Summary Basis for Regulatory Action

Date: August 30, 2017

From: Xiaobin Victor Lu, Ph.D., Chair of the Review Committee

BLA/ STN#: 125646/0

Applicant Name: Novartis Pharmaceuticals Corporation

Date of Submission: February 2, 2017

Goal Date: October 3, 2017

Proprietary Name: KYMRIAH

Proper Name: tisagenlecleucel

Indication: KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

Recommended Action: Approval

Review Office Signatory Authority: Wilson Bryan, MD, Director, 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.**

The table below indicates the material reviewed when developing the SBRA

Document title	**Reviewer name**
Clinical Review(s) • *Clinical (product office)* • *Clinical Branch Chief Review* • *Clinical Division Director Review* • *Postmarketing safety epidemiological review (OBE/DE)* • *Bioresearch Monitoring (OCBQ/DIS)* • *Pharmacometrics Analysis Working Group (CBER/OBE and CDER/OCP)*	Maura O'Leary, MD (OTAT/DCEPT) Donna Przepiorka, MD, PhD (OCE) Bindu George, MD (OTAT/DCEPT) Tejashri Purohit-Sheth (OTAT/DCEPT) Marc Theoret, MD (OCE) Jaspal Ahluwalia, MD *(OBE/DE)* Dennis Cato (OCBQ/DIS/BMB) Hong Yang (OBE) Million Tegenge (OBE) Richard Forshee (OBE) Shiowjen Lee (OBE) Xue (Mary) Lin (OBE)

• *Clinical Outcome Assessment (CDER/OND)*	Chao Liu (CDER/OCP) Justin C. Earp (CDER/OCP) Stacy Shord (CDER/OCP) Yaning Wang (CDER/OCP) Nam Atiqur Rahman (CDER/OCP) Nikunj Patel (CDER/OND)
Statistical Review • *Clinical data* • *Non-clinical data*	Xue (Mary) Lin, PhD (OBE)
CMC Review(s) • *CMC (product office)* • *Facilities review (OCBQ/DMPQ)* • *Vector Substance and Vector Product (OCBQ/DMPQ)* • *Establishment Inspection Reports (OCBQ/DMPQ)* • *Review of Bioburden, Endotoxin, Compendial Sterility Method Qualifications (OCBQ/DBSQC/LMIVTS)*	Xiaobin (Victor) Lu, PhD (OTAT/DCGT) Andrew Byrnes, PhD (OTAT/ DCGT) Kimberly Schultz, PhD (OTAT /DCGT) Elena Gubina, PhD (OTAT/DCGT) Tom Finn, PhD (OTAT/DCGT) Denise Gavin, PhD (OTAT/DCGT) Joan Johnson, MS (OCBQ/DMPQ) Randa Melhem, PhD (OCBQ/DMPQ) Ashley Burns, PharmD (OCBQ/DMPQ) Richard Heath Coats (OCBQ/DMPQ) Simleen Kaur (OCBQ/DBSQC) Cheryl Hulme (OCBQ/DMPQ/PRB) Marie Anderson, MS, PhD (OCBQ/DBSQC)
Pharmacology/Toxicology Review(s) • *Toxicology (product office)* • *Developmental toxicology (product office)* • *Animal pharmacology*	Ying Huang, PhD (OTAT/DCEPT)
Clinical Pharmacology Review	Iftekhar Mahmood (OTAT/DCEPT)
Labeling Review • *APLB (OCBQ/APLB)*	Dana Jones (OCBQ/APLB)
Other Review(s) • *DSCSA Exemption Request (OCBQ)* • *DRISK (CDER/DRISK)*	Jean Makie (OCBQ) Naomi Redd (DRISK)

1. INTRODUCTION

Novartis Pharmaceuticals Corporation submitted a Biologics License Application (BLA), STN 125646, for licensure of tisagenlecleucel. The proprietary name is KYMRIAH. KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

KYMRIAH is comprised of genetically modified antigen-specific autologous T cells (from the patient) reprogrammed to target cells that express CD19. CD19 is an antigen expressed on the surface of B cells and tumors derived from B cells. The KYMRIAH chimeric antigen receptor (CAR) protein has a murine anti-CD19 single chain antibody fragment (scFv) and signaling domains (CD3-ζ) and 4-1BB. These intracellular signaling domains play critical roles in KYMRIAH functions, including T cell activation, persistence *in vivo*, and anti-tumor activity.

This document summarizes the basis for approval for KYMRIAH, highlighting topics of key review discussions. One clinical trial, CCTL019B2202 (B2202), conducted under a Special Protocol Assessment, provided the basis for the BLA submission for a regular approval for KYMRIAH. B2202 is a multicenter, open-label, single-arm, trial to determine the efficacy and safety of KYMRIAH in pediatric and young adult patients with relapsed or refractory B-cell ALL. The primary objective was to evaluate the efficacy of KYMRIAH therapy as measured by overall remission rate (ORR) during the 3 months after KYMRIAH administration, which includes complete remission (CR) and CR with incomplete blood count recovery (CRi) as determined by an Independent Review Committee (IRC) assessment.

The B2202 trial was adequate and well controlled and the review team concluded that the BLA contains substantial evidence to demonstrate effectiveness for the proposed indication. For the 63 patients in the efficacy analysis population, the CR rate was 63% (95% CI: 50%, 75%), and all patients in CR were MRD negative. With a median follow-up of 4.8 months, the median duration of CR was not reached.

The major risks of KYMRIAH include:

- Cytokine release syndrome, which occurred in 79% of the patients and can be fatal or life-threatening
- Transient neurologic toxicity which occurred in 65% of the patients
- Febrile neutropenia which occurred in 38% of the patients
- Cytopenias not resolved by day 28 which occurred in 53% of the patients
- Infections which occurred in 59% of the patients

Overall the benefit/risk profile for these heavily-pretreated pediatric and young adult patients with relapsed/refractory (R/R) B-cell precursor ALL is favorable with appropriate risk mitigation strategies in place. During the trial the applicant provided on-site training for participants, restricted study sites to transplant centers, and closely monitored safety events. This risk mitigation strategy was successful in reducing morbidity of KYMRIAH and will be continued in the Risk Evaluation Mitigation Strategy (REMS) with Elements To Assure Safe Use (ETASU) detailed later in this review.

