LATE-CYCLE MEETING MATERIALS

BLA 125646/0 **June 22, 2017**

Novartis Pharmaceuticals Corporation
Attention: Manisha Patel, PharmD
One Health Plaza, Bldg 315, Office 3450B
East Hanover, NJ 07936

Dear Dr. Patel:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for KYMRIAH, tisagenlecleucel.

Attached are our meeting materials, including our agenda, for the Late-Cycle Meeting (LCM) scheduled for June 29, 2017.

If you have any questions, please contact the Regulatory Project Manager, Erica Giordano, at (240) 402 - 8298.

/s/

/s/

Raj K. Puri, M.D., Ph.D.
Director
Division of Cellular and Gene Therapies
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Materials

Late-Cycle Meeting Materials

Meeting Date and Time:	June 29, 2017 – 10:30 AM to 12:00 PM ET
Meeting Location:	White Oak, building 71 room 1206 Food and Drug Administration Center for Biologics Evaluation and Research 10903 New Hampshire Ave. Silver Spring, MD 20993-0002
Application Number:	BL 125646/0
Product Name:	tisagenlecleucel
Indication:	For the treatment of pediatric and young adult patients with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (ALL)
Sponsor/Applicant Name:	Novartis Pharmaceuticals Corporation

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authorities, division directors, and application Chair. Therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that could be submitted to address any identified issues. We may also discuss whether the submission of such information would be expected to trigger an extension of the PDUFA goal date if the review committee should decide, upon receipt of the information, to review it during the current review cycle.

Please note: if you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC meeting is planned, we may not be prepared to discuss that information at this meeting.

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues to be discussed during the LCM

The following substantive review issues have been identified to date:

CMC issues

a. Discussion of additional process validation data package for tisagenlecleucel:

FDA issued a form FDA-483 dated 4/7/2017 as the result of the pre-license inspection at the Cell Manufacturing facility in Morris Plains, New Jersey USA. Observation #1 states that process validation for CTL019 manufacturing (b) (4)) for pALL was incomplete at the time of the inspection. On 5/9/2017, Novartis submitted the initial response and presented approaches and timeline to address this observation.

The initial response was satisfactory.

The additional validation package was emailed to FDA on June 7, 2017 and submitted through the FDA Gateway on June 16, 2017.

We are reviewing the data package and may have additional information requests.

b. Discussion of in-process and lot release specifications:

The CMC review team is reviewing the in-process and lot release specifications for commercial manufacturing of tisagenlecleucel. We may have additional information requests regarding further adjustment of the lot release specifications.

We would also like to discuss the related clinical plans for disposition of occasional out-of-specification lots of tisagenlecleucel in the commercial setting.

Regarding the justification of specifications for vector substance and vector product, an IR was sent to Novartis on June 16, 2017. Specific adjustments to the specifications were requested. Novartis has responded and agreed to adjust the specifications for vector lot release as recommended by the review team.

c. Discussion of the FMO control of the flow cytometry test for transduction efficiency for tisagenlecleucel:

An IR was sent to Novartis on June 16, 2017 regarding the fluorescence minus one (FMO) control recommended to be added to the test for detection of CAR-positive cells by flow cytometry. The FMO control is considered necessary for the flow cytometry assays detecting low frequency (b) (4) cell populations due to possible background signals that cannot be measured without the FMO negative control. Further discussion is needed on this issue.

d. Discussion of the MOI assay:

An IR was sent to Novartis regarding the MOI assay for vector product before it is used for transduction of patient autologous T cells. An amendment was submitted on 5/30/2017 (amendment 30, SN29). The review of the response is in progress. Additional information requests are possible.

Pharmacovigilance Issues

e. Postmarketing Requirement (PMR)

An IR was sent to Novartis regarding clarification of long-term follow-up (LTFU) for IND patients and the registry for those who receive the product commercially (IND protocol B2205B and the registry B2401). Both the IND LTFU and the registry need to follow patients and look specifically at lentivirus vector persistence and monitor for secondary malignancy. The registry will need to be a PMR. We will need more specific information on the follow-up for replication competent retrovirus (RCR) testing, potential vector integration, and persistence of tisagenlecleucel and how this testing will be done.

f. Postmarketing Commitment (PMC)

A revalidation of the mycoplasma test method for vector product performed by (b) (4) with (b) (4) will be performed as part of a PMC. Novartis will provide a PMC proposal with a timeline. Novartis estimated that it may require about 6 months to complete the study. This issue was discussed in the teleconference call on May 31, 2017.

