Building and evaluation of a PBPK model for tefibazumab in healthy adults

Version	**1.0-OSP12.1**
based on *Model Snapshot* and *Evaluation Plan*	https://github.com/Open-Systems-Pharmacology/Tefibazumab-Model/releases/tag/v1.0
OSP Version	12.1
Qualification Framework Version	3.3

This evaluation report and the corresponding PK-Sim project file are filed at:

https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/

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1 Introduction

Tefibazumab is a humanized monoclonal antibody (IgG1) against the clumping factor A (ClfA) of *Staphylococcus aureus*. Tefibazumab shows a pharmacokinetic (PK) behavior which is typical for an antibody without endogenous target.

The herein presented evaluation report evaluates the performance of the physiologically based pharmacokinetic (PBPK) model for tefibazumab in healthy adults.

The presented Tefibazumab PBPK model as well as the respective evaluation plan and evaluation report are provided open-source (https://github.com/Open-Systems-Pharmacology/Tefibazumab-Model).

2 Methods

2.1 Modeling Strategy

The development of the large molecule PBPK model in PK-Sim® has previously been described by Niederalt et al. (Niederalt 2018). In short, the model was built as an extension of the PK-Sim® model for small molecules incorporating (i) the two-pore formalism for drug extravasation from blood plasma to interstitial space, (ii) lymph flow, (iii) endosomal clearance and (iv) protection from endosomal clearance by neonatal Fc receptor (FcRn) mediated recycling.

For model development and evaluation, PK data were used from compounds with a wide range of solute radii and from different species. The PK data used for parameter estimation were from the following compounds: antibody–drug conjugate BAY 79-4620 in mice (Bayer in house data), antibody 7E3 in wild-type and FcRn knockout mice (Garg 2007, Garg2009), domain antibody dAb2 in mice (Sepp 2015), antibodies MEDI-524 and MEDI-524-YTE in monkeys (Dall'Acqua 2006), and antibody CDA1 in humans (Taylor 2008). The PK data used for model evaluation were from inulin in rats (Tsuji1983) and tefibazumab in humans (Reilly 2005).

The PBPK model including the estimated physiological parameters as described by Niederalt et al. (Niederalt 2018) is available in the Open Systems Pharmacology Suite from version 7.1 onwards.

This evaluation report focuses on the PBPK model for the antibody antibodies tefibazumab.

Details about input data (physicochemical, *in vitro* and PK) can be found in Section 2.2.

Details about the structural model and its parameters can be found in Section 2.3.

2.2 Data

2.2.1 In vitro / physico-chemical Data

A literature search was performed to collect available information on physicochemical properties of tefibazumab. The obtained information from literature is summarized in the table below.

Parameter	Unit	Value	Source	Description
MW	g/mol	150000	Lobo 2004	Molecular weight
r	nm	5.34	Taylor 1984	Hydrodynamic solute radius
Kd (FcRn)	µM	0.63	Zhou 2003	Dissociation constant for binding of a human IgG1 antibody to human FcRn at pH 6

2.2.2 PK Data

Published clinical PK data on tefibazumab in healthy adults were used.

Publication	Description
Reilly 2005	The plasma concentration–time profiles after single dose 15 min i.v. infusion of 2, 5, 10, or 20 mg/kg body weight in healthy adults were used.

2.3 Model Parameters and Assumptions

2.3.1 Absorption

There is no absorption process since tefibazumab was administered intravenously.

2.3.2 Distribution

The standard lymph and fluid recirculation flow rates and the standard vascular properties of the different tissues (hydraulic conductivity, pore radii, fraction of flow via large pores) from PK-Sim were used (Niederalt 2018).

2.3.3 Metabolism and Elimination

The FcRn mediated clearance present in the standard PK-Sim model was used as only clearance process. The standard physiological parameters related to FcRn mediated clearance were used (rate constants for endosomal uptake and recycling, association rate constant for FcRn binding and concentration of FcRn in the endosomal space) (Niederalt 2018).

2.3.4 Automated Parameter Identification

The Kd(FcRn) was fitted to the experimental plasma concentrations.

Model Parameter	Optimized Value	Unit
`Kd(FcRn)`	0.85	µM

3 Results and Discussion

The PBPK model for tefibazumab was evaluated with clinical PK data.

The next sections show:

1. the final model parameters for the building blocks: Section 3.1.
2. the overall goodness of fit: Section 3.2.
3. simulated vs. observed concentration-time profiles for the clinical studies used for model building and for model verification: Section 3.3.

3.1 Final input parameters

The compound parameter values of the final PBPK model are illustrated below.

Compound: Tefibazumab

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	9999 mg/l	Other-/Dummy value not used in the simulation	Measurement	True
Reference pH	7	Other-/Dummy value not used in the simulation	Measurement	True
Lipophilicity	-5 Log Units	Other-/Dummy value not used in the simulation	Measurement	True
Fraction unbound (plasma, reference value)	1	Other-Assumption	Measurement	True
Is small molecule	No			
Molecular weight	150000 g/mol	Publication-Lobo2004		
Plasma protein binding partner	Unknown			
Radius (solute)	0.00534 µm	Publication-Taylor1984		
Kd (FcRn) in endosomal space	0.85 µmol/l	Parameter Identification		

Calculation methods

Name	Value
Partition coefficients	PK-Sim Standard
Cellular permeabilities	PK-Sim Standard

Processes

3.2 Diagnostics Plots

Below you find the goodness-of-fit visual diagnostic plots for the PBPK model performance of all data used presented in Section 2.2.2.

The first plot shows observed versus simulated plasma concentration, the second weighted residuals versus time.

