Mid-Cycle Meeting Agenda/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 8, 2017, 12pm to 2pm
Committee Chair: Xiaobin (Victor) Lu, PhD
RPM: Erica Giordano

Attendees:

Discipline	Name [with credentials (not title)]	Attended meeting?
Regulatory Project Manager (RPM)	Erica Giordano	Y
Chair	Xiaobin (Victor) Lu, PhD	Y
Clinical Reviewer	Maura O'Leary, MD	Y
Clinical Reviewer	Donna Przepiorka, MD, PhD	Y
CMC Reviewer	Xiaobin (Victor) Lu, PhD	Y
CMC Reviewer	Andrew Byrnes, PhD	Y
CMC Reviewer	Kimberly Schultz, PhD	N
CMC Reviewer	Elena Gubina, PhD	Y
CMC Reviewer	Tom Finn, PhD	Y
Animal Pharmacology Reviewer	N/A	N/A
Clinical Pharmacology Reviewer	N/A	N/A
Toxicology Reviewer	Ying Huang, PhD	Y
Developmental Toxicology Reviewer	N/A	N/A
OCBQ/DMPQ RPM	Debra Vause, RN	Y
OCBQ/DMPQ Reviewer	Joan Johnson, MS	Y
OCBQ/DMPQ Reviewer	Randa Melhem, PhD	Y
OCBQ/DMPQ/PRB Reviewer	Cheryl Hulme	N
Statistical Reviewer of clinical data	Xue (Mary) Lin, PhD	Y
Statistical Reviewer of non-clinical data	N/A	N/A
Postmarketing Safety Epidemiological Reviewer	Jaspal Ahluwalia,MD	Y
OCBQ/APLB Reviewer	Loan Nguyen, PharmD	Y
OCBQ/BIMO Reviewer	Dennis Cato	Y
OCBQ/DBSQC Reviewer	Marie Anderson, MS, PhD	Y
OCBQ/DBSQC Reviewer	Noel Baichoo	N
OCBQ/DBSQC Reviewer	Simleen Kaur	Y
Consult Reviewer(s): CDER/COA	Nikunj Patel	N
CDER/COA	Selena Daniels	N
CDER/OTS/OCP/DCPV	Chao Liu	Y

Discipline	Name [with credentials (not title)]	Attended meeting?
CDER/OTS/OCP/DCPV	Justin Earp	N
CDER/OTS/OCP/DCPV	Stacy Shord	Y
CDER/OSE	Naomi Redd	Y
CDER/OSE	Doris Auth	Y
CBER/OBE	Hong Yang	Y
CBER/OBE	Million Tegange	N
CBER/OBE	Richard Forshee	Y
OCBQ/DMPQ/Lead Inspector	Joan Johnson, MS	Y
OCBQ/DMPQ/Lead Inspector	Randa Melhem, PhD	Y
CMC Inspector	Xiaobin (Victor) Lu, PhD	Y
CMC Inspector	Denise Gavin, PhD	Y
CMC Inspector	Richard Coats	Y
CMC Inspector	Ashley Burns, PharmD	Y
CMC Inspector	Kimberly Schultz, PhD	N
Labeling Reviewer	N/A	N/A
Other Attendee(s)	Rick Pazdur, MD	Y
	Marc Theoret, MD	Y
	Gregory Reaman	Y
	Ke Liu, MD, PhD	Y
	Carolyn Renshaw	Y
	Ann Farrell, MD	Y
	Adnan Jaigirdar, MD	Y
	Wilson Bryan, MD	Y
	Steven Oh, PhD	Y
	Bindu George, MD	Y
	Ramjay Vatsan, PhD	Y
	Najat Bouchkouj, MD	Y
	Shiowjen Lee, PhD	Y
	Qiao Bobo	Y
	Raj Puri, MD, PhD	Y
	Nannette Cagungun	Y
	Carrie Mampilly	Y
	Dianne Spillman	Y
	Angelo De Claro	Y
	Elizabeth Everhart	Y
	Kimberly Benton, PhD	Y
	Laurie Norwood	Y
	Kate Oswell	Y
	Amy McKee	Y
	Elleni Alebachew	Y
	Ingrid Chapman	Y
	Katie Rivers	Y

Discipline	Name [with credentials (not title)]	Attended meeting?
	Elizabeth Valenti	Y

Discussion Summary:

The review team should access and review eMRP on a daily basis to initiate and resolve any applicable tasks.

Report and Discuss:

1. Reviewer Reports
    a. Xiaobin Victor Lu, Andrew Byrnes, Kimberly Shultz, Elena Gubina, and Thomas Finn – CMC
        i. Substantive issues identified
            1. Analytical procedures
                a. The outstanding IR addresses inadequate control and validation of the MOI determination assay for the vector and the comparability of WBC phenotyping by flow cytometry used during the clinical trial and proposed for commercial use. Both impact patient dosing.
                b. 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.
                c. Revalidation of Mycoplasma test for Vector (b) (4) performed by (b) (4) was requested. FDA asked Novartis to repeat Limit of detection and Specificity tests
            2. 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.
                a. The product lots used for the process validation studies were manufactured before the validation protocol was formally approved by the Novartis quality unit and before the commercial process was established. This was not a prospectively designed validation study and is inconsistent with what FDA recommended during the pre-BLA meeting discussion.
                b. Clinical batch records rather than commercial batch records were used for manufacture of lots used in the process validation study. FDA notes that there were multiple 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 format change required 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.

c. 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.
d. FDA questioned the acceptance criteria for critical process parameters (CPP) and key process parameters (KPP) used in the process performance qualification (PPQ) studies. Some of the CPP and KPP ranges are quite wide, and were based on data not submitted in the BLA. These ranges are sufficiently broad such that they would not help define a validated and controlled commercial manufacturing process. During the discussion with Novartis during the inspection, the FDA recommended that the acceptable ranges for CPPs and KPPs should be revised to reflect the accumulated manufacturing data and experience. FDA indicated that a simple 3 times the standard deviation may not be a suitable approach given the wide ranges of the available data.
e. Some unit operation holding times were not defined (e.g. (b) (4) , volume reduction, beads wash).
f. 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 and commercial batch record as they become available.

3. Process control - As the result of process validation discussions mentioned above, the final version of the manufacturing process control description in the BLA should be revised to reflect the changes implemented for better controls.

4. Lot release specifications - Although Novartis has tightened the lot release specifications for CTL019 from clinical to commercial production, some lot release specifications are still being evaluated by FDA. FDA may request additional information as needed 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.
   In addition, lot release testing specifications for CTL019 (murine) HIV-1 vector substance and vector product are being reviewed and may be revised if necessary.
5. Chain-of-Identity system - Novartis has provided a general description of the chain-of-identity (COI) system which controls an array of important activities from scheduling patients, maintaining traceability, issuing labels and 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 determining if the system is indeed validated. An internal consult review for computer software used in the COI system may be requested after the OTAT review.

ii. Date the primary discipline review will be complete: The CMC review will be completed after receipt of all outstanding assay validation IRs, 483 responses, and completion of all facility inspection reports. Novartis' responses to these items will impact the review timeline.

b. Maura O'Leary, Donna Przepiorka – Clinical

i. Substantive issues identified: None.
   Study CCTL019B2202 (product manufactured in New Jersey) is the primary study for efficacy. This study was conducted under a Special Protocol Assessment originally agreed upon with the sponsor on July 23, 2014.

   Primary objective: Evaluate the efficacy of CTL019 therapy as measured by overall remission rate (ORR), which includes CR and CR with incomplete blood count recovery (CRi) as determined by IRC assessment.

   Eligible population: 67 subjects to allow for 50 treated subjects who were age 3 at screening to age 21 at the time of initial diagnosis. Subjects were to have been relapsed (second or greater BM relapse or primary refractory

(failed two induction regimens) pediatric and young adult acute lymphoblastic leukemia (ALL). Subjects with Ph+ ALL, CNS 2, Down Syndrome, and ineligible for allogeneic stem cell transplant were allowed. Subject were to have >5% blasts in their bone marrow at screening. Organ function was stipulated to be in the normal range with the exception of liver function which could be greater than 5 times the upper limit of normal and performance scores (Karnofsky and Lansky) of ≥ 50%.

Trial design: Subjects were treated on a single-arm, open-label, multi-institutional, international study of CTL019.

Treatment:
There were multiple phases to the therapy plan:
Screening: subjects evaluated for compliance with eligibility criteria.

Leukapheresis: all subjects who completed screening successfully were leukapheresed at their local institution and the cells were sent to the Novartis manufacturing site in New Jersey.

Manufacturing Phase: While awaiting their CTL019, subjects were allowed to receive Bridging Chemotherapy for control of their ALL. This was investigator choice.

Lymphodepletion: Once a product was available, subjects were given chemotherapy to induce lymphopenia. The recommended regimen was:

- Fludarabine (30 mg/m2 intravenously [i.v.] daily for 4 doses) and cyclophosphamide (500 mg/m2 i.v. daily for 2 doses starting with the first dose of fludarabine).

This was not required in subjects with WBC ≤ 1000 within a week prior to CTL019 infusion.

CTL019 Infusion was given as a single dose after lymphodepleting therapy.

- Dose: A dose of CTL019 transduced cells for pediatric patients will consist of a single infusion of 2 to 5 x 10e6 CTL019 transduced cells/kg (range 0.2 -5 x 10e6 CTL019 transduced cells/kg) , with a maximum dose of 1- 2.5 x 10e8 CTL019 transduced cells (range 0.1-2.5 x 10e8 CTL019 transduced cells) for subjects > 50 kg.(non-weight adjusted).

Statistical considerations for Efficacy

- The pre-specified primary efficacy endpoint was overall remission rate (ORR) (=CR + CRi) per IRC assessment; defined as:
  Complete Remission: All of the following Criteria are met:

Bone Marrow: trilineage and < 5% blasts
Peripheral Blood:
Neutrophils > 1.0 x 10e9/L and
Platelets > 100 x 10e9/L and
Circulating blasts < 1%

Extramedullary Disease (EMD): no evidence of EMD on physical exam and for the central nervous system a lumbar puncture was required at Day 28 (primary assessment)

Transfusion independency

Complete Remission with incomplete count recovery (CRi): all of the above except neutrophils ≤ 1.0 x 10e9/L or, platelets ≤ 100 x 10e9/L or transfusions required.

No Response: failure to attain the above criteria

Relapsed Disease: subjects who achieve a CR or CRi and have reappearance of blasts in the blood (≥ 1%) or bone marrow (≥ 5%) or EMD after CR, CRi.

Unknown: "Unknown" is assigned in case the baseline assessment or the response assessment is not done, incomplete, indeterminate, or not performed within the respective time frame

Efficacy Results

- 88 subjects were screened. 68 were infused with CTL019 (63 manufactured in the New Jersey site). 50 subjects have been followed or discontinued from the study for at least 6 months. Overall 82 % (98.9% CI: 64.5, 93.3) of subjects who received CTL019 achieved a CR or CRi per Independent review committee (IRC) in the interim efficacy analysis set (IEAS) which included 50 subjects who completed or withdrew within the initial 3 months post infusion. The lower bound of the 98.9% exact CI exceeded the pre-specified threshold of clinical relevance of 20%, so the study met its primary endpoint. All but one subject was minimum residual disease (MRD) negative. In a pre-defined sensitivity analysis of the subjects who discontinued prior to CTL019, but met all eligibility requirements, the ORR by the IRC was 60.3% with the lower bound of 95% CIs above the pre-specified success criterion of 20% The median time from enrollment (defined as the point at which the subject meets all clinical inclusion/exclusion criteria, and the patients' leukapheresis product is received and accepted by the manufacturing facility) to CTL019 infusion was 43.5 days (range 30 to 105 days)
- Manufacturing failures: 5 in initial submission (6.2%).
- Duration of remission in the initial submission:
    - Month 3 EFS 94.9% (81, 98.7)
    - Month 6 EFS 60.2% (35.8, 77.8)
    - Month 9 EFS 51.6 (26.1, 72.2)

