U.S. FOOD & DRUG ADMINISTRATION

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Epidemiology (DE)

MEMORANDUM

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To:	Wilson Bryan, MD Director, Office of Tissues and Advanced Therapeutics
Through:	Deepa Arya, MD, MPH, MBA Branch Chief, AEB, DE, OBE Scott Proestel, MD Director, DE, OBE
Subject:	Review of Pharmacovigilance Plan, Post Marketing Requirement, and Risk Evaluation and Mitigation Strategy
Sponsor:	Novartis
Product:	Kymriah®; tisagenlecleucel
Application:	BLA/STN 125646/0
Proposed Indication:	Treatment of pediatric and young adult patients 3 to 25 years of age with relapsed or refractory B-cell acute lymphoblastic leukemia
Submission Date:	February 2, 2017
Action Due Date:	August 30, 2017

1. Objective

- The purpose of this review is to assess the applicant's pharmacovigilance plan (PVP), and determine whether any Post Marketing Requirements (PMRs) or a Risk Evaluation and Mitigation Strategy (REMS) are required for Kymriah®.

2. Product Information

- Product description
  - Kymriah is a genetically-modified autologous immunotherapy indicated for the treatment of pediatric and young adult patients 3 to 25 years of age with relapsed or refractory (r/r) B-cell precursor acute lymphoblastic leukemia (ALL).
  - The patient's T cells are extracted by leukophoresis and then modified *ex vivo* using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor. These modified cells are infused back into the patient's body, where they bind to the ALL cells and normal B cells to promote T-cell expansion, activation and target cell elimination of the ALL cells. The patient must receive lymphodepleting chemotherapy prior to receiving Kymriah. The intended setting in which the drug is likely to be administered is an inpatient hospital or its associated clinic (i.e., infusion center).
- Proposed dosing regimen(s) and formulation(s)
  - Kymriah is a single, one-time treatment with the proposed following dose:
    - For patients 50 kg and below: IV infusion of $0.2 – 5.0 \times 10^6$ transduced viable T cells/kg of body weight
    - For patients above 50 kg: IV infusion of $0.1 – 2.5 \times 10^8$ transduced viable T cells

3. Pertinent Regulatory History

- Kymriah was granted orphan drug designation on January 31, 2014, and Breakthrough Therapy Designation on April 7, 2016.
- Kymriah is currently not marketed in any country.
- On, July 12, 2017, the Oncologic Drug Advisory Committee (ODAC) meeting discussed (1) post-marketing considerations for risk mitigation for short-term toxicities, particularly cytokine release syndrome, and (2) long-term follow-up for anticipated safety concerns related to the potential for insertional mutagenesis and secondary malignancies, and (3) whether the benefits justify the risks for a marketing approval of Kymriah for the proposed indication. They voted 10:0 in favor of the benefits outweighing the risks.

4. Materials Reviewed

Materials reviewed in support of this assessment include:

- Sponsor's Pharmacovigilance plan (PVP) (Section 1.16 of 125646/0)
- Sponsor's Proposed label (Section 1.14 of 125646/0)
- Sponsor's Proposed REMS (Section 1.16 of 125646/0)
- Sponsor's Clinical Summary of Safety (Section 2.7.4 of 125646/0)
- Sponsor's Proposed Post-marketing Study (Section 1.16 of 125646/0)
- Safety issues identified by Clinical reviewer (FDA ODAC Briefing Document)
- Novartis ODAC Briefing Document
- IND Long Term Follow Up protocol CCTL019A2205B (RMS-BLA IND#(b) (4)

5. Pivotal Trial for Kymriah

The sponsor conducted one pivotal trial, namely CCTL019B2202, referred to as B2202 hereafter. This was a Phase II, single arm, multicenter trial to determine efficacy and safety. There were 25 centers total, with 13 being in the US. Enrollment occurred from April 8, 2015 to August 17, 2016. A total of 88 subjects were enrolled and 68 used in the efficacy analyses and 63 in safety analyses. The median follow-up time was 6.9 months (range of 9 days to 17.7 months). The safety findings from this trial will be discussed in detail in section 7.

6. Sponsor's Pharmacovigilance Plan[1]

The following tables summarize the risks and missing information for this product and the corresponding PV and other risk mitigation strategies, as enumerated by the sponsor in the BLA.

