Translational PK-RO modelling for a mAb to predict the outcome of the first in human study

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Context

In the European guideline [1] for first in human (FIH) study, the strategies to mitigate and manage risks for trial participants refer specifically to the calculation of the starting dose to be used in humans, the subsequent dose escalation steps, the criteria for maximum dose and the criteria to stop the study.

PK/PD modelling can help to define the minimal anticipated biological effect level (MABEL) in humans, the dose escalation steps and the corresponding receptor occupancy (RO).

In preclinical development, monkey is the reference species to predict the pharmacokinetics (PK) of monoclonal antibodies (mAb) in human. Allometric scaling can be used to transpose the PK model from monkeys to support the FIH study in healthy volunteers.

The compound in development is a mAb (S 95011 / OSE-127) developed in collaboration between Servier and OSE Immunotherapeutics.

Objectives

The objectives of this work are to:

- Predict doses and RO in healthy volunteers (HV) for the FIH study
- Compare the predicted concentrations and RO with the observations in the FIH study
- To build a population PK model with the first results of the FIH study (single ascending dose (SAD) to predict doses and interval between 2 doses for the multiple ascending dose (MAD).

Methods

1) Prediction of the PK and RO for the FIH study:

- PK models for S 95011 (OSE-127) in monkeys
  - IV 3 dose levels (8 animals, ♂ and ♀)
  - SC 1 dose (1 ♂ and 1 ♀)
- *Ex-vivo* PK/PD relationship between the mAb concentration and the RO

2) Transposition of the PK model in humans:

- Allometric scaling of the PK model
- Using the *ex-vivo* PK/PD relationship, calculation of RO in humans and time during which RO > 95 %
- Recommendation of doses based on criteria and simulations

3) Comparison of human predictions and observations in FIH study and population PK model in HV:

- Comparison predictions versus observations
- Population PK model with data from the SAD
- Simulations designs for the MAD

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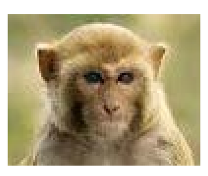
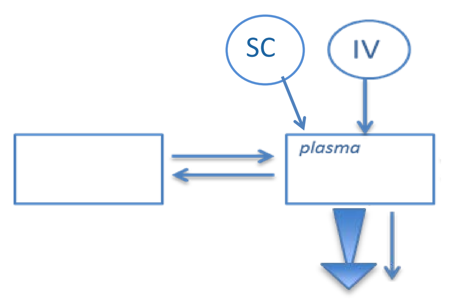
Results

1) Population PK in monkeys:



➢ *Population PK parameters:*

	Estimate	RSE (%)
CL (L/h)	0.000297	37.0
VC (L)	0.188	20.8
VP (L)	0.0695	29.2
Q (L/h)	0.00637	63.9
Vmax	0.0340	17.7
Km	0.804	83.2
CLADA* (L/h)	0.00154	18.3
Ka (/h)	0.0207	29.4
F (%)	88.1	8.60

