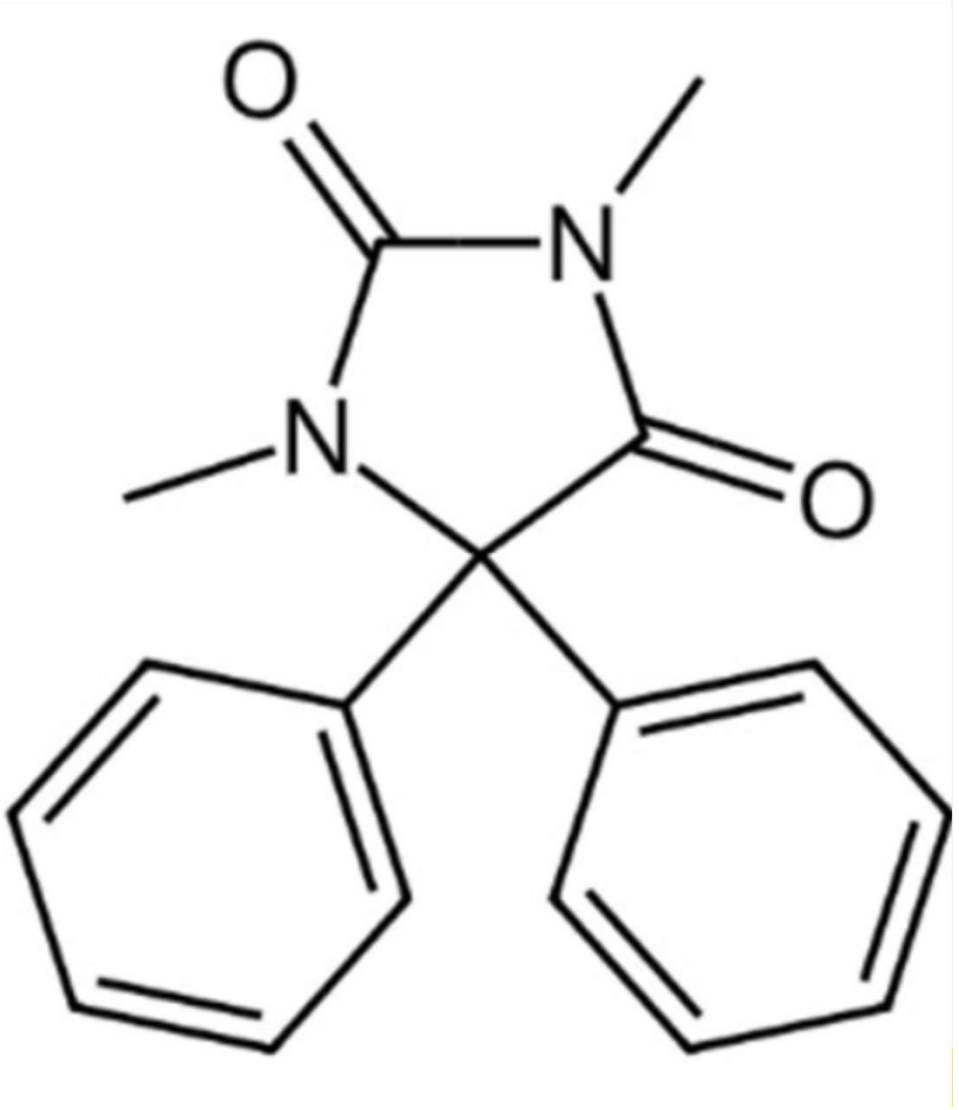
Fachhochschule Nordwestschweiz

Funytoin

Transition from IV to a tablet

Denis Schatzmann



Fachhochschule Nordwestschweiz

Research question

Research question

Primary objective:

- What dose for tablets matches the AUC 0h-6h of 150 mg Funytoin IV in patients weighting 70 kg?

Research question

Secondary objectives:

- What is the absolute bioavailability (F) of the oral tablet?
- What is the variability between patients?
- What is the impact of the covariates on the clearance and volume of distribution?