Table 3-1: GMFE for Goodness of fit plot for concentration in plasma

Group	GMFE
10 mg/kg dose	1.11
2 mg/kg dose	1.43
20 mg/kg dose	1.15
5 mg/kg dose	1.15
All	1.20

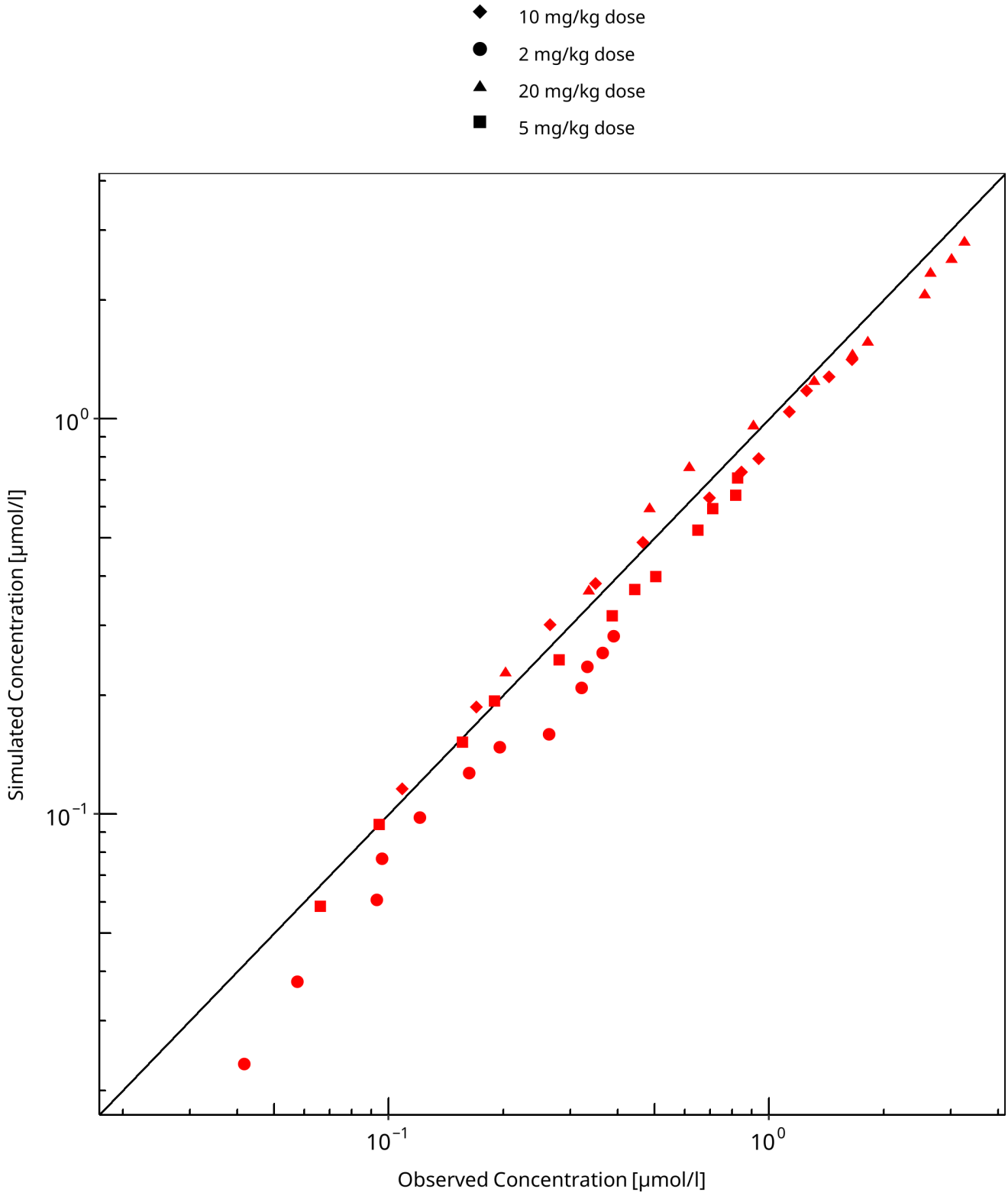

Figure 3-1: Goodness of fit plot for concentration in plasma

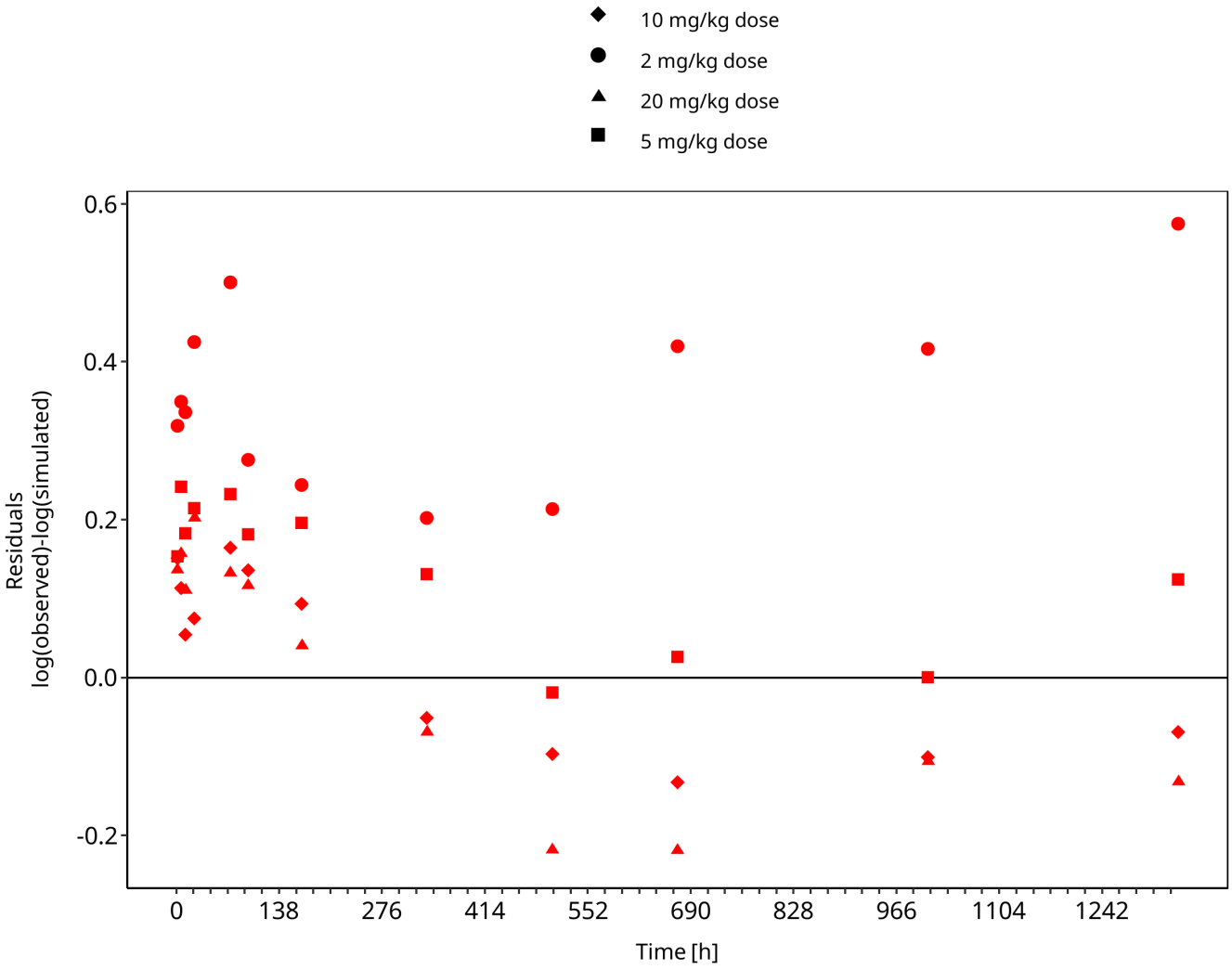

