

Population pharmacokinetics and pharmacogenetics analysis of mitotane in adrenocortical carcinoma patients towards individualized dosing

Aim

- Develop a population pharmacokinetic (PK) model to characterize and predict mitotane concentrations in adrenocortical carcinoma (ACC) patients.
- Identify covariates, especially genetic variance, that affect mitotane PK and thereby facilitate mitotane dose optimization and individualization for ACC patients.

Introduction

- Mitotane is the only agent approved for treatment of ACC patients[1].
- The inability to predict mitotane concentrations may result in a suboptimal time period to reach the therapeutic window or unexpected toxicity[2].
- It would be beneficial if pharmacogenetic polymorphisms can also be taken into account to further elucidate the variability of mitotane PK profile.

Methods

- TDM data and a limited amount of intensive sampling data was collected retrospectively from ACC patients from the Dutch Adrenal Network.
- The mitotane plasma concentrations were determined by a validated gas liquid chromatography - Mass Spectrometry assay at the Department of Clinical Pharmacy and Toxicology in the LUMC [3].
- Modelling analysis was performed with NONMEM (version 7.4.1).
- Data below LLOQ (3.6% of the data) was omitted.
- Absorption rate constant (KA) was estimated based on the data of patients who contributed drug absorption information and then fixed to analyze the full dataset.
- DNA samples were analyzed using DMET™ plus array[4] (Affymetrix UK Ltd), and SNPs with call rate $\geq 97\%$ and minor allele frequency ≥ 0.1 were included.
- Association between genotypes and CL/F for each SNP was assessed with R software (version 3.4.1), with ANOVA test or t-test which depended on the number of genotype groups.
- Covariate analysis: stepwise covariate modelling (SCM) function[5]
- Model evaluation: prediction corrected VPC (pcVPC) and Bootstrap
- Simulations were performed with RxODE package implemented in R.
- Optimization aim: mean time to reach target ≤ 90 days; mean percentage of mitotane concentration higher than 20 mg/L during the first 200 days $\leq 10\%$

- Simulation design (for included patients) :

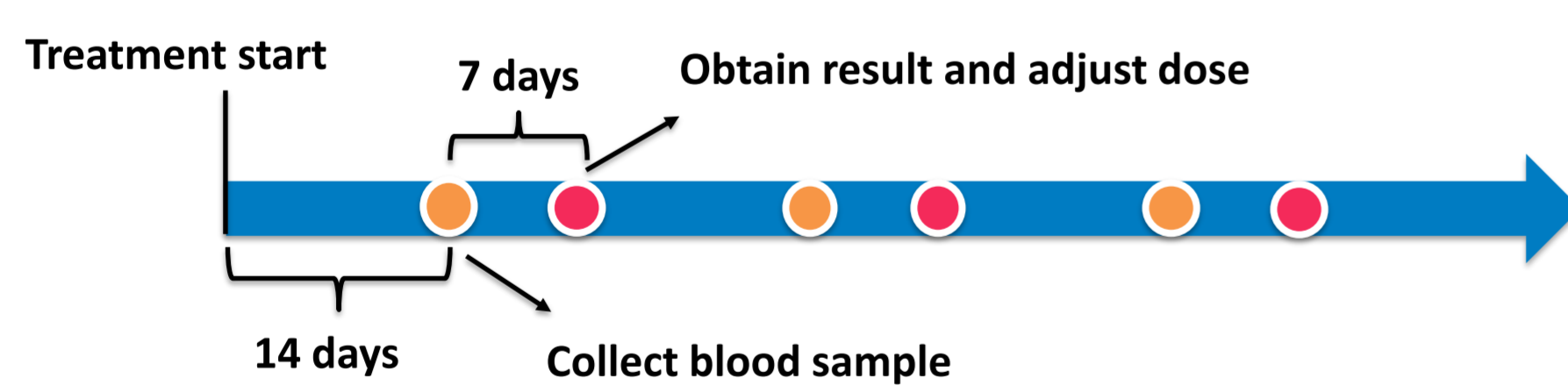


Table1 Simulation scenarios (regimens)

