Development of a Target-Mediated Drug Disposition Model for the Prediction of Target Occupancy of MEN1112/OBT357, an Anti Bst1/CD157 Humanized Antibody for the Treatment of Acute Myeloid Leukaemia

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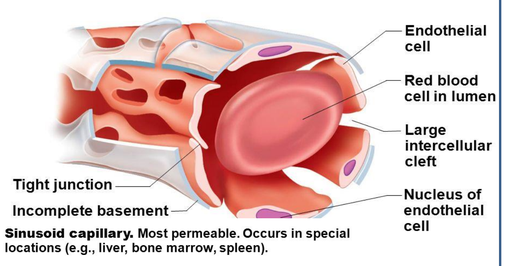
OBJECTIVE

MEN1112 is a humanized de-fucosylated monoclonal IgG1 antibody directed against human Bst1/CD157, currently under development in relapsed/refractory acute myeloid leukaemia (AML) (ARMY-1 study). In absence of receptor occupancy assessments in target or surrogate tissues, the aim of the present work was to develop a mechanistic target-mediated drug disposition (TMDD) model (i) to describe MEN1112 pharmacokinetics and (ii) to provide an *in silico* projection of receptor occupancy (RO) in peripheral blood and at the target site (i.e. bone marrow (BM)).

METHODS

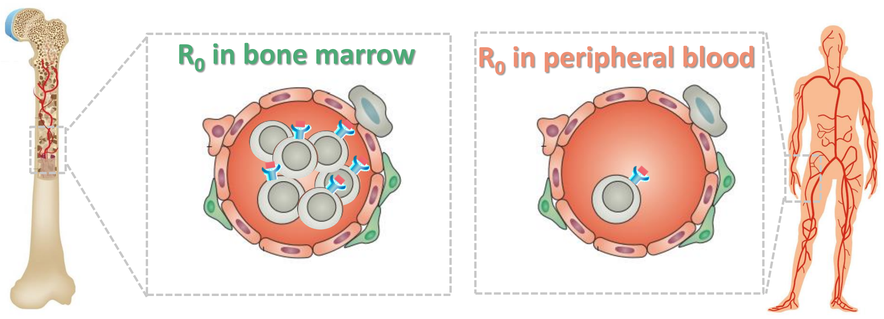
- Circulating free MEN1112 serum concentrations from 32 R/R AML patients subjects from FIH ARMY-1 study after multiple IV administration at five escalating doses of MEN1112 (0.1-1.7 mg/kg) injected weekly for two 3-week cycles were used for model building. Extensive PK sampling scheme (~30 samples/patient over 2 cycles) was adopted in the FIH study to fully characterize the expected TMDD behaviour of the drug
- The quasi-equilibrium (QE) approximation [1] of the general TMDD model [2] was implemented. NONMEM version 7.3 was used to develop the model
- The next step was to project RO at the target site (i.e. bone marrow) under two major data limitations: neither the partition coefficient between BM and peripheral blood is known, nor the receptor density in BM

- With regard to the first limiting factor, literature data [3] suggest that monoclonal antibodies can freely cross the sinusoidal clefts found in highly vascularized organs, such as liver, spleen, and bone marrow, leading to an exposure to the free antibody of the same extent as the one reached in peripheral blood



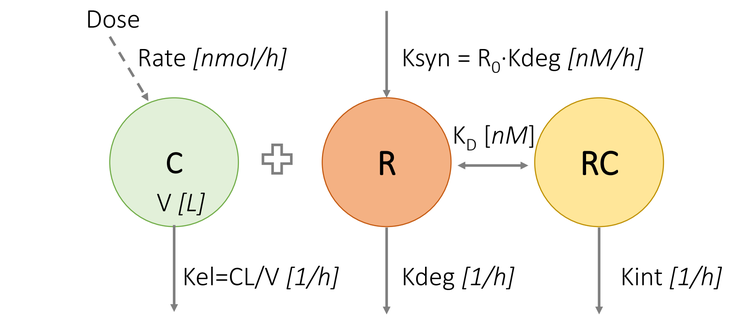
Sinusoid capillary. Most permeable. Occurs in special locations (e.g., liver, bone marrow, spleen).

