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Case 1: Meropenem

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Introduction

Meropenem (Antibiotic Carbapenem)

➢ Indication:
  - Complicated Intra-abdominal Infections
  - Complicated Skin and Skin Structure Infections
  - Bacterial Meningitis in Adults/Pedeatrics

➢ Standard dose:
  - Adults: 0,5 g – 2,0 g,   every 8 h
  - Children (3+):   10 mg - 40 mg / kg,   every 8 h

➢ MoA (Bactericidal Activity):
  ➢ Inhibition of Cell Wall Synthesis
  ➢ Penetrates Cell Wall of most G- & G+ Bacteria to bind Penicillin-Binding-Protein (PBP)

PK/PD Targets for population:

➢ %fT / MIC (Antibiotic/Bacteria specific)

➢ PK/PD Target: 40 % (Bactericidal effects)

Population PK Model

Table I — Summary of Demographic Characteristics of the Studied Patients

Covariate	Symbol	Mean (SD)	Median (Range)
Weight, kg	WT	73.0 (16.1)	70 (40.6-127)
Height, cm	HT	169.5 (8.7)	170 (147-185.4)
Sex, no. of male/female	SEX	61/18	—
Age, y	AGE	39.6 (18.2)	35 (18-93)
Serum creatinine, mg/dL	SCR	1.1 (0.8)	1.0 (0.4-6.9)

A total of 341 concentrations from 79 patients.

Parameters for typical Patient

Interindividual variability of PK parameters:

%CV(CL) =

    34,35

%CV(Q) =

    53,85

%CV(V1) =

    37,82

%CV(V2) =

    31,94

Between Subject Variability

- 0.5, 1, or 2 g Meropenem over a 0.5- or 3-hour infusion.
- 2-Compartment I.V. Infusion Model
- Most significant Covariates:
  - ➢ *Creatinine Clearance*
  - ➢ *Age*
  - ➢ *Body weight*

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Changes in Concentration Time Profile

	Age		Weight		Height		Creatinine	
	20	93	45	127	147	185	0.4	1
%fT > MIC	-	+	+	-	No Change		-	+
C_max	-	+	+	-			-	+

➤ Effects of Covariate Changes as expected

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Effect of body weight on Clearance

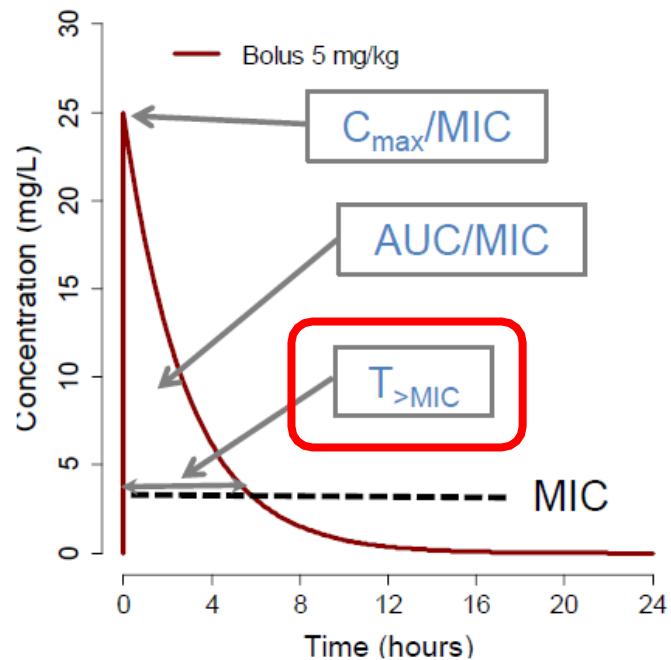$$V_d = \frac{Dose}{\boxed{Plasmaconcentration}} \downarrow$$

$$CL = k * V_d \uparrow$$

➢ Increased Weight decreases Plasmaconcentration

➢ Increased Elimination

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Impact of Characteristics on PTA

- PK Target: T > MIC = 40 %

- Toxicity Target: /

- Relevant PK/PD Index:

Impact of Characteristics on PTA
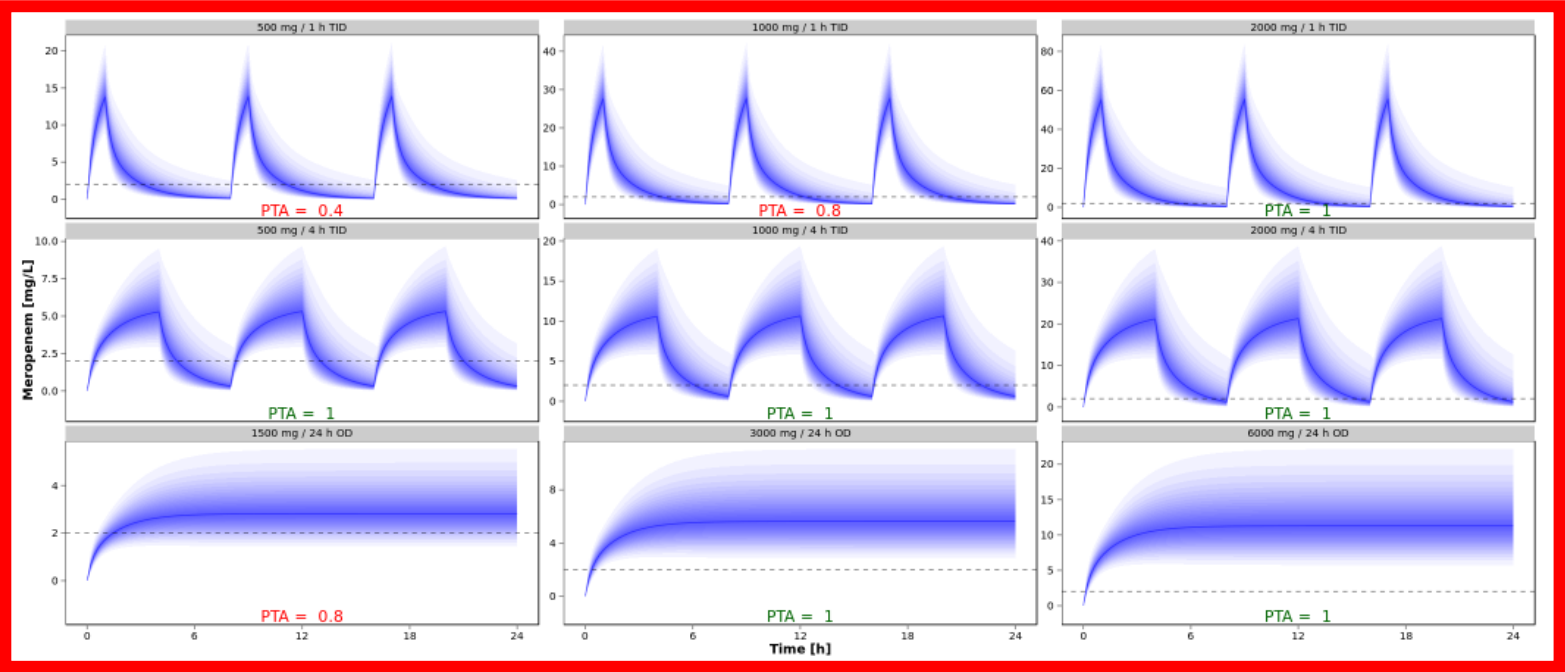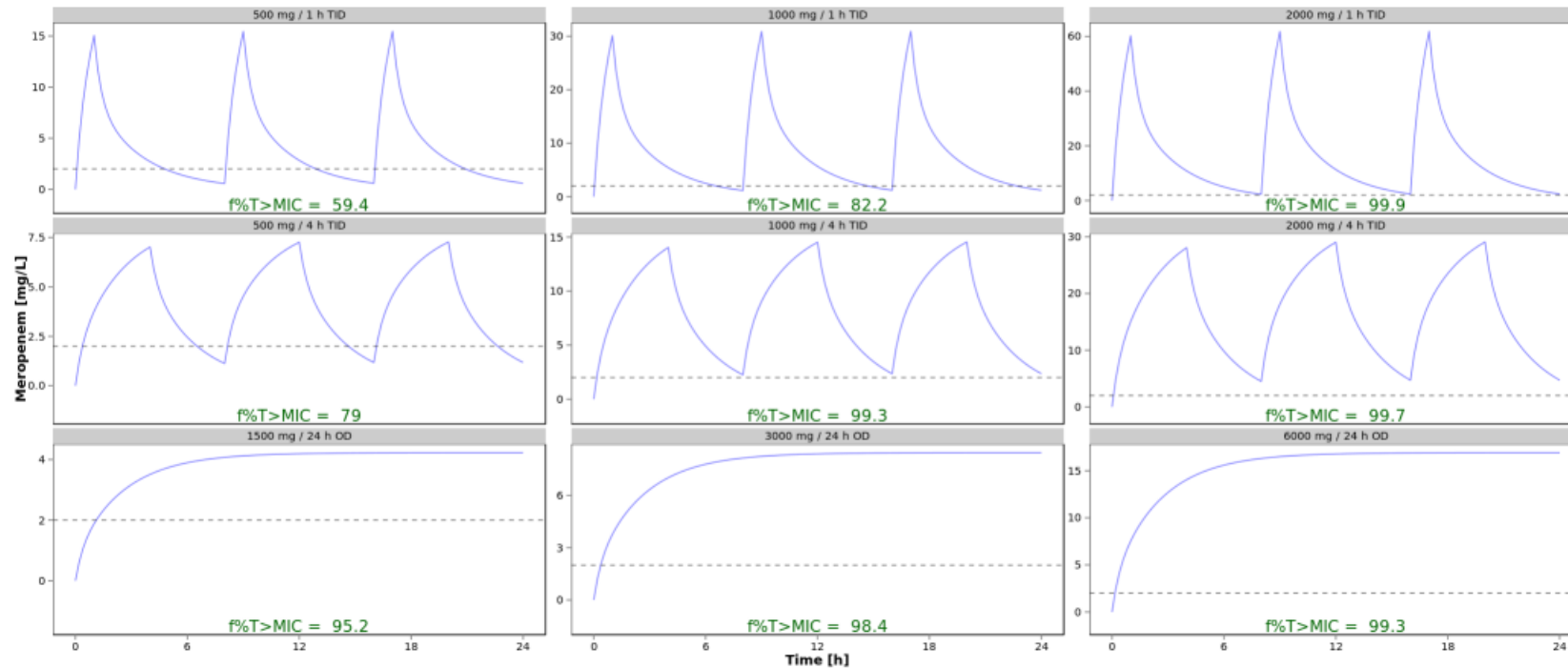

Probabilistic Dosing Scenarios; Base Model for Comparison with varied Parameters

Comparison-Matrices: Probabilistic Dosing Scenarios

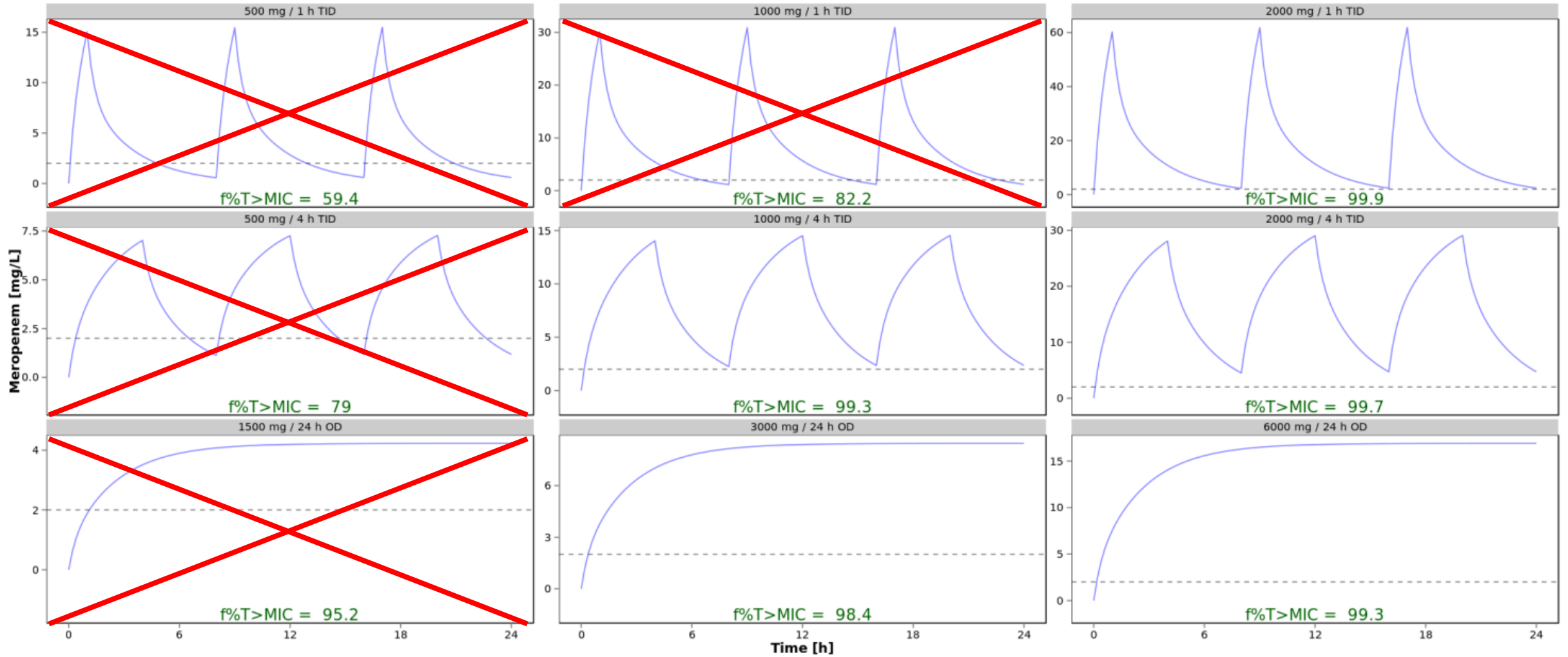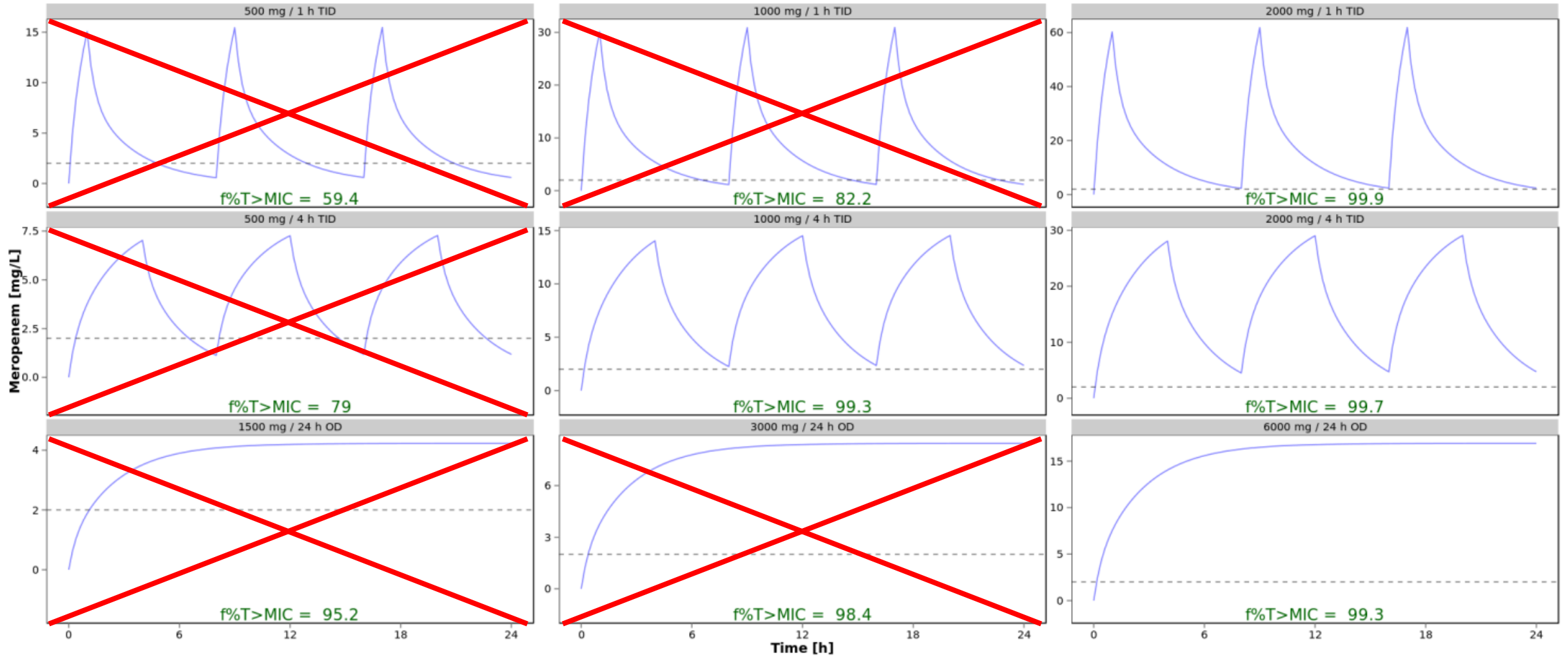|	Dose	Dosing Interval	Infusion Duration
Effect on p(PTA)	+	+	+

Bayesian Dosing

Bayesian Dosing: Patient M.P.; Triple Dose (8h); c(Meropenem) = 1.5 mg/L

➢ Plots allow identification regimes that maximizes the attainment of the PK/PD Target

➢ All dosing regimens for the patient reached target (+3)
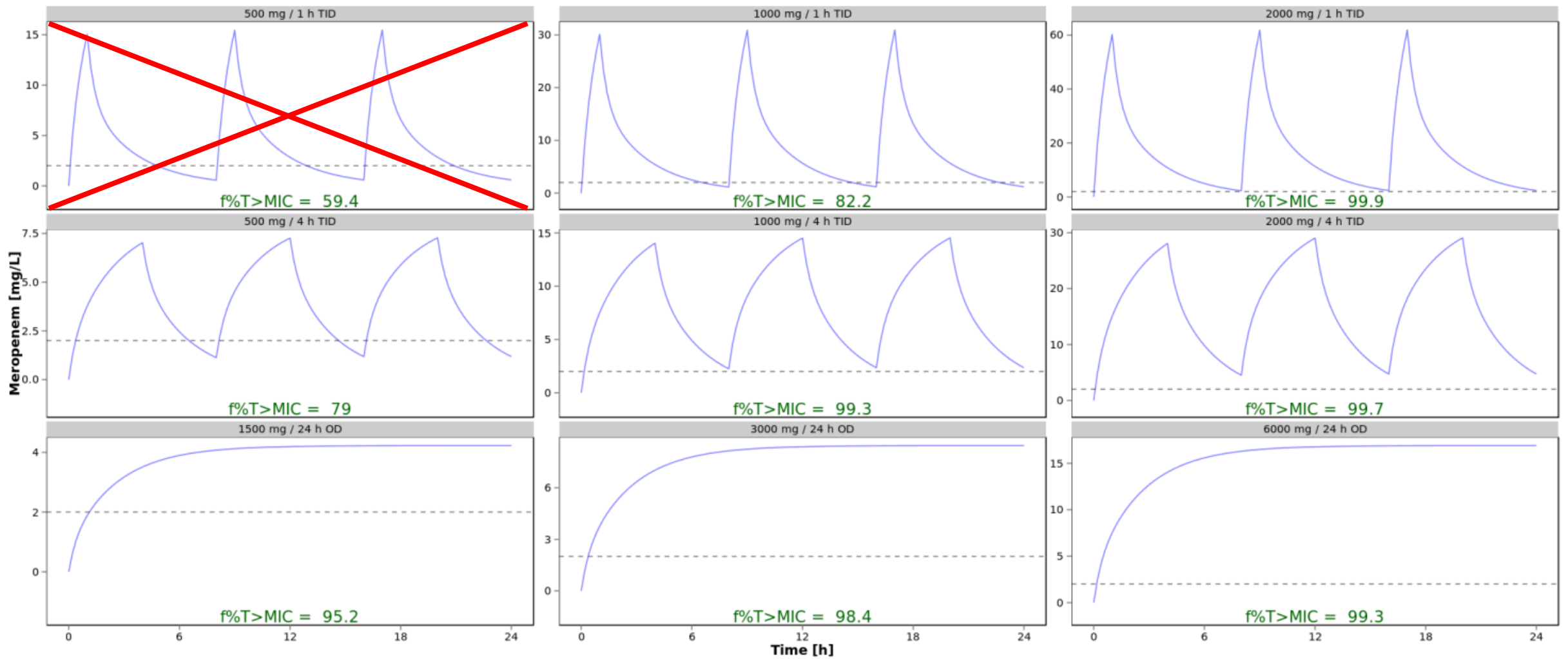
✓ FASS: 0.5g to 2g every 8 hours

MIC = 8 mg/L

T > MIC = 99 %

C_mem = 0

Conclusion

➢ TDMx Simulation suitable for Patient M.P.

➢ Impact of different patient characteristics and MIC on concentration-time profile and PTA was investigated

➢ No Bayesian Simulation possible without Patient sample measurement