Starting dose/regimen	Next dose	Dose adjustment according to mitotane level (therapeutic window: 14-20 mg/L [1])			
		<14mg/L	≥ 14 mg/L <18mg/L	≥ 18 mg/L <20mg/L	≥ 20 mg/L
1-1 According to literature [6]	According to TDM	+1g	Maintain	Maintain	-50%
1-2					-75%
2-1 4g	According to TDM	+1g	Maintain	-1g	-3g
2-2 Make PRED reach target on 98 th day					
3-1 4g	According to TDM	Before target/126 th day: +0.5 g	Maintain	-1g	-3g
3-2 Make PRED reach target on 98 th day		After: +1.5g			
4 Make PRED reach target on 98 th day	According to TDM	Before target/105 th day: maintain	Maintain	-1g	-3g
5 4g	Estimate individual parameters, then make IPRED reach target on 98 th day	After: +1.5g			

Results

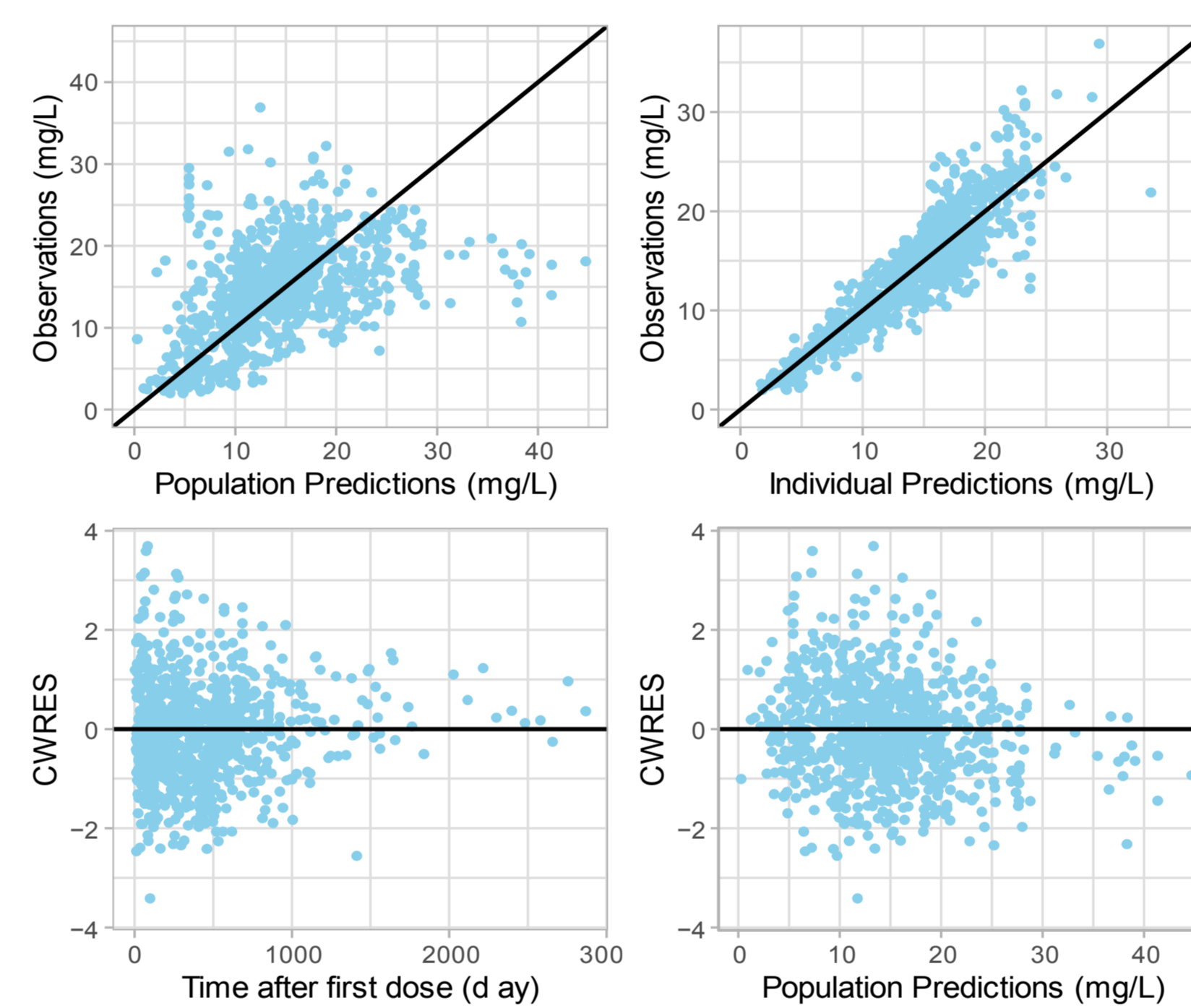
- A 2-compartment model with first-order absorption and elimination best described the 881 concentration data points collected from 48 patients (21 males, 27 females).
- 170 SNPs out of 959 SNPs were included for a genotype association test. 12 SNPs were identified to be potentially associated with mitotane clearance ($p < 0.05$) and were included in the covariate analysis.

