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Development and validation of a PBPK model of gepotidacin in rats to predict exposure in human prostate

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Introduction

Gepotidacin is a novel antibiotic currently under phase 3 development for uncomplicated urinary tract infection and uncomplicated gonorrhoea. The objective of the current study was to assess the possibility of predicting its human prostate pharmacokinetics by combining preclinical data and physiologically based pharmacokinetic (PBPK) modeling.

Materials and methods

1

20 rats
Gepotidacin IV Bolus 20 mg/kg single dose

In vivo microdialysis serial sampling over 5h from blood, muscle and prostate

LC-MS/MS assay

Unbound plasma, muscle and prostate gepotidacin concentrations

Step 1: PK study of gepotidacin pharmacokinetics in blood, muscle and prostate using multiple time-points *in vivo* microdialysis

2

Rat physiological parameters from literature

Rat unbound plasma, muscle and prostate data

PBPK model fitting and selection

Best rat PBPK model

Step 2: Development of a PBPK model for gepotidacin in rats

3

26 participants
Oral Gepotidacin 1500 mg single dose

Prostatectomy followed by *ex vivo* microdialysis

Serial plasma concentrations

Plasma sampling over 48h

LC-MS/MS assay

One prostate time-point per participant

Step 3: Composite human prostate concentration-time profile constructed from *ex vivo* microdialysis samples in a clinical study (NCT04484740/P2463).

4

Best rat PBPK model

Human physiological parameters from literature

Human PBPK model

Human prostate data

Validation

Human plasma data

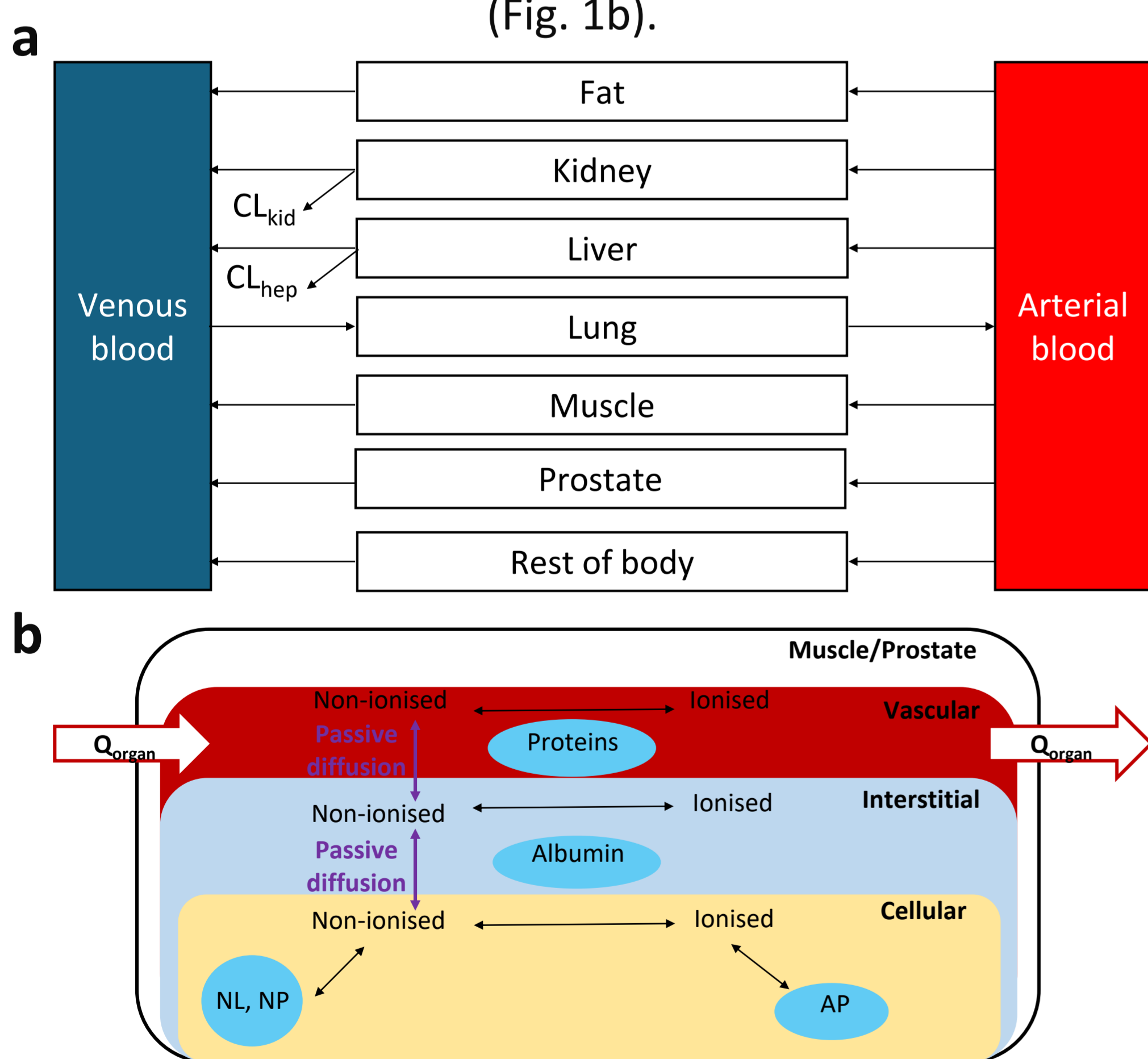
Step 4: Development and validation of a PBPK model for gepotidacin in humans