- With regard to the second limiting factor, different simulation scenarios, consisting on evaluating RO assuming different ratios of receptor density between BM and peripheral blood, have been considered:
  1. Receptor density in BM to be equal to the estimate obtained from serum data (R_0)
  2. Receptor density in BM to be 30, 50, 100 and 200% higher than R_0 (most plausible scenarios given that the majority of patients had baseline leukopenia)



CONCLUSIONS

- It has to be taken into account that data obtained in the literature for another monoclonal antibody, isatuximab, indicates that the relationship found between *in vitro* and BM receptor occupancy with respect to plasma concentrations was similar [4-5]
- These evidences corroborates the likelihood that this pharmacometric evaluation allows the prediction of MEN1112 RO at all doses planned in ARMY-1 trial



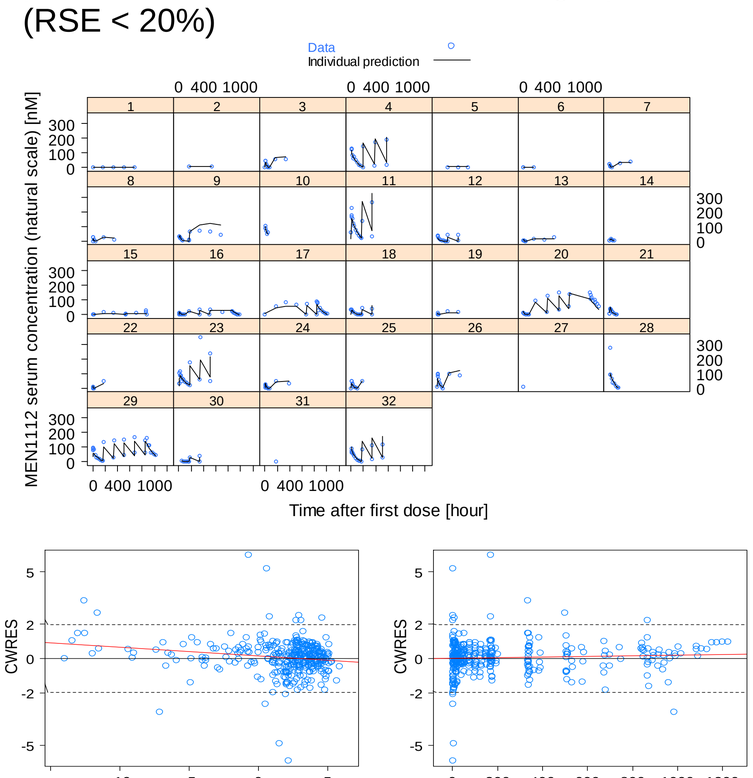
$$C_{tot} = C + RC$$
$$R_{tot} = R + RC$$
$$\begin{cases} \frac{dC_{tot}}{dt} = \frac{Rate}{V} - K_{int} RC - K_{el} C \\ \frac{dR_{tot}}{dt} = K_{syn} - (K_{int} - K_{deg})(C_{tot} - C) - K_{deg} R_{tot} \end{cases}$$
$$R_{tot}(t=0) = R_0$$
$$C = 0.5\left[(C_{tot} - R_{tot} - K_D) + \sqrt{(C_{tot} - R_{tot} - K_D)^2 + 4K_D C_{tot}}\right]$$

C = free drug in serum R = free receptor RC = drug-receptor complex

TMDD Model diagram and its QE approximation equations

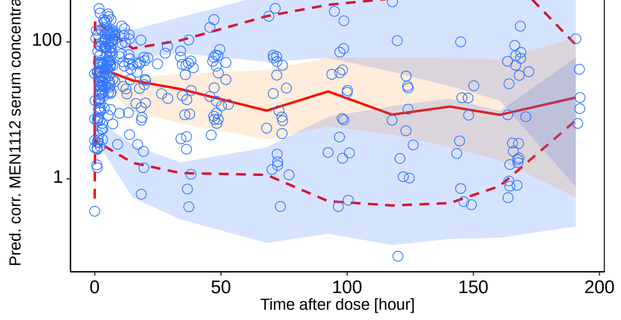
RESULTS

- A TMDD model using the QE approximation including IIV on initial receptor density (R_0) and additive residual error provided a very good description of the individual profiles, and all parameters were estimated with high precision (RSE < 20%)

