PK and PD as predictors of clinical effect

- drug **action**
  - the interaction of the drug molecule at the binding site

    e.g. receptor, carrier, channel
- drug **effect**
  - a measurable consequence of drug binding or drug action

    e.g. EEC change, QT prolongation
- drug **response**
  - a desirable or undesirable clinical outcome

    e.g. reduced frequency of seizures, reduction in blood pressure

How do we find and test new drugs?

preclinical

- screening (empirical)
- molecular modeling
- molecular design

clinical

- dose ranging (empirical)
- PKPD modeling
- optimal study design

screening → learning → design

…modeling may be understood as mechanized intuition

applying the rules of

- biology
- logic
- mathematics
- statistics

to learn from experience

to develop models based on data……what data do we need?

Preclinical:

- affinities of active drug molecules for the binding site (in vitro, in situ, in vivo)
- mechanism between binding and measurable effect including auto-regulation (feedback, synthesis)
- in vivo: dose(time) – concentration(time) – measurable effect(time)

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to learn from experience

to develop models based on data……what data do we need?

Clinical:

- ideally everything measured in the preclinical program (in vivo affinities will be difficult to obtain), but at least the following:

  dose(time)

  concentration(time)

  effect(time)

- in addition, drug response data as a function of time

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How can this strategy be incorporated into R&D planning?

- Every preclinical experiment and every clinical study is designed to add data to the PKPD knowledge base.
- The modeling and simulation (M&S) scientist participates in the project teams.
- For the M&S scientist there exists no boundary between preclinical and clinical development.

The design route will prove to be faster than the “shortcut”.

…from the work of EMF-Consulting: Example1

Selection of optimal doses for a new anti-epileptic drug to be tested in patients.

M. Marchand[1], O. Petricoul[1], E. Fuseau[1], D. Bentley[2], D. Critchley[2]
[1] EMF consulting, BP 2, 13545 Aix en Provence, France
[2] EISAI Global Clinical Development, 3 Shortlands, London W6 8EE, UK

- Rufinamide modulates the activity of sodium channels thus suppressing seizures induced by electroshock (maximal electroshock, MES) or by injection of pentylenetrazole (PTZ) in mice (PD). In clinical studies, rufinamide significantly reduced seizure frequency (PD).

- Drug X is a new chemical entity with a novel mechanism of action. It shows anticonvulsant effects in rodents. The dose(time)-concentration(time) relationship (PK) was studied in epileptic patients.

PKPD workshop: Example 1

- **PKPD modeling in mice:**

  - Population PKPD modeling used NONMEM.
  - A one-compartment model with first order elimination was chosen for both rufinamide and Drug X.
  - For PKPD modelling, drug concentrations were predicted in male mice according to weight, the administered dose in mg/kg, population PK parameters (previously estimated), and time of test.

PKPD workshop: Example 1

PKPD modeling in mice – where are the problems?

+ mice are cheap

+ mice are genetically well defined

+ small interindividual variability

– mice are small

– difficult to dose accurately

– difficult to obtain more than one blood sample

PKPD workshop: Example 1

PKPD modeling in mice – Population approach:

Population PK model based on toxicokinetic data

-free choice oral dosing (continuous input during dark hours)

-blood sampling at steady state

-destructive, only one sample per mouse

$$Cl/F = \frac{DR}{C_{ss}}$$

-oral dosing by gavage (controlled time of drug input)

-blood sampling after single or multiple doses

-destructive, only one sample per mouse

$$C(t) = \frac{D \cdot ka}{V/F \cdot (ka - k)} \cdot (e^{-k \cdot t} - e^{-ka \cdot t})$$

PKPD modeling in mice – Population approach:

Population PD model using predicted individual concentrations at the time of the effect measurement

Individual concentrations are predicted based on:

-the dose given at the PD experiment

-the gender and weight of the mouse

-the time of the effect measurement after the dose

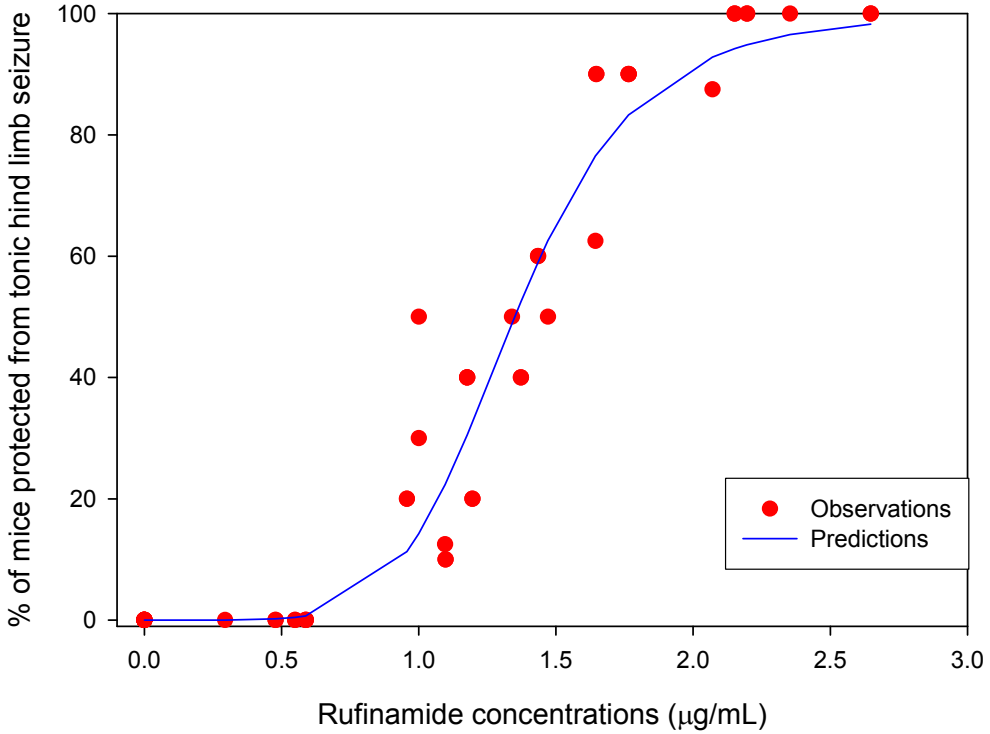
-the population PK model

PKPD workshop: Example 1

Rufinamide data: Observed and predicted % of protected mice from MES Test

$$DV = \frac{CONC^{\gamma} \cdot E_{\max}}{CONC^{\gamma} + C_{50}{}^{\gamma}}$$

E_{max} = 100% (FIXED)
C_{50} = 1.35 μg/mL
γ = 5.98



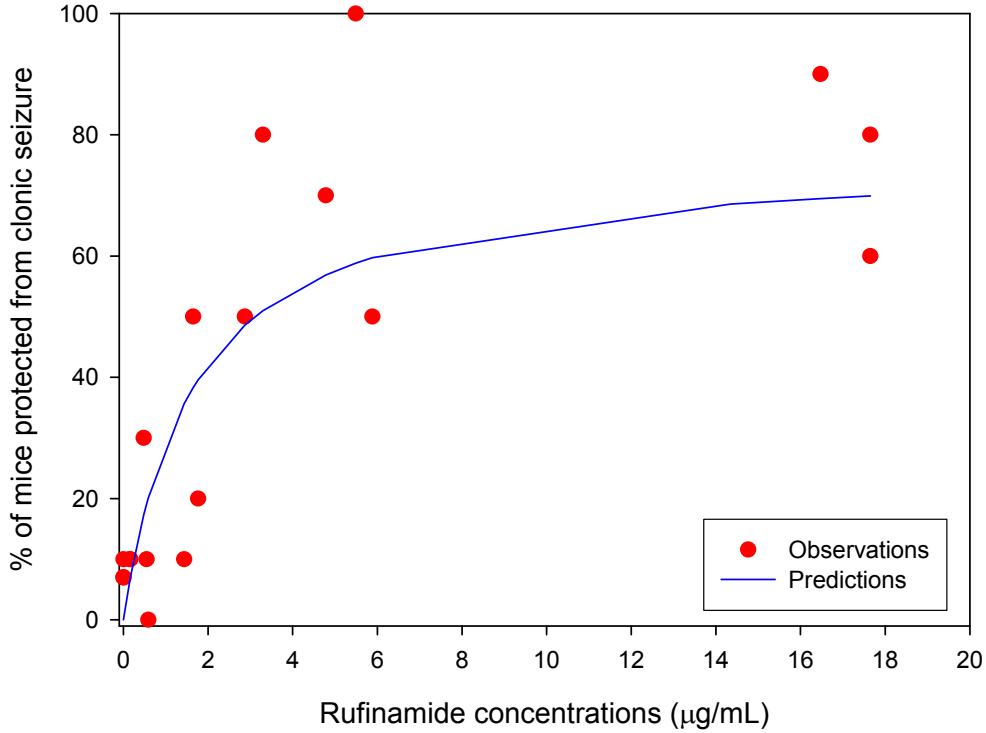
PKPD workshop: Example 1

Rufinamide data: observed and predicted % of protected mice from PTZ Test

$$DV = \frac{CONC \cdot E_{max}}{CONC + C_{50}}$$

E_{max} = 76.4%

C_{50} = 1.64 μg/mL

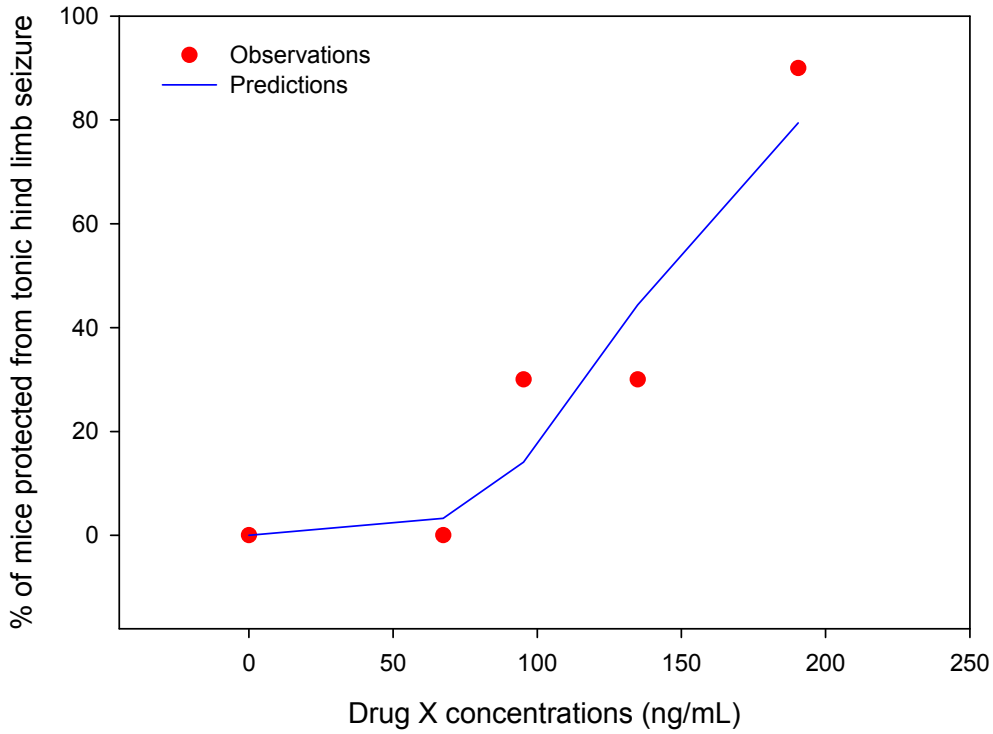


PKPD workshop: Example 1

Drug X data: observed and predicted % of protected mice from MES Test

$$DV = \frac{CONC^{\gamma} \cdot E_{max}}{CONC^{\gamma} + C_{50}{}^{\gamma}}$$

E_{max} = 100% (FIXED)
C_{50} = 141.6 ng/mL
γ = 4.56



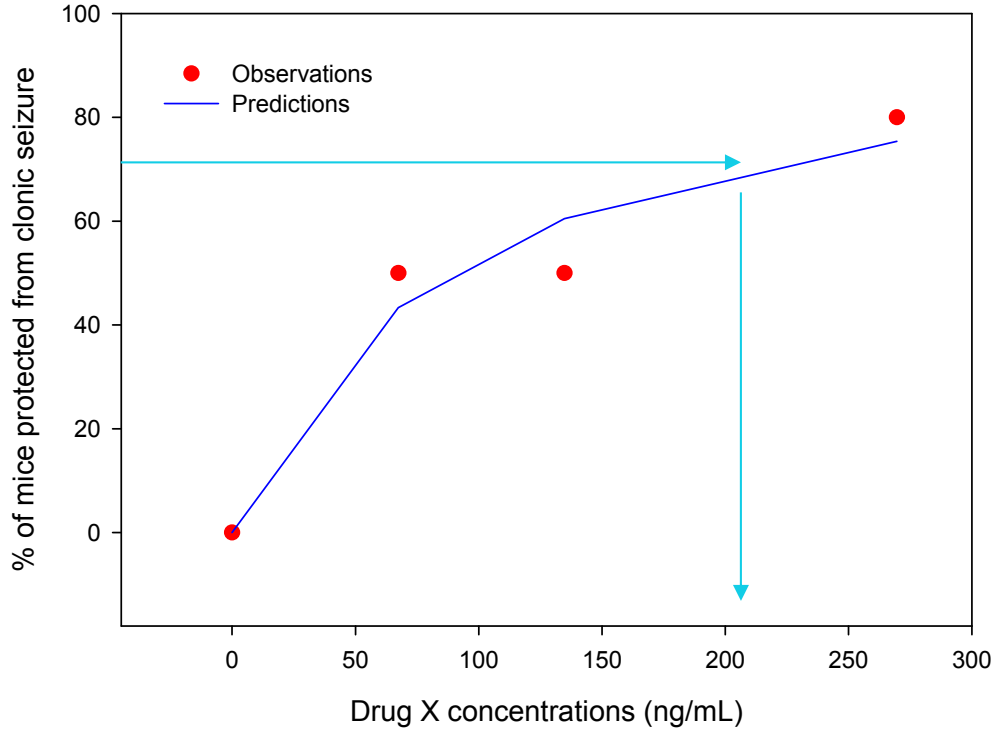
PKPD workshop: Example 1

Drug X data: observed and predicted % of protected mice from PTZ Test

$$DV = \frac{CONC \cdot E_{max}}{CONC + C_{50}}$$

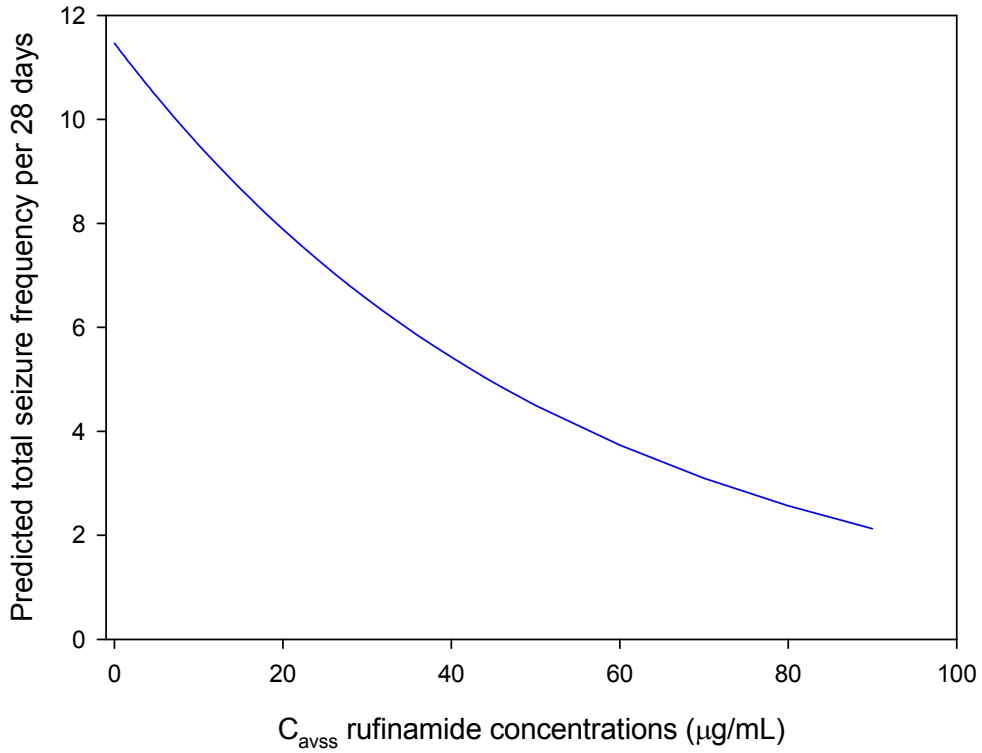
E_{max} = 100% (FIXED)

C_{50} = 88.1 ng/mL



PKPD modeling in patients:

Rufinamide: PD model based on clinical data



$$Log_e(total\ seizure\ \ frequency) = -0.893 - 0.0187 \cdot C_{avss}$$

PKPD workshop: Example 1

Link from mice to humans:

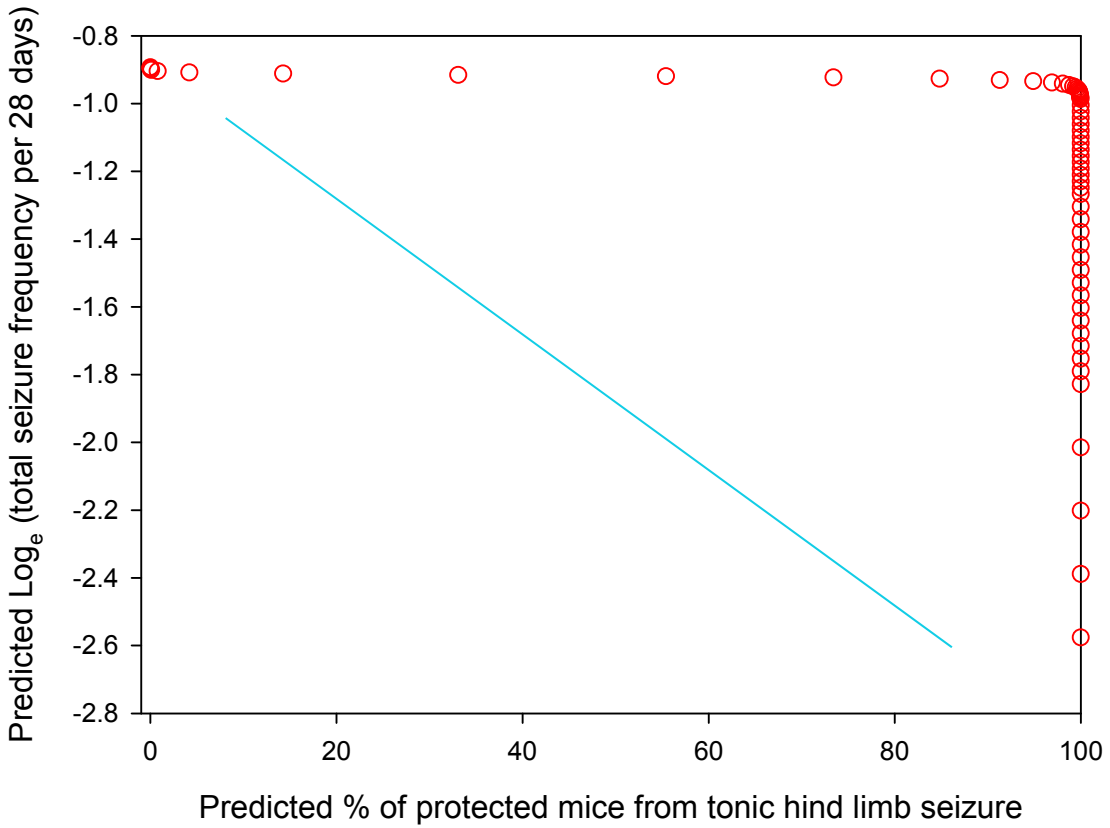
assumes that the effective concentrations in mice are also effective in humans

A generic mathematical **link function** (Weibull) was used to relate rufinamide preclinical effects to its clinical response (Log_e of total seizure frequency over a period of 28 days).

PKPD workshop: Example 1

Rufinamide preclinical effect (MES test): the **link function** shows that effective concentrations in the preclinical MES test are not effective clinically.

Is the approach wrong? Not necessarily, but MES is definitely not a suitable preclinical test.



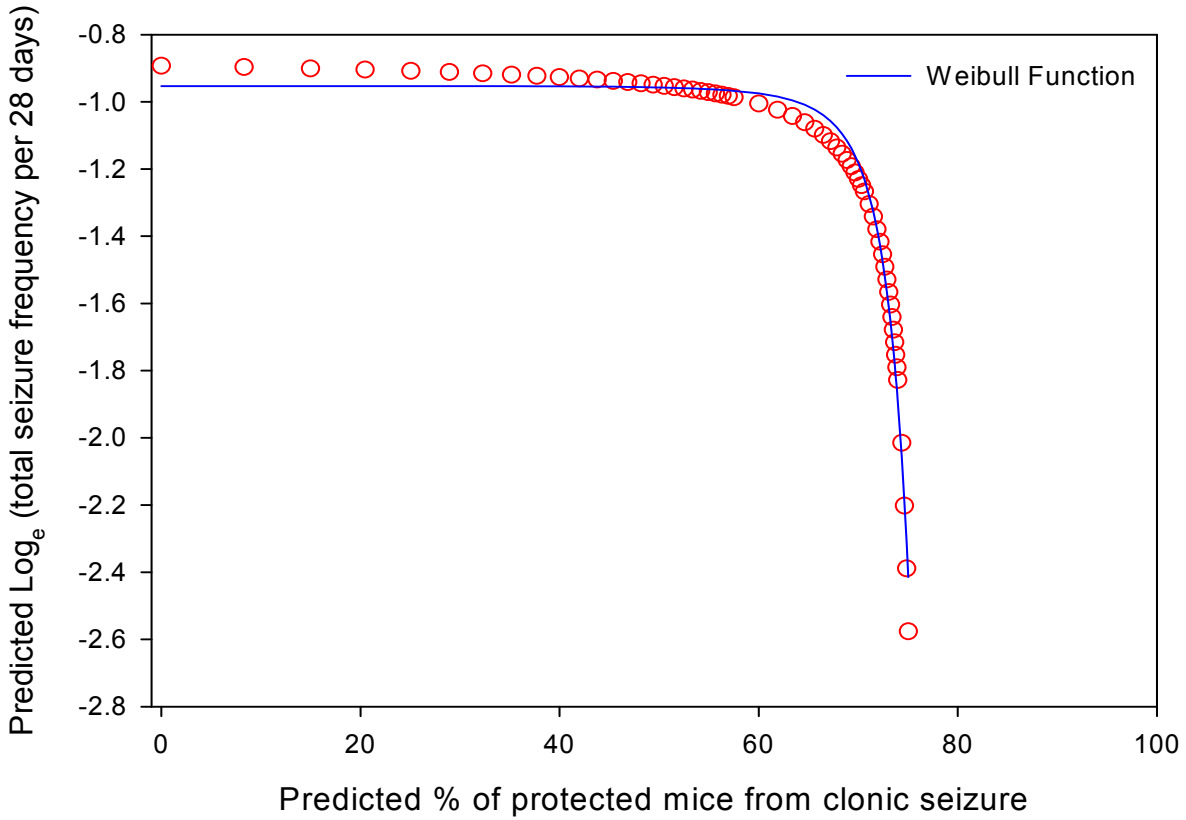
an ideal relationship:

50% protected mice are related to half the maximal reduction in seizure frequency in patients.

emf consulting

PKPD workshop: Example 1

Rufinamide preclinical effect (PTZ test): the **link function** shows that concentrations which protect more than 50% of mice also reduce total seizure frequency per 28 days in patients. The relationship is not ideal but sensitive enough to be used for the following extrapolation (next slide).



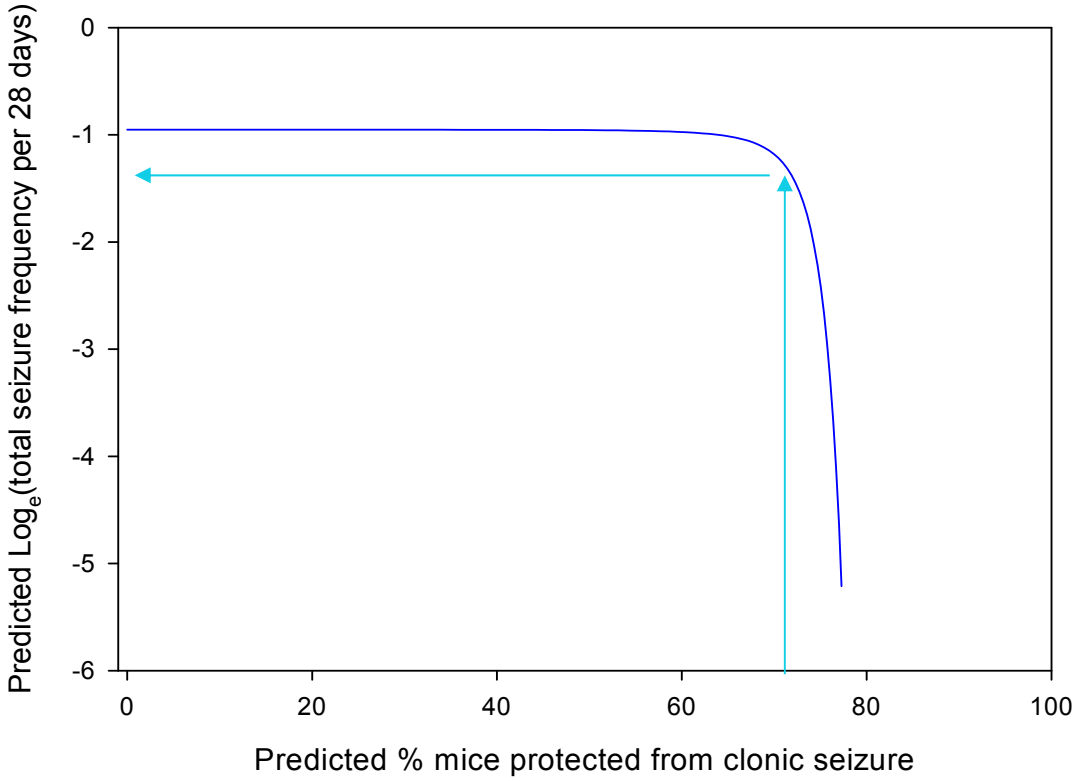
PKPD workshop: Example 1

- **Extrapolation from known to unknown:**

- assuming that the link between the preclinical and the clinical test is generally valid and independent of the pharmacologic agent used to cause the response,
- the PTZ **preclinical effect** measurements of Drug X are used to predict total seizure frequency per 28 days (**clinical response**).

PKPD workshop: Example 1

The **link function** is now applied to drug X: whatever drug X concentration is related to 70% of mice protected from seizures (PTZ test) is expected to be related to a clinical response of $28 \cdot e^{-1.3} = 7.6$ seizures in 28 days, a minimal response.



Answer: ~200ng/ml

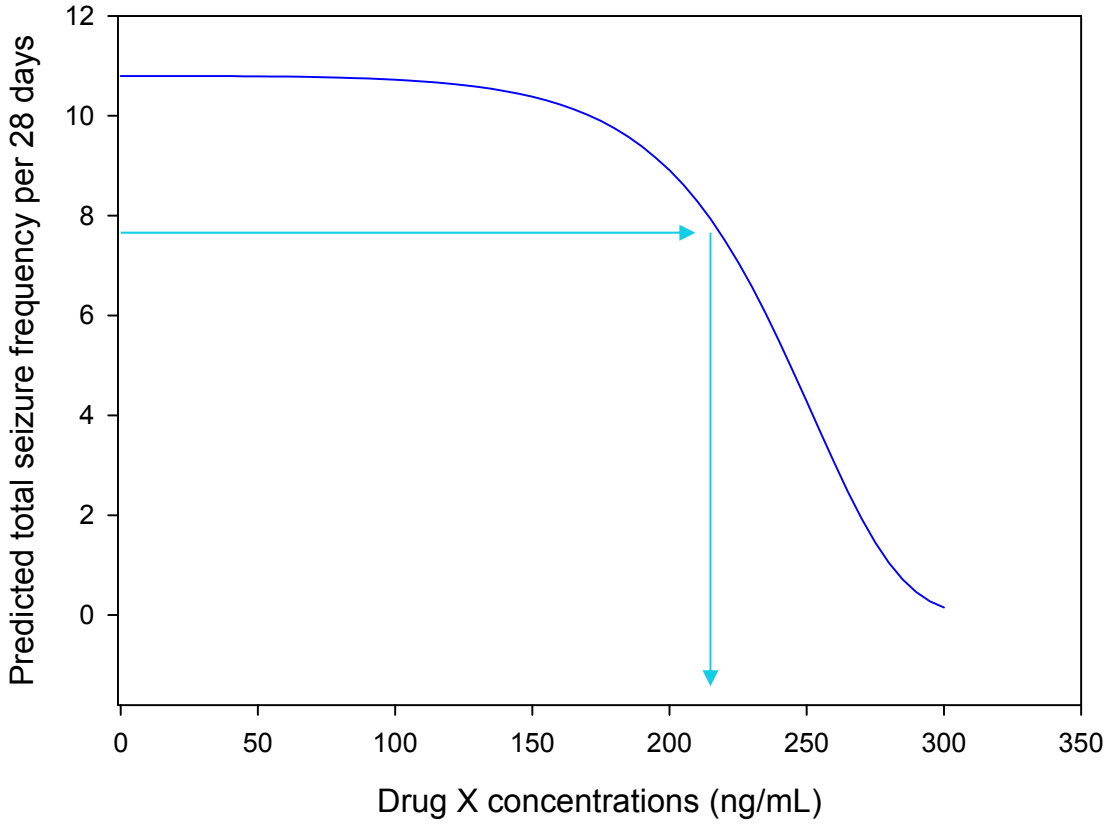
PKPD workshop: Example 1

- **Extrapolation from response to concentration:**

- the preclinical PD model for PTZ test of Drug X is used to predict the concentration in humans necessary to achieve a certain clinical response.
- knowing… that for rufinamide the **link function** relates effective concentrations in mice to effective concentrations in humans.
- assuming… that the **link function** has general applicability and is thus also valid for drug X.

PKPD workshop: Example 1

Drug X: Finding the necessary concentrations to achieve a certain total seizure frequency per 28 days (response)



PKPD workshop: Example 1

- **Extrapolation from concentration to dose:**

- a PK model for Drug X established in epileptic patients in a phase IIa pilot study is used to predict the dosing regimen to produce the necessary concentrations.
- this PK model takes the drug interaction with CYP3A4 inducers into account. The recommended dosage is stratified accordingly:

PKPD workshop: Example 1

In order to achieve similar decrease (2.8 per 28 days) of total seizure frequency as with a typical C_{avss} (15 µg/ml) of rufinamide, the following daily doses for Drug X are likely to produce a Cavss of 215 ng/mL:

- Sub-population 1, without co-administration of CYP3A4 inducers: 1.8 units
- Sub-population 1, with co-administration of CYP3A4 inducers: 7.7 units
- Sub-population 2, without co-administration of CYP3A4 inducers: 4 units
- Sub-population 2, with co-administration of CYP3A4 inducers: 15 units

Note: a C_{avss} of 215 ng/mL was observed in healthy subjects following repeated daily doses of 4 units which were well tolerated.

PKPD workshop: Example 1

workshop…*english*

atelier……..*français*

Werkstatt…*deutsch*

This is not a place to shop for work but a place to work.

Before I go on to my second example I would like to solicit contributions, comments, anecdotes… from the attendees.

…from the work of EMF-Consulting: Example 2

Selection of an optimal biomarker for neutral endopeptidase (NEP) inhibitors in humans.

A.C. Heatherington, S. Sultana, R. Hidi, M. Boucher, E. Fuseau, M. Marchand, P. Ellis, S.W. Martin
Pfizer Ltd, Sandwich, UK; EMF Consulting, Aix-en-Provence, France

Objectives:

- to select a reliable soluble biomarker for NEP inhibitors
- to compare clinical PD models to *in vitro* PD models
- to build a suitable PKPD model to optimally design future clinical studies

PKPD workshop: Example 2

Background:

Neutral endopeptidase (NEP) is a metallopeptidase enzyme involved in the degradation of a number of endogenous peptides, including

- vasoactive intestinal peptide (VIP)
- substance P
- endothelins (hydrolysis of big endothelin, Big ET-1, to endothelin)
- atrial natriuretic peptide (ANP).

It is hypothesized that **NEP inhibitors** would increase VIP leading to enhanced vasodilatation in genital tissues. Two molecules, UK-447,841 (*in vitro* IC50 10 nM) and UK-505,749 (*in vitro* IC50 1.1nM), have undergone pharmacological evaluation to assess their effect on plasma Big ET-1 and ANP levels.

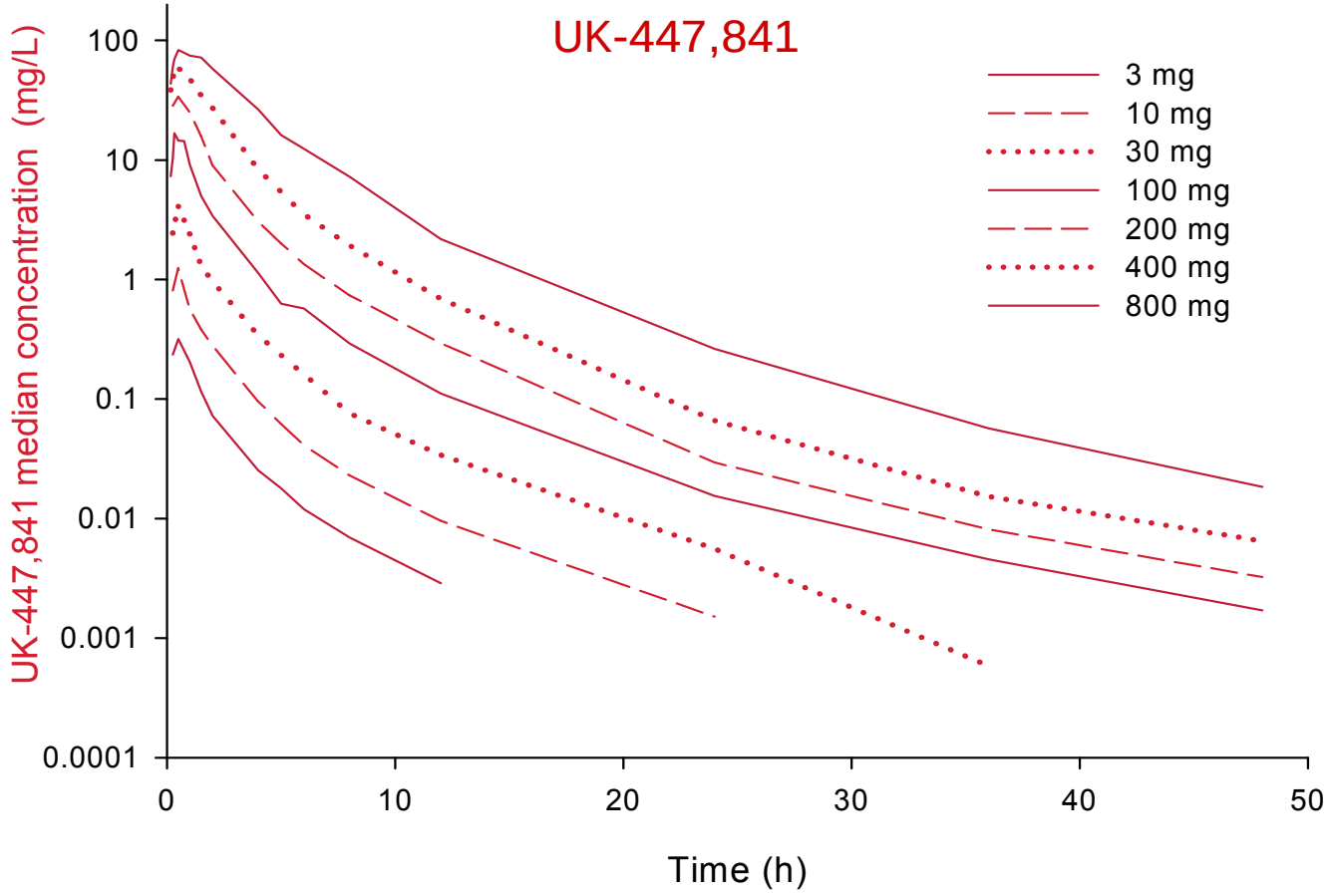
PKPD workshop: Example 2

Studies: Double-blind, randomized, placebo-controlled phase 1 studies in healthy volunteers

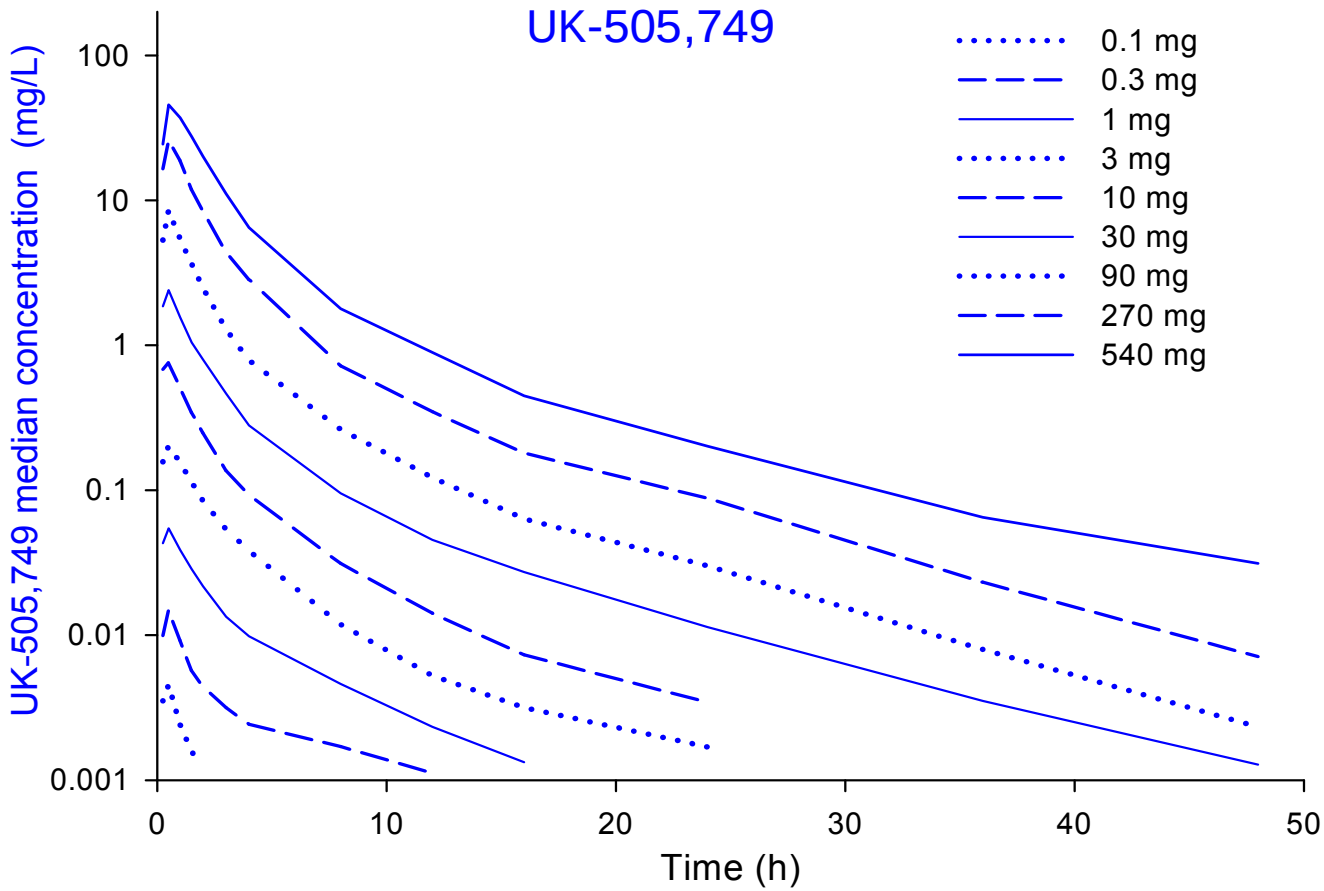
	UK-447,841		UK-505,749
Design	Cross-over	Parallel group	Cross-over
Dosing	Single escalating oral doses, 3 to 800 mg	Multiple daily oral doses, 100, 400 and 800 mg	Single escalating oral doses, 0.1 to 540 mg
PK data	14 samples up to 48 h	13 + 15 up to 48h	14 samples up to 48h
PD data (big ET-1 and ANP)	3 samples up to 8h	7 samples up to 12h	7 samples up to 12h

PKPD workshop: Example 2

median PK data, Phase I, healthy volunteers



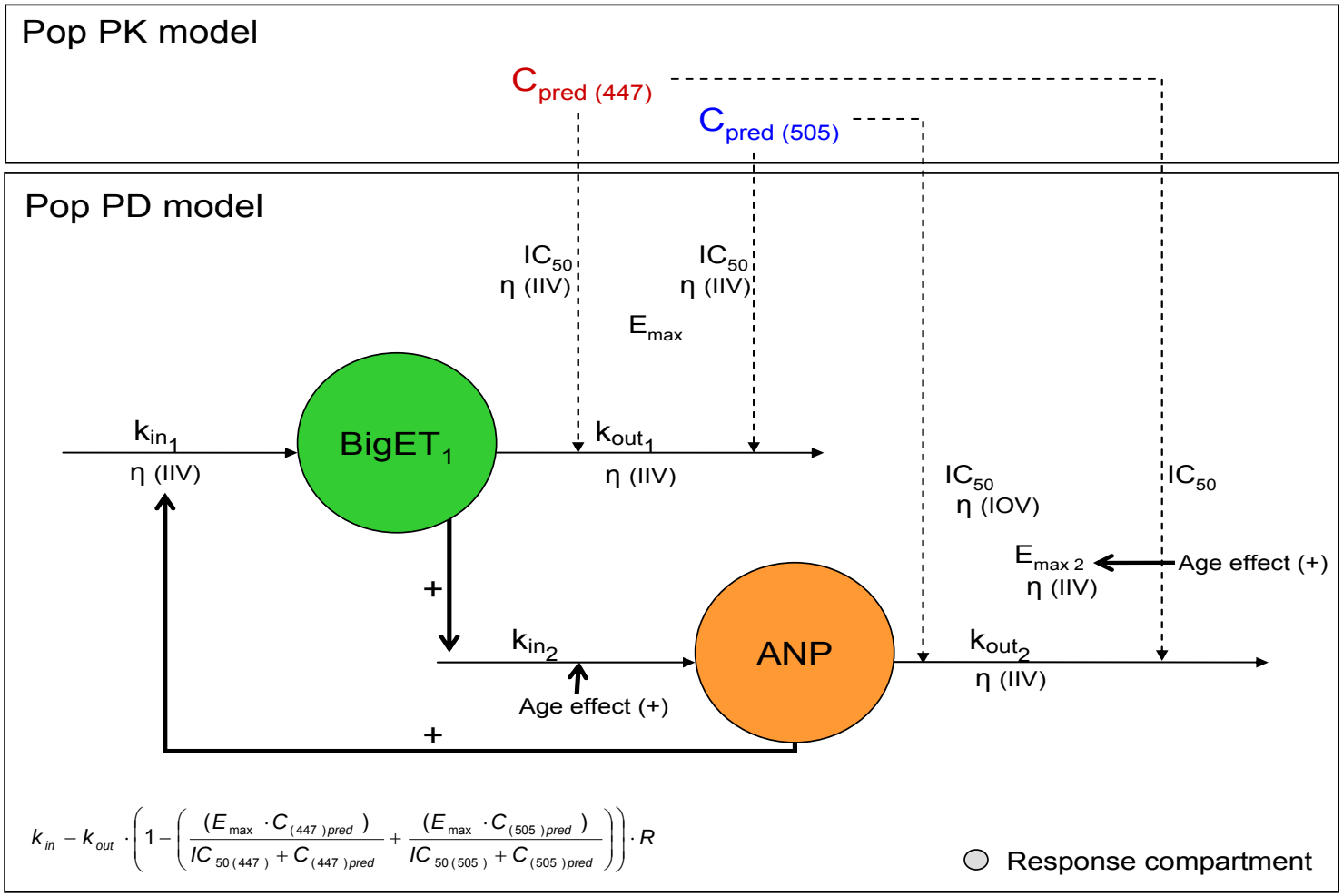
median PK data, Phase I, healthy volunteers



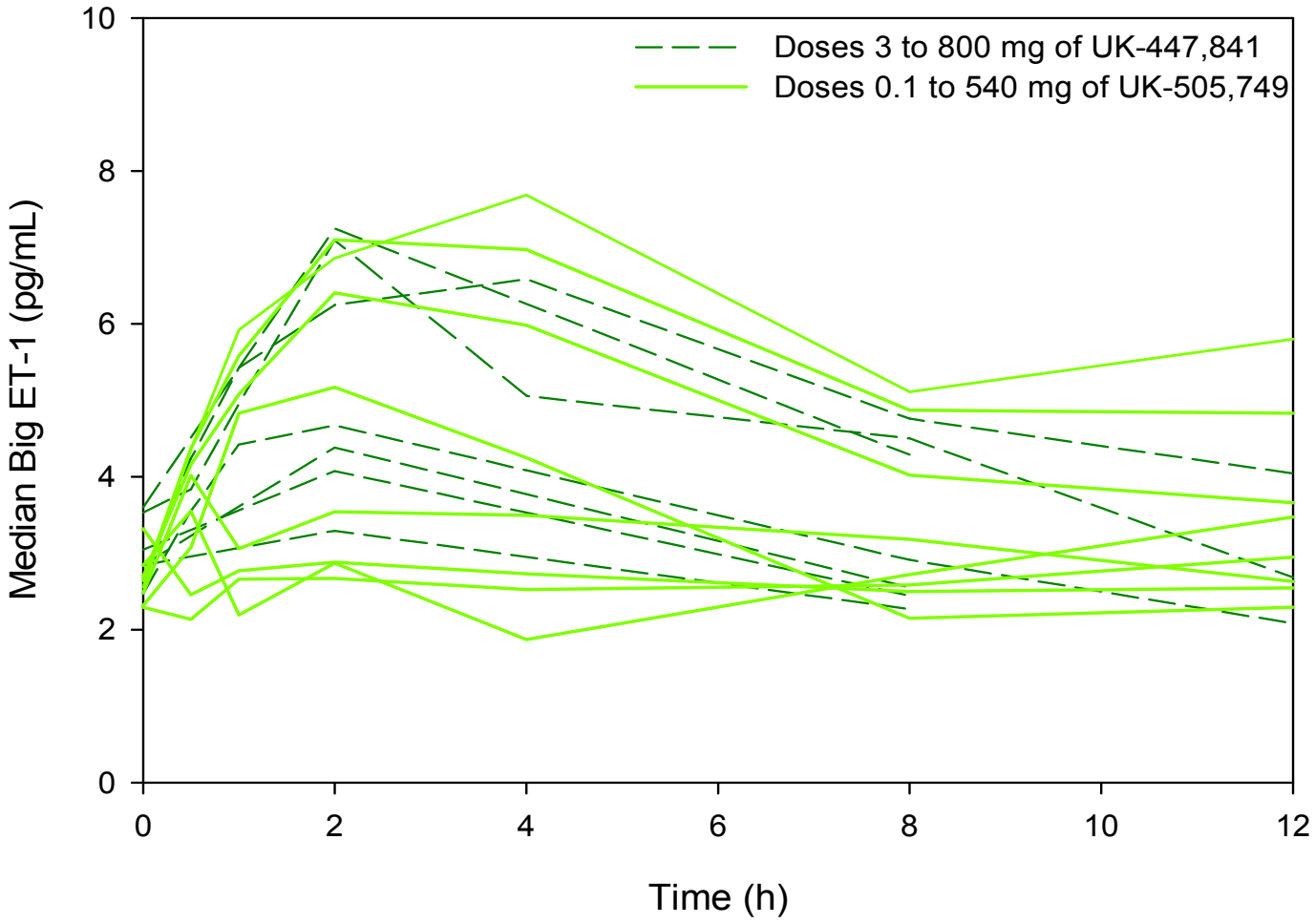
Combined PKPD population model (NONMEM) for two drugs (PK) and two biomarkers (PD indirect response model for Big ET-1 and ANP)

- the NEP inhibitors slow down the degradation ($kout_{1,2}$) of Big ET-1 and ANP
- Big ET-1 stimulates production rate (kin_2) of ANP
- ANP stimulates production rate (kin_1) of Big ET-1
- age enhances production rate (kin_2) of ANP
- E_{max} , the maximum decrease in k_{out} , is the same for both drugs but different for ANP (41%) and for Big ET-1 (66%)
- age increases E_{max} for ANP
- IC_{50}, the drug concentration at half-maximal effect, if different for Big ET-1 and ANP and different for UK-505,749 and UK-447,841
- also *in vivo* UK-505,749 is 10 times more potent than UK-447,841

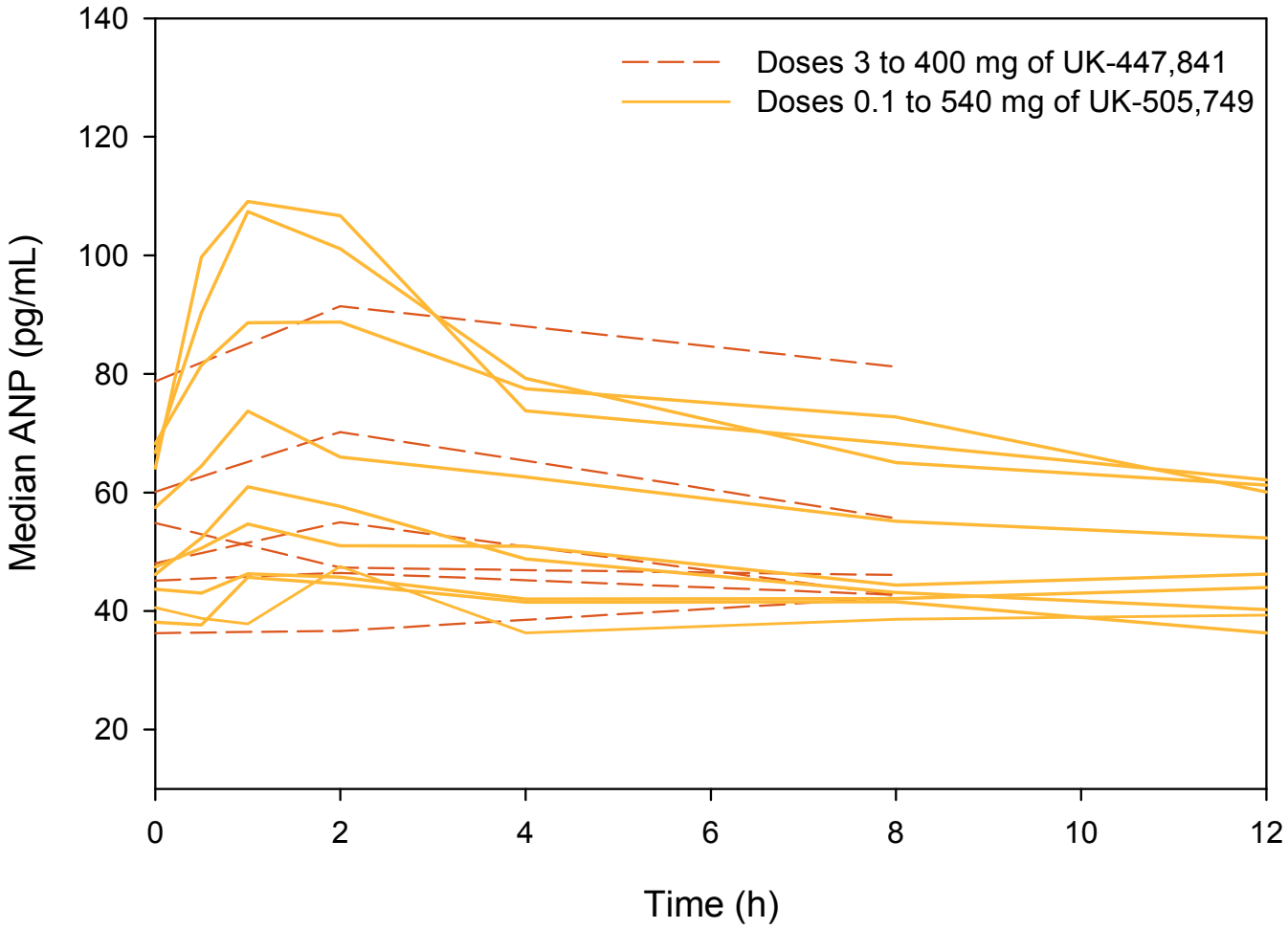
PD indirect response model for Big ET-1 and ANP



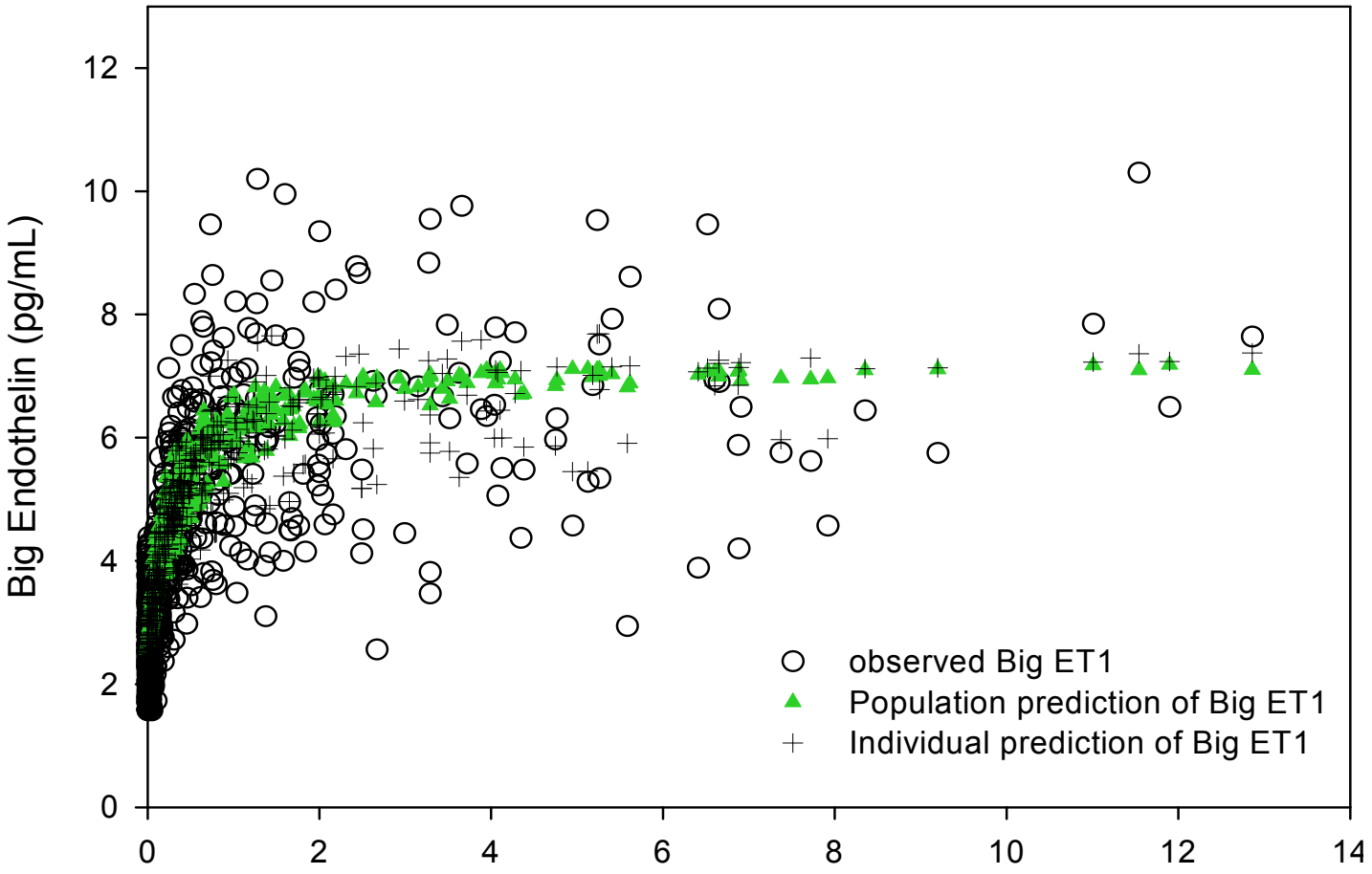
PKPD workshop: Example 2



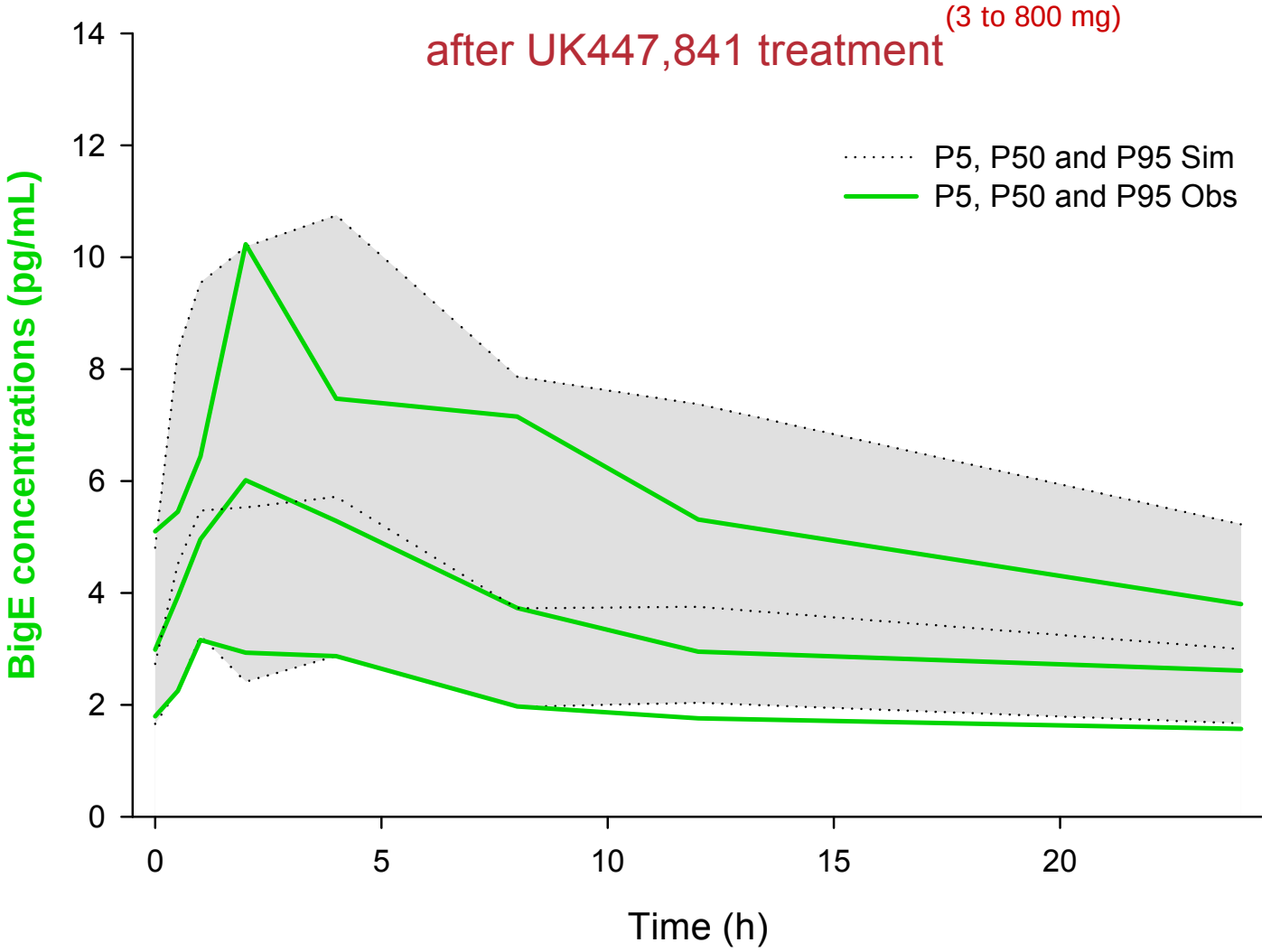
PKPD workshop: Example 2



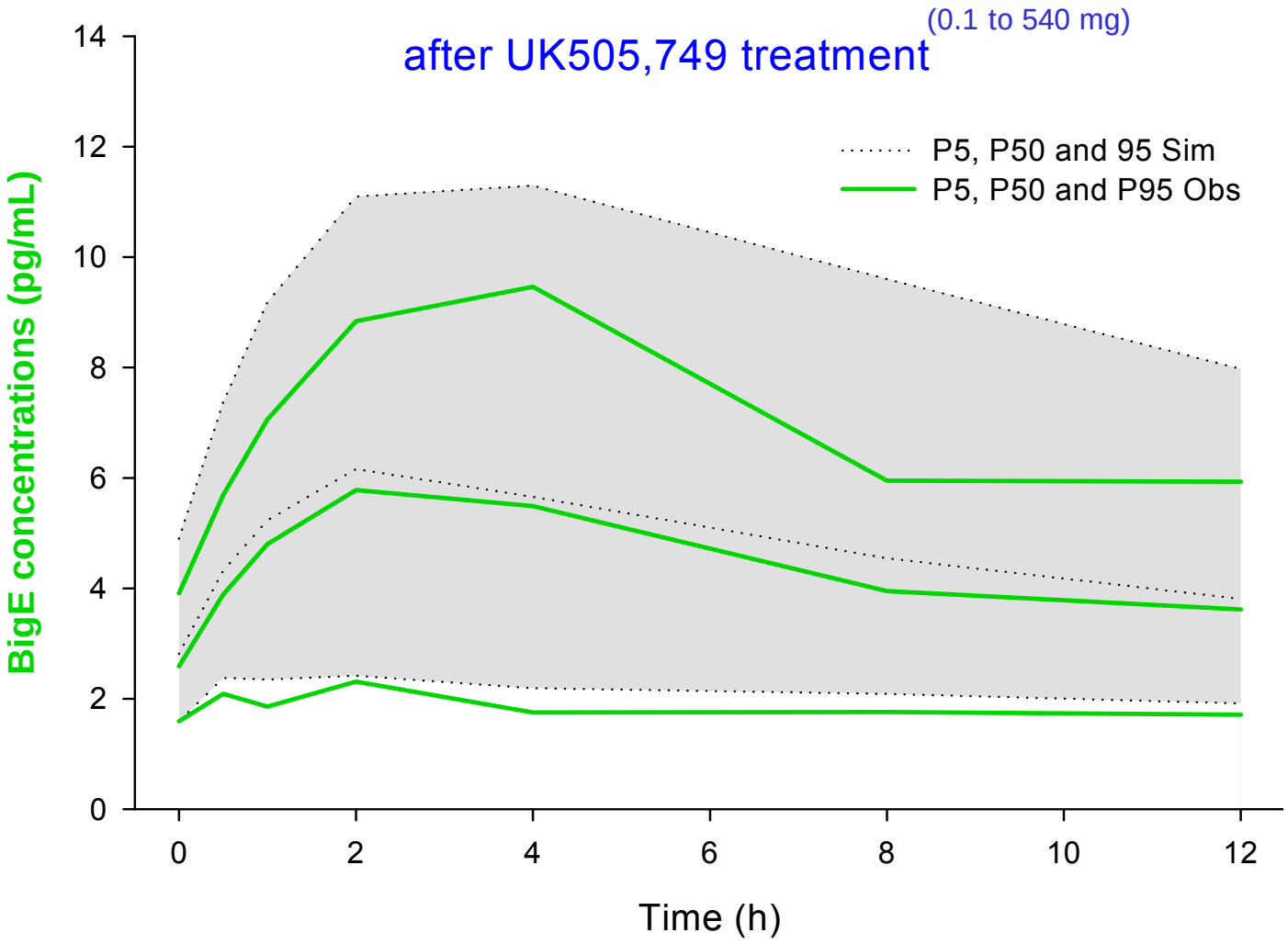
PKPD workshop: Example 2



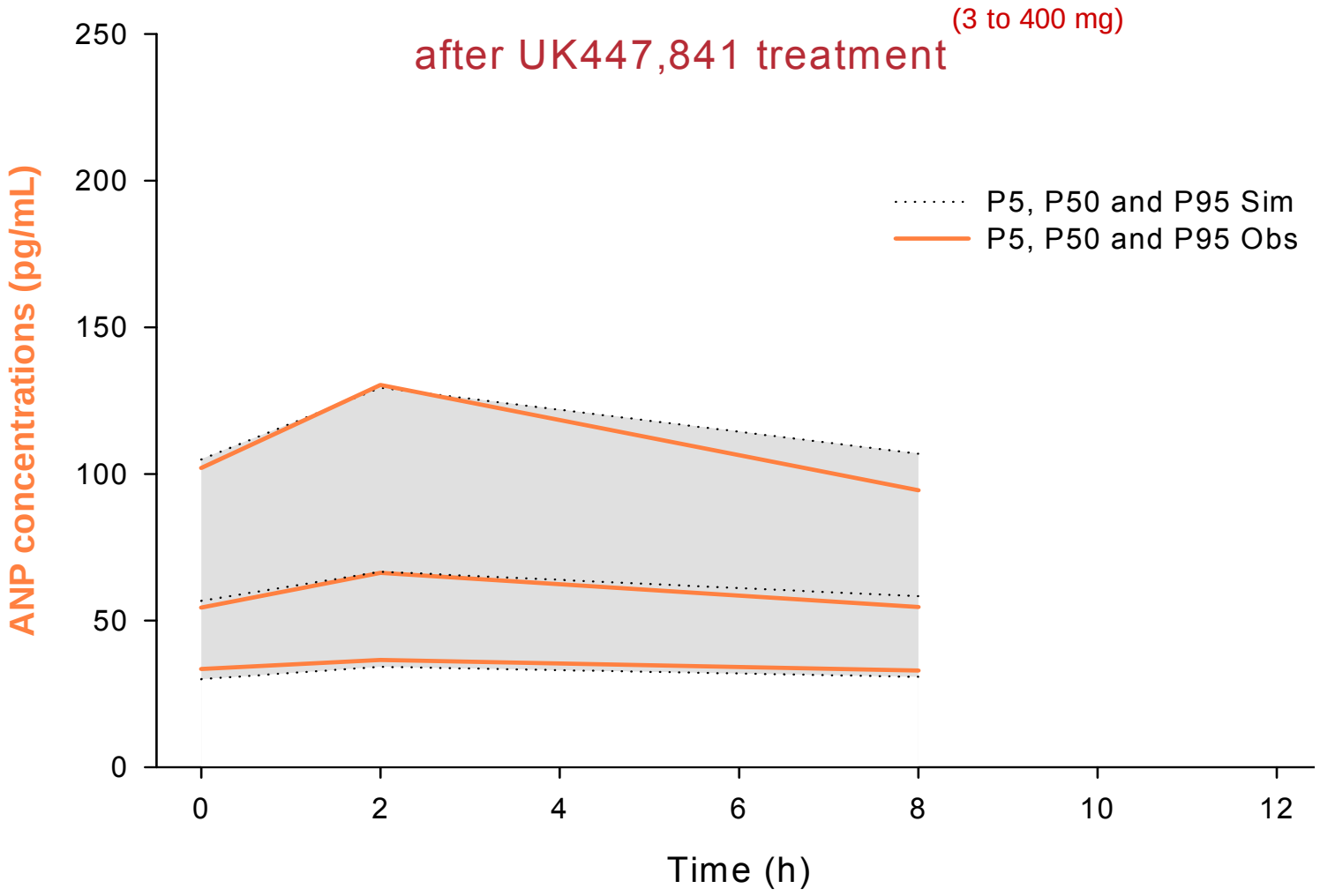
PKPD workshop: Example 2



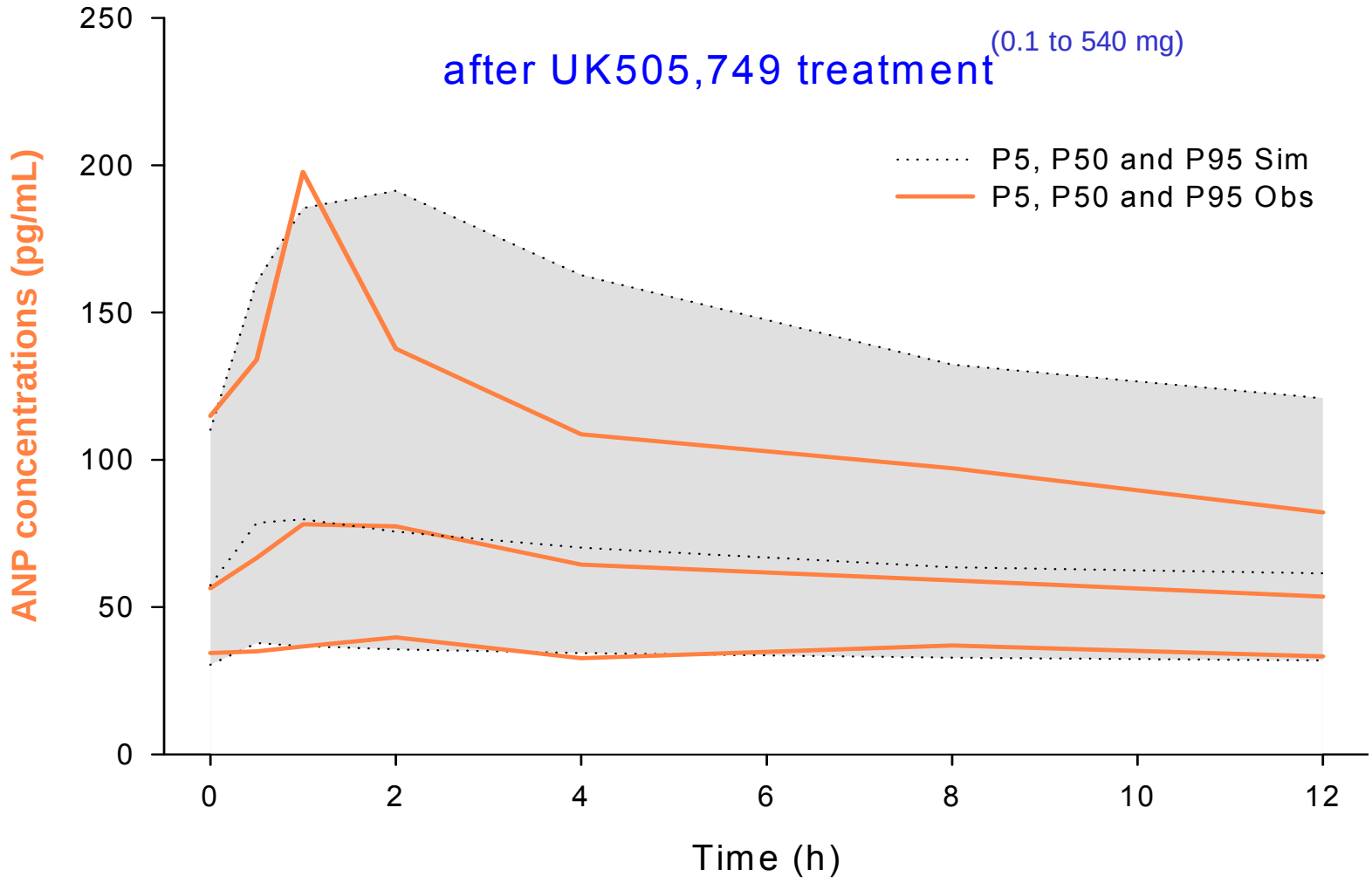
PKPD workshop: Example 2



PKPD workshop: Example 2



PKPD workshop: Example 2



Conclusion

- Big ET-1 plasma concentration and, to a lesser extent, ANP plasma concentration can be used as a pharmacological biomarker for the inhibitory drug effect on enzyme (NEP) activity in healthy volunteers.
- Big ET-1 has ideal characteristics of a soluble biomarker: it demonstrates dose-concentration-effect, time-linearity, reproducibility of effect with similar E_{max} for two NEP inhibitors.
- The ratio of the *in vivo* IC_{50} of the 2 compounds is similar to the *in vitro* ratio. This allows extrapolation between species and between different drugs.

PKPD workshop at AGAH/Club Phase I

I hope to meet many of you again at the PAGE meeting in June 2007 in Copenhagen!