Supplemental Materials

Supplemental 1. Some key systems parameters for Chinese in Simcyp® version 18

CYP Phenotype

CYP enzymes	EM (Frequency)	PM (Frequency)	IM (Frequency)	UM (Frequency)
CYP2C9	0.998	0.002	0	0
CYP2C19	0.87	0.13	0	0
CYP2D6	0.597	0.003	0.39	0.01
CYP3A4	1	0	0	0

Liver Enzyme abundance (pmol/mg-protein)

CYP enzymes	EM	PM	IM	UM
CYP2C9	60	24	0	0
CYP2C19	8	0	0	0
CYP2D6	10.5	0	3.9	20.9
CYP3A4	120	0	0	0

GFR (mL/min)

Gender	Reference value 20 ~ 30 years old
Male	130
Female	120

Supplemental 2. Some key systems parameters for Japanese in Simcyp® version 18

CYP Phenotype

CYP enzymes	EM (Frequency)	PM (Frequency)	IM (Frequency)	UM (Frequency)
CYP2C9	0.992	0.008	0	0
CYP2C19	0.82	0.18	0	0
CYP2D6	0.75	0.004	0.23	0.016
CYP3A4	1	0	0	0

Liver Enzyme abundance (pmol/mg-protein)

CYP enzymes	EM	PM	IM	UM
CYP2C9	59.2	23.5	0	0
CYP2C19	4.1	0	0	0
CYP2D6	10.5	0	3.9	20.9
CYP3A4	112.2	0	0	0

GFR (mL/min)

Gender	Reference value 20 ~ 30 years old
Male	130
Female	120

CYP: cytochrome P450; EM: extensive metabolizer; GFR: glomerular filtration rate; IM: intermediate metabolizer; PM: poor metabolizer; UM: ultra metabolizer.

Supplemental 3. Some key systems parameters for Japanese in Simcyp® version 19

CYP Phenotype

CYP enzymes	EM (Frequency)	PM (Frequency)	IM (Frequency)	UM (Frequency)
CYP2C9	0.992	0.008	0	0
CYP2C19	0.817	0.172	0	0
CYP2D6	0.74	0.004	0.24	0.016
CYP3A4	1	0	0	0

Liver Enzyme abundance (pmol/mg-protein)

CYP enzymes	EM	PM	IM	UM
CYP2C9	59.2	23.5	0	0
CYP2C19	4.4	0	0	8.7
CYP2D6	10.5	0	3.3	20.9
CYP3A4	112.2	0	0	0

GFR (mL/min)

Gender	Reference value 20 ~ 30 years old
Male	130
Female	120

CYP: cytochrome P450; EM: extensive metabolizer; GFR: glomerular filtration rate; IM: intermediate metabolizer; PM: poor metabolizer; UM: ultra metabolizer.

Supplemental 4. Some key systems parameters for Healthy Volunteer in Simcyp® version 18

CYP Phenotype

CYP enzymes	EM (Frequency)	PM (Frequency)	IM (Frequency)	UM (Frequency)
CYP2C9	0.94	0.06	0	0
CYP2C19	0.976	0.024	0	0
CYP2D6	0.865	0.082	0	0.053
CYP3A4	1	0	0	0

Liver Enzyme abundance (pmol/mg-protein)

CYP enzymes	EM	PM	IM	UM
CYP2C9	73	29	0	0
CYP2C19	14	0	0	0
CYP2D6	8	0	0	16
CYP3A4	137	0	0	0

GFR (mL/min)

Gender	Reference value 20 ~ 30 years old
Male	130
Female	120

CYP: cytochrome P450; EM: extensive metabolizer; GFR: glomerular filtration rate; IM: intermediate metabolizer; PM: poor metabolizer; UM: ultra metabolizer.

Supplemental 5. Some key systems parameters for Healthy Volunteer in Simcyp® version 19

CYP Phenotype

CYP enzymes	EM (Frequency)	PM (Frequency)	IM (Frequency)	UM (Frequency)
CYP2C9	0.94	0.06	0	0
CYP2C19	0.59	0.092	0	0.318
CYP2D6	0.865	0.082	0	0.053
CYP3A4	1	0	0	0

Liver Enzyme abundance (pmol/mg-protein)

CYP enzymes	EM	PM	IM	UM
CYP2C9	73	29	0	0
CYP2C19	4.4	0	0	8.7
CYP2D6	9.4	0	0	18.8
CYP3A4	137	0	0	0

GFR (mL/min)

Gender	Reference value 20 ~ 30 years old
Male	130
Female	120

CYP: cytochrome P450; EM: extensive metabolizer; GFR: glomerular filtration rate; IM: intermediate metabolizer; PM: poor metabolizer; UM: ultra metabolizer.

Supplemental 6A. Drug A Input Parameters for SimCYP Simulation

Parameters	Value
Molecular weight (g/mol)	263.4
LogP	0.21
Compound type	Monoprotic base
pK_a	8.34
Fu_{plasma}	0.705
B/P ratio	1.1
Fa	0.95
k_a (h^{-1})	0.171
T_{lag} (h)	0.1
Fu_{gut}	1
Q_{gut} (L/h)	11.6
V_{ss} (L/kg)	3.4
CL_{int} (CYP3A4), $\mu L \cdot min^{-1} \cdot pmol^{-1}$	0.00325
CL_{int} (Other HLM), $\mu L \cdot min^{-1} \cdot mg^{-1}$	3.789
CL_r (L/h)	11.1

Supplemental 6B. Predicted and Observed PK Parameters of Drug A In Westerner, Chinese, and Japanese

Population/Dose		C_{max} (ng/mL)	AUC_{inf} (ng*h/mL)	$t_{1/2}$ (h)	C_{trough} (ng/mL)
Westerner	**Observed**	**158**	**3931**	**9.23**	**NA**
(100 mg PO)	**Predicted**	**157.5**	**3946**	**9.40**	**NA**
Chinese	**Observed**	**259.8**	**5710**	**8.71**	**NA**
(100 mg PO)	**Predicted**	**193.4**	**4478**	**8.49**	**NA**
Japanese	**Observed**	**233**	**5541**	**9.48**	**NA**

(100 mg PO)	**Predicted**	**209**	**4280**	**7.07**	**NA**

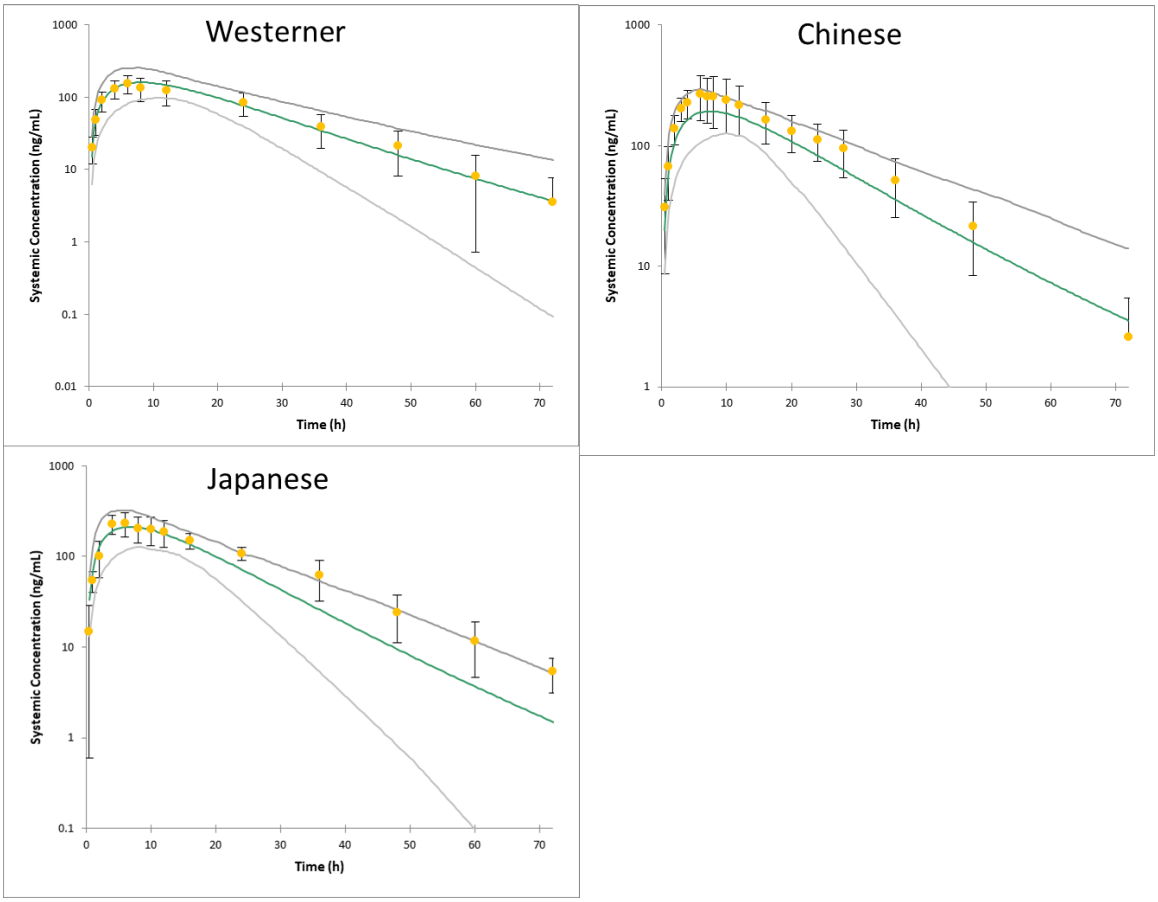
C_{max} and AUC_{inf} are reported as geometric mean; $t_{1/2}$ is reported as arithmetic mean.

Supplemental 6C. Ratios of Predicted and Observed PK Parameters of Drug A In Chinese and Japanese vs Westerner

	Chinese vs Westerner			**Japanese vs Westerner**		
	Pred_C/Pred_W	**Obs_C/Obs_W**	**Ratio**	**Pred_J/Pred_W**	**Obs_J/Obs_W**	**Ratio**
C_{max}	**1.23**	**1.64**	**0.75**	**1.33**	**1.47**	**0.90**
AUC_{inf}	**1.13**	**1.45**	**0.78**	**1.08**	**1.41**	**0.77**
$t_{1/2}$	**0.90**	**0.94**	**0.96**	**0.75**	**1.03**	**0.73**
C_{trough}	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**

Obs_C, Obs_J and Obs_W are observed in Chinese, Japanese, and Westerner, respectively; Pred_C, Pred_J, and Pred_W are predicted in Chinese, Japanese, and Westerner, respectively; Ratio is (Pred_C/Pred_W)/(Obs_C/Obs_W) and (Pred_J/Pred_W)/(Obs_J/Obs_W), respectively.

Supplemental 6D. Predicted and Observed PK Profiles of Drug A In Westerner, Chinese, and Japanese



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 7A. Drug B Input Parameters for SimCYP Simulation

Parameters	Value
Molecular weight (g/mol)	447.54

LogP	0.99
Compound type	Diprotic base
pK_a1	7.3
pK_a2	4.1
Fu_{plasma}	0.147
B/P ratio	1.63
Fa	0.85
k_a (h^{-1})	0.12
T_{lag} (h)	1.66
Fu_{gut}	0.73
Q_{gut} (L/h)	11.28
V_{ss} (L/kg)	14.3
CL_{int} (CYP3A4), $\mu L \cdot min^{-1} \cdot pmol^{-1}$	0.44
CL_{int} (Other HLM), $\mu L \cdot min^{-1} \cdot mg^{-1}$	37.65
CL_r (L/h)	6.6
CYP3A4 inhibition K_{app} (μM) k_{inact} (1/h)	-- 10 2.16

Supplemental 7B. Predicted and Observed PK Parameters of Drug B In Westerner, Chinese, and Japanese

Population/Dose		**C_{max} (ng/mL)**	**AUC_{inf} (ng*h/mL)**	**$t_{1/2}$ (h)**	**C_{trough} (ng/mL)**
Westerner	**Observed**	**46.8**	**1447**	**24.54**	**64.9**
(125 mg PO)	**Predicted**	**47.98**	**1744**	**20.48**	**61.51**
Chinese	**Observed**	**83.1**	**2416**	**27.26**	**67.55**
(125 mg PO)	**Predicted**	**70.8**	**2616**	**22.58**	**105.77**
Japanese	**Observed**	**65.4**	**2018**	**23.48**	**79.5**
(125 mg PO)	**Predicted**	**51.4**	**2123**	**25.61**	**83.39**

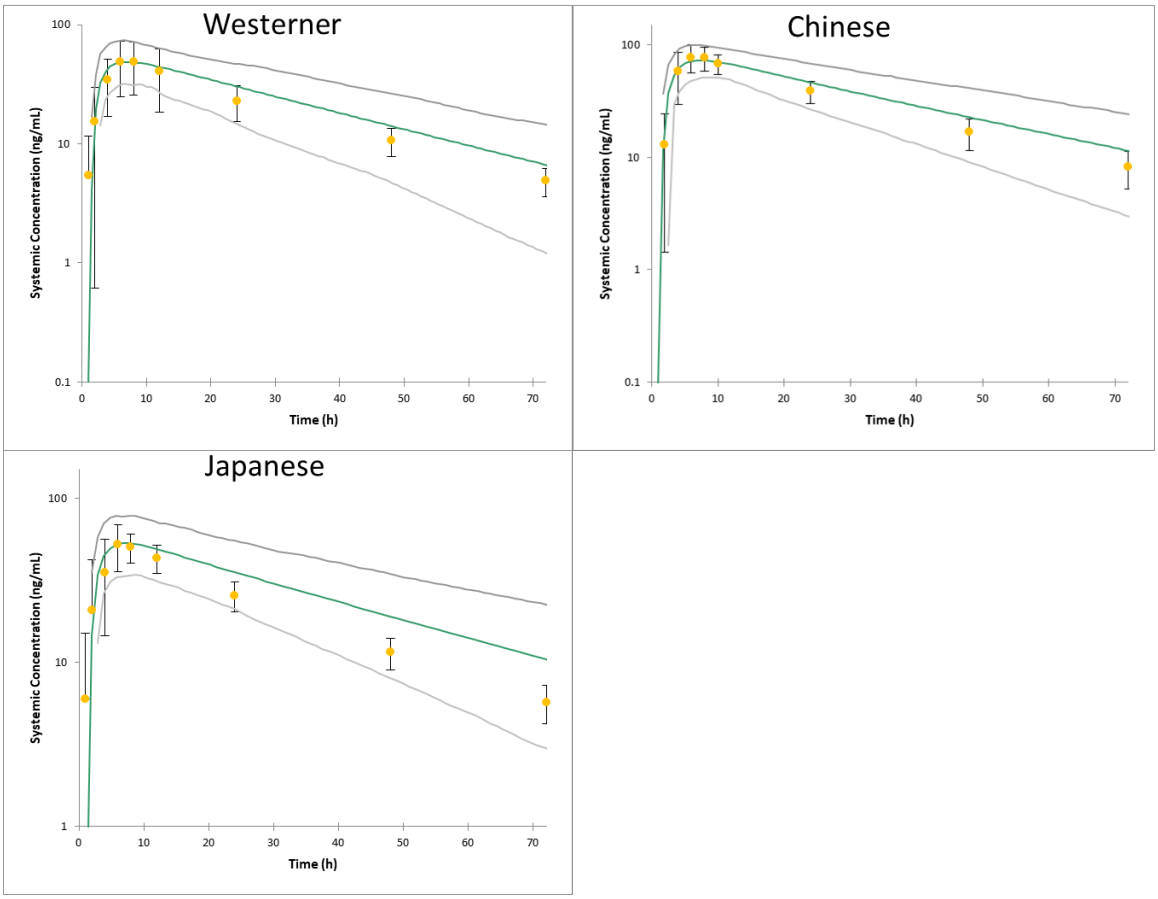
C_{max}, C_{trough}, and AUC_{inf} are reported as geometric mean; $t_{1/2}$ is reported as arithmetic mean; Steady state C_{trough} is derived from multiple daily doses of Drug B at 125 mg PO.

Supplemental 7C. Ratios of Predicted and Observed PK Parameters of Drug B In Chinese and Japanese vs Westerner

	Chinese vs Westerner			**Japanese vs Westerner**		
	Pred_C/Pred_W	**Obs_C/Obs_W**	**Ratio**	**Pred_J/Pred_W**	**Obs_J/Obs_W**	**Ratio**
C_{max}	**1.48**	**1.78**	**0.83**	**1.07**	**1.40**	**0.76**
AUC_{inf}	**1.5**	**1.67**	**0.90**	**1.22**	**1.39**	**0.88**
$t_{1/2}$	**1.10**	**1.11**	**0.99**	**1.25**	**0.96**	**1.3**
C_{trough}	**1.72**	**1.04**	**1.65**	**1.36**	**1.22**	**1.11**

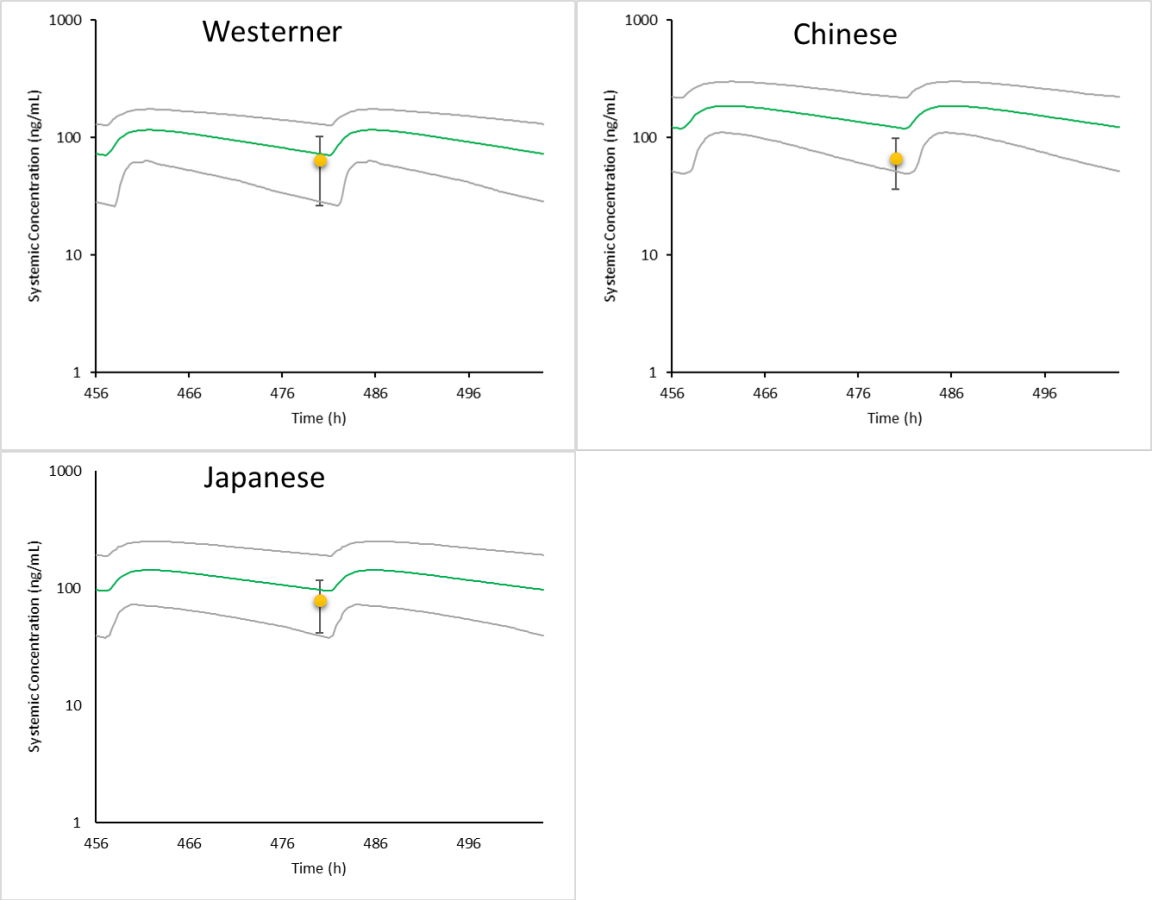
Obs_C, Obs_J and Obs_W are observed in Chinese, Japanese, and Westerner, respectively; Pred_C, Pred_J, and Pred_W are predicted in Chinese, Japanese, and Westerner, respectively; Ratio is (Pred_C/Pred_W)/(Obs_C/Obs_W) and (Pred_J/Pred_W)/(Obs_J/Obs_W), respectively.

Supplemental 7D. Predicted and Observed PK Profiles of Drug B In Westerner, Chinese, and Japanese



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 7E. Predicted and Observed Ctrough of Drug B In Westerner, Chinese, and Japanese After Multiple Doses



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 8A. Drug C Input Parameters for SimCYP Simulation

Parameters	Value
Molecular weight (g/mol)	470
LogP	5.3
Compound type	Diprotic base

pK_a1	5.03
pK_a2	8.46
Fu_{plasma}	0.0192
B/P ratio	1.08
Fa	1
k_a (h^{-1})	0.2
Human Peff ($x10^{-4}$ cm/s)	1.06
V_{ss} (L/kg)	25
V_{max} (CYP2D6), $\mu L \cdot min^{-1} \cdot mg^{-1}$	0.28
K_m (CYP2D6), µM	0.0637
CL_{int} (CYP2C9), $\mu L \cdot min^{-1} \cdot mg^{-1}$	3.5
CL_{int} (CYP3A4), $\mu L \cdot min^{-1} \cdot mg^{-1}$	23
CL_{int} (Other HLM), $\mu L \cdot min^{-1} \cdot mg^{-1}$	33
Biliary CL_{int}, $\mu L \cdot min^{-1} \cdot million^{-1}$	30.4
CL_r (L/h)	0.28
Additional system CL (L/h)	8.2
CYP3A4 Ki (µM)	8
CYP2D6 Ki (µM)	0.032

Supplemental 8B. Predicted and Observed PK Parameters of Drug C In Westerner, Chinese, and Japanese

Population/Dose		**C_{max} (ng/mL)**	**AUC_{inf} (ng*h/mL)**	**$t_{1/2}$ (h)**	**C_{trough} (ng/mL)**
Westerner	**Observed**	**17.8**	**1234**	**67.2**	**64.32**

