Towards Supporting Biosimilarity Assessment Without the Need for Efficacy Trial: Neupogen

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Objectives: To demonstrate how pharmacometric analysis can be used to leverage quantitative information of a reference product for exemption from clinical efficacy studies for a new biosimilar product using data from published clinical trials of Zarxio, a recently FDA approved biosimilar product of Neupogen [1].

Methods: The pharmacokinetics (PK) profile of Neupogen and Zarxio was described using a target mediated drug disposition model coupled with the first order elimination rate constant [2, 3]. The proliferation, and maturation of neutrophils and elimination from the blood stream (PD) were described using signal transduction model [2, 3, 4]. Emax model was used to link both products PK to PD in both healthy subjects and in cancer patients. The effect of docetaxel on the proliferation of neutrophils in cancer patients was modeled with 3-compartment PK model [5] and Emax model.

Results: The PK/PD model used adequately described the PK profile and the corresponding absolute neutrophil count (ANC) of both products after single and multiple doses. PK comparison of the reference and biosimilar products was demonstrated. The model showed that both products elicited similar time course of ANC in both healthy and cancer patients treated with docetaxel. Statistical analysis of the model predicted data showed that the clinical efficacy primary endpoints, namely duration of neutropenia in patients receiving docetaxel during the 1st cycle of chemotherapy treatment were also similar between the two products. Additionally, clinical trial simulations showed no added value of having longer duration of study.

Conclusions: The work showed that the clinical end point (similarity in the duration of neutropenia between the two products) at the end of cycle-1 (3-week) is sufficient enough to meet the criteria for the primary endpoint and can be used for exemption from large comparative clinical efficacy with longer study duration of 18-weeks.

References: