BLA 125646/0 July 13, 2017

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

Dear Dr. Patel:

Attached is a copy of the memorandum summarizing your June 29, 2017 Late-Cycle 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 in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in 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

Late-Cycle Meeting Summary

Meeting Date and Time:	June 29, 2017 – 10:30 AM to 12:00 PM ET
Meeting Location:	Teleconference
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
Meeting Chair:	Xiaobin (Victor) Lu, PhD
Meeting Recorder:	Erica Giordano

FDA ATTENDEES

Jaspal Ahluwalia, MD, Medical Epidemiologist, CBER/OBE/DE/AEB
Rachel Anatol, PhD, Deputy Director, OTAT
Kimberly Benton, PhD, Associate Director for Regulatory Management, OTAT
Wilson W. Bryan, MD, Director, OTAT
Ashley Burns, PharmD, CMC Reviewer, CBER/OCBQ/DMPQ/BII
Andrew Byrnes, PhD, Gene Transfer and Immunogenicity Branch Chief, CBER/OTAT/DCGT/GTIB
Dennis Cato, Consumer Safety Officer, CBER/OCBQ/DIS/BMB
Heba Degheidy, MD, PhD, Visiting Associate, CBER/OTAT/DCGT/CTTB
John Eltermann Jr, RPh, MS, Director, CBER/OCBQ/DMPQ
Elizabeth Everhart, MSN, RN, ACNP, Senior Drug Risk Analyst, CDER/OSE/OMEPRM/DRISK
Denise Gavin, PhD, Chief, CBER/OTAT/DCGT/GTB
Bindu George, MD, Branch Chief, CBER/OTAT/DCEPT/CHB
Erica Giordano, Consumer Safety Officer, CBER/OTAT/DRPM/RPMB1
Elena Gubina, PhD, Biologist, CBER/OTAT/DCGT/CTB
Ilan Irony, MD, Deputy Director, CBER/OTAT/DCEPT
Joan Johnson, MS, CMC Facility Reviewer, CBER/OCBQ/DMPQ/BI
Simleen Kaur, MSc, Team Lead, CBER/OCBQ/DBSQC/LMIVTS
James Kenney, DSc, Branch Chief, CBER/OCBQ/DBSQC/LMIVTS
Shiowjen Lee, PhD, Team Leader, CBER/OBE/DB/TEB
Xue (Mary) Lin, PhD, Biostatistics Reviewer, CBER/OBE/DB/TEB
Xiaobin (Victor) Lu, PhD, Microbiologist, CBER/OTAT/DCGT/GTB
Carrie Mampilly, MPH, Director, CBER/OCBQ/DIS/PSB
Amy McKee, MD, Supervisory Associate Director, CDER/OND/OHOP
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
Richard Pazdur, MD, Director, Oncology Center of Excellence, FDA
Scott Proestel, MD, Division Director, CBER/OBE/DE

Raj Puri, MD, PhD, Director, CBER/OTAT/DCGT
Tejashri Purohit-Sheth, MD, Director, CBER/OTAT/DCEPT
Donna Przepiorka, MD, PhD, Medical Officer, Team Lead, CDER/OHOP/DHP
Carolyn Renshaw, Branch Chief, CBER/OCBQ/DMPQ/BI
Becky Robinson-Zeigler, PhD, Branch Chief, CBER/OTAT/DCEPT/PTB2
Kimberley Schultz, PhD, Biologist, CBER/OTAT/DCGT/GTB
Ramani Sista, PhD, Director, CBER/OTAT/DRPM
Dianne Spillman, Lead Regulatory Project Mgr, Oncology Program, CDER/OND/OHOP
Marc Theoret, MD, CDER/OND/OHOP
Ramjay Vatsan, PhD, Team Leader, Biologics, CBER/OTAT/DCGT/GTB
Debra Vause, Regulatory Project Manager, CBER/OCBQ/DMPQ/ARB
Yvette Waples, PharmD, Supervisory Team Leader, CDER/OEP/DACCM
Hong Yang, Ph.D. Biologist, CBER/OBE/ABRA

APPLICANT ATTENDEES
Narin Ahmed Hussain (Sr. Associate Director, Regulatory)
Mariana Cota (Global Clinical Lead)
Lamis Eldjerou (US Medical Director)
Miriam Fuchs (Global Program Regulatory Director)
Shanthi Ganeshan (North American Regulatory Affairs Head, Oncology)
Jason Hamilton (Senior Fellow, Analytical Stewardship)
Kristen Harrington-Smith (US Commercial Head, CAR-T)
Albin Karimattam (US Head, Safety Risk Management, REMS)
David Lebwohl (Executive Global Program Head)
(b) (4)
Karen T Mueller (Clinical Pharmacology Fellow)
Arvind Natarajan (Head, Technical Project Management)
Manisha Patel (Sr. Associate Director, Regulatory)
Kirsten Powel (Product Quality Leader)
Clement Purcell (Principal Fellow, CMC)
Cynthia Riggins (Associate Director, Regulatory CMC)
Erik Rutjens (Global Head, QC Bioanalytics)
Kapildeb Sen (Biostatistics Program Lead)
Tetiana Taran (Sr. Global Clinical Program Head)
Keith Wonnacott (Director, Regulatory CMC)
Patricia Wood (Sr. Global Clinical Lead)

BACKGROUND

BLA 125646/0 was submitted on February 2, 2017 for tisagenlecleucel.

Proposed indication(s): For the treatment of pediatric and young adult patients with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (ALL)

PDUFA goal date: October 3, 2017

In preparation for this meeting, FDA issued the Late-cycle Meeting Materials on June 22, 2017 and issued Advisory Committee Briefing Materials on June 20, 2017.

DISCUSSION

1. 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

      Additional Discussion: The applicant provided clarification that study B2401 is a non-interventional registry study and the A2205B LTFU study is on-going and expected to stay open after potential approval for all patients who received treatment only in IND studies.

      FDA understands and agrees the chances of RCL are low. The FDA informed the applicant that this will be a discussion point for the AC meeting.

      With respect to product persistence monitoring, the FDA acknowledged the applicant's proposal to use B cell level as a surrogate measure for tisagenlecleucel persistence appears reasonable. B cell count data will be monitored when the treated patients come in for regular checkup which are described in the clinical registry protocol. Insertion of persistent product monitoring will be discussed at the AC meeting.

      The FDA suggested the applicant update the pharmacovigilance plan in the BLA because the most recent version is dated January 2017.

   b. Discussion of the preliminary REMS plan

      Additional Discussion: The applicant plans to provide the requested information by July 7, 2017

      The FDA clarified the ETASU should reference testing at 6 months and yearly thereafter.

      REMS materials should be provided to the FDA review team before feedback can be provided.

      The FDA requested the applicant propose a plan for expanding beyond the 30-35 sites. Also include plans for expanding manufacturing as site locations are increased.

   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

Additional Discussion: Various controls have been incorporated that are appropriate for flow cytometry. Novartis requested clarification on why the FMO control is needed for accessing CAR expression. The FDA clarified the FMO control is needed for lot release testing CAR transduction efficiency only and should not impact ability to meet dosing.

With regard to mycoplasma validation the FDA acknowledge the applicant's plan to provide the RFI protocol, details on execution and the final report by mid-July is acceptable.

g. Discussion of the temporary storage site at (b) (4) for vector product
h. Discussion of the MOI assay

2. Discussion of Minor Review Issues – 00 minutes

3. Additional Applicant Data – 00 minutes

4. Information Requests – 10 minutes

a. Request for clarification of how RCR 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)

5. 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

Additional Discussion: The applicant received notice that the redactions Novartis have proposed are acceptable. The FDA acknowledged an update should have been made to table 10. The FDA will make a note of it when it is discussed at the AC meeting.

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

Additional Discussion: The FDA CMC team will modify the presentation during the AC meeting based on the applicant's presentation to avoid duplication. The FDA CMC team requested to use a figure of the overall

manufacturing process and data for variability of leukapheresis materials. The applicant agreed this is acceptable.

The FDA clinical team will focus on the benefit-risk profile and setup the presentation in the context of safety.

Post Meeting Comment: The FDA does not plan to provide a draft agenda before the AC meeting but the agenda will be made public on July 7, 2017. FDA may not be able to share the slide presentations prior to the AC meeting.

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

7. Postmarketing Requirements/Postmarketing Commitments

8. Major Labeling Issues

   Additional Discussion: The FDA plans to provide labeling comments earlier than the previously discussed September 1, 2017 date.

9. Review Plans

   Additional Discussion: The FDA explained the focus is on a regular approval instead of an accelerated approval.

10. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.