Table2 Parameter estimates and bootstrap results of the final mitotane PK model

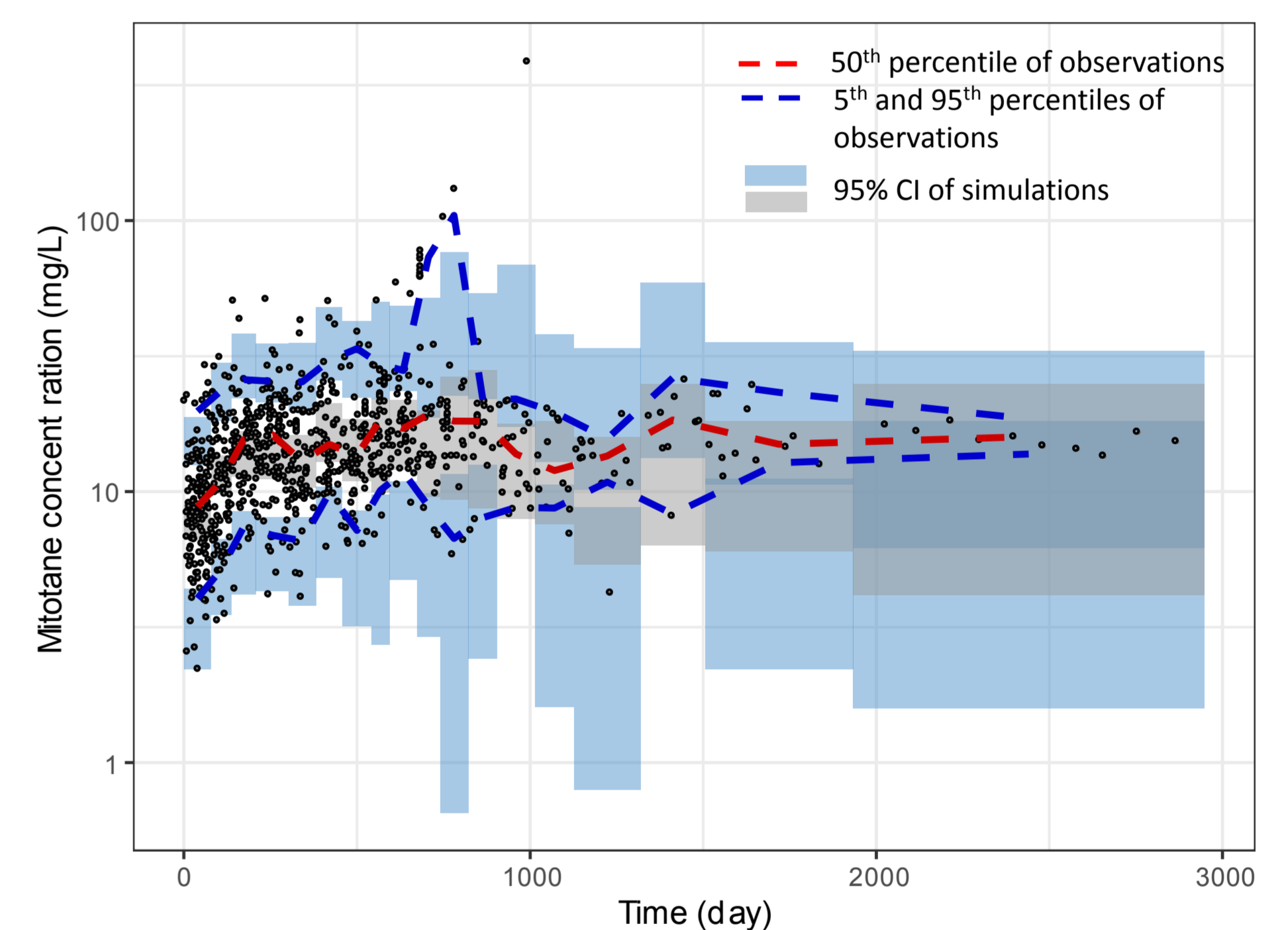
Parameters	Estimate	RSE (%)	IIV (CV%) [shrinkage]	IOV* (CV%)	Bootstrap	
					Mean	95% CI
CL/F (L/day)	294	16	43.4 [16%]	32.1	285.6	195.4-421.1
CL_SNP2 (GA/AA)	0.548	16	-	-	0.592	0.385-0.881
CL_SNP4 (AG/GG)	0.605	20	-	-	0.622	0.421-0.912
CL_SNP6 (CC)	0.773	17	-	-	0.786	0.571-1.07
CL_SNP6 (TT)	2.53	31	-	-	2.82	0.977-6.16
CL_LBW	1.11	31	-	-	1.05	0.179-2.11
V _c /F (L)	6720	22	40.7 [55%]	-	6758.9	3273.0-10354.1
V _c -FAT	1.2	20	-	-	1.26	0.465-2.14
V _p /F (L)	18000	11	86.7 [17%]	-	18535	11545-27332
Q/F (/day)	763	17	111.4 [31%]	-	789.4	355.8-1414.3
KA (/day)	15 FIX	-	-	-	15	15-15
Residual error						
Additive (mg/L)	0.902	16	-	-	0.889	0.352-1.319
Proportional (CV%)	16.6	6	-	-	16.6	14.2-18.8

