Memorandum

Date: August 01, 2017

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Through: Carrie M. Mampilly, Director, Division of Inspections and Surveillance

To: Xiaobin Lu, Review Chair
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Subject: Bioresearch Monitoring Discipline Review Memo

BLA/STN: 125646/0
IND: 16130
Sponsor: Novartis Pharmaceuticals Corp.
Product: KYMRIAH

EXECUTIVE SUMMARY for SBRA

Bioresearch Monitoring (BIMO) inspections were issued for two foreign and four domestic clinical study sites that participated in the conduct of Study CCTL019B2202. All of the inspections were completed and the Establishment Inspection Reports (EIRs) were received and reviewed. The inspections revealed no substantive problems impacting the data submitted in this original Biologics License Application (BLA).

REVIEW SUMMARY

BIMO inspections were performed at two foreign and four domestic clinical study sites that conducted Study CCTL019B2202 in support of BLA STN: 125646/0, Novartis Pharmaceuticals' KYMRIAH. The pivotal study entitled: *A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia* was conducted under IND 16130. The primary objective of the study was to evaluate the efficacy of CTL019 therapy from all marketing facilities as measured by overall remission rate (ORR) during the three months after CTL019 administration, which includes complete remission (CR) and CR with incomplete blood count recovery as determined by an Independent Review Committee assessment. The inspections have all been completed and the EIRs were received. A review of the inspection reports did not reveal problems that significantly impact the data submitted in the application.

BACKGROUND

Clinical investigator inspection assignments were issued for two foreign and four domestic clinical study sites in support of this BLA review. There were a total of twenty five study centers across 11 countries that participated in the conduct of the study, and enrolled a combined total of 81 subjects. The six study sites inspected enrolled a total of 26 subjects, which represented approximately 32 percent of all subjects (N=81) enrolled in the CCTL019B2202 study.

Bioresearch monitoring inspections are conducted in accordance with the FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The inspection assignments included specific questions related to the study protocol, and verification of the study data on efficacy and safety endpoints submitted by the sponsor in the BLA.

PROTOCOL AUDITED

A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. (Protocol CCTL019B2202)

INSPECTION SUMMARY

The table below summarizes the inspection results:

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
1404	University of Michigan Comprehensive Cancer Center	Ann Arbor, Michigan	2	VAI
1406	University of Minnesota	Minneapolis, Minnesota	3	NAI
1412	Doernbecher Children's Hospital	Portland, Oregon	2	VAI

NAI = No Action Indicated; VAI = Voluntary Action Indicated

FINANCIAL DISCLOSURE

The Clinical Investigator Compliance Program directs the FDA investigator to ask the clinical investigator if and when s/he disclosed information about her/his financial interests to the sponsor and/or interests of any sub-investigators, spouse(s) and dependent children including if and when the information was updated. Each inspected study site had a copy of the financial disclosure forms on hand for the clinical investigators and sub-investigators.

INSPECTIONAL FINDINGS

Sponsor/Monitor Issues

A review of the EIR did not revealed any sponsor related issues.

Clinical Investigator Study Site Issues

A review was conducted of testing records, regulatory binders, study specific standard operating procedures, and general study conduct. In addition, source documents, including records of adverse events, protocol deviations, and subject dispositions were reviewed and the information contained was compared to the data tables submitted by the sponsor in the application. Individual site observations are listed below:

Site 1100: Sainte Justine Hospital: A Form FDA 483 was not issued at close of this inspection, and the inspection received a final classification of NAI.

Site 1351: Hospital Sant Joan de Deu: A Form FDA 483 was not issued at close of this inspection, and the inspection received a final classification of NAI.

Site 1401: The Children's Hospital of Philadelphia: A Form FDA 483 was issued at close of this inspection. A review of the inspection report, the Form FDA 483, and the clinical investigator's letter written in response to the Form FDA 483, revealed minor deviations involving the PedsQL and EQ-5D questionnaires, and the timely review of laboratory results. Specifically, the FDA investigator reported that PedsQL and EQ-5D questionnaires were not completed for two of 10 subjects, and laboratory test results were not being reviewed and initialed in a timely manner. In a letter written in response to the Form FDA 483, the clinical investigator explained that the questionnaires could not be completed because of the subjects' comfort level and state of agitation. In addition, the clinical investigator provided subsequent documentation demonstrating a timely review of the laboratory results in question.

Site 1404: University of Michigan Comprehensive Cancer Center: A Form FDA 483 was issued at close of this inspection. A review of the inspection report revealed a minor deviation involving the use of an informed consent form that was not approved by the IRB. In a letter written in response to the Form FDA 483, the clinical investigator acknowledged the deviation and provided a corrective and preventative action plan that is acceptable, if successfully implemented.

Site 1406: University of Minnesota: A Form FDA 483 was not issued at close of this inspection, and the inspection received a final classification of NAI.

Site 1412: Doernbecher Children's Hospital: At close of this inspection, a Form FDA 483 was issued for inaccurate case histories. A review of the inspection report and the Form FDA 483 revealed the following deviations:

a. For one of two subjects enrolled, the following four medications were not recorded into the electronic case report form (eCRF), but were present in the subject's chart notes:
    - Prednisone – Taken during the subject's screen period.
    - Propofol and alfentanil – Given during a bone marrow procedure for sedation on 1/11/2016.
    - Amoxicillin – Reported by the subject as being prescribed for a common cold by an outside physician and recorded in the subject's chart.

    In a letter, written in response to the Form FDA 483, the clinical investigator stated that the Prednisone, Propofol, and Alfentanil were not recorded due to inadvertent oversight,

and that the Amoxicillin was prescribed to the subject by an outside physician but was never taken.

b. The following discrepancies were noted between source documents and the eCRF for two of two subjects enrolled:
   - Bone marrow lymphocyte differential collected on 10/12/2016 for subject (b) (6) was listed as 4 in the subject's chart and reported as 1 in the eCRF.
   - The CBC differential count, which was collected 3/21/2016, was reported in the eCRF in place of a bone marrow differential collected at the same time for subject (b) (6)
   - For subject (b) (6), a bone marrow collected on 5/16/2016 was recorded as "Clot obtained" in the subject's chart but checked as "Clot not obtained" in the eCRF.
   - The marrow cell count collected on 5/16/2016 for subject (b) (6) was not listed in the subject's chart, but was reported as 20 in the eCRF.
   - On 7/14/2016, subject (b) (6) had a recorded temperature of 36.3 in the subject's chart but reported in the eCRF as 36.6.
   - The diastolic blood pressure collected on 4/19/2016 at 12:06 for subject (b) (6) was listed in source documents as 79 and was recorded in the eCRF as 70.

   In the letter written in response to the Form FDA 483, the clinical investigator acknowledged these errors and stated that the institution has developed an educational session for the interpretation of marrow reports and will conduct additional quarterly internal audits of data entry for the discrepant items.

BIMO ADMINISTRATIVE FOLLOW-UP

Information letters were issued for all clinical sites inspected. Please contact me should you have any questions about this memo or any aspect of Bioresearch Monitoring.

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CC:
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