

Mid-Cycle Meeting Agenda/Summary

Application type and number: BL 125643/0

Product name: Axicabtagene ciloleucel

Proposed Indication: Relapsed/refractory aggressive B-cell NHL

Applicant: Kite Pharma, Inc.

Meeting date & time: July 14, 2017 11:30am - 1:00pm

Committee Chair: Michael Havert, PhD

RPM: Mark L. Davidson, RHIA

Attendees:

Discipline	Name [with credentials (not title)]	Attended meeting?
RPM	Mark Davidson	Y
Clinical Reviewer	Najat Bouchkouj, MD, DCEPT	Y
	Bindu George, MD DCEPT	Y
	Yvette Kasamon, MD, OCE	Y
	R. Angelo de Claro, MD, OCE	Y
CMC Reviewer	Mike Havert, PhD, DCGT	Y
	Anna Kwilas, PhD, DCGT	Y
	Jakob Reiser, Ph.D., DCGT	Y
	Graeme Price, PhD DCGT	Y
Animal Pharmacology and Toxicology Reviewer	Jinhua Lu, PhD, DCEPT	Y
Clinical Pharmacology Reviewer	Xiaofei Wang, PhD, CBER/OBRR	Y
Statistical Reviewer of clinical data	Xue (Mary) Lin, PhD, OBE	Y
Postmarketing Safety Epidemiological Reviewer	Adamma C. Mba-Jonas, MD, OBE	Y
OCBQ/APLB Reviewer	Oluchi Elekwachi, Pharm.D	Y
OCBQ/BIMO Reviewer	Colonious King, OCBQ/BIMO	Y
DBSQC Regulatory Coordinator	Marie Anderson, PhD	Y
DBSQC Reviewer (Sterility, Endotoxin, Myotoxin)	Hyesuk Kong, PhD	Y
DMPQ/Lead Facility Inspector & Reviewer	Donald Ertel, CMDR	Y
DMPQ Facility Inspector	Wang Wei, PhD	Y
Labeling Reviewer	Dana Jones, Pharm. D, OCBQ	Y
Other Attendee(s)	Richard Pazdur, MD	Y
	Laurie Norwood	Y
	Ramani Sista, PhD	Y
	Lori Tull	Y
	Denise Gavin, PhD	Y
	Wilson Bryan, MD	Y
	Steven Oh, PhD	Y
	Raj Puri, MD, PhD	Y

Discipline	Name [with credentials (not title)]	Attended meeting?
	Tejashri Purohit-Sheth, MD Shiowjen Lee, PhD Lisa Stockbridge Ramani Sista, PhD Rachael Anatol, PhD	Y Y Y Y Y
	Kimberly Benton, PhD Larrissa Lapteva, MD Dennis Cato, PhD Tara Waterman, MD Deborah Trout Amy McKee, MD Sarah Lee	Y Y Y Y Y Y Y

Report and Discuss:

1. Reviewer Reports/Status:

- a. **CMC Discipline Review-** [Mike Havert, PhD] Preliminary review is complete. Anticipated primary review completion is July 28. The following issues have been identified:
 - i. The Applicant's stability data does not support the proposed shelf life for the (b) (4) vector or the final product. For (b) (4) vector, the proposed shelf life is (b) (4), but Applicant has not demonstrated (b) (4) beyond (b) (4) of storage. For Final product the proposed shelf life is 12 months, but Applicant has not demonstrated stability from patient lots beyond 6 months.
 - ii. The Applicant's analytical method Validation is incomplete, information currently outstanding includes:
 - Accuracy of axicabtagene ciloleucel viability determination
 - Report for axicabtagene ciloleucel (b) (4) validation conducted at (b) (4) (including additional information on samples used)
 - Intermediate precision of axicabtagene ciloleucel (b) (4)

- during assay transfer from (b) (4)
- (b) (4) vector (b) (4) assay: validation of sensitivity and robustness, (b) (4) and additional information on samples used
 - (b) (4) release assay was validated as if it was a limit test which we do not agree with; requesting further validation

- RCR Test Operator Worksheet (or detailed description of test method) and RCR raw data for (b) (4) lots

b. **DMPQ Discipline Review and Establishment Inspection Report (EIR)** [Don Ertel]

Inspectional Status and Findings:

Pre-license inspections of the Kite Pharma, Inc. (b) (4) facility and the (b) (4) (Contract Vector Manufacturer) were completed 06/16/17 and (b) (4) respectively. A 483 was issued at the end of each inspection. Kite has responded to their 483 observation, preliminary response appears adequate. (b) (4) response is pending receipt, due 07/14/17. EIR and Inspectional close-out expected by August 2017.

I anticipate for my primary discipline review to completed 21 July 2017. If I have any review issues, I will identify IR as part of my primary review, and follow-up with the response from those IRs in an addendum review. The following IRs are drafted so far and will be sent to Kite for response send by 21 July 2017:

Reference the revised 3.2.A.1, Facilities and Equipment, sent in an amendment (rec'd 06/26/17): Section 1.1.1 Overview [first paragraph] has not been updated to reflect the current qualification status of the manufacturing suites. Please provide an updated document in an amendment to the application.

In reference to the Kite (b) (4) facility, please provide a summary of the alert and action limits for Environmental Monitoring that you have established for all room classifications.

In reference to APV at (b) (4) Facility:

How did you select the (b) (4) (Suite (b) (4) BSCs and the (b) (4) BSC (Suite (b) (4) for use in your Aseptic Processing Validation? Was a risk assessment performed to identify the specific BSCs used in the initial studies?

Do you plan to include the use of the other BSCs in subsequent AOQs? If so, please provide your general plan. If not, please provide a justification.

Reference your qualification of the Kite Final Product Shipper (for axicabtagene ciloleucel): Was physical testing such as drop and vibration testing performed as part of your qualification study?

In reference to (b) (4) EM program, please provide the Environmental Monitoring Limits for non-viable Particulate and viable Airborne and Surface sampling for Grade (b) (4) areas (i.e. BSCs)

In reference to (b) (4) purified water system program, please provide the action and alert limits that established for the (b) (4) testing for Bioburden, Endotoxin, Conductivity, pH, and Total Organic Carbon.

Please provide a summary of the Aseptic Processing Simulation for aseptic processing of (b) (4) performed at (b) (4)

Please provide a summary of the Container Closure Integrity Testing qualification for the (b) (4) cryostorage (b) (4) used for (b) (4).

All Facilities are listed in RMS-BLA per JA 910.01, Facility Data Entry Job Aid.

Categorical Exclusion is warranted, and my concurrence is included in my Primary Review memo.

EIR completion is expected August 2017

c. **Pharmacology/Toxicology** [Jinhua Lu, Ph.D.]

- All nonclinical related information is under review and no issues have been identified. Anticipated completion date is July 19, 2017.

d. **Clinical Reports**

Clinical Efficacy Review- [Yvette Kasamon, M.D.] -Slides Presentation

- Under review ongoing - anticipated completion by July 31, 2017

Statistical [Mary Lin PhD] –Slide Presentation

- Under review ongoing - anticipated completion by July 31, 2017

Clinical Safety Review- [Najat Bouchkouj, M.D.] -Slides Presentation

- The preliminary review is complete and the final review will be completed on July 31, 2017. The following study has not yet been reviewed: ZUMA-2: r/r Mantle Cell Lymphoma (MCL)

1.) Safety exposure:

Data from 147 subjects were submitted for the safety analysis.

- a. ZUMA-1 study (r/r B-NHL) is the primary study for safety. Seven subjects from Phase 1 and 101 subjects from Phase 2 cohorts form the basis of the safety review.

- b. Supportive data from ZUMA-2 study (r/r MCL) will be included in the integrated safety analysis (11 subjects).
- c. The following additional studies were submitted in the integrated summary of safety:
 - (b) (4)
 - ZUMA-3 (r/r adult B-precursor Acute Lymphoblastic Leukemia [ALL]): Four subjects
 - ZUMA-4 (r/r pediatric B-precursor ALL): 4 subjects

2.) Safety Results:

Adverse events of special interest include:

- Cytokine Release Syndrome (CRS)
- Neurotoxicity
- Prolonged cytopenia
- Infection

Potential impact the substantive issues: Risk Evaluation and Mitigation Strategy (REMS): Due to substantial risk (mainly CRS and neurotoxicity) associated with the administration of this product, a REMS is indicated to ensure the maintenance of the benefit/risk profile of this product. The applicant has addressed the need for REMS in the BLA submission; however, the current plan will need revisions to ensure that local sites, investigators, and patients are properly educated on the safety profile of the product. An Elements To Assure Safe Use (ETASU) is recommended. We will discuss the REMS with CBER OBE (pharmacovigilance), CBER Safety Working Group and CDER DRISK.

