NOVARTIS

Patient Safety & Pharmacovigilance

Tisagenlecleucel

CTL019

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Tisagenlecleucel
Product(s) concerned (brand name(s)):	Kymriah®
Document status:	Final
Version number:	8.1
Data lock point for this RMP	CCTL019B2202 cut-off: 13-Apr-2018 CCTL019C2201 DLP: 11-Dec-2018 CCTL019B2205J DLP: 24-May-2019 CTL019B2001X DLP: 13-Oct-2020 CCTL019E2202 DLP: 29-Mar-2021 PSUR cut-off date: 12-Aug-2022
Date of final sign off	01-Apr-2025

Rationale for submitting an updated RMP:

This current EU Safety Risk Management Plan (RMP) 8.1 has been updated to address comments from PRAC received in the context of procedure EMEA/H/C/004090/II/0092.

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v8.0
Part I	No changes
Part II	Module SVII.3: The language related to monitoring after infusion was updated in relevant sections aligned with latest SmPC
Part III	No changes.
Part IV	No changes.
Part V	The language related to monitoring after infusion was updated in relevant sections aligned with latest SmPC
Part VI	No changes
Part VII	Annex 4: No changes
	Annex 6: The language related to monitoring after infusion was updated in relevant sections aligned with latest SmPC

Other RMP versions under evaluation

No RMP versions are currently under evaluation.

Details of the currently approved RMP:

Version number: 7.1 (dated 18-Dec-2024)

Approved with procedure: EMEA/H/C/004090/IB/0090

Date of approval (opinion date): 14-Jan-2025

QPPV name: Dr Justin Daniels, PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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List of abbreviations

ADF	Apheresis Data Form
ADR	Adverse drug reaction
AE	Adverse event
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
AS	Apheresis site
ATC	Anatomical Therapeutic Chemical
B-ALL	B-cell acute lymphoblastic leukemia
BMI	Body mass index
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CI	Confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CNS	Central nervous system
COI	Chain of identity
CR	Complete response
CRS	Cytokine release syndrome
CRi	Complete response with incomplete blood count recovery
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DIN	Donor Identification Number
DLBCL	Diffuse large B-cell lymphoma
DLI	Donor lymphocyte infusion
DLP	Data lock point
DNA	Deoxyribonucleic acid
DOB	Date of birth
DOR	Duration of response
EBMT	European Society for Blood and Marrow Transplantation
EEA	European Economic Area
EFS	Event-free survival
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
FL	Follicular lymphoma
FPFV	First Patient First Visit
GMP	Good Manufacturing Practice
GTex	Genotype-tissue expression
GVHD	Graft-versus-host disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

HLH	Hemophagocytic lymphohistiocytosis
HSCT	Hematopoietic stem cell transplantation
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICU	Intensive care unit
ID	Identification
IFNγ	Interferon gamma
INN	International Nonproprietary Name
IPI	International Prognostic Index
ISBT	International Society for Blood Transfusion
IVIg	Intravenous immunoglobulin
LDH	Lactate dehydrogenase
LISA	Lentivirus insertion site analysis
MAP	Managed Access Program
MAS	Macrophage activation syndrome
mCAR19	Murine CAR19
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MMc	Maternal microchimerism
NA	Not applicable
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NIS	Non-interventional study
NK	Natural killer
NOD	Nondiabetic disease
NSG	Nondiabetic disease serious combined immune deficiency gamma
OR	Odds ratio
ORR	Overall response rate
OOS	Out-of-Specification
OS	Overall survival
PASS	Post-authorization safety study
PD	Pharmacodynamic
Penn	University of Pennsylvania
PFS	Progression free survival
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
PT	Preferred Term
qPCR	Quantitative polymerase chain reaction
r/r	Relapsed or refractory
RCL	Replication-competent lentivirus
R-DHAP	Rituximab, dexamethasone, high-dose cytarabine, and cisplatin
R-GDP	Rituximab, gemcitabine, dexamethasone, and cisplatin
R-ICE	Rituximab, ifosfamide, carboplatin, and etoposide
RMP	Risk Management Plan

RNA	Ribonucleic acid
RNAseq	RNA sequencing
RT-PCR	Real-time polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
scFv	Single chain variable fragment
SCID	Serious combined immune deficiency
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	Standard deviation
SEC	Single European Code
SEER	The Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
TKI	Tyrosine kinase inhibitor
TLS	Tumor lysis syndrome
TNFα	Tumor necrosis factor-alpha
UK	United Kingdom
US	United States
VSV-G	Vesicular stomatitis virus - G
WBC	White blood cell
WOCBP	Women of child-bearing potential

1 Part I: Product(s) Overview

Table 1-1 Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Tisagenlecleucel
Pharmacotherapeutic group(s) (ATC Code)	L01XL04
Marketing Authorization <Holder> <Applicant>	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Kymriah®
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Kymriah is an immunocellular therapy containing tisagenlecleucel, autologous T cells genetically modified *ex vivo* using a lentiviral vector encoding an anti-CD19 CAR.
	Summary of mode of action: Tisagenlecleucel is an autologous, immunocellular cancer therapy which involves reprogramming a patient's own T cells with a transgene encoding a CAR to identify and eliminate CD19 expressing malignant and normal cells. The CAR is comprised of a murine single chain antibody fragment which recognizes 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 antitumor 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.
	Important information about its composition: The product is formulated as a tisagenlecleucel dispersion at a batch-dependent concentration of autologous T cells genetically modified to express an anti-CD19 CAR (CAR-positive viable T cells). 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 in case of B-ALL also on the patient's body weight. The medicinal product contains per mL 2.43 mg sodium, 11 mg dextran 40, and 82.5 mg dimethyl sulfoxide.
Hyperlink to the Product Information	[Current SmPC]
Indication(s) in the EEA	Current: Kymriah is indicated for the treatment of: • Pediatric and young adult patients up to and including 25 years of age with B-ALL that is refractory, in relapse post-transplant or in second or later relapse.

	• Adult patients with r/r DLBCL after two or more lines of systemic therapy. • Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.
	Proposed: Not applicable
Dosage in the EEA	Current: Dosage in pediatric and young adult B-ALL patients: • For patients 50 kg and below: 0.2 to 5.0 × 10^6 CAR-positive viable T cells/kg body weight. • For patients above 50 kg: 0.1 to 2.5 × 10^8 CAR-positive viable T cells (non-weight based). Dosage in adult DLBCL patients: • 0.6 to 6.0 × 10^8 CAR-positive viable T cells (non-weight based). Dosage in adult FL patients: • 0.6 to 6.0 × 108 CAR-positive viable T cells (non-weight based).
	Proposed: Not applicable
Pharmaceutical form and strengths	Current: Dispersion for infusion. 10 mL – 50 mL per bag.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication: Pediatric and young adult relapsed or refractory B-cell acute lymphoblastic leukemia

2.1.1 Incidence

The incidence of ALL is relatively homogeneous across countries ranging between one and two cases per 100000 person-years. Acute lymphoblastic leukemia represents approximately 11% of all leukemias, but is the most common childhood acute leukemia, accounting for approximately 25% of cancers and 80% of all leukemias in children (Katz et al 2015, Siegel et al 2016). B-lineage ALL is the most frequent subtype diagnosed in 80% of patients (Czuczman et al 1999, Dugas et al 2003, Toft et al 2012) and about 20% to 30% of all newly diagnosed B-ALL develop r/r disease (Martin et al 2012, Teachey and Hunger 2013, Katz et al 2015).

In Europe, the highest ALL incidence rates are observed in Southern Europe and the lowest in Eastern Europe (Table 2-1).

Table 2-1 Incidence and prevalence of ALL

	Incidence rate per 100000			Prevalence; number of patients alive (year)		
Region/Country	**All ages**	**0-19 years**	**20-29 years**	**All ages**	**0-19 years**	**20-29 years**
Australia	1.6	2.8	0.7	-	-	-
Canada	1.4	3.6	0.4	-	-	-
Europe						
EU 28	1.42	2.9	0.6	15-year prevalence 60104 (2014)	34440	8369
Northern Europe (Iceland, Norway, Sweden)	1.68	3.0	0.5	1788*	1025	434
UK and Ireland	1.53	2.9	0.6	8176*	4685	1138
Central Europe (Austria, Belgium, France, Germany, Switzerland, The Netherlands)	1.57	3.0	0.7	22685*	12999	5512
Southern Europe (Italy, Malta, Portugal, Slovenia, Spain)	1.86	3.4	0.7	14252*	8166	3463
Eastern Europe (Poland, Slovakia)	1.20	2.3	0.4	5150*	2951	1251
United States	1.6	3.4	0.8	Complete prevalence 96213 (2016)	Complete prevalence 33713 (2016)	Complete prevalence 23552 (2016)

Source:

Australia. AIHW 2016. Age-adjusted to the 2001 Australian population (year 2012, cases: 356).

Canada. Canadian Cancer Registry. Age adjusted to 2011 Canadian population (year 2013, cases: 480).

Europe. RARECAREnet. Information comes from 18 European countries covering 39% of European population. The results are projected to the whole EU based on the population in each country. Calculations are based on new cases diagnosed during 1995-2002. Rates per region are age-adjusted to the 2008 European population. Estimated new cases in 2014: 7383. Incidence rates per European region and age were calculated based on data from Cancer Incidence in five Continents (International Agency for Research on Cancer).

(*) The number of patients was calculated according to the proportion of population in each European region in 2014. Total 2014 EU population was about 506 million (Eurostat). Prevalence in the EU 28 in 2014 was 1.19 per 10000. Number of prevalent pediatric and young adult patients in Europe is calculated assuming same age distribution as in the 15-year US prevalence (57.3% of patients are 0-19 years old and 24.3% 20-29 years old).

US. Age-adjusted to the 2000 US standard population (period 2000-2016). The number of estimated new cases in 2019 is 5930 (SEER CanQues 2019; SEER 2019). Complete prevalence represents the number or proportion of people alive at a certain time who were diagnosed with ALL, regardless of how long ago the

diagnosis was made. Fifteen-year prevalence represents the number or proportion of people alive at a certain time who were diagnosed with ALL in the past 15 years.

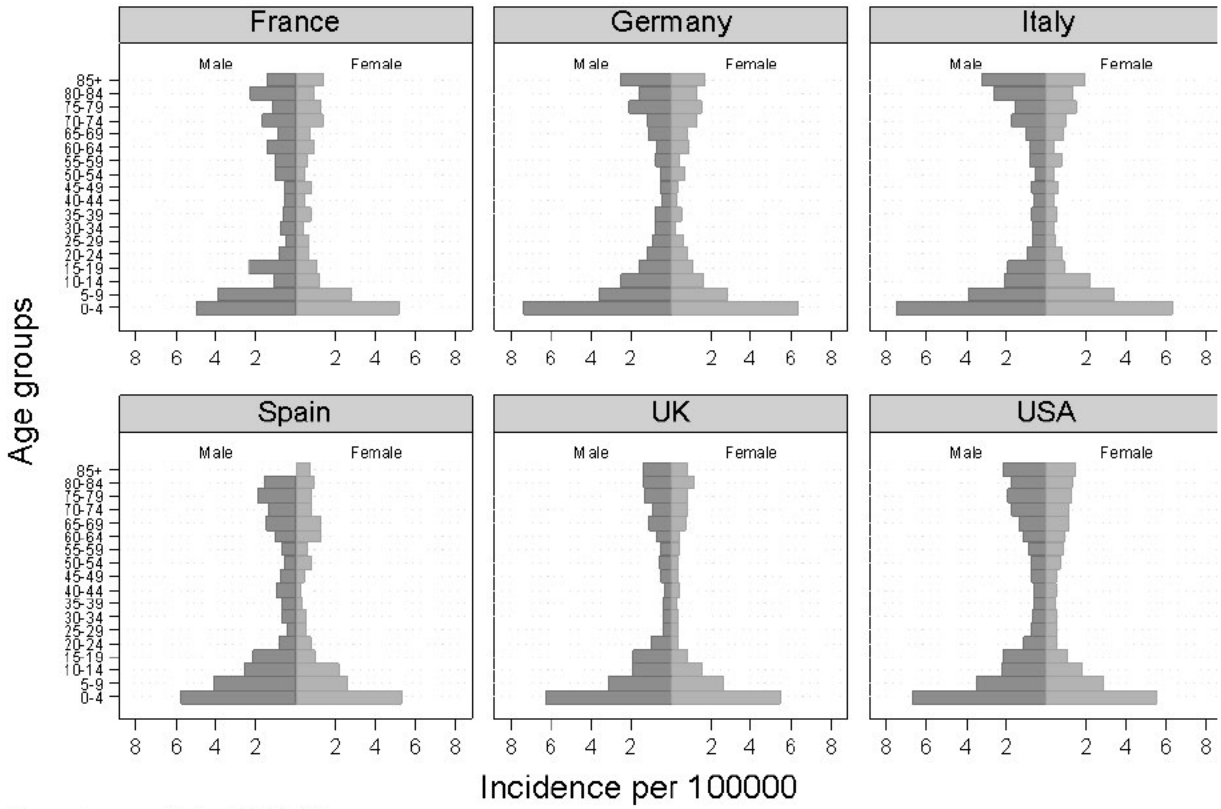
2.1.2 Prevalence

Acute lymphoblastic leukemia is a rare medical condition. In the 28 EU member states and based on data from RARECAREnet, the estimated 15-year prevalence in 2014 was 1.19 per 10000. The total number of people living with the disease was 60104 (Table 2-1). In the US, the complete prevalence in 2016 was estimated to be 2.99 per 10000 corresponding to a total of 96213 people living with the disease (SEER CanQues 2019).

2.1.3 Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease

Although ALL can occur at any age, it has a bimodal incidence and is more commonly seen in children with a peak incidence between 2 and 5 years (Pui et al 2008). The incidence rises again after the age of 60 (Howlader et al 2013). The overall incidence rate is between 1 and 2 per 100000 person-years but affects 3 to 8 per 100000 persons during the first decade of life and 1.5 to 4 per 100000 around the fifth decade of life. Approximately 60% of cases are diagnosed in patients younger than 20 years old, with a median age at diagnosis of 15 years. The incidence rate is slightly higher in males (ratio male/female: 1.13, 95% CI: 0.82 1.55). This age trend is consistently observed in EU countries and in the US (Smith et al 2011, SEER Stat Fact ref 2017, Siegel et al 2016) (Figure 2-1).

Figure 2-1 Age and sex distribution of ALL incidence

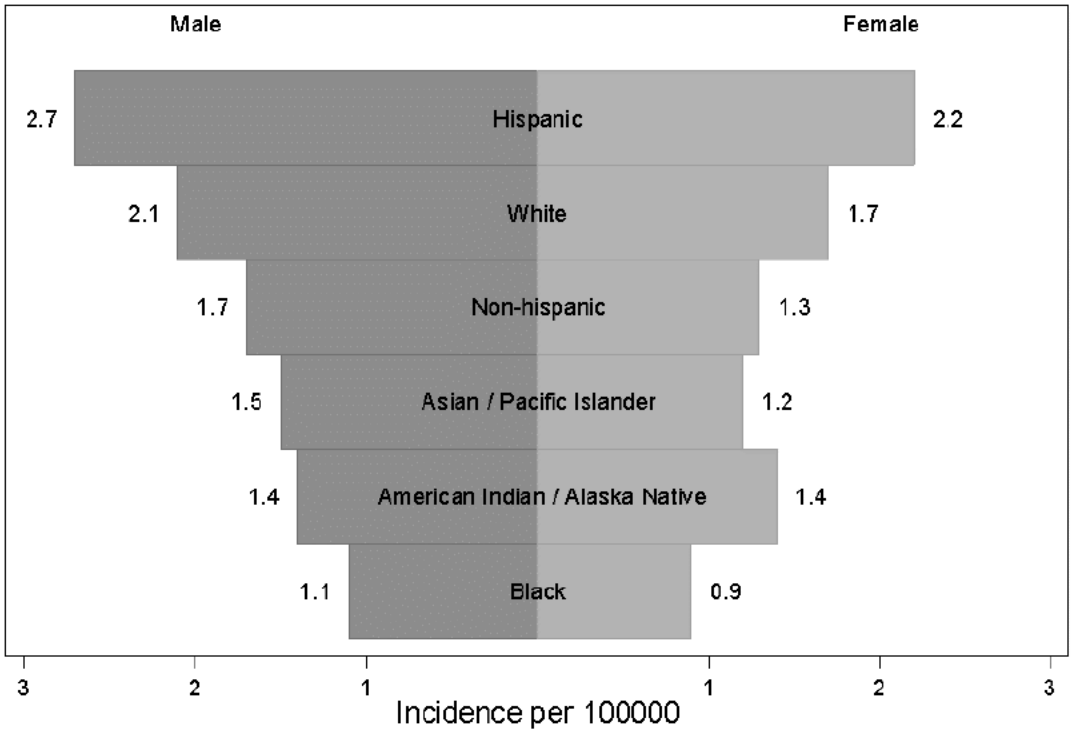


Cases diagnosed during 2003-2007

Source: International Agency for Research on Cancer.

The incidence of ALL varies also with race and ethnicity. Hispanic and white populations show usually higher rates. Across different races and ethnicities, a consistently higher incidence of ALL in males were reported (Figure 2-2).

Figure 2-2 Incidence of ALL according to race/ethnicity and sex



SEER 18 2010-2014, Age-adjusted rates
Source of data. SEER Stat Fact Sheets: Acute Lymphocytic Leukemia (ALL)

Source: SEER Stat Fact Sheets.

Initiation and progression of ALL are driven by successive mutations that alter cellular functions, including an enhanced ability of self-renewal, a subversion of control of normal proliferation, a block in differentiation, and an increased resistance to death signals (apoptosis).

The etiology of most cases of ALL is unknown. Risk factors associated with the development of ALL include (NCI PDQ 2019):

- Prenatal exposure to X-rays
- Postnatal exposure to high doses of radiation (e.g., therapeutic radiation as previously used for conditions such as tinea capitis and thymus enlargement)
- Previous treatment with chemotherapy
- Genetic conditions including Down syndrome, Neurofibromatosis, Bloom syndrome, Fanconi anemia, Ataxia telangiectasia, Li-Fraumeni syndrome, constitutional mismatch repair deficiency (biallelic mutation of MLH1, MSH2, MSH6, and PMS2), low- and high-penetrance inherited genetic variants, and carriers of a constitutional Robertsonian translocation involving chromosomes 15 and 21

Approximately 20% of children diagnosed with ALL will relapse. Demographic and clinical features, genetic features and response to treatment are factors associated with increased risk of relapse (Inaba et al 2013, Hunger and Mullighan 2015):

- Demographic and clinical features
  - Age: in children < 1 or ≥ 10 years

  - Sex: male
  - Race or ethnic group: black, native American, Hispanic
  - Initial white-cell count: $\geq 50000/mm^3$
- Genetic features
  - Cytogenetic: BCR-ABL1, mixed lineage leukemia rearrangements, hypodiploidy
  - Genomic: IKZF1 deletions or mutations, Philadelphia chromosome-like ALL with kinase gene alterations
- Response to treatment
  - Poor response to prednisone after one week of glucocorticoid therapy, marrow blasts $\geq$ 5% after one to two weeks of multi agent therapy
  - Persistence of minimal residual disease ($\geq$ 0.01%) during, at end of induction or after three to four months

The NCI/Rome relapse risk criteria divide B-ALL patients into two risk groups based on age and WBC counts. Infants younger than 1 year are a special subgroup of patients with worse outcomes (Smith et al 1996, Teachey and Hunger 2013):

- Standard risk with WBC $< 50 \times 10^9$/L and age 1.00 to 9.99 years
- High risk with WBC $\geq 50 \times 10^9$/L and/or age $\geq$ 10.00 years

Patients with NCI high risk B-ALL treated on Children's Cancer Group protocols from 1996 to 2002 had a 5-year EFS rate of 70% versus 81% for NCI standard risk B-ALL patients (Gaynon et al 2010).

Factors associated with induction failure that may indicate refractory disease are > 6 years old, high leukocyte count, leukemia with a T-cell phenotype, Philadelphia chromosome and 11q23 rearrangement (Schrappe et al 2012).

2.1.4 Main existing treatment options

Cure rates and survival outcomes have improved over time mainly in children. However, at least one-third of standard-risk patients and up to two-thirds of high-risk patients eventually experience relapse, which is still a major therapeutic challenge (Gokbuget et al 2016). Even though risk-stratified and more intensive frontline therapy exist, 20%–25% of children still relapse, thereby accounting for a large number of pediatric cancer patients and representing a major cause of death among children (Freyer et al 2011).

Re-induction of patients with relapsed B-ALL commonly includes conventional agents largely identical to those used at initial diagnosis. Allogeneic HSCT represents the sole potentially curative treatment modality to date, but it is only available to a highly selected group of patients. Allogeneic HSCT is associated with a 10%-20% risk of peri-transplantation mortality, depending on the donor type, and has a substantial relapse rate. The EFS ranges between 33% and 52% depending on the type of allogeneic HSCT (Ko et al 2010, Brandwein 2011, Martin et al 2012). In patients with relapsed disease after allogeneic HSCT, a second allogeneic transplant or DLI can be considered (NCCN ALL 2021). In a retrospective study on 214 children with ALL who received a second allogeneic transplant following relapse after their first allogeneic HSCT, the cumulative relapse rate was 47% and OS was 33% at 5 years (Yaniv et al 2018). For DLI, different studies report a median OS of less than 6 months and of 13% at 3 years, respectively; no patient achieved a complete remission with DLI alone and the

development of GVHD occurred as an important complication (reviewed in Loren and Porter 2008).

Newer chemotherapeutic treatments for r/r B-ALL comprise the purine nucleoside clofarabine (for patients 21 years old or younger after two prior regimens of chemotherapy) and a liposomal formulation of the vinca alkaloid vincristine (for adult patients with Philadelphia chromosome-negative B-ALL after second relapse or disease progression after two therapies) (NCCN pediatric ALL 2021, NCCN ALL 2021). Clofarabine has demonstrated an overall remission rate of between 20% as monotherapy and 44% to 76% in combination therapies, and an OS at 12 months of 20% to 33% (Table 2-2; Jeha et al 2006, Hijiya et al 2011, Locatelli et al 2009). High-dose vincristine sulfate liposome injection achieved an overall remission rate (CR and CRi) of 20% in adult patients and 25% in adolescent and young adult patients with r/r B-ALL, with a median OS of less than 5 months (O'Brien et al 2013, Schiller et al 2018).

Moreover, bispecific antibodies and antibody-drug conjugates are novel treatment options for subsets of patients with r/r B-ALL (Jammal et al 2020).

The bispecific T-cell engaging antibody blinatumomab is approved for both adult and pediatric patients with r/r B-ALL; in addition, it has been used for the eradication of minimum residual disease and as a bridge to transplant. In two randomized clinical trials in high-risk pediatric and adolescent/young adult patients with r/r B-ALL, blinatumomab was investigated in sequential combination with chemotherapy, as compared to chemotherapy alone, in high-risk patients with first relapse and before transplantation. One study only included patients less than 18 years of age and showed an EFS rate at two years of 66.2% in the blinatumomab group versus 27.1% in the control group, together with an overall hazard ratio for OS of 0.43 (Locatelli et al 2021). The other study included patients up to 30 years of age, and while no significant difference in the disease-free survival rate at two years could be demonstrated (54.4% in the blinatumomab group versus 39% in the control group), the hazard ratio for mortality was 0.62 (Brown et al 2021).

The CD22 antibody drug conjugate inotuzumab ozogamicin is only approved for adult patients with r/r B-ALL to date, while its use in the pediatric population is being investigated in clinical trials (Malard and Mohty 2020). In the randomized, multicenter, open-label Phase 3 INO-VATE trial, adult patients with r/r B-ALL achieved a CR/CRi rate of 73.8% and an OS of 7.7 months in the inotuzumab ozogamicin arm (versus 30.9% and 6.2 months in the standard of care arm), with a greater risk of veno-occlusive disease in the inotuzumab arm (Kantarjian et al 2019).

Table 2-2 Efficacy of available treatments for pediatric and young adult r/r B-ALL patients

	Clofarabine mono[1]	Clofarabine + etoposide + cyclo[2]	Clofarabine + etoposide + cyclo[3]	Blinatumomab[4]
Patients, N	61	25	17	70
≥ 3 prior regimens	62%	28%	NA	7%
ORR (CR+CRi)	20%	44%	76%	39%
Median OS	3.0 months	2.5 months	9.0 months	7.5 months
12 months OS	20%	30%	33%	40%

Early mortality (within 30 days)	25%	20%	NA	7%

Source: 1.Jeha et al 2006, 2. Hijiya et al 2011, 3. Locatelli et al 2009, 4. von Stackelberg et al 2016.

For Philadelphia chromosome positive B-ALL and for Philadelphia chromosome-like B-ALL, TKIs are important therapeutic options in the frontline setting as well as the r/r setting (NCCN ALL 2021).

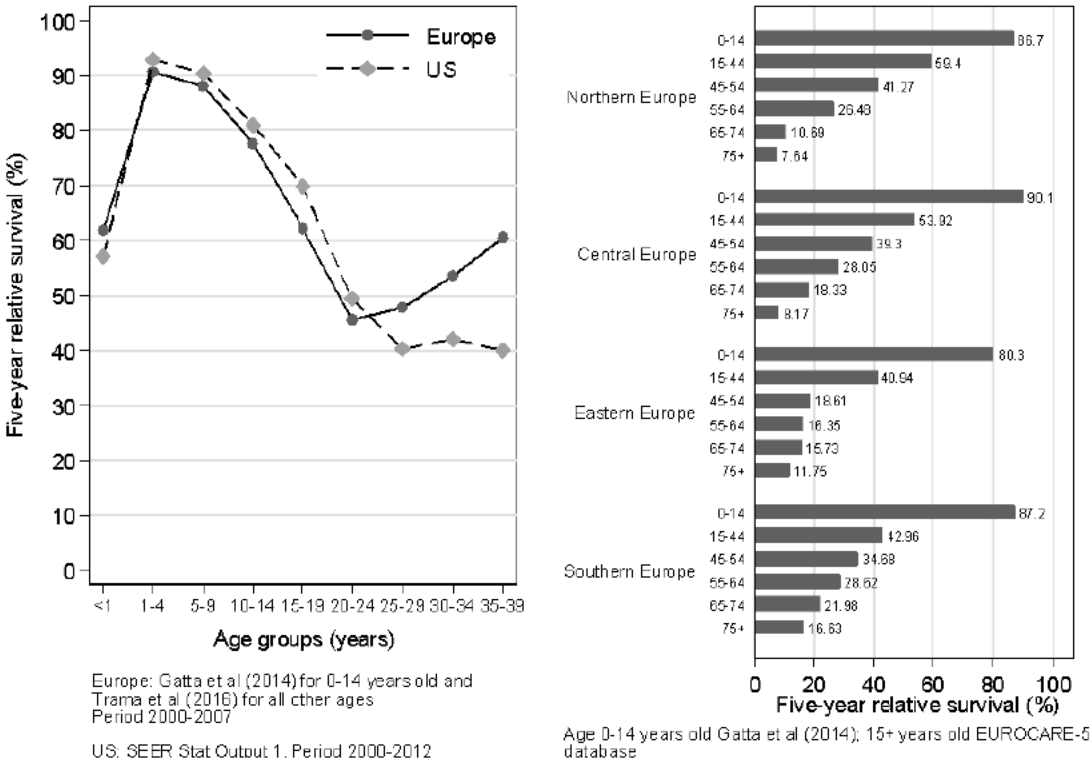
While there are a number of available therapeutic options for r/r B-ALL, there is no standard of care salvage therapy regimen.

2.1.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity

Mortality

Improvements of risk-adapted chemotherapy and supportive care over the past two decades have led to overall cure rates of newly diagnosed childhood ALL that are approaching 90% in many developed countries (Pui et al 2015). Survival is usually better at younger ages except for patients under one year old, who have worse outcomes (Figure 2-3).

Figure 2-3 Five-years survival of ALL according to age



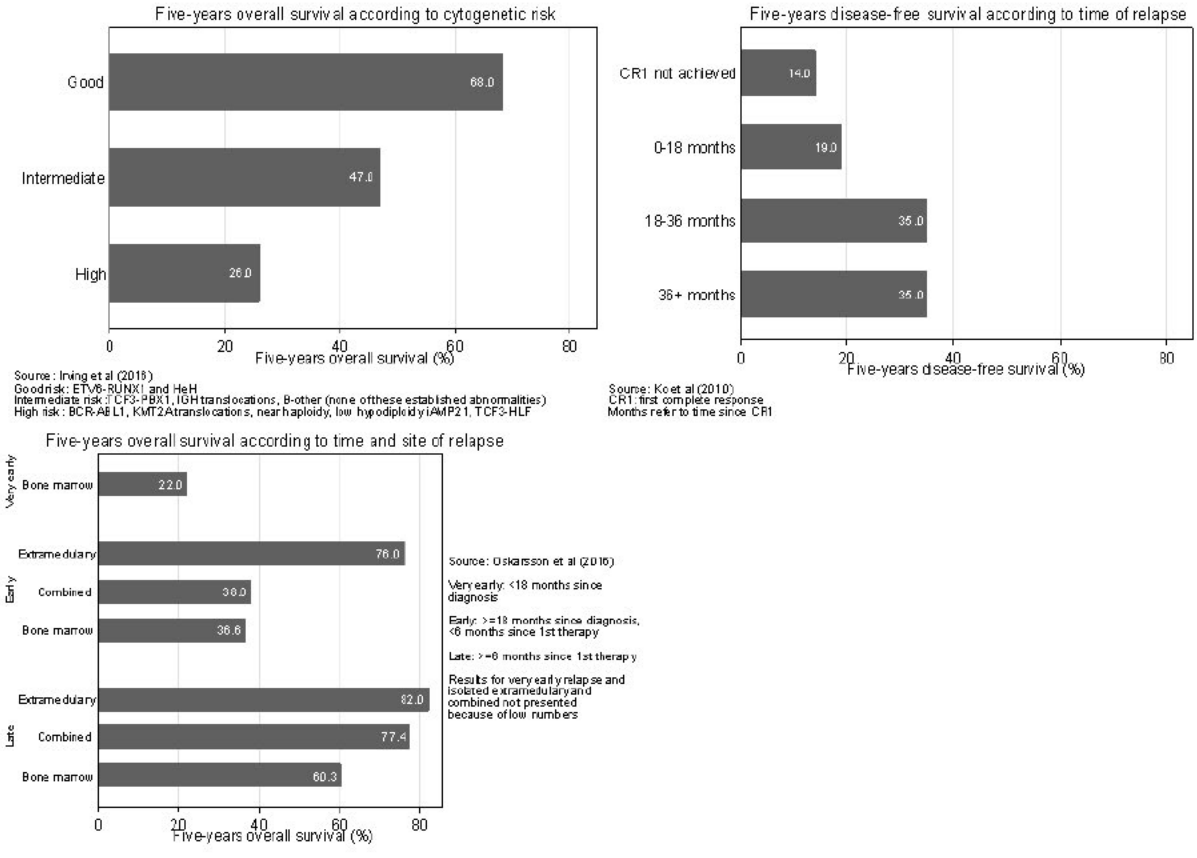
Source: Gatta et al 2014, Trama et al 2016, EUROCARE 5 database, SEER Stat Outputs.

Little progress has been made in the treatment of relapsed ALL in past decades. A study involving 1961 patients with relapsed ALL treated on Children's Oncology Group protocols between 1988 and 2002 found that survival of patients with first relapse was similar regardless

of early versus late treatment era (36.2% versus 36.6%) (Nguyen et al 2008, Bhojwani and Pui 2013). However, in more recent years, outcomes in patients with relapsed ALL have improved significantly. In the Nordic European countries OS was markedly higher for patients who relapsed between the years 2002-2011 (5 years OS 58%) compared to 1992-2001 (5-year OS 45%). This improvement may be related to a lower proportion of relapses occurring very early or early after primary therapy in the later period (Oskarsson et al 2016).

Time to relapse and site of relapse are the strongest predictors of post-relapse survival together with immunophenotype, cytogenetics and therapy response with minimal residual disease (Martin et al 2012, Bhojwani and Pui 2013, Eckert et al 2013, Irving et al 2016). Although factors such as age greater than 10 years, male sex, high-risk (according to the NCI Rome criteria) and CNS disease at diagnosis are associated with a poor response after relapse, these are not used clinically. In Figure 2-4, the outcome associated to different prognostic factors after relapse is presented.

Figure 2-4 Outcomes in patients with relapsed ALL according to prognostic factors



Source: Ko et al 2010, Irving et al 2016, Oskarsson et al 2016.

Morbidity

In patients with r/r B-ALL many different conditions may occur associated with the toxicity profiles of the therapeutic options. In a review (Hummel et al 2016) on AEs reported in clinical trials that included patients with r/r B-ALL (patients with HSCT were excluded; the review included 17 papers with at least 20 patients, nine studies with -Philadelphia chromosome negative r/r B-ALL patients) the following events were observed and classified according to the type of treatment:

- Chemotherapy and its combinations: Hematological AEs were most common (100% reported in 6 out of 9 studies), followed by infections (56%-100%). The most common gastrointestinal event was mucositis (20%-78%). Neurologic toxicity was the most common side effect associated with liposomal vincristine (8%-63%).
- Tyrosine kinase inhibitor-based treatments: Hematological events were very common (majority of studies 80%-100%), but infections were less frequently reported (9%-18%). Nausea, vomiting, and diarrhea are the predominant gastrointestinal AEs after receipt of TKIs (8%-29%).

Treatment related mortality or early/induction mortality was similar between both therapeutic options: chemotherapy 0%-30% (8 studies), TKIs 1%-27% (2 studies).

Life-threatening AEs in children and adolescents include TLS, thrombosis, bleeding, and infection:

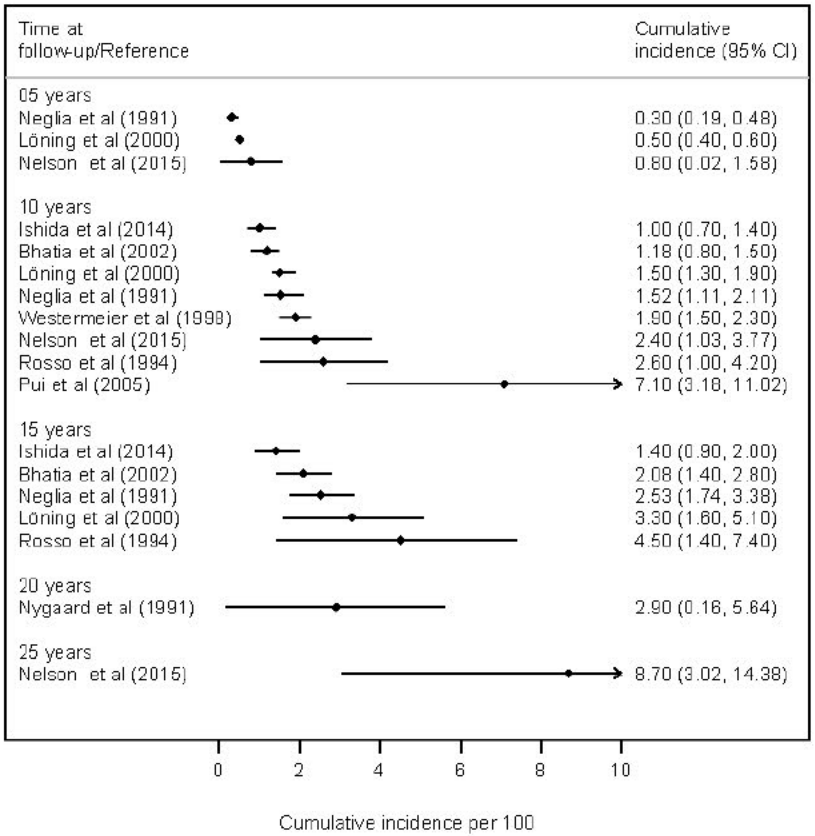
- TLS: In a study involving 328 children with ALL, 23% of patients met criteria for TLS (Truong et al 2007).
- Thrombosis: A meta-analysis of 1752 children with ALL reported that 5.2% patients developed a thrombosis at some time during treatment (i.e., from the start of induction through the end of maintenance). Most of these events (83%) occurred during induction therapy (Caruso et al 2006).
- Bleeding: Hemorrhage in children with ALL was usually caused by thrombocytopenia. Patients, who had platelet counts < 10000/µL, were at greatest risk (Chiaretti et al 2013). Children with thrombocytopenia typically had bleeding from the skin or mucus membranes.

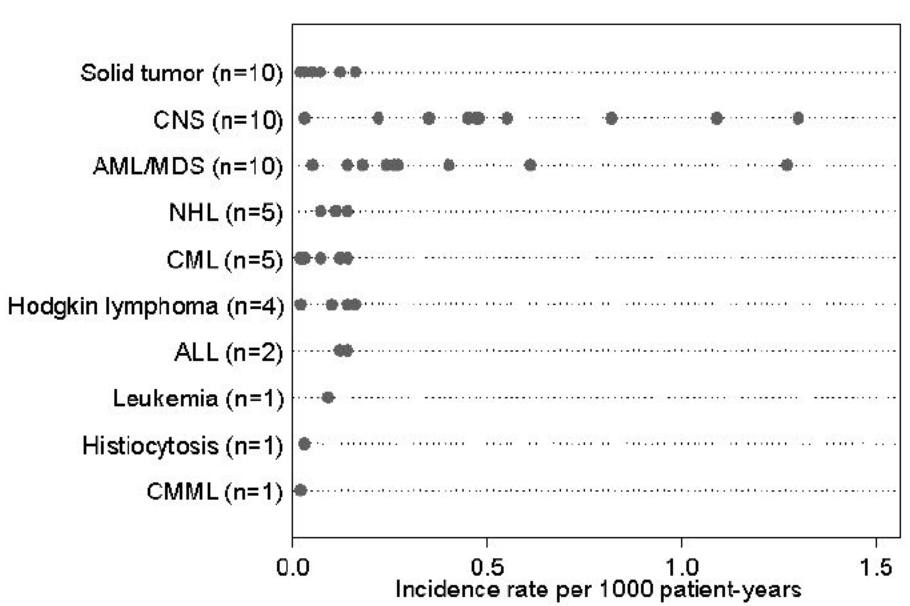
In a retrospective review, 19.5% of 425 children, who received induction therapy for ALL at a single tertiary Canadian center, experienced at least one microbiologically documented infection (Afzal et al 2009).

2.1.6 Important co-morbidities

The increase in the rate of survival observed in patients with childhood ALL comes with a significant long-term morbidity. Studies in long-term cancer survivors have shown that many patients have significant late effects due to their treatment, including subsequent risk of secondary malignancies, premature mortality, congestive heart failure, stroke, obesity, neurocognitive dysfunction, and osteonecrosis (Fulbright et al 2011, Essig et al 2014). Additionally, male and female pediatric ALL survivors have blunted fertility but no overall elevated risk for congenital anomalies in offspring (Fulbright et al 2011, Seppanen et al 2016).

Figure 2-5 Incidence of subsequent malignancies reported in childhood and young adults ALL survivors





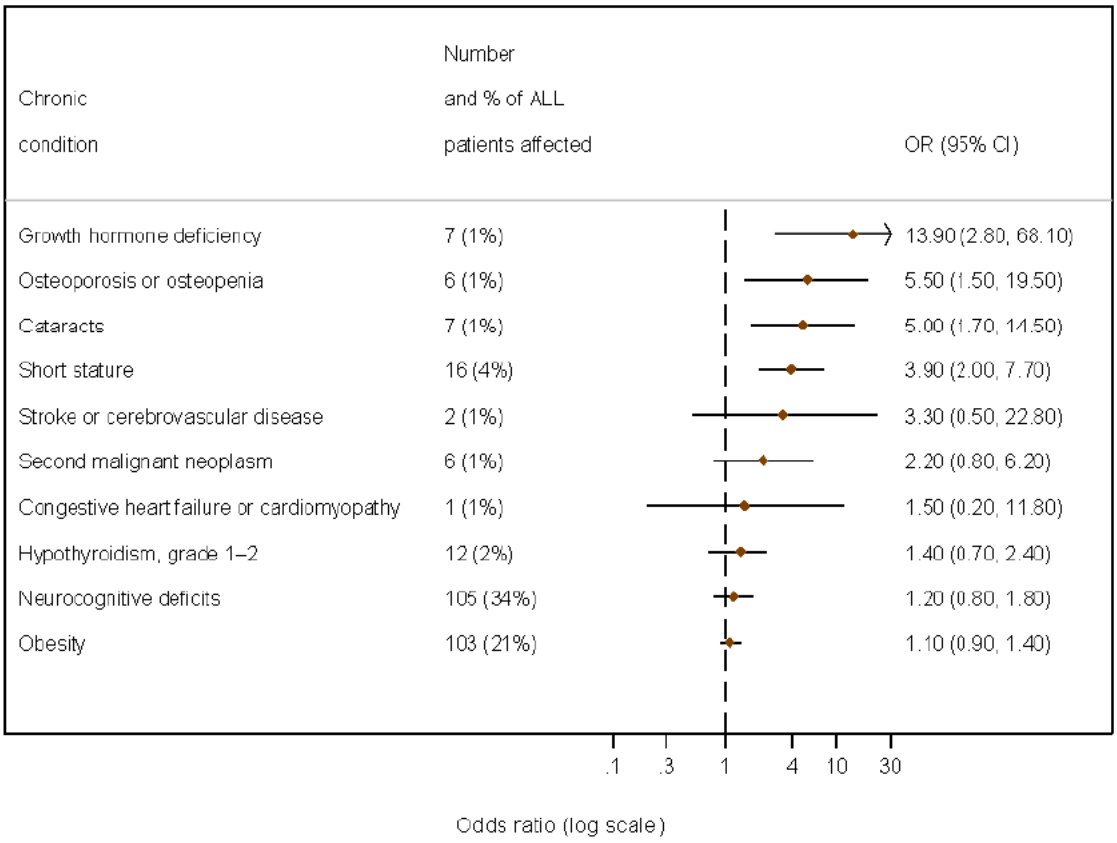
Only hematologic and central nervous system malignancies are reported individually
n refers to the number of studies reporting the incidence rate for the specific malignancy
Dots represent the incidence observed in each specific study

Source: Neglia et al 1991, Nygaard et al 1991, Rosso et al 1994, Westermeier et al 1998, Loning et al 2000, Nelson et al 2015, Ishida et al 2014, Bhatia et al 2002.

The risk of subsequent secondary malignancies when compared with the general population is increased; the standardized incidence ratio ranges between 3 and 27 (Perkins et al 2013, Nelson et al 2015). The incidence of subsequent malignancies following diagnosis of ALL in children is estimated to range from 0.69 to 5.76 per 1000 person-years across varied studies (Jenkinson et al 2004, Hijiya et al 2007). Central nervous system tumors, AML, and MDS are the most frequently reported new malignancies, although their incidence varies significantly across studies (Figure 2-5).

Other comorbidities observed in patients with previous ALL were analyzed based on data from the Childhood Cancer Survivor Study cohort (Essig et al 2014) including 556 patients treated for ALL and 2232 siblings. The risk of death was higher compared with the general population (standardized mortality ratio 3.5, 95% CI: 2.3–5.0) and 57% of deaths were due to causes other than recurrence of ALL. Patients with a previous ALL had a higher frequency of any chronic health condition when compared with siblings (odds ratio: 1.3; 95% CI: 1.1-1.6). In Figure 2-6, the incidence of different chronic disorders and their association with previous ALL is presented.

Figure 2-6 Chronic conditions observed in patients who survived ALL



Source: Essig et al (2014)
ORs compare ALL survivors with siblings
ORs adjusted for sex and age at response to questionnaire
Median follow-up of survivors 5 years after diagnosis was 18·4 years (range 0·0–33·0)

Source: Essig et al 2014.

2.2 Indication

Adult relapsed or refractory diffuse large B-cell lymphoma ineligible for autologous stem cell transplant

2.2.1 Incidence

Diffuse large B-cell lymphoma is the most common subtype of NHL constituting up to 30% of all cases (Sehn 2012).

The incidence per 100000 in 2013 in the EU was 3.44 and in the US 6.91; the incidence was relatively homogeneous across European regions (Figure 2-3).

Table 2-3 Incidence and prevalence of DLBCL

Country / region	Incidence per 100000 (year 2013)	Prevalence (number of patients alive, EU 28 in 2014 and US in 2017)
EU 28	3.44	145321
North Europe	2.48	2901
UK & Ireland	3.96	18056
Central Europe	3.88	56304
South Europe	3.44	36826
East Europe	2.03	18234
US	6.91	160373

Europe - Source RARECAREnet. In 2013, the number of new cases in the EU was 24377. RARECAREnet provides complete prevalence for 2008. To calculate 2014 complete prevalence the increase (1.4%) of the 15-year prevalence from 2008 (119296) to 2014 (120961) for the whole EU was applied to the 2008 complete prevalence. EU 28 population in 2014 according to Eurostat was 506,973,868 what gives a complete prevalence per 10000 of 2.87.

US - Source SEER Stat Outputs. In 2017, the number of new cases was 22570 (incidence in 2013 applied to population in 2017 according CDC Wonder 326,625,791). Prevalent patients in 2017 was obtained by applying the 38-year prevalence (4.91 per 10000; SEER Stat Outputs) to the US population in 2017.

2.2.2 Prevalence

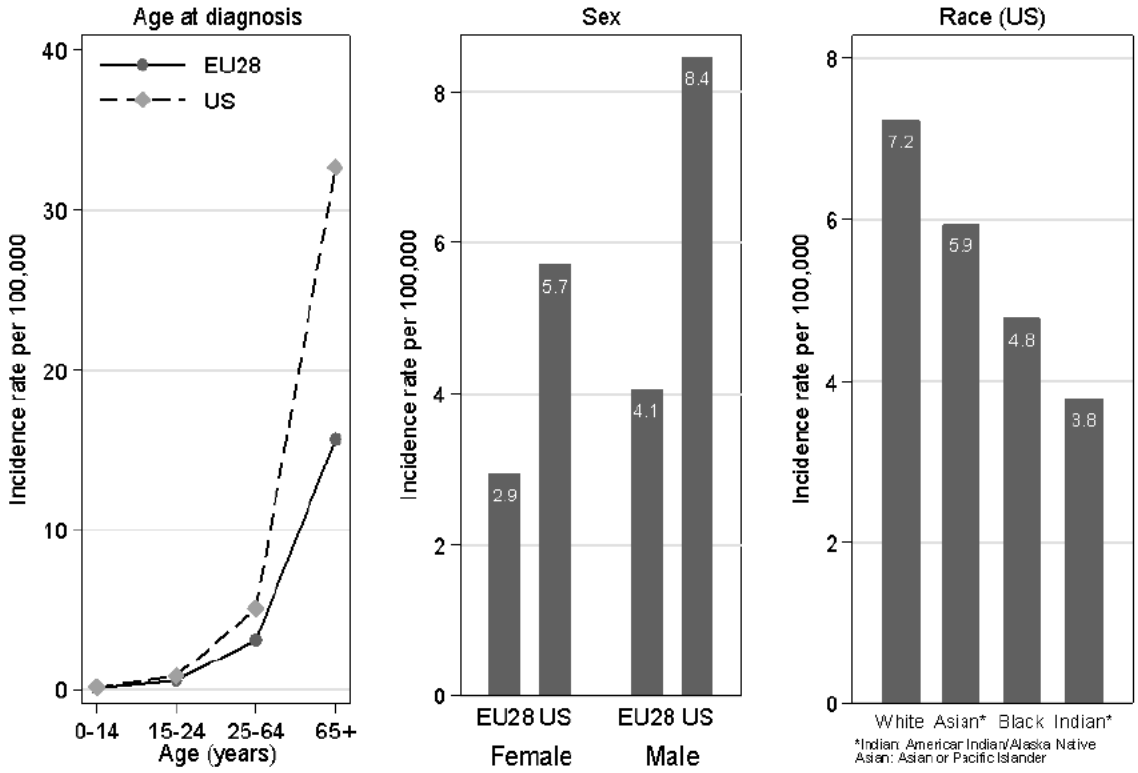
The prevalence per 10000 in the EU in 2014 was 2.87 and in the US in 2017 4.85 (Table 2-3).

Whereas outcomes in DLBCL have improved with the addition of rituximab, approximately 15%-25% of patients exhibit primary refractory disease (non-response or relapse within six months of therapy) and an additional 20%-30% relapse after initial response to therapy (Coiffier and Sarkozy 2016).

2.2.3 Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease

Age, gender, and ethnicity affect a person's likelihood of developing DLBCL. Although DLBCL has been found in people of all age groups, it is diagnosed most commonly in thosemiddle aged or elderly. The average age at the time of diagnosis is 64 years (Shenoy et al 2011). Men are at a higher risk of developing DLBCL than women, and white patients are at a higher risk compared with other races (Figure 2-7).

Figure 2-7 Demographic characteristics of patients with DLBCL



Source: for EU 28: RARECAREnet, for US: SEER Stats Outputs.

Risk factors for the disease

Several predictors of r/r DLBCL have been identified, including the IPI (The International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993, Sehn et al 2007, Zhou et al 2014) score at presentation, CNS involvement, immunoblastic histology, molecular markers such as c-myc and bcl-2, stromal signatures and results of interval positron emission tomography scan (Friedberg 2011).

Based on the number of negative prognostic features present at the time of diagnosis (age, Ann Arbor Stage III/IV disease, normalized LDH level, ECOG performance status ≥ 2, extranodal disease), four discrete outcome groups were identified; low (0-1), low-intermediate (2-3), high-intermediate (4-5), and high (6-8) (Zhou et al 2014).

2.2.4 Main existing treatment options

For r/r DLBCL patients, who are deemed eligible for high dose chemotherapy and autologous HSCT (approximately 50% of all r/r DLBCL patients), salvage therapy with rituximab and high dose platinum-based chemotherapy regimens (i.e., R-DHAP), R-ICE, R-GDP, followed by autologous HSCT is considered standard of care (Tilly et al 2015).

While approximately 50%-60% of patients with r/r DLBCL remain sensitive to conventional second line therapy, only about 30% will eventually proceed to autologous HSCT (Gisselbrecht

et al 2010, Crump et al 2014). To date, only a modest portion of patients undergoing autologous HSCT after salvage therapy are cured, and patients with high risk DLBCL, i.e., relapsing within a year from first line treatment, obtain a limited survival advantage by undergoing autologous HSCT (van Den Neste et al 2016).

Three new drugs have been approved for r/r DLBCL.

Tafasitamab, an anti-CD19 humanized monoclonal antibody, has been approved by the FDA and EMA in combination with lenalidomide for r/r FL and r/r DLBCL not eligible for autologous HSCT based on a second Phase 2 trial conducted in 81 patients, in which this combination showed an ORR of 60% and 43% CR. At 12 months follow-up, PFS was 16.3 months while OS and DOR were both not reached (Salles et al 2020).

Polatuzumab, a drug immunoconjugate targeting CD79b, has been approved by the FDA and EMA in combination with anti-CD20 (rituximab or obinutuzumab) and bendamustine for r/r DLBCL not eligible for autologous HSCT on the basis of a Phase 1b/2 trial (Sehn et al 2020) in which CR rate was 40%, with median PFS of 9.5 months, and median OS of 12.4 months.

In Jun-2020, FDA has given accelerated approval to selinexor, an oral exportin-1 inhibitor, for adult patients with r/r DLBCL after at least 2 lines of systemic therapy. The approval was based on a multicenter, single-arm, Phase 2 trial in patients with DLBCL after 2 to 5 systemic regimens. The ORR was 28%, with CR in 12% (Kalakonda et al 2020).

In addition to tisagenlecleucel, other CAR T-cell therapies have been approved by the FDA and other regulatory agencies for patients with r/r DLBCL (including high-grade B-cell lymphoma, primary mediastinal B-cell lymphoma, and transformed FL) after 2 prior lines of therapy based on data from single-arm Phase 2 trials. These studies demonstrated 40%-60% CR rates (Locke et al 2019, Schuster et al 2019). In the ZUMA-1 trial evaluating axicabtagene ciloleucel, approximately 60% of responding patients progressed, and median PFS was 5.9 months. Furthermore, the median DOR for those with incomplete responses was 1.9 months (Locke et al 2019).

The TRANSCEND trial investigating lisocabtagene maraleucel enrolled a broad range of patients with r/r large B-cell lymphomas, including high-risk features such as CNS involvement. The ORR was 73% with a complete response rate of 53%. At 18-month follow-up, 12-month DOR was 54.7% and 12-months PFS was 44.1% (Abramson et al 2020).

2.2.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity

Mortality

Patients with r/r DLBCL have a poor prognosis. If left untreated, r/r DLBCL has a life expectancy of 3 to 4 months, particularly those who do not respond to second line chemotherapy (Friedberg 2011).

The median OS of r/r DLBCL patients not eligible for autologous HSCT was reported in three European studies including France, Italy and the UK, and varied between 3.4 months and 10.8 months, while the median PFS ranged from 1.5 months to 8.8 months (Amorim et al 2016, Arcari et al 2016, Eyre et al 2016).

In the US, a retrospective series based on SEER-Medicare data that including 426 relapsed and 206 refractory patients 65 years old or older, observed a median OS of 16 months among relapsed patients and of 11 months among refractory patients (Danese et al 2017). Nagle et al (2013) reported a median survival in months from date of relapse among 56 adult patients who underwent autologous HSCT for relapsed or primary refractory DLBCL of IPI 0: 19.5 (n=12), IPI 1: 13.1 (n=15), IPI 2: 6.0 (n=13), and IPI 3-5: 3.4 (n=16).

Morbidity

Oncologic emergencies and treatment-related toxicities can occur in patients with r/r DLBCL.

While between 10% and 35% of patients have primary extranodal lymphoma at diagnosis, approximately 50% of patients develop extranodal disease (secondary extranodal disease) during the course of their disease. Potentially emergent complications are:

- Spinal cord compression: 0.1 to 6.5% of patients at the time of recurrence (Seo et al 2014)
- Pericardial tamponade: Cardiac involvement is observed in 10-20% of NHL. However, primary cardiac lymphoma is rare comprising only 0.5% of all lymphomas. More than 80% are diffuse B-cell and mostly are large cell type. Patients may present with signs of heart failure, arrhythmias, and/or pericardial effusion (Antoniades et al 2009).
- Hyperleukocytosis: Bone marrow infiltration by neoplastic circulating cells may occur in lymphomas, giving rise to a leukemic phase. Patients present with anemia, thrombocytopenia and leukocytosis. Extra nodal involvement is frequent (Muringampurath-John et al 2012)
- Lymphomatous meningitis and/or CNS mass lesions: CNS relapse ranges between 2% and 10% (Fletcher and Kahl 2014)
- Hyperuricemia and TLS: Observed in 19.6% (hyperuricemia) and 6.1% (TLS) of NHL patients (Annemans et al 2003)
- Severe hepatic dysfunction: Clinically apparent NHL infiltration of the liver at presentation occurs in 5%-14% of cases. In patients with advanced stages of NHL, the incidence may increase up to 60% (Ghobrial et al 2004)
- Venous thromboembolic disease: In patients with NHL thrombosis may occur in 11.6% of them (Caruso et al 2010)
- Severe autoimmune hemolytic anemia and/or thrombocytopenia: Patients with NHL are at an increased risk of autoimmune diseases such as autoimmune hemolytic anemia and immune thrombocytopenic purpura when compared with the general population; standardized incidence ratio 27.2 (95% CI: 21.5-34.0) and 7.5 (95% CI: 5.9-9.4), respectively (Fallah et al 2014).

Treatment-related hematologic toxicities are the most frequently reported events based on a systematic review of clinical trials (N=7) that included patients with r/r DLBCL (Colosia et al 2014). The frequency of events was:

- Leucopenia and neutropenia: 80%-90%

- Thrombocytopenia: 20%-50%
- Anemia: 0%-30%
- Febrile neutropenia: 5%-40%

Colosia et al (2014) also reported infection-related pneumonia as a common event in 49% to 71% of the cycles in two trials. In another trial included in Colosia et al (2014), infections were frequent (16% in both arms of the clinical trial).

Toxicity-related death occurred in two clinical trials:

- One patient treated with rituximab, ifosfamide, carboplatin and etoposide (R-ICE) (0.5%, 1 out of 197 patients) and in 3 patients treated with rituximab-dexamethasone high-dose ara-C platinol (R-DHAP) (1.6%, 3 out of 191 patients)
- One patient (4.5%, 1 out of 22) treated with mitoxantrone, etoposide and prednisone.

2.2.6 Important co-morbidities

Approximately 80% of patients over the age of 60 years with aggressive NHL have a comorbid condition at presentation compared to 48% in patients < 60 years of age (Janssen-Heijnen et al 2005a). The most prevalent comorbidities are cardiovascular disease (18%), hypertension (13%-32%), chronic pulmonary disease (9%-16%) and diabetes mellitus (7%-25%) (van Spronsen et al 1999, Janssen-Heijnen et al 2005b). Table 2-4 presents the prevalence of comorbidities reported across different studies in NHL patients in the US and the EU.

Patients with DLBCL have been reported to be at an increased risk of subsequent primary malignancies as compared to the general population. In a study using data from the population-based California Cancer Registry, among patients diagnosed with DLBCL between 2001 and 2012, who survived at least 1 year beyond diagnosis, the standardized incidence ratios (SIR) for subsequent AML, Hodgkin lymphoma, and solid tumors were 8.7 (95% CI: 6.62-11.22), 7.99 (95% CI: 4.57-12.98), and 1.08 (95% CI: 1.01-1.16) respectively. The cumulative incidence of subsequent malignancies was 5.41% (95% CI: 4.99-5.84) and 10.47% (95% CI: 9.74-11.22) at 5 and 10 years after the initial diagnosis of DLBCL. The most frequent types of solid tumors were lung cancer and prostate cancer. Among solid tumors, the increase in risk was highest for thyroid cancer and liver cancer with SIR of 2.27 (95% CI: 1.44-3.41) and 1.66 (95% CI: 1.12-2.37) respectively (Tao et al 2017).

Table 2-4 Comorbidities in patients with NHL

Comorbidity	Prevalence
Overweight (BMI 25-29) - Obesity (BMI ≥ 30)	37% - 32%[1]
Hyperlipidemia	32%[2]
Hypertension	13%[3] - 32%[1]
Cardiovascular disease	18%[3]
Diabetes mellitus	7%[4] - 25%[5]

Comorbidity	Prevalence
Renal failure men, women (creatinine > 140 mmol/L in men and > 105 mmol/L in women) - Renal disease	5% - 20%[4]
Anemia (hemoglobin < 12 g/dL)	19%[4]
Osteoporosis	13%[2]
Ongoing solid tumor/previous cancer	11%[2] - 19%[3]
Chronic pulmonary disease	9%[4] - 16%[5]
Hyperthyroidism – hypothyroidism	6% - 8%[2]
Gallstones (history)	8%[1]
Ulcer disease	4%[4]
Goiter	4%[2]
Dementia	3%[4]
Liver disease	2%[4]

Source: [1] Cerhan et al 2005; [2] Gebauer et al 2015; [3] van Spronsen et al 1999; [4] Thieblemont et al 2008; [5] Hester et al 2016.

2.3 Indication

Follicular lymphoma

2.3.1 Incidence

Follicular lymphoma is the second most common form of NHL, accounting for approximately 20%–30% of all NHL cases (Le et al 2019).

In Europe, the overall crude annual incidence of FL was 2.2 per 100000 population according to the HAEMACARE project (Sant et al 2010). The underlying study reported a lower age-adjusted (European) incidence in Eastern Europe (0.8 per 100000) than in Central Europe (2.5 per 100000) or UK and Ireland (2.2 per 100000). According to the population-based Haematological Malignancy Research Network in the UK, the age-adjusted (European) incidence of FL is 2.8 per 100000 (Smith et al 2015). In France, the world age-standardized rate of FL was estimated at 2.2 per 100000 persons per year during the period between 2000 and 2009 (Dandoit et al 2015).

In the US, an estimated 13960 FL cases were diagnosed in 2016, representing 12.4% of mature NHLs (Teras et al 2016). The age-adjusted incidence rate (2000 US standard population) of FL was 2.7 per 100000 persons per year based on data from 2014 and 2018 (SEER 2021). In Singapore, the age-adjusted (world) incidence rate was 1.0 per 100000 during 2008-2012 (Lim et al 2015), while the incidence in Japan was 1.1 per 100000 in 2008 (Chihara et al 2014) reported that.

The incidence of FL has been reported to be significantly lower in Asian and sub-Saharan African countries than in the Western world, which may be attributable to a combination of genetic and environmental factors and differences in life expectancy (Le et al 2019).

2.3.2 Prevalence

Compared with other cancers, there is little accurate information available on the total prevalence of hematological malignancy subtypes. This is partly because these complex cancers are identified using a combination of diagnostic tools, and this range and depth of data are difficult for cancer registries to access systematically (Li et al 2016).

Using data from the UK's specialist population-based register, the Haematological Malignancy Research Network, Li et al (2016) estimated that the observed prevalence (7-year prevalence) of FL was 18.5 per 100000 persons in 2011, while the total prevalence was estimated at 38.5 per 100000 persons. Using the same database, Smith et al (2015) estimated the 3, 5 and 10-year prevalence of FL at 9.7, 14.8 and 25.2 per 100000, respectively. In a study by Ekberg et al (2020) in Sweden, the 2-year prevalence was 7.1 per 100000, the 5-year prevalence was 16.9 per 100000, and the 10-year prevalence was 28.4 per 100000.

2.3.3 Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease

According to SEER data from 2013 to 2017, the median age of diagnosis of FL is 63 years (SEER 2021). FL is most commonly diagnosed in older individuals, with an increasing incidence from 35 years of age and peaking at 70 years (Carbone et al 2019). The distribution of age at the time of diagnosis is as below (SEER 2021):

- Approximately 0.4% of the patients diagnosed were under the age of 20 years
- 1.9% between 20 and 34 years
- 6.5% between 35 and 44 years
- 17.2% between 45 and 54 years
- 27.4% between 55 and 64 years
- 27% between 65 and 74 years
- 14.8% between 75 and 84 years
- 4.8% over 84 years of age.

The incidence of FL has been reported to be similar in males and females (Table 2-5). Among both men and women, the incidence is highest in white individuals as compared to other race/ethnic groups. Although the incidence of FL is lower in black populations, the average age of diagnosis is approximately five years younger in black patients than in white patients (Shenoy et al 2011).

Table 2-5 Incidence rates by race/ethnicity and sex adjusted to the US population

Race/Ethnicity	Men (/100000)	Women (/100000)
All races	2.9	2.5
White	3.2	2.8

Race/Ethnicity	Men (/100000)	Women (/100000)
Black	1.2	1.1
Asian/Pacific Islander	1.7	1.4
American Indian/Alaska Native	1.3	1.5
Hispanic	2.5	2.6
Non-Hispanic	3.0	2.4

Source: SEER 2021 (data from 2013-2017, age-adjusted)

In a study conducted across Spain, a total of 2099 adult patients were registered in 63 medical centers from 2014 to 2018. Distribution by sex was 44.5% male and 55.5% female, and the median age was 63 years (range: 16-98 years) (Bastos-Oreiro et al 2020). In a Danish cohort of 2773 FL patients in the rituximab era from 2000–2015, males (48.0%) and females (52.0%) were almost equally represented with the median age at diagnosis of 63 years (range: 19-97 years) (Madsen et al 2020).

Risk factors for the disease

Linet et al (2014) performed a large multivariate assessment of a broad range of putative risk factors for FL in 3530 cases and 22639 controls from 19 case–control studies in the InterLymph consortium.

The risk to develop FL was increased in persons:

- With a first-degree relative with non-Hodgkin lymphoma (OR = 1.99; 95% CI = 1.55 to 2.54); with greater body mass index as a young adult (OR = 1.15; 95% CI = 1.04 to 1.27 per 5 kg/m2 increase)
- Who worked as spray painters (OR = 2.66; 95% CI = 1.36 to 5.24)
- Among women with Sjögren syndrome (OR = 3.37; 95% CI = 1.23 to 9.19).

Lower risks to develop FL were observed in persons:

- With asthma, hay fever, and food allergy (ORs = 0.79–0.85)
- Who received blood transfusions (OR = 0.78; 95% CI = 0.68 to 0.89)
- With high recreational sun exposure (OR = 0.74; 95% CI = 0.65 to 0.86, fourth vs first quartile)
- Who worked as bakers or millers (OR = 0.51; 95% CI = 0.28 to 0.93)
- Who were university/higher education teachers (OR = 0.58; 95% CI = 0.41 to 0.83).

Elevated risks specific to women included current and longer duration of cigarette use, whereas reduced risks included current alcohol use, hay fever, and food allergies.

Approximately 85% of patients with FL have a t(14;18) chromosomal translocation which results in the overexpression of the BCL-2 protein, a member of a family of proteins that blocks apoptosis. However, it is likely that multiple genetic events are required for the development of

FL since the t(14;18) translocation can be identified in B cells from normal individuals and patients with DLBCL (Freedman and Jacobsen 2020).

2.3.4 Main existing treatment options:

Follicular lymphoma is considered incurable in most of the patients due to its relapsing remitting nature. Current therapeutic approaches in first line include 'watchful waiting', radiotherapy, and anti-CD20 monoclonal antibodies with or without chemotherapy. Patients with Stage II-IV FL are usually not cured with conventional treatment. Remissions can be attained, and multiple relapses are common. Treatment focuses on the alleviation of symptoms, reversal of cytopenias, and improvement of quality of life. While not curative, chemoimmunotherapy prolongs survival (Freedman and Jacobsen 2020). Patients relapsing within 2 years of therapy with rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone constitute approximately 20% of cases (Rummel et al 2013) with a median 5-year survival of only 50% (Casulo et al 2015).

Patients with r/r FL experience progressively shorter PFS to subsequent treatments, which decreases from 6.6 years after the first line of therapy to 1.5 and 0.83 years after the second and third line of therapy, respectively (Link et al 2019). Hence, the available data suggest need for novel therapies for r/r FL.

The therapeutic options of r/r FL include non-cross resistant agents (such as bendamustine-obinotuzumab), lenalidomide, PI3K inhibitors, and tazemetostat. These treatments showed a complete response rate of 8%-34%, thus failing to eradicate the disease in the majority of patients. Furthermore, the DOR > 6 months of treatments specifically indicated in the third or later line setting ranges between 18% and 30% (Salles et al 2017, FDA 2017, FDA 2018, Flinn et al 2019, Leppa et al 2019, FDA 2020).

Autologous and allogeneic HSCT present alternative treatment options in the r/r setting. Autologous HSCT does not result in significant OS benefit in patients with r/r FL when compared to those treated with conventional chemoimmunotherapy and PFS is around 1 year (Epperla and Hamadani 2017, Sesques et al 2020). Allogeneic HSCT, a potentially curative therapy, can be considered for a selected subgroup of patients with either refractory disease or early relapse. However, it is associated with high transplant-related mortality of 8%-17% at 1 year (Epperla and Hamadani 2017) and up to 25% at 3 years based on real world data from registries conducted EBMT and CIBMTR (Robinson et al 2013).

In Apr-2021, the anti-CD19 CAR T-cell therapy axicabtagene ciloleucel has been approved by FDA for the treatment of patients with r/r FL in the third or later line setting, showing an ORR of 91% and CR of 60% (Jacobson et al 2020).

2.3.5 Natural history of the indicated condition in the population, including mortality and morbidity

Follicular lymphoma is an indolent lymphoma with largely favorable outcomes, although some patients are at risk of disease progression and adverse outcomes (Carbone et al 2019).

In the rituximab era, the OS of FL patients has improved significantly (Freedman and Jacobsen 2020). Based on data from the Swedish Lymphoma Registry, the estimated 10-year OS from

2003-2010 were 90%, 78%, 68%, and 32% in the age groups 18-49 years, 50-59 years, 60-69 years, and ≥ 70 years, respectively (Junlen et al 2015). An analysis of US and French cohorts reported 10-year OS of 80% in the French and 77% in the US cohorts. However, lymphoma remained the primary cause of death with disease specific mortality of 10% at 10 years (Sarkozy et al 2019). In Spain, the OS at 2 years after diagnosis was 92% in patients with FL (Bastos-Oreiro et al 2020).

The clinical course in patients with FL can be very heterogeneous with some patients being safely observed over many years without ever requiring treatment compared to other patients having more rapidly progressive disease requiring multiple lines of treatment for disease control (Hanel and Epperla 2021). Patients with FL generally present with asymptomatic lymphadenopathy, which may wax and wane for years. Bone marrow involvement is present in at least 70% of patients, whereas involvement of other organs is uncommon. Less than 20% of patients present with B symptoms. Similarly, less than 20% of patients present with an increased serum LDH. One unique presentation of disease is in the intestine where FL is usually early stage and has a very favorable prognosis. Histologic transformation of FL to DLBCL occurs in 10% to 70% of patients over time, with a risk of 2% per year. Transformation is associated with rapid progression of lymphadenopathy, extranodal disease (besides the marrow), B symptoms, hypercalcemia, elevated serum LDH, high Follicular Lymphoma International Prognostic Index score, and non-response to initial therapy (Freedman and Jacobsen 2020).

Patients with FL have an increased risk of developing other medical conditions, such as infections (Carbone et al 2019) and secondary neoplasms (Giri et al 2017). According to a large population-based study in the US using the SEER database, the cumulative incidence of second primary malignancy is about 11% at 10 years (Giri et al 2017). During chemotherapy, infections are usually bacterial, however, with the use of immunotherapy such as rituximab, reactivation of HBV and other viral infections is possible (Carbone et al 2019).

2.3.6 Important co-morbidities

Given that the median age at the time of diagnosis of FL is above 60 years, it is expected that patients with FL will experience comorbidities that are common in the elderly. Kenzik et al (2018) used SEER data to identify individuals aged ≥ 66 years with incident FL (6109 patients), who were diagnosed between 2000 and 2011, to examine the long-term risk of congestive heart failure. Preexisting hypertension and diabetes were present in 79% and 19%, respectively. Congestive heart failure, cardiovascular disease/acute myocardial infarction were present in 7.6% and 7.1%, while any other comorbidity, including chronic renal failure, peripheral vascular disease, chronic obstructive pulmonary disease, liver disease, rheumatoid arthritis, gastric ulcers, paralysis, and acquired immune deficiency syndrome were detected in 25.5% of FL patients.

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

The classical toxicology program for low molecular weight or biological drugs was not conducted, because of the incompatibility of tisagenlecleucel with animal biology. Consequently, the majority of clinical risks discussed in Table 3-1, such as CRS, TLS, or neurological events, could not be assessed in non-clinical studies.

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Single and repeat-dose toxicity: The only animal model currently available to investigate genetically modified human T cells is the immunocompromised mouse model based on genetic manipulations leading to either the NSG or the NOD-SCIDβ2-/- phenotype. These mice can be successfully reconstituted with human lymphocytes without immediate rejection, because of an impaired immune system being devoid of murine T, B, and NK cells. They can be brought into a leukemic state by infusion of human leukemia cells (e.g., B-ALL), enabling the investigation of a number of efficacy and safety endpoints. The investigation in these immunocompromised mice assessed the uncontrolled cell growth of CAR vector transduced T cells, bio-distribution and persistence, which revealed no deviations of tisagenlecleucel in comparison to mock-transduced control T cells.	Cell dose-toxicity relationships derived from a study in immunocompromised mice, therefore data did not support the dose finding for clinical trials. The scope focused on cell growth control and distribution of cells into organs. This mainly supported the carcinogenicity risk assessment (see 'Genotoxicity/mutagenicity' and 'Carcinogenicity studies' below).
Genotoxicity/mutagenicity: Classical genotoxicity testing is not appropriate for assessing the risk of insertional mutagenesis. Tisagenlecleucel uses a third generation self-inactivating lentiviral vector. Insertional mutagenesis was addressed in two LISA studies where 12 batches of manufactured patient product ready for infusion and two batches of product manufactured from healthy donor cells were analyzed. The results indicate that there was no preferential integration near genes of concern, no preferential sites of integration (hot spots), and no preferential outgrowth of cells harboring integration sites of concern.	No such events were observed in the clinical trials to date.
Carcinogenicity studies Classical lifetime studies in rodents are not appropriate for genetically modified cell therapy products. However, in B-ALL xenografted mice,	Tisagenlecleucel is based on autologous, fully differentiated T cells and therefore the carcinogenicity risk is considered to be low in

Key Safety findings (from non-clinical studies)	Relevance to human usage
treatment with tisagenlecleucel (see 'single and repeat-dose toxicity') did not lead to uncontrolled T cell growth in mice kept for 6 to 7 months. A longer follow-up of animals in these immunocompromised mice is limited due to the shorter life expectation in comparison to wild type mice. In addition, in vitro, expansion studies with transduced T cells from healthy donors and leukemia patients did not reveal a transforming or immortalizing potential of the lentiviral vector. Oncogenicity due to transduction of tissue/cells by residual vector in the final product, or by generation of RCL, or by transduction of non-T cells during the manufacturing process is extremely unlikely, because of the self-inactivating vector construct and stringent design of manufacturing processes for both the vector (4-plasmid system) and the tisagenlecleucel product. For other details also refer to Section 7.2.7.2.	comparison to genetic modification or repair such as hematopoietic stem cells. In a review of CAR T-cell therapies, Bonifant et al (2016) as well as Mohanlal et al (2016) discussed that to date no cases of malignant transformation have been reported for genetic modification of T cells and there is no evidence for vector-induced immortalization, clonal expansion, or enrichment for integration sites near genes implicated in growth control or transformation. This is supported by the results of the LISA studies performed during the development of tisagenlecleucel (see 'Genotoxicity/ mutagenicity').
Tissue cross reactivity A murine CD19 CAR scFv (NVP-LYS631) equal to the one transduced into tisagenlecleucel cells was used for cross-reactivity testing in a human membrane surface protein array (Study 1470028). 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. CD19-specific immunohistochemistry and in situ hybridization on human and cynomolgus monkey tissues was conducted to contribute to the clarification of the pathogenesis of neurological events observed in clinical studies (Study 1420055). 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 demonstrate CD19 messenger RNA in the brain. Anti-CD19 human-scFv (from tisagenlecleucel) rabbit-Fc and anti-CD19 murine-scFv rabbit-Fc chimeric tool reagents were also developed. They detected CD19 on human cell lines and normal human tissue but did not produce a specific reaction in human brain tissue. In addition, real-time polymerase chain reaction (RT-PCR) analysis of the expression of 5 human and 3 cynomolgus CD19 splice variants in respective brain tissues was negative (Study 1420059).	Human CD19 is exclusively expressed on malignant and normal B cells, but not on B-cell progenitors and plasma cells. Consequently, no clinical effects related to cross-reactivity to cells/tissues other than B cells - normal and malignant - were reported thus far. Since in clinical trials, some patients showed transient effects on the CNS after receiving tisagenlecleucel infusion, the non-clinical investigation of CD19 expression in the brain was investigated (see left column). The non-clinical findings do not suggest a target directed activity of tisagenlecleucel in mediating CNS effects.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Cytokine release syndrome and Tumor lysis syndrome Due to the poor predictive nature of in vivo animal models, cytokine release was not assessed in the in vivo safety study in NSG mice. In this mouse safety study, there was no indication of TLS, most likely because the optimal tumor graft size in immuno-compromised mice is lower than the tumor cell load in patients.	Tumor lysis syndrome as well as CRS were clinically observed contemporaneously to tisagenlecleucel-cell expansion.
Neurological events No preclinical data are available. Due to the poor predictive nature of in vivo animal models, neurologic events were not assessed in the in vivo safety study in NSG mice. No other animal models have been studied. Tissue cross reactivity studies (see 'Tissue cross reactivity') and gene expression analysis using normal human brain tissues did not reveal expression of CD19 by CNS tissues. Thus, a direct effect of tisagenlecleucel on CNS tissue can be ruled out.	Cases of neurological events, mostly occurring concurrently with CRS, have been seen clinically
Hematopoietic cytopenias The NSG mice used in the non-clinical safety study generally show strongly reduced T, B-cell and NK cell counts due to their genetic manipulation, which make them irrelevant for assessment of lymphopenia. Red blood indices and platelet counts did not suggest a specific effect by tisagenlecleucel when compared to reference values of these mice. Neutrophils were not specifically monitored in the non-clinical NSG mouse study. However, WBC counts did not indicate any cytopenias in mice treated with tisagenlecleucel. No other animal models have been studied.	Cytopenias (neutropenia, leukopenia, lymphopenia and anemia) lasting > 28 days have been reported in clinical trials. Febrile neutropenia has been observed clinically in connection with both tisagenlecleucel and lymphodepleting therapy.
Graft-versus-host disease In a human B-ALL NOD/SCID-γc -/- murine leukemia xenograft study, αCD19-ζ and αCD19-BB-ζ (tisagenlecleucel) transduced viable T cells were administered in a 1:1 ratio in three T cell dose groups of both transduced and mock transduced cells, given intravenously three weeks after leukemia was established. Control groups were included to evaluate any vector-driven transformation and profile leukemia progression in the absence of therapy. Full necropsies were performed at planned sacrifice points of 42 and 56 days, respectively, post leukemia establishment as well as upon animal death or planned terminal sacrifice at Day 217. Unscheduled animal deaths	The likelihood of GVHD occurring in patients is low, but it is a potential risk with tisagenlecleucel therapy in patients with donor chimerism from a prior allogeneic HSCT. A study of activated DLIs (ex vivo activated cells collected from the donor and grown in the same fashion as tisagenlecleucel but without the CAR introduction) did not show high rates of GVHD (2/18 patients with grade 3 GVHD and none with grade 4) (Porter et al 2006). Of 18 ALL patients treated with autologous tisagenlecleucel therapy, who had relapsed after prior allogeneic HSCT with residual donor chimerism, none have developed GVHD after

Key Safety findings (from non-clinical studies)	Relevance to human usage
were attributed to GVHD and B-ALL tumor progression. The cause of death for animals after the second scheduled sacrifice was due to B-ALL tumor or to development of GVHD. At the highest T-cell dose of 20.0×10^6 cells, animals treated with untransduced T cell (mock) developed GVHD quickly. However, the animals treated with tisagenlecleucel presented with a lower incidence of GVHD, since tisagenlecleucel directly targeted CD19-positive tumor cells, thereby controlling leukemia. In general, the tisagenlecleucel treated group with tumor cells suffered less from GVHD than the mock treated groups. The non-clinically observed GVHD cases were a consequence of the study design, where human cells were exposed to a murine tissue environment. These cases are therefore not indicative of clinical GVHD cases.	autologous tisagenlecleucel infusion (Maude et al 2014). Long-term data on tisagenlecleucel are currently limited.
Prolonged depletion of normal B cells No adequate animal models are available, which would allow investigation of tisagenlecleucel in this context.	Transient or prolonged B-cell depletion is a risk with tisagenlecleucel therapy, since normal B cells express CD19. Loss of B cells can lead to hypo- or agammaglobulinemia, which can be supported with periodic IVIg infusions and other supportive measures.
Developmental and reproductive toxicity Developmental and reproductive toxicity studies were not conducted, because of the incompatibility of tisagenlecleucel with an animal tissue environment.	Not studied in clinical trials.

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

4.1.1 Exposure to tisagenlecleucel in B-ALL (CCTL019B2202, CCTL019B2205J, CCTL019B2001X), DLBCL (CCTL019C2201), and FL (CCTL019E2202)

This RMP contains safety information from pivotal Study CCTL019B2202 (hereafter referred to as 'B2202') that has been pooled with two supportive studies CCTL019B2205J (hereafter referred to as 'B2205J') and CTL019B2001X (hereafter referred to as 'B2001X') in addition to the pivotal studies CCTL019C2201 (hereafter referred to as 'C2201') and CCTL019E2202 (hereafter referred to as 'E2202'). The respective studies have been conducted in the following indications:

- **Pediatric/young adult r/r B-ALL – B2202+B2205J+B2001X**

At the data cut-off dates (B2202: 13-Apr-2018; B2205J: 24-May-2019; B2001X: 13-Oct-2020), 212 patients were treated with tisagenlecleucel.

- Study B2202 is a completed Phase 2, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric and young adult patients with r/r B-ALL. This trial has been the registration study in this indication.
- Study B2205J is a completed Phase 2, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients and young adult patients with r/r B-ALL.
- Study B2001X is a completed Phase 3b, single arm, multicenter trial to provide pediatric and young adult patients with r/r B-cell ALL access to tisagenlecleucel treatment after enrollment in Study B2202 trial was closed while either tisagenlecleucel marketing authorization, commercial product availability, or local reimbursement was still pending.

- **Adult r/r DLBCL – C2201**

Study C2201 is a completed Phase 2, single arm, multicenter trial to determine the efficacy and safety of tisagenlecleucel in adult patients with r/r DLBCL. This trial has been the registration study in this indication. At the data cut-off date 11-Dec-2018, 115 patients were treated with tisagenlecleucel.

- **Adult r/r FL – E2202**

Study E2202 is an ongoing Phase 2, single arm, multicenter trial to determine the efficacy and safety of tisagenlecleucel in adult patients with r/r FL. This trial has been the registration study in this indication. At the data cut-off date 29-Mar-2021, 97 patients were treated with tisagenlecleucel.

The distribution of exposure in studies B2202, B2205J, B2001X, C2201, and E2202 is displayed by age, gender, race, and ethnicity in Table 4-1. Exposure to tisagenlecleucel by dose for all three indications in addition to weight adjusted dose for B-ALL is presented in Table 4-2

Table 4-1 **Clinical trial exposure in pooled pediatric and young adult B-ALL studies B2202, B2205J, and B2001X, adult DLBCL Study C2201, and adult FL Study E2202, overall and by subgroup – Safety set**

	Pediatric and young adult r/r B-ALL B2202[#]+B2205J+B2001X	Adult r/r DLBCL C2201	Adult r/r FL E2202
	N=212 n (%)	N=115 n (%)	N=97 n (%)
Total number of patients infused	212 (100)	115 (100)	97 (100)
Age Group			
< 10 years	86 (40.6)	-	-
≥ 10 years to < 18 years	85 (40.1)	-	-
≥ 18 years	41 (19.3)	-	-
≥ 18 years to < 40 years	-	17 (14.8)	9 (9.3)
≥ 40 years to < 65 years	-	72 (62.6)	64 (66.0)
≥ 65 years	-	26 (22.6)	24 (24.7)
Gender			
Male	116 (54.7)	71 (61.7)	64 (66.0)
Female	96 (45.3)	44 (38.3)	33 (34.0)
Race			
White	162 (76.4)	98 (85.2)	73 (75.3)
Asian	19 (9.0)	10 (8.7)	13 (13.4)
Black or African American	4 (1.9)	4 (3.5)	1 (1.0)
American Indian or Alaska native	2 (0.9)	0	0
Unknown	10 (4.7)	2 (1.7)	0
Other	15 (7.1)	1 (0.9)	0
Missing	0	0	10 (10.3)
Ethnicity			
Hispanic or Latino	45 (21.2)	1 (0.9)	2 (2.1)
Not Hispanic or Latino	126 (59.4)	63 (54.8)	84 (86.6)
Not reported	22 (10.4)	42 (36.5)	11 (11.3)

	Pediatric and young adult r/r B-ALL B2202[#]+B2205J+B2001X	Adult r/r DLBCL C2201	Adult r/r FL E2202
Unknown	19 (9.0)	9 (7.8)	0

B2202 data cut-off date: 13-Apr-2018, B2205J data cut-off date: 24-May-2019, B2001X data cut-off date: 13-Oct-2020; C2201 data cut-off date: 11-Dec-2018; E2202 data cut-off date: 29-Mar-2021.
[#]In study B2202, post the data cut-off date (13-Apr-2018), one additional patient, PD [redacted] was infused with tisagenlecleucel (0.6×10^8 CAR-positive viable T cells; 3.6×10^6 CAR-positive viable T cells/kg) on PD [redacted] 2019 thus, a total of 80 patients were infused.
Source: [Annex 7 - Table 1-1.1]

Table 4-2 Clinical trial exposure overall and by dose in pooled pediatric and young adult B-ALL studies B2202, B2205J, and B2001X, adult DLBCL Study C2201, and adult FL Study E2202 - Safety set

	Pediatric/young adult r/r B-ALL B2202[#]+B2205J+B2001X	Adult r/r DLBCL C2201	Adult r/r FL E2202
	N=212	N=115	N=97
CTL019 transduced cell dose infused (10^8 cells)			
n	212	115	97
Mean	1.07	3.07	2.13
SD	0.848	1.189	0.981
Median	1.00	3.00	2.06
Minimum	0.01	0.10	0.10
Maximum	9.00	6.00	6.00
Weight adjusted CTL019 transduced cell dose infused (10^6 cells/kg), total N			
n	212	-	-
Mean	2.76	-	-
SD	1.500	-	-
Median	2.74	-	-
Minimum	0.01	-	-
Maximum	11.5	-	-
Weight adjusted CTL019 transduced cell dose infused (10^6 cells/kg), patients ≤ 50kg			
n	144	-	-
Mean	2.91	-	-
SD	1.373	-	-
Median	2.98	-	-

	Pediatric/young adult r/r B-ALL B2202#+B2205J+B2001X	Adult r/r DLBCL C2201	Adult r/r FL E2202
	N=212	N=115	N=97
Minimum	0.04	-	-
Maximum	7.32	-	-
CTL019 transduced cell dose infused (10^8 cells), patients > 50kg			
n	68	-	-
Mean	1.54	-	-
SD	1.158	-	-
Median	1.42	-	-
Minimum	0.01	-	-
Maximum	9.00	-	-

B2202 data cut-off date: 13-Apr-2018, B2205J data cut-off date: 24-May-2019, B2001X data cut-off date: 13-Oct-2020; C2201 data cut-off date: 11-Dec-2018; E2202 data cut-off date: 29-Mar-2021.
Weight adjusted dose for B2202, B2205J, and B2001X is based on weight used for manufacturing.
#In study B2202, post the data cut-off date (13-Apr-2018), one additional patient, PD [redacted] was infused with tisagenlecleucel (0.6 × 10^8 CAR-positive viable T cells; 3.6 × 10^6 CAR-positive viable T cells/kg) on PD [redacted] 2019 thus, a total of 80 patients were infused.
Source: [Annex 7 - Table 1-1.2].

