

# Pharmacokinetics, pharmacodynamics and safety of a human anti-IL-6 monoclonal antibody (sirukumab) in healthy subjects in a first-in-human study

Zhenhua Xu, Esther Bouman-Thio, Craig Comisar, Bart Frederick, Bart Van Hartingsveldt, Joseph C. Marini, Hugh M. Davis & Honghui Zhou

Centocor Research & Development, Inc., 200 Great Valley Parkway, Malvern, PA 19355, USA

## Correspondence

Dr Honghui Zhou PhD FCP,  
Biologics Clinical Pharmacology, Centocor  
Research & Development, Inc., 200 Great  
Valley Parkway, Malvern, PA 19355, USA.  
Tel.: +1 610 240 8796  
Fax: +1 610 993 7801  
E-mail: hzhou2@its.jnj.com

## Keywords

first-in-human study, interleukin-6,  
monoclonal antibody, pharmacokinetics,  
sirukumab

## Received

3 January 2011

## Accepted

6 March 2011

## Accepted Article

11 March 2011

## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Interleukin (IL)-6 is a cytokine known for pleiotropic and pro-inflammatory functions. IL-6 is involved in various disease processes including lupus erythematosus, rheumatoid arthritis, insulin resistance and malignancy.
- Anti-IL-6 receptor therapy has recently been demonstrated to be effective in the treatment of patients with rheumatoid arthritis.

## WHAT THIS STUDY ADDS

- Sirukumab, a human monoclonal antibody against soluble IL-6, has been found to bind to human IL-6 with high affinity and specificity and thus suppress the biological activity of IL-6. Preclinical studies have demonstrated the safety of sirukumab in cynomolgus monkeys, a toxicologically relevant animal species, following repeated intravenous and subcutaneous administrations.
- This study shows that sirukumab has desirable pharmacokinetic characteristics (linear pharmacokinetics with long half-life), a low incidence of immunogenicity and a well-tolerated safety profile in healthy subjects, supporting further development of sirukumab as a potentially valuable therapeutic agent.

## AIMS

To assess the safety, tolerability, pharmacokinetics (PK) and immunogenicity of sirukumab (CNTO 136) following intravenous (i.v.) infusion in healthy subjects.

## METHODS

Forty-five healthy adult subjects (38 men and seven women) were randomly assigned to receive a single i.v. dose of placebo or sirukumab (0.3, 1, 3, 6 or 10 mg kg<sup>-1</sup> in a dose-escalating manner). All treated subjects were observed for 96 h post infusion and underwent 20-week follow-up evaluations. Serum samples were collected to measure sirukumab concentrations, pharmacodynamic biomarkers and antibodies to sirukumab. Non-compartmental analysis and population PK modelling were conducted to characterize the PK of sirukumab.

## RESULTS

Adverse events were generally brief in duration, mild or moderate in intensity and non-dose-dependent. No serious adverse events were observed in the sirukumab-treated subjects. Both  $C_{max}$  and  $AUC(0,\infty)$  increased in an approximately dose-proportional manner. Median terminal half-life ranged from 18.5 to 29.6 days. A two-compartment model adequately described the PK of sirukumab following i.v. administration. Population estimates for the clearance (CL), the central volume of distribution ( $V_1$ ), the inter-compartmental clearance (Q) and the peripheral volume of distribution ( $V_2$ ) were 0.364 l day<sup>-1</sup>, 3.28 l, 0.588 l day<sup>-1</sup> and 4.97 l, respectively. Compared with placebo subjects, a sustained decrease from baseline in C-reactive protein was observed in all sirukumab-treated dose groups, although no clear dose-response relationship was observed. No subjects were positive for antibodies to sirukumab.

## CONCLUSIONS

Sirukumab had a well-tolerated safety profile, desirable PK characteristics and a low incidence of immunogenicity following an i.v. infusion of 0.3 to 10 mg kg<sup>-1</sup> in healthy subjects.