Exposure-Response Analysis of Dupilumab on Forced Expiratory Volume in 1 Second (FEV₁) in Uncontrolled Persistent Asthma

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Objectives: Dupilumab, a fully human anti-interleukin (IL)-4/IL-13 receptor α mAb, inhibits signaling of IL-4/IL-13, key drivers of type 2/Th2-mediated inflammation. Patients with uncontrolled persistent asthma receiving medium-to-high-dose inhaled corticosteroids plus a long-acting β₂-agonist (ICS+LABA) require additional treatment options. We aimed to investigate the exposure-response (E-R) effect of dupilumab as add-on therapy on FEV₁ in asthma patients and identify factors influencing the E-R relationship for phase 3 dose selection.

Methods: The FEV₁ E-R model was developed with data from the pivotal phase 2b dose-ranging study (NCT01854047) in 776 patients with uncontrolled persistent asthma on medium-to-high-dose ICS+LABA, who were randomized (1:1:1:1:1) to receive 24 weeks of add-on therapy with subcutaneous dupilumab 200/300 mg or placebo every 2 (q2w) or 4 weeks (q4w). Simulations were performed to assess the expected FEV₁ response for different dose regimens, to support dose selection for phase 3 study.

Results: FEV₁ time profiles were adequately characterized by a semi-mechanistic model, including treatment effect (characterized by a serum dupilumab concentration-dependent sigmoidal Eₘₐₓ model) and a placebo effect described by an empirical time-dependent function. Population mean estimates of dupilumab treatment effect were: Eₘₐₓ=0.15 L and EC₅₀=1.97 mg/L. Covariate analysis revealed that dupilumab maximum treatment effect (Eₘₐₓ) positively correlated with baseline eosinophil counts; baseline FEV₁ increased in patients of younger age, greater weight, and male sex. Simulation suggested that mean improvement of FEV₁ >0.10 L was achieved throughout the dosing interval with q2w regimens in the intent-to-treat population and in subgroups with ≥300 and <300 eosinophils/µL (Figure).

Conclusions: FEV₁ time profiles in the phase 2b study were well characterized; baseline blood eosinophil count was identified as a significant covariate for the dupilumab treatment effect. Simulations indicated that q2w dosing with either 200 or 300 mg dupilumab achieved the targeted FEV₁ response and maintained efficacy irrespective of blood eosinophil counts, supporting further evaluation of these regimens in phase 3 studies.
Figure. Model-predicted mean placebo-corrected improvement in FEV₁ after multiple subcutaneous dupilumab administrations in patients with uncontrolled persistent asthma for the intent-to-treat population (A) and the ≥300 (B) and <300 (C) eosinophils/µL subgroups.

200 mg q2w and q4w used a loading dose of 400 mg; 300 mg q2w and q4w used a loading dose of 600 mg.