The review team recommends approval of this BLA with postmarketing requirements (PMR) for a REMS with ETASU for the management of cytokine release syndrome and neurologic toxicity, training and assessment of sites and the use of tocilizumab and a postmarketing observational

study to assess short and long-term toxicities of KYMRIAH (B2401). B2401 will include short-term CRS, neurologic, and other adverse event reporting as well as long-term observational follow-up for the potential of second malignancy with tumor assessment at the time of occurrence of a new (second) malignancy.

2. BACKGROUND

Disease background

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia can be of B or T cell origin. Approximately 80-85% of pediatric ALL diagnoses are B cell precursor in origin and CD19 positive (CD19+). CD19 is an antigen on the membrane of the cell, not only at initial diagnosis, but at relapse.

CD19 is not expressed by pluripotent blood stem cells. Since CD19 is limited to normal B cells or B cell malignancies, this made CD19 a natural target for immunotherapy. The strategy with KYMRIAH was to produce genetically modified chimeric antigen receptor (CAR) T cells transduced with a lentiviral vector encoding the chimeric antigen receptor genes to target CD19 exclusively.

Pediatric and Young Adult B cell Precursor Relapsed or Refractory (R/R) Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) occurs in children and adults. Each year 3100 new cases are seen in children and adolescents in the U.S. ALL comprises 25% of all cancer diagnoses in children less than 15 years and 19% of all cancers in patients less than 20 years old. While the 5-year survival rate for ALL in children is now 90%, after relapse only 40% are able to achieve a durable remission. Fifteen to 20% of pediatric B cell precursor ALL patients relapse after their initial remission.

Survival after relapse is dependent on the timing of the relapse and the type of the relapse. Those patients who relapse on therapy, or have relapsed multiple times, have a poor prognosis. The only potential cure for relapsed systemic pediatric ALL is allogeneic stem cell transplantation (HSCT). With more aggressive therapies for front-line treatment, salvage therapy has become less effective. Relapsed ALL remains a leading cause of cancer deaths in children in the US.

Available Therapies

The standard of care approach to relapsed disease in pediatric and young adult ALL is to re-induce with combination chemotherapy to achieve a second or subsequent complete remission with minimal residual disease (MRD) negative status. Then, the patient is able to have the available curative therapy, hematopoietic stem cell transplantation (HSCT). In the absence of complete response to combination chemotherapy (standard of care regimens), single agents are available as detailed in Table 1 below. These combination induction regimens mimic those used with initial treatment: corticosteroid, vincristine, asparaginase, and an anthracycline.

Table 1. FDA Approved Therapies for R/R ALL in Pediatric and Young Adult Patients

FDA-Approved Products	Approval/ Year	Results
Clofarabine (CLOLAR)	2004, accelerated	CR 11.5%
Vincristine lyophilized injection (MARQIBO)	2012, accelerated	CR 4.6%
Blinatumomab (BLINCYTO)	2014	CR 17.1%; Median DOR 6.0 months
Inotuzumab ozogamicin (BESPONSA)	2017	CR 35.8%; Median DOR 8.0 months

8/21/2017
CR: complete remission; DOR: duration of response;
Source: USPI for CLOLAR, BLINCYTO, MARQIBO, BESPONSA

Regulatory History and Considerations

Key regulatory milestones in the development of KYMRIAH are summarized below.

Table 2. Regulatory Activity

Date	Milestone
4/22/2013	PreIND Meeting
3/03/2014	PreIND Meeting
3/04/2014	Special Protocol Assessment (SPA)
9/23/2014	IND 16130 submission
9/23/2014	Rare Disease Designation
1/31/2014	Orphan Designation: Acute Lymphoblastic Leukemia
4/08/2015	First subject enrolled into Study CCTL019B2202
2/29/2016	Breakthrough Therapy Designation
11/21/2016	Pre-BLA Meeting
11/23/2016	Efficacy Assessment: Data Cut-off
12/16/2016	CCTL019B2202 Interim Analysis with 6 months follow-up
1/19/2017	Deaths and SAEs in ongoing studies cut-off
2/02/2017	BLA 125646 submission
3/15/2017	Rare Pediatric Disease Designation
3/28/2017	BLA 125646 filed
7/12/2017	Oncologic Drugs Advisory Committee Meeting
10/03/2017	PDUFA Action Due Date

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

Product Description

KYMRIAH is composed of autologous T cells that are genetically modified with a lentiviral vector encoding a chimeric antigen receptor (CAR). The CAR specifically recognizes the CD19 protein present on CD19+ B lineage tumor cells as well as normal B cells.

KYMRIAH is a rationally designed immunotherapy, and the presumed mechanism of action is direct cytolytic killing of tumor cells. Briefly, T cell activation begins with scFv binding to CD19, which physically brings the CAR T cells to the CD19+ tumor cells. The interaction of the CAR and CD19 results in formation of immune synapses, similar to the natural T cell activation pathways. Formation of immune synapses triggers a cascade of T cell signaling that leads to T cell activation. Upon activation, T cells produce cytokines, perforin and granzymes to initiate direct cytolytic tumor cell killing. Activation of the CAR T cells also promotes cell expansion and differentiation.

Manufacturing Summary

The manufacturing process starts with receipt of the patient's white blood cells collected by leukapheresis at one of the apheresis centers that have been qualified by Novartis. The cellular composition of the leukapheresis material determines which of two manufacturing pathways is used for T cell enrichment. The enriched T cells are pre-stimulated with CD3/CD28 antibody-conjugated beads and then transduced with the lentiviral vector. The CAR-expressing autologous T cells are then expanded in culture for up to (b) (4) to reach sufficient numbers. The cells are washed to remove impurities (including the CD3/CD28 antibody conjugated beads) and formulated with infusion media for cryopreservation in a vapor-phase liquid nitrogen freezer. Upon request from the clinical center, KYMRIAH is shipped in a vapor phase liquid nitrogen dry shipper (dewar) to the clinical infusion center by a qualified courier. The chain-of-identity of the entire process from leukapheresis to infusion and throughout all manufacturing steps is controlled by a computer based system to ensure the product's identity and product traceability.

The manufacturing process for the vector used for KYMRIAH production can be divided into two stages: vector substance and vector product. The vector substance manufacturing begins with (b) (4)

. Vector product is manufactured by (b) (4)

. Additional lot release tests are conducted to release the final vector product.

Manufacturing Controls or Control Strategy

Manufacturing process consistency is mainly controlled by (1) raw material and reagent qualification programs, (2) in-process monitoring, (3) in-process control testing, including decision points for alternative manufacturing pathways, (4) lot release tests, (5) traceability by using a chain-of-identity system, and (6) validation of the manufacturing process. Within individual unit operations of the manufacturing process, critical process parameters and key process parameters were established based on process characterization and manufacturing risk assessment studies during the process development stages. The critical process parameters and key process parameters define the acceptable operating ranges for each manufacturing step necessary to ensure a consistent final product that meets the predefined product quality attributes (lot release specifications).

The raw material qualification program consists of risk assessment of the source materials, vendor qualification and audits, and an incoming materials management system that consists of visual examination of the package, identity testing, and confirmation of the certificate of analysis upon receipt of the raw material and the reagent.

While the in-process monitoring activities ensure each unit operation is on the right track, in-process control testing is used to make appropriate decisions for the next manufacturing steps. Lot release testing serves as the final confirmation of product quality before releasing the product for commercial use.

Process Validation

The KYMRIAH manufacturing process was validated, including (b) (4) T cell enrichment pathways. (b) (4) batches were manufactured using the commercial manufacturing and commercial master batch records. Deviations during the manufacturing process validation were investigated and closed. The results of the process validation (i.e., process performance qualifications) met the predefined validation acceptance criteria.

As part of the process validation, a continued process verification (CPV) protocol was established to monitor the process by trending manufacturing data, deviations, out-of-specification batches, and other unexpected manufacturing quality incidents. A media fill study was also conducted to validate the aseptic process. A chain-of-identity system was also validated to support product traceability from leukapheresis to infusion. Shipping and receiving of leukapheresis materials and the final cell product were validated for shipments between the apheresis/infusion centers and the Morris Plains manufacturing facility. As part of the overall manufacturing process validation, the manufacturing processes for vector substance and vector product have also been validated.

Specifications

The final lot release specifications are shown in the table below.

Table 1. KYMRIAH Lot Release Specifications

Test	Requirements for commercial use	Sample used for testing
Appearance	Colorless to slightly yellow	Formulated product (b) (4)
Identity by CAR q-PCR	Positive for PCR signal	(b) (4)
Percentage of viable T cells	(b) (4)	Final product (b) (4)
Determination of transduction efficiency by CAR-q-PCR	(b) (4)	(b) (4)
Cell viability	(b) (4)	Final product (b) (4)
Determination of residual beads by microscopy	(b) (4)	(b) (4)
Percentage of viable CD19+ B cells	(b) (4)	Final product (b) (4)
Total cell count[4]	Report cells/mL	Final product (b) (4)
Number of viable cells (calculated)	(b) (4) total viable cells	Final product (b) (4)

Dose (calculated)	• 0.2 to 5.0 × 10^6 CAR positive viable T cells/kg body weight (≤50 kg) • 0.1 to 2.5 ×10^8 CAR positive viable T cells (> 50 kg)	Final product (after thaw)[2] Calculation formula: *(%CAR expression x Viable cell concentration x Volume per dose)/100 (per patients (≤ 50 kg this number is divided per Kg body weight)*
Determination of CAR expression by flow cytometry	(b) (4)	Final product (b) (4)
Release of IFNγ in response to CD19-expressing target cells	• (b) (4) • (b) (4)	Final product (b) (4)
Bacterial Endotoxins	(b) (4)	Final product (b) (4)
Sterility	Negative	Formulated product (b) (4)
Mycoplasma	Negative	(b) (4)
Determination of VSV-G DNA by quantitative PCR (qPCR)	(b) (4)	(b) (4)

[1]Post-harvest samples are taken before the addition of cryopreservation media, to avoid potential interference of (b) (4) present in the final formulation.
[2]Final product (after thawing) sample tests are performed on an aliquot of the final formulation of the cellular product, collected just prior to filling the drug product bag, stored in the vapor phase of liquid nitrogen (≤ -120°C), and thawed at the time of analysis.
[3] Testing for residual beads is performed using a sample collected (b) (4) prior to dose formulation, to allow for accurate measurement of residual beads present per (b) (4), without being impacted by the range of concentrations of cells per mL at which final dose may be formulated.
[4] No specification is set for Total cell count since it is not a critical quality attribute; result from Total cell count is used to calculate Number of viable cells, essential for the Dose calculation.
[5] Pre-harvest samples are taken from the cell culture supernatant at the end of cell culture just prior to harvest processing steps and final formulation, to provide maximal opportunity to detect any contaminating mycoplasma present in the manufacturing process.

Impurity Profile

CAR-positive T cells are the active ingredient in KYMRIAH. The entire T cell population, including non-transduced T cells, is considered a part of the product and the purity of KYMRIAH is defined as the percentage of viable T cells as a whole.

Impurities can be classified into product-related (cellular impurities) and process-related impurities. Cellular impurities are those derived from leukapheresis material such as red blood cells, granulocytes, dead cells, and B cells/B-lineage lymphoblasts. Process-related impurities include ancillary materials and reagents that are not intended to be present in the final product.

Cell viability is a lot release specification with an acceptance criterion of (b) (4). Non-viable cells represent a potential clinical safety issue. Cell viability is controlled during the manufacturing and formulation process, and the percentage of total dead cells in KYMRIAH has been consistently low.

B-lineage cells including B cell blasts can interfere with the cell manufacturing process and are a potential safety concern if present in the final product. Therefore, B-lineage cells are removed during the manufacturing process. An acceptance criterion of (b) (4) B cells in KYMRIAH was established using the validated analytical method with a LOQ = (b) (4). No residual B-lineage

cells have been detected in any batch manufactured at the Novartis Morris Plains Facility. However, the possibility still exists for residual B cell blasts to be transduced, survive the manufacturing process, and be present in a trace amount in KYMRIAH.

No lot release test is performed for natural killer (NK) cells, despite detection of low levels in some lots during clinical development, because the biological activities of autologous NK cells are not considered to be a safety concern.

The percentages of hematocrit are measured and reported by the leukapheresis collection sites. The majority of incoming patient leukapheresis material met the recommended target for red blood cells (RBC), which is (b) (4) The KYMRIAH manufacturing process is capable of removing RBC even if present in large numbers in the patient leukapheresis starting material. The acceptance criterion for appearance is colorless to slightly yellow. High levels of RBCs in the final product would cause a lot release failure due to color outside of the acceptable limit.

There are significant levels of antibody conjugated beads (CD3/CD28) at the end of the cell expansion step before harvest (at maximum (b) (4) in 10 mL solution). The antibody conjugated beads (CD3/CD28) are actively removed (b) (4) to meet the acceptance criterion of no more than (b) (4)

Reduction of process-related residuals is a consequence of a series of washes and volume replacement processes. There are multiple washing and bead removal steps in the manufacturing process that are capable of removing impurities. Overall, this represents up to a 5000-fold reduction of residual carry-over by volume replacement.

Viral Safety

The potential risks from adventitious viral agents for KYMRIAH are addressed through assessment of source materials and testing programs during vector and KYMRIAH manufacturing. Animal and human or recombinant technology-derived raw materials are qualified and tested for their origin and suitability to minimize the potential contaminations with various adventitious viruses and TSE/BSE risk. Therefore, the infusion of KYMRIAH presents an overall low risk of patient infection from viral adventitious agents.

Container Closure-DS, DP

KYMRIAH is filled and cryopreserved at ≤ -120°C in (b) (4) bags, as a single-dose cell suspension, which is thawed prior to infusion. The (b) (4) cryobags are used for final product volumes of 10-30 mL of cell suspension, and the (b) (4) cryobags are used for final product volumes of 30-(b) (4) cell suspension.

The (b) (4) bags, which are non-pyrogenic and sterilized by (b) (4), are 510(k) cleared devices (b) (4) The bags have sterile fluid paths including two spike ports, an inlet tube, and a Y-connector with female luer-lock caps.
The container closure integrity of the bags is tested and inspected for leaks by the vendor (b) (4). Additional container closure integrity testing is performed by Novartis on the filled (b) (4) cryobags using a (b) (4) method. The frozen filled bags containing surrogate media are thawed at different time points to demonstrate the integrity of the bags for the duration of the final product shelf life of nine months. Results of container closure integrity testing at $Time_0$ and $Time_{6months}$ were acceptable.

Manufacturing Risks

Manufacturing failures
As an autologous, single-dose product, manufacturing failures would have a direct impact on patients for whom KYMRIAH is prescribed. In the clinical study protocol B2202, 7 of the 78 lots manufactured failed due to either termination of manufacturing or out-of-specification results (an approximately 9% failure rate).

Replication Competent Lentivirus
Generation of replication-competent lentivirus (RCL) during the manufacturing process for KYMRIAH is a theoretical safety concern. To date, no RCL has been detected in any clinical trials using a lentiviral vector transduced cell product, as tested on the vector product with a sensitive co-culture RCL assay or on the final transduced cell product with the same RCL assay or a PCR-based RCL assay.

Insertional Mutagenesis
Insertional mutagenesis due to vector integration is a potential risk for inducing secondary malignancies following KYMRIAH administration. Integration of the vector into the patient's cells might inadvertently activate a cellular proto-oncogene or disrupt a tumor suppressor gene, leading to malignant transformation events. To mitigate the risk of insertional mutagenesis, the vector used for KYMRIAH manufacturing was designed to remove any known viral enhancer elements (self-inactivating design). In addition, the average vector copy number per cell is limited to less than (b) (4) per cell for KYMRIAH.

b) CBER Lot Release

An exemption has been granted from CBER Lot Release, with no requirement for submission of lot release protocols or product samples to CBER. The basis for this decision is that KYMRIAH is an autologous product; each lot will treat a single patient. Lot release testing would negatively impact the often limited quantity of cells available to the patient and failure of a single lot will have a minimal potential impact on public health.

c) Facilities Review/Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of KYMRIAH are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Table 2. Manufacturers for KYMRIAH drug product, vector substance and vector product

Name/Address	FEI number	DUNS number	Inspection /Waiver	Justification /Results
Final Product Drug Substance Drug Product Release Testing Cell & Gene Therapies Facility (CGT), 220 East Hanover Avenue, Morris Plains, NJ 07950 USA Manufacture of KYMRIAH Drug Substance (DS) and Drug Product (DP)	3010353512	078640106	Pre-License Inspection	CBER April 3 – 7, 2017 VAI

Quality Control and Stability Testing of KYMRIAH DS and DP. Quality Control of vector (functional test of expressed transgene and MOI assay) Testing and release of vector as incoming material				
Lentiviral vector (with CAR transgene) Manufacturing and Release Testing (b) (4) Manufacturing and storage of lentiviral vector (with CAR transgene) Batch release, stability testing and QC of lentiviral vector	(b) (4)	(b) (4)	(b) (4)	CBER (b) (4) VAI
Lentiviral vector (with CAR transgene) Manufacturing and Release testing (b) (4) Sterilization, concentration, filling storage and labeling of the lentiviral vector (with the CAR gene) QC testing (b) (4) of the lentiviral vector	(b) (4)	(b) (4) 2	(b) (4)	CBER (b) (4) VAI

CBER performed a Pre-License Inspection (PLI) at Novartis Pharmaceuticals Corporation Cell and Gene Therapy Facility (CGT) in Morris Plains, New Jersey from April 3-7, 2017 for the manufacture of KYMRIAH suspension for intravenous infusion.

At the end of the inspection, CBER issued a Form FDA 483. The firm responded to the observations, and the corrective actions were reviewed and found to be acceptable. All inspectional issues are considered to be satisfactorily resolved.

CBER also performed two PLIs at the facilities involved in the manufacturing of the lentiviral vector (with CAR transgene):

- (b) (4) – a contract manufacturer (CMO) for Novartis. The inspection was conducted (b) (4) for the manufacture of the lentiviral vector. CBER issued a Form FDA 483 at the end of the inspection.

  The firm responded to the observations, and the corrective actions were reviewed and found to be acceptable. All inspectional issues are considered to be satisfactorily resolved.

- (b) (4). The inspection was conducted from (b) (4) for the sterilization, concentration and filling of the lentiviral vector. CBER issued a Form FDA 483 at the end of the inspection.

  The firm responded to the observations, and the corrective actions were reviewed and found to be acceptable. All inspectional issues are considered to be satisfactorily resolved.

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not significantly alter the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

e) Product Comparability

The CD19 CAR-positive T cell product that was the predecessor to KYMRIAH was originally developed at the University of Pennsylvania using a lentiviral vector for stable integration and expression of the CD19-specific CAR for the treatment of B cell leukemia and lymphoma. Novartis made numerous changes in the (b) (4) and the manufacturing process.

