performed to evaluate the impact of dose on the probability of CRS in the SCP Pool. Results of the logistic regression analysis showed that there is no apparent impact of dose on grade 3/4 CRS. There is a slight trend for increased risk of grade 4 CRS with higher CAR-positive viable T cell dose for patients ≤ 50kg (weight adjusted); (Figure 9).



The model is logistic regression of CRS. Included in the model are log(dose), study, weight category, study by log(dose) and weight by log dose interaction. Dashed curves are the 95% CI of the log dose interaction. B2202 transduced cell dose is determined from post-thaw measurements.

Figure 5 Logistic regression of CRS vs. dose, overlaid with observed data (SCP Pool) (FAS)

There is no notable increased risk for neurological events with increasing dose (data not shown). There is no apparent impact of dose on the time to the resolution of neutropenia and thrombocytopenia (data not shown).

A further analysis indicated a minimal apparent difference in time to resolution of hematopoietic cytopenias depending on dose. The hazard ratio for a doubling of total dose was 1.00 (95% CI: 0.79, 1.26) for neutropenia while for thrombocytopenia it was 0.93 (95% CI: 0.65, 1.32).

Exposure-response relationship

Exposure-efficacy analysis

Exposure-response analyses were conducted to explore the relationship between tisagenlecleucel exposure metrics and efficacy endpoints including Day 28 response, DOR, and EFS.

- Exposure versus event-free survival - EFS

Summary statistics of cellular kinetic parameters based on EFS category in the SCP Pool (EFS ≥ 3 months, EFS event <3 months, EFS censor <3 months, Treatment failure, and other) showed that patients with EFS category ≥ 3 months tend to have higher exposure (AUC0-28d and Cmax) compared with patients with EFS event <3 months and treatment failure patients. For pooled data, EFS categories <3 months and treatment failures tend to have prolonged Tmax (median of 21.0 and 19.5 days respectively) compared with EFS ≥ 3 months (median 9.84 days).The geometric mean and arithmetic mean (SD) concentration-time profiles for transgene in peripheral blood, by EFS categories revealed sustained persistence for patients with EFS ≥ 6 months and an earlier and more rapid loss of transgene in patients with an EFS< 6 months . Similar results were seen in B2101J.

- Exposure versus day 28 response

The logistic regression of Day 28 response on $AUC_{0\text{-}28d}$ and C_{max} showed a flat relationship was observed between Day 28 response and cellular kinetic parameters ($AUC_{0\text{-}28d}$ and C_{max}) in Studies B2202 and B2205J. Since patients with unknown response have high exposure based on summary statistics, including them in the logistic regression analysis as non-responders may have made any potential relationship between exposure and response less obvious. Therefore additional logistic regressions were done excluding patients with unknown response as sensitivity analyses. These logistic regressions models showed that there is still minimal impact of AUC0-28d and Cmax on Day 28 response when patients with unknown response were excluded.

Analyses of Day 28 response by quartile of qPCR $AUC_{0\text{-}28d}$ and Cmax was performed by study and in SCP Pool which indicated that the Day 28 disease response was similar across the exposure quartiles in the SCP Pool. In study B2202, CR/CRi patients have higher and longer exposure to tisagenlecleucel transgene (measured by qPCR) as compared to NR patients. Cmax was approximately 1.7-fold higher in CR/CRi patients, compared to NR patients. Cellular kinetics measured by CD3+CAR+ levels (measured by flow cytometry), also indicated minimal expansion of CD3+/CTL019+ cells in non-responders compared with responders. In study B2101J also, CR/CRi patients, the transgene level in peripheral blood reveal a kinetic profile with an initial rapid expansion followed by a slower decay function with some fluctuations of transgene over time resulting in higher $AUC_{0\text{-}28d}$, C_{max} and longer T1/2 compared to NR patients who tended to have a lower expansion and faster decay (i.e. shorter T1/2) of CAR-positive T cells. The flow cytometry results substantiate the trend for higher exposures observed in CR/CRi patients relative to NR patients.

- Exposure versus DOR

There does not appear to be a difference in DOR for patients with an $AUC_{0\text{-}28d}$ or $AUC_{0\text{-}84d}$ greater than the median compared with patients with $AUC_{0\text{-}28d}$ or $AUC_{0\text{-}84d}$ less than the median. Based on the SCP Pool the risk of relapse does not appear to be impacted by $AUC_{0\text{-}84d}$. The KM analysis of DOR by median of $AUC_{0\text{-}28d}$ and $AUC_{0\text{-}84d}$ in study B2101J suggests that patients with low baseline tumour burden tend to have had more durable remission irrespective of exposure category, and patients with high tumour burden had less durable remission. The median DOR was not reached in patients with low tumour burden for patients with above or below median AUC0-28d. Among patients with high tumour burden, those who had AUC0-28d higher than the median appeared to have more durable remission (median DOR 15.7 months) compared to those who had AUC0-28d less than the median (median DOR 3.8 months). The Cox regression analysis for study B2101J indicated limited impact of AUC0-84d on DOR after adjusting for tumour burden. AUC0-28d, AUC0-84d,and Cmax were approximately 307%, 344%, and 208% higher in high tumour burden patients compared with low tumour burden patients (B2101J).

- Exposure versus B-cell recovery

There was a trend for patients with AUC0-28d greater than the median to have slower B-cell recovery than in patients with lower AUC0-28d. Based on the Cox regression for Study B2202, the hazard ratio for a doubling in AUC0-28d was 0.64 (95% CI: 0.46, 0.87). In Study B2202, the KM plot of time to B-cell recovery by median of AUC0-28d indicated a separation between two curves. There were a limited number of patients with sufficient follow-up. The results based on Study B2205J were consistent with the expected pharmacodynamic on-target effect of tisagenlecleucel of causing B-cell aplasia.

The KM analysis for the SCP Pool included a total of 85 patients. The median AUC0-28d was used in the analysis. B-cell recovery was the pharmacodynamic endpoint included in this analysis and defined as the earliest time when the percentage of CD19+ total B -cell among viable white blood cells is at least 1%.

The relation between B-cell aplasia and tisagenlecleucel persistence was determined by an analysis of tisagenlecleucel transgene by B-cell recovery times (≤3 months, >3 months to ≤6 months, >6 months). This analysis showed that patients with B-cell recovery occurring before 3 months or between 3 and 6 months had more rapid loss of transgene compared with patients that had sustained B-cell aplasia beyond 6 months.

Patients with CD19+ relapse have a rapid loss of transgene and limited expansion compared with patients that have sustained CR/CRi.

- Cellular kinetics by CD19 status at time of relapse

Patients with CD19 negative relapse have an absence of CD19 on the cell surface enabling the tumour to evade CAR T-mediated recognition and clearance despite having persistent transgene. This analysis showed the type of relapse (CD19 negative vs CD19 positive) will influence the persistence of transgene compared with patients that maintain CR/CRi status.

Exposure-safety analysis

Cytokine release syndrome was observed in patients treated with tisagenlecleucel. Higher transgene expansion (Cmax and AUC0-28d) was associated with increasing CRS grades based on logistic regression analysis and boxplots in Studies B2202, B2205J and the SCP Pool. Logistic regression analyses showed a higher probability of any grade CRS was associated with increasing expansion. Similarly, a higher probability of grade 3/4 and grade 4 only CRS was associated with increasing expansion. The odds ratio for having grade 3/4 CRS from the logistic regression model was 2.17 (95% CI: 1.402, 3.359) for Study B2202 for a doubling in Cmax. Analysis of CRS post tisagenlecleucel infusion by quartile of qPCR AUC0-28d revealed that a higher proportion of any grade CRS, grade 3/4 and grade 4 events were associated with increasing tisagenlecleucel transgene expansion (Cmax and AUC0-28d). Tocilizumab or other anti-cytokine therapies were administered as per the CRS treatment algorithm to effectively manage CRS. Tocilizumab did not appear to impact the rate or extent of tisagenlecleucel transgene exposure.

Neurological events were observed in patients treated with tisagenlecleucel; grade 1 and grade 2 neurological events were observed in 28 patients (27%). Ten (9.6%) patients had grade 3 neurological events and only one (1.0%) had grade 4 neurological events. Logistic regression analysis showed an increased probability of ≥ grade 2 neurological events with increasing Cmax and AUC0-28d. Neurological events often occurred concurrently with CRS, therefore, the relationship between neurological events and increasing expansion is consistent with the relationship observed between expansion and CRS.

In the SCS pool, forty-eight (46.2%) patients had grade 3/4 low platelet count not resolved by Day 28. 32 of the 48 patients (66.7%) had resolution to grade 2 or below after Day 28. The estimated probability of resolution by KM analysis among patients with grade 3/4 low platelet count at Day 28 was 76.7% by Month 3 and 83.4% by Month 6. Thrombocytopenia events resolved within 3 months, independent of transgene levels. Similar findings were observed for the relationship between exposure and resolution of neutropenia, whereby, the majority of patients with neutropenia resolved within 3 months, independent of the cellular kinetics (Cmax and AUC0-28d). Cox regression analysis was performed to evaluate the impact of AUC0 -28d on time to resolution of hematopoietic cytopenias which indicated that there was minimal influence of AUC0-28d on the time required to resolve neutropenia and thrombocytopenia events.

- **r/r DLBCL indication**

Rationale for the proposed dose specification

The protocol specified dose range of 1.0×10^8 to 5.0×10^8 CAR-positive viable T cells in the C2201 study, was selected based on previous clinical experience from paediatric and young adult r/r B cell ALL and adult CLL studies according to the Applicant. In past and ongoing trials in r/r CLL (dose optimisation study CTL019A2201) and non-Hodgkin's lymphomas (NHL) (study CTL019A2101J) patients, the upper range of the target dose tested (i.e., 5.0×10^8 CAR-positive viable T cells) were effective and safe.

The relationship between tisagenlecleucel dose and response (efficacy and safety) in DLBCL was explored using efficacy and safety analysis sets, respectively. Efficacy endpoints evaluated to assess the impact of dose on response, included response at month 3, duration of response (DOR), time to response, event free survival (EFS), and progression free survival (PFS). The efficacy analysis set (N = 83) was used for these analyses.

The impact of dose on the occurrence of cytokine release symptom (CRS), including any grade and grade 3/4, and neurological events and time to resolution of hematopoietic cytopenia were also explored. Based on the exposure-safety, exposure-efficacy and dose response analysis, the following dose was recommended adult patients with relapsed and refractory DLBCL:

The proposed dose specification range: 0.6 to 6.0×10^8 CAR-positive viable T cells.

Dose-response relationship – r/r DLBCL

Dose versus efficacy

Even if the protocol specified dose range in the CTL019C2201 study was 1.0 to 5.0×10^8 CAR-positive viable T cells, the doses administered ranged from 0.089 to 6.0×10^8 viable T cells, and responses were observed across the whole range. The manufacturing site always attempted to produce doses within the protocol specified range; however, in some cases doses lower or higher than the target dose were manufactured. Given the anticipated benefit in this patient population with high unmet needs, the doses below and above the protocol specified range were therefore infused.

There were a total of five patients that received doses less than 1.0×10^8 cells, and out of these, two were responders. Five patients received doses greater than 5.0×10^8 cells, and out of these, also two patients were responders.

Similar responses as for r/r DLBCL were observed across dose-quartiles in paediatric and young adult patients with r/r B-cell ALL. There was, however, an increasing trend of response with increase in dose

at low doses (<1.0×10^8 cells). The dose-response curve reached a plateau at doses greater than 1.0×10^8 CAR-positive viable cells. Therefore, the occurrence of a relatively flat dose-response curve for tisagenlecleucel is evident in both adult patients with r/r DLBCL and paediatric and young adult patients with r/r B-cell ALL according to the Applicant.

Dose vs. month 3 response

A logistic regression model was used to analyse the probability of response (CR and PR) at month 3 for patients in Study C2201.

Across the wide range of dose administered, the logistic regression dose-response curve, for both rounded and unrounded doses, showed that there is no apparent impact of dose on response at month 3. However, unrounded doses were used for proposed dose specification. The model estimate suggested that doubling in the dose was associated with 3% increase in the odds of a response (95%CI: 0.624, 1.685).

Dose versus DOR/Time to response

In Study C2201, the median dose was 3.1×10^8 CAR-positive viable T cells. The Kaplan-Meier analysis of duration of response (DOR, time from achievement of CR or PR to an event of PD or death due to DLBCL) for patients indicated a similar DOR in patients treated with doses greater (n=26) than and equal/less (n=18) than the median cell dose. There is, however, limited follow-up and number of events to make definitive assessment of impact of dose on DOR. Similarly, analysis by quartile of dose infused shows no difference in DOR among the quartiles of dose. Kaplan-Meier analysis of time to response (time from infusion to first documented clinical response of CR or PR) by median cell dose was performed which indicated a similar time to response in patients treated with doses greater than and less than the median cell dose.

Dose versus PFS/EFS

Kaplan-Meier analyses for the relationship of dose-PFS and dose -EFS were performed on patients in the C2201 study.

Dose versus safety

Results from the C2201 study indicated that the probability of CRS increased with dose in adult patients with r/r DLBCL.

CRS was generally manageable with the introduced CRS management algorithm and no death was attributed to CRS in adult patients with r/r DLBCL. Kaplan-Meier plot and Cox regression analyses on the relationship of dose-neurological events and dose-hematopoietic cytopenia suggested no apparent impact of dose on any grade or grade 3/4 neurologic events or time to resolution of hematopoietic cytopenia. The safety analysis set (N=99) was used for these analyses.

Dose versus CRS

According to the Applicant, given the high unmet need in this patient population with positive risk benefit ratio associated with tisagenlecleucel administration and no substantial increase in the probability of CRS from 5.0×10^8 to 6.0×10^8 CAR-positive viable T cells, the upper range of the dose for commercial specification was proposed as 6.0×10^8 CAR-positive viable T cells.

Adult patients with r/r DLBCL treated with higher doses have an increased probability of all grades and grade 3/4 CRS. However, the frequency and severity of CRS observed in adult patients with r/r DLBCL

was lower than that in paediatric and young adult r/r B-cell ALL (23.3% patients with grade 3/4 CRS in Study **C2201**; and 48.4% patients with grade 3/4 CRS in Study **B2202**).

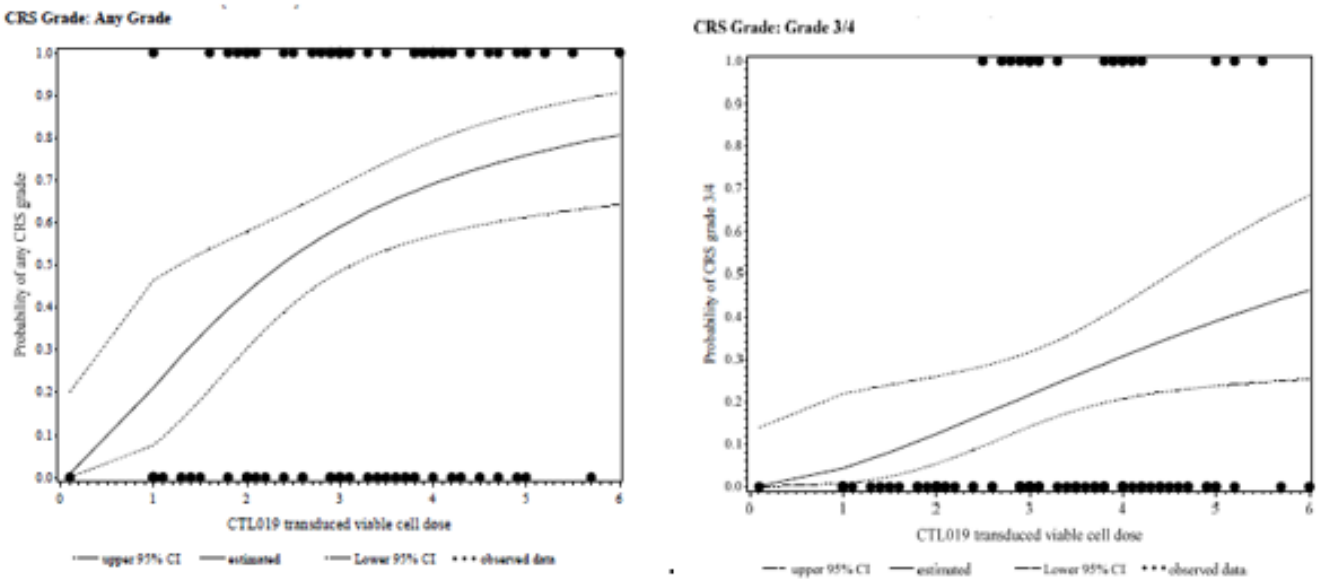


Figure 6. Logistic regression of CRS vs. CAR-positive viable T cell dose, overlaid with observed proportions (Safety analysis set)

Dose versus neurological events and hematopoietic cytopenia

Logistic regression analysis was performed to evaluate the impact of dose on neurological events, and also to explore the relationship between dose and time to resolution of hematopoietic cytopenias, including neutropenia and thrombocytopenia.

Exposure-response relationship

The relationship between tisagenlecleucel exposure and response (efficacy and safety) in r/r DLBCL, was explored using the efficacy and safety analysis sets in study C2201, respectively. Efficacy endpoints evaluated to assess the impact of exposure on response included response at month 3, duration of response (DOR), time to response, event free survival (EFS), and progression free survival (PFS). Safety endpoints evaluated included, CRS grade, neurotoxicity grade and time to resolution of hematopoietic cytopenia.

Exposure versus efficacy

Efficacy analysis dataset (N = 83) was used for the exposure versus efficacy analyses to ensure each patient had achieved month 3 response. There was no apparent exposure-efficacy relationship observed. Logistic regression was performed to evaluate the relationship between disease response versus exposure (e.g. AUC0- 84d based on qPCR, tisagenlecleucel transgene concentration measured by qPCR and concentration of CAR-positive viable T cells measured by flow cytometry at month 3). There was no relationship observed between exposure (AUC $_{-84d}$ or concentration) and month 3 response. Kaplan-Meier plot and Cox Regression analyses performed to assess the impact of exposure efficacy endpoints (*i.e.* DOR, time to response, EFS, and PFS), suggested no apparent impact.

Tisagenlecleucel showed a clinically meaningful and statistically significant response for the primary endpoint in Study C2201.

Efficacy analysis dataset (N = 83) was used for these analyses to ensure each patient had achieved month 3 response. The subsequent sections describe the key analysis results.

Kaplan-Meier, Cox regression and quartile analysis was planned to investigate the relationship between exposure and time to response. However, only four patients with cellular kinetic data available responded later than the Day 28 visit, so results of these analyses are not interpretable.

Exposure versus PFS/EFS

Kaplan-Meier analyses for the relationship of exposure-PFS and exposure-EFS were performed. The results suggested that exposure has no apparent impact on PFS and EFS.

The PFS was grouped by $AUC_{0\text{-}84d}$ quartiles and concentration quartiles. The EFS was also grouped by $AUC_{0\text{-}84d}$ and concentration quartiles. The event free probability was similar across all quartiles at month 3 by AUC0 -84d quartiles (56.3% to 83.3%) and by concentration quartiles (70.1% to 81.8%). However, due to a rather small number of events, additional follow up is needed for a strong conclusion regarding this end-point.

Exposure versus safety

The exposure-safety analyses were conducted to evaluate the relation between tisagenlecleucel exposures and cytokine release syndrome grades. Similarly, the relation between tisagenlecleucel exposures and neurological events and hematopoietic cytopenia was also explored. The PK analysis set (N=99) was used for these analyses.

Exposure versus CRS

Logistic regression analysis evaluating the impact of tisagenlecleucel exposures on CRS indicated that a higher probability of any grade or grade 3/4 CRS was associated with higher tisagenlecleucel exposures. Patients with higher $AUC_{0\text{-}28d}$ and C_{max} showed higher probability of having CRS grade 3/4 than patients with lower exposure. A similar exposure-CRS relationship was also observed in paediatric and young adult r/r B-cell ALL. Two cellular kinetic parameters, $AUC_{0\text{-}28d}$ and C_{max}, were selected for the analysis because CRS is generally resolved within seven days of the tisagenlecleucel infusion and these parameters are useful for characterising expansion.

The relation between expansion and CRS grade was explored for both adult patients with r/r DLBCL and paediatric and young adult patients with r/r B-cell ALL, based on data from Study B2202 with data cut-off date of 17 August 2016, to investigate any indication-specific differences in the exposure-safety (CRS) relationship. The results showed that the trend of higher expansion associated with higher severity of CRS was consistent for both indications, despite lower expansion in the adult patients with r/r DLBCL as compared to paediatric and young adult patients with r/r B-cell ALL.

These results further explains the lower proportion of patients with higher grades of CRS in r/r DLBCL (23.3% patients with grade 3/4 CRS) indication relative to paediatric and young adult r/r B-cell ALL (46.6% patients with grade 3/4 CRS), based on the updated data with data cut-off date of 25 April 2017.

A scatter plot of onset time of CRS versus T_{max} and C_{max} showed no impact of time and extent of *in vivo* expansion (C_{max} and T_{max}) on the onset time of CRS. Correlation between the time for maximal expansion of tisagenlecleucel (T_{max}) and the CRS grade categories and time for the onset of CRS showed no impact on T_{max} on severity of CRS events.

With increasing exposure ($AUC_{0\text{-}28d}$ and C_{max}), no increase in the probability of any grade or grade 3/4 neurological events was observed. In addition, no definitive conclusion can be drawn regarding prolonged cytopenia and exposure, due to limited number of patients with this adverse effect.

2.4.4. Discussion on clinical pharmacology

Based data from paediatric/young adult ALL patients (B2202, B2205J), the tisagenlecleucel cellular kinetic profile showed an initial rapid expansion phase achieving maximal expansion around Day 10 followed by a slower bi-exponential decline in responding (CR/CRi) patients based on Day 28 response. Cmax and AUC0-28d were 67.7% and 43% higher respectively in CR/CRi patients relative to NR patients, and a slower median Tmax (20 vs. ~10 days) and shorter median persistence (Tlast 28.9 vs. 170 days) were observed in NR patients vs. responders. Comparable findings were observed in study B2101J. Regression and modelling analysis of exposure parameters suggested that AUC0-28d was proportional to Cmax), thus those covariates that affect Cmax may also impact the AUC0-28d. Tisagenlecleucel transgene persistence was also demonstrated in bone marrow of responders for the complete sampling period of six months.

Cellular kinetic data from adult r/r DLBCL patients (C2201) showed a rapid expansion after infusion of tisagenlecleucel with maximal expansion around day 9, followed by a bi-exponential decline with median persistence (Tlast) of 87 days (range 21.9 to 367 days). The geometric mean Cmax, AUC0-28d and AUC0-84d in CR/PR patients was similar to that in non-responding patients based on clinical response at Month 3. Also, time to Cmax was similar. A longer mean persistence was observed in responders vs. non-responders with median Tlast of 180 vs. 59.9, respectively, however the follow up period was not similar in the two populations. The results indicate a high extent of bone marrow penetration, however there are limited data from non-responders.

When comparing cellular kinetic parameters between the two proposed indications, the geometric mean estimates of Cmax and AUC0-28d in responding adult patients (CR/PR) with r/r DLBCL were nearly 80-84% lower compared to responding paediatric and young adult r/r B-cell ALL patients (CR/CRi). This is potentially due to differences in primary location of the disease; in DLBCL the tisagenlecleucel target is mainly in the lymph tissue, whereas ALL cancer cells is found primarily in peripheral blood. A faster expansion was observed in the responding ALL patients vs. responding DLBCL patients (median Tmax ~10 vs. 20 days), while Tlast were comparable between indications. Inter-individual variability in cellular kinetic parameters was high, indicating that numerous factors could impact on the expansion of tisagenlecleucel. Both Tlast and T1/2 are dependent on the time of data cut off (data not shown). Persistence in blood will be measured up to month 60 irrespective of disease progression. The CHMP recommended that after study completions, additional data will be available and should be provided for determination of these parameters and for further analysis of impact of CRS co-medications on persistence.

The data, although limited, did not indicate that the site of manufacturing affected cellular kinetics.

No apparent dose-exposure relationship was detected (data not shown). This is not unexpected considering the MoA of tisagenlecleucel which includes the capacity of tisagenlecleucel to proliferate *in vivo*.

Overall, similar findings of the impact of available intrinsic and extrinsic factors were observed between ALL and DLBCL populations. The intrinsic and extrinsic factors were not found to impact on cellular kinetics with the exception of co-medications administered to manage CRS (ALL, DLBCL) and pre-

infusion tumour burden (ALL). In the ALL SPC pool, responding patients treated with tocilizumab (N=22) to manage CRS had approximately 333% and 220% higher AUC0-28d and Cmax, respectively, compared with responding patients that did not receive tocilizumab (N=58). CR/CRi patients that received corticosteroids (N=35) had 68% higher AUC0-28d and comparable Cmax and Tmax vs. CR/CRi patients that did not receive corticosteroids (N=45). The administration of tocilizumab or corticosteroid was required for management of severe CRS; these patients often had higher expansion. The higher transgene expansion in these patients might also be attributed to a higher baseline tumour burden. AUC0-28d, AUC0-84d and Cmax were approximately 307%, 344%, and 208% higher in high tumour burden patients compared with low tumour burden patients (B2101J). Similar as for the ALL indication, exposure in DLBCL patients (C2201) was higher in patients experiencing grade 3-4 CRS (approximately 3-4 fold higher), which also correlated with tocilizumab co-medication.

In general, variability of cellular kinetic parameters were very high and several of the investigated subpopulations were small which hampers interpretations of findings. The high variability is expected considering the type of the medicinal product.

Although it overall appears that there is no impact of age on cellular kinetics, data showed that children <18 years of age have up to 1.8 fold higher Cmax and AUC0-28d as compared to adults (ALL).

The scatter plots of cellular kinetic parameters versus age (22-76 years) revealed no relevant relationship between cellular kinetic parameters (AUC0 28d and Cmax) with age (SmPC, section 5.2).

There is limited evidence that race/ethnicity impact the expansion of Kymriah in paediatric and young adult ALL and DLBCL patients. In Studies B2202 and B2205J there were 79.8% Caucasian, 7.7% Asian and 12.5% other ethnic patients. In Study C2201 there were 88% Caucasian, 5% Asian, 4% Black or African American patients, and 3 patients (3%) of unknown race (SmPC, section 5.2).

Gender is not a significant characteristic influencing tisagenlecleucel expansion in B cell ALL and DLBCL patients (SmPC, section 5.2).

The CHMP recommended the applicant to investigate the cellular kinetic parameters including transgene persistence and the impact of covariates on cellular kinetics, following completion of studies B2202, B2205J, and C2201.

2.4.5. Conclusions on clinical pharmacology

Tisagenlecleucel cellular kinetics and exposure responses have been generally well characterised. Therefore, the current application for tisagenlecleucel in ALL and DLBCL is acceptable from clinical pharmacology point of view.

The CHMP endorses the CAT assessment regarding the conclusions on the clinical pharmacology as described above.

2.5. Clinical efficacy

2.5.1. Dose response studies

- ALL indication

Dosage was based on pre-clinical studies and results of Phase I/ IIA CTL019B2101J trial where 20 paediatric and young adult B-cell ALL patients received only a single infusion of tisagenlecleucel due to

the onset of fever with a cell range of 1.1×10^{6} to 6.3×10^{6} total CAR-positive T cells per kg and with an acceptable safety and efficacy profile.

Since the experience with higher doses is study CTL019B2101J is limited, a cut off of 2.5×10^{8} cells as a maximum dose, based upon a weight >50 kg, was proposed to avoid any potential safety issues.

Additional experience of dosage comes from study CTL019B2102J, a Phase II CLL trial where the dose was given as a single infusion of 1.0 to 5.0×10^{7} or 1.0 to 5.0×10^{8} CAR-positive T cells; single infusion was clinically well tolerated. In responding CLL patients with CR or lasting partial response, the tisagenlecleucel transduced cell numbers infused have ranged from 1.4×10^{7} to 1.1×10^{9} cells.

- DLBCL indication

In DLBCL, the relationship between dose and efficacy endpoints (months 3 response, time to response PFS and EFS) were investigated, where no apparent impact of dose of any of the studied efficacy endpoint was observed. Increasing dose was associated with increased probability of CRS with no higher grade CRS observed with doses lower than 2.4×10^{8} CAR-positive viable T cells.

Logistic regression for dose-safety relationship showed that the probability for CRS any grade or grade 3/4 increased with higher doses in adult patients with r/r DLBCL.

The true influence of tocilizumab on expansion cannot be ascertained directly. This observation may have been confounded as tocilizumab is given for high grade CRS and high grade CRS is correlated to higher doses and exposure.

2.5.2. Main studies

- **ALL indication - Study B2202**

Methods

This was a Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in paediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia.

Study Participants

The target population for the main study B2202 was paediatric and young adult patients with B-cell ALL of ages 3-25 who were primary refractory, chemo-refractory, relapsed after allogeneic SCT, or were otherwise ineligible for allogeneic SCT.

Main inclusion criteria

Relapsed or refractory paediatric B-cell ALL

a. 2nd or greater bone marrow (BM) relapse or
b. Any BM relapse after allogeneic SCT and was ≥ 6 months from SCT at the time of tisagenlecleucel infusion or

c. Primary refractory as defined by not achieving a CR after 2 cycles of a standard chemotherapy regimen or chemorefractory as defined by not achieving a CR after 1 cycle of standard chemotherapy for relapsed leukaemia or
d. Patients with Philadelphia chromosome positive ALL were eligible if they were intolerant to or had failed two lines of tyrosine kinase inhibitor (TKI) therapy, or if TKI therapy was contraindicated or
e. Ineligible for allogeneic SCT because of:
    i. Comorbid disease
    ii. Other contraindications to allogeneic SCT conditioning regimen
    iii. Lack of suitable donor
    iv. Prior SCT
    v. Declined allogeneic SCT as a therapeutic option after documented discussion, including expected outcomes, about the role of SCT with a BM transplantation physician not part of the study team

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

3. Adequate organ function defined as:

    a. Renal function defined as: serum creatinine based on age/gender per Table 15.

Table 11 Maximum serum creatinine (mg/dL)

	Maximum serum creatinine (mg/dL)	
Age	Male	Female
1 to <2 years	0.6	0.6
2 to <6 years	0.8	0.8
6 to <10 years	1.0	1.0
10 to <13 years	1.2	1.2
13 to <16 years	1.5	1.4
≥ 16 years	1.7	1.4

b. Alanine aminotransferase ≤ 5 times the upper limit of normal for age
c. Bilirubin <2.0 mg/dL
d. Had to have a minimum level of pulmonary reserve defined as ≤ grade 1 dyspnea and pulse oxygenation >91% on room air
e. Left ventricular shortening fraction ≥ 28% confirmed by echocardiogram, or left ventricular ejection fraction (LVEF) ≥ 45% confirmed by echocardiogram or multiplegated acquisition scan within 7 days of Screening

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

5. Life expectancy >12 weeks

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

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

8. Had to meet the institutional criteria to undergo leukapheresis or have an acceptable, stored leukapheresis product

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

Main exclusion criteria

1. Isolated extra-medullary disease relapse
2. Patients with concomitant genetic syndromes associated with BM failure states: such as patients with Fanconi anaemia, 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/leukaemia (i.e. patients with mature B-cell ALL, leukaemia with B-cell [sIg positive and kappa or lambda restricted positivity] ALL, with French-American-British (FAB) 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. Treatment with any prior gene therapy product, or had prior treatment with any anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy
6. Active or latent hepatitis B or active hepatitis C (test within 8 weeks of screening), or any uncontrolled infection at screening
7. Human Immunodeficiency Virus (HIV) positive test within 8 weeks of screening
8. Presence of grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD)
9. Patient has participated in an investigational research study using an investigational agent within the last 30 days prior to screening
10. The following medications were excluded:
    a. Steroids: Therapeutic systemic doses of steroids must be stopped >72 hours prior to tisagenlecleucel infusion. However, the following physiological replacement doses of steroids are allowed: <12 mg/m^2/day hydrocortisone or equivalent
    b. Allogeneic cellular therapy: Any donor lymphocyte infusions must be completed >6 weeks prior to tisagenlecleucel infusion
    c. GVHD therapies: Any systemic drug used for GVHD must be stopped >4 weeks prior to tisagenlecleucel infusion to confirm that GVHD recurrence is not observed (e.g. calcineurin inhibitors, methotrexate or other chemotherapy drugs, mycophenolyate, rapamycin, thalidomide, or immunosuppressive antibodies such as anti-CD20 (rituximab), anti-tumour necrosis factor [anti-TNF], anti-interleukin 6 [anti-IL6] or anti-interleukin 6 receptor [anti-IL6R], systemic steroids)
    d. Chemotherapy:
        i. Tyrosine kinase inhibitors and hydroxyurea must be stopped >72 hours prior to tisagenlecleucel infusion
        ii. The following drugs must be stopped >1 week prior to tisagenlecleucel infusion and should not be administered concomitantly or following LD chemotherapy: vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate <25 mg/m^2, cytosine arabinoside <100 mg/m^2/day, asparaginase (non-pegylated)
        iii. The following drugs must be stopped >2 weeks prior to tisagenlecleucel infusion: salvage chemotherapy (e.g. clofarabine, cytosine arabinoside >100 mg/m^2, anthracyclines, cyclophosphamide, methotrexate ≥ 25 mg/m^2), excluding the required LD chemotherapy drugs
        iv. Pegylated-asparaginase had to be stopped >4 weeks prior to tisagenlecleucel infusion

e. CNS disease prophylaxis: CNS prophylaxis treatment had to be stopped >1 week prior to tisagenlecleucel infusion (e.g. intrathecal methotrexate)

f. Radiotherapy
    i. Non-CNS site of radiation had to be completed >2 weeks prior to tisagenlecleucel infusion
    ii. CNS directed radiation had to be completed >8 weeks prior to tisagenlecleucel infusion

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

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

12. Pregnant or nursing (lactating) women. NOTE: female study participants of reproductive potential had a negative serum or urine pregnancy test performed within 48 hours before infusion

13. Active CNS involvement by malignancy, defined as CNS3 per National Comprehensive Cancer Network guidelines. Note: Patients with history of CNS disease that has been effectively treated were eligible

Prior to CTL019 infusion the following criteria must be met:

1. Influenza Testing test within 10 days prior to the CTL019 infusion. If positive, complete a full course of oseltamivir phosphate or zanamivir.

2. Performance Status: Patient should not experience a significant change in clinical or performance status compared to initial eligibility criteria that would increase the risk of adverse events associated with experimental cell infusion.

3. No Laboratory Abnormalities that may impact subject safety or the subjects' ability to receive the CTL019 infusion.

4. Leukemia Disease Status: Prior to CTL019 infusion and following lymphodepleting (LD) chemotherapy, patients must not have accelerating disease. Patients should not receive CTL019 infusion if they exhibit significant progression of disease during or following LD chemotherapy as evidenced by

- Significant and increasing circulating blasts
- Significant increases in organomegaly
- Clinical evidence of new CNS disease

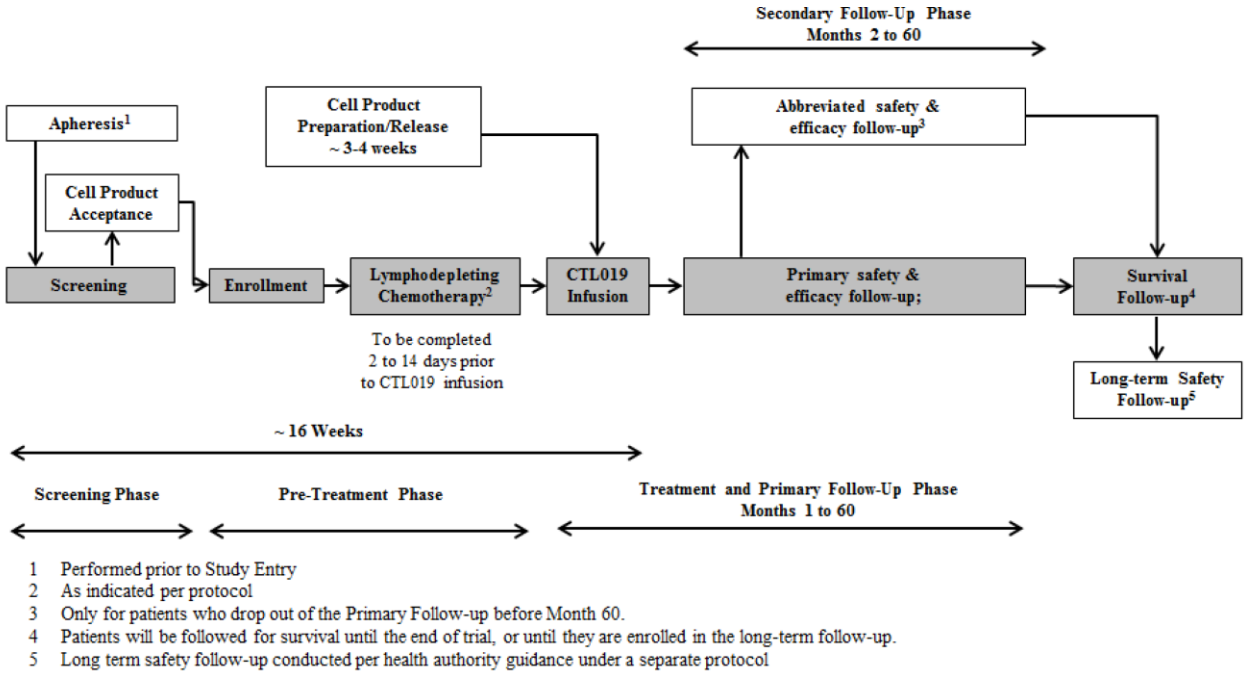
5. Chemotherapy Toxicity: Patients experiencing toxicities from their preceding lymphodepleting chemotherapy will have infusion schedule delayed until toxicities have been resolved (to grade 1 or baseline). The specific toxicities warranting delay of CTL019 cell infusion include:

a. Pulmonary: Requirement for supplemental oxygen to keep saturation greater than 91% or presence of progressive radiographic abnormalities on chest x-ray
b. Cardiac: New cardiac arrhythmia not controlled with medical management. Preinfusion ECG also required
c. Hypotension: requiring vasopressor support

6. Infection: CTL019 infusion must be delayed if there is an uncontrolled active infection, as evidenced by positive blood cultures for bacteria, fungus, or PCR positivity for viral DNA within 72 hours of CTL019 cell infusion.

Treatments

The study included a screening period including leukapheresis, enrolment, a conditioning chemotherapy period, an IMP treatment period, a primary and a secondary post treatment assessment and a long term-follow up period (see Figure 11).



Lymphodepleting chemotherapy: fluarabine (30mg/m2 IV daily for 4 doses)+ cyclophosphamide (500 mg/m2 IV daily for 2 doses)

Figure 7 Study design B2202 (and Study B2205J)

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

Bridging chemotherapy: Bridging chemotherapy was allowed pr Investigator choice.

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

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

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

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

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

Tisagenlecleucel infusion: Investigational treatment for paediatric and young adult patients consisted of a single iv infusion with a target dose range of 2.0 to 5.0×10^6 tisagenlecleucel cells (i.e. CAR-positive viable T-cells) per kg body weight (for patients ≤ 50 kg) or of 1.0 to 2.5×108 tisagenlecleucel cells (for patients >50 kg).

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

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

The released tisagenlecleucel dose is reported as CAR-positive viable T-cells for patients >50 kg and as CAR-positive viable T-cells/kg body weight for patients less or equal to 50 kg. Numerical rounding of the dose was performed by the manufacturing site.

Products falling below the minimum values in the above allowable cell dose ranges (i.e. 0.2×10^6 CAR-positive viable T-cells per kg or 1.0×10^8 CAR-positive viable T-cells) were not released for infusion.

The tisagenlecleucel dose was administered via a single iv infusion.

Objectives

The primary objective was to evaluate the efficacy of tisagenlecleucel therapy as measured by overall remission rate (ORR), which included complete response (CR) and CR with incomplete blood count recovery (CRi) as determined by Independent Review Committee (IRC) assessment, within 3 months after tisagenlecleucel administration.

Key secondary objectives included the following:

- Evaluate the efficacy of tisagenlecleucel therapy from US manufacturing facility as measured by ORR during the 3 months after tisagenlecleucel administration, which includes CR and CRi as determined by IRC assessment.
- Evaluate the percentage of patients who achieve a best overall response (BOR) of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry among all patients who received tisagenlecleucel from all manufacturing facilities.
- Evaluate the percentage of patients who achieved a BOR of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry among all patients who receive tisagenlecleucel from US manufacturing facility.

Outcomes/endpoints

Overall remission rate was defined as the proportion of patients with a best overall disease response of CR or CRi, where the best overall disease response is defined as the best disease response recorded from tisagenlecleucel infusion until the start of new anticancer therapy. Remission status was required to be maintained for at least 28 days without clinical evidence of relapse.

Best response was to be assigned according to the following order: − CR; − CRi ; No response (NR): no evidence of a response; Unknown: patients who did not have an evaluation for CR or CRi in compliance with the guidelines.

Table 12. Definition of CR, CRi and Relapse

Response Category	Definition
Complete remission (CR)	All of the following criteria are met:
	Bone Marrow • < 5% blasts
	Peripheral Blood Neutrophils > 1 x 10^9/L, and Platelets > 100 x 10^9/L, and Circulating blasts < 1%
	Extramedullary disease • No evidence of extramedullary disease (by physical exam, *spinal tap (D 28 or to ascertain CR/CRi)*, and symptom assessment
	Transfusion independency • No platelet and/or neutrophil transfusion ≤ 7 days before peripheral blood sample for disease assessment
Complete remission with incomplete blood count recovery (CRi)	All criteria for CR as defined above are met, with the exception that the following exist: • Neutrophils ≤ 1 x 10^9/L, and/or • Platelets ≤ 100 x 10^9/L and/or • Platelet and/or neutrophil transfusions ≤ 7 days before peripheral blood sample for disease assessment
Relapsed Disease	Only in patients who obtained a CR or CRi: • Reappearance of blasts in the blood (≥ 1%), or • Reappearance of blasts in the bone marrow (≥ 5%), or • (Re-)appearance of any extramedullary disease after CR or CRi

Sample size

In a study of clofarabine in patients with r/r B-cell ALL who have had 2 or more prior regimens, the reported ORR was 20% (95% CI [10%, 34%] [25]. Hence, an ORR of 45% that excludes a 20% ORR at the 0.025 significance level could indicate meaningful efficacy in this highly refractory population.

The final analysis of the primary endpoint was to be performed after all patients infused with CTL019 completed 3 months follow-up from study day 1 infusion or discontinued earlier. The sample size for the final analysis of the primary endpoint was up to 76 patients.

Based on the null hypothesis of ORR ≤ 20% and alternative hypothesis of ORR >20%, 76 patients in the FAS would provide more than 95% power to demonstrate statistical significance at one-sided

cumulative 0.025 level of significance, if the underlying ORR is 45% and taking into account the interim analysis. In this setting, an ORR of 23/76=30% was be needed to claim success.

Within the expected sample size of 76 patients with CTL019, at least 10 patients were to be treated with CTL019 manufactured by the Fraunhofer Institute. If there were at least 6 patients among them who achieved best overall response of CR or CRi, the lower bound of the 95% confidence interval would be higher than 20%. The probability of observing at least 6 CR or CRi among the 10 patients would be 26% if the true ORR is 45%, and would be 84% if the true ORR is 70%.

Randomisation

This was a single arm study.

Blinding (masking)

This was an open-label study.

Statistical methods

The primary efficacy analysis was performed by testing whether the ORR within 3 months is greater than 20% at overall one-sided 2.5% level of significance, i.e., H0: $p \leq 0.2$ vs. Ha: $p > 0.2$.

The primary efficacy endpoint, ORR within 3 months, was analysed at the interim look and final look following a group sequential design. The ORR was summarized along with the 2-sided exact Clopper-Pearson confidence intervals (CI) with coverage level determined by the O'Brien-Fleming type α-spending approach according to Lan-DeMets as implemented in East 6.3. The study was considered successful if the lower bound of the 2-sided exact confidence interval for ORR was greater than 20%, so that the null hypothesis that the ORR is less than or equal to 20% could be rejected.

