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

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Objectives: Obinutuzumab is a novel, humanized type II anti-CD20 monoclonal antibody (mAb) with a glycoengineered Fc region. The analysis aimed to establish a predictive population model that describes PK of GA101 following IV administration and to identify covariate factors that influence its disposition.

Methods: Serum concentrations (12,634) of 678 patients (50.4% with CLL) from 4 Phase I - III studies were analyzed in NONMEM. The full model approach was used for covariate model development.

Results: Consistent with other mAbs targeting B-cells, the two-compartment population PK model with time-dependent clearance ($CL=CL_{inf}+CL_T.\exp(-k_{des}t)$) described GA101 concentrations. Parameters were estimated precisely (Table 1), and predictive check procedures indicated good predictive abilities of the model. CL_T was 2.8-fold higher than CL_{inf}. Both values depended on diagnosis. They were 17% lower for B-cell lymphomas and diffuse large B-cell lymphomas, and 75% higher for Mantle cell lymphomas compared to CLL. For patients with CLL and baseline tumor size (BSIZ) > 1750 mm^2, decline of time-dependent clearance ($t_{1/2}$ = 19 days) led to steady-state after approximately 4 months for 1000 mg q4w dosing (with 2 additional doses at weeks 1 and 2 of cycle 1). Clearance declined faster (higher k_{des}) for patients with NHL (by 108%) and patients with BSIZ< 1750 mm^2 (by 165%). The results are consistent with target-mediated CL (with higher CL for higher tumor burden and higher CD20 expression) that decreases with elimination of target cells.

The parameters at steady-state were typical for mAbs. CL_{inf}, CL_T, and Vc were higher in males and increased with body weight, but differences in steady-state exposure based on weight and gender were <30%.

GA101 PK was independent of age, renal function or anti-drug antibodies (detected in 17 subjects).

Conclusions: In CLL patients, the expected differences in steady-state exposure based on weight and gender do not warrant a dose modification for the proposed 1000 mg IV q4w dosing regimen.

Table 1. Parameter Estimates of the Final Model

Parameter	Estimate	%RSE	Parameter	Estimate	%RSE
k_{des} (1/day)	0.0359	10.8	$CL_{T,DIS23}$=$CL_{inf,DIS23}$	0.834	3.54
CL_T (L/day)	0.231	8.43	$CL_{T,DIS4}$ =$CL_{inf,DIS4}$	1.75	17
CL_{inf} (L/day)	0.0828	3.37	$k_{des,BSIZ<1750}$	2.65	11.9
V_C (L)	2.76	1.38	ω^2_{kdes}	CV=127%	7.95 [b]
V_P [a] (L)	1.01	4.47	ω^2_{CLT}	CV=95.3%	11.1 [b]
Q (L/day)	1.29	11.5	ω^2_{CLinf}	CV=39.9%	7.12 [b]
$CL_{inf,WT}$ = $CL_{T,WT}$	0.615	14.8	ω^2_{Vc}	CV=18.5%	9.03 [b]
$V_{C,WT}$	0.383	12.1	ω^2_{Vp}	CV=60.1%	10.6 [b]
$CL_{T,SEX}$	1.49	9.7	ω^2_{Q}	CV=94.3%	17.5 [b]
$CL_{inf,SEX}$	1.22	3.6	ω^2_{EPS}	CV=52.3%	10 [b]
$V_{C,SEX}$	1.18	1.83	$\sigma^2_{proportional}$	CV=17.8%	4.52 [b]
$k_{des,NHL}$	2.08	12.3	$\sigma^2_{additive}$ $(\mu g/mL)^2$	SD=0.165	69.1 [b]

[a] Parameters Q and V_P were scaled as $(BW/75)^{3/4}$ and (BW/75), respectively.

[b] Relative Standard Error (%RSE) for the estimate of variance

CL_{inf}, non-specific time-independent clearance; CL_T, initial value of time-dependent clearance; k_{des}, decay coefficient of time-dependent clearance; ω^2_{EPS}, variance of inter-individual error on proportional residual error. P_{COV}, effect of covariate COV on parameter P, where DIS23 is B-cell lymphoma and diffuse large B-cell lymphoma; DIS4 is mantle cell lymphoma; WT is weight; SEX is sex; BSIZ is the baseline tumor size (mm^2).