Safety Results:

- CRS:

Toxicity Criteria	Grade	CTL019
PENN	1	5 (7.35%)
	2	16 (23.53%)
	3	14 (20.59%)
	4	18 (26.47%)
	Subjects	53 (77.94%)
	Total	68

- Neurotoxicity

Toxicity Criteria	Grade 3-4	Dictionary Derived Term	CTL019 (n=68)
CTCAE		Encephalopathy	4 (5.88%
		Delirium	3 (4.1%)
		Mental Status Changes	2 (2.94%)
		Headache	2 (2.94%)
		Decreased consciousness	1 (1.47%)

- Adverse Events of Special Interest
  - Opportunistic Infections:
    - Strep pneumonia encephalitis
    - HHV6 encephalitis
    - Fungal infections
    - Gram negative sepsis
    - Fungal sepsis
  - Macrophage Activating reaction or hemophagocytic lymphohistiocytosis associated with treatment in subjects with rapidly and uncontrolled ALL or infection
  - Hypogammaglobulinemia
  - Graft versus Host Disease
  - Cardiac toxicity
  - Second Malignancy: one CAR B cell leukemia on CCTL019B2205J

ii. Date the primary discipline review will be complete: For Late-Cycle meeting - June 30, 2017

c. Ying Huang – Toxicology Reviewer
   i. Substantive issues identified: N/A
   ii. Date the primary discipline review will be complete: May 31, 2017 (tentative)

d. Xue Lin – Statistical
   i. Substantive issues identified: N/A

ii. Date the primary discipline review will be complete: August 1, 2017 (tentative)

e. Joan Johnson – DMPQ (CMC Facilities)
   i. Substantive issues identified: There are no substantive issues or deficiencies from DMPQ perspective at this time. Review of the original BLA submission related to manufacturing facility is complete however, review of the IR responses submitted as amendment 10 and 13 is still on going.
   ii. Date the primary discipline review will be complete: The primary discipline review memos will be completed by June 30, 2017

f. Dennis Cato – Bioresearch Monitoring (BIMO)
   i. Substantive issues identified: A complete review of the EIRs is still pending. The table below summarizes the inspection results for all six study sites inspected:

Site Number	Study Site	Location	Number of Subjects	Classification
1100	Sainte Justine Hospital	Montreal, QC, Canada	4	NAI
1351	Hospital Sant Joan de Deu	Barcelona, Spain	5	NAI
1401	The Children's Hospital of Philadelphia	Philadelphia, Pennsylvania	10	VAI – 1 Observation Study not conducted according to Investigational Plan. PedsQL and EQ-5D questionnaire not performed for 4 subjects. Also laboratory results not reviewed in a timely manner.
1404	University of Michigan Comprehensive Cancer Center	Ann Arbor, Michigan	2	VAI – 1 Observation ICF used not approved by the IRB
1406	University of Minnesota	Minneapolis, Minnesota	3	NAI
1412	Doernbecher Children's Hospital Pediatrics Hematology Oncology	Portland, Oregon	2	VAI – 1 Observation Inaccurate case histories. Differences in subjects' results in source versus eCRF

   ii. Date the primary discipline review will be complete: after all of the EIRs have been received and reviewed

g. Jaspal Ahluwalia - Postmarketing Safety Epidemiological Reviewer
   i. Substantive issues identified
      1. Cytokine Release Syndrome - Current REMS may be inadequate. Being discussed internally.
   ii. Date the primary discipline review will be complete: September 1, 2017

