DrugA

1. Mechanism of action

DrugA is a human monoclonal antibody that binds to both the soluble and transmembrane bioactive forms of human TNFa (UniProt Acc: P01375). This interaction prevents the binding of TNFa to its receptors, thereby inhibiting the biological activity of TNFa (a cytokine protein). There was no evidence of DrugA antibody binding to other TNF superfamily ligands; in particular, the DrugA antibody did not bind or neutralize human lymphotoxin. DrugA did not lyse human monocytes expressing transmembrane TNF in the presence of complement or effector cells.

2. Pharmacokinetics

Following subcutaneous administration of DrugA to healthy subjects and patients with active RA, the median time to reach maximum serum concentrations (Tmax) ranged from 2 to 6 days. A subcutaneous injection of 50 mg DrugA to healthy subjects produced a mean maximum serum concentration (Cmax) of approximately 2.5 µg/mL. DrugA exhibited dose-proportional pharmacokinetics (PK) in patients with active RA over the dose range of 0.1 to 10.0 mg/kg following a single intravenous (IV) dose. Following a single IV administration over the same dose range in patients with active RA, mean systemic clearance of DrugA was estimated to be 4.9 to 6.7 mL/day/kg, and mean volume of distribution ranged from 58 to 126 mL/kg. The volume of distribution for DrugA indicates that DrugA is distributed primarily in the circulatory system with limited extravascular distribution. Median terminal half-life values were estimated to be approximately 2 weeks in healthy subjects and patients with active RA, PsA, or AS. By cross-study comparisons of administration of DrugA, the absolute bioavailability of subcutaneous DrugA was estimated to be approximately 53%.

When DrugA was administered subcutaneously to patients with RA, PsA, or AS every 4 weeks, serum concentrations appeared to reach steady state by Week 12. With concomitant use of methotrexate (MTX), treatment with 50 mg DrugA subcutaneous every 4 weeks resulted in a mean steady-state trough serum concentration of approximately 0.4-0.6 µg/mL in patients with active RA, approximately 0.5 µg/mL in patients with active PsA, and approximately 0.8 µg/mL in patients with active AS. Patients with RA, PsA, and AS treated with DrugA 50 mg and MTX had approximately 52%, 36%, and 21% higher mean steady-state trough concentrations of DrugA, respectively, compared with those treated with DrugA 50 mg without MTX. The presence of MTX also decreased anti-DrugA antibody incidence from 7% to 2% (see Adverse Reactions (6.1)). For RA, DrugA should be used with MTX. In the PsA and AS trials, the presence or absence of concomitant MTX did not appear to influence clinical efficacy and safety parameters (see Drug Interactions (7.1) and Clinical Studies (14.1)).

3. ADME

Population PK analyses indicated that concomitant use of NSAIDs, oral corticosteroids, or sulfasalazine did not influence the apparent clearance of DrugA. Population PK analyses showed there was a trend toward higher apparent clearance of DrugA with increasing weight. However, across the PsA and AS populations, no meaningful differences in clinical efficacy were observed among the subgroups by weight quartile. The RA trial in MTX-experienced and TNF-blocker-naïve patients (Study RA-2) did show evidence of a reduction in clinical efficacy with

increasing body weight, but this effect was observed for both tested doses of DrugA (50 mg and 100 mg). Therefore, there is no need to adjust the dosage of DrugA based on weight.

Population PK analyses suggested no PK differences between male and female patients after body weight adjustment in the RA and PsA trials. In the AS trial, female patients showed 13% higher apparent clearance than male patients after body weight adjustment. Subgroup analysis based on gender showed that both female and male patients achieved clinically significant response at the proposed clinical dose. Dosage adjustment based on gender is not needed.

4. Biodistribution

After IV administration, DrugA has a volume of distribution of about 58 to 126 mL/kg. This means that DrugA stays mostly in the circulatory system.

5. Target binding

kon 0.1154 (1/picomole*day)

koff 12.52 (1/day)

Initial concentration of DrugA is 302.44nM

Apparent Volume is 3.43 L

The drug is administered subcutaneously.

6. Pharmacodynamics

In clinical studies, decreases in C-reactive protein (CRP), interleukin (IL)-6, matrix metalloproteinase 3 (MMP-3), intercellular adhesion molecule (ICAM)-l and vascular endothelial growth factor (VEOF) were observed following DrugA administration in patients with RA, PsA, and AS.

7. Abbreviations

TNF - Tumor Necrosis Factor, RA - Rheumatoid Arthritis, PsA - Psoriatic Arthritis, AS - Ankylosing Spondylitis, IV - Intravenous, PK - Pharmacokinetics, AUC - Area Under the Curve, tmax - Time to Maximum Concentration, Cmax - Maximum Concentration, FDR - False Discovery Rate, MTX - Methotrexate, NSAIDs - Non-Steroidal Anti-Inflammatory Drugs, ADAs - Anti-Drug Antibodies, CRP - C-reactive Protein