NOVARTIS

Regulatory Affairs

Kymriah®

Summary of the Risk Management Plan (RMP) v1.3 for Kymriah®

(Tisagenlecleucel)

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Summary of the risk management plan for Kymriah (tisagenlecleucel)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of Kymriah® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the „Arzneimittelinformation“ approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Kymriah in Switzerland is the „Arzneimittelinformation“ (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the here published summary RMP of Kymriah®.

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 25 years of age with B-cell acute lymphoblastic leukemia (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.

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 prescribing information (‘Fachinformation’) and package leaflet (‘Patienteninformation’) 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.

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 1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	• Cytokine release syndrome • Infections • Serious neurological adverse reactions • Tumor lysis syndrome • Prolonged depletion of normal B-cells/ Agammaglobulinemia • Hematopoietic cytopenias not resolved by day 28

List of important risks and missing information	
Important potential risks	• Cerebral edema • Generation of replication competent lentivirus • Secondary malignancies (including vector insertion site oligo/monoclonality) • New occurrence or exacerbation of an autoimmune disorder • Hematological disorders (incl. aplastic anemia and bone marrow failure) • Aggravation of graft-versus-host disease • Transmission of infectious agents • Decrease in cell viability due to inappropriate handling of the product
Missing information	• Use in pregnancy and lactation • Use in patients with HBV/HCV/HIV • Use in patients with active CNS involvement by malignancy • Long-term safety • Immunogenicity

Summary of important risks

Table 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. Severe and life-threatening 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 ALL and adult r/r DLBCL, CRS was graded using criteria predefined in the study protocols (Penn CRS grading scale). In the majority of patients, development of CRS occurred between 1 to 10 days (median onset: 3 days) after tisagenlecleucel infusion for pediatric and young adult r/r B-ALL patients and between 1 and 9 days (median onset: 3 days) after the tisagenlecleucel infusion for adult r/r DLBCL patients. The median duration of CRS was 8 days in pediatric/young adult r/r B-ALL and 7 days in r/r DLBCL patients. Symptoms of CRS may include high fever, rigors, myalgia, arthralgia, nausea, vomiting, diarrhea, diaphoresis, rash, anorexia, fatigue, headache, hypotension, encephalopathy, dyspnea, tachypnea, and hypoxia. Additional organ system adverse events (AEs), including transient cardiac insufficiency and arrhythmia, renal insufficiency, elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), and elevated bilirubin have been observed. In some cases, disseminated intravascular coagulation, with low fibrinogen levels, or capillary leak syndrome. Hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) occurring in the context of tisagenlecleucel and other CAR-T-cell therapies are considered a manifestation of severe CRS.
Risk factors and risk groups	Risk factors for severe CRS in paediatric and young adult B-ALL patients are high pre-infusion tumour burden, uncontrolled or accelerating tumour burden following lymphodepleting chemotherapy, active infection and early onset of fever or CRS following tisagenlecleucel infusion. Risk factors for developing severe CRS in adult DLBCL patients is high tumor burden. Infections may also occur during CRS and increase the risk of a fatal event.
Risk minimization measures	**Routine risk minimization measures** • Prescribing information Section Posology and method of administration • Prescribing information Section Special warnings and precautions for use

	• Prescribing information Section Interaction with other medicinal products and other forms of interaction • Prescribing information Section Undesirable effects • Package leaflet, Section What you need to know before you are given Kymriah • Package leaflet, Section How Kymriah is given • Package leaflet, Section Possible side effects • Package leaflet, Section How to store Kymriah **Additional risk minimization measures** • Controlled distribution program • Educational program including the Healthcare Professional Training Material and the Patient Educational Leaflet
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B: Long-term follow-up of patients exposed to lentiviral-based CD19 directed CAR-T-cell therapy. • CCTL019B2401: A registry to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel.

Table 3 Important identified risk: Infections

Evidence for linking the risk to the medicine	Serious infections 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** • Prescribing information Section Posology and method of administration • Prescribing information Section Special warnings and precautions for use • Prescribing information Section Interaction with other medicinal products and other forms of interaction • Prescribing information Section Undesirable effects

	• Package leaflet, Section What you need to know before you are given Kymriah • Package leaflet, Section How Kymriah is given • Package leaflet, Section Possible side effects • Package leaflet, Section How to store Kymriah **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B: Long-term follow-up of patients exposed to lentiviral-based CD19 directed CAR-T-cell therapy. • CCTL019B2401: A registry to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel.

