Novartis BLA 125646

June 20, 2017

Draft Clinical Comments to the Applicant:

1. Your proposed prescribing information includes instructions for management of cytokine release syndrome (CRS), but we are unable to confirm that your instructions are appropriate. Please provide the following information for all five clinical studies in the BLA (CTL019B2101J, CTL019B2202, CTL019B2205J, CTL019A2101, and CTL019B2102J):

a. For each of the 5 studies, please provide brief narrative statements and/or tables and/or protocol page number describing:
   - What criteria you used for grading CRS,
   - The instructions for use of tocilizumab for treatment of CRS
   - The criteria used to determine responses to tocilizumab for treatment of CRS

b. For each of the subjects who developed CRS or who received tocilizumab for treatment of CRS in the five clinical studies, please provide in the ISS folder an integrated xpt data file (and define file) with the following variables:

   - Study identifier
   - Unique subject ID #
   - CRS onset date
   - CRS maximum grade
   - CRS initial treatment
   - CRS grade at time of tocilizumab infusion
   - Duration of CRS
   - Response to 1st tocilizumab declared for the subject? (Y/N)
   - Date of response to 1st tocilizumab declared for the subject
   - Total number of doses of tocilizumab administered
   - Tocilizumab dose 1 dose (mg/kg)
   - Tocilizumab dose 1 date
   - Tocilizumab dose 2 dose (mg/kg)
   - Tocilizumab dose 2 date
   - Tocilizumab dose 3 dose (mg/kg)
   - Tocilizumab dose 3 date
   - Corticosteroids given (Y/N)
   - Name of corticosteroids
   - Corticosteroids given date
   - Corticosteroids given dose (mg/kg)
   - Other systemic anticytokins therapy given (Y/N)

- Name of other systemic anticytokins therapy given
- Dose of other systemic anticytokins therapy given
- Other systemic anticytokins therapy given date
- Date of death
- Cause of death
- Toxicities from tocilizumab infusion (Y/N)

c. Please provide brief statements and summary tables to describe the efficacy of tocilizumab for treatment of CRS in each of the five clinical studies and across all five studies.

d. Please provide brief statements (and summary tables if warranted) to describe the safety of tocilizumab for treatment of CRS in each of the five clinical studies and across all studies submitted in your BLA.

2. Please confirm that your proposed instruction statements regarding how to use tocilizumab (such as dose, schedule) to treat CRS (such as grade, symptoms) are supported by the results in your BLA.