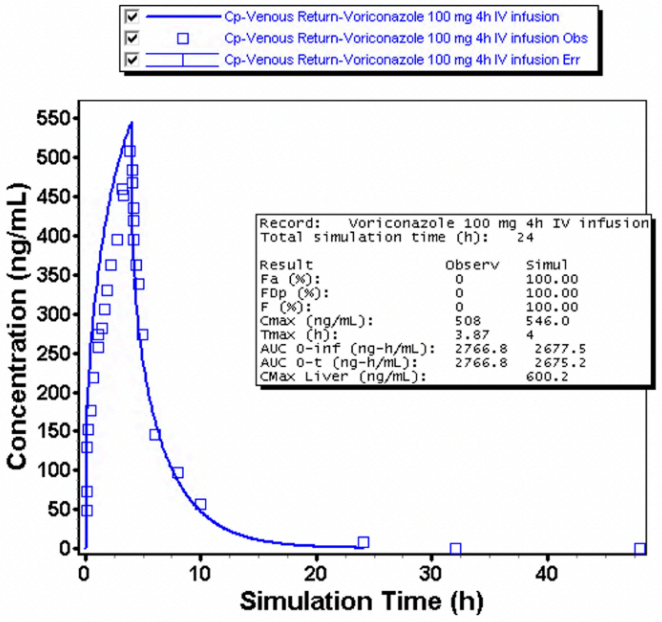
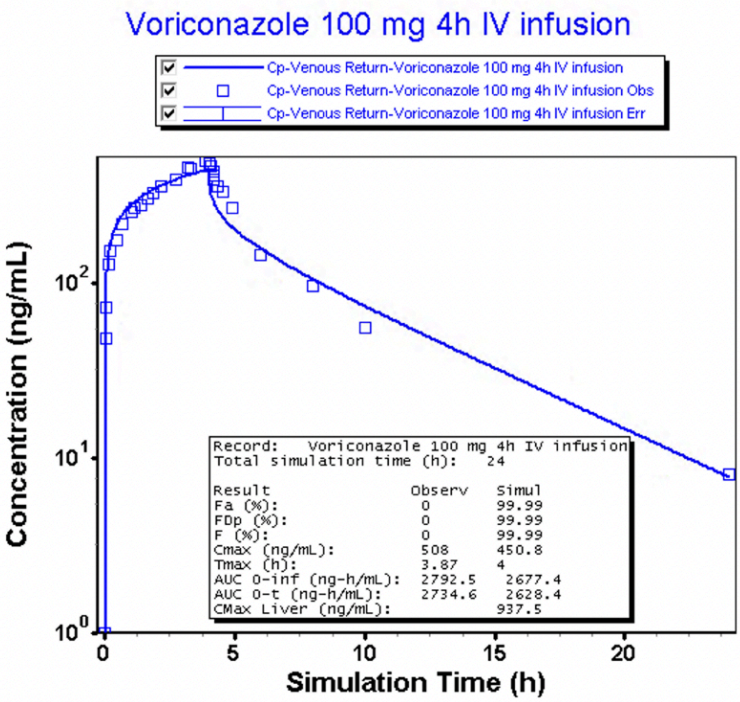
Week 4 Report: Voriconazole
Jiaqi Fu and Nicole Mohajer

Week 3



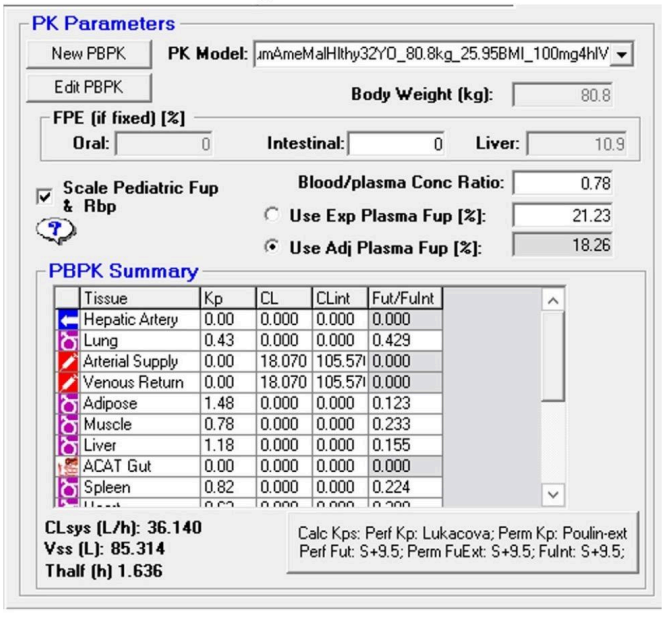
Week 4



Note: observed AUC values differ because some (inaccurate) data points were removed.

