したプロトコールを用いることによって、民族差は著しく縮小することが示された。

E. 健康危険情報

該当無し

F. 研究発表

1．論文発表

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- Kaniwa N, Saito Y, Aihara M, Matsunaga K, Tohkin M, Kurose K, Furuya H, Takahashi Y, Muramatsu M, Kinoshita S, Abe M, Ikeda H, Kashiwagi M, Song Y, Ueta M, Sotozono C, Ikezawa Z, Hasegawa R HLA-B*1511 is a risk factor for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients. Epilepsia. 2010 Dec; **51**(12): 2461-5.

2．学会発表

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- Tohkin M Activities and Outcomes of Study Group on Ethnic Factors in Clinical Data from East Asian Populations 2010/9/14 (Seoul)
- Maekawa K, Harakawa N, Yoshimura T, Kim SR, Fujimura Y, Aohara F, Sai K, Katori N, Tohkin M, Naito M, Hasegawa R, Okuda H, Sawada J, Niwa T, Saito Y. CYP3A4*16 and CYP3A4*18 alleles found in East Asians exhibit differential catalytic activities for seven CYP3A4 substrate drugs. The International Society for the Study of Xenobiotics Annual Meeting 2010

/10/15 (Istanbul)

- 頭金　正博　東アジア民族における薬物動態の比較；モキシフロキサシン動態試験　平成22年度薬物動態談話会特別例会　平成22年11月5日（浜松）
- 頭金　正博　薬物動態における民族差の検討＿最新の研究報告　欧州製薬団体連合会技術委員会全体会議　平成22年12月13日（東京）

G. 知的財産権の出願・登録状況

（予定を含む）

1．特許取得

なし

2．実用新案登録

なし

3．その他

なし

表１

	薬剤	日本での販売会社	日本人データ	中国人データ	韓国人データ	欧米人データ	総合評価
1	amitriptyline	萬有製薬	×	○	○	×	×
2	amlodipine	ファイザー	○	○	○	○	○
3	clarithromycin	大正製薬	○	○	○	△	×
4	cyclosporin A	ノバルティス	○	×	○	○	×
5	diazepam	大鵬薬品	○	○	○	△	×
6	diclofenac	ノバルティス	○	○	○	○	×
7	digoxin	中外製薬	○	×	△	○	×
8	doxazosin	ファイザー	○	○	○	○	○
9	enalapril	萬有製薬	△	△	△	△	×
10	felodipine	アストラゼネカ	○	○	×	○	×
11	fluconazole	ファイザー	○	○	○	○	○
12	5-fluorouracil	協和醗酵	○	○	△	○	×
13	glimepiride	サノフィ・アベンティス	○	○	○	○	×
14	haloperidol	メルク製薬	×	×	×	×	×
15	indinavir	萬有製薬	○	△	○	○	×
16	irinotecan	第一三共	△	×	△	△	×
17	lansoprazole	武田薬品	○	○	△	○	○
18	levofloxacin	第一三共	○	○	○	△	×
19	lornoxicam	大正富山医薬品	○	○	○	×	×
20	meloxicam	日本ベーリンガーインゲルハイム	○	○	○	○	○
21	midazolam	アステラス	○	×	○	○	×
22	nifedipine	バイエル薬品	○	○	○	○	○
23	nitrendipine	田辺三菱製薬	△	○	△	○	×
24	nortriptyline	大日本住友製薬	○	○	○	○	○
25	omeprazole	アストラゼネカ	○	×	○	○	○
26	pioglitazone	武田薬品	○	○	×	○	○
27	ranitidine	GSK	○	○	○	○	○
28	risperidone	ヤンセン ファーマ	○	△	○	△	×
29	rosiglitazone	未発売	○	○	○	○	○
30	rosuvastatin	アストラゼネカ	○	○	○	○	○
31	simvastatin	萬有製薬	○	△	△	○	△
32	tolubutamide	サノフィ・アベンティス	○	○	○	○	○
33	tolterodine	ファイザー	○	○	○	○	○
34	trimetazidine	大日本住友製薬	△	○	○	×	×
35	valproic acid	協和醗酵	○	△	×	○	×
36	adefovir	GSK	○	○	○	○	×
37	alosetron	GSK	○	○	×	○	×
38	sorafenib	バイエル薬品	○	○	×	○	○
39	Moxfloxacin	バイエル薬品	○	○	×	○	○
40	caffeine	-	○	○	○	○	○
41	nicotine	-	○	×	○	○	○

○：データあり、△：条件を満たしたデータでない、×：データなし

表 2　臨床試験機関および研究責任者

日本　臨床研究機関コード：00001 北里大学臨床薬理研究所　バイオアトリックセンター センター長　蓮沼智子 住所：〒108-8642　東京都港区白金台五丁目 9 番 1 号 TEL：+81-3-5791-6178　FAX：+81-3-3400-5469
中国　臨床研究機関コード：00002 Peking University First Hospital Cui Yimin 住所：No.8, Xishiku Street, Western District, Beijing, China TEL：＋86-10-6655-1122 (内線 2043, 3456)
韓国　臨床研究機関コード：00003 Seoul National University Hospital In-Jin Jang 住所：28 Yeongeon-dong Jongno-gu Seoul, 110-744, Korea TEL：＋82-2-2720-8290　FAX：＋82-2-2745-7996
米国　臨床研究機関コード：00004 SNBL Clinical Pharmacology Center, Inc. Masaru Kaneko 住所：800 W. Baltimore St., 6th FL, Baltimore, MD 21201, USA TEL：＋1-410-706-8926　FAX：＋1-410-706-8964

図1

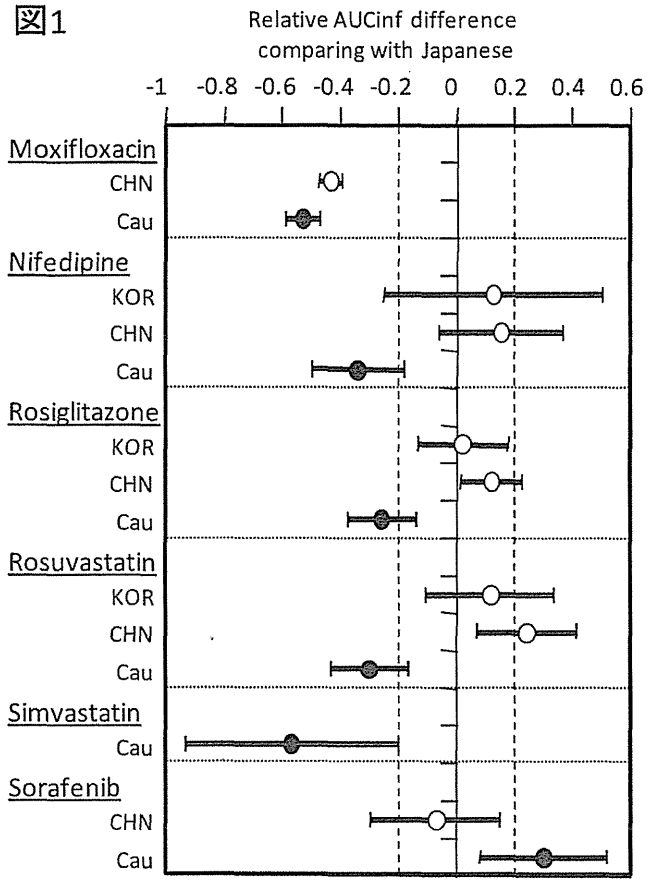

Relative AUCinf difference
comparing with Japanese
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
Moxifloxacin
CHN
Cau
Nifedipine
KOR
CHN
Cau
Rosiglitazone
KOR
CHN
Cau
Rosuvastatin
KOR
CHN
Cau
Simvastatin
Cau
Sorafenib
CHN
Cau

図2

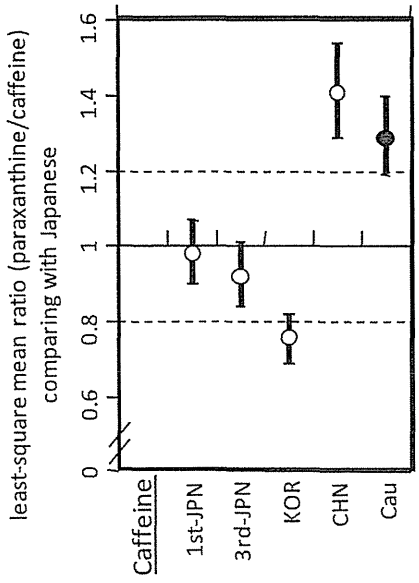

least-square mean ratio (paraxanthine/caffeine)
comparing with Japanese
0
0.6
0.8
1
1.2
1.4
1.6
Caffeine
1st-JPN
3rd-JPN
KOR
CHN
Cau

図3

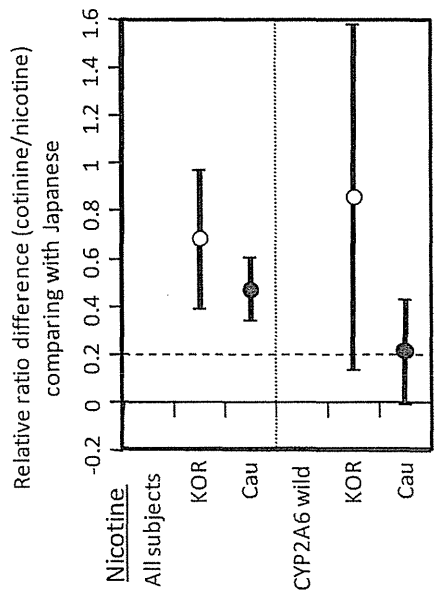

Relative ratio difference (cotinine/nicotine)
comparing with Japanese
-0.2
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
Nicotine
All subjects
KOR
Cau
CYP2A6 wild
KOR
Cau

図4

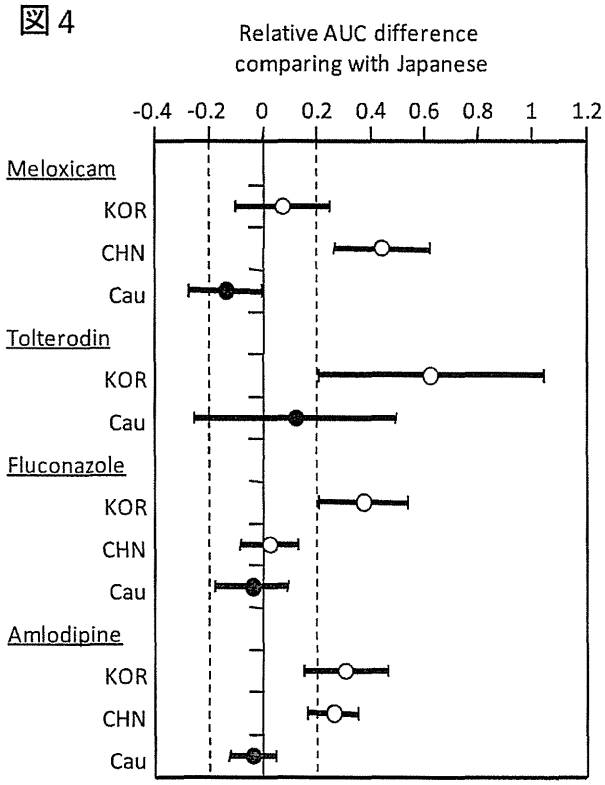


図5

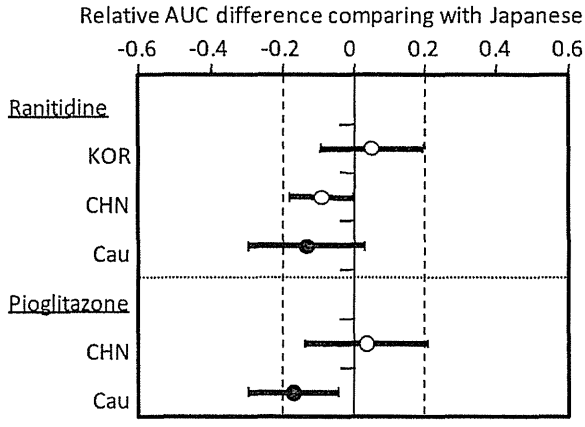


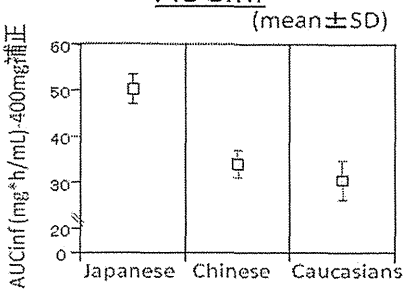
図1, 4, 5: Relative AUC difference compared with Japanese and other races (Korean, Chinese and Caucasian). Black bars indicated 90%CI of relative AUC difference. 図2: Metabolic ratio of paraxanthine/caffeine. 95% least-square mean ratio compared with Japanese and other races (Korean, Chinese and Caucasian). Black bars indicated 95%CI of least-square mean ratio. 図3: Relative metabolic ratio of Cotinine/nicotine compared with Japanese and other races (Korean and Caucasian).
1st-JPN: 1st-generation Japanese, 2nd-JPN: 2nd-Japanese, KOR: Korean, CHN: Chinese, Cau: Caucasian.

図 6

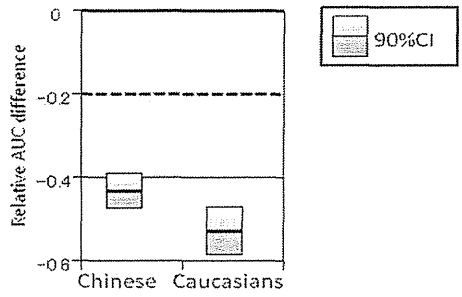
SULT2A1, UGT1A1

Moxifloxacin

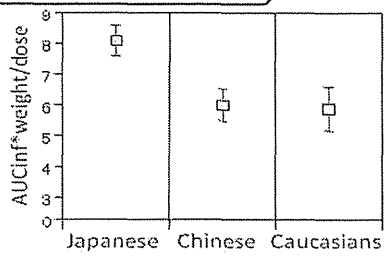
AUCinf (mean±SD)



Relative AUC difference



AUCinf*weight/dose



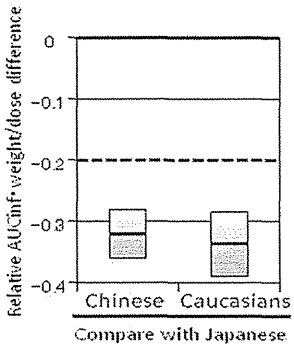


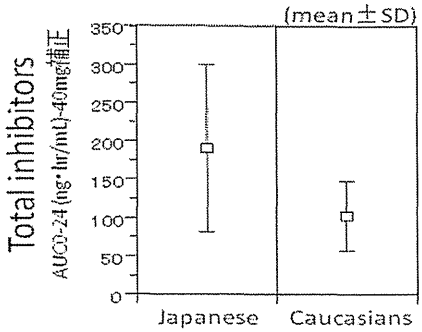
図 7

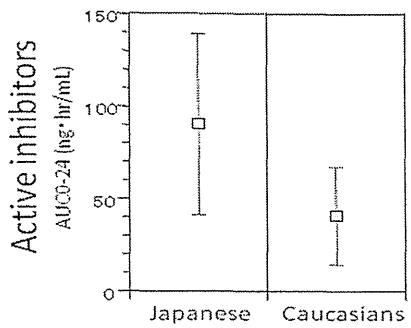
CYP3A4

Simvastatin

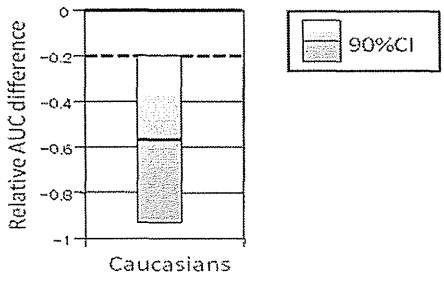
AUCinf

(mean±SD)





Relative AUC difference



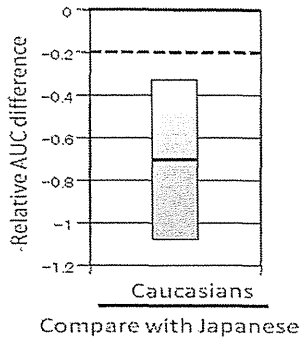
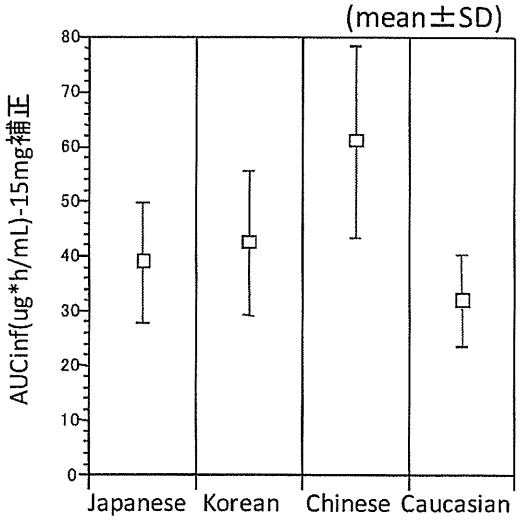


図8 CYP2C9, partially CYP3A4

Meloxicam

AUCinf



Relative AUC difference

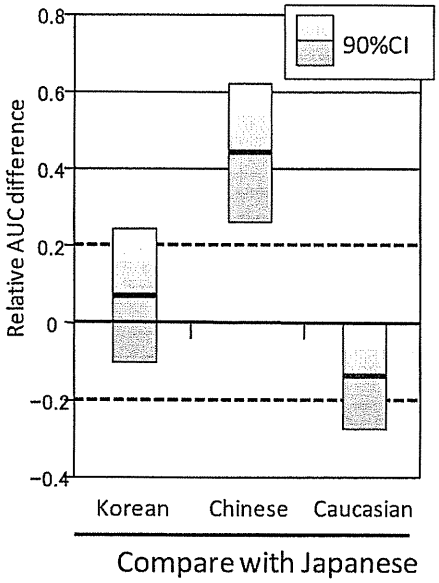


表3. Demographic characteristics of healthy volunteers

	N	Age (y)	Body weight (kg)	BMI	Body hight (cm)	Creatinine clearance (mL/mim)
Japanese	20	23.0 (3.9)	63.8 (6.7)	21.6 (1.9)	171.7 (5.5)	122.1 (19.3)
Chinese	20	29.2 (4.2)	68.9 (5.9)	24.6 (1.5)*	167.5 (5.6)	118.7 (17.5)
Korean	19	25.7 (3.6)	72.9 (9.9)*	23.3 (2.4)	176.7 (7.0)	125.8 (20.6)
Caucasian	20	28.0 (4.8)	77.0 (12.4)*	24.2 (3.0)*	178.2 (7.7)*	101.5 (14.4)*

Data are presented as mean and SD.

BMI, Body mass index.

*, $P < 0.05$ of 1-way analysis of variance and Dunnett multiple comparison ($\alpha = 0.05$) with data of Japanese.

表4. Genotype and allele frequencies of *UGT1A1* in 4 ethnic population

	Japanese	Chinese	Korean	Caucasian
UGT1A1 genotype	20	20	19	20
**1/*1*	10 (50)	6 (30)	9 (47.4)	10 (50)
**1/*6*	7 (35)	8 (40)	6 (31.6)	1 (5)
**1/*28*	3 (15)	3 (15)	3 (15.8)	8 (40)
**6/*6*	-	1 (5)	-	-
**6/*28*	-	1 (5)	1 (5.3)	-
**28/*28*	-	1 (5)	-	1 (5)

Date are presented number of subject and parcentage.