Table 4 Important identified risk: Serious neurological adverse reactions

Evidence for linking the risk to the medicine	Early neurological events, recently suggested to be named CAR-T-cell-related encephalopathy syndrome (CRES) is the second most-common adverse reaction associated with CAR-T therapies. CRES typically manifests as a toxic encephalopathy with wide range of variable symptoms such as aphasia, confusion, delirium, tremors, occasionally seizures and rarely life-threatening cerebral edema. The manifestation of CRES is biphasic, with the first phase occurring concurrently with cytokine release syndrome (CRS) symptoms typically within the first 5 days after CAR-T-cell therapy, and the second phase after CRS subsides. Delayed neurological events with seizures or episodes of confusion 3-4 weeks following CAR-T-cell therapy have been reported to occur in approximately 10% of patients. While the majority of neurological events following tisagenlecleucel infusion were observed within 8 weeks, neurological events with later onset and not in the context of CRS have also been reported. 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.

	Notably, the onset of neurological events can be concurrent with CRS, following resolution of CRS or in the absence of CRS. Onset of neurological events may be concurrent with high fever during the development and at the time of maximal grade of CRS. The incidence appeared to be greater with higher CRS severity and prior history of CNS leukemia and history of other prior CNS diseases. Encephalopathy typically occurred after peak CRS symptoms and tended to be self-limiting with some exceptions. Delayed onset of neurological events may also occur as CRS is resolving or after CRS has completely resolved. There is currently limited evidence that CAR therapies are associated with a late onset of neurological events (i.e., onset > 8 weeks after infusion). 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 CNS disease/injury or CNS leukemic involvement. In addition, higher grade CRS may predispose.
Risk minimization measures	**Routine risk minimization measures** • Prescribing information Section Posology and method of administration • Prescribing information Section Special warnings and precautions for use • Prescribing information Section Effects on ability to drive and use machines • Prescribing information Section Undesirable effects • Package leaflet, Section What you need to know before you are given Kymriah • Package leaflet, Section How Kymriah is given • Package leaflet, Section Possible side effects • Package leaflet, Section How to store Kymriah **Additional risk minimization measures**

	• Controlled distribution program • Educational program including the Healthcare Professional Training Material and the Patient Educational Leaflet
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B: Long-term follow-up of patients exposed to lentiviral-based CD19 directed CAR-T-cell therapy. • CCTL019B2401: A registry to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel.

Table 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 TLS had a grade 3 in Common Terminology Criteria for Adverse Events (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.
Risk minimization measures	**Routine risk minimization measures** • Prescribing information Section Posology and method of administration • Prescribing information Section Special warnings and precautions for use • Prescribing information Section Undesirable effects • Package leaflet, Section What you need to know before you are given Kymriah • Package leaflet, Section How Kymriah is given • Package leaflet, Section Possible side effects • Package leaflet, Section How to store Kymriah **Additional risk minimization measures** • None

Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B: Long-term follow-up of patients exposed to lentiviral-based CD19 directed CAR-T-cell therapy. • CCTL019B2401: A registry to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel.

Table 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 infections, especially with encapsulated organisms; and viral reactivation such as herpes viruses and progressive multifocal leukoencephalopathy (PML) - a rare viral disease. Prolonged hypogammaglobulinemia, defined as lasting for more than 11 months, has been reported after rituximab exposure. Progressive multifocal leukoencephalopathy is has been reported with the use of other B-cell depleting therapy (rituximab) and has also been observed after chemotherapy and bone marrow transplantation. In 2006 the FDA issued a warning about the development of PML in patients taking rituximab.
Risk factors and risk groups	Patients with B-cell aplasia are at increased risk for bacterial infections especially with encapsulated organisms; and viral reactivation such as herpes viruses and B hepatitis and PML.
Risk minimization measures	**Routine risk minimization measures** • Prescribing information Section Posology and method of administration • Prescribing information Section Special warnings and precautions for use • Prescribing information Section Fertility, pregnancy and lactation • Prescribing information Section Undesirable effects • Package leaflet, Section What you need to know before you are given Kymriah • Package leaflet, Section How Kymriah is given

	• Package leaflet, Section Possible side effects • Package leaflet, Section How to store Kymriah **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B: Long-term follow-up of patients exposed to lentiviral-based CD19 directed CAR-T-cell therapy. • CCTL019B2401: A registry to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel.

Table 7 Important identified risk: Hematopoietic cytopenias not resolved by day 28

Evidence for linking the risk to the medicine	Cytopenias not resolved by day 28 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, and lymphodepleting chemotherapy are at enhanced risk.
Risk minimization measures	**Routine risk minimization measures** • Prescribing information Section Posology and method of administration • Prescribing information Section Special warnings and precautions for use • Prescribing information Section Undesirable effects • Package leaflet, Section What you need to know before you are given Kymriah • Package leaflet, Section How Kymriah is given • Package leaflet, Section Possible side effects • Package leaflet, Section How to store Kymriah **Additional risk minimization measures** • None

Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B: Long-term follow-up of patients exposed to lentiviral-based CD19 directed CAR-T-cell therapy. • CCTL019B2401: A registry to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel.