An interim analysis was planned when the first 50 patients infused have completed 3 months from study day 1 infusion or discontinued earlier. The interim analysis was performed by testing the null hypothesis of ORR within 3 months being less than or equal to 20% against the alternative hypothesis of ORR within 3 months being greater than 20% at overall one sided 2.5% level of significance.

The study was not planned to be stopped for outstanding efficacy at the interim analysis regardless of the interim result.

An α-spending function according to Lan-DeMets (O'Brien-Fleming), as implemented in East 6.3, was used to construct the efficacy stopping boundaries (Lan and DeMets 1983). At the time of this interim analysis, assessment of all endpoints was based only on patients who receive CTL019 manufactured from US manufacturing facility because there was no patients treated with CTL019 manufactured from other manufacturing facilities.

In addition, sensitivity analysis was performed using the local investigator's response assessment instead of the IRC's assessment.

The efficacy boundary at the final analysis was based on the actual number of patients and the alpha already spent at the interim analysis. If the number of patients in the final analysis deviated from the expected number of patients, the final analysis criteria would have been determined so that the overall significance level across all analyses was maintained at one-sided 0.025.

The final analysis of the primary endpoint was to be performed after all patients infused with CTL019 have completed 3 months from study day 1 infusion or discontinued earlier.

Analysis tests

The Screened set comprised of all patients who had signed informed consent/assent and were screened in the study.

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

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

The Interim efficacy analysis set (IEAS) comprised the first 50 patients who received tisagenlecleucel infusion (used for the interim analysis).

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

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

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

The Tocilizumab Pharmacokinetic Analysis set (TPAS) consisted of patients in FAS who had taken at least one dose of tocilizumab and provided at least one tocilizumab PK concentration.

Results

Participant flow

Table 13 Overall patient disposition (Enrolled set- Study B2202)

Disposition Reason	All patients N=92 n (%)
Enrolled in the study	92 (100)
Discontinued without tisagenlecleucel infusion	17 (18.5)
Death	7 (7.6)
Tisagenlecleucel product related issues	7 (7.6)
Adverse event prior to tisagenlecleucel infusion	3 (3.3)
Tisagenlecleucel infusion pending	0
Tisagenlecleucel infused	75 (81.5)
Study follow-up completed	0
Study follow-up ongoing	48 (52.2)
Discontinued study follow-up	27 (29.3)
Death post-tisagenlecleucel infusion	11 (12.0)
Lack of efficacy (i.e. non-responder or relapse from response)	9 (9.8)
New therapy for study indication while in remission	5 (5.4)
Subject/guardian decision	2 (2.2)

Recruitment

Study B2202 enrolled and treated paediatric and young adult patients with r/r B-cell ALL in 25 in investigative centres across US, EU, Canada, Australia, and Japan.

Study initiation date was 8 April 2015 (first patient first visit). Data cut-off date for the primary analysis was 25 April 2017.

Conduct of the study

Protocol amendments

The study protocol was amended 5 times. These amendments were minor to the overall study design (data not shown).

Protocol deviations

Seven patients were excluded from the PPS, one due to a major protocol deviation related to missing or incomplete documentation of disease at Baseline (i.e. for Patient B2202-1406003 the CNS classification could not be obtained at enrollment due to failed attempt of lumbar puncture). Six patients were excluded from the PPS due to tisagenlecleucel viable T-cells received were less than the minimum target dose.

Protocol deviations were reported by 22 patients (29.3%) with the majority being minor. The most common protocol deviations were related to cardiac evaluation either cardiac safety entry criteria not met prior to enrollment (in five patients), or the patient had a screening cardiac evaluation >6 weeks at pre-infusion but was not repeated (in five patients). Good clinical practice deviations were reported (in four patients) due to source documentation issues; one was related to biomarker sample collection time, one due to missing infusion form, one due to Investigator failed to review PedsQL for AEs and one was a missing PedsQL source documentation. Missing or incomplete documentation of disease post-baseline was reported and written informed consent not obtained prior to screening procedures were reported in four patients each. Other minor protocol deviations were reported in only one more patient.

Baseline data

The demographic and Baseline disease characteristics were representative of the r/r paediatric and young adult B-cell ALL patient population are presented in Table 18 and Table 19.

Table 14 Demographic summary (Full analysis set- Study B2202)

Demographic variable Statistics	All patients N=75
Age (years)	
n	75
Mean (SD)	12.0 (5.28)
Median	11.0
Min-Max	3 - 23
Age category (years) - n (%)	
<10	31 (41.3)
≥ 10 to <18	31 (41.3)
≥ 18	13 (17.3)
Sex - n (%)	
Female	32 (42.7)
Male	43 (57.3)
Race - n (%)	
White	58 (77.3)
Asian	6 (8.0)
Other	11 (14.7)
Ethnicity - n (%)	
Hispanic or Latino	14 (18.7)
Other	61 (81.3)
Weight for tisagenlecleucel manufacturing (kg)	
n	75
Mean (SD)	42.4 (23.72)
Median	33.8
Min-Max	14.4 - 137.0
Karnofsky/Lansky performance status - n (%)	
100	26 (34.7)
90	23 (30.7)
80	13 (17.3)
70	8 (10.7)
60	2 (2.7)
50	3 (4.0)
<50	0

SD: standard deviation

Table 15 Enrolment ALL disease characteristics (Full analysis set- Study B2202)

Characteristic	All patients N=75
MRD in bone marrow by flow cytometry (%)	
n	70
Mean (SD)	51.946 (31.4675)
Median	62.740
Min-Max	0.16 - 97.37
Morphologic blast count in bone marrow (%) [1]	
n	75
Mean (SD)	63.04 (30.937)
Median	74.00
Min-Max	5.0 - 98.5
CNS status classification - n (%)	
CNS-1	63 (84.0)
CNS-2	10 (13.3)
CNS-3	1 (1.3)
Unknown [2]	1 (1.3)
Extramedullary disease presentation at physical exam - n (%)	
Yes	11 (14.7)
No	64 (85.3)

ALL: acute lymphoblastic leukemia; CNS: central nervous system; MRD: minimal residual disease; SD: standard deviation.

[1] Morphologic blasts count in bone marrow is the max from biopsy or aspirate if both are available.

[2] Lumbar puncture was performed but was unsuccessful.

The primary disease history and prior antineoplastic therapies are presented in Table 20.

Table 16 Primary disease history and prior antineoplastic therapies FAS = 75 (100)

Category	Subcategory	N (%)
Age at initial diagnosis (years)	Mean (SD) Median Min-Max	7.5 (4.94) 6.00. 4 - 21
Age at initial diagnosis category (years) - n (%)	<10 ≥ 10	52 (69.3) 23 (30.7)
Prior stem-cell transplantation – n (%)	0 1 2	29 (38.7) 40 (53.3) 6 (8.0)
Disease status - n (%)	Primary refractory[1] Relapsed disease[2]	6 (8.0) 69 (92.0)
Number of previous lines of therapy	Mean (SD) Median Min-Max	3.4 (1.55) 3.0 1 - 8
Time since initial diagnosis to first relapse (months) [3]	n Mean (SD) Median Min-Max	69 32.8 (16.22) 32.9 1.0 - 70.0
Time since initial diagnosis to first relapse category (months) - n (%) [3]	<18 18 to 36 >36	15 (21.7) 24 (34.8) 30 (43.5)
Time since most recent relapse to tisagenlecleucel infusion (months) [3]	n Mean (SD)	69 4.2 (2.69)

	Median Min-Max	3.5 1.5 - 13.8
[1]Primary refractory: Never had a morphologic complete remission (CR) prior to the study; [2]Relapsed disease: Had at least one relapse prior to the study [3]Calculated for relapsed disease patients only.		

Numbers analysed

Table 17 Analysis sets (Study B2202)

Analysis set	All patients N=107 n (%)
Screened set	107 (100)
Enrolled set	92 (86.0)
Full analysis set	75 (70.1)
Safety set	75 (70.1)
Per-protocol set	68 (63.6)
Pharmacokinetic analysis set	75 (70.1)
Tocilizumab Pharmacokinetic Analysis Set	28 (26.2)

Outcomes and estimation

Primary endpoint-ORR

The interim analysis performed on the first 50 patients infused with tisagenlecleucel with Data cut-off (DCO) of 17 August 2016. At the updated analysis at the DCO (25 April 2017) median duration from tisagenlecleucel infusion to DCO was 13.1 months (range 2.1 to 23.5) for the FAS.

Table 18: BOR and ORR during 3 months post-tisagenlecleucel infusion by IRC assessment FAS(Study B2202)

Interim efficacy analysis set = 50 first patients who receive tisagenlecleucel infusion				
		n (%)	**All patients N=50 95% CI**	**p-value**
BOR	CR CRi NR or unknown ORR: (CR+CRi)	34 (68.0) 7 (14.0) 9 (18.0) 41 (82.0)	(68.6, 91.4)	<0.0001 [1]
Full analysis set: 25-Apr-2017 cutoff				
		n (%)	**All patients N=75 95% CI**	**p-value**
BOR	CR CRi No response Unknown (UNK) ORR: (CR+CRi)	45 (60.0) 16 (21.3) 6 (8.0) 8 (10.7) 61 (81.3)	(70.7,89.4)	<0.0001 [2]
[1] Indicates statistical significance (one-sided) at the 0.0057 level so that the null hypothesis that ORR ≤ 0.2 is rejected. [2] No formal significance testing was conducted. Nominal p-value is presented.				

A sensitivity analysis for the ORR was performed using the local Investigator's assessment. The ORR was 82.7% (62/75) (95% CI: 72.2 to 90.4).

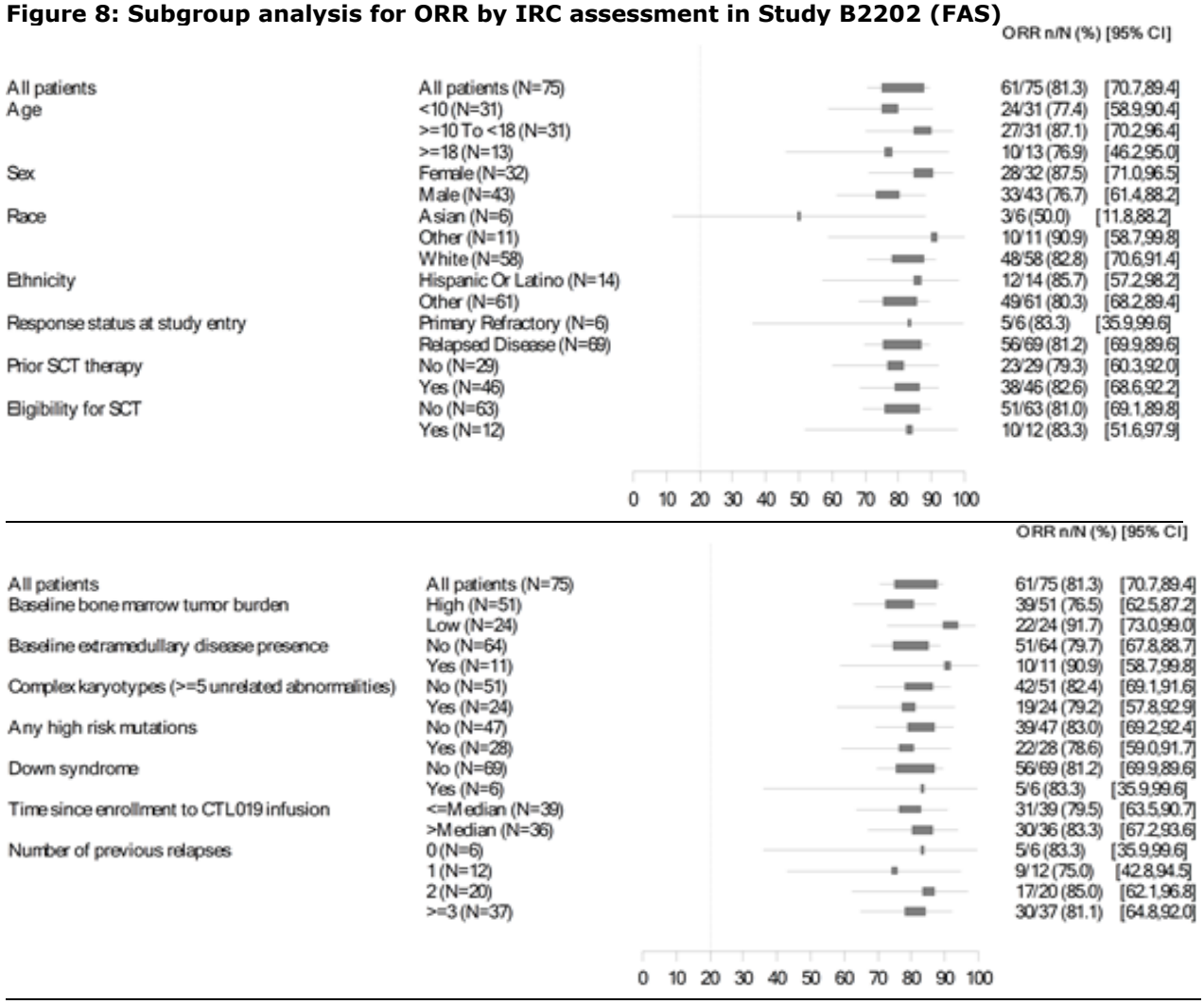
The results of predefined sensitivity analyses are displayed in Table 23.

Table 19 ORR by IRC assessment- Sensitivity analysis (Study B2202)

	All Patients	
	n/N (%)	95% CI
ORR (CR+Cri		
FAS (Primary analysis)	61/75 (81.3)	(70.7,89.4)
Per-protocol set	56/68 (82.4)	(71.2,90.5)
Enrolled set	61/92 (66.3)	(55.7,75.8)
All patients who satisfy all clinical eligibility	61/96 (63.5)	(53.1,73.1)

The results of the pre-planned subgroup analyses are displayed in Figure 12.

Figure 8: Subgroup analysis for ORR by IRC assessment in Study B2202 (FAS)



Note; area of each box is proportional to the number of patients in the particular grouping. The 95% CIs are exact Clopper-Pearson CIs calculated for each subgroup.

Secondary endpoint-Bone marrow MRD status during 3 months by IRC assessment at interim analysis

Forty-one patients of the first 50 treated patients (82.0%, 95% CI: 68.6, 91.4; p<0.0001) achieved BOR of CR or CRi per IRC assessment during 3 months post-tisagenlecleucel infusion with bone. All patients who achieved BOR also achieved bone marrow MRD negative remission (data not shown).

Secondary endpoint-Duration of remission

Seventeen of the 61 patients (27.9%) who achieved a CR or CRi relapsed after tisagenlecleucel per IRC review. The relapses occurred between 48 and 269 days after onset of remission. Responses were ongoing and censored at data cut-off date in 30 patients. Fourteen more patients were censored for DOR as follows: 7 patients for SCT while in remission, 6 patients for new cancer therapy while in remission other than SCT (4 humanized CD19 CAR-T cells, one received vincristine sulfate and blinatumomab, and one received ponatinib), one patient for adequate assessment no longer available. The estimated relapse-free rate among responders at Month 6 after onset of remission was 79.5% (data not shown).

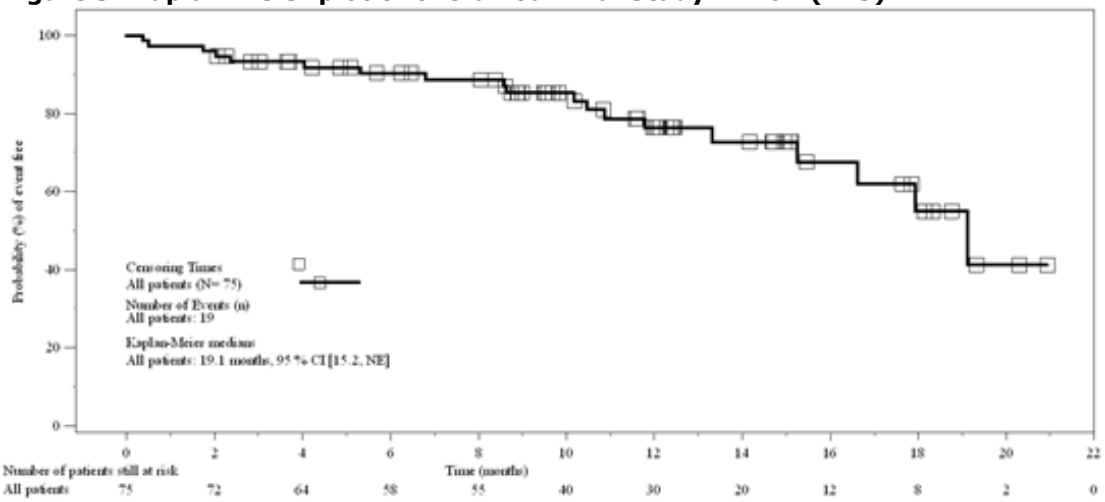
Secondary endpoint-Relapse-free survival

Among patients with a BOR of CR or CRi, there was no due to reasons other than the underlying cancer, and thus RFS was the same as DOR (data not shown).

Secondary endpoint-Overall survival

In the FAS, 19/75 patients (25.3%) died after tisagenlecleucel infusion and the probability of survival was 90.3% (95% CI: 80.7 to 95.3) at Month 6 and 76.4% (95% CI: 62.7 to 85.5) at Month 12. The KM plot of OS in the FAS is shown below.

Figure 9: Kaplan-Meier plot of overall survival Study B2202 (FAS)



CI: confidence interval; NE: not estimated; FAS: full analysis set.
Time is relative to first tisagenlecleucel infusion date. 1 month=30.4375 days.

The results of the OS for both the infused and the enrolled patients are presented in table 24.

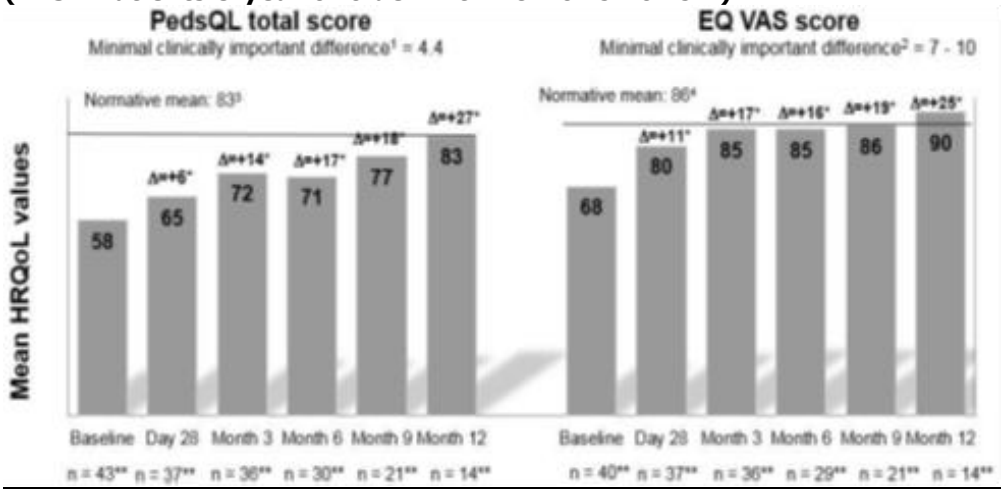
Table 20. OS (Study B2202)

	Infused patients N=75	**Enrolled patients N=92**
Overall survival (OS)		
% survival probability at 6 months	90.3	77.4
% survival probability at 12 months	76.4	70.3
Median (months) (95% CI)	19.1 (15.2, NE)	19.4 (14.8, NE)

Secondary endpoint-Quality of Life outcomes

Health-related quality of life (HRQoL) was evaluated by PedsQL and EQ-5D questionnaires completed by patients aged 8 years and above (n=58). Among patients responding (n=48), the mean_(SD) change from baseline in the PedsQL total score was 13.5 (13.5) at month 3, 16.9 (17.6) at month 6 and 27.2 (21.7) at month 12, and the mean (SD) change from baseline in the EQ-5D VAS score was 16.5 (17.5) at month 3, 15.9 (20.1) at month 6 and 24.7 (18.6) at month 12, indicating overall clinically meaningful improvement in HRQoL following Kymriah infusion (SmPC, section 5.1).

Figure 10 PedsQL scores, EQ VAS scores and change from baseline by visit in Study B2202 (FAS - Patients 8-year or older with BOR of CR or CRi)



*Mean change from baseline in patients who had both baseline and post-baseline score. **Only patients 8 years or older were required to complete the assessments n for each time point is the number of patients with non-missing score at that time point.

Ancillary analyses

Efficacy in patients infused with tisagenlecleucel from the EU manufacturing facility

For the 12 patients infused with tisagenlecleucel from the EU manufacturing facility, the ORR during 3 months per IRC assessment was 75.0% (9/12) (95% CI: 42.8, 94.5). Five patients (41.7%) achieved BOR of CR and four (33.3%) achieved BOR of CRi during 3 months post-tisagenlecleucel infusion. Two patients had unknown response: one patient did not have CSF assessment and for the other patient site considered the response as CRi however IRC determined the response as unknown as there was no differential count available and the patient's bone marrow biopsy and aspirate showed aplasia. All nine patients who achieved BOR as CR or CRi also achieved bone marrow MRD negative remission. Of the 9 patients who achieved remission, responses were ongoing in eight patients and for one patient the duration of remission was 64 days. As of the data cut-off date of 25 April 2017, all 12 patients were alive.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Title: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in paediatric patients with relapsed and refractory B-cell acute lymphoblastic leukaemia			
Study identifier	CCTL019B2202 (B2202), EudraCT no. 2013-003205-25		
Design	global, multicentre, single-arm, open-label Phase II study		
	Duration of main phase:		The duration of the study for individual subjects varied depending on their response. For a subject who remained in response and completed the entire protocol from the date of informed consent through the completion (5 years) and subsequently entered the long-term follow-up (LTFU) protocol (A2205B), the total follow-up duration was planned to be up to 15 years.
Hypothesis	The primary efficacy analysis in patients with ALL was performed by testing the null hypothesis of ORR being less than or equal to 20% against the alternative hypothesis that the RR was > 20% at an overall one-sided 2.5% level of significance, powered for an ORR of 45%.		
Treatments groups	tisagenlecleucel		For patients ≤ 50 kg: 0.2 to 5.0×10^6 CAR+ viable T-cells/kg body weight For patients >50 kg: 0.1 to 2.5×10^8 CAR+ viable T-cells Single Infusion. Novartis process Novartis Morris Plains facility (N=6; Fraunhofer-Institut für Zelltherapie
Endpoints and definitions	Primary endpoint	ORR	Overall remission rate (ORR) assessment during the 3 months after tisagenlecleucel administration; ORR includes CR and CRi, as determined by independent review committee (IRC) assessment from all manufacturing sites.
	Key Secondary endpoint	ORR	IRC assessed ORR (CR + CRi) during 3 months after infusion of tisagenlecleucel from *US* manufacturing Sites
		MRD	% of patients with BOR of CR or CRi with MRD negative bone marrow by flow cytometry during the 3 months after CTL019 infusion among all patients who are infused with CTL019 from all manufacturing facilities
		MRD	% of patients with BOR of CR or CRi with MRD negative bone marrow by flow cytometry during the 3 months after CTL019 infusion among all patients who are infused with CTL019 from US manufacturing facilities
	Other Secondary endpoints	ORR	% CR/CRi pts at Month 6 *w/o* SCT btw infusion and Month 6 % CR/CRi pts at Month 6 *with* SCT btw infusion and Month
		DOR	Duration of remission based on Kaplan-Meier estimate based on IRC assessment
		RFS	Relapse Free Survival time based on Kaplan-Meier estimate
		EFS	Progression Free Survival time based on Kaplan-Meier estimate
		OS	Overall Survival based on Kaplan-Meier estimate
Database lock	**25-Apr-2017**		
Results and Analysis			

Analysis description	**Primary Analysis**			
Analysis population and time point description	Based on the full analysis set (FAS)			
Primary Endpoint	Treatment group	US facility	EU facility	All manufacturing sites
	Number of subject	63	12	75
	ORR (CR+CRi), n(%)	52 (82.5)	9 (75)	61 (81.3)
	95% CI	(70.9, 90.9)	(42.8, 94.5)	(70.7, 89.4)
	CR, n (%)	40 (63.5)	5(41.7)	45 (60.0)
	CRi, n (%)	12(19.0)	4(33.3)	16 (21.3)
	NR [1], n (%)	5 (7.9)	1 (8.3)	6 (8.0)
	Unknown n (%)	6 (9.5)	2 (16.7)	8 (10.7)
	Primary endpoint	Tisagenlecleucel group		ORR vs 20% historic ORR
		P-value		< 0.0001
		IA cut-off date 17-Aug-2016		Primary data cut-off date 25-Apr-2017
Key Secondary Endpoints		N=50		N=75
CR or CRi with MRD negative bone marrow N (%) 95% CI P-value		 41 (82.0) (68.6, 91.4) < 0.0001		 61 (81.3) (70.7, 89.4) < 0.0001
DOR N % event free probability at 6 months (95% CI) % event free probability at 12 months (95% CI) Median DOR months (95% CI)		 41 60.2 (35.8, 77.8) - Not reached (4.9, NE)		 61 79.5 (65.1, 88.5) 50.5 (41.1,72.5) Not reached (8.6, NE)
Other Secondary Endpoints		N=62		N=75
EFS Events/Total (%) Median follow-up (months) Median EFS (months) (95% CI) % Event-free probability est at Month 12 (95% CI)		 18/62 (29.0) 3.65 7.1 (5.8, NE) 42.7 (21.1, 62.8)		 27/75 (36.0) 5.98 NE (8.9, NE) 50.5 (41.1, 72.5)
OS % event free probability at 6 months (95% CI) % event free probability at 12 months (95% CI) Events/Total (%) Median OS (months) (95% CI)		 88.5 (75.7, 94.7) 72.4 (49.7, 86.1) 9/62 (14.5) Not reached (8.6, NE)		 90.3 (80.7, 95.3) 76.4 (62.7,85.5) 19/75 (25.3) 19.1 (15.2, NE)

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

N/A

Clinical studies in special populations

Not applicable.

Supportive studies

Study B2205J enrolled 35 paediatric and young adult patients with r/r B-cell ALL with a median age of 12 years (range: 3 to 25 years. Twenty-nine patients were infused with tisagenlecleucel. All infused patients had Karnofsky/Lansky performance status ≥ 50%, and included high risk cytogenetics, following a median of 3 prior therapies (range: 1 to 9), of which 58.6% of patients had failed prior allogeneic SCT. The study also included patients with active central nervous system (CNS) leukaemia involvement defined as CNS3. Patients with other forms of CNS3 leukemic involvement (non-CSF involvement) were eligible if disease stabilization for at least 3 months prior to tisagenlecleucel infusion. Patients with other forms of active CNS3 leukemic involvement such as CNS parenchymal or ocular disease, cranial nerve involvement or significant leptomeningeal disease were not eligible.

Study B2101J was a single-arm, single-site phase I/II study in 56 paediatric and young adult patients 1 to 24 years of age with CD19+ B cell malignancies with no available curative treatment options (such as autologous or allogeneic stem cell transplantation) who had limited prognosis (several months to <2 year survival) with currently available therapies. Tisagenlecleucel treatment was administered using an intra-patient dose escalation approach: 10% on day 0, 30% on day 1, possibly followed by 60% on day 14 (or later) with a total dose goal of ~1.5 $x10^7$ to 5 $x10^9$ (~0.3$x10^6$ to 1.0$x10^8$/kg) T cells.

Of four patients with active CNS leukaemia (i.e. CNS-3) included in study B2101J, three experienced cytokine release syndrome (Grade 2-4) and transient neurological abnormalities (Grade 1-3) that resolved within 1-3 months of infusion. One patient died due to disease progression and the remaining three patients achieved a CR or CRi and remain alive 1.5-2 years after infusion.

A summary of efficacy in Studies B2205J and B2101J (FAS) is displayed in Table 25.

Table 21 Summary of efficacy in Studies B2205J and B2101J (FAS)

		Study B2205J	Study B2101J non-CNS3 ALL
Efficacy parameter		**N (%)**	**N (%)**
ORR [1]	N ORR (CR + CRi), n (%)) (95% CI) p-value CR, n (%) CRi, n (%) NR [2], n (%) Unknown [2], n (%)	29 20 (69.0) (43.6, 88.1) <0.0001 [5] 18 (62.1) 2 (6.9) 7 (24.1) 2 (6.9) [3]	**56** 53 (94.6) (85.1, 98.9) N/A 42 (75.0) 11 (19.6) 3 (5.4) 0
Response with MRD-negative bone marrow	n (%) (95% CI)	18 (62.1) (42.3, 79.3)	48 (85.7) [6] (73.8, 93.6)
DOR	Events/Responders (%) Median follow-up (months) Median DOR (months) (95% CI) % Event-free probability estimates at Month 12 (95% CI)	8/20 (40.0) 6.4 Not reached 66.4 (39.3, 83.6)	21/53 (39.6) 8.6 33.4 (8.0, NE) 73.2 (58.1, 83.5)
EFS	Events/Total (%) Median follow-up (months) Median (months) (95% CI) % Event-free probability estimates at Month 6 (95% CI) [4]	17/29 (58.6) 5.7 6.9 (1.5, NE) 55.0 (35.3, 70.9)	24/56 (42.9) 8.2 28.8 (8.6, NE) 73.9 (59.9, 83.7)
OS	Events/Total (%) Median follow-up (months) Median OS (months) (95% CI) % Event-free probability estimates at Month 12 (95% CI) [4]	10/29 (34.5) 7.3 Not reached 75.7 (55.7, 87.6)	22/56 (39.3) 22.1 37.9 (22.7, NE) 85.7 (73.5, 92.6)

[1] Study B2205J: ORR was a primary endpoint, responses were assessed by IRC, BOR lasting for at least 28 days during 6 months after infusion. Study B2101J: ORR was a secondary endpoint, ORR assessed by Investigator at Day 28.
[2] Includes relapse from response without maintaining for at least 28 days in B2205J
[3] Unknown: 2 patients died before the first scheduled assessment
[4] % event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. % Event-free probability estimates are obtained from the Kaplan- Meier survival estimates; Greenwood formula is used for CIs of Kaplan-Meier estimates.
[5] One-sided exact p-value threshold 0.0052 (adjusted for interim). The null hypothesis of ORR ≤ 20% was rejected.
[6] At Day 28.

A Phase I Study B2102J, with tisagenlecleucel in adult ALL patients have been completed. 6 adult patients with r/r ALL (one female, 5 males) were infused with a median total tisagenlecleucel cell dose of 9.2×10^7 cells (range: 6.8×107 to 9.6×108 cells). The median age was 50.5 years (range: 25 to 71 years), all of the patients had received ≥ 2 prior treatment regimens, with no prior HSCT. Three had prior radiotherapy.

The ORR (CR/CRi) for these 6 adult patients was 83.3% (95% CI: 35.9, 99.6). Four patients had a CR, 1 had CRi and 1 had NR/ disease progression. 3 patients (50.0%) had CR/CRi with MRD-negative bone marrow. The median DOR was 18.4 months (95% CI: 2.1, NE) (data not shown).

Main Study C2201 - Adult DLBCL indication

Methods

The pivotal phase 2 study in DLBCL is an open-label, multicentre, single arm study in adult patients with r/r DLBCL. As this was a single arm study, the efficacy results of study C2201 are compared with three historical data sets (SCHOLAR-1, the pooled CORAL extensions and the PIX301 trial).

Study Participants

The target population was adult patients ≥ 18 years with r/r DLBCL after ≥ 2 lines of chemotherapy and not eligible for SCT. A minimum of 25 patients in each of the two most common subtypes of DLBCL: germinal centre B-cell (GCB) type and activated B-cell (ABC) type were treated in the main study cohort. Patients with T cell rich/histiocyte rich large B-cell lymphoma, primary cutaneous DLBCL, primary mediastinal B-cell lymphoma, Epstein-Barr virus-positive DLBCL of the elderly, Richter's transformation, and Burkitt lymphoma were not allowed.

Main inclusion criteria – Study C2201

1. Histologically confirmed DLBCL at last relapse (by central pathology review before enrollment).
2. Relapsed or refractory disease after ≥ 2 lines of chemotherapy, including rituximab and anthracycline, and either having failed autologous SCT, or being ineligible for or not consenting to autologous SCT.
3. Measurable disease at time of enrollment:
    a. Nodal lesions greater than 20 mm in the long axis, regardless of the length of the short axis
    b. Extra-nodal lesions (outside lymph node or nodal mass, but including liver and spleen) ≥ 10 mm in long AND short axis (based on [26])
4. Life expectancy ≥ 12 weeks
5. Eastern Cooperative Oncology Group (ECOG) performance status that was either 0 or 1 at screening
6. Adequate renal, hepatic, pulmonary, and cardiac functions
7. Adequate bone marrow reserve without transfusions defined as:
    i. Absolute neutrophil count >1.000/mm^3
    ii. Absolute lymphocyte count >300/mm^3, and absolute number of CD3+ T-cells >150/mm^3
    iii. Platelets ≥ 50.000/mm^3
    iv. Haemoglobin >8.0 g/dL
8. Must have an apheresis product of non-mobilized cells accepted for manufacturing.
9. Women of child-bearing potential defined as all women physiologically capable of becoming pregnant and all male participants, used highly effective methods of contraception for at least

12 months following tisagenlecleucel infusion and until CAR T cells were no longer present by quantitative polymerase chain reaction (qPCR) on two consecutive tests.

Main exclusion criteria – Study C2201

1. Patients with T-cell rich/histiocyte rich large B-cell lymphoma, primary cutaneous large B-cell lymphoma, primary mediastinal B-cell lymphoma, Epstein-Barr virus-positive DLBCL of the elderly, Richter's transformation, and Burkitt lymphoma.
2. Patients with active neurological auto immune or inflammatory disorders (e.g. Guillain-Barré Syndrome, amyotrophic lateral sclerosis)
3. Prior treatment with any adoptive T cell therapy or other gene therapy product, any anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy
4. Prior allogenic SCT, or eligible for and consenting to autologous SCT
5. Active CNS involvement by malignancy
6. Chemotherapy other than LD chemotherapy within 2 weeks of infusion
7. Investigational medicinal product within the last 30 days prior to screening. Note: Investigational therapies were not used at any time while on study until the first progression following tisagenlecleucel infusion.
8. The following medications were excluded:
    a. **Steroids:** Therapeutic doses of steroids were stopped >72 hours prior to leukapheresis and >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. **Immunosuppression:** Any other immunosuppressive medication was stopped ≥ 2 weeks prior to leukapheresis and ≥ 2 weeks prior to tisagenlecleucel infusion. This could include checkpoint inhibitors (monoclonal antibodies and small molecule modulators).
    c. **Antiproliferative therapies** other than LD chemotherapy within 2 weeks of leukapheresis and 2 weeks prior to infusion
        i. Short acting drugs used to treat leukemia or lymphoma (e.g. TKIs, and hydroxyurea) was stopped >72 hour prior to leukapheresis and >72 hours prior to tisagenlecleucel infusion.
        ii. Other cytotoxic drugs, including low dose daily or weekly maintenance chemotherapy, were not given within two weeks prior to leukapheresis and within two weeks prior to tisagenlecleucel infusion.
        iii. Fludarabine may be associated with prolonged lymphopenia. This was taken into consideration when evaluating the optimal timing for leukapheresis collection.
    d. **Antibody use** including anti-CD20 therapy within four weeks prior to infusion or five half-lives of the respective antibody, whichever is longer. Note: Rituximab is excluded within four weeks prior to infusion.

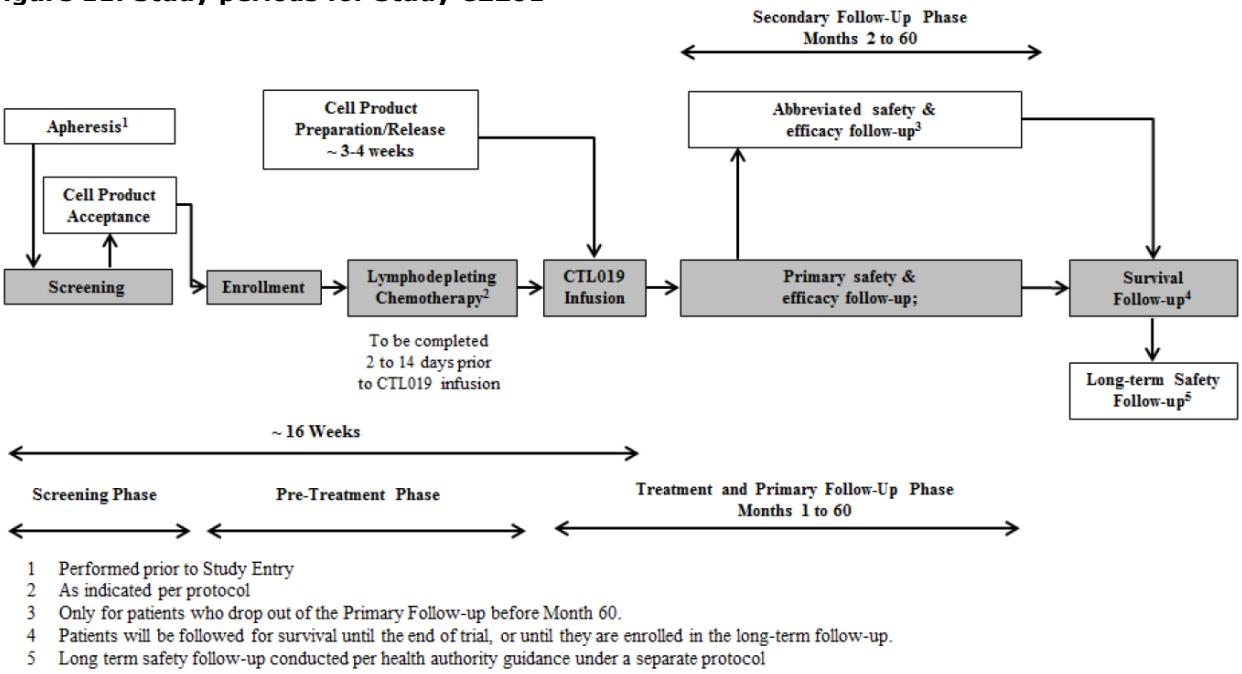
e. **CNS disease prophylaxis** must be stopped >1 week prior to tisagenlecleucel infusion (e.g. intrathecal methotrexate)

9. Prior radiation therapy within 2 weeks of infusion
10. Active replication of or prior infection with hepatitis B or active hepatitis C (hepatitis C virus ribonucleic acid-positive)
11. Human immunodeficiency virus-positive patients
12. Uncontrolled acute life threatening bacterial, viral or fungal infection (e.g. blood culture positive ≤ 72 hours prior to infusion)
13. Unstable angina and/or myocardial infarction within 6 months prior to screening
14. Cardiac arrhythmia not controlled with medical management
15. 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 has been completely resected and in complete remission for ≥ 5 years
16. Pregnant or nursing (lactating) women. Note: female study participants of reproductive potential had a negative serum or urine pregnancy test performed within 24 hours before lymphodepletion

Treatments

Study C2201 is a single-arm open-label study, the various sequences of the study is outlined in

Figure 11: Study periods for Study C2201



1 Performed prior to Study Entry
2 As indicated per protocol
3 Only for patients who drop out of the Primary Follow-up before Month 60.
4 Patients will be followed for survival until the end of trial, or until they are enrolled in the long-term follow-up.
5 Long term safety follow-up conducted per health authority guidance under a separate protocol

Patients were enrolled and assigned to treatment upon confirmation of all clinical eligibility criteria by the investigator and acceptance of the leukapheresis product for manufacturing.

Conditioning lymphodepleting (LD): After apheresis, 14 to 5 days prior to tisagenlecleucel infusion, subjects received a 3-day-cycle of conditioning lymphodepleting (LD) chemotherapy consisting of fludarabine (25 mg/m^2 intravenous daily for 3 doses) and cyclophosphamide (250 mg/m^2 intravenous daily for 3 doses starting with the first dose of fludarabine). The cyclophosphamide-based regimens was the agents of choice for LD chemotherapy since there is most experience with the use of these agents in facilitating adoptive immunotherapy. However, if there was previous grade IV haemorrhagic cystitis or the patient demonstrated resistance to a previous cyclophosphamide-containing regimen, then bendamustine 90 mg/m^2 intravenous daily for 2 days was recommended to be used. For patients who had a WBC count ≤ 1000 cells/µL within one week prior to tisagenlecleucel infusion, LD chemotherapy was not required. Patients who experienced toxicities from their preceding chemotherapy had their tisagenlecleucel infusion delayed. In case a period of delay was 4 or more weeks from completing LD chemotherapy and the WBC>1000/µL, the patient had to be re-treated with LD chemotherapy.

The tisagenlecleucel product was intended to be prepared and released by the manufacturing facility to the study site approximately 4-5 weeks after manufacturing has commenced.

Premedication: All patients was pre-medicated with acetaminophen/paracetamol and diphenhydramine or another H1-antihistamine. These medications was repeated every 6 hours as needed. Non-steroidal anti-inflammatory medications (NSAIDs) were prescribed if the patient continued to have fever not relieved with acetaminophen/paracetamol. Steroids should not be used for premedication. Infusions were performed 2 to 14 days after completion of LD chemotherapy. The targeted dose of tisagenlecleucel for adult patients consisted of a single infusion of 5.0×10^8 viable tisagenlecleucel transduced cells, which were administered via intravenous infusion. The acceptable dose range was considered as 1.0×10^8 to 5.0×10^8 viable tisagenlecleucel transduced cells. Prior to protocol amendment 4, doses between 0.5 to 1.0×10^8 cells were rounded to 1×10^8 cells and were infused. With

protocol amendment 4, doses below 1.0×10^8 cells were no longer released for infusion. However, for patients with manufactured cell numbers falling below the above specified recommended dose ranges, tisagenlecleucel therapy may have been administered.

Bridging chemotherapy/Concomitant medication: After signing the informed consent, patients were allowed to receive bridging therapies if required for stabilization of patient's disease while waiting for tisagenlecleucel manufacturing and infusion.

Objectives

Primary objective

To evaluate the efficacy of tisagenlecleucel therapy in the Main Cohort (i.e., patients treated with tisagenlecleucel manufactured at the Novartis manufacturing facility in Morris Plains, United States (US), referred to as "US manufacturing facility") as measured by the overall response rate (ORR). ORR was based on the Lugano Classification [26] assessed by a central independent review committee (IRC).

Secondary objectives

The main secondary objectives were evaluate safety of tisagenlecleucel, time-to-response (TTR), duration of overall response (DOR), event-free survival (EFS), progression-free survival (PFS), overall survival (OS) and efficacy and safety in histological and molecular subgroups.

Outcomes/endpoints

Primary endpoint

The primary endpoint was the ORR as determined centrally by IRC assessment. The ORR was defined as the proportion of patients with CR and PR based on the Lugano Classification criteria [26] interpreted by Novartis own Image guideline. The ORR was defined as the proportion of patients with a BOR of CR or PR, where the BOR was defined as the best disease response recorded from tisagenlecleucel until PD or start of new anticancer therapy. The results of central evaluations were used for primary analysis, and local investigator assessments were used for treatment decision making.

The efficacy evaluation was based on recommendations by the International Malignant Lymphomas Imaging Working Group [26], [27]). Efficacy of tisagenlecleucel was assessed at Day 28 (±7 days) and at 3, 6, 9, 12, 18, 24 months (±14 days) and then every 12 months for 5 years until documented disease relapse or disease progression.

A positron emission tomography (PET)-computed tomography (CT) (or CT/MRI and fluorodeoxyglucose (FDG)-PET when PET-CT were not available) was performed for disease assessments based on the Lugano classification within four weeks prior to scheduled infusion of the tisagenlecleucel product but prior to start of LD therapy and 3 months post-infusion, only. Response assessment at a given visit was based on the three components of the assessment: PET score and PET-CT based time point response assessment, CT based time point response assessment and integration of PET-CT based assessment, and CT based assessment to give overall response. CT/MRI scan was performed at baseline and/or 3 months (if no PET-CT was available) and at the other pre-defined time points (specified above) for efficacy assessment.

