Simcyp Population Based Simulator

5/5/2015 6:56

Simcyp Version 13 Release 2 (04/04/2014)

Substrate		Inhibitor 1		Inhibitor 2	
Compound Name	Raloxifene ADAM	Compound Name	Silybin A	Compound Name	Silybin B
Version number	Not applicable	Version number	Not applicable	Version number	Not applicable
Route	Oral	Route	Oral	Route	Oral
Sub : Dose Units	Dose (mg)	Inh 1 : Dose Units	Dose (mg)	Inh 2 : Dose Units	Dose (mg)
Sub : Dose	60.000	Inh 1 : Dose	240.000	Inh 2 : Dose	320.000
Start Day	1.000	Start Day	1.000	Start Day	1.000
Start Time	9h0m	Start Time	9h0m	Start Time	9h0m
Dosing Regimen	Single Dose	Dosing Regimen	Multiple Dose	Dosing Regimen	Multiple Dose
Compound Type	Small Molecule	Dose Interval (h)	8.000	Dose Interval (h)	8.000
		Number of Doses	12.000	Number of Doses	12.000
PhysChem and Blood Binding		Compound Type	Small Molecule	Compound Type	Small Molecule
Mol Weight (g/mol)	510.050	PhysChem and Blood Binding		PhysChem and Blood Binding	
log P	6.860				
Compound Type	Monoprotic Base	Mol Weight (g/mol)	482.440	Mol Weight (g/mol)	482.440
pKa 1	9.980	log P	6.860	log P	6.860
BP Input	User Input	Compound Type	Diprotic Acid	Compound Type	Diprotic Acid
B/P	1.000	pKa 1	6.870	pKa 1	6.870
Haematocrit	45.000	pKa 2	8.900	pKa 2	8.900
fu Input	User	BP Input	User Input	BP Input	User Input
fu	0.050	B/P	1.000	B/P	1.000
Reference Binding Component	HSA	Haematocrit	45.000	Haematocrit	45.000
Protein Reference Conc (g/L)	45.000	fu Input	User	fu Input	User
% Bound to Lipoprotein	0.000	fu	0.050	fu	0.050
% Bound to Lipoprotein (CV %)	0.000	Reference Binding Component	HSA	Reference Binding Component	HSA
		Protein Reference Conc (g/L)	45.000	Protein Reference Conc (g/L)	45.000
Absorption		% Bound to Lipoprotein	0.000	% Bound to Lipoprotein	0.000
		% Bound to Lipoprotein (CV %)	0.000	% Bound to Lipoprotein (CV %)	0.000
Absorption Model	ADAM				
Input Type	Predicted	Absorption		Absorption	
fu(Gut)	0.050				
Peff,man Type	Regional	Absorption Model	1st order	Absorption Model	1st order
Permeability Assay	Papp	Input Type	Entered	Input Type	Entered
Activity	Passive	fa	1.000	fa	1.000
Value	8.000	CV fa (%)	30.000	CV fa (%)	30.000
Slope	0.752	ka (1/h)	0.500	ka (1/h)	2.000
Intercept	-0.544	CV ka (%)	30.000	CV ka (%)	30.000
Degradation Rate Stomach (1/h)	0.000	lag time (h)	0.000	lag time (h)	0.000
Degradation Rate Duodenum (1/h)	0.000	CV lag time (%)	30.000	CV lag time (%)	30.000
Degradation Rate Jejunum I (1/h)	0.000	fu(Gut)	1.000	fu(Gut)	1.000
Degradation Rate Jejunum II (1/h)	0.000	Q(Gut) Input	User	Q(Gut) Input	User
Degradation Rate Ileum I (1/h)	0.000	Q(Gut) (L/h)	7.600	Q(Gut) (L/h)	7.600
Degradation Rate Ileum II (1/h)	0.000	CV Q(Gut) (%)	30.000	CV Q(Gut) (%)	30.000
Degradation Rate Ileum III (1/h)	0.000	Peff,man Type	n/a	Peff,man Type	n/a
Degradation Rate Ileum IV (1/h)	0.000	Permeability Assay	Physicochemical	Permeability Assay	Physicochemical
Degradation Rate Colon (1/h)	0.000	PSA(Å²)	50.000	PSA(Å²)	50.000
Input Form	Solid Formulation	HBD	0.000	HBD	0.000
Formulation	Immediate Release (IR)				
Dissolution Type	Solubility	Distribution		Distribution	
Solubility pH Type	Intrinsic				
Solubility (mg/mL)	0.050	Distribution Model	Full PBPK Model	Distribution Model	Minimal PBPK Model
Precipitation Rate Const. (1/h)	4.000	Replacement Organ?	No	SAC kin (1/h)	0.000
Maximum Supersaturation Ratio	10.000	Organ Replaced	n/a	SAC kout (1/h)	0.000
Solubility Factor 1	1000.000	User-defined Additional Organ	No	SAC CLin (L/h)	0.000
Dispersion Type	Monodispersed	Type	n/a	SAC CLout (L/h)	0.000
Radius (µm)	10.000	Vss mode	Predicted	Volume [Vsac] (L/kg)	1.00E-05
Particle density (g/mL)	1.200	Prediction Method	Method 1	Vss mode	Predicted
Diffusion coeff. type	Predicted	Concentration-dependent volume	No	Prediction Method	Method 1
Diffusion coeff, ionised (10-4 cm2/min)	3.685	log Po:w	6.860	Concentration-dependent volume	No
Diffusion coeff, micelle (10-4 cm2/min) mean	0.780	fut switch	Predicted	log Po:w	6.860
Diffusion coeff, micelle CV (%)	20.000	fut value	0.095	fut switch	Predicted
Diffusion coeff. (10E-4 cm²/min)	3.685	logDvo:w (pH=7.4) switch	Predicted	fut value	0.095
Effective diffusion layer thickness (µm)	10.000	logDvo:w (pH=7.4) value	5.643	logDvo:w (pH=7.4) switch	Predicted
Bile Micelle mediated solubilisation	On	logP vo:w	Predicted	logDvo:w (pH=7.4) value	5.643
Bile solubilisation: type	Predicted	logP vo:w value	6.299	logP vo:w	Predicted
Bile Micelle Partition: Slope	0.740	Compound Type	Diprotic Acid	logP vo:w value	6.299
Bile Micelle Partition: Offset	2.290	pKa 1	6.870	Compound Type	Diprotic Acid
Bile Micelle Partition: Ionised Species Correction	1.000	pKa 2	8.900	pKa 1	6.870
		B/P	1.000	pKa 2	8.900
Distribution		Haematocrit	45.000	B/P	1.000
		fu	0.050	Haematocrit	45.000
Distribution Model	Full PBPK Model	Adipose Input Type	Predicted	fu	0.050
Replacement Organ?	No	Adipose Value	11.526	Adipose Input Type	Predicted
Organ Replaced	n/a	Bone Input Type	Predicted	Adipose Value	11.526
User-defined Additional Organ	No	Bone Value	17.857	Bone Input Type	Predicted
Type	n/a	Brain Input Type	Predicted	Bone Value	17.857
Vss mode	Predicted	Brain Value	16.324	Brain Input Type	Predicted
Prediction Method	Method 2	Gut Input Type	Predicted	Brain Value	16.324
Concentration-dependent volume	No	Gut Value	12.874	Gut Input Type	Predicted
log Po:w	6.860	Heart Input Type	Predicted	Gut Value	12.874
logP vo:w	Predicted	Heart Value	3.959	Heart Input Type	Predicted
logP vo:w value	6.299	Kidney Input Type	Predicted	Heart Value	3.959
Compound Type	Monoprotic Base	Kidney Value	6.141	Kidney Input Type	Predicted
pKa 1	9.980	Liver Input Type	Predicted	Kidney Value	6.141
B/P	1.000	Liver Value	10.177	Liver Input Type	Predicted
Haematocrit	45.000	Lung Input Type	Predicted	Liver Value	10.177
fu	0.050	Lung Value	1.370	Lung Input Type	Predicted
Adipose Input Type	Predicted	Muscle Input Type	Predicted	Lung Value	1.370