Mathematical methods and software :

- Three model structures were tested : Full PBPK, Reduced PBPK and PermQ PBPK (1)
- Three partition coefficient (Kp) calculation methods were tested, Rodgers and Rowland's traditional method (2), Rodgers and Rowland's method taking lysosomal trapping into account (3) and Schmitt's method (4)
- Rat prostate partition coefficients were determined experimentally, human prostate partition coefficient were fixed to the rat value
- Plasma PK parameter estimation was performed with Monolix (5).

Results

The best PBPK model (**Figure 1**) was a flow limited reduced PBPK model (Fig. 1a). Muscle and prostate were separated into vascular, interstitial and cellular spaces (Fig. 1b).



As seen on **Figure 2**, rat unbound plasma, muscle and prostate concentrations were adequately described by the PBPK model with more than 80% of the predicted concentrations within 2-fold of the observed concentrations.

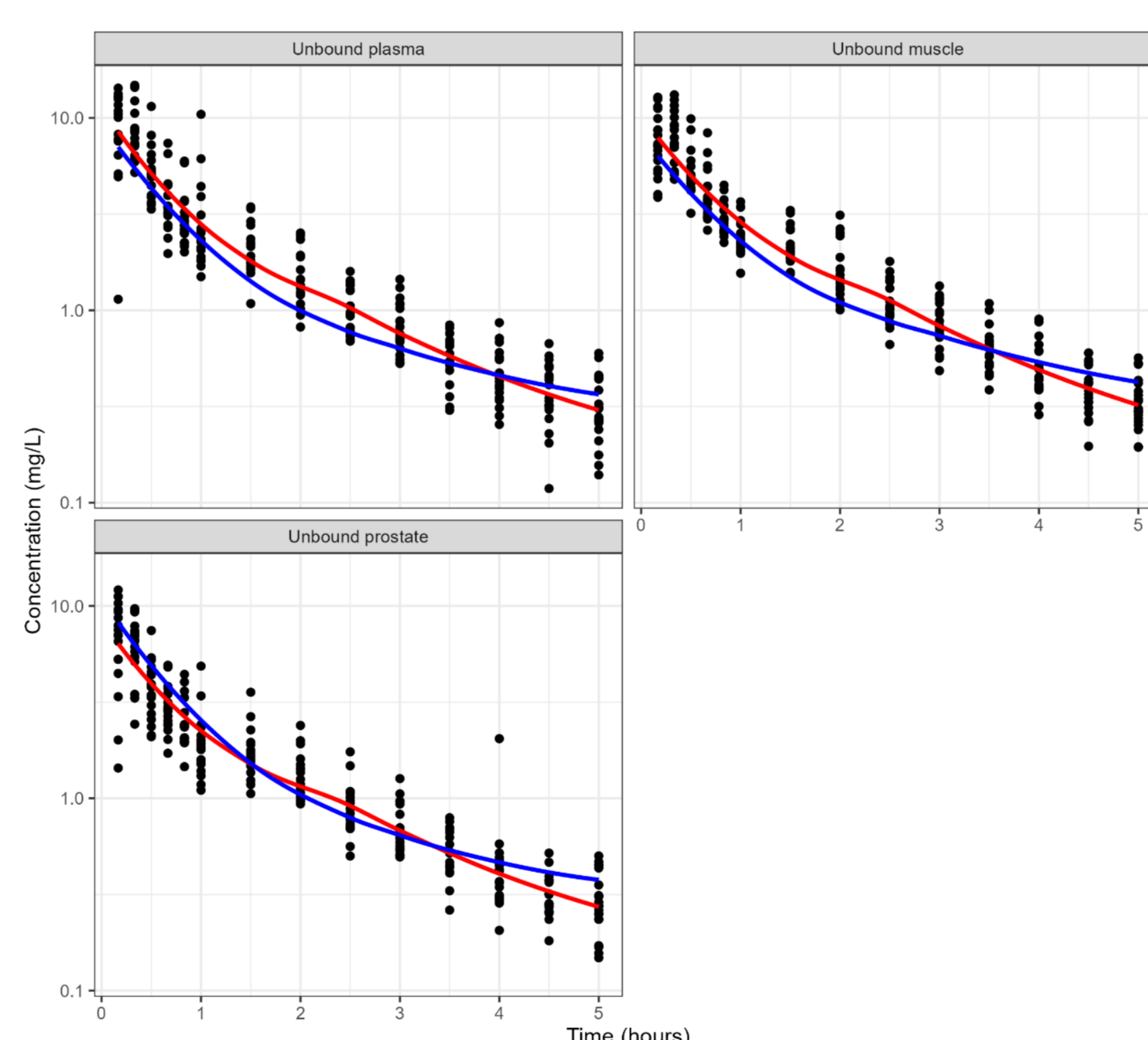


Figure 2: Rat measured concentrations (points) with observation mean (red) and prediction mean (blue).