Table 8 Important potential risk: Cerebral edema

Evidence for linking the risk to the medicine	No fatal cerebral edemas have been reported in the tisagenlecleucel clinical development program or the post-marketing setting to date that would resemble five fatal events reported for JCAR015 (Juno), which presents a very different construct of anti-CD19 CAR-T-cell products compared to 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 of these five cases, it is believed that these fatal cerebral edemas 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, possibly due to inflammatory cytokine surge. Potential baseline risk factors 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 KTE-019 infusion that may be worthwhile to mention for completeness. 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.
Risk factors and risk groups	Risk factors and risk groups are unknown.
Risk minimization measures	**Routine risk minimization measures** • Prescribing information Section Posology and method of administration • Prescribing information Section Special warnings and precautions for use • Prescribing information Section Effects on ability to drive and use machines • Prescribing information Section Undesirable effects • Package leaflet, Section What you need to know before you are given Kymriah • Package leaflet, Section How Kymriah is given • Package leaflet, Section Possible side effects • Package leaflet, Section How to store Kymriah **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B: Long-term follow-up of patients exposed to lentiviral-based CD19 directed CAR-T-cell therapy. • CCTL019B2401: A registry to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel.

Table 9 Important potential risk: Generation of replication competent lentivirus

Evidence for linking the risk to the medicine	Generation of an RCL following infusion of the vector product remains a theoretical possibility. RCL will be detected by q-PCR for VSV-G of peripheral blood.
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: Long-term follow-up of patients exposed to lentiviral-based CD19 directed CAR-T-cell therapy.

Table 10 Important potential risk: Secondary malignancies (including vector insertion site oligo/monoclonality)

Evidence for linking the risk to the medicine	Vector-mediated insertional mutagenesis and subsequent malignant cell transformation after gene correction based on autologous HSC gene therapy has been observed in X-linked severe combined immunodeficiency (SCID-X1), chronic granulomatous disease (CGD), and Wiskott-Aldrich syndrome (WAS), where first-generation gamma-retroviral vectors harboring long terminal repeats (LTRs) with strong enhancer/promoter sequences were used. In contrast, tisagenlecleucel uses third generation self-inactivating lentiviral vector. Insertional mutagenesis was addressed in two lentivirus insertion site analysis (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.

	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 HSC. As discussed in a recent 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 lentivirus insertion site analysis (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** • Prescribing information Section Special warnings and precautions for use • Prescribing information Section Preclinical safety data **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B: Long-term follow-up of patients exposed to lentiviral-based CD19 directed CAR-T-cell therapy. • CCTL019B2401 (as feasible): A registry to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel.

Table 11 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 normal B-cells. The occurrence of new occurrence or exacerbation of an autoimmune disorder has not been observed with tisagenlecleucel. Prior chemotherapy, radiation or concomitant treatment may also contribute to the risk. The use of tocilizumab, a monoclonal antibody against the interleukin 6 receptor, can exacerbate demyelinating disease, and therefore its use is to be used with precaution in such conditions.
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** • CCTL019A2205B: Long-term follow-up of patients exposed to lentiviral-based CD19 directed CAR-T-cell therapy. • CCTL019B2401: A registry to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel.

Table 12 Important potential risk: Hematological disorders (incl. aplastic anemia and bone marrow failure)

Evidence for linking the risk to the medicine	Delayed toxicity of hematologic origin (e.g., such as myelodysplastic syndrome, aplastic anemia, bone marrow failure) has been associated with prior treatment with chemotherapy and radiation and were observed in the tisagenlecleucel development program.
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** • CCTL019A2205B: Long-term follow-up of patients exposed to lentiviral-based CD19 directed CAR-T-cell therapy. • CCTL019B2401: A registry to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel.

Table 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 Hematopoietic stem cell transplantation (HSCT) post-tisagenlecleucel due to the milieu provided by robust activation of the transduced viable T-cells.

	A study of activated donor lymphocyte infusions (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. Long term data are currently limited.
Risk factors and risk groups	Patients with the presence of active GVHD from prior HSCT.
Risk minimization measures	**Routine risk minimization measures** • Prescribing information Section Posology and method of administration • Prescribing information Section Special warnings and precautions for use • Prescribing information Section Undesirable effects • Package leaflet, Section What you need to know before you are given Kymriah • Package leaflet, Section How Kymriah is given • Package leaflet, Section Possible side effects • Package leaflet, Section How to store Kymriah **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B: Long-term follow-up of patients exposed to lentiviral-based CD19 directed CAR-T-cell therapy. • CCTL019B2401: A registry to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel.