The new (b) (4) developed by Novartis for KYMRIAH was designed to improve the (b) (4) safety features while maintaining the same CAR transgene. The new (b) (4) is expected to have reduced potential for generation of replication competent lentivirus and insertional mutagenesis-mediated oncogenesis. An equivalency study comparing the new and the original (b) (4) was conducted to demonstrate that the new (b) (4) was able to transduce human T cells and produce CD19 CAR-positive T cells with the same critical product attributes.

Novartis significantly modified the manufacturing process for CD19 CAR-positive T cells developed by the University of Pennsylvania. The most significant changes were designed to improve the manufacturing process controls for product consistency and yield. These changes have been designed to reduce non-T cells that negatively affect manufacturing ability, maximize the yield, and improve the quality of the final cell product.

A site-to-site comparability study was conducted at the Novartis and University of Pennsylvania facilities, and demonstrated that CD19 CAR-positive T cells manufactured by both facilities met all lot release specifications. However, the characterization of cell growth and transduction efficiency showed statistically significant differences. Thus, the products produced by the University of Pennsylvania and Novartis are not considered to be comparable.

Significantly, the modified manufacturing process at the Novartis Manufacturing Facility at Morris Plains is able to produce a more pure intermediate T cell population before the transduction steps. This important change is expected to improve the vector transduction efficiency and cell growth. Furthermore, from safety standpoint, this change is expected to reduce the chance of transduction of non-T cells (e.g., B cell blast, residual levels of stem cells) that would pose a potential risk for the patients.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The nonclinical studies conducted for KYMRIAH included: 1) evaluation of the specificity of the CD19-binding domain using a human plasma membrane protein array, 2) assessment of *in vivo* anti-tumor activity of KYMRIAH in mouse xenograft tumor models, 3) evaluation of selected toxicology parameters, cell distribution, and persistence of KYMRIAH in tumor-bearing mice, and 4) genomic insertion site analysis of lentiviral integration into the human genome. The genomic insertion site analysis was performed on KYMRIAH from 14 individual donors (2

healthy donors and 12 patients with pediatric ALL or diffuse large B-cell lymphoma). The transduced samples exhibited conventional lentivirus integration site patterns with no preferential insertion sites near genes of concern or clonality observed. Genotoxicity assays, *in vivo* carcinogenicity studies, and developmental and reproductive toxicity studies were not conducted. No safety concerns were identified in the resulting data from the nonclinical studies.

5. CLINICAL PHARMACOLOGY

Based on Population pharmacokinetic (PK) analysis of KYMRIAH, the following conclusions can be drawn from the study:

- KYMRIAH exhibited an initial rapid expansion phase achieving maximal concentration (C_{max}) around day 10 followed by a slower bi-exponential decline in complete remission/complete remission with incomplete hematologic recovery (CR/CRi) patients on day 28.
- C_{max} and $AUC_{0\text{-}28d}$ of KYMRIAH were higher in CR/CRi patients as compared with non-responder (NR) patients.
- No difference in the pharmacokinetics of KYMRIAH was noted for race and gender.
- Children <10 years of age have higher C_{max} and AUC (1.5 to 2-fold) than adults. Both C_{max} and $AUC_{0\text{-}28d}$ decreased with increasing age. However, due to small sample size and high variability, it was difficult to assess a definitive impact of age on the PK of KYMRIAH.
- C_{max} and $AUC_{0\text{-}28d}$ of KYMRIAH were higher with greater tumor burden.
- CR/CRi patients (n=18) treated with tocilizumab had 183% and 265% higher KYMRIAH C_{max} and $AUC_{0\text{-}28d}$, respectively, as compared to patients (N=44) who did not receive tocilizumab as measured by qPCR
- CR/CRi patients who received corticosteroids had 89% higher $AUC_{0\text{-}28d}$ compared with CR/CRi patients who did not receive corticosteroids

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

B2202 provided the basis for the BLA submission for a regular approval for KYMRIAH. B2202 evaluated the safety and effectiveness of KYMRIAH for the treatment of pediatric and young adult patients with second or later relapse or primary refractory B cell precursor ALL. This study was conducted under a Special Protocol Assessment initially agreed upon on March 3, 2014.

Study Description

CCTL019B2202 (B2202) is a multicenter, open-label, single-arm, trial to determine the efficacy and safety of KYMRIAH in pediatric and young adult patients with relapsed or refractory B-cell precursor ALL. The primary objective was to evaluate the efficacy of KYMRIAH therapy as measured by overall remission rate (ORR) during the 3 months after KYMRIAH administration, which includes CR and CR with incomplete blood count recovery (CRi) as determined by an Independent Review Committee (IRC) assessment. CR is a bone marrow with < 5% blasts; peripheral blood counts with neutrophils > 1×10^9/L and platelets > 100×10^9/ L and < 1% circulating blasts; no extramedullary disease; and no platelet or neutrophil transfusion for ≤ 7 days. CRi is a CR except for neutrophils ≤ 1×10^9/L and/or platelets ≤ 100×10^9/L.

The key secondary objectives

- Evaluate the percentage of patients who achieve a best overall response (BOR) of CR or CRi with an MRD-negative bone marrow by central analysis using flow cytometry.

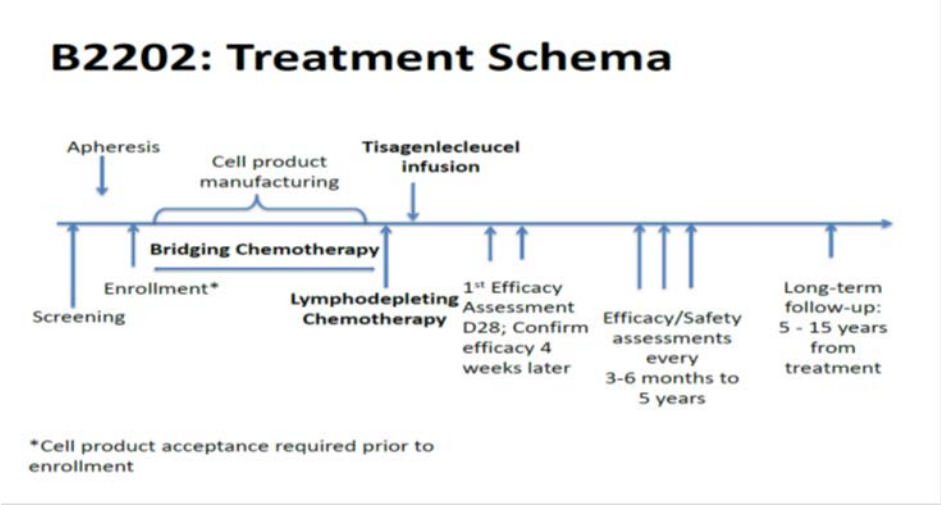
Other secondary objectives (selected)

- Duration of response

Primary efficacy endpoint

- Overall remission rate (ORR) assessment during the 3 months after KYMRIAH administration; ORR includes CR and CRi, as determined by independent review committee (IRC) assessment from all manufacturing sites.

Clinical Efficacy Findings



Of the 107 subjects who signed an informed consent, 88 were enrolled. Sixty-eight subjects received KYMRIAH with products manufactured at the Morris Plains (MP), New Jersey (n=63) and Fraunhofer Institut (FH), Germany (n=5) and were included in the Safety Set. Since the comparability of the MP product with the FH product has not been completed, the Efficacy Set or primary efficacy analysis will be restricted to the 63 subjects who were treated with KYMRIAH manufactured at the MP site.

Table 5. Efficacy Analysis Results

	Efficacy Analysis Set: Primary Endpoint* (n=63)
ORR (95% CI)	82.5% (95% CI 70.9, 91.0)
CR	63.5% (95% CI 50.4, 75.3)
Cri	19.0%
NR/UNK	17.5%

Source: FDA clinical and statistical reviewers;. Dataset ADEFIRC1
*All CR and CRi were MRD negative

For the pre-specified primary efficacy endpoint of overall remission rate (ORR), a total of 52 subjects (82.5%) had a best overall disease response of complete remission (CR) or CR with incomplete blood count recovery (CRi) during the 3 months after KYMRIAH administration, as determined by Independent Review Committee (IRC). As a result, the lower limit of the 95% exact Clopper-Pearson confidence interval for ORR is 70.9%, which is above the pre-set null hypothesis rate of 20%. Forty subjects (63.5%) had the best response of CR within the first 3 months after infusion, and 12 subjects (19.0%) had the best response of CRi. Among the 52 responders, the median duration of response (DOR) was not yet reached (range: 1.2 to 14.1+ months) with the median follow-up of 4.8 months.

Efficacy Review Issues

The ORR is better than that reported for the treatment of relapsed disease, where the average remission rate is 40%, when patients are treated with combination therapy, approved single-agent therapy, or HSCT if done in either relapse or remission for this population. The analysis for the primary endpoint focuses on a three month assessment for ORR. However, the duration of response is a crucial assessment and that the remissions are sustainable in this heavily pre-treated population is an important result. The median duration of response has not been reached with a median follow-up time of 4.8 months. Therefore, while the additional issue of a small sample size is noted, the ORR rate is a marked improvement over all available therapies and has produced sustained remissions without additional therapy. In addition, twenty-nine of the confirmed responders are alive in remission without further therapy.

Bioresearch Monitoring

Bioresearch Monitoring inspections were issued for two foreign and four domestic clinical study sites that participated in the conduct of Study CCTL019B2202. The inspections did not reveal substantive problems that impact the data submitted in this BLA.

Efficacy Conclusion

The B2202 trial was adequate and well controlled. Based on the results of B2202, the review team concludes that the BLA contains substantial evidence of the effectiveness for the proposed indication. For the 63 patients in the efficacy analysis population, the CR rate was 63% ((95% CI, (50%, 75%)), and all patients in CR were MRD negative. With a median follow-up of 4.8 months, the median duration of CR was not reached.

b) Pediatrics

This study B2202 was conducted in a pediatric population ages: 2 to < 12 (50%); 12 to < 17 (25%); and ≥ 17 (25%) in the enrolled set. Similar percentages were noted in the safety and efficacy sets. No differences in efficacy or safety were observed between the different age subgroups or in comparison to the young adults in the trial. The FDA issued a written request (WR) for B2202 December 1, 2016. The applicant completed the WR and submitted the results for review prior to the submission of the BLA. These data were reviewed by the Pediatric Review Committee and the CBER Pediatric Exclusivity Board. The applicant met their endpoints for the WR.

c) Other Special Populations

None

7. SAFETY

The primary safety population for B2202 was the 63 subjects who received KYMRIAH manufactured in the U.S. (the efficacy population) and 5 subjects who received KYMRIAH manufactured at the Fraunhofer Institut in Germany. These 68 subjects comprise the Safety population for KYMRIAH. Comparability studies for the two site products have not been completed. All subjects experienced at least one adverse event after KYMRIAH. Eight-four percent (n=57) experienced Grade 3 or higher events. Serious adverse events and adverse events

of special interest included CRS, infection, transient neurologic events, febrile neutropenia, cytopenias lasting greater than 28 days, and infections. CRS was defined by clinical symptoms and medical status: fever, ICU status, hypotension, dyspnea, tachypnea, hypoxia, organ failure (intubation, dialysis), and acute respiratory symptoms.

Table 6. Adverse Events of Special Interest Post-Infusion

Study B2202 N=68	**Grade 3 N (%)**	**Grade 4 N (%)**	**All Grades N (%)**
CRS	14 (21)	19 (28)	54 (79)
Transient neurologic events	12 (18)	0	44 (65)
Febrile Neutropenia	24 (35)	2 (3)	26 (38)
Hematopoietic cytopenia not resolved by Day 28	13 (19)	12 (18)	36 (53)
Infections	17 (24)	2 (3)	40 (59)

Source: FDA analysis ADSL, ADAE, ADAERISK

- Severe Cytokine Release Syndrome (CRS) (Grade 3 and 4) events were noted in 49% (n= 33) of patients in the safety analysis set. Severe CRS occurred within 6 days, with a median duration of 9 days.
    - These events are life-threatening and can be fatal and require supportive measures
        - Thirty two (47%) patients required ICU admission.
        - Thirty six (53%) patients required blood pressure support.
        - Eleven (16%) required mechanical ventilation.
        - Eight patients (12%) required dialysis.
        - Twelve patients (18%) developed disseminated intravascular coagulation (DIC) resulting in 9 bleeding events
- Two fatal outcomes were related to severe CRS; one with a coagulopathy resulted in death of a patient from cerebral hemorrhage; and the second was the recurrence of leukemia and the onset of CRS that resulted in death 11 days after KYMRIAH infusion.

