

FILING MEETING AGENDA/SUMMARY

Application type and number: BL 125643/0
Product name: axicabtagene ciloleucel
Indication: Relapsed/refractory aggressive B-cell NHL
Applicant: Kite Pharma, Inc.
Meeting date & time: May 8, 2017, 2:00-3:00pm
Meeting Chair: Michael Havert, DCGT, Chair Product Review
Meeting Recorder: Mark L. Davidson, OTAT, RPM

Background: This is an original Biologics License Application submitted by Kite Pharma for axicabtagene ciloleucel (YESCARTA®). The product is an autologous, genetically-modified T-cell therapy directed to CD19. Axicabtagene ciloleucel has been studied as an investigational agent under IND 16278 for the treatment of adult patients with relapsed/refractory aggressive B-cell non Hodgkin lymphoma (NHL), who are ineligible for autologous stem cell transplant. This BLA is focused on data from a Phase 1/2 clinical study (KTE-C19-101; ZUMA-1) in subjects with refractory NHL, which includes diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL). Kite Pharma has developed a commercial scale manufacturing process for axicabtagene ciloleucel. The BLA provides information on manufacturing process validation at the commercial production facility ((b) (4) product chain-of-custody and chain-of-identity, and validation of analytical methods. Kite Pharma has been granted Orphan Drug and Breakthrough designation.

Table 1: Review Committee and Discipline Filing Decision Summary

Discipline/Organization	Name	Attended meeting	Fileable	RTF	Deficiencies Identified
Regulatory Project Manager (RPM)	Mark L. Davidson, OTAT, RPM	Yes			
Chair	Michael Havert, DCGT	Yes	X		
Division Director	Raj Puri, MD, PhD	Yes			
Division Director/Deputy	Steven Oh, PhD, DCGT	Yes			
DCEPT Division Director	Tejashri Purohit-Sheth, MD	No			
DCEPT Deputy Director	Ilan Irony, MD	Yes			
Office Director OTAT	Wilson Bryan, MD	Yes			
Office Deputy Director	Rachael Anatol, PhD	Yes			
Associate Director for Regulatory Management	Kimberly Benton, PhD	Yes			
Clinical Reviewer	Najat Bouchkouj, MD, DCEPT, (MOR) (Safety)	Yes	X		
Clinical Reviewer	Yvette Kasamon, MD, CDER, (Efficacy)	Yes	X		
Clinical Reviewer	R. Angelo de Claro, MD, CDER, OHOP/DHP, Clinical Team Lead	Yes	X		
Clinical Pharmacology Reviewer	Xiaofei Wang, MD	No	X		
Toxicology Reviewer	Jinhua Lu, PhD, DCEPT,	Yes	X		
CMC Reviewer	Anna Kwilas, PhD, DCGT	Yes	X		
CMC Reviewer	Jakob Reiser, Ph.D., DCGT	Yes	X		
CMC Reviewer	Don Fink, PhD DCGT	Yes	X		
CMC Reviewer	Graeme Price, PhD DCGT	No	X		
OCBQ/DMPQ RPM	Sarah Lee, RPM	Yes			
OCBQ/DMPQ/Reviewer	Donald Ertel	Yes	X		
OCBQ/DMPQ/ Reviewer	Wang Wei, PhD	Yes	X		
OCBQ/APLB Reviewer	Oluchi Elekwachi	No	X		
OCBQ/BIMO Lead Inspector	Colonious King, DIS	Yes	X		
OCBQ/DBSQC or OVRRL/LIB Reviewer	Hyesuk Kong, DBSQC	Yes	X		
OCBQ/DMPQ/Lead Inspector	Donald Ertel, DMPQ	Yes	X		
OCBQ/DMPQ/ Inspector	Wei Wang, DMPQ	Yes	X		
Statistical Reviewer of clinical data	Xue (Mary) Lin, OBE	Yes	X		
Postmarketing Safety Epidemiological/Pharmacologo	Adamma C. Mba-Jonas, PhD	Yes			