Table 14 Important potential risk: Transmission of infectious agents

Evidence for linking the risk to the medicine	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** • Prescribing information Section Posology and method of administration • Prescribing information Section Special warnings and precautions for use • Prescribing information Section Shelf life • Prescribing information Section Special precautions for storage • Prescribing information Section Nature and contents of container and special equipment for use, administration or implantation • Prescribing information Section Special precautions for disposal and other handling

	• Package leaflet, Section What you need to know before you are given Kymriah • Package leaflet, Section How Kymriah is given • Package leaflet, Section How to store Kymriah • Prescribing information Section Other sources of information **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B: Long-term follow-up of patients exposed to lentiviral-based CD19 directed CAR-T-cell therapy. • CCTL019B2401: A registry to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel.

Table 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** • Prescribing information Section Posology and method of administration • Prescribing information Section Shelf life • Prescribing information Section Special precautions for storage • Prescribing information Section Nature and contents of container and special equipment for use, administration or implantation • Prescribing information Section Special precautions for disposal and other handling • Package leaflet, Section How Kymriah is given • Package leaflet, Section How to store Kymriah • Prescribing information 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 16 Missing information: Use in pregnancy and lactation

Risk minimization measures	**Routine risk minimization measures** • Prescribing information Section Fertility, pregnancy and lactation • Prescribing information Section Preclinical safety data • Package leaflet, Section What you need to know before you are given Kymriah • Package leaflet, Section How to store Kymriah **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401: A registry to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel.

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

Risk minimization measures	**Routine risk minimization measures** • Prescribing information Section Posology and method of administration • Prescribing information Section Special warnings and precautions for use • Prescribing information Section Special precautions for disposal and other handling • Package leaflet, Section What you need to know before you are given Kymriah • Package leaflet, Section How Kymriah is given • Package leaflet, Section How to store Kymriah

	• Prescribing information Section Other sources of information **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** CCTL019B2401: A registry to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel.

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

Risk minimization measures	**Routine risk minimization measures** • Prescribing information Section Special warnings and precautions for use • Prescribing information Section Pharmacodynamic properties – Patients with active CNS leukemia **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401: A registry to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel.

Table 19 Missing information: Long-term safety

Risk minimization measures	**Routine risk minimization measures** • None **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B: Long-term follow-up of patients exposed to lentiviral-based CD19 directed CAR-T-cell therapy. • CCTL019B2401: A registry to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel.

Table 20 Missing information: Immunogenicity

Risk minimization measures	**Routine risk minimization measures** • Prescribing information Section Pharmacokinetic properties **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B: Long-term follow-up of patients exposed to lentiviral-based CD19 directed CAR-T-cell therapy.

Post-authorization development plan

Studies which are conditions of the marketing authorization

Table 21 Studies which are condition of the marketing authorization

Study short name	Rationale and study objectives
CCTL019B2401	The objective of the Novartis registry is to further characterize the tisagenlecleucel safety specification in addition to evaluate selected AEs and outcome reported in patients up to 15 years following treatment with tisagenlecleucel based on secondary use of tisagenlecleucel data prospectively collected through the existing European Society for Blood and Marrow Transplantation (EBMT) (Europe) and Center for International Blood and Marrow Transplant Research (CIBMTR) (US), respectively, registries for cellular therapy.
Observational study in DLBCL	In order to further evaluate the efficacy of Kymriah in patients with relapsed/refractory DLBCL, Novartis will conduct a prospective, observational study in patients with r/r DLBCL with efficacy outcome measures in line with study C2201, including details of the manufacturing turnaround time.

Other studies in post-authorization development plan

Table 22 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
CCTL019A2205B	The purpose of this study is to monitor all patients exposed to lentiviral vector based CD19 CAR-T therapy for 15 years from the last CD19 CAR-T infusion, to assess the risk of delayed AEs suspected to be related to CD19 CAR-T therapy, monitor for vectors persistence and replication competent lentivirus (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 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.
Report on real-world evidence for Kymriah in children below the age of 3 years with B-ALL (based on registry CCTL019B2401)	In order to further evaluate the efficacy and safety of Kymriah in B-ALL patients below the age of 3 years, Novartis will conduct and submit a study based on data from a disease registry in B-ALL patients.
CCTL019C2201	In order to further characterize long-term efficacy and safety of Kymriah in relapsed/refractory DLBCL, Novartis will submit the 24-month follow-up for patients in the main Cohort and 24-month follow-up of all infused patients from study C2201. In addition, Novartis will submit the final CSR including 5 years of follow-up.
CCTL019H2301	In order to further characterize the benefit/risk of Kymriah in relapsed/refractory DLBCL, Novartis will submit the results of study CCTL019H2301, an open-label, Phase III study of Kymriah versus standard of care in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma.