EMA EFPIA workshop

Breakout Session 3

Assumption setting in a semi-mechanistic population PKPD model across a wide range of patients

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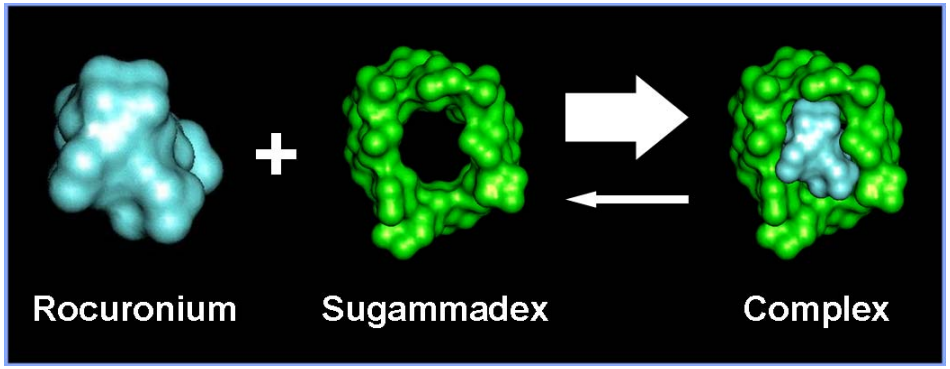
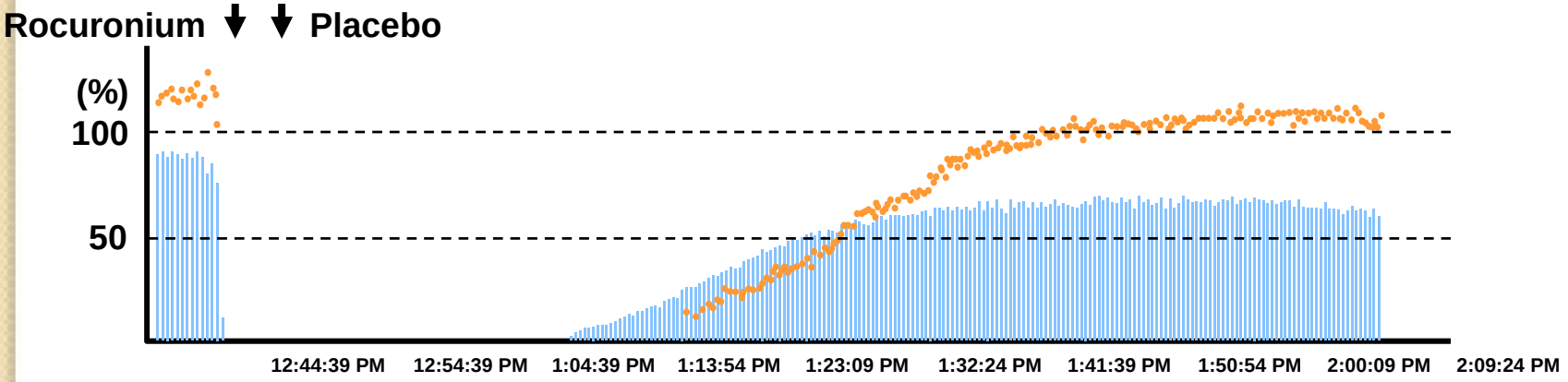
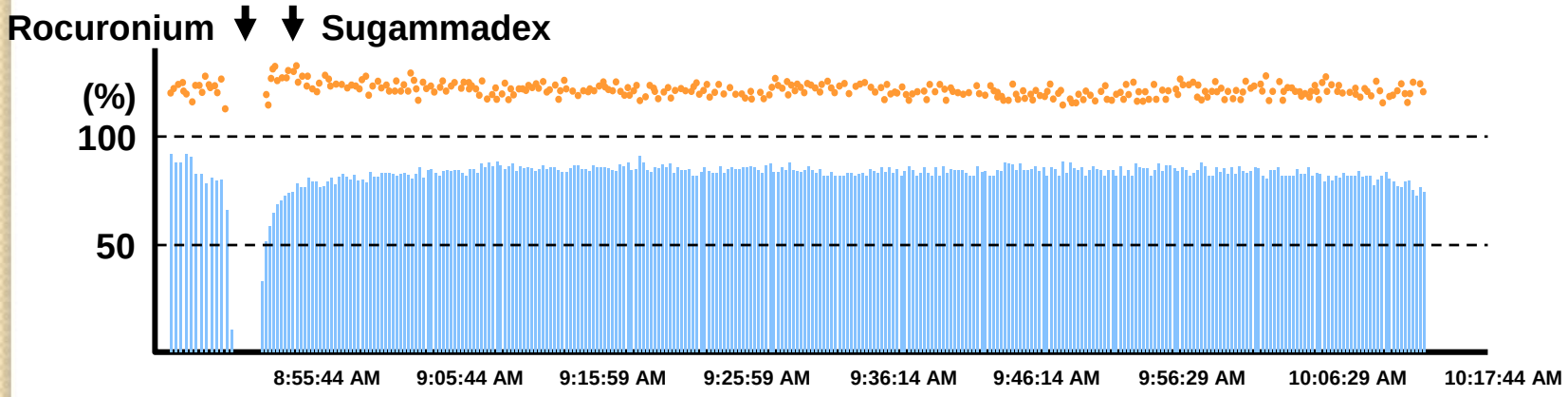
Mechanism of Action

Rocuronium causes neuromuscular block



Sugammadex causes fast reversal of neuromuscular block



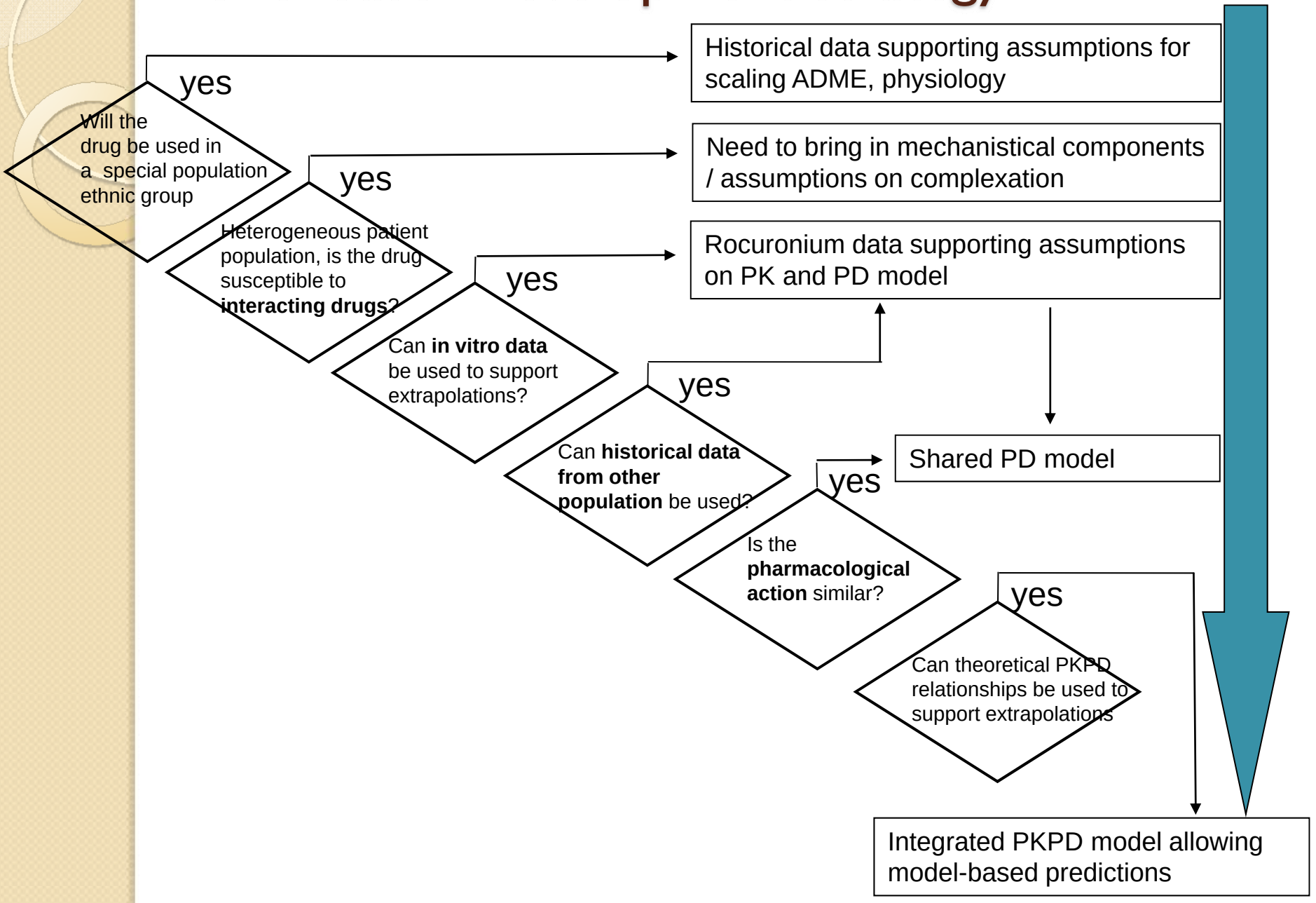


Background

- Semi-mechanistical population PKPD model to facilitate filing and post-approval process in Europe

- Objectives:
  - Provide 'evidence' for dose regimen in pediatric and renal impaired populations
  - Provide 'evidence' on drug interactions
    - displacement of rocuronium, possible reoccurence of NMB
  - Be ready for simulating what if questions

Model-based development strategy

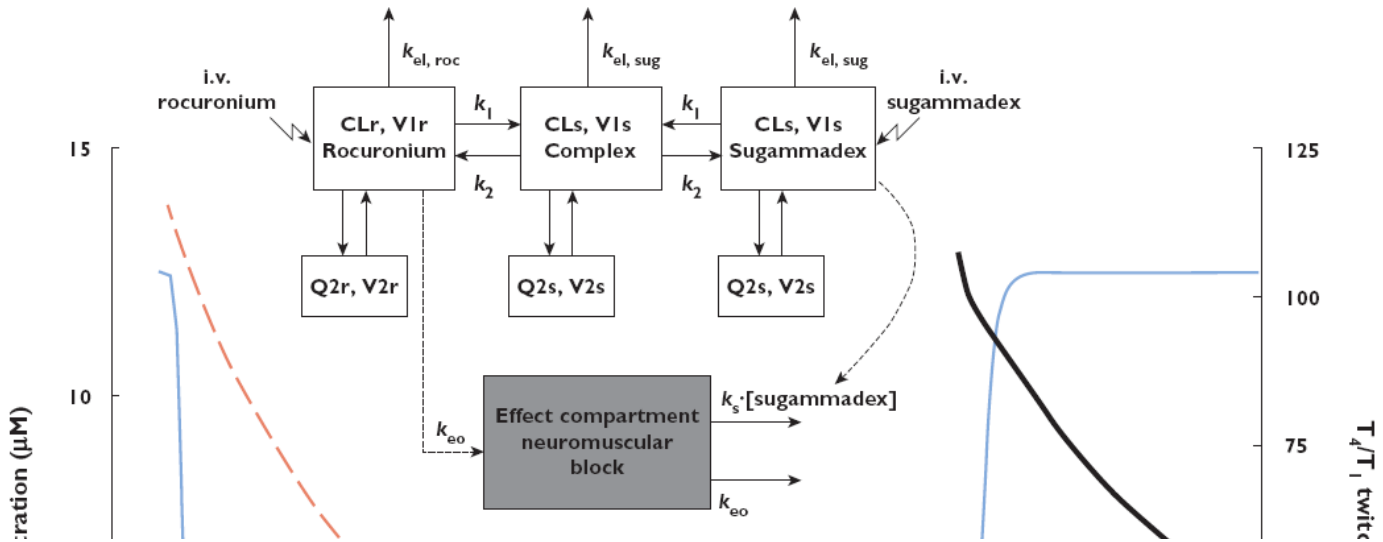


Data

- 9 trials (phase 1 – 3), 446 patients
- Age range 1 – 91 yrs
  - Infant 4
  - Child 17
  - Adolescent 21
  - Adult 247
  - Elderly 50

- BW range 9.6 – 139 kg
- CLCR range 4.3 – 229 mL/min
- Gender 289 males / 157 females
- Ethnicity 393 non-asian / 53 asian

PK-PD model assumptions



(1) Complexation rocuronium and sugammadex mechanistically described by interaction model using in-vitro determined association constant.

(2) Encapsulated rocuronium pharmacokinetically behaves like sugammadex

(3) Free rocuronium drives PD. Encapsulated it is pharmacodynamically inactive

(4a) Allometric scaling by bodyweight of CL, V

(4b) Sugammadex CL driven by renal function

(5) PD model structure on literature data

(6) Allometric scaling PD rate constants, distribution effects cause PD delay. Enables faster reversal in pediatrics!

Special populations

Mean onset time in infants and children at an intubation dose of 0.6 mg/kg is slightly shorter than in adults. The duration of relaxation and the time to recovery tend to be shorter in children compared to infants and adults.

plex ( );)

Simulations – effects of age and renal clearance on recovery time

Anaesthesia Scenario	Reversal time to TOF90 (min) No sevoflurane Infant 1 year	Child 7 years	Adolescent 15 years	Adult 40 years	Elderly 75 years
Reversal 3 min after rocuronium	0.5	0.8	0.8	0.8	0.8
16 mg kg^{-1} sugammadex at 3 min after 1.2 mg kg^{-1} rocuronium	0.3–2.5	0.3–2.8	0.3–3.3	0.3–3.3	0.3–3.5
Deep blockade reversal	0.8	1.0	1.3	1.5	1.8
4 mg kg^{-1} sugammadex at 15 min after 0.6 mg kg^{-1} rocuronium	0.3–3.3	0.3–4.3	0.3–5.5	0.5–6.0	0.5–6.5
Moderate blockade reversal	1.0	1.3	1.3	1.4	1.5
2 mg kg^{-1} sugammadex at reappearance of T_2	0.3–3.8	0.5–4.8	0.5–5.5	0.5–5.5	0.5–6.0

Median + 90%CI

- Size effects translates to recovery time
- Effects of other covariates on PK hardly visible on reversal time

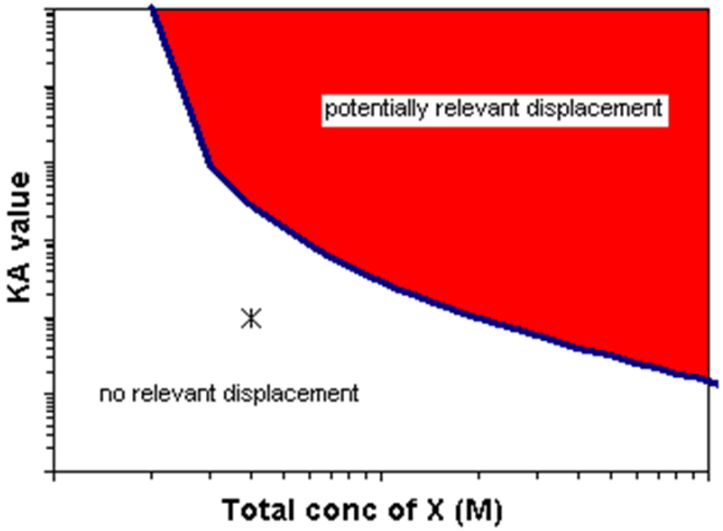
Effects not clinically relevant, supports the approach of one dose fits all

Simulations – risk of displacement and reoccurrence of NMB

$$K_A, roc = \frac{[Roc - Sug]}{[Roc][Sug]} \quad K_{A,X} = \frac{[X - Sug]}{[X][Sug]}$$

In-vitro assessed $K_{A,roc}$ and $K_{A,x}$

- The in vivo situation is modeled as a single “well-stirred” compartment with rocuronium, sugammadex and third compound X and an effect parameter, the TOF ratio, which depends on the unbound concentration of rocuronium.
- Sugammadex and rocuronium are present in this compartment at clinical relevant concentrations. The plasma concentrations are calculated from the population PK interaction model. The third compound is present at a variable concentration.
- The unbound fractions of all three compounds are determined by the two association constants (KA) under the assumption of instantaneous equilibrium.
- The relationship between TOF ratio and unbound rocuronium concentration as given in the PKPD model



SPC text - Section 4.5 driven by M&S

4.5 Interaction with other medicinal products and other forms of interaction

The information in this section is based on binding affinity between sugammadex and other medicinal products, non-clinical experiments, clinical studies and simulations using a model taking into account the pharmacodynamic effect of neuromuscular blocking agents and the pharmacokinetic interaction between neuromuscular blocking agents and sugammadex. Based on these data, no clinically significant pharmacodynamic interaction with other medicinal products is expected, with exception of the following:For toremifene and fusidic acid displacement interactions could not be excluded (no clinically relevant capturing interactions are expected).

Conclusions

- Model-based predictions indicated somewhat faster reversal in pediatric population. Simulations supported the approach for one dose fits all

- Model-based predictions allowed evaluation of potential drug interaction and identification of possible critical interactions

backup

Calculation CLcr over age range 1 – 91 yrs

- For adults and elderly creatinine clearance is calculated according to the formula of Cockcroft – Gault [5].

$$CLcr[mL/\min] = \frac{(140 - age[yrs]) \times bodyweight[kg]}{72 \times \text{serum creatinine}[mg/dL]}$$

- For pediatrics (<18 yrs) creatinine will be based upon the formula of Schwartz [6].

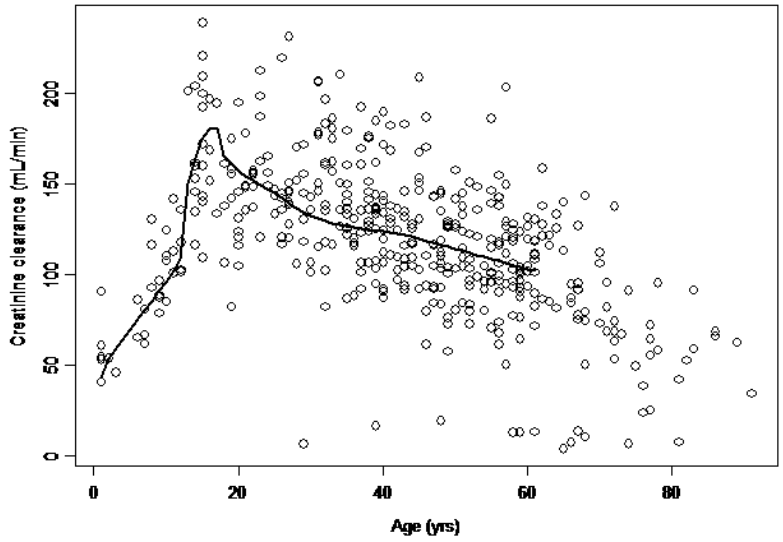
$$CLcr[mL/\min/1.73m^2] = \frac{height[cm] \times k}{\text{serum creatinine}[mg/dL]}$$

k = 0.45 for infants 1 to 52 weeks old
k = 0.55 for children 1 to 12 years old
k = 0.55 for adolescent females 13-18 years old
k = 0.7 for adolescent males 13-18 years old

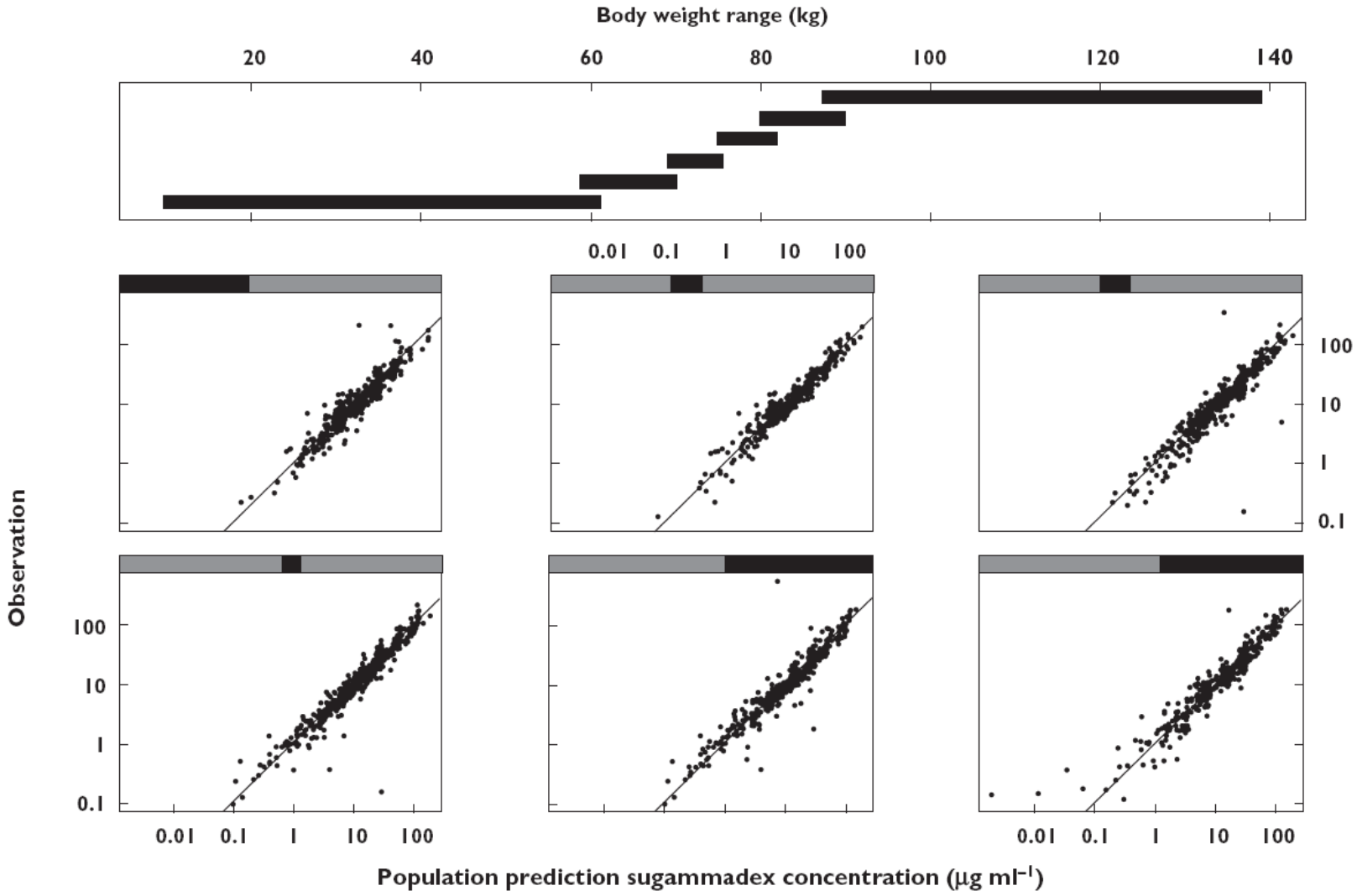
- BSA normalization in Schwartz derived CLcr was removed

- BSA derived from height and weight using Dubois – Dubois equation

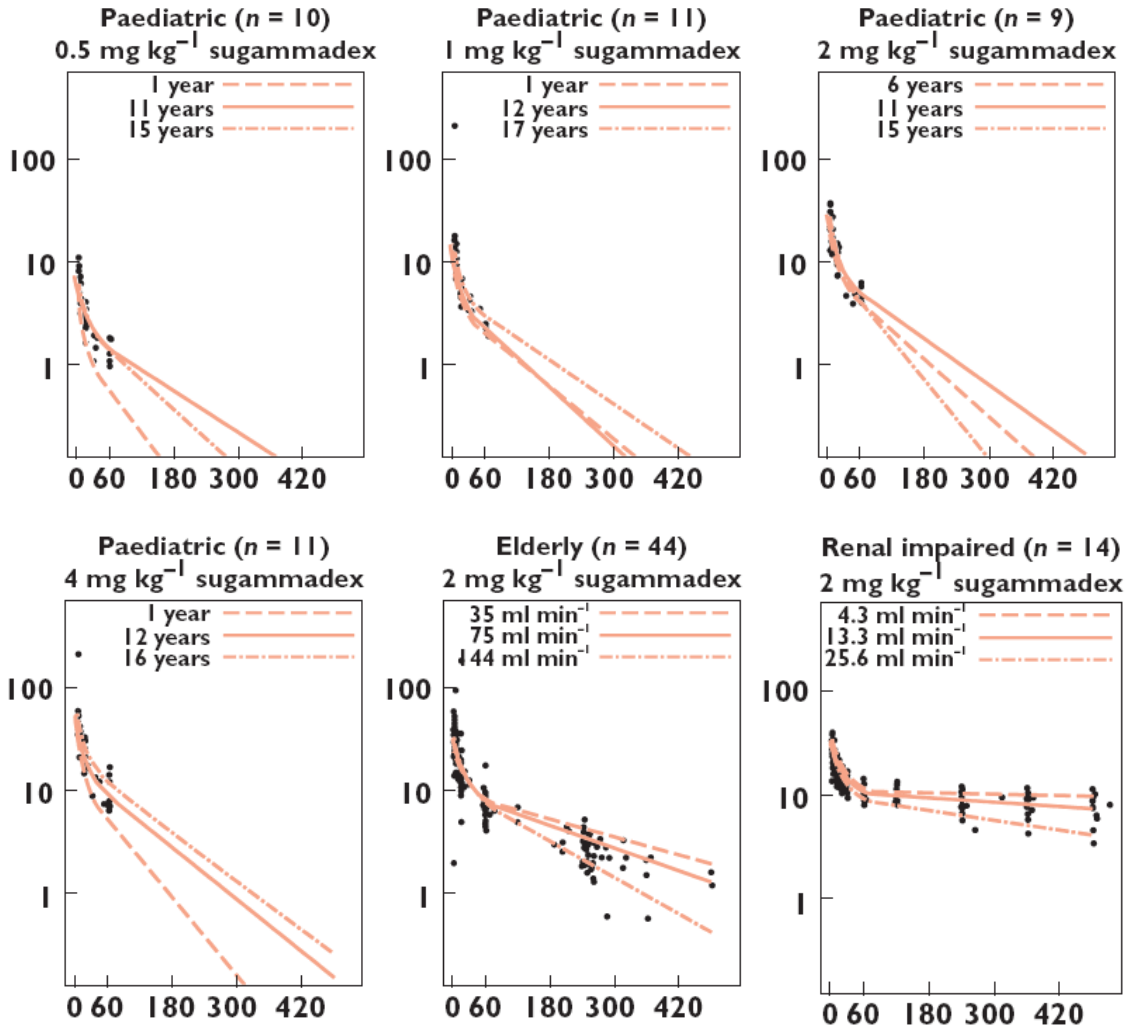
$$BSA = W^{0.425} \times H^{0.725} \times 71.84$$



Sugammadex concentrations adequately predicted Allometric scaling



Model predictions in special populations



Observed and population-predicted sugammadex plasma concentrations for adult, paediatric, elderly and renally impaired populations conditioned on sugammadex dose (one subject treated with sugammadex 0.1 mg kg^{-1} is not shown). Red lines represent population predictions for three typical subjects reflecting variability in renal function for adults or age for paediatric subjects. Demographic data from patients with lowest, median and highest creatinine clearance, or age in case of the paediatric population, within the depicted populations were used to define typical subjects; all data are shown up to 10 h postdose