

Population Name:	Healthy Volunteer (Caucasian)
Prefix:	Sim
Species:	Human
Simcyp Version this document relates to:	V19R1 and V20R1

Prepared: April 2021

The Sim-Healthy Volunteer model within the Simcyp Population Database has been used with the following setting: age range between 20 to 50 years and 50% of the population were female. At least ten trials were simulated for each Simcyp (Sim-, SV-, and RES-) compound using 50 subjects in each trial.

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1. Diagnostic plots

The dashed lines represent lines of unity and the dotted lines a 2-fold difference in the following figures.

Comparison plot of the simulated CL

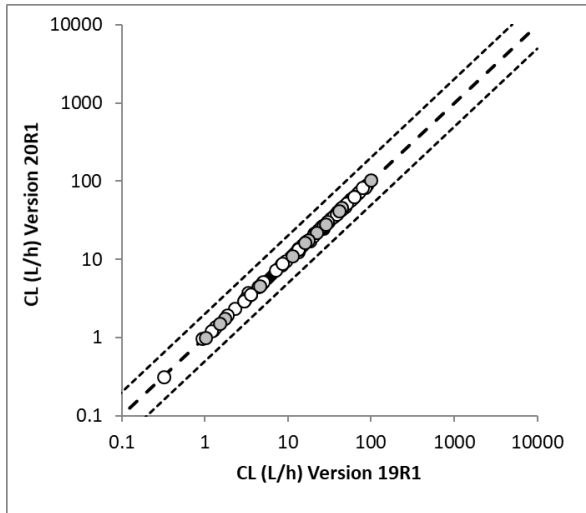


Figure 1 - Mean simulated IV clearance for the Sim- (black squares), SV-compounds (white circles), and RES-compounds (grey circles) using the Simcyp Simulator Version 19 Release 1 or Version 20 Release 1.

Comparison plot of the simulated CL_{po}

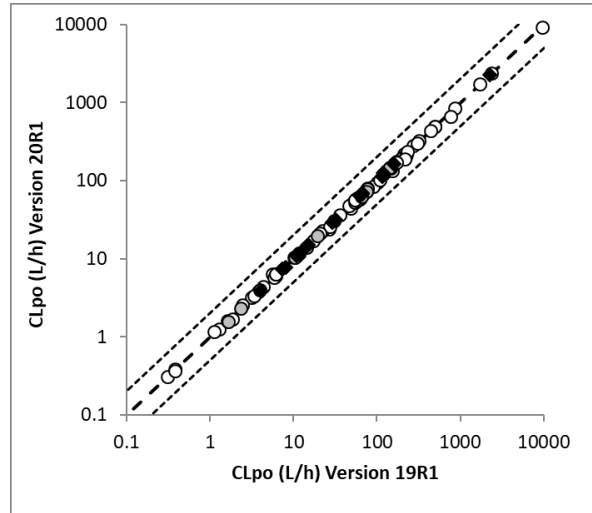
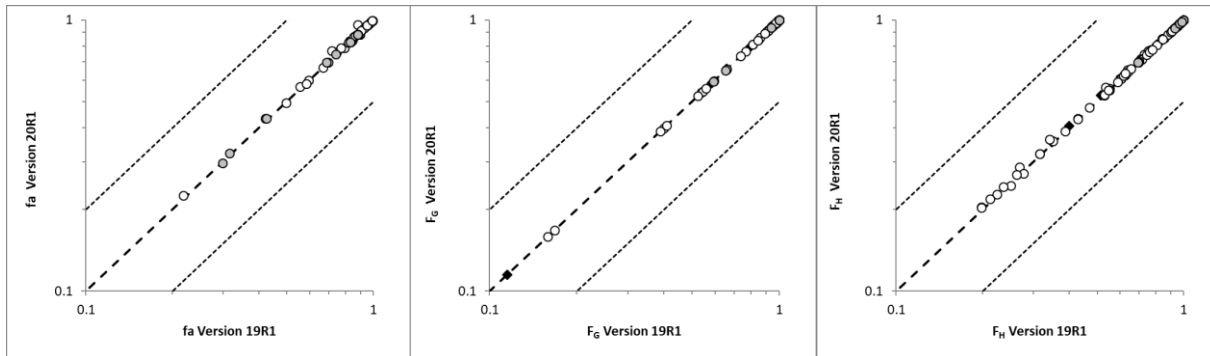


Figure 2 - Mean simulated oral clearance for the Sim- (black squares), SV-compounds (white circles), and RES-compounds (grey circles) using the Simcyp Simulator Version 19 Release 1 or Version 20 Release 1.



Comparison plot of the simulated fa, F_G and F_H in the PK-Parameter setting

Figure 3 - Mean simulated fa, F_G and F_H for the Sim- (black squares), SV-compounds (white circles), and RES-compounds (grey circles) using the Simcyp Simulator Version 19 Release 1 or Version 20 Release 1.

Comparison plot of the simulated AUC (mg/L.h)

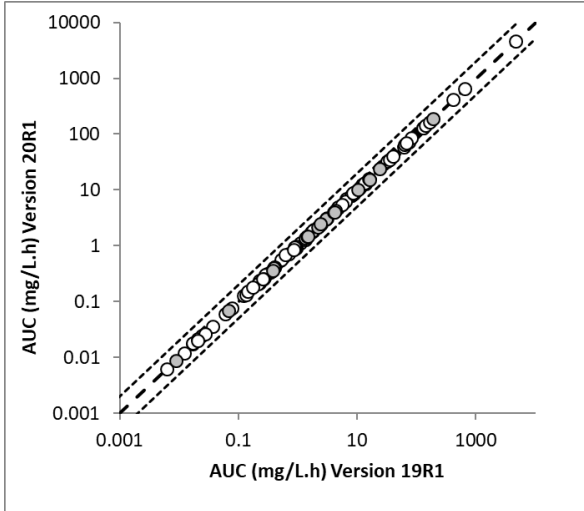


Figure 4 - Mean simulated AUC for the Sim- (black squares), SV-compounds (white circles), and RES-compounds (grey circles) using the Simcyp Simulator Version 19 Release 1 or Version 20 Release 1.

Comparison plot of the simulated CL (Dose/AUC) (L/h)

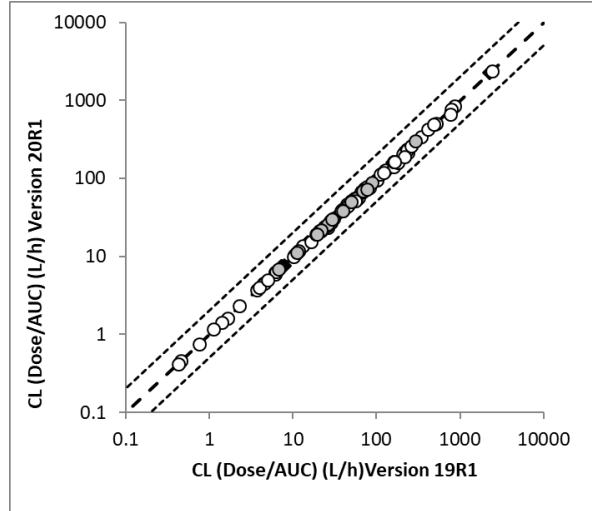


Figure 5 - Mean simulated CL (Dose/AUC) for the Sim- (black squares), SV-compounds (white circles), and RES-compounds (grey circles) using the Simcyp Simulator Version 19 Release 1 or Version 20 Release 1.

Comparison plot of the simulated C_{max} (mg/L)

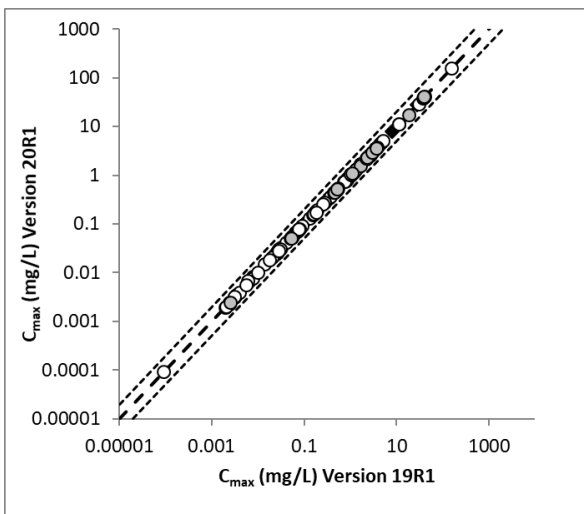


Figure 6 - Mean simulated C_{max} for the Sim- (black squares), SV-compounds (white circles), and RES-compounds (grey circles) using the Simcyp Simulator Version 19 Release 1 or Version 20 Release 1.

Comparison plot of the simulated t_{max} (h)

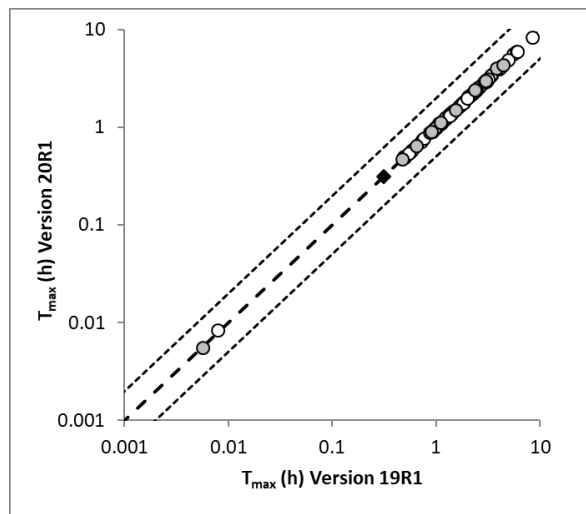


Figure 7 - Mean simulated t_{max} for the Sim- (black squares), SV-compounds (white circles), and RES-compounds (grey circles) using the Simcyp Simulator Version 19 Release 1 or Version 20 Release 1.

Comparison plot of the simulated V_{ss} (L/kg)

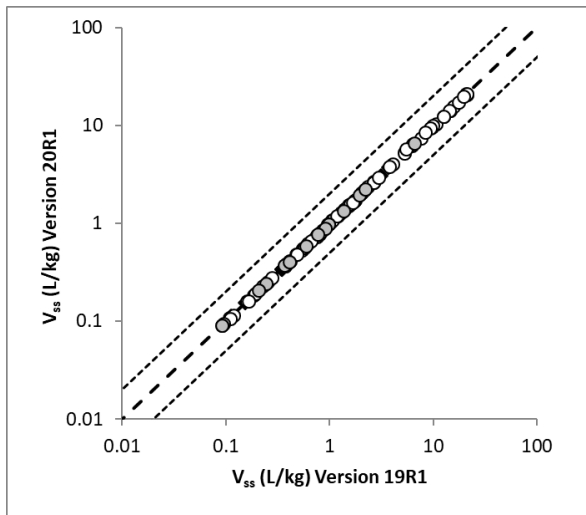


Figure 8 - Mean simulated V_{ss} for the Sim- (black squares), SV-compounds (white circles), and RES-compounds (grey circles) using the Simcyp Simulator Version 19 Release 1 or Version 20 Release 1.

2. Deviations

Individual comparison of some key PK parameters for the SV-compound files

SV files	V20R1 B157 as % of V19R1 B96										
	PKPD Parameters							PKPD Profiles			
Compound	CL	CL _{po}	fa	F _g	F _H	F	V _{ss}	C _{max}	t _{max}	AUC	CL
1-OH-Itraconazole	101	100	100	100	101	102	103	100	100	102	100
3-MethoxyMorphinan (with 3HM)	96	92	100	100	103	103	98	106	101	107	93
3-OH-Morphinan	103	99	100	100	102	102	100	105	100	99	99
3-OH-quinidine	CLIV	100	100	100	100	100	100	99	100	97	99
5-OH-Methyltolterodine	98	94	100	100	103	103	98	104	101	105	94
Alfentanil	101	101	100	99	101	100	98	100	99	99	101
Alprazolam	102	101	100	100	100	100	98	101	100	100	101
Atazanavir	102	101	101	100	101	102	100	100	100	101	101
Atomoxetine	95	89	100	101	103	104	98	105	102	104	90
Atorvastatin (new in V20)	101	103	99	100	100	99	100	101	100	102	98
Bupropion	102	102	100	100	102	102	98	103	100	101	102
Carbamazepine (with metabolite)	102	102	100	100	100	100	97	103	99	101	102
Carbamazepine epoxide	CLIV	100	100	100	100	100	98	99	99	97	100
Celecoxib	100	97	101	100	101	102	100	101	101	104	98
Cimetidine	100	98	100	100	100	100	100	99	100	99	102
Cinacalcet (new in V20)	102	101	100	100	103	103	98	103	98	102	100
Ciprofloxacin	100	92	100	100	101	101	100	99	100	101	93
Clarithromycin	101	101	100	100	100	101	99	101	100	100	101
Crizotinib	101	98	102	100	101	103	100	100	101	102	101
Cyclosporine_M1	102	102	100	100	100	100	100	100	100	100	101
Cyclosporine_M17	102	102	100	100	100	100	100	99	105	101	101
Cyclosporine_Neoral	103	103	100	100	100	100	100	97	101	98	103
Dabigatran	101	100	100	100	100	100	100	99	103	100	100
Dabigatran etexilate (Dabigatran)	102	95	103	99	103	106	100	103	103	107	92
Desipramine	96	88	100	101	106	106	99	107	102	107	89
Dexamethasone (new in V20)	102	102	100	100	100	100	99	101	98	101	102
Dextromethorphan (with all three metabolites)	100	86	100	101	107	108	99	114	100	106	86
Dextrorphan (with 3HM)	102	101	100	100	103	103	100	104	100	101	101
Digoxin (run in the Livermore solver)	100	98	101	100	100	101	100	99	101	103	96
Efavirenz	112	113	100	100	100	99	100	94	100	95	103
Erythromycin (updated in V20)	101	92	101	100	101	101	98	101	100	101	91
Erythromycin_EC (updated in V20)	101	99	100	100	101	101	96	101	99	94	106
Esomeprazole (New in V20)	103	102	101	100	100	101	100	102	99	104	102
Ethinylestradiol	101	100	101	99	100	100	99	103	100	101	100
Fluconazole	99	98	100	100	100	100	100	101	100	101	99
Fluoxetine (with metabolite)	95	93	100	100	101	102	97	105	101	105	96
Fluvoxamine	102	102	100	100	100	100	98	101	100	101	101
Ibrutinib (new in V20)	103	101	100	100	103	102	99	100	99	100	101
Imipramine (updated in V20)	103	92	109	100	100	109	98	112	98	107	91
Itraconazole_capsule (with metabolite)	102	102	100	100	101	101	99	98	101	99	100
Itraconazole_solution (with metabolite)	102	102	100	100	101	102	99	99	101	100	98
Lansoprazole (new in V20)	103	103	100	100	100	100	100	100	99	103	103
Lorazepam	100	98	101	100	100	102	102	101	97	103	98
Metformin (CVODES)	101	100	100	100	101	100	100	98	99	97	103
Metoprolol	103	104	100	100	100	100	100	99	100	96	104
Mirabegron (new in V20)	101	98	101	102	101	104	100	100	100	113	91
Nebivolol (new in V20)	104	100	102	100	98	100	100	98	97	95	100
Norfluoxetine	102	102	100	100	100	100	101	100	100	101	102
Norverapamil	102	102	100	100	100	101	100	101	101	100	102
OH-Bupropion	102	102	100	100	100	100	98	102	100	102	100
Omeprazole	103	103	100	100	100	101	100	102	99	110	103
Ondansetron (new in V20)	101	103	99	100	101	100	100	100	101	101	100
Paroxetine	104	102	101	98	98	96	99	101	99	98	104
Phenobarbital	CLIV	100	100	100	100	100	98	101	100	101	99
Phenytoin	103	104	100	100	100	100	99	100	100	100	103
Pravastatin	101	96	102	100	100	103	100	102	101	100	99
Probenecid	101	100	101	100	100	101	100	101	101	102	101
Raltegravir	99	98	100	100	102	102	99	102	100	103	98
Repaglinide	101	100	100	100	100	101	100	101	100	102	98
Rifabutin	102	98	100	103	100	103	100	101	100	102	98
Rifampicin_MD	103	101	101	100	100	101	98	101	99	100	101
Rifampicin-SD (IV)	100	100	100	100	100	100	100	96	99	103	98
Rifampicin-SD (PO)	100	99	101	100	100	101	100	101	102	103	95
Ritonavir_ADAM (updated for V20)	103	103	100	100	100	100	100	104	102	105	94
Ritonavir_FO (updated for V20)	102	101	100	100	101	100	100	96	101	98	102
Rosiglitazone	101	101	100	100	100	100	100	101	100	102	101
Rosuvastatin	100	95	103	100	100	103	100	100	100	99	104
Sildenafil	102	101	100	100	100	100	101	98	101	99	101
S-Mephenytoin*	103	102	100	100	100	101	98	103	100	104	102
Sulphaphenazole	CLIV	100	100	100	100	100	97	102	100	99	99
S-Warfarin	98	97	100	100	100	100	97	103	101	103	97
Ticlopidine	102	101	101	100	103	103	100	102	99	103	101
Tolbutamide	104	104	100	100	100	100	97	101	99	102	104
Tolterodine	99	89	100	100	106	107	98	107	100	100	89
Triazolam	103	101	100	100	100	100	99	98	100	98	101
Trimethoprim	CLIV	103	101	100	100	101	100	100	101	100	102
Valsartan	101	91	107	100	100	107	100	101	99	100	101
Verapamil (run in the RKS solver)	102	100	100	100	103	102	103	103	97	102	101
Zidovudine	101	100	100	100	102	102	100	101	101	103	100
Zidovudine 5'- O-glucuronide	101	100	100	100	100	100	100	103	105	100	100

The acceptance criteria (highlighted in green) are set as $100 \pm 15\%$.

Simulations for the SV-Ritonavir file and SV-Mirabegron file were performed using the RK5 solver with a relative tolerance when ADAM is used of $1E-15$. For both compounds 10 trials for 50 subjects were run. For the SV-Metformin simulations the custom CVODES solver was used.

Individual comparison of some key PK parameters for the Sim-compound files

Sim files	V20R1 B157 as % of V19R1 B96											
	PKPD Parameters							PKPD Profiles				
Compound	CL	CL _{po}	fa	F _G	F _H	F	V _{ss}	C _{max}	t _{max}	AUC	CL	
Bufuralol	102	102	100	100	100	100	98	109	98	97	102	
Caffeine	96	95	100	100	100	101	98	103	101	103	95	
Clozapine	100	98	100	100	101	101	98	102	100	102	98	
Desmethyldiltiazem	101	100	100	100	100	101	100	101	100	101	100	
Diltiazem (with metabolite)	101	101	100	100	102	102	97	105	99	102	101	
Gemfibrozil	101	99	100	102	100	102	100	100	101	101	101	
Gemfibrozil-glucuronide	100	98	100	100	100	100	100	101	101	101	98	
Ketoconazole 200mg BID	CLIV	100	100	100	100	100	98	100	99	96	100	
Ketoconazole 200mg QD	CLIV	100	100	100	100	100	98	99	99	96	100	
Ketoconazole 400mg QD	CLIV	100	100	100	100	100	98	100	99	96	100	
Midazolam	102	103	100	100	100	100	98	99	99	98	103	
Nifedipine	102	102	100	100	100	100	100	99	100	99	102	
Phenacetin	101	97	100	100	102	102	98	102	100	102	98	
Quinidine	101	100	100	100	100	101	99	105	99	101	100	
Simvastatin	102	100	100	100	102	101	98	100	99	100	100	
Theophylline	97	97	100	100	100	100	98	101	101	102	97	
Zolpidem	101	101	100	100	100	100	100	100	100	101	101	

The acceptance criteria (highlighted in green) are set as $100 \pm 15\%$.

Individual comparison of some key PK parameters for the RES-compound files

Research file	V20R1 B157 as % of V19R1 B96											
	PKPD Parameters							PKPD Profiles				
Compound	CL	CL _{po}	fa	F _G	F _H	F	V _{ss}	C _{max}	t _{max}	AUC	CL	
V17-Docetaxel (IV)	102						100	99	99	99	100	
V17-Methotrexate	99	98	100	100	100	100	101	99	102	99	100	
V17-Paclitaxel_80mgm2 (IV)	101						100	99	100	99	101	
V17-Paclitaxel_135mgm2 (IV)	101						100	99	100	100	101	
V17-Paclitaxel_175mgm2 (IV)	101						100	99	100	100	101	
V17-Propofol (IV)	103						100	106	98	98	101	
V18-Ranitidine	99	97	102	100	100	102	100	101	102	103	95	
V18-Sufasalazine	100	96	102	100	100	102	100	97	106	100	103	
V19-Aprepitant	102	101	100	100	100	100	98	100	100	101	101	
V20-Adefovir (IV)	101						100	99	100	97	102	
V20-Adefovir_DP	99	97	102	100	100	102	100	99	102	97	102	
V20-Benzylpenicilin	101	103	100	99	101	100	100	99	100	99	104	
V20-Chlorzoxazone	CLIV	100	100	100	100	100	100	97	99	96	100	
V20 Pitavastatin	100	98	101	101	100	101	100	100	100	101	97	

The acceptance criteria (highlighted in green) are set as $100 \pm 15\%$.

3. New and updated compounds released in V20

The version comparison exercise highlighted some key differences between compound files in V19 and V20. All of the parameter changes highlighted in the figures and tables above are the result of intended changes in the compound or population file between V19 and V20. The full list of changes in the compound files are listed in Table 31.2.1.1 of the V20 Simcyp Simulator help file.

The **SV-Imipramine**, **SV-Erythromycin**, **SV-Erythromycin_EC**, **SV-Ritonavir_ADAM** and **SV-Ritonavir_FO** files were updated for V20R1. The comparison is therefore between new V20R1 files and corresponding inputs in V19R1 to match the SV-file input values for V20.

New files were released for **SV-Atorvastatin, SV-Cinacalcet, SV-Dexamethasone, SV-Esomeprazole, SV-Lansoprazole, SV-Mirabegron, SV-Nebivolol, and SV-Ondansetron** in V20R1. The comparison is therefore between the new V20R1 file and corresponding inputs in V19R1.

For further detailed information on these updated and new files for V20, please see the Release Notes V20R1 and the corresponding Release Webinar (V20 Compound Files).

The replaced and removed (legacy) files are available on the Consortium Members' Area of the Simcyp website.