Figure 3-2: Goodness of fit plot for concentration in plasma

3.3 Concentration-Time Profiles

Simulated versus observed concentration-time profiles of all data listed in Section 2.2.2 are presented below.

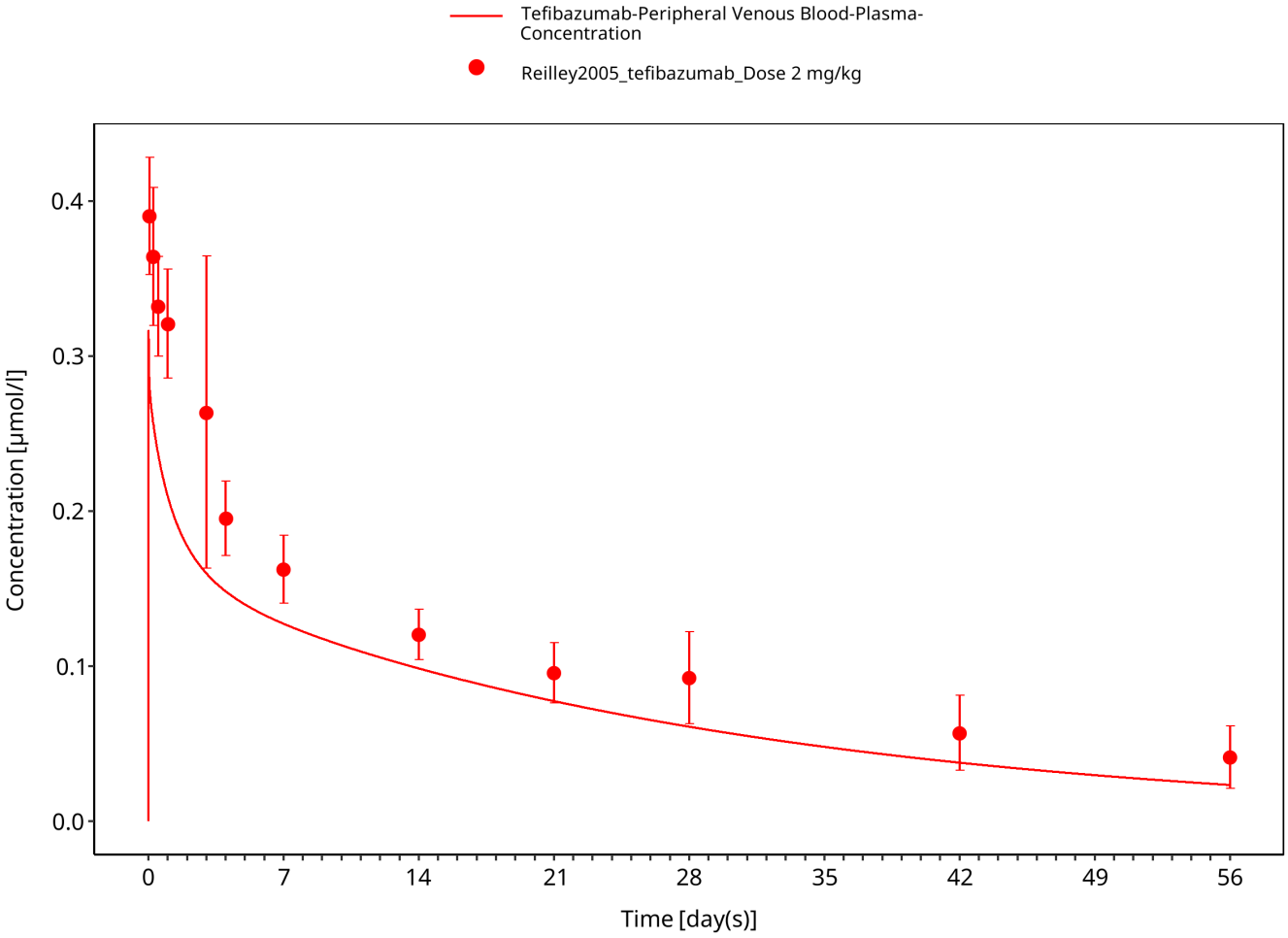

Figure 3-3: Plasma concentration - 2 mg/kg dose (linear scale)

