Summary Basis for Regulatory Action Template

Date: April 13, 2018

From: Roger Kurlander, M.D., Chair of the Review Committee

BLA/ STN#: 125646/76

Applicant Name: Novartis Pharmaceuticals Corporation

Date of Submission: October 30, 2018

Goal Date: May 1, 2018

Proprietary Name: KYMRIAH™

Established Name: tisagenlecleucel

Indication: for adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitations of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma

Recommended Action: Regular approval

Review Office(s) Signatory Authority(ies): Tejashri Purohit-Sheth, M.D, Director, Division of Clinical Evaluation and Pharmacology/Toxicology/Office of Tissues and Advanced Therapies

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Office of Compliance and Biologics Quality Signatory Authority: Mary A. Malarkey Director, Office of Compliance and Biologics Quality

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA.

Document title	**Reviewer name, Document date**
CMC Review(s) • *CMC (product office)* • *Facilities review (OCBQ/DMPQ)* • *Establishment Inspection Report (OCBQ/DMPQ)*	Not applicable
Clinical Review(s) • *Clinical (product office)* • *Postmarketing safety epidemiological review (OBE/DE)* • *BIMO*	Roger Kurlander, MD (OTAT/DCEPT) Aviva Krauss, MD (OCE) Bindu George, MD (OTAT/DCEPT) Jaspal Ahluwalia, MD (OBE/DE) Marc Theoret, MD (OCE) Tejashri Purohit-Sheth, MD (OTAT/DCEPT)
Statistical Review(s) • *Clinical data* • *Non-clinical data*	Zhenzhen Xu, PhD (OBE/DB)
Pharmacology/Toxicology Review(s) • *Toxicology (product office)* • *Developmental toxicology (product office)* • *Animal pharmacology*	Not applicable
Clinical Pharmacology Review(s)	Xiaofei Wang, PhD (OTAT/DCEPT)
Labeling Review(s) • *APLB (OCBQ/APLB)*	Dana Jones (OCBQ/DCM)
Other Review(s) • *additional reviews not captured in above categories* • *consult reviews*	Not applicable

1. Introduction

KYMRIAH was initially approved on August 30, 2017 for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL).

On October 27, 2017 Novartis Pharmaceuticals Corporation submitted a Biological License Application Supplement (sBLA), STN 125646/76, requesting approval of tisagenlecleucel (KYMRIAH), a CD19-directed genetically modified autologous T cell immunotherapy, for the treatment of adult patients with relapsed or refractory large B-cell Lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. The indication includes a Limitation of Use indicating that KYMRIAH is not indicated for patients with primary central nervous system lymphoma.

KYMRIAH is comprised of genetically modified autologous T cells reprogrammed using a lentiviral vector to target cells that express CD19, a surface antigen expressed on B cells and many tumors derived from B cells. The KYMRIAH chimeric antigen receptor (CAR) protein responsible for reprogramming contains a murine anti-CD19 single chain antibody fragment (scFv) linked to the signaling domains CD3-ζ and 4-1BB which play critical roles in KYMRIAH T cell activation, persistence in vivo, and anti-tumor activity.

This document summarizes the basis for approval of KYMRIAH for this new indication. CCTL019C2201 (C2201), a single arm, phase 2, multicenter, open-label trial was the data source used to assess the efficacy and safety of KYMRIAH for treatment of DLBCL. The recommendation for approval was based on the complete response rate and duration of response demonstrated in this study.

The review team recommends regular approval of KYMRIAH for this indication. The major risks of KYMRIAH include cytokine release syndrome (CRS), neurologic toxicity, infection, febrile neutropenia, and prolonged cytopenias. Based on the severity of CRS and neurotoxicity which can be life threatening or fatal, the review team recommends implementation of a Risk Evaluation Mitigation Strategy (REMS) with Elements To Assure Safe Use (ETASU) for the management of these toxicities. The review committee also recommends as a postmarketing requirement (PMR), a 15-year postmarketing observational study to monitor long-term toxicities of KYMRIAH and the potential risk of secondary malignancies linked to the use of a lentiviral vector for genetic modification.