4.1.2 Exposure to tisagenlecleucel in the clinical development program (excluding the pivotal studies B2202, C2201, and E2202)

CCI [redacted]

At the DLP 12-Aug-2022 of the Kymriah PSUR, reporting interval from 13-Aug-2021 to 12-Aug-2022 (hereafter referred to as 'PSUR'), the cumulative exposure of patients treated with tisagenlecleucel across various indications in the clinical development program (excluding the pivotal studies B2202, C2201, and E2202) is 871, including 434 patients in 14 completed studies and 437 patients in 5 ongoing studies. For further information, refer to the PSUR.

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Patients with HBV, HCV, and HIV infection	Patients in particular with active Hepatitis B (and to a lesser extent with active Hepatitis C infection) are at risk of viral reactivation and liver failure. Patients who are HIV positive have a risk of loss of HIV viral suppression. Currently, tisagenlecleucel is not manufactured for patients testing positive for active HBV, HCV and HIV. Investigations on measures to be taken to enable manufacturing for these patients are ongoing.	Yes	Not applicable.
Known hypersensitivity to tisagenlecleucel or to any component of the product formulation	There is a risk of severe and life-threatening to fatal hypersensitivity reactions upon exposure.	No	Routine pharmacovigilance and risk minimization are well understood.
Patients with active, uncontrolled infection	Resolution or control of infection prior to infusion of tisagenlecleucel is required.	No	In the post-authorization setting resolution of active uncontrolled infection prior to tisagenlecleucel infusion remains recommended
Pregnant women and WOCBP	The risk to a pregnant woman and her fetus is not known following tisagenlecleucel infusion. There is a theoretical potential for tisagenlecleucel cells to be transferred to the fetus, which may cause fetal toxicity including B-cell lymphocytopenia.	Yes	Not applicable.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Breastfeeding women	There is no data whether tisagenlecleucel may be transferred through breast milk, has an effect on the milk production in a lactating woman, or may have effects on the breastfed child.	Yes	Not applicable.
Children below 3 years of age	Early manufacturing experience in patients with r/r B-ALL < 3 years of age indicated manufacturing challenges based on leukapheresis (i.e., high manufacturing failure rate).	No	There is evolving manufacturing experience in patients < 3 years of age in the post-marketing setting. This age group is not expected to differ in the safety profile from patients ≥ 3 years and up to and including 25 years of age based on the consistent safety experience with tisagenlecleucel across a broad age range of children with r/r B-ALL. Notably, this age range is not relevant for the adult r/r DLBCL and adult r/r FL indications.
Active CNS leukemia and active CNS lymphoma	Risk-benefit and potential to exacerbate underlying CNS disease is not known.	Yes	Not applicable.
Patients with evidence of histologic transformation or FL grade 3B.	Evidence of histologic transformation or FL grade 3B would indicate that the hematological malignancy is progressing from indolent FL to DLBCL.	No	DLBCL would not be representative of the target indication FL.

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of ADRs that are rare and/or are delayed in onset, such as ‘generation of RCL’ or ‘secondary malignancies (including vector insertion site oligo/monoclonality)'. These ADRs are theoretically possible but have a remote probability.

The occurrence of 'generation of RCL' is highly unlikely, since elements are incorporated in the design of the lentiviral vector system that minimize vector recombination and generation of RCL. In addition, the vector used to transduce the product undergoes sensitive assays for detection of RCL before tisagenlecleucel cell product is released to the patient.

Adverse events of 'secondary malignancies (including vector insertion site oligo/monoclonality)' may only be detected with more patients exposed to tisagenlecleucel and longer duration of follow-up. In addition, the assessment of causality can be particularly difficult in these critically ill patients, where complications of the underlying disease and anti-cancer therapy (e.g., chemotherapy, radiation) present confounding factors.

Patients exposed to lentiviral vector based tisagenlecleucel therapy are intended to be followed for 15 years from the last infusion in the long-term follow-up PASS CCTL019A2205B (hereafter referred to as 'A2205B') enrolling patients treated in the clinical trial setting and in the PASS CCTL019B2401 (hereafter referred to as 'B2401') evaluating patients treated in the commercial setting (see Section 10.2).

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women Breastfeeding women	No pregnant or lactating women were included in the clinical development program
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	No dedicated PK-PD study to assess tisagenlecleucel in patients with hepatic impairment was performed, since tisagenlecleucel does not undergo hepatic metabolism or elimination. Similarly, no dedicated PK PD study in patients with renal impairment was performed, since tisagenlecleucel does not undergo renal elimination. To be included in the tisagenlecleucel clinical trial program patients had to have adequate renal, hepatic and cardiac function as described in the respective study protocols. Patients with a disease severity different from the inclusion criteria were not included in clinical trials. Patients were required to stop or complete immunosuppressive therapies within the protocol specified time frames.

Population with relevant different ethnic origin	Population from different ethnic origins were included in the clinical development program (refer to Table 4-1).
Subpopulations carrying relevant genetic polymorphisms	A total of eight pediatric patients with Down's syndrome were included in Studies B2202, B2205J, and B2101J.

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

Tisagenlecleucel is given as infusion at treatment centers qualified by Novartis. The estimated exposure is based on the records of product shipped to these centers. Since tisagenlecleucel administration in patients might have been delayed for various reasons or patients might have died during the shipping time, this exposure number could be slightly higher than the number of patients actually infused with tisagenlecleucel.

6.1.2 Part II Module SV.1.2. Exposure

At the DLP (12-Aug-2022) of PSUR, the estimated cumulative exposure of patients treated with tisagenlecleucel across the B-ALL and DLBCL indications in the post-marketing setting across regions includes:

- 6303 patients who received tisagenlecleucel meeting the final product release specification (Table 6-1).
- 594 patients who received tisagenlecleucel OOS final product, which was manufactured on the basis of a commercial prescription and did not meet the commercial release specifications (Table 6-2). Of note, the majority of OOS final products to treat patients in certain countries are provided within the ongoing dedicated OOS MAP CCTL019B2003I (hereafter referred to as 'B2003I') in which an estimated CCI patients were exposed to tisagenlecleucel.

For further details refer to PSUR.

Table 6-1 Estimated cumulative exposure to tisagenlecleucel from marketing experience to tisagenlecleucel by region and by indication

Region Indication	Cumulative exposure through 12-Aug-2022 (number of patients)
Worldwide	
Total	6303
B-ALL	1927
DLBCL	4302
FL	74
EU/EEA (excluding UK)	
Total	2233
B-ALL	529
DLBCL	1637

Region **Indication**	**Cumulative exposure through 12-Aug-2022 (number of patients)**
FL	67
CCI	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

Region Indication	Cumulative exposure through 12-Aug-2022 (number of patients)
CCI	

Table 6-2 Estimated post-marketing (non-clinical trial) exposure to OOS CTL019 by countries/region and indication

Indication	Cumulative exposure through 12-Aug-2022 (number of patients)
Worldwide	
Total	594
B-ALL	161
DLBCL	433
EU/EEA (excluding UK)	
Total	133
B-ALL	31
DLBCL	102

Indication	Cumulative exposure through 12-Aug-2022 (number of patients)
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]

Indication	Cumulative exposure through 12-Aug-2022 (number of patients)
CCI	

6.1.3 Exposure in completed and ongoing Managed Access Programs

Novartis and CCI include either Individual Patient Programs, Expanded Access Programs or French Temporary Authorization of Use. At the DLP (12-Aug-2021) of PSUR, the estimated cumulative exposure of patients treated with tisagenlecleucel in MAPs is CCI, including CCI patients in four completed MAPs and CCI patients in three ongoing MAPs.

At the DLP (12-Aug-2022), of note, the majority of OOS final products that were manufactured based on a commercial prescription are provided within the ongoing MAP B2003I, in which an estimated CCI patients were exposed at the DLP; the main exposure data of these patients has already been captured in Table 6-2.

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

Based on the nature of drug, mode of action and the fact that it will be administered only at treatment centers qualified by Novartis, there is no recreational or abuse potential for tisagenlecleucel.

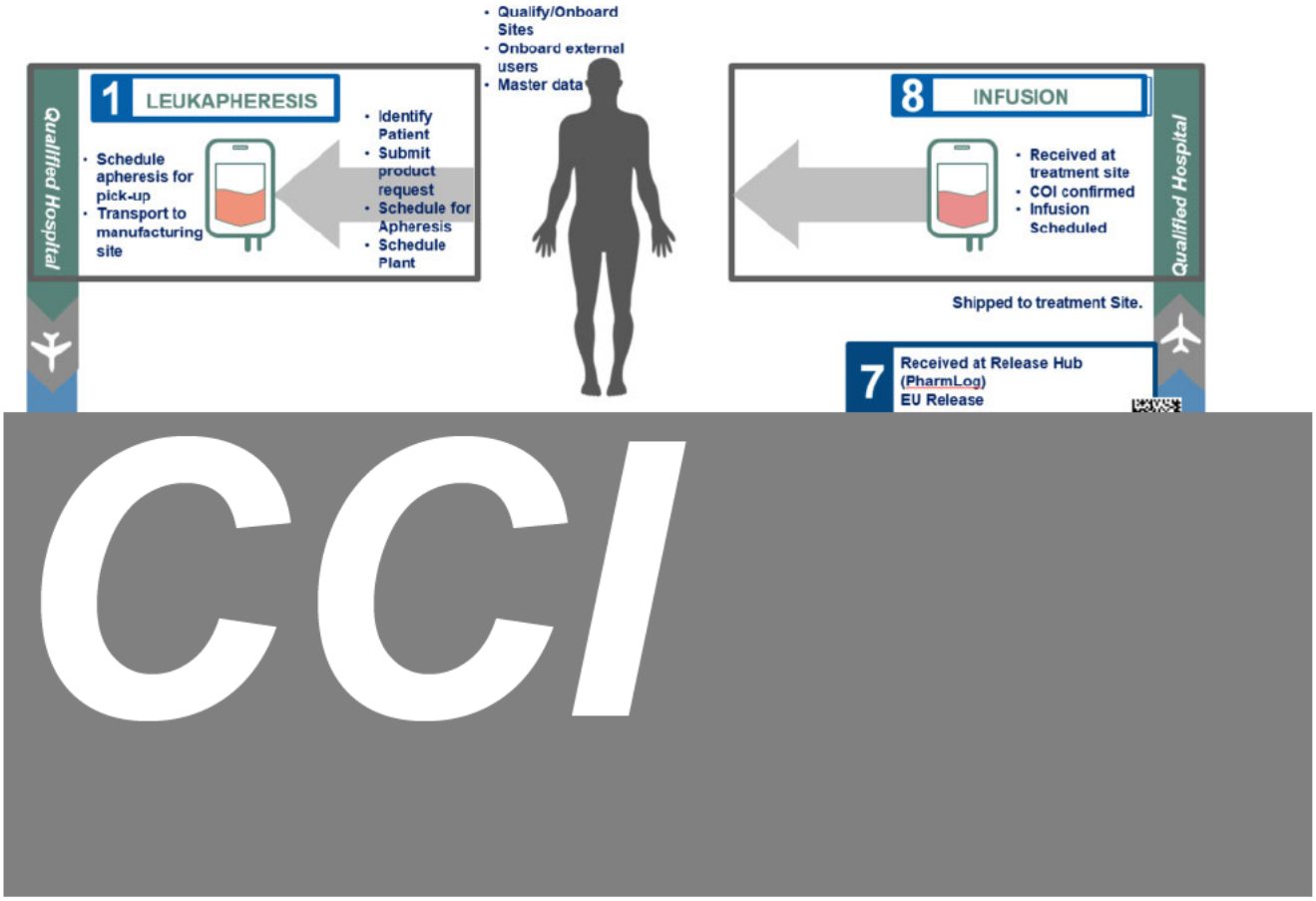
7.2 Specific risks of advanced therapy medicinal products

7.2.1 Flow-Chart of the logistics of the therapy

The logistics of tisagenlecleucel therapy are presented in Figure 7-1 below.

The main risk linked to the logistics of the product is related to the maintenance of the COI, since tisagenlecleucel is an autologous product. This section summarizes the controls in place to minimize risks with respect to the handling and collection of leukapheresis material and product COI until administration to the patient.

Figure 7-1 Leukapheresis collection, manufacturing, distribution of tisagenlecleucel



Tisagenlecleucel is an autologous product manufactured from the patient's own T cells collected by leukapheresis and cryopreserved prior to shipping to the manufacturing facility. The third party establishment ('center') that collects and processes the leukapheresis material from eligible patients is referred to as AS. The production of the leukapheresis material requires several steps including leukapheresis collection, processing (e.g., testing, cryopreservation), storage, and preparation for shipment. These steps typically involve a collection centre and a cell processing laboratory. The term AS will apply generically to the leukapheresis collection centre and to the cell-processing site.

The AS needs to be qualified by Novartis before any supplied leukapheresis material can be used for tisagenlecleucel manufacturing, as demonstrated by accreditations and licenses, according to Directive 2002/98, as well as based on their experience with the required processes. The AS should be actively implementing ISBT 128 labelling standards, including registration with the International Council for Commonality in Blood Banking Automation. Additionally, the qualification process includes the conduct of a site assessment by Novartis, and where necessary, the completion of a third party quality survey. The site assessment includes the evaluation of the AS for quality criteria such as the presence of a formal quality management system, personnel training and qualifications, business risks including experience and facilities, and material handling and storage. Only after the AS is considered qualified by Novartis, the site can be functional to support manufacturing. The implementation process includes any required training, equipment qualification, mock shipments, and logistical support. A dedicated COI system has been developed by Novartis to ensure traceability of the cells. This system is controlled by a validated computerized solution called CellChain, which provides a single, unique identifier for the final product, the Batch ID.

The Batch ID interlinks all of the patient identifiers, which may include the SEC that is generated at the time of leukapheresis collection by the AS according to Directive European Commission 2015/564 on requirements for the coding of human tissues and cells, the DIN for ISBT qualified sites or apheresis identity number (for non-ISBT qualified sites), patient name and patient DOB. An explanation of the entire CellChain COI system as well as the rationale for the use of ISBT and non-ISBT qualified sites is provided below. Access to CellChain is granted only to users at centers that have qualified or demonstrated the requirements of additional risk minimization measures (see Section 12.2.1).

A flow-chart detailing the logistics of tisagenlecleucel is presented in Figure 7-2.

CCI

CCI

CCI

CCI

CCI

CCI

7.2.2 Risks to living donors (where applicable)

The starting material for producing tisagenlecleucel are the patient's autologous (i.e., donor and recipient are the same) non-mobilized peripheral blood mononuclear cells collected by leukapheresis. The risks to the donor/recipient are the risks due to standard leukapheresis methods as no mobilization is taking place prior to collection.

7.2.3 Risks to patients in relation to quality characteristics, storage and distribution of the product

7.2.3.1 Transmission of infectious agents

Transmission of infectious material via product could potentially derive from the patient's own leukapheresis material prepared from autologous blood, other material including the tisagenlecleucel viral vector required to manufacture tisagenlecleucel, through contamination during the manufacturing process or inadequate storage. Therefore, the risk of transmission of infectious agents to close contacts including personnel involved in the tisagenlecleucel manufacturing process or health care providers involved in leukapheresis and administering tisagenlecleucel or patients treated with tisagenlecleucel is considered an important potential risk (see Section 8.3.1.1).

Accordingly, personnel involved in manufacturing and healthcare professionals involved in leukapheresis and administration of tisagenlecleucel infusion should employ appropriate precautions (e.g., wearing gloves and glasses) when handling leukapheresis material or tisagenlecleucel infusion to avoid potential transmission of infectious diseases as for any human-derived material.

The patient's cells after collection are shipped to the manufacturing facility frozen in the vapor phase of liquid nitrogen (< -120°C) and kept stored in these conditions until manufacturing.

All reagents of biological and human origin used in the manufacturing process are fully tested for adventitious agents in accordance with the relevant guidelines. Microbiological testing of the product is performed before release and shipping back to the patient.

7.2.3.2 Decrease in cell viability due to inappropriate handling of the product

Following manufacturing, each infusion bag (one individual treatment dose comprises 1 or more infusion bags) is placed into an aluminum cassette, then placed in an outer protective packaging. Tisagenlecleucel product must be stored and shipped frozen below -120°C, e.g., in a container for cryogenic storage (Dewar) in the vapor phase of liquid nitrogen. The product should be stored in the original cassette protecting the infusion bag.

Tisagenlecleucel product should be transported within the facility in closed, break-proof, leak-proof containers. It should not be irradiated.

The infusion bag(s) should be examined for any breaks or cracks prior to thawing. If an infusion bag appears to have been damaged or to be leaking, it should not be infused and should be disposed of according to local procedures on handling of biological waste.

The product should not be thawed until it is ready to be used. The timing of thaw and infusion of tisagenlecleucel should be coordinated. The infusion time should be confirmed in advance, and the start time for thaw adjusted so that tisagenlecleucel is available for infusion when the recipient is ready.

The infusion bag should be placed inside a second sterile bag during thawing to protect ports from contamination and avoid spills in the unlikely event of the bag leaking. Tisagenlecleucel product should be thawed at 37°C using either a water bath or dry thaw method, until there is no visible ice in the infusion bag. The bag should be removed immediately from the thawing device and kept at room temperature (20-25°C) until infusion.

Once tisagenlecleucel product has been thawed and is at room temperature (20-25°C), it should be infused within 30 minutes including any interruption during the infusion to maintain maximum product viability. If more than one infusion bag has been received for the treatment dose, the next bag should only be thawed after the contents of the preceding bag have been infused. Refer to the batch certificate for number of bags constituting one dose.

Tisagenlecleucel product should not be manipulated, such as washed (i.e., spun down and re-suspended in new media) prior to infusion.

Since tisagenlecleucel product contains genetically-modified human blood cells, unused medicinal product and all material that has been in contact with tisagenlecleucel (solid and liquid waste) should be handled and disposed in accordance with local guidelines on handling biological waste.

7.2.3.3 Manufacturing failure and manufactured product that is Out-of-Specification

In some cases, it may either not be possible to manufacture tisagenlecleucel or the release specifications are not met due to factors such as poor cell quality, patient characteristics, patient medical history, or manufacturing failure. In instances where the product cannot be manufactured or if the manufactured product is OOS, the treating healthcare professional will be informed as early as possible by Novartis in accordance with Section 11.5 of Volume 4 of the GMP guideline specific to Advanced Therapy Medicinal Products that appropriate measures for the safety of the patient can be taken (European Commission 2017).

Batch provision under exceptional circumstances may become necessary, if a tisagenlecleucel batch manufactured does not pass one or more release specifications (i.e., it is OOS). In the instance a tisagenlecleucel batch proves to be OOS, Novartis assesses the anticipated efficacy and safety risks pertaining to this respective OOS finding. The risk assessment will take into consideration prior experience with tisagenlecleucel infusion in clinical trials and/or the commercial setting as available and published literature. Importantly, the risk assessment does not provide infusion recommendations but is meant to inform the treating physician of the anticipated risks associated with a potential infusion of such OOS product.

The Novartis risk assessment is communicated to the treating physician to allow the physician to perform an independent evaluation of the anticipated benefit-risk of this OOS product and either request the product to be provided for infusion or consider alternative options, such as other anti-cancer treatment or re-manufacturing of a new batch (if feasible taking into account

the medical status of the patient). The infusion of OOS product needs to be carefully considered by the physician and a decision should be made based on the patient's clinical presentation and the anticipated benefit-risk associated with the specific OOS attribute. The supply and administration of the product should only occur to avoid any significant hazard to the life of the patient in the presence of a positive benefit-risk assessment by the treating physician.

The patients treated with such tisagenlecleucel OOS product in the post-marketing setting should be offered enrolment into one of the registries for cellular therapies for 15-year long-term follow-up.

The exceptional provision of OOS products is performed in line with national regulations.

7.2.4 Risks to patients related to administration procedures

Tisagenlecleucel is infused by intravenous infusion through latex-free intravenous tubing without a leukocyte depleting filter at approximately 10-20 mL per minute by gravity flow. If the volume of Kymriah to be administered is $\leq$ 20 mL, intravenous push may be used as an alternative method of administration.

Infusion may theoretically cause ADRs based on hemodynamic effects or the release of factors like cytokines through administration into the systemic circulation. There is literature reporting of clinical experience with administering large numbers of unmanipulated and ex vivo expanded hematopoietic human stem cells to patients requiring stem cell transplantation. This includes human stem cells harvested from multiple sources namely bone marrow, peripheral blood and umbilical cord.

From this experience, up to 9×10^7 ex vivo expanded umbilical cord blood cells have been safely infused per kg body weight (Delaney et al 2010) in an allogenic HSCT setting and no toxicities or other safety concerns were observed acutely during or after transplant. Thus, considering potential risks that may come from the infusion of large numbers of ex vivo expanded human stem cells, there is published clinical evidence in patients receiving ex vivo expanded allogeneic HSCT that the administration of up to 9×10^7 cells/kg is safe. Even higher cell doses of up to 4×10^9 cells/kg have reportedly been safely infused in the absence of ex vivo expansion in autologous mobilized peripheral blood stem cell transplantation (Weaver et al 1995). In a review, Gill and June (2015) discussed CAR T-cell therapy clinical trials run by different investigators with cell doses up to 5.5×10^7cells/kg, which would correspond to 3.9×10^8 cells per 70 kg patient. From these trials with high CAR T-cell counts, patients tolerated therapy well with most patients experiencing rigors, chills, and transient fevers within 24 hours of modified T-cell infusions. However, one patient experienced persistent fever, developed a sepsis-like syndrome with hypotension and renal failure, and died within 48 hours of T-cell infusion (Brentjens et al 2011). It is noteworthy that this CAR T-cell product differs from tisagenlecleucel, because it has the CD28 as a co-stimulatory domain in the CAR construct (19-28z+ T cells).

7.2.5 Risks related to interaction of the product and the patient

7.2.5.1 Immunogenicity

Although CAR T cells are autologous cellular product, host immune responses may result from presentation of CAR transgene expressing immunogenic epitopes derived from the murine scFv extracellular binding domain (fused to the intracellular signaling domains of 4-1BB and CD3zeta) or novel epitopes arising at junctions between components of the CAR fusion polypeptide (Park et al 2007, Lamers et al 2006, Lamers et al 2007, Lamers et al 2011). Humoral and cellular immunogenicity is being measured following tisagenlecleucel infusion as indicated in the clinical trial protocols. Based on the totality of available data (see below), humoral immunogenicity does not impact cellular kinetics or clinical outcome, and no notable cellular immunogenicity signals were observed. Since data are still limited to date, immunogenicity is considered missing information (see Table 8-37).

Humoral immunogenicity

Humoral immunogenicity was measured by determination of anti-mCAR19 antibodies in serum samples pre- and post-tisagenlecleucel infusion and their potential impact on cellular kinetics and clinical response. A validated flow cytometry assay was used to determine the presence of anti-mCAR19 antibodies in serum of patients who received tisagenlecleucel treatment and levels were reported by median fluorescence intensity. A positive treatment induced immunogenicity response was determined by a positive fold change from the baseline value to the post-treatment value.

In pediatric and young adult B-ALL Study B2202, 88.7% of patients tested positive for pre-existing anti-mCAR19 antibodies (pooled B2202+B2205J: 84%; B2001X: 89.9%). Treatment induced (boosted) immunogenicity was detected in 40.5% of patients in Study B2202 (in studies B2205J and B2001X, treatment induced/boosted anti-mCAR19 antibodies were not analyzed) (B-ALL SCP addendum ROW 2019; Study B2202 Interim CSR data cut-off 13-Apr-2018, B2205J Final CSR, Study B2001X Final CSR).

In DLBCL, most patients (93.9%) tested positive for pre-dose anti-mCAR19 antibodies. Treatment-induced (boosted) anti-mCAR19 antibodies were observed in 8.7% of patients in the PK analysis set, while the majority of patients tested negative (DLBCL SCP addendum ROW 2019; Study C2201 Interim CSR data cut-off 11-Dec-2018).

In FL, 66.0% of the patients tested positive and 22.7% of the patients tested negative for pre-dose anti-mCAR19 antibodies. For some patients, the baseline anti-mCAR19 antibody status was not available. Treatment-induced or boosted anti-mCAR19 antibodies were observed in 27 patients in the cellular kinetic analysis set, while 56 patients did not show induced or boosted response (FL SCP and Study E2202 CSR - Extended follow-up).

In all indications, the presence of pre-existing and treatment induced anti-mCAR19 antibodies did not appear to have an impact on the cellular kinetics and clinical response (i.e., efficacy) (B-ALL SCP addendum ROW 2019; DLBCL SCP addendum ROW 2019, FL SCP).

Cellular immunogenicity

Activation of T cells in peripheral blood mononuclear cells collected from patients in response to mCAR19-derived peptides was used to assess the cellular immunogenicity against tisagenlecleucel. T-cell activation was measured by the percentage of IFNγ positive cells detected by intracellular staining and subsequent flow cytometric analysis. Cellular responses to mCAR19 peptides were measured pre-dose (enrollment) and up to 12 months (B2202 and C2201); these are scheduled to be collected for up to 24 months (E2202) post-tisagenlecleucel infusion.

In the pediatric and adult B-ALL, DLBCL, and FL indications, cellular responses were consistent over time, demonstrating that cellular immunogenicity did not fluctuate over time. Furthermore, no apparent relationship between cellular immunogenicity and clinical outcomes (i.e., tumor response at Month 3) was observed for two mCAR19 peptide pools (Study B2202 Interim CSR data cut-off 13-Apr-2018; Study C2201 Interim CSR data cut-off 11-Dec-2018, Study E2202 CSR - Extended follow-up).

Since characterization of immunogenicity requires the use of additional endpoints including cellular kinetics and clinical response, this is most appropriately addressed in the context of clinical studies. Humoral and cellular immunogenicity is measured in all ongoing studies including long-term follow-up PASS A2205B; long-term immunogenicity data are being collected.

7.2.6 Risks related to scaffolds, matrices and biomaterials

Not applicable.

7.2.7 Risks related to persistence of the product in the patient

7.2.7.1 B-cell aplasia and immunoglobulin depletion

B-cell aplasia is an expected on-target effect of CD19-directed CAR T-cell therapy, and is a useful surrogate reflecting the persistence of CAR T cells and effectiveness of treatment in pediatric and young adult patients with r/r B-ALL. B-cell aplasia is observed in all responding pediatric and young adult patients with r/r B-ALL, following tisagenlecleucel. As long as the modified T cells persist in the patient, it is expected that B-cell aplasia continues. This may result in hypo- or agammaglobulinemia, potentially rendering the patients more susceptible to infections.

Long-term data show that prolonged depletion of normal B cells or agammaglobulinemia persists for > 5 years across indications (Study A2205B Annual Safety Report 2021). B-cell aplasia can be adequately managed by immunoglobulin replacement therapy (Doan and Pulsipher 2018). Infection precautions, antibiotic prophylaxis and immunoglobulin replacement should be performed per age and local guidelines.

Given the similar effects of rituximab on B cells and widespread use of rituximab in DLBCL, the role of B-cell aplasia as a marker of persistence of CD19-directed CAR T-cell therapy in DLBCL is less certain. B-cell aplasia is an expected on-target toxicity of tisagenlecleucel and prior rituximab treatment. All patients in Study C2201 received rituximab as prior line therapy before entering the study. 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 contributes to sustained aplasia (DLBCL SCS addendum ROW-Section 3.3).

'Prolonged depletion of normal B cells/Agammaglobulinemia' is an important identified risk as presented in Section 8.3.1.5, list of safety concerns in Section 9 and following sections.

7.2.7.2 Secondary malignancies (including vector insertion site oligo/monoclonality)

Cancer patients are at increased risk to develop second primary malignancies (hereafter referred to as 'secondary malignancies'), i.e., newly occurring malignancies other than the primary malignancy, as a result of previous anti-cancer therapy (such as chemotherapy, immunochemotherapy, radiation or HSCT). Increased rates within families have also been observed (Friedman et al 2010). The rate of new malignancy detection following tisagenlecleucel therapy will need to take into account these additional confounding risk factors.

Although the tisagenlecleucel lentiviral vector has been specifically designed to safeguard against the potential oncogenic effects, there is a theoretical concern that transduction of a patient's T cells with the lentiviral vector could result in:

- uncontrolled T-cell proliferation
- insertional oncogenic effect(s) that could result in a T-cell leukemia or lymphoma or maybe other malignancies

Ruella et al (2018) reported a B-ALL patient treated in an early clinical study at Penn/Children's Hospital of Philadelphia with CTL019 as manufactured by Penn. The patient showed an initial response to treatment and relapsed 9 months after infusion with CD19-negative leukemia cell that aberrantly expressed the anti-CD19 CAR. The CAR gene was unintentionally introduced into a single leukemic B cell during CAR T cell manufacture at Penn and its product bound in cis to the CD19 epitope on the surface of leukemic cells, masking it from recognition by and conferring resistance to the CAR-T.

The Novartis manufacturing process for tisagenlecleucel is designed to significantly reduce the probability of contaminating B cells in the T-cell culture. Therefore, the risk of CAR transduction of B cells as observed at the early CTL019 study at Penn and described in the publication by Ruella et al (2018) can be considered low with the current Novartis manufacturing process.

Evaluation of secondary malignancy

Secondary malignancies are evaluated through routine pharmacovigilance in all interventional clinical trials and in the post-marketing setting. This also includes patients, who are eligible to enroll in the long-term follow-up PASS A2205B following tisagenlecleucel infusion in a clinical trial, and for patients treated with commercial tisagenlecleucel, including those enrolled in the PASS B2401 study in the post-marketing setting. Both of these studies foresee a total of 15 years of follow-up post-infusion (see Section 10.2).

Upon clinical confirmation of a secondary malignancy, blood samples in addition to tumor tissue samples (if applicable and previously collected as standard of care in diagnosing or treating the secondary malignancy) for analysis, such as CAR transgene and RCL, are intended to be collected in clinical trials (including in long-term follow-up PASS A2205B) and, as feasible, from post-marketing commercial tisagenlecleucel patients (including OOS and/or MAP patients and those who may be enrolled in the PASS B2401).

Testing for confirmed secondary malignancies is managed according to the effective Novartis Secondary Malignancy Guidance Document and process. Testing for confirmed secondary malignancies of T-cell origin will be managed, once in place, in the planned PASS B2402, a Non-Interventional Study (NIS) to characterize secondary T-cell malignancies following CART-cell therapy using a lentiviral vector (see Section 10.2).

Pathology Work-up

A redacted copy of the official pathology report, along with any ancillary analyses used to diagnose secondary T cell malignancy, is required to confirm the diagnosis for enrolling a patient in the planned PASS B2402 study. In addition, pathology review of a tumor sample is conducted if Novartis receives samples from the treating site. A board-certified pathologist at the Novartis laboratory examines the tumor slides to determine if the tissue specimen contains at least 20% of the reported secondary malignancy.

Tumor Sample Collection

Diagnosis of relapse or recurrence of the treated disease or a new onset T-cell malignancy is performed by the treating physician. For a patient treated with tisagenlecleucel in post marketing setting, there is no requirement for the treating clinician to provide biopsy specimen in cases of recurrence, nor for a secondary cancer developing after the tisagenlecleucel administration. These patients are managed clinically by the clinician/site and Novartis is not involved in patient management. Nevertheless, every effort will be made to encourage the clinician to participate in the PASS B2402 and enroll/consent the patient.

According to the non-interventional study (NIS) protocol B2402, submission of archived secondary tumor or stored archived DNA from patient blood is requested for testing. For patients who have died or are unable to provide consent for various reasons, consideration will be given to prior tumor specimen banks and/or consent from family members or representatives.

Novartis encourages efforts to obtain tissue (archived) and/or stored DNA extracted from blood for testing. For cases where bone marrow is involved with the secondary T-cell malignancy, bone marrow aspirate is the ideal sample for testing. When bone marrow aspirate is not available, bone marrow biopsy may be considered for testing. However, bone marrow biopsy or any tissue containing bone, requires an additional step of decalcification, which may affect the ability to do qPCR testing. In these cases Immunohistochemistry (IHC) may be considered as the first testing step rather than qPCR.

Testing Algorithm including Transgene Analysis

Testing process includes instructions on prioritization of analyses to be conducted in case of limited availability of tumor tissue sample, bone marrow aspirate, and/or blood from the patient. Novartis will attempt to collect appropriate specimens and test for CTL019 CAR transgene

presence by quantitative polymerase chain reaction (qPCR) or droplet digital PCR (ddPCR) on DNA stored from peripheral blood and in secondary malignancy tissue samples (including bone marrow aspirate) when available and applicable. Bone marrow biopsy and/or tissue containing bone is discouraged but may be considered on a case-by-case basis if this is the only tissue available.

Based on the clinical trial experience, qPCR data were observed to be more robust than the flow cytometry data. Therefore, as a first step, the transgene levels will be quantified using the qPCR method. These bioanalytical data will be generated by Novartis in cases where CAR transgene is detected in DNA stored from peripheral blood and/or secondary malignancy tissue, the levels will be compared for the previous "on study" time points/visits with the average VCN levels observed in peripheral blood and/or bone marrow in the pivotal clinical studies to understand the fold-change in transgene presence. Currently, no robust reference data are available from clinical studies to understand the trafficking of CAR T cells in lymph nodes or other tissues outside blood and bone marrow. In case of a CAR-driven secondary malignancy, all secondary malignancy cells are expected to contain the CAR transgene and therefore the qPCR signal would be expected to be very strong and significantly above average blood levels at that time point post tisagenlecleucel infusion.

In line with the [FDA Guidance for Industry - Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up, January 2020], peripheral blood and secondary malignancy biopsy samples will also be tested for RCL at Novartis using the VSVg qPCR assay.

Once Novartis results for transgene and/or RCL become available, a decision will be made regarding the need for additional analyses. Additional analyses may include immunophenotyping, in situ hybridization, and LISA. This analysis will involve retained LK vials (leukapheresis cells prior to manufacture) and/or retained vials from manufactured product characterization in addition to the tumor tissue sample and stored DNA from blood or fresh blood. Additional analysis decisions are made in collaboration with expert scientists, clinical team and pathologist at Novartis. These additional analyses may include genome wide sequencing, transcriptomics or specific genetic testing that is informed by the LISA results, when applicable.

Secondary malignancies of T-cell origin' is an important identified risk (Section 8.3.1.7) and 'Secondary malignancies (except secondary malignancy of T-cell origin) including vector insertion site oligo/ monoclonality' is an important potential risk (Section 8.3.1.10).

7.2.8 Risks to healthcare professionals, care givers, offspring and other close contacts with the product or its components, or with patients

No preclinical reproductive studies have been conducted with tisagenlecleucel to assess whether it can cause fetal harm when administered to a pregnant woman. The human placenta forms an incomplete barrier for blood cells, allowing bidirectional passage of nucleated blood cells. Circulating maternal cells transfer to the fetus during pregnancy, where they may integrate with the fetal immune and organ systems, creating a state of MMc (Loubiere et al 2006, Stevens 2016). Hence, there is a potential risk that immunologically active maternal tisagenlecleucel positive T cells may cross the placenta. Currently, the potential impact of tisagenlecleucel on the offspring's B cells such as inducing B-cell lymphocytopenia or other potential toxicities including effects on the development of autoimmune disease (see below) is not known.

Maternal microchimerism has been observed in healthy fetus and adults. It was found in up to 42% of cord blood samples from healthy newborns (Müller et al 2001). Another study of tissues from five second-trimester fetuses, terminated for non-medical reasons, reported MMc in 4 out of 5 healthy fetuses; cells were found in thymus, lung, heart, pancreas, liver, spleen, kidney, adrenal gland, ovary, testis and brain (Jonsson et al 2008).

While the survival of normal maternal cells in the fetus is usually limited owing to effective rejection by an immunocompetent target, MMc has been implicated in the triggering or perpetuation of chronic inflammatory autoimmune diseases such as SCID, characterized by long-term engraftment of maternal T cells. The histocompatibility antigen disparity between mother and fetus has been considered as causative of some autoimmune diseases. It was hypothesized that normal host tolerance against maternal antigens might be initiated in utero, when regulatory T cells producing anti-inflammatory molecules in response to maternal antigens are induced. However, injury or infection may upregulate maternal histocompatibility antigen expression, allowing the antigen load to exceed the T-cell activation threshold for the otherwise-tolerated host (Stevens 2016).

The testicular environment is usually immunosuppressive to T cells, leading to control and low numbers of T lymphocytes including CD19 CAR T cells (Hedger and Meinhardt 2000). If transferred to female reproductive tract along with sperm, T cells are likely to be recognized as non-self by the female immune system and therefore be destroyed. A fundamental risk may arise from the presence of RCL the female organism may be exposed to after sexual intercourse. However, the principal design of the vector and the analytic measures taken during manufacturing of tisagenlecleucel will exclude the presence of RCL with highest probability, and the female risk for exposure to tisagenlecleucel and/or RCL is considered extremely low.

Due to the uncertainties outlined above, the pregnancy status for WOCBP should be verified prior to starting treatment with tisagenlecleucel. Tisagenlecleucel administration is not recommended during pregnancy and in WOCBP not using contraception. Notably, no data are currently available to determine the duration of contraception for WOCBP after receiving tisagenlecleucel. Pregnant women should be advised on the potential risks to the fetus. Pregnancy after tisagenlecleucel therapy should be discussed with the treating physician. Assessment of immunoglobulin levels is indicated in newborns of mothers treated with tisagenlecleucel.

No data exist, whether tisagenlecleucel is excreted in human milk or has effects on milk production. Therefore, a risk to the breastfed child cannot be excluded.

It is not known whether tisagenlecleucel can affect fertility.

'Use in pregnancy and lactation' is a topic of missing information that is discussed in Section 8.3.2.1 and following sections.

Patients treated with tisagenlecleucel should not donate blood, organs, tissues, or cells.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

8.1.1 Part II Module SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

The list of risks and ADRs that were not considered important for inclusion in the list of safety concerns in the RMP and the reasons for non-inclusion are provided below.

Table 8-1 Risks not considered important for inclusion in the list of safety concerns

Safety concern	Reason for non-inclusion as an RMP safety concern
Abnormal blood chemistries (e.g., glucose, calcium phosphorous, uric acid, magnesium)	Well known risks in cancer patients receiving chemotherapy and polypharmacy; no further characterization and are followed up via routine pharmacovigilance activities and adverse reaction reporting.
Vascular disorders: Hypo- and hypertension, capillary leak syndrome	Known risk that does not impact the risk-benefit profile. Usually associated with CRS which is an important identified risk.
Gastrointestinal events: Vomiting, abdominal pain, diarrhea, nausea	Well known risks in cancer patients receiving chemotherapy and polypharmacy; no further characterization and are followed up via routine pharmacovigilance activities and adverse reaction reporting.
Musculoskeletal pain	Well known risk associated with CAR T-cell expansion. This risk is of minimal clinical impact on patients in relation to the severity of the indication treated
Acute kidney injury	Acute kidney injury has occurred in the presence of CRS, TLS and hypotension. It is not a specific risk with tisagenlecleucel. Some chemotherapeutic agents and concomitant medications may lead to kidney injury. This risk will be followed through routine pharmacovigilance activities and adverse reaction reporting.
General events: Pyrexia, fatigue, edema, chills, decreased appetite	Well known risks in malignancy patients receiving chemotherapy and polypharmacy; no further characterization and are followed up via routine pharmacovigilance activities and adverse reaction reporting.
Coagulopathy with hypofibrinogenemia	Occurs primarily in context of moderate-severe CRS and is managed with supportive therapy.
QT prolongation	QT prolongation is not a risk with CAR T-cell therapy. United States FDA regulators granted a waiver for a thorough QT study.

