PK – PD of Crohn’s Disease Activity Index after treatment with risankizumab, an IL-23 inhibitor

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Objectives: To develop a longitudinal PK-PD model of Crohn’s disease activity index (CDAI) after at least 12 weeks of induction treatment with two doses of risankizumab vs. placebo in an ongoing Proof of Concept trial.

Methods: Moderate-to-severely active CD Patients (N=121) were treated with 200 or 600 mg risankizumab or placebo every 4 weeks (q4w) intravenously (IV) for 12 weeks, followed by 600 mg IV q4w from week 14 until week 26 in patients who were not in deep remission (CDAI <150 and CDEIS ≤4 [≤2 for isolated ileal disease]) at week 12. Patients achieving clinical remission at week 26 continued with 180 mg SC q8w through week 52 in a maintenance period. Risankizumab pharmacokinetics (humanized IgG) were described using a two compartment model, based on phase I and II studies in psoriasis and CD. An indirect response PK-PD model accounted for patients’ dosing history, demographics, individual-level PK and available CDAI data.

Results: Current model adequately described available CDAI time-course data, reflecting the characteristics of this combined re-/induction and maintenance study. At week 12, typical 600 mg IV q4w treatment was estimated to achieve CDAI remission of 29% (CDAI < 150 points) vs. 21% for 200 mg IV q4w and was predicted to increase with time. Body weight was noted to be inversely related to risankizumab exposure and baseline CDAI scores. Compared to patients who proceeded into maintenance, patients who had their last observation between week 12 and 26 were less likely to improve, expressed in terms of a higher IC₅₀ parameter.

Conclusions: The model represents the initial characterization of risankizumab exposure vs. CDAI time course. Beyond week 26, lower, SC dosing may suffice for maintenance of clinical efficacy. This may be partially due to protocol-specified enrichment of patients exhibiting lower IC₅₀ estimates and a low baseline CDAI, since only patients with clinical remission continued beyond week 26.

Figure 1. Visual predictive check for the CDAI model stratified by starting treatment (“FIRSTDOSE”). Observation times were binned using planned visit times. The solid black line denotes the predicted median CDAI, the solid red line denotes the observed median CDAI. The dashed lines represent predicted (black) and observed (red) 2.5th and 97.5th percentiles. The blue and red areas represent 95% confidence intervals around the predicted percentiles.