2. Background

Disease Background

DLBCL, which comprises 25-30% of non-Hodgkin lymphomas (NHLs), typically presents with rapid enlargement of lymphoid tissue at one or more sites. It is an aggressive disease, and without effective treatment survival is measured in months. Standard multiagent, chemoimmunotherapy can induce a complete response (CR) in about half of newly diagnosed patients, and in most cases these remissions are durable. The standard of care for patients who relapse or are refractory to first-line chemoimmunotherapy has been treatment with one of

several intense salvage chemotherapy regimens. If disease responds to this therapy, patients may undergo potentially curative autologous stem cell transplantation (ASCT). This second line therapy cures a subset of patients, but those who are refractory to primary therapy, relapse less than a year after ASCT, or who relapse after 2 or more lines of therapy have a poor prognosis with a median overall survival rate of 6-7 months despite additional chemotherapy. As discussed below, the recent approval of another CAR T cell-based treatment has improved the outlook for those with relapsed, refractory (r/r) disease.

Available Therapies

On October 18, 2017, axicabtagene ciloeucel (YESCARTA), an CD19-directed, genetically-modified, autologous T cell immunotherapy produced by Kite Pharma, Inc., was approved by the FDA for treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. In its registration trial, YESCARTA produced a 72% overall response rate (ORR) with 51% complete responses (CR). The median duration of response for CR was not yet reached after a median follow-up of 7.9 months. This response rate was superior to the anticipated outcome for standard of care therapy cited above; however, significant toxicity was noted. Cytokine release syndrome (CRS), a syndrome characterized by fever/chills, hypotension, tachycardia, and hypoxia, and neurotoxicity characterized by encephalopathy, headache, tremor, dizziness, or other neurologic complaints, was observed in 94% and 87% of patients respectively with a 4% incidence of death from toxicity. In addition, as a consequence of its anti-CD19 activity, YESCARTA induced normal B-cell aplasia in most treated patients.

KYMRIAH, like YESCARTA, is a CD19-directed genetically-modified autologous T cell product designed to kill CD19-positive B-cells including tumor cells, but the two products differ in several respects. The YESCARTA construct uses a retroviral vector to transduce T cells and the intracellular domain of CD28 to co-stimulate T cells, while KYMRIAH uses a lentiviral vector and the intracellular domain from 4.1-BB for the same purposes. There are other, more subtle, structural differences between the two products, as well as substantial differences in the proprietary methods used for generation and expansion of CAR T cells ex vivo.

Regulatory History and Considerations

Date	Milestone and Comments
Regulatory activity of KYMRIAH for treatment of DLBCL	
04/12/2017	Breakthrough Therapy Designation for DLBCL
08/04/2017	Pre-sBLA meeting for DLBCL indication.
08/29/2017	Orphan Designation for DLBCL.
10/30/2017	sBLA 125646/76 submission for DLBCL
11/21/2017	sBLA 125646/80 – submission for changes in manufacture
11/22/2017	sBLA 125646/76 – 30-day safety and efficacy update received
02/28/2018	sBLA 125646/76 – 120-day safety update received

Negotiations between FDA and applicant concerning duration of response required to establish efficacy of KYMRIAH in DLBCL

At the pre-sBLA meeting of August 4, 2017, the sponsor proposed to assess efficacy based on an interim analysis of 81 patients using a data cut-off date of March 8, 2017. Using this timetable, the applicant would be able to submit complete 3-month response and follow-up data for all 81 patients, but only 46 would have completed 6 months of follow-up. The FDA clinical reviewers indicated this duration of follow-up would not be sufficient to demonstrate durable benefit for responders. After several telecommunication interchanges, the applicant proposed on August 23, 2017 (Amendment 16130/967) to supplement their initial submission with a 30-day efficacy and safety update (with a data cut-off date of September 6, 2017) and a final 120-day safety update for a total of 92 patients. This timetable would provide 9 month assessments for all observed responders and more extensive safety data. This amendment also included additional modifications in the organization of the datasets as requested by the FDA and clarifications concerning the adjudication rules. The FDA indicated agreement with this proposal in a telecommunication on October 12, 2017.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

KYMRIAH CMC was reviewed and approved in the initial BLA submission, 125646/0. The product used in these clinical studies under Protocol C2201 conforms with the product used in the initial submission. Consequently, module 3 (Quality) was not included in Amendment 76, and no facility review/inspections are required.

The applicant has also proposed significant changes in KYMRIAH CMC in a Prior Approval Supplement (PAS) 125646/80, submitted on November 21, 2017. This document is currently under review. No changes in KYMRIAH manufacturing for use in the treatment of DLBCL will be implemented until after supplement 80 approval.

b) CBER Lot Release (only applicable for BLAs)

Not applicable. No changes in lot release criteria were requested to this supplement.

c) Facilities review/inspection

No GMP facilities inspections were conducted for this application.

d) Environmental Assessment

The BLA requests categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c).

e) Product Comparability

Not applicable.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No new nonclinical pharmacology/toxicology information was included in this supplement.

5. CLINICAL PHARMACOLOGY

KYMRIAH is prepared by transduction of normal autologous T cells with a lentiviral vector encoding a chimeric antigen receptor (CAR) composed of a murine single chain antibody variable fragment (scFv) specific for CD19, linked to intracellular signaling domains from 4-1BB (CD137) and CD3-zeta. The former enhances the expansion and persistence of KYMRIAH cells while the latter initiates T-cell activation and antitumor activity. Anti-tumor activity, cellular proliferation, and persistence are all triggered by CAR binding to CD19 positive target cells.

KYMRIAH expands rapidly following infusion into adult r/r DLBCL patients. Median time to peak levels in these studies was around 9-days post-infusion followed by a bi-exponential decline. Transduced cells persisted up to 18 months (the longest follow-up time available) in the peripheral blood and approximately 9 months in the bone marrow of treated patients. No significant relationship was identified between intrinsic factors (age, gender, race, body weight, disease stage and burden of disease) or extrinsic factors (prior ASCT status, number of prior lines of therapy and KYMRIAH exposure (Cmax and $AUC_{(0\text{-}28d)}$)). Within the limitations imposed by small sample size and high inter-subject variability, no dose-exposure, dose-response, or exposure-efficacy relationships were apparent. Time to reach peak levels of KYMRIAH were similar between responding and non-responding subjects.

Higher levels of KYMRIAH exposure and expansion rate were associated with higher CRS grade. Subjects with Grade 3 or higher CRS had significantly higher KYMRIAH exposure (Cmax and $AUC_{(0\text{-}28d)}$) compared to subjects with Grade 2 or lower CRS. In contrast, KYMRIAH exposure in subjects with Grade 3 or higher versus Grade 2 or lower neurological events were comparable. Evaluation of B cell aplasia was complicated by the frequent use of rituximab in prior lymphoma management. Consequently, B cell aplasia was noted in 80% of patients before CTL019 treatment. The continued absence of B cells 1 year post treatment in half of the treated patients (in the presumed absence of additional rituximab) strongly supports a role for KYMRIAH in prolonging B cell aplasia. Replication-competent lentiviruses (RCL) were not detected.

Tocilizumab and corticosteroids used in management of CRS and neurologic events did not prevent continued KYMRIAH proliferation, but more subtle impacts of these agents on expansion cannot be ruled out in this uncontrolled trial format.

A Pharmacometrics Consultation performed by Chao Liu, PhD (CDER/OCP) reached similar conclusions.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

Study CTL019C2201 forms the basis for the review team's recommendation of regular approval of KYMRIAH for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from

follicular lymphoma. KYMRIAH is not indicated for the treatment of patients with primary central nervous system lymphoma.

Study Description
Study CTL019C2201 was a single-arm, open-label, phase 2 multicenter study for adult patients with relapsed or refractory DLBCL after ≥2 prior lines of chemotherapy including rituximab and an anthracycline, and who either had previously been treated with, were ineligible for, or did not consent to autologous hematopoietic stem cell transplantation (AHSCT). Bridging chemotherapy was permitted at investigator discretion to support patients with progressive disease while awaiting product manufacture. Patients were treated with an intravenous infusion of 1-5 x 10^8 viable KYMRIAH cells after lymphodepletion with cyclophosphamide/fludarabine or bendamustine if the blood white blood cell count was ≥ 1x10^6 cells/µl. The primary endpoint was the objective response rate (ORR) to KYMRIAH defined as the sum of the percent complete responses and partial responses (% CR + %PR) at the time of best overall response (BOR). Responses were assessed by an independent review committee (IRC) based on the Lugano Classification (2014). The durability of response, a critical secondary endpoint, was assessed from time of initial response to time of relapse or last observation.

Clinical Efficacy Assessment
Of the 160 subjects enrolled, 49 were withdrawn before receiving KYMRIAH because of manufacturing failure (11), patient death (16), physician decision (16), adverse events (3) or other criteria (3). The applicant identified a cohort of 92 patients treated with KYMRIAH manufactured at the Morris Plains (MP) New Jersey facility as the efficacy analysis set. Ninety percent of these patients received bridging chemotherapy to suppress lymphoma growth while awaiting KYMRIAH manufacture.

On review, the FDA judged 23 of these patients as inevaluable for efficacy analysis because documentation of continued measurable disease between completion of bridging chemotherapy and KYMRIAH infusion were not available. In 8 cases, presumably because of a clinical response to bridging chemotherapy, the patients' previously measurable PET-positive disease was no longer detectable at baseline studies before KYMRIAH treatment. Thirteen others did not have valid baseline CT and PET imaging studies after completion of bridging chemotherapy available. Both groups were excluded because the reviewers adjudged that without documentation of continued measurable disease after bridging chemotherapy is completed, the independent contribution of KYMRIAH to clinical response cannot be determined. One additional patient was excluded because of initial misclassification of a neuroendocrine malignancy as DLBCL. Consequently, the efficacy analysis was based on the results in a cohort of 68 evaluable patients.

The median time from leukapheresis to product infusion for this group was 113 days (range 47 to 106 days), and the median dose was 3.4 x 10^8 transduced KYMRIAH cells. Seventy eight percent of patients had de novo DLBCL, and the remainder developed DLBCL by transformation from Follicular Lymphoma. Ten patients (15% of the group) had confirmed double- or triple-hit lymphoma. The median age was 56 years with 21% ≥ 65; the median number of prior therapies was 3; 44% had previously had a AHSCT; and 56% were refractory to their last line of therapy.

Primary Efficacy Endpoint
The ORR in the evaluable efficacy set was 50% with 95% confidence intervals (CI, 95%) of 37.6% and 62.4%. The CR rate was 32.4% with 95% CI of 21.5% and 44.8% (see the table below).

Primary Endpoint: Overall Response Rate	
Best Overall Response	Evaluable Efficacy Set N=68
	% (N)
CR	32.4% (22)
PR	17.7% (12)
SD	17.7% (12)
PD	23.5% (16)
UNK	8.8% (6)
ORR (CI)	50.0% (37.6, 62.4)
CR (CI)	32.4% (21.5, 44.8)

Source: FDA clinical reviewer
CR, complete remission; PR, partial remission; CI, 95% Confidence Intervals.

Secondary Endpoint
The duration of response in the evaluable efficacy set of patients is summarized below.

Duration of Response for KYMRIAH responders	
Overall DOR for responders (months)	N= 34
median	NE[a]
(95% CI)	(5.1, NE)[b]
Range	0.03 – 11.3+
Median Follow-up for DOR (95% CI)	9.4 (7.9, 10.8)[b]
DOR if BOR is CR	N=22
median	NE
(95% CI)	(10.0, NE)
Range	1.5 – 11.3+
Median Follow-up for DOR (95% CI)	8.4 (7.4, 10.5)
DOR if BOR is PR	I. N=12
median	3.4
(95% CI)	(1.0, NE)
Range	0.03 -11.3+
Median Follow-up for DOR (95% CI	11.1 (1.7, 11.3)

DOR, duration of response; [a] Not estimable; [b] Kaplan-Meier estimate

Median DOR for the overall group and for CRs was not reached after median follow-ups of 9.4 and 8.4 months respectively. By comparison patients with PR had only a 3.3-month median

duration of response. Though the duration of follow-up is limited, this data demonstrates KYMRIAH can produce durable responses, particularly in patients who achieve a CR.

Efficacy Review Issues

1) Yescarta, another CD19-directed CAR T cell product, has already received regular approval for a similar clinical indication. The endpoints of CR and durability of CR are considered clinical benefit endpoints, hence KYMRIAH was reviewed for regular approval.

2) The applicant initially proposed earlier submission of this efficacy supplement based on less extended follow-up, but as described in greater detail in the Regulatory History in section 2, after discussions with the FDA, the applicant delayed submission until ≥ 6-month follow-up was available for all responders and could be provided to the FDA within 30 days after supplement submission.

3) As noted in the clinical efficacy assessment section above, 23 patients were excluded from efficacy assessment because the timing or therapeutic efficacy of bridging chemotherapy interfered with the documentation of baseline measurable disease after bridging chemotherapy needed to assess the independent contribution of KYMRIAH to patient's overall response. This methodologic decision was necessary for evaluation in a registrational single arm trial, but it does not imply any judgment concerning the benefits or risks of using bridging chemotherapy in association with KYMRIAH in the treatment of DLBCL. Clarification of this issue may require additional controlled prospective studies.

Bioresearch Monitoring

Bioresearch Monitoring inspections were issued for three domestic clinical study sites that participated in the conduct of Study CCTL019C2201. The inspections did not reveal substantive problems that impact the data submitted in this BLA.

Post Marketing Requirements (PMR) and Post Marketing Commitments

Risk Evaluation Mitigation Strategies (REMS)

Seventy eight of 106 (74%) subjects treated with KYMRIAH experienced CRS, and 23 of 78 (29%) of the subjects had CRS of Grade 3 or higher. CRS results in a constellation of inflammatory symptoms ranging from a flu-like syndrome to severe multi-organ system failure and death. Specifically, Grade 3/4 CRS required treatment in ICU settings. Treatment of CRS was based on a complex grading system and treatment algorithm requiring supportive care, tocilizumab and corticosteroids. Of the 78 subjects with CRS, 16 (21%) required 1-2 doses of tocilizumab and 12 (15%) received corticosteroid. Three patient deaths, at least in part, were attributed to CRS. In addition, 58% (62 of 106) of subjects experienced neurotoxicity (defined as events within the neurologic or psychiatric SOC, or gait disturbance). Eighteen percent were grade≥ 3. There no deaths attributable to neurotoxicity. Monitoring for neurotoxicity required frequent neurological evaluations. Treatment focused on ensuring an open airway, availability of seizure prophylaxis, and systemic corticosteroid treatment.

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.
Two Elements to Assure Safe Use (ETASU) are required to mitigate the known risks of CRS and neurotoxicity, as follows:

- Pharmacies, practitioners, or health care settings that dispense the drug must be specially certified and must have immediate access to tocilizumab. 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.
- Those who prescribe, dispense or administer KYMRIAH must be trained about the management of CRS and neurotoxicity.

The REMS ETASU requires Novartis to ensure:

- Pharmacies, practitioners and health care settings dispensing KYMRIAH are certified through a live training program and knowledge assessment.
- Sites report all cases of CRS and neurotoxicity
- Sites have a minimum of two doses of tocilizumab available on site
- Processes and procedures are followed for the KYMRIAH REMS program.
- REMS assessments are sent to the Agency at 6 months, 12 months, and annually thereafter.

Materials provided as part of the REMS included:

- KYMRIAH REMS Program Live Training for Hospitals
- KYMRIAH REMS Program Knowledge Assessment
- KYMRIAH REMS Program Hospital Enrollment Form
- KYMRIAH REMS Program Website
- KYMRIAH REMS Program Patient/Caregiver Wallet Card

Since the original approval for KYMRIAH included this REMS for childhood B-ALL, a major modification will be completed by the sponsor to include all pertinent training information for the DLBCL indication.

Post Marketing Requirements (PMR) Study
The use of retroviral and lentiviral vectors in the genetic modification of human cells exposes patients to potential long-term risks such as prolonged persistence of transduced T cells, the formation of oncogenic replication-competent lentiviruses through recombination of lentiviral elements with endogenous retroviruses, and the development of secondary malignancies triggered by insertion of transduced lentivirus into the genome of normal cells. In view of these potential risks, long-term monitoring of safety for patients treated for the DLBCL indication necessitates a post-marketing requirement (PMR). The applicant previously proposed Study CCTL019B2401 (B2401) a multicenter, prospective, observational, non-interventional, safety study as a post-marketing required study for 15 years in at least 1000 ALL patients who receive KYMRIAH. This protocol will be amended to include 1500 DLBCL patients who received KYMRIAH. Patients will be enrolled over a 5-year period with enrollment of each subject to begin within 3 months of KYMRIAH infusion. Patients will receive clinical evaluation and

follow-up as per standard of care for patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma. The primary endpoint will be evaluation for secondary malignancy which will include if possible, tissue acquisition by the Applicant for analysis of possible lentiviral mediated oncogenic events. Secondary endpoints will be adverse events of CRS and neurologic toxicities and disease outcomes (survival). The time table for data collection starts upon commercialization and ends December 31, 2037. Safety reports will be submitted periodically in accordance with local regulatory requirements for the duration of the study. and the Final report of study results is December 31, 2038.

b) Pediatrics

Not applicable. There are no pediatric data in the intended population and the application does not trigger Pediatric Research Equity Act (PREA), as KYMRIAH has orphan designation for this indication.

c) Other Special Populations

None

7. SAFETY

The primary safety population for C2201 consisted of 106 patients who received KYMRIAH, 93 whom received product manufactured in the US and an additional 13 who received KYMRIAH manufactured in (b) (4) (Cohort A). All subjects experienced at least one adverse event following KYMRIAH infusion, and 95 (90%) experienced at least one Grade 3 or greater event. Serious adverse events (SAEs) were observed in 67 (63%) patients. Adverse events of special interest (AESI) included cytokine release syndrome (CRS), neuropsychiatric toxicities, febrile neutropenia, cytopenias lasting greater than 28 days, infections and hypogammaglobulinemia. CRS was assessed based on the Penn Grading Scale (PGS-CRS) which included clinical signs and symptoms and supportive care interventions in the context of supportive cytokine levels. The following table summarizes the incidence of all grade and grade ≥3 AESI.

Adverse Events of Special Interest post-KYMRIAH Infusion, C2201 (N=106)

	All Grades n (%)	Grade ≥3 n (%)
CRS	78 (74%)	24 (23%)
Neuropsychiatric toxicities	62 (58%)	19 (18%)
Infections	54 (51%)	33 (31%)
Hematopoietic cytopenia beyond day 2	n/a	56 (52%)
Neutropenia		26 (25%)
Thrombocytopenia		41 (39%)
Febrile neutropenia	18 (17%)	18 (17%)
Hypogammaglobulinemia	14 (13%)	3 (3%)

Source: FDA reviewer

Overall, 46 patient deaths were reported from the time of informed consent to the data cut-off for the 30-day safety update report 09/06/2017). Three deaths (3%) occurred within 30 days of the KYMRIAH infusion, and 13 deaths (12%) occurred within 60 days of the infusion. The majority

of deaths (35; 33%) were due to progressive disease. Seven deaths (6.6%) were assessed to be at least possibly related to KYMRIAH therapy, including 4 cases where distinguishing between CRS/tumor flare versus progressive disease as the root cause of death was not possible. All 3 patients who died within 30 days of infusion had CRS in the setting of stable to progressive underlying disease. One patient died in the setting of a fatal infection, and 2 had fatal hemorrhages, one of which was in the setting of persistent thrombocytopenia 105 days from the infusion.

The median time to onset of CRS was 3 days, and, except for one case on day 51, all cases occurred on days 1 through 9 post-infusion. Median time to CRS resolution was 6 days (range 1-30). CRS required intensive support measures including new hospitalizations (8% of patients), extended hospital stays (41%), including ICU admissions (25%), intubations (8%), use of vasopressors (12%) and dialysis (5%). Sixteen patients (15%) received at least 1 dose of tocilizumab, and 15 patients (14%) received at least one dose of steroids.