*UGT1A1 wild type, UGT1A1*1/*1; UGT1A1 hetero, UGT1A1*1/*6 and UGT1A1*1/*28; UGT1A1 homo, UGT1A1*6/*6, UGT1A1*6/*28* and *UGT1A1*28/*28.*

図 9

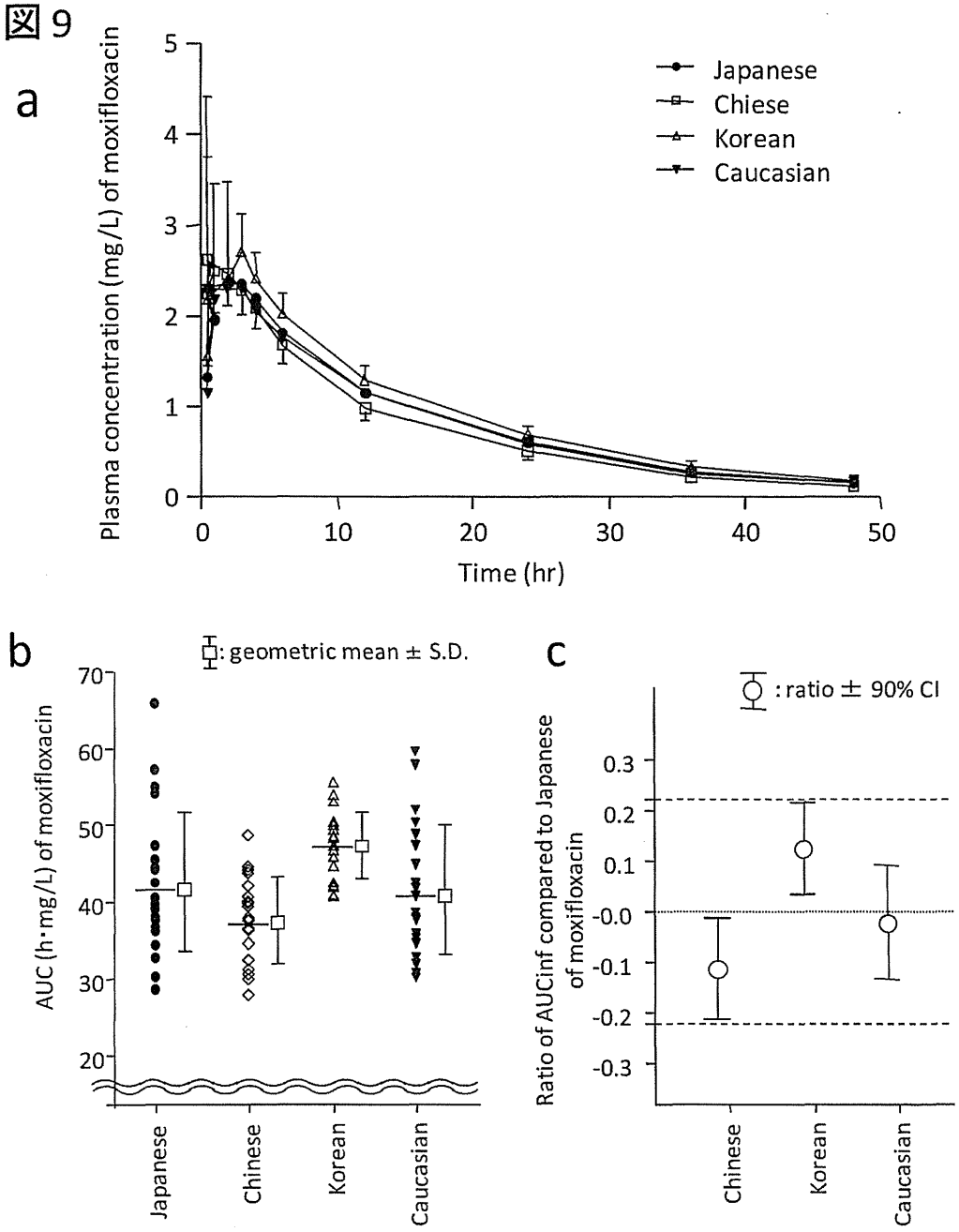


Fig 9. (a) Plasma concentration-time curve of moxifloxacin after administration of a single 400-mg dose in 4 ethnic population (geometric mean and SD). (b) Individual data and geometric mean with SD of the AUCinf of moxifloxacin in 4 ethnic populations and (c) the ratio with 90% confidence interval (CI) of geometric mean AUCinf of the moxifloxacin comparing Chinese, Korean and Caucasian to Japanese.

