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Title: Population pharmacokinetics of tralokinumab, an investigational anti-IL-13 monoclonal antibody, in asthmatic and healthy adults

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Body: Interleukin-13 (IL-13) is considered a critical mediator in the development and maintenance of asthma. Tralokinumab (CAT-354), a human IgG4 monoclonal antibody that specifically neutralizes IL-13, is currently trialled in subjects with uncontrolled, severe asthma. The aim of this study was to develop and evaluate a population pharmacokinetic (PK) model of tralokinumab. Four phase 1 studies and one phase 2a study constitute the data to be analysed comprising a population of 247 healthy and asthmatic adults. Nonlinear mixed-effects modeling of pooled data was conducted using the software NONMEM7. The influence of demographic features on tralokinumab PK was evaluated by covariate analysis. Predictive performance of the model was assessed through simulations. The PK parameters for a 2-compartment model after IV and SC dosing were all precisely estimated (RSE<26%) with mean values (CV% of between-subject variability) of clearance (CL), central volume (Vc), inter-compartment clearance (Q), and peripheral volume (Vp) respectively equal to 0.22 L·day-1 (33%), 2 L (64%), 3.4 L (28%), and 1.4 L·day-1 (64%). Body weight explained a minor portion of the variability in CL and Vp, 11% and 34% respectively. No PK difference was detected between healthy and asthmatic subjects. SC bioavailability was estimated at 82%. Model appropriateness was demonstrated by good predictive behaviours of the model. The population PK model successfully described the concentration time-course of tralokinumab and adequately predicted the variability in the studied population. It therefore constitutes a useful tool for guiding the design and dosing of tralokinumab in future clinical trials.