- Transient Grade 3 neurotoxicity such as encephalopathy, delirium, aphasia, and seizures occurred in 18% (n=12) of all patients.

- Severe infectious complications were noted in 26% (18/68) of patients, with three deaths occurring within 60 days and related to HHV6, bacterial pneumonia, and fungal infection.

- Prolonged neutropenia was noted in 40% of patients.

- Three patients experienced Grade 3 or 4 congestive heart failure requiring treatment for management. One remains on therapy.

- Successful treatment with KYMRIAH resulted in acquired hypogammaglobulinemia due to the loss of normal B cells. Patients need to be maintained on supplemental treatment with intravenous gamma globulin (IV IgG).

- Twenty seven patients experienced 61 episodes of bleeding pre- and post-KYMRIAH. The cerebral hemorrhage occurred post-KYMRIAH and was fatal as detailed above. Bleeding was controlled with clinical care with and without transfusions of fibrinogen, fresh frozen plasma and platelets.

- As described in the CMC review, 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.

Deaths:

Overall, 29 deaths have been reported from time of informed consent to the data cut-off of the study (November 23, 2016) as submitted for the BLA. To be screened, one had to sign an informed consent. Six patients died in the failed screened population, 12 pre-infusion, awaiting manufacture of KYMRIAH (6 from ALL, 5 from infection, and one respiratory failure) and 11 patients died post-infusion. Of the 29 deaths, two were attributable to the product and were considered by the FDA as related to CRS and are described above with CRS.

Selected Post-Infusion Adverse Events

Table 7. Selected Adverse Events (≥10%): Safety Population: Post- KYMRIAH

Body System	Preferred Term	Post-infusion period n (%)	Grade 3 or Higher n (%)
Subjects		68 (100%)	57 (84%)
Blood And Lymphatic System Disorders	Anemia	21 (31%)	9 (13%)
	Febrile Neutropenia	26 (38%)	26 (38%)
Cardiac Disorders	Tachycardia	18 (26%)	3 (4%)
Gastrointestinal Disorders	Abdominal Pain	11 (16%)	2 (3%)
	Vomiting	18 (26%)	1 (1%)
General Disorders And Administration Site Conditions	Chills	7 (10%)	0
	Fatigue	15 (22%)	0
	Fever	27 (40%)	10 (15%)
Immune System Disorders	Cytokine Release Syndrome	54 (79%)	33 (49%)
	Hypogammaglobulinemia	29 (43%)	5 (7%)
Infections And Infestations		40 (59%)	19 (27%)
	Fungal Infectious Disorders	9 (13%)	5 (7%)
Metabolism And Nutrition Disorders	Decreased Appetite	25 (37%)	10 (15%)
	Fluid Overload	7 (10%)	5
Musculoskeletal And Connective Tissue Disorders	Arthralgia	8 (12%)	1 (1%)
	Back Pain	7 (10%)	2 (3%)
	Myalgia	10 (15%)	0
	Pain In Extremity	11 (16%)	1 (1%)
Nervous System Disorders	Encephalopathy	23 (34%)	7(10%)

	Headache	25 (37%)	2 (3%)
Psychiatric Disorders	Agitation	6 (9%)	0
	Anxiety	9 (13%)	2 (3%)
	Confusional State	7 (10%)	0
	Delirium	14 (21 %)	3 (4%)
Renal And Urinary Disorders	Acute Kidney Injury	15 (16%)	9 (10%)
Respiratory, Thoracic And Mediastinal Disorders	Cough	13 (19%)	0
	Hypoxia	16 (24%)	12 (18%)
	Nasal Congestion	7 (10%)	0
	Pleural Effusion	7 (10%)	3 (4%)
	Pulmonary Edema	11 (16%)	7 (10%)
	Tachypnea	8 (12%)	4 (6%)
Vascular Disorders	Hypertension	13 (19%)	4 (6%)
	Hypotension	21 (31%)	15 (22%)

Source: ADSL ADAE JReview

Postmarketing Requirements

Risk Evaluation Mitigation Strategies (REMS)

Fifty four of 68 (79%) subjects treated with KYMRIAH experienced CRS, and 33/68 (49%) of the subjects had Grade 3/4 CRS. 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 and tocilizumab. Of the 54 subjects with CRS, 27 (50%) required 1-3 doses of tocilizumab. Two deaths were attributed to CRS. In addition, 65% (44 of 68) of subjects had neurotoxicity (defined as events such as aphasia, tremor, seizures, confusion, and encephalopathy) within the first 8 weeks, with 18 % being grade 3 (and none being grade 4). Monitoring for neurotoxicity required frequent neurological evaluations and treatment with systemic corticosteroids. The severity of the adverse events described above and the risk mitigation measures implemented in the study suggest that, post-approval, a Risk Evaluation and Mitigation Strategy (REMS) is indicated to ensure that the benefits of KYMRIAH outweigh the risks of Cytokine Release Syndrome (CRS) and neurotoxicity. The REMS includes Elements to Assure Safe Use (ETASU) to mitigate the known risks of CRS and neurotoxicity, as follows:

- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified.

- KYMRIAH is dispensed to patients only in certain health care settings.

The REMS ETASU requires Novartis to ensure that:

a) Pharmacies, practitioners and health care settings dispensing KYMRIAH are certified through a live training program and knowledge assessment.
b) Sites report all cases of CRS and neurotoxicity.

c) Novartis maintains documentation that processes and procedures are followed for the KYMRIAH REMS program.
d) Novartis conducts audits to ensure that training processes and procedures are in place.
e) Sites verify that a minimum of two doses of tocilizumab are available on site.

Materials provided as part of the REMS included:

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

Postmarketing Requirement (PMR) Study

Study CCTL019B2401 (B2401) is a multicenter, prospective, observational safety study. The study will include 1000 subjects enrolled within 3 months of the KYMRIAH infusion over a period of 5 years. All enrolled subjects will be followed for 15 years from their KYMRIAH infusion. Patients will receive clinical evaluation and follow-up according to standard of care for pediatric and young adult ALL patients. The primary endpoint will be evaluation for second malignancy (including T cell leukemia) which will include tissue work-up by the applicant for these events. Secondary endpoints will be adverse events and laboratory abnormalities, adverse events of special interest (CRS, neurotoxicity, infections, prolonged cytopenias), growth and development, reproductive status and pregnancy outcomes, and disease outcomes (ORR, OS).