Plan for addressing issues: Issues identified in the review will be addressed by labeling and do not affect approval.

Clinical Pharmacology [Xiaofei Wang] -Slide Presentation

- Under review (ongoing) - anticipated completion by July 31, 2017

e. **Lot Release** [Marie Anderson]

The Laboratory Quality Product Testing Plan (TP) has been drafted and routed to PO and DBSQC reviewers. A response of Friday, 21 Jul 2017 has been requested. We will ask Kite Pharma to submit release lot annual reports.

f. **Quality Control** [Hyesuk Kong]

- Drug product: Section 3.2.P.5.3- (b) (4) system for sterility; (b) (4) for mycoplasma testing; and (b) (4) endotoxin test method using (b) (4) test system.
- Drug substance (Vector Substance): Section 3.2.S.4.3 - (b) (4)

There are no major substantive issues to resolve. Date to complete primary review is the end of July or early August 2017, tentative.

g. **Bioresearch Monitoring** [Colonious King]

Bioresearch Monitoring issued three domestic clinical investigator inspection assignments, and a sponsor inspection for Protocol KTE-C19-101- A phase ½ multi-center study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive non-hodgkin lymphoma (NHL) (ZUMA-1). The inspections are still pending in the ORA district offices. Anticipate BIMO will complete the discipline review after the EIR for the inspections have been received between 24 July 2017 – 04 August 2017. **There are no major substantive issues to resolve.**

h. **Postmarketing Safety Epidemiological** [Adamma C. Mba-Jonas, MD]

Key findings and substantive issues with the information and data in the application:

The sponsor has identified cytokine release syndrome (CRS) and neurologic events (NE) as important risks that warrant the establishment of REMS. The stated purpose of the REMS is to mitigate these severe toxicities by ensuring that Health Care Providers (HCPs) are educated about how to manage these adverse events (including with regards to the use of tocilizumab for treatment of CRS) and that patients are aware of the symptoms of CRS and NE and are prepared to seek immediate medical care after onset of these symptoms.

The REMS as outlined by the sponsor is a communication plan that includes the following elements:

- a) Provision of an Adverse Reaction Management Guide to all prescribers of YESCARTA; the guide will instruct prescribers on the management of CRS and NE and will be distributed to HCPs “during initial visits” of Kite’s medical field-based personnel with HCPs. New prescribers will be contacted by phone, email, or live meeting to reiterate risks of YESCARTA.

- b) Communication Letters targeted at HCPs who are likely to prescribe YESCARTA and relevant professional societies; these letters will include information regarding the potential severity of CRS and NE as well as links to a patient wallet card (PWC) for dissemination to recipients of YESCARTA and the Adverse Reaction Management Guide.
- c) Establishment of a REMS website which provides access to all the REMS materials, the Prescribing Information, and the PWC.

The sponsor plans to assess the efficacy of this communication plan by REMS assessments that include periodic surveys of random samples of HCPs, including YESCARTA providers, to assess understanding of the identified and potential risks of YESCARTA and knowledge of CRS/NE management strategies as well as whether they received REMS communications. The sponsor will also assess a random selection of YESCARTA recipients with regards to whether they received/recalled receiving the PWC as recommended as well as their awareness of the risks associated with YESCARTA. The sponsor indicates that they will submit REMS assessments to the FDA at a minimum by 18 months, by 3 years, and in the seventh year from the date of approval of the REMS.

The sponsor has indicated that risk mitigation for CRS and NE will also be accomplished with additional surveillance strategies, including:

- 1) Routine PV, including collection and periodic aggregation and evaluation of AE reports from multiple sources (spontaneous reporting from healthcare professionals and consumers, regulatory agencies, scientific literature, clinical trials, and post-marketing studies, i.e., registries, safety studies) as well as use of guided questionnaires for collecting data about a specific safety concern
- 2) A post-market registry of all recipients of YESCARTA, to be created and maintained by the (b) (4) (protocol not yet submitted)
- 3) Ongoing YESCARTA clinical trials, including ZUMA-1, the pivotal trial for this BLA (final report due 2032), as well as trials underway for future additional indications

Additional safety concerns and the suggested surveillance/risk mitigation strategies are below:

- a.) Identified risks
 - 1) Cytopenias and Febrile Neutropenia - routine PV, a post-market registry, and ongoing YESCARTA clinical trials

