Population Pharmacokinetics (PK) of Tocilizumab Following Intravenous (IV) and Subcutaneous (SC) Administration to Patients with Rheumatoid Arthritis (RA)

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Objectives: Tocilizumab is a recombinant humanized anti-IL-6R monoclonal antibody. The analysis aimed to establish a predictive population PK model of tocilizumab following administration of 8 mg/kg IV Q4W (IV1), and 162mg SC QW (SC1) and Q2W (SC2), including identification of covariate factors influencing tocilizumab exposure.

Methods: Serum concentrations (13,642) of 1759 RA patients from two 24-week Phase III studies were analyzed.

Results: A two-compartment model with parallel linear and Michaelis-Menten elimination and first-order SC absorption accurately described tocilizumab concentrations. Parameter estimates (Table 1) were consistent with earlier results[1]. Tocilizumab clearance increases with weight (BW). For IV1, steady-state C_{trough} (ssC_{trough}) was 30% lower for BW<60kg and 65% higher for BW>100kg compared with BW=60-100kg. For SC1 (SC2), ssC_{trough} was 48% (122%) higher for BW<60kg and 46% (78%) lower for BW>100kg compared with BW=60-100 kg. Nonlinear clearance was more prevalent at low concentrations which led to stronger weight-dependence of exposure for SC2 compared to SC1. Apart from WT effect on linear clearance and volume parameters, no other covariates had clinically relevant effects on tocilizumab PK. ssC_{mean} was similar for SC1 (49.1μg/mL) and IV1 (58.7μg/mL), while trough concentrations were 2.4-fold higher (45.3 vs. 18.8μg/mL) and peak concentrations 3-fold lower (51.3 vs. 152.7μg/mL) following SC1. Nonlinear clearance led to more than dose-proportional increase in exposure for SC1 and SC2, with ssC_{trough} (ssC_{mean}) of 45.3μg/mL (49.1μg/mL) and 5.9μg/mL (10.3μg/mL), respectively.

Conclusions: The model indicated that nearly complete target saturation was achieved at steady-state during the entire dosing interval for 162 mg QW SC and 8 mg/kg Q4W IV regimens. For 162 mg Q2W SC regimen, the target-mediated elimination pathway was not completely saturated at steady-state, which led to high total clearance and high fluctuation of clearance over the entire dosing interval.

References:

[1] Frey N, Grange S, Woodworth T. J.Clin.Pharmacol. 2010;50(7):754-66.

Table 1. Parameter Estimates for the Final PK Model

Parameter	Estimate	%RSE		Parameter	Estimate	%RSE
CL (L/day)	0.216	1.18		$V_{M,CRCLN}$	0.229	7.43
V_2 (L)	4.51	1.61		$k_{a,age}$	-0.442	17.2
Q (L/day)	0.274	2.2		$k_{a,\ study}$	0.61	3.54
V_3 (L)	2.77	1.7		$F_{SC,thigh}$	1.11	0.712
V_M (mg/L/day)	1.85	1.04		σ_{study}	1.94	3.1
K_M (mcg/mL)	0.343	2.49		ω^2_{CL}	CV=27.6	4.49[a]
k_a (1/day)	0.233	2.68		ω^2_{V2}	CV=22.5	5.04[a]
F_{SC}	0.795	1.05		$R\omega_{V2}\omega_{V3}$	R=0.661	8.26[a]
CL_{WT}, Q_{WT}	0.512	4.36		ω^2_{V3}	CV=30.3	7.22[a]
$V_{2,WT}$, $V_{3,WT}$	0.683	3.86		ω^2_{ka}	CV=46.5	6.3[a]
CL_{HDL}	-0.256	10.9		ω^2_{EPS}	CV=53.8	3.72[a]
$V_{albumin}$	-0.672	9.38		σ^2	CV=20.7	3.99[a]
$V_{protein}$	0.728	12.2		[a] %RSE for the estimate of variance		