(45 mg PO)	**Predicted**	**16.52**	**1545**	**65.56**	**66.6**
Chinese	**Observed**	**21.5**	**1669**	**62.66**	**NA**
(45 mg PO)	**Predicted**	**18.85**	**1865**	**63.77**	**NA**
Japanese	**Observed**	**17.6**	**1541**	**80.03**	**64.9**
(45 mg PO)	**Predicted**	**21.4**	**2012**	**58.07**	**79.21**

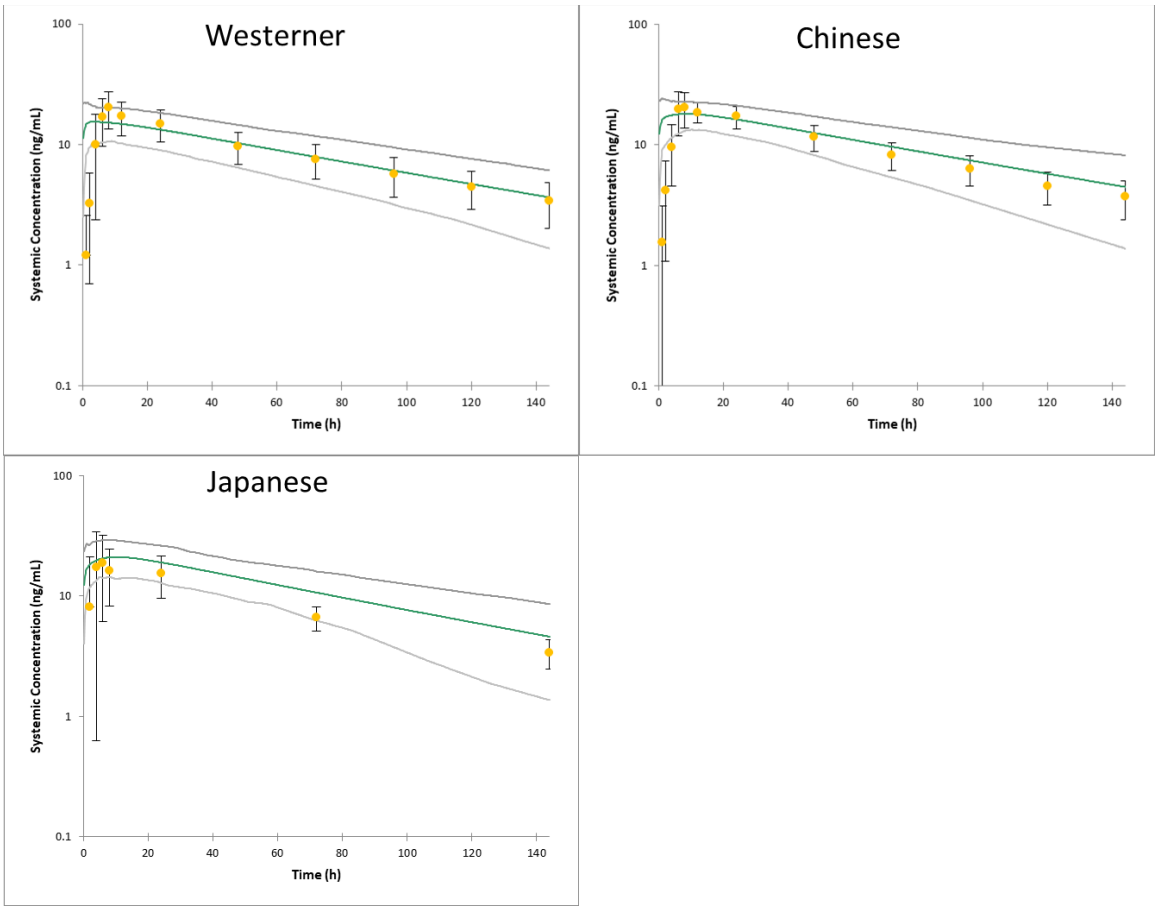
C_{max}, C_{trough}, and AUC_{inf} are reported as geometric mean; $t_{1/2}$ is reported as arithmetic mean; steady state C_{trough} is derived from multiple daily doses of Drug C at 45 mg PO.

Supplemental 8C. Ratios of Predicted and Observed PK Parameters of Drug C In Chinese and Japanese vs Westerner

	Chinese vs Westerner			**Japanese vs Westerner**		
	Pred_C/Pred_W	**Obs_C/Obs_W**	**Ratio**	**Pred_J/Pred_W**	**Obs_J/Obs_W**	**Ratio**
C_{max}	**1.14**	**1.21**	**0.94**	**1.21**	**1.35**	**0.90**
AUC_{inf}	**1.21**	**1.35**	**0.90**	**1.30**	**1.25**	**1.04**
$t_{1/2}$	**0.97**	**0.93**	**1.04**	**0.89**	**1.19**	**0.75**
C_{trough}	**NA**	**NA**	**NA**	**1.19**	**1.01**	**1.18**

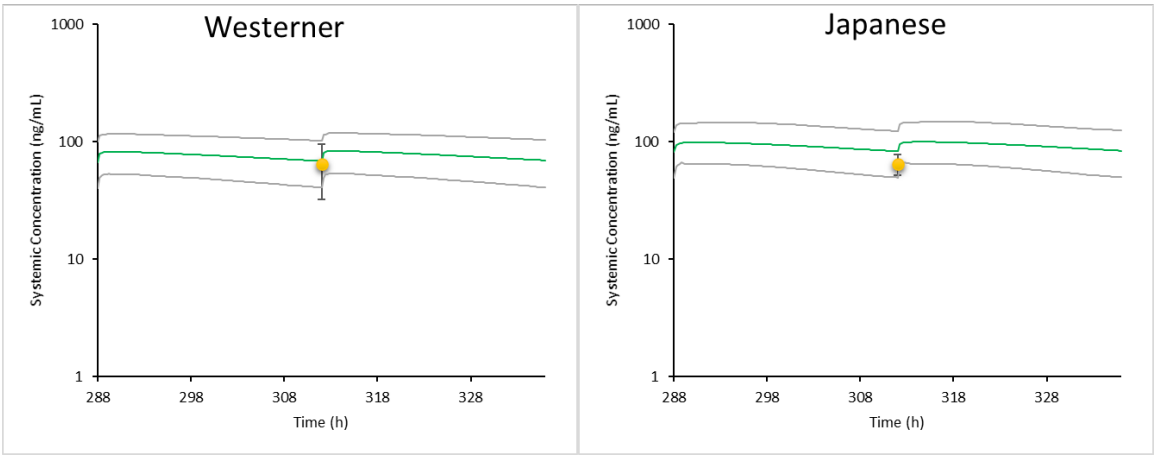
Obs_C, Obs_J and Obs_W are observed in Chinese, Japanese, and Westerner, respectively; Pred_C, Pred_J, and Pred_W are predicted in Chinese, Japanese, and Westerner, respectively; Ratio is (Pred_C/Pred_W)/(Obs_C/Obs_W) and (Pred_J/Pred_W)/(Obs_J/Obs_W), respectively.

Supplemental 8D. Predicted and Observed PK Profiles of Drug C In Westerner, Chinese, and Japanese



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 8E. Predicted and Observed Ctrough of Drug C In Westerner, and Japanese After Multiple Doses



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 9A. Drug D Input Parameters for SimCYP Simulation

Parameters	**Value**
Molecular weight (g/mol)	159.23
LogP	-1.35
Compound type	Ampholyte
pK_a1	4.2
pK_a2	10.6
Fu_{plasma}	1
B/P ratio	0.86
Fa	1
k_a (h^{-1})	4.18
T_{lag} (h)	0.166
Fu_{gut}	1
Q_{gut} (L/h)	10

V_{ss} (L/kg)	0.52
CL_{int} (Other HLM), $\mu L \cdot min^{-1} \cdot mg^{-1}$	0.0073
CL_r (L/h)	4.37

Supplemental 9B. Predicted and Observed PK Parameters of Drug D In Westerner, Chinese, and Japanese

Population/Dose		**C_{max} (ng/mL)**	**AUC_{inf} (ng*h/mL)**	**$t_{1/2}$ (h)**	**C_{trough} (ng/mL)**
Westerner	**Observed**	**2.95**	**21.9**	**6.10**	**1.967**
(100 mg PO)	**Predicted**	**2.33**	**21.74**	**5.70**	**1.63**
Chinese	**Observed**	**2.1**	**14.4**	**5.20**	**NA**
(75 mg PO)	**Predicted**	**2.02**	**16.1**	**5.12**	**NA**
Japanese	**Observed**	**5.0**	**32.1**	**5.82**	**1.28**
(150 mg PO)	**Predicted**	**3.84**	**37.1**	**6.52**	**1.39**

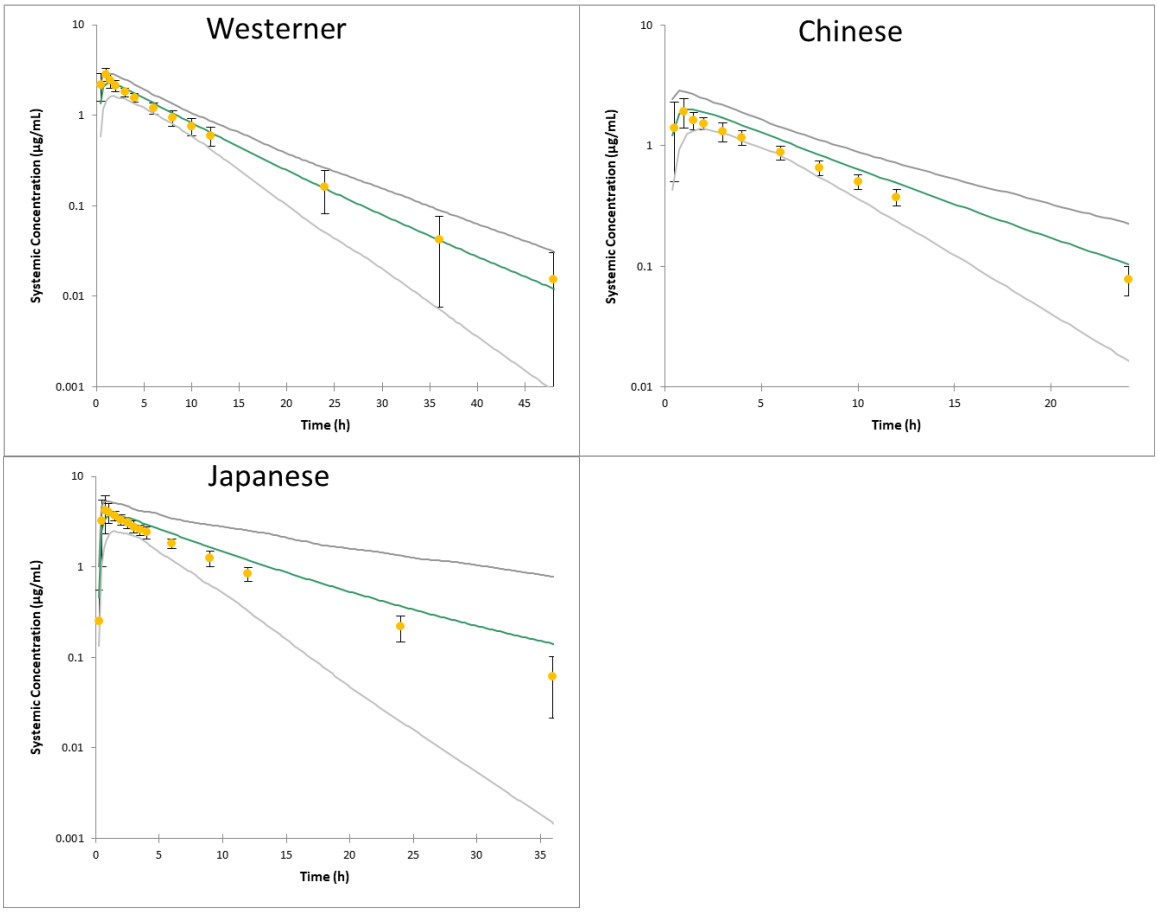
C_{max}, C_{trough}, and AUC_{inf} are reported as geometric mean; $t_{1/2}$ is reported as arithmetic mean; steady state C_{trough} is derived from multiple dose of Drug D at 100 mg PO three times a day in Westerner, and 150 mg PO twice a day in Japanese.

Supplemental 9C. Ratios of Predicted and Observed PK Parameters of Drug D In Chinese and Japanese vs Westerner

	Chinese vs Westerner			Japanese vs Westerner		
	Pred_C/Pred_W	Obs_C/Obs_W	Ratio	Pred_J/Pred_W	Obs_J/Obs_W	Ratio
C_{max}	0.87	0.71	1.23	1.65	1.69	0.98
AUC_{inf}	0.74	0.66	1.12	1.71	1.47	1.16
$t_{1/2}$	0.90	0.85	1.06	1.14	0.95	1.2
C_{trough}	NA	NA	NA	0.85	0.65	1.31

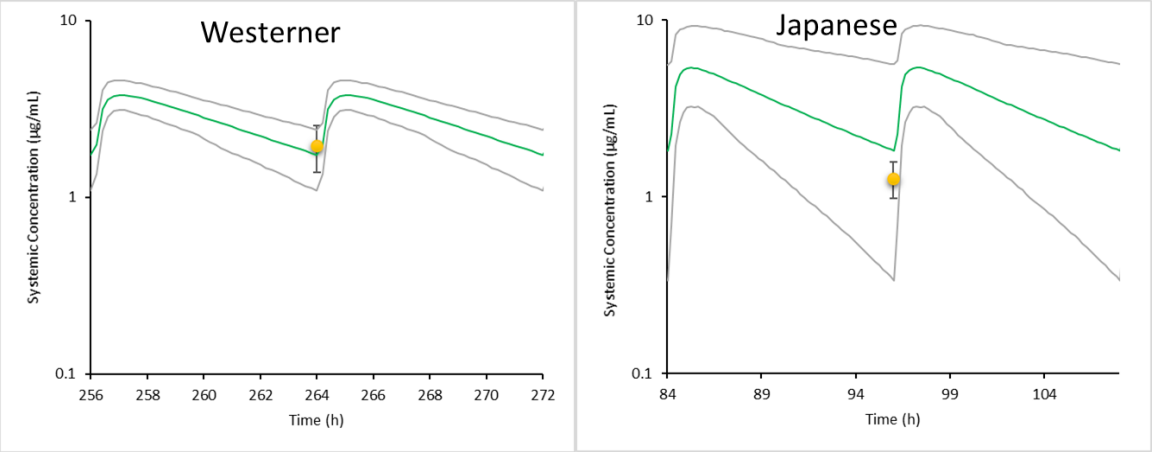
Obs_C, Obs_J and Obs_W are observed in Chinese, Japanese, and Westerner, respectively; Pred_C, Pred_J, and Pred_W are predicted in Chinese, Japanese, and Westerner, respectively; Ratio is (Pred_C/Pred_W)/(Obs_C/Obs_W) and (Pred_J/Pred_W)/(Obs_J/Obs_W), respectively.

Supplemental 9D. Predicted and Observed PK Profiles of Drug D In Westerner, Chinese, and Japanese



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 9E. Predicted and Observed Ctrough of Drug D In Westerner, and Japanese After Multiple Doses



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 10A. Drug E Input Parameters for SimCYP Simulation

Parameters	**Value**
Drug E	
Molecular weight (g/mol)	398.48
LogP	3.1
Compound type	Monoprotic base
pK_a	8.5
Fu_{plasma}	0.05
B/P ratio	1.17
Fa	0.791
k_a (h^{-1})	0.236
T_{lag} (h)	0.527
Fu_{gut}	0.05
Q_{gut} (L/h)	4.26

V_{ss} (L/kg)	22.9
CL_{int} (CYP3A4), $\mu L \cdot min^{-1} \cdot pmol^{-1}$	0.603
CL_{int} (Other HLM), $\mu L \cdot min^{-1} \cdot mg^{-1}$	41.6
CL_r (L/h)	4.05
Drug E-M1	
Molecular weight (g/mol)	370.42
LogP	1.88
Compound type	Monoprotic base
pK_a	10.96
Fu_{plasma}	0.1
B/P ratio	1.17
Fu_{gut}	0.1
V_{ss} (L/kg)	42.3
CL (L/h)	36.8

Supplemental 10B. Predicted and Observed PK Parameters of Drug E In Westerner, Chinese, and Japanese

Population/Dose		**C_{max} (ng/mL)**	**AUC_{0-24} (ng*h/mL)**	**$t_{1/2}$ (h)**	**C_{trough} (ng/mL)**
Westerner	**Observed**	**27.7**	**420**	**NA**	**44**
(50 mg PO)	**Predicted**	**29.8**	**465**	**NA**	**41.85**
Chinese	**Observed**	**5.0**	**290**	**NA**	**NA**
(10 mg PO)	**Predicted**	**5.98**	**349**	**NA**	**NA**
Japanese	**Observed**	**32.5**	**1367**	**NA**	**NA**
(50 mg PO)	**Predicted**	**31.3**	**1720**	**NA**	**NA**

AUC_{0-24} for Westerner, and AUC_{inf} for Chinese and Japanese; C_{max}, C_{trough}, and AUC are reported as geometric mean; $t_{1/2}$ is reported as arithmetic mean; steady state C_{trough} is derived from multiple dose of Drug E at 50 mg PO daily doses in Westerner.

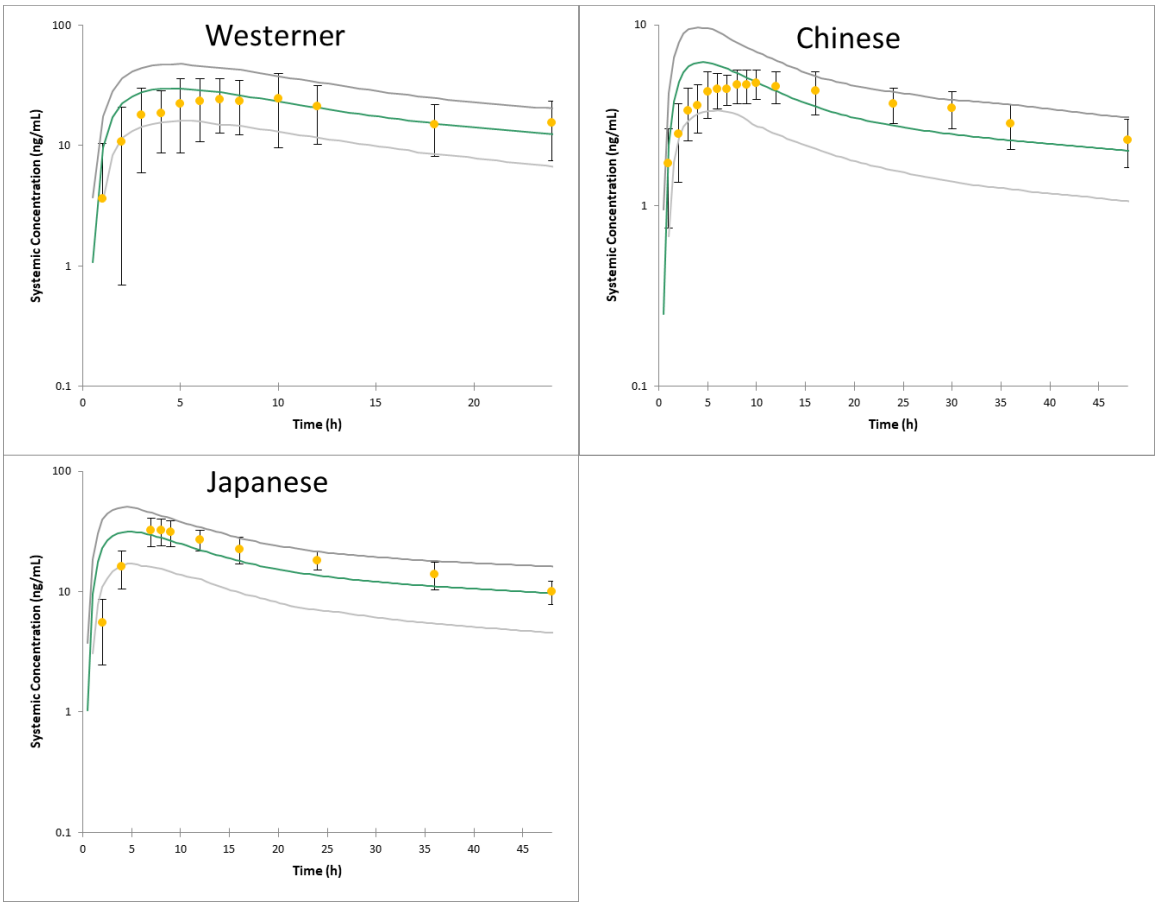
Supplemental 10C. Ratios of Predicted and Observed PK Parameters of Drug E In Chinese and Japanese vs Westerner

	Chinese vs Westerner			Japanese vs Westerner		
	Pred_C/Pred_W	Obs_C/Obs_W	Ratio	Pred_J/Pred_W	Obs_J/Obs_W	Ratio
C_{max}	1.00	0.90	1.11	1.05	1.17	0.90
AUC_{inf}	NA	NA	NA	NA	NA	NA
$t_{1/2}$	NA	NA	NA	NA	NA	NA
C_{trough}	NA	NA	NA	NA	NA	NA

Chinese dose normalized to 50 mg for ratios calculation.

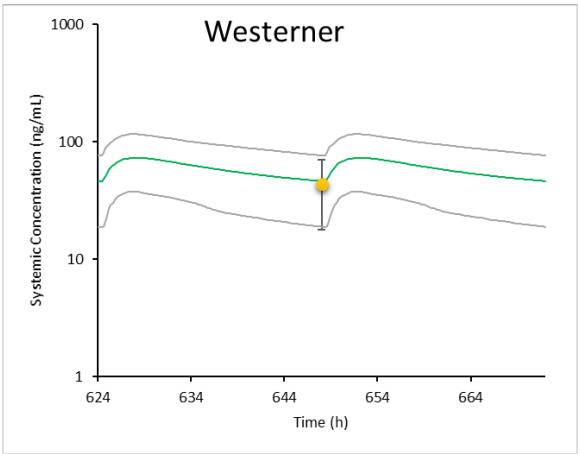
Obs_C, Obs_J and Obs_W are observed in Chinese, Japanese, and Westerner, respectively; Pred_C, Pred_J, and Pred_W are predicted in Chinese, Japanese, and Westerner, respectively; Ratio is (Pred_C/Pred_W)/(Obs_C/Obs_W) and (Pred_J/Pred_W)/(Obs_J/Obs_W), respectively.

Supplemental 10D. Predicted and Observed PK Profiles of Drug E In Westerner, Chinese, and Japanese



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 10E. Predicted and Observed Ctrough of Drug E In Westerner After Multiple Doses



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 11A. Drug F Input Parameters for SimCYP Simulation

Parameters	**Value**
Molecular weight (g/mol)	312.4
LogP	1.15
Compound type	Monoprotic base
pK_a	5.07
Fu_{plasma}	0.61
B/P ratio	1.2
Fa	0.93
k_a (h^{-1})	5.7

Fu_{gut}	1
Q_{gut} (L/h)	10
V_{ss} (L/kg)	1.24
IV CL, $L \cdot h^{-1}$	24.7
CL_{int} (CYP2C19), $\mu L \cdot min^{-1} \cdot pmol^{-1}$	0.149
CL_{int} (CYP3A4), $\mu L \cdot min^{-1} \cdot pmol^{-1}$	0.048
CL_r (L/h)	7.62

Supplemental 11B. Predicted and Observed PK Parameters of Drug F In Westerner, Chinese, and Japanese

Population		**C_{max} (ng/mL)**	**AUC_{inf} (ng*h/mL)**	**$t_{1/2}$ (h)**	**C_{trough} (ng/mL)**
Westerner	**Observed**	**88**	**289**	**2.61**	**NA**
(10 mg PO)	**Predicted**	**62.75**	**277.3**	**2.82**	**NA**
Chinese	**Observed**	**98.5**	**276**	**3.32**	**4.69**
(10 mg PO)	**Predicted**	**87.2**	**394**	**2.85**	**4.17**
Japanese	**Observed**	**127**	**513**	**3.14**	**NA**
(15 mg PO)	**Predicted**	**130**	**645**	**3.29**	**NA**

Cmax, C_{trough}, and AUC_{inf} are reported as geometric mean; $t_{1/2}$ is reported as arithmetic mean; steady state C_{trough} is derived from multiple dose of Drug F at 10 mg PO twice daily doses in Chinese.

Supplemental 11C. Ratios of Predicted and Observed PK Parameters of Drug F In Chinese and Japanese vs Westerner

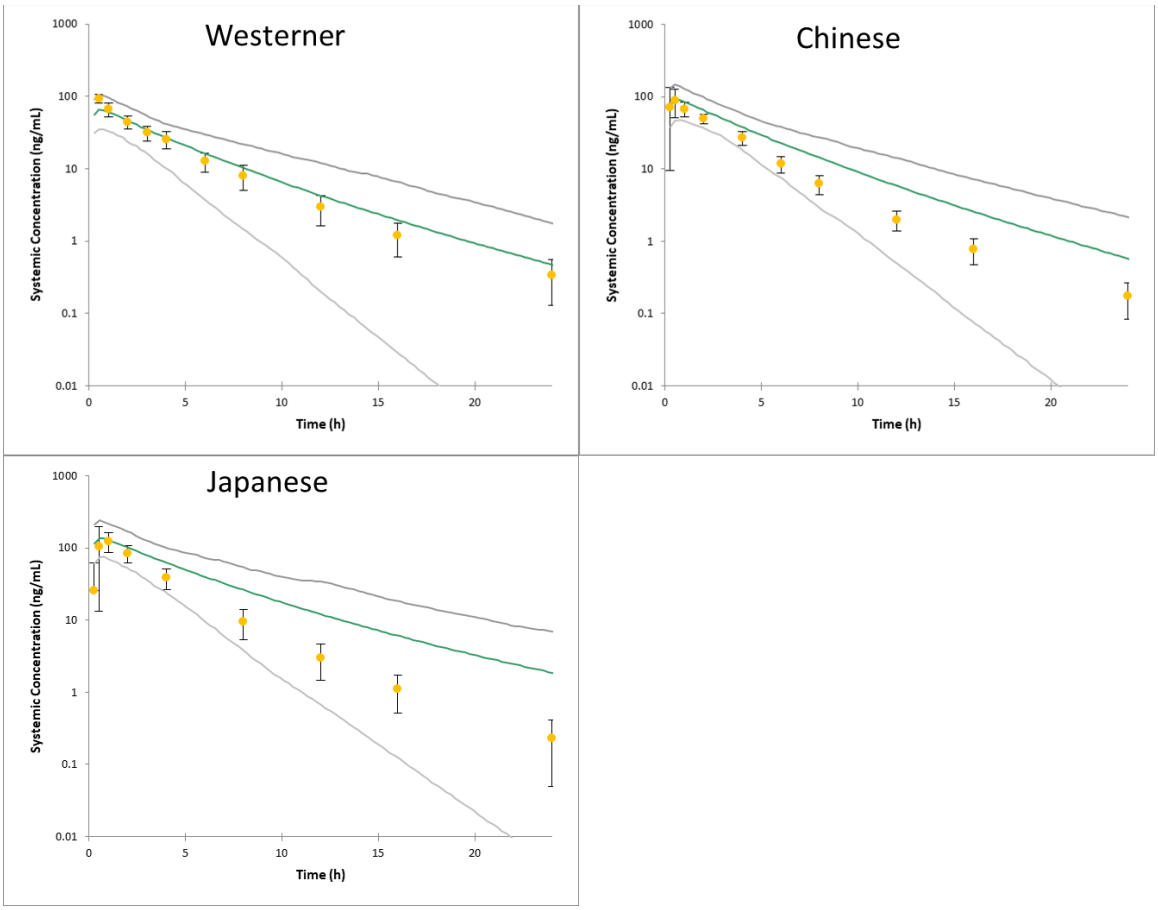
	Chinese vs Westerner			**Japanese vs Westerner**		
	Pred_C/Pred_W	**Obs_C/Obs_W**	**Ratio**	**Pred_J/Pred_W**	**Obs_J/Obs_W**	**Ratio**
C_{max}	**1.39**	**1.12**	**1.24**	**1.38**	**0.96**	**1.44**
AUC_{inf}	**1.42**	**0.96**	**1.48**	**1.55**	**1.18**	**1.31**

$t_{1/2}$	1.01	1.27	0.80	1.17	1.20	0.98
C_{trough}	NA	NA	NA	NA	NA	NA

Japanese dose normalized to 10 mg for ratios calculation.

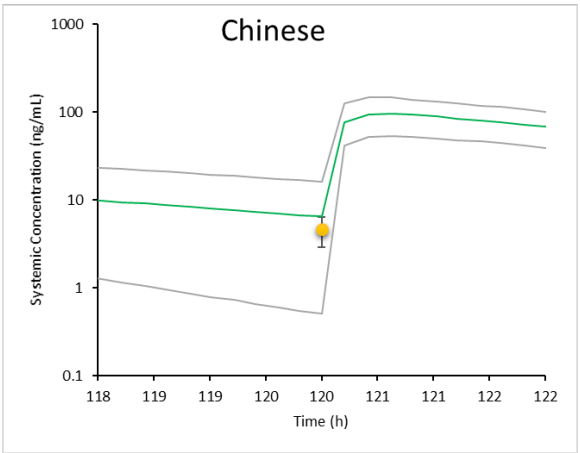
Obs_C, Obs_J and Obs_W are observed in Chinese, Japanese, and Westerner, respectively; Pred_C, Pred_J, and Pred_W are predicted in Chinese, Japanese, and Westerner, respectively; Ratio is (Pred_C/Pred_W)/(Obs_C/Obs_W) and (Pred_J/Pred_W)/(Obs_J/Obs_W), respectively.

Supplemental 11D. Predicted and Observed PK Profiles of Drug F In Westerner, Chinese, and Japanese



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 11E. Predicted and Observed Ctrough of Drug F In Chinese After Multiple Doses



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 12A. Drug G Input Parameters for SimCYP Simulation

Parameters	**Value**
Molecular weight (g/mol)	381.37
LogP	3.83
Compound type	Monoprotic acid
pK_a	10.9
Fu_{plasma}	0.027
B/P ratio	0.945
Fa	0.85
Human Peff ($x10^{-4}$ cm/s)	2.86
Fu_{gut}	1
Q_{gut} (L/h)	12.11
V_{ss} (L/kg)	5.05
V_{max} (CYP3A4), $\mu L \cdot min^{-1} \cdot pmol^{-1}$	3.08
K_m (CYP3A4), µM	16.76

CL_{int} (Other HLM), $\mu L \cdot min^{-1} \cdot mg^{-1}$	16.2
CL_r (L/h)	0.584

Supplemental 12B. Predicted and Observed PK Parameters of Drug G In Westerner, and Japanese

Population/Dose		C_{max} (ng/mL)	AUC_{inf} (ng*h/mL)	$t_{1/2}$ (h)	C_{trough} (ng/mL)
Westerner	**Observed**	**797**	**6272**	**7.57**	**NA**
(200 mg PO)	**Predicted**	**665.8**	**5500**	**10.9**	**NA**
Japanese	**Observed**	**944**	**6701**	**5.6**	**311.2**
(200 mg PO)	**Predicted**	**1262**	**7587**	**8.17**	**238.1**

Cmax, C_{trough}, and AUC_{inf} are reported as geometric mean; $t_{1/2}$ is reported as arithmetic mean; steady state C_{trough} is derived from multiple doses of Drug G at 200 mg PO twice daily doses in Japanese.

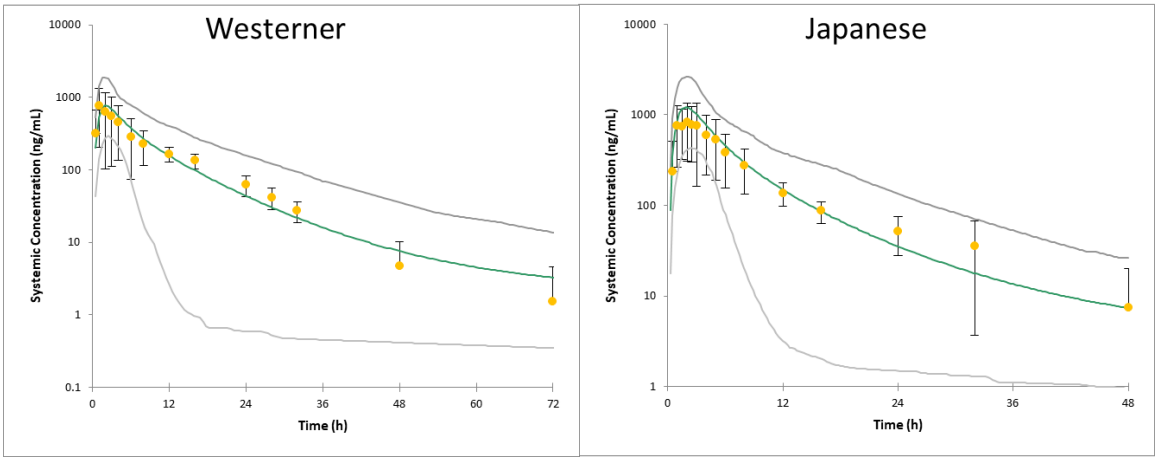
Supplemental 12C. Ratios of Predicted and Observed PK Parameters of Drug G In Japanese vs Westerner

Japanese vs Westerner

	Pred_J/Pred_W	Obs_J/Obs_W	Ratio
C_{max}	1.90	1.18	1.61
AUC_{inf}	1.38	1.07	1.29
$t_{1/2}$	0.75	0.74	1.01
C_{trough}	NA	NA	NA

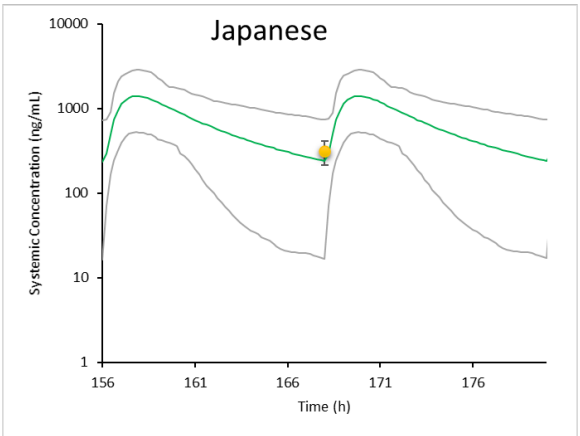
Obs_J and Obs_W are observed in Japanese and Westerner, respectively; Pred_J and Pred_W are predicted in Japanese and Westerner, respectively; Ratio is (Pred_J/Pred_W)/(Obs_J/Obs_W).

Supplemental 12D. Predicted and Observed PK Profiles of Drug G In Westerner, Chinese, and Japanese



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 12E. Predicted and Observed Ctrough of Drug G In Japanese After Multiple Doses



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 13A. Drug H Input Parameters for SimCYP Simulation

Parameters	Value
Molecular weight (g/mol)	436
LogP	2.5
Compound type	Neutral
Fu_{plasma}	0.064
B/P ratio	0.66
Fa	1
k_a (h^{-1})	1.2
T_{lag} (h)	0.5
Fu_{gut}	0.064
Q_{gut} (L/h)	5.62
V_{ss} (L/kg)	1.23

CL_{iv}, L/h	11.2
CL_{int} (CYP3A4), $\mu L \cdot min^{-1} \cdot pmol^{-1}$	0.041
CL_{int} (CYP3A5), $\mu L \cdot min^{-1} \cdot pmol^{-1}$	0.006
CL_{int} (CYP2C8), $\mu L \cdot min^{-1} \cdot pmol^{-1}$	0.011
CL_{int} (UGT1A9), $\mu L \cdot min^{-1} \cdot mg^{-1}$	35
CL_{int} (UGT2B7), $\mu L \cdot min^{-1} \cdot mg^{-1}$	8
CL_r (L/h)	0.1

Supplemental 13B. Predicted and Observed PK Parameters of Drug H In Westerner, Chinese, and Japanese

Population/Dose		**C_{max} (ng/mL)**	**AUC_{0-24} (ng*h/mL)**	**$t_{1/2}$ (h)**	**C_{trough} (ng/mL)**
Westerner	**Observed**	**81.3**	**398**	**NA**	**NA**
(5 mg PO)	**Predicted**	**79.3**	**382.4**	**NA**	**NA**
Chinese	**Observed**	**113**	**602**	**NA**	**NA**
(5 mg PO)	**Predicted**	**102**	**525**	**NA**	**NA**
Japanese	**Observed**	**91.8**	**478**	**NA**	**NA**
(5 mg PO)	**Predicted**	**92.3**	**453**	**NA**	**NA**

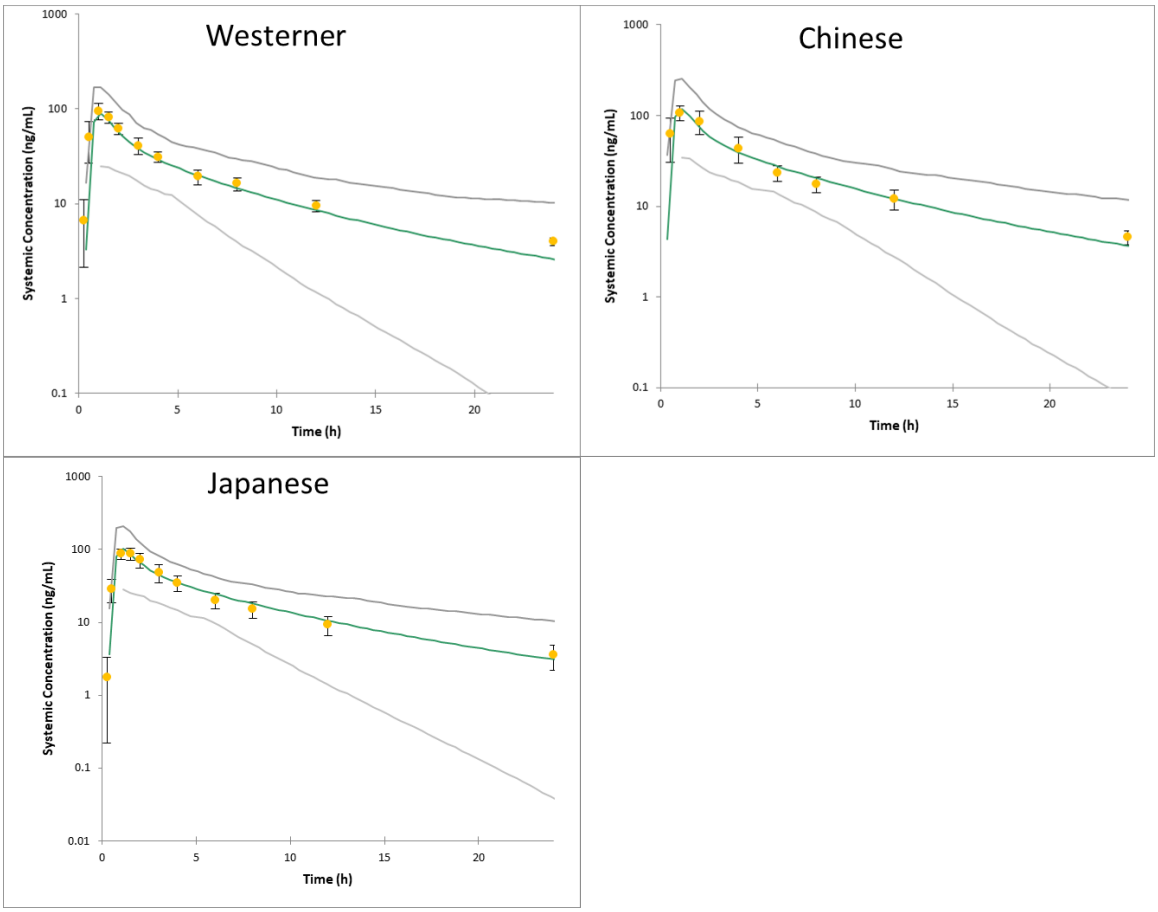
C_{max} and AUC_{inf} are reported as geometric mean; $t_{1/2}$ is reported as arithmetic mean

Supplemental 13C. Ratios of Predicted and Observed PK Parameters of Drug H In Chinese and Japanese vs Westerner

	Chinese vs Westerner			Japanese vs Westerner		
	Pred_C/Pred_W	Obs_C/Obs_W	Ratio	Pred_J/Pred_W	Obs_J/Obs_W	Ratio
C_{max}	1.29	1.39	0.93	1.16	1.13	1.03
AUC_{inf}	1.37	1.51	0.91	1.18	1.20	0.98
$t_{1/2}$	NA	NA	NA	NA	NA	NA
C_{trough}	NA	NA	NA	NA	NA	NA

Obs_C, Obs_J and Obs_W are observed in Chinese, Japanese, and Westerner, respectively; Pred_C, Pred_J, and Pred_W are predicted in Chinese, Japanese, and Westerner, respectively; Ratio is (Pred_C/Pred_W)/(Obs_C/Obs_W) and (Pred_J/Pred_W)/(Obs_J/Obs_W), respectively.

Supplemental 13D. Predicted and Observed PK Profiles of Drug H In Westerner, Chinese, and Japanese



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 14A. Drug I Input Parameters for SimCYP Simulation

Parameters	**Value**
Molecular weight (g/mol)	341.5
LogP	3.7
Compound type	Monoprotic base
pK_a	10.5
Fu_{plasma}	0.49
B/P ratio	1

Fa	0.7
k_a (h^{-1})	0.17
T_{lag} (h)	0
Fu_{gut}	1
Q_{gut} (L/h)	9.75
V_{ss} (L/kg)	2.4
CL_{int} (CYP2D6), $\mu L \cdot min^{-1} \cdot pmol^{-1}$	2.067
CL_{int} (CYP3A4), $\mu L \cdot min^{-1} \cdot pmol^{-1}$	0.121
CL_r (L/h)	14.4

Supplemental 14B. Predicted and Observed PK Parameters of Drug I In Westerner, Chinese, and Japanese

Population/Dose		**C_{max} (ng/mL)**	**AUC_{inf} (ng*h/mL)**	**$t_{1/2}$ (h)**	**C_{trough} (ng/mL)**
Westerner	**Observed**	**4.69**	**52.6**	**7.21**	**NA**
(8 mg PO)	**Predicted**	**4.37**	**59.59**	**4.68**	**NA**
Japanese	**Observed**	**10.9**	**113**	**7.56**	**NA**
(16 mg PO)	**Predicted**	**11.5**	**134**	**4.64**	**NA**

C_{max} and AUC_{inf} are reported as geometric mean; $t_{1/2}$ is reported as arithmetic mean

Supplemental 14C. Ratios of Predicted and Observed PK Parameters of Drug I In Japanese vs Westerner

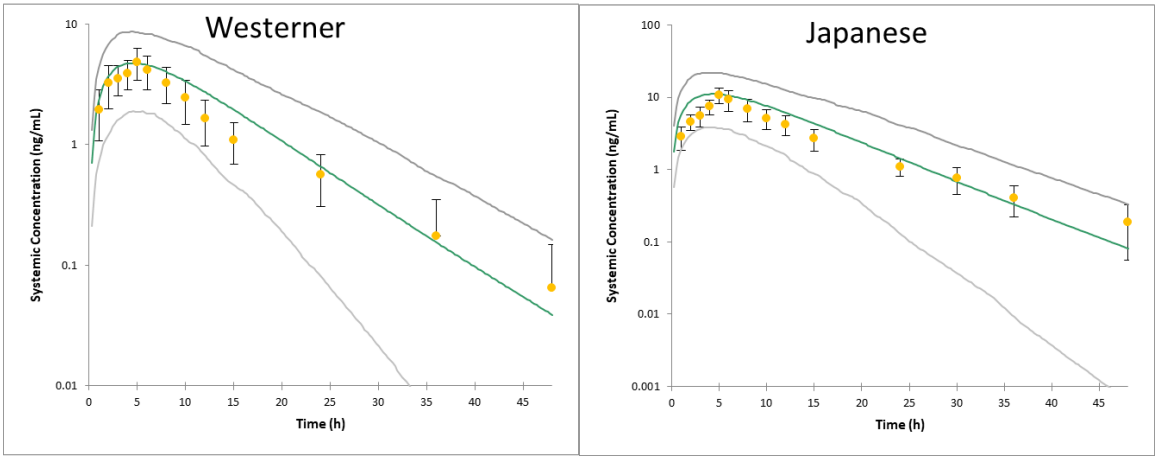
	Japanese vs Westerner		
	Pred_J/Pred_W	**Obs_J/Obs_W**	**Ratio**
C_{max}	**1.32**	**1.16**	**1.14**
AUC_{inf}	**1.12**	**1.07**	**1.05**

$t_{1/2}$	**0.99**	**1.05**	**0.94**
C_{trough}	**NA**	**NA**	**NA**

Japanese dose normalized to 8 mg.

Obs_J and Obs_W are observed in Japanese and Westerner, respectively; Pred_J and Pred_W are predicted in Japanese and Westerner, respectively; Ratio is (Pred_J/Pred_W)/(Obs_J/Obs_W).

Supplemental 14D. Predicted and Observed PK Profiles of Drug I In Westerner, Chinese, and Japanese



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 15A. Drug J Input Parameters for SimCYP Simulation

Parameters	**Value**
Molecular weight (g/mol)	474.58
LogP	2.97

Compound type	Monoprotic base
pK_a	6.5
Fu_{plasma}	0.036
B/P ratio	0.63
Fa	1
k_a (h^{-1})	2.58
T_{lag} (h)	0
Fu_{gut}	0.383
Q_{gut} (L/h)	10.17
V_{ss} (L/kg)	1.2
CL_{int} (CYP2C9), $\mu L \cdot min^{-1} \cdot pmol^{-1}$	1.511
CL_{int} (CYP3A4), $\mu L \cdot min^{-1} \cdot pmol^{-1}$	2.864
CL_r (L/h)	0.72

Supplemental 15B. Predicted and Observed PK Parameters of Drug J In Westerner, Chinese, and Japanese

Population/Dose		**C_{max} (ng/mL)**	**AUC_{inf} (ng*h/mL)**	**$t_{1/2}$ (h)**	**C_{trough} (ng/mL)**
Westerner	**Observed**	**75.74**	**184**	**2.51**	**NA**
(20 mg PO)	**Predicted**	**67.81**	**211.1**	**1.79**	**NA**
Chinese	**Observed**	**296**	**765**	**2.82**	**NA**
(50 mg PO)	**Predicted**	**195**	**764**	**2.09**	**NA**
Japanese	**Observed**	**166**	**450**	**2.33**	**NA**
(50 mg PO)	**Predicted**	**225**	**907**	**2.32**	**NA**

C_{max} and AUC_{inf} are reported as geometric mean; $t_{1/2}$ is reported as arithmetic mean

Supplemental 15C. Ratios of Predicted and Observed PK Parameters of Drug J In Chinese and Japanese vs Westerner

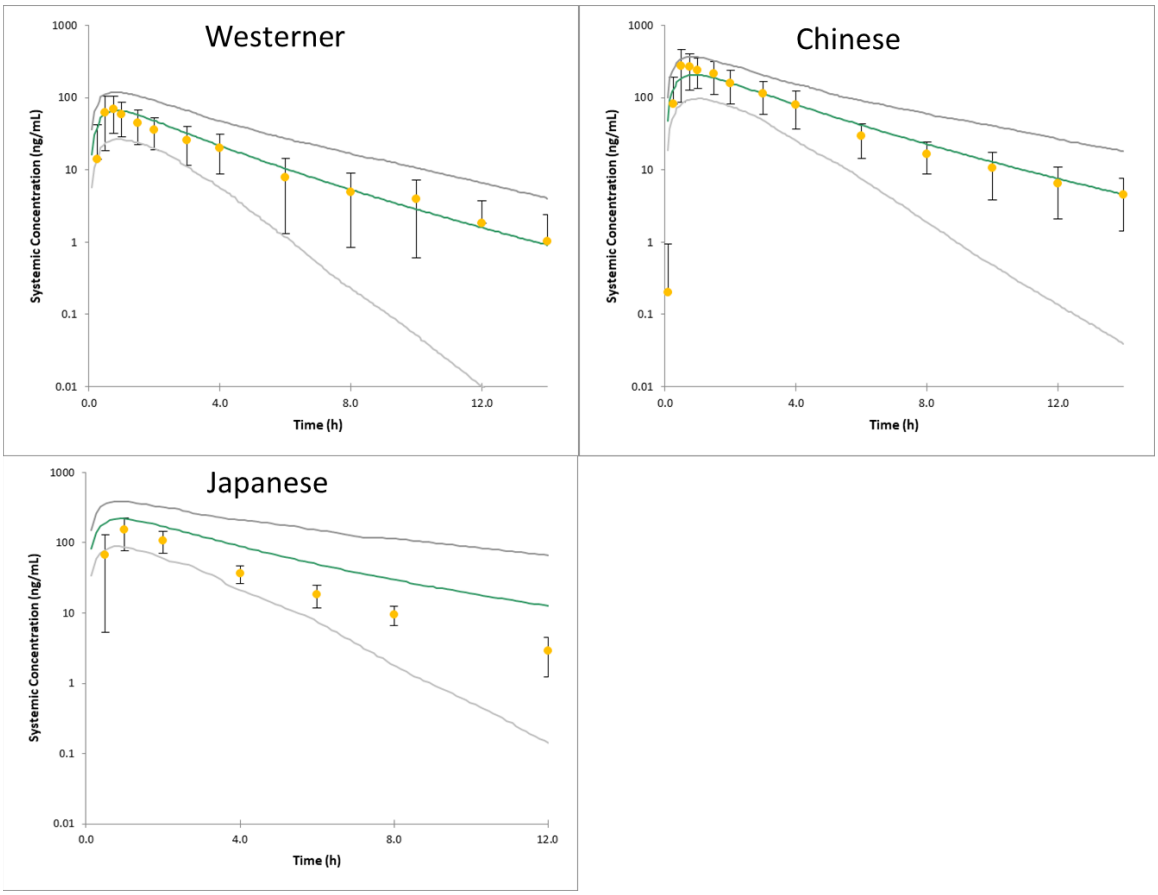
Chinese vs Westerner	**Japanese vs Westerner**

	Pred_C/Pred_W	Obs_C/Obs_W	Ratio	Pred_J/Pred_W	Obs_J/Obs_W	Ratio
C_{max}	1.15	1.56	0.74	1.33	0.88	1.51
AUC_{inf}	1.45	1.66	0.87	1.72	0.98	1.76
$t_{1/2}$	1.17	1.12	1.04	1.30	0.93	1.40
C_{trough}	NA	NA	NA	NA	NA	NA

Westerner dose normalized to 50 mg for calculation of ratios.

Obs_C, Obs_J and Obs_W are observed in Chinese, Japanese, and Westerner, respectively; Pred_C, Pred_J, and Pred_W are predicted in Chinese, Japanese, and Westerner, respectively; Ratio is (Pred_C/Pred_W)/(Obs_C/Obs_W) and (Pred_J/Pred_W)/(Obs_J/Obs_W), respectively.

Supplemental 15D. Predicted and Observed PK Profiles of Drug J In Westerner, Chinese, and Japanese



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 16A. Drug K Input Parameters for SimCYP Simulation

Parameters	**Value**
Molecular weight (g/mol)	211
LogP	1.1
Compound type	Monoprotic base
pK_a	9.9
Fu_{plasma}	0.8

B/P ratio	1
Fa	1
k_a (h^{-1})	1.2
T_{lag} (h)	0
Fu_{gut}	1
Q_{gut} (L/h)	14.96
V_{ss} (L/kg)	2
$CL_{int,Hep}$, $\mu L \cdot min^{-1} \cdot million^{-1}$	0.3394
CL_r (L/h)	7

Supplemental 16B. Predicted and Observed PK Parameters of Drug K In Westerner, Chinese, and Japanese

Population/Dose		**C_{max} (ng/mL)**	**AUC_{inf} (ng*h/mL)**	**$t_{1/2}$ (h)**	**C_{trough} (ng/mL)**
Westerner	**Observed**	**4.48**	**97.6**	**20.0**	**NA**
(1 mg PO)	**Predicted**	**5.35**	**89.17**	**10.11**	**NA**
Chinese	**Observed**	**4.9**	**89.1**	**15.23**	**4.58**
(1 mg PO)	**Predicted**	**6.46**	**101**	**9.42**	**5.34**
Japanese	**Observed**	**5.3**	**42.5[a]**	**NA**	**7.261**
(1 mg PO)	**Predicted**	**5.98**	**53.7[a]**	**NA**	**5.04**

a: AUC_{0-12}

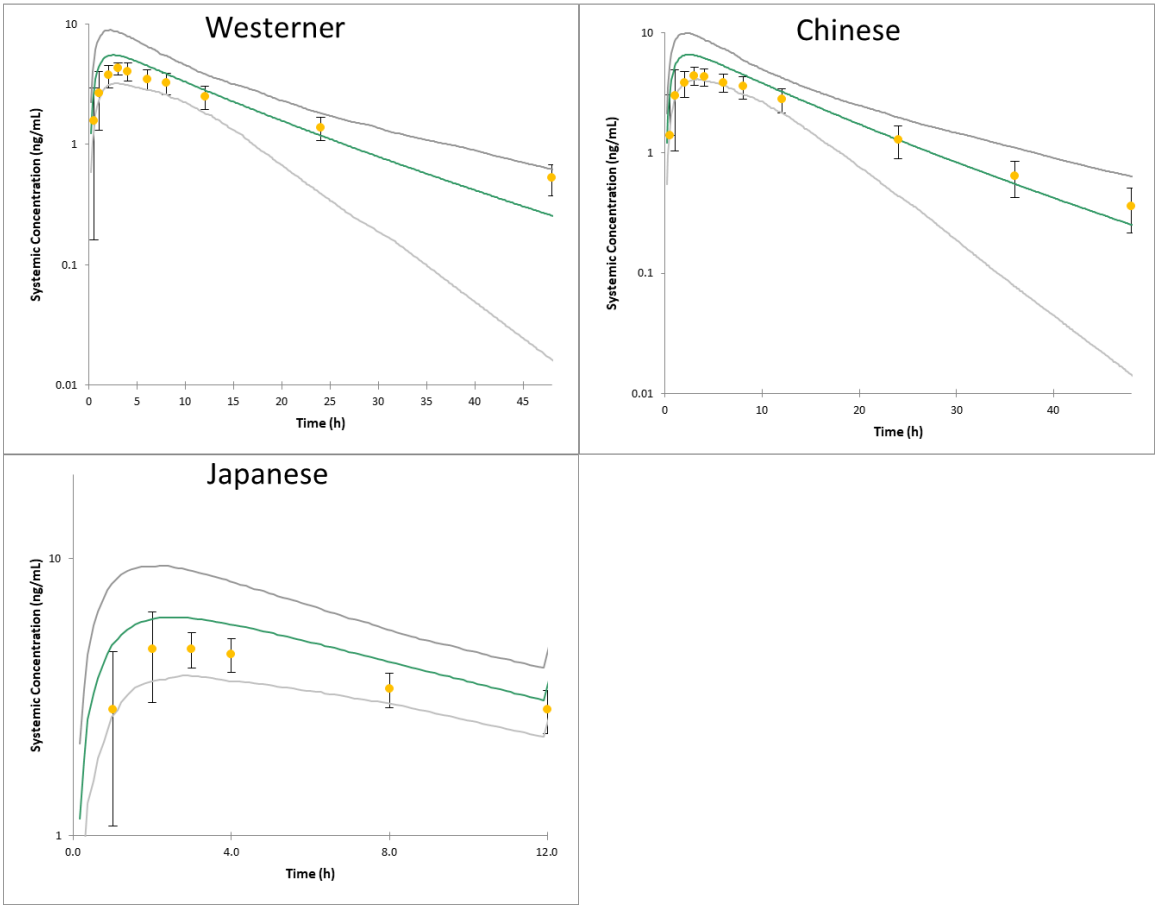
C_{max}, C_{trough}, and AUC are reported as geometric mean; $t_{1/2}$ is reported as arithmetic mean; steady state C_{trough} is derived from multiple dose of Drug K at 1 mg PO twice daily doses in Chinese and Japanese.