図10

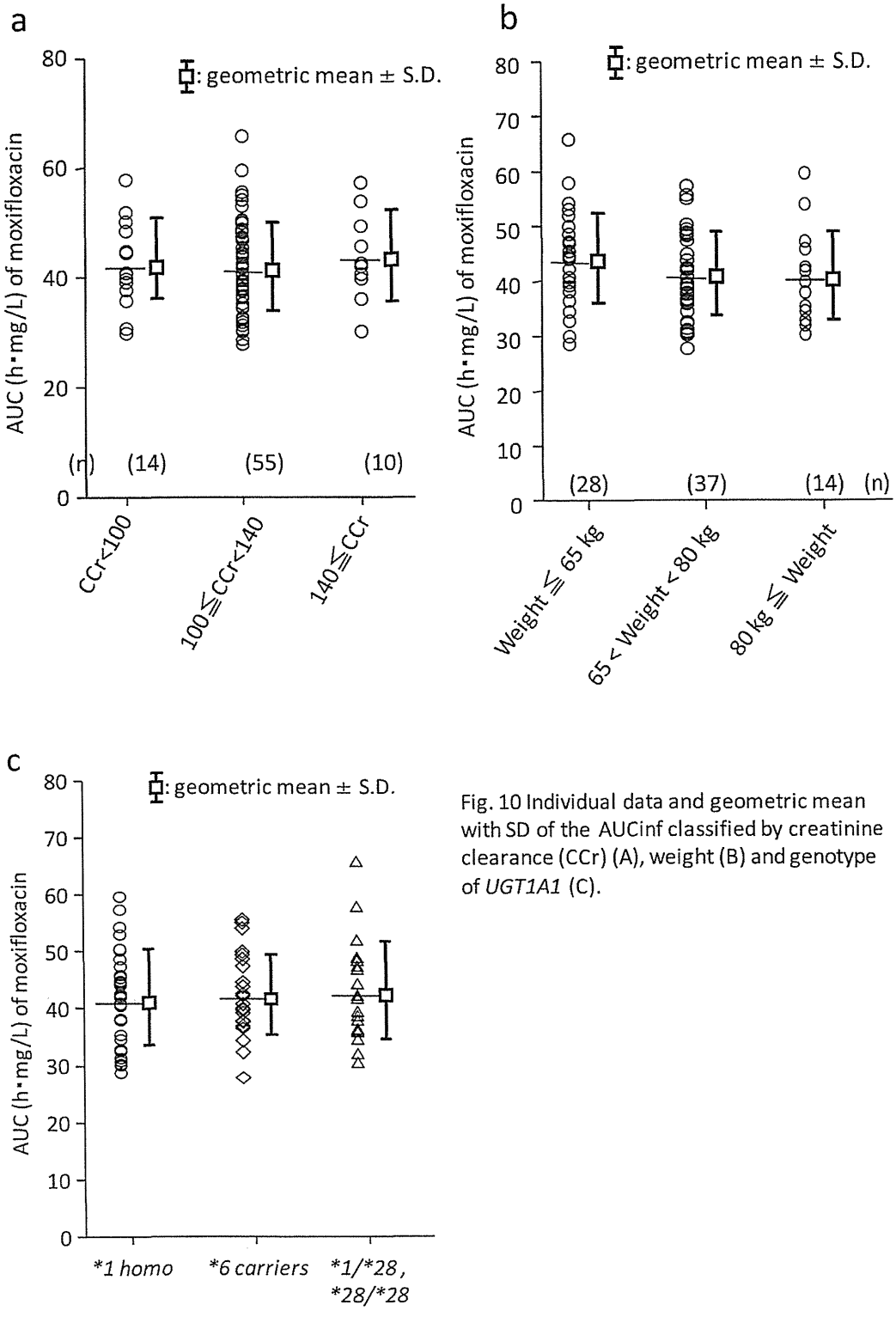


Fig. 10 Individual data and geometric mean with SD of the AUCinf classified by creatinine clearance (CCr) (A), weight (B) and genotype of *UGT1A1* (C).

図11

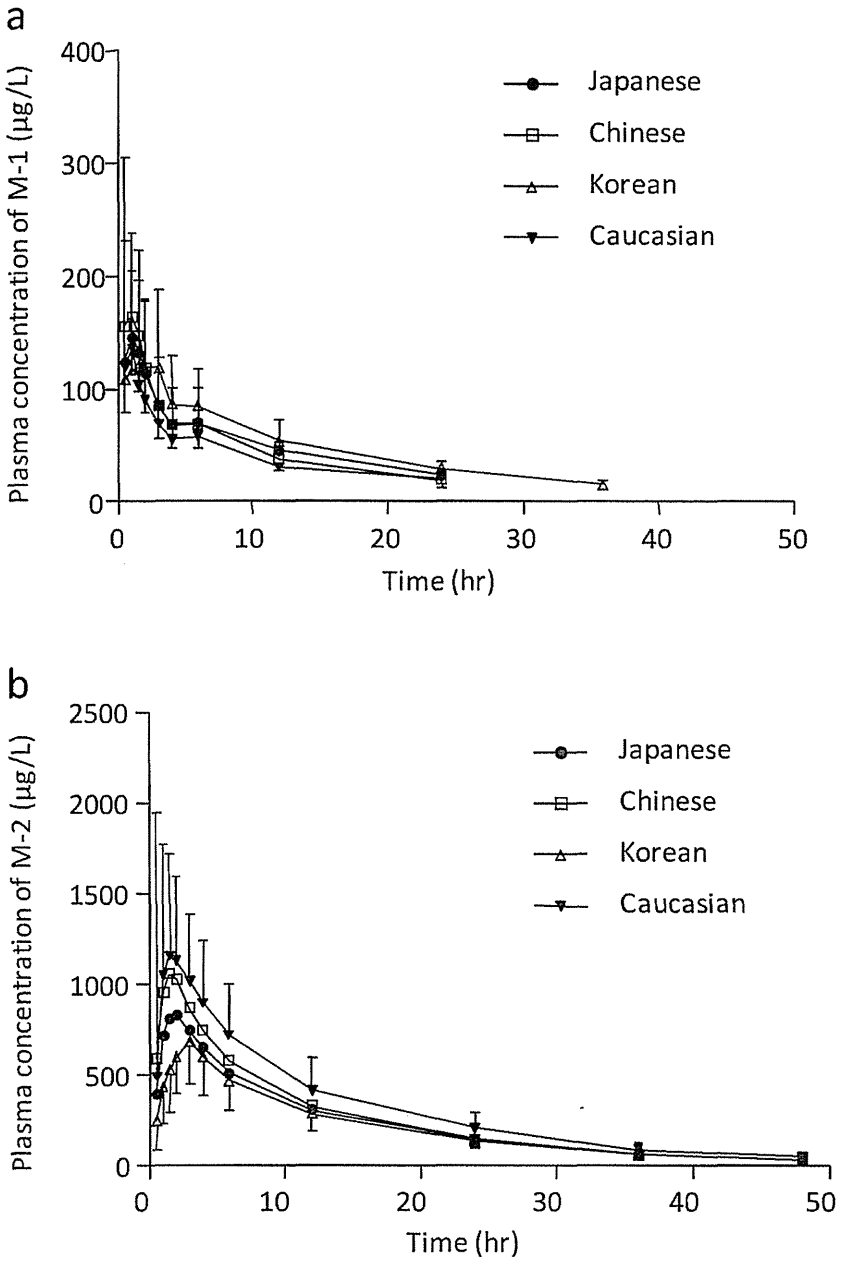


Fig 11. Plasma concentration-time curve of M-1 (sulfate conjugate) (a) and M-2 (glucronate conjugate) (b) after administration of a single 400-mg dose in 4 ethnic population (geometric mean and SD).

図12

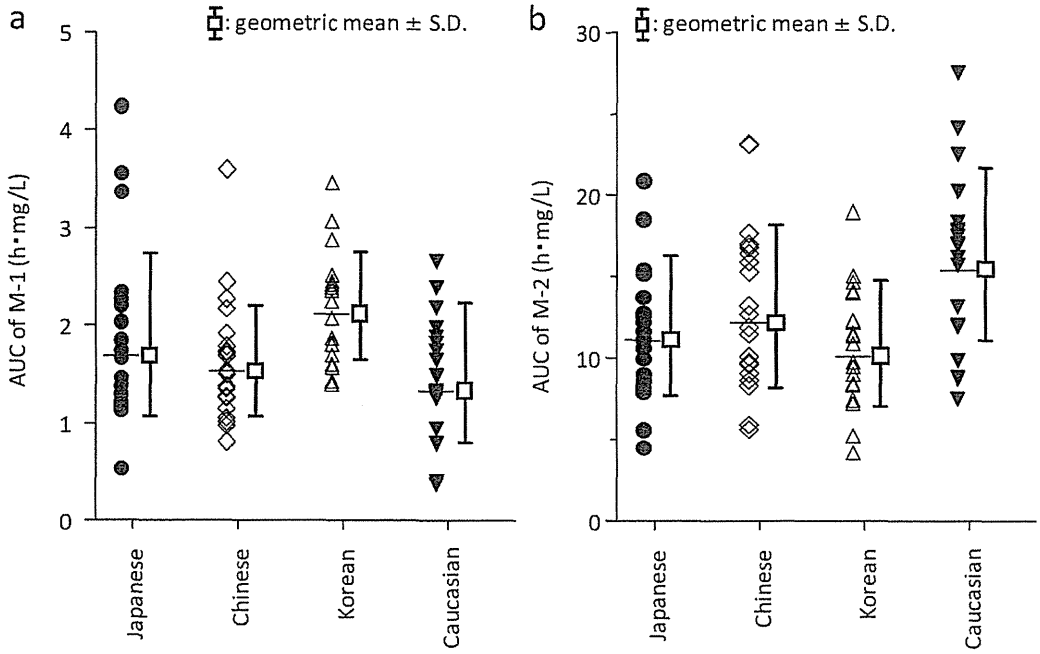


Fig 12. Individual data and geometric mean with SD of the AUCinf of M-1 (a) and M-2 (b) in 4 ethnic populations.

図13

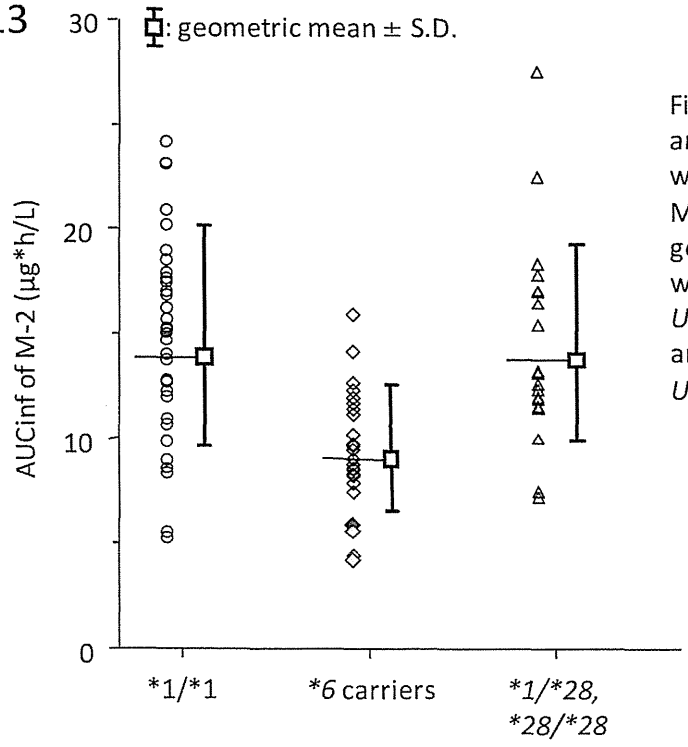


Fig 13. Individual data and geometric mean with SD of the AUCinf of M-2 in the 3 *UGT1A1* genotypes. Solid argyle was indicated *UGT1A1*6/*6*. Gray argyle were indicated *UGT1A1*6/*28*.

図14

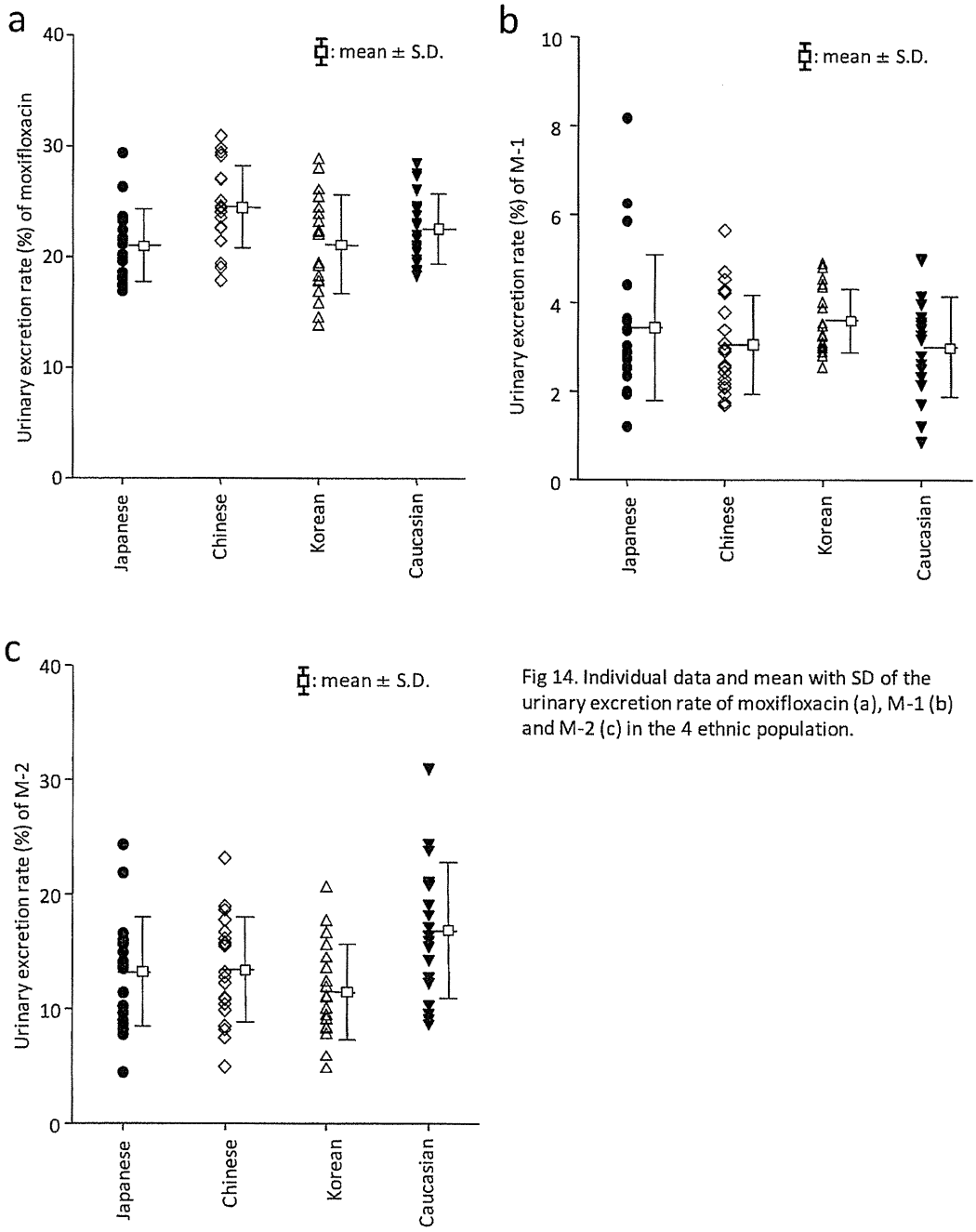


Fig 14. Individual data and mean with SD of the urinary excretion rate of moxifloxacin (a), M-1 (b) and M-2 (c) in the 4 ethnic population.

図15

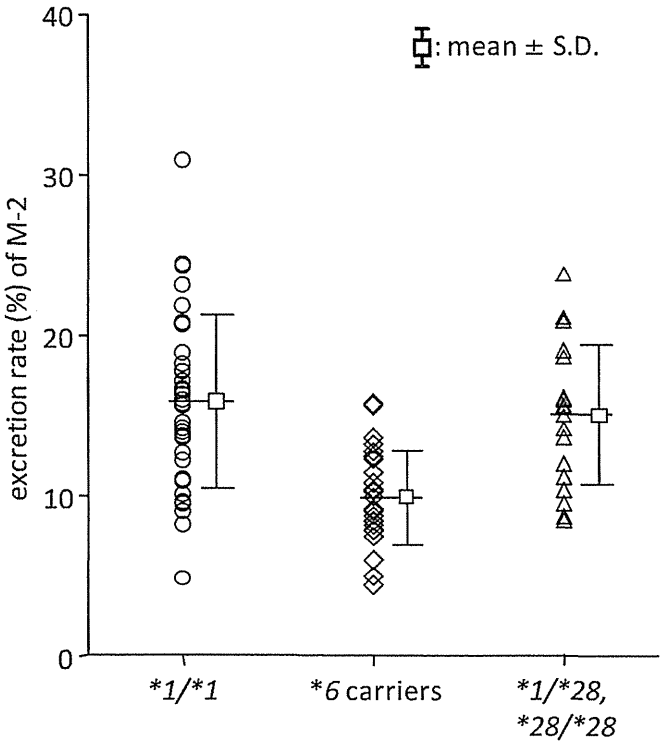


Fig 15. Individual data and mean with SD of the urinary excretion rate of M-2 in the 4 *UGT1A1* genotype.

表5. Summary of moxifloxacin, M-1and M-2 pharmacokinetic parameters in 4 ethnic population after administration of a single 400-mg dose of moxifloxacin

	Japanese	Chinese	Korean	Caucasian
n	20	20	19	20
Moxifloxacin				
AUC_{inf} (hr·mg/L)				
Geometric mean	41.6	37.1	47.2	40.8
CV%	21.9	15.3	9.36	20.6
SD	33.5 to 51.6	31.9 to 43.2	43.0 to 51.8	33.2 to 50.0
C_{max} (mg/L)				
Geometric mean	2.63	3.04	3.38	2.65
CV%	12.0	17.4	15.2	22.5
SD	2.33 to 3.00	2.55 to 3.61	2.91 to 3.93	2.12 to 3.31
$t_{1/2}$ (hr)				
Geometric mean	12.2	11.7	12.7	12.1
CV%	12.3	12.2	10.4	12.5
SD	13.8 to 10.8	10.4 to 13.3	11.4 to 14.0	10.7 to 13.7
t_{max} (hr)				
Median	1.50	1.25	1.50	1.50
Range	0.50 to 4.00	0.50 to 2.00	0.50 to 3.00	0.50 to 3.00
M-1				
AUC_{inf} (hr·mg/L)				
Geometric mean	1.69	1.53	2.11	1.32
CV%	50.7	37.3	26.3	55.4
SD	1.05 to 2.73	1.06 to 2.19	1.63 to 2.74	0.79 to 2.22
C_{max} (mg/L)				
Geometric mean	0.184	0.202	0.194	0.164
CV%	59.9	42.8	37.4	48.5
SD	0.106 to 0.320	0.134 to 0.304	0.135 to 0.279	0.104 to 0.260
$t_{1/2}$ (hr)				
Geometric mean	11.6	10.4	13.9	11.9
CV%	16.8	15.2	13.6	21.9
SD	9.82 to 13.7	8.94 to 12.1	12.2 to 16.0	9.57 ot 14.8
t_{max} (hr)				
Median	1.00	0.50	1.00	0.50
Range	0.50 to 3.00	0.50 to 2.00	0.50 to 3.00	0.50 to 3.00
M-2				
AUC_{inf} (hr·mg/L)				
Geometric mean	11.1	12.2	10.1	15.4
CV%	39.2	41.5	38.7	34.5
SD	7.6 to 16.2	8.2 to 18.1	7.0 to 14.7	11.0 to 21.6
C_{max} (mg/L)				
Geometric mean	0.930	1.14	0.792	1.27
CV%	41.7	45.9	38.6	32.5
SD	0.624 to 1.39	0.734 to 1.76	0.545 to 1.15	0.922 to 1.74
$t_{1/2}$ (hr)				
Geometric mean	11.1	10.5	11.7	11.2
CV%	14.1	10.4	11.1	9.88
SD	9.62 to 12.7	9.50 to 11.7	10.5 to 13.1	10.2 to 12.4
t_{max} (hr)				
Median	1.25	1.00	2.00	1.50
Range	0.50 to 3.02	1.00 to 3.00	0.50 to 4.02	1.00 to 3.00

AUC_{inf}, Area under the plasma concentration-time curve time 0 to infinity; C_{max}, maximum plasma concentration; $t_{1/2}$, terminal elimination half-life; t_{max}, maximum drug concentration time.

表6. Summary of moxifloxacin, M-1and M-2 urinary pharmacokinetic parameters in 4 ethnic population after administration of a single 400-mg dose of moxifloxacin

	Japanese	Chinese	Korean	Caucasian
n	20	20	19	20
Urine volume (ml)				
mean	2440	6973	2678	4426
SD	759	2353	1048	1319
urine excretion rate (%)				
Moxifloxacin				
mean	21.0	24.5	21.1	22.6
SD	3.31	3.71	4.46	3.15
M-1				
mean	3.45	3.06	3.61	3.00
SD	1.64	1.13	0.721	1.14
M-2				
mean	13.2	13.3	11.4	16.8
SD	4.76	4.59	4.18	5.93

表7. Demographic characteristics of healthy volunteers in the clinical study of simvastatin

	n	Age (y)	Body weight (kg)	BMI	Height (cm)
Japanese	40	25.0 ±3.95	63.6 ±7.46	21.6 ±2.44	171.6 ±6.34
Chinese	40	31.5 ±2.91*	65.9 ±8.37	23.5 ±2.43*	167.3 ±4.93*
Korean	40	23.5 ±2.66	67.9 ±9.36	22.5 ±2.58	173.6 ±5.52
Caucasian	40	25.7 ±4.03	77.5 ±10.3*	24.9 ±2.77*	176.4 ±6.85*

Data are presented as mean and SD.

BMI, Body mass index.

*, $P < 0.05$ of 1-way analysis of variance and Dunnett multiple comparison ($\alpha = 0.05$) with data of Japanese.

表 8. Allele and Genotype frequencies of *CYP3A5*3* and *SLCO1B1 c.521T>C* in 4 ethnic populations in the clinical study of simvastatin

	Japanese	Chinese	Korean	Caucasian
n	40	40	40	40
Allele frequency*				
*CYP3A5*3*	49 (0.612)	61 (0.763)	64 (0.8)	75 (0.938)
SLCO1B1 c.521T>C	8 (0.1)	4 (0.05)	5 (0.063)	14 (0.175)
Genotype frequency**				
CYP3A5				
wild type	4 (0.1)	3 (0.075)	0 (0)	0 (0)
**1/*3*	23 (0.575)	13 (0.325)	16 (0.4)	5 (0.125)
**3/*3*	13 (0.325)	24 (0.6)	24 (0.6)	35 (0.875)
SLCO1B1				
c.521 TT	32 (0.8)	36 (0.9)	35 (0.875)	26 (0.65)
c.521 TC	8 (0.2)	4 (0.1)	5 (0.125)	14 (0.35)
c.521 CC	0 (0)	0 (0)	0 (0)	0 (0)

*Date are presented number of allele and percentage.

**Date are presented number of subject and percentage.

表 9. Summary of simvastatin and simvastatain acid pharmacokinetic parameters in 4 ethnic population after administration of a single 20-mg dose of simvastatin

	Japanese	Chinese	Korean	Caucasian
n	40	40	40	40
simvastatin				
C_{max} (nM)				
Geometric mean	5.02	7.14	7.86	7.85
SD	2.92 to 8.64	3.91 to 13.05	4.25 to 14.52	4.40 to 14.02
CV%	58.5	66.2	67.7	63.2
AUC_{INF} (h·nM)				
Geometric mean	23.09	32.28	29.04	29.85
SD	12.99 to 41.05	19.82 to 52.57	14.22 to 59.30	15.31 to 58.17
CV%	62.6	51.8	81.5	74.9
AUClast (h·nM)				
Geometric mean	21.03	29.48	26.55	26.84
SD	11.77 to 37.57	18.09 to 48.03	13.48 to 52.26	14.47 to 49.80
CV%	63.3	51.9	76.3	68.2
$t_{1/2}$ (h)				
Geometric mean	3.97	4.84	4.43	4.93
SD	2.53 to 6.22	2.72 to 8.62	2.63 to 7.48	2.42 to 10.01
CV%	47.3	62.9	56.0	80.8
T_{max} (h)				
Median	1.50	1.50	1.50	1.00
Range	0.50 to 6.00	0.50 to 5.00	0.50 to 5.23	0.50 to 5.00
Vz_F (L)				
Geometric mean	11842	10333	10525	11379
SD	7119 to 19699	5616 to 19010	5649 to 19609	7005 to 18484
CV%	54.4	67.1	68.8	51.5
CL_F (L/h)				
Geometric mean	2069	1480	1646	1601
SD	1164 to 3679	909 to 2411	806 to 3360	821 to 3120
CV%	62.6	51.8	81.5	74.9
MRTlast (h)				
Geometric mean	4.49	4.91	4.32	4.48
SD	2.95 to 6.83	3.13 to 7.70	2.65 to 7.05	2.65 to 7.57
CV%	43.9	47.4	52.1	56.3
MRT_{INF} (h)				
Geometric mean	5.75	6.42	5.60	6.17
SD	3.60 to 9.20	3.69 to 11.18	3.12 to 10.05	3.06 to 12.46
CV%	49.6	59.9	63.8	79.8

AUC_{inf}, Area under the plasma concentraion-time curve time 0 to infinity; C_{ma}x, maximum plasma concentration; $t_{1/2}$, terminal elimination half-life; t_{max}, maximum drug concentration time.

表 10. Summary of simvastatin and simvastatain acid pharmacokinetic parameters in 4 ethnic population after administration of a single 20-mg dose of simvastatin

	Japanese	Chinese	Korean	Caucasian
n	40	40	40	40
Simvastatin acid				
C_{max} (nM)				
Geometric mean	3.20	2.49	3.68	2.05
SD	1.87 to 5.48	1.46 to 4.24	2.10 to 6.44	1.25 to 3.36
CV%	57.8	57.4	60.6	52.7
AUC_{INF} (h·nM)				
Geometric mean	24.94	24.59	28.21	18.16
SD	14.55 to 42.77	13.74 to 44.01	16.25 to 48.96	10.10 to 32.65
CV%	58.1	63.5	59.6	64.1
AUClast (h·nM)				
Geometric mean	28.32	29.31	32.94	23.17
SD	17.25 to 46.50	17.44 to 49.25	19.48 to 55.72	13.05 to 41.12
CV%	52.8	55.6	56.4	62.4
$t_{1/2}$ (h)				
Geometric mean	4.84	5.73	5.16	6.88
SD	3.32 to 7.07	3.85 to 8.53	3.49 to 7.63	4.16 to 11.37
CV%	39.2	41.4	40.6	53.6
T_{max} (h)				
Median	4.00	5.00	4.00	4.50
Range	2.00 to 6.03	3.00 to 12.00	2.00 to 8.00	1.50 to 12.00
Vz_F (L)				
Geometric mean	11302	12923	10358	19614
SD	6658 to 19183	7211 to 23160	5973 to 17960	11460 to 33570
CV%	56.8	63.7	59.5	57.9
CL_F (L/h)				
Geometric mean	1618	1563	1391	1977
SD	985 to 2656	930 to 2627	822 to 2352	1114 to 3509
CV%	52.8	55.6	56.4	62.4
MRTlast (h)				
Geometric mean	7.01	8.56	7.16	7.76
SD	5.46 to 8.98	6.76 to 10.84	5.62 to 9.12	5.89 to 10.24
CV%	25.3	23.9	24.6	28.2
MRT_{INF} (h)				
Geometric mean	8.97	11.37	9.44	11.90
SD	6.66 to 12.07	8.15 to 15.85	6.72 to 13.27	7.75 to 18.26
CV%	30.4	34.2	35.04	44.9

AUC_{inf}, Area under the plasma concentraion-time curve time 0 to infinity; C_{max}, maximum plasma concentration; $t_{1/2}$, terminal elimination half-life; t_{max}, maximum drug concentration time.