- 2) Infections - routine PV, a post-market registry, and ongoing YESCARTA clinical trials Potential risks
 - 3) Secondary malignancy - routine PV, a post-market registry, and ongoing YESCARTA clinical trials
 - 4) Autoimmune disorders - routine PV, a post-market registry, and ongoing YESCARTA clinical trials
 - 5) Immunogenicity - ongoing YESCARTA clinical trials; the sponsor posits that the lack of these AEs in ZUMA-1 to date suggests that there is no need to conduct surveillance for this in the registry, given that this would require periodic blood testing
 - 6) Generation of Replication-competent Retrovirus - ongoing YESCARTA clinical trials
- 5) Cerebral edema - routine PV, a post-market registry, and ongoing YESCARTA clinical trials
 - Use in special populations (pregnancy/lactation, patients with hepatic/renal impairment – routine PV, a post-market registry
 - Use in pediatric populations – routine PV, upcoming clinical trial for expanded pediatric indication
- b.) Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline:
 - c.) Discussions with DRISK to finalize REMS plan are ongoing.
 - d.) Plan for addressing issues and the reason for the suggested approach:

OBE's assessment is that the REMS plan submitted by the sponsor may not constitute adequate risk mitigation, as the designed communication plan does not ensure that YESCARTA is dispensed only in certified hospitals and clinics that have on-site immediate access to tocilizumab. Elements to Assure Safe Use may be a more effective and appropriate risk mitigation strategy.

The planned registry of YESCARTA recipients is being proposed as a post-marketing commitment; in order to align with the pharmacovigilance plans of similar products, a post-marketing requirement is being considered. The protocol has yet to be reviewed.

Plan for addressing issues and the reason for the suggested approach:

OBE's assessment is that the REMS plan submitted by the sponsor may not constitute adequate risk mitigation, as the designed communication plan does not ensure that YESCARTA is dispensed only in certified hospitals and clinics that

have on-site immediate access to tocilizumab. Elements to Assure Safe Use may be a more effective and appropriate risk mitigation strategy.

The planned registry of YESCARTA recipients is being proposed as a post-marketing commitment; in order to align with the pharmacovigilance plans of similar products, a post-marketing requirement is being considered. The protocol has yet to be reviewed.

Anticipated primary discipline review completion date is July 31, 2017.

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

Review team will continue with information request emails.

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

Axicabtagene ciloleucel (YESCARTA) will not be discussed at ODAC Advisory Committee.

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

Risk Evaluation Mitigation Strategy (REMS) will be indicated.

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

National Drug Code and package Bar Code label to be determined. Are the regulations and guidance on NDC are applicable to cell and gene therapy products? The preliminary advice is that a different product code should be used when indications will require a different dose (range)/amount of cells.

6. Proper naming convention.

The proper name of the product is Axicabtagene ciloleucel.

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

(b) (4) and Kite facility inspections are complete, 483 responses due 7/14/17, EIR target completion is 8/14/17. BIMO inspections are ongoing until 8/4/17.

Upcoming Review Milestones

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).

Remaining Milestone dates:		Expedited Dates
Mid-Cycle Review Meeting	14-Jul-17	14-Jul-17
Mid-Cycle Communication Meeting Package:	28-Jul-17	21-Jul-17
Mid-Cycle Communication with Applicant:		25-Jul-17
Telecon		
Send Information Requests as needed		24-Jul-17
Complete Discipline Reviews(Primary)	25-Aug-17	31-Jul-17
Complete Discipline Reviews -Secondary	08-Sep-17	28-Aug-17
Send Discipline Review Letters as completed		31-Jul-17
Internal Late-Cycle Meeting	14-Sep-17	11-Aug-17
Promotional labeling review (APLB)	31-Aug-17	20-Jul-17
Complete inspection reports	29-Sep-17	28-Aug-17
Send Late Cycle briefing package	01-Sep-17	30-Aug-17
External Late-Cycle Meeting		11-Sept-17
Circulate draft press release or Draft PI to OCOD	30-Oct-17	18-Sept-17
PMR/PMC, if any	30-Oct-17	18-Sept-17
Labeling Target (First time PI sent to applicant)	30-Oct-17	18-Sept-17
All Discipline Concurred Reviews must be entered into EDR.	30-Oct-17	18-Sept-17
Draft & Circulate the approval letter		01-Oct-17
SBRA First Draft Branch Chief		18-Sept-17
SBRA to Discipline DD		02-Oct-17
SBRA to Kim Benton, Mary Malarkey, Wilson Bryan (A new License # will be issued for this		09-Oct-17
Complete Supervisory Review	30-Oct-17	
Request Compliance Check, Lot Release	15-Nov-17	04-Oct-17
Send Press Release to OCTMA	15-Nov-17	04-Oct-17
T-minus date	15-Nov-17	04-Oct-17
Send FDA Action Letter	29-Nov-17	18-Oct-17
Post-Action Debrief Meeting	12-Jan-18	01-Dec-17

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

Labeling meetings are scheduled starting with Friday, July 28, 2017 and throughout the month of August 2017. Additional meetings can be added to schedule based on need to complete the labeling review in a timely manner.

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.**

Components Information Table is complete. Review of ABC database input is ongoing.

- 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.**

This product is exempt and there will be no lot release testing for this product.

- 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.**

Request sent to CBER SRS 5/16/17

- 14. PeRC presentation**

As noted in the May 8, 2017 Filing meeting this product has received orphan designation and is exempt from PeRC.

- 15. Action Items:**

- a. RPM will schedule additional labeling meetings as needed.

- 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).

Mid-Cycle Communication Agenda/Summary

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

CMC

We have identified issues regarding proposed shelf life. The stability data does not support the proposed shelf life for the (b) (4) vector and axicabtagene ciloleucel final product. For (b) (4) vector the proposed shelf life is (b) (4), but Kite has not demonstrated (b) (4) beyond (b) (4) of storage. For axicabtagene ciloleucel final product the proposed shelf life is 12 months, but Kite has not demonstrated stability from patient lots in final container beyond 6 months.

We have also identified issues with the post approval stability commitments. For the (b) (4) vector post approval stability commitment, please conduct stability testing according to the schedule provided on samples from each manufacturing campaign (from either (b) (4) lots). For the final product post approval stability commitment, please conduct stability testing on multiple unused patient lots at each time point, as they become available.

2. Information regarding major safety concerns.

Fatal and life-threatening Cytokine Release Syndrome (CRS) and neurotoxicity events were associated with axicabtagene ciloleucel and are major safety concerns.

Patients exposed to retroviral based CD19 directed CART cell therapy are at risk for long term complications of secondary malignancies.

We may have additional information requests or may identify additional safety concerns after review of the updated safety information due on July 31, 2017

3. Preliminary review committee thinking regarding risk management.

The Risk Evaluation and Mitigation Strategy (REMS) is under review. Additional communication regarding the REMS will be sent to the applicant at a later time.

The pharmacovigilance plan for YESCARTA includes a registry of YESCARTA recipients; additional information regarding plans for this registry will be reviewed when submitted and discussed at the time of the late cycle meeting.

4. Any information requests sent and responses not received

CMC

Analytical Method Validation is incomplete, information currently outstanding includes:

- i. Accuracy of axicabtagene ciloleucel viability determination
- ii. Report for axicabtagene ciloleucel (b) (4) validation conducted at (b) (4) (including additional information on samples used)
- iii. Intermediate precision of axicabtagene ciloleucel (b) (4) during assay transfer from (b) (4)
- iv. (b) (4) vector (b) (4) assay: validation of sensitivity and robustness, (b) (4) and additional information on samples used

- v. (b) (4) release assay was validated as if it was a limit test which we do not agree with; requesting further validation
 - vi. RCR Test Operator Worksheet (or detailed description of test method) and RCR raw data for (b) (4) lots
5. Any new information requests to be communicated
- Efficacy
Regarding ZUMA1 ADTTE.xpt submitted on July 12, for paramcd='PFS_CS1', three subjects (KTE-C19-101-002-012, KTE-C19-101-009-008 and KTE-C19-101-025-001) received new cancer therapy but were not censored at the last tumor assessment before the new therapy. Please submit an updated ADTTE.xpt with corrected PFS_CS1 for these three subjects.
6. Proposed date(s) for the Late-Cycle meeting (LCM)
- The LCM between you and the review committee is currently scheduled for September 11, 2017 from 1:00 am to 2:00 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
The Advisory Committee Meeting will not be scheduled.
8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.

External Late-Cycle Meeting: September 11, 2017
Labeling Target Date: October 30, 2017
PMC Target Date: October 30, 2017