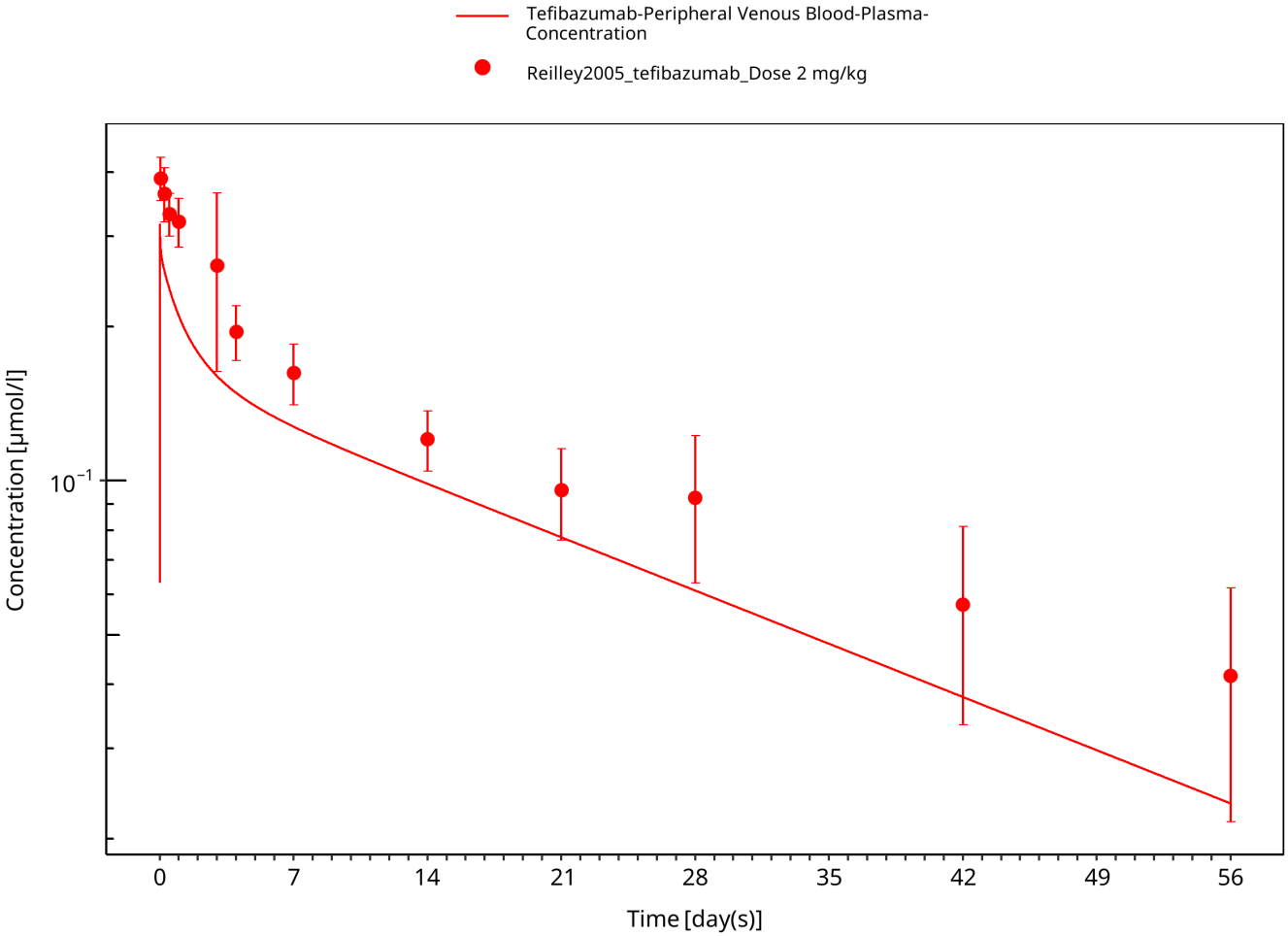

Figure 3-4: Plasma concentration - 2 mg/kg dose (log scale)

