

Application of neural ordinary differential equations (neural-ODE) framework to predict unknown exposure profile in first-in-human (FIH) single ascending trial: comparative analysis with observed data



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Introduction

First in human (FIH) clinical trials aim to study the human pharmacology, tolerability and safety of an investigational medicinal product (IMP). The highest priority in conducting a FIH trial is ensuring the safety and well-being of the recruited subjects [1]:

- ▶ In the dose escalation meeting, the decision is taken to continue with the next dose cohort.
- ▶ Any data that are relevant to assess safety have to be taken into account in order to make a good informed decision.
- ▶ The time frame for receiving the latest exposure data and the dose escalation meeting is often a time delying factor.
- ▶ Purely data-driven modelling (AI) approach could be beneficial to "shorten" the time required for model development and prediction of exposure of next anticipated dose.
- ▶ No assumptions of the structural model (compartment structure) are needed.
- ▶ We have demonstrated that a deep learning approach using neural-ODE is suitable for predicting untested exposure in FIH trials [2].

Methods

The single ascending dose (SAD) part of the FIH trial:

- ▶ 6 cohorts with different doses (starting dose and applying the following dose escalation factors: 3, 2.5, 2.7, 2.0 and 1.5).
- ▶ 6 subjects per cohort
- ▶ PK sampling scheme: 0, 0.5, 1, 1.5, 2.5, 4, 5, 8, 10, 12, 14, 24, 28, 32, 38, 48 and 72 h. post-dose.

The neural-ODE model [3] was adapted for SAD data:

- ▶ Extended by transfer learning technique (two stage training).
 - ▶ Simulated data derived from a pre-clinical allometric popPK model[4] was used to train the base model.
 - ▶ Following the SAD trial design, we retrained the base model with the encoder layers frozen using all lower dose levels to predict the individual response at the next planned higher dose.
 - ▶ Model performance was evaluated by graphical display.
- ▶ Optimization of hyperparameters.
 - ▶ Learning rate (lr) of 4.5e-4, L2 regularization (l2) of 1e-6 and 100 epochs for the base model.
 - ▶ l2 of 1e-7 for a second training via transfer learning on the trial data.
- ▶ The prediction error (PE) [%] ($100 \times (|\text{observed} - \text{predicted}|) / \text{observed}$) was calculated for $C_{\max}$ and $AUC_{t=0-24\text{ h}}$.

Literature

1 Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (europa.eu). https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-and-mitigate-risks-first-human-and-early-clinical-trials-investigational-medicinal-products-revision-1_en.pdf last accessed 10. Mar 2025.

2 K. Lindauer, A. Ahmad, F. Khalil, L. Kraske et al. Application of a neural-ODE framework to support dose escalation decision during safety review meetings in first-in-human clinical trial. PAGE 32 (2024) last accessed 10. Mar 2025.

3 Lu J, Deng K, Zhang X, Liu G, Guan Y. Neural-ODE for pharmacokinetics modeling and its advantage to alternative machine learning models in predicting new dosing regimens. iScience. 2021 Jun 30;24(7):102804.

4 K. Lindauer, K. Pasikanti, F. Khalil, M. Gautrois, S. Engelen, B. Manning Allometric Scaling for Efficacious First-in-Human Dose Prediction of Pharmacologically-Active Parent and Metabolite Based on Rat, Dog and Monkey PK data. PAGE 31 (2023) Abstr 10540 [www.page-meeting.org/?abstract=10540] last accessed 10. Mar 2025.

Conclusions

Neural-ODE modeling proved to be a valuable, data-driven and time-efficient complement to population PK modeling in FIH trials, offering a dynamic approach to dose prediction with generally increasing accuracy as more data accumulates.

The neural-ODE framework:

- ▶ Demonstrated a strong potential for predicting exposure at higher dose levels.
- ▶ Was validated in the SAD part of a FIH trial as a tool for forecasting individual PK profiles with linear dose exposure relationship.
- ▶ As additional trial data became available, model performance improved, reducing bias in the simulated predictions.
- ▶ Supporting dose escalation decisions in real time.
- ▶ Can effectively capture linear dose-exposure relationships.
- ▶ Early-stage predictions were highly dependent on simulations and data augmentation due to limited clinical trial data.
- ▶ Increased prediction error (PE) of cohort 5 could be caused by differences in the intra-individual variability within each cohort.

Results - Model Prediction

The trained network predicted the respective concentration profiles of the next unknown dose cohort.

- ▶ $C_{\max}$.
 - ▶ The average PE ranged from 8.2 to 38.2 %, with an average mean PE of 21.8%.
 - ▶ The maximum PE ranged from 23.8 to 53.0 %. with an average mean PE of 37.5%.
- ▶ $AUC_{t=0-24\text{ h}}$.
 - ▶ The average PE ranged from 5.4 to 31.5 %, with an average mean PE of 21.6%.
 - ▶ The maximum PE ranged from 21.4 to 79.7 %, with an average mean PE of 44.0%.
- ▶ With increasing dose levels, the neural-ODE PE of $C_{\max}$ tended to increase, whereas the $AUC_{t=0-24\text{ h}}$ PE showed a decreasing trend.

The PE for $C_{\max}$ and $AUC_{t=0-24\text{ h}}$ is summarized in Table 1 and the profiles are shown in Table 2.

Cohort	2		3		4		5		6	
	mean	max	mean	max	mean	max	mean	max	mean	max
$C_{\max}$ PE [%]	20.2	28.6	28.1	53.0	8.2	32.8	38.2	49.1	14.3	23.8
$AUC_{t=0-24\text{ h}}$ PE [%]	18.2	79.7	31.5	47.1	28.1	32.3	24.6	39.4	5.4	21.4
No. of subject in clinical trial data	6		12		18		24		30	
	110		110		110		110		110	
No of subjects in test data	6		6		6		6		6	

Table 1: Quantitative assessment of the degree of goodness-of-fit of the validation dataset. The mean and maximum (max) prediction error refer to the mean and the maximum of the observed and predicted values of the respective cohort.

Prediction Error

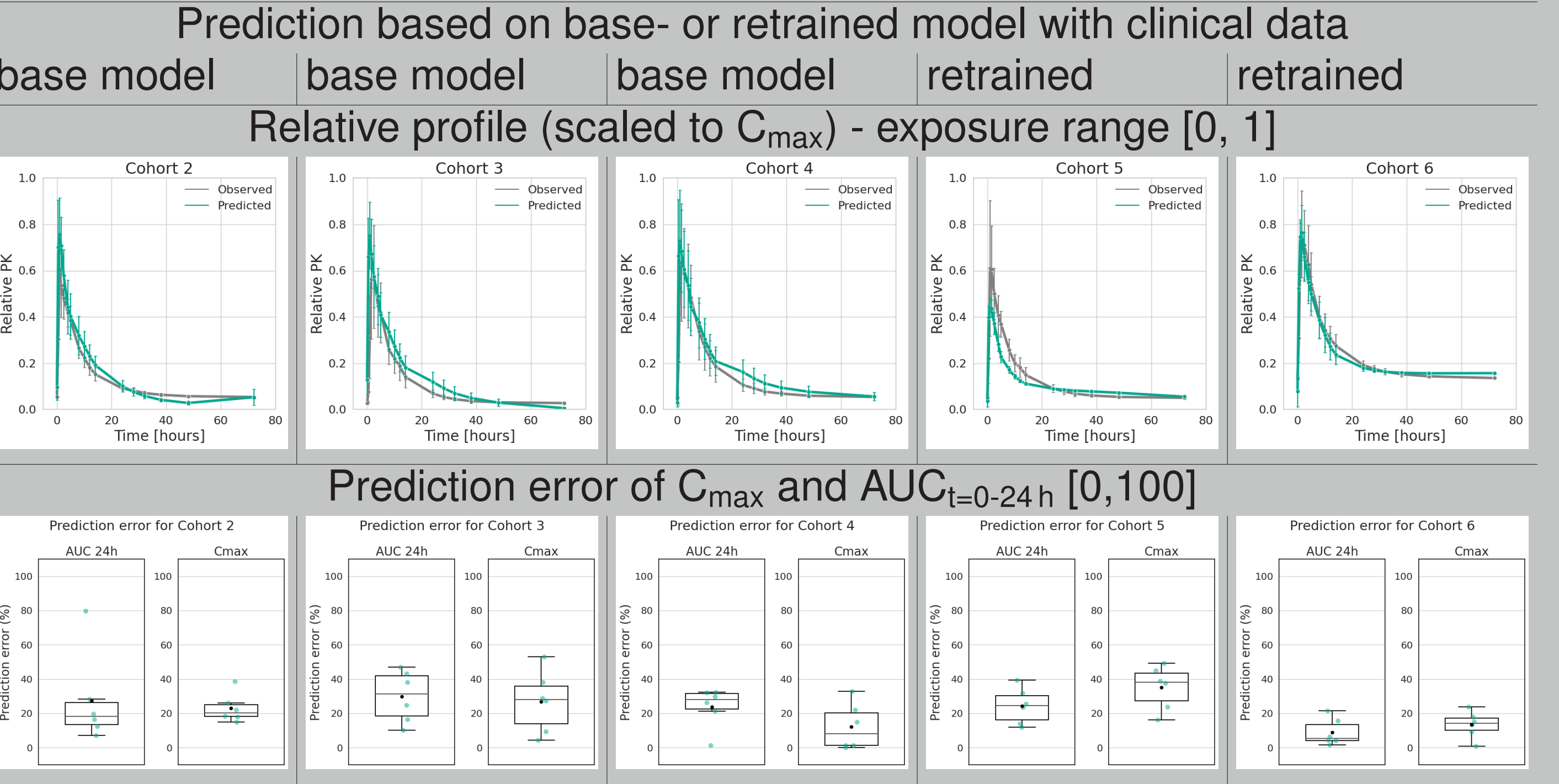
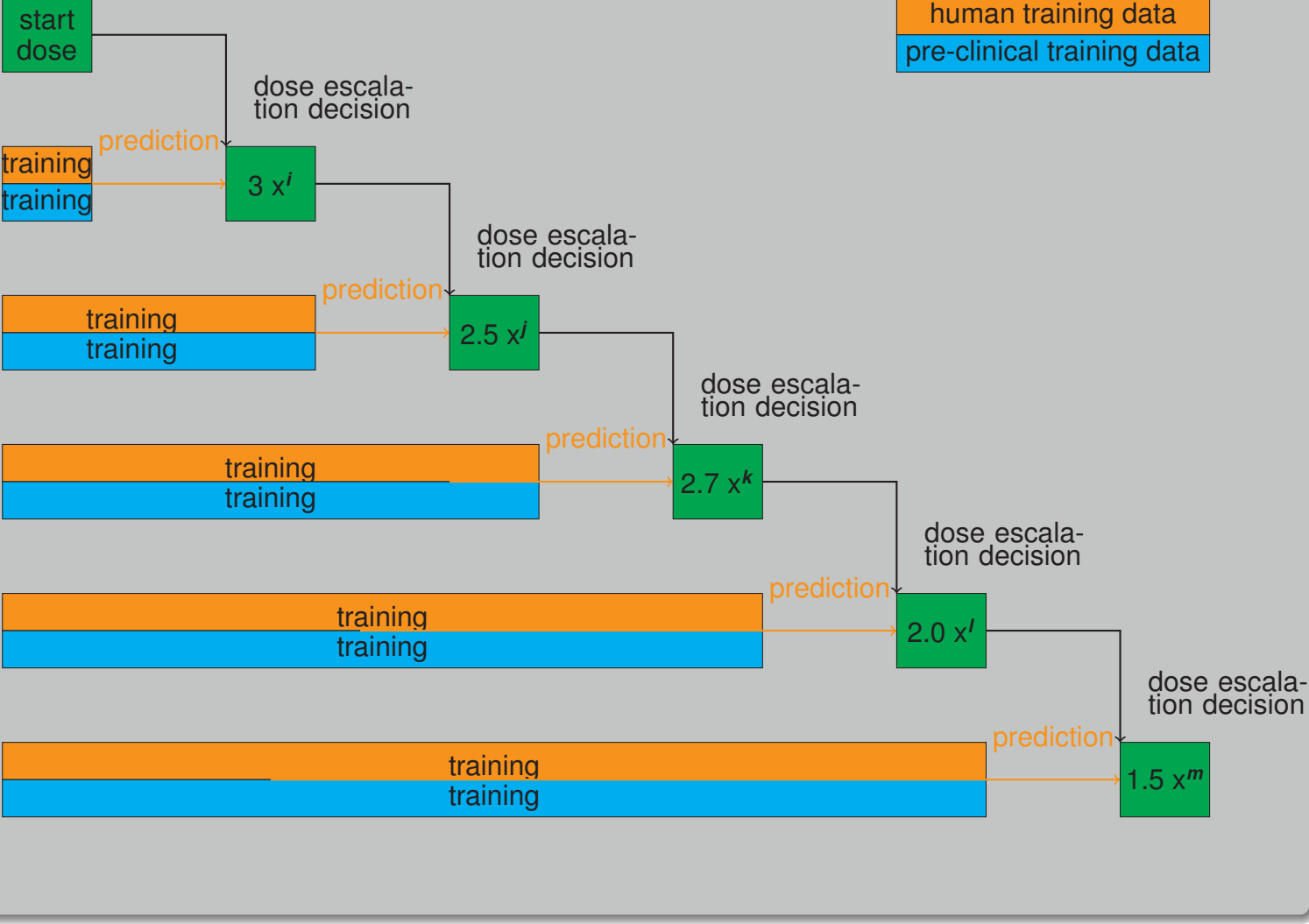


Table 2: The prediction error of $C_{\max}$ and $AUC_{t=0-24\text{ h}}$ and the respective profile scaled to the maximum exposure are shown.

Objectives

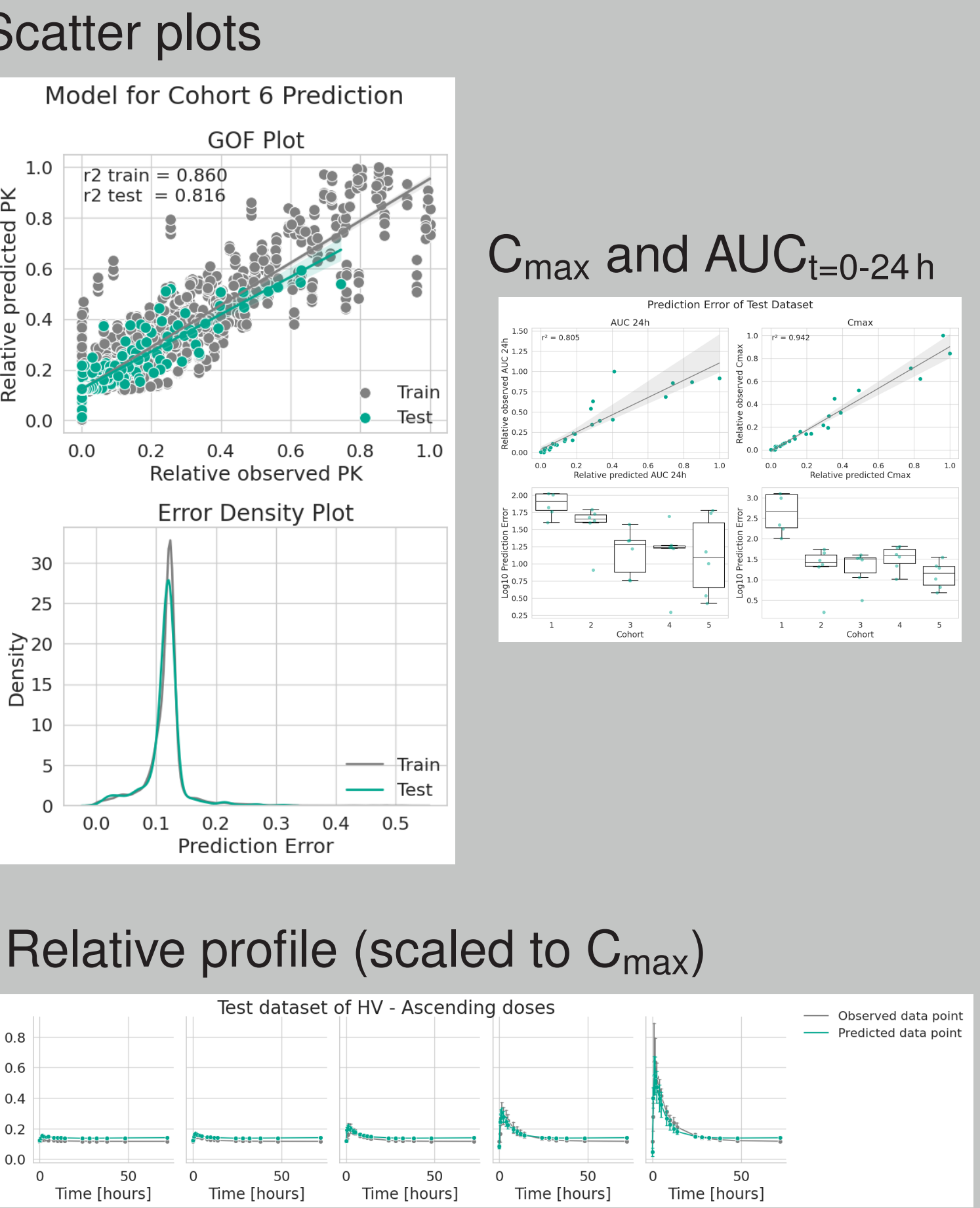
Application of the neural-ODE framework to predict unknown exposure in FIH trial and estimate the prediction error (PE) of maximal exposure ($C_{\max}$) and $AUC_{t=0-24\text{ h}}$.

Outline of SAD trial



Model Performance

Training dataset - up to cohort 5
Goodness-of-fit



Training dataset - cohort 1
Goodness-of-fit - scatter plots

