Population pharmacokinetics of andecaliximab, an inhibitor of MMP9, for the treatment of advanced solid tumors

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Objectives: Matrix metalloproteinase 9 (MMP9) is involved in primary tumor growth, metastasis, angiogenesis and tumor-associated immune suppression. Andecaliximab (andeca), an IgG4 monoclonal antibody, is a selective inhibitor of MMP9. The objective is to develop a population pharmacokinetic (PK) model to characterize andeca PK in subjects with solid tumors, and evaluate the influence of potential covariates on clearance and volume.

Methods: Results from a phase 1b dose-escalation (part A: 200, 600, and 1800 mg, q2week IV) and expansion (part B: 800 mg q2week and 1200 mg q3week, IV) study in subjects with advanced solid tumors were used for the analysis. The model development dataset included 991 plasma concentrations from 88 subjects. A nonlinear mixed effects approach (NONMEM 7.3) was used for population PK modeling and R v3.3.2 was used for data processing/visualization. Covariates evaluated were baseline body weight, albumin, gender, age, and type of cancer.

Results: Andeca PK was best described by a two compartment model with dual (saturable [CL\textsubscript{sat}] and linear [CL\textsubscript{linear}]) elimination pathways, inter-individual variability on CL\textsubscript{linear}, CL\textsubscript{sat} and V1 and a proportional error model. The mean (%CV) values for key parameters were CL\textsubscript{linear} = 0.106 (71.5) L/day, CL\textsubscript{sat} = 1.24 (30.5) L/day, Q = 0.360 L/day, V1 = 6.50 (67.2) L, V2 = 1.22 L and C\textsubscript{50} = 31.0 µg/mL. None of the covariates tested were statistically significant on clearance or volume. A dose dependent decrease in CL\textsubscript{sat} approaching PK linearity at andeca doses > 600 mg was observed, indicating saturation of MMP9.

Conclusion: A population PK model for andeca, accounting for a nonlinear elimination mechanism, was developed. The structural model parameters were in agreement with typical characteristics of circulating IgG antibodies. The results indicate that andeca 800 mg q2week IV is expected to saturate the target (MMP9), and therefore supports further evaluation of this dose in a Phase 3 study for the first line treatment of subjects with gastric cancer.