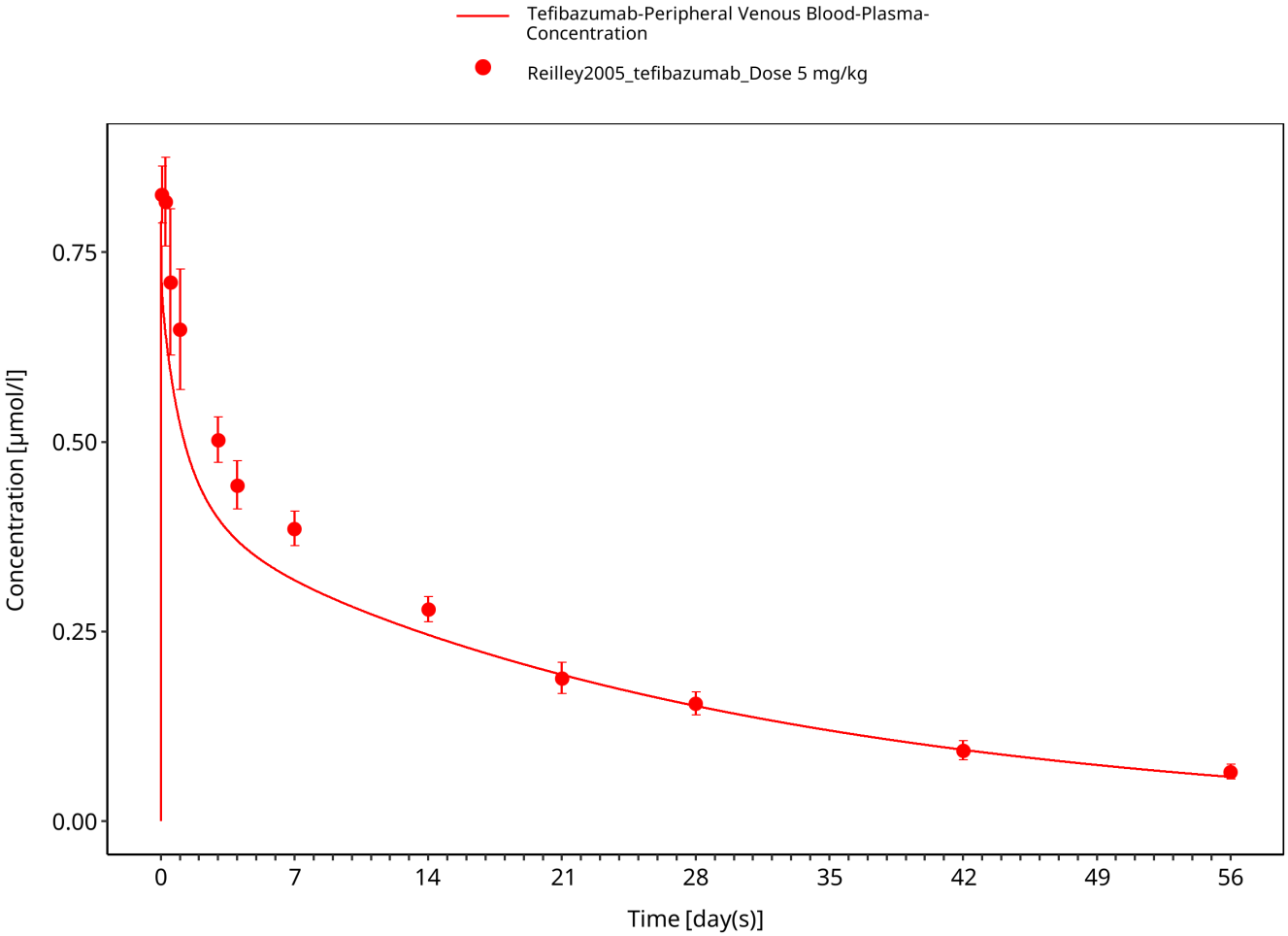

Figure 3-5: Plasma concentration - 5 mg/kg dose (linear scale)

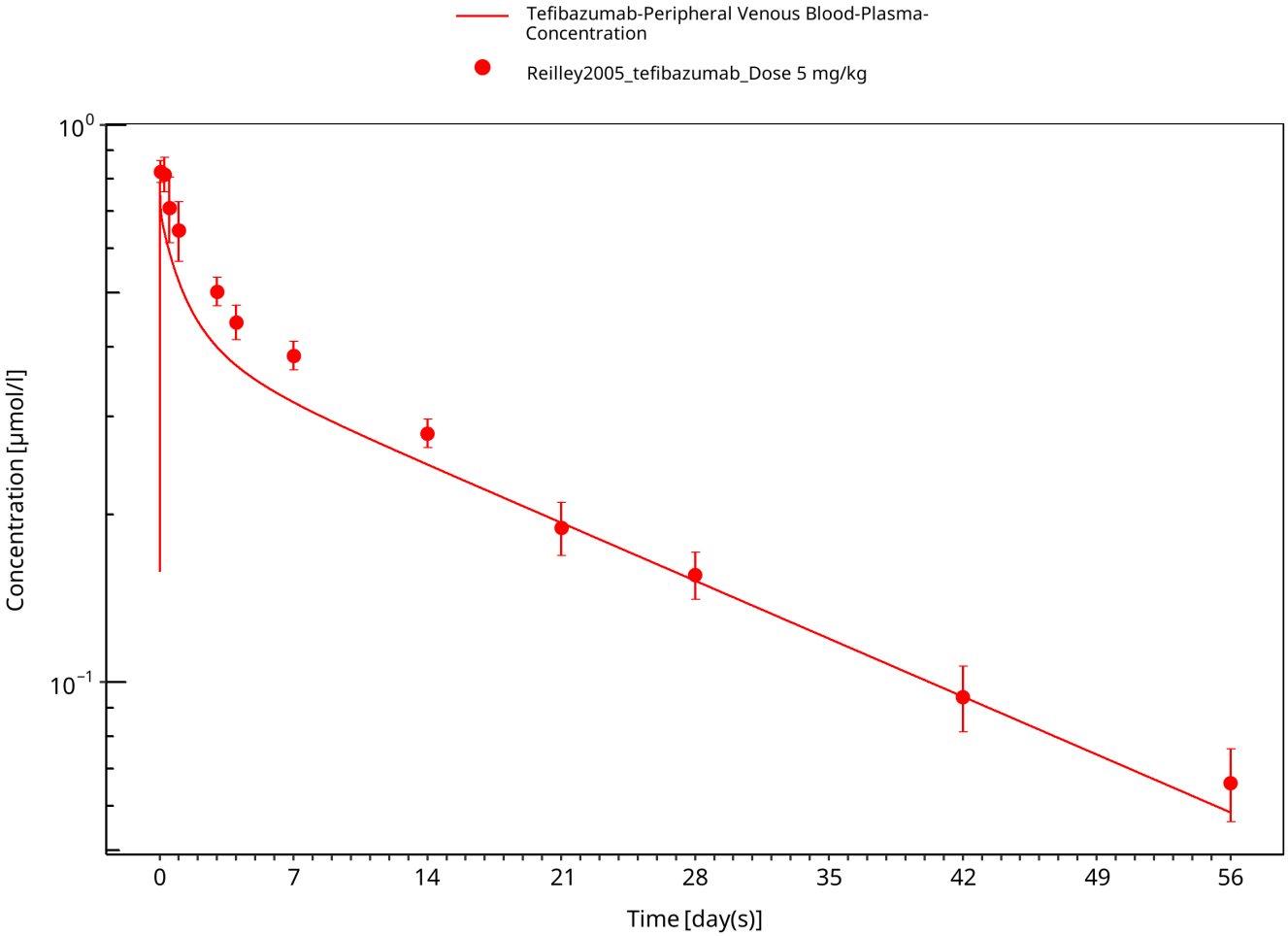

Figure 3-6: Plasma concentration - 5 mg/kg dose (log scale)

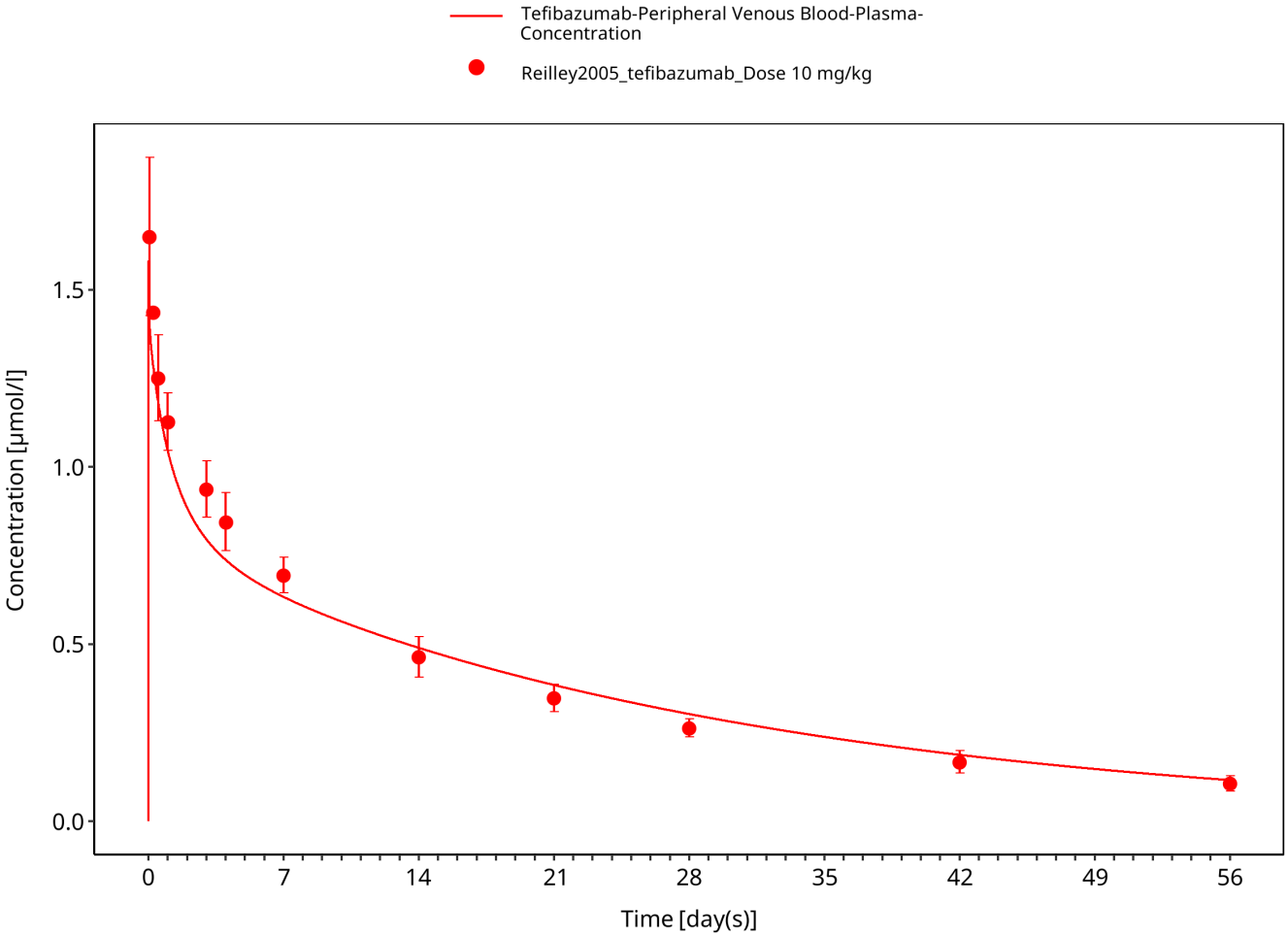

Figure 3-7: Plasma concentration - 10 mg/kg dose (linear scale)