Discipline/Organization	Name	Attended meeting	Fileable	RTF	Deficiencies Identified
vigilance Reviewer					
Labeling Reviewer	Loan Nguyen, OCBQ, APLB	Yes	X		
Other Attendee(s)	Richard Pazdur, MD Laurie Norwood John Eltermann, Jr, RPh, MS Carolyn Renshaw Ramani Sista, PhD Lori Tull Mercedes Serabian Iwen Wu, PhD Ramjay Vatsan, PhD Denise Gavin, PhD Bindu George, MD Maura O'Leary, MD Ke Liu, MD, PhD Kristin Baird, MD Shiojjen Lee, PhD Lisa Stockbridge Christine Drabick				

REGULATORY CONCLUSIONS / DEFICIENCIES

- 1. Does the application, on its face, appear to be suitable for filing or is the application unsuitable for filing and will require a RTF letter?**

Yes, the application is suitable for filing.

- 2. If fileable, list any substantive deficiencies or issues that have significant impact on the ability to complete the review or approve the application:**

Day 74 clinical review comments:

1. You seek an indication for relapsed/refractory disease (b) (4) [REDACTED].” You have therefore not established that KTE-C19 is superior to available salvage therapies for (b) (4) refractory disease.

2. You seek an indication for “aggressive B-cell NHL.” However, this is not a World Health Organization diagnosis and the term is overly broad, encompassing many types of lymphoma that were not studied.
3. You seek an indication for patients who are ineligible for autologous HSCT. However, transplant ineligibility was not the entry criterion for ZUMA1 cohorts 1 and 2. The term “ineligible for transplant” is also ambiguous, because reasons for transplant ineligibility include not only comorbidities, but absence of remission. According to the proposed indication, a fit patient with first, untreated relapse could receive KTE-C19 rather than standard salvage chemotherapy, because he has not yet entered the remission typically required for HSCT. This issue also makes the eligibility criteria for ZUMA1 cohort 3 problematic.
4. No rationale was provided for the target dose of KTE-C19, and only one target dose of KTE-C19 was studied in the intended population. As such, the optimal dose of KTE-C19 is not defined.
5. You monitored anti-CD19 CAR T cells levels in blood samples using a (b) (4) assay. However, you did not submit method validation report and bioanalytical report for measurement of anti-CD19 CAR T cell levels in blood samples using this (b) (4) assay for your clinical studies # KTE-C19-101 and (b) (4). Please provide above information.
6. For clinical studies # KTE-C19-101 and (b) (4), you conducted pharmacokinetic (PK) assessment for anti-CD19 CAR T cells by evaluating peak levels (Cmax), area under the blood concentration vs time curve (AUC) from Day 0 to Day 28 (AUC0-28). Please provide 1) individual subject concentration-time plots; and 2) individual subject PK data (Cmax, AUC0-28, and Tmax) and arithmetic mean and standard deviation for above two clinical studies.

3. If RTF, list any substantive deficiencies or issues that would make this application unsuitable for filing:

Does not apply.

FILING MEETING DISCUSSION, IF FILED:

4. Indicate any comments on the status of the proprietary name review (PNR).

CBER/APLB has completed the name review Yescarta® and find no objections to the name. We will revisit the marketing name again and discuss prior to June 29, 2017 review deadline.

5. Indicate whether the product sh/would be subject to lot release, surveillance, or exempt from lot release. Verify sample availability.

Axicabtagene ciloleucel will not be subject to CBER lot release testing.

6. Confirm review schedule of this application.

Priority Review 6 Month. This BLA will be reviewed on a priority review clock with a target completion date of the end November 2017. The team will attempt an expedited review, with the timeline becoming more clear following product inspections in June 2017

7. Indicate the decision regarding the need for an Advisory Committee.

An Advisory Committee Meeting is not planned for this product.

8. Indicate whether the submission triggers PREA; if yes, a PeRC meeting is needed.

This product has received orphan designation and does not trigger PREA.

