



V23 comparison

Population name	Healthy volunteer (Caucasian)
Prefix	Sim
Species	Human

Simcyp Version this document relates to: V23 (Release 2)

Prepared: February 2025

The Sim-Healthy Volunteer population within the Simcyp Simulator database has been used for these simulations with the following settings: age range 20-50; 50% of subjects were female. At least 10 trials were simulated for each compound file with 50 subjects per trial. Simulations were run for all compounds (substrates, metabolites and inhibitors) within the Simcyp database.

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Certara Predictive Technologies,
Level 2 - Acero, 1 Concourse Way,
Sheffield, S1 2BJ, United Kingdom

Please contact Simcyp.support@certara.com for more information

Model Performance

Diagnostic plots - Dynamic simulations

The solid line represents the line of unity and the dashed lines a 2-fold difference in the following plots.

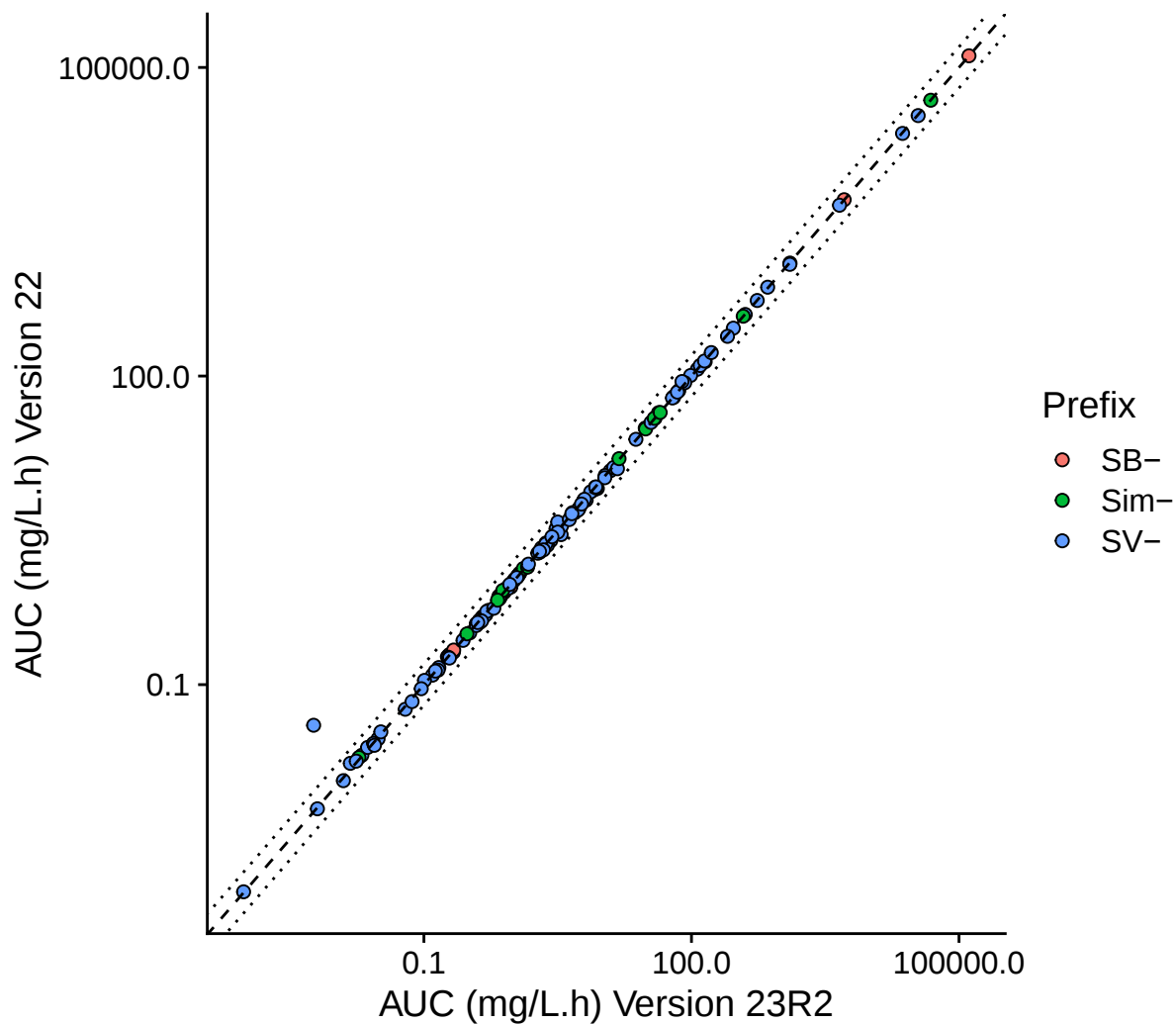


Figure 1. Mean simulated AUC (mg/L*h) for the Sim- (green), SV-(blue) and SB-(red) compound files using the Simcyp Simulator Version 22 release 1 or Version 23 release 2.

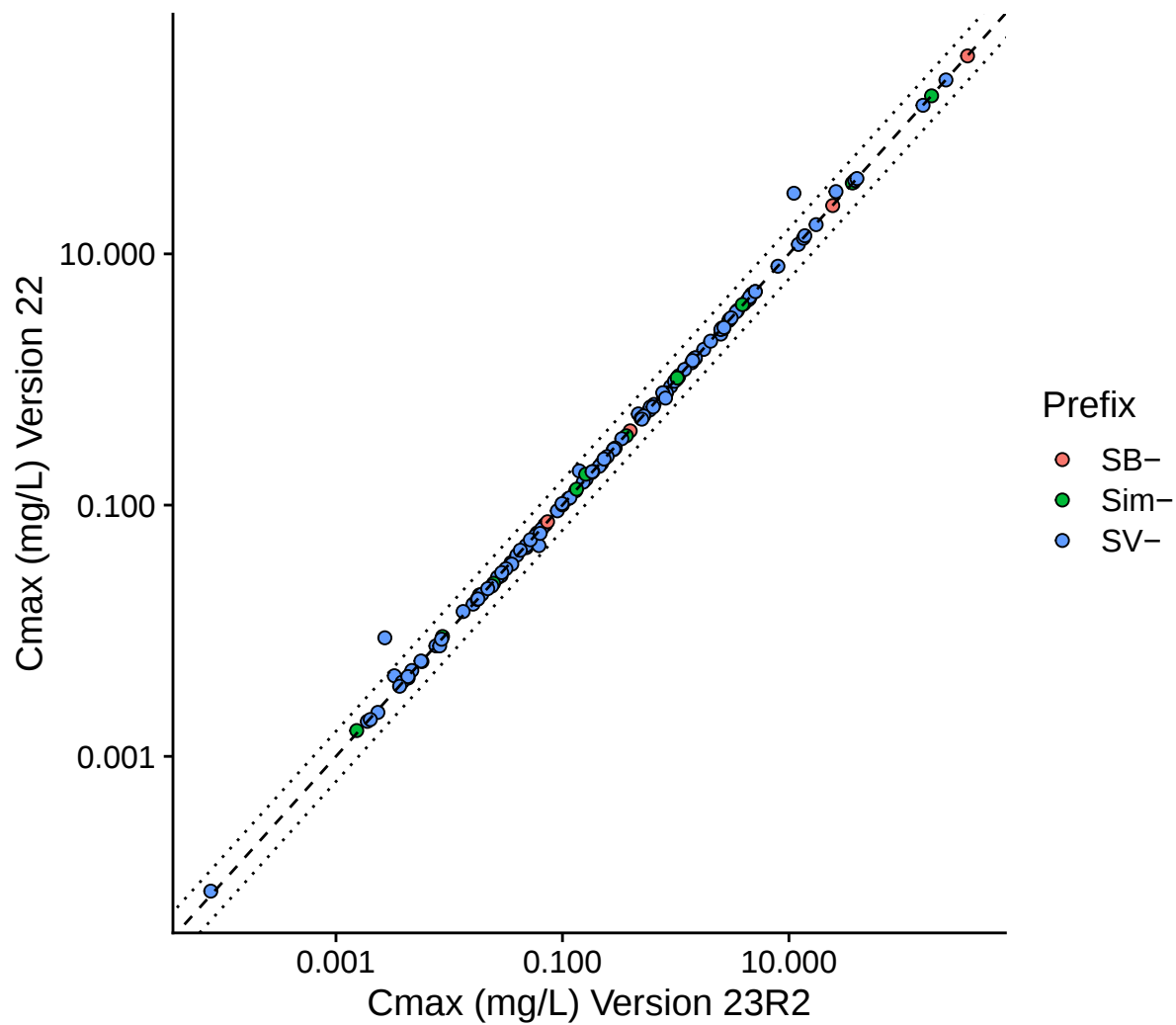


Figure 2. Mean simulated C_{max} (mg/L) for the Sim- (green), SV-(blue) and SB-(red) compound files using the Simcyp Simulator Version 22 release 1 or Version 23 release 2.

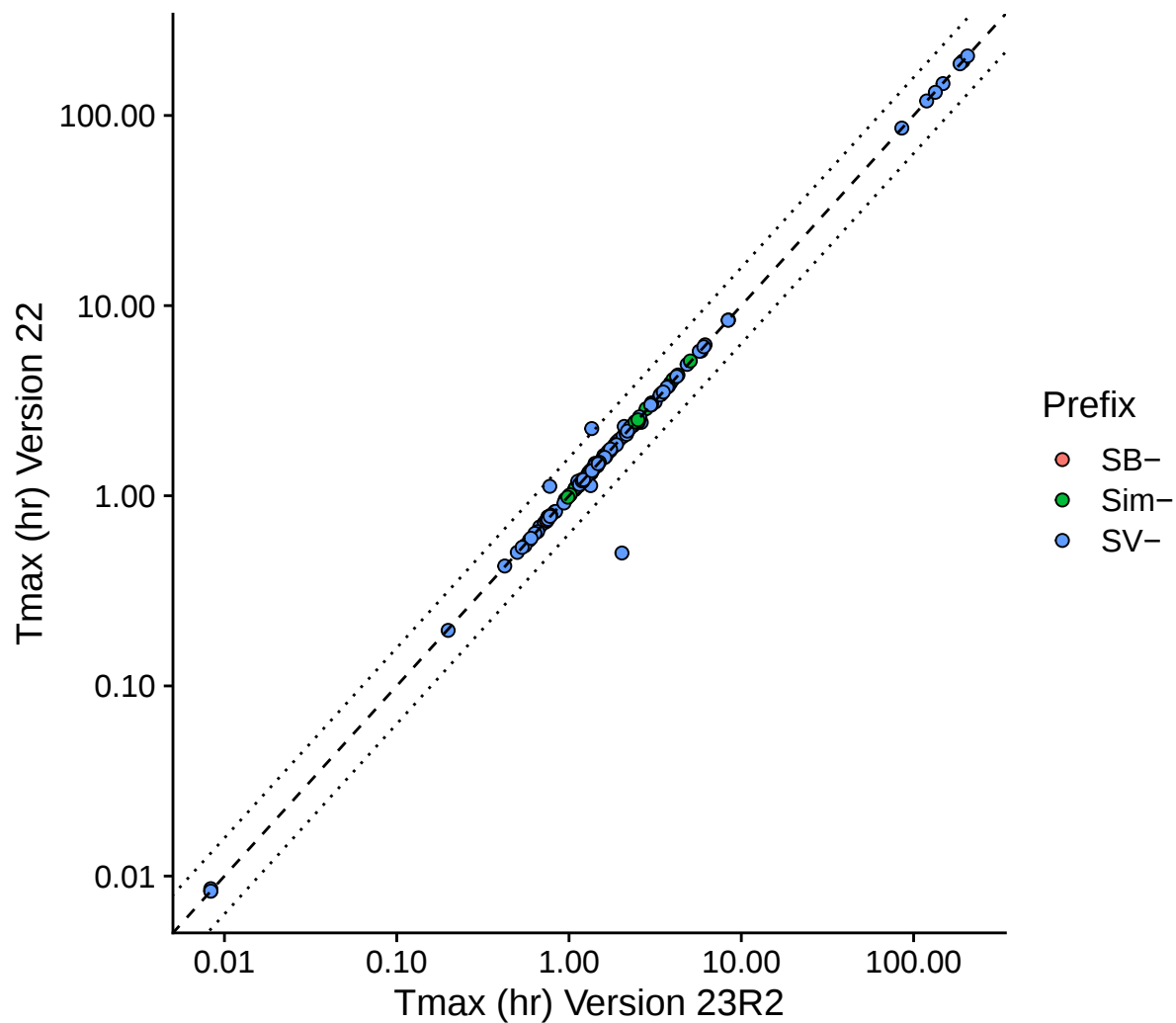


Figure 3. Mean simulated Tmax (hr) for the Sim- (green), SV-(blue) and SB-(red) compound files using the Simcyp Simulator Version 22 release 1 or Version 23 release 2.

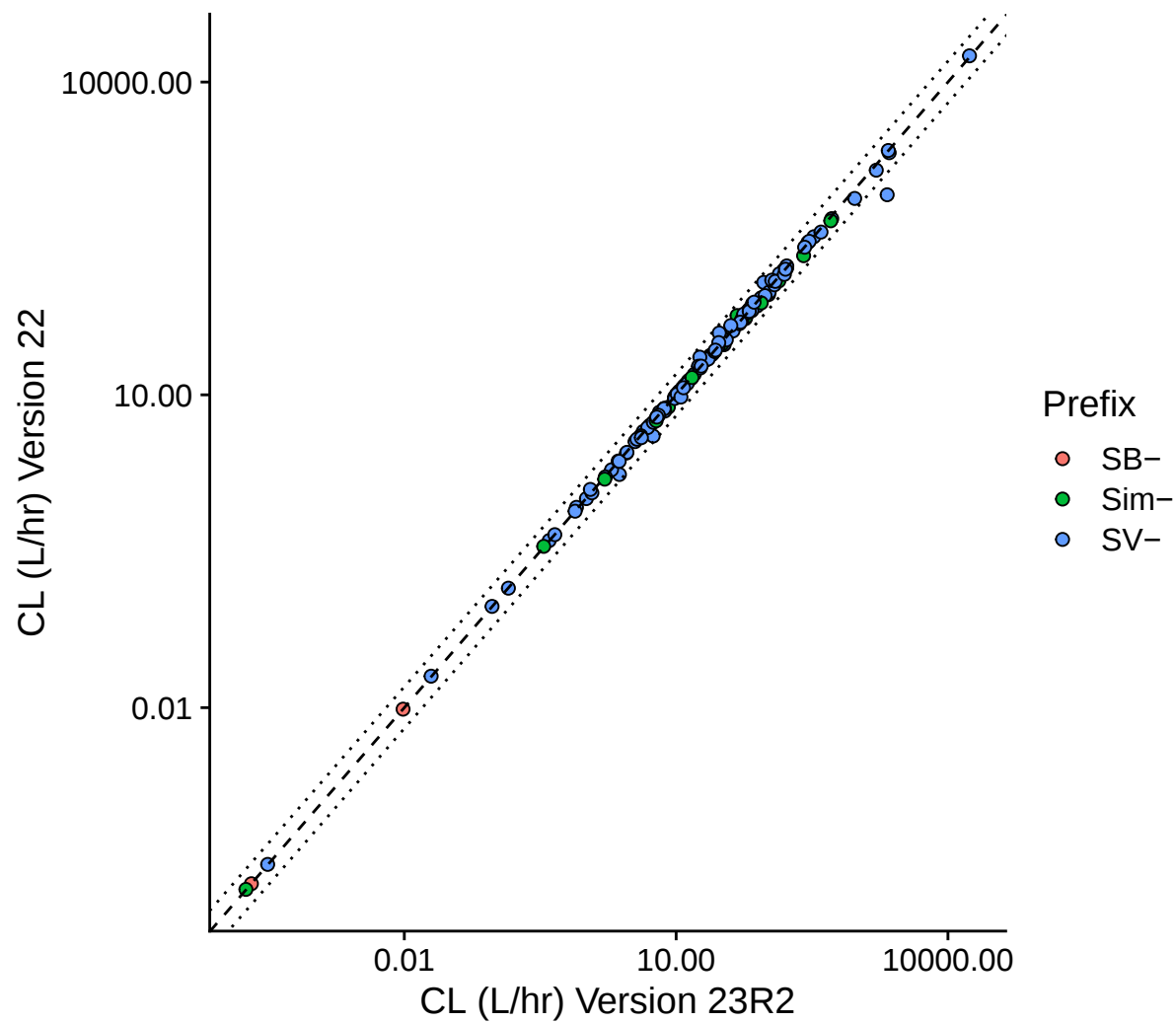


Figure 4. Mean simulated CL (L/hr) for the Sim- (green), SV-(blue) and SB-(red) compound files using the Simcyp Simulator Version 20 release 1 or Version 23 release 2.

Diagnostic plots - Static simulations

The solid line represents the line of unity and the dashed lines a 2-fold difference in the following plots.

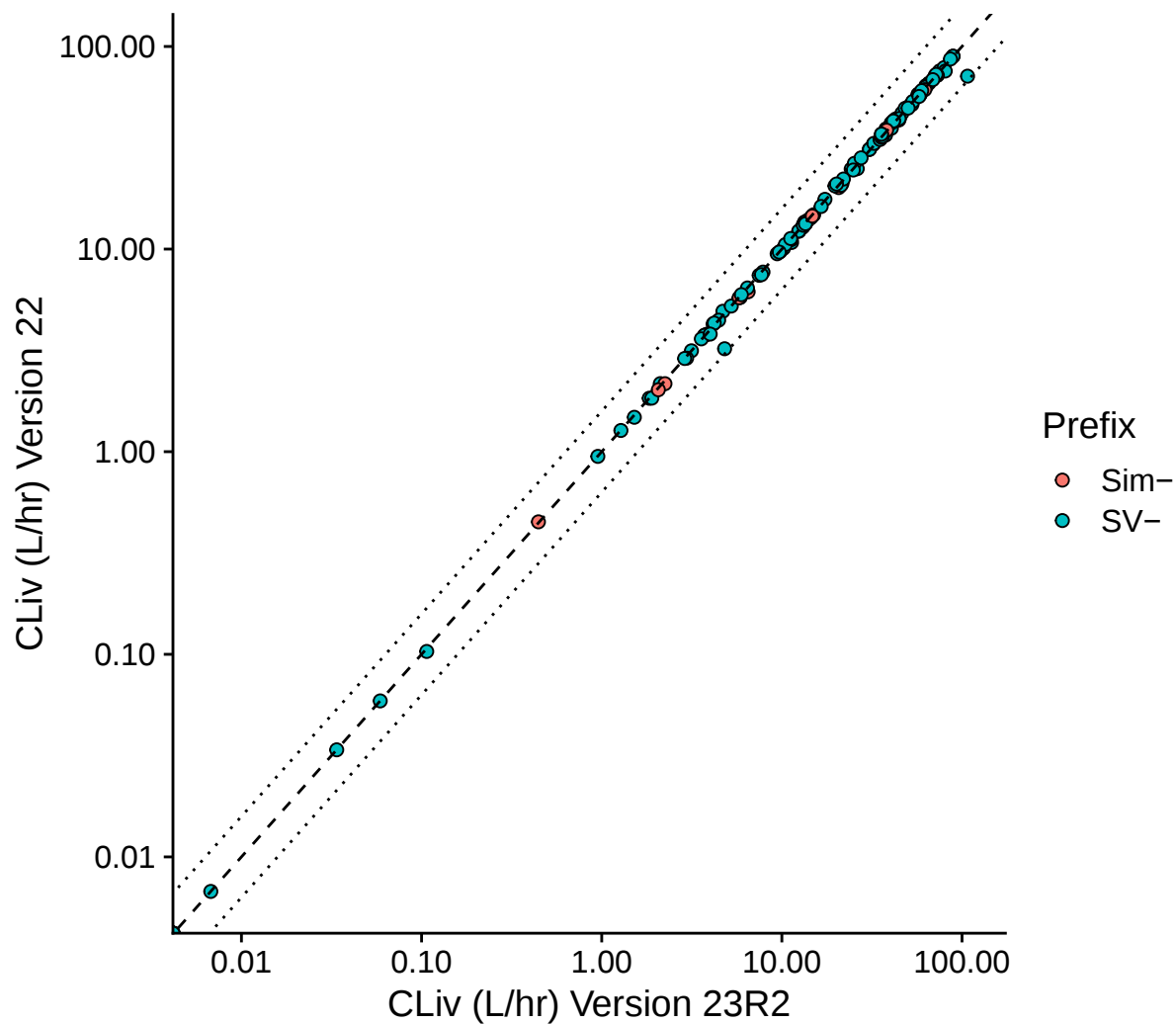


Figure 5. Mean simulated CLiv (L/hr) for the Sim- (red) and SV-(blue) compound files using the Simcyp Simulator Version 22 release 1 or Version 23 release 1.

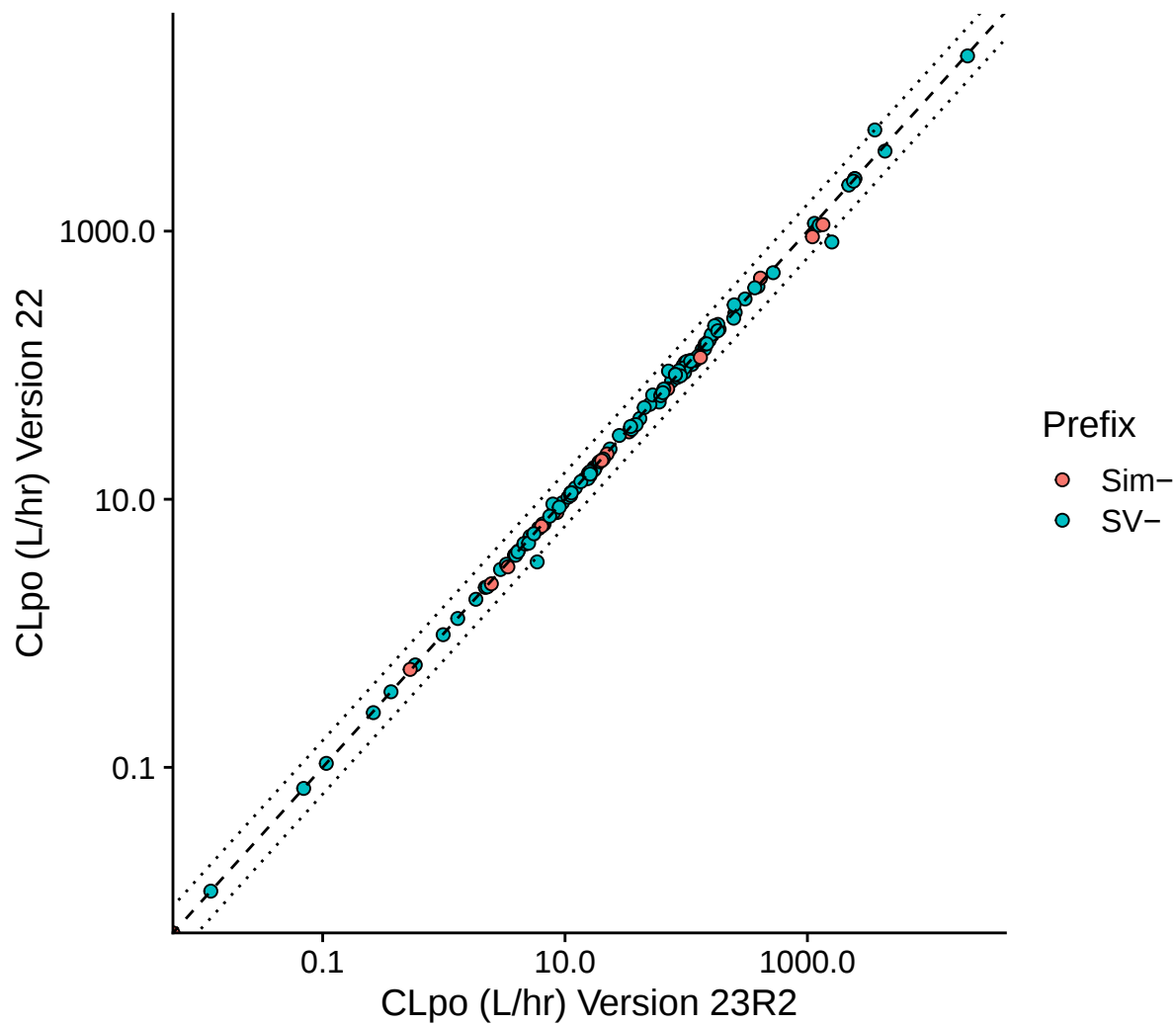


Figure 6. Mean simulated CLpo (L/hr) for the Sim- (red) and SV-(blue) compound files using the Simcyp Simulator Version 22 release 1 or Version 23 release 2.

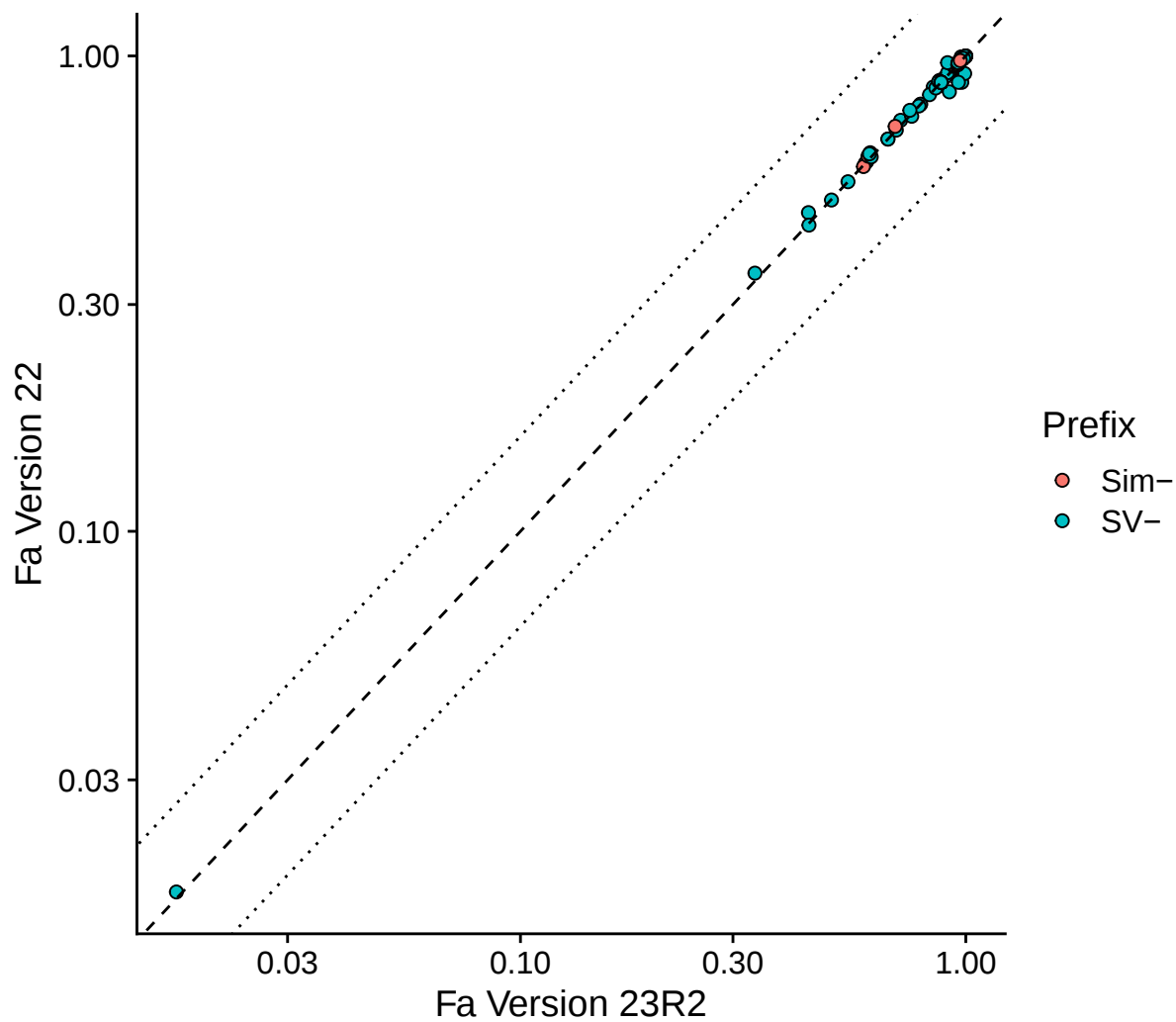


Figure 7. Mean simulated fa for the Sim- (red) and SV-(green) compound files using the Simcyp Simulator Version 22 release 1 or Version 23 release 2.

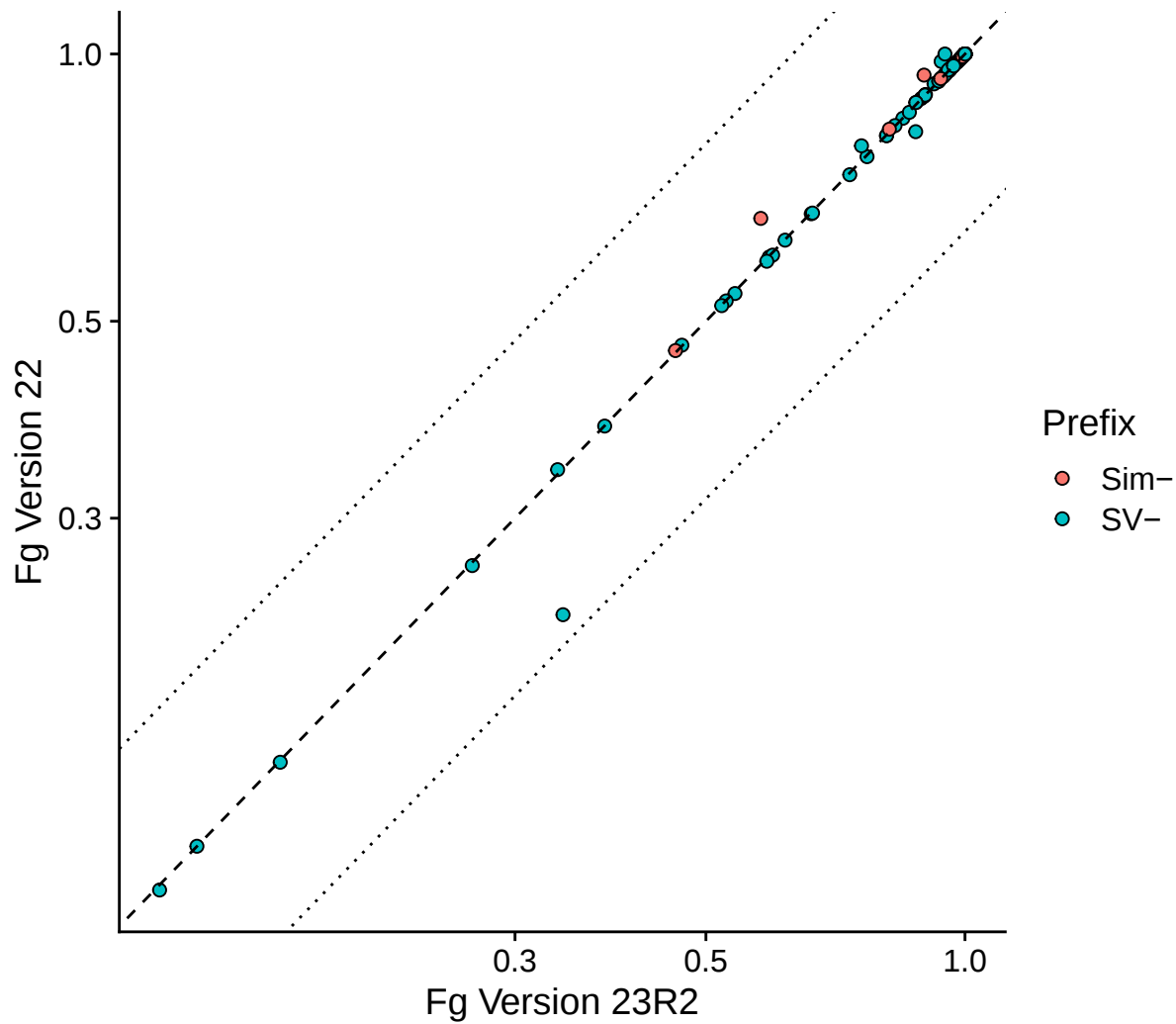


Figure 8. Mean simulated F_g for the Sim- (red) and SV-(green) compound files using the Simcyp Simulator Version 22 release 1 or Version 23 release 2.

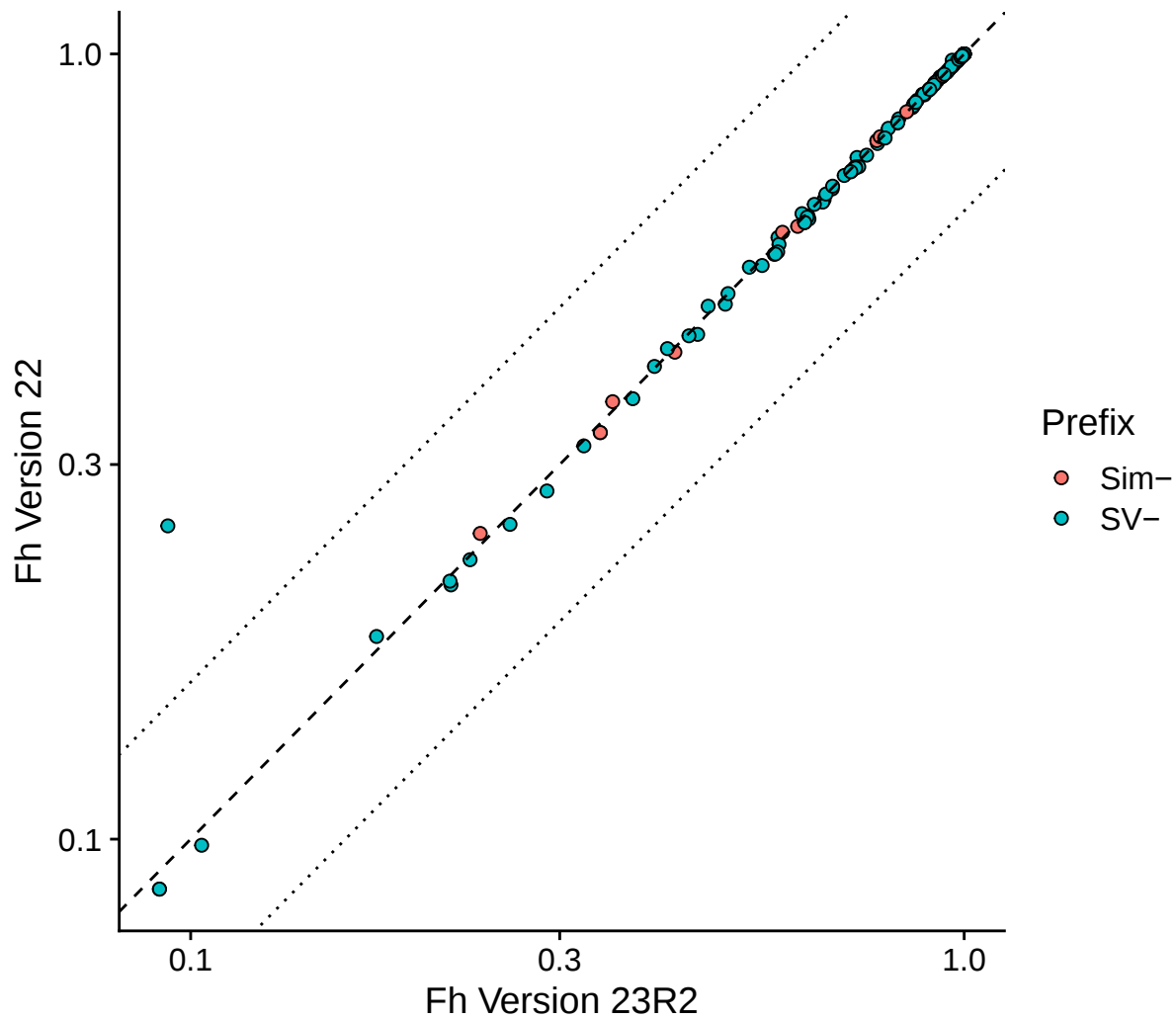


Figure 9. Mean simulated F_h for the Sim- (red) and SV-(blue) compound files using the Simcyp Simulator Version 22 release 1 or Version 23 release 2.

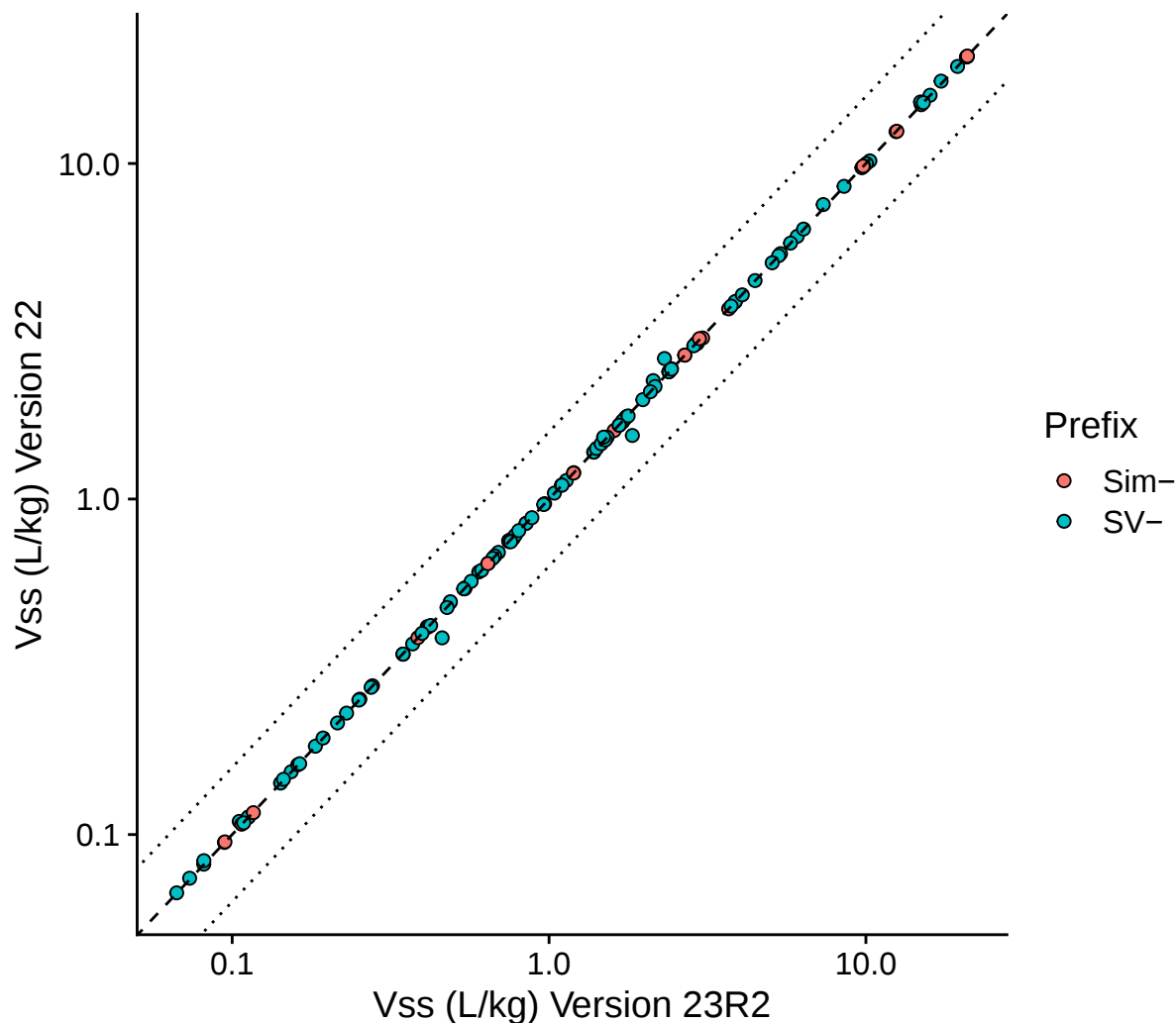


Figure 10. Mean simulated V_{ss} (L/kg) for the Sim- (red) and SV-(blue) compound files using the Simcyp Simulator Version 22 release 1 or Version 23 release 2.

Deviations

The table below shows the relative difference in pharmacokinetic parameters for the SV and Sim Compound files when they are run in V22 and V23. Results are presented as a percentage with 100% meaning no difference in the results for that compound between V22 and V23.

Name	PKPD Parameters						PKPD Profiles			
	CLiv	CLpo	Fa	Fg	Fh	Vss	Cmax	Tmax	AUC	Dose/AUC
5-hydroxy methyl Tolterodine	101	103	100	100	100	100	101	100	100	103
Adalimumab	100	100	100	100	100	99	101	100	100	100
Alfentanil	98	99	100	101	101	100	102	100	107	101
Alprazolam	97	97	100	100	100	100	101	101	104	97
Atazanavir	98	98	98	100	103	99	102	99	103	97

(continued)

Name	CLiv	CLpo	Fa	Fg	Fh	Vss	Cmax	Tmax	AUC	Dose/AUC
Atezolizumab	NaN	NaN	100	100	100	99	100	100	100	100
Atomoxetine	105	113	100	100	98	100	101	98	98	112
Atomoxetine	101	102	100	100	100	100	102	100	101	102
Atorvastatin	99	102	99	100	101	100	75	101	87	122
Bufuralol	103	110	100	100	98	100	101	99	99	110
Bufuralol	100	101	100	100	100	100	101	100	103	101
Buprenorphine	99	100	100	101	102	95	103	97	103	98
Bupropion_SR	100	101	100	100	99	100	100	98	99	101
Caffeine	106	108	100	100	100	100	99	99	97	108
Carbamazepine	98	98	100	100	100	101	98	101	103	99
Carbamazepine-10,11-epoxide	NaN	100	100	100	100	100	100	100	100	100
Celecoxib	98	98	100	100	101	100	103	100	102	97
Cimetidine	101	88	109	100	100	100	109	100	109	87
Cinacalcet	100	101	100	100	101	100	105	99	102	101
Ciprofloxacin	101	93	100	100	100	100	101	100	100	93
3-cis-hydroxy-glyburide	101	101	100	100	100	100	100	99	99	101
Clarithromycin	99	99	100	100	101	100	103	100	105	100
Clozapine	102	105	100	100	99	100	100	100	100	105
Cobicistat	100	100	100	100	105	100	99	100	100	137
Cobicistat	100	100	100	100	105	100	102	100	106	109
Crizotinib	99	104	98	100	101	100	75	108	92	114
Cyclosporine_Neoral	95	79	111	101	102	118	106	96	120	77
Cyclosporine_M1 (AM9)	100	100	100	100	100	100	101	100	100	100
Cyclosporine_M17 (AM1)	100	100	100	100	100	100	100	99	100	100
Dabigatran etexilate	99	103	95	100	103	100	99	101	98	97
Dabigatran	100	101	100	100	100	100	100	99	100	100
Desipramine	101	101	100	100	100	100	100	100	100	101
Desipramine	103	110	100	100	99	100	100	99	98	110
Desmethyldiltiazem (MA)	99	105	100	95	101	100	96	100	98	105
Dexamethasone	99	99	100	100	100	100	101	101	105	100
Dextromethorphan (peripheral sampling)	102	103	100	100	100	98	99	99	99	102
Dextromethorphan (peripheral sampling)	101	113	100	100	96	100	97	99	95	113
Dextrophan	107	107	100	100	102	100	101	98	95	107
Digoxin	101	102	99	100	100	100	105	97	101	99
Diltiazem	99	98	100	100	101	101	100	101	102	98
Drospirenone	99	100	100	100	100	100	105	100	103	100
Duloxetine	102	107	100	100	98	97	100	99	96	107
Efavirenz	99	100	100	100	100	100	104	100	101	101

(continued)

Name	CLiv	CLpo	Fa	Fg	Fh	Vss	Cmax	Tmax	AUC	Dose/AUC
Efavirenz	99	100	100	100	100	100	102	100	101	101
Efalizumab	100	100	100	100	100	99	101	97	102	99
Enzalutamide	100	101	100	100	100	100	102	100	102	101
Erythromycin_EC	99	98	100	100	101	99	101	100	104	99
Erythromycin	99	98	100	100	101	100	102	101	103	99
Esomeprazole	102	105	99	100	100	100	98	102	98	105
Esomeprazole	98	96	99	100	101	100	102	101	106	96
Etanercept	100	100	100	100	100	96	101	100	101	99
Ethinylestradiol	102	103	99	100	100	100	93	100	98	103
Fedratinib	98	101	98	100	101	100	101	99	104	108
Fluconazole	100	101	100	100	100	101	99	102	99	101
Fluoxetine	105	107	100	100	99	101	97	99	98	102
Flurbiprofen	99	99	100	100	100	100	101	99	100	99
Fluvoxamine	103	106	100	100	99	100	103	99	101	105
Gemfibrozil 1-O-b Glucuronide	101	102	100	100	100	100	100	100	99	102
Gemfibrozil	101	108	98	96	100	100	83	118	97	107
Glyburide_Micronized	99	100	100	100	100	100	103	98	101	96
3- HydroxyMorphinan	150	192	100	100	37	88	31	69	14	257
Ibrutinib	100	63	108	146	105	100	130	60	99	107
Imipramine	100	101	100	100	101	98	105	98	103	101
Itraconazole_Fasted Soln	99	88	109	100	103	100	114	90	118	79
Itraconazole_Fed Capsule	99	92	101	100	103	100	103	98	101	82
Ketoconazole-200 mg BID	NaN	100	100	100	100	100	100	100	100	100
Ketoconazole-200 mg QD	NaN	102	100	100	100	100	99	99	98	102
Ketoconazole-400 mg QD	NaN	100	100	100	100	100	100	100	100	100
Lansoprazole	96	94	100	100	101	100	102	100	105	94
Letermovir	102	103	99	100	100	100	102	101	104	95
Lorazepam	100	101	100	100	100	100	99	102	98	101
S-Mephenytoin	103	103	100	100	100	100	100	100	98	102
S-Mephenytoin	98	95	100	99	102	100	103	101	107	95
Metformin	100	100	100	100	101	100	99	100	99	99
3- MethoxyMorphinan	103	107	100	100	99	100	99	99	99	106
Metoprolol	101	102	100	100	100	101	99	100	99	102
Metoprolol	103	110	100	100	98	100	99	99	97	110
Midazolam	97	91	100	101	103	100	105	101	108	90
Mirabegron	100	102	99	100	100	100	102	100	103	99
Modafinil	NaN	100	99	100	100	100	100	99	101	99
Montelukast	95	86	101	107	100	99	88	104	83	138
Nebivolol	102	107	97	100	100	100	98	102	99	102
Nebivolol	101	120	98	99	97	100	95	99	95	109

(continued)

Name	CLiv	CLpo	Fa	Fg	Fh	Vss	Cmax	Tmax	AUC	Dose/AUC
Nifedipine	97	97	100	100	101	100	103	101	106	97
Norfluoxetine	100	100	100	100	100	100	100	100	100	100
Norverapamil	97	95	100	100	102	100	102	100	104	97
OH Bupropion	100	100	100	100	100	100	100	100	100	100
OH-Itraconazole	98	104	100	96	101	100	98	101	102	104
3OH-Quinidine	NaN	100	100	100	100	100	100	100	99	100
Omalizumab	100	100	100	100	100	97	101	101	102	99
Omeprazole	102	103	100	100	100	99	99	102	99	103
Omeprazole	98	95	100	100	102	100	104	100	110	94
Ondansetron	101	104	99	100	100	100	100	98	101	103
Oxycodone	100	103	99	100	100	100	101	99	101	102
Paroxetine	101	121	99	99	97	100	97	99	97	118
Phenacetin	102	106	100	100	99	100	99	99	98	107
Phenobarbital	NaN	100	100	100	100	100	100	100	100	100
Phenytoin	102	102	100	100	100	100	101	100	99	102
Pioglitazone	100	101	100	100	100	100	101	101	106	101
Posaconazole DR Tablet	103	104	100	100	100	100	100	100	100	104
Pravastatin	101	108	98	100	100	100	107	100	106	99
Probenecid	104	105	99	100	100	100	99	98	100	105
Quinidine	99	100	100	100	100	100	101	101	103	100
Raltegravir	100	101	100	100	100	100	100	100	101	101
Repaglinide	98	101	99	100	100	100	100	101	103	106
Rifabutin	99	101	100	100	100	100	102	100	104	101
Rifampicin-MD	100	101	99	100	100	101	99	100	100	101
Rifampicin-SD	149	173	94	95	98	119	36	406	88	119
Ritonavir	97	96	100	100	102	99	105	99	108	87
Ritonavir_FO	97	87	100	100	103	99	102	99	103	76
Rivaroxaban	99	100	100	100	100	100	102	100	101	100
Rosiglitazone	101	102	100	100	100	100	101	99	105	101
Rosuvastatin	101	108	96	100	100	100	93	99	92	109
Ruxolitinib	100	100	100	100	100	100	100	100	101	100
Sildenafil	99	115	100	89	101	100	91	100	93	114
Simvastatin	99	99	100	101	102	97	109	100	108	99
Siponimod	98	98	100	100	100	100	100	100	102	98
Sulphaphenazole	NaN	100	100	100	100	100	100	100	100	100
Tenofovir	103	102	101	100	100	100	102	94	99	101
Theophylline	105	106	100	100	100	100	100	99	97	106
Ticlopidine	99	97	100	100	103	100	104	101	107	96
Tolbutamide	103	102	100	100	100	100	99	99	98	102
Tolterodine	102	104	100	100	100	100	100	100	99	103
Tolterodine	102	110	100	100	98	100	101	100	97	109
4-trans-hydroxy- glyburide	101	105	98	100	100	100	99	98	97	103
Trastuzumab	NaN	NaN	100	100	100	99	100	100	100	99
Triazolam	96	93	100	100	101	100	102	102	107	93
Trimethoprim	NaN	100	100	100	100	100	100	100	99	100
Valsartan	102	108	98	100	100	100	98	99	98	107

(continued)

Name	CLiv	CLpo	Fa	Fg	Fh	Vss	Cmax	Tmax	AUC	Dose/AUC
Verapamil	99	102	97	99	104	100	96	100	100	101
Voriconazole	97	96	99	99	102	100	103	100	104	91
Voriconazole	97	96	99	99	102	100	100	100	106	94
Voriconazole N-oxide	100	100	100	100	100	100	100	100	100	100
S-Warfarin	99	98	100	100	100	100	100	100	101	98
Zidovudine 5'- O-glucuronide	101	110	97	100	100	100	100	100	99	101
Zidovudine	100	101	100	100	100	100	100	100	100	101
Zolpidem	101	103	99	100	100	100	99	100	101	102

NaN = no value is calculated for this compound and parameter pair.

Discussion

The following compounds show more than 15% difference between V22 and V23: atorvastatin, cobicistat (multiple dose), cyclosporine, gemfibrozil, itraconazole, lansoprazole, montelukast, paroxetine and ritonavir. The majority of these changes are expected based on the changes to compound files between V22 and 23 as outlined in the paragraphs below.

Updates have been made to the following compounds.

Atorvastatin - changes to Pgp and BCRP kinetics

Crizotinib - intrinsic aqueous solubility was updated using measured values for melting point (replacing previously optimized values).

Sildenafil - Qgut updated with 50 mg oral data

Cimetidine - The fa %CV was changed from 30% to 5% to ensure the PK parameters and concentration profiles for cimetidine were similar when used in either the substrate or inhibitor slots.

3-hydroxymorphinan - B/P ratio and distribution method updated. Elimination updated to enzyme kinetics model.

Dextrophan - the renal clearance was updated with clinical data.

Gemfibrozil - the MechPeff model was used to predict permeability to better capture Tmax and Cmax.

Ketoconazole - the P-gp Ki was optimized base on interaction with fexofenadine in gut wall and liver.

Itraconazole fasted solution – fa and ka predicted using PSA.

Itraconazole fed capsule - fa and ka %CV was optimized to 10% to ensure the PK parameters and concentration profiles for itraconazole were similar when used in either the substrate or inhibitor slots.

Trimethoprim - updated MATE Ki.

Ondansetron - updated MATE Ki.

Probenecid - OAT3 Ki included in file.

Montelukast - absorption updated to include dissolution of film coated tablets and permeability was predicted from Caco-2 data, with a basolateral scalar of 0.1 to recover the observed Fg after grapefruit juice administration.

Cyclosporine - the fa and ka %CV was optimized from 30% to 5% to ensure the PK parameters and concentration profiles for cyclosporine were similar when used in either the substrate or inhibitor slots.

Rifampicin FO - fa and ka %CV was optimized to 10% to ensure the PK parameters and concentration profiles for ritonavir were similar when used in either the substrate or inhibitor slots.

New compounds for V23

The new compounds introduced into Simcyp V23 are:

Rifampicin - new model accounting for auto-induction, induction and transporter DDI and uses the PERL model for rifampicin. This will replace the previously available SV-Rifampicin-SD file. In this version comparison the new Rifampicin file is compared to the SV-Rifampicin-SD file from V22.

Docetaxel - developed as a CYP3A4, P-gp, and OATP1B1/1B3 substrate.

Prednisolone - developed as a CYP3A4/5 substrate

Methotrexate - developed as an OAT3, MRP2, MRP4, and BCRP substrate.

Furosemide - developed as an OAT3 and MRP4 substrate.

In addition due to limitations that prevent adequate performance verification of the files the following files will be made available as research files and will be available for download from the members area

Dapagliflozin

Apalutamide/N-desmethyapalutamide

Fexofenadine

Dolutegravir

R and S Carvedilol

R and S Nebivolol and hydroxy metabolites

Lomitapide

Desogestrel/etonorgestrel

Venetoclax

Simvastatin/Simvastatin Acid - more mechanisms included than in the standard simvastatin file. The file requires some changes to the population to run correctly and to make this easier will be provided as a

workspace on the members area.