From:	Patel, Manisha
To:	Giordano, Erica
Cc:	Ahmed, Narin
Subject:	RE: BL 125646 Clinical Pharmacology Information Request
Date:	Wednesday, June 07, 2017 10:54:02 AM
Attachments:	image001.png
Sensitivity:	Confidential

Thanks Erica

From: Giordano, Erica [mailto:Erica.Giordano@fda.hhs.gov]
Sent: Wednesday, June 07, 2017 10:51 AM
To: Patel, Manisha <manisha.patel@novartis.com>
Cc: Ahmed, Narin <narin.ahmed@novartis.com>
Subject: RE: BL 125646 Clinical Pharmacology Information Request
Sensitivity: Confidential

Hi Manisha,

Please see the notes next to the Novartis proposed age ranges:
Novartis proposed age ranges:

Group 1 (children): 0-5 FDA = 0-<6 years
Group 2 (children): 6 – 12 FDA = OK
Group 3 (adolescents): 13 - 18 FDA = >12-<18
Group 4 (adults): greater than 18 FDA = OK

Please let me know if you have any questions.

Thanks
Erica

From: Patel, Manisha [mailto:manisha.patel@novartis.com]
Sent: Tuesday, June 06, 2017 4:17 PM
To: Giordano, Erica
Cc: Ahmed, Narin
Subject: RE: BL 125646 Clinical Pharmacology Information Request
Sensitivity: Confidential

Dear Erica,

Can you confirm if the Novartis proposed age ranges below are acceptable for the requested analysis (I refer to FDA request #6 in the email below *[...]Your analysis should be based on age (adults, children 0-5 years, 5-12 years, and adolescents). [...]).*

Novartis proposed age ranges:

Group 1 (children): 0-5
Group 2 (children): 6 - 12
Group 3 (adolescents): 13 - 18

Group 4 (adults): greater than 18

Kind regards,
Manisha

From: Patel, Manisha
Sent: Tuesday, June 06, 2017 12:20 PM
To: 'Erica.Giordano@fda.hhs.gov' <Erica.Giordano@fda.hhs.gov>
Cc: Riggins, Cindy <cindy.riggins@novartis.com>; Ahmed, Narin <narin.ahmed@novartis.com>
Subject: RE: BL 125646 Clinical Pharmacology Information Request
Sensitivity: Confidential

Dear Erica,
I confirm receipt of this request.

Kind regards,
Manisha

From: Giordano, Erica [mailto:Erica.Giordano@fda.hhs.gov]
Sent: Tuesday, June 06, 2017 11:46 AM
To: Patel, Manisha <manisha.patel@novartis.com>
Cc: Riggins, Cindy <cindy.riggins@novartis.com>; Ahmed, Narin <narin.ahmed@novartis.com>
Subject: BL 125646 Clinical Pharmacology Information Request
Sensitivity: Confidential

Good afternoon,

Please see the information request below and provide a response by noon on June 19, 2017 and follow up by submitting the information as an official amendment to the BLA.

There is a lot of emphasis on C_{max} of CTL019 in your population PK (POPK) report. Please describe the clinical significance (relationship with efficacy or adverse effects) of C_{max} of CTL019.

You state that Patients who received tocilizumab had higher peak tisagenlecleucel-T transgene levels (2 fold higher C_{max}). What is the clinical relevance of this 2-fold increase in C_{max} of tisagenlecleucel-T transgene levels? Did tocilizumab also alter the AUC and clearance of tisagenlecleucel-T transgene?

Is there any concentration-toxicity relationship (tisagenlecleucel-T transgene levels vs cytokine release syndrome (CRS))?

Clearance and volume of distribution are two important PK parameters and were not reported in your POPPK report. Please explain.

Although, your POPOK model is innovative and new but is without validation (external data). Therefore, the accuracy of the parameter estimates is uncertain. Furthermore, the model only estimates C_{max} and AUC. Why not use a traditional POPPK model?

Your sampling time points are extensive and you can estimate PK parameters of CTL019 by non-compartmental analysis (NCA). Your analysis should be based on age (adults, children 0-5 years, 5-12 years, and adolescents). In addition, you should analyze (NCA) data separately based on co-medication (tocilizumab and corticosteroids). Please provide the PK parameters (at least Cmax and AUC) for each subject with mean and standard deviation of the population. Please calculate AUC from the very first concentration (not after tmax).

Please provide concentration-time data for each subject.

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