An exposure response model to describe the relationship between ixekizumab concentrations and the temporal profiles of ACR response in psoriatic arthritis patients

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BACKGROUND: Ixekizumab is a high-affinity monoclonal antibody that selectively targets interleukin (IL)-17A. It has been approved to treat adult patients with moderate-to-severe plaque psoriasis and is in development for the treatment of psoriatic arthritis (PsA). The objective of this analysis was to characterize the exposure-efficacy relationship and time course of 20, 50, and 70% improvement in the American College of Rheumatology criteria (ACR 20, 50, and 70, respectively) using data from 2 Ph3 PsA studies.

METHODS: In both Ph3 studies, Ixekizumab was administered subcutaneously as a 160mg starting dose followed by repeated 80mg doses given every 2 weeks (Q2W) or every 4 weeks (Q4W). ACR responses were measured at various time points. A latent variable model, modified from a published method [1], was constructed and implemented in NONMEM to describe the temporal relationship between ixekizumab serum concentrations and ACR response rates up to 24 weeks. Data from placebo patients were also included in the model fitting to allow estimation of the placebo effect. Using this model, ACR20/50/70 responses were fit simultaneously, and patient specific factors affecting the ACR response rates were explored.

RESULTS: Ixekizumab pharmacokinetics were described with a 2-compartment model which drove the ACR responses. The ACR model adequately characterized the time course of ACR20/50/70 responses. The model results suggested similar efficacy between the 80mg Q2W and Q4W dosing regimens, consistent with the trial observations, and a relatively flat exposure - ACR response relationship in the ixekizumab serum concentration range observed in the trials.

CONCLUSIONS: The exposure response analyses suggest that increasing the dosing frequency from Q4W to Q2W would not offer additional clinically important ACR improvement in patients with active PsA.

REFERENCES: