IND 16130

WRITTEN REQUEST
December 1, 2016

Novartis Pharmaceuticals Corporation
Attention: Manisha Patel, PharmD
Associate Director, Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Patel:

Reference is made to your August 5, 2016, Proposed Pediatric Study Request for CTL019 (tisagenlecleucel-T).

The study, CCTL019B2202, investigated the potential use of CTL019 (tisagenlecleucel-T) in the treatment of relapsed/refractory (r/r) acute lymphoblastic leukemia (ALL) in pediatric and young adult patients.

Background:

Despite the current treatment modalities, many pediatric patients with relapsed or refractory ALL remain incurable; prognosis remains poor in infants, pediatric subtypes and adults. Innovative treatments are urgently needed for the treatment of r/r ALL; for this patient population no effective treatment regimens exist. Novel approaches are also needed to supplement or even replace traditional chemotherapy and stem cell transplantation.

Relapsed/refractory B-cell acute lymphoblastic leukemia in pediatric patients remains a disease with an unmet medical need. Optimal use of anti-leukemic agents, many of which have been developed decades ago, together with the use of prognostic factors for risk-directed therapy has led to a good prognosis in pediatric ALL patients with a cure rate of greater than 80% in developed countries (Pui 2008). Approximately twenty percent of pediatric patients will relapse, with relapsed ALL being still one of the leading causes of death in pediatric cancer (Tallen 2010). Though most pediatric patients (>85%) with relapsed ALL will achieve a second remission, the challenge remains to maintain this second remission as most patients who relapse once will relapse again, and will ultimately succumb to their disease (Tallen 2010; Martin 2012; Ko 2010).

> CTL019 (tisagenlecleucel-T): is an adoptive cellular immunotherapy that uses the autologous peripheral blood T cells that have been genetically modified *ex vivo* with a lentiviral vector to target CD19 on the surface of B cells. The chimeric antigen receptor (CAR) approach uses genetically programmed lymphocytes transduced with chimeric receptor genes to combine the effector functions of T lymphocytes with the ability of antibodies to recognize predefined surface antigens with high specificity in a non-MHC restricted manner (Gross 1989,

Pinthus 2003). These receptors have the ability to recognize intact membrane proteins independent of antigen processing. The tumor antigen binding function of CAR is usually accomplished by the inclusion of a single chain variable fragment (scFv) antibody, containing the heavy chain variable domain (VH) and light chain variable domain (VL) chains joined by a peptide linker of about 15 residues in length (Mullaney et al, 2001). CTL019 is a second generation CAR T-cell cell. Comparability between the Novartis CTL019 and the University of Pennsylvania product (UPenn CTL019) has not been evaluated. There are minor differences in the (b) (4) between products and different manufacturing methods.

UPenn CTL019 is a cell and gene therapy approach that was developed at the University of Pennsylvania (Penn), Pennsylvania, USA. To date, over 250 patients have been infused with UPenn CTL019 in various Phase 1 and 2 studies in r/r B-cell malignancies under Penn IND 13,960 at Penn (adult patients) and the Children's Hospital of Philadelphia (CHOP, pediatric patients). Early results from ongoing clinical trials of UPenn CTL019 in r/r B -cell pediatric acute lymphoblastic leukemia (ALL) have shown promising and durable anti-tumor efficacy (Grupp 2013, Maude 2014). Specifically, in the two ongoing clinical trials of UPenn CTL019 in r/r pediatric and young adult B-cell ALL (CCTL019B2101J (Penn single center) and CCTL019B2205J (Penn/Novartis multicenter) clinical results to date have shown CR of 70-95% (Grupp 2013, Maude 2014). This study CCTL019B2202 (Novartis/multicenter) will use the Novartis CTL019. The toxicities include cytokine release syndrome (CRS) and persistent B cell aplasia. It is anticipated that CTL019 will provide a therapeutic alternative for patients with r/r B – cell ALL and will offer a greater durability of response than current salvage therapies. The trials have been restricted to subjects over 3 years of age. Neonates and infants are not included because apheresis technology has not been adapted to these age groups.