h. Simleen Kaur - OCBQ/DBSQC/LMIVTS- Microbiological tests
    i. Substantive issues identified: Mycoplasma assay validation performed by (b) (4) has deficiencies in their Limit of Detection and Specificity studies. IR to be sent out soon.
    ii. Date the primary discipline review will be complete: July 15, 2017 (tentative)

i. Consult:
    i. DRISK
        1. Requestor: OBE/DE – Jaspal Ahluwalia
        2. Reviewer: Naomi Redd, Doris Auth
        3. Update: Discussion is ongoing
    ii. COA
        1. Requestor: Clinical – Maura O'Leary
        2. Reviewer: Nikunj Patel, Selena Daniels
        3. Update: Reviewers recently received the documents for review. Draft feedback will be provided by the week of 14May17 and a final concurred memo will be provided by the end of May 2017.
    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: The working group, with CDER participants, and modeling group has been established and the models are being specified. A detailed analysis to examine two clinical outcomes is being done. The first clinical outcome is safety for CRS with three categories and the second clinical outcome is efficacy for overall recovery and duration of response.

2. For PDUFA V Program submissions, indicate whether discipline review letters will be issued.

    CMC may have a discipline review letter depending on the sponsor's response to validation.

    All other disciplines confirmed a discipline review letter will not be needed.

3. If the application will be discussed at an Advisory Committee (AC), review potential issues for presentation.

    CMC: There will be a morning session for CMC discussion. Both FDA and Novartis will present. The FDA's briefing document and presentation slides will be provided to Novartis prior to the scheduled AC meeting. FDA and Novartis will attempt to exchange presentation materials to minimize potential overlapping content before the AC meeting.

Clinical: The afternoon session of the Advisory Committee will have a clinical focus. Both Novartis and the FDA will present. FDA's briefing document and presentation slides will be sent to the Novartis prior to the AC for review. We will work with Novartis to avoid overlap of content material. The clinical focus 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 to exposure to a genetically modified cell therapy.

4. Determine whether Postmarketing Requirements (PMRs), Postmarketing Commitments (PMCs), or a Risk Evaluation Mitigation Strategy (REMS) are needed.

   It is too early in the review cycle to discuss PMRs and PMCs. This topic will be re-addressed during the post AC meeting. 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. Risk management strategies are under discussion as part of the review process. There are ongoing discussions regarding REMS.

5. National Drug Code (NDC) assignments to product/packaging (excludes devices).

   Discussion regarding the NDC will take place after OCBQ presents its assessment of the applicant's Drug Supply Chain Security Act (DSCSA) exemption request on May 9, 2017.

6. Proper naming convention.

   The proper name of the product is Tisagenlecleucel.

7. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval and the establishment inspection report (EIR).

   a. CMC Facilities: A pre-license inspection for the manufacturing of the CTL-019 drug product at Novartis CGT facility at Morris Plains, NJ was performed April 3-7, 2017. A 483 containing two deficiency items was issued at the conclusion of the inspection. The findings are summarized below:

      1) Process validation for CTL-019 manufacturing (b) (4) for pALL was incomplete at the time of the inspection. Specifically: the process performance qualification (PPQ) study was based on clinical batches made before the commercial process(es) were defined in the commercial master batch record (MBR) and changes made to the commercial

manufacturing process were not evaluated during validation, such as leukapheresis materials containing high monocytes were not part of the PPQ study; methods used in the PPQ study were not the same as those specified in the commercial batch record (i.e. cell count/viability assay, mycoplasma testing, flow cytometry method). In addition, Hold steps are not defined in the Master Batch Record (e.g., (b) (4)

2) Deviations were not initiated and therefore not investigated for numerous action level excursions for microbial monitoring of ISO 5 operators during Q1-Q3, 2016.

