

# Population pharmacokinetic analysis of intravenous telavancin in healthy subjects undergoing plasma and tissue microdialysis

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## Background

- Telavancin is a novel lipoglycoprotein used to treat complicated skin and soft tissue infections and hospital acquired pneumonia with MRSA.
- Increased emergence of microbial resistance as well as poor penetration abilities of vancomycin have increased the importance of telavancin which exhibits a dual mechanism of action against Gram positive pathogens.
- Non-compartmental analysis of systemic total telavancin concentrations in a microdialysis study gave an average calculated target index ( $AUC_{0-24}/MIC$ ) slightly below the proposed value [1].
- The aim of this evaluation [1] was the development of a compartmental population pharmacokinetic model and its application to assess the tissue distribution of telavancin and PK/PD target attainment at steady state.

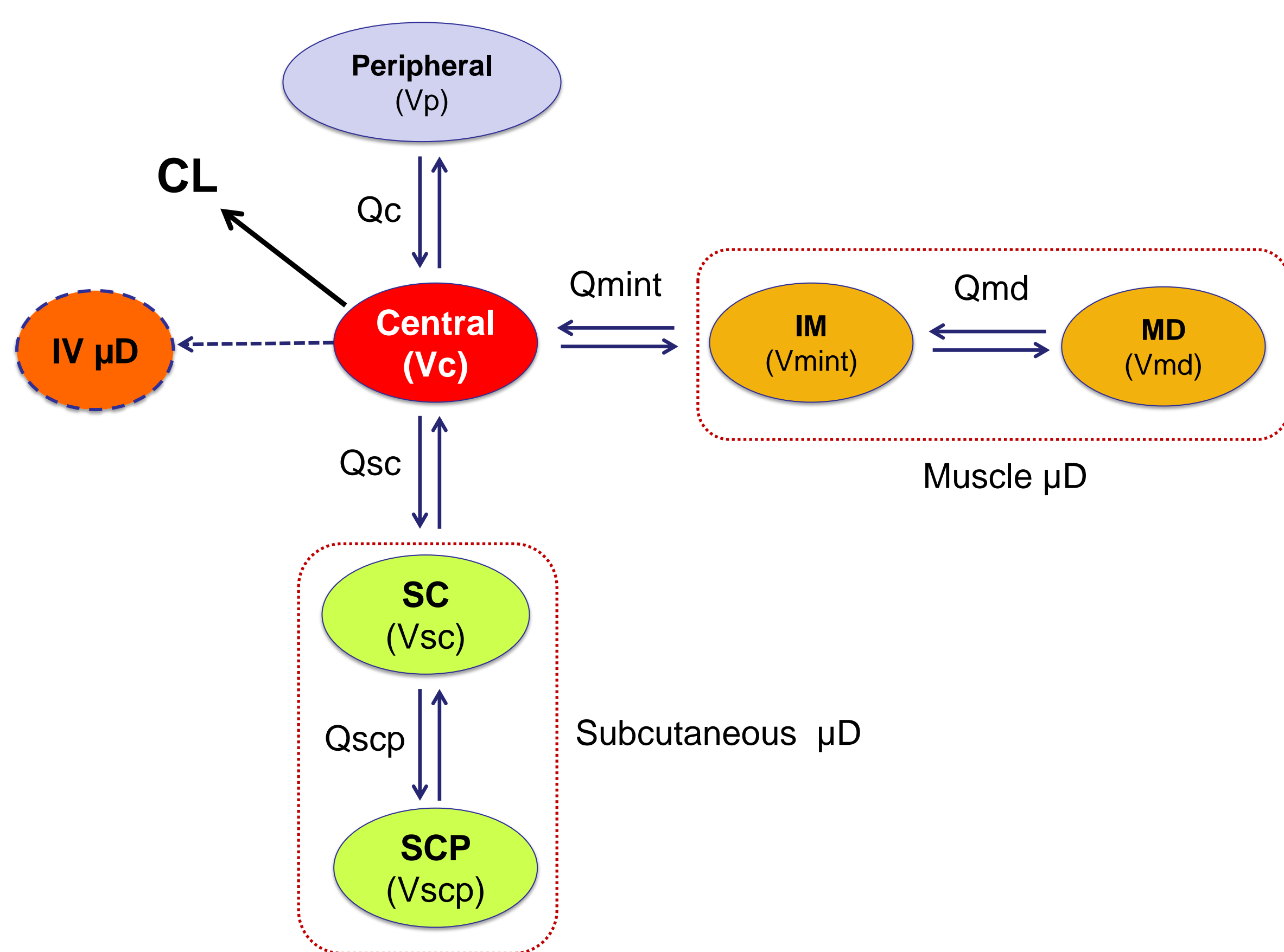
## Materials and Methods

- Data was available for eight male healthy subjects (median [range] age and body weight of 27 [23-35] years and 76.5 [67.0-83.4] kg). A single intravenous infusion of telavancin (10mg/kg within 1 hour) was given to all subjects.
- Plasma samples and microdialysis samples, representing unbound telavancin concentrations in plasma, muscle and subcutaneous tissue, were taken at pre-defined intervals[1].
- Population pharmacokinetic modeling and Monte Carlo simulations were performed using NONMEM VII and Monolix suite 2016R1. Bootstrap analysis and visual predicted checks (VPCs) were performed in order to evaluate performance of the model.

## Results & Discussion

Plasma concentrations of telavancin were best described by a two compartment model with saturable protein binding. Clearances and volumes were scaled allometrically. Two additional compartments each (interstitial and peripheral) described the distribution into muscle and subcutaneous tissue (Fig. 1).

The probability of target attainment (PTA) was only 39% after the first dose but was 97 % at steady state. Time over MIC ( $T_{>MIC}$ ) was 100% both after single dose and steady state in plasma, muscle and subcutaneous tissue at a MIC range of 0.016-0.25 mg/L.



