Errata to FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

BLA 125646
Tisagenlecleucel
Novartis Pharmaceuticals Corporation

On 12th page (Table 2. Regulatory Milestones), listed as:

2/29/2016	Breakthrough Therapy Designation

Corrected to Read:

4/7/2016	Breakthrough Therapy Designation

On 17th page, listed as:

The length and topology of the spacer and transmembrane domains are critical in providing an appropriate steric orientation for specific antigen recognition and subsequent T cell activation.

Corrected to Read:

The length and topology of the spacer and transmembrane domains are important in providing an appropriate steric orientation for specific antigen recognition and subsequent T cell activation.

On page 24th page, listed as:

Currently, each batch of tisagenlecleucel is tested for RCR using a quantitative PCR (qPCR) for VSV-G sequences. In addition, each batch of vector is tested twice for RCR (once on the vector itself, and once on the end of production cells used to manufacture the vector) using a sensitive culture-based assay. During clinical trials, patient peripheral blood samples were tested for RCR (using VSV-G qPCR) at pre-specified infusion time points after administration of tisagenlecleucel. The applicant has proposed a phase 4 registry that will continue such monitoring for RCR in samples from future patients who receive tisagenlecleucel.

Corrected to Read:

Currently, each batch of tisagenlecleucel is tested for RCR using a quantitative PCR (qPCR) for VSV-G sequences. In addition, each batch of vector is tested twice for RCR (once on the vector itself, and once on the end of production cells used to manufacture the vector) using a sensitive culture-based assay. During clinical trials, patient peripheral blood samples were tested for RCR (using VSV-G qPCR) at pre-specified infusion time points after administration of tisagenlecleucel.

On page 27th page, listed as:

The applicant has two clinical protocols: proposed for commercial product; CTL019B2401 Phase 4 with a registry and ongoing CCTL019A2205B LTFU for patients who received tisagenlecleucel under the IND. Both the registry and the long-term follow-up study are designed to follow patients for up to 15 years post-treatment, as summarized below.

Corrected to Read:

The applicant has two clinical protocols proposed for long-term follow-up of patients after receiving tisagenlecleucel: CTL019B2401 Phase 4 observational Patient Registry for patients who receive commercial product and ongoing CCTL019A2205B LTFU for patients who received tisagenlecleucel under the IND. Both the registry and the long-term follow-up study are designed to follow patients for up to 15 years post-treatment, as summarized below.

On page 27th page, listed as:

The primary objective is to evaluate adverse events of special interest (AESIs) after treatment with tisagenlecleucel. This will include short-term AESIs and long-term AESIs.

Corrected to Read:

The primary objective is to evaluate the safety of patients with B lymphocyte malignancies treated with tisagenlecleucel in a real-world setting as measured by the type, frequency and severity of AEs and laboratory abnormalities.

On page 27th page, listed as:

The secondary objectives include the following:
Evaluate other AEs potentially related to tisagenlecleucel therapy
Evaluate incidence and outcome of any pregnancy
Assess any hematologic malignancy, secondary malignancy, or B-cell aplasia
Monitor for presence of RCR (by q-PCR for VSV-G sequences in peripheral blood at pre-specified time points after administration of tisagenlecleucel)Monitor for presence of RCL (by q-PCR for VSV-G sequences in peripheral blood at pre-specified time points after administration of tisagenlecleucel)
Monitor for presence of RCL (by q-PCR for VSV-G sequences in peripheral blood at pre-specified time points after administration of tisagenlecleucel)

Corrected to Read:

Secondary objectives are as follows:

- Describe the growth, development, and female reproductive status for patients who were aged < 18 years at the time of the tisagenlecleucel infusion.
- Evaluate incidence and outcome of any pregnancy occurring in women of child-bearing potential after treatment with tisagenlecleucel.
- Evaluate the long-term effectiveness of tisagenlecleucel for each type of hematologic malignancy with an authorized indication (i.e. ALL and lymphoma) as follows:
- Evaluate the overall response rate (ORR)
- Evaluate duration of overall response (DOR)
- Evaluate relapse incidence
- Evaluate event-free survival (EFS)

- Evaluate overall survival (OS)

On page 36th page, listed as:

- Adverse events of Special Interest for safety analyses included TLS, febrile neutropenia, CRS, infection, transient neuropsychiatric events lasting greater than 28 days.

Corrected to Read:

- Adverse events of Special Interest for safety analyses included TLS, febrile neutropenia, CRS, infection, transient neuropsychiatric events, and cytopenias lasting greater than 28 days.

On page 43rd page, listed as:

Sixty-three subjects received product manufactured in Morris Plains, New Jersey and 5 manufactured in Fraunhofer, Germany

Corrected to Read:

Sixty-three subjects received product manufactured in Morris Plains, New Jersey and 5 manufactured at the Fraunhofer Institut, Germany.

On page 44th page, listed as:

The applicant had 7 manufacturing failures on Study B2202 in the products manufactured at the Morris Plains, New Jersey plant. One manufacturing failure occurred at the Fraunhof, Germany plant. The remaining subjects with failed production went off-study with no additional attempt at manufacturing an acceptable product.

Corrected to Read:

The applicant had manufacturing failures for 6 patients on Study B2202 in the products manufactured at the Morris Plains, New Jersey plant, and manufacturing failure for 1 patient in the products manufactured at Fraunhofer Institut, Germany plant. Re-manufacturing was attempted for 2 of the patients with manufacturing failures at Morris Plains, but re-manufacturing was unsuccessful in both attempts. All patients with failed production runs went off-study.

On page 47th page, listed as:

- During CRS, subjects developed a coagulopathy marked by hypofibrinogenemia – Grade 3 in 14 subjects and Grade 4 in 18 subjects. One subject died after recovery from CRS, with death due to ongoing coagulopathy with intracranial hemorrhage.

Corrected to Read:

- During CRS, subjects developed a coagulopathy marked by Grade ¾ hypofibrinogenemia – in 5/18 subjects with Grade 4 CRS. One subject died after recovery from CRS, with death due to ongoing coagulopathy with intracranial hemorrhage.

On page 47th page, listed as:

Study B2202 CRS (All Grades)	N=53
Systemic Anticytokine given [n (%)]	26 (49)
Tocilizumab • 1 dose • 2 doses • 3 doses	 26 (49) 16 (30) 7 (13)

Corrected to Read:

Study B2202 CRS (All Grades)	N=53
Systemic Anticytokine given [n (%)]	26 (49)
Tocilizumab • 1 dose • 2 doses • 3 doses	 16 (30) 7 (13) 3 (6)

On page 52nd page, listed as:

The applicant has proposed two post-marketing studies to evaluate long-term safety, including an observational long-term follow-up study (referred to as "LTFU") for subjects who received tisagenlecleucel. These subjects who received tisagenlecleucel on the IND clinical trials will be followed according to protocol CCTL019A2205B.

Additionally, there is a prospective registry, protocol CTL019B2401, for patients treated with tisagenlecleucel after commercial availability (Table 10).

Corrected to Read:

The applicant has proposed two studies to evaluate long-term safety, including an ongoing long-term follow-up study CCTL019A2205B (referred to as "LTFU") for subjects who received tisagenlecleucel on the IND clinical trials.

Additionally, there is a prospective observational Patient Registry, protocol CTL019B2401, for patients treated with tisagenlecleucel after commercial availability (Table 10).