Secondary endpoints

IRC assessment were used in the main analysis of secondary endpoints that involved the disease response. The most important secondary endpoints were TTR, DOR, EFS, PFS, OS and safety.

Sample size

Based on the null hypothesis of ORR ≤ 20% and alternative hypothesis of ORR >20%, 80 patients in the primary analysis would provide 94% cumulative power to demonstrate statistical significance, using a 2-look Lan-DeMets group sequential design with O'Brien-Fleming type boundary and an exact CI at one-sided cumulative 0.025 level of significance, if the underlying ORR was 38%. In this setting, an ORR of 24/80=30% was needed to claim success. The sample size was appropriate to demonstrate a statistically significant result in the primary analysis.

Randomisation

This was a single arm study.

Blinding (masking)

This was an open-label study.

Statistical methods

The primary efficacy analysis was performed by testing the null hypothesis of ORR being less than or equal to 20% against the alternative hypothesis that ORR is greater than 20% at overall one-sided 2.5% level of significance, i.e., H0: $p \leq 0.2$ vs. Ha: $p>0.2$

The ORR was summarized along with the 2-sided 95% exact Clopper-Pearson confidence intervals. Taking into account the interim analysis, the study was considered successful if the lower bound of the 2-sided 95.28% exact confidence interval for ORR was greater than 20%, so that the null hypothesis that the ORR is less or equal to 20% could be rejected.

The primary objective of the study was to evaluate the efficacy of CTL019 therapy as measured by overall response rate (ORR), which includes complete response (CR) and partial response (PR) as determined by IRC assessment in the FAS in main cohort (patients treated with CTL019 from US manufacturing facility).

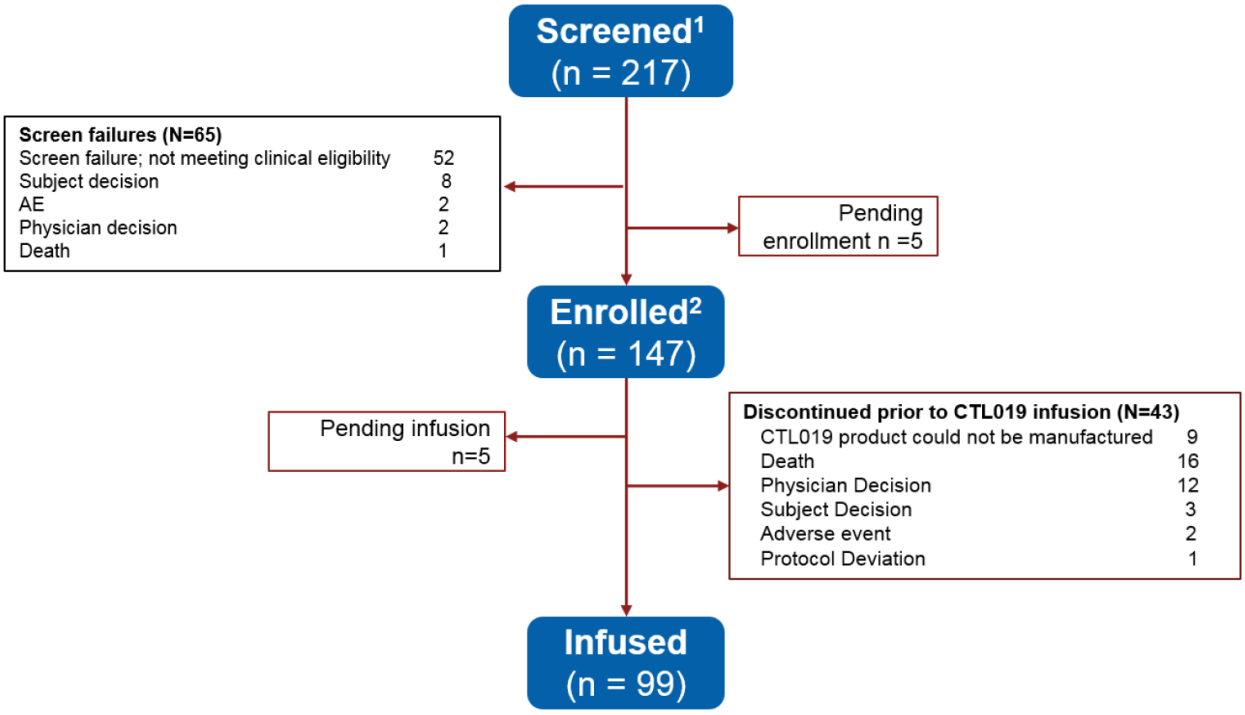
The study was ongoing at the time of interim analysis and primary analysis, when 50 and 80 patients respectively from main cohort had 3 month follow-up or discontinued earlier. Therefore EAS was used to assess the primary endpoint to these milestones to ensure that patients included in the analysis had the opportunity to be followed-up for 3 months. FAS will be used for the final update of the primary endpoint after all infused patients in the main cohort have been followed 3 months or discontinued earlier.

In addition, sensitivity analyses were to be performed using the local investigator response assessments instead of the IRC assessment.

Results

Participant flow

Figure 12 Participant flow in study C2201



[1] Screened patients are all patients who have signed informed consent. [2] Enrollment requires patient meeting clinical eligibility and having leukapheresis product accepted by manufacturing facility.

Table 22: Overall patient disposition (Enrolled set)

Disposition Reason	All patients N=147 n (%)
Enrolled in the study	**147 (100)**
Discontinued prior to tisagenlecleucel infusion	**43 (29.3)**
Death	16 (10.9)
Physician decision	12 (8.2)
Tisagenlecleucel product-related issues (tisagenlecleucel manufacturing failure)	9 (6.1)
Patient decision	3 (2.0)
Adverse event	2 (1.4)
Protocol deviation	1 (0.7)
Tisagenlecleucel infusion pending	**5 (3.4)**
Tisagenlecleucel infused	**99 (67.3)**
Study follow-up ongoing	64 (43.5)
Study follow-up completed	0
Discontinued study follow-up	**35 (23.8)**
Death	20 (13.6)
Progressive disease	10 (6.8)
Patient decision	3 (2.0)
Adverse event	1 (0.7)
Physician decision	1 (0.7)

Among the 99 patients who received tisagenlecleucel infusion, 92 received infusion from the US manufacturing facility (Main Cohort) and seven received infusion from the EU manufacturing facility (Cohort A). A total of 83 patients were infused at least 3 months (90 days) prior to the data cut-off date, 81 in the Main Cohort and two in Cohort A. Among the 81 patients with at least 3 months follow-up, 46 patients had ≥ 6 months follow-up, 24 patients had ≥ 9 months follow-up and nine patients had ≥ 12 months follow-up. The median times from screening and enrolment to tisagenlecleucel infusion were 119 days (range: 49 to 396) and 54 days (range: 30 to 357), respectively, and the median time from tisagenlecleucel infusion to data cut-off date was 5.6 months (range: 0.0 to 17.1).

Of the 217 screened patients, 165 patients fulfilled the eligibility criteria, 147 patients were enrolled and 99 patients were infused. Thus, there is a large difference between the numbers of screened, eligible, enrolled and infused patients.

Recruitment

Study initiation date was 29-Jul-2015 (first patient first visit). Data cut-off (DCO) date for the primary analysis was 08-Mar-2017 (the study is ongoing). The main contributing country in study C2201 were USA (12 centres), but a significant number of European centres (7 centres) also recruited patients into the study. Additional follow-up data from the study were provided with a data cut-off of 06-Sep-2017.

Conduct of the study

There were four global amendments over the course of the study and before the data cut-off date for the primary analysis (08/03/2017). Amendment 1 added an interim analysis (IA) when approximately

50 DLBCL patients had been treated and followed up for 6 months. Based on the α-spending function according to Lan-DeMets (O'Brien-Fleming), if the lower bound of 99.08% exact confidence interval for ORR was greater than 20% then statistical significance could be declared. If the predicted probability of success (i.e, positive result at the end of the study) was less than 10% then the study may be terminated due to futility. This amendment also added a safety run-in stage -to enrol at least 3 patients to assess the acute safety profile and product characteristics of the Novartis manufactured tisagenlecleucel cell product- and modified the inclusion and exclusion criteria to ensure a homogenous population. Allogeneic HSCT were removed from inclusion criteria. The exclusion of patients with T cell rich/histiocyte rich large B-cell lymphoma, primary cutaneous DLBCL, primary mediastinal B-cell lymphoma, Epstein-Barr virus-positive DLBCL of the elderly, Richter's transformation, and Burkitt lymphoma were introduced in protocol amendment 2 along with a redefinition of the term of final enrolment. Furthermore, the decision to prohibit release of tisagenlecleucel doses lower than the protocol specified range was introduced in protocol amendment 4.

Protocol deviations were reported on 48 patients in the Main Cohort (59.3%) in the EAS and 57 patients (57.6%) in the FAS with the majority being considered minor deviations. There was one major protocol deviation for a patient who had single lung lesion thought to be progression of DLBCL and was enrolled based on central confirmation of DLBCL from an archival tumour sample; however, based on a subsequent biopsy done after relapse, this patient was determined by the Investigator to have had neuroendocrine carcinoma at the time of study entry rather than DLBCL.

The most common protocol deviations fell into the following categories: Assessments not being repeated before tisagenlecleucel infusion as per protocol requirements; Signed written informed consent not obtained prior to any study procedures ; GCP not followed (GCP deviations (16 in total) were mostly (n=13) related to late reporting of SAEs (more than 24 hours) to the Novartis Safety Department. These SAEs were all ultimately captured in the database); Patients were not dosed as per protocol requirements (doses above or below dosing range); Response assessments were not performed as described in the protocol; Testing for influenza was not done 10 days prior to planned tisagenlecleucel infusion.

Baseline data

Baseline data

The demographic and baseline disease characteristics were representative of the r/r DLBCL patient population as defined by the protocol criteria (see Table 27).

Table 23: Demographics (FAS)

Demographic variable Statistics	All patients N=99
Age (years)	
n	99
Mean (SD)	54.0 (13.04)
Median	56.0
Min-Max	22.0-76.0
Age category (years) – n (%)	
<40	14 (14.1)
≥ 40 to <65	62 (62.6)
≥ 65	23 (23.2)
Sex – n (%)	
Female	36 (36.4)
Male	63 (63.6)
Race – n (%)	
White	90 (90.9)
Asian	4 (4.0)
Black	4 (4.0)
Other	1 (1.0)
Ethnicity - n (%)	
Hispanic or Latino	1 (1.0)
Other [1]	98 (99.0)
ECOG performance status - n (%)	
0	54 (54.5)
1	45 (45.5)

Table 24: Primary disease history and prior antineoplastic therapies (FAS)

Disease history	All patients N=99
Bone marrow involvement at initial diagnosis - n (%)	
No	78 (78.8)
Yes	18 (18.2)
Missing	3 (3.0)
Bone marrow involvement at study entry - n (%)	
No	92 (92.9)
Yes	7 (7.1)
Predominant histology/cytology - n (%)	
Diffuse large B-cell lymphoma	79 (79.8)
Transformed lymphoma	19 (19.2)
Other [1]	1 (1.0)
Stage at initial diagnosis - n (%)	
Stage I	9 (9.1)
Stage II	20 (20.2)
Stage III	16 (16.2)
Stage IV	50 (50.5)
Unknown	3 (3.0)
Missing	1 (1.0)
Stage at study entry - n (%)	
Stage I	7 (7.1)
Stage II	16 (16.2)
Stage III	21 (21.2)
Stage IV	55 (55.6)
IPI at initial diagnosis - n (%)	
<2 risk factors	25 (25.3)
≥ 2 risk factors	56 (56.6)
Unknown	18 (18.2)
IPI at study entry - n (%)	
<2 risk factors	27 (27.3)
≥ 2 risk factors	72 (72.7)
Prior hematopoietic stem cell transplant [3] - n (%)	
No	52 (52.5)
Yes	47 (47.5)
Disease status - n (%)	
Refractory to last line	51 (51.5)
Relapsed to last line	48 (48.5)
Molecular subtype (cell of origin)	
Germinal center B-cell type	51 (51.5)
Activated B-cell type	42 (42.4)
Missing	6 (6.1)

Disease history	All patients N=99
Double/Triple hits in MYC/BCL2/BCL6 genes	
CMYC+BCL2+BCL6	4 (4.0)
CMYC+BCL2	8 (8.1)
CMYC+BCL6	3 (3.0)
Negative	42 (42.4)
Not done [4]	36 (36.4)
Missing	6 (6.1)
Time since most recent relapse/progression prior to tisagenlecleucel infusion (months)	
n	99
Mean (SD)	6.1 (2.98)
Median	5.4
Min-Max	2.1-21.5
Number of prior lines of anti-neoplastic therapy- n (%)	
1 [2]	5 (5.1)
2	44 (44.4)
3	31 (31.3)
4	14 (14.1)
5	4 (4.0)
6	1 (1.0)

IPI: international prognostic index; SD: standard deviation.

[1] Patient with predominant histology/cytology being large cell neuroendocrine carcinoma; [2] Five patients with only one line of prior chemotherapy for DLBCL; [3] Autologous stem cell transplantation; [4] A cut-off of 40% MYC expression by immunohistochemistry was used to further test for rearrangements involving MYC, BCL2 and BCL6 by FISH; cases where this analysis was not done are not suspected to be high risk "double/triple hit" lymphomas.

Bridging chemotherapy and Lymphodepleting chemotherapy

Among the 99 patients who received tisagenlecleucel infusion, 89 patients (90%) had received antineoplastic therapy after enrollment and prior to tisagenlecleucel infusion. The most frequently used (≥ 15% of patients) bridging therapies were rituximab (54.5%), gemcitabine (38.4%), dexamethasone (25.3%), etoposide (22.2%), cytarabine (19.2%), cisplatin (18.2%), and cyclophosphamide (15.2%).

Among the 99 patients who received tisagenlecleucel infusion, 92 (92.9%) patients received LD chemotherapy after enrolment and prior to tisagenlecleucel infusion.

With the updated cut off in Study C2201, 165 patients were enrolled, 111 of whom were infused (93 patients in the Main Cohort and 18 patients in Cohort A).

Table 25 Comparison of demographics of the non-infused and infused patient populations – updated cut-off DCO: 08-Dec-2017

	Infused N = 111 n (%)	Non-infused N = 54 n (%)	Enrolled N = 165 n (%)
Age (years)			
Mean (standard deviation)	53.9 (12.95)	60.0 (11.79)	55.9 (12.87)

	Infused N = 111 n (%)		Non-infused N = 54 n (%)		Enrolled N = 165 n (%)	
Median (minimum – maximum)	56	(22 - 76)	63	(32 - 76)	59	(22 - 76)
Age category (years) – n (%)						
< 65 years	86	(77.5)	32	(59.3)	118	(71.5)
≥ 65 years	25	(22.5)	22	(40.7)	47	(28.5)
Sex – n (%)						
Male	68	(61.3)	35	(64.8)	103	(62.4)
Female	43	(38.7)	19	(35.2)	62	(37.6)
Race – n (%)						
White	98	(88.3)	39	(72.2)	137	(83.0)
Asian	6	(5.4)	10	(18.5)	16	(9.7)
Black	4	(3.6)	4	(7.4)	8	(4.8)
Other	3	(2.7)	1	(1.9)	4	(2.4)
Ethnicity – n (%)						
Hispanic or Latino	1	(0.9)	1	(1.9)	2	(1.2)
Other	110	(99.1)	53	(98.1)	163	(98.8)
ECOG performance status – n (%)						
0	61	(55.0)	16	(29.6)	77	(46.7)
1	50	(45.0)	38	(70.4)	88	(53.3)

Table 26: Comparison of the baseline disease characteristics of the non-infused and infused patient populations DCO: 08-Dec-2017

	Infused N = 111 n (%)		Non-infused N = 54 n (%)		Enrolled N = 165 n (%)	
Primary site of cancer – n (%)						
Lymphoma: non-Hodgkin's disease	111	(100)	54	(100)	165	(100)
Bone marrow involvement at initial diagnosis – n (%)						
No	86	(77.5)	42	(77.8)	128	(77.6)
Yes	20	(18.0)	8	(14.8)	28	(17.0)
Missing	5	(4.5)	4	(7.4)	9	(5.5)
Bone marrow involvement at study entry – n (%)						
No	103	(92.8)	48	(88.9)	151	(91.5)
Yes	8	(7.2)	6	(11.1)	14	(8.5)
Predominant histology/cytology – n (%)						
Diffuse large B-cell lymphoma	88	(79.3)	39	(72.2)	127	(77.0)
Transformed follicular lymphoma	21	(18.9)	13	(24.1)	34	(20.6)
Transformed lymphoma – other	1	(0.9)	2	(3.7)	3	(1.8)
Other	1	(0.9)	0		1	(0.6)
Stage at study entry – n (%)						
Stage I	8	(7.2)	1	(1.9)	9	(5.5)
Stage II	19	(17.1)	8	(14.8)	27	(16.4)
Stage III	22	(19.8)	14	(25.9)	36	(21.8)
Stage IV	62	(55.9)	31	(57.4)	93	(56.4)
IPI at study entry – n (%)						

	Infused N = 111 n (%)		Non-infused N = 54 n (%)		Enrolled N = 165 n (%)	
< 2 risk factors	31	(27.9)	3	(5.6)	34	(20.6)
≥ 2 risk factors	80	(72.1)	51	(94.4)	131	(79.4)
Prior hematopoietic stem cell transplant (SCT) – n (%)						
No	57	(51.4)	36	(66.7)	93	(56.4)
Yes	54	(48.6)	18	(33.3)	72	(43.6)
Molecular subtype – n (%)						
Germinal center B-cell type	63	(56.8)	31	(57.4)	94	(57.0)
Activated B-cell type	45	(40.5)	19	(35.2)	64	(38.8)
Missing	3	(2.7)	2	(3.7)	5	(3.0)
Cannot be determined	0		2	(3.7)	2	(1.2)
Double/triple hits in MYC/BCL2/BCL6 gene						
CMYC+BCL2+BCL6	5	(4.5)	3	(5.6)	8	(4.8)
CMYC+BCL2	10	(9.0)	6	(11.1)	16	(9.7)
CMYC+BCL6	4	(3.6)	1	(1.9)	5	(3.0)
Negative	51	(45.9)	20	(37.0)	71	(43.0)
Not done	38	(34.2)	18	(33.3)	56	(33.9)
Missing	3	(2.7)	6	(11.1)	9	(5.5)
Disease status – n (%)						
Refractory to last line of therapy	61	(55.0)	35	(64.8)	96	(58.2)
Relapse to last line of therapy	50	(45.0)	19	(35.2)	69	(41.8)
Time since most recent relapse/progression to tisagenlecleucel infusion (months)						
N	111		-		111	
Mean (standard deviation)	6	(2.95)	-		6	(2.95)
Median (minimum, maximum)	5.4	(1.6, 21.5)	-		5.4	(1.6, 21.5)
Number of prior lines of antineoplastic therapies (%)						
1	5	(4.5)	1	(1.9)	6	(3.6)
2	49	(44.1)	23	(42.6)	72	(43.6)
3	34	(30.6)	17	(31.5)	51	(30.9)
4	15	(13.5)	6	(11.1)	21	(12.7)
5	7	(6.3)	3	(5.6)	10	(6.1)
6	1	(0.9)	1	(1.9)	2	(1.2)
7	0		2	(3.7)	2	(1.2)
8	0		1	(1.9)	1	(0.6)

Numbers analysed

Numbers analysed

The Full Analysis set (FAS) and Safety set consisted of 99 patients, and the first 83 infused patients were included in the Efficacy Analysis set (EAS) (81 patients in the Main Cohort and two patients in Cohort A; those 81 patients who received tisagenlecleucel infusion from the US manufacturing facility and at least 3 months prior to data cut-off were included in the efficacy analysis set (EAS), which was the primary analysis population. In total, 80 patients were included in the per-protocol set (PPS).

Table 27: Analysis sets

Analysis set	All patients N=217 n (%)
Screened Set	217 (100)
Enrolled Set	147 (67.7)
Full Analysis Set	99 (45.6)
Safety Set	99 (45.6)
Efficacy Analysis Set	83 (38.2)
Per-Protocol Set	80 (36.9)
Pharmacokinetic Analysis Set	99 (45.6)
Tocilizumab Pharmacokinetic Analysis Set	14 (6.5)

At the data cut-off for the additional follow-up analysis (DCO: 06-Sep-2017), 160 patients were enrolled in study C2201 and 106 patients were infused with tisagenlecleucel (+7 patients compared to the primary analysis), and included in the full analysis set (FAS). In total were 92 patients followed-up for longer than 3 months and therefore included in the EAS for this update analysis (an additional 11 patients compared to the primary analysis).

At a further update based on the updated DCO of 08-Dec-2017 among the 165 patients enrolled in study C2201, 111 patients were infused and comprise the FAS, 95 of these received tisagenlecleucel manufactured at the Morris Plains facility (Main Cohort) and 16 of them from the Fraunhofer Institute (Cohort A). The primary endpoint for patients in the Main Cohort was analysed in the EAS, which consisted of 93 patients who were followed for ≥ 3 months (or had discontinued earlier). Two patients in the Main Cohort who were followed for < 3 months were not included in the EAS. Of the 54 non-infused patients, 50 were scheduled to receive tisagenlecleucel from the US manufacturing facility and 4 patients from the Fraunhofer Institute.

Outcomes and estimation

Outcomes and estimation

Primary efficacy results

Table 28: Study C2201: ORR and DOR results in the ITT population (N=-165, 08-Dec-2017 DCO)

	Enrolled patients
Primary endpoint	**N=165**
Overall response rate (ORR) (CR+PR)[1], n (%) 95% CI	**56 (33.9)** (26.8, 41.7)
CR, n (%)	40 (24.2)
PR, n (%)	16 (9.7)
Response at month 3	N=165
ORR (%)	39 (23.6)
CR (%)	33 (20.0)
Response at month 6	N=165
ORR (%)	34 (20.6)
CR (%)	30 (18.2)
Duration of response (DOR)[2]	**N=56**
Median (months) (95% CI)	Not reached (10.0, NE[4])
% relapse free probability at 6 months	66.7
% relapse free probability at 12 months	63.7

Data from 81 patients enrolled in the Main Cohort who received tisagenlecleucel and who were followed for at least 3 months (or discontinued earlier) in patients with r/r DLBCL are presented in Table 33. Forty-three of 81 (53.1%) patients demonstrated complete (32 patients; 39.5%) or partial (11 patients; 13.6%) response within 3 months after infusion.

Table 29: BOR and ORR post tisagenlecleucel infusion by IRC assessment for Main Cohort patients (EAS, 08-Mar-2017 DCO)

	All Patients N=81		
	n (%)	**95% CI**	**p-value**
BOR			
CR	32 (39.5)		
PR	11 (13.6)		
SD	11 (13.6)		
PD	18 (22.2)		
Unknown	9 (11.1)		
ORR (CR+PR)	43 (53.1)	(41.7, 64.3)	<.0001*

Table 30: Disease response by IRC assessment at Month 3 and Month 6 (EAS)

	ORR (%)	**CR (%)**
Disease response		
Month 3 [1]	31/81 (38.3)	26/81 (32.1)
Month 6 [2]	17/46 (37.0)	14/46 (30.4)

ORR Sensitivity analyses

The robustness of the primary analysis of ORR (per IRC assessment) was confirmed by the results of a series of predefined sensitivity analyses (Table 35).

Table 31: ORR by IRC assessment - Sensitivity analyses

	All patients	
	n/N (%)	95% CI
ORR (CR+PR)		
Main cohort patients in EAS	43/81 (53.1)	(41.7, 64.3)
Main cohort patients in PPS	43/80 (53.8)	(42.2, 65.0)
Main cohort patients EAS plus enrolled but not infused patients from the Main Cohort	43/125 (34.4)	(26.1, 43.4)
EAS excluding patients with no evidence of disease at baseline prior to tisagenlecleucel infusion who remain CR after infusion [1]	37/75 (49.3)	(37.6, 61.1)

[1] Six patients with no evidence of disease (CR) at baseline prior to tisagenlecleucel infusion who remain CR after infusion

ORR per local investigator assessment and concordance with IRC

The ORR as assessed by local Investigator was consistent with the results by IRC assessment. Discrepancy in terms of BOR assessment between IRC and the local Investigator was found in 14/81 patients (17.3%), which corresponds to 83% BOR assessment agreement (data not shown).

Secondary efficacy results

Time-to-response (TTR) by IRC assessment

Among the 43 responders per IRC assessment in the Main Cohort, the median time to response was 0.9 months (95% CI: 0.9, 1.0). Almost all responses were observed within the first month following infusion. The median time to response among the 43 responders per IRC assessment in the Main Cohort was 0.9 months (95% CI: 0.9, 1.0). The majority of the responders (79.1%; 34/43) achieved their disease control (CR or PR) within the first month after tisagenlecleucel infusion.

DOR per IRC assessment

At the data cut-off date for the protocol defined primary analysis, the median follow-up time from the onset of response was 2.17 months. The median DOR per IRC assessment was not reached.

Table 32: DOR by IRC assessment (EAS, 08-Mar-2017 DCO)

	All patients N=81
Events/Responders (%)	8/43 (18.6)
Maximum follow-up (months)	11.3
Median follow-up (months)	2.17
Percentiles (95% CI) [1]	
25th	5.1 (1.5, NE)
50th	NE
75th	NE
% Event-free probability estimates (95% CI) [2]	
Month 3	79.7 (61.7, 89.9)
Month 6	73.5 (52.0, 86.6)
Month 9	73.5 (52.0, 86.6)
Month 12	NE

Event-free survival

At the data cut-off date (08-Mar-2017 DCO), 59 EFS events per IRC assessment occurred with a median follow-up time of 2.17 months.

Table 33 EFS by local investigator and IRC assessment (FAS)

	Main Cohort Patients in EAS		All Patients in FAS	
	Local assessment N=81	IRC assessment N=81	Local assessment N=99	IRC assessment N=99
Events/Total (%)	53/81 (65.4)	50/81 (61.7)	62/99 (62.6)	59/99 (59.6)
Maximum follow-up (months)	11.5	12.1	11.5	12.1
Median follow-up (months)	2.73	2.69	2.20	2.17
Percentiles (95% C.I) (months) [1]				
25%	0.9 (0.8, 1.6)	1.0 (0.9, 1.8)	1.0 (0.8, 1.5)	1.0 (0.9, 1.5)
Median	2.8 (2.1, 3.1)	2.8 (2.1, 3.5)	2.6 (1.9, 3.0)	2.6 (2.1, 3.1)
75%	9.0 (3.2, NE)	9.3 (5.3, NE)	7.3 (3.1, NE)	9.3 (3.5, NE)
% Event-free probability estimate (95% C.I) [2]				
3 months	39.1 (28.0 , 50.0)	42.4 (31.0 , 53.4)	37.1 (26.7 , 47.4)	39.9 (29.3 , 50.3)
6 months	33.3 (22.4 , 44.6)	34.9 (23.7 , 46.3)	30.1 (20.1 , 40.8)	31.5 (21.2 , 42.2)
9 months	26.6 (15.4 , 39.3)	32.2 (20.9 , 44.0)	24.1 (13.9 , 35.9)	29.0 (18.8 , 40.1)
12 months	NE	21.4 (6.5 , 41.9)	NE	19.4 (6.0 , 38.3)

PFS per IRC assessment

At the data cut-off date (08-Mar-2017 DCO), 47 PFS events per IRC assessment occurred (see Table 38).

Table 34: PFS by IRC assessment (FAS)

	All Patients N=99
Events/Total (%)	47/99 (47.5)
Maximum follow-up (months)	12.1
Median follow-up (months)	2.14
Percentiles (95% CI) [1]	
25th	1.3 (0.9, 1.9)
50th	2.9 (2.2, 6.2)
75th	NE (6.2, NE)
% Event-free probability estimates (95% CI) [2]	
Month 3	43.8 (32.2, 54.9)
Month 6	40.0 (28.4, 51.3)
Month 9	37.0 (25.0, 48.9)
Month 12	37.0 (25.0, 48.9)

No patients proceeded to SCT while maintaining a response to tisagenlecleucel therapy. Therefore, the sensitivity analysis per IRC of DOR, EFS, and PFS without censoring SCT was identical to the main analysis of these time-dependent secondary endpoints (i.e. with censoring SCT).

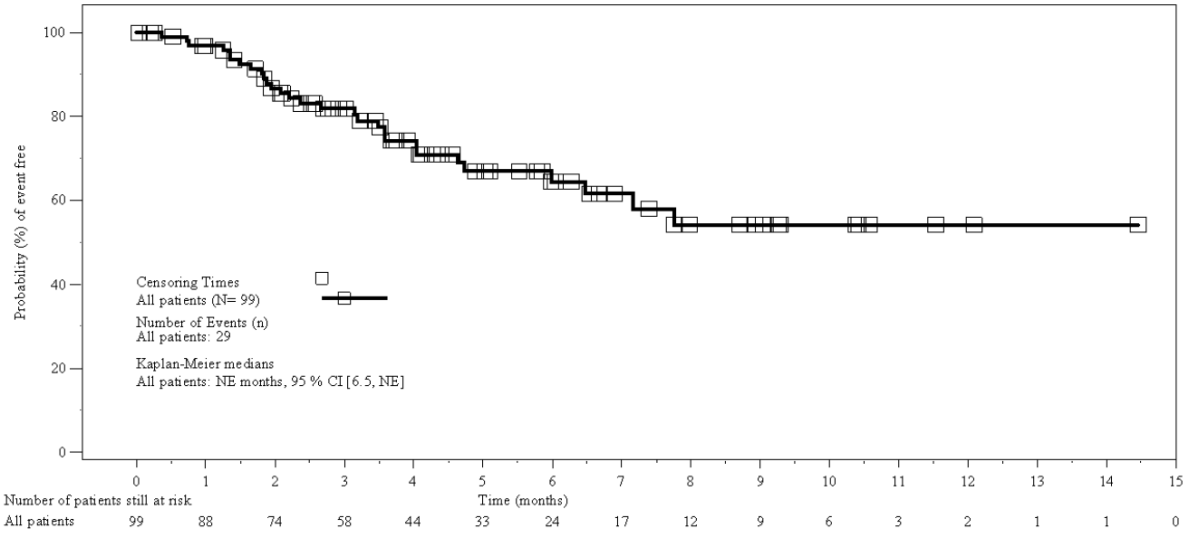
Overall survival

At the data cut-off date (08-Mar-2017 DCO), a total of 29 patients died after tisagenlecleucel infusion in the FAS. The median OS was not reached. The results should be interpreted with caution due to short median follow-up time (see Table 39 and Figure 16).

Table 35: Overall survival (FAS)

	All Patients N=99
Events/Total (%)	29/99 (29.3)
Maximum follow-up (months)	14.5
Median follow-up (months)	3.58
Percentiles (95% CI) [1]	
25th	3.6 (2.2, 6.0)
50th	NE (6.5, NE)
75th	NE
% Event-free probability estimates (95% CI) [2]	
Month 3	81.8 (71.9, 88.4)
Month 6	64.5 (51.5, 74.8)
Month 9	54.1 (38.5, 67.3)
Month 12	54.1 (38.5, 67.3)

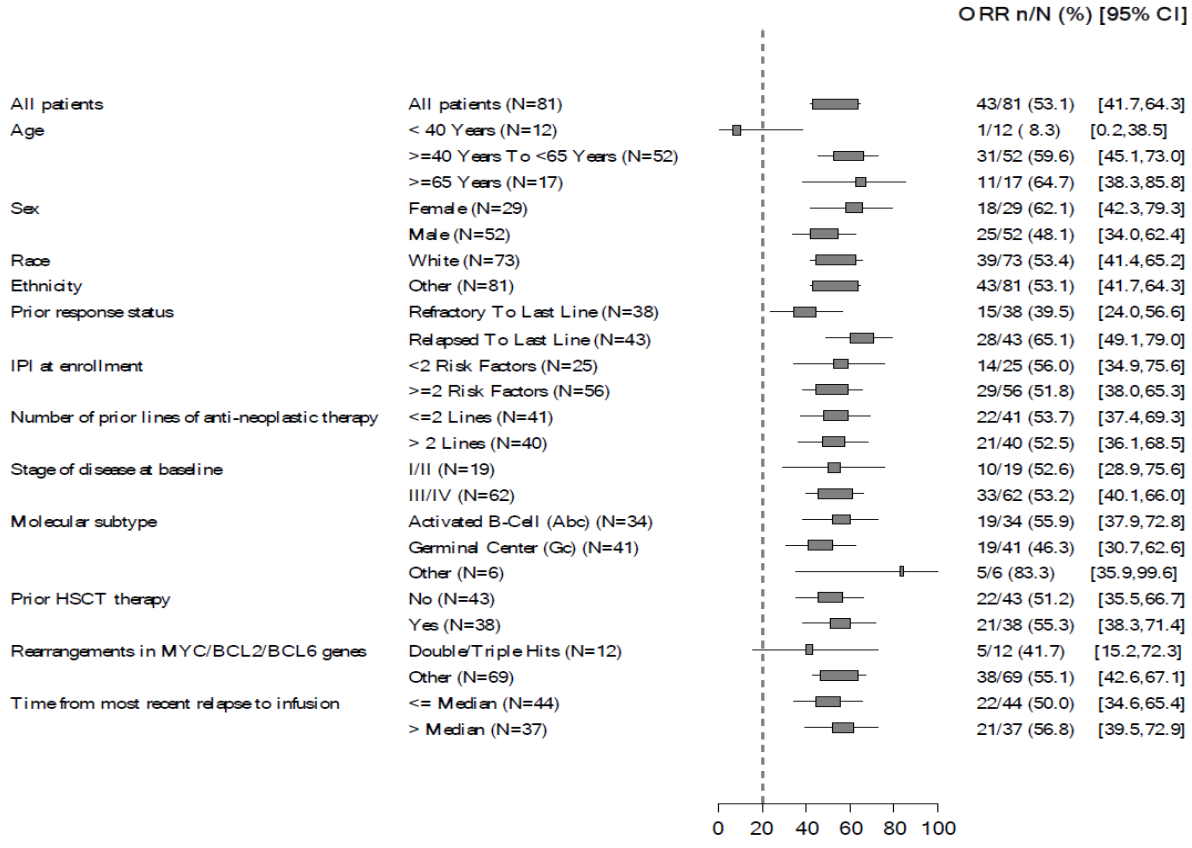
Figure 13: Kaplan-Meier plot of overall survival (FAS)



Exploratory efficacy results

ORR subgroup analysis

Table 36: ORR by IRC assessment for patients in Main Cohort– subgroup analysis (EAS)



Patient reported outcomes

Quality of life (QoL) assessments were performed with FACT-Lym questionnaire (disease specific) and the SF-36 questionnaire. The QoL instruments were completed by 76 patients (94%) at baseline and 34 patients (42%) at Month 3. Among the 34 patients who reported PRO at 3 months, 29 patients had a CR or PR. The PRO results indicate that there is a small increase in QoL after 3 months for patients who responded in terms of ORR to treatment.

Updated efficacy results in Study C2201 (data cut-off (DCO) 06 Sep 2017 and 08 Dec 2017)

Based on the first update (DCO 06 Sep 2017), the median time from tisagenlecleucel infusion to the data cut-off was 11.4 months (range: 2.1 to 23.1), 5.8 months longer than in the primary efficacy analysis (median: 5.6 months). Overall, 92 patients from the Main Cohort had more than 6 months of follow-up, or discontinued earlier. All 43 patients with a CR or PR at the time of the data cut -off for the primary analysis (08-Mar- 2017) were followed for at least 9 months or discontinued earlier. The updated analysis of the Main Cohort including 92 patients (EAS) infused with tisagenlecleucel is consistent with the primary analysis (Table 41). The robustness of the primary analysis of ORR (per IRC assessment) was confirmed by the results of a series of pre-defined sensitivity analyses.

Table 37: Overview of efficacy in Study C2201

Parameter	Primary analysis Cut-off: 08-Mar-2017	Update analysis Cut-off: 06-Sep-2017
ORR, N [1], [4] (EAS)	81	92
ORR (CR + PR), n (%) (95% CI)	43 (53.1) (41.7, 64.3)	48 (52.2) (41.5, 62.7)
CR, n (%)	32 (39.5)	35 (38.0)
PR, n (%)	11 (13.6)	13 (14.1)
Response at Month 3, N [4] (EAS)	81	92
CR, n (%)	26 (32.1)	30 (32.6)
PR, n (%)	5 (6.2)	5 (5.4)
Response at Month 6, N [4] (EAS)	46	92
CR, n (%)	14 (30.4)	27 (29.3)
PR, n (%)	3 (6.5)	3 (3.3)
DOR, Responders, N [2], [4] (EAS)	43	48
Median (months), (95% CI)	NR	NR (10.0, NE)
% relapse-free probability at Month 6 (95% CI)	73.5 (52.0, 86.6)	67.4 (51.1, 79.4)
% relapse-free probability at Month 9 (95% CI)	73.5 (52.0. 86.6)	67.4 (51.1, 79.4)
OS, N [3] (FAS)	99	106
Median (months), (95% CI)	NR	10.3 (6.7, NE)
% event-free probability at Month 6 (95% CI)	64.5 (51.5, 74.8)	63.2 (52.7, 71.9)
% event-free probability at Month 9 (95% CI)	54.1 (38.5, 67.3)	54.8 (43.8, 64.6)

CI = Confidence interval; CR = complete response; DOR = duration of response; IRC = Independent Review Committee; NE = not estimable; NR = not reached; ORR = overall response rate; OS = overall survival; PR = partial response

[1] Patients in the Main Cohort who received tisagenlecleucel infusion and were followed for at least 3 months. [2] DOR was defined as time from achievement of CR or PR, whichever occurs first, to relapse or death due to DLBCL [3] OS was defined as time from date of tisagenlecleucel infusion to the date of death due to any cause. [4] Assessed by IRC.

Among 35 patients in remission (CR + PR) at Month 3 post-tisagenlecleucel infusion, 30 patients (85.7%) continued to be in remission at Month 6 and 25 patients (71.4%) continued to be in remission at Month 9.

Table 38 Study C2201: Comparison of Efficacy results of infused vs all enrolled patients (updated DCO 08-December – 2017)

	Infused patients	**Enrolled patients**
Primary endpoint	**EAS main cohort N=93**	**N=165**
Overall response rate (ORR) (CR+PR) n (%) 95% CI	**48 (51.6)** (41.0, 62.1)	**56 (33.9)** (26.8, 41.7)
CR, n (%)	37 (39.8)	40 (24.2)
PR, n (%)	11 (11.8)	16 (9.7)
Response at month 3		N=165
ORR (%)	35 (37.6)	39 (23.6)
CR (%)	30 (32.3)	33 (20.0)
Response at month 6	N=92	N=165
ORR (%)	30 (32.6)	34 (20.6)
CR (%)	27 (29.3)	30 (18.2)
Duration of response (DOR)	**N=48**	**N=56**
Median (months) (95% CI)	Not reached (10.0, NE)	Not reached (10.0, NE)
% relapse free probability at 6 months	68.2	66.7
% relapse free probability at 12 months	65.1	63.7
Other secondary endpoints	**FAS N=111**	**N=165**
Overall survival (OS)		
% survival probability at 6 months	62.1	56.2
% survival probability at 12 months	49.0	40.2
Median (months) (95% CI)	11.7 (6.6, NE)	8.2 (5.8, 11.7)

Table 39: Overview of key efficacy endpoints in Study C2201 (Infused vs Enrolled patients in EAS)

	Infused patients EAS[1]/FAS[2]	Enrolled patients[3]
	EAS Main Cohort (N=93)	**EAS Main Cohort + enrolled & non-infused Main Cohort (N=143)**
Overall Response Rate (ORR)[4]		
CR+PR, n (%)	48 (51.6)	48 (33.6)
95% CI	(41.0, 62.1)	(25.9, 41.9)
CR, n (%)	37 (39.8)	37 (25.9)
PR, n (%)	11 (11.8)	11 (7.7)
	FAS (N=111)	**All enrolled (N=165)**
Progression-free survival (PFS) from enrollment[5]		
Events, n (%)	66 (59.5)	95 (57.6)
Median (months) (95% CI)	5.1 (4.4, 5.8)	4.4 (3.6, 5.1)
Probability event-free at 6 months (%)	40.2 (30.5, 49.7)	33.9 (25.8, 42.2)
Overall survival (OS) from enrollment[8]		
Events, n (%)	53 (47.7)	84 (50.9)
Median (months) (95% CI)	12.9 (8.4, NE)	8.2 (5.8, 11.7)
Probability event-free at 12 months (%)	50.6 (40.2, 60.1)	40.2 (31.6, 48.6)
Overall survival (OS) from last relapse[7]		
Events, n (%)	53 (47.7)	84 (50.9)
Median (months) (95% CI)	16.3 (11.1, NE)	10.6 (8.3, 16.1)
Probability event-free at 12 months (%)	57.4 (47.1, 66.5)	45.6 (37.0, 53.9)

[1] Efficacy analysis set (EAS) includes patients infused with tisagenlecleucel followed for at last 3 months or discontinued earlier.
[2] Full analysis set (FAS) includes all patients infused with tisagenlecleucel
[3] Patients who met all inclusion/exclusion criteria, and whose apheresis product was received and accepted by the manufacturing facility.

Ancillary analyses

Table 40: Overall Response rate by ECOG performance status in EAS main cohort

	All patients n/N (%)	95% CI
Overall response rate	48/93 (51.6)	(41.0, 62.1)
ECOG performance status		
0	25/49 (51.0)	(36.3, 65.6)
1	23/44 (52.3)	(36.7, 67.5)

Table 41: Duration of bridging chemotherapy prior to infusion of tisagenlecleucel

Duration of bridging chemotherapy[1]	N (%)
<3 weeks	24 (23.8%)
3 to <6 weeks	30 (29.7%)
6 to <9 weeks	18 (17.8%)

Duration of bridging chemotherapy[1]	N (%)
9 to <12 weeks	11 (10.9%)
>= 12 weeks	18 (17.8%)
[1]Duration of bridging chemotherapy is calculated as the sum of the durations of each bridging chemotherapy regimen taken by the patient.	

Table 42: Bridging therapy ORR prior to tisagenlecleucel infusion

	FAS N=111		EAS main cohort N=93	
	n (%)	95% CI	n (%)	95% CI
Patients who took bridging therapy	102 (91.9)		85 (91.4)	
Response to bridging therapy*				
CR	7 (6.9)		7 (8.2)	
PR	14 (13.7)		13 (15.3)	
SD	23 (22.5)		17 (20.0)	
PD	38 (37.3)		28 (32.9)	
Unknown	20 (19.6)		20 (23.5)	
Bridging therapy ORR (CR+PR)	21 (20.6)	(13.2, 29.7)	20 (23.5)	(15.0, 34.0)

* Percentages are based on number of patients who took bridging therapy.
CI: confidence interval; CR: complete response; ORR: overall response rate; PD: progressive disease; PR: partial response; SD: stable disease.
The 95% CIs were exact Clopper-Pearson CIs

Note: Initially it was indicated that n=102 infused patients had received bridging chemotherapy, however as subsequently corticosteroids were removed from the definition of bridging chemotherapy, it resulted to one less patient having received bridging.

