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Development of a Target-Mediated Drug Disposition Model for the Prediction of Target Occupancy of MEN1112, an Anti Bst1/CD157 Humanized Antibody for the Treatment of Acute Myeloid Leukaemia

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Poster: Drug/Disease modelling - Oncology

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Objectives: The pharmacokinetics of MEN1112, a humanized de-fucosylated monoclonal IgG1 antibody directed against human Bst1/CD157, has been described in relapsed/refractory (R/R) acute myeloid leukaemia (AML) patients. Under the assumption that the degree of target engagement at the site of action drives clinical response, the aim of the present work was to develop a mechanistic target-mediated drug disposition (TMDD) model [1] to provide an *in silico* projection of receptor occupancy (RO) in peripheral blood (PB) and bone marrow (BM) under different dosing schedules supporting dose selection for next clinical trials.

Methods: Circulating free MEN1112 serum concentrations from R/R AML patients subjects from FIH study [2] after multiple intravenous administration at five escalating doses of MEN1112 injected weekly were used for model building. The quasi-steady state (QSS) approximation of the general TMDD model [3-5] was implemented. NONMEM VII was used to develop the model. Model performances were evaluated through changes in Objective Function, GoF plots and VPCs. The next step was to project RO at the target site (i.e. bone marrow) under two major data limitations: neither the target concentration in BM is known, nor the partition coefficient between BM and plasma. Assumptions regarding the similarity between target and plasma MEN1112 concentrations were considered conscientiously, and the results from such analysis served as the rationale to design the different scenarios of a simulation study consisting on evaluating RO assuming different ratios of target concentration between BM and plasma: (1) receptor density in BM to be equal to the estimate obtained from serum data (R0), and (2) receptor density in BM to be 30, 50, 100 and 200 % higher than R0 (most plausible scenarios given that the majority of patients had baseline leukopenia).

Results: A TMDD model using the QSS approximation including inter-patient variability on initial target density and additive residual error provided a very good description of the individual profiles, and all parameters were estimated with high precision [relative standard errors (RSE) < 20%]. Sensitivity analysis showed that MEN1112 concentration vs time profiles are sensitive to changes in main parameters related to TMDD kinetics, supporting parameter identifiability. The estimate of the drug-receptor dissociation constant resembles very well the result obtained from *in vitro* binding experiments, supporting the mechanistic nature of the model. RO in peripheral blood was predicted to be 50 and 75% at steady-state concentrations of MEN1112 at the highest doses explored so far. Lower doses were associated with RO lower than 30%. At Cmax median RO in BM, assuming receptor density 50, 100 and 200% greater than R0, is predicted to be ≥ 75% at the next dose levels according to the dose escalation. With respect to Cmin, median RO ≥ 75% was obtained only for the highest planned dose in the escalation in all simulation scenarios.

Conclusions: In conclusion, this pharmacometric evaluation has integrated all information available (in a comprehensive and mechanistic quantitative way). It therefore allows to rational discuss about potential receptor occupancy in next clinical trials, as well as to suggest design characteristics improving the understanding of drug response and making less uncertain the outcome of future clinical trials.