Trial Design	
Use Pop Representative	No
Population Size	16.000
Number of Trials	1.000
No of Subjects per Trial	16.000
Population name	Sim-Healthy Volunteers
Version number	13.1.1
Minimum Age (years)	18.000
Maximum Age (years)	65.000
Propn. of Females	0.500
Fasted/Fed	Fasted
Fluid intake with dose (mL)	250.000
Fluid intake with dose CV (%)	30.000
PKPD Parameters	On
PKPD Profiles	On
Start Day/Time	Day 1, 09:00
End Day/Time	Day 5, 09:00
Study Duration (h)	96.000
Sub : Route	Oral
Sub : Dose Units	Dose (mg)
Sub : Dose	60.000
Inh 1 : Route	Oral
Inh 1 : Dose Units	Dose (mg)
Inh 1 : Dose	240.000
Inh 2 : Route	Oral
Inh 2 : Dose Units	Dose (mg)
Inh 2 : Dose	320.000
Random Generator	Simcyp Linear Congruential Generator
Seed	Fixed
Seed Value	1.000
Output sampling interval (h)	0.050
Memory Size	1140457472.000
Number of time samples	200.000
Solubility Cap (mg/mL)	500.000
Differential Solver	5th-order Runge-Kutta
Maximum number of steps	1000000.000
Relative Tolerance	0.000
Relative Tolerance when ADAM is used	0.000
Integration error tolerance	0.020
Paediatric Module	Not Loaded
No. Differential Equations	560.000

Software Version Detail	
Simulation Duration(seconds)	28.000
Windows Version	Version 5.1 (Build 2600: Service Pack 3)
Source File Location	C:\Program Files (x86)\Simcyp\Simcyp Simulator V13
Data Path Location	C:\Users\Public\Documents
Excel Embedded Workspace	Yes
Simcyp.exe	
File Version	13.2.89.0
Date Modified	04/04/2014
File Size (bytes)	8291328
BayesianPluginV13.dll	
File Version	12.0.88.0
Date Modified	04/04/2014
File Size (bytes)	559104
Common.dll	
File Version	1.0.0.2
Date Modified	04/04/2014
File Size (bytes)	78336
CompoundImportBackendV13.dll	
File Version	11.1.88.0
Date Modified	04/04/2014
File Size (bytes)	239104
DBSupportLib.dll	
File Version	13.2.89.0
Date Modified	04/04/2014
File Size (bytes)	156160
DataStore13.dll	
File Version	13.2.89.0
Date Modified	04/04/2014
File Size (bytes)	2430976
EPPlus.dll	
File Version	3.0.0.2
Date Modified	04/04/2014
File Size (bytes)	459776
lua5.1.dll	
File Version	
Date Modified	04/04/2014
File Size (bytes)	167936
lua51.dll	
File Version	
Date Modified	04/04/2014
File Size (bytes)	11264
Login name	BRANDON-PC\fishe_000
Computer name	BRANDON-PC
Licence type	Desktop
Key	AALJIJHKAINJJCBOAI
Expiry	1082015
Login name	BRANDON-PC\fishe_000
Computer name	BRANDON-PC
Licence type	Desktop
Key	AALJIJHKAINJJCBOAI
Expiry	1082015

Adipose Value	20162.971	Muscle Value	6.237	Muscle Input Type	Predicted
Bone Input Type	Predicted	Skin Input Type	Predicted	Muscle Value	6.237
Bone Value	6900.634	Skin Value	7.623	Skin Input Type	Predicted
Brain Input Type	Predicted	Spleen Input Type	Predicted	Skin Value	7.623
Brain Value	6308.783	Spleen Value	6.256	Spleen Input Type	Predicted
Gut Input Type	Predicted	Pancreas Input Type	Predicted	Spleen Value	6.256
Gut Value	4975.530	Pancreas Value	10.520	Pancreas Input Type	Predicted
Heart Input Type	Predicted	Kp Scalar Value	1.000	Pancreas Value	10.520
Heart Value	1530.570			Kp Scalar Value	1.000
Kidney Input Type	Predicted	Elimination			
Kidney Value	2373.532			Elimination	
Liver Input Type	Predicted	Allometric Scaling	Not Used		
Liver Value	3933.148			Allometric Scaling	Not Used
Lung Input Type	Predicted	Clearance Type	Enzyme Kinetics		
Lung Value	529.886	Fl Correction	Not used	Clearance Type	Enzyme Kinetics
Muscle Input Type	Predicted	PLR Correction	Not Used	Fl Correction	Not used
Muscle Value	2410.778	In vitro metabolic system	Recombinant	PLR Correction	Not Used
Skin Input Type	Predicted			In vitro metabolic system	Recombinant
Skin Value	2945.971	Pathway 1	0.000		
Spleen Input Type	Predicted	Enzyme	UGT1A8	Pathway 1	0.000
Spleen Value	2418.152	Vmax	760.000	Enzyme	UGT1A8
Pancreas Input Type	Predicted	Km	55.000	Vmax	940.000
Pancreas Value	4065.971	fu mic	1.000	Km	39.000
Kp Scalar Value	10.000			fu mic	1.000
		Pathway 1	0.000		
Elimination		Enzyme	UGT1A10	Pathway 1	0.000
		Vmax	2000.000	Enzyme	UGT1A10
Allometric Scaling	Not Used	Km	33.000	Vmax	14000.000
		fu mic	1.000	Km	81.000
Clearance Type	Enzyme Kinetics			fu mic	1.000
Fl Correction	Not used	Feed formed renal metabolite into kidney	No		
PLR Correction	Not Used			Feed formed renal metabolite into kidney	No
In vitro metabolic system	Recombinant	Use Allelic variants for Enzyme 1	No		
		Enzyme	CYP2C9	Use Allelic variants for Enzyme 1	No
Pathway 1	1.000			Enzyme	CYP2C9
Enzyme	UGT1A8	Use Allelic variants for Enzyme 2	No		
Vmax	550.000	Enzyme	CYP1A2	Use Allelic variants for Enzyme 2	No
Km	5.500			Enzyme	CYP1A2
fu mic	0.500	Human intestine preparation method	HIMms		
rUGTSystem	User	Additional HIM ms CLint	71.000	Ontogeny Profile	No Profile Used
rUGTScalar - Liver	0.000	Additional HIM ms CV (%)	30.000	Biliary CLint (Hep) (µL/min/10^6)	0.000
rUGTScalar - Intestine	3.000	Additional HIM ms fumic	1.000	CV Biliary CLint (Hep) (%)	30.000
rUGTScalar - Kidney	0.000	Ontogeny Profile	No Profile Used	Ontogeny Profile	No Profile Used
		Biliary CLint (Hep) (µL/min/10^6)	0.000	Active Uptake into Hepatocyte	1.000
Pathway 1	1.000	CV Biliary CLint (Hep) (%)	30.000	CL R (L/h)	0.000
Enzyme	UGT1A10	Ontogeny Profile	No Profile Used		
Vmax	1100.000	Active Uptake into Hepatocyte	1.000	CYPs and/or UGTs Interaction	
Km	0.870	CL R (L/h)	0.000		
fu mic	0.500			Enzyme	UGT1A1
rUGTSystem	User	CYPs and/or UGTs Interaction		Ki (µM)	3.300
rUGTScalar - Liver	0.000			fu mic	0.900
rUGTScalar - Intestine	3.000	Enzyme	UGT1A1		
rUGTScalar - Kidney	0.000	Ki (µM)	5.000	Enzyme	UGT1A3
		fu mic	0.900	Ki (µM)	2.800
Pathway 1	2.000			fu mic	0.900
Enzyme	UGT1A9	Enzyme	UGT1A3		
Vmax	110.000	Ki (µM)	4.200	Enzyme	UGT1A8
Km	1.500	fu mic	0.900	Ki (µM)	47.000
fu mic	0.500			fu mic	0.900
rUGTSystem	User	Enzyme	UGT1A8		
rUGTScalar - Liver	0.000	Ki (µM)	40.000	Enzyme	UGT1A9
rUGTScalar - Intestine	3.000	fu mic	0.900	Ki (µM)	19.000
rUGTScalar - Kidney	0.000			fu mic	0.900
		Enzyme	UGT1A9		
Pathway 1	2.000	Ki (µM)	67.000	Enzyme	UGT1A10
Use User UGT Option	Yes	fu mic	0.900	Ki (µM)	74.000
UGT User	1			fu mic	0.900
Enzyme	User UGT1A10	Enzyme	UGT1A10		
Ontogeny Profile	No Profile Used	Ki (µM)	79.000	Use User UGT Option	Yes
Vmax	130.000	fu mic	0.900	UGT User	1
Km	0.960			Enzyme	User UGT1A10
fu mic	0.500	Use User UGT Option	Yes	Ki (µM)	65.000
rUGTSystem	User	UGT User	1	fu mic	1.000
rUGTScalar - Liver	0.000	Enzyme	User UGT1A10		
rUGTScalar - Intestine	3.000	Ki (µM)	72.000		
rUGTScalar - Kidney	0.000	fu mic	0.900		
Pathway 1	1.000	Transport			
Enzyme	UGT1A1				
Vmax	88.000				
Km	4.300				
fu mic	0.500				
rUGTSystem	User				
rUGTScalar - Liver	3.000				
rUGTScalar - Intestine	3.000				
rUGTScalar - Kidney	1.000				
Pathway 1	2.000				
Enzyme	UGT1A3				
Vmax	92.000				
Km	3.600				
fu mic	0.500				
rUGTSystem	User				
rUGTScalar - Liver	3.000				
rUGTScalar - Intestine	3.000				

rUGTScalar - Kidney	1.000
Feed formed renal metabolite into kidney	No
Use Allelic variants for Enzyme 1	No
Enzyme	CYP2C9
Use Allelic variants for Enzyme 2	No
Enzyme	CYP1A2
Ontogeny Profile	No Profile Used
Biliary CLint (Hep) (µL/min/10^6)	0.000
CV Biliary CLint (Hep) (%)	30.000
Ontogeny Profile	No Profile Used
Percentage available for re-absorption (%)	100.000
Active Uptake into Hepatocyte	1.000
CL R (L/h)	0.000
Transport	
Assume Colon SS	No