Table 43: Overview of efficacy for patients with different subtypes prior to DLBCL diagnosis in Study C2201 (EAS or FAS)

	DLBCL N=74		TFL N=18	
	n (%)	95% CI	n (%)	95% CI
BOR				
CR	25 (33.8)		12 (66.7)	
PR	8 (10.8)		3 (16.7)	
SD	14 (18.9)		0	
PD	20 (27.0)		3 (16.7)	
Unknown	7 (9.5)		0	
ORR (CR+PR)	33 (44.6)	(33.0, 56.6)	15 (83.3)	(58.6, 96.4)
ORR **at 3 months**	25 (33.8)	(23.2, 45.7)	10 (55.6)	(30.8, 78.5)
ORR **at 6 months**	21 (28.8)	(18.8, 40.6)	9 (50.0)	(26.0, 74.0)
DOR per IRC in EAS Main Cohort	74		18	
Events/Responders (%)	12/33 (36.4)		3/15 (20.0)	
Median (95% CI) (months) [1]	NE	(5.1, NE)	NE	(2.0, NE)
% event-free (95% CI) [2]				
Month 3	81.4	(63.1, 91.2)	76.9	(44.2, 91.9)
Month 6	64.9	(45.6, 78.9)	76.9	(44.2, 91.9)
Month 9	64.9	(45.6, 78.9)	76.9	(44.2, 91.9)
OS in FAS, N	88		21	
Events/Total (%)	45/88 (51.1)		7/21 (33.3)	
Median (95% CI) (months) [1]	10.1	(5.6, 17.9)	NE	(6.0, NE)
% event-free (95% CI) [2]				
Month 6	59.1	(47.4, 69.0)	71.4	(47.2, 86.0)
Month 12	45.1	(33.3, 56.1)	66.7	(42.5, 82.5)

DLBCL vs DLBCL arising from TFL

The initial diagnosis of the lymphoma was DLBCL in 88 patients (79.3%), 21 patients (18.9%) had DLBCL arising from TFL, and 2 patients (1.8%) had other transformed lymphoma reported in disease history.

The ORR in patients with DLBCL arising from TFL was 83.3% (95% CI: 58.6, 96.4), whereas the ORR for the remaining patients (n=74) was 44.6% (95% CI: 33.0, 56.6). The probability for being remission-free 3 months after infusion was similar in responding patients with DLBCL and those with DLBCL arising from TFL (81.4% vs 76.9%). The median OS in the DLBCL subgroup was 10.1 months (95% CI: 5.6, 17.9), while the median OS for patients with DLBCL arising from TFL was not yet reached.

Table 44: Primary disease history and prior antineoplastic therapies by DOR duration censoring HSCT by IRC assessment for main cohort patients in Study C2201 – Updated EAS

Disease history	Non-responders N=45	DOR<3 Months N=14	DOR>=3 Months N=34	All Patients N=93
Primary site of cancer - n(%)				
Lymphoma: non-hodgkin's disease	45 (100)	14 (100)	34 (100)	93 (100)
Bone marrow involvement at initial diagnosis - n(%)				
No	37 (82.2)	12 (85.7)	24 (70.6)	73 (78.5)
Yes	6 (13.3)	2 (14.3)	9 (26.5)	17 (18.3)
Missing	2 (4.4)	0	1 (2.9)	3 (3.2)
Bone marrow involvement at study entry - n(%)				
No	42 (93.3)	12 (85.7)	32 (94.1)	86 (92.5)
Yes	3 (6.7)	2 (14.3)	2 (5.9)	7 (7.5)
Predominant histology/cytology - n(%)				
Diffuse large B-cell lymphoma	41 (91.1)	8 (57.1)	25 (73.5)	74 (79.6)
Transformed follicular lymphoma	3 (6.7)	6 (42.9)	9 (26.5)	18 (19.4)
Other	1 (2.2)	0	0	1 (1.1)
Stage at initial diagnosis - n(%)				
Stage I	6 (13.3)	0	2 (5.9)	8 (8.6)
Stage II	9 (20.0)	4 (28.6)	8 (23.5)	21 (22.6)
Stage III	5 (11.1)	2 (14.3)	8 (23.5)	15 (16.1)
Stage IV	22 (48.9)	7 (50.0)	16 (47.1)	45 (48.4)
Unknown	2 (4.4)	1 (7.1)	0	3 (3.2)
Missing	1 (2.2)	0	0	1 (1.1)
Stage at study entry - n(%)				
Stage I	3 (6.7)	0	3 (8.8)	6 (6.5)
Stage II	8 (17.8)	2 (14.3)	5 (14.7)	15 (16.1)
Stage III	6 (13.3)	4 (28.6)	10 (29.4)	20 (21.5)
Stage IV	28 (62.2)	8 (57.1)	16 (47.1)	52 (55.9)
IPI at initial diagnosis - n(%)				
<2 risk factors	10 (22.2)	4 (28.6)	11 (32.4)	25 (26.9)
>=2 risk factors	27 (60.0)	7 (50.0)	18 (52.9)	52 (55.9)
Unknown	8 (17.8)	3 (21.4)	5 (14.7)	16 (17.2)
IPI at study entry - n(%)				
<2 risk factors	11 (24.4)	4 (28.6)	10 (29.4)	25 (26.9)
>=2 risk factors	34 (75.6)	10 (71.4)	24 (70.6)	68 (73.1)
IPI at initial diagnosis - n(%)				
<3 risk factors	18 (40.0)	7 (50.0)	19 (55.9)	44 (47.3)
>=3 risk factors	12 (26.7)	3 (21.4)	9 (26.5)	24 (25.8)
Unknown	15 (33.3)	4 (28.6)	6 (17.6)	25 (26.9)
IPI at study entry - n(%)				
<3 risk factors	21 (46.7)	10 (71.4)	21 (61.8)	52 (55.9)
>=3 risk factors	24 (53.3)	4 (28.6)	13 (38.2)	41 (44.1)
Prior Hematopoietic Stem Cell Transplant (SCT) - n(%)				
No	26 (57.8)	7 (50.0)	19 (55.9)	52 (55.9)
Yes	19 (42.2)	7 (50.0)	15 (44.1)	41 (44.1)
Molecular subtype - n(%)				
Germinal center B-cell type	26 (57.8)	8 (57.1)	16 (47.1)	50 (53.8)
Activated B-cell type	19 (42.2)	5 (35.7)	16 (47.1)	40 (43.0)
Missing	0	1 (7.1)	2 (5.9)	3 (3.2)
Double/Triple hits in MYC/BCL2/BCL6 genes - n(%)				
CMYC+BCL2+BCL6	1 (2.2)	3 (21.4)	0	4 (4.3)
CMYC+BCL2	6 (13.3)	1 (7.1)	2 (5.9)	9 (9.7)
CMYC+BCL6	1 (2.2)	1 (7.1)	1 (2.9)	3 (3.2)
Negative	23 (51.1)	5 (35.7)	14 (41.2)	42 (45.2)
Not done	13 (28.9)	3 (21.4)	16 (47.1)	32 (34.4)
Missing	1 (2.2)	1 (7.1)	1 (2.9)	3 (3.2)
Disease status - n (%)				
Refractory to all lines with prior HSCT	2 (4.4)	0	2 (5.9)	4 (4.3)

Disease history	Non-responders N=45	DOR<3 Months N=14	DOR>=3 Months N=34	All Patients N=93
Refractory to all lines without prior HSCT	8 (17.8)	1 (7.1)	6 (17.6)	15 (16.1)
Refractory to last line but not all lines with prior HSCT	7 (15.6)	0	4 (11.8)	11 (11.8)
Refractory to last line but not all lines without prior HSCT	12 (26.7)	1 (7.1)	5 (14.7)	18 (19.4)
Relapsed to last line with prior HSCT	10 (22.2)	7 (50.0)	9 (26.5)	26 (28.0)
Relapsed to last line without prior HSCT	6 (13.3)	5 (35.7)	8 (23.5)	19 (20.4)
Time since end of last prior antineoplastic therapy to enrollment (months)				
n	43	14	33	90
Mean	4.1	5.7	8.6	6.0
SD	4.43	7.43	9.35	7.29
Median	2.8	3.8	5.1	3.4
Minimum	-1.6	0.9	-1.4	-1.6
Maximum	22.5	30.9	35.9	35.9
Time since most recent relapse/progression to CTL019 infusion (months)				
n	45	14	34	93
Mean	5.5	6.7	6.8	6.1
SD	2.56	4.38	2.93	3.06
Median	5.4	5.5	5.9	5.4
Minimum	1.6	3.7	3.4	1.6
Maximum	14.9	21.5	13.6	21.5
Number of prior lines of anti-neoplastic therapy - n(%)				
1	1 (2.2)	1 (7.1)	3 (8.8)	5 (5.4)
2	22 (48.9)	7 (50.0)	15 (44.1)	44 (47.3)
3	12 (26.7)	6 (42.9)	9 (26.5)	27 (29.0)
4	6 (13.3)	0	6 (17.6)	12 (12.9)
5	4 (8.9)	0	0	4 (4.3)
6	0	0	1 (2.9)	1 (1.1)

Data cut-off of C2201: 8-Dec-2017; Efficacy analysis set (EAS) = all patients treated with CTL019 at least 3 months prior to the clinical data cut-off.

Summary of main studies

The following tables summarise the efficacy results from the pivotal study C2201 supporting the present application for the r/r DLBCL indication. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 45: Summary of efficacy for trial C2201

Title: A phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)		
Study identifier	CCTL019C2201; EudraCT no. 2014-003060-20	
Design	A phase 2, multicenter, non-randomized, single arm, open-label efficacy and safety study in adult patients with r/r DLBCL	
	Duration of main phase:	Treatment and Primary Follow-up: 1 to 60 months. Secondary Follow-up, if applicable: 2 to 60 months
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	The duration of the study for individual patients varied depending on their response. For a subject who remained in response and completed the entire protocol from the date of informed consent through the completion of the long-term follow-up (LTFU) period, the duration of the study is planned to be up to 15 years

Hypothesis	The primary efficacy analysis was performed by testing the null hypothesis of ORR being less than or equal to 20% against the alternative hypothesis that ORR is greater than 20% at overall one-sided 2.5% level of significance, i.e., H0: $p \leq 0.2$ vs. Ha: $p>0.2$. The study was considered successful if the lower bound of the 2-sided 95.28% exact CI for ORR was greater than 20%, so that the null hypothesis that the ORR was less or equal to 20% could be rejected.		
Treatments groups	Tisagenlecleucel		Single infusion with a protocol-specified target dose of 1.0-5.0x10^8 CTL019 cells
	Main Cohort		Patients who received tisagenlecleucel infusion from the US manufacturing facility (Morris Plains)
	Cohort A		Patients who received tisagenlecleucel infusion from the EU manufacturing facility (Frauenhofer institute [FH], Germany)
Endpoints and definitions	Primary endpoint	Overall Response Rate (ORR)	ORR is defined as the proportion of patients with BOR of CR and PR based on the Lugano Classification criteria (Cheson et al. 2014) interpreted by Novartis. BOR was defined as the best disease response recorded from tisagenlecleucel until PD or start of new anticancer therapy.
	Secondary endpoint	Time-to-Response (TTR)	TTR is defined as the time between date of tisagenlecleucel infusion until first documented disease response (CR or PR). The analysis included all responders.
	Secondary endpoint	Duration of Overall Response (DOR)	DOR is defined as the time from achievement of CR or PR, whichever occurs first, to relapse or death due to DLBCL.
	Secondary endpoint	Event-Free Survival (EFS)	EFS is defined as the time from date of tisagenlecleucel infusion to the date of first documented disease progression or relapse, new treatment for lymphoma (excluding HSCT) or death due to any cause.
	Secondary endpoint	Progression-Fee Survival (PFS)	PFS is defined as the time from date of tisagenlecleucel infusion to the date of first documented disease progression or death due to any cause.
	Secondary endpoint	Overall Survival (OS)	OS is defined as the time from date of tisagenlecleucel infusion to the date of death due to any cause.
Data cut-off (DCO) of the analyses	Interim analysis: 20-Des-2016 *Primary analysis: 08-Mar-2017* Updated efficacy analysis: 06-Sep-2017 and 08-Dec-2017		

Results and Analysis

Analysis description	Primary Analysis on ITT			
Analysis population and time point description	The efficacy analysis was based on the ITT analysis on the basis of all enrolled patients and the efficacy analysis set (EAS) which included all patients in the Main Cohort who received tisagenlecleucel infusion at least 3 months prior to data cut-off.			
Primary Endpoint	Analysis set	Enrolled patrients	Infused patients EAS	
	Number of subject	165	93	

	ORR (CR+PR), n(%)	33.9%	51.6%	
	95% CI	(26.8, 41.7)	(41.0, 62.1)	
	CR, n(%)	20	32.3	

Effect estimate per comparison	Primary endpoint All Enrolled patients	Comparison groups	ORR vs. 20% historic ORR
		P-value	0.0047
	Primary endpoint *Infused patients (EAS)*	Comparison groups	ORR vs. 20% historic ORR
		P-value	p<0.0001
Notes	The primary endpoint was determined centrally by IRC assessment 3 months post-infusion. The applicant refers to an external control: SCHOLAR-1, a study of outcomes (e.g. ORR and CR) in patients with refractory or relapsed DLBCL. SCHOLAR-1 (salvage therapies) has pooled data of 636 patients from two phase 3 clinical trials and two observational cohorts. 73 patients from the company database were matched to those in the SCHOLAR-1 study. Overall response rate in the SCHOLAR-1 study was 26%.		
Analysis description	Secondary analysis		
Secondary endpoints	Analysis set	*All enrolled/ Responders*	Infused / Responders
	Number of subject	*N=56*	N=48
	DOR, Responders 95% CI	NR NR (10.0, NE)	NR NR (10.0, NE)
	% relapse free probability at 6 months	66.7	68.2
	% relapse free probability at 12 months	63.7	65.1
	Number of subjects	N= 165	N=111 (FAS)
	Other secondary endpoints		
	Overall Survival	99	106
	Median OS (months) 95% CI % survival probability at month 6 % survival probability at month 12	8.2 (5.8, 11.7) 56.2 40.2	11.7 (6.6, NE) 49.2
Notes	IRC assessment was used in the main analysis of secondary endpoints that involved the disease response. OS was assessed in all patients who received tisagenlecleucel infusion (full analysis set; FAS). NE = Not estimated; NR = Not reached.		

Clinical studies in special populations

No individual efficacy studies or analyses in specific populations were conducted. Almost one forth (23.2%) of the 99 patients in the FAS of study C2201 were ≥ 65 years, and none above 76 years.

Analysis performed across trials

The efficacy outcomes in the single-arm pivotal trial (C2201) were indirectly compared to three external datasets (SCHOLAR-1, the pooled CORAL extension studies, and the PIX301 study).

SCHOLAR-1 study

SCHOLAR-1 was an international, multicohort retrospective non-Hodgkin lymphoma research study, evaluating responses and OS rates in patients with refractory NHL, including DLBCL, transformed follicular lymphoma (TFL) and primary mediastinal B cell lymphoma (PMBCL).

Methods

SCHOLAR-1 pooled data from the observational follow up of 2 phase 3 clinical trials (Lymphoma Academic Research Organization-CORAL and Canadian Cancer Trials Group LY.12) and 2 observational cohorts (MD Anderson Cancer Center (MDACC) and University of Iowa/Mayo Clinic (IA/MC) Lymphoma Specialized Program of Research Excellence).

Only the published aggregated data for SCHOLAR-1 was submitted [28].

Study participants

Subjects were included in the outcome analyses if they were determined to be refractory and had commenced the next line of systemic therapy for refractory disease. Refractory disease was defined as progressive disease (PD) or stable disease (SD) as best response to last line of chemotherapy (≥ 4 cycles of first-line or 2 cycles of later-line therapy) or relapse ≤ 12 months after autologous stem cell transplantation (ASCT). Patients must have received an anti-CD20 monoclonal antibody and an anthracycline as 1 of their qualifying regimens. Patients with primary central nervous system lymphoma were excluded.

Thus, the population in SCHOLAR-1 (relapsed) differs from the patient population in study C2201 (relapsed and refractory). In the cross study comparison this was solved by including only those patients from C2201 who met the refractory criteria applied to SCHOLAR-1 in the analyses.

Inclusion criteria for the four individual cohorts were not presented. From the limited information provided it seems that, compared to study C2201 (which included patients with PS 0-1 and no evidence of major organ dysfunction), the SCHOLAR-1 included a much broader patient population.

Treatments

No information regarding the salvage chemotherapies in SCHOLAR-1 was provided. Pixuvri received a conditional approval by the EMA in 2012 in adult patients with multiply relapsed or refractory aggressive Non-Hodgkin B-cell Lymphomas (NHL), demonstrating a moderate improvement in ORR compared to salvage therapy. It is not clear if any patients in SCHOLAR-1 received Pixuvri. Thus it could be questioned if the SCHOLAR-1 results are fully representative of what could be expected from currently approved therapies in the r/r DLBCL indication.

Outcomes/endpoints

RR, CR and OS from the time that salvage therapy for refractory disease was initiated. Response was assessed using the 1999 International Working Group (IWG) response criteria per local review/ investigator assessment.

Sample size

No sample size calculations were performed. All patients eligible were analysed.

Randomisation/blinding

Not applicable.

Statistical methods

Higgin's Q-statistic was used to assess the heterogeneity of response rate between the source databases. If the p-value was > 0.10, data from the 4 institutions were to be pooled for analysis. Data were pooled at the patient-record level, and response rates were estimated from the pooled data with a random effects model.

Based on the Higgin's Q statistic the authors concluded that heterogeneity was low and it was appropriate to pool the studies. The power of Q statistic depends on the effective sample size (ESS) and should not be the sole determinant of heterogeneity. The heterogeneity test results should be considered alongside a qualitative assessment of the combinability of studies. The key differences are the retrospective vs prospective collection of data, the differences in inclusion criteria (unselected patients in the observational cohorts vs patients eligible for ASCT in the randomized cohorts), different time points at which the patients were included (time of primary refractoriness vs refractory to second-line or later-line), differences response assessment (local vs investigator), potential differences in follow up schedule (limited information), potential differences in the management of patients (i.e. who are considered eligible for second SCT, limited information).

Results

Table 46 Baseline Patient Characteristics for SCHOLAR-1

Characteristic	MDACC (n = 165)	IA/MC (n = 82)	LY.12 (CCTG) (n = 219)	CORAL (LYSARC) (n = 170)	Pooled (N = 636)
Median (range) age, y	56 (20-81)	60 (20-80)	54 (24-70)	54 (19-65)	55 (19-81)
Male sex, %	64	62	61	69	64
Primary diagnosis, %					
DLBCL*	76	89	84	100	87
PMBCL	1	0	5	0	2
TFL	3	0	10	0	4
Indeterminate/missing	0	8	0	0	1
ECOG PS, %					
0-1	42	72	89	84	73
2-4	10	24	11	15	14
Missing	49	4	0	1	13
Disease stage, %					
I-II	18	20	33	32	27
III-IV	82	79	67	67	72
Missing	0	1	0	1	<1
IPI risk classification,† %					
Low risk	5	22	36	32	25
Low-intermediate risk	7	31	30	29	24
High-intermediate to high risk	23	48	35	34	33
Missing or incompletely assessed	65	0	0	5	18
Refractory category, %					
Primary refractory	0	24	51	28	28
Refractory to ≥second-line therapy	90	51	21	46	50
Relapsed ≤12 mo post-ASCT	10	24	28	26	22
Total no. of lines of chemotherapy and ASCT received, %					
1	0	24	51	28	28
2	90	50	21	46	49
3	0	1	0	0	<1
≥4	-	-	-	5	-

According to the SCHOLAR-1 publication [28], covariates were determined at diagnosis for the observational cohorts and at randomization (i.e. at relapse/refractoriness to first line treatment) in the randomized study cohorts. For all cohorts, in some cases, covariates were also measured later in the treatment course. For summaries of patient characteristics, the covariate measured closest in time to the determination of refractory status was used. Thus, it is understood that for most patients, the reported baseline characteristics were recorded at potentially a much earlier time point than the date at which the therapy for refractory disease was initiated.

Numbers analysed

SCHOLAR-1 analysed 636 subjects identified from a total pooled population of 861 subjects. Of the 636 extracted patients, response rates were evaluable for 523 patients and survival was evaluable in 603 patients.

Outcomes and estimations

Response rates

Table 47 Response Rates to Chemotherapy After Refractory Disease SCHOLAR-1

	MDACC (n = 165)	IA/MC (n = 82)	LY.12 (CCTG) (n = 219)	CORAL (LYSARC) (n = 170)	Pooled* (N = 636)
Patients evaluated for response, n†	165	82	106	170	523
Response rate (95% CI), %	20	26	26	31	26 (21, 31)
CR rate	7	7	2	15	7 (3, 15)
PR rate	13	18	25	16	18 (13, 23)
Response rate by refractory category (95% CI), %					
Primary refractory					
RR	—	25	27	10	20 (11, 34)
CR rate	—	10	1	2	3 (1, 11)
Refractory to second-line or later-line therapy					
RR	20	21	20	40	26 (17, 39)
CR rate	7	5	20	18	10 (5, 20)
Relapse ≤12 mo post-ASCT					
RR	19	35	—	39	34 (24, 45)
CR rate	6	10	—	25	15 (6, 31)

Data for disease stage and IPI, were available for only 239 (46%) and 228 (44%) of 523 patients, respectively.

Overall survival

The median OS was estimated as 6.3 months (95% CI: 5.9, 7.0), with a range across cohorts of 5.0-6.6 months. Survival in patients who achieved (complete) response to therapy, was 14.9 months (median) and in patients who underwent ASCT following salvage therapy was 14.4 months (CIs and p-values not reported, KM graphs not shown).

The amount of missing data is large, with OS data being reported in only 81 of the 136 patients (60%) who achieved response to treatment for refractory disease. Furthermore, the published report for SCHOLAR-1 states the following: When covariates assessed after commencement of therapy for refractory status were used in survival models, survival time was calculated from the day of covariate assessment.

Matching-adjusted indirect comparison (MAIC) against SCHOLAR-1

The MAIC approach, a form of propensity score weighting, was used to further adjust for cross-study difference in patient characteristics. All available data were utilized for this analysis: patient-level data from C2201 and published aggregate data from SCHOLAR-1. The comparison was first conducted by matching inclusion criteria between the C2201 and the SCHOLAR-1 studies. Patients from the EAS main cohort of the C2201 trial (n=92) were eligible for inclusion if they met the refractory criteria applied to SCHOLAR-1 (i.e. progressive disease (PD) or stable disease (SD) as best response to chemotherapy or relapse ≤12 months post-ASCT) (n=73).

Subsequently, patient characteristics potentially associated with treatment response, based on clinical input, and consistently reported in both studies were matched. Specifically, the matched variables included primary diagnosis (DLBCL vs. non-DLBCL), IPI risk classification (<2 vs. ≥2), and refractory category (primary refractory, refractory to ≥2nd line therapy, relapsed ≤12 months post ASCT). The Applicant was unable to match on the total number of lines of prior chemotherapy and ASCT received

because the information reported for SCHOLAR-1 was incomplete (approximately 22% of patients with missing data).

Before matching, compared to SCHOLAR-1, more patients in C2201 had a diagnosis of TFL (16% vs 4%), ECOG PS 0-1 (100% vs 73%), IPI score intermediate to high (77% vs 57%), primary refractory disease (41% vs 28%) and >2 number of lines of prior chemotherapy/ASCT (52% vs <1%). Baseline characteristics after matching showed a full match. The effective sample size was 63, a considerable drop from 99 (FAS) or 81 (EAS).

Outcomes

Response rates

In both populations, only those with response evaluated were included in the comparison of efficacy outcomes. Response was evaluated for 63 patients (out of the 73 patients) who received tisagenlecleucel infusion at least 3 months (90 days) prior to data cut-off date (8-March-2017) included from C2201.

Before matching, tisagenlecleucel was associated with significantly higher CR and ORR compared to salvage therapies in SCHOLAR-1 (CR: 36.5% vs. 7.0%, P-value<0.01; ORR: 47.6% vs. 26.0%, P-value<0.01). After matching on the primary diagnosis (DLBCL or others), IPI risk classification, and refractory category, the differences in CR and ORR remained significant (CR: 38.0% vs. 7.0%, P-value<0.01; ORR: 47.4% vs. 26.0%, P-value<0.01). CTL019 was associated with a 31.0% (95% CI: 19.1%, 43.0%) higher CR rate and a 21.4% (8.8%, 34.1%) higher ORR compared to salvage therapies.

Table 48: Comparison of Efficacy Outcomes of CTL019 AND Salvage Therapies Before and After Matching

	Before Matching						After Matching					
	JULIET[1] (CTL019) [A]	SCHOLAR-1[2] (Salvage Therapies) [B]	Response Difference (95% CI) [A] - [B]		P-value[3]		JULIET[4] (CTL019) [C]	SCHOLAR-1[2] (Salvage Therapies) [D]	Response Difference (95% CI) [C] - [D]		P-value[5]	
Response Rates												
CR	36.5%	7.0%	29.5%	(17.3%, 41.7%)	<0.01	*	38.0%	7.0%	31.0%	(19.1%, 43.0%)	<0.01	*
ORR (CR + PR)	47.6%	26.0%	21.6%	(8.6%, 34.6%)	<0.01	*	47.4%	26.0%	21.4%	(8.8%, 34.1%)	<0.01	*

** Denotes p-value <0.05*

Abbreviations: CI: Confidence Interval; CR: Complete Response; ORR: Overall Response Rate; PR: Partial Response.

Notes: The ORR was defined as the proportion of patients with the best overall disease response of CR or PR in JULIET

Based on the updated DCO for the JULIET study (Dec 2017), additional post-hoc analyses were performed comparing JULIET to the three historical controls:

JULIET (C2201) vs SCHOLAR-1:

- ORR/CR: JULIET infused patients in the Main Cohort of EAS who met SCHOLAR-1 criteria vs. SCHOLAR-1 patients.
- OS: JULIET infused patients in both cohorts (FAS) who met SCHOLAR- 1 criteria vs. SCHOLAR-1 patients

Sensitivity analyses were conducted using a similar approach in the JULIET enrolled population.

JULIET (C2201) vs. pooled CORAL extension studies

Patient Population

All JULIET patients, regardless of number of prior lines of therapy, were included in the analyses to provide sufficient sample sizes for baseline adjustment in comparisons to the CORAL extension studies, which only included patients who had failed two lines of prior therapy.

Outcomes

The following two sets of analyses were performed:

- Comparison of ORR/CR: JULIET infused patients in the Main Cohort of EAS vs. pooled CORAL patients
- Comparison of OS: JULIET infused patients in both cohorts (FAS) vs. pooled CORAL patients

Sensitivity analyses were conducted using a similar approach in the JULIET enrolled population.

In CORAL OS was defined as a) the time from relapse post-ASCT (in patients who had ASCT as the most recent therapy) or b) time from failure of CORAL induction therapy, to death from any cause. To align with this definition, OS in JULIET was defined as time from a) relapse after the most recent therapy, b) the last dose of the most recent therapy, or c) the most recent ASCT, whichever occurred the latest before enrolment, to death from any cause.

Unadjusted Comparisons of Efficacy Outcomes

As described for the JULIET vs SCHOLAR-1 comparison.

Adjusted Comparisons of Efficacy Outcomes (MAIC)

Baseline characteristics were measured at screening in the JULIET trial and at second relapse (after ASCT) or CORAL failure (patients who failed to proceed to ASCT) in CORAL. Variables included in the matching adjustment were gender, IPI risk classification (<3 vs. ≥3), ASCT as the most recent therapy and relapsed after ASCT (yes vs. no). The same methods as described for the JULIET vs SCHOLAR-1 comparison were used to conduct the MAIC analyses.

JULIET (C2201) vs. PIX301 All JULIET patients in the EAS Main Cohort were included in the comparison. Patients from the PIX301 trial with prior rituximab treatment use who received pixantrone as third or fourth line treatment were included. In the primary analysis comparing ORR/CR, JULIET infused patients in the Main Cohort of EAS were included. In the sensitivity analysis, JULIET enrolled patients in the EAS Main Cohort were included. In the PIX301 trial, tumour response was assessed by an independent panel based on the 1999 IWG response criteria. An ORR of 30% and a CR of 20% were seen in PIX301.Unadjusted Comparisons of Efficacy Outcomes was as described for the JULIET vs SCHOLAR-1 comparison.

Results

Table 49: MAICs of tisagenlecleucel in Study C2201 versus historical controls-Infused patients

Comparison	ORR Difference (95% CI)	CR Difference (95% CI)	OS Hazard ratio (95% CI)
C2201 vs SCHOLAR-1	20.5% (8.9%, 32.0%)**	30.8% (19.9%, 41.8%)**	0.681 (0.48, 0.96)*
C2201 vs Pooled CORAL extensions	12.2% (0.6%, 23.7%)*	12.2% (1.1%, 23.3%)*	0.412 (0.31, 0.54)**

* P-value < 0.05. ** P-value < 0.01. 1. OS from treatment. 2. OS from last relapse.

Table 50: MAICs of tisagenlecleucel in Study C2201 versus historical controls (enrolled patients)

Comparison	ORR Difference (95% CI)	CR Difference (95% CI)	OS Hazard ratio (95% CI)
C2201 vs SCHOLAR-1	6.1% (-3.6%, 15.8%)	19.2% (10.3%, 28.1%)**	0.781 (0.59, 1.04)
C2201 vs Pooled CORAL extensions	-5.0% (-14.7%, 4.8%)	-1.7% (-10.7%, 7.2%)	0.532 (0.42, 0.68)**

* P-value < 0.05. ** P-value < 0.01. 1. OS from enrollment in Study C2201. 2. OS from last relapse.

KM Curves JULIET vs. SCHOLAR-1

Figure 14: Juliet infused (FAS, both cohorts) vs. SCHOLAR-1 after matching

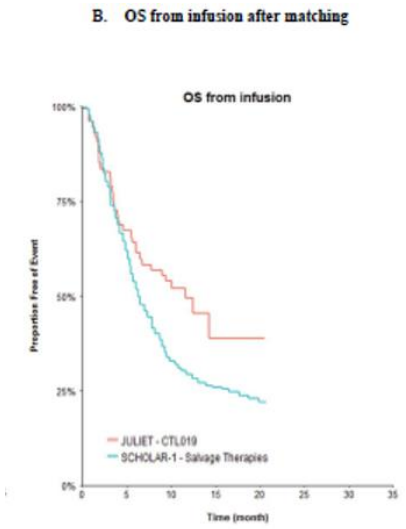
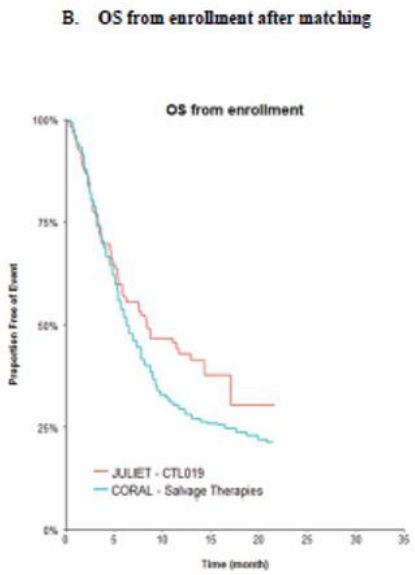


Figure 15: JULIET enrolled (both cohorts) vs. SCHOLAR-1 after matching



Post-hoc analyses: KM Curves JULIET vs. CORAL

Figure 16: JULIET Infused (FAS, Both Cohorts) vs. CORAL. OS from most recent relapse, after matching (truncated at JULIET maximum follow-up)

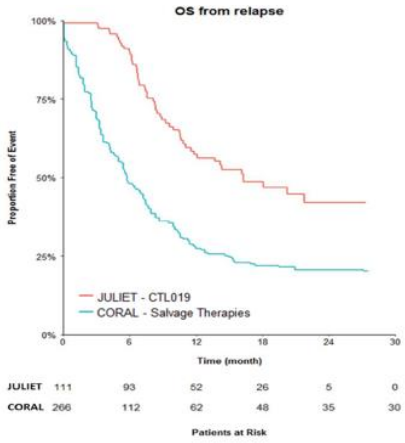
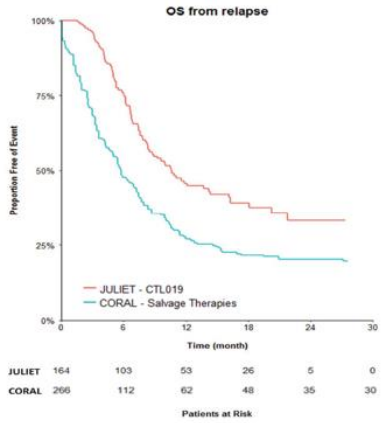


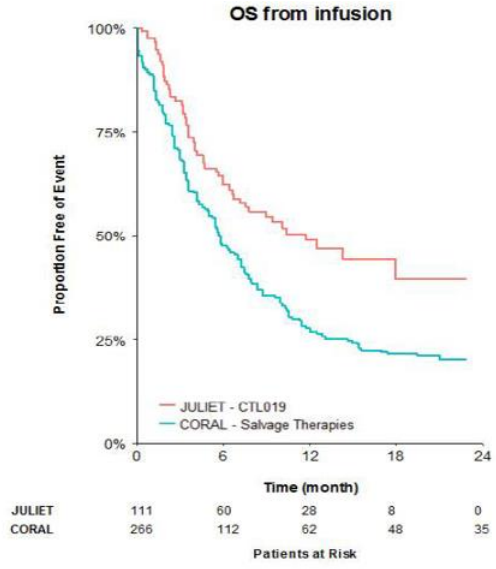
Figure 17: JULIET Enrolled (Both Cohorts) vs. CORAL. OS from most recent relapse, after matching (truncated at JULIET maximum follow-up)



Sensitivity analysis of OS JULIET (from infusion) vs CORAL (from last relapse)

As all enrolled and infused patients by definition had already survived the period of screening and wait to infusion, the OS curve for JULIET demonstrates an early plateau. In order to assess the impact of these factors on OS comparisons between JULIET (Study C2201) vs CORAL extensions, the Applicant provided an additional sensitivity analysis, of JULIET vs Pooled CORAL extensions, moving the time of start of measurement of OS in JULIET to the time of infusion.

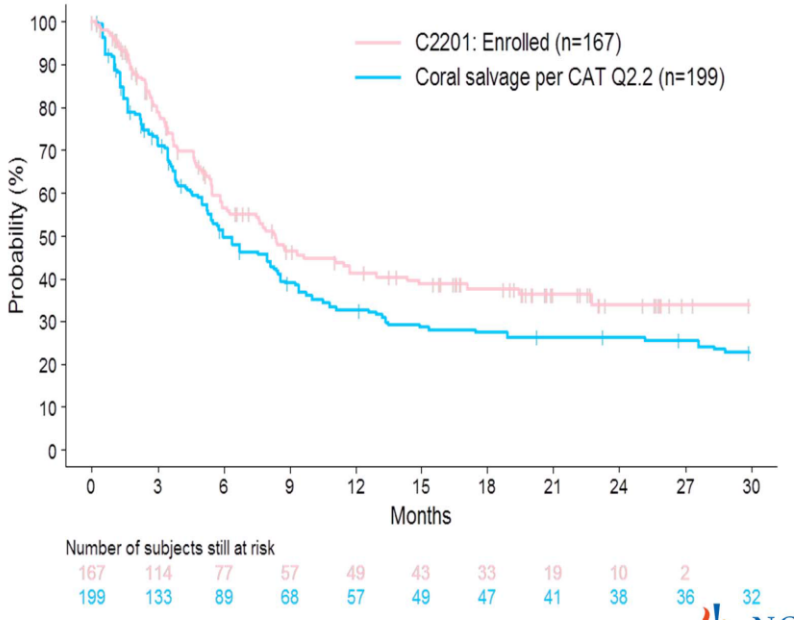
Figure 18: JULIET Infused (FAS, Both Cohorts) and Pooled CORAL Extension Studies with OS from infusion (truncated at JULIET maximum follow-up)



Retrospective modification of data underlying the published analysis of the CORAL salvage study was requested by the CAT. For this analysis, patients from the CORAL salvage study that had died or were censored within the first 2 months were excluded from the comparative analysis and the origin for OS was moved to 2 months for the remainder of the patients. This analysis is presented in Figure 22. The

JULIET KM curve was based on data up to 21 May 2018 that was undergoing data–cleaning and had not been locked.

Figure 19 Juliet infused vs CORAL extension studies (excludes patients dead or censored within first 2 months and origin for OS moved to 2 months for the rest of the patients)



Comparisons of OS in JULIET vs. CORAL for responders and non-responders

KM curves were submitted comparing JULIET vs CORAL for the subset of complete responders, overall responders and non-responders. Descriptive statistics were not provided.

Figure 20: Kaplan -Meier Curves of OS Comparing JULIET Infused (CR Subset, FAS, Both Cohorts) and Pooled CORAL Extension Studies (CR/CRu Subset)

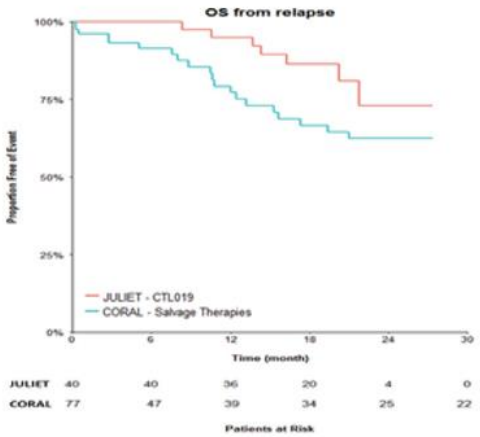


Figure 21: Kaplan-Meier Curves of OS Comparing JULIET Infused (CR/PR Subset, FAS, Both Cohorts) and Pooled CORAL Extension Studies (CR/PR Subset), OS from most recent relapse (truncated at JULIET maximum follow-up) – no match

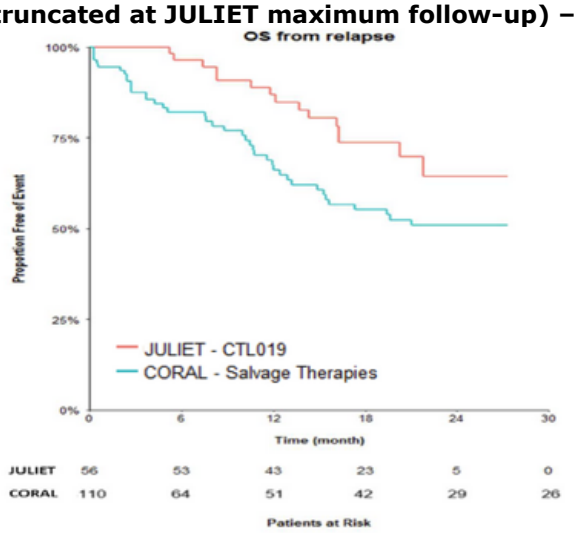
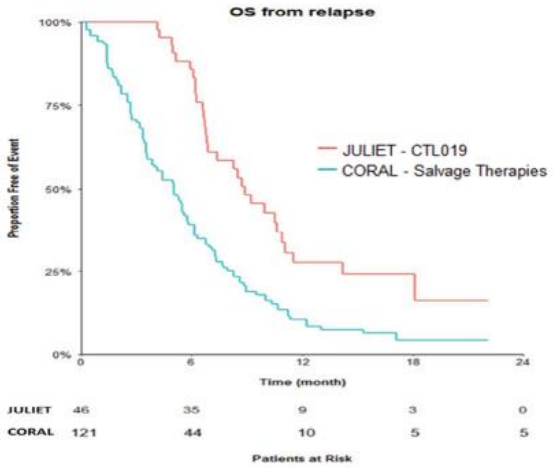


Figure 22: KM of OS Comparing JULIET Infused (SD/PD Subset, FAS, Both Cohorts) and Pooled CORAL Extension Studies (SD/PD Subset).
OS from most recent relapse (truncated at JULIET maximum follow-up) – no match



2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

- *ALL indication*

Study B2202, included patients with high risk cytogenetics, following a median of 3 prior therapies of which 61.3% of patients had failed prior allogeneic SCT. Overall, the study population reflects the clinical population of paediatric and young adult patients with r/r B-cell ALL. Study schedules and duration of follow up is considered appropriate.

There was a delay of up to 3 months between staging tumour burden for each subject (done at enrolment to study) and administration of study product. Tumour burden may have either progressed during the delay or regressed in response to bridging therapies. There is, therefore, uncertainty in tumour burden status of subjects at the time of exposure to study product. It would have been preferred for tumour burden to have been assessed just prior to exposure to study product. However in the majority of patients with refractory ALL following multiple relapses and remission, CR/CRi achieved by the bridging chemotherapy is expected to be rare and of short duration. Hence, this is not considered to have significantly biased the results of the efficacy analyses.

There does not appear to be a discernible dose-response relationship with the number of CAR-positive viable T-cells infused (see section 1.1.3 ''pharmacodynamics''. This is likely the result of the CAR-positive T cells' ability to proliferate and expand extensively (e.g. 1000 to >10000-fold) in vivo. Thus, the administered dose does not correlate with the number of CAR-positive T cells in vivo following engraftment and expansion, which will vary from patient to patient. Additional considerations in this dose selection take into account the manufacturing feasibility of producing adequate numbers of CAR-positive cells.Given the poor prognosis and lack of effective treatment options for patients with ALL, the general safety profile of tisagenlecleucel, and the lack of apparent direct relationship between the number of CAR-positive T-cells infused and clinical outcome, infusion of a "low dose product" is considered preferable to the alternatives of further salvage chemotherapy or supportive treatment. Therefore, administration of a dose of 0.2 to 5.0×10^6 CAR-positive viable T-cells/kg for patients ≤ 50 kg and 0.1 to 2.5×10^8 CAR-positive viable T-cells for patients >50 kg is considered justified.

Only patients with second or greater bone marrow (BM) relapse were included in the study. This was not reflected in the applied indication for tisagenlecleucel and the indication has been revised to include paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse. The added words "*in relapse post transplant*" reflect 5 patients in the population studied which is acceptable.

There is currently no experience with manufacturing Kymriah for patients testing positive for HBV, HCV and HIV.Screening for HBV, HCV and HIV must be performed in accordance with clinical guidelines before collection of cells for manufacturing (SmPC, section 4.4).

The requirement for CD19 tumour expression confirmed within 3 months of study entry was to ensure that treatment failures were not due to the treatment of ALL that was not positive for CD19. The CHMP raised a major objection regarding a requirement for CD19 tumour expression to be reflected in the SmPC. However additional data showed a lack of consistency between CD19 levels and response to tisagenlecleucel. While, it still seems likely that a minimum expression level would be necessary for efficacy, it is accepted that this could indeed be below the threshold for detection with current methods used in the clinic. Therefor there is no need for further investigation.

Patients who had prior treatment with any anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy where excluded from receiving tisagenlecleucel. Successful treatment with CD19 directed CAR-T's in patients failing Blincyto has been reported. It is nevertheless conceivable that these patients would trend toward low CD19 tumour expression and therefore not respond to tisagenlecleucel. In Study B2101J, three of the six patients who received prior blinatumomab had a BOR of CRi. A single patient had a BOR of CR and relapsed 2 years and 10 months after tisagenlecleucel infusion. There is limited experience with Kymriah in patients exposed to prior CD19-directed therapy. Kymriah is not recommended if the patient has relapsed with CD19-negative leukaemia after prior anti-CD19 therapy (SmPC, section 4.4).

The choice of a cut-off of 3-25 years in the indication is a reflection of the inclusion criteria of the pivotal study B2202. In response to the comments made by CAT on the List of Questions (16/03/2018), the applicant submitted in its responses of 25/04/2018 a revised SmPC with the broader indication with regard the paediatric population. The eligibility criteria in the pivotal Study B2202 and supportive Study B2205J included patients from age 3 years was based on early experience where there was a high failure rate with the product from patients < 3 years. During the past 2 years the Applicant has implemented a number of improvements/modifications to the manufacturing process of tisagenlecleucel ensuring that leukapheresis material from patients < 3 years can be used for successful manufacture of tisagenlecleucel and their manufacturing facilities accept leukapheresis from patients ≥ 6 kg. To date, tisagenlecleucel has been manufactured for 2 patients < 3 years of age in the commercial setting and 4 patients in the trials B2101J (n=1) and B2208J (n=3), the latter evaluating the earlier use of tocilizumab for the management of CRS in paediatric patients with r/r B-cell ALL. There is no clinical basis to suggest a difference in safety or efficacy of tisagenlecleucel in children < 3 years of age. In order to further evaluate the efficacy and safety of Kymriah in ALL patients below the age of 3 years, the applicant should conduct and submit a study based on data from a disease registry in ALL patients (see Annex II).