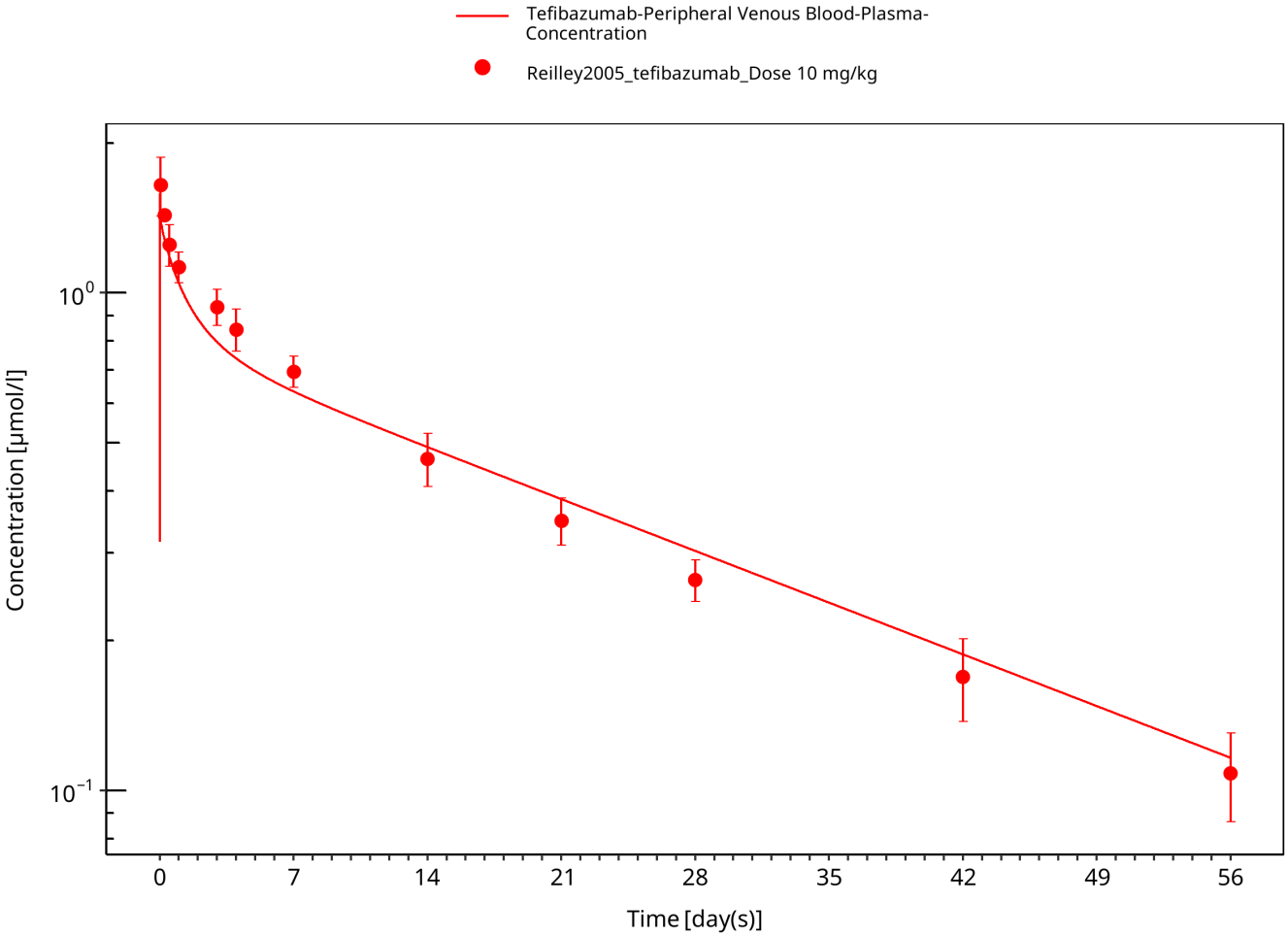

Figure 3-8: Plasma concentration - 10 mg/kg dose (log scale)

