From:	Patel, Manisha
To:	Giordano, Erica
Cc:	Riggins, Cindy; Ahmed, Narin
Subject:	RE: BL 125646 Clinical Information Request
Date:	Monday, August 21, 2017 1:38:12 PM
Attachments:	image001.png
Sensitivity:	Confidential

Dear Erica,

Please find below a response to FDA's request:

> *Based on the 45 patients treated with the recommended dose for the first episode of grade 3-4 CRS, we confirm that we have identified 9 (20%) who responded within 2 days, 26 (57.8%) who responded within 7 days, and 31 (68.9%) who responded within 14 days. All numbers match FDA's.*

Kind regards,
Manisha

From: Giordano, Erica [mailto:Erica.Giordano@fda.hhs.gov]
Sent: Friday, August 18, 2017 5:05 PM
To: Patel, Manisha <manisha.patel@novartis.com>
Cc: Riggins, Cindy <cindy.riggins@novartis.com>; Ahmed, Narin <narin.ahmed@novartis.com>
Subject: RE: BL 125646 Clinical Information Request
Sensitivity: Confidential

Good afternoon,

Thank you for your response on August 11, 2017. In your response to Item 4 (of FDA information request of August 9, 2017), your reported response rates are different from FDA's. We note that your response rates were calculated based on 58 patients treated with tocilizumab, rather than just the 45 patients treated with the recommended dose for the first episode of grade 3-4 CRS (variable EFFPOP=Y).

You have confirmed that 45 patients were treated with the recommended dose for the first episode of grade 3-4 CRS. Based on these 45 patients treated with the recommended dose for the first episode of grade 3-4 CRS, we identified 9 (20.0%) who responded within 2 days, 26 (57.8%) who responded within 7 days, and 31 (68.9%) who responded within 14 days.

Please confirm that you verify these response rates and provide a response by 4 pm on Monday August 21, 2017.

Please confirm receipt of this request.

Thank you,

Erica Giordano
Regulatory Project Manager
Center for Biologics Evaluation and Research
Office of Tissues and Advanced Therapies
U.S. Food and Drug Administration

Tel: 240-402-8298
Erica.Giordano@fda.hhs.gov

From: Giordano, Erica
Sent: Friday, August 11, 2017 3:58 PM
To: 'Patel, Manisha'
Cc: Riggins, Cindy; Ahmed, Narin
Subject: RE: BL 125646 Clinical Information Request
Sensitivity: Confidential

I am confirming receipt.

Thanks
Erica

From: Patel, Manisha [mailto:manisha.patel@novartis.com]
Sent: Friday, August 11, 2017 3:55 PM
To: Giordano, Erica
Cc: Riggins, Cindy; Ahmed, Narin
Subject: RE: BL 125646 Clinical Information Request
Sensitivity: Confidential

Dear Erica,

Please find attached a response to your below request.

Kind regards,
Manisha

From: Giordano, Erica [mailto:Erica.Giordano@fda.hhs.gov]
Sent: Wednesday, August 09, 2017 3:38 PM
To: Patel, Manisha <manisha.patel@novartis.com>
Cc: Riggins, Cindy <cindy.riggins@novartis.com>; Ahmed, Narin <narin.ahmed@novartis.com>
Subject: BL 125646 Clinical Information Request
Sensitivity: Confidential

Good afternoon,

Please see the information request below and provide a response by 4 pm on August 11, 2017. Please send a response directly to this e-mail and follow-up by submitting the information as an official amendment to the BLA.

We have reviewed your responses submitted June 30 and July 7, 2017, for our Information Request sent on June 20, 2017, and we have the following comments:

1. Variable CRSYN in adcrs.xpt identifies whether patients developed CRS. Please clarify whether this flag used data elements taken from a case report form question about CRS, from a report of CRS as an adverse event, or some other derived method.

2. We have identified 58 patients treated with tocilizumab for cytokine release syndrome (CRS) after receiving a CTL019 product on CTL019B2101J, CTL019B2202, CTL019B2205J, CTL019A2101, and CTL019B2102J. See data file NOVDEM.xpt and verify that these are the 58 patients that you cited in Appendix 3 of your response document.

3. You propose to include in your prescribing information that for treatment of severe or life-threatening cytokine release syndrome (CRS), the healthcare provider should administer tocilizumab 8 mg/kg (12 mg/kg for patients <30 kg). We identified 45 patients treated with the recommended dose for the first episode of grade 3-4 CRS (variable EFFPOP=Y). Please confirm that patients in the data file NOVDEM.xpt with EFFPOP=Y received the recommended dose for the first dose of tocilizumab for the first episode of grade 3-4 CRS. Variables used:
   TOCIDSGP – FDA-derived first toci dose from adcmcrs.xpt
   RECDOS – FDA-derived Y if patient received recommended dose (based on weight group > or < 30 kg))
   CRSEPIN – FDA confirms Sponsor's derived CRS episode number
   CRSGR- Sponsor's reported grade of CRS at start of toci

4. You indicated in Section 2.2 of the response document that resolution of CRS was defined as the date when the patient was afebrile for 24 hours and off vasopressors for 24 hours. We identified responders as patients who had resolution of CRS within a specified timeframe after the first tocilizumab dose using no more than 2 doses of tocilizumab and without any additional drugs other than corticosteroids. We identified 9 (20.0%) who responded within 2 days, 26 (57.8%) who responded within 7 days, and 31 (68.9%) who responded within 14 days. Please verify these response rates.
   Variables used:
   NTOCI – FDA confirms sponsor's number of toci doses given
   OANCYT – FDA confirms sponsor's report of other drugs used (FDA-derived variable from con med file is OTHRX)
   INTT1END – FDA-derived interval from first toci dose to end of CRS (element 0=CRS ended the same day as toci administration)
   TOC1DT – Sponsor's reported date of first toci dose
   CRSENDT- Sponsor's reported date of end of CRS

5. Please confirm that your CRS treatment algorithm requires an interval of at least 12 hours between the 1st and 2nd doses of tocilizumab.

Please confirm receipt of this request.

Thank you,

Erica Giordano
Regulatory Project Manager
Center for Biologics Evaluation and Research
Office of Tissues and Advanced Therapies
U.S. Food and Drug Administration
Tel: 240-402-8298
Erica.Giordano@fda.hhs.gov