Prediction of CNTO 5825 Pharmacokinetics in Human Subjects Using Preclinical Data from Rats and Cynomolgus Monkeys
I. P. Nnane, M. Xu, H. Zhou, H. Davis
Janssen Research and Development

Purpose
To predict pharmacokinetics (PK) of CNTO 5825, a potent and specific monoclonal antibody against human anti-interleukin-13, in human subjects using PK data from rats and cynomolgus monkeys.

Methods
PK properties of CNTO 5825 were determined following single IV administration of 1, 3 and 10 mg/kg in rats and cynomolgus monkeys. The species time-invariant method, with allometric exponent of 0.9 for CL and 1.0 for Vss, was used to predict PK parameters of CNTO 5825 in human subjects using combined PK data from rats and cynomolgus monkeys.

Results
In rats, the mean clearance (CL) of CNTO 5825 after IV administration ranged from 9.98 mL/day/kg to 11.49 mL/day/kg, and mean volume of distribution at steady state (Vss) ranged from 151.52 to 155.64 mL/kg across all dose groups. In cynomolgus monkeys, mean CL after IV administration ranged from 5.78 mL/day/kg to 7.19 mL/day/kg, and mean Vss ranged from 49.77 to 61.10 mL/kg. The PK properties of CNTO 5825 appeared to be dose-proportional in the 1–10 mg/kg dose range in rats and cynomolgus monkeys. The predicted serum concentrations of CNTO 5825 in human subjects declined bi-exponentially with a terminal half-life of 11 days. The predicted CL and Vss of CNTO 5825 in a 70 kg human subject based on time-invariant method with combined PK data from rats and monkeys were 4.84 ± 1.13 ml/day/kg and 68.93 ± 35.55 ml/kg, respectively.

Conclusion
The predicted human PK profile of CNTO 5825 was used to support dose selection for the first-in-human study of CNTO 5825 in healthy subjects. The observed mean CL and Vss of CNTO 5825 in healthy subjects following IV administration of single doses (0.1 to 10 mg/kg) ranged from 2.39 to 4.78 ml/day/kg and 57.80 to 144.15 ml/kg, respectively. The predicted CL and Vss were within 2-fold of observed values in human subjects. Thus, the predicted human concentration-time profile for CNTO 5825 was reasonably well predicted from combined PK data in rats and cynomolgus monkey using time-invariant method with fixed exponent of 0.9 for CL and 1.0 for Vss.