Safety concern	Reason for non-inclusion as an RMP safety concern
Chain of identity failure	There are multiple controls in place to ensure specific traceability based on the SEC, patient ID and the batch number (see Section 7.2.1).
Infection associated with use of live vaccines	The risk of infection associated with live vaccine is clearly stated in the Warnings and Precautions section of the SmPC; no other pharmacovigilance activities or risk minimization measures are needed. This is a known risk that does not impact the risk-benefit profile.

8.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Table 8-2 Important identified risks

Risk	Reasons for classification as important identified risk (risk-benefit impact)
Cytokine release syndrome	Cytokine release syndrome is a systemic inflammatory response and an expected on-target toxicity, which has been observed with other types of T-cell directed therapies. It is caused by cytokines that are released by activated T cells and bystander cells (monocytes, macrophages, dendritic cells, and others), as a result from tisagenlecleucel cell expansion, activation, and tumor cell killing. Life-threatening or fatal events have been observed in tisagenlecleucel clinical trials. Given the first-in-class status of tisagenlecleucel, the potential severity and seriousness of the event and the absence of information on the effectiveness of the CRS management algorithm in the post-authorization setting, CRS is classified as an important identified risk.
Serious neurological adverse reactions	This risk refers to neurological events, excluding cerebral edema, after tisagenlecleucel infusion. Neurological events have been observed with CAR T-cell therapies including tisagenlecleucel. While the majority of neurological events following tisagenlecleucel infusion were observed ≤ 8 weeks, neurological events with later onset > 8 weeks and not in the context of CRS have also been reported. Most neurological events ≤ 8 weeks were transient or self-limiting in nature. Frequently, AEs included encephalopathy, confusional state and delirium. Other manifestations reflected a multifarious set of signs and symptoms such as seizures, aphasia, speech disorder, and tremor. Some of the events are severe and may have a life-threatening outcome. The underlying pathophysiological mechanism is not well understood. Serious neurological adverse reactions are classified as an important identified risk given the observed severity and seriousness of events.
Infections	Infections commonly occur in patients with hematological malignancies due to their immunocompromised condition involving several pathomechanisms caused by the underlying disease and

Risk	Reasons for classification as important identified risk (risk-benefit impact)
	preceding anticancer treatment such as chemotherapy, immunochemotherapy, radiation, HSCT or lymphodepleting chemotherapy. Serious infections were observed in patients after lymphodepleting chemotherapy and tisagenlecleucel infusion, some of which were life-threatening or fatal. Infections are classified as an important identified risk due to the observed severity and seriousness.
Tumor lysis syndrome	Adoptive CAR T-cell therapy leads to the release of nucleic acids, catabolites, and intracellular ions from tumor cells into the circulation which may manifests as TLS. It typically occurs in patients with large tumor burden and/or highly proliferative malignancies, particularly acute leukemia, and can be life-threatening. Most cases observed with tisagenlecleucel in clinical trials were of grade 3 severity. Tumor lysis syndrome is classified as an important identified risk based on the potential severity and seriousness.
Prolonged depletion of normal B-cells/Agammaglobulinemia	B-cell aplasia is an on-target effect of tisagenlecleucel and therefore a patient may experience hypo- or agammaglobulinemia for as long as tisagenlecleucel persists. Given that a typical T-lymphocyte has a lifespan of 40 years, tisagenlecleucel may potentially be detectable in a patient for a prolonged period. Hypo- or agammaglobulinemia may render the patients more susceptible to infections especially with encapsulated organisms. Viral reactivation such as herpes viruses may occur. Prolonged depletion of normal B-cells/Agammaglobulinemia is classified as an important identified risk given the potential of developing severe and serious events.
Hematopoietic cytopenias not resolved by day 28	Grade 3 and 4 cytopenias not resolved by day 28 have been observed in patients infused with tisagenlecleucel and also with other CAR T-cell therapies. The etiology of these cytopenias may be either the underlying B-cell malignancy, the CAR T-cell therapy itself, the lymphodepleting chemotherapy administered prior to the infusion or a combination. Prolonged neutropenia has been associated with increased risk of infection. It is classified as an important identified risk based on its potential severity and seriousness.

Table 8-3 Important potential risks

Risk	Reasons for classification as important potential risk (risk-benefit impact)
Cerebral edema	Five fatal cerebral edemas to date occurred after treatment with another anti-CD19 CAR T-cell product that is differently constructed than tisagenlecleucel. These cerebral edemas were characterized by rapid evolution soon after infusion, appeared to be resistant to anti-cytokine therapy and resulted in brain death within 1-2 days after diagnosis. Such events have not occurred in

Risk	Reasons for classification as important potential risk (risk-benefit impact)
	the tisagenlecleucel program to date. However, cerebral edema is included as an important potential risk based on these reports.
Generation of replication competent lentivirus	Although RCL could be generated during the tisagenlecleucel manufacturing or subsequently after infusion of the product to the patient, RCL resulting from manufacturing is highly unlikely. Elements are incorporated in the design of the vector system that minimize the probability of recombination events, and therefore minimize the potential for generation of RCL. Based on this theoretical concern, the generation of an RCL following infusion of the vector product is classified as an important potential risk.
Secondary malignancies (including vector insertion site oligo/monoclonality)	Secondary malignancies in cancer patients are increased as a result of previous anti-cancer therapies or partly due familial predisposition. Patients treated with tisagenlecleucel may develop secondary malignancies or relapse of their leukemia or lymphoma. There is in particular a theoretical concern that transduction of a patient's T cells with tisagenlecleucel lentiviral vector could result in an oncogenic effect that could result in a T-cell leukemia or lymphoma and maybe other malignancies. Consequently, this is classified as an important potential risk.
New occurrence or exacerbation of an autoimmune disorder	Modulation of an individual's immune status following chemotherapy or tisagenlecleucel infusion can cause new occurrence or exacerbation of an autoimmune disorders. This has been described both for diseases with and without an obvious underlying autoimmune cause. Autoimmune disorders following tisagenlecleucel have not been observed thus far. The risk of autoimmune reaction with tisagenlecleucel is considered low, since CD19 is not present on most normal tissue other than normal B cells. New occurrence or exacerbation of an autoimmune disorders is classified as an important potential risk based on theoretical concerns with this immunologic therapy, as CD19 presents a minimal risk of autoimmune disease.
Hematological disorders (incl. aplastic anemia and bone marrow failure)	There is potential risk of a hematologic disorder (i.e., MDS, aplastic anemia, bone marrow failure) based on drug class, i.e., tisagenlecleucel is a genetically modified cell product that affects hematopoietic cell function and potential for damage to bone marrow from prior chemotherapy and radiation.
Aggravation of graft-versus-host disease	The chance of GVHD occurring in patients after tisagenlecleucel infusion per se is considered low, but there is a potential risk of aggravation of pre-existing GVHD in patients with donor chimerism from a prior allogeneic HSCT post-tisagenlecleucel due to the milieu provided by robust activation of the transduced viable T cells.
Transmission of infectious agents	Transmission of infections agents could lead to new infections and reactivation of pre-existing viral disease (e.g., HBV, HCV, or HIV), respectively, in close contacts including personnel involved in the tisagenlecleucel manufacturing process or health care providers involved in leukapheresis and administering tisagenlecleucel in

Risk	Reasons for classification as important potential risk (risk-benefit impact)
	addition to patients treated with tisagenlecleucel. The risk associated with tisagenlecleucel is considered low.
Decrease in cell viability due to inappropriate handling of the product	Inappropriate handling of the manufactured product including reception, storage, handling 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.

Table 8-4 Missing information

Missing information	Reasons for classification as missing information (risk-benefit impact)
Use in pregnancy and lactation	Pregnant and breastfeeding women were excluded from all clinical studies with tisagenlecleucel. It is not known, if tisagenlecleucel constitutes a risk to pregnant women or fetuses, however, tisagenlecleucel cells may have the potential to cross the placenta and be transferred to the fetus leading to fetal toxicity including B-cell lymphocytopenia. It is not known, if tisagenlecleucel is excreted into breast milk or has effects on milk production. There are no data on the effects of tisagenlecleucel on the breastfed child.
Use in patients with HBV/HCV/HIV	Patients with HBV, HCV and HIV infection were excluded from all clinical studies, and no data is available in this population. Patients with active HBV or HCV have been excluded from clinical studies with tisagenlecleucel, because of the potential risk of viral reactivation and the risk of hepatic failure. HIV positive patients have been also excluded, because of the possible effect on HIV viral suppression. In addition, there is currently no experience with manufacturing tisagenlecleucel for patients testing positive for HBV, HCV and HIV.
Use in patients with active CNS involvement by malignancy	Patients with active CNS involvement of the underlying hematological malignancy were excluded from all the studies, therefore, a risk-benefit has not been established in this population.
Long-term safety	Current safety experience with tisagenlecleucel was evaluated up to 12 months following infusion. Longer-term safety data through 15 years after tisagenlecleucel infusion will be collected in the long-term follow-up PASS A2205B, enrolling patients treated with tisagenlecleucel in clinical trials. In addition, data will be evaluated in PASS B2401, utilizing data collected in two registries for cellular therapies that also enroll patients treated with tisagenlecleucel in the post-marketing setting.
Immunogenicity	Tisagenlecleucel product consists of autologous T cells that have been genetically modified to express a CAR to identify and eliminate CD19 expressing cells. Immunogenicity may result from host immune responses against CD19-specific CAR transgene expressing immunogenic epitopes derived from the murine scFv extracellular binding domain (fused to the intracellular signaling

Missing information	Reasons for classification as missing information (risk-benefit impact)
	domains of 4-1BB and CD3zeta) or novel epitopes arising at junctions between components of the CAR fusion polypeptide. Based on the totality of available data to date, humoral and cellular immunogenicity does not appear to impact cellular kinetics or clinical outcome, and no notable cellular immunogenicity signals were observed in the pediatric and young adult r/r B-ALL, adult r/r DLBCL, and adult r/r FL. However, data is still limited.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

The wording of the important potential risk 'secondary malignancies (except T-cell origin) including vector insertion site oligo monoclonality' is changed to 'Secondary malignancies (except secondary malignancy of T-cell origin) including vector insertion site oligo/monoclonality'.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

Adverse event and laboratory data are presented from the following studies:

- Pediatric and young adult patients with r/r B-ALL: Pooled dataset including pivotal Study B2202 (data cut-off date: 13-Apr-2018) and two supportive studies (B2205J (data cut-off date: 24-May-2019) and B2001X (data cut-off date: 13-Oct-2020). The pooled Safety set includes 212 patients exposed to tisagenlecleucel.

Since the data cut-off date of B2202 is 13-Apr-2018, AE data for the patient who was infused with tisagenlecleucel on 23-Oct-2019 has been excluded from further analysis.

- Adult patients with r/r DLBCL: Pivotal Study C2201 (data cut-off date 11-Dec-2018). The Safety set includes 115 patients exposed to tisagenlecleucel.

Adult patients with r/r FL: Pivotal Study E2202 (data cut-off date 29-Mar-2021). The Safety set includes 97 patients exposed to tisagenlecleucel.

8.3.1.1 Important Identified Risk: Cytokine release syndrome

Table 8-5 Clinical trial data of cytokine release syndrome

	Pediatric/young adult r/r B-ALL	Adult r/r DLBCL	Adult r/r FL

	B2202+B2205J+B2001X N=212 n (%)	C2201 N=115 n (%)	E2202 N=97 n (%)
Number of patients with at least one event at any time post tisagenlecleucel; (95% CI)	158 (74.5) (68.1, 80.2)	66 (57.4) (47.8, 66.6)	48 (49.5) (39.2, 59.8)
Maximum grade			
Grade 3 AEs	34 (16.0)	16 (13.9)	0
Grade 4 AEs	45 (21.2)	10 (8.7)	0
Treatment-related AEs	157 (74.1)	66 (57.4)	47 (48.5)
SAEs	119 (56.1)	31 (27.0)	19 (19.6)
AE outcome*			
Recovered/resolved	152 (96.2)	61 (92.4)	47 (97.9)
Recovered/resolved with sequelae	1 (0.6)	4 (6.1)	0
Recovering/resolving	1 (0.6)	0	NA
Not recovered/not resolved	3 (1.9)	1 (1.5)	0
Fatal	1 (0.6)	0	1 (2.1)
Unknown	0	0	0

B2202 data cut-off date: 13-Apr-2018, B2205J data cut-off date: 24-May-2019, B2001X data cut-off date: 13-Oct-2020; C2201 data cut-off date: 11-Dec-2018; E2202 data cut-off date: 29-Mar-2021.
Numbers (n) represent counts of patients.
* Percentage calculated based on number of patients with at least one event.
MedDRA version 24.1 was used.
Source: Attachment to [Annex 7 - Table 2-1.1a]

Table 8-6 Important identified risk cytokine release syndrome: Other details

Name of the risk Cytokine release syndrome	**Details**
Potential mechanisms	Cytokine release syndrome is a direct mechanism based systemic inflammatory response associated with tisagenlecleucel cell expansion, activation, and tumor cell killing. The activated T cells release cytokines and chemokines as do bystander immune cells, such as macrophages, monocytes, dendritic cells, and others (Neelapu et al 2018, Norelli et al 2018, Norelli et al 2018, Maus et al 2020, Morris et al 2021). High levels IFNγ, interleukin 6, and TNFα levels are frequently detected. The incidence and severity of CRS following tisagenlecleucel infusion appears greater when patients have large tumor burden, probably due to higher levels of T-cell activation.
Evidence source(s) and strength of evidence	Cytokine release syndrome is a direct mechanism based toxicity that occurs as a result of high-level immune activation. It is a systemic inflammatory response caused when cytokines are released by activated T cells, which has been observed in other types of T-cell directed therapies. This syndrome has become

Name of the risk Cytokine release syndrome	**Details**
	increasingly important with the use of new and more potent immunotherapies. The level of immune activation with these newer therapies occurs at levels greater than that occurring in nature. The severity ranges from mild to severe with a fatal outcome sometimes (Neelapu et al 2018, Norelli et al 2018, Norelli et al 2018, Maus et al 2020, Morris et al 2021). Life-threatening and fatal events have been observed in tisagenlecleucel clinical trials. In the Novartis tisagenlecleucel clinical study programs for the indications of pediatric and young adult r/r B-ALL, adult r/r DLBCL, and adult r/r FL, CRS was graded using criteria predefined in the study protocols (Penn CRS grading scale for Study B2202, Study B2205J, Study B2001X, and Study C2201; Lee grading criteria for Study E2202). In the majority of patients, CRS after tisagenlecleucel infusion occurred with a median time to onset of 3 days in both pediatric and young adult r/r B-ALL and adult r/r DLBCL patients, and 4 days in adult r/r FL. For details see below. Symptoms of CRS may include high fever, hypotension, hypoxia, dyspnea, tachypnea, rigors, myalgia, arthralgia, nausea, vomiting, diarrhea, diaphoresis, rash, anorexia, fatigue, tachycardia, and headache. In addition, multiple organ dysfunction, including transient cardiac failure, renal impairment, and liver injury with elevated hepatic enzymes have been observed. Disseminated intravascular coagulation, with low fibrinogen levels, or capillary leak syndrome may also occur. In the setting of severe CRS following CAR T-cell therapies including tisagenlecleucel, patients may develop a clinical phenotype that shares signs and symptoms of HLH and MAS, as further evidenced by similar laboratory findings. There is a significant overlap across CRS, MAS and HLH, reflecting a group of severe systemic immunological disorders characterized by hyperactivation of macrophages and lymphocytes, pro-inflammatory cytokine production, lymphohistiocytic tissue infiltration, and immune-mediated multiorgan failure. In the majority of patients, MAS/HLH responds to CRS resolution. Given this overlap, MAS/HLH may be considered to reflect manifestations of CRS of higher severity. However, it should be distinguished from late-onset, tocilizumab-refractory HLH/MAS-like toxicity that may represent a distinct and separate pathology than conventional CRS and requires a different treatment approach (Maus et al 2020).
Characterization of the risk:	In general, AEs of CRS were manageable and resolved with standard supportive case and concomitant medication as per protocol-specified CRS management algorithm. Of note, the algorithm implemented in Study E2202 allowed use of tocilizumab and low-dose corticosteroids at an earlier severity stage of CRS in reflection of current clinical practice (Lee et al 2019; Maus et al 2020). **Pediatric/young adult r/r B-ALL (B2202+B2205J+B2001X)** A total of 158 (74.5%) patients experienced AEs indicative of the risk 'cytokine release syndrome'. All events were suspected to be causally related to treatment with tisagenlecleucel by the Investigator, except for 1 patient who experienced CRS due to treatment with blinatumomab on Day 144. Thirty-four (16%) patients

Name of the risk Cytokine release syndrome	**Details**
	had AEs of severity grade 3 and 45 (21.2%) grade 4. Serious adverse events of CRS were reported in 119 (56.1%) patients. Preferred Terms reported included cytokine release syndrome in 158 (74.5%) and haemophagocytic lymphohistiocytosis in 9 (4.2%) patients. Adverse events occurred with an onset of: ≤ 8 weeks post tisagenlecleucel infusion – in 157 (74.1%) patients and > 8 weeks to 1 year - 1 (0.5%). In almost all cases (n = 151; 95.6%), the time to CRS onset ranged from 1 to 10 days (median: 3 days). The median duration was 8.0 days (range: 1-36 days). A total of 77 (36.3%) patients were admitted to the ICU for a median duration of 8 days (range: 0-24 days). Sixty-three (29.7%) patients with CRS were treated with systemic anti-cytokine therapy such as tocilizumab, siltuximab, corticosteroids, or others (e.g., infliximab, etanercept). A total of 1, 2, 3, and 4 doses of tocilizumab were required in 32 (15.1%), 19 (9%), 7 (3.3%), and 2 (0.9%) patients, respectively. Twenty-nine (13.7%) patients received corticosteroids, and 7 (3.3%) patients received siltuximab. Forty-seven (22.2%) patients required high-dose vasopressors, 74 (34.9%) patients required oxygen supplementation, 23 (10.8%) patients were intubated, and 14 (6.6%) patients required dialysis. Adverse event outcome at the time of the data cut-off: Resolved in 152 (96.2%) patients, resolved with sequelae in 1 (0.6%) patient, resolving in 1 patient (0.6%), not resolved in 3 patients (1.9%), and fatal in 1 patient (0.6%), who died due to CRS and TLS, secondary to ALL on Day 17, post-CTL019 infusion. Source: Annex 7; Study B2202 Interim CSR data cut-off 13-Apr-2018, B2205J Final CSR, Study B2001X Final CSR. **Adults with r/r DLBCL (C2201)** A total of 66 (57.4%) patients experienced AEs indicative of the risk 'cytokine release syndrome', all of which were suspected to be related to treatment with tisagenlecleucel by the Investigator. Sixteen (13.9%) patients had AEs of severity grade 3 and 10 (8.7%) grade 4. Serious adverse events of CRS were reported in 31 (27.0%) patients. Preferred Terms reported included cytokine release syndrome in 66 (57.4%) and haemophagocytic lymphohistiocytosis in 2 (1.7%) patients. All of the CRS AEs occurred with an onset ≤ 8 weeks of tisagenlecleucel infusion. The median time to onset was 3.0 days and except for one patient with time to onset on Day 51, all events of CRS occurred 1 to 9 days post infusion. The median CRS duration was 7.0 days (range: 2 to 30 days). Twenty-seven (23.5%) patients were admitted to the ICU for a median duration of 5.5 days (range: 2 to 34 days). Nineteen (28.8%) patients were treated with systemic anti-cytokine therapy; 18 (27.3%) patients were treated with tocilizumab, 12 (18.2%) with corticosteroids, and none with siltuximab. No patients received more than 2 doses of tocilizumab. Seven (10.6%) patients required high-dose vasopressors, 8 (12.1%) patients required invasive ventilation, and 5 (7.6%) patients required dialysis.

Name of the risk Cytokine release syndrome	**Details**
	Adverse event outcome at the time of the data cut-off: Resolved in 61 (92.4%) patients and resolved with sequelae in 4 (6.1%). CRS was ongoing in 1 (1.5%) patient at the time of the death due to DLBCL disease progression. There was no fatal CRS. Source: Annex 7; Study C2201 Interim CSR data cut-off 11-Dec-2018. **Adults with r/r FL (E2202)** A total of 48 (49.5%) patients experienced AEs indicative of the risk 'cytokine release syndrome' at any time post tisagenlecleucel infusion, of which 47 (48.5%) patients had AEs suspected to be causally related to treatment with tisagenlecleucel by the Investigator. Except for one fatal case of CRS (refer to PD , all patients had CRS of severity grade 1 or grade 2. Serious adverse events of CRS were reported in 19 (19.6%) patients. Preferred Terms reported included cytokine release syndrome in 48 (49.5%) patients and haemophagocytic lymphohistiocytosis in 1 (1.0%) patient. Adverse events occurred with an onset within 8 weeks post tisagenlecleucel infusion – in 47 (48.5%) patients; 2 (2.1%) patients had AEs after 8 weeks: • PD This patient experienced 3 episodes of CRS with onset on Day 207, Day 214 and Day 222 (Day 1 defined as tisagenlecleucel infusion date). CRS was attributed to initiation of new anti-cancer investigational treatment (T-cell engaging bi-specific antibody) that was administered due to FL disease progression. • PD This patient experienced CRS grade 1 on Day 7 from which PD recovered. After nearly 1 year post tisagenlecleucel infusion, PD further clinical course was complicated by pneumonia, sepsis, hypotension, pancytopenia, encephalopathy, renal and hepatic failure and atrial fibrillation. By means of exclusion, the Investigator diagnosed CRS (onset: Day 368) and HLH (Day 369) in the context of negative work-up for sepsis and autoimmune disorder. On Day 375, the patient died from CRS. Transgene levels at Month 3 were 96 copies/µg, and at Month 6 and Month 9 (6 and 3 months before the death, respectively) were below the limit of sensitivity, which makes a new onset of CRS at Month 12 due to tisagenlecleucel unlikely. For AEs that occurred within 8 weeks post tisagenlecleucel infusion (n=47; 48.5%), the median time to onset was 4.0 days (range: 1 to 14 days). The median CRS duration was 4.0 days (range: 1 to 24 days). Four (8.5%) patients were admitted to the ICU for a median duration of 8 days (range: 3 to 10 days). Sixteen (34.0%) patients were treated with systemic anti-cytokine therapy: all of whom were treated with tocilizumab, 3 (6.4%) with corticosteroids, and none with siltuximab. A total of 1, 2, and 3 doses of tocilizumab were required in 8 (17.0%), 5 (10.6%), and 3 (6.4%) patients, respectively. Three (6.4%) patients received vasopressor. None of the patients required high-dose vasopressors, invasive ventilation, or dialysis. Adverse event outcome at the time of the data cut-off: Resolved in 47 (97.9%) patients and fatal in 1 (2.1%) patient.

Name of the risk Cytokine release syndrome	**Details**
	Source: Annex 7; Study E2202 CSR - Extended follow-up.
Risk factors and risk groups	Risk factors for severe CRS in pediatric and young adult B-ALL patients are high pre-infusion tumor burden, uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy, active infection and early onset of fever or CRS following tisagenlecleucel infusion. Risk factor for developing severe CRS in adult DLBCL patients is high tumor burden prior to tisagenlecleucel infusion. Infections may also occur during CRS and increase the risk of a fatal event.
Preventability	Prior to administration of tisagenlecleucel in pediatric and young adult B-ALL patients, adult DLBCL patients, and adult FL patients, efforts should be made to lower and control the patient's tumor burden. Tisagenlecleucel infusion should be delayed in case of significant clinical worsening of leukemia or rapid progression of lymphoma following lymphodepleting chemotherapy. Appropriate prophylactic and therapeutic treatment for infections should be provided, and complete resolution of any existing infections should be ensured before tisagenlecleucel infusion. Since signs and symptoms of CRS occur in most cases within two weeks after tisagenlecleucel infusion, in the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for potential CRS, but also for neurological events and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalization at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion. Patients need to be informed to seek immediate medical attention should signs or symptoms of CRS occur at any time. Management of CRS is based on clinical presentation and according to the CRS management algorithm provided in the label. Alternative CRS management strategies may be implemented based on appropriate institutional or academic guidelines. Anti-interleukin 6 based therapy such as tocilizumab and corticosteroids have been administered for CRS associated with tisagenlecleucel. One dose of tocilizumab for use in the event of CRS must be available per patient prior to infusion on site; the treatment center must have access to additional doses of tocilizumab within 8 hours. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the EMA shortage catalogue, the treatment center must have access to suitable alternative measures instead of tocilizumab to treat CRS. 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 antagonists are not recommended for management of CRS associated with tisagenlecleucel.

Name of the risk Cytokine release syndrome	**Details**
Impact on the benefit-risk balance of the product	The benefit-risk balance with respect to CRS remains positive. The risk is generally manageable with appropriate monitoring and therapy. The severity ranges from mild to severe with rare fatal outcome noted during the clinical development.
Public health impact	With control of tumor burden and prompt treatment where indicated, the public health concern is low to moderate.

8.3.1.2 Important identified risk: Serious neurological adverse reactions

Table 8-7 Clinical trial data of serious neurological adverse reactions

	Pediatric/young adult r/r B-ALL	**Adult r/r DLBCL**	**Adult r/r FL**
	B2202+B2205J+B2001X N=212 n (%)	**C2201 N=115 n (%)**	**E2202 N=97 n (%)**
Number of patients with at least one event at any time post tisagenlecleucel; (95% CI)	74 (34.9) (28.5, 41.7)	27 (23.5) (16.1, 32.3)	11 (11.3) (5.8, 19.4)
Maximum grade			
Grade 3 AEs	24 (11.3)	10 (8.7)	2 (2.1)
Grade 4 AEs	1 (0.5)	5 (4.3)	1 (1.0)
Treatment-related AEs	55 (25.9)	17 (14.8)	8 (8.2)
SAEs	23 (10.8)	9 (7.8)	3 (3.1)
AE outcome*			
Recovered/resolved	55 (74.3)	19 (70.4)	10 (90.9)
Recovered/resolved with sequelae	1 (1.4)	0	0
Recovering/resolving	0	1 (3.7)	NA
Not recovered/not resolved	18 (24.3)	7 (25.9)	1 (9.1)
Fatal	0	0	0
Unknown	0	0	0

B2202 data cut-off date: 13-Apr-2018, B2205J data cut-off date: 24-May-2019, B2001X data cut-off date: 13-Oct-2020; C2201 data cut-off date: 11-Dec-2018; E2202 data cut-off date: 29-Mar-2021.
Numbers (n) represent counts of patients.
* Percentage calculated based on number of patients with at least one event.
MedDRA version 24.1 was used.
Source: Attachment to [Annex 7 - Table 2-1.1a]

Table 8-8 Important identified risk Serious neurological adverse reactions: Other details

Name of the risk Serious neurological adverse reactions	**Details**
Potential mechanisms	Neurotoxicity including events indicative of encephalopathy and delirium of non-infectious origin, have been observed with CAR T-cell therapies such as tisagenlecleucel. While the clinical phenomenon has been well described, its pathophysiology in particular in case of late events remains inadequately understood. Although intravenously infused anti-CD19 CAR T cells can cross the blood brain barrier to a sufficient degree irrespective of CNS malignancy status as shown by CAR T-cell trafficking to cerebrospinal fluid, CAR T-cell associated neurotoxicity is thought to be related to generalized T-cell mediated inflammation rather than direct toxicity of CAR T cells on the brain. Animal models and clinical studies in patients with neurotoxicity post CAR-therapy suggest brain endothelial activation resulting in disseminated intravascular coagulation, capillary leak, and breakdown of the blood brain barrier with increased permeability. In consequence, the blood brain barrier fails to protect the cerebrospinal fluid from high concentrations of systemic cytokines, including IFNγ, which induces brain vascular pericyte stress and their secretion of endothelium-activating cytokines leading to further increase of blood brain barrier permeability (Maus et al 2014, Tey 2014, Gust et al 2017, Neelapu et al 2018, Hunter et al 2019, Morris et al 2021, Gust et al 2020). A direct off-tumor on target action by CD19 CAR T cells to the CNS was proposed by Parker et al (2020). The authors presented their investigations using single-cell RNA sequencing data and perivascular staining at the protein level, which showed CD19 expressed by mural cells in the brain, which surround the endothelium and are considered critical for blood-brain-barrier integrity. Novartis investigations could neither detect CD19 protein nor a CD19-specific nucleotide sequence using CD19-specific immunohistochemistry and in situ hybridization on human and cynomolgus monkey brain tissues (data on file). In addition, RT-PCR analysis of the expression of five human and three cynomolgus CD19 splice variants in respective brain tissues was negative (data on file). In a more recent study, in situ hybridization with RNA scope probes for the full length CD19 mRNA and the pericyte marker CD248 also failed to localize CD19 mRNA in pericytes (data on file). The results from this Novartis investigation do not suggest an on-target mechanism for neurotoxicity in CD19-directed therapies. Furthermore, the staining pattern and quality of the pericyte staining by Parker et al (2020) were considered an artifact produced by endogenous cell components like lipofuchsin rather than representing a significant, true finding. As reported in the publicly available GTEx RNAseq data set (Gtexportal 2021) and the internal target expression profile database, CD19 is detected at very low levels in multiple brain regions (mean values of < 0.1 to < 0.01 transcripts per million) and may originate from intravascular B cells in circulation. Further analysis of the GTEx data (Tregt 2021) indicated that the CD19 transcript in brain tissue proposed by Parker et al (2020) represents a truncated version not able to be translated into a functional CD19 protein. This may explain the discrepancy between the single-cell RNAseq data analysis in Parker et al (2020) and Novartis' inability to detect CD19 protein or full length mRNA expression in this tissue.

Name of the risk Serious neurological adverse reactions	**Details**
	To date, no clear predictors of neurologic toxicity have been identified. Confounders, such as preceding or newly induced anti-cancer treatment regimens might be involved.
Evidence source(s) and strength of evidence	Neurotoxic events, suggested to be named 'CAR-T-cell-related encephalopathy syndrome' (Neelapu et al 2018) and subsequently termed 'immune effector cell-associated neurotoxicity syndrome' (ICANS) (Lee et al 2019), is the second most-common adverse reaction associated with CAR T-cell therapies. Neurotoxicity typically manifests as a toxic encephalopathy with wide range of variable symptoms such as confusion, delirium, tremors, aphasia, speech disorders, motor findings, and seizures. For fatal cerebral edema that occurred with other CAR T-cell products differently constructed than tisagenlecleucel, see Table 8-19 and Table 8-20. Notably, the onset of neurological events can be concurrent with CRS, typically during high fever and at the time of maximal grade of CRS, following resolution of CRS or in the absence of CRS. Severe ICANS symptoms are more frequently observed in cases when CRS develops early, which may be due to a high dose of CAR T cells, or unusually robust and rapid CAR T cell proliferation (Gust et al 2020). Encephalopathy typically occurred after peak CRS symptoms and tended to be self-limiting with some exceptions. Neurological events with seizures or episodes of confusion 3-4 weeks following CAR T-cell therapy have been reported to occur (Neelapu et al 2018). The majority of neurological events following tisagenlecleucel infusion were observed within 8 weeks; there is currently limited evidence that CAR therapies are associated with a late onset of neurological events (i.e., onset > 8 weeks after infusion). Most neurological events observed within 8 weeks were transient or self-limiting in nature. Frequently, encephalopathy, confusional state and delirium were observed. Other manifestations include a multifarious set of signs and symptoms including seizures, aphasia, speech disorder, and tremor. Some of the events are severe and may have a life-threatening outcome. The causality assessment of neurological events in patients treated with tisagenlecleucel can be confounded, as CNS toxicity can be associated with chemotherapy used for lymphodepletion and the presence of co-morbid conditions such as CRS, fever and infections.
Characterization of the risk:	Note that the risk term 'Serious neurological adverse reactions' refers to both non-serious and serious AEs. **Pediatric/young adult r/r B-ALL (B2202+B2205J+B2001X)** Adverse events indicative of the risk 'serious neurological adverse reactions' at any time post-infusion were reported in 74 (34.9%) patients, including 55 (25.9%) patients with AEs suspected to be causally related to treatment with tisagenlecleucel by the Investigator. Twenty-four (11.3%) patients had AEs of severity grade 3 and 1 (0.5%) had severity grade 4. Serious adverse events were reported in 23 (10.8%) patients.

Name of the risk Serious neurological adverse reactions	**Details**
	The most frequently reported PTs (> 5.0% patients) were confusional state (16 patients; 7.5%), delirium, encephalopathy, and seizure (14 each; 6.6%), tremor (12; 5.7%), and agitation (11; 5.2%). Adverse events occurred with an onset of: ≤ 8 weeks post tisagenlecleucel infusion – in 67 (31.6%) patients, > 8 weeks to 1 year - 9 (4.7%), > 1 year to 2 years - 2 (2.0%), > 2 years – 1 (3.4%). For AEs that occurred post-infusion at any time, the median time to onset of the first episode was 8.5 days (range: 2 to 964 days) and the median time to resolution was 7.0 days (95% CI: 4, 12 days). Resolution occurred within 3 weeks in 73.5% of patients (95% CI: 63.6, 82.6). Adverse event outcome at the time of the data cut-off: Resolved in 55 (74.3%) patients, resolved with sequelae in 1 (1.4%) patient, and not resolved in 18 (24.3%) patients. There was no fatal neurotoxic AE. Source: Annex 7; Study B2202 Interim CSR data cut-off 13-Apr-2018, B2205J Final CSR, Study B2001X Final CSR. **Adult r/r DLBCL (C2201)** Adverse events indicative of the risk 'serious neurological adverse reactions' at any time post-infusion were reported in 27 (23.5%) patients, including 17 (14.8%) patients with AEs suspected to be causally related to treatment with tisagenlecleucel by the Investigator. Ten (8.7%) patients had AEs of severity grade 3 and 5 (4.3%) patients had AEs grade 4. Serious adverse events were reported in 9 patients (7.8%). The most frequently reported PTs (> 5.0% patients) were confusional state in 10 (8.7%), and encephalopathy in 7 patients (6.1%). Adverse events occurred with an onset of: ≤ 8 weeks post tisagenlecleucel infusion - in 23 (20.0%) patients, > 8 weeks to 1 year - 5 (5.0%), and > 1 year to 2 years - 1 (2.3%) patient. For AEs that occurred post-infusion at any time, the median time to onset of the first episode was 6.0 days (range 1 to 323 days) and the median time to resolution was 13.0 days (95% CI: 6, 23 days). Resolution occurred within 3 weeks in 59.7% of patients (95% CI: 42.7, 77.3). Adverse events outcome at the time of the data cut-off: Resolved in 19 (70.4%) patients and resolving in 1 (3.7%) patient. In 7 (25.9%) patients, the neurotoxic events were not recovered, when they died due other reasons than neurotoxicity. There was no fatal neurotoxic AE. Source: Annex 7; Study C2201 Interim CSR data cut-off 11-Dec-2018. **Adult r/r FL (E2202)** Adverse events indicative of the risk 'serious neurological adverse reactions' at any time post-infusion were reported in 11 (11.3%) patients, including 8 (8.2%) patients with AEs suspected to be causally related to treatment with tisagenlecleucel by the Investigator. Two (2.1%) patients had AEs of severity

Name of the risk Serious neurological adverse reactions	**Details**
	grade 3 and 1 (1.0%) patient had AEs of severity grade 4. Serious adverse events were reported in 3 patients (3.1%). The most frequently reported PTs (> 2.0% patients) were immune effector cell-associated neurotoxicity syndrome in 4 (4.1%), encephalopathy in 3 (3.1%), and tremor in 2 patients (2.1%). Adverse events occurred with an onset within 8 weeks post tisagenlecleucel infusion - in 9 (9.3%) patients and > 8 weeks to 1 year – 2 (2.1%). For AEs that occurred post-infusion at any time, the median time to onset of the first episode was 9 days (range 4 to 345 days), and the median time to resolution was 2 days (95% CI: 1 to 4 days). Resolution occurred within 3 weeks in 91.2% of patients (95% CI: 67.7, 99.5 days). The majority of the tisagenlecleucel-related serious neurological adverse reactions required no specific protocol-defined intervention other than supportive care, unless an additional identified cause was defined (e.g., infection). Adverse event outcome at the time of the data cut-off: Resolved in 10 (90.9%) patients and not resolved in 1 (9.1%) patient. There was no fatal neurotoxic AE. Source: Annex 7; Study E2202 CSR - Extended follow-up.
Risk factors and risk groups	Risk factors are not known but may include prior medical history of CNS disease/injury or CNS leukemic involvement. In addition, higher grade CRS may predispose.
Preventability	In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for potential neurological events, but also for CRS and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalization at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion. 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.
Impact on the benefit-risk balance of the product	The benefit risk balance with respect to neurological events remains positive. The majority of these events were transient and reversible. Some of the events are severe and may have a life-threatening outcome.
Public health impact	Impact is low to moderate with appropriate monitoring, diagnostic work-up and effective management.

8.3.1.3 Important identified risk: Infections

Table 8-9 Clinical trial data of infections

	Pediatric/young adult r/r B-ALL B2202+B2205J+B2001X N=212 n (%)	Adult r/r DLBCL C2201 N=115 n (%)	Adult r/r FL E2202 N=97 n (%)
Number of patients with at least one event at any time post tisagenlecleucel; (95% CI)	149 (70.3) (63.6, 76.3)	67 (58.3) (48.7, 67.4)	48 (49.5) (39.2, 59.8)
Maximum grade			
Grade 3 AEs	57 (26.9)	32 (27.8)	15 (15.5)
Grade 4 AEs	20 (9.4)	7 (6.1)	0
Treatment-related AEs	48 (22.6)	20 (17.4)	13 (13.4)
SAEs	66 (31.1)	23 (20.0)	17 (17.5)
AE outcome*			
Recovered/resolved	111 (74.5)	44 (65.7)	42 (87.5)
Recovered/resolved with sequelae	1 (0.7)	0	1 (2.1)
Recovering/resolving	5 (3.4)	3 (4.5)	NA
Not recovered/not resolved	24 (16.1)	17 (25.4)	4 (8.3)
Fatal	5 (3.4)	1 (1.5)	0
Unknown	3 (2.0)	2 (3.0)	1 (2.1)

B2202 data cut-off date: 13-Apr-2018, B2205J data cut-off date: 24-May-2019, B2001X data cut-off date: 13-Oct-2020; C2201 data cut-off date: 11-Dec-2018; E2202 data cut-off date: 29-Mar-2021.
Numbers (n) represent counts of patients.
* Percentage calculated based on number of patients with at least one event.
MedDRA version 24.1 was used.
Source: Attachment to [Annex 7 - Table 2-1.1a]

Table 8-10 Important identified risk infections: Other details

Name of the risk Infections	**Details**
Potential mechanisms	There is an increased risk and severity of infections in patients with longer and more intense immunosuppression. Patients treated with tisagenlecleucel are at risk of infection for several reasons: • Underlying bone marrow disease or dysfunction increases the risk of infections. • Patients with prolonged and profound immunosuppression are at enhanced risk for more frequent and severe opportunistic infections. This may result from preceding anti-cancer treatment, including

Name of the risk Infections	**Details**
	chemo(immune)therapy, radiation, HSCT, bridging chemotherapy during the tisagenlecleucel manufacture waiting time in addition to lymphodepleting chemotherapy just prior to treatment with tisagenlecleucel causing severe cytopenias involving neutrophils and lymphocytes. • B-cell depletion is known to be associated with hypo- or agammaglobulinemia that contributes to the risk.
Evidence source(s) and strength of evidence	Serious infections, which may occur late, were observed in patients after tisagenlecleucel infusion, some of which were life-threatening or fatal.
Characterization of the risk:	**Pediatric/young adult r/r B-ALL (B2202+B2205J+B2001X)** A total of 149 (70.3%) patients experienced AEs of infections at any time post tisagenlecleucel infusion, of which 48 (22.6%) patients had AEs suspected to be causally related to treatment with tisagenlecleucel by the Investigator. A total of 57 (26.9%) patients had AEs of grade 3 severity and 20 (9.4%) had grade 4 severity. Serious adverse events of infections were reported in 66 (31.1%) patients including 5 (3.4%) deaths. The AEs included infections caused by unspecified pathogen (116; 54.7%), viral infections (66; 31.1%), bacterial (51; 24.1%), fungal (26; 12.3%), cutaneous neoplasm benign (PT skin papilloma) (2; 0.9%), and helminthic disorders (PT helminthic infection) (1; 0.5%). The AEs occurred with an onset of: ≤ 8 weeks post tisagenlecleucel infusion - in 86 (40.6%) patients, > 8 weeks to 1 year - 107 (56.3%), > 1 year to 2 years – 28 (28.6%) and > 2 years in 5 (17.2%). Adverse event outcome at the time of the data cut-off: Resolved in 111 (74.5%) patients, not resolved in 24 (16.1%), resolving in 5 (3.4%), unknown outcome in 3 (2.0%), and resolved with sequelae in 1 (0.7%). Five (3.4%) patients died from an infection. These included fungal infection (death on Day 62) and encephalitis (death on Day 53), which were suspected to be causally related to tisagenlecleucel by the Investigator; fatal infections not suspected to be causally related to tisagenlecleucel by the Investigator comprised respiratory tract infection (death on Day 1038), sepsis (death on Day 201) and embolic stroke with concurrent toxicity of septic embolus (death on Day 25; suspected to be causally related to lymphodepleting chemotherapy by the Investigator). Source: Annex 7; Study B2202 Interim CSR data cut-off 13-Apr-2018, B2205J Final CSR, Study B2001X Final CSR. **Adult r/r DLBCL (C2201)** A total of 67 (58.3%) patients experienced AEs of infections at any time post tisagenlecleucel, of which 20 (17.4%) patients had AEs assessed as causally related to treatment with tisagenlecleucel by the Investigator. A total of 32 (27.8%) patients had AEs of grade 3 severity and 7 (6.1%) patients had grade 4 severity. Serious adverse events of infections were reported in 23 patients (20%).

