Population Pharmacokinetic and Pharmacodynamic Modeling of Thymus and Activation-Regulated Chemokine (TARC) Response to Dupilumab in Uncontrolled Persistent Asthma

Li Zhang¹, Meng Li¹, Zhaoling Meng¹, Yongtao Li¹, John D. Davis², Brian N. Swanson¹, Vanaja Kanamaluru¹, Qiang Lu¹

¹Sanofi, Bridgewater, NJ; ²Regeneron Pharmaceuticals, Inc., Tarrytown, NY; USA

Objectives: Dupilumab, a fully human anti-interleukin (IL)-4Rα mAb, inhibits signaling of IL-4/IL-13, key drivers of type 2/Th2-mediated inflammation. TARC (a key regulator of type 2-mediated inflammation) is evaluated as a pharmacodynamic (PD) biomarker for target engagement and dupilumab action through the type 2 pathway in asthma. We aimed to develop a population pharmacokinetic (PK)/PD model to characterize the time course of exposure-response for serum TARC in asthma patients receiving dupilumab.

Methods: The TARC PK/PD base model was developed with data from the pivotal phase 2b dose-ranging study (NCT01854047) in patients with uncontrolled persistent asthma on medium-to-high-dose inhaled corticosteroids plus a long-acting β₂-agonist randomized (1:1:1:1:1) to receive 24 weeks of add-on therapy with subcutaneous dupilumab 200 mg every 2 weeks (q2w) or every 4 weeks (q4w) (loading dose [LD] 400 mg); dupilumab 300 mg q2w or q4w (LD 600 mg); or placebo. Clinical trial simulation was conducted to evaluate biomarker response with the different dose regimens, to support dose selection for the phase 3 study.

Results: The time course of TARC concentration changes was best described by an indirect-response model for which TARC formation was suppressed by serum dupilumab concentration. The estimated mean values (% relative standard error) of PD parameters were: \( IC_{50} = 1.81 \ (12.0) \) mg/L and \( I_{\text{max}} = 37.7\% \ (1.8) \). The mean calculated \( IC_{90} \) is 16.6 mg/L, consistent with the observation that a near-maximal suppression of TARC (>34%) is achieved throughout the dosing interval with q2w regimens only (Figure).

Conclusions: The exposure-response relationship of TARC during dupilumab treatment in the phase 2b study was well characterized. For dupilumab 200/300 mg q2w (with LD), but not 200/300 mg q4w, simulation suggested that near-maximum TARC suppression is achieved by 4 weeks, and maintained throughout the treatment interval, supporting further evaluation of the q2w regimens that were selected for the phase 3 study.

Figure. Model-predicted mean dupilumab serum concentration (A) and percentage change from TARC baseline (B) in patients with uncontrolled persistent asthma after multiple subcutaneous dupilumab administrations.