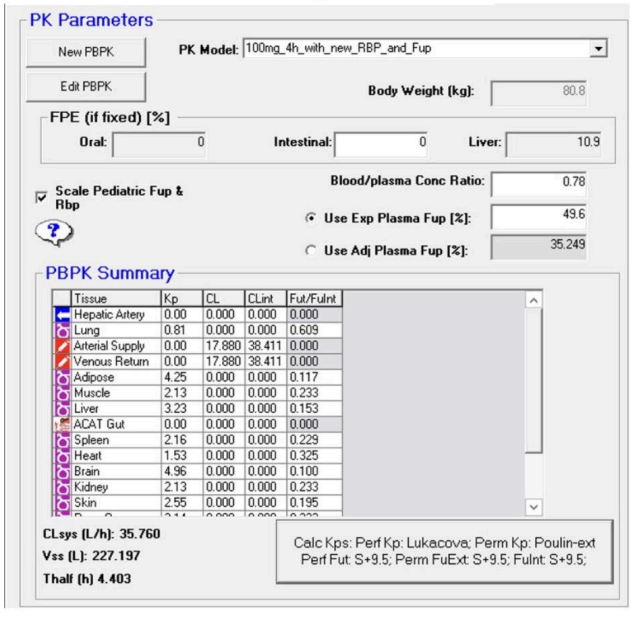
Week 3

100 mg 4h

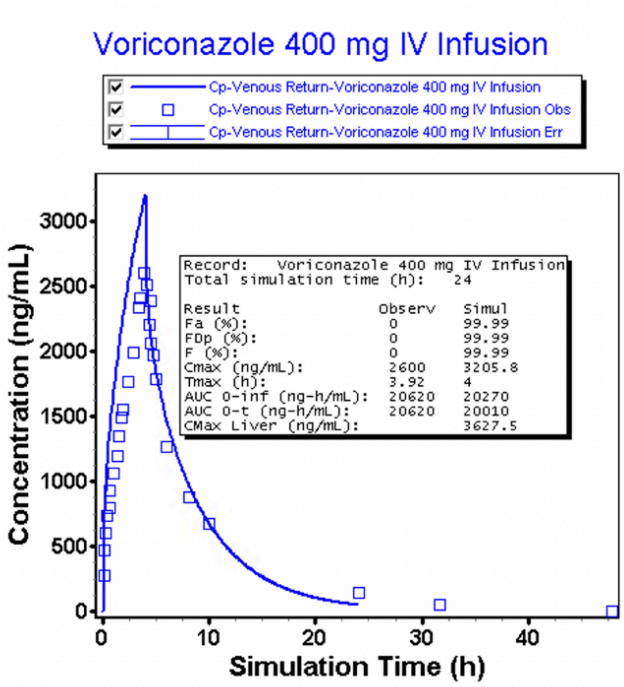


Week 4

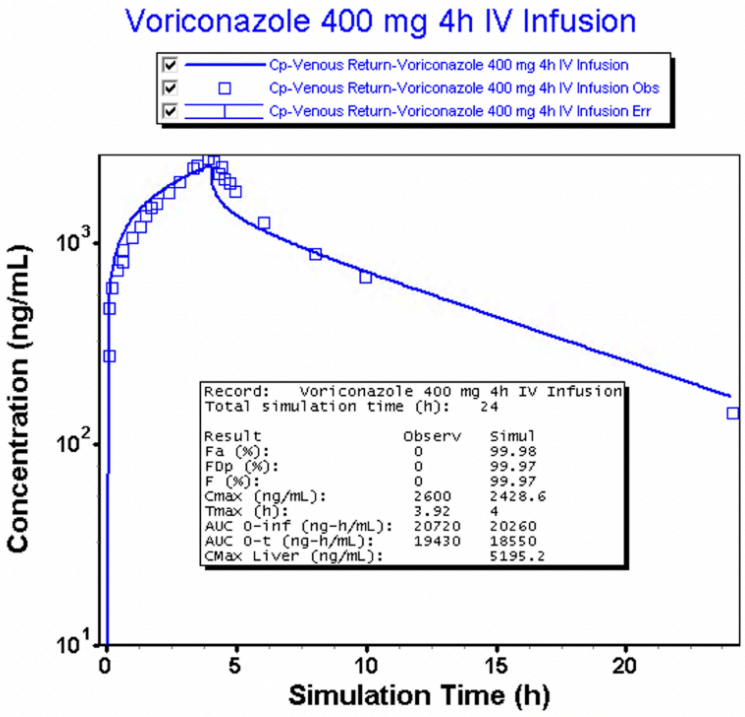
100 mg 4h



Week 3



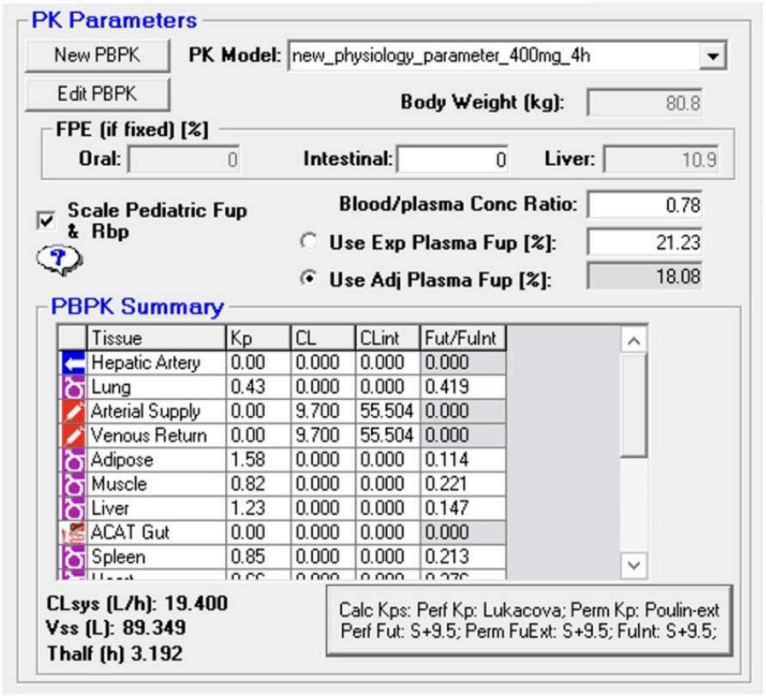
Week 4



Note: observed AUC values differ because some (inaccurate) data points were removed.

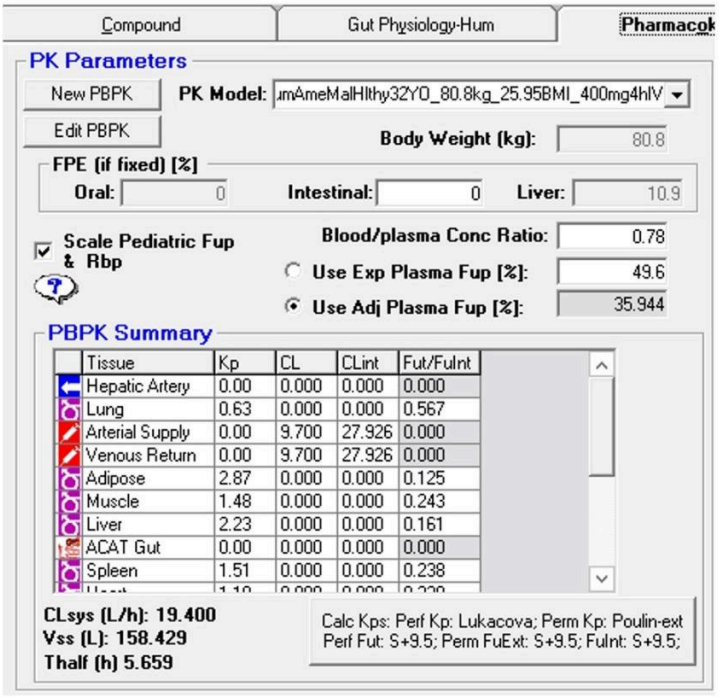
Week 3

400 mg 4h



Week 4

400 mg 4h



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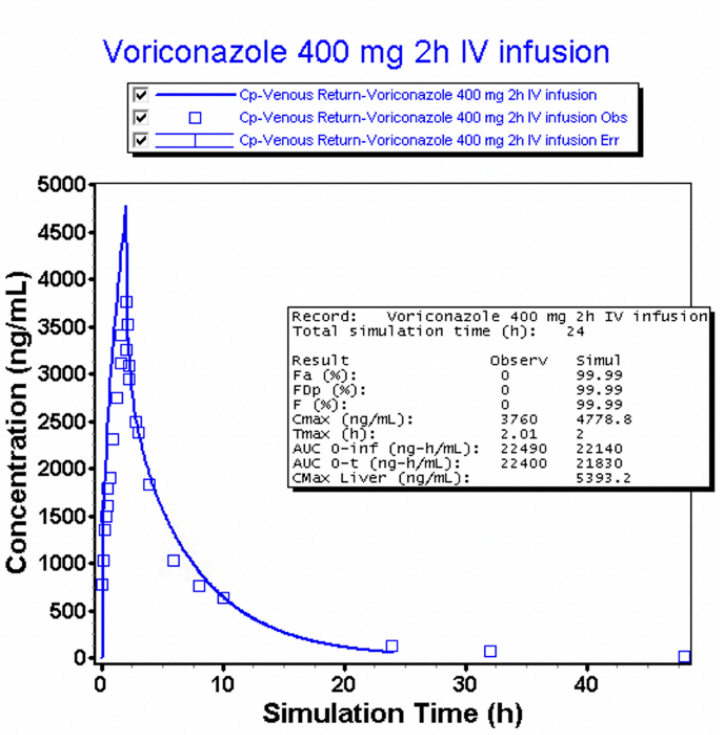

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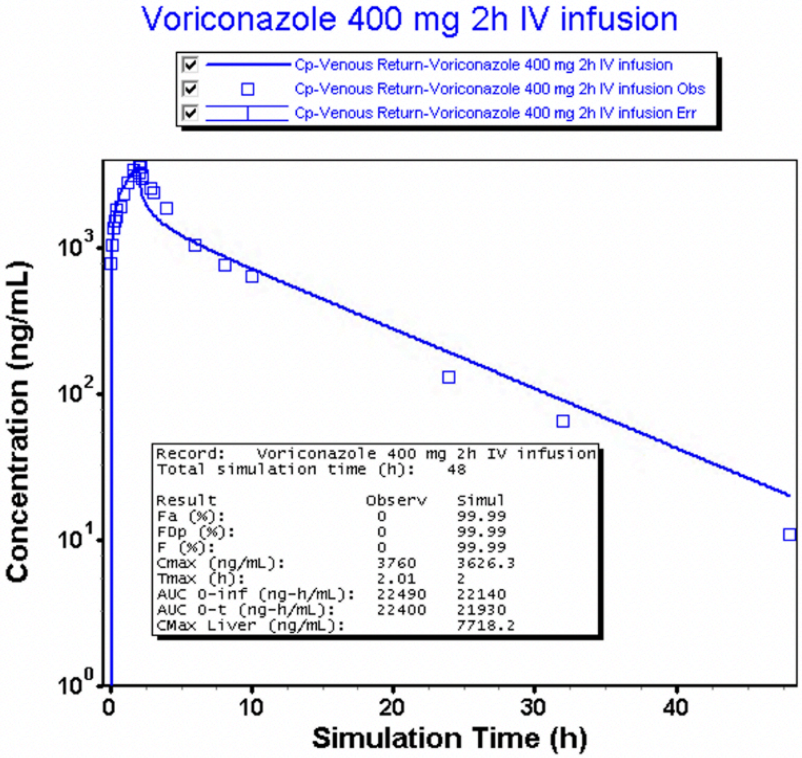


Week 3

400 mg 2h

File Edit Database Simulation Setup Controlled Release Tools Modules (Optional)

Compound | Gut Physiology-Hum | Pharmaco

PK Parameters

New PBPK | **PK Model:** new_physiology_parameter_400mg_2hl

Edit PBPK | **Body Weight (kg):** 80.8

FPE (if fixed) [%]

Oral: 0 **Intestinal:** 0 **Liver:** 10.9

Scale Pediatric Fup & Rbp

Blood/plasma Conc Ratio: 0.78

Use Exp Plasma Fup [%]: 21.23

Use Adj Plasma Fup [%]: 18.08

PBPK Summary

Tissue	Kp	CL	CLint	Fut/Fulnt
Hepatic Artery	0.00	0.000	0.000	0.000
Lung	0.43	0.000	0.000	0.419
Arterial Supply	0.00	8.890	50.723	0.000
Venous Return	0.00	8.890	50.723	0.000
Adipose	1.58	0.000	0.000	0.114
Muscle	0.82	0.000	0.000	0.221
Liver	1.23	0.000	0.000	0.147
ACAT Gut	0.00	0.000	0.000	0.000
Spleen	0.85	0.000	0.000	0.213
Heart	0.66	0.000	0.000	0.276
Brain	1.84	0.000	0.000	0.098

CLsys (L/h): 17.780
Vss (L): 89.364
Thalf (h) 3.483

Calc Kps: Perf Kp: Lukacova; Perm Kp: Poulin-ext
Perf Fut: S+9.5; Perm FuExt: S+9.5; Fulnt: S+9.5;

Week 4

400 mg 2h

PK Parameters

New PBPK | **PK Model:** µmAmeMalHlthy32YO_80.8kg_25.95BMI_400mg2hIV

Edit PBPK | **Body Weight (kg):** 80.8

FPE (if fixed) [%]

Oral: 0 **Intestinal:** 0 **Liver:** 10.9

Scale Pediatric Fup & Rbp

Blood/plasma Conc Ratio: 0.78

Use Exp Plasma Fup [%]: 49.6

Use Adj Plasma Fup [%]: 35.944

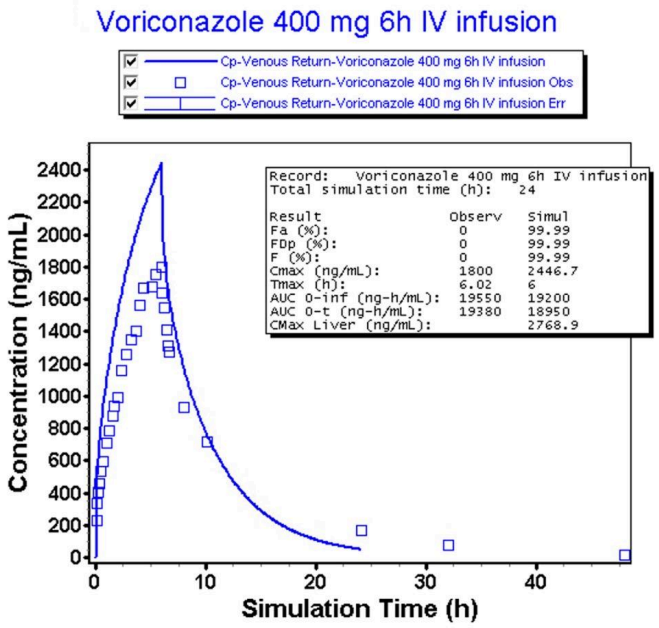
PBPK Summary

Tissue	Kp	CL	CLint	Fut/Fulnt
Hepatic Artery	0.00	0.000	0.000	0.000
Lung	0.63	0.000	0.000	0.567
Arterial Supply	0.00	8.890	25.520	0.000
Venous Return	0.00	8.890	25.520	0.000
Adipose	2.87	0.000	0.000	0.125
Muscle	1.48	0.000	0.000	0.243
Liver	2.23	0.000	0.000	0.161
ACAT Gut	0.00	0.000	0.000	0.000
Spleen	1.51	0.000	0.000	0.238

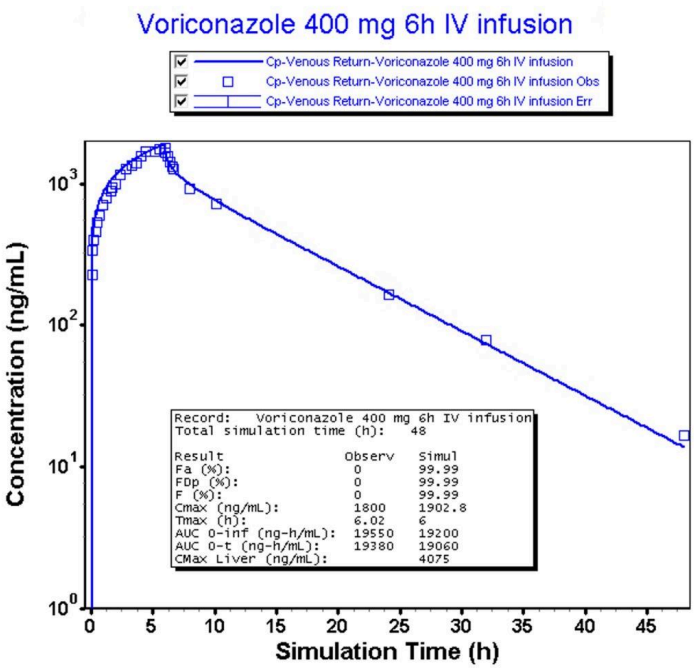
CLsys (L/h): 17.780
Vss (L): 158.444
Thalf (h) 6.176

Calc Kps: Perf Kp: Lukacova; Perm Kp: Poulin-ext
Perf Fut: S+9.5; Perm FuExt: S+9.5; Fulnt: S+9.5;

Week 3

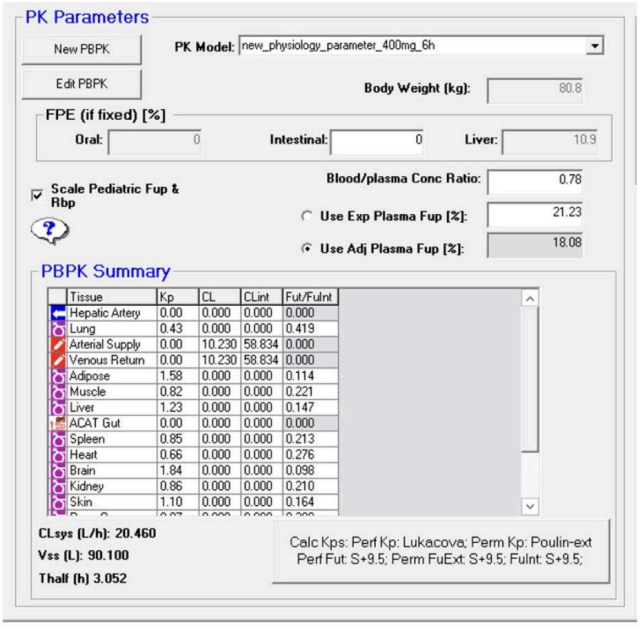


Week 4



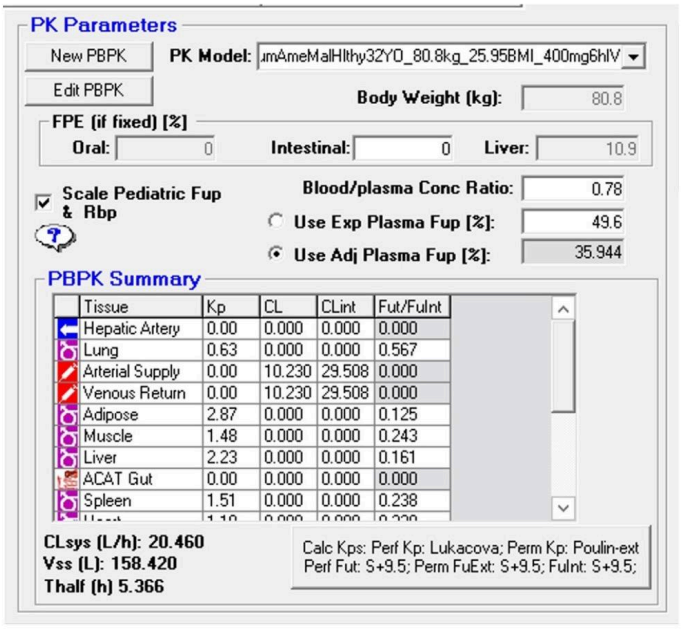
Week 3

400 mg 6h



Week 4

400 mg 6h



The first picture on the next page is the statistics on observation data and how a set of PK parameters change after adding Fup(49.6%). Moreover, we also added statistics from week 3, in order to compare the influence of adding two models(NAC CL and Fup) on AUC and Cmax:

100mg 4h		Observation	After adding Fup value/ Percentage difference(%)		Before adding Fup (Only NAC CL model)	After adding Fup value/ Percentage difference(%)
	AUC(ng-h/ml)	2734.6	2628.4 / -3.88%	Vss(L)	85.314	227.197 / +116.31%
	Cmax(ng/ml)	508	450.8 / -11.23%	Thalf(h)	1.636	4.403 / +169.13%
400mg 4h		Observation	After adding Fup value/ Percentage difference(%)		Before adding Fup (Only NAC CL model)	After adding Fup value/ Percentage difference(%)
	AUC(ng-h/ml)	19430	18550 / -4.53%	Vss(L)	89.349	158.429 / +77.31%
	Cmax(ng/ml)	2600	2428.6 / -6.59%	Thalf(h)	3.192	5.659 / +77.29%
400mg 2h		Observation	After adding Fup value/ Percentage difference(%)		Before adding Fup (Only NAC CL model)	After adding Fup value/ Percentage difference(%)
	AUC(ng-h/ml)	22400	21930 / -2.10%	Vss(L)	89.364	158.444 / +77.30%
	Cmax(ng/ml)	3760	3626.3 / -3.56%	Thalf(h)	3.483	6.176 / +77.32%
400mg 6h		Observation	After adding Fup value/ Percentage difference(%)		Before adding Fup (Only NAC CL model)	After adding Fup value/ Percentage difference(%)
	AUC(ng-h/ml)	19380	19060 / -1.65%	Vss(L)	90.1	158.42 / +75.83%
	Cmax(ng/ml)	1800	1902.8 / +5.71%	Thalf(h)	3.052	5.366 / +75.82%

400 mg - 4h (From Week3 Report):

	Before adding NCA CL value/ Percentage difference(%)	After adding NCA CL value/ Percentage difference(%)
AUC(ng-h/ml)	40240 / +95.15%	20010 / -2.96%
Cmax(ng/ml)	3069.3 / +18.05%	3205.8 / +23.3%

400 mg - 2h (From Week3 Report):

	Before adding NCA CL value/ Percentage difference(%)	After adding NCA CL value/ Percentage difference(%)
AUC(ng-h/ml)	41040 / +83.21%	21830 / -2.54%
Cmax(ng/ml)	3275.8 / -12.88%	4478.8 / +19.11%

400 mg - 6h (From Week3 Report):

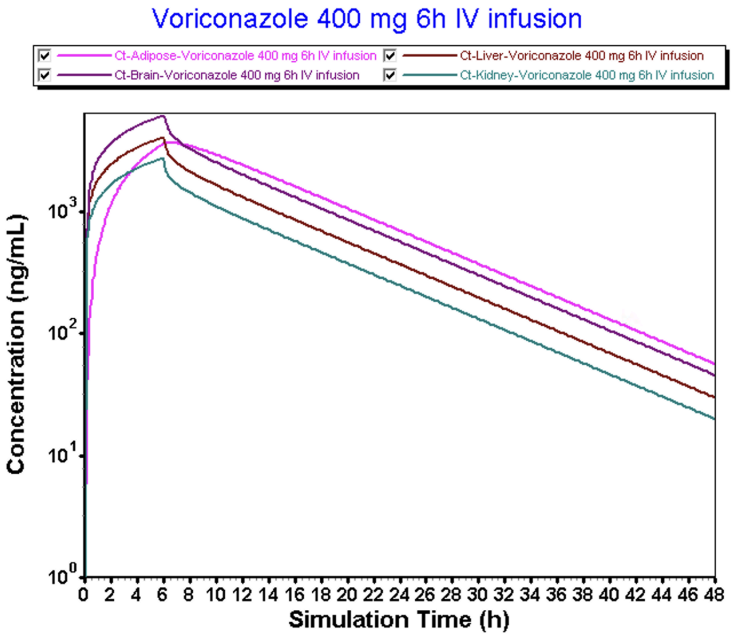
	Before adding NCA CL value/ Percentage difference(%)	After adding NCA CL value/ Percentage difference(%)
AUC(ng-h/ml)	39360 / +103.10%	18950 / -2.22%
Cmax(ng/ml)	2881 / +60.06%	2446.7 / +35.93%

100 mg - 4h (From Week3 Report):

	Before adding NCA CL value/ Percentage difference(%)	After adding NCA CL value/ Percentage difference(%)
AUC(ng-h/ml)	10060 / +263.60%	2675.2 / -3.31%
Cmax(ng/ml)	767.3 / +51.04%	546 / +7.48%

1. A brief review from last week's assignment: we adjusted the age, weight and BMI, more importantly, added NAC CL and did the simulation. This week, we kept the same age, weight, BMI, and NAC CL value but adjusted the Fup (percentage of drug that does not bind with plasma protein).
2. Based on our drug's physicochemical properties: log P is 2.13; pKa is 1.76(base), we know that when our drug in the system circulation where pH is 7.4, it will be in a neutral form; being lipophilic, it can cross membranes easily, indicating that permeability is not the rate-limiting step. Thus, the amount of drug that enters into tissue, as well as the rate of the distribution is based on how much drug is binding with the plasma protein.
3. Compared with the Fup = 21.23% in the previous week, when we increased the Fup to 49.6%, it means that there should be more drug entering into the tissue. Thus, in an ideal situation, we observe a lower AUC and Cmax compared to those values under the NCA CL model; also, we observe a more steep slope in the Cp-time curve which indicates a faster distribution process.
4. Now, looking at the values in the sheet: for 400mg 2h with the only NAC CL model, the AUC bias from on the observation data is -2.54%; while after adjusting Fup, the AUC bias from observation data is -2.10%. This indicates that by increasing Fup, the simulation is closer to the observation. However, after adjusting Fup, the AUC (n=21930) is larger than the AUC (n=21830) only with the NAC CL model. The same thing happens to 400mg 6h. For 400mg 6h with the only NAC CL model, the AUC bias from on the observation data is -2.22%; while after adjusting Fup, the AUC bias from observation data is -1.65%. This indicates that by increasing Fup, the simulation is closer to the observation. However, after adjusting Fup, the AUC(n=19060) is larger than the AUC (n=18950) only with the NAC CL model.

Please see below for explanations of Vss and $t_{1/2}$: After incorporating the newly-added fraction unbound in plasma (fup) data, the maximum concentration time (Tmax) was expected to shift rightward, indicating a slower distribution, while the volume of distribution at steady state (Vss) increased across all dose levels, with both parameters showing substantial increases ranging from 75.82% to 169.13% compared to their counterparts in the non-compartmental clearance model.



It could remain unchanged for adipose tissue because our model is perfusion-based, and that is tissue with lower blood flow.

Part 2:

Voriconazole is primarily cleared through the liver via N-oxidation. This clearance is facilitated by CYP450 enzyme isoforms CYP2C19, CYP2C9, and CYP3A4. The half life of Voriconazole is approximately 6 hours. It is excreted through the urine primarily as metabolites (Theuretzbacher et al., 2006). In the observed data (independent of dose), Voriconazole reaches its peak concentration (C_{max}) in ~ 3-5 hours and clearance begins thereafter. The literature also suggests that Voriconazole is extensively metabolized by the liver, with only 2% remaining unchanged (Barbarino., 2017). Therefore, it could be that after reaching peak concentrations, Voriconazole is rapidly cleared, matching the data. The change in the data after adding the calculated fup also matches the literature when observing the $t_{1/2}$. Before adding the fup data, $t_{1/2}$ was calculated closer to 1-3 hours. Now it is between 4-6 hours.

Barbarino, J. M., Owusu Obeng, A., Klein, T. E., & Altman, R. B. (2017). PharmGKB summary: voriconazole pathway, pharmacokinetics. *Pharmacogenetics and genomics*, *27*(5), 201–209. https://doi.org/10.1097/FPC.0000000000000276

Theuretzbacher, U., Ihle, F., & Derendorf, H. (2006). Pharmacokinetic/pharmacodynamic profile of voriconazole. Clinical pharmacokinetics, 45(7), 649–663. https://doi.org/10.2165/00003088-200645070-00002