Pharmacokinetic/Receptor Occupancy/Pharmacodynamic Modeling of FR104, an Anti-CD28 Pegylated Fab' Ab, in Healthy Subjects with or without KLH Challenge

Songmao Zheng1, Ian Gourley2, Bernard Vanhove3, Weirong Wang1

1Biologics Development Sciences, JBIO, Janssen R&D US; 2Translational Medicine Science, Immunology, Janssen R&D US; 3OSE Immunotherapeutics S.A., Nantes F44200, France

Objectives: FR104 is a monovalent pegylated Fab' Ab, antagonist of CD28, under development for treatment of autoimmune diseases. This study aims to quantify the relationship between the pharmacokinetics (PK), receptor occupancy (RO) and pharmacodynamics (PD) in healthy subjects using population modeling approaches.

Methods: FR104 was evaluated in a first-in-human study (1). Sixty-four subjects were randomly assigned to four single ascending dose (SAD) groups, two multiple ascending dose groups and four SAD groups challenged with keyhole limpet hemocyanin (KLH). Blood samples were collected for measurement of PK and CD28 RO on T cells in the peripheral blood. A target-mediated drug disposition (TMDD)-based PK/RO model was developed to characterize data from all dose groups, and an RO/PD model was developed to link observed RO and inhibition of KLH-induced IgG response.

Results: Following FR104 dosing, a clear dose-dependent CD28 RO was observed. CD28 RO by FR104 was saturated at the first sampling time point (0.5 h) at doses above 0.02 mg/kg and the duration of CD28 RO is dose-dependent. Baseline CD28 level was identified through modeling as a significant covariate that can affect RO. The TMDD model successfully captured PK and RO data in all groups simultaneously, with or without KLH challenge. Inhibition of anti-KLH antibody response was apparent at doses at or above 0.02 mg/kg, and inhibition correlated with CD28 RO. One set of RO/PD model parameters, incorporating transit compartments, was able to fit the time course and fold-change from baseline IgG response in the control and all treatment groups.

Conclusions: The observed immunosuppressive activity indicated the therapeutic potential of FR104 for autoimmune diseases. The developed PK/RO/PD model can be used to guide patient dose selection.