The upper age limit in Studies B2202 and B2205J was based on current clinical practice where paediatric oncologists often treat patients up to 21 years of age and this was the upper age for inclusion of patients in the multi-centre program. However, the actual age when receiving tisagenlecleucel was up to age 23 in Study B2202 and up to age 25 in Study B2205J and consequently this was used in the indication. This data-driven age-cut-off is considered acceptable.

- *DLBCL indication*

The pivotal study C2201 is an open-label, single arm, multicentre phase 2 study evaluating the efficacy and safety of tisagenlecleucel in adult patients with DLBCL (including TFL) who have r/r disease after ≥ 2 lines of chemotherapy (including rituximab and anthracycline), and who are ineligible for, have failed or are not consenting to autologous stem cell transplant (ASCT). Supporting evidence is derived from an ongoing phase 2a case-series study (study A2101J).

The study consists of the following sequential periods: screening including acceptance of leukapheresis product, pre-treatment with bridging- and lymphodepleting (LD) chemotherapy, one single dose of tisagenlecleucel infusion (dose range: 1.0-5.0x10^8) and primary follow-up, secondary follow-up, survival follow-up and long-term follow-up (consisting of semi-annual and annual evaluations for up to 15 years from the date of infusion on all patients under a separate long-term follow-up protocol. All patients were allowed to receive bridging therapies constituting standard 3rd-line antineoplastic therapy based on the investigators choice to stabilize the disease while waiting for tisagenlecleucel infusion.

Among those 101 infused patients who received bridging chemotherapy prior to infusion in study C2201, the median number of bridging regimens each of these patient received was 1 (range 1-5) and the mean number was 1.7 regimen. The median treatment duration of bridging chemotherapy (calculated as the sum of the durations of each bridging chemotherapy regimen) was 40 days with a mean duration of 48.8 days. Patients who received bridging therapy in the FAS, and who had two available disease assessments pre-infusion, obtained an ORR of 20.6% (95% CI: 13.2, 29.7) and those in the EAS an ORR of 23.5% (95% CI: 15.0, 34.0). Thus, some of the patients who received bridging chemotherapy had already a response to their last treatment when they were given tisagenlecleucel infusion. Consequently, the type and numbers of various bridging therapies each individual patient received prior to infusion may have had an impact on the efficacy outcome of this

CAR-T cell therapy, as a potential carry-over effect from the bridging chemotherapy, cannot be excluded. The LD therapy was limited to one preferred cyclophosphamide-based regimen of fludarabine and cyclophosphamide, which is endorsed, as several options may cause variation in the response to tisagenlecleucel infusion. In patients intolerant or resistant to cyclophosphamide, bendamustine was recommended instead as per clinical practice.

In the study protocol, the applicant pre-specifies a manufacturing time of tisagenlecleucel of around 4-5 weeks. This is longer than what is to be expected based on the product's quality specifications (~3weeks) and longer than what has been seen with other CAR-T products. The median time from enrolment to infusion in study C2201 at the time of the primary analysis (DCO: 08-mar-2017; 99 patients infused [FAS]) was 54 days (range: 30 to 357), with a median time from screening to infusion of 119 days (range: 49 to 396). This considerable time span from screening and enrolment to infusion is a concern, especially as tisagenlecleucel is intended for the treatment of patients with an advanced disease expected to progress rapidly.

According to the applicant, this high turnaround time was due to the prolonged production time, secondary to limited capacity at the US manufacturing facility, in the beginning of the study and it was clarified the manufacturing capacity was improved in August 2016, when the EU manufacturing site (Fraunhofer) started to actively produce tisagenlecleucel. In fact the actual manufacturing time did not change throughout the study, staying consistent at a median of 30-34 days which is consistent with the pre-specified 4-5 weeks. In the commercial setting, the time from receipt of leukapheresis to product shipment is currently 24 days and is targeted to be 22 days going forward. This is now reflected in the product information and educational material.

No classic dose-finding studies were conducted in any of the indications. The protocol specified dose range in study C2201 was therefore based on the experience in the Penn (UPCC13413) study in r/r lymphoma (18 DLBCL, 8 FL), whereas preliminary clinical experiences also were taking into consideration. Some patients were given tisagenlecleucel even though the recommended dose was not met, since these patients did not have any other effective treatment options available. Patients who received doses below (n=5) and above (n=5) the target dose range had similar response rates as those patients who received doses within the protocol-specified dose range of 1.0-5.0 x 10^8 CAR-positive viable cells.

Disease staging and response assessment was performed with PET-CT only within 28 days prior to tisagenlecleucel infusion and at 3 months post-infusion. However, for the assessment of responses at the other pre-defined time points, conventional CT or MRI was performed. Best overall response was determined according to the Lugano classification, at each recorded time-point based on the scan available (i.e. conventional CT/MRI or PET-CT). In cases where both modalities were available, PET-based responses over-ruled the CT-based responses.

The primary efficacy analysis was performed by testing the null hypothesis of ORR being less than or equal to 20% against the alternative hypothesis that ORR is greater than 20% at overall one-sided 2.5% level of significance. This was not consistent with a previous advice given by the CHMP (28/04/2016; EMEA/H/SAH/061/1/2016/ADT/II), which stated that for registration based on a phase II trial, the clinical benefit should be at least superior to that observed in the CORAL study (ORR 40.3%).

In three historical dataset controls, unadjusted ORR ranged from 26% (SCHOLAR-1) or 30% (PIX301) to 40.3% (CORAL extension studies). Similar to the JULIET (C2201) trial, the CORAL study selected for better patients, due to the anticipated toxicity of the transplant that was the intentional treatment. Therefore, the CORAL study was considered the most relevant historical dataset for indirect comparison to the JULIET (C2201) trial.

The chosen secondary endpoints of TTR, DOR, EFS, PFS, and OS were appropriate and consistent with a previous advice given by the CHMP (28/04/2016; EMEA/H/SAH/061/1/2016/ADT/II) where the applicant was recommended to use a combined interpretation of ORR and CR in particular, together with DOR, PFS and OS. The sample size was appropriate to demonstrate a statistically significant result in the primary analysis. However, the calculations of the sample size were based on the 20% ORR for the control; with a higher control ORR a larger sample size would be needed. With the current sample size, short follow-up time and a high censoring rate, meaningful conclusions from the time to event analyses are difficult to reach.

Based on a systematic literature review three historical datasets were identified where indirect comparisons to C2201 were deemed feasible: SCHOLAR-1, the pooled CORAL extensions and the rituximab treated patients in the PIX301 (the pivotal study for the Pixuvri MAA). Indirect comparisons of ORR/CR and OS were performed using 1) C2201 infused patients and 2) C2201 enrolled patients. Adjustment for baseline characteristics were conducted for two of the three datasets (SCHOLAR and CORAL). The SCHOLAR-1 comparison was first conducted by applying the refractory criteria used in SCHOLAR-1 to the C2201 study population. Subsequently, matching was performed on three variables (primary diagnosis (DLBCL vs. non-DLBCL), IPI risk classification (<2 vs. $\geq$ 2), and refractory category (primary refractory, refractory to $\geq$ 2nd line therapy, relapsed $\leq$ 12 months post ASCT). For the CORAL comparison, matching was based on 3 variables; gender, IPI risk classification (<3 vs. ≥3) and ASCT as the most recent therapy and relapsed after ASCT (yes vs. no).

Supportive Study A2101J (NCT02030834) is an ongoing Phase 2a case-series study evaluating the efficacy of tisagenlecleucel in adult patients with r/r Non-Hodgkin lymphoma (NHL) including GC and non-germinal center (NGC) DLBCL, "Double hit" DLBCL (DHL), and transformation of follicular lymphoma (tFL). Patients were eligible if they had CD19+ DLBCL or follicular lymphoma (FL) with measurable residual disease after primary and salvage therapies, had relapsed or residual disease after ASCT, or were not eligible for autologous or allogeneic SCT.

The enrolled patients received LD chemotherapy based on each patient's treatment history, blood counts, and organ function (data not shown). One single dose of tisagenlecleucel were infused 1 to 4 days after the completion of LD chemotherapy at the dose range of 1.0 to 5.0x10^8 cells. The median number of days from apheresis to infusion in study A2101J was 39 (range: 27 to 145). In total, 10 of 28 patients received bridging therapy. The primary objective of this study was to estimate the efficacy of tisagenlecleucel in NHL patients by measuring the ORR in evaluable patients at 3 months.

Efficacy data and additional analyses

- *ALL indication*

Results from the pivotal study B2202 showed that tisagenlecleucel significantly improved ORR: 61 of the 75 infused patients (81.3%) had a best overall disease response of CR or CRi as determined by IRC. As a result, using the pre-specified endpoint in the SPA for B2202, the lower limit of the 95% exact Clopper-Pearson confidence interval for ORR was 70.7% for CR/CRi, which is above the pre-set null hypothesis rate of 20%. Forty five patients (60%) had a best response of CR within the first 3 months after infusion, and 16 patients (21.3%) had a best response of CRi. The study also met its primary objective with an ORR (BOR as CR or CRi; during the 3 months after tisagenlecleucel administration in patients by IRC assessment) of 82.0% (95% CI: 68.6, 91.4) analysed based on first 50 infused patients. The robustness of the primary analysis of ORR (per IRC assessment) was confirmed by the results of a series of predefined sensitivity analyses with the ORR ranging from

63.5% to 82.4% in different analysis sets, with the lower bounds of all 95% CIs above 20%. Efficacy in patients infused with tisagenlecleucel from the EU manufacturing facility was 75% and consistent with the overall results.

Regarding the secondary endpoints the proportion of patients with BOR of CR/CRi by IRC assessment with MRD negative bone marrow (i.e., MRD <0.01%) during three months after tisagenlecleucel infusion was 61/75 (81.3%, 95% CI: 70.7, 89.4). The majority of patients who had a CR or CRi after tisagenlecleucel treatment achieved a sustained response and median DOR per IRC assessment was not reached at Primary data cut-off date 25-Apr-2017 (median duration of follow up 7.5 months). The median EFS was not reached, with 6-month EFS of 72.7%. The median OS was 19.1 months (15.2, NE), with 12-month OS of 76.4%. Results from these time-dependent endpoints provide support for sustained benefit of tisagenlecleucel.

Patients in the B2202 reported improvements in health related quality of life outcomes at 3 and 6 months among responders to therapy. Tisagenlecleucel infusion led to a decrease in the severity of problems as measured by the emotional, social, physical, and psychosocial health subscales as well as mobility, self-care, usual activities, pain/discomfort, anxiety/depression as assessed via the EQ-5D questionnaire. Thus, results indicate a meaningful improvement in patients responding to treatment.

ORR in the supportive studies B2205J and B2101J were 69% and 94.6% respectively. Overall, these results provide supportive evidence for the efficacy of tisagenlecleucel in the treatment of paediatric and young adult patients with r/r B-cell ALL.

Results from the historical controls were presented either as a comparison of pooled patients who received tisagenlecleucel or as B2202 patients alone. After adjusting for population differences via MAIC, CTL019 was estimated to have superior OS and ORR over blinatumomab, CEC, and clofarabine monotherapy. Additionally tisagenlecleucel was estimated to have superior RFS over blinatumomab. Overall, this comparison is subject to potential bias due to unobserved or unmeasurable confounding. At the same time it is noted that the degree of benefit observed was largely consistent regardless of whether the comparison was made using B2202 only or using the pooled CTL019 studies and was largely consistent between the primary analysis and sensitivity analyses across all the comparators and endpoints. Finally, the benefit of tisagenlecleucel was still consistent across all the sensitivity analyses performed. Since the populations in the studies were different the benefit of tisagenlecleucel may have been underestimated.

- *DLBCL indication*

Only those 81 patients who received tisagenlecleucel infusion from the US manufacturing facility at least 3 months prior to data cut-off were included in the efficacy analysis set (EAS), which was the primary analysis population.

In the FAS, the majority of patients were white (90.9%; 90 patients) and men (63.6%; 63 patients). The median age was 54 years (range 22-76) with 23.2% (23 patients) being ≥ 65 years, and none above 76 years. This is younger than would be expected, given that DLBCL peaks in the 7th decade, and probably reflects the eligibility criteria. The majority of patients had DLBCL histology (79.8%) and a smaller group had transformed lymphoma (19.2%). The percentage of patients who were refractory to last line (51.5%) was marginally higher than those who relapsed to last line therapy (48.5%). Approximately 50% of patients had prior autologous SCT, and 18.1% had received ≥4 prior lines of anti-neoplastic therapies. Thus, the majority of the patients in study C2201 had relapsed or were refractory to either 2/3 prior therapies (75.7%).

In the "not infused" set compared to the FAS, there was a higher proportion of patients with unfavourable prognostic factors: Age ≥65 years, 33.3% vs. 23.2%; ECOG 1, 66.7% vs. 45.5%; stage III-IV at initial diagnosis, 79.2% vs. 66.7%; stage III at study entry 29.2% vs. 21.2%; IPI ≥2 at initial diagnosis, 68.8% vs. 56.6% and IPI ≥2 at study entry, 93.8% vs. 72.7%. Fewer patients in the "not infused" set had undergone HSCT (37.5% vs. 47.5%) and a higher proportion were refractory to the last treatment line without prior HSCT (31.3% vs. 17.2%). On the other hand, a higher fraction in the "not infused" set compared to the FAS had tumours of the GBC subtype (60.4% vs. 51.5%) and a slightly higher proportion had double/triple hits in myc/bcl2/bcl6 genes (18.8% vs. 12.1%). Overall, these data indicate that the prolonged time-period from apheresis to CAR-T administration enriched the patient population included in the FAS for a better prognosis.

The mean and median time from the end of the last antineoplastic therapy to enrolment were longer in the long-term responders (8.6 and 5.1 months, respectively) than in the non-responders (4.1 and 2.8 months). The mean time from the most recent relapse/progression was also somewhat longer in the long-term responders compared to the non-responders (6.8 vs. 5.5 months). The proportion of patients with lymphomas of double/triple hits in myc/bcl2/bcl6 genes were also lowest in the long-term responders. Thus, again this indicates that inclusion in the EAS of only those patients who survived the long pre-infusion waiting period, selected for patients with a more favourable survival prognosis on current therapies, who were more likely to respond to treatment.

Among the 217 screened patients in study C2201, 165 patients fulfilled the eligibility criteria and 147 patients were enrolled. In total, 99 patients received tisagenlecleucel (FAS) at the primary analysis (DCO: 08-mar-2017), whereas 48 enrolled patients were never infused.

The study protocol specified that patients should not experience significant worsening in the clinical status compared to the initial eligibility criteria prior to infusion. Combined with the prolonged waiting period, this may have contributed to the large proportion (~30%) of poor prognosis patients dropping-out after enrolment and prior to receiving tisagenlecleucel, potentially enriching the patient population in the EAS for patients having a better prognosis. Thus, for the efficacy outcomes, the results based on the ITT (enrolled) population is considered the primary analysis set.

The best ORR based on IRC in the EAS of 81 patients was 53.1% (43/81; 95% CI: 41.7, 64.3; p<0.0001). Among the responding patients, 39.5% (32/81 patients) achieved a CR, while 13.6% (11/81 patients) obtained a PR. The ORR response at 3 months of follow-up was 38.3 % (31/81 patients) and 32% (26/81 patients) for CR. However as the overall treatment in study C2201 includes leukapheresis, bridging- and LD chemotherapy, and tisagenlecleucel infusion, efficacy analysis of tisagenlecleucel based on the infused patients only as this likely might provide unrealistic positive efficacy results of the therapy. Sensitivity analysis of ORR by IRC where all enrolled patients with the updated DCO was taken into account showed an ORR of 33.9% (56/165; 95% CI: 26.8, 41.7) - significantly lower than the ORR in the EAS. Compared to the pre-specified historical control with an ORR of around 20% (used in hypothesis testing) - 26% (pooled estimate from SCHOLAR-1) and 40.3% (estimate from the pooled CORAL extension studies), these results are not considered compelling.

The median TTR among the 43 responders per IRC assessment in the EAS Main Cohort was 0.9 months (95% CI: 0.9, 1.0). As evident form the KM plot, the majority of the responders (79.1%; 34/43) achieved their disease control (CR or PR) within the first month after tisagenlecleucel infusion. The median DOR per IRC assessment was not reached at the DCO of the primary analysis. The median follow-up time from onset of response was 2.17 months (range: 1.5, 11.3). At the DCO of the primary analysis 65.1% of the responding patients (28/43) were still in an ongoing response to tisagenlecleucel. The median EFS per IRC assessment at the DCO of the primary analysis was 2.6 months (95% CI: 2.1, 3.1). The median follow-up time of 2.17 months (range: 0.9, 12.1) was short

and 39 patients who were ongoing without an event were censored. The median PFS per IRC assessment was 2.9 months (95% CI: 2.2, 6.2). Median follow-up time at the DCO was 2.14 months (range: 0.9, 12.1). With a median follow-up time of 3.58 months (range: 2.2, 14.5) in the FAS, median OS was not yet reached (95% CI: 6.5, NE). The data of the primary analysis on DOR, EFS, PFS and OS should be interpreted with caution due to the short median follow-up time and high censoring of patients.

ORRs analysis was performed for various demographic and prognostic subgroups in the EAS Main Cohort that contained at least 5 patients in each subgroup. The ORR values by IRC assessment ranged on average from 39.5% to 83.3% in all the subgroups analysed, except for the subgroup of patients <40 years of age where only one patient achieved a PR (ORR 8.3%; 1/12). Hence, the majority of the subgroups evaluated achieved a disease control rate in line with the ORR of the primary analysis of 53.1% (95% CI: 41.7, 64.3). The lower limit of the 95% CIs for most of the subgroups, with the exception of patients <40 years and those with double/triple-hit rearrangements, were above the pre-specified historical control ORR of 20%.

Concerning the low sample sizes within each subset, these differences should be interpreted with caution. However, the data provided points to a trend of lower efficacy in terms of ORR in patients who were refractory to last line therapy and patients below 40 years of age. It is well-known that patients who are refractory to last line therapy may have a more severe outcome. The lower efficacy in r/r DLBCL patients under 40 years of age is unexpected; no association with an underlying prognostic factor could be identified.

In an updated analysis with an additional median follow-up time of 5.8 months the median time from infusion to the DCO was 11.4 months (range: 2.1 to 23.1). Best ORR based on IRC in the updated EAS of 92 patients was 52.2% (95% CI: 41.5, 62.7). In line with the results of the primary analysis, 38.0% of the responding patients achieved a CR, while 14.1% obtained a PR. The response rates of patients who achieved CR were sustained at month 3 (32.6%; 95% CI: 23.2, 43.2) and month 6 (29.3%; 95% CI: 20.3, 39.8). In line with the results of the primary analysis, the median DOR per IRC assessment was not reached in the EAS at the DCO of the updated analysis however, there is evidence that a large proportion of patients who achieve a CR sustained clinically meaningful remission. This does not seem to apply to the low number of patients who achieved a PR (N=13), with the exception of three patients. The median OS in the updated FAS of 106 patients was 10.3 months (95% CI: 6.7, NE). Although the OS support the ORR results, the data was not very mature.

Quality of life (QoL) assessments were performed with FACT-Lym questionnaire (disease specific) and the SF-36 questionnaire. The QoL instruments were completed by 76 patients (94%) at baseline and 34 patients (42%) at Month 3. Among the 34 patients who reported PRO at 3 months, 29 patients had a CR or PR. The PRO results indicate that there is a small increase in QoL after 3 months for patients who responded in terms of ORR to treatment. However, the design of the phase 2 study (uncontrolled, non-randomized, open-label) makes it difficult to conclude if any clinically relevant symptomatic improvement.

In the updated results from Study C2201 based on a DCO date of 08-Dec-2017 165 patients were enrolled and 111 patients infused and comprise the FAS: 95 received tisagenlecleucel manufactured at the Morris Plains facility (EAS Main Cohort) and 16 at the Fraunhofer Institute (Cohort A). The median duration of follow-up is 13.9 months with a median duration of follow-up of 7.7 months. All responding patients were followed for ≥ 9 months after response. The set of 'all eligible patients who underwent leukapheresis' was the same as the set of 'all enrolled' patients.

Efficacy results showed an ORR of 51.6% (48/93) in infused patients versus 33.6% (48/143) in enrolled patients in the EAS Main cohort and 33.9 % (56/165) in all enrolled - which is at the same level as at initial DCO. Median OS from enrolment date was 12.9 months (95% CI: 8.4, NE) in the infused population and 8.2 months (95% CI: 5.8, 11.7) in the enrolled population. The median OS from infusion was 11.7 months in the infused population, this increased as compared to the 10.3 months at the DCO of 06-Sep-2017. In the non-infused patients median PFS was 2.1 months versus 4.4 months in all enrolled and 5.1 months FAS. Furthermore, the median OS from enrolment was considerably lower in the non-infused patients (median 2.4 months); similarly the median OS from last relapse was FAS 16.3 months, all enrolled 10.6 months, non-infused 5.0 months.

There is a concern that the use of the EAS for all efficacy outcomes ignores the impact of waiting time and bridging therapy thus leading to an enrichment of the patient population in the EAS for patients having a better prognosis, and an overestimation of efficacy for tisagenlecleucel. In the update, baseline characteristics were also given for the non-infused patients, showing that these patients had a higher representation of patients who were ≥65 years (FAS 22.5% vs non-infused 40.7%), ECOG 1 (FAS 45% vs non-infused 70.4%), IPI≥2 (FAS 94.4% vs non-infused 72.1%) at study entry and refractory to last treatment (FAS 55% vs non-infused 64.8%). In general, baseline characteristics were worse in this group.

Furthermore, an analysis on OS from last relapse in patients with SD or PD following salvage/bridging therapy was provided. According to this, such patients in the JULIET trial had a similar KM curve as the subset of SD/PD patients in the CORAL study, both subsets showing a far lower OS than in the SD/PD subset of the infused patients in the JULIET trial. This indicates that not including these patients in the efficacy analyses introduces a bias that is not present in the CORAL trial.

Updated efficacy results were presented for DLBCL versus DLBCL arising from TFL (18.9%; 21/111). The ORR in the subgroup of 18 patients with DLBCL / TFL was 83.3% (95% CI: 58.6, 96.4), whereas the ORR for the remaining patients (n=74) was 44.6% (95% CI: 33.0, 56.6). The median OS in the DLBCL subgroup was 10.1 months (95% CI: 5.6, 17.9), while the median OS for patients with DLBCL arising from TFL was not yet reached. Of note, a larger proportion of the patients with DLBCL arising from TFL responded to tisagenlecleucel, and 33 % (6/18) and 50 % (9/18) of these were short- and long-term responders. Overall, the data provided reveal a better efficacy outcome in patients with DLBCL arising from TFL.

SCHOLAR-1 analysed 636 subjects identified from a total pooled population of 861 subjects. Compared to study C2201, SCHOLAR-1 had fewer patients with a diagnosis of TFL (4% vs 16%), ECOG PS 0-1 (73% vs 100%), IPI score intermediate to high (57% vs 77%), primary refractory disease (28% vs 41%) and >2 number of lines of prior chemotherapy/ASCT (<1% vs 52%). It is however not clear to what extent the baseline characteristics reflect the status of the patient at the time of initiation of savage therapy. Response rates (evaluated for 523 patients) was estimated as 26% (95% CI: 21%, 31%), ranging from 20% to 31% across cohorts (95% CI not reported). The CR was 7% (95% CI: 3%, 15%), ranging from 2-15% (95% CI not reported). The median OS was estimated as 6.3 months (95% CI: 5.9, 7.0), with a range across cohorts of 5.0 - 6.6 months.

In overall it seems that accounting for all uncertainties and applying conservative approaches, efficacy of Kymriah in patients with relapsed/refractory DLBCL is seen and further data including details of the manufacturing turnaround time, (i.e. time from last relapse or confirmed refractory status, time from decision to treat, and time from leukapheresis to infusion) will be obtained from post-authorisation studies; a prospective, observational study in patients with r/r DLBCL based on data from registry with efficacy outcome measures in line with study C2201; further follow-up (24 months) for patients in the EAS Cohort and all infused patients from study C2201; and study CCTL019H2301 - open-label, Phase

III study of Kymriah versus standard of care in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma.

Further to the uncertainties identified during the assessment of the DLBCL indication as the study design, study conduct and study analysis (use of historical comparisons) the CAT considered that the SAG Oncology should be consulted.

Additional expert consultation

The SAG Oncology was consulted on the following issues:

Population

1. How representative do you view the population that was administered Kymriah of the population encountered in the clinical setting considering that patients dropped out due to the delay in manufacturing (i.e. the selection of patients from the ITT to the mITT population) and received bridging chemotherapy?

   As a general comment, it is important to stress that the ITT analysis set (all enrolled patients, regardless of treatment actually received) is the most relevant population to estimate the efficacy of bridging chemotherapy plus Kymriah in the real-life setting. Other analysis sets (infused, evaluable, responders) are likely to introduce important selection bias.

   Concerning the ITT population, it is likely that selection bias has been introduced by the eligibility criteria (ECOG PS 0-1; adequate organ function), and patients >65 years old are likely to be under-represented. The views within the group were slightly diverging in terms of generalizability. However, it was acknowledged that this type of selection is common for clinical trials and the uncertainties in terms of generalization to the normal population did not pose any major concerns. Indeed, when an intensive regimen is proposed to patients, there is anyway a selection.

   The initial manufacturing problems and delay in infusion of Kymriah have to be taken into account and improvements in the lymphoma progression prior to infusion are expected on the basis of improvements in the manufacturing speed. Thus, the results observed in the ITT population likely represent a conservative estimate for the target patient population.

   However, concerning deviations from the ITT analysis set, such as in the infused "mITT" population, further selection bias is likely and it is difficult rule out important over-estimation of the treatment effect. (It is understood, that traditionally the results are given for the ITT and for the patient submitted to treatment, i.e., infused patients and that both set of data should be described.)

   In conclusion, the ITT population was considered relevant and representative based on reasonable assumptions and extrapolations.

2. How does the selection of patients from the ITT to the mITT population, due to the delay in administration, impact your evaluation of the efficacy of Kymriah?

   Other analysis sets (infused, evaluable, responders) than the ITT set may be useful for exploratory analyses but are likely to introduce important selection bias. The relevant estimate of the probability of experiencing benefits to inform treatment decisions is the probability of response at the start of treatment procedure (i.e., ITT) and not the probability of response conditional on some future event like actually receiving an infusion or being evaluable for response.

Treatment outcomes

3. Can in your experience complete responses of relevant duration be observed in the population of interest (i.e. DBCL that have relapsed or are refractory to several lines of standard therapy) with salvage treatment (chemotherapy/radio therapy/SCT) only?

   The data in this population are limited. In the C2201 trial, bridging chemotherapy was associated with a <10% proportion of CR. A 28% CR rate was observed in the follow-up cohorts of the CORAL-1/2 studies (N=278), which is similar to what observed in the ITT population for trial C2201 (with all limitations of indirect comparisons, see also answer to question 5), but the population of the C2201 trial was mostly pretreated by more lines of therapy than in the CORAL trial.

   Concerning exploratory subgroups (acknowledging the selection bias, see answer to question 1), for the infused population the ORR was 52% with 40% CR rate associated with prolonged duration of response in the last evaluation presented. Allogeneic stem cell transplantation performed only in responding patients leading to a selection of the patients and the chemorefractory ones are excluded from this procedure. Allogeneic stem cell transplantation is associated with high response rate but only few patients in this situation make it to the procedure (and ranges will vary nationally depending on local practice) and transplant mortality is seen by many as prohibitively high (10% to more than 30% depending on the series).

4. How do you evaluate the impact of bridging chemotherapy on the efficacy outcomes?

   The effect is likely to be small and of little impact although the estimated complete response rate was almost 10% in patients who did not receive Kymriah. Some SAG members raised potential risks if the bridging therapy was to be modified significantly. In any case, bridging therapy should be considered as an essential element of the treatment strategy. The ITT analysis assesses the efficacy of the whole strategy of bridging therapy plus Kymriah (and not Kymriah alone).

5. In this context can you comment on the relevance of the data from the CORAL study for interpretation of the Kymriah results?

   Comparison between the two studies is difficult due to the different study populations (population in C2201 more heavily pre-treated) and the known problems with indirect comparison. Still, the CORAL studies provide a reasonable comparison for exploratory purposes. As a comment, it is possible that in the future such indirect comparisons could additionally be conducted on the basis of population-based registry data (although it is acknowledged that this may be possible only in selected countries and often on the basis of less extensive data collection on patient characteristics). In conclusion, the comparison is relevant to contextualise the observed effects.

6. What conclusions can be drawn on clinical benefit given the limitations of the follow-up time for time-dependent endpoints and the single arm trial design?

   Based on the ITT analysis set that is considered the most relevant and conservative to estimate the effect of the treatment strategy, the complete response rate observed is in the range of what has been observed with other treatment modalities (CORAL studies). However, the duration of response is considered remarkable with more than 60% of responders still responding after a median follow-up of 19 months. Taken together, based on the response rate and duration of response, given the available treatment options, the group agreed by consensus that the clinical benefit is considered established despite the limitations for time-dependent endpoints in single arm trials. Concerning OS, a number of suitable approaches have been explored based on matching. While informative, it is difficult to draw conclusions on the basis of the analyses presented since important biases (including lead time bias) cannot be excluded.

7. For which patients with DLBCL would Kymriah be a treatment option given available data on efficacy and safety?

   Based on the available data, Kymriah may be a treatment option for patients failing or relapsing after at least 2 lines of therapy . It is difficult to further specify criteria to select patients for whom Kymriah might be a treatment option. This has to be left to informed clinical decisions that can assess patient preferences, and the benefits, risks, and uncertainties of all available treatment options, including stem cell transplantation and clinical trials. Treatment should only be initiated in centres that are experienced also in these types of procedures.

   Furthermore, if possible, research on identification of biomarkers predictive of response should continue, with the aim to guide treatment decisions.

2.5.4. Conclusions on the clinical efficacy

- *ALL indication*

Results of the B2202 study demonstrated that a single infusion with tisagenlecleucel showed a high increase of ORR in aggressive relapsed or refractory ALL. Despite limited follow up, the results from time-dependent secondary endpoints such as DOR, EFS and OS provide support for sustained benefit of tisagenlecleucel.

The CAT considers the following measures necessary:

- PAES: In order to further evaluate the efficacy and safety of Kymriah in ALL patients below the age of 3 years, the applicant should conduct and submit a study based on data from a disease registry in ALL patients.

- DLBCL indication

Whereas the efficacy of tisagenlecleucel in terms of ORR/CR was modest based on the most conservative analyses, the duration of response in complete responders is substantial and therefore clinically relevant in the patient population.

The CAT considers the following measures necessary:

- PAES: In order to further evaluate the efficacy of Kymriah in patients with relapsed/refractory DLBCL, the applicant should conduct and submit a prospective, observational study in patients with r/r DLBCL based on data from registry with efficacy outcome measures in line with study C2201, including details of the manufacturing turnaround time, (i.e. time from last relapse or confirmed refractory status, time from decision to treat, and time from leukapheresis to infusion).
- PAES: In order to further characterise long-term efficacy and safety of Kymriah in relapsed/refractory DLBCL, the applicant should submit the 24 months follow-up for patients in the main Cohort and 24 months follow-up of all infused patients from study C2201. In addition the applicant should submit the final CSR including 5 years of follow-up.
- PAES: In order to further characterise the long-term efficacy and safety of Kymriah in relapsed/refractory DLBCL, the applicant should submit the results of study CCTL019H2301 - open-label, Phase III study of Kymriah versus standard of care in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma.

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

2.6. Clinical safety

- *ALL indication*

The safety assessment is assessed based on the below studies:

Study B2202 (patients enrolled: N=92, patients infused: N =75), study B2205J (patients enrolled: N=35, patients infused: N=29). Pool and study B2101J (patients enrolled: N=73, patients infused: N=62 including 56 non-CNS3 ALL patients, 4 CNS3 ALL and 2 lymphoma patients). For all studies the follow-up of safety post-tisagenlecleucel infusion was daily to every third day until day 28, thereafter monthly first 6 month, thereafter every third month until 24 months. Thereafter every sixth month to yearly until 60 months for studies in the SCS Pool.

Safety in studies B2202 and B2205J is presented as pooled data.

- *DLBCL indication*

Evaluation of safety is based on data from Study C2201 in 27 sites. Planned follow-up is 60 months. Patients were assessed for AEs at each clinic visit: Daily to every third day until day 28, thereafter monthly first 6 months, thereafter every third month until 24 months, thereafter every sixth month until 60 months.

Patient exposure

- *ALL indication*

In the SCS Pool the median (range) dose of tisagenlecleucel infused was 1.06×10^8 (range: 0.03×10^8 to 2.6×10^8) CAR-positive viable T cells for all patients regardless of weight. The median (range) weight adjusted dose of tisagenlecleucel infused was 3.2×10^6 CAR-positive viable T cells/kg (range: 0.2×10^6 to 5.4×10^6).

The clinical dose selected for the supportive study B2101J included a wide range from 1.5×107 to 5×10^9 (0.3×10^6 to 1.0×10^8 cells per kg) total T cells. The total number of CAR-positive T cells varied among batches (range: 1 x 10^7 to 1 x 10^9). The total dose in this study was administered in three divided fractions in this study (i.e. 10%, 30%, 60% of the total cell dose) to ensure safe tisagenlecleucel administration. Subsequent doses were held with the onset of fever or other acute events. Within the first 28 days of the study, the median total tisagenlecleucel dose infused was 1.6×10^8 cells (range 0.1×10^8 to 9.1×10^8). The median weight adjusted tisagenlecleucel dose infused was 4.8×10^6 CAR-positive cells/kg (range 0.6×10^6 to 16.4×10^6). Anytime during the study, the median total tisagenlecleucel dose infused was 3.4×10^8 cells (range 0.1×10^8 to 11.4 $\times10^8$). The median weight adjusted tisagenlecleucel dose infused was 7.5×10^6 CAR-positive cells/kg (range 0.6×10^6 to 22.6 $\times10^6$).

In the SCS Pool, all infused patients received concomitant medications after tisagenlecleucel infusion. Concomitant medications administered were representative of those routinely prescribed for paediatric and young adult patients with r/r ALL for treatment and prophylaxis of AEs. The most commonly used concomitant medications (per ATC class) included multiple medications used by 102 (98.1%) patients (including vancomycin by 46.2%), anilides (paracetamol) used by 77 (74.0%) patients, natural opium alkaloids used by 50 (48.1%) patients, immunoglobulins used by 49 (47.1%) patients, and serotonin antagonist used by 47 (45.2%) patients.

In the supportive study B2101J the most commonly used (by ≥ 70% patients) and the most relevant concomitant medications by ATC class regardless of the proportion of treated patients included: natural opium alkaloids (96.4%), immunoglobulins (75%), antibiotics (87.5%) including gentamycin and vancomycin.

- *DLBCL indication*

In total 99 adult patients treated with single intravenous tisagenlecleucel infusion of 1.0 to 5.0×10^8 CAR+ viable T cells. The median infused tisagenlecleucel dose was 3.1×10^8 cells (range: 0.10 to 6.0×10^8) and the median total cell dose infused was 10.3×10^8 cells (range: 0.9 to 39×10^8). At the data cut-off of 06 Sep 2017, a safety analysis with updated frequency data for AESI of a total of 106 patients was included. Median dose in this analysis is $3.0x10^8$ (range: 0.10-6.0), and the median total cell dose infused was $10.5x10^8$ (range: 0.9-30.0. At the cut-off date of 08 Dec 2017 (addendum dated 18.04.2018) the analysis included safety data for in total 111 patients with DLBCL indication with a median duration of follow-up of 13.9 months; this analysis is used in the assessment where possible.

Adverse events

- *ALL indication*

Table 51 Adverse events categories post-tisagenlecleucel infusion on SCS Pool (Safety set)

	Study B2202 N=75	Study B2205J N=29	All patients N=104
Number of patients with at least one AE	**75 (100)**	**29 (100.0)**	**104 (100)**
Suspected to be study drug related	71 (94.7)	28 (96.6)	99 (95.2)
Death within 30 days post-tisagenlecleucel infusion	2 (2.7)	2 (6.9)	4 (3.8)
Death >30 days post-tisagenlecleucel infusion	17 (22.7)	8 (27.6)	25 (24.0)
Patients with serious or other significant events			
Any time post-tisagenlecleucel infusion			
SAE	58 (77.3)	23 (79.3)	81 (77.9)
Suspected to be study drug related	50 (66.7)	22 (75.9)	72 (69.2)
Grade 3/4 AE	66 (88.0)	24 (82.8)	90 (86.5)
Suspected to be study drug related	55 (73.3)	22 (75.9)	77 (74.0)
Within 8 weeks post-tisagenlecleucel infusion			
SAE	51 (68.0)	23 (79.3)	74 (71.2)
Suspected to be study drug related	49 (65.3)	22 (75.9)	71 (68.3)
Grade 3/4 AE	62 (82.7)	24 (82.8)	86 (82.7)
Suspected to be study drug related	52 (69.3)	22 (75.9)	74 (71.2)
Adverse events of special interest (AESI)	70 (93.3)	26 (89.7)	96 (92.3)
Grade 3/4 AESI	59 (78.7)	20 (69.0)	79 (76.0)
Suspected to be study drug related	65 (86.7)	26 (89.7)	91 (87.5)
>8 weeks post-tisagenlecleucel infusion	**N=70**	**N=21**	**N=91**
SAE	24 (34.3)	7 (33.3)	31 (34.1)
Suspected to be study drug related	7 (10.0)	2 (9.5)	9 (9.9)
Grade 3/4 AE	32 (45.7)	10 (47.6)	42 (46.2)
Suspected to be study drug related	14 (20.0)	7 (33.3)	21 (23.1)

All deaths during both study follow-up and survival follow-up are summarized.
For the summary of >8 weeks post-tisagenlecleucel infusion, the percentage is based on the number of patients who are still in study follow-up at 8 weeks post-tisagenlecleucel infusion.
Source: [SCS Appendix 1-Table 3-22.1]

Table 52 Percentage of patients with adverse drug reactions post-tisagenlecleucel infusion in clinical studies

Adverse drug reactions	B2202 + B2205J, N=104			Frequency category (all grades)
	All grades %	Grade 3 %	Grade 4 %	
Infections and infestations[a)]				
Infections - pathogen unspecified	48	13	8	Very common
Viral infectious disorders	33	14	1	Very common
Bacterial infectious disorders	25	13	1	Very common
Fungal infectious disorders	13	4	3	Very common
Blood and lymphatic system disorders				
Febrile neutropenia	36	34	2	Very common
Disseminated intravascular coagulation	6	2	-	Common
Coagulopathy	6	2	-	Common
Histiocytosis haematophagic	5	2	1	Common
Pancytopenia	3	2	1	Common
Immune system disorders				
Cytokine release syndrome	81	20	24	Very common
Hypogammaglobulinemia[b)]	45	7	-	Very common
Graft versus host disease	1	1	-	Common
Metabolism and nutrition disorders				
Decreased appetite	40	19	1	Very common
Hypokalaemia	30	12	3	Very common
Hypophosphatasaemia	21	11	1	Very common
Hypocalcaemia	16	6	-	Very common
Hypoalbuminaemia	13	1	-	Very common
Fluid overload	11	5	-	Very common
Hyperglycaemia	10	6	1	Very common
Hyperphosphatasaemia	11	-	1	Very common
Hyperuricaemia	11	1	-	Very common
Hypomagnesaemia	6	-	-	Common
Tumor lysis syndrome	4	3	1	Common
Psychiatric disorders				
Delirium[c)]	16	3	-	Very common
Anxiety	15	3	-	Very common

Adverse drug reactions	B2202 + B2205J, N=104			Frequency category (all grades)
	All grades %	Grade 3 %	Grade 4 %	
Nervous system disorders				
Headache[d)]	35	2	-	Very common
Encephalopathy[e)]	29	6	1	Very common
Dizziness	8	-	-	Common
Tremor	6	-	-	Common
Seizure[f)]	5	2	-	Common
Cerebral haemorrhage	2	-	2	Common
Dysphasia[g)]	2	1	-	Common
Cardiac disorders				
Tachycardia[h)]	30	4	1	Very common
Cardiac failure[i)]	7	6	1	Common
Cardiac arrest	3	-	3	Common
Vascular disorders				
Hypotension	31	10	13	Very common
Hypertension	18	5	-	Very common
Capillary leak syndrome	3	1	1	Common
Flushing	3	-	-	Common
Respiratory, thoracic and mediastinal disorders				
Hypoxia	24	13	7	Very common
Cough	23	-	-	Very common
Pulmonary oedema	14	8	2	Very common
Epistaxis	13	3	1	Very common
Pleural effusion	13	3	1	Very common
Tachypnoea	10	5	-	Very common
Interstitial lung disease	1	-	1	Common
Gastrointestinal disorders				
Vomiting	36	3	-	Very common
Nausea	31	7	-	Very common
Diarrhoea	28	2	-	Very common
Abdominal pain[j)]	22	3	-	Very common
Constipation	17	-	-	Very common
Mouth haemorrhage	5	3	-	Common
Abdominal distension	4	-	-	Common
Ascites	3	-	-	Common

Adverse drug reactions	B2202 + B2205J, N=104			Frequency category (all grades)
	All grades %	Grade 3 %	Grade 4 %	
Abdominal compartment syndrome	1	-	1	Common
Hepatobiliary disorders				
Hyperbilirubinaemia	7	3	-	Common
Skin and subcutaneous tissue disorders				
Rash	10	-	-	Very common
Pruritus	8	-	-	Common
Erythema	7	-	-	Common
Hyperhydrosis	7	-	-	Common
Petechiae	6	1	-	Common
Rash maculo-papular	4	2	-	Common
Rash papular	4	-	-	Common
Musculoskeletal and connective tissue disorders				
Pain in extremity	16	1	-	Very common
Myalgia	13	-	-	Very common
Arthralgia	11	1	-	Very common
Back pain	10	3	-	Very common
Musculoskeletal pain	7	-	-	Common
Renal and urinary disorders				
Acute kidney injury[k)]	19	3	10	Very common
Haematuria	7	3	1	Common
Dysuria	4	-	-	Common
General disorders and administration site conditions				
Pyrexia	41	10	3	Very common
Fatigue	24	1	-	Very common
Chills	13	-	-	Very common
Face oedema	9	2	-	Common
Oedema peripheral	8	2	-	Common
Generalized oedema	6	-	-	Common
Multiple organ dysfunction syndrome	3	1	2	Common
Investigations				
Aspartate aminotransferase increased	30	11	7	Very common
Alanine aminotransferase increased	28	13	-	Very common
Blood bilirubin increased	15	9	-	Very common
International normalised ratio increased	15	1	-	Very common

Adverse drug reactions	B2202 + B2205J, N=104			Frequency category (all grades)
	All grades %	Grade 3 %	Grade 4 %	
Blood creatinine increased	13	4	1	Very common
Prothrombin time prolonged	9	1	-	Common
Blood fibrinogen decreased	9	2	2	Very common
Activated partial thromboplastin time prolonged	7	1	-	Common

[1)]The frequency of ADRs observed is the crude incidence rate
[a)]Infections and infestations are high level group terms.
[b)]Hypogammaglobulinemia includes PTs of immunoglobulins decreased, blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased and hypogammaglobulinaemia
[c)] Delirium includes PTs of agitation, delirium, hallucination, visual hallucination, irritability, and restlessness
[d)] Headache includes PTs of headache and migraine
[e)] Encephalopathy includes PTs of depressed level of consciousness, mental status changes, automatism, cognitive disorder, confusional state, disturbance in attention, encephalopathy, myoclonus, somnolence and lethargy
[f)]Seizure includes PTs of generalized tonic-clonic seizure, and seizure.
[g)]Dysphagia includes PTs of dysphagia, dysarthria, speech disorder, and aphasia
[h)] Tachycardia includes PTs of sinus tachycardia and tachycardia.
[i)] Cardiac failure includes PTs of cardiac failure, left ventricular dysfunction, cardiac failure congestive and right ventricular dysfunction
[j)]Abdominal pain includes PTs of abdominal pain, abdominal pain lower gastrointestinal pain and abdominal pain upper
[k)]Acute kidney injury includes PTs of acute kidney injury, anuria, azotaemia, renal failure, renal tubular dysfunction and renal tubular necrosis

- *DLCBL indication*

AEs were primarily observed within 8 weeks post-infusion; within 8 weeks and after 8 weeks postinfusion were reported in 84.8% and 28.2% of patients, respectively. No adverse reactions were reported after more than 1 year post-infusion.

An overview of adverse reactions in patients with DLBCL is given in the following table.

Table 5-8 Adverse drug reactions in patients treated with tisagenlecleucel

Adverse drug reaction	C2201, N=111		
	All grades %	Grade 3/4 %	Frequency category
Infections and infestations[a)]			
Infections - pathogen unspecified	44	24	Very common
Bacterial infectious disorders	10	7	Very common
Fungal infectious disorders	10	5	Very common
Viral infectious disorders	8	2	Common
Blood and lymphatic system disorders			
Febrile neutropenia	16	15	Very common
Disseminated intravascular coagulation	3	2	Common
Histiocytosis haematophagic	1	-	Common
Immune system disorders			
Cytokine release syndrome	58	22	Very common
Hypogammaglobulinaemia[b)]	15	4	Very common
Metabolism and nutrition disorders			
Hypokalaemia	23	8	Very common
Hypomagnasaemia	17	-	Very common
Hypophosphataemia	17	14	Very common
Decreased appetite	12	4	Very common
Hyponatraemia	8	5	Common
Hyperglycaemia	5	2	Common
Hypoalbuminaemia	5	3	Common
Tumour lysis syndrome	1	1	Common
Psychiatric disorders			
Anxiety	11	1	Very common
Delirium[c)]	5	3	Common
Nervous system disorders			
Headache[d)]	23	1	Very common
Encephalopathy[e)]**	16	12	Very common
Dizziness[f)]	12	2	Very common
Paraesthesia[g)]	6	-	Common
Speech disorder[h)]	5	1	Common
Tremor	5	-	Common
Neuralgia	3	1	Common
Seizure[i)]	3	1	Common
Ischaemic cerebral infarction	1	1	Common
Cardiac disorders			
Tachycardia[j)]	14	3	Very common
Arrhythmia[k)]	6	2	Common
Cardiac failure[l)]	1	1	Common
Vascular disorders			
Hypotension	26	9	Very common
Hypertension	3	3	Common
Capillary leak syndrome	1	-	Common

Respiratory, thoracic and mediastinal disorders			
Dyspnoea[m)]	21	6	Very common
Cough[n)]	18	-	Very common
Hypoxia	8	4	Common
Pleural effusion	5	2	Common
Gastrointestinal disorders			
Diarrhoea	32	1	Very common
Nausea	29	1	Very common
Constipation	16	1	Very common
Vomiting	9	1	Common
Abdominal pain[o)]	9	2	Common
Dry mouth	5	-	Common
Stomatitis	5	-	Common
Abdominal distension	4	2	Common
Hepatobiliary disorders			
Hyperbilirubinaemia	3	3	Common
Skin and subcutaneous tissue disorders			
Night sweats	5	-	Common
Petechiae	5	-	Common
Pruritus	5	-	Common
Rash[p)]	8	-	Common
Hyperhidrosis	4	-	Common
Erythema	2	1	Common
Musculoskeletal and connective tissue disorders			
Arthralgia	10	-	Very common
Back pain	5	1	Common
Myalgia	5	-	Common
Renal and urinary disorders			
Acute kidney injury[q)]	17	6	Very common
General disorders and administration site conditions			
Pyrexia	35	5	Very common
Fatigue	26	6	Very common
Oedema[r)]	23	2	Very common
Pain[s)]	14	3	Very common
Chills	13	-	Very common
Asthenia	7	-	Common
Influenza like illness	7	-	Common
Multiple organ dysfunction syndrome	3	3	Common

Other events of interest

- *ALL indication*

The most frequently reported AESI within 8 weeks post-tisagenlecleucel infusion was CRS (80.8%).

Table 53 Adverse events of special interest (AESI) within 8 weeks post tisagenlecleucel infusion, regardless of study drug relationship, by group term and maximum grade for SCS Pool (Safety set)

	Study B2202 N=75			Study B2205J N=29			All patients N=104		
Group 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 (%)
Cytokine release syndrome	58 (77.3)	16 (21.3)	19 (25.3)	26 (89.7)	5 (17.2)	6 (20.7)	84 (80.8)	21 (20.2)	25 (24.0)
Febrile neutropenia	26 (34.7)	24 (32.0)	2 (2.7)	10 (34.5)	10 (34.5)	0	36 (34.6)	34 (32.7)	2 (1.9)
Hematopoietic cytopenias not resolved by day 28	28 (37.3)	12 (16.0)	12 (16.0)	9 (31.0)	3 (10.3)	4 (13.8)	37 (35.6)	15 (14.4)	16 (15.4)
Infections	32 (42.7)	16 (21.3)	2 (2.7)	14 (48.3)	2 (6.9)	1 (3.4)	46 (44.2)	18 (17.3)	3 (2.9)
Neurological events	30 (40.0)	9 (12.0)	1 (1.3)	9 (31.0)	1 (3.4)	0	39 (37.5)	10 (9.6)	1 (1.0)
Tumor Lysis Syndrome	3 (4.0)	3 (4.0)	0	0	0	0	3 (2.9)	3 (2.9)	0

A patient with multiple adverse events within a group term is counted only once in the total row.
A patient with multiple occurrences of an AE is counted only once in the AE category at the maximum toxicity grade.
Preferred terms are presented within group term in descending frequency of all grades column, as reported in the All patients column.

ALL indication and DLBLC indication

Cytokine release syndrome

In the ongoing clinical studies in paediatric and young adult B-cell ALL (N=75), cytokine release syndrome was reported in 77% of patients (47% with Grade 3 or 4). Two deaths occurred within 30 days of Kymriah infusion: one patient died with cytokine release syndrome and progressive leukaemia and the second patient had resolving cytokine release syndrome with abdominal compartment syndrome, coagulopathy and renal failure when death occurred due to an intracranial haemorrhage. In the ongoing clinical study in DLBCL (N=111), cytokine release syndrome was reported in 58% of patients, (22% with Grade 3 or 4) (SmPC, section 4.8).

Cytokine release syndrome was graded with the Penn scale as follows: Grade 1: mild reactions, e.g. reactions requiring supportive care; Grade 2: moderate reactions, e.g. reactions requiring intravenous therapies; Grade 3: severe reactions, e.g. reactions requiring low-dose vasopressors or supplemental oxygen; Grade 4: life-threatening reactions, e.g. those requiring high-dose vasopressors or intubation; Grade 5: death (SmPC, section 4.8).

Table 54 Clinical trial data of Cytokine release syndrome

	Pediatric/young adult r/r ALL		Adult r/r DLBCL
	Pooled data (B2202+B2205J) N=104 n (%)	B2101J* N=56 n (%)	C2201 N=99 n (%)
Number of patients with at least one event (95% CI)	84 (80.8) (71.9,87.8)	50 (89.3) (78.1, 96.0)	57 (57.6) (47.2,67.5)
Maximum grade			

Grade 3 AEs	21 (20.2)	12 (21.4)	15 (15.2)
Grade 4 AEs	25 (24.0)	14 (25.0)	8 (8.1)
Treatment-related AEs	84 (80.8)	50 (89.3)	57 (57.6)
SAEs	67 (64.4)	46 (82.1)	29 (29.3)
AE outcome			
Recovered/resolved	81 (77.9)		52 (52.5)
Recovered/resolved with sequelae	1 (1.0)		4 (4.0)
Recovering/resolving	0		0
Not recovered/not resolved	2 (1.9)		1 (1.0)
Fatal	0		0
Unknown	0		0

Numbers (n) represent counts of subjects.
*=AE outcome for Study B2101J was not collected.
Case Retrieval Strategy version 02-Jun-2017.

In the majority of patients, development of CRS occurred between 1 to 11 days (median onset: 3 days, range 1-22 days) after tisagenlecleucel infusion in ALL patients and between 1 and 9 days (median onset: 3 days) after the tisagenlecleucel infusion in DLBCL patients. The median duration of CRS was 8 days (range 1-36 days) in ALL patients and 7 days (median 2-18 days) in DLBCL patients.

CRS and dose: In the individual Studies B2202 and B2205J in ALL patients, there is no apparent relationship between CRS grade and tisagenlecleucel dose. DLBCL patients were safely treated up to the highest dose of $6.0x10^8$ CAR+ viable T cells.

CRS and fever: In the SCS Pool of the 84 ALL patients with CRS, 80 (95.2%) had high fever with a median duration of fevers of 6 days (range: 1-36), with the onset being earlier among patients with grade 4 CRS. In DLBCL high fevers were reported in 94.7% of patients. The median duration of high fever was 4.0 days (range 1-17).

CRS and hypotension: Among the patients in the SCS Pool with CRS, 49 (58.3%) patients had hypotension that required intervention. High-dose vasopressors were required for 28 (33.3%) patients. Oxygen supplementation was required in 42 (50%) patients and of those patients 16 required intubation for a median duration of 8.0 days (range 4-26). In DLBCL patients hypotension that required intervention among patients with CRS was reported for 28 patients (49.1%); use of high dose vasopressors was reported in 6 patients (10.5%).

CRS and disseminated intravascular coagulation and fibrinogen levels: Tisagenlecleucel associated coagulopathy during CRS can be associated with severe hypofibrinogenemia as observed in the Phase I Study B2101J [29],[30],[31]. In the SCS Pool, analysis of fibrinogen levels during the first episode of CRS by CRS grade showed that patients with grade 4 CRS had a lower median fibrinogen level compared to those patients with the CRS grade of 1-3. The low fibrinogen levels were successfully managed by replacement therapy with cryoprecipitate or fibrinogen concentrate. Disseminated intravascular coagulation (DIC) was observed in 12 (14.3%) ALL patients and bleeding events were observed in 15 (17.9%) of patients. Among DLBCL patients disseminated intravascular coagulation concurrent with CRS was reported in 3 patients (5.3%), no relationship between fibrinogen level and CRS severity was apparent.

In the ALL patients anti-cytokine therapy was received by 35 (41.7%) of the patients with CRS, tocilizumab was administered to all 35 patients; 19 of whom required only 1 dose of tocilizumab. Five

patients (6%) received siltuximab and 19 patients (23%) had treatment with corticosteroids in addition to other anti-cytokine drugs (Table 59).

Table 55 Anti-cytokine therapy during CRS (Safety set - Patients with CRS)

	Study B2202 N=58	Study B2205J N=26	All patients N=84
Systemic anti-cytokine therapy given - n (%)	28 (48.3)	7 (26.9)	35 (41.7)
Tocilizumab	28 (48.3)	7 (26.9)	35 (41.7)
1 dose	17 (29.3)	2 (7.7)	19 (22.6)
2 doses	8 (13.8)	2 (7.7)	10 (11.9)
3 doses	3 (5.2)	3 (11.5)	6 (7.1)
4 doses	0	0	0
>4 doses	0	0	0
Siltuximab	5 (8.6)	0	5 (6.0)
Corticosteroids	14 (24.1)	5 (19.2)	19 (22.6)
Other	2 (3.4)	5 (19.2)	7 (8.3)

Tisagenlecleucel positive cells continued to expand and persist after administration of tocilizumab. The administration of anti-IL6 agents and corticosteroids did not result in lower tisagenlecleucel expansion profiles as determined by AUC0-28d and Cmax. Corticosteroids are administered at low doses over short duration and weaned rapidly following a poor response to tocilizumab per the CRS treatment algorithm. Anti-cytokine therapy in DLBCL patients are summarised in Table 60.

Table 56 Anti-cytokine therapy during CRS (Safety set - Patients with CRS)

	All patients N=57
Systemic anti-cytokine therapy given - n (%)	16 (28.1)
Tocilizumab	15 (26.3)
1 dose	6 (10.5)
2 doses	9 (15.8)
Corticosteroids	11 (19.3)

An algorithm was set up to manage CRS events:

Cytokine release syndrome severity	Management
Prodromal syndrome: Low-grade fever, fatigue, anorexia	Observe in person; exclude infection; administer antibiotics per local guidelines if neutropenic; provide symptomatic support.
Cytokine release syndrome requiring mild intervention - one or more of the following: – High fever – Hypoxia – Mild hypotension	Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.
Cytokine release syndrome requiring moderate to aggressive intervention - one or more of the following: – Haemodynamic instability despite intravenous fluids and vasopressor support – Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation – Rapid clinical deterioration	• Administer high-dose or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. • Administer tocilizumab. - Patient weight less than 30 kg: 12 mg/kg intravenously over 1 hour - Patient weight ≥30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg) Repeat tocilizumab as needed at a minimum interval of 8 hours if there is no clinical improvement. If no response to second dose of tocilizumab, consider a third dose of tocilizumab or pursue alternative measures for treatment of cytokine release syndrome. Limit to a maximum total of 4 tocilizumab doses. • If no clinical improvement within 12 to 18 hours of the first tocilizumab dose, or worsening at any time, administer methylprednisolone 2 mg/kg as an initial dose, then 2 mg/kg per day until vasopressors and high-flow oxygen are no longer needed, then taper.

Tumor lysis syndrome (TSL)

The reporting of TLS in both indications are summarised in Table 61.

Table 57. Clinical trial data of Tumor lysis syndrome

	Pediatric/young adult r/r ALL		Adult r/r DLBCL
	Pooled data (B2202+B2205J) N=104 n (%)	**B2101J* N=56 n (%)**	**C2201 N=99 n (%)**
Number of patients with at least one event (95% CI)	4 (3.8) (1.1, 9.6)	3 (5.4) (1.1, 14.9)	1 (1.0) (0.0, 5.5)
Maximum grade			
Grade 3 AEs	3 (2.9)	3 (5.4)	1 (1.0)
Grade 4 AEs	1 (1.0)	0	0
Treatment-related AEs	3 (2.9)	2 (3.6)	1 (1.0)
SAEs	2 (1.9)	1 (1.8)	0
AE outcome			
Recovered/resolved	4 (3.8)		1 (1.0)
Recovered/resolved with sequelae	0		0
Recovering/resolving	0		0
Not recovered/not resolved	0		0
Fatal	0		0
Unknown	0		0

Numbers (n) represent counts of subjects.
*=AE outcome for Study B2101J was not collected.
Case Retrieval Strategy version 02-Jun-2017.

Infections

In B-cell ALL patients severe infections (Grade 3 and higher), which can be life-threatening or fatal, occurred in 44% of patients after Kymriah infusion. The overall incidence (all grades) was 65% (unspecified 49%, viral 32%, bacterial 24% and fungal 15%) (see section 4.4). 43% of the patients experienced an infection of any type within 8 weeks after Kymriah infusion.

In DLBCL patients severe infections (Grade 3 and higher), which can be life-threatening or fatal, occurred in 32% of patients. The overall incidence (all grades) was 54% (unspecified 44%, bacterial 10%, fungal 10% and viral 8%) (see SmPC, section 4.4). 34% of the patients experienced an infection of any type within 8 weeks (see SmPC, section 4.8).

Table 62 gives an overview of reported infections in both indications:

Table 58 Clinical trial data of Infections

	Pediatric/young adult r/r ALL		Adult r/r DLBCL
	Pooled data (B2202+B2205J) N=104 n (%)	**B2101J* N=56 n (%)**	**C2201 N=99 n (%)**
Number of patients with at least one event (95% CI)	70 (67.3) (57.4,76.2)	39 (69.6) (55.9, 81.2)	52 (52.5) (42.2,62.7)
Maximum grade			

Grade 3 AEs	27 (26.0)	13 (23.2)	25 (25.3)
Grade 4 AEs	13 (12.5)	1 (1.8)	4 (4.0)
Treatment-related AEs	29 (27.9)	34 (60.7)	14 (14.1)
SAEs	33 (31.7)	12 (21.4)	14 (14.1)
AE outcome			
Recovered/resolved	52 (50.0)		42 (42.4)
Recovered/resolved with sequelae	1 (1.0)		0
Recovering/resolving	3 (2.9)		3 (3.0)
Not recovered/not resolved	10 (9.6)		5 (5.1)
Fatal	3 (2.9)		1 (1.0)
Unknown	1 (1.0)		1 (1.0)
Numbers (n) represent counts of subjects. *=AE outcome for Study B2101J was not collected. Case Retrieval Strategy version 02-Jun-2017.			

In the ALL indication, the SCS Pool, anytime post-tisagenlecleucel infusion ADRs of infections and infestations were reported as bacterial infectious disorders in 25% patients, viral infectious disorders in 33%, fungal infections disorders in 13%, and unspecified infections in 48% of patients. The most frequent preferred terms (PTs, reported in >5% of patients) were upper respiratory tract infection (11.5%), rhinovirus infection (7.7%), staphylococcal infection (5.8%) and viral upper respiratory tract infection (5.8%).

Patients with active, uncontrolled infections did not start tisagenlecleucel treatment until the infection was controlled. Prior to tisagenlecleucel infusion, infection prophylaxis follows local guidelines based on the degree of preceding immunosuppression. After infusion, patients were monitored for signs and symptoms of infection and treated appropriately with prophylactic antibiotics. Surveillance testing prior to and during treatment with tisagenlecleucel was employed.

In patients achieving complete remission following tisagenlecleucel treatment, resulting low immunoglobulin levels can increase the risk for infections. In patients with low immunoglobulin levels pre-emptive measures such as immunoglobulin replacement and rapid attention to signs and symptoms of infection are implemented as per age and local specific guidelines.

Febrile neutropenia

Severe febrile neutropenia (Grade 3 or 4) was observed in 36% of paediatric and young adult B-cell ALL patients and 15% of DLBCL patients (SmPC, section 4.8). Table 63 summarises reported febrile neutropenia in both indications:

Table 59. Clinical trial data of febrile neutropenia

	Pediatric/young adult r/r ALL		**Adult r/r DLBCL**
	Pooled data (B2202+B2205J) N=104 n (%)	**B2101J* N=56 n (%)**	**C2201 N=99 n (%)**
Number of patients with at least one event (95% CI)	37 (35.6) (26.4,45.6)	44 (78.6) (65.6, 88.4)	13 (13.1) (7.2,21.4)
Maximum grade			

Grade 3 AEs	35 (33.7)	36 (64.3)	11 (11.1)
Grade 4 AEs	2 (1.9)	8 (14.3)	2 (2.0)
Treatment-related AEs	29 (27.9)	44 (78.6)	11 (11.1)
SAEs	25 (24.0)	40 (71.4)	7 (7.1)
AE outcome			
Recovered/resolved	37 (35.6)		13 (13.1)
Recovered/resolved with sequelae	0		0
Recovering/resolving	0		0
Not recovered/not resolved	0		0
Fatal	0		0
Unknown	0		0
Numbers (n) represent counts of subjects. *=AE outcome for Study B2101J was not collected			

Hematopoietic cytopenias

Cytopenias are very common with Kymriah therapy. In paediatric and young adult B-cell ALL patients, Grade 3 and 4 cytopenias not resolved by day 28 were reported based on laboratory findings and included leukopenia (55%), neutropenia (53%), lymphopenia (43%), thrombocytopenia (41%) and anaemia (12%)(SmPC, section 4.8).

In adult DLBCL, patients, Grade 3 and 4 cytopenias not resolved by day 28 were reported based on laboratory findings and included thrombocytopenia (41%), lymphopenia (28%), neutropenia (24%), leukopenia (21%) and anaemia (14%)(SmPC, section 4.8).

Table 64 summarises an overview of occurrence of cytopenias in both indications.

Table 60 Clinical trial data of Hematopoietic cytopenias lasting greater or equal to 28 days

	Paediatric/young adult r/r ALL*	**Adult r/r DLBCL**
	Pooled data (B2202+B2205J) N=104 n (%)	**C2201 N=99 n (%)**
Number of patients with at least one event (95% CI)	37 (35.6) (26.4,45.6)	36 (36.4) (26.9,46.6)
Maximum grade		
Grade 3 AEs	15 (14.4)	15 (15.2)
Grade 4 AEs	16 (15.4)	12 (12.1)
Treatment-related AEs	19 (18.3)	19 (19.2)
SAEs	4 (3.8)	2 (2.0)
AE outcome		
Recovered/resolved	26 (25.0)	19 (19.2)
Recovered/resolved with sequelae	0	0
Recovering/resolving	4 (3.8)	3 (3.0)
Not recovered/not resolved	6 (5.8)	14 (14.1)
Fatal	0	0
Unknown	1 (1.0)	0
*= This AE was not collected for Study B2101J Numbers (n) represent counts of subjects.		

Case Retrieval Strategy version 02-Jun-2017.

Neurological events

The majority of neurological events occurred within 8 weeks following infusion and were transient. In The majority of neurological events occurred within 8 weeks following infusion and were transient. In paediatric and young adult B-cell ALL patients, manifestations of encephalopathy and/or delirium occurred in 40% of patients (13% were Grade 3 or 4) within 8 weeks after Kymriah infusion. In DLBCL patients, manifestations of encephalopathy and/or delirium occurred in 21% of patients (12% were Grade 3 or 4) within 8 weeks after Kymriah infusion (SmPC, section 4.8).

Table 65 gives an overview of neurological events in both indications.

Table 61. Clinical trial data of Neurological events (early)

	Pediatric/young adult r/r ALL		Adult r/r DLBCL
	Pooled (B2202+B2205J) N=104 n (%)	**B2101J* N=56 n (%)**	**C2201 N=99 n (%)**
Number of patients with at least one event (95% CI)	39 (37.5) (28.2, 47.5)	28 (50.0) (36.3, 63.7)	21 (21.2) (13.6, 30.6)
Maximum grade			
Grade 3 AEs	10 (9.6)	12 (21.4)	8 (8.1)
Grade 4 AEs	1 (1.0)	1 (1.8)	4 (4.0)
Treatment-related AEs	30 (28.8)	27 (48.2)	16 (16.2)
SAEs	6 (5.8)	17 (30.4)	7 (7.1)
AE outcome			
Recovered/resolved	32 (30.8)		15 (15.2)
Recovered/resolved with sequelae	0		0
Recovering/resolving	0		1 (1.0)
Not recovered/not resolved	7 (6.7)		5 (5.1)
Fatal	0		0
Unknown	0		0

Numbers (n) represent counts of subjects.

*=AE outcome for Study B2101J was not collected.

Case Retrieval Strategy version 02-Jun-2017.

ALL indication

Neurological event incidence and severity were associated with higher CRS grades both in the SCS Poll and in the supportive study B2101J.

Table 62 Neurological events within 8 weeks of infusion by maximum CRS grade in SCS pool (safety set)

	Patients with neurological events		
	All grades n (%)	**Grade 3 n (%)**	**Grade 4 n (%)**
No CRS (N=20)	4 (20.0)	1 (5.0)	0
Grade 1/2 CRS (N=38)	9 (23.7)	1 (2.6)	0
Grade 3 CRS (N=21)	9 (42.9)	2 (9.5)	0
Grade 4 CRS (N= 25)	17 (68.0)	6 (24.0)	1 (4.0)

DLBCL indication

Table 63 Neurological events within 8 weeks post-tisagenlecleucel infusion, regardless of study drug relationship, by group term, preferred term and maximum CTC grade (Safety set)

	All patients N=99		
Group term Preferred term	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Neurological events	**21 (21.2)**	**8 (8.1)**	**4 (4.0)**
Confusional state	8 (8.1)	2 (2.0)	0
Encephalopathy	6 (6.1)	1 (1.0)	3 (3.0)
Dysphagia	4 (4.0)	1 (1.0)	0
Aphasia	3 (3.0)	1 (1.0)	0
Delirium	3 (3.0)	2 (2.0)	0
Tremor	3 (3.0)	0	0
Dyskinesia	2 (2.0)	0	0
Mental status changes	2 (2.0)	2 (2.0)	0
Somnolence	2 (2.0)	1 (1.0)	1 (1.0)
Agitation	1 (1.0)	1 (1.0)	0
Disturbance in attention	1 (1.0)	0	0
Irritability	1 (1.0)	0	0
Lethargy	1 (1.0)	0	0
Loss of consciousness	1 (1.0)	0	0
Memory impairment	1 (1.0)	1 (1.0)	0
Metabolic encephalopathy	1 (1.0)	1 (1.0)	0
Seizure	1 (1.0)	0	0
Speech disorder	1 (1.0)	0	0
Thinking abnormal	1 (1.0)	0	0

A patient with multiple occurrences of an AE is counted only once in the AE category at the maximum toxicity grade.

Preferred terms are presented within group term in descending frequency of all grades column, as reported in the All patients column.

- *DLBCL indication*

Neurological events within 8 weeks post-infusion were reported in 21 patients (21.2%); grade 3 events were reported in 8.1% of patients and grade 4 events in 4.0%. The most frequently reported events were confusional state (8.1%), encephalopathy (6.1%), and dysphagia (4.0%).

Among the 21 patients (21.2%) with neurological events within 8 weeks post-infusion, 12 patients experienced multiple neurological events. Seventeen of the 21 patients also experienced CRS and 4/21 patients did not present with CRS. In the 21 patients who experienced a neurological event, there were a total of 49 neurological events reported, and of those, 4 events occurred before CRS, 23 events during CRS, 6 events after CRS and 16 events in patients with no CRS.

Cardiac events

In the SCS Pool, the majority of cardiac events were reported within 8 weeks post-tisagenlecleucel infusion in 46 (44.2%) patients (these included events related to fluid resuscitation and acute respiratory distress syndrome such as pulmonary oedema, fluid overload, and oedema peripheral, as well as tachycardia, dizziness). Any time post-tisagenlecleucel infusion, 49 (47.1%) patients had cardiac events; grade 3 events were reported in 14 (13.5%) and grade 4 in 8 (7.7%) of patients. Within 8 weeks to 1 year events were reported in 9 patients (9.9%) and after 1 year post-infusion cardiac event was reported in 1 of the 29 patients monitored.

Within 8 weeks post-infusion, grade 3/4 events were reported in 20 patients (19.2%); 14 with maximum grade 3 events and 6 with grade 4 events:

- Cardiac rhythm-related disorders include tachycardia (24.0%), sinus tachycardia (7.7%), bradycardia (2.9%), atrioventricular block first degree (1%), atrioventricular block second degree (1%) and sinus bradycardia (1%).
- Cardiac function-related disorders include left ventricular dysfunction (4.8%), right ventricular dysfunction (1.0%), cardiac arrest (1.0%), mitral valve dysfunction (1.0%).
- Oedema-related events include pulmonary oedema (14.4%), oedema peripheral (6.7%) and fluid overload (9.6%)

The majority, 18 out of 20 patients had grade 3/4 cardiac events concurrent with CRS.

In the supportive study B2101J, cardiac events were reported anytime post-tisagenlecleucel infusion in 66.1% of patients with non-CNS3 ALL with 14.3% being grade 3/4, the majority of events occurred concurrently with CRS episodes.

Cardiac events -DLBCL indication

In the DLBCL Study C2201, 48.6% of patients presented with a cardiac event any time post-infusion. The most frequent (≥10% of patients) cardiac events any time post infusion were dyspnoea (17.1%), oedema peripheral (15.3%), dizziness (11.7%), and tachycardia (10.8%). Grade 3 events were reported in 11.7% of patients and grade 4 events in 3.6%. Except for 3 patients (one patient with a grade 3 event of atrial fibrillation, one patient with a grade 3 event of syncope, and one patient with a grade 4 event of cardio-respiratory arrest), grade 3 or 4 cardiac events occurred within 8 weeks of the infusion.

Notable cardiac events occurring any time post-infusion included: cardiac arrest (2.7%), cardiac failure congestive (0.9%), cardio-respiratory arrest (0.9%), fluid overload (2.7%), pulmonary oedema (1.8%), and acute pulmonary oedema (0.9%). Since the data cut-off for the primary CSR analysis, two additional patients were reported to have grade 4 cardiac arrest.

Renal dysfunction requiring dialysis

In Study B2202, 7 patients underwent renal dialysis for fluid overload and/or renal failure; all events occurred during CRS and were attributable to investigational treatment. Four patients in Study B2205J had renal dialysis, two of which continued until the patients died. In Study B2202, the number of patients that had renal failure (2 patients) was much lower than the patients that had dialysis indicating that dialysis was often used primarily just for management of fluid overload.

No patient in the supportive study B2101J had renal dysfunction requiring dialysis within 28 days post-infusion.

Clinically significant bleeding events

In the SCS Pool, 30 (28.8%) patients had bleeding events within 8 weeks post-infusion; 8 patients had grade 3 events and 2 patients had grade 4 events. The most frequently reported events were epistaxis reported in 10 patients, disseminated intravascular coagulation (6 patients), haematuria, mouth haemorrhage, petechiae, each reported in 5 patients and conjunctional haemorrhage reported in 4 patients. All other bleeding events were reported in two or fewer patients. Ten patients had bleeding

events >8 weeks to 1 year post-tisagenlecleucel infusion; three patients had grade 3 events and 1 patient had grade 4 event. Grade 3/4 bleeding events were reported in 14 (13.5%) patients during anytime post-infusion. Among the 84 patients with CRS post-tisagenlecleucel infusion, 15 (17.9%) patients had bleeding events and blood product support was given for 14 (16.7%) patients.

In the supportive study B2101J up to the cut-off for this analysis (30-Jan-2017), 14 non-CNS3 ALL patients experienced epistaxis post-tisagenlecleucel infusion. Of these, three AEs were grade 3, suspected to be study treatment related but resolved within one day with medication or non-drug therapy given. One of them was a SAE (Day 6 post-infusion) which resolved with medical therapy within one day. Five (10%) non-CNS3 ALL patients out of 50 patients with CRS required blood product support specifically for bleeding. No cases of intracranial bleeding were reported.

Prolonged depletion of normal B cells/ Agammaglobulinemia

Based on the pooled data (B2202+B2205J) 39 patients (37.5%) reported AEs related to prolonged depletion of normal B-cells (PT 'hypogammaglobulinaemia). Most of these events were of grade 1/2 severity, with grade 3 AEs reported in five patients (4.8%) and no patients reported grade 4 AEs. Most of the AEs (35 patients, 33.7%) were suspected to be related to tisagenlecleucel treatment.

In study C2201, prior to tisagenlecleucel infusion, one patient had normal levels of CD19+ B-cells (normal range: 80-616 cells/µL), while the majority of the patients had CD19+ B-cell levels below lower limit of quantitation (LLOQ=0.2 cells/µL). After tisagenlecleucel infusion, two patients showed CD19+ B-cell levels within normal range (or slightly above normal) as of the data cut-off date. Some patients with CD19+ B-cells below LLOQ at pre-infusion visit had detectable CD19+ B-cells at post-infusion time points (but still below the normal range values). In this study, four patients (4.0%) reported AEs related to prolonged depletion of normal B-cells, all of which were suspected to be related to tisagenlecleucel treatment and all the events were ongoing at the time of the cut-off date. Of these, one patient reported grade 3 AE and was treated with immunoglobulins. No patient reported grade 4 AE. No SAEs or fatalities associated with AEs of prolonged depletion of normal B-cells were reported.

Serious adverse event/deaths/other significant events

- *ALL indication - Serious adverse events*

SAEs were reported in 77.9% of infused patients. Febrile neutropenia was reported in 25 (24%) patients; grade 3 in 24 (23.1%) patients and grade 4 in 1 patient. Grade 3/4 hypotension was reported in 12 (13.2%) patients, and is a known consequence of CRS.

Table 64 Serious adverse events post-tisagenlecleucel infusion, regardless of study drug relationship, preferred term, maximum grade (>3 patients, all patients, all grades) in SCS Pool (Safety set)

	Study B2202 N=75			Study B2205J N=29			All patients N=104		
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 SAE	58 (77.3)	21 (28.0)	33 (44.0)	23 (79.3)	8 (27.6)	13 (44.8)	81 (77.9)	29 (27.9)	46 (44.2)
Cytokine release syndrome	47 (62.7)	15 (20.0)	19 (25.3)	20 (69.0)	5 (17.2)	6 (20.7)	67 (64.4)	20 (19.2)	25 (24.0)
Febrile neutropenia	15 (20.0)	14 (18.7)	1 (1.3)	10 (34.5)	10 (34.5)	0	25 (24.0)	24 (23.1)	1 (1.0)
Hypotension	8 (10.7)	1 (1.3)	7 (9.3)	4 (13.8)	1 (3.4)	3 (10.3)	12 (11.5)	2 (1.9)	10 (9.6)
Pyrexia	7 (9.3)	1 (1.3)	0	2 (6.9)	0	0	9 (8.7)	1 (1.0)	0
Hypoxia	5 (6.7)	3 (4.0)	2 (2.7)	2 (6.9)	1 (3.4)	1 (3.4)	7 (6.7)	4 (3.8)	3 (2.9)
Acute kidney injury	5 (6.7)	2 (2.7)	3 (4.0)	1 (3.4)	0	1 (3.4)	6 (5.8)	2 (1.9)	4 (3.8)
Respiratory failure	5 (6.7)	0	5 (6.7)	1 (3.4)	0	1 (3.4)	6 (5.8)	0	6 (5.8)

A patient with multiple occurrences of an AE is counted only once in the AE category at the maximum toxicity grade.
Preferred terms are presented in descending frequency of all grades column, as reported in the All patients column

In study B2202 in total 71 patients (94.7%) had at least one hospitalization and most patients required 1 or 2 hospitalizations. Among patients with at least one hospitalization, the median total duration of hospitalization was 29.0 days (range 5 to 214 days). There were 40 patients admitted to the ICU, and the median duration of intensive care unit stay was 7 days (range from 0.5 to 51) among these 40 patients.

In study B2101J SAEs occurred in 89.3% of non-CNS3 ALL patients at any time post tisagenlecleucel infusion. The most common (≥ 20% of patients) SAEs were CRS (82.1%), febrile neutropenia (71.4%), hypotension (39.3%), encephalopathy (26.8%) and pyrexia (23.2%). The majority of patients (83.9%) had at least one SAE which was related to study treatment. The frequency of febrile neutropenia and hypotension was higher in Study B2101J compared to the SCS pool.

- *DLBCL indication - serious adverse events*

At the time of the 08.12.17 cut-off, 72 patients (64.9%) had at least one SAE regardless of study drug relationship. Serious adverse events with suspected relationship to study drug were reported in 52 patients (46.8%). Serious AEs occurred more frequently within 8 weeks post-tisagenlecleucel infusion (49.5%) than >8 weeks to one year post-tisagenlecleucel (29.2%)

The most frequent SAEs (reported in >5% of patients) regardless of study drug relationship were CRS (27.0%), febrile neutropenia (8.1%), and pyrexia (7.2%). Most of these SAEs were suspected to be related to study drug. These SAEs were expected CRS-related events and were managed by standard supportive care and concomitant medications and, when indicated, anti-cytokine therapy per the protocol-defined CRS algorithm in a hospital setting.

Table 65 SAEs post-infusion in study C2201 by PT and max grade in at least 2% of all patients (safety set)

	All patients N=111			Cohort A N=16		
Preferred term	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 SAE	72 (64.9)	31 (27.9)	31 (27.9)	10 (62.5)	2 (12.5)	7 (43.8)
Cytokine release syndrome	30 (27.0)	11 (9.9)	8 (7.2)	2 (12.5)	0	1 (6.3)
Febrile neutropenia	9 (8.1)	6 (5.4)	3 (2.7)	0	0	0
Pyrexia	8 (7.2)	5 (4.5)	0	1 (6.3)	0	0
Acute kidney injury	4 (3.6)	1 (0.9)	2 (1.8)	0	0	0
Encephalopathy	4 (3.6)	1 (0.9)	3 (2.7)	2 (12.5)	0	2 (12.5)
Fatigue	4 (3.6)	4 (3.6)	0	0	0	0
Clostridium difficile infection	3 (2.7)	3 (2.7)	0	0	0	0
Confusional state	3 (2.7)	3 (2.7)	0	0	0	0
Dyspnoea	3 (2.7)	2 (1.8)	0	1 (6.3)	1 (6.3)	0
Multiple organ dysfunction syndrome	3 (2.7)	0	3 (2.7)	1 (6.3)	0	1 (6.3)
Neutrophil count decreased	3 (2.7)	1 (0.9)	2 (1.8)	1 (6.3)	0	1 (6.3)
Pneumonia	3 (2.7)	3 (2.7)	0	1 (6.3)	1 (6.3)	0

PT: preferred term; SAE: serious adverse events
A patient with multiple occurrences of an AE is counted only once in the AE category at the maximum toxicity grade.

ALL indication – deaths

Among the 127 enrolled patients, 18 died prior to tisagenlecleucel infusion, which included 10 deaths due to disease progression and 8 deaths due to AEs, mainly infections (6 cases - pneumonia in 3 patients, fungal infections in 2 patients, and sepsis in 1 patient). There were 4 deaths within 30 days of tisagenlecleucel infusion: 2 patients died due to disease progression, 1 due to cerebral hemorrhage in the setting of disseminated intravascular coagulation (DIC) and 1 due to embolic stroke from an intracardiac mucormycotic mass. No deaths occurred within 30 days of first tisagenlecleucel infusion in Study B2101J. Two patients died during the LD chemotherapy period due to multi-organ dysfunction syndrome failure and respiratory failure.

Four patients died within 30 days of tisagenlecleucel infusion; 2 due to disease progression and 2 due to nervous system disorders (one cerebral haemorrhage in the setting of DIC, causality was related to multiple factors including chemotherapy and continuous venovenous hemodiafiltration (CVVH); and one embolic stroke from an intracardiac mucormycotic mass, causality was related to lympho-depleting chemotherapy).

Twenty-five patients died more than 30 days after tisagenlecleucel infusion, including 20 due to disease progression. All the remaining 5 deaths occurred in Study B2202, 3 patients died due to infections; namely encephalitis (related to viral infection/tisagenlecleucel/autoimmune), lower respiratory tract bacterial infection (not related to study drug) and systemic mycosis (related to tisagenlecleucel/prolonged pancytopenia that predated tisagenlecleucel infusion), one due to hepatobiliary disease (not related to study drug), and one death was due to unknown reason.

Table 66 Deaths by preferred term for SCS Pool (Enrolled set)

Preferred term	Study B2202	Study B2205J	All patients
Patients enrolled	**N=92**	**N=35**	**N=127**
Any time before tisagenlecleucel infusion	14 (15.2)	4 (11.4)	18 (14.2)
Acute lymphocytic leukaemia	8 (8.7)	2 (5.7)	10 (7.9)
Fungaemia	1 (1.1)	0	1 (0.8)
Multiple organ dysfunction syndrome	0	1 (2.9)	1 (0.8)
Pneumonia	1 (1.1)	1 (2.9)	2 (1.6)
Pneumonia fungal	1 (1.1)	0	1 (0.8)
Pneumonia klebsiella	1 (1.1)	0	1 (0.8)
Respiratory failure	1 (1.1)	0	1 (0.8)
Sepsis	1 (1.1)	0	1 (0.8)
Patients infused	**N=75**	**N=29**	**N=104**
Any time post-tisagenlecleucel infusion	**19 (25.3)**	**10 (34.5)**	**29 (27.9)**
Any time within 30 days of tisagenlecleucel infusion	2 (2.7)	2 (6.9)	4 (3.8)
Acute lymphocytic leukaemia	1 (1.3)	1 (3.4)	2 (1.9)
Cerebral haemorrhage	1 (1.3)	0	1 (1.0)
Embolic stroke	0	1 (3.4)	1 (1.0)
Any time >30 days after tisagenlecleucel infusion	17 (22.7)	8 (27.6)	25 (24.0)
Acute lymphocytic leukaemia	12 (16.0)	8 (27.6)	20 (19.2)
Death	1 (1.3)	0	1 (1.0)
Encephalitis	1 (1.3)	0	1 (1.0)
Hepatobiliary disease	1 (1.3)	0	1 (1.0)
Lower respiratory tract infection bacterial	1 (1.3)	0	1 (1.0)
Systemic mycosis	1 (1.3)	0	1 (1.0)

Preferred terms are presented in descending frequency as reported in the All patients column.

In supportive study B2101J at the time of the data cut-off (30-Jan-2017), 22 non-CNS3 ALL patients (39.3%) had died any time following their first tisagenlecleucel infusion, all due to disease progression. No deaths were reported within 30 days of the first tisagenlecleucel infusion whereas 3 non- CNS3 ALL patients (5.4%) died within 30 days from the time of the last tisagenlecleucel infusion; (16, 22 and 27 days after last infusion).

Laboratory findings

- *ALL indication*

Haematology

Grade 3/4 hematopoietic cytopenias not resolved by Day 28 were seen among patients who received tisagenlecleucel and are discussed above under AESIs. Although data for long term follow-up are limited, the occurrence of higher grades haematology parameters generally decreased over time indicating resolution of the events.

Clinical chemistry

Based on CTC grade, new or worsened biochemistry abnormalities were reported mainly as grade 1/2.

Most commonly reported (in at least 5 patients) worst post-baseline grade 3 biochemistry abnormalities within 8 weeks post-tisagenlecleucel infusion were for hypokalaemia (21.2%), bilirubin (17.3%), alanine aminotransferase (ALT) (16.3%), aspartate aminotransferase (AST) (16.3%),

phosphate (11.5%), hyperglycaemia (8.7%), creatinine (5.8%), hyponatremia (5.8%). Worst post-baseline grade 4 biochemistry abnormalities within 8 weeks post-tisagenlecleucel infusion were reported for AST (10.6%), phosphate (4.8%), hypokalaemia (3.8%), ALT (2.9%), urate (2.9%), creatinine (1.9%), hyperglycaemia (1.9%), hypernatremia (1%), hyponatremia (1.0%), and bilirubin (1%).

The proportion of patients with worst post-baseline grade 3/4 biochemistry abnormalities decreased at further timepoints >8 weeks to 1 year post-tisagenlecleucel infusion with no post-baseline grade 3/4 biochemistry abnormalities >1 year post-tisagenlecleucel infusion.

The most commonly reported biochemistry abnormalities (in >15% for all patients) that worsened from grade 0/2 to grade 3/4 post-baseline, post-tisagenlecleucel infusion were for AST (28.8%), potassium (26.5%), ALT (19.5%), bilirubin (17.5%), and phosphate (15.5%).

Hepatic reactions: In the SCS pool ALT or AST > 3x upper limit of normal (ULN) & bilirubin > 2x ULN & alkaline phosphatase (ALP) < 2x ULN within 8 weeks after tisagenlecleucel infusion (seen in 19 patients) were not observed at any time >8 weeks post-infusion. These abnormalities occurred during and toward the end of CRS and were reversible. In Study B2101J, there were 5 non-CNS3 ALL patients with concurrent ALT or AST > 3x ULN & bilirubin > 2x ULN & ALP < 2x ULN within 8 weeks after tisagenlecleucel infusion. One patient had concurrent ALT or AST > 3x ULN & bilirubin > 2x ULN & ALP < 2x ULN between 8 weeks to 1 year with no events occurring post 1 year.

Generation of replication competent lentivirus (RCL)

No positive replication-competent lentivirus findings were reported in Studies B2202, B2205J and B2101J.

Electrocardiograms/echogardiograms

In Study B2202 and B2205J, evaluation of 12-lead electrocardiograms (ECG) (locally assessed) was assessed at Screening and prior to tisagenlecleucel infusion. In Study B2202 and B2205J, there were no scheduled ECG assessments post tisagenlecleucel infusion in this study. In Study B2202, ECG assessments at Screening, prior to tisagenlecleucel infusion and unscheduled visits shows infrequent significant abnormalities (7 patients). In Study B2101J echocardiograms were taken during the apheresis visit prior to tisagenlecleucel infusion. No or only clinically insignificant cardiac abnormalities were detected. There were no scheduled ECG assessments post tisagenlecleucel infusion in this study.

- *DLBCL indication*

Clinical chemistry

Most newly occurring or worsening clinical chemistry abnormalities reported post-tisagenlecleucel infusion were low in severity (grade 1/2).

The most frequently reported new or worsened grade 3 toxicities any time post infusion were hypophosphatemia (23.4%), hypokalaemia (12.6%), hypoalbuminemia), and hyponatremia both (9.9%), hyperbilirubinemia, increased alanine aminotransferase (ALT) and increased blood creatinine (5.4% each), and hypermagnesemia (3.0%). New or worsened grade 4 biochemistry abnormalities were reported for urate in 4 patients (3.6%), aspartate aminotransferase in two patients (1.8%), and bilirubin, hypophosphatemia and hyponatremia in one patient each (0.9%). Liver enzyme abnormalities generally occurred within 8 weeks post-tisagenlecleucel (during and towards the end of CRS), and were reversible.

Haematology

Shifts of haematology values to grade 3 or 4 (e.g. low lymphocytes, leukocytes, platelet and neutrophil counts) were most frequently seen within 8 weeks post-tisagenlecleucel infusion, and declined substantially from 8 weeks to 1 year post-infusion.

B-cell aplasia (data based on follow-up of 99 infused patients): Prior to tisagenlecleucel infusion, i.e. at the pre-infusion visit, only 1 patient had normal levels of CD19+ B cells (normal range: 80-616 cells/µL), while the majority of the patients had CD19+ B cell levels below the lower limit of quantification (LLOQ) (0.2 cells/µL). After tisagenlecleucel infusion, 2 patients showed CD19+ B cell levels within normal range (or slightly above normal) as of of the data cut-off (08-March- 2017). Some patients with CD19+ B cells below the LLOQ at the pre-infusion visit had detectable CD19+ B cells at post-infusion time points (but still below the normal range values). It should be noted that post-infusion B cell results can be influenced by duration of the follow-up period, and the patients' B cell levels could further increase over time. The impact of tisagenlecleucel on B-cell aplasia during the study cannot be directly ascertained due to the confounding effect of high rituximab levels in the majority of patients post-infusion (i.e. at Day 7 and Day 21). Rituximab-mediated B–cell aplasia is expected to last approximately 6 months to 1 year based on the terminal half-life (T1/2) of rituximab, i.e. 22 days. However, it is possible that tisagenlecleucel could contribute to or cause sustained aplasia.

Safety in special populations

- *ALL indication*

In the SCS Pool, 40 patients were <10 years, 44 patients were ≥ 10 to < 18 years and 20 patients were ≥ 18 years. The frequency and nature of events were reported in similar proportions of patients among the age subgroups.

DLBCL indication

Populations according to molecular subtype (cell of origin):

Patients with germinal centre B-cell of origin comprised 51.5% and patients with activated B-cell type comprised 42.4% of infused patients. The incidence rate of AEs overall and grade 3/4 AEs was similar in both subtypes.

Age

Table 67: Adverse events in age groups- DLBCL indication

	<65 years N=86 n (%)	65 - <75 years N=23 n (%)	75 - <85 years N=2 n (%)	All patients N=111 n (%)
Any adverse events	86 (100)	23 (100)	2 (100)	111 (100)
Serious adverse events	54 (62.8)	16 (69.6)	2 (100)	72 (64.9)
-Fatal	6 (7.0)	3 (13.0)	0	9 (8.1)
Multiple organ dysfunction syndrome	1 (1.2)	1 (4.3)	0	2 (1.8)
Cerebral haemorrhage	0	1 (4.3)	0	1 (0.9)
Chronic kidney disease	1 (1.2)	0	0	1 (0.9)
Duodenal ulcer haemorrhage	1 (1.2)	0	0	1 (0.9)
Infection	1 (1.2)	0	0	1 (0.9)
Neuroendocrine carcinoma	0	1 (4.3)	0	1 (0.9)
Pulmonary haemorrhage	1 (1.2)	0	0	1 (0.9)
Sepsis	1 (1.2)	0	0	1 (0.9)
Adverse events leading to study discontinuation				
-Total	5 (5.8)	2 (8.7)	0	7 (6.3)
Cerebral haemorrhage	0	1 (4.3)	0	1 (0.9)
Chronic kidney disease	1 (1.2)	0	0	1 (0.9)
Febrile neutropenia	1 (1.2)	0	0	1 (0.9)
Infection	1 (1.2)	0	0	1 (0.9)
Multiple organ dysfunction syndrome	0	1 (4.3)	0	1 (0.9)
Pneumonia aspiration	1 (1.2)	0	0	1 (0.9)
Pulmonary haemorrhage	1 (1.2)	0	0	1 (0.9)
Psychiatric disorders				
-Total	27 (31.4)	7 (30.4)	0	34 (30.6)
Anxiety	10 (11.6)	2 (8.7)	0	12 (10.8)
Confusional state	6 (7.0)	4 (17.4)	0	10 (9.0)
Insomnia	8 (9.3)	0	0	8 (7.2)
Sleep disorder	5 (5.8)	0	0	5 (4.5)

Delirium	1 (1.2)	2 (8.7)	0	3 (2.7)
Mental status changes	2 (2.3)	1 (4.3)	0	3 (2.7)
Agitation	2 (2.3)	0	0	2 (1.8)
Depression	2 (2.3)	0	0	2 (1.8)
Irritability	1 (1.2)	0	0	1 (0.9)
Tearfulness	1 (1.2)	0	0	1 (0.9)
Thinking abnormal	0	1 (4.3)	0	1 (0.9)
Nervous system disorders				
-Total	43 (50.0)	11 (47.8)	2 (100)	56 (50.5)
Headache	21 (24.4)	3 (13.0)	1 (50.0)	25 (22.5)
Dizziness	10 (11.6)	3 (13.0)	0	13 (11.7)
Encephalopathy	5 (5.8)	1 (4.3)	1 (50.0)	7 (6.3)
Tremor	4 (4.7)	0	1 (50.0)	5 (4.5)
Paraesthesia	4 (4.7)	0	0	4 (3.6)
Aphasia	3 (3.5)	0	0	3 (2.7)
Disturbance in attention	3 (3.5)	0	0	3 (2.7)
Hypoaesthesia	2 (2.3)	1 (4.3)	0	3 (2.7)
Dysgeusia	0	1 (4.3)	1 (50.0)	2 (1.8)
Dyskinesia	1 (1.2)	1 (4.3)	0	2 (1.8)
Myoclonus	1 (1.2)	0	1 (50.0)	2 (1.8)
Neuralgia	1 (1.2)	1 (4.3)	0	2 (1.8)
Neuropathy peripheral	1 (1.2)	1 (4.3)	0	2 (1.8)
Phantom pain	2 (2.3)	0	0	2 (1.8)
Seizure	1 (1.2)	1 (4.3)	0	2 (1.8)
Somnolence	1 (1.2)	1 (4.3)	0	2 (1.8)
Syncope	2 (2.3)	0	0	2 (1.8)
Acute polyneuropathy	1 (1.2)	0	0	1 (0.9)
Ataxia	0	0	1 (50.0)	1 (0.9)
Brain oedema	0	0	1 (50.0)	1 (0.9)
Cerebral haemorrhage	0	1 (4.3)	0	1 (0.9)
Cognitive disorder	0	0	1 (50.0)	1 (0.9)
Demyelinating polyneuropathy	1 (1.2)	0	0	1 (0.9)
Dysarthria	1 (1.2)	0	0	1 (0.9)
Dysmetria	1 (1.2)	0	0	1 (0.9)
Horner's syndrome	1 (1.2)	0	0	1 (0.9)
Hyperaesthesia	0	1 (4.3)	0	1 (0.9)
Hypotonia	0	1 (4.3)	0	1 (0.9)
Ischaemic cerebral infarction	1 (1.2)	0	0	1 (0.9)
Lethargy	0	1 (4.3)	0	1 (0.9)
Loss of consciousness	0	1 (4.3)	0	1 (0.9)
Memory impairment	0	1 (4.3)	0	1 (0.9)
Meningeal disorder	1 (1.2)	0	0	1 (0.9)
Metabolic encephalopathy	1 (1.2)	0	0	1 (0.9)
Migraine	1 (1.2)	0	0	1 (0.9)
Nerve compression	0	1 (4.3)	0	1 (0.9)
Peripheral sensory neuropathy	1 (1.2)	0	0	1 (0.9)
Polyneuropathy	1 (1.2)	0	0	1 (0.9)
Presyncope	1 (1.2)	0	0	1 (0.9)
Psychomotor skills impaired	0	0	1 (50.0)	1 (0.9)
Sciatica	1 (1.2)	0	0	1 (0.9)

Speech disorder	1 (1.2)	0	0	1 (0.9)
Status epilepticus	0	1 (4.3)	0	1 (0.9)
Stupor	1 (1.2)	0	0	1 (0.9)
Vith nerve paralysis	1 (1.2)	0	0	1 (0.9)
Accidents and injuries (narrow)				
-Total	7 (8.1)	2 (8.7)	0	9 (8.1)
Contusion	2 (2.3)	1 (4.3)	0	3 (2.7)
Fall	3 (3.5)	0	0	3 (2.7)
Eye contusion	1 (1.2)	0	0	1 (0.9)
Head injury	1 (1.2)	0	0	1 (0.9)
Tendon injury	0	1 (4.3)	0	1 (0.9)
Traumatic haematoma	1 (1.2)	0	0	1 (0.9)
Upper limb fracture	1 (1.2)	0	0	1 (0.9)
Accidents and injuries (broad)				
-Total	8 (9.3)	3 (13.0)	0	11 (9.9)
Contusion	2 (2.3)	1 (4.3)	0	3 (2.7)
Fall	3 (3.5)	0	0	3 (2.7)
Eye contusion	1 (1.2)	0	0	1 (0.9)
Head injury	1 (1.2)	0	0	1 (0.9)
Hypothermia	1 (1.2)	0	0	1 (0.9)
Nerve compression	0	1 (4.3)	0	1 (0.9)
Skin abrasion	1 (1.2)	0	0	1 (0.9)
Tendon injury	0	1 (4.3)	0	1 (0.9)
Traumatic haematoma	1 (1.2)	0	0	1 (0.9)
Upper limb fracture	1 (1.2)	0	0	1 (0.9)
Cardiac disorders				
-Total	20 (23.3)	5 (21.7)	1 (50.0)	26 (23.4)
Tachycardia	10 (11.6)	2 (8.7)	0	12 (10.8)
Atrial fibrillation	2 (2.3)	3 (13.0)	0	5 (4.5)
Bradycardia	2 (2.3)	1 (4.3)	0	3 (2.7)
Cardiac arrest	3 (3.5)	0	0	3 (2.7)
Sinus tachycardia	3 (3.5)	0	0	3 (2.7)
Cardiac failure congestive	1 (1.2)	0	0	1 (0.9)
Cardio-respiratory arrest	1 (1.2)	0	0	1 (0.9)
Palpitations	1 (1.2)	0	0	1 (0.9)
Supraventricular tachycardia	1 (1.2)	0	0	1 (0.9)
Ventricular extrasystoles	0	0	1 (50.0)	1 (0.9)
Vascular disorders				
-Total	27 (31.4)	9 (39.1)	1 (50.0)	37 (33.3)
Hypotension	22 (25.6)	6 (26.1)	1 (50.0)	29 (26.1)
Hypertension	3 (3.5)	0	0	3 (2.7)
Deep vein thrombosis	2 (2.3)	0	0	2 (1.8)
Hot flush	2 (2.3)	0	0	2 (1.8)
Orthostatic hypotension	2 (2.3)	0	0	2 (1.8)
Capillary leak syndrome	1 (1.2)	0	0	1 (0.9)
Embolism	0	1 (4.3)	0	1 (0.9)
Lymphoedema	1 (1.2)	0	0	1 (0.9)
Pallor	1 (1.2)	0	0	1 (0.9)
Peripheral ischaemia	0	1 (4.3)	0	1 (0.9)
Thrombophlebitis superficial	1 (1.2)	0	0	1 (0.9)

Thrombosis	0	1 (4.3)	0	1 (0.9)
Vena cava thrombosis	1 (1.2)	0	0	1 (0.9)
Venous thrombosis	0	1 (4.3)	0	1 (0.9)
Cerebrovascular disorders (narrow)				
-Total	1 (1.2)	1 (4.3)	0	2 (1.8)
Cerebral haemorrhage	0	1 (4.3)	0	1 (0.9)
Ischaemic cerebral infarction	1 (1.2)	0	0	1 (0.9)
Cerebrovascular disorders (broad)				
-Total	5 (5.8)	1 (4.3)	0	6 (5.4)
Aphasia	3 (3.5)	0	0	3 (2.7)
Cerebral haemorrhage	0	1 (4.3)	0	1 (0.9)
Dysarthria	1 (1.2)	0	0	1 (0.9)
Ischaemic cerebral infarction	1 (1.2)	0	0	1 (0.9)
Infections and infestations				
-Total	42 (48.8)	16 (69.6)	2 (100)	60 (54.1)
Upper respiratory tract infection	12 (14.0)	1 (4.3)	0	13 (11.7)
Urinary tract infection	4 (4.7)	4 (17.4)	0	8 (7.2)
Pneumonia	6 (7.0)	0	0	6 (5.4)
Clostridium difficile infection	2 (2.3)	2 (8.7)	1 (50.0)	5 (4.5)
Infection	2 (2.3)	2 (8.7)	1 (50.0)	5 (4.5)
Nasopharyngitis	4 (4.7)	1 (4.3)	0	5 (4.5)
Conjunctivitis	4 (4.7)	0	0	4 (3.6)
Sinusitis	2 (2.3)	2 (8.7)	0	4 (3.6)
Bacteraemia	3 (3.5)	0	0	3 (2.7)
Herpes simplex	1 (1.2)	2 (8.7)	0	3 (2.7)
Lung infection	1 (1.2)	2 (8.7)	0	3 (2.7)
Otitis media	2 (2.3)	0	1 (50.0)	3 (2.7)
Respiratory tract infection	2 (2.3)	1 (4.3)	0	3 (2.7)
Sepsis	3 (3.5)	0	0	3 (2.7)
Bronchitis	1 (1.2)	1 (4.3)	0	2 (1.8)
Device related infection	2 (2.3)	0	0	2 (1.8)
Gingivitis	1 (1.2)	1 (4.3)	0	2 (1.8)
Oral herpes	1 (1.2)	1 (4.3)	0	2 (1.8)
Paronychia	1 (1.2)	1 (4.3)	0	2 (1.8)
Pneumocystis jirovecii pneumonia	1 (1.2)	0	1 (50.0)	2 (1.8)
Rhinitis	0	1 (4.3)	1 (50.0)	2 (1.8)
Skin infection	1 (1.2)	1 (4.3)	0	2 (1.8)
Adenovirus infection	0	1 (4.3)	0	1 (0.9)
Bronchopulmonary aspergillosis	1 (1.2)	0	0	1 (0.9)
Campylobacter gastroenteritis	1 (1.2)	0	0	1 (0.9)
Candida infection	0	1 (4.3)	0	1 (0.9)
Cellulitis	1 (1.2)	0	0	1 (0.9)
Cerebral toxoplasmosis	0	1 (4.3)	0	1 (0.9)
Cystitis	1 (1.2)	0	0	1 (0.9)
Cytomegalovirus infection	1 (1.2)	0	0	1 (0.9)
Enterococcal infection	1 (1.2)	0	0	1 (0.9)
Escherichia infection	1 (1.2)	0	0	1 (0.9)
Eye infection	1 (1.2)	0	0	1 (0.9)
Febrile infection	0	1 (4.3)	0	1 (0.9)
Folliculitis	1 (1.2)	0	0	1 (0.9)

Fungal infection	0	1 (4.3)	0	1 (0.9)
Fungal paronychia	1 (1.2)	0	0	1 (0.9)
Gastroenteritis viral	1 (1.2)	0	0	1 (0.9)
Influenza	1 (1.2)	0	0	1 (0.9)
Laryngitis	1 (1.2)	0	0	1 (0.9)
Lower respiratory tract infection	1 (1.2)	0	0	1 (0.9)
Mucosal infection	1 (1.2)	0	0	1 (0.9)
Onychomycosis	0	1 (4.3)	0	1 (0.9)
Oral fungal infection	1 (1.2)	0	0	1 (0.9)
Parainfluenzae virus infection	1 (1.2)	0	0	1 (0.9)
Periodontitis	1 (1.2)	0	0	1 (0.9)
Pharyngitis	0	1 (4.3)	0	1 (0.9)
Postoperative wound infection	1 (1.2)	0	0	1 (0.9)
Pseudomonas infection	1 (1.2)	0	0	1 (0.9)
Purulent discharge	0	1 (4.3)	0	1 (0.9)
Rhinovirus infection	1 (1.2)	0	0	1 (0.9)
Staphylococcal bacteraemia	1 (1.2)	0	0	1 (0.9)
Staphylococcal infection	1 (1.2)	0	0	1 (0.9)
Systemic infection	1 (1.2)	0	0	1 (0.9)
Upper respiratory fungal infection	1 (1.2)	0	0	1 (0.9)
Urinary tract infection bacterial	0	1 (4.3)	0	1 (0.9)
Urinary tract infection fungal	1 (1.2)	0	0	1 (0.9)
Urinary tract infection staphylococcal	1 (1.2)	0	0	1 (0.9)
Urinary tract infection viral	0	1 (4.3)	0	1 (0.9)
Urosepsis	1 (1.2)	0	0	1 (0.9)
Vaginal infection	1 (1.2)	0	0	1 (0.9)
Vulvitis	1 (1.2)	0	0	1 (0.9)
Vulvovaginal mycotic infection	0	1 (4.3)	0	1 (0.9)
Anticholinergic syndrome (narrow)				
-Total	0	0	0	0
Anticholinergic syndrome (broad)				
-Total	52 (60.5)	14 (60.9)	2 (100)	68 (61.3)
Pyrexia	32 (37.2)	7 (30.4)	0	39 (35.1)
Dizziness	10 (11.6)	3 (13.0)	0	13 (11.7)
Tachycardia	10 (11.6)	2 (8.7)	0	12 (10.8)
Confusional state	6 (7.0)	4 (17.4)	0	10 (9.0)
Dry mouth	5 (5.8)	0	1 (50.0)	6 (5.4)
Dysphagia	1 (1.2)	3 (13.0)	0	4 (3.6)
Gait disturbance	3 (3.5)	1 (4.3)	0	4 (3.6)
Visual impairment	3 (3.5)	1 (4.3)	0	4 (3.6)
Delirium	1 (1.2)	2 (8.7)	0	3 (2.7)
Vision blurred	2 (2.3)	0	1 (50.0)	3 (2.7)
Agitation	2 (2.3)	0	0	2 (1.8)
Somnolence	1 (1.2)	1 (4.3)	0	2 (1.8)
Urinary retention	1 (1.2)	1 (4.3)	0	2 (1.8)
Ataxia	0	0	1 (50.0)	1 (0.9)
Dry eye	1 (1.2)	0	0	1 (0.9)
Loss of consciousness	0	1 (4.3)	0	1 (0.9)
Presyncope	1 (1.2)	0	0	1 (0.9)
Stupor	1 (1.2)	0	0	1 (0.9)

Thinking abnormal	0	1 (4.3)	0	1 (0.9)
Quality of life decreased				
-Total	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures				
-Total	31 (36.0)	9 (39.1)	2 (100)	42 (37.8)
Hypotension	22 (25.6)	6 (26.1)	1 (50.0)	29 (26.1)
Dizziness	10 (11.6)	3 (13.0)	0	13 (11.7)
Fall	3 (3.5)	0	0	3 (2.7)
Orthostatic hypotension	2 (2.3)	0	0	2 (1.8)
Syncope	2 (2.3)	0	0	2 (1.8)
Ataxia	0	0	1 (50.0)	1 (0.9)
Loss of consciousness	0	1 (4.3)	0	1 (0.9)
Presyncope	1 (1.2)	0	0	1 (0.9)
Other AE appearing more frequently in older patients (>=10% of all patients) n(%)				
-Total	85 (98.8)	23 (100)	2 (100)	110 (99.1)
Cytokine release syndrome	52 (60.5)	10 (43.5)	2 (100)	64 (57.7)
Anaemia	38 (44.2)	14 (60.9)	1 (50.0)	53 (47.7)
Pyrexia	32 (37.2)	7 (30.4)	0	39 (35.1)
Neutrophil count decreased	30 (34.9)	7 (30.4)	1 (50.0)	38 (34.2)
Platelet count decreased	31 (36.0)	5 (21.7)	1 (50.0)	37 (33.3)
White blood cell count decreased	27 (31.4)	9 (39.1)	1 (50.0)	37 (33.3)
Diarrhoea	25 (29.1)	9 (39.1)	1 (50.0)	35 (31.5)
Nausea	23 (26.7)	8 (34.8)	1 (50.0)	32 (28.8)
Hypotension	22 (25.6)	6 (26.1)	1 (50.0)	29 (26.1)
Fatigue	20 (23.3)	7 (30.4)	1 (50.0)	28 (25.2)
Headache	21 (24.4)	3 (13.0)	1 (50.0)	25 (22.5)
Hypokalaemia	20 (23.3)	5 (21.7)	0	25 (22.5)
Neutropenia	16 (18.6)	6 (26.1)	0	22 (19.8)
Cough	13 (15.1)	5 (21.7)	1 (50.0)	19 (17.1)
Dyspnoea	12 (14.0)	6 (26.1)	1 (50.0)	19 (17.1)
Hypophosphataemia	14 (16.3)	5 (21.7)	0	19 (17.1)
Constipation	13 (15.1)	5 (21.7)	0	18 (16.2)
Febrile neutropenia	14 (16.3)	4 (17.4)	0	18 (16.2)
Oedema peripheral	12 (14.0)	5 (21.7)	0	17 (15.3)
Thrombocytopenia	8 (9.3)	6 (26.1)	0	14 (12.6)
Decreased appetite	9 (10.5)	2 (8.7)	2 (100)	13 (11.7)
Dizziness	10 (11.6)	3 (13.0)	0	13 (11.7)
Blood creatinine increased	9 (10.5)	3 (13.0)	0	12 (10.8)
Arthralgia	7 (8.1)	4 (17.4)	0	11 (9.9)
Pain in extremity	7 (8.1)	3 (13.0)	1 (50.0)	11 (9.9)
Confusional state	6 (7.0)	4 (17.4)	0	10 (9.0)
Hypogammaglobulinaemia	6 (7.0)	3 (13.0)	0	9 (8.1)
Hypoxia	6 (7.0)	3 (13.0)	0	9 (8.1)
Asthenia	4 (4.7)	3 (13.0)	1 (50.0)	8 (7.2)
Urinary tract infection	4 (4.7)	4 (17.4)	0	8 (7.2)
Atrial fibrillation	2 (2.3)	3 (13.0)	0	5 (4.5)
C-reactive protein increased	2 (2.3)	2 (8.7)	1 (50.0)	5 (4.5)
Clostridium difficile infection	2 (2.3)	2 (8.7)	1 (50.0)	5 (4.5)

Infection	2 (2.3)	2 (8.7)	1 (50.0)	5 (4.5)
Dysphagia	1 (1.2)	3 (13.0)	0	4 (3.6)
Fluid retention	1 (1.2)	3 (13.0)	0	4 (3.6)

Data cutoff: C2201: 8-Dec-2017
Safety set = All patients who received an infusion of tisagenlecleucel
Only AEs occuring post infusion are summarized
Source: [D120 RtoQ Safety-Table 3-4.1]

Serious adverse event cases on tisagenlecleucel retrieved from the [company] ARGUS database are presented by case and SAE counts, age group and seriousness criteria in Table 72.

Table 68 Courts of cases and events (preferred terms) of tisagenlecleucel from the Novartis safety database (cut-off: 08 December 2017

Seriousness criteria [1]	Age <65 years		Age ≥ 65 to 74 years		Total	
	Number of cases	Number of events	Number of cases	Number of events	Number of cases	Number of events
Death	4	26	5	19	9	45
Life threatening	2	11	-	-	2	11
Disability	2	8	-	1	2	9
Hospitalization	16	57	8	28	24	85
Medically significant	4	8	-	1	4	9

[1] For cases and events with multiple criteria, only the most serious was counted.
Source: ARGUS data on file

Considering the known age distribution in study C2201 with > 75 % of patients being younger than 65 years of age, the incidence of SAE cases and SAEs appear comparable between patients < 65 years and ≥ 65 to 74 years. As anticipated for patients of advanced age, the death rate appeared to be higher in the older age group although the numbers were overall small.

Use in pregnancy and lactation

No data provided in the current studies for any of the two indications.

Safety related to drug-drug interactions and other interactions

During lymphodepleting chemotherapy

In the SCS Pool, 60 patients (59.4%) experienced at least one AE (regardless of study drug relationship) requiring medication or therapy during LD chemotherapy; 15 patients (14.9%) due to grade 3 events and 13 patients (12.9%) due to grade 4 events.

Post-tisagenlecleucel infusion

Within 8 weeks post-tisagenlecleucel infusion, 98 patients (94.2%) experienced at least one AE (regardless of study drug relationship) requiring medication or therapy; 30 patients (28.8%) due to grade 3 events and 48 patients (46.2%) due to grade 4 events. Between 8 weeks and 1 year post-tisagenlecleucel infusion, 65 patients (71.4%) experienced at least one AE requiring medication or therapy; 14 patients (15.4%) due to grade 3 events and 15 patients (16.5%) due to grade 4 events.

After 1 year post-tisagenlecleucel infusion, 6 patients (20.7%) experienced at least one AE requiring medication or therapy; 2 patients due to grade 3 events and 1 patient due to grade 4 event.

Discontinuation due to adverse events

- *ALL indication*

During pre-treatment period

In the SCS Pool, 10 patients (7.9%) experienced at least one AE (regardless of study drug relationship) leading to study discontinuation during the pre-treatment period; grade 3 in 2 patients and grade 4 in 7 patients. The AEs leading to study discontinuation were due to infections and infestations in 5 patients (grade 4 in 4 patients: aspergillus infection, pneumonia, pneumonia fungal and trichosporon infection; grade 3 in 1 patient: systemic mycosis), metabolism and nutrition disorders in 2 patients (hypoalbuminemia and grade 4 tumour lysis syndrome), and due to the PTs multiple organ dysfunction syndrome (grade 4), graft versus host disease (grade 3), haemorrhage intracranial (grade 4) and respiratory failure (grade 4) in one patient each.

During lymphodepleting chemotherapy

In the SCS Pool, 2 patients (2.0%) experienced at least one AE (regardless of study drug relationship) leading to study discontinuation during LD chemotherapy; both patients experienced at least 1 grade 4 event.

Post tisagenlecleucel infusion

Within 8 weeks post tisagenlecleucel infusion, 2 patients in the SCS Pool, one from Study B2202 (due to grade 4 candida infection) and one from Study B2205J (due to grade 4 embolic stroke) experienced an AE (regardless of study drug relationship) leading to study discontinuation. Between 8 weeks and 1 year post tisagenlecleucel infusion, one patient had an event of cardiac arrest (grade 4) that led to study discontinuation. No AEs leading to discontinuation were reported after 1 year.

- *DLBCL indication*

AEs leading to study discontinuation that occurred within 8 weeks post-tisagenlecleucel infusion were reported in 3 patients (2.7%); 1 patient (0.9%) due to febrile neutropenia, 1 patient (0.9%) due to aspiration pneumonia and 1 patient (0.9%) due to pulmonary haemorrhage.

Further, 3 additional patients discontinued the study due to an AE that occurred more than 8 weeks and less than 1 year post-tisagenlecleucel infusion; reasons were: AE of grade 4 cerebral haemorrhage, an AE of grade 3 chronic kidney disease (note: the patient had a medical history that included bladder cancer, kidney fibrosis and renal failure – the patient who died from chronic kidney disease) and a grade 4 infection.

None of the AEs leading to study discontinuation were considered to have a relationship to tisagenlecleucel treatment.

Post marketing experience

Tisagenlecleucel is approved since 30 August 2017 by the FDA for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse. However no post marketing data was available at the time of the submission of the MAA.

2.6.1. Discussion on clinical safety

- *ALL indication*

The safety assessment is based on two phase II clinical trials and one phase I/IIa study including in total 104 evaluable patients. Median follow-up have been 6.37 months, 9.9 months and 11.5 months.

The most common non haematological adverse reactions were cytokine release syndrome (77%), infections (65%), hypogammaglobulinaemia (47%), pyrexia (40%) and decreased appetite (39%)(SmPC, section 4.8).

Grade 3 and 4 adverse reactions were reported in 88% of patients. The most common Grade 3 and 4 non haematological adverse reaction was cytokine release syndrome (47%) (SmPC, section 4.8).

The most common Grade 3 and 4 haematological laboratory abnormalities were white blood cells decreased (99%), neutrophils decreased (95%), lymphocytes decreased (95%), platelets decreased (77%) and haemoglobin decreased (53%)(SmPC, section 4.8).

All patients infused experienced at least 1 adverse event (AE).The most frequently reported AEs post-tisagenlecleucel infusion suspected to be study drug related were cytokine related syndrome (CRS) (80.8%), hypogammaglobulinaemia (32.7%), pyrexia (28.8%), febrile neutropenia (27.9%), hypotension (26.9%), decreased appetite (25.0%), and aspartate aminotransferase (AST) increased (23.1%).

Grade 3 and 4 adverse reactions were more often observed within the initial 8 weeks post infusion (83% of patients) compared to after 8 weeks post infusion (46% of patients) (SmPC, section 4.8).

The most frequently reported SAEs post-tisagenlecleucel infusion were CRS (64.4%), febrile neutropenia (24.0%), and hypotension (11.5%). Serious adverse events were more frequently reported within the initial 8 weeks post-infusion (71.2% of patients; with grade 3 SAEs in 27.9% of patients and grade 4 in 35.6%) compared with >8 weeks to 1 year (31.9% of patients; grade 3 in 18.7% and grade 4 in 13.2%).

Eighteen (14.2%) among the 127 enrolled patients died prior to tisagenlecleucel infusion, which included 10 deaths due to disease progression and 8 deaths due to other causes, mainly infections (6 cases). There were 4 (3.8%) deaths within 30 days of tisagenlecleucel infusion: 2 patients died due to disease progression, 1 due to cerebral haemorrhage in the setting of disseminated intravascular coagulation (DIC) and 1 due to embolic stroke from an intracardiac mucormycotic mass. No deaths occurred within 30 days of first tisagenlecleucel infusion in Study B2101J. Any time 30 days after tisagenlecleucel infusion 25 (24.0%) died, 20 (19.2%) due to disease progression.

No differences in efficacy or safety were observed between different age subgroups (SmPC, section 4.8).

- *DLBCL indication*

The safety assessment is based on 111 adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) as per the third analysis presented in the addendum 2, in trial C2201. Median follow-up from the primary analysis has increased from 3.7 months to 13.9 months.

All except 1 patient experienced an adverse event (AE) post-tisagenlecleucel infusion (note: the patient with no AE received tisagenlecleucel infusion on the day of the data cut -off).

The most common non-haematological adverse reactions were cytokine release syndrome (58%), infections (54%), pyrexia (35%), diarrhoea (32%), nausea (29%), hypotension (26%) and fatigue (26%). The most common (>25%) Grade 3 and 4 haematological laboratory abnormalities were lymphocyte count decreased (95%), neutrophil count decreased (81%), white blood cell count decreased (77%), haemoglobin decreased (59%) and platelet count decreased (55%).

Serious adverse events (SAEs) were reported in 64% of patients. The relationship of adverse events to treatment with tisagenlecleucel can be difficult to assess due to the temporal proximity of chemotherapy to tisagenlecleucel infusion. Lymphodepleting chemotherapy regimens were received by 92.8% of patients infused with tisagenlecleucel. AEs with a suspected relationship to tisagenlecleucel treatment any time post-infusion were reported for most (89.2%) patients.

Adverse reactions to tisagenlecleucel treatment within 8 weeks after infusion were reported in 86.5% of patients. Grade 3/4 AEs with a suspected relationship to tisagenlecleucel treatment were reported in 70 patients (63.1%); grade 3 in 32.4% and grade 4 in 30.6% of patients. Adverse reactions were primarily observed in the first 8 weeks post-infusion. Adverse reactions after 8 weeks post-infusion were reported in 31.3%. AEs with a suspected relationship to tisagenlecleucel treatment that occurred more than 1 year post-infusion were reported in 2 patients (one patient with leukopenia and one patient with respiratory tract infection, both AEs <grade 3).

Three patients died within 30 days post-infusion, all due to lymphoma progression. An additional 47 deaths occurred more than 30 days post-tisagenlecleucel infusion, 42 of which were due to lymphoma progression, and three due to chronic kidney disease, pulmonary haemorrhage and sepsis, respectively.

- *Both indications*

The safety profile for patients treated with tisagenlecleucel is influenced by cytotoxic chemotherapy involved in bridging therapy and lymphodepletion pre-tisagenlecleucel infusion and medication needed to treat AEs post-tisagenlecleucel infusion like antibiotics, gammaglobulines, antipyretics and anti-IL-6 based therapy (tocilizumab).

Overall, the safety profile is similar in both ALL in children and DLBCL in adults, with minor differences in frequency. One difference between the two patient groups is that many of the DLBCL patients have been treated with rituximab pre-tisagenlecleucel infusion, which may have influence on the pattern of AEs observed post-tisagenlecleucel.

AESIs were CRS, infections, neurological events, TLS, hypogammaglobulinaemia, febrile neutropenia, infections and hematopoietic cytopenias. All of these are serious and can be life-threatening. For the B/R of the product it is important this can be managed in a correct and prompt way, in particular the

CRS, infections and febrile neutropenia. Additional risk minimisation measures are important including the proposed CRS algorithm and educational material/guiding documents on AEs to be expected, time to onset, how to handle them and the expected duration of these events. Such information material should be part of special education of all kind of HCPs treating the patients from enrolment to tisagenlecleucel therapy until post-tisagenlecleucel infusion period. For the patients it is as well of greatest importance to get information about what AEs to be expected and how they or their carers should react when symptoms appear.

The most frequently reported AEs post-tisagenlecleucel infusion suspected to be study drug related were CRS (ALL indication: 80.8% in the SCS Pool and 89.3% in study B2101J, DLBCL indication 57.7%). CRS was reversible in most cases and was managed with supportive care and as-needed anti-cytokine therapy (tocilizumab was required in 41.7% of patients). Approximately half of the patients with CRS required intensive care unit level care (56.0%) at a median of 6 days after the infusion, where they remained for a median duration of 7 days.

The frequency of deaths reported in DLBCL patients have increase over time, which is expected for patient groups included in this clinical trial. It may be anticipated that additional information on clinical safety will be gathered via the routine post-marketing pharmacovigilance activities.

The most serious and life-threatening AE is CRS observed in 81% of ALL patients and in 38% in DLBCL patients. CRS occurred between 1 to 11 days (median onset: 3 days) in ALL patients and between 1-9 days (median 3 days) in the DLBCL patients. All occurred within first 8 weeks post-tisagenlecleucel infusion. CRS was one of events associated with three cases of fatal outcome. To prevent CRS being life-threatening, a revised algorithm with minor changes from the one used in the clinical trials, is proposed for managing this AE.

Cytokine release syndrome, including fatal or life-threatening events, has been frequently observed after Kymriah infusion (see SmPC section 4.8). In almost all cases, development of cytokine release syndrome occurred between 1 to 10 days (median onset 3 days) after Kymriah infusion. The median time to resolution of cytokine release syndrome was 7 days(SmPC, section 4.4).

Symptoms of cytokine release syndrome may include high fever, rigors, myalgia, arthralgia, nausea, vomiting, diarrhoea, diaphoresis, rash, anorexia, fatigue, headache, hypotension, encephalopathy, dyspnoea, tachypnoea, and hypoxia. Additional organ system adverse reactions, including transient cardiac insufficiency and arrhythmia, renal insufficiency, elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT) and elevated bilirubin have been observed. In some cases, disseminated intravascular coagulation (DIC), with low fibrinogen levels, capillary leak syndrome (CLS), and haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) have been reported in the setting of cytokine release syndrome. Patients should be closely monitored for signs or symptoms of these events, including fever (SmPC, section 4.4).

Risk factors for severe cytokine release syndrome in paediatric and young adult B-cell ALL patients are: high pre-infusion tumour burden, uncontrolled or accelerating tumour burden following lymphodepleting chemotherapy, active infection and early onset of fever or cytokine release syndrome following Kymriah infusion. Risk factors for developing severe cytokine release syndrome in adult DLBCL patients are not known (SmPC, section 4.4).

In all indications, appropriate prophylactic and therapeutic treatment for infections should be provided, and complete resolution of any existing infections should be ensured. Infections may also occur during cytokine release syndrome and may increase the risk of a fatal event (SmPC, section 4.4).

Cytokine release syndrome is managed solely based on clinical presentation and according to the cytokine release syndrome management algorithm provided in Table 1. Anti-IL-6 based therapy such

as tocilizumab has been administered for moderate or severe cytokine release syndrome associated with Kymriah and a minimum of four doses of tocilizumab must be on site and available for administration prior to Kymriah infusion. Corticosteroids may be administered in cases of life-threatening emergencies. Tisagenlecleucel continues to expand and persist following administration of tocilizumab and corticosteroids. Patients with medically significant cardiac dysfunction should be managed by standards of critical care and measures such as echocardiography should be considered. Tumour necrosis factor (TNF) antagonists are not recommended for management of Kymriah-associated cytokine release syndrome (SmPC, section 4.4). Cytokine release syndrome has been categorized as identified risk (see Risk Management Plan).

Neurological events are AEs of concern, observed in 38% in ALL patients and in 21% in DLBCL patients. These events were often seen as part of the CRS, in particular with high fever and occurred within few days following tisagenlecleucel infusion. Neurological events occurring first 8 weeks post-infusion is called "early" neurological events. The majority of neurologic events occurred first 30 days after tisagenlecleucel infusion. Most common symptoms were agitation, encephalopathy, seizures, tremor, confusional state, delirium, irritability and somnolence. The majority of neurological events resolved completely, however, 7% of patients with neurological events with ALL indication and 5% with the DLBC indication were not recovered at the time of cut-off. History of CNS disease is considered a risk factor. Treatment with tocilizumab did not reverse the symptoms. No neurological events are suggested to be part of any death. It is not clear if delayed or late neurological events (occurring >8 weeks post-infusion) have been observed. In a recent publication [33], neurotoxicity associated with CAR-T cells are mentioned CAR-T-cell-related encephalopathy (CRES) and a management guide is proposed. This guide is considered useful for HCPs and is included in the educational material for HCPs.

Other manifestations included seizures, aphasia and speech disorder. The majority of neurological events occurred within 8 weeks following Kymriah infusion and were transient. The median time to onset of neurological events was 7 days in B-cell ALL and DLBCL. The median time to resolution was 7 days for B-cell ALL and 12 days for DLBCL. Neurological events can be concurrent with cytokine release syndrome, following resolution of cytokine release syndrome or in the absence of cytokine release syndrome. Patients should be monitored for neurological events. In case of neurological events, patients should be diagnostically worked-up and managed depending on the underlying pathophysiology and in accordance to local standard of care (SmPC, section 4.4). Serious neurological adverse reactions have been categorized as identified risk (see Risk Management Plan).

Due to the time sequence and frequency of severe CRS and (early) neurological events > Grade 3, patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential cytokine release syndrome, neurological events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion. After the first 10 days following the infusion, the patient should be monitored at the physician's discretion. Patients should be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion (SmPC, section 4.2).

Hypogammaglobulinaemia was seen in 45% in the ALL indication and in 15% in DLBCL indication. Immunoglobulin replacement therapy was given in 19.2% of those with hypogammaglobulinemia in the DLBCL indication. Immunoglobulin levels should be monitored after treatment with Kymriah. In patients with low immunoglobulin levels pre-emptive measures such as infection precautions, antibiotic prophylaxis and immunoglobulin replacement should be taken according to age and standard guidelines (SmPC, section 4.4).

Patients treated with Kymriah may develop secondary malignancies or recurrence of their cancer. Life-long for secondary malignancies should be monitored. In the event that a secondary malignancy

occurs, the company should be contacted to obtain instructions on patient samples to collect for testing (SmPC, section 4.4).

Based on the pooled data (B2202+B2205J) 39 patients (37.5%) reported AEs related to prolonged depletion of normal B-cells. In study C2201, prior to tisagenlecleucel infusion, one patient had normal levels of CD19+ B-cells (normal range: 80-616 cells/µL), while the majority of the patients had CD19+ B-cell levels below lower limit of quantitation (LLOQ=0.2 cells/µL). Transient or prolonged B-cell depletion is a risk with tisagenlecleucel therapy, since normal B-cells express CD19. Prolonged depletion of normal B cells/ agammaglobulinemia has been categorized as identified risk (see Risk Management Plan).

Hematopoietic cytopenias was seen in 36% of both ALL and DLBCL patients and was observed within 28 days as well as several months post-tisagenlecleucel. Management was blood product support, growth factors and/or antibiotics as indicated. Myeloid growth factors are not recommended until CRS has been resolved and typically not before 28 days have elapsed following tisagenlecleucel infusion. Hematopoietic cytopenias not resolved by 28 days have been categorized as identified risk (see Risk Management Plan).

Pyrexia (41% in the ALL indication and 35% in DLBCL indication) and febrile neutropenia (36% in ALL indication, 16% in DLBCL indication) were managed with standard practice of hospital admission, culture surveillance, antibiotics and supportive care.

Infections were seen caused by several different pathogens related to respiratory infections, urinary tract infections, gastrointestinal infections etc. Bacteria, viral as well as fungal infections were seen and treated with antibiotics according to local guidance.

Patients with active, uncontrolled infection should not start Kymriah treatment until the infection is resolved. Prior to Kymriah infusion, infection prophylaxis should follow standard guidelines based on the degree of preceding immunosuppression. Serious infections, including life-threatening or fatal infections, occurred frequently in patients after Kymriah infusion. Patients should be monitored for signs and symptoms of infection and treated appropriately. As appropriate, prophylactic antibiotics should be administered and surveillance testing should be employed prior to and during treatment with Kymriah. Infections are known to complicate the course and management of concurrent cytokine release syndrome (SmPC, section 4.4). Infections have been categorized as identified risk (see Risk Management Plan).

Febrile neutropenia was frequently observed in patients after Kymriah infusion and may be concurrent with cytokine release syndrome. In the event of febrile neutropenia, infection should be evaluated and managed appropriately with broad spectrum antibiotics, fluids and other supportive care, as medically indicated (SmPC, section 4.4).

In patients achieving complete remission following Kymriah, resulting low immunoglobulin levels can increase the risk for infections. Attention to signs and symptoms of infection should be implemented according to age and standard specific guidelines (SmPC, section 4.4).

Patients may continue to exhibit cytopenias for several weeks following Kymriah infusion and should be managed according to standard guidelines. The majority of patients who had cytopenias at day 28 following Kymriah treatment resolved to Grade 2 or below within three months after treatment. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), have the potential to worsen cytokine release syndrome symptoms and are not recommended during the first 3 weeks after Kymriah infusion or until cytokine release syndrome has resolved (SmPC, section 4.4).

Delayed toxicity of hematologic origin (e.g., such as myelodysplastic syndrome, aplastic anaemia, bone marrow failure) has been associated with prior treatment with chemotherapy and radiation and were observed in the tisagenlecleucel development program. Haematological disorders (incl. aplastic anaemia and bone marrow failure) have been categorized as potential risk (see Risk Management Plan).

Two cases of fatal cerebral oedema and one case of papilledema have been observed post-tisagenlecleucel infusion. All the 2 fatal events clearly present the pathophysiological consequence of preceding events and conditions that are considered the primary aetiology of the death in these patients. Therefore, these 2 events must be unmistakably distinguished from the clinical pattern of fatal cerebral oedema observed with the JCAR015 product. Therefore cerebral oedema has been categorized as potential risk (see Risk Management Plan).