SNP2: CYP2C19*2 ;SNP4: SLCO1B3 A1125/I233M ;SNP6: SLCO1B1, rs4149057; LBW, lean body weight; FAT, fat amount
* Every 200 days of dosing was defined as an occasion

GOF plots of the final model:



pcVPC result of the final model:



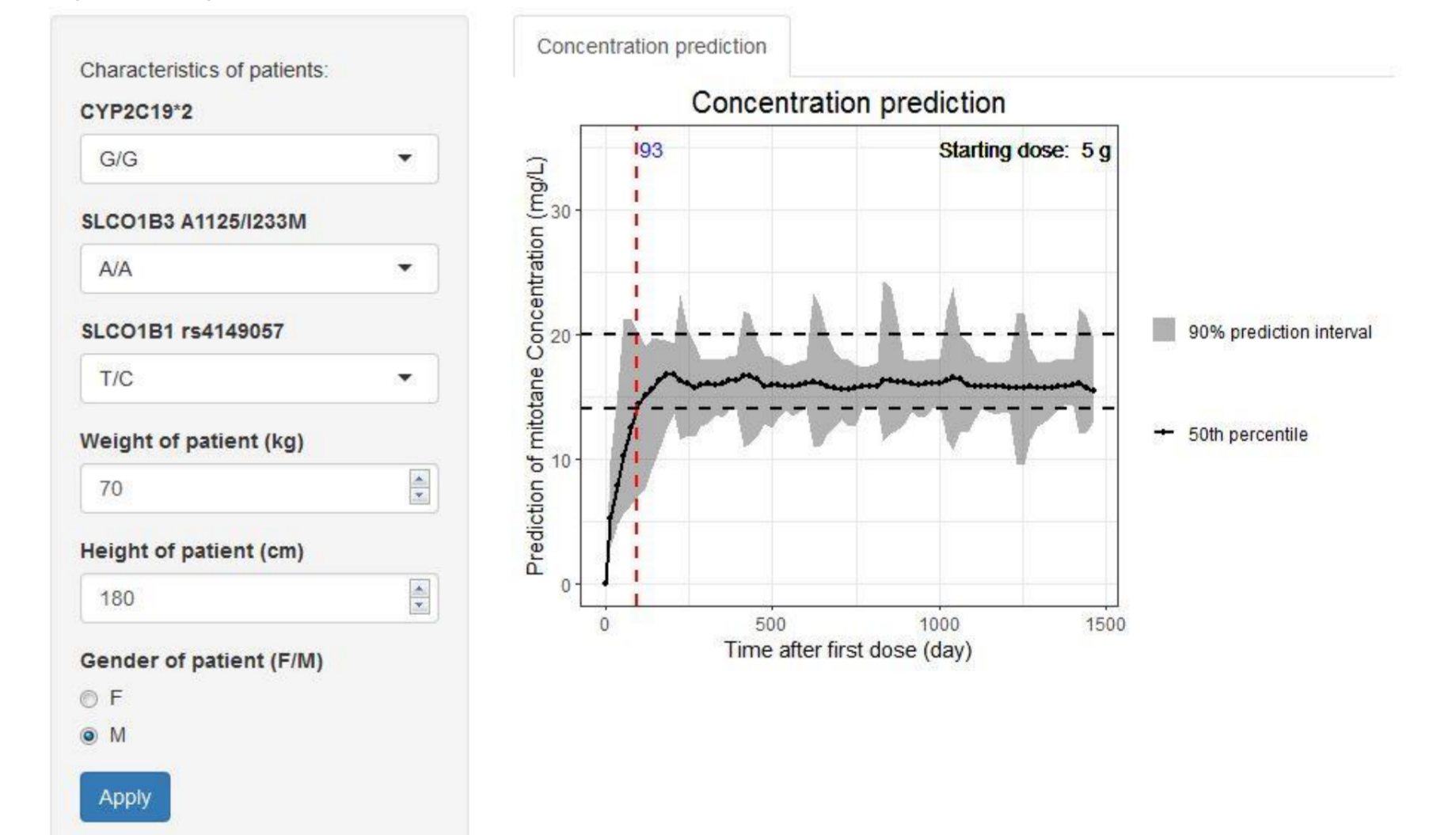
Model simulation results

Table3 Simulation results of different treatment regimens for included patients who originally reached the target (N=41).

Scenario (Table 1)	Mean time to reach target	Mean percentage of CONC > 20mg/L	N of patients with percentage > 20%
1-1	53.80	23.27	23
1-2	53.80	15.29	10
2-1	74.15	13.61	13
2-2	80.02	14.48	13
3-1	89.20	6.80	4
3-2	84.15	8.11	6
4	89.49	6.78	4
5	86.34	5.70	5

CONC, simulated mitotane concentration

- Simulation results (100 times) of a random patient with regimen 3-2 (Table1)



Conclusion

- A 2-compartment model demonstrated a good characterization of mitotane PK in ACC patients.
- LBW, genotypes of SLCO1B1 (rs4149057), CYP2C19*2, and SLCO1B3 (A1125 / I233M) were identified to affect mitotane CL/F and FAT was identified to affect the central V/F.
- Optimal treatment schedule was developed by simulating with the final model.

References

- [1] Paragliola, R.M., et al., Endocrine Oncology, 2018.
- [2] Kerkhofs, T.M., et al., Ther Drug Monit, 2015.
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- [5] Jonsson, E.N. and M.O. Karlsson, Pharmaceutical Research, 1998.
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Acknowledgements

- We would like to thank Dutch Adrenal Network for the contribution of data.
- This work was partially supported by HRA Pharma.

