

Supplementary Material to Härtter et al. “Pharmacokinetics and pharmacodynamics in Japanese and Caucasian subjects after oral administration of dabigatran etexilate” (Thromb Haemost 2012; 107.2)

Supplementary Table 1: Summary of studies included in the retrospective analysis.

Study design	Population (No. on dabigatran)	Gender	Origin	Age (years)	BMI (kg/m ²)	CrCl (mL/min)	Dose (mg)
Single-dose Phase I Studies							
R, DB, PC, SR (1)	HV (32) ^a	40 M	20 C	24.1 (20-37)	22.2 (20-24.8)	121.0 (102-136.8)	50, 150
			20 J	27.6 (21-36)	21.4 (18.6-24.9)	115.0 (87.0-153.6)	
NON-R, OL, SR (2)	HV (42)	42 M	21 C	27 (20-45)	22.3 (19.0-25.0)	140.6 (102.0-168.0)	150, 220, 300
			21 J	29.9 (20-45)	21.5 (19.0-25.0)	128.8 (90.0-164.0)	
R, OL, 2-way CO (3)	HV (28)	23 F, 5 M	28 C	36.1 (18.5-55)	22.6 (19.3-27.8)	NR	150
R, OL, 3-way CO ± food or pantoprazole (4)	HV (18)	18 M	18 C	37 (21-44)	25.4 (20.2-28.9)	NR	150
R, OL, 3-way CO (5)	HV (12)	12 M	12 C	34.5 (19-48)	24.4 (19.9-28.8)	NR	150
R, partly DB, PC, 4- way CO ± moxifloxacin (6)	HV (40)	20 M, 20 F	40 C	38.6 (24-53)	24.2 (19.9-29.7)	NR	150, 600
NON-R, OL, PG (7)	HV, renal impairment (35) ^b	28 M, 7 F	35 C	49.8 (20–69)	24.9 (20.0-30.2)	53.9 (13-141)	50 ^c , 150
NON-R, OL, PG(8)	HV, hepatic impairment (24) ^d	14 M, 10 F	24 C	55.0 (38-68)	27.9 (19.2-34.6)	105.1 (75.0-194.0)	150

Supplementary Table 1: cont. Summary of studies included in the retrospective analysis.

Study design	Population (No. on dabigatran)	Gender	Origin	Age (years)	BMI (kg/m²)	CrCl (mL/min)	Dose (mg)
Multiple-dose Phase I Studies							
NON-R, OL, MR (2)	HV (40) ^e	42 M	21 C	27.0 (20-45)	22.3 (19.0-25.0)	140.6 (102.0-168.0)	150, 220 qd, 150 bd ^f for 7 days
			21 J	29.9 (20-45)	21.5 (19.0-25.0)	128.8 (90.0-164.0)	
NON-R, OL (9)	HV (48)	48 M	24 C	30.2 (22-43)	23.4 (19-27.2)	132.2 (103.5-166.6)	110, 150 bd for 7 days
			24 J	24.6 (20-33)	22.9 (19.5-27.7)	144.7 (100.9-184.4)	
NON-R, OL (10)	HV (7)	7 M	7 J	24.4 (21-30)	20.0 (18.0-24.0)	128.1 (114.1-142.9)	150 bd for 7 days
R, OL, 3-way CO ± diclofenac (11)	HV (24)	12 M, 12 F	24 C	38.7 (21-54)	24.0 (18.8-29.7)	NR	150 bd for 1-3 days, 150 od on day 4
R,OL, GC ± amiodarone (12)	HV (24)	12 M, 12 F	1 A, 23 C	30.8 (19-49)	23.6 (18.4-28.4)	NR	150 bd for 4 days
R, OL, 3-way CO ± atorvastatin (13)	HV (22) ^g	12 M, 12 F	24 C	43.3 (19-64)	25.1 (18.4-29.7)	NR	150 bd for 4 days
R, OL, 3-way CO ± digoxin (14)	HV (23) ^h	12 M, 11 F	22 C,1 B	39.3 (19-58)	24.1 (19.9-29.6)	NR	150 bd for 4 days

Supplementary Table 1: cont. Summary of studies included in the retrospective analysis.

Study design (Study No.)	Population (No. on dabigatran)	Gender	Origin	Age (years)	BMI (kg/m ²)	CrCl (mL/min)	Dose (mg)
Phase II Studies							
R, DB, AC, PG, 3 x 3 factorial (15)	AF (427) ⁱ	349 M, 78 F	424 C, 2 B, 2 A	69.9 (40-90)	29.0 (17.2-48.4)	80.4 (23.2-210.4)	50, 150, 300 bd for 12 weeks
R, OL, AC, PG (16)	AF (103) ⁱ	88 M, 15 F	103 J	68.4 (43-87)	24.9 (16.0-37.0)	76.2 (36.8-160.9) ^j	110, 150 bd for 12 weeks
R, DB, AC, PG (17)	THR and TKR (1435) ⁱ	568 M, 867 F ⁱ	1428C, 5 B, 2A	65.9 (21-93)	28.1 (13.9-50.8)	96.2 (20.5-321.1)	50, 150, 225 bd, 300 od for 6 to 10 days
R, DB, PG, PC (18)	TKR (272) ⁱ	44 M, 228 F	272 J	71.6 (26-93) ⁱ	26.5 (18.0-43.0) ⁱ	83.8 (33.0-229.0) ^j	110, 150, 220 od for 11 to 14 days

Data presented as mean (range). ^aIncluded a further 8 volunteers on placebo; ^bIncluded 6 healthy volunteers (5 M and 1 F) and 29 patients in 4 renal impairment groups; ^c50 mg dose given to 6 patients with end stage renal failure on dialysis, remainder received 150 mg dose; ^dIncluded 12 healthy volunteers (7 M and 5 F) and 12 patients with hepatic impairment (Child-Pugh classification B); ^eTwo patients discontinued participation in the trial after completing single-dose treatment prior to multiple dosing treatment; ^f300 mg was administered in the morning on day 7 by mistake in 5 Japanese and 6 Caucasians; ^gA total of 24 healthy subjects were randomised. Two subjects were withdrawn from the study and 22 subjects completed the study according to the study protocol; ^hA total of 24 subjects (12 M and 12 F) were randomised in this study. One female withdrew consent after the first treatment period (digoxin alone) and 23 subjects completed the study according to the study protocol. ⁱNumber of patients undergoing pharmacokinetic assessment in the individual trial; ^jData based on total population (including comparator group). A, Asian; AC, active controlled; B, Black; bd, twice-daily; BMI, body mass index; C, Caucasians; CO, cross over; CrCl, creatinine clearance; DB, double blind; DE, dose escalation; DR, dose ranging; F, female; GC, group-comparison; HV, healthy volunteers; J, Japanese; od, once-daily; OL, open label; M, male; MR, multiple rising; NR, Not reported; NON-R, Non-randomised; PC, placebo controlled; PG, parallel-group; R, randomized; SR, single rising.

Supplementary Table 2: Pooled AUC data ($AUC_{0-\infty}$ after single/first dose and $AUC_{\tau,ss}$ after once- or twice-daily doses) grouped by race after oral administration of dabigatran etexilate 150 mg in healthy subjects (1-13,19).

Value	Total dabigatran	
	Japanese (n=41)	Caucasians (n=298)
Median (10 th and 90 th percentiles)	1110 (644 – 1824) ng·h/mL	924 (420 – 1654) ng·h/mL
Variability (CV%)	47.0%	61.4%

Variability (CV%) results are presented as geometric mean. AUC, area under the plasma concentration-time curve; $AUC_{0-\infty}$, area under the plasma concentration-time curve over the time interval from 0 extrapolated to infinity; $AUC_{\tau,ss}$, area under the plasma concentration-time curve at steady state over a uniform dosing interval τ ; CV%, coefficient of variation (%).

Supplementary Tables Reference List

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