Supplemental 16C. Ratios of Predicted and Observed PK Parameters of Drug K In Chinese and Japanese vs Westerner

	Chinese vs Westerner			Japanese vs Westerner		
	Pred_C/Pred_W	Obs_C/Obs_W	Ratio	Pred_J/Pred_W	Obs_J/Obs_W	Ratio
C_{max}	1.21	1.09	1.11	1.12	1.18	0.95
AUC_{inf}	1.13	0.91	1.24	NA	NA	NA
$t_{1/2}$	0.93	0.76	1.22	NA	NA	NA
C_{trough}	NA	NA	NA	NA	NA	NA

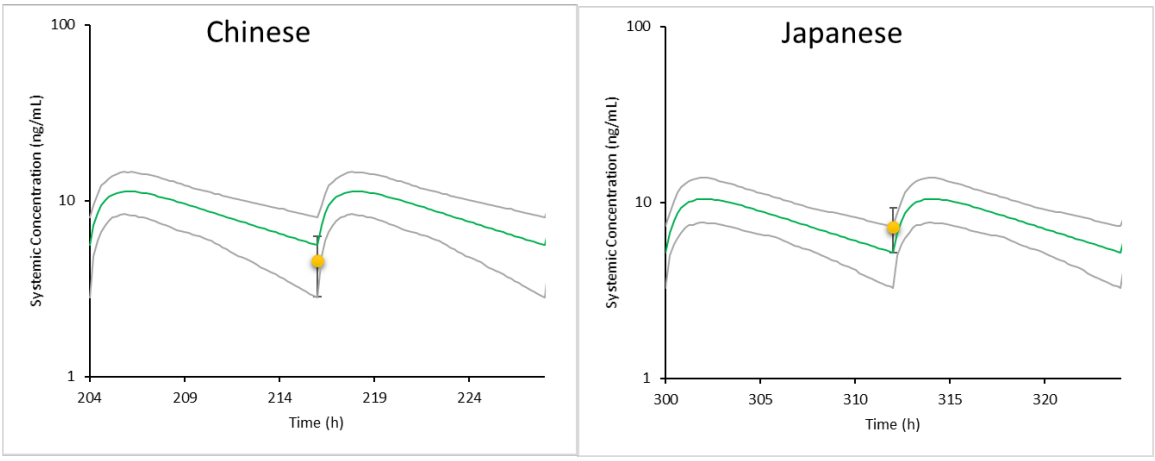
Obs_C, Obs_J and Obs_W are observed in Chinese, Japanese, and Westerner, respectively; Pred_C, Pred_J, and Pred_W are predicted in Chinese, Japanese, and Westerner, respectively; Ratio is (Pred_C/Pred_W)/(Obs_C/Obs_W) and (Pred_J/Pred_W)/(Obs_J/Obs_W), respectively.

Supplemental 16D. Predicted and Observed PK Profiles of Drug K In Westerner, Chinese, and Japanese



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 16E. Predicted and Observed Ctrough of Drug K In Chinese, and Japanese



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.

Supplemental 17A. Drug M Input Parameters for SimCYP Simulation

Parameters	**Value**
Molecular weight (g/mol)	349
LogP	1.8
Compound type	Monoprotic base
pK_a	1.63
Fu_{plasma}	0.42
B/P ratio	0.89
Fa	0.96
k_a (h^{-1})	1.44
T_{lag} (h)	0
Fu_{gut}	1
Q_{gut} (L/h)	14.61
V_{ss} (L/kg)	1.88

V_{max} (CYP2C9), $\mu L \cdot min^{-1} \cdot pmol^{-1}$	0.1
K_m (CYP2C9), µM	11
V_{max} (CYP2C19), $\mu L \cdot min^{-1} \cdot pmol^{-1}$	7
K_m (CYP2C19), µM	3.5
V_{max} (CYP3A4), $\mu L \cdot min^{-1} \cdot pmol^{-1}$	0.31
K_m (CYP3A4), µM	15

Supplemental 17B. Predicted and Observed PK Parameters of Drug M In Westerner, and Japanese Separated by CYP2C19 Polymorphisms

Population/Dose		C_{max} (µg/mL)	AUC_{0-12} (µg*h/mL)	$t_{1/2}$ (h)	C_{trough} (µg/mL)
Westerner - EM	**Observed**	**2.22**	**10.8**	**NA**	**0.36**
(200 mg PO)	**Predicted**	**1.57**	**13.4**	**NA**	**0.62**
Westerner - HEM	**Observed**	**2.82**	**17.6**	**NA**	**0.75**
(200 mg PO)	**Predicted**	**2.76**	**26.5**	**NA**	**1.5**
Westerner - PM	**Observed**	**6.84**	**61.6**	**NA**	**4.27**
(200 mg PO)	**Predicted**	**4.12**	**43.4**	**NA**	**2.97**
Japanese - EM	**Observed**	**2.15**	**12**	**NA**	**0.49**
(200 mg PO)	**Predicted**	**1.87**	**16.2**	**NA**	**0.77**
Japanese - HEM	**Observed**	**3.36**	**20**	**NA**	**0.97**
(200 mg PO)	**Predicted**	**3.18**	**31**	**NA**	**1.81**
Japanese - PM	**Observed**	**6.87**	**65**	**NA**	**4.74**
(200 mg PO)	**Predicted**	**5.94**	**65.2**	**NA**	**4.69**

C_{max} and AUC_{0-12} are reported as geometric mean; $t_{1/2}$ is reported as arithmetic mean; steady state C_{trough} is derived from multiple dose of Drug M at 200 mg PO twice daily doses in Westerner and Japanese.

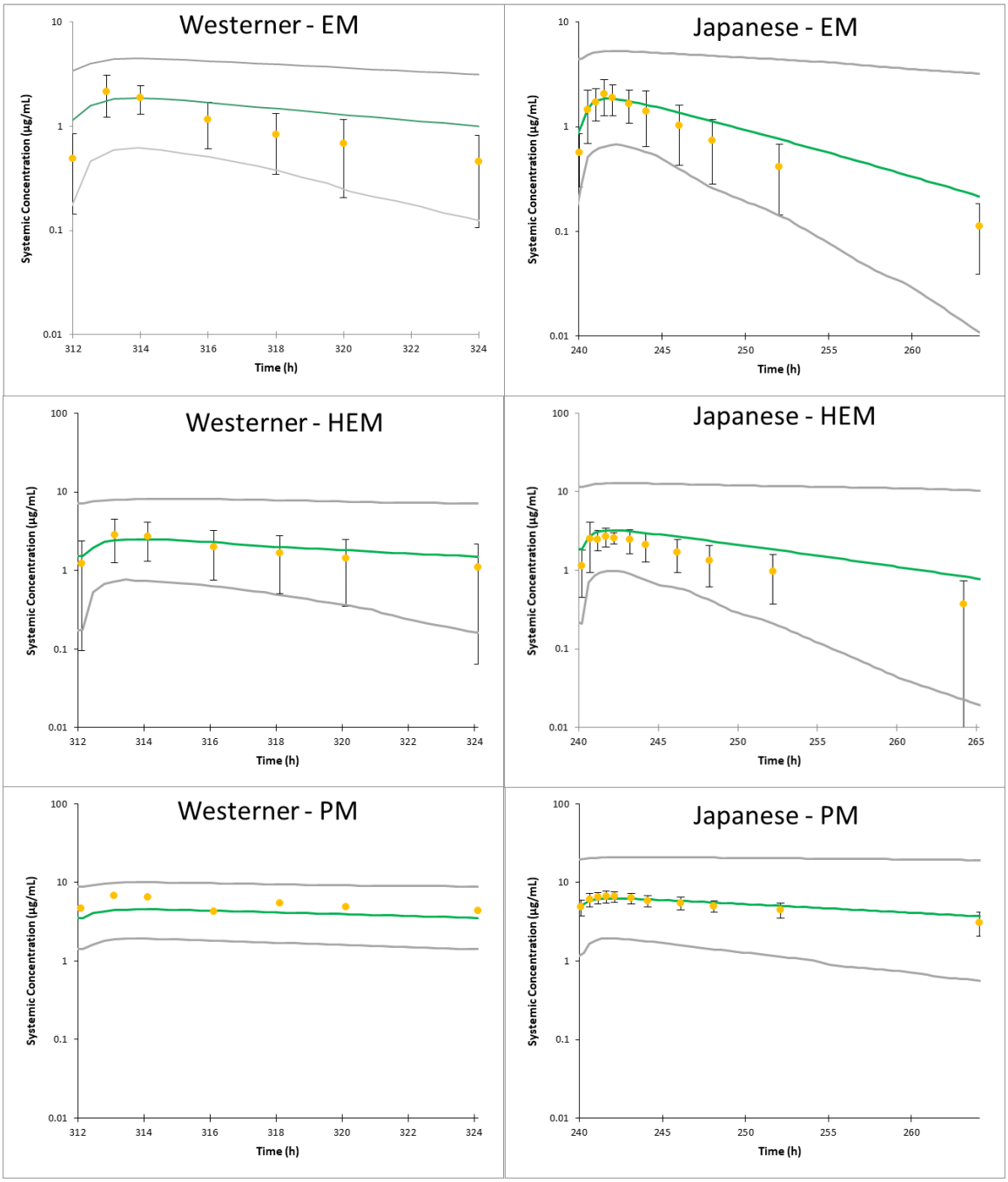
Supplemental 17C. Ratios of Predicted and Observed PK Parameters of Drug M In Japanese vs

Westerner Separated by CYP2C19 Polymorphisms

	Japanese vs Westerner - EM			Japanese vs Westerner - HEM			Japanese vs Westerner - PM		
	Pred_J/ Pred_W	Obs_J/ Obs_W	Ratio	Pred_J/ Pred_W	Obs_J/ Obs_W	Ratio	Pred_J/ Pred_W	Obs_J/ Obs_W	Ratio
C_{max}	1.19	0.97	1.23	1.15	1.19	0.97	1.44	1.00	1.44
AUC_{0-12}	1.21	1.11	1.09	1.17	1.14	1.03	1.50	1.06	1.42
$t_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA
C_{trough}	1.24	1.36	0.91	1.21	1.29	0.94	1.58	1.11	1.42

Obs_J and Obs_W are observed in Japanese and Westerner, respectively; Pred_J and Pred_W are predicted in Japanese and Westerner, respectively; Ratio is (Pred_J/Pred_W)/(Obs_J/Obs_W).

Supplemental 17D. Predicted and Observed PK Profiles and Ctrough of Drug M In Westerner, and Japanese Separated by CYP2C19 Polymorphisms



Green lines represent the predicted mean; gray lines represent the predicted 5th and 95th percentile; orange circle and error bar represent the observed mean and standard deviation.