Table 1: Identified Risks

	Safety Concern	Pharmacovigilance Action
1	Cytokine Release Syndrome	routine PV and **REMS**, severe adverse events (SAE's) will be followed up on a case-by-case basis
2	Neurologic and psychiatric events	routine PV and **REMS**, SAE's will be followed up on a case-by-case basis
3	Tumor lysis syndrome	routine PV and SAE's will be followed up on a case-by-case basis
4	Febrile Neutropenia	routine PV and SAE's will be followed up on a case-by-case basis
5	Infection	routine PV and SAE's will be followed up on a case-by-case basis
6	Hematopoietic cytopenias lasting greater or equal to 28 days	routine PV and SAE's will be followed up on a case-by-case basis
7	Graft versus host disease	routine PV and SAE's will be followed up on a case-by-case basis
8	Prolonged depletion of normal B cells/Agammaglobulinemia	routine PV and SAE's will be followed up on a case-by-case basis

Reviewer Comment: The REMS (as proposed by the sponsor) and as modified and mandated by the agency will be discussed later in the memo.

Table 2: Potential Risks

	Safety Concern	Pharmacovigilance Action
1	Vector insertion site (oligo/monoclonality)	routine PV and SAE's will be followed up on a case-by-case basis; **PMR; LTFU* from clinical trial**
2	Vector virus replication	routine PV and SAE's will be followed up on a case-by-case basis; **PMR; LTFU from clinical trial**

[1] All of the tables in Section 6 are derived from the sponsor's Pharmacovigilance plan (PVP) (Section 1.16 of 125646/0)

3	New incidence of a hematological disorder	routine PV and SAE's will be followed up on a case-by-case basis; **PMR; LTFU from clinical trial**
4	New incidence or exacerbation of an existing autoimmune disorder	routine PV and SAE's will be followed up on a case-by-case basis
5	New incidence or exacerbation of an existing neurological event	routine PV and SAE's will be followed up on a case-by-case basis

*LTFU, Long term follow up

Reviewer Comments: The LTFU from clinical trial refers to a long term follow up protocol which is part of the IND pivotal trial for this product (B2205). Those who have received this product under IND will continue to be followed under that protocol for 15 years. The PMR (as proposed by the sponsor) and as modified and mandated by the agency will be discussed later in the memo in section 8, along with the pertinent differences with the LTFU.

Table 3: Missing Information

	Safety Concern	Pharmacovigilance Action
1	No studies in the elderly patients	Labeled product indication is not for patients older than 25 years of age; routine PV
2	No studies in patients who may be pregnant or nursing	Label states that this therapy is not recommended for this patient population; routine PV
3	No studies in patients with co-morbidities such as HIV or Hepatitis B or C	Label states that this therapy is not recommended for patients with these co-morbidities; routine PV

7. Analysis of Sponsor's Pharmacovigilance Plan (PVP)

- Cytokine Release Syndrome (CRS):
  - The most serious adverse event for Kymriah is CRS, and 53 of 68 (78%) subjects treated with the product experienced CRS (which includes fever, hypotension, acute kidney injury, and hypoxia). Additionally, 32/68 (47%) of subjects had Grade 3/4 CRS[2], which requires ICU care. CRS onset occurred at a median of 3 days post Kymriah infusion, with a range of 1-22 days. The median duration of CRS was 8 days. There were no deaths from CRS in this trial. The protocol mandated the use of tocilizumab (interleukin-6 (IL-6) receptor antagonist) in the management of CRS, which was required to be onsite and immediately available to those getting Kymriah. A boxed warning for CRS was proposed by the sponsor and DE agrees that it is appropriate. The sponsor's PVP states that these adverse events will be reported as required under 21 CFR 600.80, which is appropriate. Additionally, due to the common, rapidly developing, and potentially fatal nature of this adverse event, a REMS is required for this this safety concern. The REMS will be discussed later in this memo in section 8.
- Neurotoxicity:
  - Neurotoxicity was reported in 44% (n=30) of the subjects who received Kymriah. Ten (15%) of those subjects had Grade 3 neurotoxicity[2], which required ICU support. In

[2] Tisagenlecleucel-therapy associated Grading for Adverse Events: Penn Grading Scale; FDA Briefing Document, Oncologic Drugs Advisory Committee Meeting, page 61

general, neurologic events were concurrent with CRS but 6 cases occurred after CRS. Neurological toxicities included encephalopathy, delirium, hallucinations, somnolence, cognitive disorder, seizures, depressed level of consciousness, mental status changes, dysphagia, muscular weakness, and dysarthria. Resolution of symptoms occurred over weeks and lagged behind CRS recovery. There were no reported cases of cerebral edema with Kymriah. Treatment for neurotoxicity has been symptomatic treatment, which includes close monitoring and observation to assure an open airway, seizure prophylaxis, and corticosteroids (dexamethasone). A boxed warning for neurotoxicity was proposed by the sponsor and DE agrees that it is appropriate. The sponsor's PVP states that these adverse events will be reported as required under 21 CFR 600.80, which is appropriate. Additionally, since early recognition of neurotoxicity and treatment with corticosteroids is the only way to prevent even more severe sequalea, DE recommends that a REMS should also be required for this safety concern.

- Tumor Lysis Syndrome (TLS):
    - CAR T-cell therapy can potentially lead to TLS; however, with the use of prophylaxis as described in the studies, only a limited number of patients (4%) developed TLS post-infusion. The sponsor's PVP states that these adverse events will be reported as required under 21 CFR 600.80, which is appropriate.
- Febrile Neutropenia
    - Prolonged neutropenia and thrombocytopenia (after 30 days) has been noted after treatment with Kymriah. Twenty-five of the 52 responders to Kymriah had incomplete hematologic recovery. Neutropenia was prolonged but resolved over time. Grade 3[3] poor recovery occurred in 10 subjects (14.7%), and Grade 4 occurred in 12 (17.6%) subjects. Recovery was achieved by 6 months with improvements noted by 3 months. The sponsor's PVP states that these adverse events will be reported as required under 21 CFR 600.80, which is appropriate.
- Infections within 8 weeks after Kymriah administration
    - Twenty-nine subjects on Study B2202 developed infections in the first 8 weeks after Kymriah administration. Sixteen infections were Grade 3, and two were Grade 4, and required ICU support. The infections included gram-positive and gram-negative systemic infections, Clostridium difficile, Candida, herpes simplex, and human herpesvirus 6. Two fatalities (one due to a systemic fungal infection and one attributed to encephalitis [human herpes virus-6 (HHV-6)]) occurred. The sponsor's PVP states that these adverse events will be reported as required under 21 CFR 600.80, which is appropriate.
- Hematopoietic cytopenias lasting greater or equal to 28 days
    - Persistent grade 3 and grade 4 cytopenias (reported as an AE in 13.4% and 16.5% of patients, respectively) were observed beyond day 28 post-infusion. Prolonged neutropenia (based on laboratory reporting) was associated with grade 3/4 infections in 8.1% of patients, requiring ICU support. Cytopenias are generally manageable with standard clinical measures. Two fatalities (one due to a systemic fungal infection and one attributed to encephalitis [human herpes virus-6 (HHV-6)]) occurred where prolonged neutropenia (both pre- and post-infusion) was considered to have played a contributory role. The sponsor's PVP states that these adverse events will be reported as required under 21 CFR 600.80, which is appropriate.

[3] Tisagenlecleucel-therapy associated Grading for Adverse Events: Penn Grading Scale; FDA Briefing Document, Oncologic Drugs Advisory Committee Meeting, page 61

- Graft vs. Host Disease
    - CAR T-cell therapy can potentially lead to graft-versus-host disease. In Study B2202, there was 1 case. The sponsor's PVP states that these adverse events will be reported as required under 21 CFR 600.80, which is appropriate.
- B cell aplasia/Acquired hypogammaglobulinemia
    - As part of its mechanism of action, Kymriah not only kills pre-B ALL cells, it also kills normal B cells because they are CD19+. As a result, successful treatment with Kymriah renders the trial participants with acquired hypogammaglobulinemia. Subjects have been maintained on supplemental treatment with intravenous gamma globulin (IV IgG) post-infusion. The sponsor's PVP states that these adverse events related to B cell aplasia will be reported as required under 21 CFR 600.80, which is appropriate.