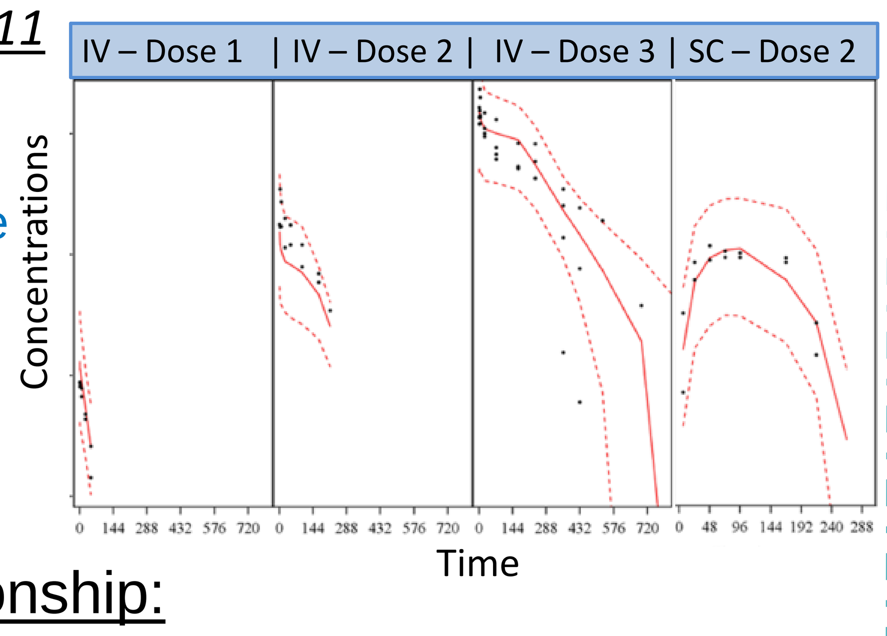


** CL for anti-drug antibody (ADA)*

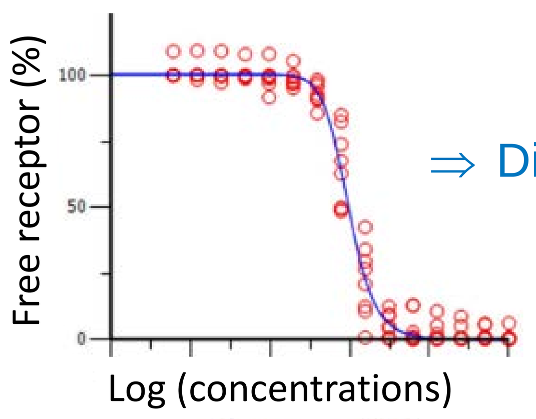
➢ *VPC after S 95011 administration:*

⇒ Quite good description of the concentrations

⇒ No systematic bias

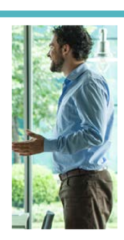


Ex-vivo relationship:



⇒ Direct sigmoïd E_{max} model

2) Transposition of the PK model in humans:

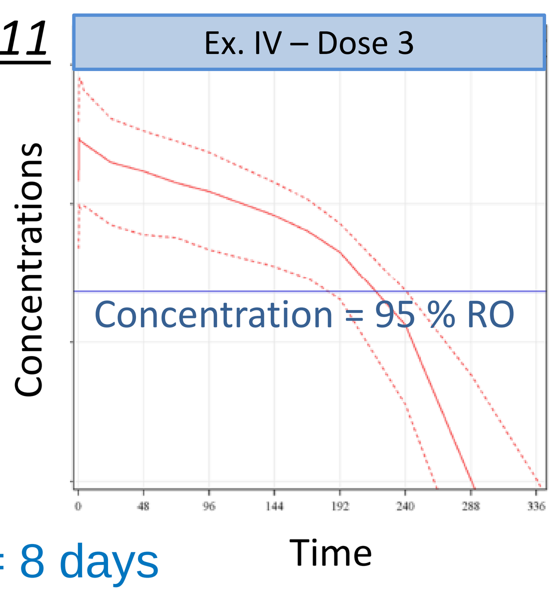


⇒ Inter-species translation
Allometric scaling [2] [3] [4]

$$\theta_{monkey} = \theta_{mouse} \cdot \left(\frac{BW_{monkey}}{BW_{mouse}}\right)^{\alpha}$$

$\alpha = 1$ for volumes
$\alpha = 0.85$ for CL and Vmax
$\alpha = -0.25$ for rate constants Ka
No scaling for Km and F

➢ *Simulation after S 95011 for Dose 3:*



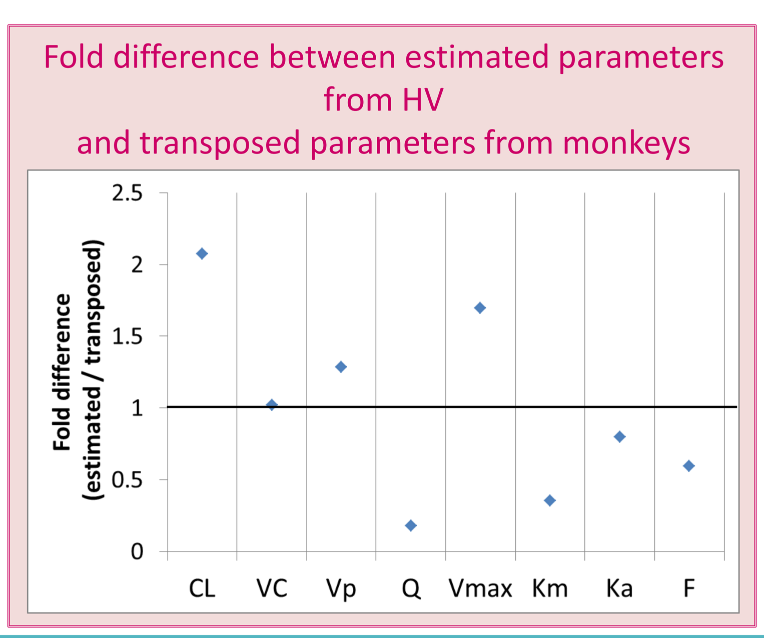
At Dose 3:
maximum RO = 100 %
Duration for RO > 95 % = 8 days

Recommendation of doses for FIH study:

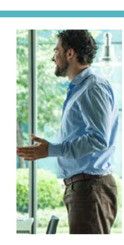
⇒ First dose: maximum RO < 20 % in plasma