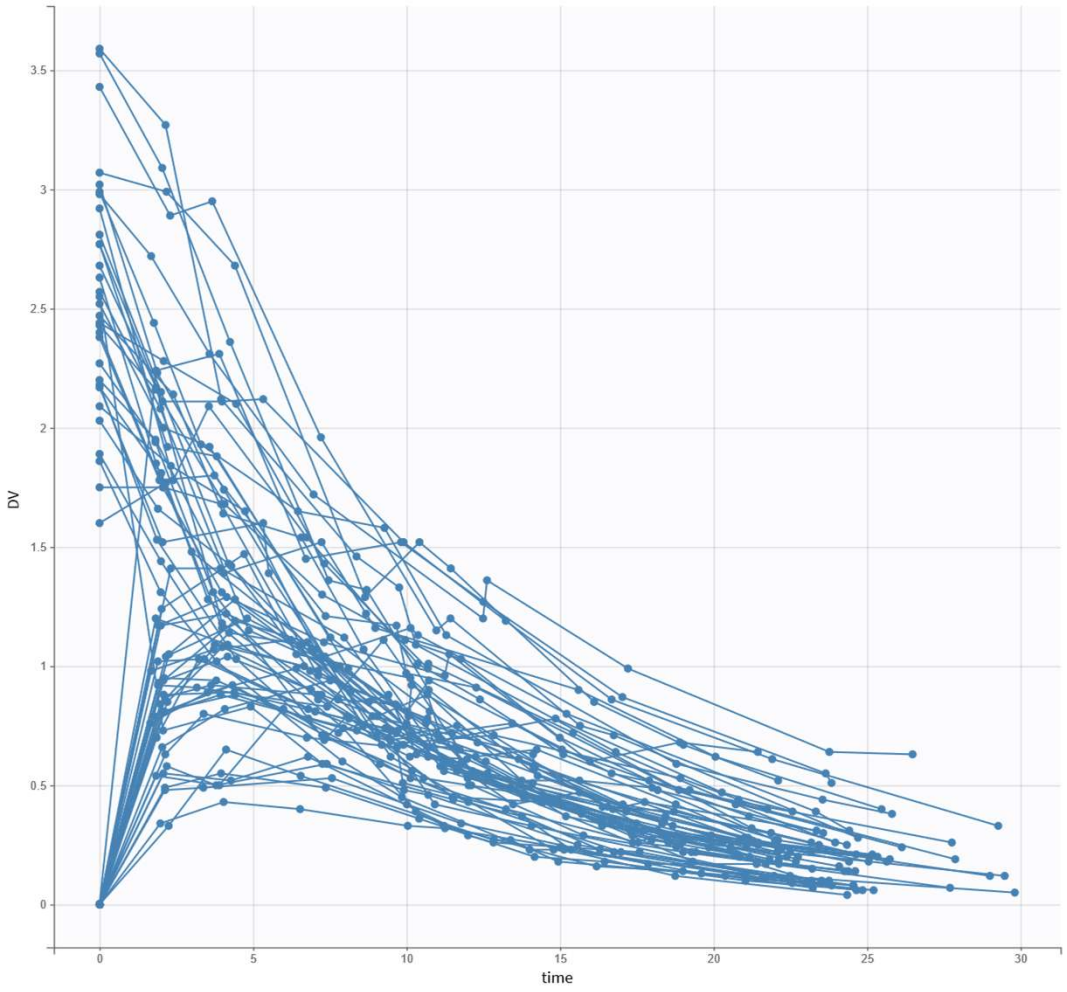
Fachhochschule Nordwestschweiz

Data overview

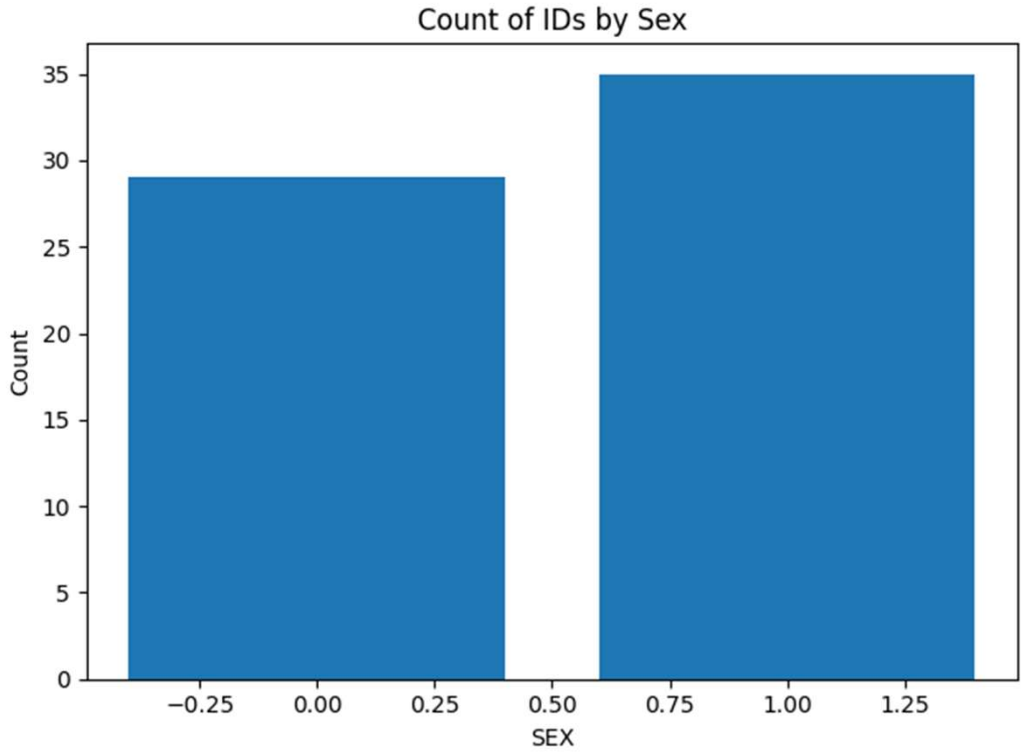
Fachhochschule Nordwestschweiz

Observed data

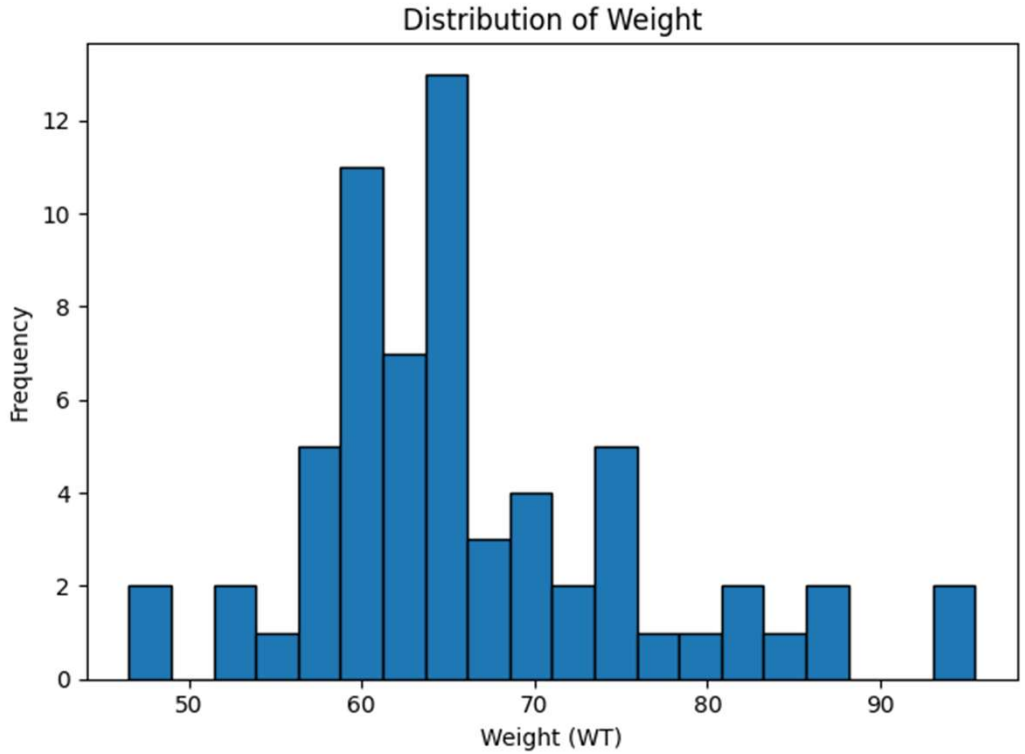
- 64 Patients
- 9 measurements each
- IV and oral route



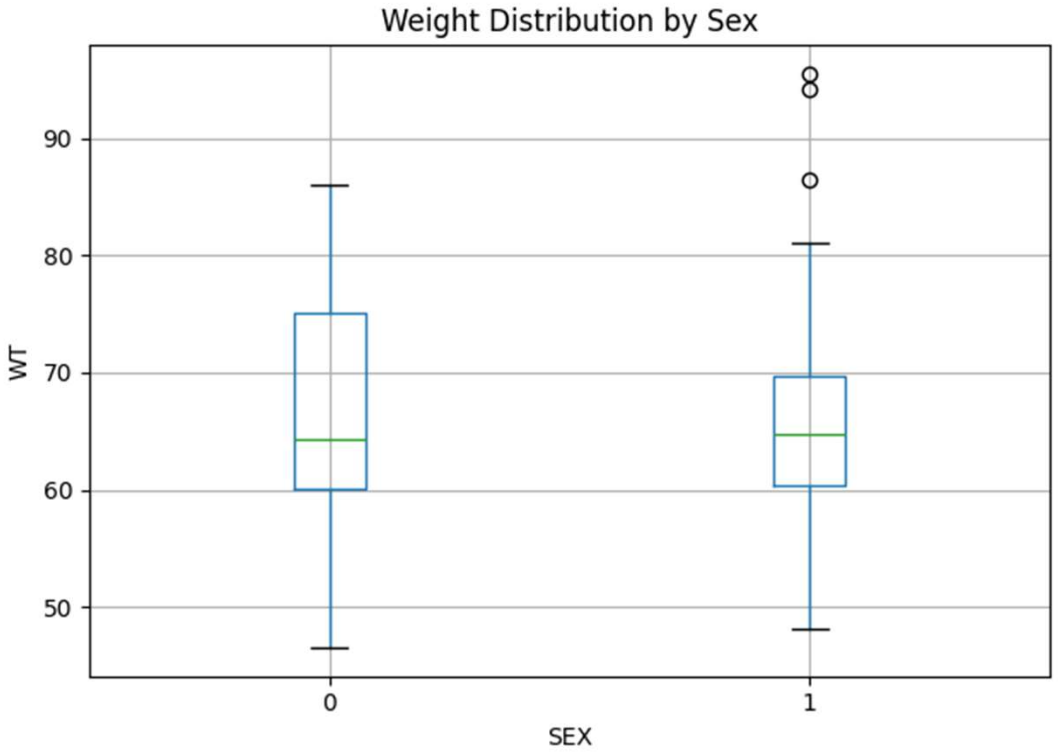
Distribution of gender



Distribution of weight



Gender vs Weight



Fachhochschule
Nordwestschweiz

Final model

Strucutral model

```
[LONGITUDINAL]
input = {F, ka, V, Cl}

PK:
; PK model definition
compartment(cmt = 1, volume = V, concentration = Cc)

; IV Administration (Matches Data ADM=2)
iv(adm = 2, cmt = 1)

; Oral Administration (Matches Data ADM=1)
; Uses First-Order Absorption (ka) and Bioavailability (F)
oral(adm = 1, cmt = 1, ka, p = F)

elimination(cmt = 1, Cl)

OUTPUT:
output = {Cc}
```

- PK
- One-compartment model
- First order
- Linear elimination
- Administration IV and oral
- Estimations for Cl, V, ka, F

Error model

- Combined error model (additive + proportional)

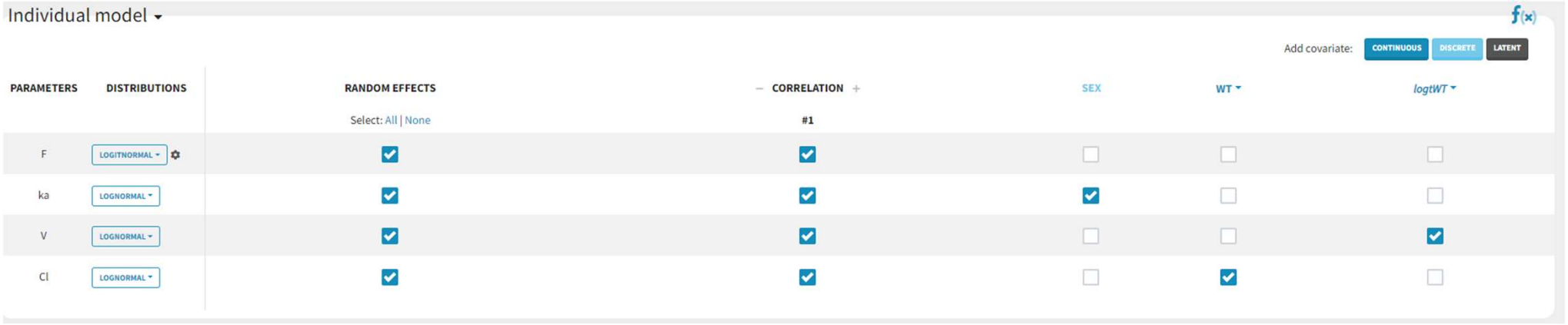
Fachhochschule Nordwestschweiz

Random effects model IIV

Log-normal distribution: CL, V, ka
Logit-normal distribution: F

Fachhochschule Nordwestschweiz

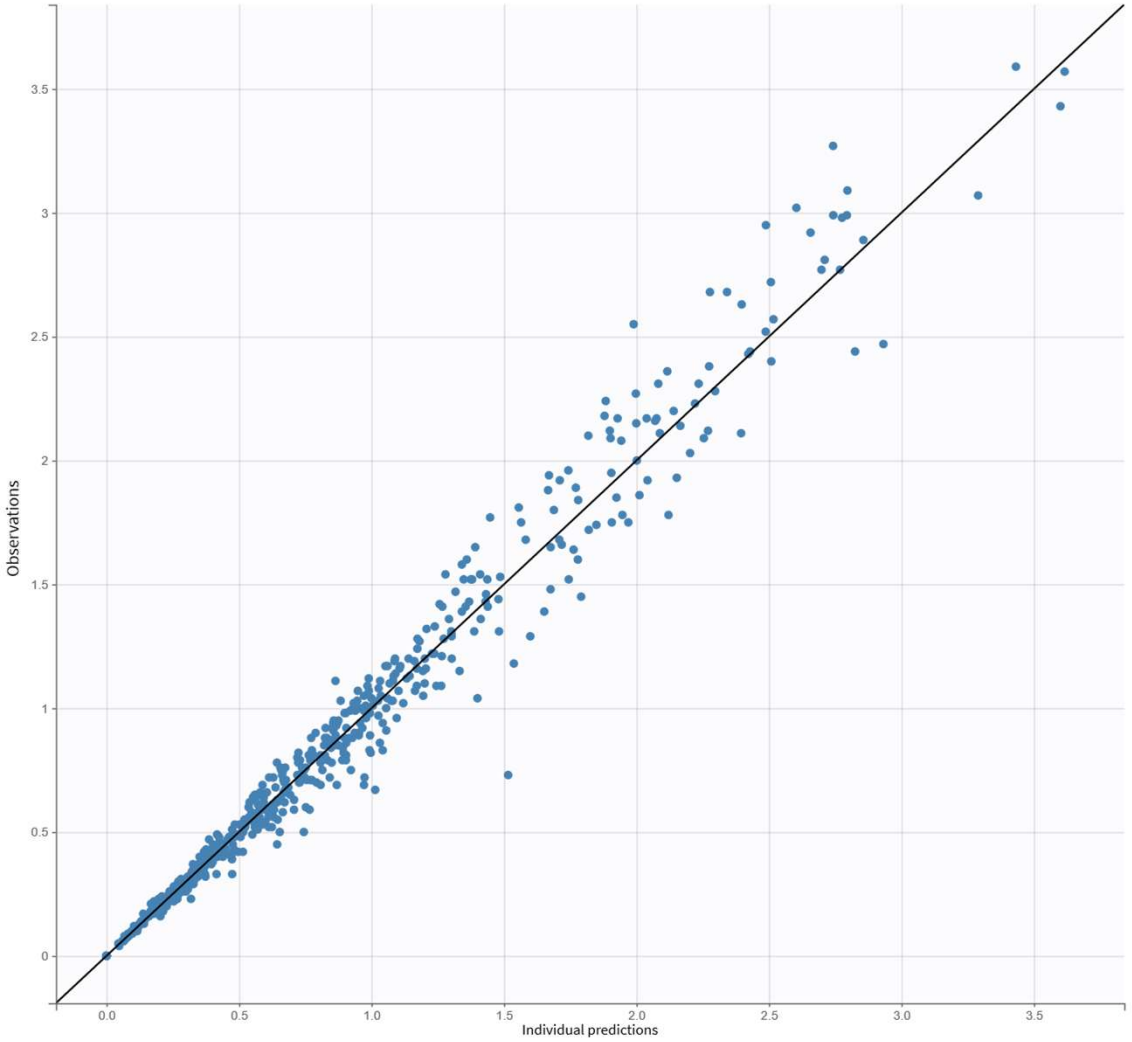
Used covariates



- Bodyweight used for clearance
- Log-bodyweight used for Volume of distribution
- Sex used for absorbtion rate
- Correlations between all PK parameters

Fachhochschule Nordwestschweiz

Results

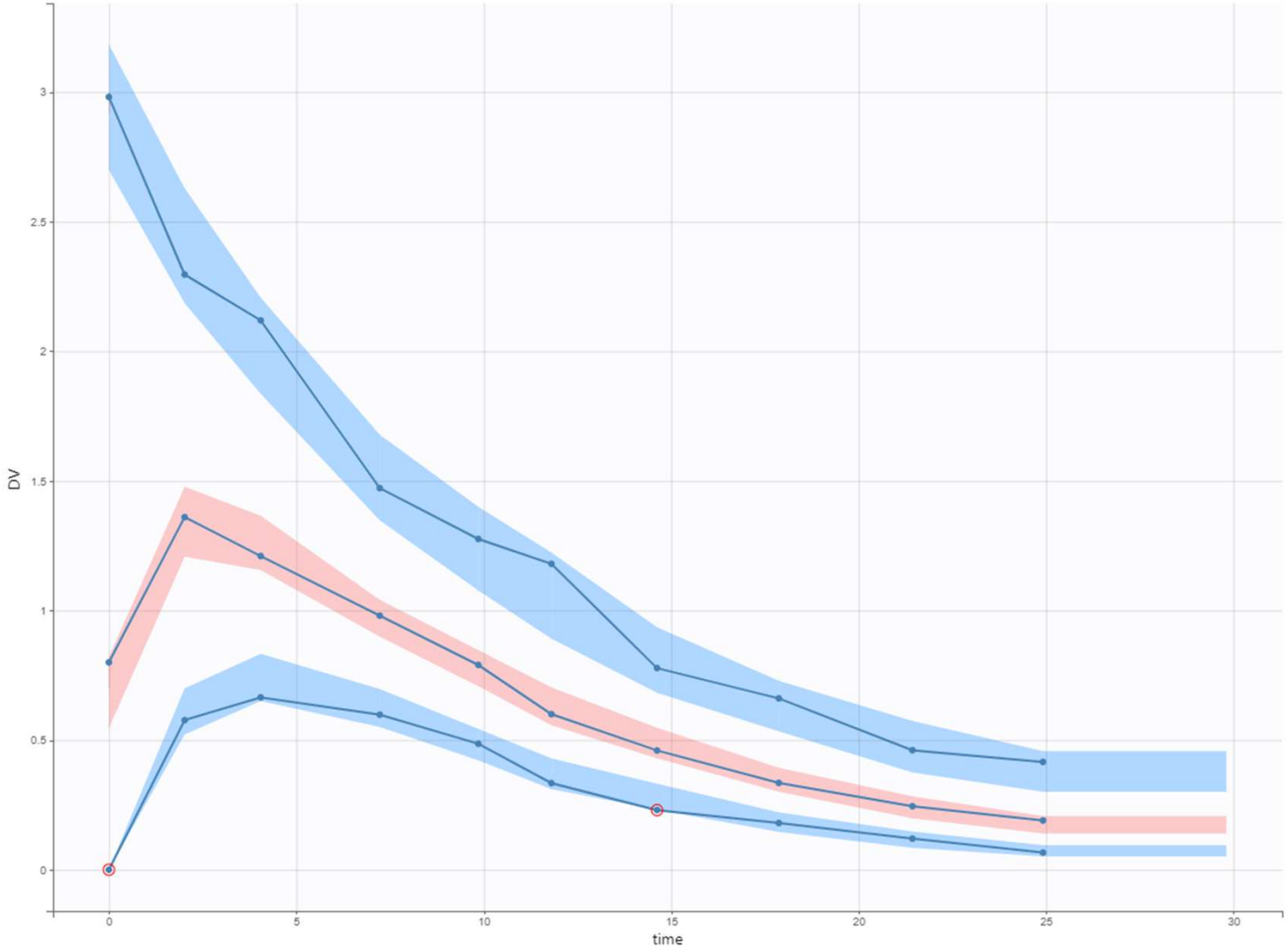


Fachhochschule Nordwestschweiz

Residuals

Fachhochschule Nordwestschweiz

VPC



Estimated parameters

		S.E.	R.S.E.(%)
Fixed Effects			
F_pop	0.7	0.06	8.51
ka_pop	0.56	0.05	8.90
beta_ka_SEX_1	-0.28	0.098	35.6
V_pop	70.07	2.29	3.27
beta_V_logtWT	1.16	0.15	13.3
Cl_pop	2.24	0.56	25.1
beta_Cl_WT	0.016	0.0036	22.4

Dosage calculation

Dosage oral: 150mg / F_{pop} = 214.3mg

Fachhochschule Nordwestschweiz

Simulations

Scenario patients

Two covariates:

- Weight: 70kg
- Sex: 1

Simulated 1000 patients

Scenario treatments

- Reference IV 150mg
- Oral 150mg
- Oral: 210mg
- Oral: 250mg
- Oral: 300mg

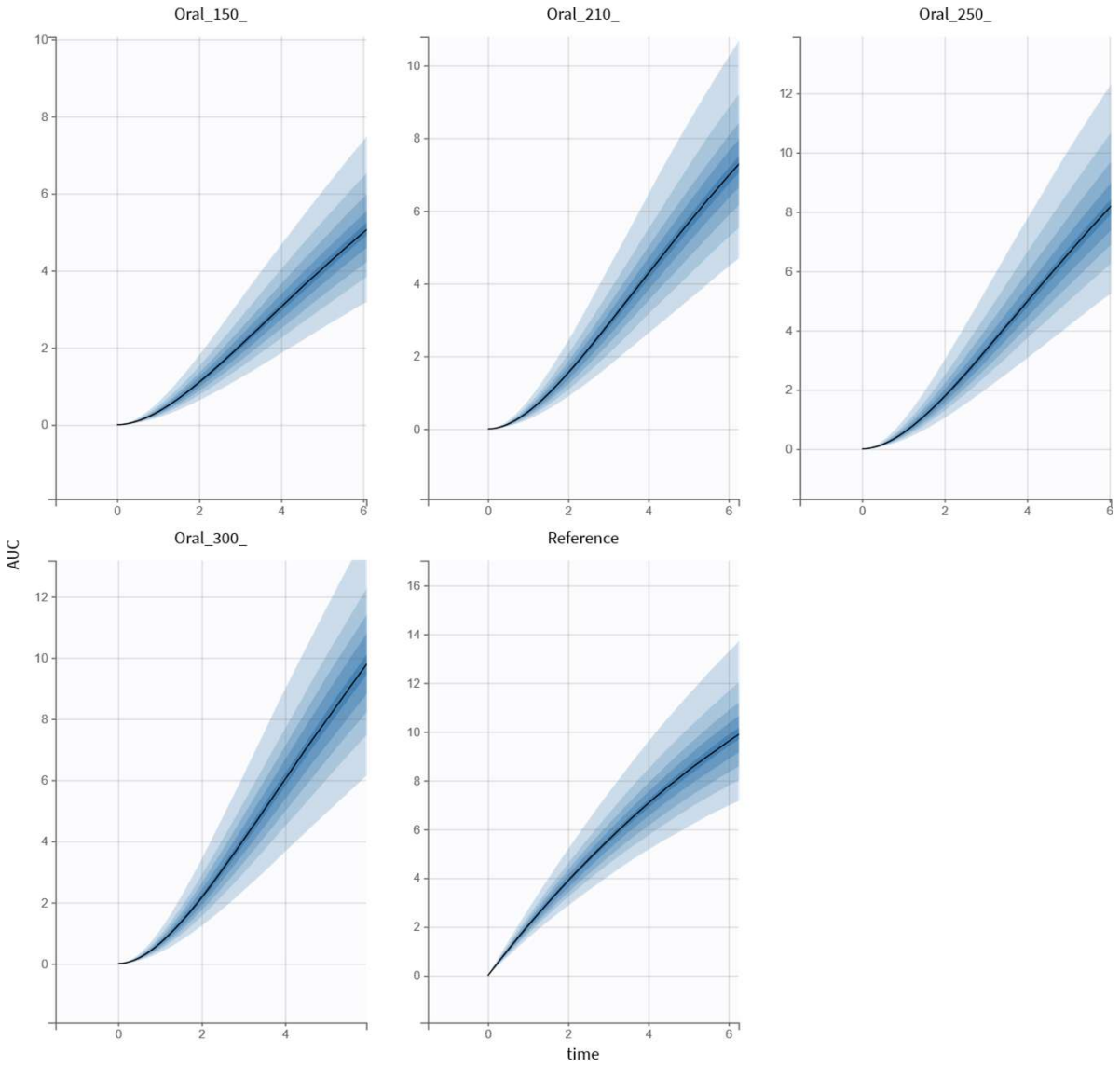
Scenario outputs

- Grid from 0 to 6h for AUC with 0.1 stepsize
- Grid from 0 to 6h for concentration with 0.1 stepsize
- Grid from 0 to 30h for AUC with 1 stepsize
- Grid from 0 to 30h for concentration with 1 stepsize

Fachhochschule Nordwestschweiz

$AUC_{0\text{-}6h}$ Median

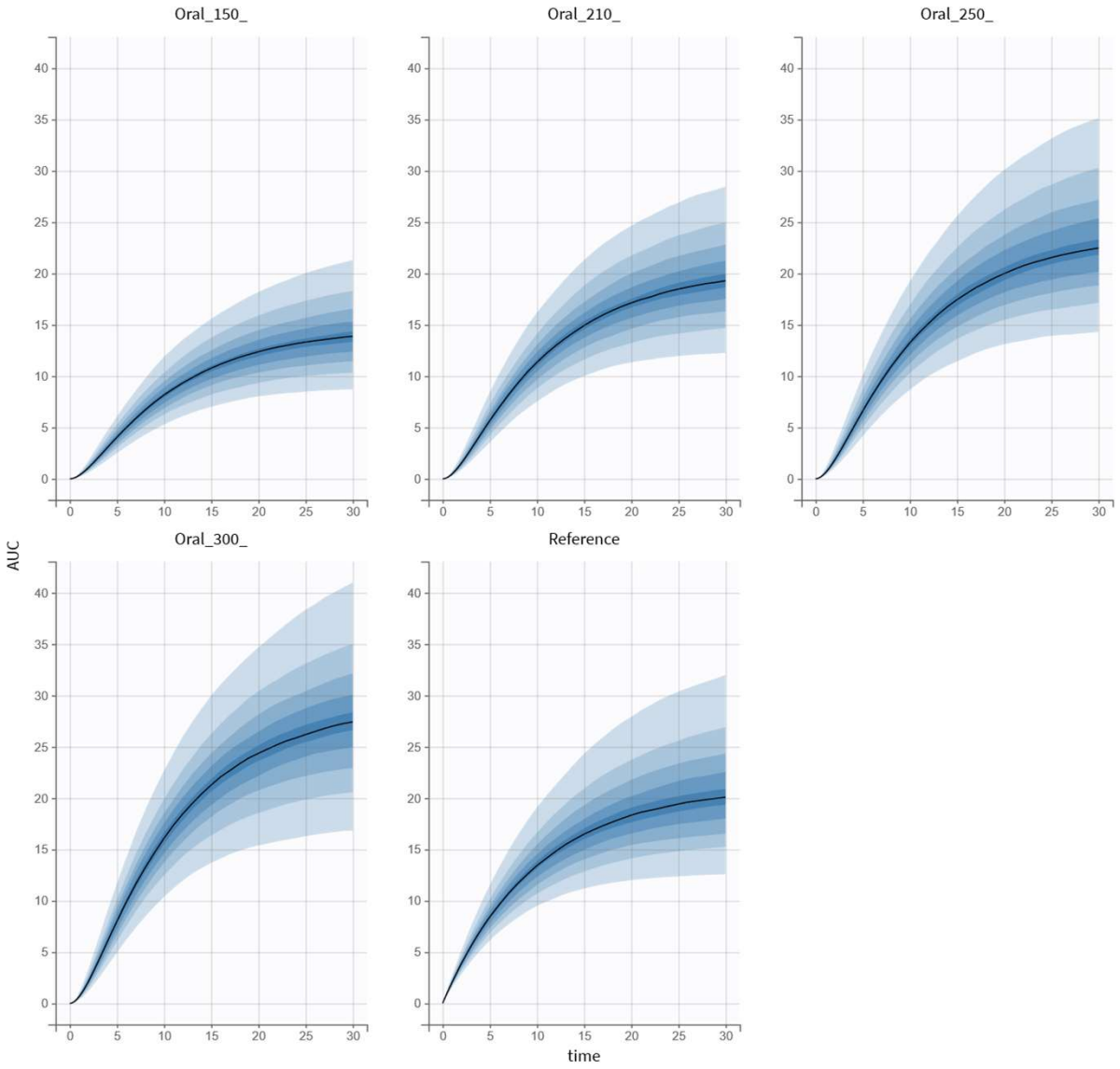
IV Ref	Oral 150	Oral 210	Oral 250	Oral 300
9.61	4.98	6.97	8.14	**9.87**



