Our Reference: BL125646/0

Date: June 7, 2017

Novartis Pharmaceuticals Corporation

ATTENTION: Manisha Patel, Pharm D
One Health Plaza, Bldg. 315, Office 3450B
East Hanover, NJ 07936

Dear Dr. Patel:

Attached is a copy of the summary for your May 18, 2017 Mid-Cycle Communication teleconference with CBER. This memorandum constitutes the official record of the Teleconference. If your understanding of the Teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to BL 125646 in your future submissions related to the subject product.

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

Sincerely,

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

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Mid-Cycle Communication Teleconference Summary

Application type and number: BL 125646/0
Product name: Tisagenlecleucel
Proposed Indication: For the treatment of pediatric and young adult patients with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (ALL)
Applicant: Novartis Pharmaceuticals Corporation
Meeting date & time: May 18, 2017, 3PM ET
Committee Chair: Xiaobin (Victor) Lu
RPM: Erica Giordano

FDA Attendees:
Deepa Arya, MD, MPH, MBA, Branch Chief, CBER/OBE/DE/AEB
Doris Auth, CDER/OSE/OMEPRM/DRISK
Kimberly Benton, PhD, Associate Director for Regulatory Management, OTAT
Ashley Burns, PharmD, CMC Reviewer, CBER/OCBQ/DMPQ/BII
Andrew Byrnes, PhD, Gene Transfer and Immunogenicity Branch Chief, CBER/OTAT/DCGT/GTIB
John Eltermann Jr, RPh, MS, CBER/OCBQ/DMPQ
Tom Finn, PhD, Microbiologist, CBER/OTAT/DCGT/CTB
Richard Forshee, PhD, CBER/OBE
Denise Gavin, PhD, Chief, CBER/OTAT/DCGT/GTB
Erica Giordano, Consumer Safety Officer, CBER/OTAT/DRPM/RPMB1
Xue (Mary) Lin, PhD, Biostatistics Reviewer, CBER/OBE/DB/TEB
Anthony Lorenzo, CBER/OCBQ/DMPQ/BII
Randa Melhem, PhD, CBER/OCBQ/DMPQ/BII
Steven Oh, PhD, Cell Therapies Branch Chief, CBER/OTAT/DCGT/CTB
Maura O'Leary, MD, Medical Officer, Team Leader, CBER/OTAT/DCEPT/CHB
Nikunj Patel, PharmD, Clinical Outcome Assessments Reviewer, CDER/OND
Scott Proestel, MD, Division Director, CBER/OBE/DE
Donna Przepiorka, MD, PhD, CDER/OND/OHOP/DHP
Raj Puri, MD, PhD, Director, CBER/OTAT/DCGT
Tejashri Purohit-Sheth, MD, Director, CBER/OTAT/DCEPT
Naomi Redd, CDER/OSE/OMEPRM/DRISK
Ramani Sista, PhD, Director, CBER/OTAT/DRPM
Dianne Spillman, Lead Regulatory Project Mgr, Oncology Program, CDER/OND/OHOP
Million Tegenge, RPh, PhD, Clinical Pharmacologist, CBER/OBE
Marc Theoret, MD, CDER/OND/OHOP
Joyce Weaver, PharmD, Senior Risk Management Analyst, CDER/OSE/OMEPRM/DRISK

Applicant Attendees:
Shanthi Ganeshan, PhD, VP, North America Regulatory Affairs Head, Oncology
Narin Ahmed Hussain, PharmD, Sr. Associate Director, Regulatory Affairs
Margit Jeschke, PhD, Head, Analytical Development
David Lebwohl, MD, Sr. VP, Executive Global Program Head
Yoko Momonoi, Sr. Fellow, Process Transfer

Arvind Natarajan, PhD, MBA, Head, Project Management Office, Cell & Gene Technical Development and Manufacturing
Manisha Patel, PharmD, Sr. Associate Director, Regulatory Affairs
Cynthia (Cindy) Riggins, PhD, Associate Director, Regulatory Affairs CMC
Kapil Sen, PhD, Biostatistics Program Lead
Tetiana (Tanya) Taran, MD, VP, Sr. Global Clinical Program Head
Ryan Tyburczy, Product Quality Leader
Keith Wonnacott, PhD, Director, Regulatory Affairs CMC
Patricia A. Wood, MD, PhD, Sr. Global Clinical Lead

Agenda:

To discuss the progress of the review.

Discussion Summary:

1. Any significant issues/major deficiencies identified by the review committee to date

    a. OTAT CMC

        i. Manufacturing process validation:

        During the pre-license inspection (PLI) at the Novartis Morris Plains Manufacturing Facility for CTL019, the FDA identified deficiencies in the process validation studies. Specifically, the process performance qualification (PPQ) study was conducted according to the clinical manufacturing process rather than the intended commercial process, and, clinical batch production records were used rather than commercial batch production records. In addition, some methods used in the PPQ study were not the same as those specified in the commercial batch record. Some critical process parameters (CPP) and key process parameters (KPP) were too broad to ensure meaningful process controls. The PPQ study also did not include leukapheresis materials that contain high levels of monocytes, which is one of the intended starting materials. Finally, some hold steps were not defined in the Master Batch Production Record.

        As the result, the FDA issued a 483 letter to capture these issues. Novartis has responded to the 483 letter and proposed to submit additional validation data and revised commercial batch records by June 7, 2017 to address the 483 issues.

        ii. Lot release specifications

Although Novartis has made an attempt to tighten the lot release specifications for the commercial CTL019 drug product compared to clinical production, some lot release specifications may need to be further evaluated.

Analysis of batch records and lot release data will impact the review of the proposed specifications. Progressive implementation of process control parameters during process development appear to have resulted in a more consistent product being produced later in the manufacturing timeline. Therefore, more recent historical manufacturing data may have more weight in defining the lot release specifications.

The suitability of the final lot release specifications will be determined during the ongoing review of the BLA, and in conjunction with the pending additional validation data from the PPQ study to be submitted by June 7, 2017.

In addition, lot release testing specifications for CTL019 (murine) HIV-1 vector substance and vector product are being reviewed and may be tightened if necessary.

iii. Process control

As a result of the additional PPQ runs and revision of the commercial Master Batch Production Records, the final version of the manufacturing process control description in the BLA needs to be revised to reflect these changes. In addition, data collected from healthy donors during process qualification studies should be submitted to the BLA and reflected in the CPP and KPP analyses and acceptance criteria.

iv. Analytical procedures

The outstanding information requests address the following analytical procedure issues:

1. Inadequate control and validation of the multiplicity of infection (MOI) determination assay for the vector, which could impact dosing.

2. Comparability of WBC phenotyping by flow cytometry used during the clinical trial and proposed for commercial use, which could impact dosing.

3. Revalidation of Mycoplasma test for Vector (b) (4) performed by (b) (4) FDA asked Novartis to repeat Limit of detection and Specificity tests

b. OTAT Clinical – The focus of the clinical review is on the safety profile of the process that is required to receive CTL019. Our main concern is the management of risk for the patients and this is under review.

Discussion Summary: This item was not discussed during the meeting.

2. Information regarding major safety concerns.

The management of cytokine release syndrome and other adverse events of special interest (profound hypogammaglobulinemia, opportunistic infections, monitoring for late effects as a result of therapy with a genetically modified cell therapy, cardiac, and renal toxicity) are major safety concerns.

Discussion Summary: The FDA agreed it is acceptable for the applicant to begin with the preliminary training program.

3. Preliminary review committee thinking regarding risk management

Risk management strategies are under discussion as part of the review process. There are ongoing discussions regarding REMS.

Discussion Summary: The FDA explained the information regarding risk management that was originally submitted is not robust enough. Internal discussion is on-going and the FDA will provide feedback as soon as possible. FDA confirmed the expectation that Novartis will send (b) (4) a Letter of Authorization to cross-reference the BLA data regarding management of CRS with tocilizumab. FDA recommended that Novartis contact CDER directly regarding any other questions about how the Novartis data would be used.

4. Any information requests sent and not received

a. The CMC information request regarding the MOI assay and the CTL019 phenotyping assay was sent on May 4, 2017, and a response is expected by noon on May 17, 2017. We are expecting additional validation data for the MOI assay by June 7, 2017.

b. An information request regarding the endotoxin test release specification for the CTL019 final product was sent on May 10, 2017 and a response is expected by noon on May 24, 2017.

c. A DBSQC information request to submit the results of repeat LOD and Specificity tests and comparability study was sent on May 16, 2017 and a response is expected by June 23, 2017.

d. A clinical information request regarding the role of therapy for Cytokine Release Syndrome over time was sent on May 16, 2017 and a response is expected by May 23, 2017.

Discussion Summary: This item was not discussed during the meeting.

5. Any new information requests to be communicated

   There are no new information requests to send at this time.

   Discussion Summary: This item was not discussed during the meeting.

6. Proposed date(s) for the Late-Cycle Meeting and the Late-Cycle Meeting Materials

   The LCM between you and the review committee is currently scheduled for June 29, 2017 from 10:30 am to 12 pm ET.

   We intend to send the LCM meeting materials to you approximately 5 business days in advance of the LCM.

   If these timelines change we will communicate updates to you during the course of the review.

   Discussion Summary: This item was not discussed during the meeting.

7. Updates regarding plans for the AC meeting

   For both the morning (CMC) and afternoon (Clinical) sessions, both the FDA and Novartis will present. The FDA's briefing document (CMC and Clinical) and their presentation slides will be sent to Novartis for review. FDA and Novartis will work to minimize overlapping content before the AC Meeting.

   (Clinical perspective) The afternoon session of the Advisory Committee will have a clinical focus. The clinical focus for the FDA will be on the safety profile of the product. In particular, the management of risk will be a focus of the discussion. This includes the risks to a patient awaiting manufacture of the product, the risks of bridging chemotherapy and/or lymphodepletion, and the risk of unique reactions such as immediate cytokine release syndrome, profound and prolonged B cell aplasia, and exposure to a genetically modified cell therapy.

   Discussion Summary:

   - The current agenda allows for a 45-minute presentation each from the FDA and the applicant on CMC in the morning and a 45-minute presentation each from the FDA and the applicant on clinical in the afternoon. The Advisory Committee team subsequently agreed to modify

the agenda to allow a 30-35 minute CMC presentation by the applicant in the morning and a one hour clinical presentation by the applicant in the afternoon.

- The FDA team agreed to discuss the slide deck with the applicant once the briefing document has been sent.

- The FDA explained the label should include information regarding the risk during the manufacturing period while the patient is waiting for the infusion.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.

   Advisory Committee Meeting: July 12, 2017
   Post Advisory Committee Meeting: July 26, 2017, 1pm – 2pm ET (will be cancelled if not needed)
   Labeling Target Date: September 1, 2017
   PMC Target Date: September 1, 2017

   Discussion Summary: If these timelines change the FDA will communicate updates to the applicant during the course of the review.