



Physiologically-based Pharmacokinetic and Pharmacodynamic modeling of Enzalutamide and N-Desmethyl Enzalutamide

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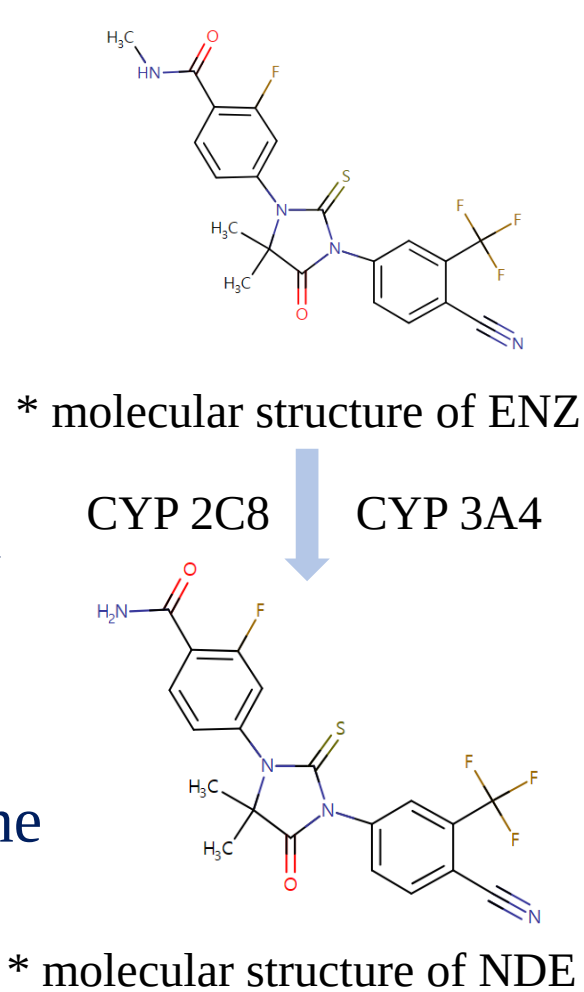
BACKGROUND

Enzalutamide and metabolite treatment of Prostate cancer patients

- **Enzalutamide (ENZ)** is a 2nd generation androgen receptor of castration-resistant prostate cancer(CRPC) patients.
- **N-Desmethyl Enzalutamide (NDE)** is active metabolite of ENZ

Main pharmacokinetic(PK) characteristics of ENZ

- Majorly metabolized by **CYP2C8** and **CYP3A4**.
- Peak concentration of ENZ are typically reached within **1 to 2 hours**.
- A relatively long half-life of **5.8 days**, steady state was achieved by **day 28**.
- The contribution of **CYP2C8** and **CYP3A4** in the metabolism of Enzalutamide is estimated to be 87% and 13% following single dose Drug-Drug interaction study



Main pharmacokinetic characteristics of NDE

- Although NDE is not metabolized by Cytochrome P450, probably metabolized to the inactive carboxylic acid metabolite by carboxylesterase 1.
- A longer half-life than ENZ of **7.8 days**.
- NDE is contribute to the clinical effects of ENZ with **similar efficacy and safety** to ENZ.

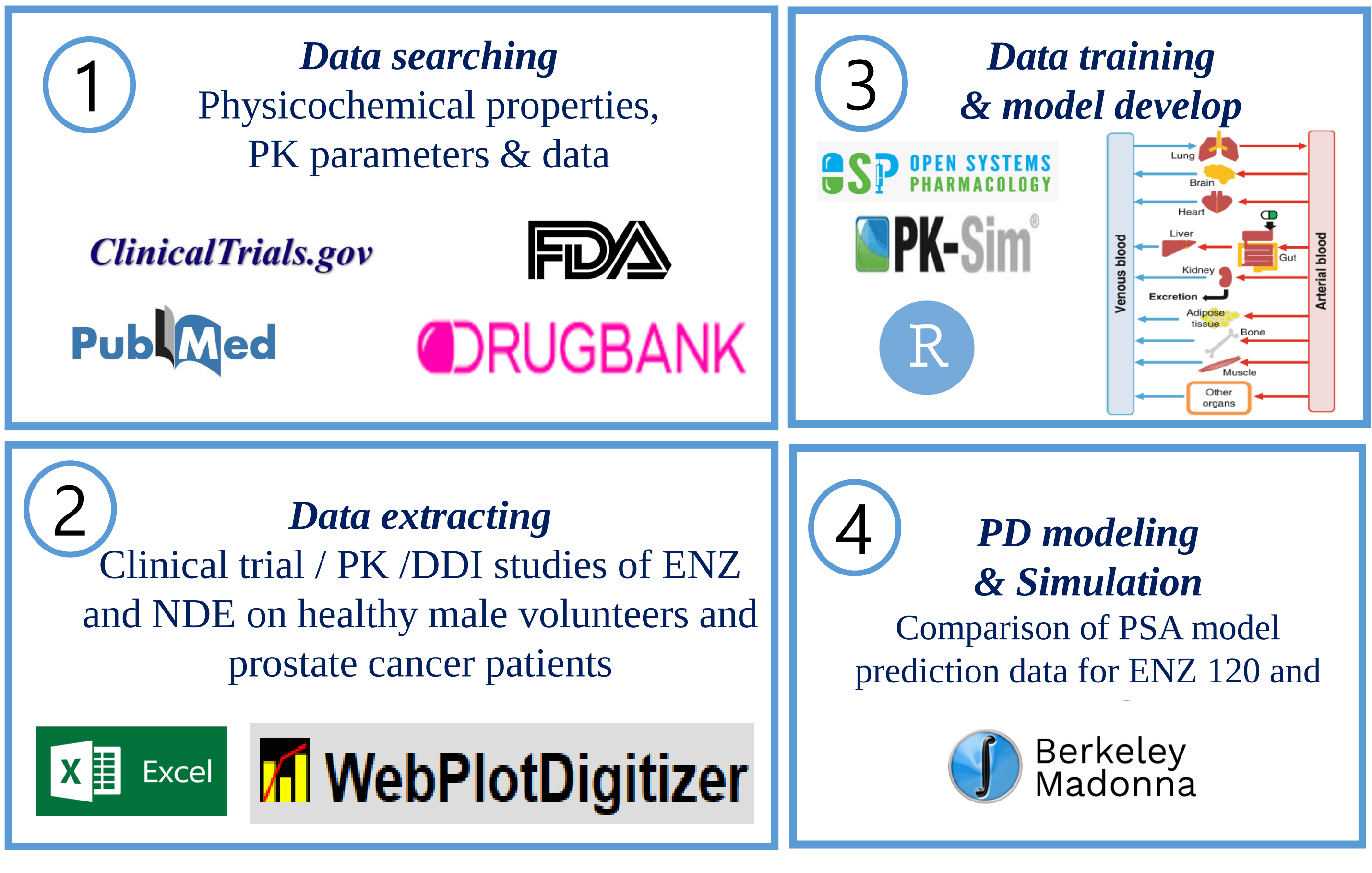
Prstate – specific antigen (PSA)

- **PSA is biomarker** of CRPC patients.
- typically, CRPC is associated with increases in serum PSA levels, suggesting that the disease continues to be driven by Androgen Receptor signaling.
- ENZ and NDE can reduce abnormally elevated PSA levels by targeting the androgen receptor signaling pathway with a once-daily regimen of registered dose of ENZ 160mg. However, due to the occurrence of adverse reactions, there are several opinions to reduce the dose from 160mg to 120mg.

OBJECTIVES

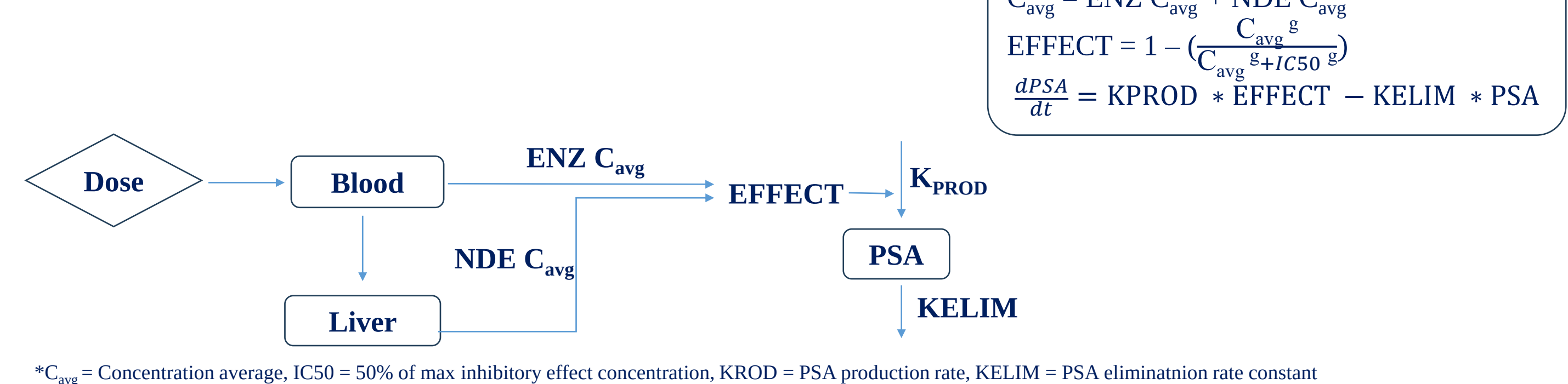
1. **Develop a physiologically based pharmacokinetic model of ENZ and NDE**
Developing a physiologically based pharmacokinetic (PBPK) model for the prediction of ENZ and NDE pharmacokinetic features.
2. **Develop a Pharmacodynamic(PD) model of ENZ and NDE**
Development of a PSA response PD model using data from the developed PBPK model and comparison of 120mg and 160mg

METHODS



RESULTS

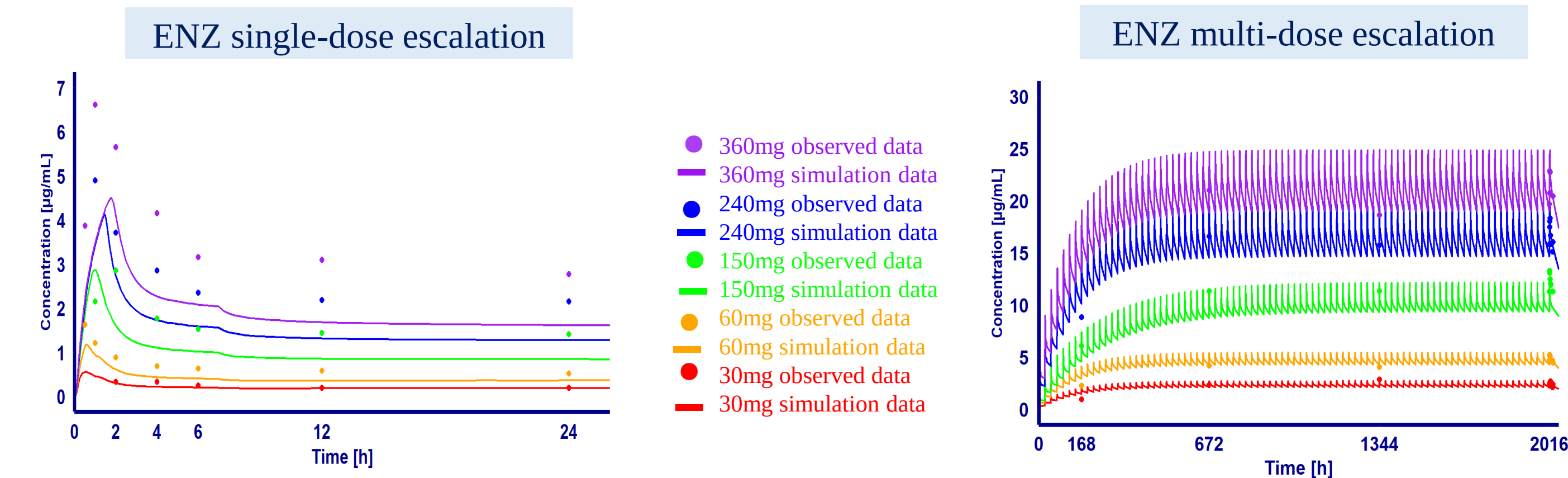
PK-PD Model scheme



Results of PBPK model

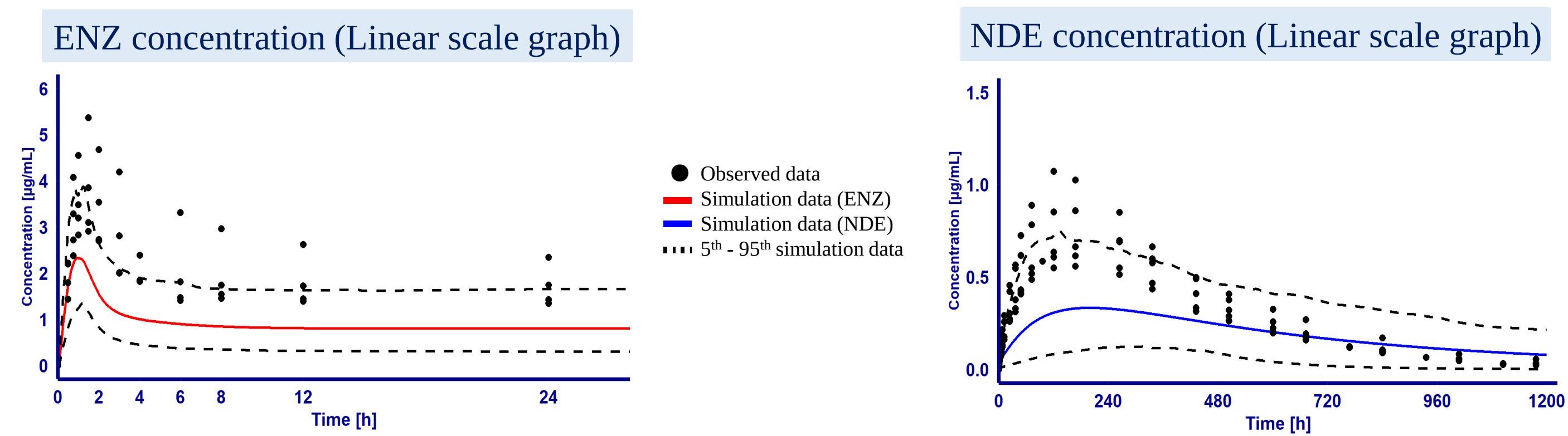
- PK data of ENZ/NDE were extracted from 4 single dose studies and 2 multi dose studies at 160mg oral dose. Additionally, single and multi ascending dose-escalation (30, 60, 150, 240, 360mg) data were used to train the PBPK model at other doses.
- Data on the physicochemical properties, absorption, distribution, metabolism, and excretion of the drug were initial values in the literature and were fine-tuned to model multiple doses.

- Dose escalation simulation

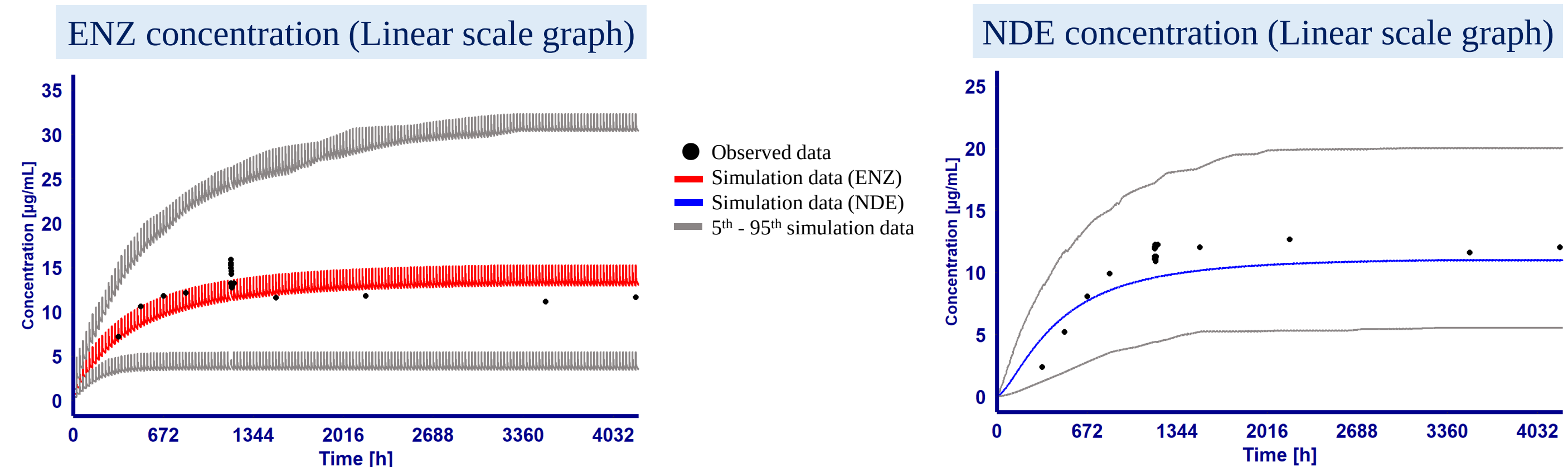


RESULTS

- Single-dose simulation 160mg dose of ENZ/NDE plasma concentration

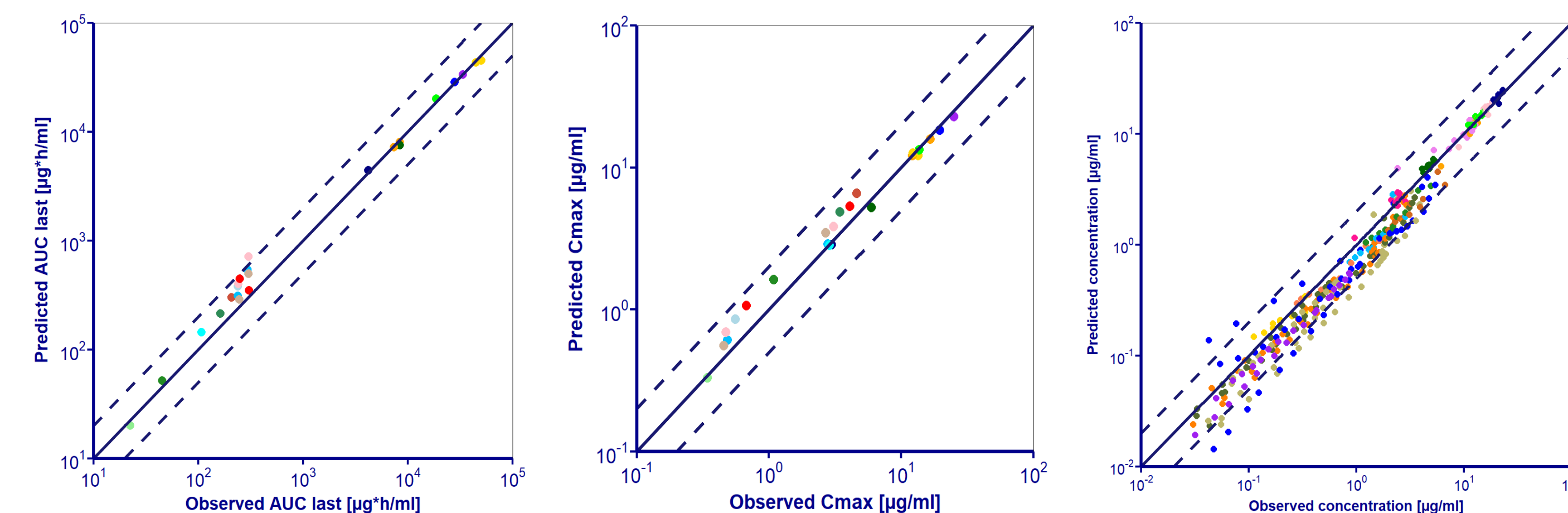


- Multi-dose simulation 160mg dose of ENZ/NDE plasma concentration



Predicted vs observed values of ENZ and NDE

AUC_{inf}, C_{max} and Plasma concentration



- The ENZ MRD of predicted plasma level were 1.39.
- The ENZ GMFE values of AUC_{inf} & C_{max} were 1.27 &1.16.respectively.
- The NDE MRD of predicted plasma level were 1.41.
- The NDE GMFE values of AUC_{inf} & C_{max} were 1.35 &1.29.respectively.

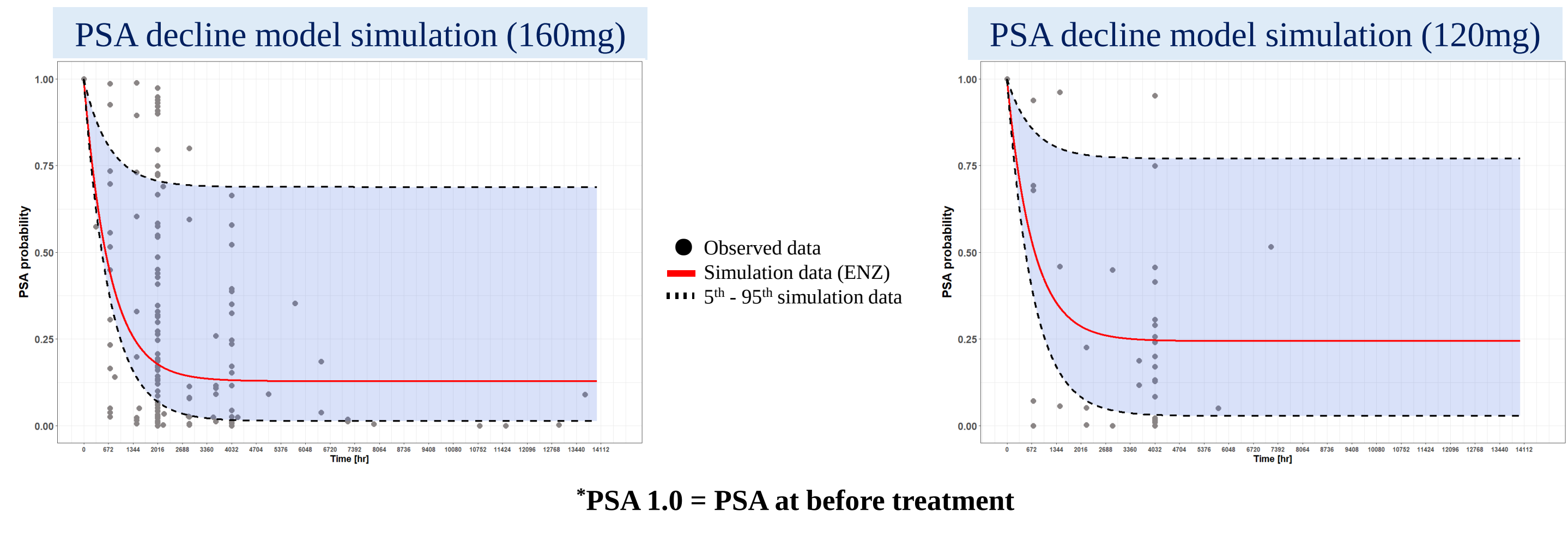
*MRD = Mean relative deviations, GMFE = Geometric mean fold errors

$MRD = 10^x$, with $x = \frac{1}{n} \sum_{i=1}^n (\log_{10} C_{pred,i} - \log_{10} C_{obs,i})^2$

$GMFE = 10^x$, with $x = \frac{1}{n} \sum_{i=1}^n |\log_{10} PK_{pred,i} - \log_{10} PK_{obs,i}|$

Results of PD model

- PSA data were extracted from 5 multi dose studies, and only patients with reduced PSA in the studies.
- Determined that there was no difference between 120 and 160 mg in the data collected.
- The concentration of PSA in CRPC patients were highly variable, thus we set the baseline to 1.0 rather than the individual concentration to check the probability of PSA decline.



CONCLUSION & DISCUSSION

What we got:

1. We successfully developed a PBPK model to characterize the PKs of ENZ and NDE in combined population for healthy male volunteers and CRPC patients
2. Development of a PSA PD model using C_{avg} from PBPK model

What are our limits :

1. We did not know the decrease in PSA time profile, so we used the time point when PSA nadir per individual.
2. The number of studies for 120 mg dose group was fewer than the 160mg group

Acknowledgement

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