Based on the pooled (B2202+B2205J) 39 patients (37.5%) reported AEs related to hypersensitivity. Most of these patients (31 out of 39) had events that were of grade 1/2 severity, with grade 3 AEs reported in seven patients (6.7%) and grade 4 AE reported in one patient. The most frequent PTs (reported in >5% of patients) were rash (9.6%) and face oedema (8.7%). In study C2201 15 patients (15.2%) reported AEs related to hypersensitivity, all of which were of grade 1/2 severity.

The safety of immunization with live viral vaccines during or following Kymriah treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Kymriah treatment, and until immune recovery following treatment with Kymriah (SmPC section 4.4).

TLS, which may be severe, has occasionally been observed. To minimise risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to Kymriah infusion. Signs and symptoms of TLS should be monitored and events managed according to standard guidelines (SmPC section 4.4). Tumour lysis syndrome has been categorized as identified risk (see Risk Management Plan).

Graft-versus-host disease (GVHD) was reported in one patient (study B2202). The patient hadgrade 1 GVHD in the past, but it was not ongoing at the time of the study entry. There were no patients with GVHD in study C2201. Aggravation of graft-versus-host disease has been categorized as potential risk (see Risk Management Plan).

Modulation of an individual’s immune status (such as what occurs with chemotherapy and CRS) can cause an exacerbation of a pre-existing autoimmune disorder. No AEs were observed in the clinical trials. New occurence or exacerbation of an autoimmune disorder has been categorized as potential risk (see Risk Management Plan).No AEs were observed in the clinical trials.

Patients with a history of active CNS disorder or inadequate renal, hepatic, pulmonary or cardiac function were excluded from the studies. These patients are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention (SmPC section 4.4).

It is not recommended that patients receive Kymriah within 4 months of undergoing an allogeneic stem cell transplant (SCT) because of the potential risk of Kymriah worsening GVHD. Leukapheresis for Kymriah manufacturing should be performed at least 12 weeks after allogeneic SCT (SmPC section 4.4).

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with medicinal products directed against B cells. There is currently no experience with manufacturing Kymriah for patients testing positive for HBV, HCV and HIV.Screening for HBV, HCV and

HIV must be performed in accordance with clinical guidelines before collection of cells for manufacturing (SmPC section 4.4).

Due to limited short spans of identical genetic information between the lentiviral vector used to create Kymriah and HIV, some commercial HIV nucleic acid tests (NAT) may give a false positive result(SmPC section 4.4).

Long-term safety is for the time being considered missing information. Regular reporting from the follow-up until 24 months and 60 months of the ongoing studies is of importance. Two studies are planned for follow-up of long-term safety in 15 years, one the follow up of ALL patients in study B2205 and a PASS for all B-cell lymphomas (see RMP).

Inappropriate handling of the manufactured product including transport, storage in addition to thawing and standing time prior to infusion may result in a decrease of viable cells. This may impact the efficacy and safety profile of tisagenlecleucel. Decrease in cell viability due to inappropriate handling of the product has been categorized as potential risk (see Risk Management Plan).

Missing information in several patient groups: safety during use in pregnancy and lactation, safety in patients with HIV/HBV/HCV, safety in patients with active CNS, involvement by malignancy, immunogenicity and long-term safety. Routine risk minimization activities recommend specific clinical measures to address these (see Risk Management Plan).

Kymriah has a major influence on the ability to drive and use machines.Due to the potential for neurological events, including altered mental status or seizures, patients receiving Kymriah are at risk for altered or decreased consciousness or coordination in the 8 weeks following infusion (SmPC, section 4.7).

This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Kymriah should therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases. (SmPC, section 4.2). Transmission of infectious agents has been categorized as potential risk (see Risk Management Plan).

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

Controlled distribution program

A controlled distribution program is proposed in the RMP as additional risk minimization activity to mitigate the risk associated with Kymriah (tisagenlecleucel) by ensuring that hospitals and their associated centres that dispense Kymriah (tisagenlecleucel) are specially qualified and have on-site, immediate access to tocilizumab.

To mitigate the risk and minimize the occurrence of severe or life-threatening CRS and neurological toxicities by ensuring that those who prescribe, dispense, and administer Kymriah (tisagenlecleucel) have completed the educational program, and have on-site, immediate access to tocilizumab. Patients receiving Kymriah (tisagenlecleucel) treatment will be counselled by treating clinician in treatment risks including CRS and neurological toxicities, and will be provided with a patient reminder card, besides the package leaflet.

Kymriah (tisagenlecleucel) will only be supplied to hospitals and associated centres that are qualified and only if the healthcare professionals involved in the treatment of a patient have completed the educational program, and have on-site, immediate access to tocilizumab.

This program is endorsed and is supposed to include management of all types of expected serious AEs.

2.6.2. Conclusions on the clinical safety

Serious and life-threatening AEs, in particular CRS, have been observed in most patients, across indications in particular first eight weeks post- Kymriah infusion. These AEs are considered manageable with the appropriate risk minimisation measures in place. Furthermore, post authorisation studies will further investigate the safety and long term safety of Kymriah. The registry will also evaluate safety of tisagenlecleucel in B-ALL patients below the age of 3 years treated in the commercial setting. In addition, follow up data on the pivotal study C2201 will be submitted by the applicant. Finally study CCTL019H2301 is a randomized open-label parallel-group multicenter Phase III trial designed to evaluate the efficacy and safety of tisagenlecleucel in adult patients with relapsed or refractory B-cell aggressive NHL after failure of rituximab and anthracycline containing first line immunochemotherapy.

The CAT considers the following measures necessary to address issues related to safety:

- Non-interventional PASS: In order to further characterise the safety including long-term safety of Kymriah, the applicant should conduct and submit a study based on data from a disease registry in ALL and DLBCL patients.

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

2.7. Risk Management Plan

Summary of the safety concerns

Table 69: Summary of the Safety Concerns

Important identified risks	• Cytokine release syndrome • Infections • Serious neurological adverse reactions • Tumor lysis syndrome • Prolonged depletion of normal B-cells/ Agammaglobulinemia • Hematopoietic cytopenias not resolved by day 28
Important potential risks	• Cerebral edema • Generation of replication competent lentivirus • Secondary malignancies (including vector insertion site oligo/ monoclonality) • New occurrence or exacerbation of an autoimmune disorder • Hematological disorders (incl. aplastic anemia and bone marrow failure) • Aggravation of graft-versus-host disease • Transmission of infectious agents • Decrease in cell viability due to inappropriate handling of the product
Missing information	• Use in pregnancy and lactation • Use in patients with HBV/HCV/HIV • Use in patients with active CNS involvement by malignancy • Long-term safety • Immunogenicity

Pharmacovigilance plan

Summary of planned additional PhV activities from RMP

Table 70 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
CCTL019B2401 Non-interventional study with secondary use of data from two registries conducted by EBMT and CIBMTR to evaluate the long term safety of patients with malignancies treated with CAR-T-cell therapies (planned) *Note:* The design of this registry and safety concerns that will be evaluated will be further defined in the final study protocol.	The objective of the Novartis study is to further characterize the tisagenlecleucel safety specification in addition to evaluate selected AEs and outcome reported in patients up to 15 years following treatment with tisagenlecleucel	• Cytokine release syndrome • Infections • Serious neurological adverse reactions • Tumor lysis syndrome • Prolonged depletion of normal B-cells/ Agammaglobulinemia • Hematopoietic cytopenias not resolved by day 28 • Cerebral edema • Secondary malignancies(including vector insertion site oligo/monoclonality) (as feasible) • New occurrence or exacerbation of an autoimmune disorder • Hematological disorders (incl. aplastic anemia and bone marrow failure) • Aggravation of graft-versus-host disease • Transmission of infectious agents • Use in pregnancy and lactation • Use in patients with HBV/HCV/HIV • Use in patients with active CNS involvement by malignancy • Long-term safety	Start of data collection Study completion date Update reports Final report of study results	Q4, 2018 December 2037 Annual safety reports and 5-yearly interim reports December 2038
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
None				
Category 3 - Required additional pharmacovigilance activities				
CCTL019A2205B Long-term follow-up of patients exposed to lentiviral- based CD19 directed CAR-T-cell therapy (ongoing)	The primary objective of the study is to describe selected, delayed AEs suspected to be related to previous CD19 CAR-T-cell therapy as outlined in current Health Authority guidelines. The secondary objectives are to monitor the persistence of CD19 CAR transgene in peripheral blood, monitor the expression of RCL, assess the long-term efficacy of CD19 CAR-T, monitor lymphocyte levels and describe the growth, development, and female reproductive status for patients who were aged <18 years at the time of the initial CD19 CAR-T-cell infusion	• Cytokine release syndrome • Infections • Serious neurological adverse reactions • Tumor lysis syndrome • Prolonged depletion of normal B-cells/ agammaglobulinemia • Hematopoietic cytopenias not resolved by day 28 • Cerebral edema • Generation of replication competent lentivirus • Secondary malignancies (including vector insertion site oligo/monoclonality) • New occurrence or exacerbation of an autoimmune disorder • Hematological disorders (incl. aplastic anemia and bone marrow failure) • Aggravation of graft-versus-host disease • Transmission of infectious agents • Long-term safety • Immunogenicity	Start of data collection Study completion date Update reports Final report of study results	2015 December 2036 Annual safety reports and 5-yearly interim reports December 2037

Additional pharmacovigilance activities to assess the effectiveness of risk minimisation measures

The effectiveness of risk minimisation measures will be assessed by analysis of data obtained in the proposed registry study (CTL019B2401).

Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC Rapporteur also considered that the planned registry in the post-authorisation development plan is sufficient to monitor the effectiveness of the risk minimisation measures.

Post-authorization efficacy studies (PAES) commitments

Report on real-world evidence for Kymriah in children below the age of 3 years with B-ALL (based on registry CCTL019B2401)

Novartis will report based on data from registry B2401 to evaluate the efficacy and safety of tisagenlecleucel in B-ALL patients below the age of 3 years treated in the commercial setting. The following will be provided as part of the annual registry reports:

- Information on manufacturing, safety and efficacy
- Information on the manufacturing experience for batches for patients below 3 years of age

Novartis will provide this information within a dedicated section of the annual report until information on 20 patients below the age of three years and infused with tisagenlecleucel is available.

Milestones:
- Start of data collection: Q4, 2018
- Study completion date: December 2037
- Update reports: Annual safety reports and 5-yearly interim reports
- Final report of study results: December 2038

Observational study in DLBCL (Category 1)

Novartis will conduct a prospective, observational PAES study in order to further evaluate the efficacy of tisagenlecleucel in patients with r/r DLBCL. Efficacy outcome measures will be line with those evaluated in study C2201. In addition, details of the manufacturing turnaround time (i.e., including time from last relapse or confirmed refractory status, time from decision to treat, and time from leukapheresis to infusion) will be reported.

Subgroup analysis will be conducted to evaluate the effectiveness in 1) all included patients, 2) patients matching the population in C2201 and 3) patients matching the population in the CORAL extension studies (i.e. receiving third line treatment or having relapsed after SCT). In addition, subgroup analysis based on important prognostic covariates will be performed. Details of the manufacturing turnaround time, (i.e. time from last relapse or confirmed refractory status, time from decision to treat, and time from leukapheresis to infusion) will be reported.

Milestone: The study protocol will be submitted within 3 months of the European Commission decision.

Study CCTL019C2201

The following reports will be prepared for pivotal study C2201 in order to further characterize long-term efficacy and safety of tisagenlecleucel in r/r DLBCL:

- Follow-up report at the data cut-off December 2018: this will provide 24 months follow-up of the 81 patients of the EAS Cohort, who were included in the initial analysis.
- Follow-up report at the data cut-off February 2020: this will provide at least 24 months follow-up of all infused patients.

- The final CSR corresponding to 5 years of follow-up once this is available.

Milestones: See above.

Study CCTL019H2301

Study CCTL019H2301 is a randomized open-label parallel-group multicenter Phase III trial to evaluate the efficacy and safety of tisagenlecleucel in adult patients with relapsed or refractory B-cell aggressive NHL after failure of rituximab and anthracycline containing first line immunochemotherapy.

Study data will support further characterization of the benefit-risk ratio of tisagenlecleucel in an earlier line of DLBCL.

Milestone: The study is planned to start in Q4 2018.

Risk minimisation measures

- **Summary of risk minimisation measures from the RMP**

Table 71 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures (routine and additional)	Pharmacovigilance activities
Important identified risks		
Cytokine release syndrome	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects • SmPC Package leaflet, Section 5 How to store Kymriah **Additional risk minimization measures** • Controlled distribution program • Educational program including the Healthcare Professional Training Material and the Patient Educational Leaflet	**Additional pharmacovigilance activities** • CCTL019A2205B • CCTL019B2401
Infections	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method	**Additional pharmacovigilance activities**

Safety concern	Risk minimization measures (routine and additional)	Pharmacovigilance activities
	of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects • SmPC Package leaflet, Section 5 How to store Kymriah **Additional risk minimization measures** • None	• CCTL019A2205B • CCTL019B2401
Serious neurological adverse reactions	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.7 Effects on ability to drive and use machines • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects • SmPC Package leaflet, Section 5 How to store Kymriah **Additional risk minimization measures** • Controlled distribution program • Educational program including the Healthcare Professional Training Material and the Patient Educational Leaflet	**Additional pharmacovigilance activities** • CCTL019A2205B • CCTL019B2401
Tumor lysis syndrome	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given	**Additional pharmacovigilance activities** • CCTL019A2205B • CCTL019B2401

Safety concern	Risk minimization measures (routine and additional)	Pharmacovigilance activities
	Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects • SmPC Package leaflet, Section 5 How to store Kymriah **Additional risk minimization measures** • None	
Prolonged depletion of normal B-cells/Agammaglobulinemia	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.6 Fertility, pregnancy and lactation • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects • SmPC Package leaflet, Section 5 How to store Kymriah **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019A2205B • CCTL019B2401
Hematopoietic cytopenias not resolved by day 28	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects • SmPC Package leaflet, Section 5 How to store Kymriah **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019A2205B • CCTL019B2401
Important potential risks		
Cerebral edema	**Routine risk minimization measures**	**Additional pharmacovigilance activities**

Safety concern	Risk minimization measures (routine and additional)	Pharmacovigilance activities
	• SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.7 Effects on ability to drive and use machines • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects • SmPC Package leaflet, Section 5 How to store Kymriah **Additional risk minimization measures** • None	• CCTL019A2205B • CCTL019B2401
Generation of replication competent lentivirus	**Routine risk minimization measures** • None **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019A2205B
Secondary malignancies (vector insertion site oligo/ monoclonality)	**Routine risk minimization measures** • SmPC Section 5.3 Preclinical safety data • SmPC Section 4.4 Special warnings and precautions for use **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019A2205B • CCTL019B2401 (as feasible)
New occurrence or exacerbation of an autoimmune disorder	**Routine risk minimization measures** • None **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019A2205B • CCTL019B2401
Hematological disorders (incl. aplastic anemia and bone marrow failure)	**Routine risk minimization measures** • None **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019A2205B • CCTL019B2401
Aggravation of graft-versus-host disease	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How	**Additional pharmacovigilance activities** • CCTL019A2205B • CCTL019B2401

Safety concern	Risk minimization measures (routine and additional)	Pharmacovigilance activities
	Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects • SmPC Package leaflet, Section 5 How to store Kymriah **Additional risk minimization measures** • None	
Transmission of infectious agents	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 6.3 Shelf life • SmPC Section 6.4 Special precautions for storage • SmPC Section 6.5 Nature and contents of container and special equipment for use, administration or implantation • SmPC Section 6.6 Special precautions for disposal and other handling • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 5 How to store Kymriah • SmPC Section Other sources of information **Additional risk minimization measures** None	**Additional pharmacovigilance activities** • CCTL019A2205B • CCTL019B2401
Decrease in cell viability due to inappropriate handling of the product	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 6.3 Shelf life • SmPC Section 6.4 Special precautions for storage • SmPC Section 6.5 Nature and contents of container and special equipment for use, administration or implantation • SmPC Section 6.6 Special precautions for disposal and other handling • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 5 How to store Kymriah • SmPC Section Other sources of information	**Additional pharmacovigilance activities** • None

Safety concern	Risk minimization measures (routine and additional)	Pharmacovigilance activities
	Additional risk minimization measures • Controlled distribution program • Educational program including the Pharmacy/Cell Lab/Infusion Center Training Material	
Missing information		
Use in pregnancy and lactation	**Routine risk minimization measures** • SmPC Section 4.6 Fertility, pregnancy and lactation • SmPC Section 5.3 Preclinical safety data • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 5 How to store Kymriah **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401
Use in patients with HBV/HCV/HIV	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 6.6 Special precautions for disposal and other handling • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 5 How to store Kymriah • SmPC Section Other sources of information **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401
Use in patients with active CNS involvement by malignancy	**Routine risk minimization measures** • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 5.1 Pharmacodynamic properties – Patients with active CNS leukemia **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401
Long-term safety	**Routine risk minimization measures** • None **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019A2205B • CCTL019B2401

Safety concern	Risk minimization measures (routine and additional)	Pharmacovigilance activities
Immunogenicity	**Routine risk communication** • SmPC Section 5.2 Pharmacokinetic properties **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019A2205B

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The IBD is 30.08.2017. The applicant did request international harmonisation of the PSUR cycle by using the forthcoming Data Lock Point 12.02.2019.

2.9. New Active Substance

The applicant declared that tisagenlecleucel has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers tisagenlecleucel to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kymriah (tisagenlecleucel) is included in the

additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applied indications are as follows:

Kymriah is indicated for the treatment of:

- Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (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.

3.1.2. Available therapies and unmet medical need

- ALL indication

For r/r ALL treatment options include high-dose chemotherapy with subsequent allogeneic stem cell transplantation (SCT), standard chemo-immunotherapy, targeted treatment with small molecule pathway inhibitors, or supportive care with non-curative palliative goals. Allogeneic SCT is the only potentially curative option for r/r pALL, but outcomes are suboptimal. Among r/r pALL patients who received allogeneic SCT in third or later remission, received allogeneic SCT with active disease or received allogeneic SCT after relapse from previous allogeneic SCT, the 1-year overall survival (OS) rates are in 25 to 55% range and 5-year OS rates are generally in 20 to 45% range.

For Ph+ patients, dasatinib (Sprycel) was approved in 2006 for the treatment of adult patients with resistance or intolerance to prior therapy. Ponatinib (Iclusig) was approved in 2013 for the treatment of adult patients with Ph+ ALL who are resistant to/ intolerant of dasatinib. Blincyto (blinatumomab), a bispecific anti-CD3/CD19 monoclonal antibody, has been approved for the treatment of adults with Ph- relapsed or refractory B-precursor ALL.

Despite the current treatment modalities, maintaining a remission in relapsed patients is difficult, the patients are being hospitalized for a long period of time with a poor QoL, and the prognosis of patients with r/r ALL still remains poor.

- DLBCL indication

The front-line standard of care for patients with DLBCL includes a combination of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) with rituximab (R-CHOP). Although rituximab has markedly improved the prognosis of DLBCL patients, 30-50% do not have long-term benefit from first-line therapy (approximately 30% relapse and 20% have refractory disease). The

recommended second-line therapy for patients with r/r DLBCL (<65-70 years) is salvage regimens with rituximab and chemotherapy (i.e. R-DHAP, R-ICE, R-GDP) followed, in responsive patients (approximately 40-60%), by high-dose chemotherapy (HDC) and ASCT. For patients who are ineligible for ASCT or relapse following ASCT, treatment options are more limited and for most patients the prognosis is poor.

3.1.3. Main clinical studies

- *ALL indication*

The clinical package of Kymriah for the ALL indication was primarily supported by data from a Phase II, single arm, multicentre trial designed to determine the efficacy and safety of CTL019 in paediatric and young adult patients with relapsed and refractory B-cell ALL (Study B2202).

- DLBCL indication

Study C2201 is an open-label, multicentre, single arm phase 2 study designed to determine the efficacy and safety of tisagenlecleucel in adult patients with r/r DLBCL (including DLBCL arising from TFL) who are ineligible for ASCT after ≥ 2 prior lines of chemotherapy (including rituximab and anthracycline).

3.2. Favourable effects

- *ALL indication*

The primary endpoint (superiority of ORR compared to a historic control ORR of 20%) was met at the April 25, 2017 cut-off. Best ORR within 3 months was 66.3% (95% CI: (55.7, 75.8). Forty five patients (48.9%) had a best response of CR, and 16 patients (17.4%) had a best response of CRi.

With respect to the secondary endpoints, all patients who achieved BOR also achieved bone marrow MRD negative remission. At a median follow up of 7.5 months (27.9% events), the median DOR was not reached. The median EFS was also not reached (95% CI: 8.9, NE), with an estimated event-free probability at Month 6 of 72.7% (95% CI: 59.9, 82.0). Median OS was 19.1 months (95% CI 15.2, NE), at a median follow up of 10.5 months (25.3% events). At the updated December 2017 data cut, median OS was not reached.

The response rates were generally consistent across various demographic and prognostic subsets, except for one (Asian n=6), for which the ORR was 50% (95% CI 11.8%, 88.2%).

- DLBCL indication

In the final update (DCO: 08-Dec-2017) on 165 patients enrolled and 111 patients infused (FAS): 95 received tisagenlecleucel manufactured at the Morris Plains facility (EAS Cohort) and 16 at the Fraunhofer Institute (Cohort A). Efficacy results showed an ORR of 51.6% (48/93) in infused patients in the EAS and 33.9% (56/165) in all enrolled patients. PFS and OS were also numerically higher in all infused patients (FAS). Median OS from enrolment date was 12.9 months (95% CI: 8.4, NE) in the infused population and 8.2 months (95% CI: 5.8, 11.7) in the enrolled population. The median OS from infusions was 11.7 months.

The response rate in the primary analysis of SCHOLAR-1 was 26% (95% CI: 21%, 31%), with a CR rate of 7% and a PR rate of 18%. When SCHOLAR-1 was compared to enrolled patients in study

C2201, the difference in CR remained significant (19.2%, p<0.01), whereas the median OS was reduced from 11.7 months vs 6.3 months (p<0.05) to 8.4 months vs. 6.3 months (p=0.12). In the C2201 vs CORAL comparison, the difference in ORR and CR was ~12%, (p<0.05), favouring tisagenlecleucel. When the analyses was based on enrolled patients, response rates were similar across the two trials (ORR: -5%, p=0.32, CR: -1.7%, p=0.71). Median OS from last relapse was significantly better in C2201 compared to CORAL both in the infused set (median 16.3 months, 95% CI: 11.5, NR) and in the enrolled set (median 10.6 months, 95% CI: 8.3, 16.3) vs. median of 5.8 months (95% CI: 4.7, 7.2) in CORAL (p<0.01).

3.3. Uncertainties and limitations about favourable effects

- ALL indication

The uncertainties that were identified during the assessment regarding the initially proposed indication for ALL were satisfactorily addressed (see discussion on clinical efficacy). The choice of a cut-off of 3-25 years in the initially proposed indication was a reflection of the inclusion criteria of the pivotal study B2202. Efficacy and safety can be extrapolated to below the age of 3 as discussed in the efficacy section. Some uncertainty about the precise estimates will be made on the basis of a registry (see Annex II and RMP).

- DLBCL indication

Longer than anticipated manufacturing times posed challenges for the treatment of patients in need resulting in a significant amount of patients withdrawing from the study (50 out of 165 enrolled patients did not receive the infusion). Thus, the efficacy as reported for the enrolled analysis set could be underestimated in case of improvements in the manufacturing time.

In order to further evaluate the efficacy of Kymriah in patients with relapsed/refractory DLBCL, the applicant should conduct and submit a prospective, observational study in patients with r/r DLBCL based on data from registry with efficacy outcome measures in line with study C2201, including details of the manufacturing turnaround time, (i.e. time from last relapse or confirmed refractory status, time from decision to treat, and time from leukapheresis to infusion) (see Annex II and RMP).

In order to further characterise long-term efficacy and safety of Kymriah in relapsed/refractory DLBCL, the applicant should submit the 24 months follow-up for patients in the EAS Cohort and 24 months follow-up of all infused patients from study C2201. In addition the applicant should submit the final CSR including 5 years of follow-up (see Annex II and RMP).

3.4. Unfavourable effects

Grade 3 and 4 adverse reactions were reported in 88% of patients. The most common Grade 3 and 4 non haematological adverse reaction was cytokine release syndrome (47%). The most common Grade 3 and 4 haematological laboratory abnormalities were white blood cells decreased (99%), neutrophils decreased (95%), lymphocytes decreased (95%), platelets decreased (77%) and haemoglobin decreased (53%).

A total of 84 patients (80.8%) reported AEs related to CRS in ALL studies B220 and B2205J over half of which (46 patients) had grade 3 or 4 severity. In all the 84 patients the AEs were suspected to be

related to tisagenlecleucel treatment. In study C2201, 57 patients (57.6%) had CRS, all of which were suspected to be related to treatment with tisagenlecleucel.

Febrile neutropenia were seen in 36% of ALL patients and in 13% of DLBCL patients and may be associated with LD therapy, and may be concurrent with CRS. Febrile neutropenia was mostly seen first eight weeks post-tisagenlecleucel and is managed appropriately with broad spectrum antibiotics, fluids and other supportive care.

Infections were seen in 67% of ALL patients and in 53% of DLBCL patients and are related to B-cell depletion and hypogammaglobulinemia and may be associated to chemotherapy/lymphodepletion therapy as well as tisagenlecleucel. Infections were primarily bacterial or viral and were frequent both first eight weeks post-tisagenlecleucel as more than eight weeks post-infusion. Infections are managed by appropriate antibiotic and immunoglobulins in case of agammaglobulinemia.

Tumour lysis syndrome was seen in 4% of ALL patients and 1% of DLBCL patients. Symptoms of TLS and events are managed according to local guidelines.

The availability of tocilizumab at all hospitals and associated centres must be ensured by the Marketing Authorisation Holder until an authorised treatment for CRS is available in the EU. Kymriah will only be supplied to hospitals and associated centres that are qualified and only if the healthcare professionals involved in the treatment of a patient have completed the educational program. To mitigate the safety risks associated with the treatment of Kymriah, it must be ensured that hospitals and their associated centres that dispense Kymriah are specially qualified (see Annex II and RMP).

3.5. Uncertainties and limitations about unfavourable effects

Due to the small safety database and short follow-up, further data on safety including long-term safety are needed. Patients will be followed up to 60 months in the clinical trials that are ongoing and regular reporting on safety data from the studies should be included in PSURs post-marketing. A disease registry in ALL and DLBCL patients will address this concern. The objective of this registry is to further characterise the safety including long-term safety of Kymriah, in the post marketing setting (Annex II and RMP).

3.6. Effects Table

- ALL indication

Table 72 Effects Table for Kymriah in paediatric and young adult patients up to 25 years of age with B cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse (data cut-off: 25 April 2017)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
Favourable effects					

ORR during the 3 months	Proportion of patients with a best overall disease response of CR or CRi.	%	66.3 (55.7, 75.8) p< 0.0001	N/A	CR[1], n (%): 45 (48.9) CRi[2], n (%): 16 (17.4)
DOR	Time since onset of CR or CRi to relapse or death due to underlying indication, whichever is earlier	months	NR (8.6, NE)		61 infused patients (FAS)
Unfavourable effects					
Cytokine release syndrome	Grade 3-4 ADRs	%	47	N/A	
Neurological events	Grade 3-4 ADRs	%	13	N/A	
Febrile Neutropenia	Grade 3-4 ADRs	%	36	N/A	
Infections	Grade 3-4 ADRs	%	44	N/A	

Abbreviations: ADRs: adverse reactions; CR: complete remission; DOR: duration of remission; N/A: not applicable; ORR: Overall remission rate
Notes: [1] CR (complete remission) was defined as <5% of blasts in the bone marrow, circulating blasts in blood should be <1%, no evidence of extramedullary disease, and full recovery of peripheral blood counts (platelets >100,000/μL and absolute neutrophil counts [ANC] >1,000/μL) without blood transfusion.
[2]CRi (complete remission with incomplete blood count recovery) was defined as <5% of blasts in the bone marrow, circulating blasts in blood should be <1%, no evidence of extramedullary disease, and without full recovery of peripheral blood counts with or without blood transfusion.

Table 73. Effects table for Kymriah in patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) after two or more lines of systemic therapy (data cut-off: 8 December 2017)

Effect	Short Description	Unit	Treatment N=165	Control	Uncertainties/ Strength of evidence		References
Complete response (CR)	Best CR per IRC review using the Lugano response criteria (Cheson et al. 2014)	%	24.2	Historical controls: SCHOLAR-1: 7% CORAL: 28.4% PIX301: 20%	Limitations of pivotal study Single-arm trial with historical control Limited sample size / Limitations of indirect comparisons Selection of population due to drop outs Impact of bridging chemotherapy on the outcomes		

Effect	Short Description	Unit	Treatment N=165	Control	Uncertainties/ Strength of evidence		References
Objective response rate (ORR)	Best ORR defined as a CR or PR per IRC review using the Lugano response criteria (Cheson et al. 2014) BOR was defined as the best disease response recorded from tisagenlecleucel until PD or start of new anticancer therapy.	%	33.9 (26.8, 41.7)	SCHOLAR-1: 26% CORAL: 40.3% PIX301: 30%	As above		
Duration of response (DOR)	Median DOR	months	Not Reached (10.0, Not estimable)		As above		
Unfavourable Effects DLBCL							
Cytokine release syndrome (CRS)	≥Grade 3	%	21.6	NA			
Neurological events	≥Grade 3	%	11.7	NA			
Tumor lysis syndrome	≥Grade 3	%	0.9	NA			
Infections	≥Grade 3	%	19.8	NA			

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

- ALL indication

The primary endpoint of the pivotal Study B2202 was met. A clinically meaningful and statistically significant ORR of 82.0% within 3 months post - Kymriah infusion was observed with the majority of patients experiencing deep responses as measured by MRD-negativity. This response rate considerably exceeds the response rates observed with clofarabine, blinatumomab or a combination therapy of clofarabine, cyclophosphamide and etoposide in a similar patient population. Furthermore, the

observed ORR is supported by time dependent endpoints with a median OS of 19.1 months with a median follow up of 22.1 months.

- DLBCL

In the DLBCL study C2201 based on the ITT analysis set that is considered the most relevant and conservative to estimate the effect of the treatment strategy, the complete response rate observed is in the range of what has been observed with other treatment modalities (CORAL studies). However, the duration of response is considered remarkable with more than 60% of responders still responding after a median follow-up of 19 months. Further strength of evidence is anticipated to be provided with agreed conditions.

For both indications serious and life-threatening AEs, in particular CRS, have been observed in most patients, in particular first eight weeks post- Kymriah infusion. These AEs are considered manageable with the appropriate risk minimisation measures in place.

3.7.2. Balance of benefits and risks

- ALL indication

Given the poor prognosis of patients with ALL, the treatment effect of Kymriah is considered clinically relevant, and has been demonstrated in the population in the single pivotal study that was submitted. The safety profile of Kymriah is acceptable in view of the therapeutic context, the observed benefits and the fact that any remaining uncertainties have been addressed.

The overall B/R of Kymriah for the ALL indication is positive.

- DLBCL indication

Whereas the efficacy of tisagenlecleucel in terms of ORR/CR was modest based on the most conservative analyses, the duration of response in complete responders is substantial and therefore clinically relevant in the patient population.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Kymriah for the treatment of paediatric and young adult patients up to 25 years of age with B cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse and for the treatment of adult patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) after two or more lines of systemic therapy is positive.

The CHMP endorses the CAT conclusion on the benefit-risk balance as described above.

The divergent position statement is appended to this report.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Kymriah is not similar to Xaluprine, Blincyto, Iclusig and Besponsa within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Kymriah is favourable in the following indication:

- Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (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 CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new

information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Key elements:

Availability of tocilizumab and site qualification

To minimise the risks associated with the treatment of KYMRIAH, the MAH must ensure that hospitals and their associated centres that dispense KYMRIAH are specially qualified in accordance with the agreed control distribution program.

The MAH must ensure on-site, immediate access to 4 doses of tocilizumab for each patient as CRS management medication prior to treating patients.

KYMRIAH will only be supplied to hospitals and associated centres that are qualified and only if the healthcare professionals involved in the treatment of a patient have completed the educational program.

The availability of tocilizumab at all hospitals and associated centres must be ensured by the MAH until an authorised treatment for CRS is available in the EU.

Educational program – Prior to the launch of KYMRIAH in each Member State the MAH must agree about the content and format of the educational materials with the National Competent Authority.

HCP Educational program

The MAH shall ensure that in each Member State where KYMRIAH is marketed, all HCPs who are expected to prescribe, dispense, and administer KYMRIAH shall be provided with a guidance document to:

- facilitate identification of CRS and serious neurologic adverse reactions
- facilitate management of the CRS and serious neurologic adverse reactions
- ensure adequate monitoring of CRS and serious neurologic adverse reactions
- facilitate provision of all relevant information to patients
- ensure that adverse reactions are adequately and appropriately reported
- ensure that detailed instructions about the thawing procedure are provided
- before treating a patient ensure that 4 doses of tocilizumab for each patient are available on site

Patient Educational program

To inform and explain to patients

- the risks of CRS and serious neurologic adverse reactions, associated with KYMRIAH
- the need to report the symptoms to their treating doctor immediately
- the need to remain in the proximity of the location where KYMRIAH was received for at least 4 weeks following KYMRIAH infusion
- the need to carry the patient alert card at all times

- **Obligation to conduct post-authorisation measures**

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

Annex II condition wording	Due date
Non-interventional PASS: In order to further characterise the safety including long-term safety of Kymriah, the applicant should conduct and submit a study based on data from a disease registry in ALL and DLBCL patients.	Update reports: Annual safety reports and 5-yearly interim reports Final report of study results: December 2038
PAES: In order to further evaluate the efficacy and safety of Kymriah in ALL patients below the age of 3 years, the applicant should conduct and submit a study based on data from a disease registry in ALL patients.	Update reports: Included as part of the annual reports of the non-interventional PASS Final report: Dec 2023
PAES: In order to further evaluate the efficacy of Kymriah in patients with relapsed/refractory DLBCL, the applicant should conduct and submit a prospective, observational study in patients with r/r DLBCL based on data from registry with efficacy outcome measures in line with study C2201, including details of the manufacturing turnaround time, (i.e. time from last relapse or confirmed refractory status, time from decision to treat, and time from leukapheresis to infusion).	June 2022
PAES: In order to further characterise long-term efficacy and safety of Kymriah in relapsed/refractory DLBCL, the applicant should submit the 24 months follow-up for patients in the main Cohort and 24 months follow-up of all infused patients from study C2201. In addition the applicant should submit the final CSR including 5 years of follow-up.	Updated reports: September 2019; November 2020 Final CSR: August 2023
PAES: In order to further characterise the long-term efficacy and safety of Kymriah in relapsed/refractory DLBCL, the applicant should submit the results of study CCTL019H2301 - open-label, Phase III study of Kymriah versus standard of care in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma.	June 2022

The CHMP endorses the CAT conclusion on the obligation to conduct post-authorisation measures as described above.

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

Not applicable.

New Active Substance Status

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

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

Appendix

1. Divergent position statement 28 June 2018

References

1. RARECARENet 2017. SEER Cancer Query System (Internet) Retrieved from http://www.rarecarenet.eu/rarecarenet/ (Accessed October 4th, 2017)

2. Sarkozy C. & Coiffier B. Diffuse large B-cell lymphoma in the elderly: a review of potential difficulties. Clin Cancer Res, 2013 Apr 1;19(7):1660-9.

3. Ghielmini M, Vitolo U, Kimby E et al. ESMO guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL). *Ann Oncol*. 2013; 24(3):561-76.

4. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature*. 2000; 403(6769):503-11.

5. Lenz G, Wright GW, Emre NC, et al. Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. *Proc Natl Acad Sci USA*. 2008; 105(36):13520-5

6. Ledbetter J, Rabinovitch P, June C, et al. Antigen-independent regulation of cytoplasmic calcium in b cells with a 12-kDa b-cell growth factor and anti-CD19. *Proc Natl Acad Sci USA*. 1988; 85(6):1897-901.

7. Stamenkovic I and Seed B. CD19, the earliest differentiation antigen of the B cell lineage, bears three extracellular immunoglobulin-like domains and an Epstein-Barr virus-related cytoplasmic tail. *The Journal of experimental medicine*. 1988; 168(3):1205-10.

8. Fearon DT and Carroll MC. Regulation of B lymphocyte responses to foreign and self-antigens by the CD19/CD21 complex. *Annual review of immunology*. 2000; 18:393-422.

9. Porter D, Levine B, Kalos M, et al. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N Engl J Med*. 2011; 365(8):725-33.

10. Katz BZ, Herishanu Y. Therapeutic targeting of CD19 in hematological malignancies: past, present, future and beyond. *Leuk Lymphoma*. 2014; 55(5):999-1006.

11. Uckun FM, Jaszcz W, Ambrus JL, et al. Detailed studies on expression and function of CD19 surface determinant by using B43 monoclonal antibody and the clinical potential of anti-CD19 immunotoxins. *Blood*. 1988; 71(1):13-29.

12. Pfreundschuh M, Kuhnt E, Trümper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2011; 12(11):1013-22.

13. Coiffier B and Sarkozy C. Diffuse large B-cell lymphoma: R-CHOP failure—what to do? *Hematology Am Soc Hematol Educ Program*. 2016; 2016(1):366-78.

14. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010; 28(27):4184-90.

15. Crump et al 2014 Crump M, Kuruvilla J, Couban, S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory agressive lymphomas: NCIC-CTG LY.12. *J Clin Oncol.* 2014; 32(31):3490-6.

16. Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Onc. 2015; 26 (Suppl 5):116–25.

17. Milone MC, Fish JD, Carpenito C, et al. Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. *Mol Ther*. 2009; 17(8):1453-64.

18. Berry CC, Nobles C, Six E et al. INSPIIRED: Quantification and Visualization Tools for Analyzing Integration Site Distributions. Mol Ther Methods Clin Dev, 2016 Dec 18;4:17-26.

19. Afzal S, Wilkening S, von Kalle C et al. GENE-IS: Time-Efficient and Accurate Analysis of Viral Integration Events in Large-Scale Gene Therapy Data. *Mol Ther Nucleic Acids*, 2017 Mar 17;6:133-139.

20. White RD, Glosson JA, Gordon DE, et al. Intravenous Safety Study in Rats Given Paramagnetic, Polystyrene Beads with Covalently Bound Sheep Anti-Mouse Immunoglobulin G (IgG). International Journal of Toxicology. Vol 14, Issue 4, pp. 251 - 265

21. Koblas T, Girman P, Berkova Z, Jirak D. Magnetic resonance imaging of intrahepatically transplanted islets using paramagnetic beads. *Transplant Proc*. 2005; 37(8):3493-5.

22. Roberts ZJ, Better M, Bot A et al. Axicabtagene ciloleucel, a first-in-class CAR T cell therapy for aggressive NHL. *Leuk Lymphoma*. 2017 Oct 23:1-12.

23. Tang XY, Sun Y, Zhang A. Third-generation CD28/4-1BB chimeric antigen receptor T cells for chemotherapy relapsed or refractory acute lymphoblastic leukaemia: a non-randomised, open-label phase I trial protocol. *BMJ Open*. 2016 Dec 30;6(12):e013904.

24. Dotan E, Aggarwal C, Smith MR. Impact of Rituximab (Rituxan) on the Treatment of B-Cell Non-Hodgkin's Lymphoma. *P & T*. 2010; 35(3):148-57.

25. Jeha S, Razzouk B, Rytting M et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute myeloid leukemia. *J Clin Oncol*. 2009; 27(26):4392-7.

26. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin lymphoma: The Lugano classification. *J Clin Oncol*. 2014; 32:3059-67.

27. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol*. 2014; 32:3048-58.

28. Crump M, Neelapu SS, Farroq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: Results from the international SCHOLAR-1 study. *Blood*. 2017; 130(16):1800-1808.

29. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. *Bone Marrow Transplant*. 2017; 52(2):216-21.

30. Fitzgerald JC, Weiss SL, Maude SL, et al. Cytokine release syndrome after chimeric antigen receptor T cell therapy for acute lymphoblastic leukemia. *Crit Care Med*. 2016;45(2):e124-31.

31. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med*. 2014; 371: 1507–17.

APPENDIX 1

DIVERGENT POSITION DATED 22 JUNE 2018

DIVERGENT POSITION DATED 22 JUNE 2018

Kymriah EMEA/H/C/4090

The below mentioned members of the CAT did not agree with the CAT's positive opinion recommending the granting of the marketing authorisation for Kymriah indicated for the treatment of:

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

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

The reasons for divergent opinion were the following:

All below mentioned members agree that for the ALL indication a positive benefit/risk has been established, and this indication is considered approvable. However, efficacy in the diffuse large B-cell lymphoma (DLBCL) indication has not been sufficiently established. The MAA for the latter indication is based on one single pivotal, single arm trial in patients with r/r DLBCL. As explained in the CHMP points to consider on application with one pivotal study (CPMP/EWP/2330/99), in the case of licensing based on one single pivotal trial, the results should be exceptionally compelling.

For the DLBCL indication, multiple factors complicate the contextualization of the data. These include the 1) uncertainties regarding the selection bias introduced by the high drop out of (poor prognosis) patients, 2) inability to adequately adjust for baseline characteristics in the indirect comparisons, 3) inability to establish DOR or PFS benefit due to the lack of published data in the historical controls, 4) lack of benefit on response rates and overall survival across the historical data sets for the ITT (enrolled) population.

Consequently, it is at present not possible to conclude on the efficacy of Kymriah (administered on top of bridging chemotherapy) compared to currently available therapies.

The risks of treatment, both identified and theoretical ones are substantial. The early safety findings include neurological adverse reactions and severe and life threatening cytokine release syndrome (CRS). Long-term safety issues are unknown.

Due to the high degree of uncertainty in the obtained efficacy results for the DLBCL indication, the potential benefit cannot be determined for this population. Thus, the benefit/risk cannot be established and is thus not positive. As a consequence of the above considerations, and the regulatory environment where both indications were submitted under the same application, the below mentioned delegates disagree with the granting of the marketing authorisation including both indications on the ground that the potential benefit is considered not to be sufficiently demonstrated for the DLBCL indication.

Helga Haugom Olsen (Norway)

Lisbeth Barkholt (Sweden)

Carla Herberts (Netherlands)

Paolo Gasparini (Italy)

Asterios Tsiftsoglou (Greece)

APPENDIX 2

DIVERGENT POSITION DATED 28 JUNE 2018

DIVERGENT POSITION DATED 28 JUNE 2018

Kymriah EMEA/H/C/4090

The below mentioned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation for Kymriah indicated for the treatment of:

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

The reasons for divergent opinion were the following:

All below mentioned members agree that for the ALL indication a positive benefit/risk has been established, and this indication is considered approvable. However, efficacy in the diffuse large B-cell lymphoma (DLBCL) indication has not been sufficiently established. The MAA for the latter indication is based on one single pivotal, single arm trial in patients with r/r DLBCL.

For the DLBCL indication, the results in the ITT population are not compelling; moreover the follow-up time is relatively short. Further, benefit is not established through the comparison of overall survival across the historical data sets for the ITT (enrolled) population.

Consequently, it is at present not possible to conclude on the efficacy of Kymriah (administered on top of bridging chemotherapy) compared to currently available therapies.

The risks of treatment, both identified and theoretical ones are substantial. The early safety findings include neurological adverse reactions and severe and life threatening cytokine release syndrome (CRS).

Due to the high degree of uncertainty in the obtained efficacy results for the DLBCL indication, the potential benefit cannot be determined for this population. Thus, the benefit/risk cannot be established as positive. As a consequence of the above considerations, and the fact that both indications were submitted under the same application, the below mentioned delegates disagree with the granting of the marketing authorisation including both indications on the ground that the potential benefit is considered not to be sufficiently demonstrated for the DLBCL indication.

Svein Rune Andersen (Norway)

Kristina Dunder (Sweden)

Johann Lodewijk Hillege (Netherlands)

Simona Badoi (Romania)

Concepcion Prieto Yerro (Spain

Daniela Melchiorri (Italy)

Sol Ruiz