A long term post-study follow-up for lentiviral vector safety will continue under a separate destination protocol (Study CCTL019A2205B). Patients will continue to be followed until 15 years post-CTL019 infusion per FDA guidelines for genetically modified products. This study is not part of the Written Request but part of FDA Guidance for the adequate evaluation of the safety for genetically modified products. For review of the Biologics Licensing Application (BLA), a completed long-term study is not required by the FDA.

To obtain needed pediatric information on CTL019 (tisagenlecleucel-T), the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (FDCA), as amended by the Food and Drug Administration Amendments Act of 2007, and pursuant to section 351(m) of the Public Health Service Act (the PHS Act), as amended by the Biologics Price Competition and Innovation Act of 2009, that you submit information from the studies described below.

Nonclinical studies:

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

Clinical study:

Study 1: CCTL019B2202 is a single-arm, open-label, multi-center study of CTL019 (tisagenlecleucel-T) for relapsed/refractory ALL in pediatric and young adult patients.

Primary Objective of CCTL019B2202 study:

1. Evaluate the efficacy of CTL019 (tisagenlecleucel-T) therapy as measured by overall remission rate (ORR) during the 3 months after CTL019 (tisagenlecleucel-T) administration, which includes CR and CR with incomplete blood count recovery (CRi) as determined by Independent Review Committee assessment.

Secondary Objectives:

1. Evaluate the efficacy of CTL019 therapy as measured by overall remission rate (ORR) during the 3 months after CTL019 administration, which includes CR and CR with incomplete blood count recovery (CRi) as determined by IRC assessment

2. Evaluate the percentage of patients who achieve a best overall response (BOR) of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry among all patients who receive CTL019

3. Evaluate the percentage of patients who achieve CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment

4. Evaluate the percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment

Patients to be studied:

1. Age group: Age 3 to 21

2. Number of patients to be studied: Enrollment will be adjusted to support at least 50 treated subjects between the ages of 3 and 21 years, including at least

50 subjects less than the age 21 at time of screening and 10 under the age of 10. Patients older than 18 will be limited to 10. (Note: Patients may be enrolled but may not be treated in part due to the manufacturing time (up to (b) (4) days), manufacturing failure, progressive disease or the complications of late-stage disease)

Representation of Ethnic and Racial Minorities:

The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Study endpoints:

Efficacy Endpoints:

1. The primary efficacy endpoint:

    a. Overall remission rate (ORR): complete remission (CR) + CR, incomplete hematologic recovery (CRi)

2. Secondary endpoints included:

    a. ORR within 3 months of last subject infused with CTL019

    b. ORR with Minimal Residual Disease (MRD) negative bone marrow

    c. Percentage of patients with best overall response of CR or CRi with MRD negative Bone Marrow at 3 months after CTL019 infusion

    d. Percentage of patients who achieve CR or CRi at Month 6 without stem cell transplant (SCT) between CTL019 infusion and Month 6 response assessment

Safety Endpoints:

1. Type, frequency and severity of adverse events and laboratory abnormalities

2. Adverse events monitored until symptom resolution or until the condition stabilizes

3. Adverse Events of Special Interest:

    a. Cytokine Release Syndrome greater than or equal to Grade 3

    b. Neurologic Toxicity

c. Cardiac Toxicity

d. Intracranial hemorrhage

e. B cell aplasia

f. Second Malignancies

Pharmacokinetic Endpoints:

1. CTL019 transgene levels by qPCR in blood, bone marrow and CSF if available

2. Expression of CTL019 detected by flow cytometry in blood and bone marrow

3. Cmax, Tmax, AUCs and other relevant PK parameters of CTL019 in blood, bone-marrow, CSF if available

4. Persistence of CTL019 in blood, bone marrow, and CSF if available (eg Mean Residence Time [MRT] last)

Known safety concerns and monitoring:

All general toxicities and known safety concerns will be actively monitored and treated per protocol. These toxicities include acute infusion reaction, febrile reaction, tumor lysis syndrome, and B cell depletion, cytokine release syndrome (CRS).

A Data Monitoring Committee (DMC) is needed.