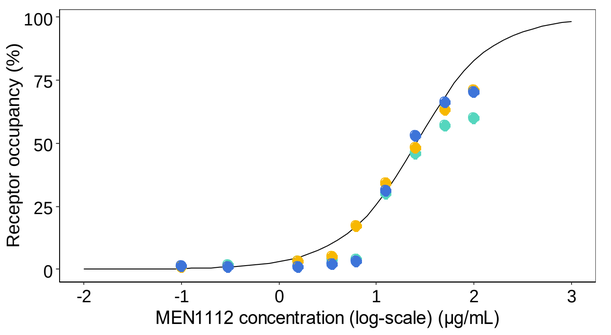


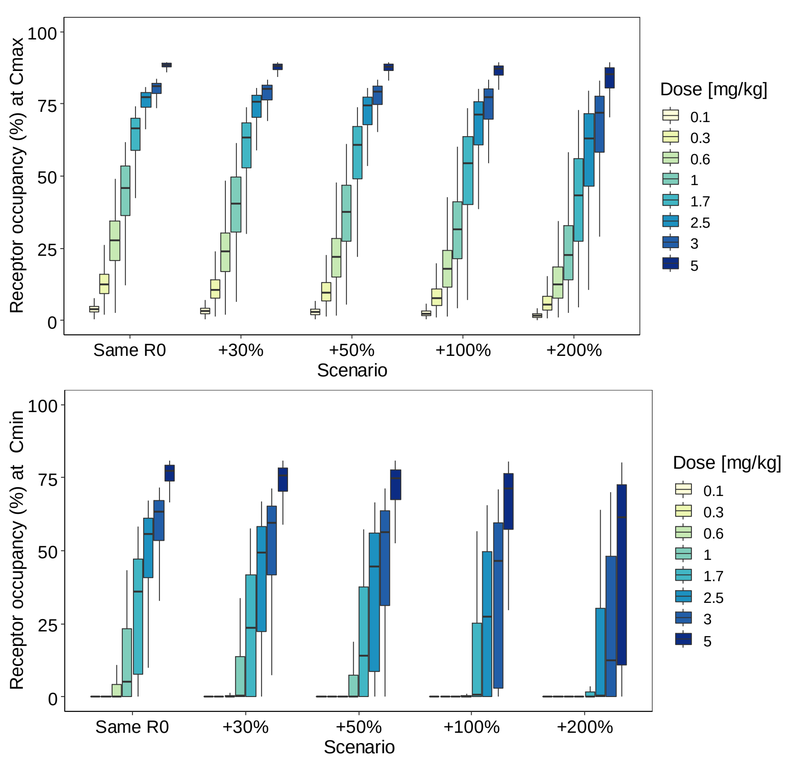
Parameter	Units	Estimate	RSE (%)
CL	L/hr	0.0171	17
V	L	4.24	4
K_D	nM	124	16
R_0	nM	90.9	19
Kdeg	1/hr	0.0053	18
Kint	1/hr	0.271	14
Inter-individual variability (IIV)			
IIV R_0	CV% [shrinkage %]	70.8 [3]	16
Residual variability [shrinkage %]		4	
Additive	nM	0.264	3

CV%: percentage coefficient of variation; RSE relative standard error.
CL: linear clearance; V: volume of the central compartment; K_D: dissociation constant; R_0: initial receptor concentration; Kdeg: receptor turnover rate constant; Kint: receptor-drug complex internalization rate constant.



- The estimate of the drug-receptor dissociation constant (K_D) resembles very well the result obtained from *in vitro* binding experiments, supporting the mechanistic nature of the model





- At Cmax and for receptor density in BM that are 50, 100 and 200% greater than R_0, a median RO ≥ 75% was achieved starting from 1.7 mg/kg, supporting the hypothesis of positive risk-benefit for patients
- With respect to Cmin, a median RO ≥ 60% was obtained only for the 5 mg/kg at all simulation scenarios, which was also associated with a median RO ≥ 75% only for the scenarios with a receptor density in BM up to 50% of that estimated for peripheral blood

References:

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MEN1112 is a development collaboration project of Menarini Ricerche and Oxford BioTherapeutics

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