Name of the risk Infections	**Details**
	Adverse events included bacterial infections (n=20; 17.4%), viral (n=13; 11.3%), fungal (n=13; 11.3%), unspecified pathogen (n=55; 47.8%), protozoal (n=1; 0.9%), and cutaneous neoplasm benign (PT Skin papilloma) (n=1; 0.9%). The AEs occurred with an onset of: ≤ 8 weeks post tisagenlecleucel infusion - in 43 (37.4%) patients, > 8 weeks to 1 year - 40 (40.0%), > 1 year to 2 years - 14 (31.8%) and > 2 years in 2 (7.4%). Adverse event outcome at the time of the data cut-off, AEs of infections resolved in 44 (65.7%) patients, did not resolve in 17 (25.4%), were resolving in 3 (4.5%) patients, and causality was unknown in 2 (3.0%) patients. One patient died from an infection (Sepsis; death on Day 41), which was not suspected to be causally related to tisagenlecleucel by the Investigator. Source: Annex 7; Study C2201 Interim CSR data cut-off 11-Dec-2018. **Adult r/r FL (E2202)** A total of 48 (49.5%) patients experienced AEs of infections at any time post tisagenlecleucel infusion, of which 13 (13.4%) patients had AEs assessed as causally related to treatment with tisagenlecleucel by the Investigator. Fifteen (15.5%) patients had AEs of grade 3 severity; none had AEs of grade 4 severity. Serious adverse events of infections were reported in 17 (17.5%) patients. Adverse events reported included bacterial infections (n=6; 6.2%), viral (n=16; 16.5%), fungal (n=2; 2.1%), and unspecified pathogen (n=35; 36.1%). The AEs occurred with an onset of: ≤ 8 weeks post tisagenlecleucel infusion – in 18 (18.6%) patients, > 8 weeks to 1 year - 37 (38.5%), and > 1 year to 2 years - 5 (7.0 %). Infections were managed with standard supportive measures and anti-infective therapy. Adverse event outcome at the time of the data cut-off: Resolved in 42 (87.5%) patients and not resolved in 4 (8.3%); resolved with sequelae and outcome unknown in 1 (2.1%) patient each. No event was fatal. Source: Annex 7; Study E2202 CSR - Extended follow-up.
Risk factors and risk groups	Severity of underlying disease and longer, more intense immunosuppression following preceding chemotherapy, radiation and/or tisagenlecleucel infusion may lead to an increased risk, severity and seriousness of infection.
Preventability	Patients with active, uncontrolled infection should not start tisagenlecleucel treatment until the infection is resolved. Prior to tisagenlecleucel infusion, infection prophylaxis should follow standard guidelines based on the degree of preceding immunosuppression. In the first week following infusion, patients should be monitored2 to 3 times, or more frequently at the physician's discretion for potential neurological events, but also for CRS and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalization at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within

Name of the risk Infections	Details
	proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion. As appropriate, prophylactic anti-infective therapy should be administered and surveillance testing prior to and during treatment with tisagenlecleucel should be employed. The possibility of opportunistic infections of the CNS should be considered in patients with neurological AEs and appropriate diagnostic evaluations should be performed. In patients with low immunoglobulin levels preventive measures such as immunoglobulin replacement and rapid attention to signs and symptoms of infection should be implemented as per age and local specific guidelines.
Impact on the benefit-risk balance of the product	The benefit risk balance with respect to infections remains positive. The risk is generally manageable with appropriate monitoring and treatment. The severity ranges from mild to severe with a small percentage of fatal outcomes noted.
Public health impact	Impact is low to moderate with prompt and appropriate treatment.

8.3.1.4 Important Identified Risk: Tumor lysis syndrome

Table 8-11 Clinical trial data of tumor lysis syndrome

	Pediatric/young adult r/r B-ALL B2202+B2205J+B2001X N=212 n (%)	Adult r/r DLBCL C2201 N=115 n (%)	Adult r/r FL E2202 N=97 n (%)
Number of patients with at least one event at any time post tisagenlecleucel; (95% CI)	8 (3.8) (1.6, 7.3)	2 (1.7) (0.2, 6.1)	2 (2.1) (0.3, 7.3)
Maximum grade			
Grade 3 AEs	6 (2.8)	1 (0.9)	2 (2.1)
Grade 4 AEs	2 (0.9)	1 (0.9)	0
Treatment-related AEs	6 (2.8)	2 (1.7)	1 (1.0)
SAEs	5 (2.4)	1 (0.9)	0
AE outcome*			
Recovered/resolved	7 (87.5)	2 (100)	2 (100)
Recovered/resolved with sequelae	0	0	0
Recovering/resolving	0	0	NA
Not recovered/not resolved	0	0	0
Fatal	1 (12.5)	0	0

	Pediatric/young adult r/r B-ALL	Adult r/r DLBCL	Adult r/r FL
Unknown	0	0	0

B2202 data cut-off date: 13-Apr-2018, B2205J data cut-off date: 24-May-2019, B2001X data cut-off date: 13-Oct-2020; C2201 data cut-off date: 11-Dec-2018; E2202 data cut-off date: 29-Mar-2021.
Numbers (n) represent counts of patients.
* Percentage calculated based on number of patients with at least one event.
MedDRA version 24.1 was used.
Source: Attachment to [Annex 7 - Table 2-1.1a]

Table 8-12 Important identified risk tumor lysis syndrome: Other details

Name of the risk Tumor lysis syndrome	**Details**
Potential mechanisms	Tumor lysis syndrome is a potentially life-threatening metabolic disorder that occurs when tumor cells undergo rapid decomposition either spontaneously or in response to cytoreductive therapy. It tends to occur particularly with highly effective therapies and in patients with high tumor burden and cancers with a high potential for cell lysis include high-grade lymphoma, acute leukemia, and other rapidly proliferating tumors. Metabolic abnormalities characteristic of TLS include hyperuricemia resulting from the breakdown of purine-containing nucleic acids and major electrolyte imbalances such as hyperkalemia, hyperphosphatemia, and hypocalcemia. Delayed recognition of the metabolic imbalances caused by the massive release of tumor cell contents may result in clinical complications such as acute kidney injury, seizures, and cardiac arrhythmias (Mughal et al 2010).
Evidence source(s) and strength of evidence	Tumor lysis syndrome was clinically observed in a timely relation to tisagenlecleucel T-cell expansion. In the clinical experience with tisagenlecleucel thus far, most cases of TLS had a grade 3 in CTCAE severity, however, the risk has been moderate to low with appropriate monitoring after lymphodepleting chemotherapy, prophylaxis and treatment as needed.
Characterization of the risk:	**Pediatric/young adult r/r B-ALL (B2202+B2205J+B2001X)** A total of 8 (3.8%) patients experienced AEs of the risk 'tumor lysis syndrome' at any time post tisagenlecleucel, of which 6 (2.8%) patients had AEs assessed as causally related to tisagenlecleucel by the Investigator. Six (2.8%) patients had TLS grade 3 and 2 (0.9%) patients had TLS grade 4. Serious adverse events of TLS were reported in 5 (2.4%) patients. All AEs comprised the PT tumor lysis syndrome. The AEs occurred with an onset of: ≤ 8 weeks post tisagenlecleucel infusion – in 6 (2.8%) patients, and > 8 weeks to 1 year - in 2 (1.1%) patients. Adverse event outcome at the time of the data cut-off: Resolved in 7 (87.5%) patients and fatal in 1 (12.5%), who died due to CRS and TLS, secondary to B-ALL on Day 17 post-CTL019 infusion. Source: Annex 7; Study B2202 Interim CSR data cut-off 13-Apr-2018, B2205J Final CSR, Study B2001X Final CSR. **Adult r/r DLBCL (C2201)**

Name of the risk Tumor lysis syndrome	**Details**
	A total of 2 patients (1.7%) experienced AEs of TLS within 8 weeks post tisagenlecleucel, all of which were assessed to be causally related to tisagenlecleucel by the Investigator. One (0.9%) patient each had an AE of grade 3 and 4 severity, respectively. In 1 (0.9%) patient, TLS was serious. All AEs comprised the PT tumor lysis syndrome. No AE occurred > 8 weeks. Adverse event outcome at the time of the data cut-off: Resolved in all 2 (100%) patients. There was no fatal TLS. Source: Annex 7; Study C2201 Interim CSR data cut-off 11-Dec-2018. **Adult r/r FL (E2202)** A total of 2 patients (2.1%) experienced AEs indicative of the risk of 'tumor lysis syndrome' at any time post tisagenlecleucel infusion, of which 1 (1.0%) patient had an AE assessed as causally related to tisagenlecleucel by the Investigator. Both (2.1%) patients had grade 3 TLS. No AE was serious. All AEs comprised the PT tumor lysis syndrome. The AEs occurred with an onset of: ≤ 8 weeks post tisagenlecleucel infusion and > 8 weeks to 1 year - in 1 (1.0%) patient each. Adverse event outcome at the time of the data cut-off: Resolved in all 2 (100%) patients. There was no fatal TLS. Source: Annex 7; Study E2202 CSR - Extended follow-up.
Risk factors and risk groups	All recipients are at risk for this concern. In general, TLS occurs more frequently in hematological malignancies than in solid tumors. The highest risk of developing TLS is observed in patients with lymphoproliferative disorders with high proliferative rate and high tumor sensitivity to chemotherapy, like B-ALL and Burkitt's lymphoma. Tumor burden, reflected by serum LDH level, initial WBC count, tumor size, and extensive bone marrow involvement are considered main predictors for the development of TLS in these patients (Belay et al 2017).
Preventability	Patients should be closely monitored for signs and symptoms of TLS both before and after lymphodepleting chemotherapy and tisagenlecleucel infusion including relevant laboratory tests. In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for potential neurological events, but also for CRS and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalization at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion. To minimise risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to tisagenlecleucel

Name of the risk Tumor lysis syndrome	Details
	infusion. Signs and symptoms of TLS should be monitored and events managed according to standard guidelines.
Impact on the benefit-risk balance of the product	The benefit-risk balance with respect to TLS remains positive. TLS can be severe but is generally manageable with prophylaxis and treatment.
Public health impact	Impact is considered low and manageable with appropriate monitoring and therapeutic treatment.

8.3.1.5 Important identified risk: Prolonged depletion of normal B cells/ Agammaglobulinemia

Table 8-13 Clinical trial data of prolonged depletion of normal B cells/ Agammaglobulinemia

	Pediatric/young adult r/r B-ALL B2202+B2205J+B2001X N=212 n (%)	Adult r/r DLBCL C2201 N=115 n (%)	Adult r/r FL E2202 N=97 n (%)
Number of patients with at least one event at any time post tisagenlecleucel; (95% CI)	105 (49.5) (42.6, 56.5)	21 (18.3) (11.7, 26.5)	16 (16.5) (9.7, 25.4)
Maximum grade			
Grade 3 AEs	20 (9.4)	8 (7.0)	1 (1.0)
Grade 4 AEs	1 (0.5)	0	0
Treatment-related AEs	97 (45.8)	17 (14.8)	10 (10.3)
SAEs	1 (0.5)	0	0
AE outcome*			
Recovered/resolved	16 (15.2)	3 (14.3)	6 (37.5)
Recovered/resolved with sequelae	0	0	0
Recovering/resolving	9 (8.6)	1 (4.8)	NA
Not recovered/not resolved	79 (75.2)	16 (76.2)	9 (56.3)
Fatal	0	0	0
Unknown	1 (1.0)	1 (4.8)	1 (6.3)

B2202 data cut-off date: 13-Apr-2018, B2205J data cut-off date: 24-May-2019, B2001X data cut-off date: 13-Oct-2020; C2201 data cut-off date: 11-Dec-2018; E2202 data cut-off date: 29-Mar-2021.
Numbers (n) represent counts of patients.
* Percentage calculated based on number of patients with at least one event.
MedDRA version 24.1 was used.

	Pediatric/young adult r/r B-ALL	Adult r/r DLBCL	Adult r/r FL

Source: Attachment to [Annex 7 - Table 2-1.1a]

Table 8-14 Important identified risk prolonged depletion of normal B cells/ Agammaglobulinemia: Other details

Name of the risk Prolonged depletion of normal B-cells/ Agammaglobulinemia	Details
Potential mechanisms	Transient or prolonged B-cell depletion is a risk with tisagenlecleucel therapy, since normal and malignant B cells express CD19. It is an expected on-target toxicity of a successful CD19-directed CAR T-cell therapy and a useful surrogate reflecting the persistence of CAR T cells and effectiveness of treatment. B-cell aplasia is observed in all responding patients. As long as the modified T cells persist in the patient, it is expected that B-cell aplasia will continue to be present. Loss of B cells can result in hypo- or agammaglobulinemia, potentially rendering the patients more susceptible to certain infections including but not limited to those caused by encapsulated bacteria and viruses (Gernez et al 2018). Given that a typical T lymphocyte may have a lifespan of 40 years, tisagenlecleucel may potentially be detectable in the patient for a very prolonged period primarily in the subset of patients who continue to demonstrate a tumor response.
Evidence source(s) and strength of evidence	Prolonged depletion of B cells is an expected on-target toxicity of CD19-directed CAR T-cell therapy. This may result in hypo- or agammaglobulinemia, potentially rendering the patients more susceptible to certain infections.
Characterization of the risk:	**Pediatric/young adult r/r B-ALL (B2202+B2205J+B2001X)** A total of 105 (49.5%) patients experienced AEs of the risk prolonged depletion of normal B-cells/agammaglobulinemia at any time post tisagenlecleucel, including 97 (45.8%) patients with AEs suspected to be causally related to treatment with tisagenlecleucel by the Investigator. Twenty (9.4%) patients had AEs grade 3 severity and 1 (0.5%) had grade 4. One (0.5%) patient had an SAE. Among the AEs reported for this risk, hypogammaglobulinemia was the most frequently reported PT in 84 (39.6%) patients. The AEs occurred with an onset of: ≤ 8 weeks post tisagenlecleucel infusion - in 81 (38.2%) patients, > 8 weeks to 1 year - 30 (15.8%), and > 1 year to 2 years - 3 (3.1%), and > 2 years - 1 (3.4%). In Study B2202, 70 patients received IVIg replacement therapy during the study, of which 65 patients received at least one IVIg dose post infusion. A total of 23 (35.4%) patients received IVIg dose post tisagenlecleucel infusion for a duration > 12 months at the time of cut-off date. In Study B2205J, 38 (59.4%) patients received IVIg replacement therapy. This included 9 of the 45 patients who achieved best overall response of CR/CRi; they received IVIg replacement

Name of the risk	Details
Prolonged depletion of normal B-cells/ Agammaglobulinemia	therapy post-tisagenlecleucel infusion for more than 12 months. In Study B2001X, 34.8% patients received IVIg replacement therapy. Of note, the use of IVIg replacement therapy might have been underestimated in this study; therefore, no further data are reported. Adverse event outcome at the time of the data cut-off: Resolved in 16 patients (15.2%), not resolved in 79 (75.2%), and resolving in 9 (8.6%); the outcome was unknown in 1 (1.0%) patient. None of the AEs was fatal. Source: Annex 7; Study B2202 Interim CSR data cut-off 13-Apr-2018, B2205J Final CSR, B2001X Final CSR. **Adult r/r DLBCL (C2201)** A total of 21 (28.3%) patients experienced AEs of prolonged depletion of normal B-cells/Agammaglobulinemia at any time post tisagenlecleucel, including 17 (14.8%) patients with AEs suspected to be causally related to treatment with tisagenlecleucel by the Investigator. Eight (7.0%) patients had AEs grade 3 severity and none had grade 4. None of the AEs was serious. Among the AEs reported for this risk, hypogammaglobulinemia was the most frequently reported PT in 9 (7.8%) patients. The AEs occurred with an onset of: ≤ 8 weeks post tisagenlecleucel infusion - in 7 (6.1%) patients, > 8 weeks to 1 year - 12 (12.0%), > 1 year to 2 years - 2 (4.5%). 41 patients received IVIg during the study; all of them received at least one IVIg dose post infusion. Twelve patients received IVIg post infusion for a duration > 12 months during the study at the data cut-off. Adverse event outcome at the time of the data cut-off: Resolved in 3 (14.3%) patients and not resolved in 16 (76.2%); resolving and outcome unknown in 1 (4.8%) patient each. None of the AEs was fatal. Source: Annex 7; Study C2201 Interim CSR data cut-off 11-Dec-2018. **Adult r/r FL (E2202)** A total of 16 (16.5%) patients experienced AEs of prolonged depletion of normal B-cells/Agammaglobulinemia at any time post tisagenlecleucel infusion, including 10 (10.3%) patients with AEs suspected to be causally related to treatment with tisagenlecleucel by the Investigator. One (1.0%) patient had AEs of grade 3 severity and none had grade 4. None of the AEs were serious. Among the AEs reported for this risk, hypogammaglobulinemia was the most frequently reported PT in 14 (14.4%) patients. The AEs occurred with an onset of: ≤ 8 weeks post tisagenlecleucel infusion - in 10 (10.3%) patients and > 8 weeks to 1 year - 7 (7.3%). Thirty-three infused patients received at least one dose of prophylactic immunoglobulin therapy, with all 33 receiving a dose post-infusion, and 11 of these patients also receiving prophylactic administration prior to infusion.

Name of the risk	**Details**
Prolonged depletion of normal B-cells/ Agammaglobulinemia	
	Adverse event outcome at the time of the data cut-off: Resolved in 6 (37.5%) patients and not resolved in 9 (56.3%) patients; the outcome was unknown for 1 (6.3%) patient. None of the AEs were fatal. Source: Annex 7; Study E2202 CSR - Extended follow-up.
Risk factors and risk groups	Patients with B-cell aplasia are at increased risk for certain infections including but not limited to those caused by encapsulated bacteria and viruses (Gernez et al 2018).
Preventability	In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for potential neurological events, but also for CRS and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalization at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion. Immunoglobulin levels should be monitored after treatment with tisagenlecleucel. 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. The safety of immunization with live vaccines during or following tisagenlecleucel treatment has not been studied. Vaccination with live vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during tisagenlecleucel treatment, and until immune recovery following treatment with tisagenlecleucel.
Impact on the benefit-risk balance of the product	The benefit-risk balance with respect to prolonged depletion of normal B-cells/Agammaglobulinemia remains positive. The risk is generally manageable with appropriate precautions, prophylaxis and treatment. Infections subsequent to hypogammaglobulinemia may be severe or fatal, but the above mentioned treatment can change the course.
Public health impact	Impact is low to moderate with the above mentioned precautions and treatment. Can be significant if remains undetected.

8.3.1.6 Important identified risk: Hematological disorders including cytopenias

Table 8-15 Clinical trial data of hematological disorders including cytopenias

	Pediatric/young adult r/r B-ALL	Adult r/r DLBCL	Adult r/r FL
	B2202+B2205J+B2001X N=212 n (%)	C2201 N=115 n (%)	E2202 N=97 n (%)
Number of patients with at least one event at any time post tisagenlecleucel; (95% CI)	145 (68.4) (61.7, 74.6)	89 (77.4) (68.7, 84.7)	76 (78.4) (68.8, 86.1)
Maximum grade			
Grade 3 AEs	46 (21.7)	21 (18.3)	26 (26.8)
Grade 4 AEs	87 (41.0)	66 (57.4)	46 (47.4)
Treatment-related AEs	99 (46.7)	57 (49.6)	42 (43.3)
SAEs	48 (22.6)	22 (19.1)	9 (9.3)
AE outcome*			
Recovered/resolved	99 (68.3)	45 (50.6)	56 (73.7)
Recovered/resolved with sequelae	0	0	1 (1.3)
Recovering/resolving	4 (2.8)	5 (5.6)	NA
Not recovered/not resolved	41 (28.3)	39 (43.8)	18 (23.7)
Fatal	0	0	0
Unknown	1 (0.7)	0	1 (1.3)

B2202 data cut-off date: 13-Apr-2018, B2205J data cut-off date: 24-May-2019, B2001X data cut-off date: 13-Oct-2020; C2201 data cut-off date: 11-Dec-2018; E2202 data cut-off date: 29-Mar-2021.
Numbers (n) represent counts of patients.
* Percentage calculated based on number of patients with at least one event.
MedDRA version 24.1 was used.
Source: Attachment to [Annex 7 - Table 2-1.1a]

Table 8-16 Important identified risk hematological disorders including cytopenias: Other details

Name of the risk	Details
Hematological disorders including cytopenias	
Potential mechanisms	The etiology of hematological disorders including cytopenias is multifactorial, likely reflecting a combination of cytotoxic effects from the underlying hematological malignancy, cytotoxicity from prior anticancer treatment, bridging chemotherapy during the tisagenlecleucel manufacture waiting time and

Name of the risk Hematological disorders including cytopenias	Details
	conditioning lymphodepleting chemotherapy just prior to tisagenlecleucel infusion in addition to the CAR T-cell therapy per se, which is frequently associated with B-cell aplasia as on-target effect. Prolonged hematological cytopenias and hematological disorders are considered a sequelae (Brudno and Kochenderfer 2016). High-grade CRS or ICANS as well as markers of acute inflammation (such as CRP and ferritin) were found to be associated with a lower probability of hematopoietic recovery 1 month following treatment with CAR T-cell therapies, suggesting that inflammation is a key factor only in the early post CAR T-cell period (Jain et al 2020), while the pathophysiology of longer-term cytopenias is still not understood.
Evidence source(s) and strength of evidence	Hematological disorders including cytopenias are commonly seen in patients receiving tisagenlecleucel. Patients may continue to exhibit cytopenias for several weeks following tisagenlecleucel infusion. Prolonged neutropenia has been associated with increased risk of infection.
Characterization of the risk:	**Pediatric/young adult r/r B-ALL (B2202+B2205J+B2001X)** **AE data** Adverse events indicative of the risk 'hematological disorders including cytopenias' at any time post-infusion were reported in 145 (68.4%) patients, including 99 (46.7%) patients with AEs suspected to be causally related to treatment with tisagenlecleucel by the Investigator. A total of 46 (21.7%) patients had AEs of severity grade 3 and 87 (41.0%) grade 4. Serious adverse events were reported in 48 (22.6%) patients. Most commonly reported PTs (reported in > 20% of patients) were white blood cell count decreased (73 patients; 34.4%), anemia (66; 31.1%), neutrophil count decreased (62; 29.2%), febrile neutropenia (57 patients; 26.9%), and platelet count decreased (54; 25.5%). Adverse events occurred with an onset of: ≤ 8 weeks post tisagenlecleucel infusion - in 135 (63.7%) patients; > 8 weeks to 1 year - 59 (31.1%), > 1 year to 2 years - 14 (14.3%), and > 2 years - 3 (10.3%). Adverse event outcome at the time of the data cut-off: Resolved in 99 (68.3%) patients, not recovered in 41 (28.3%), and resolving in 4 (2.8%), and the outcome was unknown in 1 (0.7%) patient. None of the AEs were fatal. Source: Annex 7; Study B2202 Interim CSR data cut-off 13-Apr-2018, B2205J Final CSR, Study B2001X Final CSR. **Laboratory data** *Worst post-baseline hematology shifts at any time post-infusion (N=212)* • At baseline, decreased leukocyte counts grade 0, 1, 2, 3, and 4 were noted in 0.9%, 1.4%, 3.3%, 12.7% and 81.1% of patients, respectively. At post-baseline at any time post infusion, worst value grade 3 was noted

Name of the risk	Details
Hematological disorders including cytopenias	

in 8.5% and grade 4 in 88.2% of patients. A total of 58.3% patients with baseline grades 0-2 shifted to post baseline grades 3-4.

- At baseline, decreased neutrophil counts grade 0, 1, 2, 3, and 4 were noted in 5.2%, 2.4%, 8.0%, 16.5% and 67% of patients, respectively. At post-baseline at any time post infusion, worst value grade 3 was noted in 6.6% and grade 4 in 89.6% of patients. A total of 93.9% patients with baseline grades 0-2 shifted to post baseline grades 3-4.
- At baseline, decreased lymphocyte counts grade 0, 1, 2, 3 and 4 were noted in 5.2%, 8.5%, 5.7%, 14.2% and 66% of patients, respectively. At post-baseline at any time post infusion, worst value grade 3 was noted in 21.2% and grade 4 in 73.1% of patients. A total of 82.5% patients with baseline grades 0-2 shifted to post baseline grades 3-4.
- At baseline, decreased platelet counts grade 0, 1, 2, 3, and 4 were noted in 19.8%, 25%, 9.4%, 30.7% and 14.6% of patients, respectively. At post-baseline at any time post infusion, worst value grade 3 was noted in 17.9% and grade 4 in 52.4% of patients. A total of 47% patients with baseline grades 0-2 shifted to post baseline grades 3-4.
- At baseline, decreased hemoglobin grade 0, 1, 2, 3, 4 was noted in 6.1%, 27.8%, 55.2%, 9.9% and 0 of patients, respectively. At post-baseline at any time post infusion, worst value grade 3 was noted in 45.8% and grade 4 in 0 of patients. A total of 44.4% patients with baseline grades 0-2 shifted to post baseline grades 3-4.

Source: Annex 7

Resolution of hematopoietic cytopenias grade 3 and 4 at Day 28

Persistent cytopenias grade 3 and 4 were observed beyond Day 28 post tisagenlecleucel and continued to resolve over time. The estimated probability of resolution in patients with cytopenias grade 3 and 4 at Day 28 by Month 3 and Month 6 using Kaplan-Meier analysis is presented below. By Month 6 the probability of resolution of cytopenias ranged from 80% to 93.6%.

		All patients; N=212			
		By month 3 [2]		**By month 6 [2]**	
Parameter	**Day 28 [1] n (%)**	**Patients at risk**	**Resolved probability %**	**Patients at risk**	**Resolved probability %**
WBC	107 (50.5)	31	63.5	5	93.6
Neutrophils	23 (10.8)	0	Not estimable	0	Not estimable
Lymphocytes	67 (31.6)	16	58.9	5	80.0
Platelets	118 (55.7)	36	61.0	9	88.8

Name of the risk	Details
Hematological disorders including cytopenias	

Hemoglobin	92 (43.4)	42	42.4	8	87.9

B2202 data cut-off date: 13-Apr-2018, B2205J data cut-off date: 24-May-2019, B2001X data cut-off date: 13-Oct-2020; C2201 data cut-off date: 11-Dec-2018; E2202 data cut-off date: 29-Mar-2021.
Based on laboratory results regardless of blood transfusion.
[1] Number of patients with last value ≤ Day 28 indicating grade 3 or 4 cytopenia
[2] Resolution of cytopenia is defined as achieving laboratory value ≤ grade 2. % resolved probability is among patients with cytopenia at Day 28, obtained from the Kaplan-Meier survival estimate.

Source: Annex 7

Adult r/r DLBCL (C2201)

AE data

Adverse events indicative of the risk 'hematological disorders including cytopenias' at any time post-infusion were reported in 89 (77.4%) patients, including 57 (49.6%) patients with AEs suspected to be causally related to treatment with tisagenlecleucel by the Investigator. A total of 21 (18.3%) patients had AEs of severity grade 3 and 66 (57.4%) grade 4. Serious adverse events were reported in 22 (19.1%).

Most commonly reported PTs (reported in > 30% of patients) were anemia (55 patients; 47.8%), white blood cell count decreased (41; 35.7%), neutrophil count decreased (40; 34.8%) and platelet count decreased (39; 33.9%).

The majority of AEs occurred with an onset of: ≤ 8 weeks post tisagenlecleucel infusion - 88 (76.5%) patients, > 8 weeks to 1 year - 32 (32.0%), > 1 to 2 years - 6 (13.6%), and > 2 years - 1 (3.7%).

Adverse event outcome at the time of the data cut-off: Resolved in 45 (50.6%) patients, resolving in 5 (5.6%) and not recovered in 39 (43.8%). None of the AEs was fatal.

Source: Annex 7; Study C2201 Interim CSR data cut-off 11-Dec-2018.

Laboratory data

Worst post-baseline hematology shifts at any time post-infusion (N=111)

- At baseline, decreased leukocyte counts grade 0, 1, 2, 3, and 4 were noted in 13.9%, 12.2%, 23.5%, 27.8% and 22.6% of patients, respectively. At post-baseline at any time post infusion, worst value grade 3 was noted in 34.8% and grade 4 in 43.5 of patients. A total of 59.6% patients with baseline grades 0-2 shifted to post baseline grades 3-4.
- At baseline, decreased neutrophil counts grade 0, 1, 2, 3, and 4 were noted in 32.2%, 13.9%, 11.3%, 20.9% and 21.7% of patients, respectively. At post-baseline at any time post infusion, worst value

Name of the risk	Details
Hematological disorders including cytopenias	

grade 3 was noted in 20.9% and grade 4 in 60.9% of patients. A total of 69.7% patients with baseline grades 0-2 shifted to post baseline grades 3-4.

- At baseline, decreased lymphocyte counts grade 0, 1, 2, 3 and 4 were noted in 1.7%, 7.8%, 7.0%, 32.2% and 51.3% of patients, respectively. At post-baseline at any time post infusion, worst value grade 3 was noted in 28.7% and grade 4 in 66.1% of patients. A total of 68.4% patients with baseline grades 0-2 shifted to post baseline grades 3-4.
- At baseline, decreased platelet counts grade 0, 1, 2, 3, and 4 were noted in 42.6%, 32.2%, 11.3%, 6.1% and 7.8% of patients, respectively. At post-baseline at any time post infusion, worst value grade 3 was noted in 13.9% and grade 4 in 41.7% of patients. A total of 48.5% patients with baseline grades 0-2 shifted to post baseline grades 3-4.
- At baseline, decreased hemoglobin grade 0, 1, 2, 3, 4 was noted in 7.8%, 27.0%, 48.7%, 16.5% and 0 of patients, respectively. At post-baseline at any time post infusion, worst value grade 3 was noted in 59.1% and grade 4 in 0 of patients. A total of 51.0% patients with baseline grades 0-2 shifted to post baseline grade 3.

Source: Study C2201 Interim CSR data cut-off 11-Dec-2018.

Resolution of hematopoietic cytopenias grade 3 and 4 at Day 28

Persistent cytopenias grade 3 and 4 were observed beyond Day 28 post tisagenlecleucel infusion and continued to resolve over time. The estimated probability of resolution in patients with cytopenias grade 3 and 4 at Day 28 by Month 3 and Month 6 using Kaplan-Meier analysis is presented below. By Month 6 the probability of resolution of cytopenias ranged from 58% to 100%.

		All patients (N=115)			
		By month 3 [2]		**By month 6 [2]**	
Parameter	**Day 28 event [1] n (%)**	**Patients at risk**	**Resolved probability %**	**Patients at risk**	**Resolved probability %**
WBC	24 (20.9)	0	100.0	0	100.0
Neutrophils	29 (25.2)	2	84.4	1	92.2
Lymphocytes	33 (28.7)	6	57.9	5	57.9
Platelets	45 (39.1)	8	61.5	3	78.3
Hemoglobin	16 (13.9)	0	100.0	0	100.0

Name of the risk	Details
Hematological disorders including cytopenias	Based on laboratory results regardless of blood transfusion. [1] Number of patients with last value ≤ Day 28 indicating grade 3 or 4 cytopenia. [2] Resolution of cytopenia is defined as achieving laboratory value ≤ grade 2. % resolved probability is among patients with cytopenia at Day 28, obtained from the Kaplan-Meier survival estimate. Source: Study C2201 Interim CSR data cut-off 11-Dec-2018.
	Adult r/r FL (E2202) **AE data** Adverse events indicative of the risk 'hematological disorders including cytopenias' at any time post-infusion were reported in 76 (78.4%) patients, including 42 (43.3%) patients with AEs suspected to be causally related to treatment with tisagenlecleucel by the Investigator. A total of 26 (26.8%) patients had AEs of severity grade 3 and 46 (47.4%) grade 4. Serious adverse events were reported in 9 (9.3%) patients. Most commonly reported PTs (reported in > 20% of patients) were neutropenia in 41 (42.3%) patients, anaemia 25 (25.8%) and white blood cell count decreased 21 (21.6 %). The majority of AEs occurred with an onset of: ≤ 8 weeks post tisagenlecleucel infusion - 73 (75.3%) patients, > 8 weeks to 1 year - 41 (42.7%), and > 1 year to 2 years - 8 (11.3%). Adverse event outcome at the time of the data cut-off: Resolved in 56 (73.7%) patients and not resolved in 18 (23.7%); resolved with sequelae and outcome unknown in 1 (1.3%) patient each. None of the AEs were fatal. Source: Annex 7; Study E2202 CSR - Extended follow-up. **Laboratory data** *Worst post-baseline hematology shifts at any time post-infusion (N=97)* • At baseline, decreased leukocyte counts grade 0, 1, 2, 3, and 4 were noted in 22.7%, 9.3%, 18.6%, 34.0%, and 15.5% of patients, respectively. At post-baseline at any time post infusion, worst value grade 3 was noted in 41.2% and grade 4 in 33.0% of patients. A total of 53.1% patients with baseline grades 0-2 shifted to post baseline grades 3-4. • At baseline, decreased neutrophil counts grade 0, 1, 2, 3, and 4 were noted in 46.4%, 9.3%, 19.6%, 14.4% and 10.3% of patients, respectively. At post-baseline at any time post infusion, worst value grade 3 was noted in 24.7% and grade 4 in 46.4% of patients. A total of 67.2% patients with baseline grades 0-2 shifted to post baseline grades 3-4.

Name of the risk	Details
Hematological disorders including cytopenias	

- At baseline, decreased lymphocyte counts grade 0, 1, 2, 3 and 4 were noted in 12.4%, 3.1%, 7.2%, 25.8% and 51.5% of patients, respectively. At post-baseline at any time post infusion, worst value grade 3 was noted in 34.0% and grade 4 in 52.6% of patients. A total of 62.5% patients with baseline grades 0-2 shifted to post baseline grades 3-4.
- At baseline, decreased platelet counts grade 0, 1, 2, 3, and 4 were noted in 39.2%, 44.3%, 6.2%, 6.2% and 4.1% of patients, respectively. At post-baseline at any time post infusion, worst value grade 3 was noted in 8.2% and grade 4 in 17.5% of patients. A total of 17.2% patients with baseline grades 0-2 shifted to post baseline grades 3-4.
- At baseline, decreased hemoglobin grade 0, 1, 2, 3, 4 was noted in 19.6%, 44.3%, 29.9%, 6.2% and 0 of patients, respectively. At post-baseline at any time post infusion, worst value grade 3 was noted in 24.7% and grade 4 in none of the patients. A total of 20.9% patients with baseline grades 0-2 shifted to post baseline grade 3.

Source: Study E2202 CSR - Extended follow-up.

Resolution of hematopoietic cytopenias grade 3 and 4 at Day 28

Persistent cytopenias grade 3 and 4 were observed beyond week 4 post tisagenlecleucel infusion and continued to resolve over time. The estimated probability of resolution in patients with cytopenias grade 3 and 4 at Week 4, by Month 3 and Month 6 using Kaplan-Meier analysis is presented below. By Month 6 the probability of resolution of cytopenias ranged from 70% to 100%.

		All patients (N=97)			
		By Month 3 [2]		By Month 6 [2]	
Parameter	**Week 4 event [1] n (%)**	**Patients at risk**	**Resolved probability %**	**Patients at risk**	**Resolved probability %**
WBC	13 (13.4)	5	61.5	2	84.6
Neutrophils	15 (15.5)	4	73.3	1	93.3
Lymphocytes	22 (22.7)	9	55.0	6	70.0
Platelets	16 (16.5)	7	56.3	3	81.3
Hemoglobin	3 (3.1)	0	100.0	0	100.0

Based on laboratory results regardless of blood transfusion.

[1] Number of patients with last value on or prior to Week 4 indicating Grade 3 or 4 cytopenia.

[2] Resolution of cytopenia is defined as achieving lab results of grade 2 or below. % resolved probability is among patients with cytopenia at week 4, obtained from the Kaplan-Meier survival estimates.

Name of the risk	Details
Hematological disorders including cytopenias	
	Source: Study E2202 CSR - Extended follow-up.
Risk factors and risk groups	All patients are at risk after tisagenlecleucel infusion. Extensive prior exposure to anti-cancer therapy, such as chemotherapy or radiation in addition to lymphodepleting chemotherapy in proximity to tisagenlecleucel infusion, enhance the risk.
Preventability	In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for potential neurological events, but also for CRS and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalization at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion. The risk can be managed with standard measures of observation, blood product support, growth factors and/or antibiotics as indicated. Since myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor, have the potential to worsen CRS (if it occurs), these are not recommended during the first 3 weeks after tisagenlecleucel infusion or until CRS has resolved.
Impact on the benefit-risk balance of the product	The benefit-risk balance with respect to hematological disorders including cytopenias remains positive. The risk is generally manageable with appropriate measures; some events may be severe or require blood products.
Public health impact	Impact is considered low to moderate, and manageable with appropriate monitoring and therapeutic treatment.

8.3.1.7 Important Identified Risk: Secondary malignancy of T-cell origin

Table 8-17 Clinical trial data of Secondary malignancy of T-cell origin

	Pediatric/young adult r/r B-ALL	Adult r/r DLBCL	Adult r/r FL
	B2202+B2205J+B2001X N=212 n (%)	C2201 N=115 n (%)	E2202 N=97 n (%)
Number of patients with at least one event at any time post tisagenlecleucel; (95% CI)	No events were observed		

	Pediatric/young adult r/r B-ALL	Adult r/r DLBCL	Adult r/r FL
	B2202+B2205J+B2001X N=212 n (%)	C2201 N=115 n (%)	E2202 N=97 n (%)

Source: - B2202 data cut-off date: 13Apr2018, B2205J data cut-off date: 24May2019, B2001X data cut-off date: 13Oct2020; C2201 data cut-off date: 11Dec2018; E2202 data cut-off date: 29Mar2021
- Numbers (n) represent counts of patients.
- A patient with multiple occurrences of an AE within a risk category is counted only once in the category.
- The 95% exact CI was computed using Clopper-Pearson method.
- Only post-infusion events are considered.
- * Percentage calculated based on number of patients with at least one event.
- MedDRA version 27.0 was used; CTCAE version 4.03 was used.Source:
Attachment to [Annex 7 - Table 2-1.1a]

Table 8-18 Important Identified Risk: Secondary malignancy of T-cell origin: other details

Name of the risk Secondary malignancies of T-cell origin	Details
Potential mechanisms	Insertion of lentiviral vector sequences into 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, in particular if integration occurs in proximity of an exon that might promote the expression of an endogenous oncogene or silence the expression of cellular tumor suppressor gene. This is associated with the potential risk of losing control of cell growth and developing secondary malignancies. For malignant transformation, excessive and permanent clonal outgrowth/expansion is a pre-requisite.
Evidence source(s) and strength of evidence	PRAC evaluated data on 38 cases of secondary malignancy of T-cell origin, including T-cell lymphoma and leukaemia, reported among approximately 42,500 patients who have been treated with CAR T-cell medicines. Tissue samples were tested in half of the cases, revealing the presence of the CAR construct in 7 cases. This suggests that the CAR T-cell medicine was involved in disease development. The secondary malignancies of T-cell origin have been reported within weeks and up to several years following administration of CAR T-cell medicines. (Source: Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 10-13 June 2024) Two of the 7 cases with the presence of the CAR construct were reported after tisagenlecleucel infusion. **Evidence of insertional oncogenesis**: Two cases of secondary malignancy of T-cell origin with CAR transgene detected in tumor tissue sample were reported after tisagenlecleucel infusion (both TCL). In one case, Novartis tests on the patient's PBMC sample 2 months after Kymriah infusion, apheresis material and final product with flow cytometry, ddPCR, lentiviral integration site analysis (LISA) and whole genome sequencing (WGS) confirmed CAR expression and T-cell monoclonality of the

Name of the risk Secondary malignancies of T-cell origin	Details
	expanded T-cell population in PBMC post Kymriah infusion, found dominant lentiviral insertion on 3 sites (DPF2, NPLOC4 and RAB11FIB3) which are not cancer gene, and preexisting mutations in cancer genes TET2 and DNMT3A already in apheresis material and final product. A second TET2 mutation seen in PBMC sample post Kymriah infusion with WGS was also seen in the final product and apheresis material with PacBio and Duplex Sequencing in low frequency. While direct evidence of insertional oncogenesis is not seen, the possibility of outgrowth of the preexisting malignant T-cell clone through the manufacturing process (cell expansion) or in vivo stimulation by CD19 engagement cannot be excluded. In the other case, CAR transgene was detected in tumor tissue by qPCR. LISA revealed a dominant clone with lentiviral integration in ANKHD1 EIF4EBP3, a gene that is not classified as cancer gene. Further tests (i.e. genomic sequencing, TCR repertoire analysis) are ongoing. **Comparison of T-cell malignancies frequency after Kymriah treatment with background incidence:** In a large population-based study (SEER database) covering about 28% of the US population, of the patients diagnosed with first primary BCL (N = 288,478) during 2000 to 2016 who were followed until date of diagnosis of a second primary cancer, death, lost to follow-up, or end of study (31-Dec-2017), whichever occurred first, a total of 354 T-cell lymphoma cases were observed (Chihara et al 2021). The incidence is therefore 0.123% (354/288,478). When the subtype of primary BCL is considered, of the total 80,155 DLBCL patients, 96 patients were observed with T-cell lymphoma (TCL). The incidence is therefore 0.120% (96/80155). These incidences can serve as background incidence since Kymriah, the first CAR-T approved by any health authority, was approved by FDA in October 2017 for the first indication. Reporting rate of T-cell lymphoma spontaneous report in post-marketing setting after Kymriah use: As of PSUR 9data cutoff on 12-Aug-2024, cumulatively a total of estimated 6471 DLBCL patients (6035 with in-specification product, 436 with out-of-specification product) and 741 FL patients (724 with in-specification product, 17 with out-of-specification product) had been exposed to Kymriah since August 2017, so the total exposure for B-cell lymphoma is 7212. Meanwhile, a total of 10 cases reported T-cell malignancies, of which 9 cases were T-cell lymphoma. The reporting rate with Kymriah post-marketing use is therefore 0.139% (10/7212) for T-cell malignancies and 0.125% (9/7212) for T-cell lymphoma. The latter is consistent with the background incidence of 0.123% for T-cell lymphoma in BCL patients in (Chihara et al 2021), though cases may be underreported in post-marketing setting. Incidence in Kymriah CIBMTR registry from PASS NIS study B2401 vs. background incidence: From the 2024 B2401 ASR (cutoff 05-Mar-2024): N = 1,399 patients are in the safety evaluable set for DLBCL in CIBMTR registry. A total of 3 patients were found to have T-cell lymphoma. The incidence of TCL in CIBMTR is 3 / 1,399

Name of the risk Secondary malignancies of T-cell origin	**Details**
	= 0.214% (95% CI - 0.048 to 0.684%), which looks higher than the background incidence of 0.120% in SEER data registry. However, considering the overlapping confidence intervals, the estimates are not statistically different.
Characterization of the risk:	No cases of secondary malignancies of T-cell origin, were observed in the clinical trials B2202, B2205J, B2001X, C2201, and E2202. All cases of secondary malignancies of T-cell origin were reported in post-marketing setting as spontaneous reports. As of 12-Aug-2024, a total of 10 cases were reported which include 8 cases of T-cell lymphoma, 1 case of peripheral T-cell lymphoma unspecified and 1 case of Large granular lymphocytosis (T-cell large granular lymphocyte leukemia). Onset was reported in 8 cases and ranged from 46 to 1064 days post tisagenlecleucel administration. Age was reported in 8 cases and ranged from 52 to 75 years old with 3 males and 5 females. The underlying malignancy as tisagenlecleucel indication was DLBCL in 9 patients and NHL in 1 patient. Prior lines of anticancer therapy (2 to 11 lines) were reported in 7 cases with similar chemotherapies, radiation in 4 cases and auto-HSCT in 3 cases. Three patents also had concurrent other malignancies besides the underlying DLBCL suggesting high genomic instability. One patient had EBV infection. Fatal outcome from T-cell malignancies was reported in 3 cases, with death in the context of HLH and hemorrhage in 2 cases. One case reported CAR positive T-cell lymphoma and was confirmed by Novartis investigative tests. Evidence of direct insertional oncogenesis was not found, however the possibility of outgrowth of the preexisting malignant T-cell clone through the manufacturing process (cell expansion) or in vivo stimulation by CD19 engagement cannot be excluded. A second case TCL with positive CAR detection was found; further testing with LISA revealed lentiviral insertion in ANKHD1 EIF4EBP3, a gene that is not classified as a cancer gene.
Risk factors and risk groups	Risk factors include anticancer therapies (chemotherapy, radiation therapy, and HSCT) prior to or post-tisagenlecleucel infusion. These factors are associated with the development of new malignancies. Additionally, historical or concurrent other malignancies suggest high genomic instability. Risk groups; Advanced age (>50 years old) with DLBCL.
Preventability	Unknown.
Impact on the benefit-risk balance of the product	With the rare occurrence of T-cell malignancies and the poor prognosis of indications the patients are treated for, the identified risk of secondary malignancies of T-cell origin does not impact the benefit-risk balance of the product.
Public health impact	Public health impact is considered to be low.

