# RECORD OF TELEPHONE CONVERSATION

## Submission Information

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| **Application Type** | BLA |
| **STN** | 125646/0.0 |
| **Review Office** | OTAT |
| **Applicant** | Novartis Pharmaceuticals Corporation / Lic. # 1244 |
| **Product** | Tisagenlecleucel |
| **Trans-BLA Group:** | No |

## Telecon Details

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| **Telecon Date/Time** | 23-AUG-2017 02:00 PM |
| **Author** | GIORDANO, ERICA |
| **EDR** | No |
| **Post to Web** | Yes |
| **Outside Phone Number** | 1 866 755 6294<br>324 113 8817# |
| **FDA Originated?** | No |
| **Communication Categories** | IR - Information Request |
| **Related STNs** | None |
| **Related PMCs** | None |
| **Telecon Summary** | Labeling sponsor call |

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| **FDA Participants** | Kimberly Benton, PhD, Associate Director for Regulatory Management, CBER/OTAT<br><br>Erica Giordano, Consumer Safety Officer, CBER/OTAT/DRPM<br><br>Dana Jones, Consumer Safety Officer, CBER/OCBQ/DCM<br><br>Xue (Mary) Lin, PhD, Biostatistics Reviewer, CBER/OBE/DB/TEB<br><br>Xiaobin (Victor) Lu, PhD, Microbiologist, CBER/OTAT/DCGT<br><br>Maura O'Leary, MD, Medical Officer, Team Leader, CBER/OTAT/DCEPT<br><br>Donna Przepiorka, MD, Medical Officer, CDER/OND/OHOP/DHP<br><br>Tejashri Purohit-Sheth, MD, Director, CBER/OTAT/DCEPT<br><br>Lisa Stockbridge, PhD, Branch Chief, CBER/OCBQ/DCM/APLB |

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| **Applicant Participants** | Narin Ahmed (Sr. Associate Director, Regulatory Affairs)<br><br>Eric Bleickardt (Global Program Clinical Head)<br><br>Shanthi Ganeshan (North American Regulatory Affairs Head, Oncology)<br><br>Gabriela Gruia, (Sr. VP and Global Regulatory Affairs Head, Oncology)<br><br>Kristen Harrington-Smith (US Commercial Head, CAR-T)<br><br>David Lebwohl (Executive Global Program Head)<br><br>Antonella Maniero (Executive Global Biostatistics Head)<br><br>Manisha Patel (Sr. Associate Director, Regulatory Affairs)<br><br>Patricia Wood (Sr. Global Clinical Lead)<br><br>Lan Yi (Senior Principal Biostatistician) |

**Telecon Body:**

The applicant requested further clarification regarding why patients in first relapse were not included in the indication, citing 2 cases in their trial of patients with Down syndrome and ALL treated in first relapse. FDA indicated that the two cases the applicant presented are not adequate to support a change in the indication. In order to treat patients with first relapse, a new study would be needed to demonstrate that long-term survival is as good as current therapy, as the available data did not include sufficient follow-up of patients. FDA explained that once the product is marketed, how an individual physician chooses to utilize the product is within the practice of medicine, including results that can be supported by published literature, so the indication statement should not be a limiting factor.

The applicant proposed to specify the Penn grading scale in the PI in order to clearly communicate the meaning of the grades cited. FDA agreed that it is acceptable for the applicant to use the Penn grading scale in section 5.1 CRS, but the applicant should use the appropriate terminology, and the exact reference needs to be included in the REFERENCES section, section 15, and cited in section 5.

The applicant questioned whether the intent of using CR as the basis for approval actually meant CR+CRi. FDA explained that the basis for approval was CR as stated, and referred the applicant to other examples and the 2007 cancer clinical trials endpoints guidance. The applicant proposed to use wording about CRi similar to that in the Besponsa PI. FDA asked the applicant to make a proposal, and the FDA team would evaluate and provide a response.

The applicant proposed to include a Day-28 response rate; however, FDA noted that this would not be included in the PI as an efficacy endpoint. FDA suggested providing median and range for time to response based on calendar day rather than study visit, so that healthcare providers could determine when it was futile to expect a response.

The applicant requested including a relapse-free rate of 6 months in the label. FDA explained that the time-to-event result for a single-arm trial was not interpretable, especially with the very short follow-up and as the median duration of response has not been reached. but there was information to provide physicians with the lower bound.

Regarding Sections 5 and 6:

FDA agreed with the incidence reported by the applicant for the following: tachycardia, febrile neutropenia, infections, use of corticosteroids, and prolonged cytopenia.

FDA requested a list of subjects from the applicant in order to identify the source of the discrepancy in percentage of the following: abdominal pain, acute kidney injury, bleeding.

For CRS, FDA indicated that Patient (b) (6) has been confirmed to have CRS.

For the laboratory results tables, FDA agreed that a shift table is not useful for hematological toxicities and requested that prolonged cytopenias be reported instead. The Vyxeos label was suggested as an example. FDA indicated, however, that a chemistry lab abnormalities shift table was needed.

ADR table discussion:

FDA emphasized that only adverse reactions should be included in section 6, ADVERSE REACTIONS. Adverse events that were investigations were taken out of the ADR table; a shift table including the chemistries from the adverse reactions may be included instead.

The applicant questioned use of the 10% cut-off for ADRs. FDA indicated that the applicant could propose an alternate, but 40% was not going to be acceptable.

FDA requested that the applicant provide the label by COB today, August 23, 2017. The applicant should send all labeling materials, including the revised MedGuide. The applicant plans to provide a response by COB Thursday August 24, 2017 or early Friday August 25, 2017.