For inspections: Inspections are completed. A final recommendation is pending at this time. However, if we learn of any issues from the outstanding facility inspections, the agenda will be modified accordingly.

Amendment: We acknowledge your amendments (#32, 33, and 34) submitted/received [6/16/2017, 6/16/2017, and 6/21/2017, respectively]. Reviews of these amendments are ongoing and the final decisions are pending.

3. Advisory Committee Meeting

Date of AC meeting**: July 12, 2017**

Date AC briefing package sent under separate cover by CBER's Advisory Committee Staff: June 20, 2017

Potential questions and discussion topics for AC Meeting are as follows:

Draft Discussion Point 1:

Control of product quality for tisagenlecleucel is demonstrated by the design of the CAR structure and viral vector, manufacturing controls, and product testing. Each lot (batch) of product is tested before release for administration to ensure it meets specifications for defined product quality attributes. During development, the applicant established product quality specifications to assess CAR expression and T cell activity, including transduction efficiency by flow cytometry, vector copy number per cell, and the IFN-γ

production upon stimulation of the final cell product with a CD19+ antigen presenting cell line.

Please discuss the following aspects of the control of product quality of tisagenlecleucel:

1. The design of the CAR construct and viral vector.
2. The assessment of CAR expression and T cell activity through
    a. The number of transduced T cells
    b. The number of vector copies per cell
    c. Antigen-specific T cell function (e.g., IFN-γ production and cytotoxicity upon stimulation)

Please comment on any other measurements, such as T cell subpopulations (cell surface marker characterization), that could provide greater assurance of product safety or efficacy.

Draft Discussion Point 2:

Potential safety concerns with tisagenlecleucel and other retrovirus-based gene therapy products include generation of replication-competent retrovirus (RCR) and insertional mutagenesis. Strategies to address these concerns include vector design and product testing.

1. Please discuss how vector design impacts the risk of RCR.
2. Please discuss how vector design impacts the risk that insertional mutagenesis might cause genotoxicity.
3. Please discuss the impact of product testing on mitigation of risk for RCR and insertional mutagenesis.

Background:

Study B2202 was a prospective study of tisagenlecleucel, an anti-CD19 CAR T cell product for patients with relapsed or refractory ALL.

Life-threatening Cytokine Release Syndrome (Grade 3 and 4 CRS) events were noted in subjects who received tisagenlecleucel. The applicant's treatment algorithm requires risk mitigation measures (for example, availability of tocilizumab prior to tisagenlecleucel infusion at the treatment site) and close monitoring to permit early intervention and extensive supportive care measures to manage any resultant multi-organ dysfunction and coagulopathy.

Tisagenlecleucel was also associated with transient but ≥ Grade 3 neurotoxicity (including encephalopathy, seizures). Other serious and severe adverse events included infectious complications and resulting deaths, prolonged cytopenias, hypogammaglobulinemia, and coagulopathies.

In Study B2202, training of physicians and health care providers were required. In addition pre-infusion requirements included specific safety measures in place. The benefit-risk assessment and conclusions of effectiveness from Study B2202 were made in the setting of stringent risk- mitigation strategies.

Draft Discussion Point 3:

If tisagenlecleucel is approved by the FDA, please discuss which, if any, of the following would be necessary to ensure safe use of tisagenlecleucel in patients.

a. A Warning in the Prescribing Information that describes the risk of CRS and other adverse events of special interest.

b. Detailed instructions in the Prescribing Information for management of CRS, neurotoxicity, and Adverse Events of Special Interest.

c. Information about the risks and management of CRS distributed to oncology healthcare providers (e.g., physicians, nurses, nurse practitioners, physician's assistants).

d. Product-specific training and certification for individual prescribers and healthcare facilities to educate on the management of the acute toxicities of cytokine release syndrome and neurotoxicity.

e. Restricted distribution to hospitals that have documented training for hospital-based healthcare providers (e.g., staff nurses).

f. Measures to assure that tocilizumab will be on site, and that have written procedures in place for management of patients who will receive tisagenlecleucel.

g. Real-time monitoring for, and detailed evaluation of, every case of Grade 4 CRS or any fatal events that occur within 30 days after tisagenlecleucel infusion, to facilitate revision of the risk mitigation strategy.

Please discuss each element above, along with any other measures that you recommend to assure safe use of tisagenlecleucel.

Draft Discussion Point 4:

LTFU discussion:

For the tisagenlecleucel IND studies, the FDA requires 15 years of follow-up to monitor for subsequent malignant transformation.

Please discuss the follow-up that you would recommend for patients who receive tisagenlecleucel post-marketing.

a. Please discuss the possible use of a patient registry to maintain contact with the patients for 15 years.

b. Please discuss the recommended follow-up for persistence of the transduced tisagenlecleucel cells. This should include a discussion of the frequency, duration, and type (e.g., passive or active, with blood samples stored for future evaluation if malignancy occurs) of follow-up.

Background:

Key efficacy results are shown below:

a. CR+CRi 52
   - Infused Population 52/63 (82.5%)

b. MRD-Negative CR/CRi Day 28;
   - 52 CR + CRi 52/52 (100%)

c. Duration of Response (DOR: Among the 52 responders, the median DOR was not yet reached, with the median follow-up of 4.8 months and a maximum follow-up of 14.1 months(Range: 1.2 – 14.1 months) . The estimated relapse-free rate among responders at Month 6 was 75.4% (95% CI: 57.2, 86.7).

However, tisagenlecleucel has also been associated with life-threatening adverse events including CRS and neurotoxicity.

Draft Discussion Point 5:

Based on the efficacy and safety results of Study B2202, please discuss whether the benefits justify the risks of tisagenlecleucel for treatment of pediatric and young adult patients (age 3-25) with relapsed (second or later relapse) or refractory (failed to achieve remission to initial induction or reinduction chemotherapy) B-cell acute lymphoblastic leukemia (ALL).

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:
http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm

4. Risk Management Actions (e.g., REMS)

RISK MANAGEMENT/REMS ACTIONS HAVE BEEN IDENTIFIED

The risk of cytokine release syndrome (CRS) and neurologic complications after treatment with tisagenlecleucel may necessitate a REMS with elements to assure safe use (ETASU). Specifically, the ETASU will focus on site certification, which will ensure the following: (1) training of sites and those who administer the product at those sites on the use of tocilizumab for the treatment of cytokine release syndrome and the management of neurotoxicity, (2) availability of the appropriate treatment for CRS, and (3) patient education on the risks of the product. The communication plan that was proposed by Novartis to be part of the REMS will be largely incorporated into the ETASU above.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/Chair)

   Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues – 20 minutes*:*

   Each issue will be introduced by FDA and followed by a discussion.
   a. Discussion of the PMR study for long-term follow-up
   b. Discussion of the preliminary REMS plan
   c. Discussion of additional process validation data package for tisagenlecleucel
   d. Discussion of in-process and lot release specifications
   e. Discussion of disposition plans for out-of-specification tisagenlecleucel lots in the commercial setting.
   f. Discussion of the FMO control of the flow cytometry test for transduction efficiency for tisagenlecleucel
   g. Discussion of the temporary storage site at (b) (4) for vector product
   h. Discussion of the MOI assay
3. Discussion of Minor Review Issues – 00 minutes
4. Additional Applicant Data – 00 minutes
5. Information Requests – 10 minutes

   a. Request for clarification of how RCL and persistence will be monitored for the commercial product (IR was sent on 6/21/2017)

   b. Discussion of the temporary storage site at (b) (4) for vector product (IR was sent on 6/22/2017)

6. Discussion of Upcoming Advisory Committee Meeting – 10 minutes

a. Discussion of the Sponsor's presentation versus the FDA to decrease overlap
b. Discussion of FDA's advisory committee briefing document: Redaction of proprietary CMC information

c. Brief discussion of presentations CMC and Clinical at the AC to avoid duplication

7. Risk Management Actions (e.g., REMS) – 10 minutes

a. discussion of a possible REMS (ETASU)

8. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

a. Please clarify how patients who received tisagenlecleucel will be followed for replication competent lentivirus and for the persistence of the tisagenlecleucel cells. The Phase 4 PMR study CCTL019B2401is observational. The Pharmacovigilance Plan (PVP) indicates that this follow-up will be done on CCTL019A2205B which is the investigational long-term follow-up for the IND subjects and will require that it be open through all local IRBs at treatment sites.

b. PMC for (b) (4) mycoplasma validation.

9. Major labeling issues – 00 minutes

a. Do not plan to discuss at this meeting

10. Review Plans – 00 minutes

a. Do not plan to discuss at this meeting

11. Applicant Questions –5 minutes

12. Wrap-up and Action Items – 10 minutes