

Late cycle internal meeting 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: August 11, 2017 11:30am - 12:30pm

Date of LCM with applicant: September 11, 2017

Committee Chair: Michael Havert, PhD

RPM: Mark L. Davidson, RHIA

Attendees:

Discipline/Organization	Name
Regulatory Project Manager	Mark Davidson, RHIA, DRPM
Chair	Mike Havert, PhD, DCGT
DCGT Deputy Director	Steven Oh, PhD
DCGT, Branch Chief	Denise Gavin, PhD
DCEPT Deputy Director	Ilan Irony, MD
Office Director	Wilson Bryan, MD
Office Deputy Director	Rachael Anatol, PhD
Associate Director for Regulatory Management	Kimberly Benton, PhD
Clinical Reviewer	Najat Bouchkouj, MD, DCEPT Bindu George, MD DCEPT Yvette Kasamon, MD, OCE R. Angelo de Claro, MD, OCE
CMC Reviewer	Anna Kwilas, PhD, DCGT Jakob Reiser, Ph.D., DCGT Graeme Price, PhD DCGT
Animal Pharmacology and Toxicology Reviewer	Jinhua Lu, PhD, DCEPT
Clinical Pharmacology Reviewer	Xiaofei Wang, PhD, CBER/OBRR
Statistical Reviewer of clinical data	Xue (Mary) Lin, PhD, OBE
Postmarketing Safety Epidemiological Reviewer	Adamma C. Mba-Jonas, MD, OBE Chege Wambui, MD
OCBQ/APLB Reviewer	Oluchi Elekwachi, Pharm. D
OCBQ/BIMO Reviewer	Colonious King, OCBQ/BIMO
DBSQC Regulatory Coordinator	Marie Anderson, PhD

DBSQC Reviewer (Sterility, Endotoxin, Myotoxin)	Hyesuk Kong, PhD
DMPQ/Lead Facility Inspector & Reviewer	Donald Ertel, CMDR
DMPQ Facility Inspector	Wang Wei, PhD
Labeling Reviewer	Dana Jones, CSO, OCBQ
CDER/OSE/OMEPRM/DRISK	Joyce Weaver
Other Attendee(s)	Ramani Sista, PhD Lori Tull Shiowjen Lee, PhD, OBE Ramjay Vatsan, PhD, DCGT

Late-cycle internal meeting agenda:

1. Introduction/Short summary of the submission [**Mike**]

Axicabtagene ciloleucel is a CD19-directed, genetically-modified, autologous, T-cell immunotherapy that has been developed for the treatment of patients with relapsed/ or refractory aggressive large B-cell non-Hodgkin lymphoma (NHL). Axicabtagene ciloleucel is composed of a patient's T cells that have undergone ex vivo T cell activation, gene transfer by replication-deficient retroviral vector (b) (4) Vector), and expansion. These transduced T cells are then formulated in a cryopreservation medium suitable for infusion. Each final product bag of axicabtagene ciloleucel is filled to deliver a target dose of 2.0 x 10⁶ CAR T cells/kg of patient weight. Axicabtagene ciloleucel is supplied cryopreserved at a temperature of ≤ -150°C in cryostorage bags.

Since the original BLA submission on March 31, 2017, as of August 11, 2017 Kite Pharma has submitted 49 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/Major Deficiencies raised during Review [**Mike**]

I. Clinical Safety & Efficacy Labeling Update, [**Kasamon, Yvette, MD, OCE /Najat Bouchkouj, M.D.,OTAT/DCEPT**]

II. **Adamma Mba-Jonas, MD - OBE/DE.**

A. Three major safety concerns:

- a. Cytokine release syndrome (CRS) in the acute phase after treatment
- b. Neurological sequelae in the acute phase after treatment

- c. Long-term secondary malignancy risk
- B. Review of Risk Mitigation Strategies
 - a. REMS – sponsor currently reviewing previously submitted REMS in light of REMS Notification Letter
 - b. Possible PMC/PMR - OBE awaits details of sponsor’s proposed patient registry
- 3. Review of upcoming timeline/deadlines [**Mark Davidson**]

Internal Late-Cycle Meeting	14-Sep-17	11-Aug-17
Complete inspection reports	29-Sept-17	28-Aug-17
Send Late-Cycle Briefing Package	01-Sept-17	30-Aug-17
External Late-Cycle Meeting	13-Oct-17	11-Sept-17
Circulate draft press release and Draft PI to OCOB	30-Oct-17	18-Sept-17
PMR/REMS	30-Oct-17	18-Sept-17
Labeling Target (First time PI sent to applicant)		18-Sept-17
All Discipline Concurred Reviews must be entered into EDR.		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 application)		09-Oct-17
Complete Supervisory Review	30-Oct-17	18-Sep-17
Request Compliance Check, Lot Release Clearance	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

- 4. Assess status of the review including plans for completing outstanding discipline reviews and any remaining outstanding issues [**Mike**]
 - a. All assigned CMC areas have been reviewed. Outstanding CMC IRs include requests for clarification on stability testing and product label information. Primary discipline review completed 7/28/17. [**Mike Havert, PhD, DCGT**]
 - b. Clinical efficacy has No issues. Primary review in progress. [**Kasamon, Yvette, MD, OCE**]
 - c. Clinical safety preliminary review is complete. Outstanding review: Datasets for the 120 Day safety update that the applicant submitted on August 9, 2017 and plan to complete the primary discipline review by August 17, 2017. No

substantive issue at this time. Labeling discussions are ongoing and do not effect approval. **[Najat Bouchkouj, M.D.,OTAT/DCEPT]**

- d. The first draft of primary discipline review is completed. The primary reviewer and secondary reviewer are working on review revisions. **[Xiaofei Wang, Ph.D., OTAT/Clinical Pharmacology]**
 - e. Review memo currently under revision, after team lead peer review. Final concurred memo available September 10, 2017 (tentative). **[Xue (Mary) Lin, Statistics]**
 - f. All nonclinical related information is under review and no issues have been identified. **[Jinhua Lu, PhD, OTAT/Pharmacology/Toxicology]**
 - g. The inspections are complete and the EIRs are still being reviewed, no 483s were issued during the inspections. Bioresearch Monitoring issued three domestic clinical investigator inspection assignments 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 three domestic clinical investigator inspections are complete. BIMO will complete the discipline review by August 28, 2017 pending the receipt of two outstanding EIRs. No BIMO findings or substantive issues to report. **[Colonious King, Bioresearch Monitoring]**
 - h. The Laboratory Quality Product Testing Plan (TP) has been reviewed by PO and DBSQC reviewers. Final approval is in process. **[Marie Anderson, DBSQC/ Hyesuk Kong, PhD]**
 - i. Received the response from my IR from my primary review; I am evaluating that response in an addendum review memo; expected to be completed in early September. 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. (b) (4) responded to their 483 (received 07/14/17). 483 Response Memos is progress. EIR and Inspectional close-out expected by end of August 2017. I have identified no substantive review issues/major deficiencies that have been identified to date. **[Donald Ertel, CDR; DMPQ]**
5. Reach agreement on Late-Cycle meeting materials that will be sent to the applicant. Meeting scheduled for September 11th. The Package is due to the sponsor on August 30th. **[Mike]**

The Late-Cycle meeting materials are due to the sponsor by August 30, 2017.