The timetable for the PMR study:

Final Protocol Submission: September 8, 2017
Study Completion: December 31, 2037
Final Report Submission: December 31, 2038

Immunogenicity

Because the CD19-specific chimeric antigen receptor is a foreign protein that contains murine sequences, infusion of KYMRIAH could induce antibodies against the CAR (collectively termed as anti-mCAR19 antibodies). Anti-mCAR19 antibodies may negatively impact the KYMRIAH efficacy and safety profile by impeding the KYMRIAH expansion after infusion.

In Study B2202, pre-infusion anti-mCAR19 antibodies were observed in 86% of patients treated with KYMRIAH. The pre-existing anti-mCAR19 antibodies did not impact the expansion and cellular kinetics of KYMRIAH. Post-infusion induced or boosted anti-mCAR19 antibodies were observed in 37% of patients treated with KYMRIAH. Despite the pre-existing or post-infusion induced anti-mCAR19 antibodies there was no apparent relationship between pre-existing or treatment-induced anti-mCAR19 antibodies on the cellular kinetics or impact on response or relapse.

8. ADVISORY COMMITTEE MEETING

A meeting of the Oncology Drugs Advisory Committee (ODAC) was held on July 12, 2017 in order to provide advice to FDA regarding product quality and safety, clinical safety, and overall risk-benefit assessment for KYMRIAH.

Summary of Discussion:

- The Committee agreed that the risk-mitigation measures in the B2202 study were reasonable. The Committee did not express concern about testing for replication competent retrovirus. However, the Committee considered insertional mutagenesis to be a potential risk.

- Discussion of the planned 15-year follow-up centered on the B2401 postmarketing observational trial. The committee agreed that 15-year follow-up would be sufficient.

- The Committee voted 10 (Yes) to 0 (No) to the question, "Considering the efficacy and safety results of Study B2202, is the benefit-risk profile of KYMRIAH favorable for treatment of pediatric and young adult patients (age 3-25 years) with relapsed (second or later relapse) or refractory (failed to achieve remission to initial induction or reinduction chemotherapy) B-cell precursor acute lymphoblastic leukemia (ALL)?"

9. OTHER RELEVANT REGULATORY ISSUES

Not applicable

10. LABELING

The proposed proprietary name, KYMRIAH, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on April 13, 2017, and was found to be acceptable. CBER communicated the acceptability of the proprietary name to the applicant on May 2, 2017.

The APLB found the prescribing information (PI) and container label to be acceptable from a promotional and comprehension perspective. The review committee negotiated revisions to the PI, including the INDICATIONS statement and a BOXED WARNING for Cytokine Release Syndrome and Neurotoxicity. All issues were acceptably resolved after exchange of information and discussions with the applicant. Issues identified with the proposed container labeling were resolved following discussion with the applicant.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The review team recommends regular approval (21 CFR 601.4) for KYMRIAH.

b) Risk/ Benefit Assessment

The risks of KYMRIAH center around its mechanism of action, which is activation of T cells and the destruction of CD19+ B cells, both tumor cells and normal B cells. Cytokine release syndrome, which occurred in 79% of the patients, can be life-threatening or fatal. Transient neurotoxicity occurred in 65% of the patients. Hypogammaglobulinemia persists for months and requires monitoring and intervention. Cytokine release syndrome, which occurred 79% of the patients, can be life-threatening or fatal. Transient neurotoxicity occurred in 65% of the patients. Hypogammaglobulinemia persists for months and requires monitoring and intervention.

Following review of the BLA clinical and safety data, and considering the available therapies for relapsed/refractory ALL, as well as the discussion at the ODAC meeting, the review team recommends issuing a regular approval (21 CFR 601.4 (a)) for KYMRIAH. While the safety risks, both known and theoretical are substantial, the achievement of an overall remission rate (ORR: complete remission plus complete remission with incomplete hematologic recovery) in 82.5% of the patients (52 of 63), which were MRD-negative, provides a favorable risk/benefit profile for this population of highly-resistant pediatric and young adult ALL. The durability of the response was also considered. With a median follow-up of 4.8 months, the duration of CR and CRi has not been reached (range: 1.2 to 14.1+ months). Despite limited follow-up, durability is documented. These findings support approval of KYMRIAH at the dose of 0.2-5 x 10^6/kg for patients less than or equal to 50 kg or 0.1-2.5 x 10^8 for patients over 50 kg as demonstrated in B2202.

c) Recommendation for Postmarketing Activities

The applicant submitted a postmarketing study, which is considered a postmarketing requirement. This observational study, B2401, focuses on short-term toxicity, documenting adverse events, and long-term follow-up for documentation and evaluation of secondary malignancies. Due to the potential for secondary malignancies related to replication-competent retrovirus or insertional mutagenesis, the applicant plans to make every effort to obtain tissue from second malignancies to assure that KYMRIAH did not cause the second malignancy. The plan is to enroll 1,000 patients over 5 years and follow each patient for 15 years.

Considering input from CBER Office of Biostatistics and Epidemiology and CDER Division of Risk Management, FDA determined that a Risk Evaluation and Mitigation Strategy (REMS) is indicated to ensure that the benefits of KYMRIAH outweigh the risks of Cytokine Release Syndrome (CRS) and neurotoxicity. Therefore, FDA sent the applicant a REMS notification letter on June 27, 2017. The recommended REMS includes Elements to Assure Safe Use (ETASU). The REMS ETASU focuses on mitigating the known risks of CRS and neurotoxicity, and includes site certification and restriction of use to certain health care settings.

CMC Postmarketing Commitment

The review team recommends a Postmarketing Commitment for KYMRIAH for the revalidation of the (b) (4) Mycoplasma Test Validation" for Vector (b) (4) Material performed by (b) (4) .

In amendment 57 submitted on August 28, 2017, Novartis commits to revalidate the (b) (4) mycoplasma test method for vector (b) (4) as specified in the validation protocol entitled "Validation of Mycoplasma (b) (4) assay in the presence of KYMRIAH (DOCUMENT No: VP300808.DRAFT00)" submitted on July 19, 2017 and submit a final validation report by June 30, 2018.