As seen on **Figure 3**, there is a general agreement between the mean predicted prostate concentrations and the observed mean unbound prostate concentrations with 66.7% of the of the predicted concentrations within 2-fold of the observed concentrations.

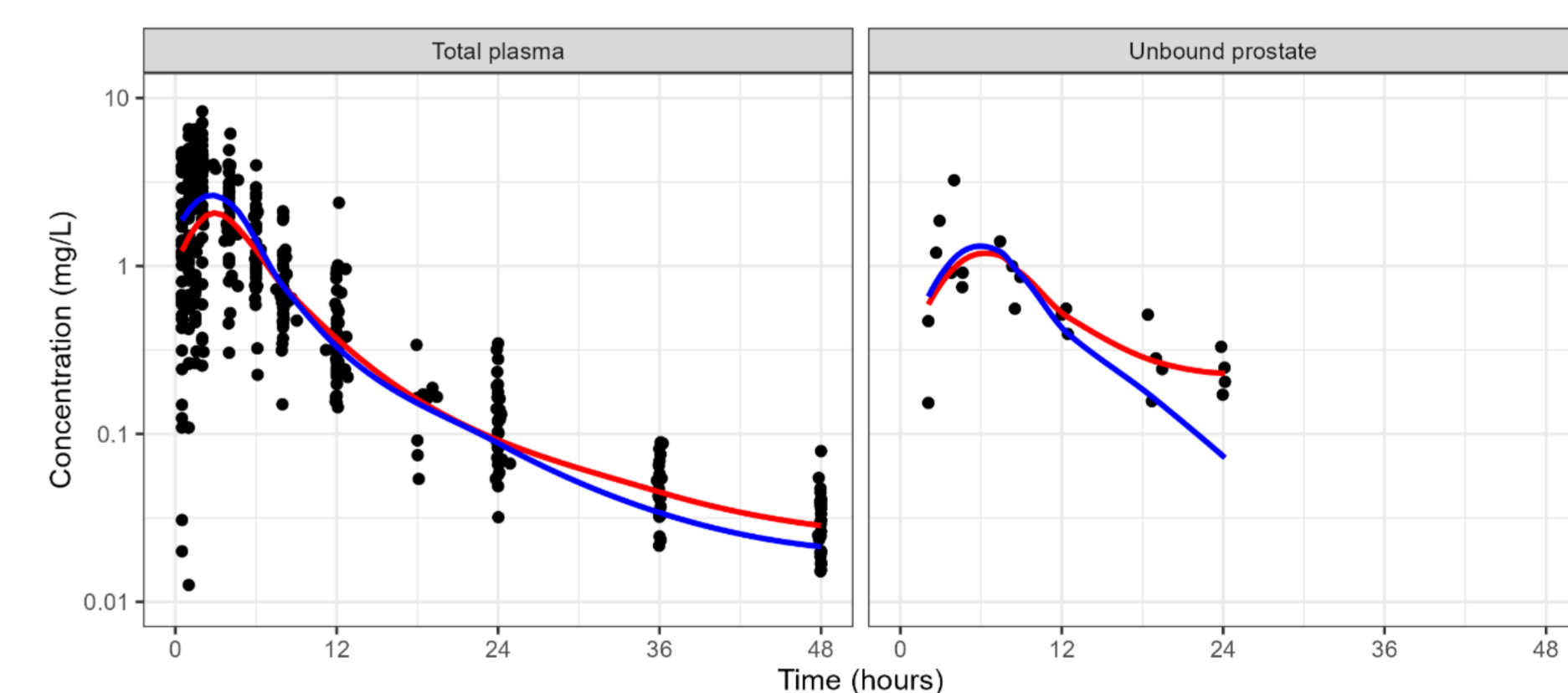


Figure 3: Human measured concentrations (points) with observation mean (red) and prediction mean (blue).

Conclusion

A PBPK model was developed with rat microdialysis data and translated to a human PBPK model to adequately predict human *ex vivo* prostate microdialysate data.

References

- 1) Korzekwa et al. [10.1111/cts.13314](https://doi.org/10.1111/cts.13314)
- 2) Rodgers and Rowland, [10.1002/jps.20322](https://doi.org/10.1002/jps.20322)
- 3) Schmitt et al. [10.1016/j.tiv.2007.09.010](https://doi.org/10.1016/j.tiv.2007.09.010)
- 4) Schmitt et al. [10.1124/dmd.120.000161](https://doi.org/10.1124/dmd.120.000161)
- 5) Monolix 2023R1, Lixoft SAS, a Simulations Plus company

Disclosure statement

GSK provided funding for the bioanalysis of samples from this study. Hwa-Ping Feng and Karen O'Dwyer are employees of and shareholders in GSK.

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