The median time to onset of neuropsychiatric toxicity was 5 days (range 1-359); only 16 events in 12 patients occurred beyond 90-days post-infusion. Fifty patients (47%) experienced both CRS and neuropsychiatric toxicities. Median time to resolution was 14 days (range 1-365), with 84% resolving within 90 days. The most common (>10%) events in this category included headache (21%), encephalopathy (16%), pain (15%) and dizziness (13%); other notable events included visual impairment (7%), tremor (7%), delirium (5%), speech disorders (3%) and seizures (3%).

Hypogammaglobulinemia resulted from loss of normal B-cells, an on-target effect of successful KYMRIAH treatment. Patients need to be maintained on supplemental treatment with intravenous gamma globulin (IVIG).

Grade 3 or greater non-hematologic laboratory abnormalities occurring in at least 10% of patients included hypophosphatemia (24%), hypocalcemia (13%), hypokalemia (12%) and hyponatremia (11%).

KYMRIAH is a genetically modified product that has the potential for integration of the lentiviral vector (insertional mutagenesis), clonal outgrowth, or neoplastic transformation of transduced host cells.

Post-infusion, non-laboratory adverse events that occurred in at least 10% of patients in the safety population on C2201, or in at least 5% of patients at Grade 3 or greater, are outlined in the table below.

Common (>10% overall, or ≥5% Grade 3 or greater) non-laboratory AEs post- Infusion, C2201

PT[a]	All grades	Grade ≥ 3
Cytokine release syndrome	78 (74%)	24 (23%)
Pyrexia	36 (34%)	6 (6%)
Diarrhoea	33 (31%)	1 (1%)
Nausea	29 (27%)	1 (1%)

Hypotension	28 (26%)	9 (8%)
Fatigue	27 (26%)	7 7%)
	24 (23%)	3 (3%)
Headache	22 (21%)	-
Cough	20 (19%)	
Dyspnoea	19 (18%)	6 (6%)
Acute kidney injury	18 (17%)	6 (6%)
Febrile neutropenia	18 (17%)	18 (17%)
Constipation	17 (16%)	1 (1%)
Encephalopathy	17 (16%)	12 (11%)
Pain	16 (15%)	3 (3%)
Chills	14 (13%)	-
Hypogammaglobulinaemia	14 (13%)	3 (3%)
Tachycardia	14 (13%)	3 (3%)
Decreased appetite	13 (12%)	4 (4%)
Dizziness	13 (12%)	2 (2%)
Upper respiratory tract infection[b]	13 (12%)	2 (2%)
Weight decreased	13 (12%)	3 (3%)
Arthralgia	11 (10%)	-
Source: FDA reviewer; [a]Includes grouped terms; [b]HLGT "infections, pathogens unspecified"		

Immunogenicity
Because the CD19-specific chimeric antigen receptor (CD19-CAR) is a foreign protein that contains murine sequences, infusion of KYMRIAH could induce humoral and cellular responses against this moiety. Humoral antibody responses against CD19-CAR were detectable in most individuals even before KYMRIAH treatment, but only 7 subjects demonstrated an increased anti-mCAR19 response following KYMRIAH treatment. T cell responses against mCD19 (b) (4) were also common pretreatment and did not fluctuate over time. Within the limitations imposed by small patient population size and high variability in sample levels, humoral and cellular immunogenicity did not significantly impact CTL019 expansion and efficacy.

8. ADVISORY COMMITTEE MEETING

No advisory committee meeting was held for this supplement because: a) KYMRIAH has already been approved for another indication and it displays a similar safety profile in the current trial, b) the trial endpoints are not novel and are acceptable in the proposed patient population, and c) the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

