Title: Population Pharmacokinetic of Obinutuzumab (GA101) in Patients with Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin's Lymphoma (NHL)

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Objectives: Obinutuzumab (OZ) is a novel, humanized type II anti-CD20 monoclonal antibody with a glycoengineered Fc region. The aim of the analysis was to establish a predictive population model that describes obinutuzumab PK following IV administration and to identify covariate factors that may influence disposition of tocilizumab.

Methods: In total, 12,634 serum concentrations from 678 patients from 4 Phase I - III studies were analyzed. The two-compartment population PK model with time-dependent clearance ($CL=CL_{inf}+CL_T \cdot \exp(-k_{des}t)$) described OZ concentrations. The full model approach was used for covariate model development. Diagnostics plots and various predictive check procedures were used for model evaluation.

Results: For a reference patient (female, CLL, 75 kg), OZ steady-state clearance, central volume, peripheral volume, and inter-compartment clearance were estimated at CL_{inf} =0.0828 L/day (95% CI: 0.0775–0.0884 L/day), V_C=2.76 L (95% CI: 2.68–2.83 L), V_P=1.01 L (95% CI: 0.922 –1.10 L), and Q=1.29 L/day (95% CI: 1.03–1.62 L/day), respectively. CL_{inf} and V_C were respectively 22% (95%CI: 14–31%) and 18% (95% CI: 14–22%) higher in males. CL_{inf}, V_C, V_P, and Q increased with body weight as power functions with the power coefficients of 0.615 (95% CI: 0.437–0.794), 0.383 (95% CI: 0.293–0.474), 1, and 0.75, respectively. CL_{inf} was 17% (95% CI: 11–22%) lower in patients with B-cell lymphomas (BCL) and diffuse large B-cell lymphomas (DLBCL), and 75% (95% CI: 25–144%) higher in patients with Mantle cell lymphomas (MCL) compared with patients with CLL. CL_T was estimated at 0.231 L/day (95% CI: 0.196–0.272 L/day), was 49% (95% CI: 23–80%) higher in males, and depended on body weight and diagnosis similarly to CL_{inf}. For patients with CLL with baseline tumor size above 1750 mm^2, time-dependent clearance declined with the half-life of 19 days, and concentrations approached the steady-state levels after approximately 4 months of dosing. Decline of time-dependent clearance was 108% (95% CI: 63–164%) faster in patients with NHL compared with patients with CLL, and 165% (95% CI: 110–235%) faster in patients with baseline tumor size below 1750 mm^2.

Conclusions: The expected differences in exposure for the proposed 1000 mg IV dosing regimen to patients with CLL do not warrant a dose modification based on gender and weight.