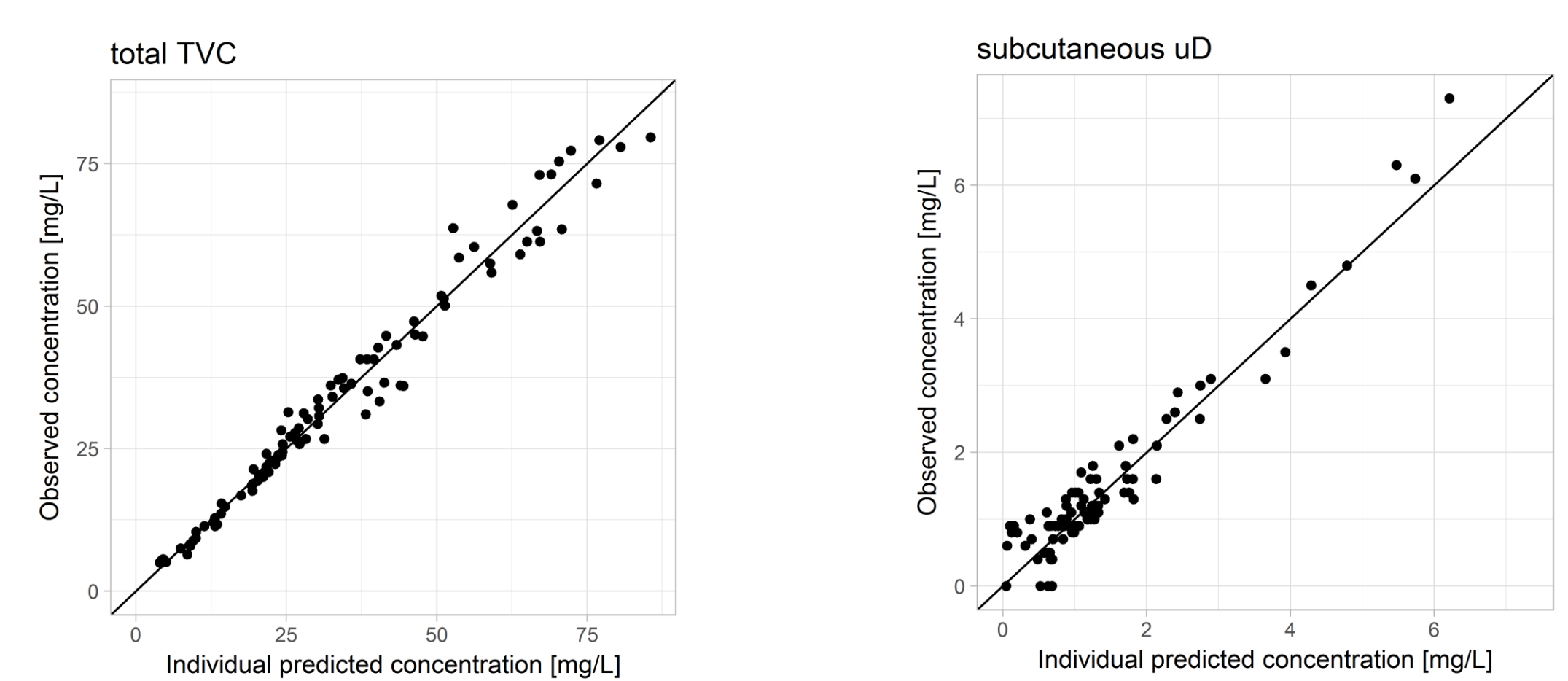
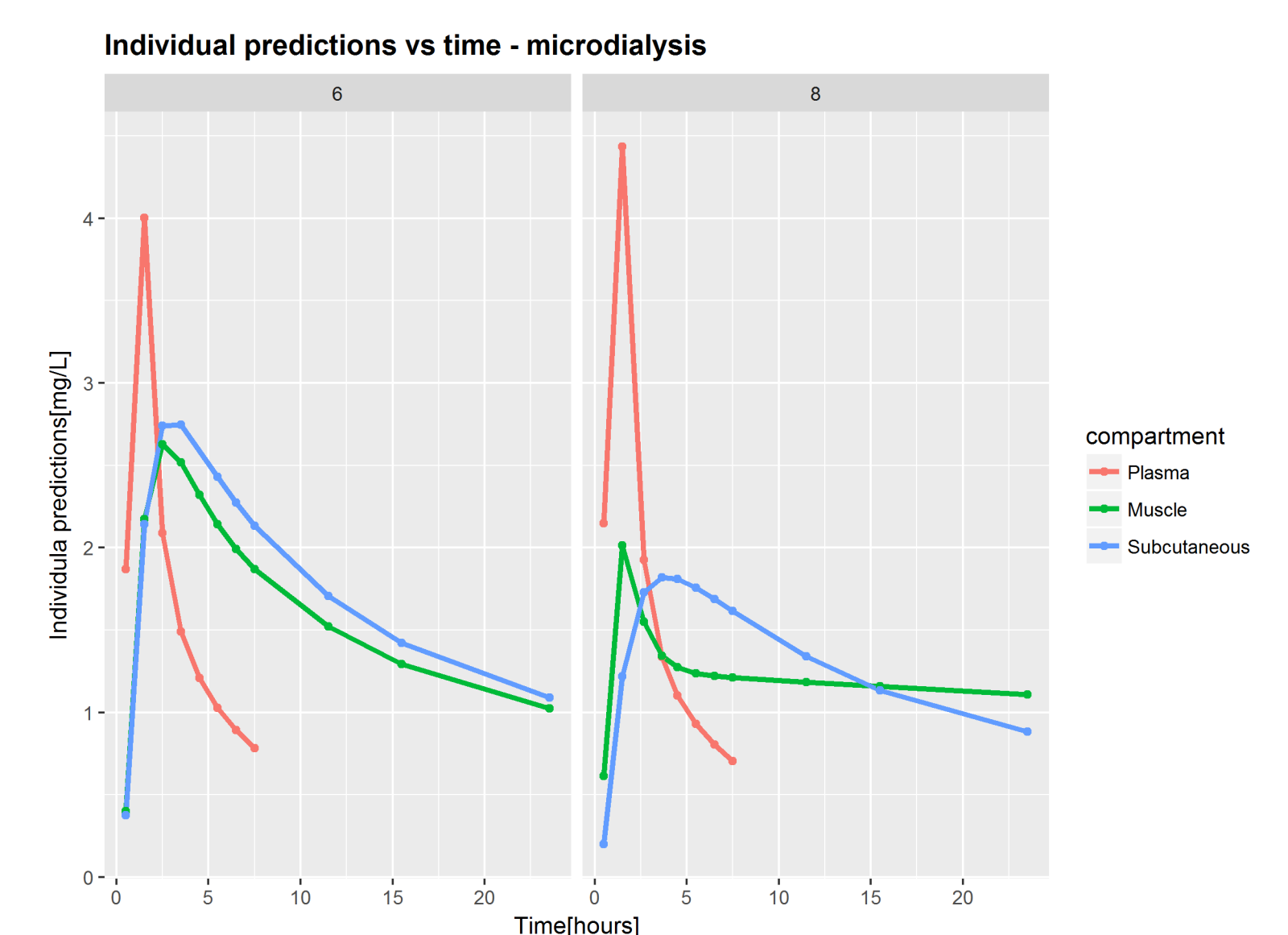
**Fig. 1. Model structure** (with CL representing elimination clearance; Vc, Vp, Vsc, Vscp, Vmint and Vmd representing volumes of distribution of central, peripheral, interstitial and peripheral subcutaneous, interstitial and peripheral muscle compartments and Qc, Qsc, Qscp, Qmint and Qmd representing inter-compartmental clearances between respective compartments.)