Fachhochschule Nordwestschweiz

$AUC_{0\text{-}30h}$ Median

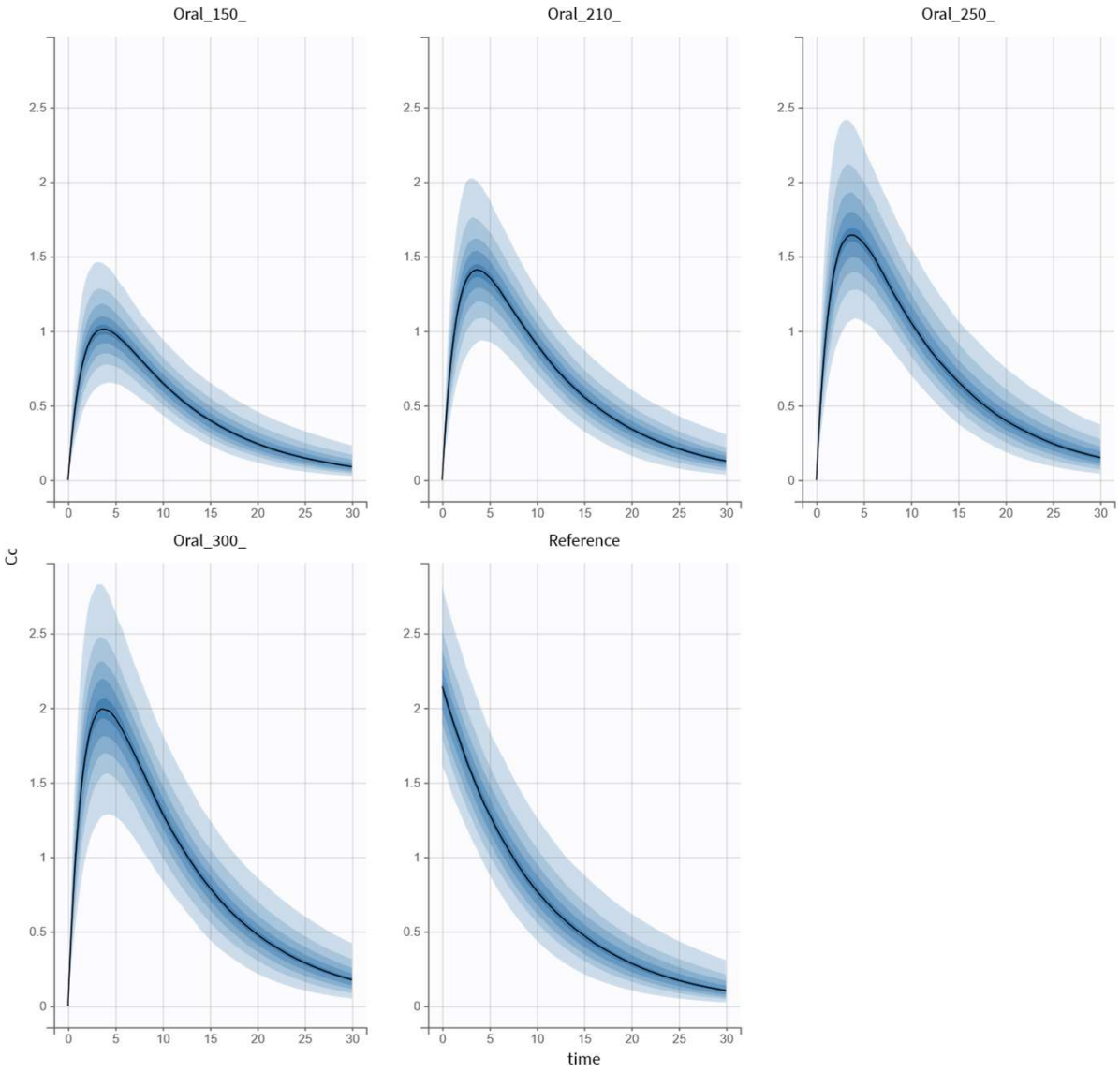
IV Ref	Oral 150	Oral 210	Oral 250	Oral 300
20.08	13.88	**19.3**	22.48	27.42



Fachhochschule Nordwestschweiz

Cc_{6h} Median

IV Ref	Oral 150	Oral 210	Oral 250	Oral 300
1.16	0.92	**1.28**	1.50	1.82



Fachhochschule
Nordwestschweiz

Conclusions

Research question

Primary objective:

- What dose for tablets matches the AUC 0h-6h of 150 mg Funytoin IV in patients weighting 70 kg?

Answer:
300mg

But:
Concentration matches better with the 210mg tablet

Research question

Secondary objectives:

- What is the absolute bioavailability (F) of the oral tablet?
  - F = 0.7 = 70%

- What is the variability between patients?
  -

	Value	C.V.(%)
omega_F	0.6	17.35
omega_ka	0.25	25
omega_V	0.16	16.31
omega_Cl	0.32	32.76

- What is the impact of the covariates on the clearance and volume of distribution?
  - Log-weight on volume of distribution: 1.16
  - Weight on clearance: 0.016

Fachhochschule
Nordwestschweiz

Questions?