9. Is a comprehensive and readily located list of all clinical sites included or referenced in the application?

Yes, Sponsor has provided this information.

10. Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?

Yes, Sponsor has provided this information.

11. Indicate any updates since the First Committee Meeting on pre-license inspection, pre-approval inspection, or BIMO sites requiring inspections (Is the establishment(s) ready for inspection?)

Product review team, DMPQ, and BIMO inspectors are in the process of planning facility inspections for June 2017.

12. If the application is affected by the Application Integrity Policy (AIP), has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

This BLA is not affected by the Application Integrity Policy (AIP).

13. Is the product an Original Biological Product or a New Molecular Entity (NME) for an NDA?

This product is an Original Biological Product.

FOR APPLICATIONS IN THE PDUFA PROGRAM (NME NDAs/Original BLAs), IF FILED

14. Confirm that any late submission components were submitted within 30 days. List any late submission components that arrived after 30 days.

During the pre-BLA meeting, chain-of-custody and chain-of-identity validation data was agreed to be accepted during the first 30 days and has been received.

15. Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?

Yes, the application was relatively complete on submission. Information requests for several disciplines have been sent to the sponsor.

ADMINISTRATIVE DETAILS, IF FILED:

16. Review the Milestone Schedule and indicate if there are any issues with the schedule. Note: This is a confirmation to capture any changes made since the First Committee Meeting.

There are no changes since the First Committee Meeting

STN BP 125643, BLA Priority 6 Month Review due on 11/29/2017. With regard to the expedited review, the review schedule will be adjusted based on the target completion date of early September.

BLA Priority 8 Month Review		
STN:		125643
Applicant:	Kite Pharma, Inc	
Product:	KTE-C19	
Indication:	Engineered autologous T-cell immunotherapy for the treatment of adult patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma (NHL) who are ineligible for autologous stem cell transplant (ASCT)	
RPM:	Mark Davidson	
Chairperson:	Mike Havert	
Review Schedule	Target Date	Expedited
DCC Receipt Date	31-Mar-17	
Complete regulatory filing review; Assign review committee	10-Apr-17	
Acknowledge receipt; Establish review schedule	14-Apr-17	
First Committee Meeting	21-Apr-17	
30 Day Late Components Due	28-Apr-17	
Filing Meeting	15-May-17	

Send Filing Determination Letter	30-May-17	
Deficiencies Identified Letter	13-Jun-17	
Proprietary Name Review	29-Jun-17	
Request initial labeling review	30-Jun-17	
Mid-Cycle Review Meeting	14-Jul-17	14-Jul-17
Mid-Cycle Communication with Applicant	28-Jul-17	28-Jul-17
Send Information Requests as needed		
Complete Discipline Reviews (Primary)	25-Aug-17	31-Jul-17
Complete Discipline Reviews (Secondary Review)	8-Sep-17	7-Aug-17
Send Discipline Review Letters as completed		
Send Late Cycle / Advisory Comm briefing package	1-Sep-17	21-Jul-17
External Late-Cycle Meeting	14-Sep-17	28-Jul-17
Advisory Committee Meeting, if needed	29-Sep-17	
Promotional labeling review (APLB)	31-Aug-17	31-Jul-17
Complete inspection reports	29-Sep-17	31-Jul-17
PeRC Meeting	18-Oct-17	
Circulate draft press release	30-Oct-17	18-Aug-17
Complete PMC Study, Labeling Review, Review Addenda	30-Oct-17	18-Aug-17
Complete Supervisory Review	30-Oct-17	18-Aug-17
Request Compliance Check, Lot Release Clearance	15-Nov-17	25-Aug-17
Send Press Release to OCTMA	15-Nov-17	25-Aug-17
<i>T-minus date</i>	15-Nov-17	
Send FDA Action Letter	29-Nov-17	1-Sep-17
Post-Action Debrief Meeting	12-Jan-18	Oct 2017