Extraordinary results:

In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

Biological product information:

Treatment Regimen:

1. Dosage form*:* transduced T cells

2. Route of administration: Intravenous

3. Lymphodepletion Regimen: Per protocol

4. CTL019 Infusion: Per protocol

Statistical information, including power of study and statistical assessments:

Primary Endpoint Analysis:

The primary efficacy analysis will be performed by testing whether the ORR within 3 months is less than or equal to 20% against the alternative hypothesis that ORR within 3 months is greater than 20% at overall one-sided 2.5% level of significance, i.e., Ho: $p \leq 0.2$ vs. Ha: $p > 0.2$.
The primary efficacy endpoint, ORR within 3 months, will be analyzed at the interim look and final look of a group sequential design. The ORR will be summarized along with the 2 - sided exact Clopper-Pearson confidence intervals with significance level determined by the O'Brien-Fleming type α-spending approach of Lan-DeMets. Assuming the underlying ORR is 45%, 76 patients in the full analysis set will provide more than 95% power to demonstrate statistical significance at a one-sided 0.025 level of significance, taking into account the interim analysis. The primary efficacy endpoint, ORR will be analyzed based on the data observed in the Interim Efficacy Analysis Set (IEAS) and the Full Analysis Set (FAS) at interim and final analysis, respectively.

Labeling that may result from the study:

You must submit proposed pediatric labeling to incorporate the findings of the study. Under section 505A(j) of the FDCA, regardless of whether the study demonstrates that CTL019 (tisagenlecleucel-T) is safe, pure, and potent, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study. Under section 505A(k)(2) of the FDCA, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study.

Format and types of reports to be submitted:

You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the FDCA, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 600.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (http://inside.fda.gov:9003/downloads/cder/officeofsurveillanceandepidemiology/ucm349727.pdf) and the Guidance addendum. (http://inside.fda.gov:9003/downloads/cder/officeofsurveillanceandepidemiology/ucm349747.pdf). You are encouraged to contact the Division for Clinical Evaluation and Pharmacology/Toxicology in CBER for further guidance.

The submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will be required in studies that start after December 17, 2016. However, we strongly encourage sponsors to use the FDA supported data standards for the submission of applications for new drugs/biologics as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical studies. For example, in clinical trials, IND sponsors should include with their protocol a study data standardization plan (http://www.fda.gov/downloads/BiologicsBloodVaccines/DevelopmentApprovalProcess/UCM209771.doc) proposing their use of the Clinical Data Interchange Standards Consortium (CDISC), Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) formats with the associated annotated case report form for SDTM (e.g., Clinical Data Acquisition Standards Harmonization (CDASH)). Sponsors whose trials began before the required CDISC start dates should consult the Study Data Technical Conformance Guide (http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf) for further information on possibly converting legacy data (non-CDISC) to CDISC.
(Additional information regarding standardized study data can be found in the Guidance for Industry: *Providing Regulatory Submissions in Electronic Format – Standardized Study Data* (http://www.fdanews.com/ext/resources/files/12-14/12-17-18-Studydataguidance.pdf?1418847293).

Timeframe for submitting reports of the study:

Reports of the above studies must be submitted to the Agency by July 1, 2017. Please keep in mind that pediatric exclusivity can attach only to existing exclusivity, if any, that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, if there is unexpired exclusivity that is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such exclusivity is otherwise due to expire.

If FDA has not determined whether CTL019 (tisagenlecleucel-T) is eligible for reference product exclusivity under section 351(k)(7) of the PHS Act, you may submit a request for reference product exclusivity with supporting data and information to the Agency. Note that neither the issuance of this formal pediatric Written Request, nor any request for exclusivity made by you confers or otherwise implies that you are eligible for reference product exclusivity under section 351(k)(7) of the PHS Act.

Response to Written Request:

Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Reports of the study must be submitted as a biologics license application (BLA) with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the FDCA, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);

2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);

3. the action taken (i.e. approval, complete response); or

4. the exclusivity determination (i.e. granted or denied)

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm122938.htm

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of

proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the PHS Act, you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

Please note the Office of Cellular, Tissue and Gene Therapies (OCTGT) is now the Office of Tissues and Advanced Therapies (OTAT) effective October 16, 2016. For additional information see http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm525907.htm

If you have any questions, call Erica Giordano, Regulatory Project Manager, at 240-402-8298.

Sincerely,

Wilson W. Bryan, MD
Director
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research