Model-Based Meta-Analyses (MBMA) of DAS28 Reduction in Support of Rheumatoid Arthritis Development Programs

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Objectives: Early development of RA drugs usually involves trials of ≥12 weeks with disease activity score, DAS28, as the efficacy endpoint. Questions facing RA early development include: (1) Can an efficacy-based decision for program advancement be made sooner than 12 weeks? (2) Can comparative efficacy of a novel RA treatment be evaluated against historical data of comparators? With the rich literature on DAS28 responses in RA patients, we employed MBMA of baseline-corrected DAS28 (ΔDAS28) to help address these questions.

Methods: Analyses were based on arm-level DAS28 records from a comprehensive database on RA trials published during 1994-2013. The analyses comprised of two parts. (I) Establishment of correlation between DAS28-ESR and DAS28-CRP. (II) MBMA of ΔDAS28. The model assumed ΔDAS28 to be a sum of placebo and drug effects. Each effect was described using a longitudinal Emax model, with baseline DAS28 as a covariate on the Emax. Each drug was modeled at the regulatory approved dose level. Simulations were conducted for arm-level ΔDAS28 for each drug at the corresponding dose.

Results: (I) The 193 paired records of DAS28-ESR and DAS28-CRP represented 7 distinct mechanisms with trial durations up to 52 weeks. The correlation, DAS28-CRP=0.554+0.957×DAS28-ESR, irrespective of mechanism and duration (Fig. 1A), supported the pooling of ΔDAS28-ESR and ΔDAS28-CRP for MBMA. (II) The MBMA included 127 trials of 7 drugs from 5 distinct mechanisms besides placebo, representing 17381 patients, mostly incomplete responders to methotrexate with or without prior exposure to biologics. The time-course ΔDAS28 for each drug was adequately described by the model. The simulated arm-level mean ΔDAS28 for each drug is shown in Fig. 1(B, C).

Conclusions: The MBMA demonstrates that ΔDAS28 profiles for placebo and active drugs begin to separate at as early as 2 weeks of treatment, supporting the plausibility of early decision making based on data prior to 12 weeks. The simulated ΔDAS28 profiles provide a benchmark for evaluation of competitiveness of new anti-RA agents.