8.3.1.8 Important potential risk: Cerebral edema

Table 8-19 Clinical trial data of cerebral edema

	Pediatric/young adult r/r B-ALL B2202+B2205J+B2001X N=212 n (%)	Adult r/r DLBCL C2201 N=115 n (%)	Adult r/r FL E2202 N=97 n (%)
Number of patients with at least one event at any time post tisagenlecleucel; (95% CI)	2 (0.9) (0.1, 3.4)	1 (0.9) (0.0, 4.7)	0
Maximum grade			
Grade 3 AEs	0	0	0
Grade 4 AEs	0	0	0
Treatment-related AEs	1 (0.5)	1 (0.9)	0
SAEs	1 (0.5)	0	0
AE outcome*			
Recovered/resolved	2 (100)	1 (100)	0
Recovered/resolved with sequelae	0	0	0
Recovering/resolving	0	0	NA
Not recovered/not resolved	0	0	0
Fatal	0	0	0
Unknown	0	0	0

B2202 data cut-off date: 13-Apr-2018, B2205J data cut-off date: 24-May-2019, B2001X data cut-off date: 13-Oct-2020; C2201 data cut-off date: 11-Dec-2018; E2202 data cut-off date: 29-Mar-2021.
Numbers (n) represent counts of patients.
* Percentage calculated based on number of patients with at least one event.
MedDRA version 24.1 was used.
Source: Attachment to [Annex 7 - Table 2-1.1b]

Table 8-20 Important potential risk cerebral edema: Other details

Name of the risk Cerebral edema	Details
Potential mechanisms	The mechanism of fulminant, rapidly evolving cerebral edema with fatal outcome observed following CAR T-cell therapies other than tisagenlecleucel is poorly understood. Notably, the rare complication 'Cerebral edema' should be distinguished from the important identified risk 'Serious neurological adverse reactions' (Section 8.3.1.2) reflective of non-infectious encephalopathy/ICANS. Available evidence suggests that the pathophysiology of cerebral edema may be different from that of the more common manifestation of encephalopathy seen with ICANS (Morris et al 2021).

Name of the risk Cerebral edema	**Details**
Evidence source(s) and strength of evidence	No fatal cerebral edemas have been reported following tisagenlecleucel infusion in the clinical development program or the post-marketing setting to date that would resemble five fatal cases reported for JCAR015 (Juno). Importantly, the risk of fatal cerebral edema appears to be dependent of the anti-CD19 CAR construct used to engineer CAR T-cell therapies; JCAR015 presents a different construct of an anti-CD19 CAR than the CAR construct of tisagenlecleucel (Morris et al 2021). These five fatal cases of cerebral edema occurred in the ROCKET study and were characterized by a rapid evolution soon after JCAR015 infusion, appeared to be resistant to anti-cytokine treatment, and ensued brain death within 1-2 days after diagnosis. Following a retrospective exploratory analysis, it is believed that the fatal cerebral edemas in these five patients emerged from rapid T-cell expansion associated with the specific CAR T-cell product construct that determines the kinetics of T-cell expansion after infusion together with other risk factors such as high baseline blood levels of interleukin 15 (JCAR015; Gilbert 2017). Key findings of this retrospective analysis of the JCAR015 cases with fatal cerebral edema showed that all five patients experienced rapid, early expansion of their CAR T cells within a week of being infused (rather than the typical time frame of 12-14 days), high levels of the CD8+ subtype and, consequently, a sharp spike in cytokines such as interleukin 2 and TNFα. Autopsy results from two of the patients showed a breakdown of the blood-brain barrier and microvascular disruption, possibly due to inflammatory cytokine surge. Potential risk factors at baseline included age younger than 30 years, Philadelphia chromosome negativity, subset of disease (i.e., B-ALL), fewer prior regimens, higher levels of interleukin 15 and decreased levels of platelets (Gust et al 2017; Gust et al 2020). Since the five fatal cases after exposure to the JCAR015 product have become known, another patient with fatal cerebral edema was reported in the ZUMA-1 trial following axicabtagene ciloleucel treatment. This patient progressed to CRS grade 4 refractory to tocilizumab and dexamethasone on Day 4, developed cerebral edema refractory to siltuximab and mannitol on Day 9, and died on Day 11 (Turtle et al 2017). The clinical course of this case treated with KTE-019 may not be comparable with those 5 cases treated with JCAR015, which is further supported by a retrospective analysis of baseline cytokine and chemokine levels in serum and cerebrospinal fluid suggesting significant pre-existing underlying inflammatory condition providing an alternate explanation (BLA Clinical Review Memorandum Yescarta 2017). Another fatal cerebral edema case following axicabtagene ciloleucel was reported in the standard of care setting (Nastoupil et al 2020).
Characterization of the risk:	**Pediatric/young adult r/r B-ALL (B2202+B2205J+B2001X)** Adverse events indicative of the risk 'cerebral edema' at any time post-infusion were reported in 2 (0.9%) patients. One patient developed idiopathic intracranial hypertension, experienced visual impairment, and was diagnosed with pseudotumor cerebri causing papilledema (SAE; grade 2) 23 days after CTL019 infusion, which resolved after treatment with acetazolamide. The SAE was suspected to be related to tisagenlecleucel treatment. The other patient had a non-serious AE of increased intracranial pressure 73 days after CTL019 infusion,

Name of the risk Cerebral edema	Details
	which resolved after treatment with acetazolamide. The AE was not suspected to be related to tisagenlecleucel treatment. No grade 3, grade 4, or fatal AEs were reported. Source: Annex 7; Study B2202 Interim CSR data cut-off 13-Apr-2018, B2205J Final CSR, Study B2001X Final CSR. **Adult r/r DLBCL (C2201)** One patient experienced a non-serious AE of cerebral edema (grade 2) on Day 8, which resolved without treatment on the next day. The AE was suspected to be related to tisagenlecleucel treatment. No further information is available for this case. No SAEs or deaths due to cerebral edema were reported. Source: Annex 7; Study C2201 Interim CSR data cut-off 11-Dec-2018. **Adult r/r FL (E2202)** No AEs indicative of the risk 'cerebral edema' were reported. Source: Annex 7.
Risk factors and risk groups	Risk factors and risk groups are unknown.
Preventability	Unknown. Patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for potential neurological events, but also for CRS and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalization at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion.
Impact on the benefit-risk balance of the product	This is a potential risk. The impact of this risk on benefit-risk balance is unknown. Occurrences of cerebral edema with CD19 directed CAR T-cell therapies, other than tisagenlecleucel, have been fatal. To date, no occurrences of fatal cerebral edema have been reported with tisagenlecleucel.
Public health impact	Impact is low with appropriate monitoring.

8.3.1.9 Important potential risk: Generation of replication competent lentivirus

Table 8-21 Clinical trial data of generation of replication competent lentivirus

	Pediatric/young adult r/r B-ALL	Adult r/r DLBCL	Adult r/r FL
	B2202+B2205J+B2001X N=212 n (%)	C2201 N=115 n (%)	E2202 N=97 n (%)
Number of patients with at least one event at any time post tisagenlecleucel; (95% CI)	No events were observed		

B2202 data cut-off date: 13-Apr-2018, B2205J data cut-off date: 24-May-2019, B2001X data cut-off date: 13-Oct-2020; C2201 data cut-off date: 11-Dec-2018; E2202 data cut-off date: 29-Mar-2021.
Numbers (n) represent counts of patients.
* Percentage calculated based on number of patients with at least one event.
MedDRA version 24.1 was used.
Source: Attachment to [Annex 7 - Table 2-1.1b]

Table 8-22 Important potential risk: Generation of replication competent lentivirus: Other details

Name of the risk Generation of replication competent lentivirus	**Details**
Potential mechanisms	Theoretically, RCL may be generated during the tisagenlecleucel manufacturing or subsequently after introduction of lentiviral vector transduced viable T cells into the patient. However, an RCL resulting from manufacturing is highly unlikely, since elements are incorporated in the design of the vector system that minimize vector recombination and generation of RCL. The lentiviral vectors used to manufacture tisagenlecleucel are third generation self-inactivating. Lentiviral vectors are produced by transient transfection of a suspension HEK293T manufacturing cell line with four plasmid constructs consisting of the transfer plasmid, the Gag/Pol packaging plasmid, the envelope packaging plasmid and the Rev packaging plasmid. This method for generating lentiviral vectors was designed to greatly reduce recombination events, which could give rise to RCL activity. In line with regulatory guidance, all lentiviral vector lots are tested for the presence of RCL (by qPCR for VSV-G) as part of release at both end of production and final lentiviral vector product, with the required specification of 'No RCL detected'. All lentiviral vector lots used for tisagenlecleucel manufacturing have tested negative for RCL activity thus far. Furthermore, final tisagenlecleucel product undergoes sensitive assays for detection of RCL before it can be released to the patient. Thus, patients will only receive cell products that meet RCL release criteria.
Evidence source(s) and strength of evidence	Tisagenlecleucel uses third generation self-inactivating lentiviral vector. Generation of an RCL following infusion of the vector product remains a theoretical possibility. Replication-competent lentivirus will be detected by qPCR for VSV-G of peripheral blood.

Name of the risk Generation of replication competent lentivirus	**Details**
	Replication-competent lentivirus has not been described in the scientific literature for lentiviral vectors that use a production method similar to the tisagenlecleucel vectors (Cornetta et al 2018). Furthermore, lentiviral vectors have been successfully used in conjunction with HIV infected patients (Chung et al 2014; Delviks-Frankenberry et al 2019; Lemiale and Korokhov 2009), with no evidence of vector mobilization after 60 days or insertional mutagenesis observed up to 36 months (Levine et al 2006). To date, no indication of RCL tisagenlecleucel batches was detected by using VSV-G DNA (specification ≤ 50 copies/µg) assay as a substitute. Furthermore, patients enrolled in interventional clinical trials have been screened for RCL with no RCL identified to date.
Characterization of the risk:	No RCL was detected in the tisagenlecleucel development program. Source: Annex 7.
Risk factors and risk groups	The development of RCL could pose a risk to both the patient and their close contacts.
Preventability	The lentiviral vector has been designed to minimize the probability non-homologous recombination, thereby preventing the generation of a RCL.
Impact on the benefit-risk balance of the product	This is a potential risk. The impact of this risk on benefit-risk balance remains unknown. The occurrence of this risk is highly unlikely.
Public health impact	Impact is low with appropriate monitoring.

8.3.1.10 Important potential risk: Secondary malignancies (except secondary malignancy of T-cell origin) including vector insertion site oligo monoclonality

Table 8-23 Clinical trial data of secondary malignancies (except secondary malignancy of T-cell origin) including vector insertion site oligo monoclonality

	Pediatric/young adult r/r B-ALL **B2202+B2205J+B2001X** **N=212** **n (%)**	**Adult r/r DLBCL** **C2201** **N=115** **n (%)**	**Adult r/r FL** **E2202** **N=97** **n (%)**
Number of patients with at least one event at any time post tisagenlecleucel; (95% CI)	11 (5.2) (2.6, 9.1)	10 (8.7) (4.2, 15.4)	4 (4.1) (1.1, 10.2)

	Pediatric/young adult r/r B-ALL	Adult r/r DLBCL	Adult r/r FL
	B2202+B2205J+B2001X N=212 n (%)	C2201 N=115 n (%)	E2202 N=97 n (%)
Maximum grade			
Grade 3 AEs	4 (1.9)	3 (2.6)	0
Grade 4 AEs	5 (2.4)	4 (3.5)	0
Treatment-related AEs	0	0	1 (1.0)
SAEs	8 (3.8)	6 (5.2)	3 (3.1)
AE outcome*			
Recovered/resolved	2 (18.2)	3 (30.0)	3 (75.0)
Recovered/resolved with sequelae	1 (9.1)	0	0
Recovering/resolving	0	0	NA
Not recovered/not resolved	6 (54.5)	5 (50.0)	1 (25.0)
Fatal	2 (18.2)	2 (20.0)	0
Unknown	0	0	0

B2202 data cut-off date: 13-Apr-2018; B2205J data cut date: 24-May-2019, B2001X data cut-off date: 13-Oct-2020; C2201 data cut-off date: 11-Dec-2018; E2202 data cut-off date: 29-Mar-2021.
[1] Includes one non-serious AE grade 2 of 'intermittend fever secondary to ALL' (verbatim) coded as ALL, which reflected the underlying study indication and not a second primary malignancy.
[2] Includes one non-serious AE grade 2 of 'intermittent abdominal and back pain due to lymphoma' (verbatim) coded as 'lymphoma', which reflected the underlying study indication and not a second primary malignancy.
Note: For the indication pediatric and young adult r/r B-ALL, only data from Study B2202 are presented. Since Study B2001X captured disease progression, relapse, or refractory status of the underlying B-ALL disease as AEs, which would have confounded the analysis of this risk, the three pediatric/young adult B-ALL studies B2202, B2205J, and B2001X have not been pooled. However, respective events of secondary malignancies (including vector insertion site oligo/monoclonality) that occurred in these studies are presented in Table 8-24.
Numbers (n) represent counts of patients.
* Percentage calculated based on number of patients with at least one event.
AEs are based on MedDRA v 27.0 (while C2201 and E2202 is based on MedDRA v24.1).
Source: Attachment to [Annex 7 - Table 2-1.1b]

Table 8-24 Important potential risk secondary malignancies (except secondary malignancy of T-cell origin) including vector insertion site oligo/monoclonality: Other details

Name of the risk Secondary malignancies (except T-cell origin) including vector insertion site oligo/ monoclonality	Details
Potential mechanisms	Insertion of lentiviral vector sequences into 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, in particular if integration occurs in proximity of an exon that might promote the expression of an endogenous oncogene or silence the expression of cellular tumor suppressor gene. This is associated with the potential risk of losing control of cell growth and developing secondary malignancies. For malignant transformation, excessive and permanent clonal outgrowth/expansion is a pre-requisite.
Evidence source(s) and strength of evidence	To date, no cases of secondary malignancy excluding those of T-cell origin have been assessed to be causally related to tisagenlecleucel by Novartis. No suspected secondary malignancies other than T-cell origin following CAR T-cell therapies developed by other pharmaceutical companies have been reported in the literature. Based on historic experience in patients with X-linked SCID, chronic granulomatous disease, and Wiskott-Aldrich syndrome, vector-mediated insertional mutagenesis and subsequent malignant cell transformation have been observed following gene correction via autologous human stem cell based gene therapy, where first-generation gamma-retroviral vectors harboring long terminal repeats with strong enhancer/promoter sequences have been used (Hacein-Bey-Abina et al 2003, Howe et al 2008, Boztug et al 2010, Stein et al 2010, Persons and Baum 2011). The potential risk of insertional oncogenesis was addressed in two LISA studies where 12 batches of manufactured tisagenlecleucel product ready for administration in patients (6 patients each from study B2202 and C2201) and two batches of product manufactured from healthy donor cells were analyzed. The results indicate that there was no preferential integration near genes of concern, no preferential sites of integration (hot spots), and no preferential outgrowth of cells harboring integration sites of concern. Tisagenlecleucel is based on autologous, fully differentiated T cells and therefore the carcinogenicity risk is considered to be low in comparison to genetic modification or repair of human stem cells. In a review of CAR T-cell therapies, Bonifant et al 2016 as well as Mohanlal et al 2016 discussed that to date no cases of malignant transformation have been reported for genetic modification of T cells and that there currently is no evidence for vector-induced immortalization, clonal expansion, or enrichment for integration sites near genes implicated in growth control or transformation. This is supported

Name of the risk Secondary malignancies (except T-cell origin) including vector insertion site oligo/ monoclonality	Details
	by the results of the LISA studies performed during the development of tisagenlecleucel. For other details refer to Section 7.2.7.2.
Characterization of the risk:	**Pediatric/young adult r/r B-ALL** **B2202+B2205J+B2001X** A total of 11 patients (5.2%) were reported with AEs under the potential risk secondary malignancies (except secondary malignancy of T-cell origin) including vector insertion site oligo/monoclonality' at any time post tisagenlecleucel infusion. Actual secondary malignancies occurred in three patients (1.4%), with two patients (0.9%) having MDS (grade 3 and grade 2) and one patient (0.5%) having glioblastoma multiforme (fatal) with acquired gene mutation (TP53 Gene mutation P.G254S). All three secondary malignancies were serious; none was suspected by the Investigator to be related to tisagenlecleucel. Time to onset was Day 262 and Day 260 post tisagenlecleucel infusion for the two MDS cases, and Day 965 for the glioblastoma multiforme case (with acquired gene mutation found on Day 271). Glioblastoma multiforme was reported with fatal outcome. The remaining eight patients were all reported with relapse, progression or symptoms of underlying ALL. These cases are not real secondary malignancy cases. Adverse event outcome at the time of the data cut-off: Not recovered in 6 (54.5 %) patients. Source: Annex 7; Study B2202 Interim CSR data cut-off 13-Apr-2018, B2205J Final CSR, Study B2001X Final CSR. **Adult r/r DLBCL (C2201)** A total of 10 patients (8.7%) experienced AEs potentially indicative of the risk secondary malignancies (except secondary malignancy of T-cell origin) including vector insertion site oligo/monoclonality'. The AEs retrieved included 1 non-serious AE grade 2 of 'intermittent abdominal and back pain due to lymphoma' (verbatim) coded as 'lymphoma', reflecting the underlying study indication and not a second primary malignancy. Excluding this case from further analysis, there were nine AEs of secondary malignancies (except secondary malignancy of T-cell origin) including vector insertion site oligo/monoclonality' reported in nine patients at any time post tisagenlecleucel infusion with the following PTs: • Prostate cancer (n = 3; time to onset Day 73, Day 574, Day 602) • Basal cell carcinoma (n = 2; time to onset Day 55, Day 307)

Name of the risk Secondary malignancies (except T-cell origin) including vector insertion site oligo/ monoclonality	Details
	• Acute myeloid leukaemia (n = 1; time to onset Day 364; 1 fatal event) • Myelodysplastic syndrome (n = 1; time to onset Day 414) • Neuroendocrine carcinoma (n = 1; time to onset Day 231; 1 fatal event) • Myelodysplastic syndrome with multilineage dysplasia (n=1; time to onset Day 356) Pre-existing pulmonary lesion suggested presence of malignancy prior to tisagenlecleucel in the case of pulmonary neuroendocrine carcinoma. No causal relationship between any of these AEs and tisagenlecleucel could be established with certainty by Novartis. Adverse event outcome at the time of the data cut-off: Resolved in 3 patients (30.0%), not resolved in 5 (50.0%; including the patient with the AE of lymphoma) and fatal in 2 (20.0%). Fatal outcome involved the AEs AML and neuroendocrine tumor. Source: Annex 7; Study C2201 Interim CSR data cut-off 11-Dec-2018. **Adult r/r FL (E2202)** A total of 4 (4.1%) patients experienced AEs potentially indicative of the risk secondary malignancies (except secondary malignancy of T-cell origin) including vector insertion site oligo/monoclonality', including 1 (1.0%) patient with 2 AEs (squamous cell carcinoma and malignant melanoma) suspected to be causally related to tisagenlecleucel by the Investigator. No AEs with grade 3 or grade 4 severity were reported. Serious adverse events were reported in 3 (3.1%) patients. The 6 AEs of 'secondary malignancies (except secondary malignancy of T-cell origin) including vector insertion site oligo/monoclonality reported in 4 patients at any time post tisagenlecleucel infusion comprised the following PTs: • Basal cell carcinoma (n = 2; time to onset Day 115 and Day 709, Day 185) • Squamous cell carcinoma (n = 2; time to onset Day 115 and Day 709, Day 283) • Malignant melanoma (n = 1; time to onset Day 324) • Bowen's disease (n = 1; time to onset Day 82) Of the 4 patients, 1 was diagnosed with both squamous cell carcinoma and basal cell carcinoma and 1 with both squamous cell carcinoma and malignant melanoma.

Name of the risk	Details
Secondary malignancies (except T-cell origin) including vector insertion site oligo/ monoclonality	
	In the latter patient, transgene and RCL test results of blood and secondary malignancy tissue samples taken from both the squamous cell carcinoma and malignant melanoma precluded transgene- or RCL-mediated clonal transformation. In all other cases, a causal relationship between the secondary malignancy and tisagenlecleucel could not be established with certainty by Novartis. Adverse event outcome at the time of the data cut-off: Resolved in 3 patients (75.0%) and not resolved in 1 (25.0%) patient. No fatal AE was reported. Source: Annex 7; Study E2202 CSR - Extended follow-up
Risk factors and risk groups	Since this is a potential risk, no attributable increase to tisagenlecleucel has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Preventability	Unknown.
Impact on the benefit-risk balance of the product	This is a potential risk. The impact of this risk on benefit-risk balance remains unknown.
Public health impact	Public health impact is considered to be low to moderate.

8.3.1.11 Important potential risk: New occurrence or exacerbation of an autoimmune disorder

Table 8-25 Clinical trial data of new occurrence or exacerbation of an autoimmune disorder

	Pediatric/young adult r/r B-ALL	Adult r/r DLBCL	Adult r/r FL
	B2202+B2205J+B2001X N=212 n (%)	C2201 N=115 n (%)	E2202 N=97 n (%)
Number of patients with at least one event at any time post tisagenlecleucel; (95% CI)	114 (53.8) (46.8, 60.6)	25 (21.7) (14.6, 30.4)	20 (20.6) (13.1, 30.0)
Maximum grade			
Grade 3 AEs	24 (11.3)	7 (6.1)	2 (2.1)
Grade 4 AEs	4 (1.9)	5 (4.3)	0

	Pediatric/young adult r/r B-ALL	Adult r/r DLBCL	Adult r/r FL
	B2202+B2205J+B2001X N=212 n (%)	C2201 N=115 n (%)	E2202 N=97 n (%)
Treatment-related AEs	101 (47.6)	19 (16.5)	12 (12.4)
SAEs	14 (6.6)	5 (4.3)	2 (2.1)
AE outcome*			
Recovered/resolved	41 (36.0)	7 (28.0)	10 (50.0)
Recovered/resolved with sequelae	1 (0.9)	0	0
Recovering/resolving	9 (7.9)	1 (4.0)	NA
Not recovered/not resolved	61 (53.5)	17 (68.0)	9 (45.0)
Fatal	1 (0.9)	0	0
Unknown	1 (0.9)	0	1 (5.0)

B2202 data cut-off date: 13-Apr-2018, B2205J data cut-off date: 24-May-2019, B2001X data cut-off date: 13-Oct-2020; C2201 data cut-off date: 11-Dec-2018; E2202 data cut-off date: 29-Mar-2021.
Numbers (n) represent counts of patients.
* Percentage calculated based on number of patients with at least one event.
MedDRA version 24.1 was used.
Source: Attachment to [Annex 7 - Table 2-1.1b]

Table 8-26 Important potential risk new occurrence or exacerbation of an autoimmune disorder: Other details

Name of the risk New occurrence or exacerbation of an autoimmune disorder	Details
Potential mechanisms	Modulation of an individual's immune status, as it may occur with anti-cancer therapy and biological drugs, may cause new occurrence or exacerbation of a pre-existing autoimmune disorder.
Evidence source(s) and strength of evidence	Most autoimmune diseases are driven by a dysfunction in the immune network consisting of B cells, T cells, and other immune cells. Reciprocal roles of T-cell help for B cells during adaptive immune responses and B-cell help in $CD4^+$ T-cell activation are being increasingly recognized (Hampe 2012). An emerging number and variety of autoimmune diseases following anti-cancer treatment including immunotherapy are reported, ranging from asymptomatic immunological alterations to life-threatening systemic autoimmune diseases (Pérez-De-Lis et al 2017). However, specific etiopathogenic mechanisms that could clearly link the induced autoimmune disorder with the immunological pathways altered by the anti-cancer treatments are not well understood. Persistent immune abnormalities after treatment with chemotherapy, development of auto-antibodies and neoantigens are proposed to be crucial in the pathogenesis of autoimmune diseases post anti-cancer treatment (Descotes and Gouraud 2008, Chang and Gershwin 2010, Amos et al 2011).

Name of the risk New occurrence or exacerbation of an autoimmune disorder	**Details**
	Based on current knowledge, the risk of autoimmune reaction is considered low with tisagenlecleucel, since CD19 is not present on most normal tissue other than B cells. The occurrence or exacerbation of an autoimmune disorder has not been observed with tisagenlecleucel to date. Prior anti-cancer therapy, such as radiation and chemotherapy, lymphodepleting chemotherapy prior to treatment with tisagenlecleucel or concomitant treatment may present additional risk factors.
Characterization of the risk:	To retrieve AEs in support of analyzing the risk 'new occurrence or exacerbation of an autoimmune disorder', the previously used MedDRA HLGT 'Autoimmune disorders' has been conservatively replaced by the SMQ 'Immune-mediated/autoimmune disorders', which has become newly available following issuance of EU RMP v3.0. This new SMQ includes a broad selection of PTs (such as hypogammaglobulinemia, encephalopathy or haemophagocytic lymphohistiocytosis), which do not reflect true autoimmune disorders in the setting of CAR T-cell therapy but rather present commonly observed ADRs of tisagenlecleucel important identified risks discussed in previous sections. As a result of this new SMQ use, the number of AEs for Studies B2202 and C2201 retrieved for the risk 'new occurrence or exacerbation of an autoimmune disorder' has increased compared to EU RMP v3.0. **Pediatric/young adult r/r B-ALL (B2202+B2205J+B2001X)** Adverse events indicative of the risk 'new occurrence or exacerbation of an autoimmune disorder' at any time post-infusion were reported in 114 (53.8%) patients, including 101 (47.6%) patients with AEs suspected to be causally related to tisagenlecleucel by the Investigator. Twenty-four (11.3%) patients had AEs of severity grade 3 and 4 (1.9%) AEs of grade 4. Serious adverse events were reported in 14 (6.6%) patients. The most frequently reported PTs (> 3.0% of patients) were hypogammaglobulinaemia (84 patients; 39.6%), encephalopathy (14; 6.6%), haemophagocytic lymphohistiocytosis (9; 4.2%), and pancreatitis (8; 3.8%). Adverse events occurred with an onset of: within 8 weeks post tisagenlecleucel infusion - in 89 (42%) patients, > 8 weeks to 1 year - 31 (16.3%), > 1 year to 2 years - 3 (3.1%) and > 2 years - 1 (3.4%). Adverse event outcome at the time of the data cut-off: Not resolved in 61 (53.5%) patients, resolved in 41 (36%), resolving in 9 (7.9%), and resolved with sequelae and outcome unknown in 1 (0.9%) patient each. There was one fatal AE (encephalitis of unknown etiology) No AE that would constitute autoimmune disease associated with tisagenlecleucel could be identified. Source: Annex 7; Study B2202 Interim CSR data cut-off 13-Apr-2018, B2205J Final CSR, Study B2001X Final CSR. **Adult r/r DLBCL (C2201)**

Name of the risk New occurrence or exacerbation of an autoimmune disorder	**Details**
	Adverse events indicative of the risk 'new occurrence or exacerbation of an autoimmune disorder' at any time post-infusion were reported in 25 (21.7%) patients, including 19 (16.5%) patients with AEs suspected to be causally related to tisagenlecleucel by the Investigator. Seven (6.1%) patients had AEs of severity grade 3 and 5 (4.3%) patients had AEs of grade 4. Serious adverse events were reported in 5 (4.3%) patients. The most frequently reported PTs (> 3.0% of patients) were hypogammaglobulinemia (9 patients; 7.8%) and encephalopathy (7; 6.1%). Adverse events occurred with an onset of: within 8 weeks post tisagenlecleucel infusion - in 16 (13.9%) patients, > 8 weeks to 1 year - 8 (8.0%), > 1 year to 2 years - 2 (4.5%) and > 2 years - 1 (3.7%). Adverse event outcome at the time of the data cut-off: Resolved in 7 (28.0%) patients and not resolved in 17 (68.0%) patients; resolving in 1 (4.0%) patient. There was no fatal AE. No AE that would constitute autoimmune disease associated with tisagenlecleucel could be identified. Source: Annex 7; Study C2201 Interim CSR data cut-off 11-Dec-2018. **Adult r/r FL (E2202)** Adverse events indicative of the risk 'new occurrence or exacerbation of an autoimmune disorder' at any time post-infusion were reported in 20 (20.6%) patients, including 12 (12.4%) patients with AEs suspected to be causally related to tisagenlecleucel by the Investigator. Two (2.1%) patients had AEs of severity grade 3; no patients had grade 4 AEs. Serious adverse events were reported in 2 (2.1%) patients. The most frequent PTs (reported in > 3.0% of patients) were hypogammaglobulinemia (14 patients; 14.4%) and encephalopathy (3; 3.1%). Adverse events occurred with an onset of: within 8 weeks post tisagenlecleucel infusion - in 12 (12.4%) patients, > 8 weeks to 1 year - 9 (9.4%), and > 1 year to 2 years - 1 (1.4%) patient. Adverse event outcome at the time of the data cut-off: Resolved in 10 (50.0%) patients, and not resolved in 9 (45.0%); the outcome was unknown in 1 (5.0%) patient. There was no fatal AE. No AE that would constitute autoimmune disease associated with tisagenlecleucel could be identified. Source: Annex 7; Study E2202 CSR - Extended follow-up.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to tisagenlecleucel has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Preventability	Unknown.

Name of the risk	Details
New occurrence or exacerbation of an autoimmune disorder	
	Autoimmunity flares can be addressed by increasing immunosuppression if clinically indicated.
Impact on the benefit-risk balance of the product	This is a potential risk. The impact of this risk on benefit-risk balance remains unknown.
Public health impact	Unknown

8.3.1.12 Important potential risk: Aggravation of graft-versus-host disease

Table 8-27 Clinical trial data of aggravation of graft-versus-host disease

	Pediatric/young adult r/r B-ALL	Adult r/r DLBCL	Adult r/r FL
	B2202+B2205J+B2001X N=212 n (%)	C2201 N=115 n (%)	E2202 N=97 n (%)
Number of patients with at least one event at any time post tisagenlecleucel; (95% CI)	6 (2.8) (1.0, 6.1)	0	1 (1.0) (0.0, 5.6)
Maximum grade			
Grade 3 AEs	2 (0.9)	0	1 (1.0)
Grade 4 AEs	0	0	0
Treatment-related AEs	2 (0.9)	0	0
SAEs	1 (0.5)	0	1 (1.0)
AE outcome*			
Recovered/resolved	3 (50.0)	0	1 (100)
Recovered/resolved with sequelae	0	0	0
Recovering/resolving	1 (16.7)	0	NA
Not recovered/not resolved	2 (33.3)	0	0
Fatal	0	0	0
Unknown	0	0	0

B2202 data cut-off date: 13-Apr-2018, B2205J data cut-off date: 24-May-2019, B2001X data cut-off date: 13-Oct-2020; C2201 data cut-off date: 11-Dec-2018; E2202 data cut-off date: 29-Mar-2021.
Numbers (n) represent counts of patients.
* Percentage calculated based on number of patients with at least one event.
MedDRA version 24.1 was used.
Source: Attachment to [Annex 7 - Table 2-1.1b]

Table 8-28 Important potential risk aggravation of graft-versus-host disease: Other details

Name of the risk Aggravation of graft-versus-host disease	**Details**
Potential mechanisms	Patients, who have host and donor hematopoietic cells (i.e., mixed chimerism) due to allogeneic HSCT prior to leukapheresis required to manufacture tisagenlecleucel, may develop GVHD or aggravation of pre-existing GVHD following administration of tisagenlecleucel infusion.
Evidence source(s) and strength of evidence	The chance of GVHD occurring in patients after tisagenlecleucel infusion per se is considered low, but there is a potential risk of aggravation of pre-existing GVHD in patients with donor chimerism from a prior allogeneic HSCT post-tisagenlecleucel due to the milieu provided by robust activation of the transduced viable T cells. A study of activated DLIs (ex vivo activated cells collected from the donor and grown in the same fashion as tisagenlecleucel but without the CAR introduction) did not show high rates of GVHD (2/18 patients with grade 3 GVHD and none with grade 4) (Porter et al 2006). Of 18 ALL patients treated with autologous tisagenlecleucel therapy who had relapsed after prior allogeneic HSCT with residual mixed chimerism, none have developed GVHD after autologous tisagenlecleucel infusion (Maude et al 2014).
Characterization of the risk:	**Pediatric/young adult r/r B-ALL (B2202+B2205J+B2001X)** Six (2.8%) patients experienced AEs indicative of the risk 'aggravation of graft-versus-host disease' at any time post tisagenlecleucel infusion: • In 4 of these patients (two of which had a medical history of HSCT prior to tisagenlecleucel infusion), 4 AEs of GVHD developed post HSCT performed after tisagenlecleucel infusion (allogeneic HSCT Day 310/GVHD Day 322; Day 124/Day 160; Day 206/Day 248; Day 246/Day 752); these AEs were not suspected to be causally related to tisagenlecleucel infusion by the Investigator. • The other 2 patients received HSCT prior to tisagenlecleucel infusion and developed 3 AEs of GVHD that were suspected to be causally related to tisagenlecleucel by the Investigator. One patient had a medical history of GVHD and developed GVHD in the gastrointestinal tract (SAE) on Day 73; the second patient developed GVHD in skin on Day 26 and a second episode of GVHD on Day 71. Source: Annex 7; Study B2202 Interim CSR data cut-off 13-Apr-2018, B2205J Final CSR, Study B2001X Final CSR. **Adult r/r DLBCL (C2201)** No AEs of aggravation of graft-versus-host disease were reported. Source: Annex 7. **Adult r/r FL (E2202)**

Name of the risk Aggravation of graft-versus-host disease	Details
	One patient (1.0%) experienced two AEs indicative of the risk 'aggravation of graft-versus-host disease', involving the events (PT) GVHD in skin (non-serious, grade 2, onset on Day 278) and GVHD in gastrointestinal tract (SAE, grade 3, onset Day 292). These AEs occurred following allogenic HSCT on Day 266 post tisagenlecleucel infusion and were not suspected to be causally related to tisagenlecleucel infusion by the Investigator. This patient recovered from both AEs. Source: Annex 7; Study E2202 CSR Extended follow-up.
Risk factors and risk groups	Patients with the presence of active GVHD from prior HSCT.
Preventability	Tisagenlecleucel infusion is not recommended within 4 months of undergoing an allogenic HSCT. Tisagenlecleucel infusion should be delayed, if a patient has active GVHD. In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for potential neurological events, but also for CRS and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalization at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion.
Impact on the benefit-risk balance of the product	This is a potential risk. The impact of this risk on benefit-risk balance remains unknown. GVHD can be severe but can be controlled with steroids and other immunosuppressants.
Public health impact	Impact is low to moderate with prompt monitoring and treatment.

8.3.1.13 Important potential risk: Transmission of infectious agents

Table 8-29 Clinical trial data of transmission of infectious agents

	Pediatric/young adult r/r B-ALL	Adult r/r DLBCL	Adult r/r FL
	B2202+B2205J+B2001X N=212 n (%)	C2201 N=115 n (%)	E2202 N=97 n (%)
Number of patients with at least one event at any time post tisagenlecleucel; (95% CI)	No events were observed		

	Pediatric/young adult r/r B-ALL	Adult r/r DLBCL	Adult r/r FL
	B2202+B2205J+B2001X N=212 n (%)	C2201 N=115 n (%)	E2202 N=97 n (%)

B2202 data cut-off date: 13-Apr-2018, B2205J data cut-off date: 24-May-2019, B2001X data cut-off date: 13-Oct-2020; C2201 data cut-off date: 11-Dec-2018; E2202 data cut-off date: 29-Mar-2021.
Numbers (n) represent counts of patients.
* Percentage calculated based on number of patients with at least one event.
MedDRA version 24.1 was used.
Source: Attachment to [Annex 7 - Table 2-1.1b]

Table 8-30 Important potential risk: transmission of infectious agents: Other details

Name of the risk Transmission of infectious agents	Details
Potential mechanisms	Transmission of infections agents could lead to new infections in close contacts including personnel involved in the tisagenlecleucel manufacturing process or health care providers involved in leukapheresis and administering tisagenlecleucel in addition to patients treated with tisagenlecleucel.
Evidence source(s) and strength of evidence	Multiple steps are required to produce tisagenlecleucel CAR T cells, involving leukapheresis to obtain patient autologous starting material, enrichment and activation, gene transduction via lentiviral vector and expansion. Transmission of infectious material via product could potentially derive from the patient's own leukapheresis material prepared from autologous blood, other material including the tisagenlecleucel viral vector required to manufacture tisagenlecleucel, through contamination during the manufacturing process or inadequate storage. The risk associated with tisagenlecleucel is considered very low. Stringent precautions to prevent introduction of viral adventitious agents and to ensure microbial safety of tisagenlecleucel are in place in compliance with principles of good manufacturing practices and regulatory guidelines. The starting material for producing tisagenlecleucel are the patient's autologous (i.e., donor and recipient are the same) non-mobilised peripheral blood mononuclear cells collected by leukapheresis. Tisagenlecleucel is composed of autologous CD4+ and CD8+ T cells genetically modified with a murine HIV-1 lentiviral vector encoding a CAR against CD19. The product is manufactured by expansion of patient T cells after transduction without any hold step. Due to the nature of the product (i.e., cells), there is no possibility to introduce terminal sterilization or dedicated viral removal and inactivation steps. Therefore, precautions to prevent introduction of viral adventitious agents and to ensure microbial safety of tisagenlecleucel product are taken as detailed below. 1. Control of raw materials and of the tisagenlecleucel vector • Control of animal and human derived raw materials entering the manufacturing process through certificates of origin and suitability. For

Name of the risk Transmission of infectious agents	Details
	human derived materials such as human serum, viral inactivation steps in the manufacturing process of these materials are performed • Control of the production of tisagenlecleucel vector using HEK293T cells, which are not known to express endogenous viruses • Additional controls through filtration of raw materials (media) performed prior to use in manufacturing • Control of the tisagenlecleucel vector through testing for adventitious viral agents • Testing for relevant human viruses as part of the patient eligibility assessment 2. Process and environmental controls • Control of the tisagenlecleucel drug product manufacturing process (antibiotics free) through use of closed systems. Where there are open steps, the process is performed under environmentally controlled conditions • Environmental controls (e.g., evaluating the quality of air, temperature, surfaces, personnel in a cleanroom environment) • Cleaning and decontamination of work surfaces and equipment • Aseptic verification, simulating all process steps and interventions is conducted to verify that the process is capable of maintaining sterility 3. Control of tisagenlecleucel by microbial contaminants testing as part of drug product release testing • Testing for bacterial endotoxin • Testing for sterility • Testing for mycoplasma Details on shipping and storage conditions of tisagenlecleucel product and disposal are described in Section 7.2.3.
Characterization of the risk:	No AEs were observed in the clinical trials B2202, B2205J, B2001X, C2201, and E2202.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to tisagenlecleucel has been established. There is a potential risk of transmission of infectious agents to close contacts including personnel involved in the tisagenlecleucel manufacturing process or health care providers involved in leukapheresis and administering tisagenlecleucel in addition to patients treated with tisagenlecleucel.
Preventability	See under 'Evidence source(s) and strength of evidence'. In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for potential neurological events, but also for CRS and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalization at the first signs/symptoms of cytokine release syndrome

Name of the risk Transmission of infectious agents	Details
	and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion.
Impact on the benefit-risk balance of the product	This is a potential risk. The impact of this risk on benefit-risk balance remains unknown.
Public health impact	The public health impact is expected to be low, considering that only those, who are in close contact to the product via the manufacturing process, leukapheresis or tisagenlecleucel administration, and patients treated with tisagenlecleucel are involved.

8.3.1.14 Important potential risk: Decrease in cell viability due to inappropriate handling of the product

Table 8-31 Clinical trial data of decrease in cell viability due to inappropriate handling of the product

	Pediatric/young adult r/r B-ALL B2202+B2205J+B2001X N=212 n (%)	Adult r/r DLBCL C2201 N=115 n (%)	Adult r/r FL E2202 N=97 n (%)
Number of patients with at least one event at any time post tisagenlecleucel; (95% CI)	No events were observed		

B2202 data cut-off date: 13-Apr-2018, B2205J data cut-off date: 24-May-2019, B2001X data cut-off date: 13-Oct-2020; C2201 data cut-off date: 11-Dec-2018; E2202 data cut-off date: 29-Mar-2021.
Numbers (n) represent counts of patients.
* Percentage calculated based on number of patients with at least one event.
MedDRA version 24.1 was used.
Source: Attachment to [Annex 7 - Table 2-1.1b]

Table 8-32 Important potential risk decrease in cell viability due to inappropriate handling of the product

Name of the risk Decrease in cell viability due to inappropriate handling of the product	Details
Potential mechanisms	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.

Name of the risk Decrease in cell viability due to inappropriate handling of the product	**Details**
Evidence source(s) and strength of evidence	Inconsistencies may arise due to product handling including subjective determination of the thaw endpoint and risk of water borne contamination.
Characterization of the risk:	No relevant AEs were observed in the clinical trials B2202, B2205J, B2001X, C2201, and E2202.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to tisagenlecleucel has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Preventability	Tisagenlecleucel should be administered at a qualified clinical facility. Qualified center personnel must follow appropriate protocols for product handling to receive, thaw, and infuse the finished tisagenlecleucel product. Instructions are provided in the SmPC and Healthcare professional information pack. In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for potential neurological events, but also for CRS and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalization at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion.
Impact on the benefit-risk balance of the product	This is a potential risk. The impact of this risk on benefit-risk balance remains unknown.
Public health impact	Impact is considered low with appropriate training.

8.3.2 Part II Module SVII.3.2. Presentation of the missing information for pediatric and young adult r/r B-ALL, adult r/r DLBCL, and adult r/r FL

8.3.2.1 Missing information: Use in pregnancy and lactation

Table 8-33 Use in pregnancy and lactation

Name of missing information Use in pregnancy and lactation	**Details**
Evidence source	This population was not studied.

Name of missing information Use in pregnancy and lactation	Details
	There are no data on the effects of tisagenlecleucel on pregnant women and on the breastfed child or the effects of tisagenlecleucel on milk production.
Anticipated risk/ consequence of the missing information:	Pregnant and breastfeeding women were excluded from all clinical studies with tisagenlecleucel. It is not known if tisagenlecleucel constitutes a risk to pregnant women or fetuses, however tisagenlecleucel cells have the potential to cross the placenta and be transferred to the fetus. This may cause fetal toxicity including B-cell lymphocytopenia. Therefore, tisagenlecleucel is not recommended for women who are pregnant. Pregnancy after therapy should be discussed with the treating physician. It is not known if tisagenlecleucel is excreted into breast milk or has effects in milk production. There are no data on the effects of tisagenlecleucel on the breastfed child. A breastfeeding woman should be advised on possible risks to the child.

8.3.2.2 Missing information: Use in patients with HBV/HCV/HIV

Table 8-34 Use in patients with HBV/HCV/HIV

Name of missing information Use in patients with HBV/HCV/HIV	Details
Evidence source	There is no safety data on the use of tisagenlecleucel in patients with HBV, HCV, and HIV infections, since patients tested positive of such infections were excluded from all clinical studies. There is no experience with manufacturing tisagenlecleucel for patients testing positive for HBV, HCV, or HIV. Leukapheresis material from these patients are currently not be accepted for manufacturing. Investigations on measures to be taken to enable manufacturing for these patients are ongoing.
Anticipated risk/ consequence of the missing information:	It is not recommended that patients receive tisagenlecleucel if they have active HBV or HBC infection, because of the potential risk of viral reactivation and the risk of hepatic failure. It is also not recommended that patients receive tisagenlecleucel, if they are HIV positive, because of the possible effect on HIV viral suppression. Patients are to be screened for any active HBV, HCV or HIV infection prior to leukapheresis.

8.3.2.3 Missing information: Use in patients with active CNS involvement by malignancy

Table 8-35 Use in patients with active CNS involvement by malignancy

Name of missing information Use in patients with active CNS involvement by malignancy	**Details**
Evidence source	Patients with active CNS involvement due to malignancy were excluded from clinical trials.
Anticipated risk/ consequence of the missing information:	There is very little experience with patients with active CNS involvement and the likelihood of obtaining additional information in this population is low. It is supposed that patients with history of active CNS disorders may be vulnerable.

8.3.2.4 Missing information: Long-term safety

Table 8-36 Long-term safety

Name of missing information Long-term safety	**Details**
Evidence source	Patients treated with tisagenlecleucel are expected to be followed up for up to 15 years post-infusion. There was no change in the known tisagenlecleucel safety profile based on the median follow-up post-tisagenlecleucel infusion in pediatric and young adult r/r B-ALL (2 years in B2202, 12 months in B2205J, and 9 months in B2001X), adult r/r DLBCL (2 years in C2201), and adult r/r FL (17 months in E2202). Long-term safety data of tisagenlecleucel is evolving based on experience in long-term follow-up PASS A2205B (clinical trial setting) and PASS B2401 (post-marketing setting); no new safety risks have been identified in these studies.
Anticipated risk/ consequence of the missing information:	Long-term safety effects of tisagenlecleucel over a longer term are unknown.

8.3.2.5 Missing information: Immunogenicity

Table 8-37 Immunogenicity

Name of missing information Immunogenicity	**Details**
Evidence source	Immunogenicity may result from host immune responses against CD19-specific CAR transgene expressing immunogenic epitopes derived from the murine scFv

Name of missing information Immunogenicity	**Details**
	extracellular binding domain (fused to the intracellular signaling domains of 4-1BB and CD3zeta) or novel epitopes arising at junctions between components of the CAR fusion polypeptide (Park et al 2007, Lamers et al 2006, Lamers et al 2007, Lamers et al 2011). There is a theoretical concern that cellular and humoral anti-CAR T-cell immune responses could potentially interfere with the functionality of the CAR T cells, and therefore, impact safety, efficacy, and persistence of CAR T cells. Based on the totality of available data on tisagenlecleucel to date, humoral and cellular immunogenicity does not impact cellular kinetics or clinical outcome, and no notable cellular immunogenicity signals were observed in the pediatric and young adult r/r B-ALL, adult r/r DLBCL, and adult r/r FL (see Section 7.2.5.1). Long-term immunogenicity data are being collected. Humoral and cellular immunogenicity is being measured following tisagenlecleucel infusion as indicated in the clinical study protocols.
Anticipated risk/ consequence of the missing information:	No apparent impact of immunogenicity on safety, efficacy, or CAR T-cell exposure has been observed; long-term data are still pending.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Part II SVIII.1: Summary of safety concerns

Important identified risks	Cytokine release syndrome
	Serious neurological adverse reactions
	Infections
	Tumor lysis syndrome
	Prolonged depletion of normal B-cells/Agammaglobulinemia
	Hematological disorders including cytopenias
	Secondary malignancy of T-cell origin
Important potential risks	Cerebral edema
	Generation of replication competent lentivirus
	Secondary malignancies (except secondary malignancy of T-cell origin) including vector insertion site oligo/monoclonality
	New occurrence or exacerbation of an autoimmune disorder
	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

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

None.

10.2 Part III.2. Additional pharmacovigilance activities

Patients should be followed-up for 15 years post tisagenlecleucel infusion.

•Patients treated with tisagenlecleucel in clinical trials are expected to be enrolled into the long-term follow-up PASS A2205B.

•Patients treated with commercial product in the post-marketing setting are expected to be enrolled into one of the registries for cellular therapies such as the registry conducted by the CIBMTR (US) or the EBMT (Europe). These two registries also enroll patients treated with other commercial CAR T-cell products beyond tisagenlecleucel. Novartis utilizes and analyzes the data collected on tisagenlecleucel in PASS B2401, which is designed as a non-interventional study with secondary use of data.

All patients with identified secondary T-cell malignancies occurring after the infusion of clinical trial CAR T (CTL019- tisagenlecleucel) or commercial CAR T (Kymriah/tisagenlecleucel) are strongly encouraged to enroll into PASS B2402, to assess the secondary T-cell malignancies following CAR T-cell therapy using a lentiviral vector .

10.2.1 CCTL019B2401 – PASS to assess the long-term safety of patients with B-cell malignancies treated with tisagenlecleucel in the post-marketing setting

Study short name and title

Post-authorization safety study B2401 is a registry study to assess the long-term safety of patients with B-lymphocyte malignancies treated with tisagenlecleucel.

Rationale and study objectives

The study will provide information on long-term, safety and effectiveness up to 15 years following treatment with tisagenlecleucel in the post-marketing setting.

The primary objective is to evaluate the long-term safety and the risk of secondary malignancies in patients with B lymphocyte malignancies treated with tisagenlecleucel in a real-world setting.

Secondary objectives are to evaluate the long-term effectiveness of tisagenlecleucel in the approved indications and to evaluate any pregnancy occurring in WOCBP or female partners of males after infusion with tisagenlecleucel.

Study design

This PASS is a non-interventional study based on secondary use of tisagenlecleucel data prospectively collected through registries for cellular therapies conducted by CIBMTR and EBMT. The scope of registry data on tisagenlecleucel available for analysis by Novartis depends on the CIBMTR and EBMT registry data collection plan and execution. Therefore, this additional pharmacovigilance activity and its timelines proposed in this RMP may be subject to modification.

Study population

Patients, who have been treated with tisagenlecleucel for hematological B-cell malignancies in the post-marketing setting, will be enrolled in one of the two registries conducted by CIBMTR and EBMT.

Post-authorization safety study B2401 will include at least 1000 pediatric and young adult patients with r/r B-cell ALL and 1500 patients with r/r large B cell lymphoma including DLBCL.

Milestones

- FPFV: Dec-2018
- Study completion date: Dec-2037
- Update reports:
    - Annual safety reports (based on CIBMTR and EBMT registry data)
    - 5-yearly interim reports (starting in 2020)
- Final report of study results: Dec-2038

10.2.2 CCTL019A2205B – PASS for long-term follow-up of patients treated with tisagenlecleucel in preceding clinical trials

Study short name and title

Study A2205B, long-term follow-up of patients exposed to lentiviral-based CD19 directed CAR T-cell therapy.

Rationale and study objectives

The purpose of this PASS is to monitor all patients treated with lentiviral vector based CD19 CAR Tcell therapy in preceding clinical trials for 15 years from the last CD19 CAR T-cell infusion, to assess the risk of delayed AEs suspected to be related to CD19 CAR T-cell therapy, monitor for vectors persistence and RCL, and record the status of the primary malignancy to assess efficacy.

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 for RCL, assess the long-term efficacy of CD19 CAR T-cell therapies, 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.

Study design

This is a prospective, long-term follow-up PASS designed as a destination or basket protocol for the long-term monitoring of safety and efficacy of all pediatric and adult patients exposed to CD19 CAR T-cell therapy. No treatment will be administered to patients.

Study population

Male or female patients of any age, who have received anti-CD19 directed CAR T-cell therapy manufactured by Novartis or Penn and participated in Novartis or Penn sponsored treatment protocols or Novartis MAPs. All patients will be included upon completion of the core study or early discontinuation. The study periods include baseline, long-term follow-up period (up to 15 years post last anti-CD19 CAR T-cell infusion) and survival follow-up period (until Last Patient Last Visit of A2205B).

Milestones:

- FPFV: Nov-2015
- Study completion date: Dec-2036
- Update reports: Annual safety reports and 5-yearly interim reports
- Final report of study results: Dec-2037

10.2.3 CCTL019B2402 - PASS to assess the secondary T-cell malignancies following CAR T-cell therapy using a lentiviral vector

Study short name and title

A Non-Interventional Study (NIS) to characterize secondary T-cell malignancies following CART-cell therapy using a lentiviral vector

Rationale and Study objectives

The primary objective is to test for muCAR19 transgene and RCL using qPCR for all identified secondary T-cell malignancies (archived tumor tissue and archived blood or DNA from blood) occurring after the infusion of clinical trial CAR T (CTL019- tisagenlecleucel) or commercial CAR T (Kymriah/tisagenlecleucel). IHC may be considered in some cases where qPCR is not feasible. Patient-specific testing and results determine whether there is any potential causal relationship (or lack thereof) of the prior CAR T therapy with the development of the secondary T cell malignancy.

The secondary objective is to explore potential causality of tisagenlecleucel with the development of secondary T cell malignancy. Additional testing will be performed for all cases where qPCR or IHC shows a positive signal for muCAR19 transgene in the T cell secondary malignancy tumor site. This additional testing may include LISA, genomics profiling on retained vials of apheresis, final product and archived patient samples (peripheral blood and tumor tissue samples).

Study Design

This is a prospective non-interventional PASS, that involves confirming the diagnosis of new patients, including Novartis' review of the redacted pathology report along with any ancillary analyses used to diagnose secondary T cell malignancy. The protocol will be provided to the site and clinician for review and approval by the local IRB/Ethics Committee to capture the prospective data using the archived tumor tissue and/or stored archived DNA from blood from the patient when feasible, provided consent is obtained.

PASS B2402, will enroll 30 confirmed cases of secondary T-cell malignancies for analysis. The study will be open for enrollment of the planned number of patients (i.e. 30 patients in combined cohort 1 & 2) or up to 15 years after the EC decision of last approved indication (i.e. adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy).

Study population

Cohort 1: Interventional clinical trial patients treated with tisagenlecleucel, who develop and have a confirmed report of secondary malignancy of T-cell origin that have previously withdrawn consent, were lost to follow-up at any time, including during the parent study, or failed to enter the long-term follow-up study A2205 upon completion of the parent study.

Cohort 2: Commercial (including OOS and MAP) tisagenlecleucel patients who develop and have a reported and confirmed secondary malignancy of T-cell origin.

Number of patients: 30 patients planned from both Cohort 1 and 2 combined.

Milestones

- Planned study protocol submission - Mar-2025
- Planned FPFV: Q4 2025*
- With each PSUR: Review of reported cases in the reporting interval and cumulative cases review
- Final report of study results: Study completion +12 months (i.e., enrollment and analysis of 30 planned patients in cohort 1 and 2 combined) or Dec-2038 whichever is earlier.

*Note: Subject to protocol approval by PRAC, case identification, and internal Novartis approvals and external approvals needed at the specific sites for patients.

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: 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 (PASS) Non-interventional study with secondary use of data from the registries conducted by CIBMTR and EBMT, respectively, to evaluate the long-term safety of patients with malignancies treated with CAR T-cell therapies (ongoing)	The primary objective is to evaluate the long-term safety and the risk of secondary malignancies in patients with B lymphocyte malignancies treated with tisagenlecleucel in a real-world setting. The main secondary objective is to evaluate the long-term effectiveness of tisagenlecleucel.	• Cytokine release syndrome • Serious neurological adverse reactions • Infections • Tumor lysis syndrome • Prolonged depletion of normal B-cells/ Agammaglobulinemia • Hematological disorders including cytopenias • Secondary malignancy of T-cell origin • Cerebral edema • Secondary malignancies (except secondary malignancy of T-cell origin) including vector insertion site oligo/monoclonality • New occurrence or exacerbation of an autoimmune disorder • 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	FPFV	Dec-2018
			Study completion date	Dec-2037
			Update reports	Annual reports (based on CIBMTR and EBMT registry data)
				5-yearly interim reports (first report in 2020)
			Final report of study results	Dec-2038

		• Long-term safety		
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				
None				
Category 3 - Required additional pharmacovigilance activities				
CCTL019A2205B (PASS) Long-term follow-up study in patients exposed to lentiviral-based CD19 directed CAR T-cell therapy in preceding clinical trials (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 • Serious neurological adverse reactions • Infections • Tumor lysis syndrome • Prolonged depletion of normal B-cells/ Agammaglobulinemia] • Hematological disorders including cytopenias • Secondary malignancy of T-cell origin • Cerebral edema • Generation of replication competent lentivirus • Secondary malignancies (except secondary malignancy of T-cell origin) including vector insertion site oligo/monoclonality • New occurrence or exacerbation of an autoimmune disorder	FPFV	Nov-2015
			Study completion date	Dec-2036
			Update reports	Annual reports
				5-yearly interim reports (first report in 2020)
			Final report of study results	Dec-2037

		• Aggravation of graft-versus-host disease • Transmission of infectious agents • Long-term safety • Immunogenicity		
CCTL019B2402 (PASS) A Non-Interventional Study (NIS) to characterize secondary T-cell malignancies following CAR-T cell therapy using a lentiviral vector (planned)	Primary objective: To test for muCAR19 transgene and RCL using qPCR for all identified secondary T-cell malignancies (archived tumor tissue and archived blood or DNA from blood) occurring after the infusion of clinical trial CAR T (CTL019-tisagenlecleucel) or commercial CAR T (Kymriah/tisagenlecleucel) . IHC may be considered in some cases where qPCR is not feasible. Patient-specific testing and results determine whether there is any	Secondary malignancy of T-cell origin	Planned protocol submission	Mar-2025
			Planned FPFV	Q4 2025*
			PSUR	With each PSUR: Review of reported cases in the reporting interval and cumulative cases review

	potential causal relationship (or lack thereof) of the prior CAR T therapy with the development of the secondary T cell malignancy. The secondary objective is to explore potential causality of tisagenlecleucel with the development of secondary T cell malignancy. Additional testing will be performed for all cases where qPCR or IHC shows a positive signal for muCAR19 transgene in the T cell secondary malignancy tumor site. This additional testing may include LISA, genomics profiling on retained vials of apheresis, final product and archived patient sample (peripheral blood and tumor tissue samples).		Final report of study results	Study completion +12 months (i.e. enrollment and analysis of 30 planned patients in cohort 1 and 2 combined) or Dec-2038 whichever is earlier
*Note: Subject to protocol approval by PRAC, to case identification, and internal Novartis approvals and external approvals needed at the specific sites for patients.				

11 Part IV: Plans for post-authorization efficacy studies

Post-authorization efficacy studies commitments are outlined in the table below.

Table 11-1 Part IV.1: Planned and ongoing post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization				
CCTL019H2301 (ongoing)	Phase 3 study to evaluate the efficacy and safety of tisagenlecleucel versus standard of care in adult patients with r/r aggressive B-cell NHL	Efficacy and safety of tisagenlecleucel in an earlier line of DLBCL Further characterize long-term efficacy and safety in r/r DLBCL	FPFV	May-2019
			Final CSR	Mar-2027

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Cytokine release syndrome	**Routine risk communication** • 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 **Routine risk minimization activities recommending specific clinical measures** • Instruction given that tisagenlecleucel infusion must be administered in a treatment center qualified by Novartis. Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of hematological malignancies and trained for administration and management of patients treated with tisagenlecleucel. One dose of tocilizumab for use in the event of CRS and emergency equipment must be available per patient prior to infusion on site; the treatment center must have access to additional doses of tocilizumab within 8 hours. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the EMA shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion (SmPC Section 4.2) • In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for signs and symptoms of potential CRS, neurological events and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalisation at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion (SmPC Section 4.2) • Instruction given that tisagenlecleucel infusion should be delayed in case of active uncontrolled infection or significant clinical worsening of leukemia burden or rapid progression of lymphoma following lymphodepleting chemotherapy. (SmPC Section 4.4) • Instruction for close monitoring of signs and symptoms of CRS (SmPC Section 4.4)

	• CRS management algorithm, which provides treatment options based on the stage and severity of CRS. One dose of tocilizumab must be on site and available for administration per patient prior to tisagenlecleucel infusion. The treatment center must have access to additional doses of tocilizumab within 8 hours. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the EMA shortage catalogue, the treatment center must have access to suitable alternative measures instead of tocilizumab to treat CRS. Alternative CRS management strategies may be implemented based on appropriate institutional or academic guidelines (SmPC Section 4.4) • Warning that high pre-infusion tumor burden, uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy, active infection and early onset of fever are risk factors for severe CRS in B-ALL. Risk factors for developing severe CRS in adult DLBCL patients is high tumor burden prior to tisagenlecleucel infusion (SmPC Section 4.4). • Guidance for monitoring of neurological events during and after resolution of CRS, monitoring for infections and febrile neutropenia during the course of CRS and management of infections (SmPC Section 4.4) • Co-administration of agents known to inhibit T-cell function has not been formally studied, administration of low dose steroids per the CRS treatment algorithm does not impact the expansion and persistence of CAR T cells. The co-administration of agents known to stimulate T-cell function has not been investigated and the effects are unknown (SmPC Section 4.5) • Guidance to inform healthcare professional about infection or if cancer is getting worse prior to tisagenlecleucel (SmPC Package leaflet, Section 2) • Guidance to measure temperature twice a day for 3-4 weeks post-tisagenlecleucel and see doctor immediately, if temperature is high (SmPC Package leaflet, Section 2) • Guidance to stay within 2 hours travel from the hospital for at least 4 weeks post-infusion. Information provided that during the first week after treatment, treating physician may recommend that patient return 2 to 3 times, or more frequently, to the hospital (SmPC Package leaflet, Section 3) • Guidance to contact healthcare professional immediately in case of signs and symptoms of CRS after tisagenlecleucel infusion (SmPC Package leaflet, Section 4)
Serious neurological adverse reactions	**Routine risk communication** • 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 **Routine risk minimization activities recommending specific clinical measures**

	• Instruction given that tisagenlecleucel infusion must be administered in a treatment center qualified by Novartis. Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of hematological malignancies and trained for administration and management of patients treated with tisagenlecleucel (SmPC Section 4.2) • In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for signs and symptoms of potential CRS, neurological events and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalisation at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion (SmPC Section 4.2) • Guidance for close monitoring of signs and symptoms of neurological events, in particular during and after resolution of CRS, diagnostic work-up and management is provided (SmPC Section 4.4) • Warning that due to the potential of neurological events in the 8 weeks following tisagenlecleucel infusion, tisagenlecleucel may have major influence on the ability to drive and use machines (SmPC Section 4.7) • Guidance to not drive, use machines or take part in activities that require alertness for 8 weeks post tisagenlecleucel (SmPC Package leaflet, Section 2) • Guidance to stay within 2 hours travel from the hospital for at least 4 weeks post-infusion. Information provided that during the first week after treatment, treating physician may recommend that patient return 2 to 3 times, or more frequently, to the hospital (SmPC Package leaflet, Section 3) • Guidance to contact healthcare professional immediately in case of signs and symptoms of neurological events after tisagenlecleucel infusion (SmPC Package leaflet, Section 4)
Infections	**Routine risk communication** • 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 **Routine risk minimization activities recommending specific clinical measures** • Instruction given that tisagenlecleucel infusion must be administered in a treatment center qualified by Novartis. Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of hematological malignancies and trained for

administration and management of patients treated with tisagenlecleucel (SmPC Section 4.2).

- In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for signs and symptoms of potential CRS, neurological events and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalisation at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion (SmPC Section 4.2)
- Information provided that there is no experience with manufacturing tisagenlecleucel for patients with a positive test for HIV, active HBV, or active HCV infection. Leukapheresis material from these patients will not be accepted for tisagenlecleucel manufacturing. Screening for HBV, HCV, and HIV must be performed in accordance with clinical guidelines before collection of cells for manufacturing (SmPC Section 4.2)
- Guidance to take precautions before handling or administering tisagenlecleucel product to avoid potential transmission of infectious diseases as for any human-derived material (SmPC Section 4.2)
- Instruction given that tisagenlecleucel infusion should be delayed in case of active uncontrolled infection (SmPC Section 4.4)
- Guidance for close monitoring of signs and symptoms of infections (SmPC Section 4.4)
- Guidance given that active, uncontrolled infection must be resolved prior to tisagenlecleucel infusion. Recommendation regarding prophylaxis prior to tisagenlecleucel infusion in addition to adequate treatment and surveillance testing prior to and during tisagenlecleucel exposure is provided (SmPC Section 4.4)
- Preventive measures for infections due to low immunoglobulin levels are provided (SmPC Section 4.4)
- Warning provided that prolonged neutropenia is associated with increased risk of infection (SmPC Section 4.4)
- Guidance to screen for HBV, HCV and HIV prior to leukapheresis. Warning that viral reactivation, e.g., HBV reactivation, can occur in patients treated with medicinal products directed against B cells and could result in fulminant hepatitis, hepatic failure and death (SmPC Section 4.4)
- Guidance for the time period of 6 weeks prior to tisagenlecleucel or until immune recovery thereafter, during which vaccination with live vaccines should be avoided (SmPC Section 4.5)
- Guidance to inform healthcare professional about infection and medical history of hepatitis B, hepatitis C, and HIV prior to tisagenlecleucel (SmPC Package leaflet, Section 2)
- Guidance about the time period of 6 weeks prior to tisagenlecleucel infusion or a few months thereafter, during which vaccination with live vaccines should be avoided (SmPC Package leaflet, Section 2)
- Guidance to measure temperature twice a day for 3-4 weeks post-tisagenlecleucel and see doctor immediately, if temperature is high (SmPC Package leaflet, Section 2)

	• Guidance to stay within 2 hours travel from the hospital for at least 4 weeks post-infusion. Information provided that during the first week after treatment, treating physician may recommend that patient return 2 to 3 times, or more frequently, to the hospital (SmPC Package leaflet, Section 3) • Guidance to contact healthcare professional immediately in case of signs and symptoms of infections after tisagenlecleucel infusion (SmPC Package leaflet, Section 4) • Information provided to monitor opportunistic infections. Possibility of opportunistic infections of the CNS including events with late onset should be considered in patients with neurological AEs and appropriate diagnostic evaluations should be performed (SmPC Section 4.4).
Tumor lysis syndrome	**Routine risk communication** • 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 **Routine risk minimization activities recommending specific clinical measures** • Instruction given that tisagenlecleucel infusion must be administered in a treatment center qualified by Novartis. Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of hematological malignancies and trained for administration and management of patients treated with tisagenlecleucel (SmPC Section 4.2) • In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for signs and symptoms of potential CRS, neurological events and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalisation at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion (SmPC Section 4.2) • Guidance for prophylaxis, close monitoring for signs and symptoms and management of TLS is provided (SmPC Section 4.4) • Guidance to stay within 2 hours travel from the hospital for at least 4 weeks post-infusion. Information provided that during the first week after treatment, treating physician may recommend that patient return 2 to 3 times, or more frequently, to the hospital (SmPC Package leaflet, Section 3) • Guidance to contact healthcare professional immediately in case of signs and symptoms of tumor lysis syndrome after tisagenlecleucel infusion (SmPC Package leaflet, Section 4)

Prolonged depletion of normal B-cells/ Agammaglobulinemia	**Routine risk communication** • 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 **Routine risk minimization activities recommending specific clinical measures** • Instruction given that tisagenlecleucel infusion must be administered in a treatment center qualified by Novartis. Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of hematological malignancies and trained for administration and management of patients treated with tisagenlecleucel (SmPC Section 4.2) • In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for signs and symptoms of potential CRS, neurological events and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalisation at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion (SmPC Section 4.2) • Guidance for monitoring of immunoglobulin levels after treatment with tisagenlecleucel in addition to infection precautions, antibiotic prophylaxis and immunoglobulin replacement as per age and local guidelines is provided (SmPC Section 4.4) • Guidance for monitoring of immunoglobulin levels in newborns of mothers treated with tisagenlecleucel, since potential fetal toxicity of tisagenlecleucel may include B-cell lymphocytopenia (SmPC Section 4.6) • Guidance to stay within 2 hours travel from the hospital for at least 4 weeks post-infusion. Information provided that during the first week after treatment, treating physician may recommend that patient return 2 to 3 times, or more frequently, to the hospital(SmPC Package leaflet, Section 3) • Guidance to contact healthcare professional immediately in case of severe or serious signs and symptoms of prolonged depletion of normal B cells or agammaglobulinemia after tisagenlecleucel infusion (SmPC Package leaflet, Section 4)
Hematological disorders including cytopenias	**Routine risk communication** • 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 **Routine risk minimization activities recommending specific clinical measures** • Instruction given that tisagenlecleucel infusion must be administered in a treatment center qualified by Novartis. Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of hematological malignancies and trained for administration and management of patients treated with tisagenlecleucel (SmPC Section 4.2) • In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for signs and symptoms of potential CRS, neurological events and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalisation at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion (SmPC Section 4.2) • Guidance for management of cytopenias was recommended as per local guidelines (SmPC Section 4.4) • Myeloid growth factors are not recommended during the first 3 weeks after tisagenlecleucel infusion or until CRS has resolved (SmPC Section 4.4) • Guidance to stay within 2 hours travel from the hospital for at least 4 weeks post-infusion. Information provided that during the first week after treatment, treating physician may recommend that patient return 2 to 3 times, or more frequently, to the hospital (SmPC Package leaflet, Section 3) • Guidance to contact healthcare professional immediately in case of severe or serious signs and symptoms of hematopoietic cytopenias not resolved by day 28 after tisagenlecleucel infusion (SmPC Package leaflet, Section 4)
Secondary malignancy of T-cell origin	**Routine risk communication** • 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 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures** • Information provided that treatment with tisagenlecleucel may induce secondary malignancy or recurrence of cancer. Guidance to monitor for secondary malignancies life-long (SmPC Section 4.4)

	• Instruction provided, 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).
Important potential risks	
Cerebral edema	**Routine risk communication** • 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 **Routine risk minimization activities recommending specific clinical measures** • Instruction given that tisagenlecleucel infusion must be administered in a treatment center qualified by Novartis. Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of hematological malignancies and trained for administration and management of patients treated with tisagenlecleucel (SmPC Section 4.2) • In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for signs and symptoms of potential CRS, neurological events and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalisation at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion (SmPC Section 4.2) • Guidance for close monitoring of signs and symptoms of neurological events, in particular during and after resolution of CRS is provided (SmPC Section 4.4) • Guidance for supportive care and diagnostic work-up are provided (SmPC Section 4.4) • Warning that due to the potential of neurological events in the 8 weeks following tisagenlecleucel infusion, tisagenlecleucel may have major influence on the ability to drive and use machines (SmPC Section 4.7) • Guidance to not drive, use machines or take part in activities that require alertness for 8 weeks post tisagenlecleucel (SmPC Package leaflet, Section 2) • Guidance to stay within 2 hours travel from the hospital for at least 4 weeks post-infusion. Information provided that during the first week after treatment, treating physician may recommend that patient return 2 to 3 times, or more frequently, to the hospital (SmPC Package leaflet, Section 3)

	• Guidance to contact healthcare professional immediately in case of signs and symptoms of neurological events after tisagenlecleucel infusion (SmPC Package leaflet, Section 4)
Generation of replication competent lentivirus	**Routine risk communication** • None **Routine risk minimization activities recommending specific clinical measures** • None
Secondary malignancies (except secondary malignancy of T-cell origin) including vector insertion site oligo/monoclonality	**Routine risk communication** • SmPC Section 4.4 Special warnings and precautions for use • 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 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures** • Information provided that treatment with tisagenlecleucel may induce secondary malignancy or recurrence of cancer. Guidance to monitor for secondary malignancies life-long (SmPC Section 4.4)
New occurrence or exacerbation of an autoimmune disorder	**Routine risk communication** • None **Routine risk minimization activities recommending specific clinical measures**: • None
Aggravation of graft-versus-host disease	**Routine risk communication** • 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 **Routine risk minimization activities recommending specific clinical measures** • Instruction given that tisagenlecleucel infusion must be administered in a treatment center qualified by Novartis. Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of hematological malignancies and trained for administration and management of patients treated with tisagenlecleucel (SmPC Section 4.2) • In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for signs and symptoms of potential CRS, neurological events and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalisation at the first signs/symptoms of cytokine release syndrome and/or

	neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion (SmPC Section 4.2) • Instruction given to delay infusion in case of active GVHD (SmPC Section 4.4) • Guidance to not treat patients with tisagenlecleucel within 4 months of undergoing an allogeneic HSCT because of the potential risk of worsening GVHD. Leukapheresis should be at least 12 weeks from allogeneic HSCT (SmPC Section 4.4) • Guidance to inform healthcare professional about stem cell transplant within the last 4 months (SmPC Package leaflet, Section 2) • Guidance to inform healthcare professional about signs and symptoms of graft-versus-host disease prior to tisagenlecleucel (SmPC Package leaflet, Section 2) • Guidance to stay within 2 hours travel from the hospital for at least 4 weeks post-infusion. Information provided that during the first week after treatment, treating physician may recommend that patient return 2 to 3 times, or more frequently, to the hospital (SmPC Package leaflet, Section 3) • Guidance to contact healthcare professional immediately in case of severe or serious signs and symptoms of GVHD after tisagenlecleucel infusion (SmPC Package leaflet, Section 4)
Transmission of infectious agents	**Routine risk communication** • 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 **Routine risk minimization activities recommending specific clinical measures** • Instruction given that tisagenlecleucel infusion must be administered in a treatment center qualified by Novartis. Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of hematological malignancies and trained for administration and management of patients treated with tisagenlecleucel (SmPC Section 4.2) • Information provided that there is no experience with manufacturing Kymriah for patients with a positive test for HIV, active HBV, or active HCV infection. Leukapheresis material from these patients will not be accepted for Kymriah manufacturing. Screening for HBV, HCV, and HIV

	must be performed in accordance with clinical guidelines before collection of cells for manufacturing (SmPC Section 4.2) • Guidance to take precautions before handling or administering tisagenlecleucel product to avoid potential transmission of infectious diseases as for any human-derived material (SmPC Section 4.2) • In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for signs and symptoms of potential CRS, neurological events and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalisation at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion (SmPC Section 4.2) • Guidance to screen for HBV, HCV and HIV prior to leukapheresis. Warning that viral reactivation, e.g., HBV reactivation, can occur in patients treated with medicinal products directed against B cells and could result in fulminant hepatitis, hepatic failure and death (SmPC Section 4.4) • Instructions to administer tisagenlecleucel infusion within 30 mins after thawing, including any interruption during infusion (SmPC Section 6.3) • Instructions on storage and transport given (SmPC Section 6.4) • Information on infusion bag given (SmPC Section 6.5) • Guidance that tisagenlecleucel is potentially infectious and healthcare professionals should take precautionary measures with regard to handling, administration, storage and disposal (SmPC Section 6.6) • Guidance to inform healthcare professional about infection and medical history of hepatitis B, hepatitis C and HIV prior to tisagenlecleucel (SmPC Package leaflet, Section 2) • Guidance to stay within 2 hours travel from the hospital for at least 4 weeks post-infusion. Information provided that during the first week after treatment, treating physician may recommend that patient return 2 to 3 times, or more frequently, to the hospital (SmPC Package leaflet, Section 3) • Guidance to apply guidelines on handling biological waste for products containing genetically modified human cells (SmPC Package leaflet, Section 5) • Guidance how to handle tisagenlecleucel product (SmPC Section Other sources of information)
Decrease in cell viability due to inappropriate handling of the product	**Routine risk communication** • 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

	Routine risk minimization activities recommending specific clinical measures • Instruction given that tisagenlecleucel infusion must be administered in a treatment center qualified by Novartis. Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of hematological malignancies and trained for tisagenlecleucel administration and management of patients treated with tisagenlecleucel (SmPC Section 4.2) • In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for signs and symptoms of potential CRS, neurological events and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalisation at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion (SmPC Section 4.2) • Guidance for instructing patient to stay in proximity (i.e., within 2 hours travel) of the qualified treatment center for at least 4 weeks post-infusion (SmPC Section 4.2) • Instructions to administer tisagenlecleucel infusion within 30 mins after thawing, including any interruption during infusion (SmPC Section 6.3) • Instructions on storage and transport given (SmPC Section 6.4) • Information on infusion bag given (SmPC Section 6.5) • Guidance that tisagenlecleucel is potentially infectious and healthcare professionals should take precautionary measures with regard to handling, administration, storage and disposal (SmPC Section 6.6) • Guidance to stay within 2 hours travel from the hospital for at least 4 weeks post-infusion. Information provided that during the first week after treatment, treating physician may recommend that patient return 2 to 3 times, or more frequently, to the hospital (SmPC Package leaflet, Section 3) • Guidance to apply guidelines on handling biological waste for products containing genetically modified human cells (SmPC Package leaflet, Section 5) • Guidance how to handle tisagenlecleucel product (SmPC Section Other sources of information)
Missing information	
Use in pregnancy and lactation	**Routine risk communication** • 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 **Routine risk minimization activities recommending specific clinical measures** • Pregnancy testing is recommended for WOCBP prior to starting treatment with tisagenlecleucel (SmPC Section 4.6)

	• Information provided that there are no data on the duration of contraception following tisagenlecleucel infusion (SmPC Section 4.6) • Guidance that it is not known whether tisagenlecleucel has the potential to be transferred to the fetus via the placenta and could cause fetal toxicity including B-cell lymphocytopenia. Due to a potential risk to the fetus, tisagenlecleucel is not recommended for women who are pregnant or are WOCBP not using contraception (SmPC Section 4.6) • Guidance given to see the prescribing information of lymphodepleting chemotherapy for the need to effective contraception as applicable (SmPC Section 4.6) • Guidance given to inform pregnant patients about the potential risks to the fetus. Pregnancy in WOCBP post tisagenlecleucel should be discussed with the treating physician (SmPC Section 4.6) • Guidance that pregnant may have hypogammaglobulinemia following tisagenlecleucel and assessment of immunoglobulin levels is indicated in newborns of mothers treated with tisagenlecleucel (SmPC Section 4.6) • Guidance on potential risks to the child during lactation should be given to the mother and breast-feeding should be discussed with the treating physician (SmPC Section 4.6) • Guidance that pregnancy testing is performed in WOCBP prior to starting treatment with tisagenlecleucel (SmPC Package leaflet, Section 2) • Guidance for women who are pregnant or breast-feeding or plan to become pregnant to ask healthcare professional for advice prior to treatment with tisagenlecleucel due to the unknown risk to the fetus and newborn/infant. Pregnancy after tisagenlecleucel infusion should be discussed with the treating physician (SmPC Package leaflet, Section 2)
Use in patients with HBV/HCV/HIV	**Routine risk communication** • 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 Section Other sources of information **Routine risk minimization activities recommending specific clinical measures** • Information provided that there is no experience with manufacturing tisagenlecleucel for patients with a positive test for HIV, active HBV, or active HCV infection. Leukapheresis material from these patients will not be accepted for tisagenlecleucel manufacturing. Screening for HBV, HCV, and HIV must be performed in accordance with clinical guidelines before collection of cells for manufacturing (SmPC Section 4.2) • Guidance to take precautions before handling or administering tisagenlecleucel product to avoid potential transmission of infectious diseases as for any human-derived material (SmPC Section 4.2) • Guidance to screen for HBV, HCV and HIV prior to leukapheresis. Warning that viral reactivation, e.g., HBV reactivation, can occur in patients treated with medicinal products directed against B cells and

	could result in fulminant hepatitis, hepatic failure and death (SmPC Section 4.4) • Guidance that tisagenlecleucel is potentially infectious and healthcare professionals should take cautionary measures with regard to handling, storage and disposal (SmPC Section 6.6) • Guidance to inform healthcare professional about infection and medical history of hepatitis B, hepatitis C and HIV prior to tisagenlecleucel (SmPC Package leaflet, Section 2) • Guidance how to handle tisagenlecleucel product (SmPC Section Other sources of information)
Use in patients with active CNS involvement by malignancy	**Routine risk communication** • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 5.1 Pharmacodynamic properties – Patients with active CNS leukemia **Routine risk minimization activities recommending specific clinical measures**: • Guidance given that patients with history of active CNS disorder were excluded from studies and are likely to be more vulnerable to the consequences of ADRs and require special attention (SmPC Section 4.4)
Long-term safety	**Routine risk communication** • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures** • None
Immunogenicity	**Routine risk communication** • SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures** • None

12.2 Part V.2. Additional Risk minimization measures

12.2.1 Controlled Distribution Program

Objectives

- To mitigate the safety risks associated with tisagenlecleucel treatment by ensuring that hospitals and their associated centers that dispense tisagenlecleucel infusion are specially qualified by Novartis
- Tisagenlecleucel product will only be supplied to hospitals and associated centers 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. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the EMA shortage catalogue, the treatment center must have access to suitable alternative measures instead of tocilizumab to treat CRS

Qualification of treatment center by Novartis

The following steps are involved in the treatment center qualification:

- Confirmed completion of the healthcare professional educational program with focus on risks of CRS and neurological events
- Full availability ensured of on-site, immediate access to one dose of tocilizumab and emergency equipment as CRS management medication per patient prior to infusion. The treatment center must have access to additional doses of tocilizumab for each patient within 8 hours. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the EMA shortage catalogue, the treatment center must have access to suitable alternative measures instead of tocilizumab to treat CRS.
    - Prior to the release of the first tisagenlecleucel product for delivery, Novartis contacts the respective treatment center to confirm that the treatment center ensures for each patient onwards immediate access to one dose of tocilizumab and emergency equipment per patient prior to tisagenlecleucel infusion in addition to access to an additional dose of within 8 hours of each previous dose.
    - In addition, Novartis will ensure that suitable alternative measures instead of tocilizumab to treat CRS are available on-site, in the exceptional case where tocilizumab is not available due to a shortage that is listed in the EMA shortage catalogue.
    - Tisagenlecleucel will only be released for shipment with confirmed availability of tocilizumab or suitable alternative measures instead of tocilizumab at the treatment center.
- Confirmed completion of the healthcare professional training on patient information pack and patient consent information
- Technical survey of apheresis institution and cell lab in accordance with the EU GMP Guidelines on GMP specific to Advanced Therapy Medicinal Products
- Technical quality assessment of apheresis center's cell processing laboratory and apheresis collection facility with a quality audit, if deemed required
- Confirmed completion of the training on the leukapheresis reference manual by Responsible Person and other personnel involved in the activities preformed on the leukapheresis material's cell collection, processing, cryopreservation and shipping
- Instructions on final product reception and storage in the cell-processing facility
- Instructions for coordination of product and patient preparation for infusion, and for infusion including handling prior to infusion, thawing procedure, administration and monitoring after infusion
- Training on tisagenlecleucel ordering process including COI education from product order via leukapheresis material collection and labelling to final product reception back at the center

Rationale for the additional risk minimization measure

There is a need to mitigate the risk and minimize occurrence of severe or life-threatening CRS and neurotoxic events.