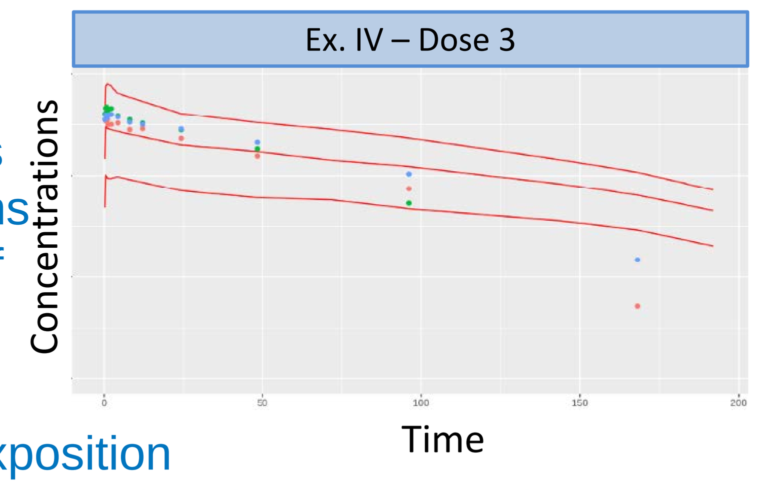
⇒ Last dose: duration for RO > 95 % < 5 months

⇒ Prediction of concentrations, maximum RO and duration for RO > 95 % in HV after 6 IV doses and 1 SC dose



3) Comparison of human predictions and observations in FIH:





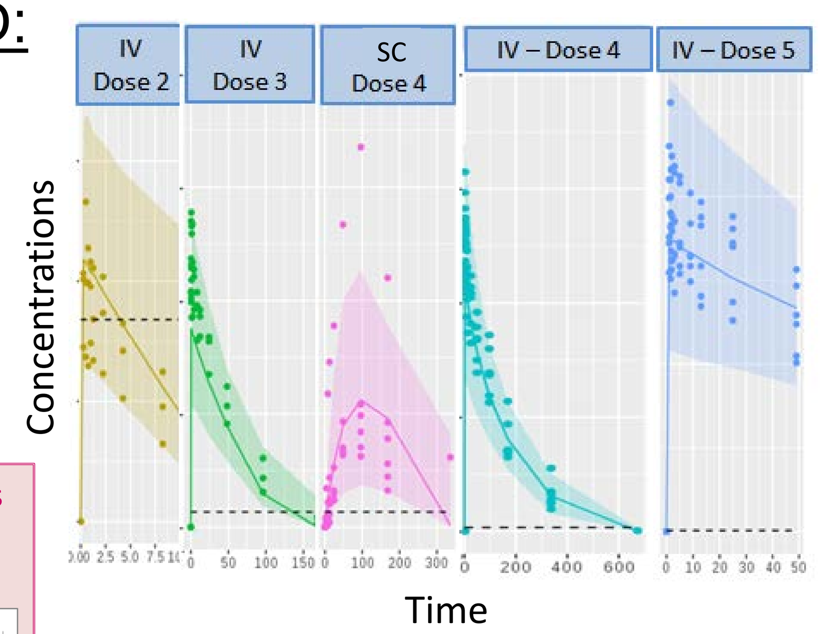
⇒ Good predictions of the observations

⇒ No adjustment of the doses during the SAD

⇒ The duration of exposition was over predicted, so the observed duration with RO > 95 % was lower than predicted (between D4 and D8 instead of 8 days for this dose)

Population PK model with SAD data to predict MAD:

➢ *VPC after S 95011:*



⇒ Good description of the concentrations

⇒ No systematic bias

⇒ Simulation of designs for MAD

Conclusion

Translational PK-RO modelling for a mAb was successfully applied for the prediction of doses for the FIH study, using allometric scaling of clearances parameters (linear and non linear), volumes and absorption rate constant.

For the phase 2 doses prediction, a target mediated drug disposition (TMDD) model will be built using concentrations and RO from the FIH study (SAD + MAD) and *in vitro* measurements of total target in HV and patients.

MID3 value: medium impact as justification of doses selection.[5]

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References

1. EMEA/CHMP/SWP/28367/07 Rev. 1 (2017) Committee for Medicinal Products for Human Use (CHMP) Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products
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4. Singh P. Quantitative Prediction of Human Pharmacokinetics for mAbs Exhibiting Target-Mediated Disposition. AAPS J. (2015) Vol. 17, No. 2 43:252-259
5. Workgroup EM, et al. Good Practices in Model-Informed Drug Discovery and Development: practice, Application, and Documentation. CPT (2016) 5 (3) : 93–122

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