For a 10 mg/kg dose, simulations on total plasma concentrations indicated an  $AUC_{0-24}/MIC$  of 3609 [range 3166-4147] and 3984 [range 3485-4577] for a MIC of 0.125 mg/L [2] after single dose and at steady state respectively.

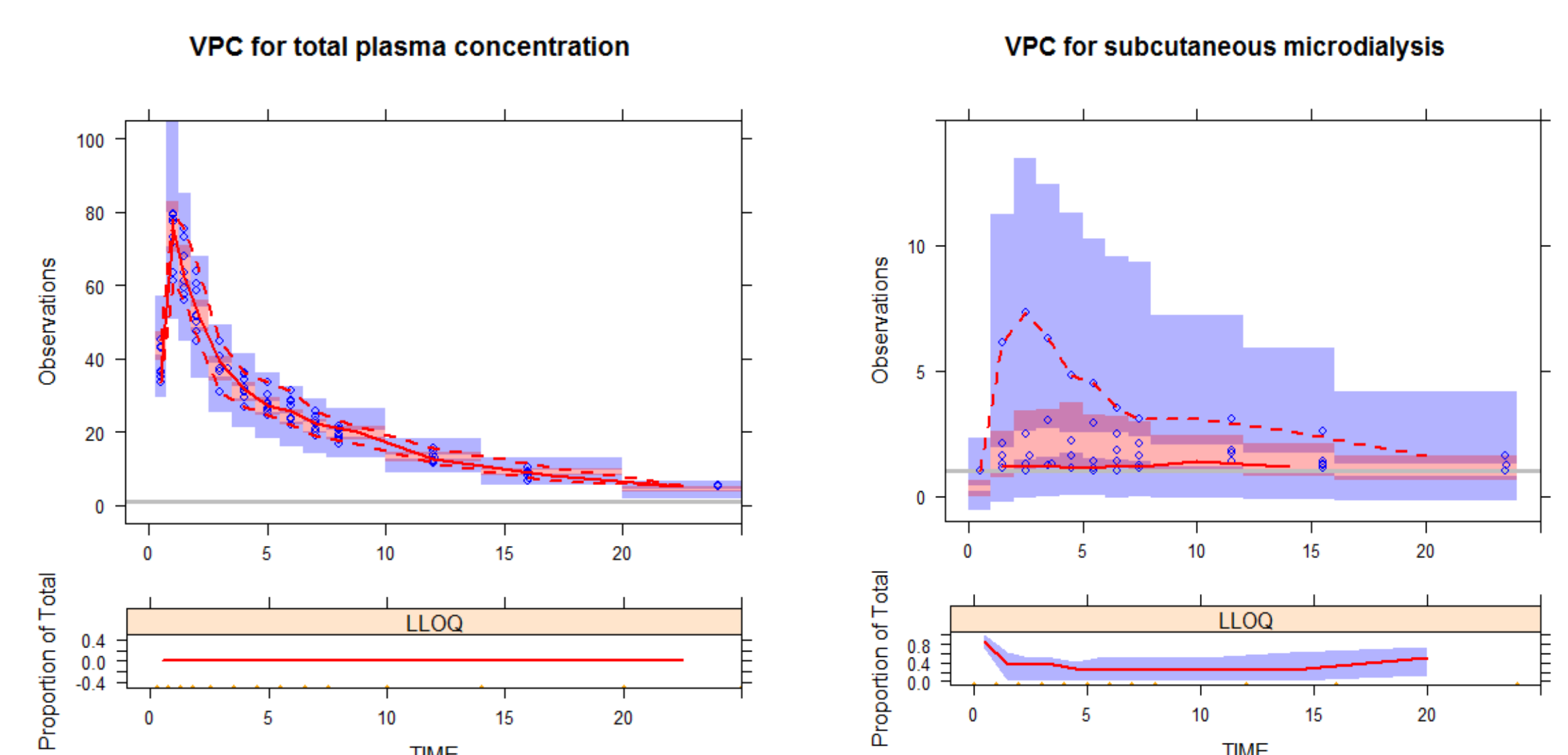
| Plasma parameters / bootstrap median (95% CI) | Subcutaneous parameters / bootstrap median (95% CI) | Muscle parameters / bootstrap median (95% CI) |
|---|---|---|
| CL (L/h)                                      | Vsc (L)   | Vmint (L)                                     |
| Vc(L)   | Qsc (L/h)   | Qmint (L/h)                                   |
| Qc (L/h)                                      | Qscp (L/h)  | Qmd (L/h)                                     |
| Vp (L)  | Vscp (L)  | Vmd (L)                                       |
| Bmax (mg/L)                                   |   |   |
| Kd (mg/L)                                     |   |   |

**Table 1. Bootstrap medians of population pharmacokinetic parameters**

**Fig 2. Exemplary predicted concentration-time curves of two selected subjects**



**Fig 3. Goodness of fit (GOF) plots (individual predictions vs observations) for total telavancin plasma and subcutaneous microdialysis measurements**



**Fig 4. Visual Predictive checks (VPCs) for total telavancin plasma and subcutaneous microdialysis measurements**

## Conclusion

The empirical model was able to describe the data and to provide a new hypothesis on telavancin plasma protein binding *in vivo*. This study suggested that PK/PD target is achieved with the current dose and elimination from the subcutaneous and muscle tissue appears to be slow which might be beneficial for treating skin and soft tissue infections.

## References

- [1] Matzneller P, Österreicher Z, Reiter B, Lackner E, Stimpfl T, Zeitlinger M. Tissue pharmacokinetics of telavancin in healthy volunteers: a microdialysis study. J Antimicrob Chemother. 2016 Nov;71(11):3179-3184.
- [2] European Committee on antimicrobial susceptibility testing (EUCAST). Consultation on Proposed EUCAST Telavancin Breakpoint Changes, June 2014 [http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST\\_files/Consultation/2014/EUCAST\\_telavancin\\_breakpoint\\_consultation\\_20140602.pdf](http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Consultation/2014/EUCAST_telavancin_breakpoint_consultation_20140602.pdf). Accessed February 26, 2017.