Target audience and planned distribution path

Qualified centers that intend to treat patients with tisagenlecleucel product need to confirm that they have completed the educational program and ensure on-site, immediate access to one dose of tocilizumab and emergency equipment per patient prior to infusion in addition to access to additional doses of tocilizumab within 8 hours. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the EMA shortage catalogue, the treatment center must have access to suitable alternative measures instead of tocilizumab to treat CRS.

Plans to evaluate the effectiveness of the interventions and criteria for success

Novartis keeps oversight of center qualification and healthcare professional training qualification. Access to CellChain is only granted to centers that are qualified and trained on severe or life-threatening CRS and neurological events.

The effectiveness of risk mitigation of severe or life-threatening CRS and neurological events will be assessed in the context of risk evaluation in the PSUR.

12.2.2 Educational program

- Pharmacy/Cell Lab/Infusion Center Training Material
- Healthcare Professional Training Material
- Patient Educational Leaflet

Objectives

- Pharmacy/Cell Lab/Infusion Center Training Material
  - Inform about reception, storage, handling, thawing and preparation for infusion of tisagenlecleucel to mitigate a decrease in cell viability of tisagenlecleucel due to inappropriate handling of the product and subsequent potential impact on the efficacy/safety profile
- Healthcare Professional Training Material
  - Mitigate the risk of severe or life-threatening CRS and neurological events by ensuring those, who prescribe, dispense, or administer tisagenlecleucel, are aware of how to manage the risks of CRS and neurological events
  - Counsel patients/guardians on instances where tisagenlecleucel cannot be successfully manufactured or the final product is OOS, the potential need for bridging chemotherapy, risk of progressive disease during manufacturing time, in addition to the risks of CRS and neurological events and actions to be taken.
  - Create awareness about the risk of secondary malignancy of T-cell origin, reporting requirement and potential need to consider testing of tumor tissue and/or blood from the patient, among health care professionals who prescribe, dispense, administer tisagenlecleucel or who follow up patients after tisagenlecleucel treatment
  - Inform about AEs reporting in the respective registry for cellular therapy and, in parallel, encourage to spontaneously report the same AEs timely, if causality to the tisagenlecleucel treatment is suspected, as adverse reactions of tisagenlecleucel to Novartis or the local Health Authorities

- Patient Educational Leaflet
  - Create awareness that there are instances, where tisagenlecleucel cannot be successfully manufactured and infusion cannot be provided, or the final manufactured product is OOS
  - Inform about the potential need for bridging chemotherapy and associated ADRs and the risk of progressive disease during the tisagenlecleucel manufacturing time
  - Educate about the risks of CRS and neurotoxicity, and when to seek medical attention.
  - Inform about monitoring requirements and potential for hospitalization following tisagenlecleucel infusion

Rationale for the additional risk minimization measure

There is a need to mitigate the risk of severe or life-threatening CRS and neurological events. Patients should be appropriately informed about any risks associated with bridging chemotherapy and waiting time for the tisagenlecleucel product.

Target audience and planned distribution path

The target audience are healthcare professionals in treatment centers qualified by Novartis. Treatment with tisagenlecleucel should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of hematological malignancies. The health care professional will receive the Pharmacy/Cell Lab/Infusion Center Training Material, the Healthcare Professional Training Material, besides having access to the SmPC.

Patients receiving tisagenlecleucel treatment will be counseled by the treating clinician about risks including CRS and neurological events, and will be provided with a Patient Educational Leaflet, besides the SmPC Package leaflet and the Patient Alert Card.

12.2.3 Plans to evaluate the effectiveness of the risk minimization measures and criteria for success

Additional risk minimization measures including the Controlled Distribution Program and Educational Material have been implemented to minimize the risks of 'Cytokine release syndrome', 'Serious neurological adverse reactions' and 'Decrease in cell viability due to inappropriate handling of the product', respectively.

The effectiveness of the additional risk minimization measures to mitigate the two risks 'Cytokine release syndrome' and 'Serious neurological adverse reactions' are evaluated through routine pharmacovigilance monitoring and additional pharmacovigilance activities in studies CCTL019A2205B (clinical trial setting) and CCTL019B2401 (post-marketing setting).

Specific benchmarks as process indicators have been defined to evaluate the effective implementation of the 'Controlled distribution program' and the distribution of and training on the 'Educational Material'. Data collected during the center onboarding qualification process and from CellChain (Section 7.2.1) are analyzed.

The results of the monitoring of the risk minimization measures will be included in each PSUR.

12.3 Part V.3. Summary of risk minimization measures

Table 12-2 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 **Additional risk minimization measures** • Controlled distribution program Educational program including the Healthcare Professional Training Material and the Patient Educational Leaflet	**Additional pharmacovigilance activities** • CCTL019B2401 CCTL019A2205B
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	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B

Safety concern	Risk minimization measures (routine and additional)	Pharmacovigilance activities
	• SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • Controlled distribution program • Educational program including the Healthcare Professional Training Material and the Patient Educational Leaflet	
Infections	**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 **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B
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 Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures**	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B

Safety concern	Risk minimization measures (routine and additional)	Pharmacovigilance activities
	• None	
Prolonged depletion of normal B-cells/Agamma globulinemia	**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 **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B
Hematological disorders including cytopenias	**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 **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B
Secondary malignancy of T-cell origin	**Routine risk communication** • 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	**Additional pharmacovigilance activities** • CCTL019B2401 (as feasible) • CCTL019A2205B • CCTL019B2402

Safety concern	Risk minimization measures (routine and additional)	Pharmacovigilance activities
	• SmPC Package leaflet, Section 4 Possible side effects • **Routine risk minimization activities recommending specific clinical measures** Information provided that treatment with tisagenlecleucel may induce secondary malignancy or recurrence of cancer. Guidance to monitor for secondary malignancies life-long (SmPC Section 4.4) Instruction provided, 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).	
Important potential risks		
Cerebral edema	**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 **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B
Generation of replication competent lentivirus	**Routine risk minimization measures** • None **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019A2205B
Secondary malignancies (except secondary	**Routine risk minimization measures** • SmPC Section 5.3 Preclinical safety data	**Additional pharmacovigilance activities** • CCTL019B2401 (as feasible)

Safety concern	Risk minimization measures (routine and additional)	Pharmacovigilance activities
malignancy of T-cell origin) including vector insertion site oligo/ monoclonality	• SmPC Section 4.4 Special warnings and precautions for use • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None	• CCTL019A2205B
New occurrence or exacerbation of an autoimmune disorder	**Routine risk minimization measures** • None **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B
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 Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B
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	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B

Safety concern	Risk minimization measures (routine and additional)	Pharmacovigilance activities
	• 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	
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 risk minimization measures** • Controlled distribution program • Educational program including the Pharmacy/Cell Lab/Infusion Center Training Material	**Additional pharmacovigilance activities** • None
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	**Additional pharmacovigilance activities** • CCTL019B2401

Safety concern	Risk minimization measures (routine and additional)	Pharmacovigilance activities
	• SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah **Additional risk minimization measures** • None	
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 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** • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B
Immunogenicity	**Routine risk communication** • SmPC Section 4.8 Undesirable effects **Additional risk minimization measures** •None	**Additional pharmacovigilance activities** • CCTL019A2205B

13 Part VI: Summary of the risk management plan for Kymriah (tisagenlecleucel)

This is a summary of the Risk Management Plan (RMP) for Kymriah. The RMP details important risks of Kymriah, how these risks can be minimized, and how more information will be obtained about Kymriah's risks and uncertainties (missing information).

Kymriah's Summary of Product Characteristics (SmPC) and the SmPC Package leaflet give essential information to healthcare professionals and patients on how Kymriah should be used.

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

Important new concerns or changes to the current ones will be included in updates to the Kymriah RMP.

13.1 Part VI: I. The medicine and what it is used for

Kymriah is a CD19-directed autologous immunotherapy indicated for the treatment of:

- Paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukemia (B-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.
- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Further information about the evaluation of Kymriah's benefits can be found in Kymriah's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/kymriah.

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

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

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the SmPC and SmPC Package leaflet addressed to healthcare professionals and patients
- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks

Together, these measures constitute routine risk minimization measures.

In the case of Kymriah, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks below.

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

If important information that may affect the safe use of Kymriah is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI: II.A: List of important risks and missing information

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

Table 13-1 List of important risks and missing information

List of important risks and missing information	
Important Identified risks	• Cytokine release syndrome • Serious neurological adverse reactions • Infections • Tumor lysis syndrome • Prolonged depletion of normal B-cells/Agammaglobulinemia • Hematological disorders including cytopenias • Secondary malignancy of T-cell origin
Important potential risks	• Cerebral edema • Generation of replication competent lentivirus • Secondary malignancies (except secondary malignancy of T-cell origin) including vector insertion site oligo/monoclonality • New occurrence or exacerbation of an autoimmune disorder • 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

13.2.2 Part VI: II.B: Summary of important risks

Table 13-2 Important identified risk: Cytokine release syndrome

Evidence for linking the risk to the medicine	Cytokine release syndrome (CRS) is a direct mechanism based toxicity that occurs as a result of high-level immune activation. It is a systemic inflammatory response caused when cytokines are released by activated T-cells, which has been observed in other types of T-cell directed therapies. This syndrome has become increasingly important with the use of new and more potent immunotherapies. The level of immune activation with these newer therapies occurs at levels greater than that occurring in nature. The severity ranges from mild to severe with a fatal outcome sometimes. Life-threatening and fatal events have been observed in tisagenlecleucel clinical trials. In the Novartis tisagenlecleucel clinical study programs for the indications of pediatric and young adult r/r B-ALL, adult r/r DLBCL, and adult r/r FL, CRS was graded using criteria predefined in the study protocols (Penn CRS grading scale for Study B2202, Study B2205J, Study B2001X, and Study C2201; Lee grading criteria for Study E2202). In the majority of patients, CRS after tisagenlecleucel infusion occurred with a median time to onset of 3 days in both pediatric and young adult r/r B-ALL and adult r/r DLBCL patients, and 4 days in adult r/r FL. Symptoms of CRS may include high fever, hypotension, hypoxia, dyspnea, tachypnea, rigors, myalgia, arthralgia, nausea, vomiting, diarrhea, diaphoresis, rash, anorexia, fatigue, tachycardia, and headache. In addition, multiple organ dysfunction, including transient cardiac failure, renal impairment, and liver injury with elevated hepatic enzymes have been observed. Disseminated intravascular coagulation, with low fibrinogen levels, or capillary leak syndrome may also occur. In the setting of severe CRS following CAR T-cell therapies including tisagenlecleucel, patients may develop a clinical phenotype that shares signs and symptoms of hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), as further evidenced by similar laboratory findings. There is a significant overlap across CRS, MAS and HLH, reflecting a group of severe systemic immunological disorders characterized by hyperactivation of macrophages and lymphocytes, pro-inflammatory cytokine production, lymphohistiocytic tissue infiltration, and immune-mediated multiorgan failure. In the majority of patients, MAS/HLH responds to CRS resolution. Given this overlap, MAS/HLH may be considered to reflect manifestations of CRS of higher severity. However, it should be distinguished from late-onset, tocilizumab-refractory HLH/MAS-like toxicity that may represent a distinct and separate pathology than conventional CRS and requires a different treatment approach.
Risk factors and risk groups	Risk factors for severe CRS in paediatric and young adult B-ALL patients are high pre-infusion tumor burden, uncontrolled or

	accelerating tumor burden following lymphodepleting chemotherapy, active infection and early onset of fever or CRS following tisagenlecleucel infusion. The risk factor for developing severe CRS in adult DLBCL patients is high tumor burden prior to tisagenlecleucel infusion. Infections may also occur during CRS and increase the risk of a fatal event.
Risk minimization measures	**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 **Additional risk minimization measures** • Controlled distribution program • Educational program including the Healthcare Professional Training Material and the Patient Educational Leaflet
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-3 Important identified risk: Serious neurological adverse reactions

Evidence for linking the risk to the medicine	Neurotoxic events, suggested to be named 'CAR-T-cell related encephalopathy syndrome' and subsequently termed 'immune effector cell-associated neurotoxicity syndrome' (ICANS), is the second most-common adverse reaction associated with CAR T-cell therapies. Neurotoxicity typically manifests as a toxic encephalopathy with wide range of variable symptoms such as confusion, delirium, tremors, aphasia, speech disorders, motor findings, and seizures. For fatal cerebral edema that occurred with other CAR-T-cell products differently constructed than tisagenlecleucel, see Table 13-9. Notably, the onset of neurological events can be concurrent with CRS, typically during high fever and at the time of maximal grade of CRS, following resolution of CRS or in the absence of CRS. Severe ICANS symptoms are more frequently observed in cases when CRS develops early, which may be due to a high dose of CAR T cells, or unusually

	robust and rapid CAR T cell proliferation. Encephalopathy typically occurred after peak CRS symptoms and tended to be self-limiting with some exceptions. Neurological events with seizures or episodes of confusion 3-4 weeks following CAR T-cell therapy have been reported to occur. The majority of neurological events following tisagenlecleucel infusion were observed within 8 weeks; there is currently limited evidence that CAR therapies are associated with a late onset of neurological events (i.e., onset > 8 weeks after infusion). Most neurological events observed within 8 weeks were transient or self-limiting in nature. Frequently, encephalopathy, confusional state and delirium were observed. Other manifestations include a multifarious set of signs and symptoms including seizures, aphasia, speech disorder, and tremor. Some of the events are severe and may have a life-threatening outcome. The causality assessment of neurological events in patients treated with tisagenlecleucel can be confounded, as CNS toxicity can be associated with chemotherapy used for lymphodepletion and the presence of co-morbid conditions such as CRS, fever and infections.
Risk factors and risk groups	Risk factors are not known but may include prior medical history of central nervous system (CNS) disease/injury or CNS leukemic involvement. In addition, higher grade CRS may predispose.
Risk minimization measures	**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 **Additional risk minimization measures** • Controlled distribution program • Educational program including the Healthcare Professional Training Material and the Patient Educational Leaflet
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-4 Important identified risk: Infections

Evidence for linking the risk to the medicine	Serious infections, which may occur late, were observed in patients after tisagenlecleucel infusion, some of which were life-threatening or fatal..
Risk factors and risk groups	Severity of underlying disease and longer, more intense immunosuppression following preceding chemotherapy, radiation and/or tisagenlecleucel infusion may lead to an increased risk, severity and seriousness of infection.
Risk minimization measures	**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 **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-5 Important identified risk: Tumor lysis syndrome

Evidence for linking the risk to the medicine	Tumor lysis syndrome was clinically observed in a timely relation to tisagenlecleucel T-cell expansion. In the clinical experience with tisagenlecleucel thus far, most cases of tumor lysis syndrome (TLS) had a grade 3 in CTCAE severity, however, the risk has been moderate to low with appropriate monitoring after lymphodepleting chemotherapy, prophylaxis and treatment as needed.
Risk factors and risk groups	All recipients are at risk for this concern. In general, TLS occurs more frequently in hematological malignancies than in solid tumors. The highest risk of developing TLS is observed in patients with lymphoproliferative disorders with high proliferative rate and high tumor sensitivity to chemotherapy, like B-ALL and Burkitt's lymphoma. Tumor burden, reflected by serum LDH level, initial WBC count, tumor size, and extensive bone marrow involvement are considered main predictors for the development of TLS in these patients.

Risk minimization measures	**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 **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-6 Important identified risk: Prolonged depletion of normal B cells/ Agammaglobulinemia

Evidence for linking the risk to the medicine	Prolonged depletion of B cells is an expected on-target toxicity of CD19-directed CAR T-cell therapy. This may result in hypo- or agammaglobulinemia, potentially rendering the patients more susceptible to certain infections.
Risk factors and risk groups	Patients with B-cell aplasia are at increased risk for certain infections including but not limited to those caused by encapsulated bacteria and viruses.
Risk minimization measures	**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 **Additional risk minimization measures** • None

Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-7 Important identified risk: Hematological disorders including cytopenias

Evidence for linking the risk to the medicine	Hematological disorders including cytopenias are commonly seen in patients receiving tisagenlecleucel. Patients may continue to exhibit cytopenias for several weeks following tisagenlecleucel infusion. Prolonged neutropenia has been associated with increased risk of infection.
Risk factors and risk groups	All patients are at risk after tisagenlecleucel infusion. Extensive prior exposure to anti-cancer therapy, such as chemotherapy or radiation in addition to lymphodepleting chemotherapy in proximity to tisagenlecleucel infusion, enhance the risk.
Risk minimization measures	**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 **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-8 Important identified risk: Secondary malignancy of T-cell origin

Evidence for linking the risk to the medicine	The PRAC evaluated data on 38 cases of secondary malignancy of T-cell origin, including T-cell lymphoma and leukemia, among approximately 42,500 patients treated with CAR T-cell medicines. Tissue samples from half of the cases revealed the presence of the CAR construct in 7 cases, suggesting involvement of the CAR T-cell medicine in disease development. These malignancies were reported within

	weeks to several years after administration. Two of the 7 cases were reported after tisagenlecleucel infusion. **Evidence of insertional oncogenesis**: Two cases of secondary T-cell malignancy with CAR transgene were reported after tisagenlecleucel infusion. In one case, tests confirmed CAR expression and T-cell monoclonality, with dominant lentiviral insertion at three non-cancer gene sites and preexisting mutations in cancer genes. No direct evidence of insertional oncogenesis was found, but the possibility of outgrowth of preexisting malignant T-cell clones cannot be excluded. In the other case, CAR transgene was detected in tumor tissue, with a dominant clone having lentiviral integration in a non-cancer gene. Further tests are ongoing. For details on comparison of T-cell malignancies frequency after Kymriah treatment with background incidence please refer to Table 8-18.
Risk factors and risk groups	Risk factors include prior anticancer therapies (chemotherapy, radiation therapy, and HSCT) or post tisagenlecleucel infusion. These factors are associated with development of new malignancies. Additionally historical or concurrent other malignancies besides the underlying indication suggesting high genomic instability. Risk groups; Advanced age (>50 years old) with DLBCL.
Risk minimization measures	**Routine risk minimization measures** 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 4 Possible side effects **Additional risk minimization measures** Information provided that treatment with tisagenlecleucel may induce secondary malignancy or recurrence of cancer. Guidance to monitor for secondary malignancies life-long (SmPC Section 4.4) Instruction provided, 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).
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** CCTL019B2401 (as feasible) CCTL019A2205B CCTL019B2402 See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-9 Important potential risk: Cerebral edema

Evidence for linking the risk to the medicine	No fatal cerebral edemas have been reported following tisagenlecleucel infusion in the clinical development program or the post-marketing setting to date that would resemble five fatal cases reported for JCAR015 (Juno). Importantly, the risk of fatal cerebral edema appears

	to be dependent of the anti-CD19 CAR construct used to engineer CAR T-cell therapies; JCAR015 presents a different construct of an anti-CD19 CAR than the CAR construct of tisagenlecleucel. These five fatal cases of cerebral edema occurred in the ROCKET study and were characterized by a rapid evolution soon after JCAR015 infusion, appeared to be resistant to anti-cytokine treatment, and ensued brain death within 1-2 days after diagnosis. Following a retrospective exploratory analysis, it is believed that the fatal cerebral edemas in these five patients emerged from rapid T-cell expansion associated with the specific CAR T-cell product construct that determines the kinetics of T-cell expansion after infusion together with other risk factors such as high baseline blood levels of interleukin 15 (JCAR015). Key findings of this retrospective analysis of the JCAR015 cases with fatal cerebral edema showed that all five patients experienced rapid, early expansion of their CAR T cells within a week of being infused (rather than the typical time frame of 12-14 days), high levels of the CD8+ subtype and, consequently, a sharp spike in cytokines such as interleukin 2 and TNFα. Autopsy results from two of the patients showed a breakdown of the blood-brain barrier and microvascular disruption, possibly due to inflammatory cytokine surge. Potential risk factors at baseline included age younger than 30 years, Philadelphia chromosome negativity, subset of disease (i.e., B-ALL), fewer prior regimens, higher levels of interleukin 15 and decreased levels of platelets. Since the five fatal cases after exposure to the JCAR015 product have become known, another patient with fatal cerebral edema was reported in the ZUMA-1 trial following axicabtagene ciloleucel treatment. This patient progressed to CRS grade 4 refractory to tocilizumab and dexamethasone on Day 4, developed cerebral edema refractory to siltuximab and mannitol on Day 9, and died on Day 11. The clinical course of this case treated with KTE-019 may not be comparable with those 5 cases treated with JCAR015, which is further supported by a retrospective analysis of baseline cytokine and chemokine levels in serum and cerebrospinal fluid suggesting significant pre-existing underlying inflammatory condition providing an alternate explanation. Another fatal cerebral edema case following axicabtagene ciloleucel was reported in the standard of care setting.
Risk factors and risk groups	Risk factors and risk groups are unknown.
Risk minimization measures	**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 **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B • CCTL019B2401 See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-10 Important potential risk: Generation of replication competent lentivirus

Evidence for linking the risk to the medicine	Tisagenlecleucel uses third generation self-inactivating lentiviral vector. Generation of a replication-competent lentivirus (RCL) following infusion of the vector product remains a theoretical possibility. Replication-competent lentivirus will be detected by qPCR for vesicular stomatitis virus-G (VSV-G) of peripheral blood. Replication-competent lentivirus has not been described in the scientific literature for lentiviral vectors that use a production method similar to the tisagenlecleucel vectors. Furthermore, lentiviral vectors have been successfully used in conjunction with HIV infected patients, with no evidence of vector mobilization after 60 days or insertional mutagenesis observed up to 36 months. To date, no indication of RCL tisagenlecleucel batches was detected by using VSV-G DNA (specification ≤ 50 copies/µg) assay as a substitute. Furthermore, patients enrolled in interventional clinical trials have been screened for RCL with no RCL identified to date.
Risk factors and risk groups	The development of RCL could pose a risk to both the patient and their close contacts.
Risk minimization measures	**Routine risk minimization measures** • None **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-11 Important potential risk: Secondary malignancies (except secondary malignancy of T-cell origin) including vector insertion site oligo/monoclonality

Evidence for linking the risk to the medicine	To date, no cases of secondary malignancy (other than T-cell origin) have been assessed to be causally related to tisagenlecleucel by

	Novartis. No suspected secondary malignancies following CAR T-cell therapies developed by other pharmaceutical companies have been reported in literature. Based on historic experience in patients with X-linked severe combined immunodeficiency, chronic granulomatous disease, and Wiskott-Aldrich syndrome, vector-mediated insertional mutagenesis and subsequent malignant cell transformation have been observed following gene correction via autologous human stem cell based gene therapy, where first-generation gamma-retroviral vectors harboring long terminal repeats with strong enhancer/promoter sequences has been used. The potential risk of insertional oncogenesis was addressed in two LISA studies where 12 batches of manufactured tisagenlecleucel product ready for administration in patients (6 patients each from study B2202 and C2201) and two batches of product manufactured from healthy donor cells were analyzed. The results indicate that there was no preferential integration near genes of concern, no preferential sites of integration (hot spots), and no preferential outgrowth of cells harboring integration sites of concern. Tisagenlecleucel is based on autologous, fully differentiated T cells and therefore the carcinogenicity risk is considered to be low in comparison to genetic modification or repair such as human stem cells. As discussed in a review of CAR T-cell therapies, no cases of malignant transformation have been reported for genetic modification of T cells to date and there is currently no evidence for vector-induced immortalization, clonal expansion, or enrichment for integration sites near genes implicated in growth control or transformation. This is supported by the results of the LISA studies performed during the development of tisagenlecleucel. Theoretically, CAR-positive viable T cells could proliferate without control of normal homeostatic mechanisms. In pre-clinical studies and clinical experience to date, CAR-positive viable T cells have only proliferated in response to physiologic signals or upon exposure to CD19 antigen. In the context of tisagenlecleucel therapy, it is expected that the T cells will proliferate in response to signals from the CD19 expressing malignant tumor and normal B cells. This could be either harmful depending on the extent of proliferation or beneficial, since clonal dominance of adoptively transferred T cells has been associated with tumor reduction in adoptive transfer trials.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to tisagenlecleucel has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.4 Special warnings and precautions for use 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 4 Possible side effects **Additional risk minimization measures** None

Additional pharmacovigilance activities	**Additional pharmacovigilance activities** CCTL019B2401 (as feasible) CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-12 Important potential risk: New occurrence or exacerbation of an autoimmune disorder

Evidence for linking the risk to the medicine	Most autoimmune diseases are driven by a dysfunction in the immune network consisting of B cells, T cells, and other immune cells. Reciprocal roles of T-cell help for B cells during adaptive immune responses and B-cell help in $CD4^+$ T-cell activation are being increasingly recognized. An emerging number and variety of autoimmune diseases following after anti-cancer treatment including immunotherapy are reported, ranging from asymptomatic immunological alterations to life-threatening systemic autoimmune diseases. However, specific etiopathogenic mechanisms that could clearly link the induced autoimmune disorder with the immunological pathways altered by the anti-cancer treatments are not well understood. Persistent immune abnormalities after treatment with chemotherapy, development of auto-antibodies and neoantigens are proposed to be crucial in the pathogenesis of autoimmune diseases post anti-cancer treatment. Based on current knowledge, the risk of autoimmune reaction is considered low with tisagenlecleucel, since CD19 is not present on most normal tissue other than B cells. The occurrence or exacerbation of an autoimmune disorder has not been observed with tisagenlecleucel to date. Prior anti-cancer therapy, such as radiation and chemotherapy, lymphodepleting chemotherapy prior to treatment with tisagenlecleucel or concomitant treatment may present additional risk factors.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to tisagenlecleucel has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	**Routine risk minimization measures** • None **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-13 Important potential risk: Aggravation of graft-versus-host disease

Evidence for linking the risk to the medicine	The chance of graft-versus-host-disease (GVHD) occurring in patients after tisagenlecleucel infusion per se is considered low, but there is a potential risk of aggravation of pre-existing GVHD in patients with donor chimerism from a prior allogeneic HSCT post-tisagenlecleucel due to the milieu provided by robust activation of the transduced viable T cells. A study of activated DLIs (ex vivo activated cells collected from the donor and grown in the same fashion as tisagenlecleucel but without the CAR introduction) did not show high rates of GVHD (2/18 patients with grade 3 GVHD and none with grade 4). Of 18 ALL patients treated with autologous tisagenlecleucel therapy who had relapsed after prior allogeneic HSCT with residual mixed chimerism, none have developed GVHD after autologous tisagenlecleucel infusion.
Risk factors and risk groups	Patients with the presence of active GVHD from prior HSCT.
Risk minimization measures	**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 **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-14 Important potential risk: Transmission of infectious agents

Evidence for linking the risk to the medicine	Multiple steps are required to produce tisagenlecleucel CAR T cells, involving leukapheresis to obtain patient autologous starting material, enrichment and activation, gene transduction via lentiviral vector and expansion. Transmission of infectious material via product could potentially derive from the patient's own leukapheresis material prepared from autologous blood, other material including the tisagenlecleucel viral vector required to manufacture tisagenlecleucel, through contamination during the manufacturing process or inadequate storage. The risk associated with tisagenlecleucel is considered very low. Stringent precautions to

prevent introduction of viral adventitious agents and to ensure microbial safety of tisagenlecleucel are in place in compliance with principles of good manufacturing practices and regulatory guidelines.

The starting material for producing tisagenlecleucel are the patient's autologous (i.e., donor and recipient are the same) non-mobilised peripheral blood mononuclear cells collected by leukapheresis.

Tisagenlecleucel is composed of autologous CD4+ and CD8+ T cells genetically modified with a murine HIV-1 lentiviral vector encoding a CAR against CD19. The product is manufactured by expansion of patient T cells after transduction without any hold step. Due to the nature of the product (i.e., cells), there is no possibility to introduce terminal sterilization or dedicated viral removal and inactivation steps. Therefore, stringent precautions to prevent introduction of viral adventitious agents and to ensure microbial safety of tisagenlecleucel product are taken as detailed below.

1. Control of raw materials and of the tisagenlecleucel vector

• Control of animal and human derived raw materials entering the manufacturing process through certificates of origin and suitability. For human derived materials such as human serum, viral inactivation steps in the manufacturing process of these materials are performed

- Control of the production of tisagenlecleucel vector using HEK293T cells, which are not known to express endogenous viruses
- Additional controls through filtration of raw materials (media) performed prior to use in manufacturing
- Control of the tisagenlecleucel vector through testing for adventitious viral agents
- Testing for relevant human viruses as part of the patient eligibility assessment

2. Process and environmental controls

- Control of the tisagenlecleucel drug product manufacturing process (antibiotics free) through use of closed systems. Where there are open steps, the process is performed under environmentally controlled conditions
- Environmental controls (e.g., evaluating the quality of air, temperature, surfaces, personnel in a cleanroom environment)
- Cleaning and decontamination of work surfaces and equipment
- Aseptic verification, simulating all process steps and interventions is conducted to verify that the process is capable of maintaining sterility

3. Control of tisagenlecleucel by microbial contaminants testing as part of drug product release testing

- Testing for bacterial endotoxin
- Testing for sterility
- Testing for mycoplasma

	Details on shipping and storage conditions of tisagenlecleucel product and disposal are described in the SmPC.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to tisagenlecleucel has been established. There is a potential risk of transmission of infectious agents to close contacts including personnel involved in the tisagenlecleucel manufacturing process or health care providers involved in leukapheresis and administering tisagenlecleucel in addition to patients treated with tisagenlecleucel.
Risk minimization measures	**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	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-15 Important potential risk: Decrease in cell viability due to inappropriate handling of the product

Evidence for linking the risk to the medicine	Inconsistencies may arise due to product handling including subjective determination of the thaw endpoint and risk of water borne contamination.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to tisagenlecleucel has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	**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 risk minimization measures** • Controlled distribution program • Educational program including the Pharmacy/Cell Lab/Infusion Center Training Material
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • None

Table 13-16 Missing information: Use in pregnancy and lactation

Risk minimization measures	**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 **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-17 Missing information: Use in patients with HBV/HCV/HIV

Risk minimization measures	**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 Section Other sources of information **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-18 Missing information: Use in patients with active CNS involvement by malignancy

Risk minimization measures	**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	**Additional pharmacovigilance activities** • CCTL019B2401 See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-19 Missing information: Long-term safety

Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-20 Missing information: Immunogenicity

Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.8 Undesirable effects

	Additional risk minimization measures • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

13.2.3 Part VI: II.C: Post-authorization development plan

13.2.3.1 II.C.1. Studies which are conditions of the marketing authorization

Table 13-21 Studies which are conditions of the marketing authorization

Study short name	Purpose of the study:
CCTL019B2401 (PASS) Non-interventional study with secondary use of data from the registries conducted by CIBMTR and EBMT, respectively, to evaluate the long-term safety of patients with malignancies treated with CAR T-cell therapies.	This study will provide further information on long-term, real-world safety and effectiveness up to 15 years following treatment with tisagenlecleucel based on secondary use of tisagenlecleucel data prospectively collected through the CIBMTR and EBMT registries for cellular therapy. The primary objective is to evaluate the long-term safety and the risk of secondary malignancies in patients with B lymphocyte malignancies treated with tisagenlecleucel in a real-world setting. The main secondary objective is to evaluate the long-term effectiveness of tisagenlecleucel.
CCTL019H2301	Phase 3 study to evaluate the efficacy and safety of tisagenlecleucel versus standard of care in adult patients with r/r aggressive B-cell aggressive NHL. To further characterize the long-term efficacy and safety in relapsed/refractory DLBCL.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

Table 13-22 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
CCTL019A2205B (PASS) Long-term follow-up study in patients exposed to lentiviral-based CD19 directed CAR T-cell therapy in preceding clinical trials	The purpose of this Novartis PASS is to monitor all patients exposed to lentiviral vector based CD19 CAR T-cell therapy for 15 years from the last CD19 CAR T-cell infusion, to assess the risk of delayed AEs suspected to be related to CD19 CAR T-cell therapy, monitor for vectors persistence and RCL, and record the status of the primary malignancy (efficacy). 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 T-cell 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.
CCTL019B2402 (PASS)	The purpose of this study is to to characterize secondary T-cell malignancies following CAR-T -cell therapy using a lentiviral vector. The primary objective is to test for CAR transgene and RCL using qPCR for all identified sSecondary T cell malignancies occurring after the infusion of clinical trial CAR T (CTL019- tisagenlecleucel) or commercial CAR T (Kymriah/tisagenlecleucel). IHC (Immunohistochemistry) (IHC) may be considered in some cases where PCR is not feasible. Patient-specific testing and results determine whether there is any potential causal

Study short name	Rationale and study objectives
	relationshipity (or lack thereof) of the prior CAR T therapy with the development of the secondary T cell malignancy. The secondary objective is to explore potential causality of CAR T with the development of secondary T cell malignancy, additional testing will be performed for all cases where qPCR or IHC shows a positive signal for transgene in the T cell secondary malignancy. This additional testing (if feasible) includes LISA, genomic profiling on retained vials of apheresis and final product sample is performed.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

No product specific checklists are proposed.

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Key messages of the additional risk minimization measures

- **Controlled distribution program objectives**
  - To mitigate the safety risks associated with tisagenlecleucel treatment by ensuring that hospitals and their associated centers that dispense tisagenlecleucel infusion are specially qualified by Novartis.
  - Tisagenlecleucel product will only be supplied to hospitals and associated centers 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. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the EMA shortage catalogue, Novartis will ensure that suitable alternative measures to treat CRS instead of tocilizumab are available on-site.
- **Educational program objectives**
  - Pharmacy/Cell Lab/Infusion Center Training Material
    - Inform about reception, storage, handling, thawing and preparation for infusion of tisagenlecleucel to mitigate a decrease in cell viability of tisagenlecleucel due to inappropriate handling of the product and subsequent potential impact on the efficacy/safety profile.
  - Healthcare Professional Training Material
    - Mitigate the risk of severe or life-threatening CRS and neurological events by ensuring those, who prescribe, dispense, or administer tisagenlecleucel, are aware of how to manage the risks of CRS and neurological events.
- Counsel patients/guardians on instances where tisagenlecleucel cannot be successfully manufactured or the final product is OOS, the potential need for bridging chemotherapy, risk of progressive disease during manufacturing time, in addition to the risks of CRS and neurological events and actions to be taken.
- Create awareness about the risk of secondary malignancy of T-cell origin, reporting requirement and potential need to consider testing of tumor tissue and/or blood from the patient, among health care professionals who prescribe, dispense, administer tisagenlecleucel or who follow up patients after tisagenlecleucel treatment.
  - Inform about AEs reporting in the respective registry for cellular therapy and, in parallel, encourage to spontaneously report the same AEs timely, if causality to the tisagenlecleucel treatment is suspected, as adverse reactions of tisagenlecleucel to Novartis or the local Health Authorities.
  - Patient Educational Leaflet

- Create awareness that there are instances, where tisagenlecleucel cannot be successfully manufactured and infusion cannot be provided, or the final manufactured product is OOS.
- Inform about the potential need for bridging chemotherapy and associated ADRs and the risk of progressive disease during the tisagenlecleucel manufacturing time.
- Educate about the risks of CRS and neurotoxicity, and when to seek medical attention.
- Inform about monitoring requirements and potential for hospitalization following tisagenlecleucel infusion.

Material provided to healthcare professionals and patients

- **Healthcare professional information pack**

  Healthcare professionals will have access to the SmPC. In addition, they must be trained with educational material that includes the Pharmacy/Cell Lab/Infusion Center Training Material and the Healthcare Professional Training Material.

  The healthcare professional information pack contains:

  - ***Summary of Product Characteristics***
  - ***Educational material: Pharmacy/Cell Lab/Infusion Center Training Material***
    - Information on reception, storage, handling, thawing and preparation for infusion of tisagenlecleucel
  - ***Educational material: Healthcare Professional Training Material***
    - Approved indications
    - Risks of CRS and neurological events
    - CRS:
      - CRS incidence, onset and duration
      - CRS signs and symptoms and associated organ dysfunction
      - Risk factors for severe CRS
      - Conditions when tisagenlecleucel infusion should be delayed

- In the first week of following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion, for signs and symptoms of potential CRS, neurological events and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalization at the first signs/symptoms of cytokine release syndrome and/or neurological events.

  - Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion

    - Management of CRS according to the CRS management algorithm. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the EMA shortage catalogue, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS.
  - Neurological events
  - Neurological event incidence, onset and duration
  - Neurological events manifestations
- In the first week of following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion, for signs and symptoms of potential CRS, neurological events and other toxicities. After the first week following the infusion, the patient should be monitored at the physician's discretion. Physicians should consider hospitalization at the first signs/symptoms of cytokine release syndrome and/or neurological events. Patients should be instructed to remain within proximity (i.e., within 2 hours travel) of a qualified clinical facility for at least 4 weeks following infusion
  - Diagnostic work-up of neurological events
  - Monitoring of patients for infections, with late occurrence in some cases. Diagnostic work-up of opportunistic infections of the CNS in patients with neurological events
  - Management of neurological events
  - Secondary malignancy of T-cell origin
    - For patients treated with tisagenlecleucel, upon diagnosis with secondary malignancy during any follow up visit, healthcare professionals should report all new secondary malignancies (subsequent neoplasm) to Novartis and arrangements should be made for testing of archived tumor sample and/or DNA extracted and saved from blood from the patient, when feasible.
    - Eligible patients should be offered enrollment in NIS PASS B2402.
    - For all other patients (including not eligible, decline consent or site declines to participate in the B2402 study) with a reported secondary T cell malignancy, the current Novartis Secondary Malignancy Guidance Document and Process will be followed.
  - Counsel patients/guardians regarding
    - In the instance, where tisagenlecleucel cannot be successfully manufactured and infusion cannot be provided, or the final manufactured product is OOS and does not pass release tests. In some instances, a second manufacturing of tisagenlecleucel may be attempted. In case of OOS, the final product may be still provided as per physician's request, if supported by a positive benefit-risk assessment
    - Potential need for bridging chemotherapy and associated ADRs, and the risk of progressive disease during the tisagenlecleucel manufacturing time
    - Risk of CRS and neurological events and actions to take

- Patients should be offered enrollment into a registry for cellular therapies
- Healthcare professionals should report AEs in the respective registry for cellular therapies according to Registry holder guidelines and, in parallel, are encouraged to spontaneously report the same AEs, if causality to the tisagenlecleucel treatment is suspected, as adverse reactions of tisagenlecleucel to Novartis at https://www.report.novartis.com or call the phone number listed in the local tisagenlecleucel prescribing information, or to the local Health Authorities

- **Patient information pack**

Patients will be provided with the SmPC Package leaflet and Patient Alert Card in addition to educational material that is the Patient Educational Leaflet

Patients receiving tisagenlecleucel treatment will be counseled by the treating healthcare professional on risks of CRS and neurological events and when to contact the healthcare professional. In addition, patients will be informed about the potential need for bridging therapy and associated adverse reactions, and the risk of progressive disease during the tisagenlecleucel manufacturing time

The patient information pack contains:

- ***SmPC Package leaflet*** and ***Patient Alert Card***
- ***Educational material: Patient Educational Leaflet***
  - Carry Patient Alert Card at all times and show it to any healthcare provider
  - Approved indications
  - Leukapheresis and tisagenlecleucel manufacturing time
  - In the instance, where tisagenlecleucel cannot be successfully manufactured and infusion cannot be provided, or the final manufactured product is OOS and does not pass release tests. In some instances, a second manufacturing of tisagenlecleucel may be attempted. In case of OOS, the final product may be still provided as per physician's request, if supported by a positive benefit-risk assessment
  - While tisagenlecleucel is being manufactured, additional bridging therapy may be needed to stabilize the underlying disease. The treating physician will inform about potential side effects of this therapy
  - While awaiting tisagenlecleucel manufacture, the underlying disease may worsen and progress
  - Before getting tisagenlecleucel, a short course of lymphodepleting chemotherapy for conditioning may be given
  - Information that CRS, neurological events and other toxicities may occur. Signs and symptoms of CRS and neurological events in addition to other clinically important side effects are outlined.
  - Patient may need to be hospitalized for side effects

- Instructions to call treating healthcare professional or go to the emergency room if certain signs and symptoms appear
- Information that patients will be monitored 2 to 3 times, or more frequently at the physician's discretion, following tisagenlecleucel infusion for signs and symptoms of potential CRS, neurological events and other toxicities. After the first week following the infusion, patients will be monitored at the physician's discretion. Physicians should consider hospitalization at the first signs/symptoms of cytokine release syndrome and/or neurological events.
- Information that tisagenlecleucel may cause false positive HIV test
- Instructions for the patient:
  - Take temperature twice a day for 3-4 weeks after administration of tisagenlecleucel. If temperature is elevated, see your doctor immediately
  - Plan to stay within 2 hours of the location where tisagenlecleucel was received for at least 4 weeks following tisagenlecleucel infusion
  - Do not drive, use machines or take part in activities that require alertness for 8 weeks after tisagenlecleucel infusion because of the risk of neurological events
  - Do not donate blood, organs, tissues or cells

- Information for the healthcare professional:
  - This patient has received tisagenlecleucel infusion, a CAR T-cell therapy for <approved indication>
  - Following tisagenlecleucel treatment, CRS and neurological events can occur typically within the first few weeks after infusion; however, later occurrence might happen
  - Please contact his/her treating oncologist before giving steroids or cytotoxic medications. Consult with his/her treating oncologist for the management of the patient