9. OTHER RELEVANT REGULATORY ISSUES

None

10. LABELING

- The APLB found the prescribing information (PI) and container labels to be acceptable from a promotional and comprehension perspective.
- The review committee negotiated revisions to the PI with the Applicant which included:
  - Warnings and Precautions: Section 5 was modified providing more detailed information about incidence of major adverse events within the trial, especially CRS and neurotoxicity.
  - Adverse Reactions: Section 6, Tables 2, 3, 5, and 6 were modified providing more detailed information about overall incidence of adverse reactions in trials using KYMRIAH.
  - Clinical Studies: Section 14.2 r/r DLBCL Clarification was provided about frequency of inpatient and outpatient administration of KYMRIAH. After exclusion of 24 patients who were inevaluable for assessment of objective response with KYMRIAH therapy, efficacy analysis presented in Section 14.2 of labeling included the subset of 68 patients with measurable disease at baseline assessment as described in section 6.1.10.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

Based on the magnitude and durability of the treatment effect demonstrated in Study CCTL019C2201, the clinical review team recommends regular approval (21 CFR 601.4) of KYMRIAH for adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. KYMRIAH is not indicated for treatment of patients with primary central nervous system (CNS) lymphoma.

b) Risk/ Benefit Assessment

The efficacy of KYMRIAH was established based on the complete remission (CR) rate and duration of response. In a population of 68 patients with relapsed or refractory disease, the objective response rate was 50% with a CR rate of 32%, and the median duration of response for responders has not yet been reached after a median follow-up of 9.4 months. This response rate exceeds that previously reported for standard chemo-immunotherapy.

The risks of KYMRIAH can be linked to its mechanism of action, which involves the activation of T cells targeted to kill CD19+ cells. Cytokine release syndrome and neurotoxicity presumably linked to T cell activation-products occurred in 65% and 79% of patients respectively, and both complications can be life-threatening or fatal. Hypogammaglobulinemia resulting from CAR T cell attack on normal CD19+ B cells may persist for months requiring monitoring and replacement therapy. A potential risk of clonal mutagenesis or secondary malignancy associated with the use of a lentiviral vector cannot be excluded.

In view of the grave prognosis of relapsed/refractory large B-cell lymphoma after treatment with conventional chemo-immunotherapy, the review team concludes that the BLA efficacy and

safety data indicate a favorable risk/benefit profile. The review team recommends regular approval of KYMRIAH at the dose of 0.6-6 x 10^8 transduced CAR-positive viable T cells. A postmarketing requirement (PMR) study to assess long-term toxicities of KYMRIAH will be conducted.

Following review of the BLA clinical and safety data, the review team recommends issuing a regular approval (21 CFR 601.4 (a)) for KYMRIAH, implementing a REMS program, and requiring a long-term follow-up program as a PMR. The Prescribing Information (PI) will include a boxed warning for CRS and neurologic toxicity and a REMS with ETASU to ensure that the product's benefits outweigh the risks.

c) Recommendation for Postmarketing Activities

The applicant previously established a long-term follow-up study B2401, as a PMR upon initial approval of KYMRIAH for treatment of patients with relapsed, refractory childhood ALL. This observational study was established to assess short-term toxicity, document adverse events, and monitor long-term for the development of secondary malignancies.
Since the lentiviral vector used to produce KYMRIAH could potentially contribute in the generation of replication-competent retroviruses or initiate insertional mutagenesis, the applicant has agreed to obtain and test tissue from second malignancies whenever possible to test whether genetic elements of KYMRIAH contributed to oncogenesis. To detect uncommon events, B2401 plans to enroll 1,000 ALL patients over 5 years and follow each patient for 15 years. Since similar concerns also arise concerning the impact of KYMRIAH on patients with DLBCL, the agency requires the applicant to amend the protocol to also enroll at least 1500 patients in this long-term study as well.

At the time of initial approval, CBER Office of Biostatistics and Epidemiology and CDER Division of Risk Management also determined that a Risk Evaluation and Mitigation Strategy (REMS) was indicated to ensure that the benefits of KYMRIAH outweigh the risks of Cytokine Release Syndrome (CRS) and neurotoxicity for patients with childhood ALL. This REMS included 2 Elements to Assure Safe Use (ETASU) i.e. site certification and restriction of use to certain health care settings for patients receiving KYMRIAH for childhood ALL. The agency now requests the applicant to modify the REMS/ETASU plan to enforce similar pharmacovigilance in the treatment of patients with DLBCL.