The product office clinical team found two more identified risks for Kymriah, in addition to those identified by the sponsor:

- Hemophagocytic Lymphohistiocytosis (HLH):
    - HLH is an inflammatory reaction that involves the activation of macrophages and T cells. It can be primary or secondary (sometimes associated with viral disease such as Epstein-Barr). In the context of CAR T cell therapy, HLH has been seen in patients with increasing tumor load as the CAR T cells are being administered. Like primary HLH, subjects can be pancytopenic, have low fibrinogen, and have hemophagocytosis in bone marrow (BM), spleen, and/or lymph nodes. Routine pharmacovigilance and reporting as required under 21 CFR 600.80 is appropriate.
- Cardiac Disorders:
    - Per the clinical study report, in an analysis of the initial 62 subject safety data, 20 had cardiac events. Grade 3 left ventricular dysfunction (LVD) was noted in three subjects (one each of Grade 2, 3, 4 CRS) and one of these subjects with LVD also had biventricular failure, mitral incompetence and had Grade 4 cardiac failure in conjunction with Grade 4 CRS. Arrhythmias and congestive heart failure (CHF) are not commonplace in a pediatric population. However, this population (r/r ALL) has a history of prior exposure to anthracyclines in 60% of the subjects, which are considered as standard-of-care and also a risk factor for cardiac events. Routine pharmacovigilance and reporting as required under 21 CFR 600.80 is appropriate.

- The discussion on potential risks identified by the sponsor will combine all of them into the following category:
    - Secondary Malignancy or Relapse:
        - Retroviral vectors provide long-term expression of the chimeric antigen receptor (CAR) in T cells and lead to the potential safety concern of secondary malignancy/relapse because of the following: generation of replication-competent retrovirus (RCR) and insertional mutagenesis.
        - There have been numerous clinical trials with T cells that were transduced with a gammaretroviral or lentiviral vector. Many of these trials used CAR T cells for malignancy indications. To date, there have been no reports of vector-induced secondary malignancies in clinical trials using T cells.
        - The vector used for Kymriah manufacturing is designed to minimize the risk of formation of RCR, and both the vector and the cell product are extensively tested for RCR during the manufacturing process. Regarding the risk of secondary malignancy, clinical long-term follow-up monitoring for clonal

outgrowth and vector-mediated delayed adverse events (e.g., secondary leukemias) have not raised any concerns for Kymriah or for other retroviral-transduced T cell products to date.

- In B2202, study subjects have not been followed for very long (maximum of 17.7 months), thus limiting the ability to assess the risk of delayed events. The potential for secondary malignancy is a concern with immunotherapy products that require gammaretroviral and lentiviral transduction. Therefore, a post marketing requirement for a registry is necessary along with the sponsor plan to report these adverse events as required under 21 CFR 600.80 . Additionally, all of the clinical trial participants will continue to be monitored in a long term follow up (LTFU) protocol which is separate but similar to the PMR. Both of these will be discussed in the following section.

- No additional safety concerns were identified by either the DE reviewer or by the clinical reviewer.

8. Post Marketing Requirement

- After reviewing the safety data for this product, there is potential for the serious risk of secondary malignancy due to replication-competent retrovirus or insertional mutagenesis. A communication was sent to the sponsor informing them that the agency will require a Post Marketing Requirement based on section 505(o)(3)(B)(iii) of FDAAA: "to identify unexpected serious risk(s) when available data indicate the potential for serious risk(s)."
- The PMR will be a Phase IV, multi-center, prospective, observational, non-interventional, post market study. The primary objective of this study would be to characterize the type, frequency, and severity of all secondary malignancies and relapses in patients who receive Kymriah and enroll at least 1,000 patients and follow them for 15 years. For all secondary malignancies, fresh tumor tissue will be obtained and sent to Novartis to analyze for persistence of the vector used in Kymriah.
- Table 4 summarizes this registry-type study proposed by the sponsor and agreed upon by the agency.

Table 4: Post Marketing Study

Study title	Prospective registry to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel
Study design	Multicenter, prospective, observational, non-interventional, post-marketing safety study. Enrollment will be offered to pediatric, young adult and adult patients with B-cell malignancies who have received (or are due to receive) the product. Patients can enroll in this study on the day of or prior to the infusion, or within 3 months of receiving the infusion. Recommended clinic visits will occur in line with standard clinical practice. This study will consist of a baseline accrual period of 5 years and a follow-up period (up to 15 years post infusion). The study duration will be approximately 20 years. All patients will be followed up for survival until the time of the last patient's last visit (LPLV) in this Registry.
Study population	Enrollment will be offered to every pediatric, young adult and adult B-cell malignancy patient who have received (or are due to receive) a product infusion for an approved indication as prescribed by their treating physician. Based on a recruitment projection at least **1,000 patients** will be enrolled in the Registry over 5 years.

