A longitudinal PKPD model describing the static Physician Global Assessment (sPGA) Response to ixekizumab in patients with moderate to severe plaque psoriasis.

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Objectives: To develop a PKPD model describing the effect of ixekizumab, an anti-IL-17A monoclonal IgG4 antibody, on the longitudinal sPGA response in patients with moderate to severe plaque psoriasis.

Methods: Ixekizumab or placebo was administered subcutaneously (SC) (10, 25, 75, or 150 mg) at 0, 2, 4, 8,12, and 16 weeks in a Phase 2 study (N=141 patients); and as a 160 mg initial dose, then 80 mg Q2W or Q4W or placebo for 12 weeks, then Q4W or Q12W up to 60 weeks in a Phase 3 study (N=1297 patients). Analyses were conducted using NONMEM 7.3.

Results: A two compartment PK model with first order absorption linked with a semi-mechanistic Type I indirect response latent-variable logistic regression model¹ was adapted to model ordered categorical sPGA scores. The structural model included a weibull-like placebo effect, a mixture model bimodal distribution of EC50, disease progression and a precursor compartment for the latent variable to describe development of tolerance. An adaptive VPC approach demonstrated the model was able to describe the data well. The model simulations were used to support the proposed induction and maintenance dosage regimens for regulatory submission.

Conclusions: The relationship between ixekizumab concentrations and sPGA response over time in patients with moderate to severe plaque psoriasis was described well using a longitudinal latent variable model and supported the proposed dose regimens for registration.

Reference: