Late cycle internal meeting 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: June 13, 2017
Committee Chair: Xiaobin (Victor) Lu, PhD
RPM: Erica Giordano

Attendees:

Discipline/Organization	Name
Regulatory Project Manager (RPM)	Erica Giordano
Chair	Xiaobin (Victor) Lu, PhD
DCGT Division Director DCGT Deputy Director DCEPT Division Director DCEPT Deputy Director	Raj Puri, MD, PhD Steven Oh, PhD Tejashri Purohit-Sheth, MD Ilan Irony, MD
Office Director Office Deputy Director Associate Director for Regulatory Management	Wilson Bryan, MD Rachael Anatol, PhD Kim Benton, PhD
Clinical Reviewer	Maura O'Leary, MD
Clinical Reviewer	Donna Przepiorka, MD, PhD
Toxicology Reviewer	Ying Huang, PhD
CMC Reviewer	Xiaobin (Victor) Lu, PhD
CMC Reviewer	Kimberly Schultz, PhD
CMC Reviewer	Elena Gubina, PhD
CMC Reviewer	Tom Finn, PhD
CMC Reviewer	Andrew Byrnes, PhD
OCBQ/DMPQ Reviewer	Joan Johnson, MS
OCBQ/DMPQ Reviewer	Randa Melhem, PhD
OCBQ/APLB Reviewer	Dana Jones
OCBQ/BIMO Reviewer	Dennis Cato
OCBQ/DBSQC	Marie Anderson, MS, PhD
OCBQ/DMPQ/Lead Inspector	Joan Johnson, MS
OCBQ/DMPQ/Lead Inspector	Randa Melhem, PhD
CMC Inspector	Xiaobin (Victor) Lu, PhD
CMC Inspector	Kimberly Schultz, PhD
CMC Inspector	Denise Gavin, PhD
Statistical Reviewer of clinical data	Xue (Mary) Lin, PhD
Postmarketing Safety Epidemiological/Pharmacologovigilance Reviewer	Jaspal Ahluwalia,MD
Other Attendee(s)	Anthony Lorenzo
Branch Chief, CBER/OTAT/DCEPT/CHB	Bindu George, MD

Medical Officer, CBER/OTAT/DCEPT/CHB	Robert Le, MD, PhD
Branch Chief, CBER/OTAT/DCEPT/PTB2	Becky Robinson-Zeigler, PhD
Regulatory project manager	Nannette Cagungun
Branch Chief, CBER/OBE/DE/AEB	Deepa Arya, MD, MPH, MBA
CBER/OCBQ/DMPQ	Laurie Norwood, MS
Director, CBER/OTAT/DRPM	Ramani Sista, PhD
Branch Chief, CBER/OCBQ/DMPQ/BI	Carolyn Renshaw
Pharmacologist, CDER/OTS/OCP/DPM	Justin Earp
Associate Director, OCE	Gregory Reaman, MD
Supervisory Mathematical Statistician, CBER/OBE/DB/TEB	Boguang Zhen
Medical Officer, CBER/OTAT/DCEPT/CHB	Megha Kaushal, MD
Clinical Pharmacologist, CBER/OBE	Million Tegenge, RPh, PhD
Division Director, CBER/OBE/DE	Scott Proestel, MD
Associate Director for Research, CBER/OBE	Richard Forshee
Acting Team Lead, CBER/OCBQ/DMPQ/BII	Ellen Huang
Branch Chief, CBER/OTAT/DCEPT/OB	Ke Liu MD, PhD
Associate Director, CBER/OTAT/DCEPT	Larissa Lapteva, MD, MHS, MBA
General Health Scientist, CDER/OSE/OMEPRM/DRISK	Naomi Redd
Science Policy Analyst, CDER/OND	Nikunj Patel, PharmD
Lead Pharmacologist, CDER/OTS/OCP/DCPV	Stacy Shord
Consumer Safety Officer, CBER/OCBQ/DIS/BMB	Christine Drabick
Chief Medical Officer, CBER/OBE/DE	Craig Zinderman

Late–cycle internal meeting agenda:

1. Short summary of the submission **[Chair]**

   Since the original BLA submission on February 2, 2017, Novartis has submitted 35 amendments in response to information requests from all review disciplines in the review process to address potential regulatory issues. These amendments have been either reviewed or are in the process of reviewing. Based on the review of the amendments, additional information may be requested.

2. Substantive issues raised during review **[Reviewer].**

   a. CMC – Xiaobin Victor Lu, Andrew Byrnes, Kimberly Shultz, Elena Gubina, and Thomas Finn

      i. Analytical procedures

         1. The baseline control "fluorescent minus one (FMO)" should be included for each lot to accurately assess transduction efficiency that is used for dose determination. Currently Novartis does not have this control in transduction efficiency assay. It is especially important to include this control in order to accurately measure the transduction efficiency of CTL019 at low levels (b) (4) of transduction.

2. Analysis of batch records will impact the review of the proposed specifications. Implementation of control parameters during manufacture may have resulted in a more consistent product being produced later in the manufacturing timeline.

ii. Manufacturing process validation for tisagenlecleucel

Based on the ongoing CMC review and results of the PLI at the Morris Plains NJ manufacturing facility, the following major CMC issues need to be resolved for approval of the BLA.

1. The conformance lots used for process validation studies were performed before the validation protocol was formally approved by the Novartis quality unit and before the commercial process was established. This is not a prospectively designed validation study and inconsistent with what FDA recommended during the pre-BLA meeting discussion.

2. Clinical batch records rather than commercial batch records were used for these conformance lots. FDA notes that there were differences between the clinical batch record used at the time of the PV and the proposed commercial batch records. In particular, the (b) (4) version was used for clinical batch records. The commercial manufacturing process should use (b) (4) There were significant test method changes as well. In particular, the methods for flow cytometry analysis, cell counting/viability, mycoplasma were modified. There were also significant format changes and the inclusion of a work procedure to provide detailed instructions. These instructions were previously in the clinical batch record. This change requires significant training of staff. The totality of the changes introduced from the clinical to the commercial process is considered significant and therefore the validation runs with the clinical process was not adequate to support the commercial process at this time.

3. Novartis did not run any batches with leukapheresis materials that contained high levels of monocytes as advised by the FDA during the pre-BLA discussion.

4. FDA questioned the acceptance criteria for CPPs and KPPs used in the PPQ studies. Some of the CPP and KPP ranges are quite wide, and were based on data not submitted in the BLA. These ranges would not help define a validated and controlled commercial manufacturing process. During the discussion with Novartis during the inspection, the FDA has recommended that the acceptable ranges for CPPs and KPPs should be revised to reflect the accumulative manufacturing data and experience. FDA indicated that a simple 3 times of standard deviation may not be a suitable approach given the wide ranges of the available data.

5. Some unit operation holding time was not defined (e.g. (b) (4)

6. 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 by June 7, 2017 to address the 483 issues. Novartis indicated that new batches for validation PPQ runs have been identified and the new commercial batch records will be submitted by June 7, 2017. The CMC review team will review the new validation data as they become available.

7. Additional validation results have been submitted. Review is pending.

iii. Manufacturing process control for vector

Based on the PLI at the (b) (4) vector substance and vector product manufacturing facilities, the following major CMC issues need to be resolved for approval of the BLA.

1. Temporary vector product storage site at (b) (4) The detailed procedures for vector storage, packaging and shipping will be reviewed. IR was orally communicated to (b) (4) as a discussion point of the PLI. A formal IR will be sent as soon as possible.

2. 483 items were issued for (b) (4) : CMC items: **1**. Vector product storage is not adequately controlled to prevent mix-ups. Specifically, rejected CTL019 vector product is not clearly identified, and is commingled with other vector products. **2**. Processing and hold time ranges for unit operations are incompletely defined in the Batch Master Record (e.g. (b) (4) The initial response to 483 was received 6/2/17. We will review the full response when submitted.

3. 483 items were issued for (b) (4) CMC item: Processing and hold time ranges for unit operations are incompletely defined in the Batch Master Record (examples include, but not limited to, no upper limit of thawing time for DNA plasmid at (b) (4) The initial response to 483 was received 6/8/17. We will review the full response when submitted.

4. The baseline control "fluorescent minus one (FMO)" should be included for each lot to accurately assess transduction efficiency that is used for dose determination. Currently Novartis does not have this control in transduction efficiency assay. It is especially important to include this control in order to accurately measure the transduction efficiency of CTL019 at low levels (b) (4) of transduction.

iv. Process controls

CTL019

As the result of process validation discussion mentioned above, the final version of the manufacturing process control description in the BLA needs to be revised to reflect the changes for better controls.

Vector substance and vector product

Additional unit operation limit ranges for vector substance and vector product are being implemented as the results of PLI at (b) (4)

v. Lot release specification

Although Novartis has tightened the lot release specifications for CTL019 from clinical to commercial production, some lot release specifications may be still need to be further evaluated. This will be addressed during the ongoing review of the BLA and in conjunction with the validation study report to be submitted by June 7, 2017. Our internal lot release data analysis will also be a part of the review for lot release specification justifications.

Lot release testing specifications for CTL019 (murine) HIV-1 vector substance and vector product have been tightened as agreed between Novartis and FDA.

vi. Chain-of-Identity system

Novartis has provided a general description of chain-of-identity system which controls an array of important activities from scheduling patients, maintain traceability, issue labels, barcodes among other things. Novartis also provided a high level validation study report to support the chain-of-identity system. This validation report contains high level conclusions and references to other supporting studies and documents as well as a list of deviations encountered during the system validation.

During the Novartis PLI at the Morris Plains Facility, FDA asked for additional supporting evidence for the validation of the COI system. Novartis provided second tier documents to support the initial high level validation study report. These reports need to be reviewed thoroughly before a determination can be made as to if the system is indeed validated. A consult review for computer software used in the COI system may be requested after the OTAT review.

b. Clinical – Maura O'Leary

i. Risk Mitigation, specifically working with OBE as they work with the sponsor to design a REMS with ETASU

ii. Current assessment of risk management issues (e.g., REMS)

iii. PMR: clarification of follow-up for subjects on Study B2202 as well as those who will receive the commercial product. [CCTL019A2205B

(IND16130 or pre-marketing exposure) CCTL019B2401 (PMR)]. The current plan is for a registry without active component.

c. OBE/DE – Jaspal Ahluwalia
Three major safety concerns:

i. Cytokine release syndrome (CRS) in the acute phase after treatment

ii. Neurological sequelae in the acute phase after treatment

iii. Long-term secondary malignancy risk

d. Consult:

i. DRISK
1. Requestor: OBE/DE – Jaspal Ahluwalia
2. Reviewer: Naomi Redd, Doris Auth
3. Update: Internal consult review is ongoing

ii. COA
1. Requestor: Clinical – Maura O'Leary
2. Reviewer: Nikunj Patel, Selena Daniels
3. Update: The review of the patient reported outcome studies is incomplete. It is a preliminary view of the population and the information is not sufficient for label purposes.

iii. Pharmacometrics
1. Requestor: Clinical – Maura O'Leary
2. CDER/OTS/OCP Reviewer: Chao Liu, Justin Earp, Stacy Shord
CBER/OBE Reviewer: Hong Yang, Million Tegange, Richard Forshee
3. Update: A preliminary report to layout the analysis for safety and efficacy endpoints has been submitted and analysis is ongoing

3. Review of upcoming timeline/deadlines **[Chair]**

Internal Late-Cycle Meeting	Jun 13, 2017
Send Late Cycle Meeting Materials to Applicant [RPM]	Jun 22, 2017
External Late-Cycle Meeting	Jun 29, 2017
Send applicant proposed labeling [RPM]	**Jul 7, 2017**
Send proposed PMR and clinical PMC language and supportive documentation to SWG Exec Sec. [RPM]	Jul 10, 2017
Advisory Committee Meeting	Jul 12, 2017
Safety Working Group meeting to discuss the PMR	Jul 13, 2017
Draft and Circulate the SBRA to the review team [Chair]	Jul 17, 2017
Circulate draft press release [Chair]	Jul 17, 2017
Send applicant proposed PMR [RPM]	**Jul 17, 2017**
Place holder for Post Advisory Committee Internal	Jul 19, 2017

Meeting	
Send Press Release to OCOD [Chair]	Jul 20, 2017
Place holder for Post Advisory Committee Sponsor Meeting	Jul 26, 2017
Complete inspection reports [Review Committee]	Jul 31, 2017
Prepare eAP [RPM]	Jul 31, 2017
Draft and circulate approval letter for office review [RPM]	Jul 31, 2017
Obtain point of contact for action package posting [RPM]	Jul 31, 2017
Email the Officer/Employee list to all review committee members [RPM]	Jul 31, 2017
SBRA to Branch Chiefs [RPM]	Aug 7, 2017
Send Primary Discipline Reviews for supervisory review and concurrence [Review Committee]	Aug 7, 2017
Final labeling negotiations	Aug 15, 2017
SBRA to Division Director [RPM]	Aug 15, 2017
Supervisory Concurred Discipline Reviews in eMRP/EDR [Review Committee]	Aug 15, 2017
Finalize eAP [RPM]	Aug 21, 2017
SBRA to OTAT Office Director and IOD [RPM]	Aug 23, 2017
Send FDA Action Letter [RPM]	Aug 31, 2017
Post-Action Debrief Meeting	Sep 25, 2017

4. Assess status of the review including plans for completing outstanding discipline reviews and any remaining outstanding issues **[Chair]**

   Outstanding review issues are listed in section 2 above and are being reviewed. The discipline reviewers are expected to complete their draft discipline review memos for supervisory review and concurrence by August 7, 2017.

5. Reach agreement on Late-Cycle meeting materials that will be sent to the applicant. **[Chair, Review Committee Members]**

   The Late-Cycle meeting materials are due to the sponsor by June 22, 2017.

6. Come to agreement on the issues to be included on the agenda for the LCM with the applicant. The timeframes for each agenda item should also be agreed to. **[Chair, Review Committee Members, Management]**

7. **Concurrence:** RPM, Chair, Division Director of the product office

Late-Cycle Meeting Agenda to applicant

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