Primary Objectives/ Endpoints	The primary variable is the type, frequency and severity of adverse events (AE's) and laboratory abnormalities, including secondary malignancies and cases of primary relapse..
Secondary Objectives/ Endpoints	• Describe the growth, development, and female reproductive status for patients who were aged < 18 years at the time of infusion. • Evaluate incidence and outcome of any pregnancy occurring in women of child-bearing potential after treatment • Evaluate the long-term effectiveness of this product for each type of hematologic malignancy with an authorized indication (i.e. ALL and lymphoma).
Data Analysis	• All cases of secondary malignancy or relapse will have clinical samples sent to Novartis for analysis the presence of the vector used in Kymriah. • All AEs observed in this Registry will be summarized by frequencies and percentages by system organ class (SOC) using MedDRA and Common Terminology Criteria for Adverse Events version 4.03 and/or preferred term, severity (based on CTCAE grading or, the Penn grading scale for CRS[4]), and type of AE. • Safety and effectiveness data will be summarized and listed by approved indication in an incremental and a cumulative manner. • Summaries of safety data pooled across indications will be reported periodically and at least annually in accordance with regulatory requirements. • The final Clinical Study Report will be prepared including all planned effectiveness and safety analyses at the end of the study after database lock. In addition, selected endpoints will be summarized by pediatric and
Study Time-Line	• Start of data collection: Upon commercialization (~Quarter 3 2017) • End of data collection: Quarter 3, 2037 • Safety reports will be submitted periodically in accordance with local regulatory requirements for the duration of the study. • Final report of study results: Quarter 1, 2039

- The LTFU protocol will continue to follow those who received the product before licensure. It is largely similar to the PMR registry, but will be collecting samples and sending them back to Novartis for presence of the vector in Kymriah for all clinic visits. The PMR will mirror standard clinical practice and will not send any samples to Novartis unless there is a case of relapse or secondary malignancy. The details of the LTFU are outside the scope of this memo since it will remain part of an IND protocol and will not include anyone who receives Kymriah after approval.

9. Risk Evaluation and Mitigation Strategy (REMS)

- Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a

[4] Tisagenlecleucel-therapy associated Grading for Adverse Events: Penn Grading Scale; FDA Briefing Document, Oncologic Drugs Advisory Committee Meeting, page 61

strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505 1(a)].

- To ensure that the benefits of Kymriah outweigh the risks of cytokine release syndrome (CRS) and neurotoxicity, it was determined that a REMS that includes elements to assure safe use (ETASU) is necessary. During the review of this BLA, it was found that that the applicant's proposed REMS, which consisted of a communication plan for healthcare providers, was not adequate to mitigate these risks. As stated earlier, over 70% of patients in the pivotal clinical trial developed CRS, and many required intensive-care level facilities and the specific use of the monoclonal antibody tocilizumab to manage this adverse event.
- ETASU B and ETASU C are required to ensure the drug's benefits outweigh the risks. The REMS for Kymriah will ensure that health care settings that administer Kymriah are specially certified and have on-site, immediate access to tocilizumab (ETASU B). Furthermore, the REMS will ensure that those who prescribe, dispense or administer Kymriah are trained about the management of CRS and neurotoxicity (ETASU C). Site-certification will also entail providing patients with information on CRS and neurotoxicity and informing them of the importance of staying within 2 hours of the hospital for at least 3 to 4 weeks after receiving treatment, since many emergency rooms and hospitals are unable to adequately treat CRS due to a lack of available tocilizumab.
- Since the REMS has ETASU, the sponsor will submit REMS assessments to the agency at 6 months, 12 months, and then annually thereafter.

10. Recommended Pharmacovigilance Actions

- DE agrees with the pharmacovigilance activities proposed by the sponsor in the PVP with adverse event reporting as required under 21 CFR 600.80. Periodic safety reports should include details of the potential risks and missing information identified in this safety review. In addition, the immediate risks of CRS and neurotoxicty necessitate a REMS, and the longer term risks of secondary malignancy necessitate a PMR.