From Animal to Human with a new monoclonal antibody: An example of the use of pharmacokinetics only to assist on the choice of first in human dose

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Background

- Drug A is a fully human antibody that binds with high affinity to a ligand binding site on Cells C.
- Drug A is able to induce expansion of Cells C in normal young mice, young and old rats and cynomolgus monkeys.
- The objective of this analysis was to assist in obtaining a minimally acceptable biological effect level (MABEL) in Human.
- No ligand concentrations and receptor occupancy data could be obtained and thus a full mechanistic PKPD model could not be identified.

Methods - Assumptions

- Rat and cynomolgus monkey are relevant species for extrapolation to human
- PD effect occurs with saturation of PK as illustrated by rat data:
- Target Mediated Drug Disposition (TMDD) observed with rat and monkey data
- Similar TMDD predicted in the human
- For a rapidly accessible target, target saturation and clearance saturation are equal
- Saturation of PK is taken to be an auxiliary biomarker that can be used for dose selection
- Assumes equivalent receptor expression across species that is supported by the equivalent TMDD exposure threshold in rat and monkey
- Similar potency between monkey and human based on *in vitro* tests
- Allometric scaling for PK:
  - Clearances scaled by body weight with an exponent of 0.75, Volumes with an exponent of 1
  - Vm scaled by body weight with an exponent of 1

Data

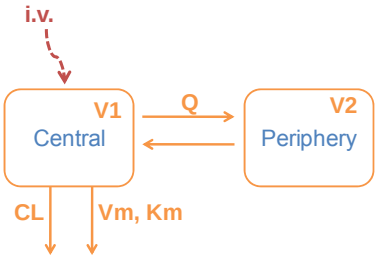
- **Pre-clinical studies:**

Toxicology studies in rats and cynomolgus monkeys (Dose Range Finding and 4 weeks toxicology study)

- **Clinical study:**

Single Ascending Dose (SAD) in healthy subjects (2 hours i.v. infusion)

Structure of the PK Model



Pre-clinical Results

Figure 1. Rat PK and PD data

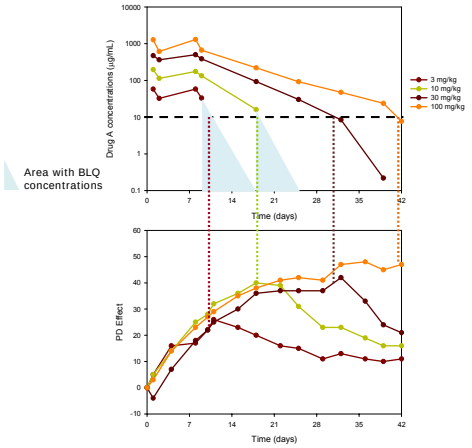
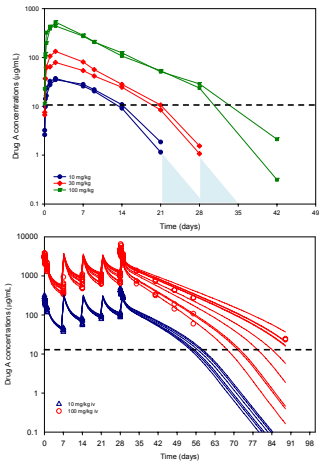


Figure 2. Cynomolgus monkey PK data



Similar Drug A concentration threshold for TMDD in rats and cynomolgus monkeys

Table 1. Estimated PK parameters for a 3.5 kg monkey

Parameters	Estimates
CL (L/d)	0.0256
V1 (L)	0.110
Q (L/d)	0.0581
V2 (L)	0.191
Vm (L/d)	0.518
Km (µg/mL)	5.1

Allometric scaling

Table 2. Predicted PK parameters for a 75 kg human based on allometric scaling

Parameters	Predictions
CL (L/d)	0.300
V1 (L)	2.40
Q (L/d)	0.675
V2 (L)	4.13
Vm (L/d)	11.1
Km (µg/mL)	5.1

Maximum Recommended Starting Dose strategy

Toxicology (rat and monkey)
[1] NOAEL 1 mg/kg
[2/3] HED 1 mg/kg

[4] Apply ≥10-fold safety factor
0.1 mg/kg

Pharmacology
[5] MABEL
- MABEL was defined as 30% receptor occupancy (assuming TMDD occurs at exposures below 100% receptor occupancy)
- 30% target saturation occurs at a concentration defined as Km*(3/7) = 2 µg/mL

Dose providing a $C_{max} \leq 2$ µg/mL = 0.1 mg/kg

0.1 mg/kg + 0.1 mg/kg

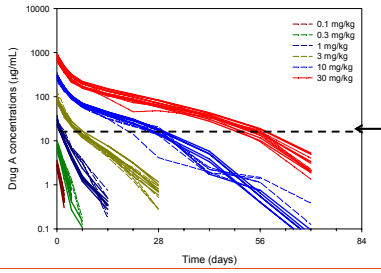
"Maximum Recommended Starting Dose"
0.1 mg/kg

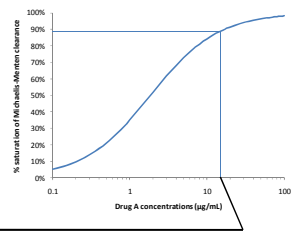
Clinical Results

Table 3. Estimated PK parameters in Human

Parameters	Estimates
CL (L/d)	0.303
V1 (L)	2.83
Q (L/d)	0.724
V2 (L)	4.43
Vm (L/d)	6.05
Km (µg/mL)	1.86

Figure 3. Human individual PK profiles (dashed) and population predictions (solid)





Threshold for 90% saturation of the clearance: 16 µg/mL

Conclusions

- First in Human Dose successfully selected from allometric scaling of PK only
- TMDD observed in Human as predicted from pre-clinical results
- Human PK parameters estimated from SAD study used to select dosing regimen in the multiple dose study

Reference
Hans Peter Grimm. Gaining insights into the consequences of target-mediated drug disposition of monoclonal antibodies using quasi-steady-state approximations. J Pharmacokinet Pharmacodyn (2009) 36: 407-420