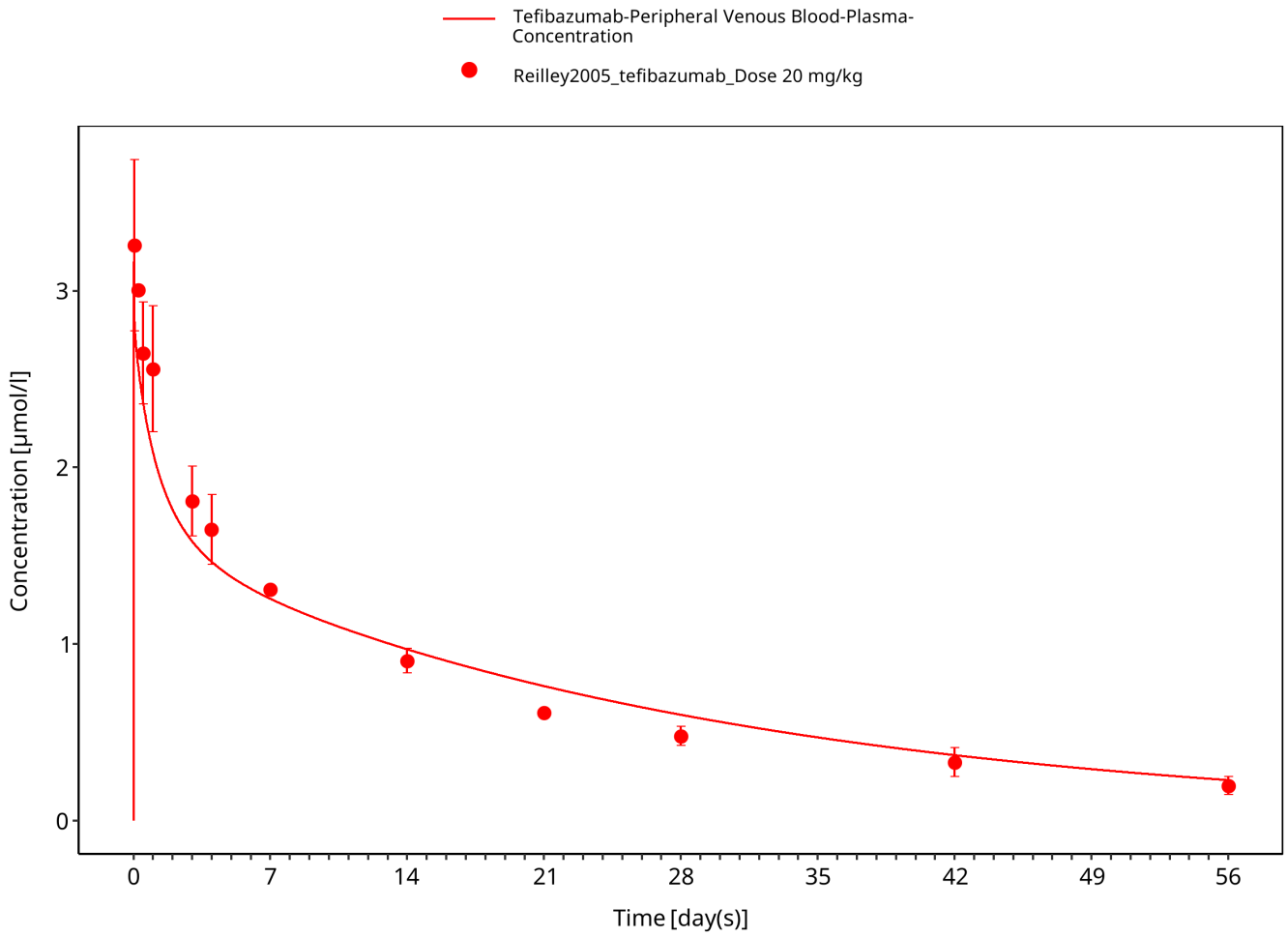

Figure 3-9: Plasma concentration - 20 mg/kg dose (linear scale)

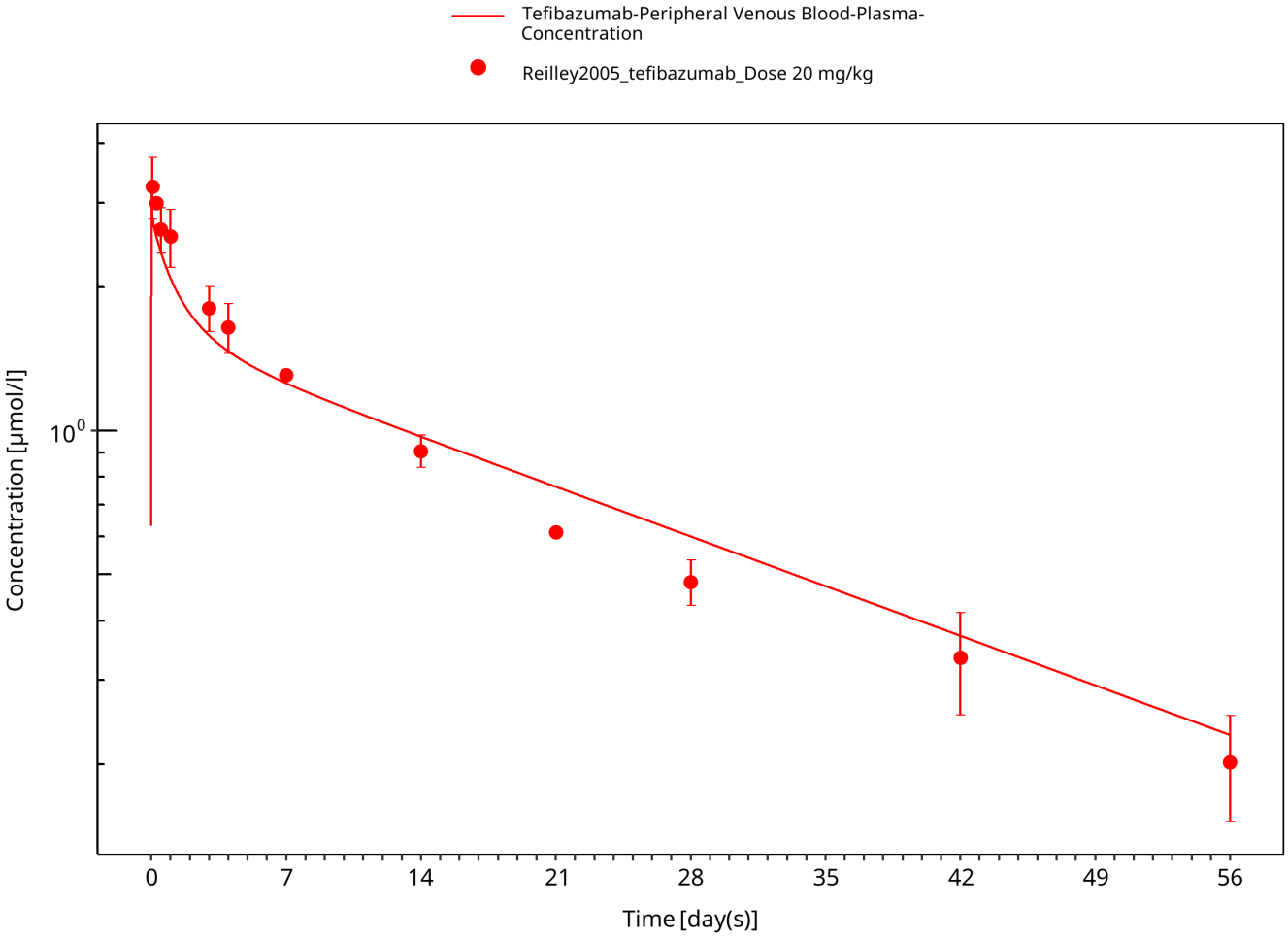

Figure 3-10: Plasma concentration - 20 mg/kg dose (log scale)

4 Conclusion

The herein presented PBPK model adequately describes the pharmacokinetics of tefibazumab in adults after adjusting the affinity to FcRn except for the lowest dose for which the plasma concentrations are underestimated. The initial plasma concentrations are slightly underestimated also for higher doses.

5 References

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