The pre-license inspections for the two vector contract facilities in (b) (4) are scheduled for (b) (4). Findings will be reported at the next BLA monthly meeting.

b. BIMO: All of the inspections have been completed, and three of the six EIRs have been received but are pending review. Of the six inspections, three study sites received a Form FDA 483 (483) and a recommended classification of Voluntary Action Indicated (VAI). The remaining three inspections did not receive a 483 and the recommended classification for these inspections were No Action Indicated (NAI).

Review

8. Major target and milestone dates from RMS/BLA. Discuss pending dates of targets and milestones (e.g. Late-Cycle meeting, Advisory Committee, labeling discussion).

MidCycle Communication with Applicant	May 18, 2017
PeRC Meeting	Jun 7, 2017
CBER Pediatric Exclusivity Board (PEB)	Jun 12, 2017
Internal Late-Cycle Meeting	**Jun 13, 2017**
Send Late Cycle / Advisory Comm briefing package	Jun 22, 2017
External Late-Cycle Meeting	**Jun 29, 2017**
Complete Discipline Reviews (Primary)	**Jun 30, 2017**
Promotional labeling review (APLB)	Jul 5, 2017
Complete Discipline Reviews (Secondary Review)	**Jul 14, 2017**
Advisory Committee Meeting	**Jul 11-13, 2017**
Place holder for Post Advisory Committee Internal Meeting	Jul 17-21, 2017

Place holder for Post Advisory Committee Sponsor Meeting	Jul 24-28, 2017
Complete inspection reports	Aug 3, 2017
Circulate draft press release	Sep 1, 2017
Complete PMC Study, Labeling Review, Review Addenda	Sep 1, 2017
Complete Supervisory Review	**Sep 1, 2017**
Request Compliance Check, Lot Release Clearance	Sep 19, 2017
Send Press Release to OCOD	Sep 19, 2017
Send FDA Action Letter	**Oct 3, 2017**
Post-Action Debrief Meeting	Nov 17, 2017

9. Establish a labeling review plan and agree on future labeling meeting activities.

   Joint AC preparation and labeling meetings are scheduled for every Friday from 10 am to 11 am.

Confirm, as applicable

10. Components Information Table was obtained and notification was sent to the Data Abstraction Team (DAT) if discrepancies were found per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*. If not complete, indicate date it will be completed.

    Notified of completion by the ABC team on April 6, 2017. The CMC team is in the process of completing the task.

11. New facility information is included in the application, requiring implementation of regulatory job aid *JA 910.01: Facility Data Entry.* If not complete, indicate date it will be completed.

    N/A

12. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan.

    DBSQC and OTAT have agreed that no in-support testing will be performed by DBSQC and this product will not be subject to CBER lot release as it is an autologous product. Justification to support this decision is currently being developed.

13. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid *JA 900.01*: *Unique Ingredient Identifier (UNII) Code* for additional information.

    UNII code process initiated on March 31, 2017.

14. PeRC presentation date is set, and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision. **Note:** Remind the review committee that PeRC forms have to be submitted two weeks in advance of scheduled PeRC meeting.

    This product has received orphan designation and does not trigger PREA. However, BPCA is applicable due to the pediatric exclusivity request. The product is scheduled to go to PeRC on June 7, 2017 to review the written request, and will be discussed by the Pediatric Exclusivity Board (PEB) on June 12, 2017.

    PeRC forms need to be sent to me COB on May 23, 2017.

15. Action Items:

a. CMC and clinical will discuss and determine who is responsible for reviewing immunogenicity, which is section 6.3 of the label.
b. RPM will schedule an internal and sponsor "post AC meeting."

16. **For applications subject to the PDUFA V Program:**

a. Reach agreement on information to be included in the Mid-Cycle Communication telecon with the applicant (see section below).
b. Reach agreement on dates for upcoming meetings such as the AC or Late Cycle Meeting. **Note:** the RPM may choose to pre-populate these dates prior to the meeting.

Mid-Cycle Communication Agenda/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.

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.

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.

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.

5. Any new information requests to be communicated

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

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.

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.

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