STUDY NUMBER: 1041

TITLE: A Pharmacokinetic Interaction Study between HMR 3647 and Cisapride in Healthy Subjects.

INVESTIGATOR(S):

OBJECTIVES:

To determine the effect of HMR 3647 on the pharmacokinetics of cisapride.

To determine the effect of HMR 3647 on the pharmacodynamics related to the safety of cisapride.

STUDY DESIGN:

This study was a single blinded with respect to HMR 3647 only, randomized complete two-period crossover design. The study is consisted of two parts and four treatments.

Part I: Treatment A: once daily oral doses of placebo for 7 days followed by a single 20 mg (2 x 10 mg) dose of cisapride on day 7.

Treatment B: placebo on day 1, once daily oral doses of 800 mg HMR 3647 (2 x 400 mg) on days 2 through 7, and cisapride 20 mg (2 x 10 mg) on day 7.

Part II: Treatment C: once daily oral doses of placebo on days 1 through 6 and cisapride 10 mg (1x10 mg) three times daily (total of 13 doses) on days 2 through 6.

Treatment D: placebo on day 1, then 800 mg HMR 3647 (2 x 400 mg) once daily on days 2 through 6 concurrently with 10 mg (1 x 10 mg) cisapride three times daily on days 2 through 6 (total of 13 doses).

There was a drug free washout period of at least 12 days for subjects randomized to treatment B followed by treatment A, and at least 8 drug free days for subjects randomized to treatment A, then treatment B. In part II, at least nine drug free days occurred between treatments.

FORMULATION: HMR-3647 400 mg tablet (batch #: RG9823)

SAMPLING:

In treatment A and B, blood samples were collected prior to dosing on days 5, 6, 7 and at 0, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, and 24 hours after the last dose of HMR 3647 and cisapride at day 7.

In treatment A and B, serial ECG (1, 1.5, 2, 2.5, 3, 6, and 12 hours after the dose) were recorded on day 1 after placebo dose and day 6 (effect of steady state HMR alone) and day 7 after coadministration of HMR3647 and cisapride (cisapride effect for treatment A and effect of steady state of HMR3647+single dose of cisapride for treatment B).

In treatment C and D, blood samples were collected at day 2,4 and 5 prior to the dose and at 0, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, and 24 hours after the last dose of HMR 3647 and cisapride at day 6. Two more samples for cisapride measurement were collected at 36 and 48 hours after the last dose.

For treatment C and D, serial ECG were recorded at day 1 after placebo and day 6 after the last dose of HMR and cisapride.

ASSAY: Cisapride concentration in plasma was determined by a validated HPLC/MS method. The performance of the assay is shown in the following:

	HMR 3647	Cisapride
Accuracy of QC samples	-4.7 % to 3.0 %	-0.8% - 3.2%
Precision (CV) of QC samples	2.5 % - 9.2 %	2.9% - 7.5%
The limit of quantification		

DATA ANALYSIS:

Pharmacokinetics:

Pharmacokinetic parameters such as C_{max}, t_{max}, $AUC_{0-\infty}$ were calculated using non-parametric method.

Statistics:

HMR 3647 plasma concentration data were to be descriptively compared to HMR 3647 plasma concentration data from previous comparable studies. Trough concentrations of HMR 3647 for measured on days 5, 6, and 7 were to be compared to determine if steady-state was reached.
A comparison of trough concentrations of cisapride on days 4, 5, and 6 within treatments C and D was made to determine achievement of steady-state.
Comparisons between treatments were to be made for cisapride plasma pharmacokinetic variables.
An ANOVA, with terms for sequence, subject within sequence, period, and treatment was to be done for each variable, from which 90% confidence intervals for the ratio of treatment means were to be calculated. Treatment B was to be compared to treatment A with treatment A as the reference treatment.
QTc data for treatment C and D subjects were to be summarized descriptively. A pharmacodynamic analysis was to be conducted to examine possible relationships between changes in QTc and plasma pharmacokinetic variables for both HMR 3647 and cisapride. However, it was decided later during the development of the clinical program to conduct an analysis of QTc and plasma pharmacokinetic variables across several studies. Thus, results of a pharmacodynamic analysis examining possible relationships between changes in QTc and plasma pharmacokinetic variables will be presented in a separate report.

RESULTS:

A total of 42 subjects completed the study; 14 subjects completed part I of the study (all male with age ranged from 23 to 45 years), and 28 subjects completed part II of the study (all male with age ranged from 20 to 44 years old).

Pharmacokinetics:

The pharmacokinetic parameters of cisapride after a single dose and multiple doses are shown in Table 1 and 2. The concentration vs time profiles are shown in Figure 1 and 2.
The concomitant administration of a single oral dose of cisapride and 800 mg HMR 3647 resulted in a 1.7-fold increase in the peak plasma concentration (Treatment B Cmax = 155.74 ng/mL, range: [redacted] ng/mL). Furthermore, the extent of absorption was 2.5 times higher for cisapride following multiple oral doses of HMR 3647 as compared to that observed after the placebo administration. The estimated AUC(0-∞) values for Treatment B ranged from 1602.8 to 3584.5 ng•h/mL, with an average of 2402.96 ng•h/mL. The co-administration of HMR 3647 resulted in a corresponding 2.5-fold decrease in the estimated cisapride CLpo (23.62 vs 8.88 L/h). The estimated mean terminal elimination half-life values of cisapride administered alone and with 800 mg HMR 3647 were 8.69 h (range: 5.50 h to 16.41 h) and 9.9 h (range: 7.64 to 12.93 h), respectively. Concomitant administration of cisapride and 800 mg HMR 3647 did not change cisapride half-life.
Concomitant administration of multiple oral doses of 10 mg cisapride and 800 mg HMR 3647 resulted in similar changes in cisapride pharmacokinetics. The peak plasma cisapride concentration at steady state on average was 71.96 ng/mL (range: [redacted] ng/mL) for treatment C and 138.49 mg/L (range: [redacted] ng/mL) for treatment D (1.92-fold increase). Concomitant administration of 800 mg HMR 3647 caused a 2.5-fold increase in the estimated AUC,ss(0-8) values for cisapride. When 800 mg HMR 3647 was concomitantly administered with cisapride, the mean cisapride CLpo was decreased from 27.15 L/h (Treatment C range: 25.31 to 47.25 L/h) to 11.24 L/h (Treatment D range: 6.73 to 16.87 L/h). However, the estimated mean terminal half-life values after treatment C (10.50 h, range: 5.83 to 22.43 h) and treatment D (11.61, range: 7.70 to 16.59 h) were not different.
Following multiple 800 mg (2 x 400 mg tablets in capsules) oral doses of HMR 3647, trough concentrations obtained on days 5, 6, and 7 exhibited an increase of about 24% per day. The difference among trough concentrations reached statistical significance. The estimated pharmacokinetic parameters of HMR 3647 after multiple 800 mg oral doses (six doses) administered together with a single 20 mg oral dose of cisapride on day 7 (treatment B) and

together with multiple 20 mg cisapride (treatment D) are shown in Table 3. The mean plasma concentration vs time profiles are shown in Figure 3.

After multiple 800 mg HMR 3647 and together with a single dose of cisapride, HMR 3647 was rapidly absorbed with mean $C_{max,ss}$ of 2.96 mg/L (range: — mg/L) and mean $t_{max,ss}$ 1.29 (range: 1-2.5). AUC(0-∞) ranged from 9.89 mg/L*h to 21.60 mg/L*h with an average of 15.48 mg/L*h. The mean steady-state oral clearance of HMR 3647 was 57.62 L/h with a range of 39.62 to 83.65 L/h. The mean terminal elimination half-life $t_{1/2(\beta)}$ and $t_{1/2(\alpha)}$ were 7.71 h (range: 6.17-10.78 h) and 1.225 h (range: 0.29-4.17 h), respectively.

After multiple 800 mg HMR 3647 and with multiple 20 mg cisapride, the observed HMR 3647 $C_{max,ss}$ value was on average 2.99 mg/L (range: — mg/L) with a mean $t_{max,ss}$ value of 1.11 h (range: 1 to 2 h). The estimated AUC(0-∞) values for HMR 3647 ranged from 4.74 to 25.39 mg•h/mL with an average of 14.65 mg*h/mL. The estimated mean $t_{1/2(\alpha)}$, $t_{1/2(\beta)}$, and $CL_{po,ss}$ were 1.17 h (range: 0.4 to 2.75 h), 8.64 h (range: 6.38 to 15.46 h), and 68.42 L/h (range: 34.25 to 176.15 L/h), respectively.

Pharmacodynamics:

ECG was recorded on day 6 and day 7 for treatment A and B in part I and descriptive analysis are shown in Table 4 for QTc and Delta QTc and Table 5 for QTf and delta QTf. The study design allowed comparing QT prolongation effect between treatments. The comparison of QT_c interval/delta QTc, QT_f interval/Delta QT_f between treatments are shown in Figure 4-7. The results indicated that QT prolongation effect of HMR 3647 is similar to that of cisapride. Coadministration of cisapride and HMR 3647 would significantly increase the QTc interval. The effect on delta QT_c are similar. The observed QT prolongation effect was less if using QT_f instead of QTc as evaluator.

Similar results were observed in Treatment C and Treatment D when multiple cisapride were given with placebo or HMR 3647 (Table 6 and Table 7). When coadministration of HMR 3647 with cisapride, the QT was significantly prolonged (Figure 8 and Figure 9).

CONCLUSION:

1. Multiple oral doses of 800 mg HMR 3647 had significant impact on the single dose plasma pharmacokinetics of cisapride. The Cmax and AUC for cisapride increased 1.7 and 2.5 times, respectively, with co-administration of multiple dose HMR 3647.
2. Multiple doses of cisapride and 800 mg HMR 3647 administered concomitantly showed a similar magnitude of change in the pharmacokinetics of cisapride.
3. It has been demonstrated that HMR 3647 is a substrate and competitive inhibitor of CYP3A4. Therefore, the observed changes in the single and multiple dose pharmacokinetics of cisapride could be attributed to both nonsystemic and systemic changes in the CYP3A4 activity by HMR 3647.
4. The maximum mean QTc interval prolongation following administration of 800 mg HMR 3647 with single and multiple doses of cisapride was similar (33 msec and 43 msec, respectively, at 1.5 hour postdose).
5. When 800 mg HMR 3647 was administered concomitantly with cisapride, pronounced increases in mean QTc interval duration were observed at 1, 1.5, 2, 2.5, 3 and 6 hour postdose, and were significantly greater than those observed when 800 mg HMR 3647 or cisapride were administered alone.
6. HMR 3647 should not be administered with cisapride.

COMMENTS:

1. ECG record was measured on day 6 in treatment A and B before cisapride was given on day 7. However, no serial blood samples were collected on day 6, therefore, the relationship

between delta QTc with HMR 3647 concentrations could not be explored. Serial ECG was recorded on day 7 when HMR 3647 and cisapride were co-administered. Therefore, the effect of QT prolongation would be attributed by both cisapride and HMR 3647.

2. Serial ECG was recorded on day 1 (placebo), day 6 (HMR 3647 at steady state) and day 7 (when cisapride and HMR 3647 were coadministered) in treatment B and on day 7 in treatment A (after cisapride only and placebo)
3. When coadministered with cisapride, Cmax and AUC of HMR after multiple dose are about 3 mg/L and 14 mg•/L, which was about 50% and 40% increased compared with Cmax and AUC of 2 mg/L and 10 mg•/L from study 1013.
4. The heart rate ranged from 48-82 bpm, 47 to 86 bpm, 53-89 bpm, 58-104 bpm after placebo, HMR 3647 treatment, single dose cisapride and coadministration of HMR 3647 + cisapride, indicating that heart beat increase not significant enough to prefer QTf to QTc.

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Table 1. Mean cisapride plasma pharmacokinetic parameters following a single oral 20 mg dose of cisapride after once daily oral dosing for 6 days with placebo (treatment A) or 800 mg HMR 3647 (treatment B)

							Pairwise comparisons [a]		
					Adjusted		Ratio		
Parameter	Trtm	N	Mean	CV%	mean	Pair	(%)	(90% CI) on ratio	P-value
AUC(0-z) (ng/mL*h)	A	14	914.55	49.09	806.85	B/A	268.88	(234.92, 307.75)	<0.001
	B	14	2286.24	28.01	2169.45				
AUC(0-inf) (ng/mL*h)	A	14	1022.55	45.36	914.35	B/A	249.85	(219.39, 284.54)	<0.001
	B	14	2402.96	27.54	2284.53				
Clpo (L/h)	A	14	23.62	45.18	21.87	B/A	40.02	(35.14, 45.58)	<0.001
	B	14	8.88	25.28	8.75				
Cmax (ng/mL)	A	14	92.77	34.43	86.88	B/A	170.62	(154.37, 188.58)	<0.001
	B	14	155.74	27.06	148.24				
$t_{1/2}$ (h)	A	14	8.69	34.68	8.23	B/A	118.16	(106.14, 131.55)	0.017
	B	14	9.90	16.56	9.73				
Tmax (h)	A	14	2.29	26.74	2.20	B/A	118.08	(99.67, 139.88)	0.106
	B	14	2.75	30.05	2.60				

Treatment A = once daily oral doses of HMR 3647 placebo for 7 days followed by a single 20 mg (2 x 10 mg) dose of cisapride on day 7.

Treatment B = placebo on day 1, once daily oral doses of HMR 3647 800 mg (2 x 400 mg) on days 2 through 7, and cisapride 20 mg (2 x 10 mg) on day 7.

a Log transformed results of the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% confidence interval.

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Table 2. Mean cisapride plasma pharmacokinetic parameters following cisapride 10 mg three times daily for 5 days concomitantly with once daily dosing for 5 days with placebo (treatment C) or 800 mg HMR 3647 (treatment D)

							Pairwise comparisons [a]		
					Adjusted		Ratio	(90% CI) on	
Parameter	Trt	N	Mean	CV	mean	Pair	(%)	ratio	P-value
AUC,ss(0-8)	C	28	399.47	28.85	383.68	D/C	238.34	(226.48, 250.83)	<0.001
(ng/mL*h)	D	28	941.31	25.00	914.48				
AUC,ss (0-z)	C	28	804.51	43.29	734.85	D/C	322.52	(299.37, 347.45)	<0.001
(ng/mL*h)	D	28	2530.29	37.52	2370.00				
AUC,ss (0-inf)	C	28	920.04	40.40	848.89	D/C	296.73	(276.30, 318.68)	<0.001
(ng/mL*h)	D	28	2688.83	37.31	2518.92				
Clpo,ss	C	28	27.15	29.60	26.06	D/C	41.96	(39.87, 44.16)	<0.001
(L/h)	D	28	11.24	23.45	10.94				
Cmax,ss	C	28	71.96	28.56	69.29	D/C	195.28	(183.26, 208.09)	<0.001
(ng/mL)	D	28	138.49	22.21	135.32				
Cmin,ss	C	28	33.14	39.29	30.39	D/C	249.36	(226.76, 274.22)	<0.001
(ng/mL)	D	28	80.41	36.10	75.79				
$t_{1/2,ss}$	C	28	10.50	34.71	9.98	D/C	113.70	(104.67, 123.51)	0.014
(h)	D	28	11.61	21.94	11.35				
tmax,ss	C	28	1.36	37.33	1.28	D/C	155.20	(133.32, 180.68)	<0.001
(h)	D	28	2.11	34.99	1.99				

Treatment C = once daily oral doses of placebo on days 1 through 6 and cisapride 10 mg (1 x 10 mg) three times daily on days 2 through 6.
Treatment D = placebo on day 1, then HMR 3647 800 mg (2 x 400 mg) once daily on days 2 through 6 concurrently with 10 mg (1 x 10 mg) cisapride three times daily on days 2 through 6.
a Log transformed results of the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% confidence interval.

Table 3. Pharmacokinetic parameters of HMR 3647 after multiple doses

	Treatment B mean±sd (CV%) [range]	Treatment D mean±sd (CV%) [range]
C_{max} (mg/L)	2.960±0.690 (23.3%)	2.99±1.05 (35.2%)
AUC(0-24)ss (mg*h/L)	14.573±3.186 (21.9%)	13.65±4.72 (34.59%)
AUC (0-inf) (mg*h/L)	15.476±3.31 (21.4%)	14.65±4.95 (33.8%)
CL (L/hr)	57.62±13.67 (23.7%)	68.42±32.59 (47.64%)
$t_{1/2}$ (h)	7.72±1.28 (16.6%)	8.64±1.97 (22.8%)
C_{min} (mg/L)	0.072±0.021 (28.8%)	0.058±0.023 (40.24%)
C_{ave} (mg/L)	0.607±0.133 (21.9%) [0.398-0.841]	0.57±0.20 (14.6%) [0.189-0.973]

Table 4. Part I descriptive statistics for expert-read QTc interval (msec) and change from day 1 average

		Day 6				Day 7			
ECG		Treatment A (placebo)		Treatment B (HMR)		Treatment A (Cisapride)		Treatment B (HMR+Cisapride)	
Time Hour after dose	Statistic	QTc interval	Delta QTc	QTc interval	Delta QTc	QTc interval	Delta QTc	QTc interval	Delta QTc
08:00	Number	14	14	14	14	14	14	14	14
1	Mean (S.D.)	390 (18)	0 (11)	401 (16)	11 (9)	403 (15)	13 (13)	416 (16)	26 (11)
	Median	387	-1	399	7	404	13	420	24
	Range	362 - 426	-18 -24	370 - 432	2 -31	367 - 431	-9 -46	385 - 435	6 -50
08:30	Number	14	14	14	14	14	14	14	14
1.5	Mean (S.D.)	391 (11)	1 (10)	404 (8)	14 (7)	400 (12)	10 (9)	423 (12)	33 (9)
	Median	392	1	404	15	404	11	429	31
	Range	370 - 413	-15 -14	390 - 421	2 -26	370 - 422	-6 -22	396 - 439	23 -48
09:00	Number	14	14	14	14	14	14	14	14
2	Mean (S.D.)	387 (12)	-3 (7)	403 (10)	13 (11)	400 (11)	10 (9)	419 (12)	28 (12)
	Median	385	-3	403	11	400	12	418	29
	Range	360 - 405	-15 -8	382 - 417	-2 -32	378 - 416	-18 -20	399 - 440	12 -54
09:30	Number	14	14	14	14	14	14	14	14
2.5	Mean (S.D.)	387 (11)	-4 (8)	400 (7)	9 (10)	395 (11)	4 (7)	416 (14)	26 (13)
	Median	388	-4	400	12	396	4	419	27
	Range	364 - 404	-18 -9	387 - 409	-9 -29	368 - 409	-8 -19	394 - 441	9 -48
10:00	Number	14	14	14	14	14	14	14	14
3	Mean (S.D.)	387 (15)	-4 (8)	398 (8)	8 (8)	399 (14)	9 (11)	417 (19)	27 (19)
	Median	386	-3	402	9	398	10	419	26
	Range	356 - 405	-16 -6	385 - 408	-6 -28	374 - 422	-12 -29	388 - 458	-4 -64
13:00	Number	14	14	14	14	14	14	14	14
6	Mean (S.D.)	391 (17)	1 (11)	398 (17)	8 (10)	397 (15)	7 (8)	413 (12)	23 (12)
	Median	396	1	401	4	399	4	415	22
	Range	360 - 414	-23 -17	368 - 428	-1 -32	367 - 418	-3 -17	393 - 435	4 -41
19:00	Number	14	14	14	14	14	14	14	14
12	Mean (S.D.)	389 (13)	-1 (8)	390 (12)	-1 (10)	398 (10)	7 (9)	403 (15)	13 (10)
	Median	385	1	392	-3	401	5	409	14
	Range	371 - 409	-19 -10	369 - 409	-18 -15	380 - 415	-5 -23	374 - 422	-6 -28

Note: Treatment A is HMR3647 placebo on days 1-7 and 20 mg cisapride on day 7; Treatment B is HMR3647 placebo on day 1, 800 mg HMR3647 on days 2-7 and 20 mg cisapride on day 7

Delta QTc - change from the Day 1 average of the 08:00, 08:30, 09:00, 09:30, 10:00, 13:00 and 19:00 ECG measurements

Table 5. Part I descriptive statistics for expert-read QTf interval (msec) and change from day 1 average

		Day 6				Day 7			
ECG		Treatment A (placebo)		Treatment B (HMR)		Treatment A (Cisapride)		Treatment B (HMR+Cisapride)	
Time Hour after dose	Statistic	QTf interval	Delta QTf	QTf interval	Delta QTf	QTf interval	Delta QTf	QTf interval	Delta QTf
08:00	Number	14	14	14	14	14	14	14	14
1	Mean (S.D.)	386 (19)	-3 (9)	391 (18)	3 (5)	393 (15)	4 (9)	399 (17)	12 (5)
	Median	380	-6	389	3	395	3	404	11
	Range	357 - 422	-14 -13	368 - 437	-5 - 15	361 - 419	-12 -26	371 - 435	2 -20
08:30	Number	14	14	14	14	14	14	14	14
1.5	Mean (S.D.)	387 (12)	-2 (7)	392 (14)	5 (6)	389 (13)	0 (5)	403 (14)	15 (4)
	Median	388	-2	391	5	388	1	404	16
	Range	365 - 412	-14 -12	372 - 428	-9 -17	362 - 418	-8 -11	380 - 436	8 -21
09:00	Number	14	14	14	14	14	14	14	14
2	Mean (S.D.)	385 (14)	-4 (7)	392 (14)	4 (7)	390 (12)	1 (7)	399 (15)	12 (7)
	Median	383	-5	392	3	390	3	396	11
	Range	358 - 408	-15 -9	372 - 424	-11 -19	368 - 417	-19 -7	380 - 436	-2 -21
09:30	Number	14	14	14	14	14	14	14	14
2.5	Mean (S.D.)	387 (13)	-2 (5)	390 (12)	2 (6)	387 (13)	-2 (5)	398 (14)	11 (7)
	Median	384	-2	389	2	387	-3	399	13
	Range	365 - 412	-10 -5	371 - 419	-5 -11	360 - 414	-9 -5	377 - 436	-4 -22
10:00	Number	14	14	14	14	14	14	14	14
3	Mean (S.D.)	387 (16)	-1 (5)	391 (13)	4 (5)	392 (13)	3 (7)	401 (16)	13 (13)
	Median	386	-1	391	4	392	6	401	13
	Range	357 - 417	-10 -9	373 - 420	-3 -14	369 - 420	-10 -17	377 - 428	-11 -42
13:00	Number	14	14	14	14	14	14	14	14
6	Mean (S.D.)	387 (17)	-1 (8)	388 (19)	0 (7)	391 (16)	2 (7)	399 (13)	11 (9)
	Median	391	-3	391	-1	395	4	400	11
	Range	359 - 418	-17 -11	357 - 428	-11 -18	357 - 414	-7 -13	374 - 418	-4 -26
19:00	Number	14	14	14	14	14	14	14	14
12	Mean (S.D.)	382 (13)	-7 (7)	382 (14)	-6 (7)	386 (11)	-3 (7)	390 (15)	2 (5)
	Median	379	-5	382	-5	385	-3	390	2
	Range	365 - 408	-19 -2	363 - 417	-18 -5	366 - 405	-16 -7	366 - 420	-7 -14

Table 6. Part II descriptive statistics for expert-read QTc interval (msec) on day 6 and change from day 1 average

ECG		Treatment C (Placebo +Cisapride)		Treatment D (HMR 3647 + Cisapride)	
Time	Statistic	QTc	Delta QTc	QTc	Delta QTc
08:00	Number	28	28	28	28
	Mean (S.D.)	395 (15)	13 (8)	422 (23)	40 (15)
	Median	395	14	421	44
	Range	372 - 426	-5 -34	369 - 470	5 -60
08:30	Number	28	28	28	28
	Mean (S.D.)	392 (20)	10 (11)	425 (17)	43 (15)
	Median	392	12	425	41
	Range	349 - 435	-24 -25	395 - 456	17 -85
09:00	Number	28	28	28	28
	Mean (S.D.)	388 (19)	6 (11)	419 (20)	37 (15)
	Median	390	4	421	41
	Range	356 - 436	-13 -26	387 - 460	-1 -71
09:30	Number	28	28	28	28
	Mean (S.D.)	382 (17)	0 (10)	412 (16)	30 (13)
	Median	386	1	410	30
	Range	352 - 410	-19 -26	384 - 444	2 -64
10:00	Number	28	28	28	28
	Mean (S.D.)	382 (17)	0 (10)	410 (18)	28 (12)
	Median	383	2	409	27
	Range	353 - 416	-18 -23	378 - 455	9 -59
13:00	Number	28	28	28	28
	Mean (S.D.)	390 (21)	8 (11)	414 (16)	32 (10)
	Median	385	10	413	30
	Range	353 - 427	-20 -28	384 - 450	17 -53
19:00	Number	28	28	28	28
	Mean (S.D.)	387 (17)	5 (8)	401 (17)	19 (10)
	Median	386	7	399	22
	Range	355 - 421	-11 - 16	373 - 446	-5 - 37

Table 7. Part II descriptive statistics for expert-read QTf interval (msec) on day 6 and change from day 1 average

ECG		Treatment C		Treatment D	
Time	Statistic+	QTf	Delta QTf	QTf	Delta QTf
08:00	Number	28	28	28	28
	Mean (S.D.)	389 (13)	6 (7)	408 (19)	26 (12)
	Median	388	5	406	27
	Range	365 - 414	-12 -19	371 - 448	2 -49
08:30	Number	28	28	28	28
	Mean (S.D.)	386 (18)	3 (11)	408 (16)	26 (12)
	Median	389	5	408	25
	Range	345 - 420	-34 -18	381 - 439	8 -62
09:00	Number	28	28	28	28
	Mean (S.D.)	383 (18)	0 (10)	403 (18)	21 (12)
	Median	382	-1	405	24
	Range	346 - 425	-19 -17	372 - 440	-7 -46
09:30	Number	28	28	28	28
	Mean (S.D.)	381 (16)	-2 (8)	399 (15)	17 (10)
	Median	383	-2	400	17
	Range	353 - 402	-17 -14	374 - 427	-2 -46
10:00	Number	28	28	28	28
	Mean (S.D.)	382 (14)	-1 (7)	400 (18)	18 (10)
	Median	383	0	398	16
	Range	357 - 404	-16 - 16	371 - 433	6 -44
13:00	Number	28	28	28	28
	Mean (S.D.)	385 (19)	2 (9)	402 (15)	20 (8)
	Median	386	3	401	20
	Range	351 - 422	-28 -19	378 - 439	5 -38
19:00	Number	28	28	28	28
	Mean (S.D.)	379 (14)	-4 (8)	389 (16)	7 (8)
	Median	381	-3	390	9
	Range	353 - 404	-19 -7	363 - 424	-6 -18

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Figure 1. Mean plasma concentrations (ng/ mL) of cisapride following a single 20 mg oral dose of the drug after q. d. x 6 days oral treatment with placebo (treatment A) or 800 mg HMR 3647 (treatment B) (Part I)

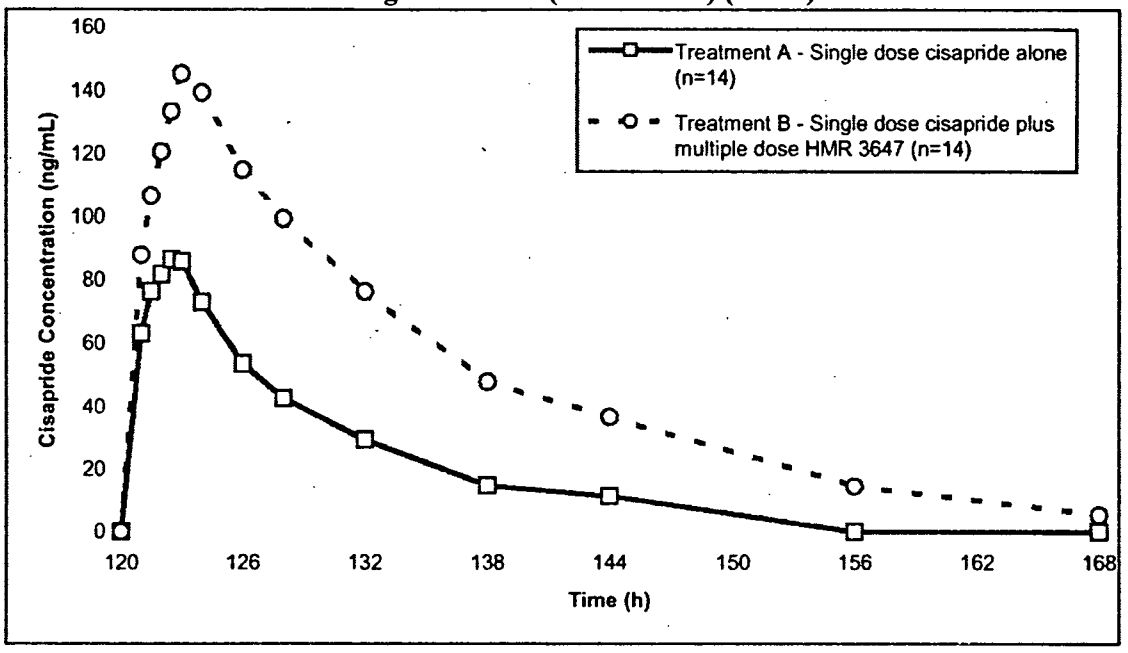


Figure 2 Mean plasma concentrations (ng/ mL) of cisapride during and following 10 mg cisapride t. i. d. x 5 days during simultaneous q. d. x 5 days oral treatment with placebo (treatment C) or 800 mg HMR 3647 (treatment D)

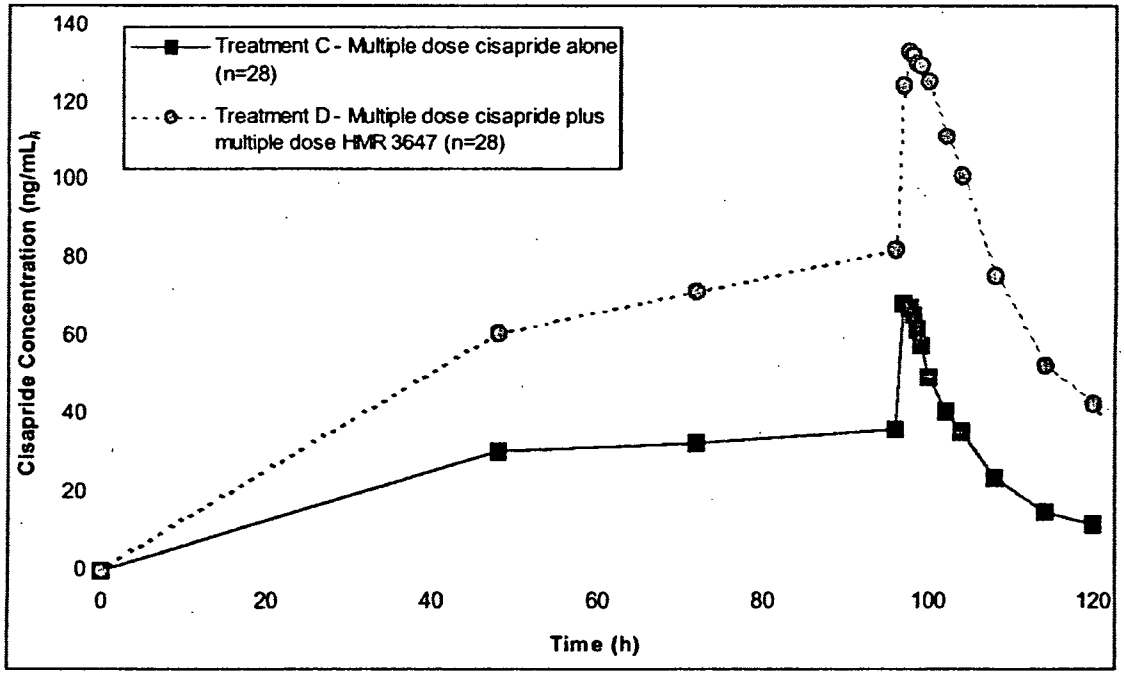
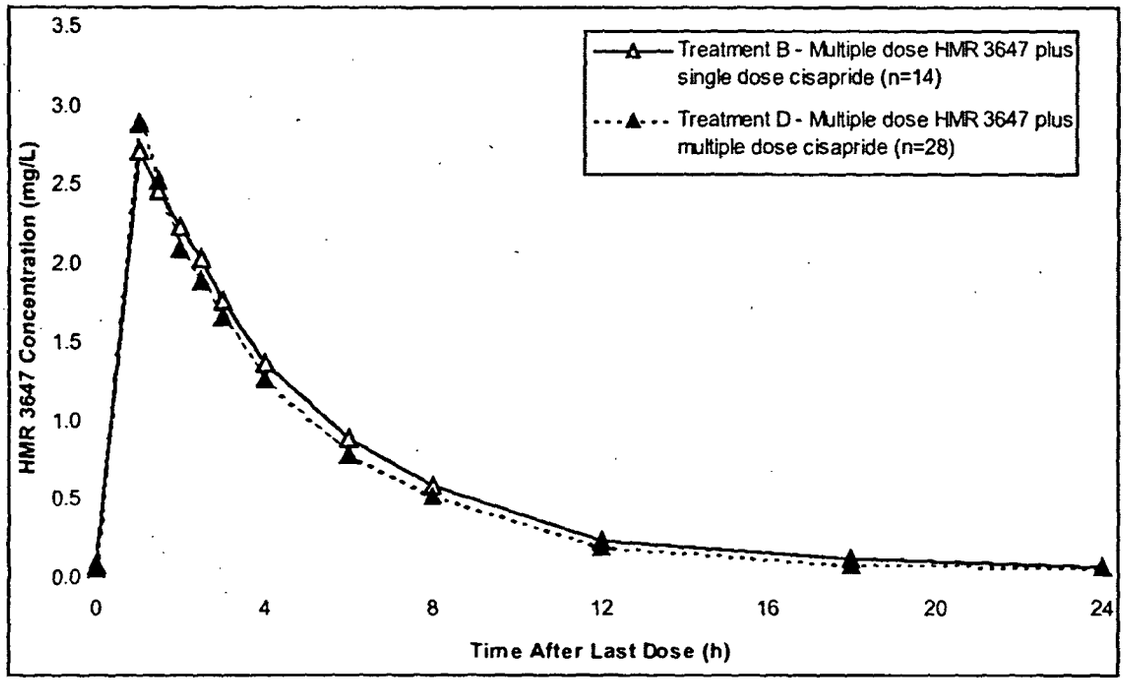


Figure 3. Comparison of mean plasma concentration profiles when 800 mg HMR 3647 was administered in the presence of single (20 mg) or multiple doses (10 mg t. i. d.) of cisapride



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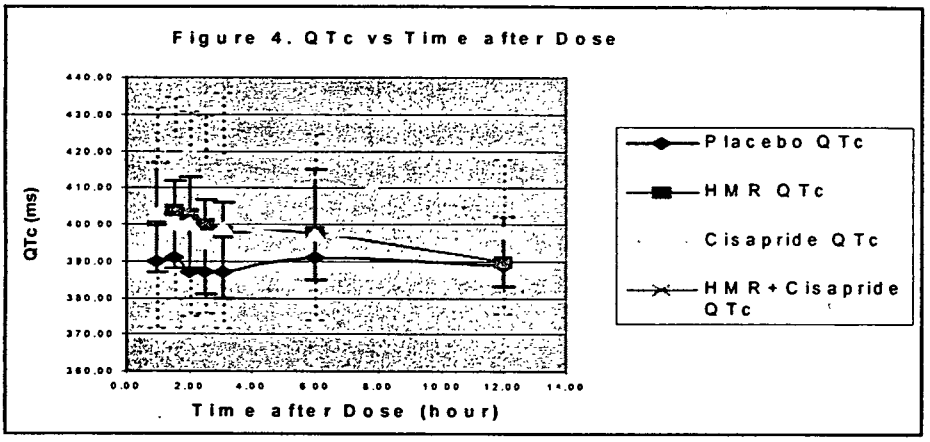
Figure 4. QTc vs Time after Dose
QTc (ms)
440.00
430.00
420.00
410.00
400.00
390.00
380.00
370.00
360.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
Time after Dose (hour)
Placebo QTc
HMR QTc
Cisapride QTc
HMR+Cisapride QTc

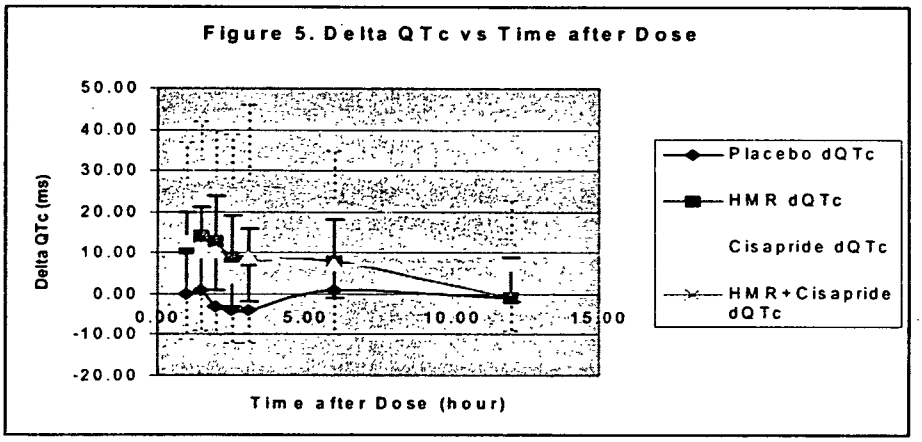
Figure 5. Delta QTc vs Time after Dose
Delta QTc (ms)
50.00
40.00
30.00
20.00
10.00
0.00
-10.00
-20.00
0.00
5.00
10.00
15.00
Time after Dose (hour)
Placebo dQTc
HMR dQTc
Cisapride dQTc
HMR+Cisapride dQTc

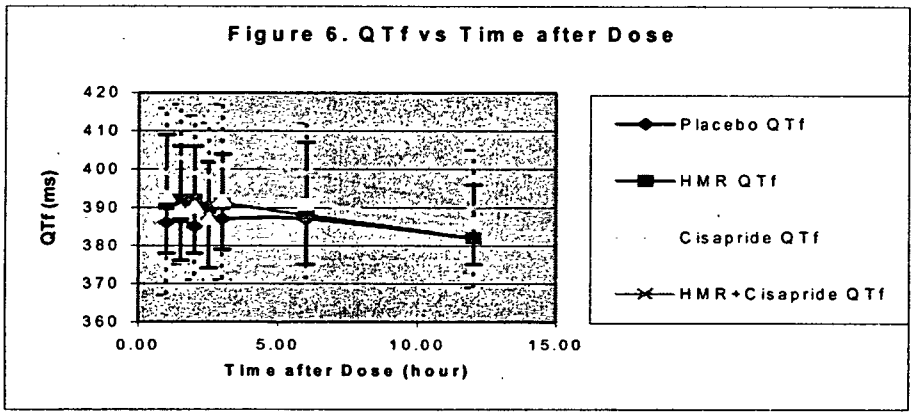
Figure 6. QTf vs Time after Dose
QTf (ms)
420
410
400
390
380
370
360
0.00
5.00
10.00
15.00
Time after Dose (hour)
Placebo QTf
HMR QTf
Cisapride QTf
HMR+Cisapride QTf

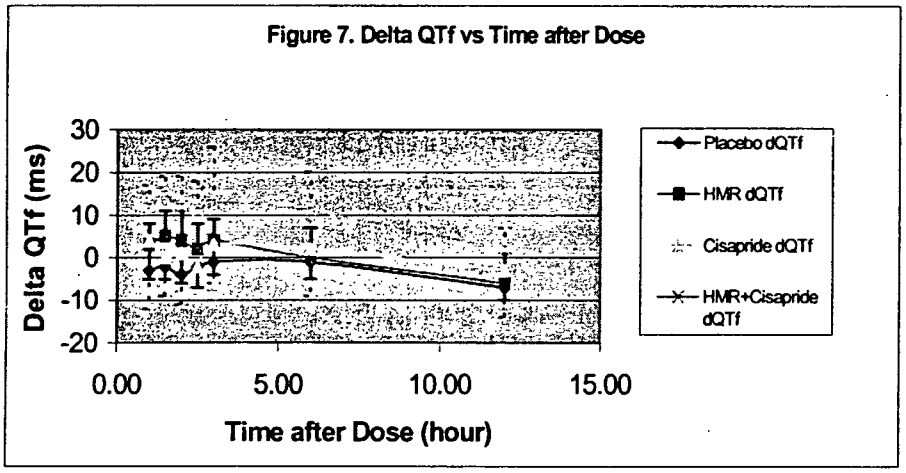
Figure 7. Delta QTf vs Time after Dose
Delta QTf (ms)
30
20
10
0
-10
-20
0.00
5.00
10.00
15.00
Time after Dose (hour)
Placebo dQTf
HMR dQTf
Cisapride dQTf
HMR+Cisapride dQTf

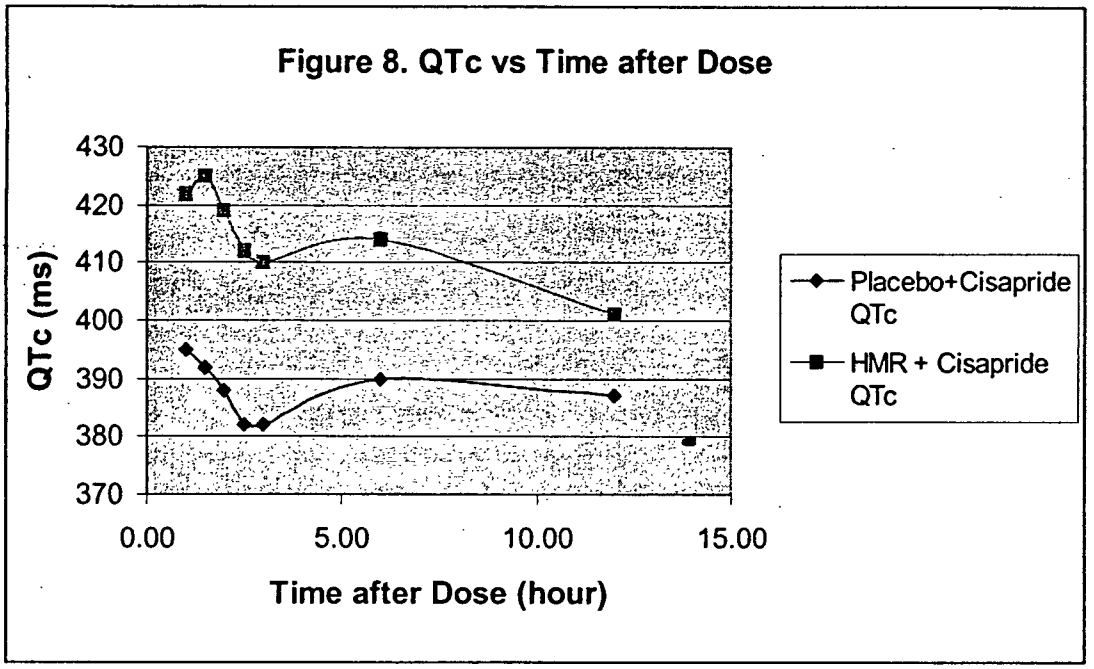
Figure 8. QTc vs Time after Dose
430
420
410
400
390
380
370
QTc (ms)
0.00
5.00
10.00
15.00
Time after Dose (hour)
Placebo+Cisapride QTc
HMR + Cisapride QTc

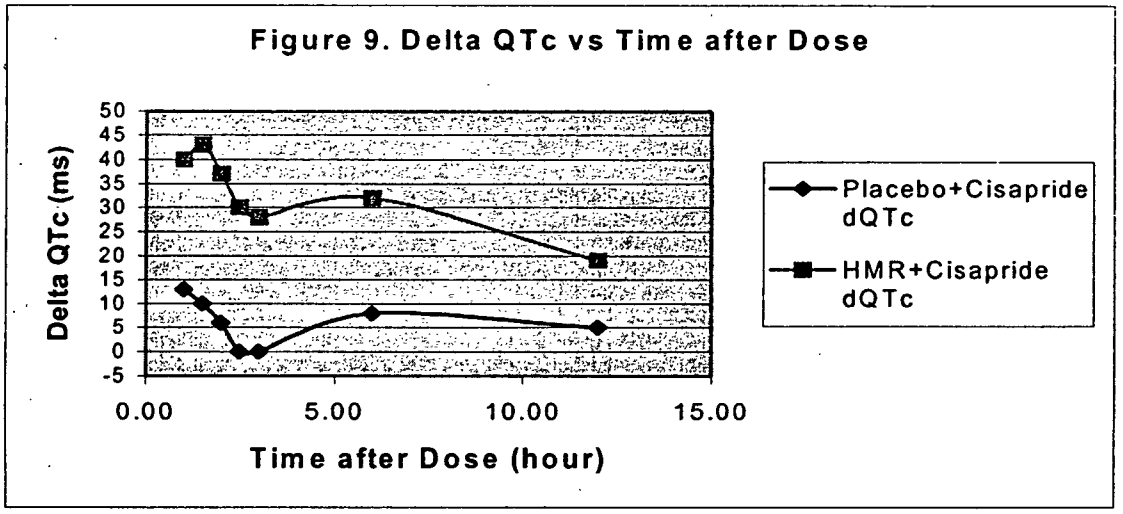
Figure 9. Delta QTc vs Time after Dose
50
45
40
35
30
25
20
15
10
5
0
-5
Delta QTc (ms)
0.00
5.00
10.00
15.00
Time after Dose (hour)
Placebo+Cisapride dQTc
HMR+Cisapride dQTc

STUDY NUMBER: 1042

TITLE: A study of the potential pharmacodynamic and pharmacokinetic interaction of HMR 3647 with low dose triphasic oral contraceptive (ethinyl estradiol/levonorgestrel) in healthy female subjects.

INVESTIGATOR(S): Dr. H.E.Scholtz, HMR Research Centre for Clinical Pharmacology, Bloemfontein, South Africa.

OBJECTIVES:

To assess the potential effect of HMR 3647 on the oral contraceptive's suppression of ovulation, using the plasma progesterone concentrations as marker of ovulation, or suppression thereof.
To assess the potential effect of HMR 3647 on the pharmacokinetics of ethinyl estradiol and of levonorgestrel.

STUDY DESIGN:

It was an open-label, non-randomized study in healthy female volunteers of childbearing potential, over three menstrual cycles.

Cycle I (including screening):

No medication. Subjects were to be screened within 4 weeks before the expected onset of Cycle II. On the 7th day before the expected onset of their next menstruation (approximately Day 21), plasma progesterone was to be determined in order to assess whether the subjects had ovulated. Women who did not ovulate during Cycle I were to be excluded from the remainder of the study.

Cycle II:

Oral contraceptive. Subjects were to receive the oral contraceptive once daily for the first 21 days of their cycle. On Day 21, plasma progesterone was to be determined in order to assess whether the subjects had ovulated. Subjects who ovulated during Cycle II were to be excluded from the remainder of the study.

Cycle III:

Oral contraceptive + HMR 3647. Subjects were to receive the oral contraceptive for the first 21 days, and 800 mg HMR 3647 once daily for 10 days, between Days 3 and 12 of the cycle. On Day 21, plasma progesterone was to be determined in order to assess whether the subjects had ovulated.

The pharmacokinetic profile was followed between Days 9 and 11 of Cycles II and III; the profile day was to be the same for Cycles II and III, within each subject.

FORMULATION: HMR-3647 400 mg tablet (batch #: MMG 27931-081)

SAMPLING: Plasma concentrations (24-hour profile) and pharmacokinetic variables of ethinyl estradiol and levonorgestrel in Cycles II and III at steady state were measured.
Plasma concentrations and pharmacokinetic variables of HMR 3647 in Cycle III at steady state were measured.
Plasma progesterone concentrations on Day 21 of Cycles I, II and III. Ovulation was assumed to have occurred if the plasma progesterone concentration exceeded 10 nmol/L on Day 21 of the cycle.

ASSAY: Plasma concentrations of HMR 3647 were measured by a validated LC/MS method.
The assays of ethinyl estradiol and levonorgestrel in plasma were performed using validated gas chromatography/mass spectrometry (GC/MS) methods. The performance of the assay is shown in the following:

	HMR 3647/Plasma	ethinyl estradiol	levonorgestrel	progesterone
Accuracy of QC samples	-9.1 % - 6.8 %	-9.4 % 10.0 %	-5.8 % - 7.9 %	-9.6 % - -1.8%
Precision (CV) of QC samples	10.1 %- 14.8 %	5.4 % - 14.6%	2.7 % - 5.1%	5.6% - 9.1%
The limit of quantification	—			

Progesterone was assayed by a validated radio-immunoassay method with a limit of quantification of —. Ovulation was assumed to have occurred if the plasma progesterone concentration exceeded 10 nmol/L on Day 21 of the cycle.

DATA ANALYSIS:

Pharmacokinetics:

Pharmacokinetic parameters such as C_{max}, t_{max}, $AUC_{0-\infty}$ were calculated using non-parametric method.

Statistics:

Analysis of variance (ANOVA) on $C_{max,ss}$ and AUC_{ss} of ethinyl estradiol and levonorgestrel (ln-transformed data); 90% confidence intervals were calculated for the mean ratio "Trinordiol®+HMR 3647 / Trinordiol®". Non-parametric analysis of t_{max}; 90% non-parametric confidence intervals were calculated for the median difference "(Trinordiol®+HMR 3647) - Trinordiol®".

The primary variable for assessment of a possible drug interaction was the proportion of subjects who ovulated during Cycle III, when the oral contraceptive and HMR 3647 were administered concomitantly. Based on this number, a one-sided exact 95% confidence interval for the risk of ovulation with concomitant treatment of HMR 3647 and Trinordiol® was calculated.

The primary variable for the assessment of a possible drug interaction was the proportion of subjects who ovulated during Cycle III, when the oral contraceptive and HMR 3647 were administered concomitantly. Based on this number, a one-sided exact 95% confidence interval of the form (0; r) for the risk of ovulation with concomitant treatment of HMR 3647 and Trinordiol® was calculated, by solving r from:

$$\sum_{t=0}^{T} {}^{n}C_{t} \; r^{t}(1-r)^{n-t} = \alpha$$ i.e.

$$\sum_{t=0}^{T} {}^{38}C_{t} \; r^{t}(1-r)^{38-t} = 0.05$$ where T is the observed number of ovulations in Cycle III.

Note: 38 subjects completed the study.

RESULTS:

Forty (40) healthy female volunteers were enrolled and treated with study medication: age 18.0-37.0 (mean: 22.0) years; weight 56.0-83.0 (mean: 65.7) kg. Thirty-eight (38) subjects completed the study, and were included in the pharmacodynamic (primary) analysis and the analysis of plasma HMR 3647. Only the first 30 subjects who completed the study were included in the analysis of plasma ethinyl estradiol and levonorgestrel.

The mean pharmacokinetic parameters for HMR 3647 are shown in Table 2.

Pharmacokinetics:

Pharmacokinetic parameters of estradiol and levonorgestrel are shown in Table 1. The mean plasma concentration vs time profiles are shown in Figure 1 and 2. Coadministration of HMR 3647 with Trinordiol caused 17% decrease in C_{max} but not AUC.The level of levonorgestrel was 19% and 50% increase in C_{max} and AUC, respectively when HMR 3647 was administered with oral contraceptive agents. However, no progesterone concentration >10 nmol/L was observed in Cycle III, i.e. none of the 38 subjects with observations, ovulated. The mean progesterone concentrations in the three cycles are shown in Table 2. In cycle I, all subjects' progesterone were higher than 10 nmol/L but in cycle II and III, none subject's progesterone level are higher than 10 nmol/L. The observed risk of ovulation with the combination of the oral contraceptive and HMR 3647 was

0%, with an upper 95% confidence limit of 7.58%. Thus, in the general population, it can be accepted with 95% certainty that the probability of an interaction will not exceed 7.58%.

The pharmacokinetic parameters of HMR 3647 are shown in Table 3. The peak steady state HMR 3647 concentrations ranged between 0.87 and 2.82 mg/L, and were observed at sampling times between 1 and 4 hours after medication. The mean AUC over 24 hours was 10.2 mg.h/L.

CONCLUSION:

1. Using progesterone as ovulation marker, it was found that concomitant HMR 3647 did not obtund the anti-ovulatory effect of the oral contraceptive in any of the 38 subjects who completed the study. In the general population it may, according to the study results, be accepted with 95% certainty that the probability of an interaction would not exceed 7.58%.
2. The AUC_{ss} of ethinyl estradiol was not affected by concomitant administration of HMR 3647, although a slight tendency towards a lower rate of absorption was observed.
3. The mean AUC_{ss} of levonorgestrel was increased by 50% with concomitant HMR 3647 administration; this was probably due to an increase of the bioavailability and a reduced rate of elimination of levonorgestrel with the combination treatment.

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Table 1. Plasma ethinyl estradiol and levonorgestrel pharmacokinetic variables Mean (CV%) and range (n=30)

Variable	Trinordiol® (Cycle II)	Trinordiol® + HMR 3647 (Cycle III)	Point estimate (90% CI)*	Intra-individual CV
Ethinyl estradiol				
$C_{max,ss}$	116.4 (27)	96.1 (30)	82.4%	14%
[pg/mL]			(77.6; 87.4%)	
t_{max}	1.50#	1.50#	0.50 h**	-
[h]			(0.25; 0.73 h)	
AUC_{ss}	917 (23)	935 (23)	102%	10%
[pg.h/mL]			(97.6; 107%)	
Levonorgestrel				
$C_{max,ss}$	4.78 (20)	5.71 (20)	120%	10%
[ng/mL]			(115; 125%)	
t_{max}	1.00#	1.00#	0.22 h**	-
[h]			(0.00; 0.25 h)	
AUC_{ss}	55.1 (27)	82.4 (25)	150%	10%
[ng.h/mL]			(144; 157%)	
$t_{½;z}$	27.0 (33)	33.7 (34)	125%	20%
[h]			(114; 136%)	

Median value

* Point estimate and 90% confidence interval for the mean ratio "(Trinordiol®+HMR 3647)/Trinordiol®", based on ln-transformed data analysis

** Point estimate and 90% confidence interval for the median difference "(Trinordiol®+HMR 3647) – Trinordiol®", based on non-parametric data analysis

Table 2. The mean values, coefficients of variation (CV%, in brackets) and ranges of the individual values of plasma progesterone in Cycles I, II and III

Variable	No medication (Cycle I, n=40)	Trinordiol® (Cycle II, n=39)	Trinordiol®+ HMR 3647 (Cycle III, n=38)
Progesterone concentration [nmol/L]	33.1 (48) 11.6 - 66.0	2.47 (40) 1.14 - 5.24	2.05 (42) 0.70 - 4.30

Table 3. The pharmacokinetic parameters for HMR 3647

Variable	Trinordiol®+ HMR 3647 (Cycle III, n=38)
$C_{max,ss}$	1.742 (29)
[mg/L]	0.873 – 2.815
t_{max}	3.00#
[h]	1.02 – 4.00
AUC_{ss}	10.18 (33)
[mg.h/L]	4.43 – 17.21

Median value

Figure 1. Plasma ethinyl estradiol concentrations [pg/mL] (Cycles II and III). Median values (N=30)

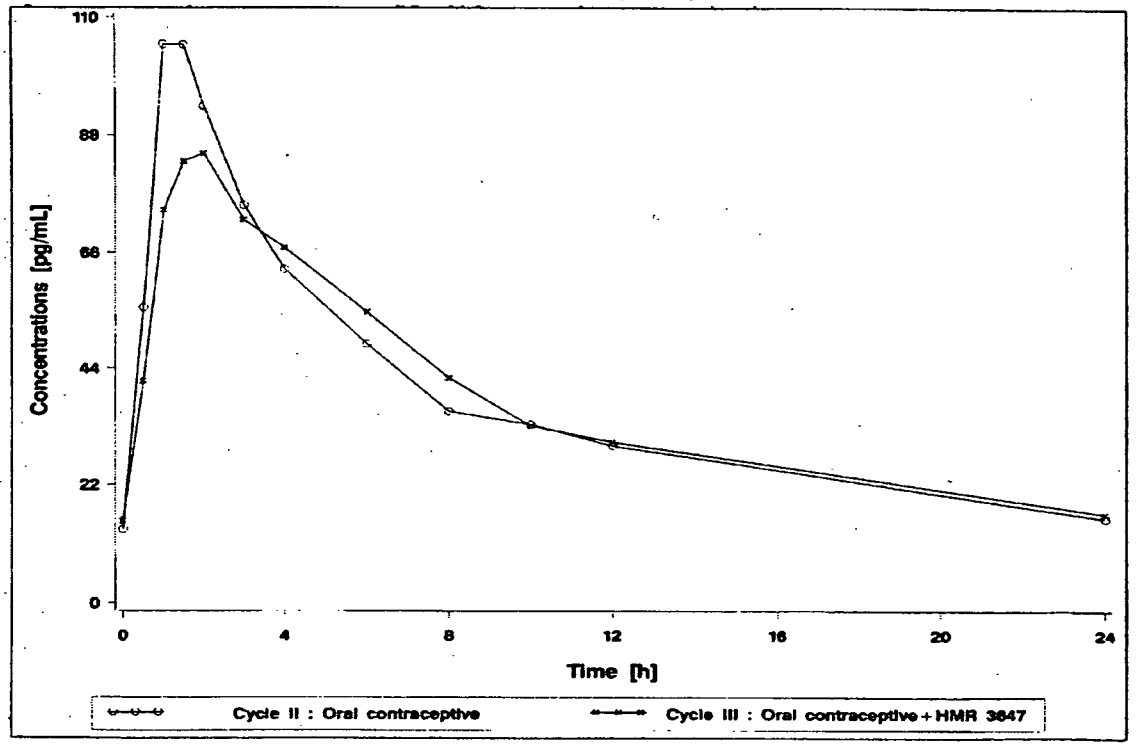


Figure 2. Plasma levonorgestrel concentrations [ng/mL] (Cycles II and III) Median values (N=30)

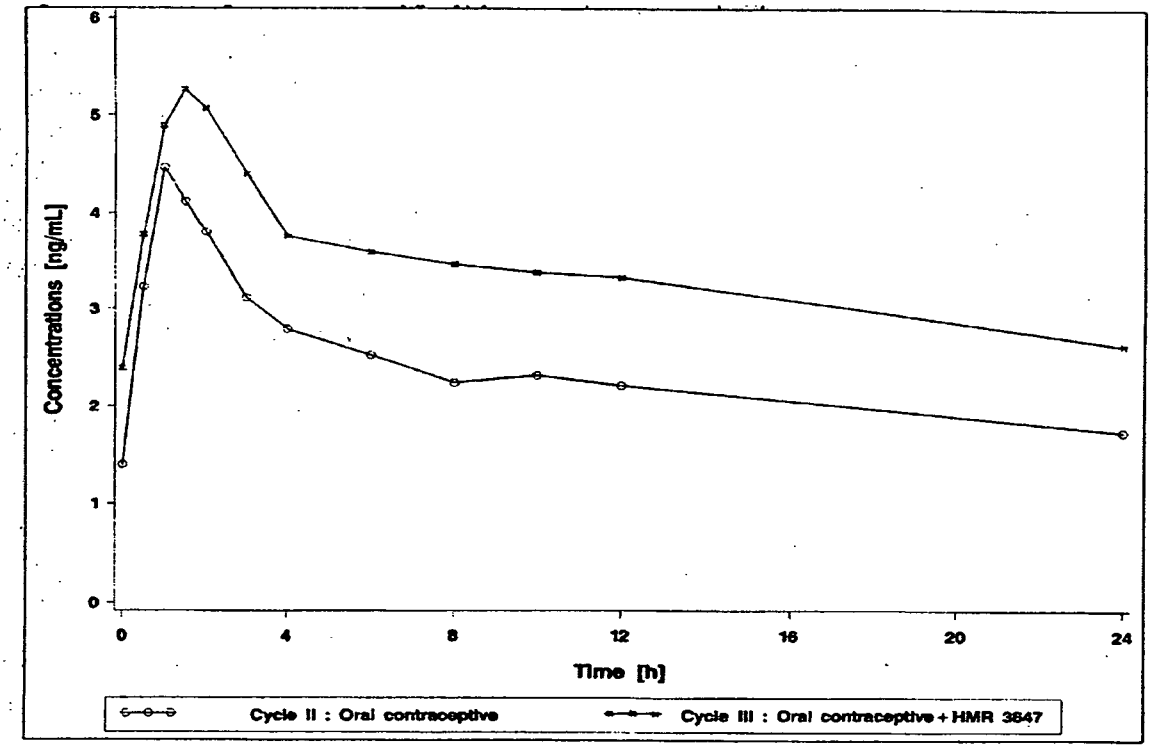
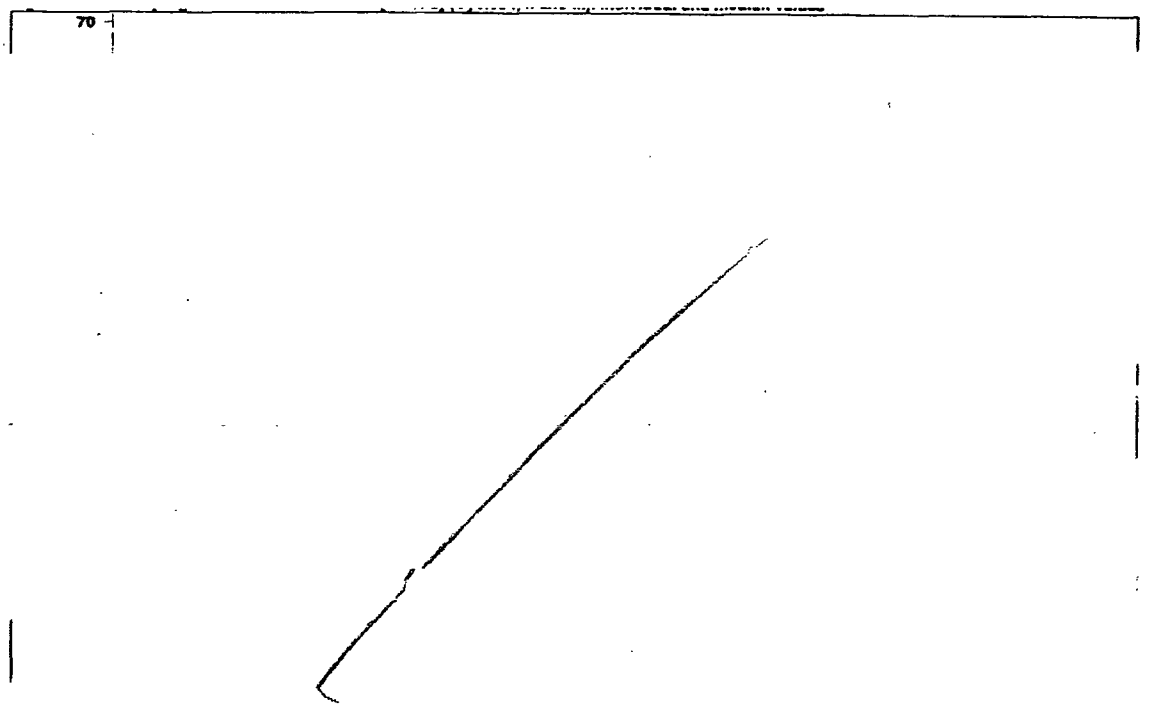


Figure 3. Plasma progesterone concentrations [nmol/L] (Cycles I, II and III). Individual and median values



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STUDY NUMBER: 1045
TITLE: The Effect of Concomitant Multiple Doses of Ketoconazole and HMR 3647 on Pharmacokinetic and ECG Measures: A Four Period Open-Label Crossover Drug-Drug Interaction Study.
INVESTIGATOR(S):

OBJECTIVES:
To determine the effect of concomitant dosing of HMR 3647 and ketoconazole on the pharmacokinetics of HMR 3647 and ketoconazole.
To determine the effect of concomitant dosing of HMR 3647 and ketoconazole on QTc interval.
STUDY DESIGN:
This was a randomized, open label, four way cross-over study. The following treatments were used in this study:
· Treatment A: HMR 3647 800 mg (2 x 400 mg oral tablets) once daily for 5 days (days 1 to 5)
· Treatment B: Ketoconazole 400 mg (2 x 200 mg tablets) once daily for 7 days (days 1 to 7)
· Treatment C: HMR 3647 800 mg (2 x 400 mg oral tablets) once daily for 5 days (days 1 to 5) and ketoconazole 400 mg (2 x 200 mg tablets) once daily for 7 days (days 1 to 7)
· Treatment D: Placebo HMR 3647 daily (2 oral capsules) for 5 days (days 1 to 5).
Washout between treatments was to be 13 days from the 72-hour sample following day 5 dosing. An erythromycin breath test was to be administered to all subjects in treatments A, B, C and D on day –1 and day 5. This test dosed subjects with 0.03 mg of radiolabeled erythromycin and 0.40 mg ethyl alcohol.
FORMULATION: HMR-3647 400 mg tablet (batch #: MD 28146-057)
SAMPLING:
Blood samples were drawn at 0 h (before drug administration), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72 and 96 h after drug administration at day 1. Blood samples were also collected before dosing on days 6-11 and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 48,5 4, 72 and 96h after the last dose of the HMR 3647 at day 5.
Urine was collected at the following fractions: 0-24, 24-48, 48-72 h after the single dose and the last dose of multiple dose.
QT interval was measured at pre-dose, and 0.5, 1, 1.5, 2, 2.5, 3, 4, and 8 hours after last dose of HMR3647 at day 5.
ASSAY: Plasma concentrations of HMR 3647 ant its major metabolite (RU 76363) were measured by a validated LC/MS method. The standard curve ranged from ng/mL for HMR 3647 and ng/mL. Plasma concentrations of ketoconazole were measured by HPLC with fluorescence detection. The concentrations of standard curve ranged from to ng/mL.
The performance of the assay is shown in the following:

	HMR 3647/Plasma	RU 76363	Ketoconazole
Accuracy of QC samples	-8.8% to 2.2 %	0%-6.7%	-5.6 to 6.1%
Precision (CV) of QC samples	5.3 %- 11.4%	3.2%-6.3%	1.7 to 3.8%
The limit of quantification			

DATA ANALYSIS:
Pharmacokinetics:
Pharmacokinetics parameters were calculated using non-parametric method.
Statistics:
Pharmacokinetic parameters were calculated from plasma concentrations of HMR 3647, RU 76363, and ketoconazole using standard validated noncompartmental techniques.

Comparisons between treatments were made for HMR 3647, RU 76363 and ketoconazole parameters. An analysis of variance (ANOVA) with terms for sequence, subject within sequence, period, and treatment was done for each parameter. From this ANOVA, least squares means for each treatment, estimated treatment differences, and 90% confidence intervals for treatment differences were calculated. These log-transformed results were transformed to the original scale by exponentiation to obtain adjusted means, treatment ratios, and 90% confidence intervals for these ratios.

For HMR 3647 and RU 76363 pharmacokinetic parameters, Treatment A (HMR 3647 alone) was compared to Treatment C (HMR 3647 concomitantly with ketoconazole), with Treatment A serving as the reference treatment. Similarity between treatments was defined as the limits of the 90% confidence interval on the ratio of treatment means falling entirely within 70% to 143%.

For ketoconazole pharmacokinetic parameters, Treatment B (ketoconazole alone) was compared to Treatment C (HMR 3647 concomitantly with ketoconazole), with Treatment B serving as the reference treatment. Similarity between treatments was defined as the limits of the 90% confidence interval on the ratio of treatment means falling entirely within 70% to 143%.

ECG analysis:

Maximal QTc and maximal QTc change from baseline on day 5 were the primary variables used for pharmacodynamic analysis. Maximal QTc interval was defined as the largest QTc interval within a 24-hour postdose period for a given subject. Maximal QTc change from baseline was the maximal QTc interval within a 24-hour period minus the baseline QTc interval for that subject for that period.

Baseline was calculated as the mean of the three predose measurements on day 1.

An ANCOVA of the primary pharmacodynamic estimates was performed, with the covariate of baseline of QTc on day 1. Treatments A (HMR 3647 alone), B (ketoconazole alone), and C (HMR 3647 concomitantly with ketoconazole) were each compared to Treatment D (placebo), with Treatment D serving as the reference treatment. Treatment C was compared to Treatments A and B, with Treatments A and B serving as the reference treatments. Similarity between treatments was assessed through the 90% confidence interval for the difference between two treatments.

RESULTS:

A total of 16 subjects were entered into the study and received study medication. Six subjects were withdrawn from the study prior to completion; three subjects (002, 004, 015) because of adverse events, one subject (001) was lost to follow-up and two subjects (010, 016) did not wish to continue in the study. Ten subjects completed the study according to the protocol.

Eleven subjects received Treatment A (800 mg HMR 3647 alone), 14 subjects received Treatment B (400 mg ketoconazole alone), 12 subjects received Treatment C (800 mg HMR 3647 administered concomitantly with 400 mg ketoconazole), and 12 subjects received Treatment D (placebo). One subject (004) who received Treatment C did not complete that period of the study and was discontinued from the study after day 2 in the Treatment C period. There were no blood samples drawn for this subject.

Pharmacokinetics:

HMR 3647:

Concomitant administration of ketoconazole with HMR 3647 did not have an effect on time to maximum plasma HMR 3647 concentration, and demonstrated a minimal effect on $t_{1/2,ss}$. In addition, concomitant administration of ketoconazole and HMR 3647 resulted in a greater exposure to HMR 3647, as indicated by a 1.51-fold increase in $C_{max,ss}$, and a 1.95-fold increase in $AUC(0\text{-}24)_{ss}$, based upon the ratio of adjusted means (Table 1.).

RU76363:

Concomitant administration of ketoconazole with HMR 3647 did not have an effect on $t_{1/2,ss}$, and demonstrated a minimal effect on time to maximum plasma RU 76363 concentration and AUC(0-

24)$_{ss}$. In addition, concomitant administration of ketoconazole and HMR 3647 resulted in a reduced maximum exposure to RU 76363, as indicated by a 27% decrease in $C_{max,ss}$ (Table 2).

Ketoconazole

Concomitant administration of ketoconazole with 800 mg HMR 3647 did not have an effect on apparent $t_{1/2,ss}$, and demonstrated a minimal effect on time to maximum plasma ketoconazole concentration. In addition, there was reduced exposure to ketoconazole as indicated by a 20% decrease in Cmax,ss, and a 20% decrease in AUC(0-24)ss, based upon the ratio of adjusted means (Table 3).

Electrocardiogram (ECG)

The study protocol specified the analysis of QTc was to be performed for both maximum QTc and maximum change in QTc from baseline. It was observed that when baseline QTc was added to the analysis model identical results were obtained for both pharmacodynamic variables – maximum QTc and maximum change in QTc from baseline. Therefore, only results from the analysis of maximum QTc are presented. The statistical analysis results are shown in table 4.

HMR3647 vs. Placebo (A/D):

The adjusted means for maximum QTc recorded for Treatment A (HMR 3647 only) and Treatment D (placebo) were similar, with the 90% confidence interval of the difference of adjusted means ranging from –2.30 to +9.00 msec.

Ketoconazole vs. Placebo (B/D) and HMR3647+ketoconazole vs Placebo (C/D):

The adjusted means for maximum QTc recorded for Treatment B (ketoconazole only) and Treatment C (HMR 3647 administered concomitantly with ketoconazole) were both different from the adjusted mean for Treatment D (placebo). The 90% confidence interval of the difference of adjusted means between Treatment B (ketoconazole alone) and Treatment D ranged from +0.92 to +11.9 msec, while the 90% confidence of difference of adjusted means between Treatment C and Treatment D ranged from +4.80 to +16.20 msec.

HMR-3647+ketoconozole vs. Ketoconazole (C/B):

The adjusted means for maximum QTc recorded for Treatment C (HMR 3647 administered concomitantly with ketoconazole) and Treatment B (ketoconazole alone) were similar with the 90% confidence interval of the difference of adjusted means ranging from –1.50 to +9.67 msec.

HMR-3647+ketoconozole vs. Ketoconazole (C/A):

The adjusted mean for maximum QTc recorded for Treatment C was different from the adjusted mean for Treatment A (HMR 3647 alone). The 90% confidence interval of difference of adjusted means between Treatment C and Treatment A ranged from +1.42 to +12.9 msec.

In summary, the administration of HMR 3647 alone did not result in an increase in maximum QTc. Increases in maximum QTc were observed when the subjects were given ketoconazole. The addition of HMR 3647 to ketoconazole did not result in an additional increase in maximum QTc.

Erythromycin Breath Test (EBT)

Following the administration of placebo, there did not appear to be a change in liver CYP3A4 activity, as demonstrated by a minimal changes and high variability in the change in the amounts of $^{14}CO_2$ collected for the EBT between day –1 and day 5. Compared to placebo (Treatment D), there were reductions in the amount of $^{14}CO_2$ collected for Treatment A (HMR 3647 alone), Treatment B (ketoconazole alone) and Treatment C (HMR 3647 concomitantly with ketoconazole). When 800 mg HMR 3647 was administered alone, there was a decrease (35.6% reduction with a 93% CV) in the change in the amount of $^{14}CO_2$ collected for the EBT between day –1 and day 5. Following the administration of 400 mg ketoconazole alone, there was a greater decrease (65.8%) and less variability (25% CV) in the change in the amount of $^{14}CO_2$ collected for the EBT between day –1 and day 5 than observed with HMR 3647 alone. These results suggest both HMR 3647 and ketoconazole produce an inhibition in liver CYP3A4 activity.

The inhibition of liver CYP3A4 observed when HMR 3647 is administered alone appeared to be less than observed when ketoconazole was administered alone. The 35.6% reduction in CYP3A4 activity (as demonstrated by changed in $^{14}CO_2$ collected between day –1 and day 5) for HMR 3647 alone is similar to the 26.2% reduction reported with clarithromycin (500 mg clarithromycin twice daily for two days) and the 37.4% reduction reported with erythromycin (500 mg three times daily for seven days). The concomitant administration of HMR 3647 with ketoconazole did not produce a greater level of CYP3A4 inhibition than observed from ketoconazole alone.

CONCLUSION:

1. A 95% increase in HMR 3647 AUC and a 51% increase in HMR 3647 Cmax at steady-state were observed when ketoconazole was co-administered with HMR 3647.
2. The rate of elimination for ketoconazole (as measured by apparent terminal elimination half-life) at steady-state were not significantly changed with the concomitant administration of HMR 3647.
3. A 20% decrease in ketoconazole AUC and maximum exposure to ketoconazole (as measured by Cmax) at steady-state was observed when ketoconazole was co-administered with HMR 3647.
4. The total systemic exposure to RU 76363 was not altered by the concomitant administration of ketoconazole with HMR 3647, indicating that ketoconazole inhibit GI P450 more significant that liver P450 which resulted in increase of AUC and Cmax of the parent compound but not the metabolite.
5. No significant changes in maximum QTc were observed with the administration of 800 mg HMR 3647 compared to placebo.
6. Ketoconazole increased the risk of HMR3647 at 800 mg in QTc prolongation. When ketoconazole coadministered with HMR 3647 at 800 mg, the maximal QTc was significantly different from HMR 3647 use alone (C/A)
7. HMR 3647 alone, ketoconazole alone, and HMR 3647 concomitantly with ketoconazole inhibit liver CYP3A4 activity.
8. Ketoconazole alone inhibited liver CYP3A4 activity more than observed with HMR 3647 alone. The level of CYP3A4 activity observed with HMR 3647 alone was similar to that reported with either erythromycin or clarithromycin.
9. Ketoconazole concomitantly with HMR 3647 did not inhibit liver CYP3A4 activity more than was observed with ketoconazole alone.

COMMENTS:

1. The sponsor should submit the analysis on delta QTc, too.
2. In this study, analysis was conducted on the maximal recorded QTc for a given subject, which is considered to be adequate.

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Table 1. Mean HMR 3647 pharmacokinetic parameters following once daily oral dosing with 800 mg HMR 3647 alone (Treatment A) or 400 mg ketoconazole administered concomitantly with 800 mg HMR 3647 (Treatment C)

							Pairwise comparisons			
				CV	Adjusted		Ratio [b]			
Parameter	Trmt [a]	N	Mean	(%)	mean [b]	Pair	(%)	90% Conf. interval [b]		P-value
AUC(0-24)ss (mg/L*h)	A	11	14.43	38.73	13.67	C/A	194.51	(150.10, 252.06)		0.002
	C	11	28.55	31.03	26.60					
$C_{max.ss}$ (mg/L)	A	11	2.02	37.92	1.93	C/A	151.31	(111.86, 204.67)		0.036
	C	11	3.13	35.82	2.91					
$t_{1/2}$ (h)	A	11	11.24	26.41	10.76	C/A	115.04	(94.53, 140.00)		0.218
	C	11	12.58	27.47	12.38					
t_{max} (h)	A	11	2.59	38.42	2.43	C/A	104.57	(81.57, 134.05)		0.743
	C	11	2.64	25.57	2.54					
CL (L/h)	A	11	64.01	40.7	NA	NA	NA	NA	NA	NA
	C	11	31.94	46.1%	NA	NA	NA	NA	NA	NA

a Treatment A - HMR 3647 800 mg (2 x 400 mg tablet) once daily for 5 days
Treatment C - HMR 3647 800 mg (2 x 400 mg tablet) once daily for 5 days and ketoconazole 400 mg (2 x 200 mg tablet) once daily for 7 days
b Log transformed results of the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% confidence interval.

Table 2. Mean RU 76363 pharmacokinetic parameters following once daily oral dosing with 800 mg HMR 3647 alone (Treatment A) or 400 mg ketoconazole administered concomitantly with 800 mg HMR 3647 (Treatment C)

							Pairwise Comparisons			
				CV	Adjusted		Ratio [b]			
Parameter	Trmt [a]	N	Mean	(%)	mean [b]	Pair	(%)	90% Conf. interval [b]		P-value
$AUC(0\text{-}24)_{ss}$ (mg/L*h)	A	11	1.43	33.60	1.37	C/A	94.59	(69.69,	128.39)	0.740
	C	11	1.34	34.00	1.29					
C_{max} (mg/L)	A	11	0.133	37.00	0.126	C/A	73.47	(54.24,	99.51)	0.096
	C	11	0.096	39.39	0.092					
$t_{1/2,ss}$ (h)	A	11	10.75	39.05	10.36	C/A	112.95	(98.04,	130.14)	0.147
	C	11	12.98	30.17	11.70					
$t_{max,ss}$ (h)	A	11	4.77	26.24	4.75	C/A	113.57	(89.31,	144.43)	0.349
	C	11	5.74	27.14	5.40					

a Treatment A - HMR 3647 800 mg (2 x 400 mg tablet) once daily for 5 days
Treatment C - HMR 3647 800 mg (2 x 400 mg tablet) once daily for 5 days and ketoconazole 400 mg (2 x 200 mg tablet) once daily for 7 days
b Log transformed results of the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% confidence interval.

Table 3. Mean ketoconazole pharmacokinetic parameters following once daily oral dosing with 400 mg ketoconazole alone (Treatment B) or 400 mg ketoconazole administered concomitantly with 800 mg HMR 3647 (Treatment C)

							Pairwise Comparisons			
				CV	Adjusted		Ratio [b]	90% Conf.		P-
Parameter	Trmt [a]	N	Mean	(%)	mean [b]	Pair	(%)	interval [b]		value
$AUC(0\text{-}24)_{ss}$	B	14	92512.7	32.4	87361.9	C/B	80.44	(67.41,	95.99)	0.052
(ng/mL*h)	C	11	73572.4	38.2	70272.4					
C_{max}	B	14	9908.3	21.7	9632.6	C/B	80.16	(70.12,	91.64)	0.017
(ng/mL)	C	11	7890.9	27.8	7721.6					
$t_{1/2}$	B	14	4.54	23.8	4.48	C/B	92.28	(82.36,	103.41)	0.223
(h)	C	11	4.33	30.7	4.13					
$t_{1/2}$	B	14	2.3	29.4	2.19	C/B	121.07	(96.70,	151.59)	0.151
(h)	C	11	2.8	28.4	2.65					

a Treatment B - Ketoconazole 400 mg (2 x 200 mg tablet) once daily for 7 days
Treatment C - HMR 3647 800 mg (2 x 400 mg tablet) once daily for 5 days and ketoconazole 400 mg (2 x 200 mg tablet) once daily for 7 days

b Log transformed results of the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% confidence interval.

c Plasma samples for the determination of elimination half-life were collected from 0 to 24 hours following ketoconazole dosing.

Since the collection interval is less than 3 times the ketoconazole terminal elimination half-life, the estimates for t1/2 represent apparent elimination half-life over 24 hours rather than terminal elimination half-life. These were calculated for the purpose of comparison of apparent elimination between treatments rather than a definitive determination of terminal elimination half-life.

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Table 5. Maximum QTc after once daily oral dosing with 800 mg HMR 3647 alone (Treatment A), 400 mg ketoconazole alone (Treatment B), 800 mg HMR 3647 concomitantly with 400 mg ketoconazole (Treatment C), or placebo (Treatment D)

						Pairwise differences		
Parameter	**Trmt**	**Mean**	**N**	**Pair**	**Est diff**	**SE of diff**	**(90% CI) on diff**	**P-value**
Maximum QTc (msec)	A	410.4	11	A-D	3.344	3.314	(-2.3, 9.00)	0.322
	B	413.4	14	B-D	6.388	3.207	(0.92, 11.9)	0.057
	C	417.5	11	C-D	10.493	3.336	(4.80, 16.2)	0.004
				C-A	7.149	3.361	(1.42, 12.9)	0.043
				C-B	4.105	3.265	(-1.5, 9.67)	0.220
	D	407.0	12					

A = HMR 3647 800 mg once daily for 5 days
B = ketoconazole 400 mg once daily for 7 days
C = HMR 3647 800 mg once daily for 5 days and ketoconazole 400 mg once daily for 7 days
D = placebo

Table 5. Percent change (from day –1 to day 5) in $^{14}CO_2$ from Eythromycin Beath Test

	Treatment A (800 mg HMR 3647 alone)	**Treatment B (400 mg ketoconazole alone)**	**Treatment C (800 mg HMR 3647 concomitantly with 400 mg ketoconazole)**	**Treatment D (placebo)**
Mean	-35.60	-65.76	-62.74	+11.80
Std Dev	33.06	16.33	20.40	19.96
CV%	92.98	24.83	32.52	169.24
Median	-44.20	-70.93	-69.78	+6.19

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Figure 1. Mean (± SEM) HMR 3647 plasma concentration- time profiles for Treatment A (800 mg HMR 3647 x 5 days) and Treatment C (800 mg HMR 3647 x 5 days concomitant with 400 mg ketoconazole x 7 days)

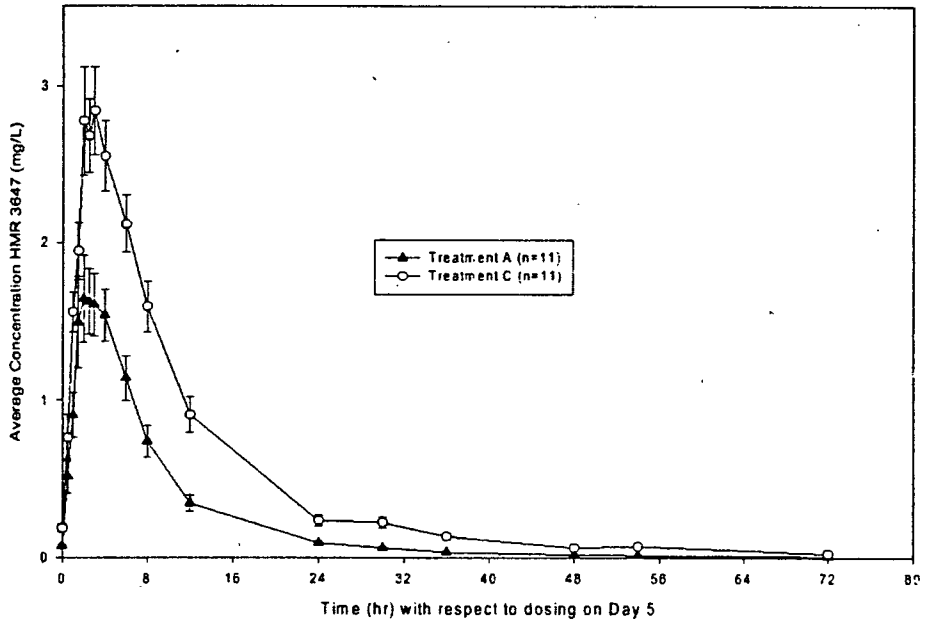


Figure 2. Mean RU 76363 plasma concentration- time profiles for Treatment A (800 mg HMR 3647 x 5 days) and Treatment C (800 mg HMR 3647 x 5 days concomitant with 400 mg ketoconazole x 7 days)

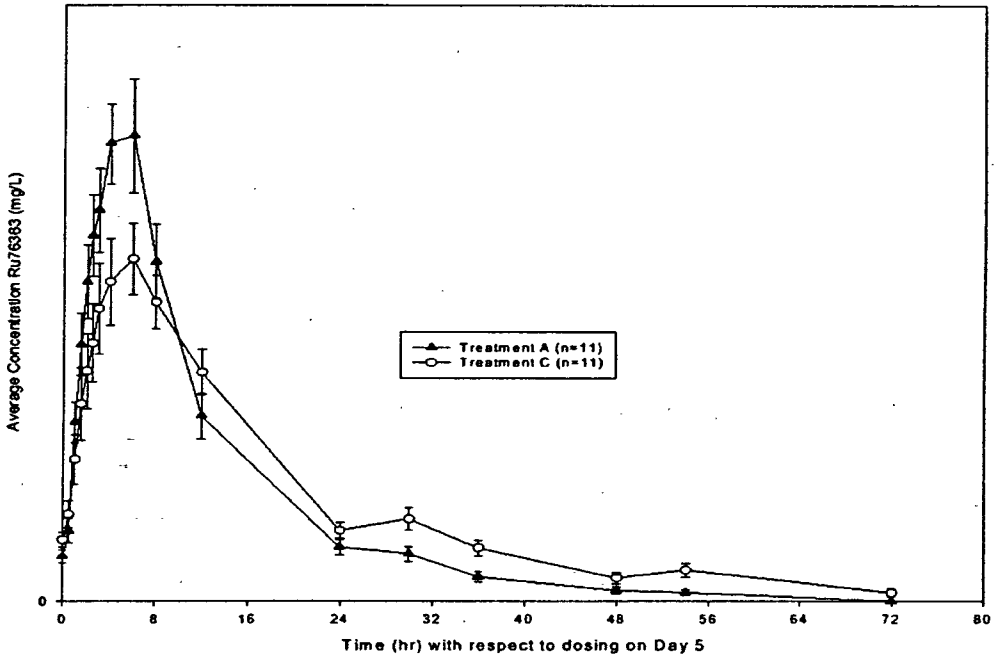
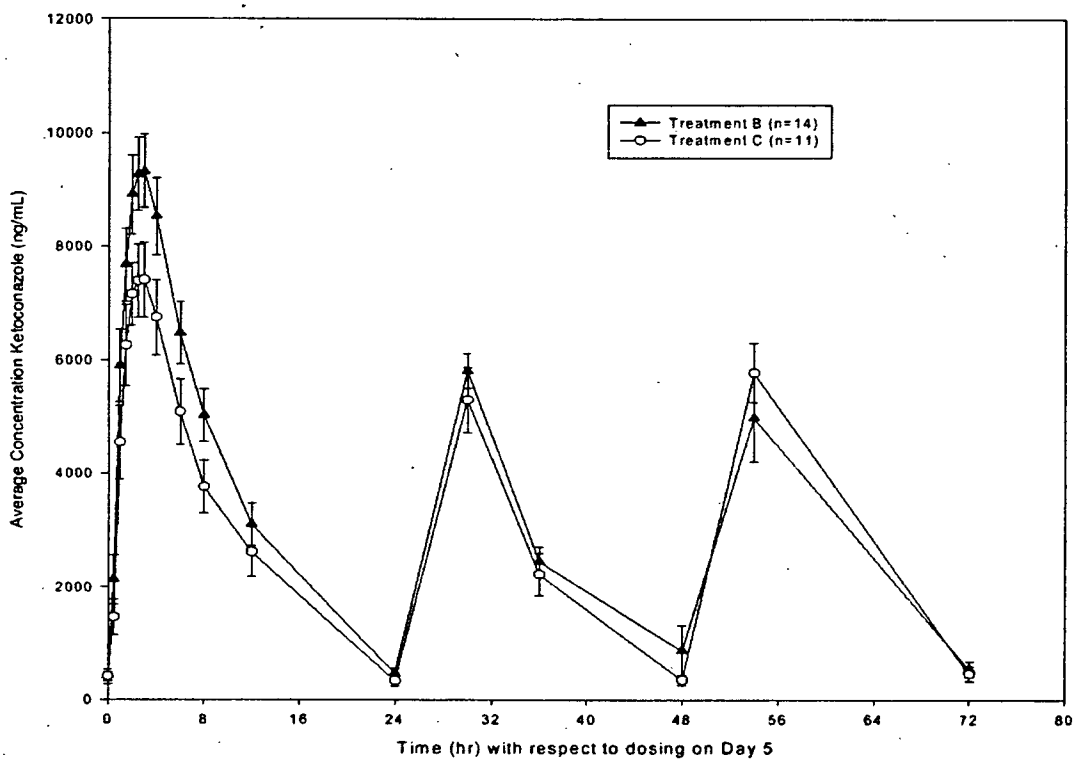


Figure 3. Mean ketoconazole plasma concentration- time profiles for Treatment B (400 mg ketoconazole x 7 days) and Treatment C(800 mg HMR 3647 x 5 days concomitant with 400 mg ketoconazole x 7 days)



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STUDY NUMBER: 1047
TITLE: The Effect of Concomitant Administration of Grapefruit Juice on the Single Dose Pharmacokinetics of HMR3647 in Healthy Male Adults.
INVESTIGATOR(S):

OBJECTIVES:
To determine the effect of concomitant administration of HMR3647 and grapefruit juice on the plasma pharmacokinetics of HMR3647 and its metabolite, RU76363.
STUDY DESIGN:
The study was designed as a single-center, open-label, randomized, two-period crossover, single dose study. There was a 12-day washout between the period 1 and the period 2 doses of HMR3647.
In each of the two study periods, subjects received one of the following treatments:
Treatment A: A single oral dose of 800 mg HMR3647 (as two 400 mg tablets) administered with 240 mL of water
Treatment B: A single oral dose of 800 mg HMR3647 (as two 400 mg tablets) administered with 240 mL of reconstituted single strength grapefruit juice
An Erythromycin Breath Test was to be administered to all subjects on day 1 (approximately 12 hours postdose) of both periods.
FORMULATION: HMR-3647 400 mg tablet (batch #: VL28095-021)
SAMPLING:
Blood samples were drawn at 0 h (before drug administration), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, 48, 54 and 72 hours after drug administration.
ASSAY: Plasma concentrations of HMR 3647 ant its major metabolite (RU 76363) were measured by a validated LC/MS method. The standard curve ranged from g/mL for HMR 3647 and ng/mL.
The performance of the assay is shown in the following:

	HMR 3647/Plasma	RU 76363
Accuracy of QC samples	-2.7 % to 1.6 %	-5.1 % - 1.7 %
Precision (CV) of QC samples	3.3 %- 8.4 %	2.8 % - 4.4 %
The limit of quantification		

Erythromycin Breath Tests (EBT) were to be administered to each subject on day 1 (approximately
12 hours postdose) of each study period. The EBT was performed to determine the activity of hepatic CYP3A4 isoenzymes during the elimination of HMR3647. CYP3A4 activity is measured by the percentage of the radiolabeled erythromycin dose that is expired as $^{14}CO_2$. A reduction in the percentage of the radiolabeled carbon dioxide indicates reduced CYP3A4 activity. EBT results were compared for Treatment A and Treatment B to determine if there was a difference in hepatic CYP3A4 activity between the treatments.
DATA ANALYSIS:
Pharmacokinetics:
Pharmacokinetic parameters were calculated from plasma concentrations of HMR3647 and RU76363 using standard noncompartmental techniques.
Statistics:
Comparisons between treatments were made with an analysis of the natural log-transformed data. An analysis of variance, with terms for sequence, subject within sequence, period, and treatment, was done for each parameter, from which 90% confidence intervals for the ratio of treatment means were obtained. Similarity between treatment comparisons was defined as the limits of the 90% confidence interval for the ratio of treatment means falling entirely within 70% to 143%.

RESULTS:

Sixteen healthy, male subjects between 18 and 45 years of age were enrolled, randomized, and treated in the study. One subject dropped from the study during period 1 for personal reasons. Fifteen subjects completed the study

Pharmacokinetics:

Mean HMR3647 and RU76363 plasma concentrations profiles of the two treatment results are presented in Figure 1 and 2. Summary statistical treatment comparison results are presented in Table 1 and Table 2. As shown in the table, the mean C_{max} are 1.46 and 1.49 mg/L without grapefruit and with grapefruit, respectively. The corresponding $AUC_{0-\infty}$ are 8.6 and 9.0 h•mg/L. No significant difference exists between the two treatments.

The EBT has been validated as a model drug probe for measuring in vivo hepatic CYP3A4 activity. After EBT administration, erythromycin is N-demethylated by CYP3A4 and the demethylated carbon appears as carbon dioxide in expelled breath. Intravenous ^{14}C erythromycin was administered approximately 12 hours after the HMR3647 dose in both treatments, and the breath test was done 20 minutes after the erythromycin dose to estimate hepatic CYP3A4 activity during the elimination phase of the drug. Since HMR3647 and RU76363 are metabolized by CYP3A4, the EBT test results were used to determine if hepatic CYP3A4 activity during the elimination phase was altered by the administration of grapefruit juice as compared to treatment with water. The investigator noted that the intravenous EBT dose may have infiltrated for Subjects 001 and 005 during Treatment B, which may explain the low ^{14}C metabolized per hour (%) results observed for these subjects. Therefore, Subjects 001 and 015 were not included in the EBT descriptive statistics for Treatment B or in the paired t-test analysis. The mean (sd) of ^{14}C metabolized per hour for treatment A and B are 1.86% (0.35) and 1.88% (0.36). A paired t-test analysis showed the two treatments were not significantly different with a p-value of 0.8881. The correlation between clearance of HMR3647 and percent of ^{14}C metabolized per hour is shown in Figure 3.

CONCLUSION:

1. Administration of grapefruit juice with HMR3647 did not effect the rate or extent of absorption of the parent compound as measured by AUC(0-∞), Cmax, and tmax .
2. A slight decrease in exposure to the metabolite, RU76363, was detected by AUC(0-∞) and Cmax with the grapefruit juice treatment.
3. Erythromycin Breath Test results indicate that administration of grapefruit juice does not appear to effect hepatic CYP3A4 activity during the elimination phase of HMR3647 or the RU76363 metabolite.

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Table 1. Statistical results for HMR 3647 pharmacokinetic parameters

Parameter (Units)	TRT	N	Mean	CV%	Adjusted LS Mean	Pair	Ratio Pair (%)	90%Conf. Interval
AUC(0-z) (hr*mg/L)	A	15	8.50	39.3	7.97	B/A	103.9	95.1-113.4
	B	15	8.89	39.0	8.28			
AUC(0-∞) (hr*mg/L)	A	15	8.60	38.8	8.08	B/A	103.9	95.2-113.4
	B	15	9.00	38.4	8.40			
C_{max} (mg/L)	A	15	1.46	41.4	1.36	B/A	100.8	90.0-112.9
	B	15	1.49	40.8	1.37			
$t_{1/2}$ (h)	A	15	11.37	52.2	10.31	B/A	92.9	76.6-112.6
	B	15	10.56	52.4	9.58			
t_{max} (h)	A	15	2.70	41.3	2.44	B/A	92.3	68.1-125.1
	B	15	2.47	41.5	2.25			

Treatment A = with water Treatment B = with grapefruit juice

Table 2. Statistical results for RU76363 pharmacokinetic parameters

Parameter (Units)	TRT	N	Mean	CV%	Adjusted LS Mean	Pair	Ratio Pair (%)	90%Conf. Interval
AUC(0-z) (hr*mg/L)	A	15	0.88	27.7	0.84	B/A	88.0	79.4-97.5
	B	15	0.78	28.7	0.74			
AUC(0-∞) (hr*mg/L)	A	15	0.92	26.5	0.88	B/A	88.8	80.5-97.8
	B	15	0.81	27.6	0.78			
C_{max} (mg/L)	A	15	0.11	26.9	0.10	B/A	82.7	73.7-92.8
	B	15	0.09	29.3	0.09			
$t_{1/2}$ (h)	A	15	7.09	40.4	6.45	B/A	115.8	98.1-136.7
	B	15	7.89	38.0	7.47			
t_{max} (h)	A	15	3.40	17.8	3.34	B/A	107.1	95.6-120.0
	B	15	3.67	26.1	3.57			

Figure 1. Mean HMR3647 plasma concentration-time profiles for treatment A (800 mg HMR3647 with water) and treatment B (800 mg HMR3647 with grapefruit juice) (n = 15)

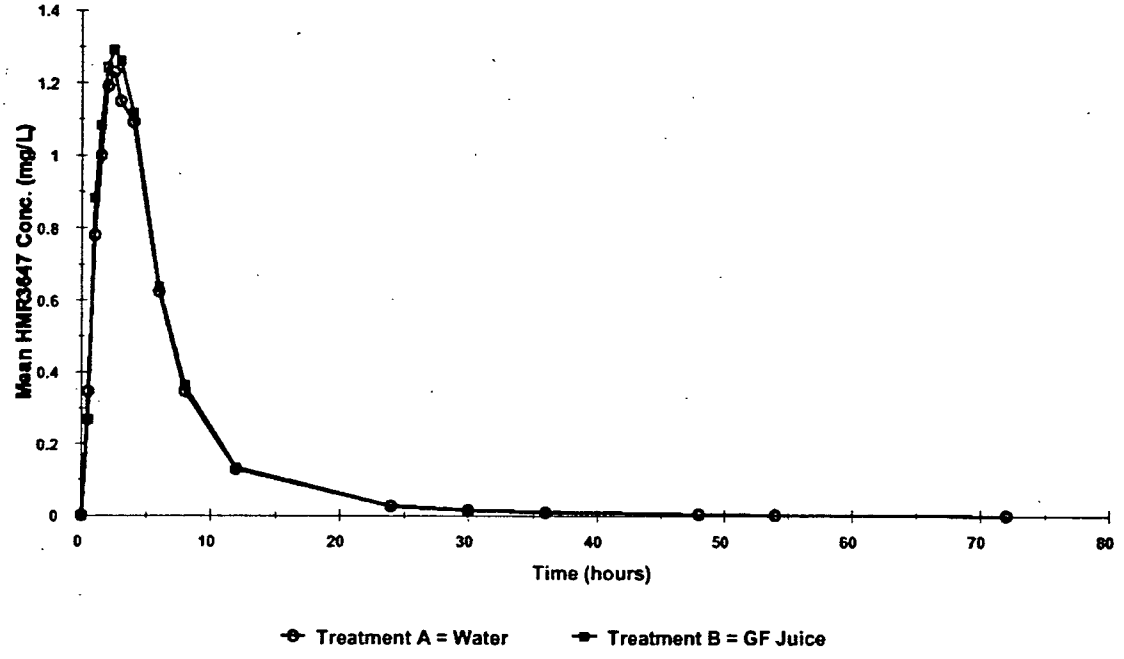


Figure 2. Mean RU76363 plasma concentration-time profiles for treatment A (800 mg HMR3647 with water) and treatment B (800 mg HMR3647 with grapefruit juice) (n = 15)

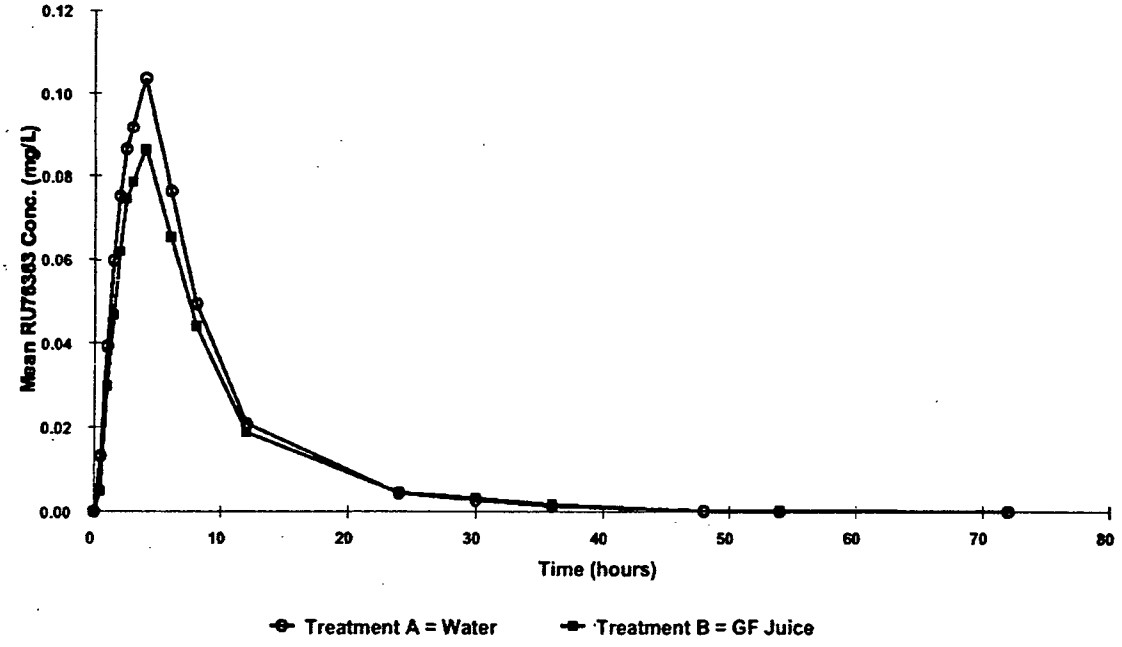
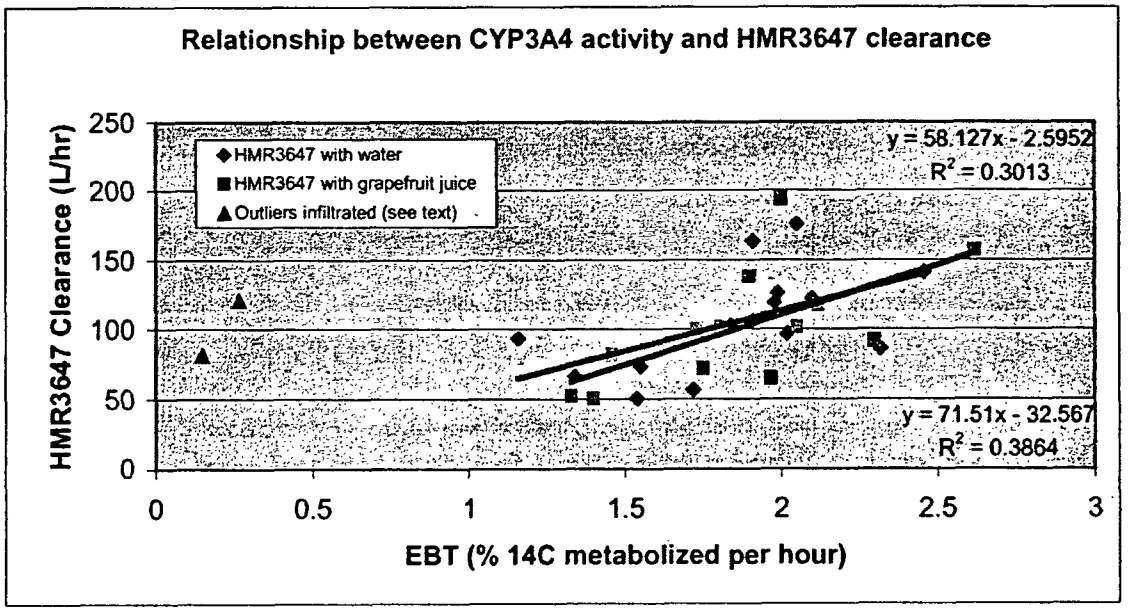


Figure 3. Relationship between CYP3A4 and HMR 3647 clearance



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STUDY NUMBER: 1048

TITLE: A study investigating a potential pharmacokinetic interaction between HMR 3647 and simvastatin in healthy male subjects.

INVESTIGATOR(S): Dr. D.H. Wessels, HMR Research Center for Clinical Pharmacology and Drug Development. University of Orange Free State, Republic of South Africa

OBJECTIVES:

To investigate whether the pharmacokinetics of simvastatin were affected by the concomitant administration of HMR 3647.

STUDY DESIGN:

The study was double blinded for HMR 3647, randomized, two-period crossover, multiple doses study. There was a at least 12-day washout between the period 1 and the period 2.

In each of the two study periods, subjects received one of the following treatments:

Treatment A: 800 mg HMR3647 (as two 400 mg tablets) administered once a day for 5 days and 40 mg of simvastatin was administered on day 5.

Treatment B: Placebo was administered once a day for 5 days and 40 mg of simvastatin was administered on day 5.

FORMULATION: HMR-3647 400 mg tablet (batch #: MMG 27931-127)

SAMPLING:

Blood samples were drawn at 0 h (before drug administration), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, and 24 hours after drug administration.

ASSAY: Plasma concentrations of HMR 3647 were measured by a validated LC/MS method. The standard curve ranged from — ng/mL for HMR 3647.

Simvastatin/simvastatin acid was measured in plasma by a validated LC/MS method. The validated method has a standard curve range of — ng/mL for simvastatin and — ng/mL for simvastatin acid. The limit of quantification is — for simvastatin and of — ng/mL for simvastatin acid.

The performance of the assay is shown in the following:

	HMR 3647/Plasma	simvastatin	simvastatin acid
Accuracy of QC samples	-4.5 % - 5.3 %	0.4 % - 8.0 %	-5.1 % - 1.7 %
Precision (CV) of QC samples	1.9 %- 5.3 %	12.5% - 18.9%	13.8% - 15.0%
The limit of quantification		—	

DATA ANALYSIS:

Pharmacokinetics:

Pharmacokinetic parameters were determined using a non-compartmental analysis.

Statistics:

HMR 3647+simvastatin was compared to placebo+simvastatin with respect to the pharmacokinetic variables C_{max}, AUC(0-t_{last}), AUC(0-∞), Cmax /AUC(0-∞) and $t_{½,z}$ for simvastatin and simvastatin acid using an analysis of variance with subject (sequence), treatment and period effects after logarithmic transformation of the data. Point estimates and 90% confidence intervals for the "HMR 3647+simvastatin/placebo+simvastatin" mean ratios of these variables were calculated. A lack of interaction between simvastatin and HMR 3647 was to be concluded if the calculated 90% confidence intervals for the mean ratios ("HMR 3647+simvastatin/placebo+simvastatin") of the above-mentioned variables fell within 70 to 143 %. In addition, a non-parametric point estimate and 90% confidence interval for the "HMR 3647+simvastatin – placebo+simvastatin" median difference of the variable t max were calculated.

The pharmacokinetic variables for HMR 3647 at steady-state, $C_{max,ss}$, $C_{min,ss}$ and AUC_{ss}, are analyzed descriptively by means of arithmetic mean values, arithmetic standard deviations, coefficient of variation and ranges.

RESULTS:

Thirty male subjects (age range from 19-27 years old) completed the study and were included in the pharmacokinetic analyses.

Pharmacokinetics:

The mean plasma concentration vs time profiles for simvastatin, simvastatin acid, and HMR 3647 are shown in Figure 1-3. The pharmacokinetics parameters are summarized in Table 1-3.
The results indicated when HMR3647 was coadministered with simvastatin, the C_{max} and AUC_{ss} of simvastatin were increased by 397% and 727%, respectively. The increased in its metabolite, simvastatin acid was more significant. C_{max} and AUC_{ss} were increased by 1418% and 982% when HMR 3647 was given with simvastatin.

CONCLUSION:

1. There was a strong pharmacokinetic interaction of HMR 3647 on simvastatin pharmacokinetics.
2. When co-administered with HMR 3647, there were a 5.3-fold increase in simvastatin C_{max}, a 8.9-fold increase in simvastatin AUC, a 15-fold increase in simvastatin acid C_{max} and a 12-fold increase in simvastatin acid AUC.
3. The elimination half lives of simvastatin and simvastatin acid were not modified.
4. These data show that HMR 3647 increases greatly the bioavailability of simvastatin and simvastatin acid due to an inhibition of their CYP3A4 dependent pre-systemic first pass.
5. In patients treated with simvastatin, precautions should be used when HMR 3647 is coadministered. In particular, the patients should be carefully monitored to detect any signs or symptoms of myopathy.

COMMENTS:

1. The possibility that HMR 3647 interacts with other HMG-CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, atorvastatin and cerivastatin are discussed.
   Several interactions between simvastatin and CYP3A4 substrates or CYP3A4 strong inhibitors have been already reported. The table below summarized the pharmacokinetic interactions assessed in formal human interaction studies in comparison to that observed for HMR 3647:

		Telithromycin	Clarithromycin	Erythromycin	Verapamil	Grapefruit juice	Itraconazole
		(HMR 3647)		[2]	[2]	[8]	[9]
Simvastatin	C_{max}	4.5-fold ↗	No formal study	3.5-fold ↗	2.6-fold ↗	9-fold ↗	> 10-fold ↗
	AUC	9-fold ↗ .	Case reports	6-fold ↗	4.6-fold ↗	16-fold ↗	> 10-fold ↗
	$t_{1/2}$	↔		-		↔	↔
Simvastatin	C_{max}	15-fold ↗	No formal study	5-fold ↗	3.4-fold ↗	7-fold ↗	17-fold ↗
acid	AUC	12-fold ↗	Case reports	4-fold ↗	2.8-fold ↗	7-fold ↗	18-fold ↗
	$t_{1/2}$	↔		-		↔	-

   No formal interaction study with clarithromycin was found in the literature but case reports of interaction are mentioned.
   Based on the pharmacokinetic properties, the interaction of other HMG-CoA reductase inhibitors with HMR 3647 are discussed.

- The pharmacokinetic properties of lovastatin are similar to those of simvastatin and clinically significant interactions with CYP3A4 substrates have been reported. Thus, one can predict

that clinically significant interaction when coadministered with HMR 3647 should be observed.

- Pravastatin is much less metabolized as 50% of the dose is excreted unchanged in urine. Its bioavailability is 10 to 25%. In addition CYP3A enzymes do not contribute significantly to pravastatin clearance or first pass. As expected, no clinically significant interaction with CYP3A4 substrates or inhibitors are reported. Thus, a metabolic interaction between HMR 3647 and pravastatin should be unlikely.
- Fluvastatin is primarily metabolized by CYP2C9. In vitro interaction studies performed with human microsomes have shown that HMR 3647 does not inhibit this isoenzyme. Therefore clinically relevant metabolic interaction with HMR 3647 is unlikely.
- Atorvastatin and cerivastatin are metabolized by CYP3A4. Their absolute bioavailability is 12 and 60% respectively. Erythromycin increases the plasma concentration of atorvastatin by 40% and increase the C_{max} and AUC of cerivastatin by 24 and 50% respectively. Precautions are recommended for coadministration of atorvastatin or cerivastatin with the azoles, macrolides or cyclosporin to avoid myopathy. HMR 3647 should produce a similar pharmacokinetic interaction by competitive inhibition of the CYP3A4 first pass and metabolism and therefore, similar precautions should be used in case HMR 3647 is coadministered. Given the better bioavailability of atorvastatin and mainly of cerivastatin as compared to simvastatin and lovastatin, given the lower magnitude of the interaction observed with erythromycin, one can predict that the magnitude of the interaction caused by HMR 3647 should be much less than that observed with simvastatin.

2. Simvastatin is a prodrug. Its metabolites, simvastatin acid is the active species. Therefore, in terms of increasing simvastatin acid exposure, the effect of HMR-3647 was stronger than erythromycin, verapermil, and grapefruit juice but similar to itraconazole.
3. It demonstrated in vitro study that HMR 3647 was a substrate of p-glycoprotein.

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Table 1. Pharmacokinetic parameters of simvastatin with and without HMR 3647

Variable	HMR 3647 + Simvastatin (Treatment A) (n=30)	Placebo + Simvastatin (Treatment B) (n=30)	Mean ratio (%)*	90% CI (%)**
C_{max} (ng/ml)	144 (47)	29.0 (61)	533	434 ; 654
t_{max} # (h)	1.00	0.50	0.50	0.25 ; 0.75
AUC (0 - t_{last}) (ng·h/ml)	434 (38)	50.8 (51)	891	787 ; 1008
AUC (0 - ∞) (ng·h/ml)	440 (38)	53.2 (51)	861	761 ; 974
$t_{½;z}$ (h)	4.10 (27) 2.52 – 6.90	4.01 (39) 1.77 – 7.17	107	96.7 ; 118.4
MRT* (h)	4.20 (18) 2.94 – 5.98	3.79 (36) 1.65 – 8.28		

*Point estimate of "Treatment A/Treatment B" mean ratio from analysis of log-transformed data.
**90% Conventional confidence interval for the "Treatment A/Treatment B" mean ratio from analysis of variance of log-transformed data.
#Medians, ranges, nonparametric point estimate of "Treatment A-Treatment B" median difference and corresponding confidence interval.

Table 2. Pharmacokinetic parameters of simvastatin acid with and without HMR 3647

Variable (unit)	HMR 3647 + simvastatin (Treatment A) (n=30)	Placebo + simvastatin (Treatment B) (n=30)	Mean ratio (%)*	90% CI (%)**
C_{max} (ng/ml)	20.8 (50)	1.37 (49)	1489	1307 ; 1697
t_{max} # (h)	2.00	3.50	-1.25	-1.75 ; -0.75
$AUC_{(0 - tlast)}$ (ng·h/ml)	116.3 (48)	9.99 (54)	1186	1044 ; 1348
AUC (0 - ∞) (ng·h/ml)	118.7 (48)	10.97 (52)	1084	964 ; 1219
Cmax/AUC (0 - ∞) (1/h)	0.18 (25)	0.13 (19)	138	127 ; 149
$t_{½;z}$ (h)	3.63 (35)	3.72 (35)	96.6	88.3 ; 105.7
MRT (h)	5.61 (25)	6.78 (26)		

*Point estimate of "Treatment A/Treatment B" mean ratio from analysis of log-transformed data.
**90% Conventional confidence interval for the "Treatment A/Treatment B" mean ratio from analysis of variance of log-transformed data.
#Medians, ranges, nonparametric point estimate of "Treatment A-Treatment B" median differenceand corresponding confidence interval.

Table 3. Pharmacokinetic parameters of HMR3647 at steady state

	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)	AUC (mg.h/L)
Arithmetic mean	2.24	0.04	9.41
CV(%)	34	30	25
Range			

Figure 1. Mean simvastatin plasma concentration-time profiles

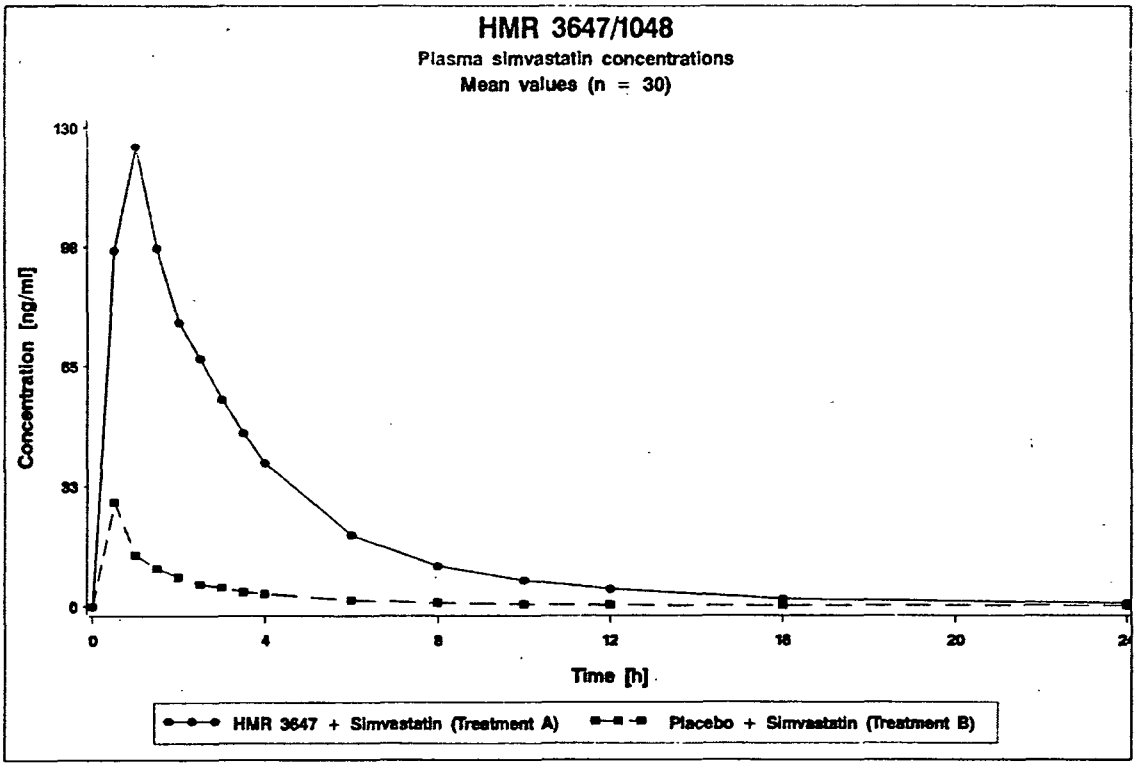


Figure 2. Mean simvastatin acid plasma concentration-time profiles with and without HMR 3647

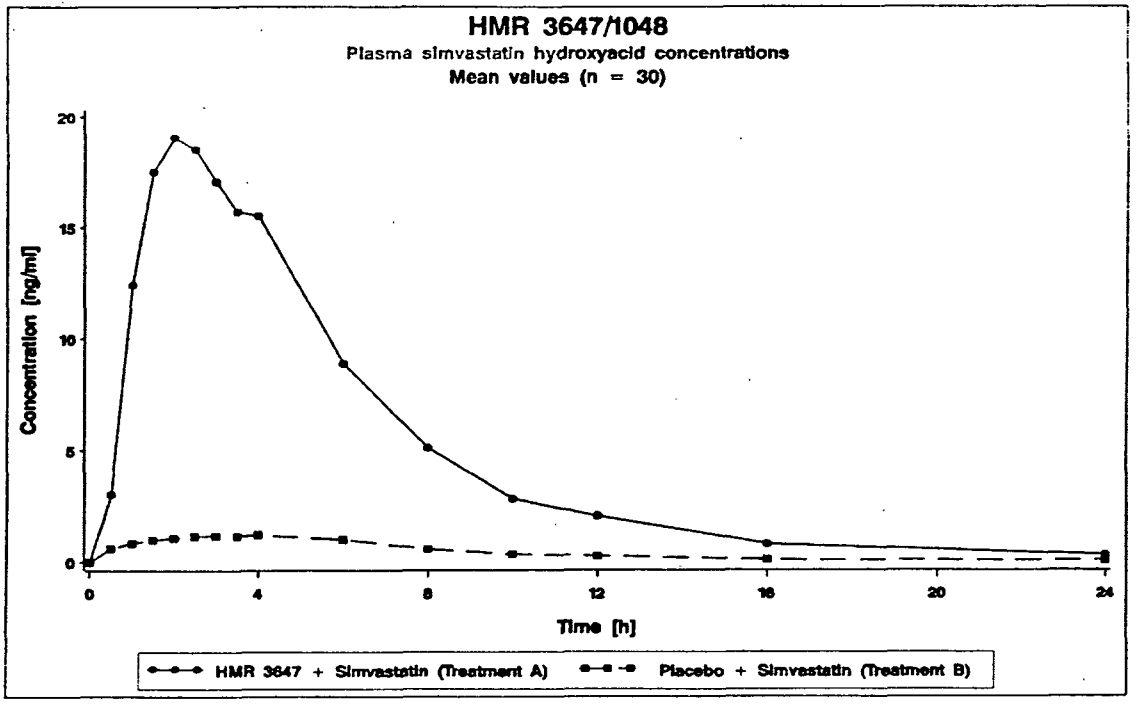
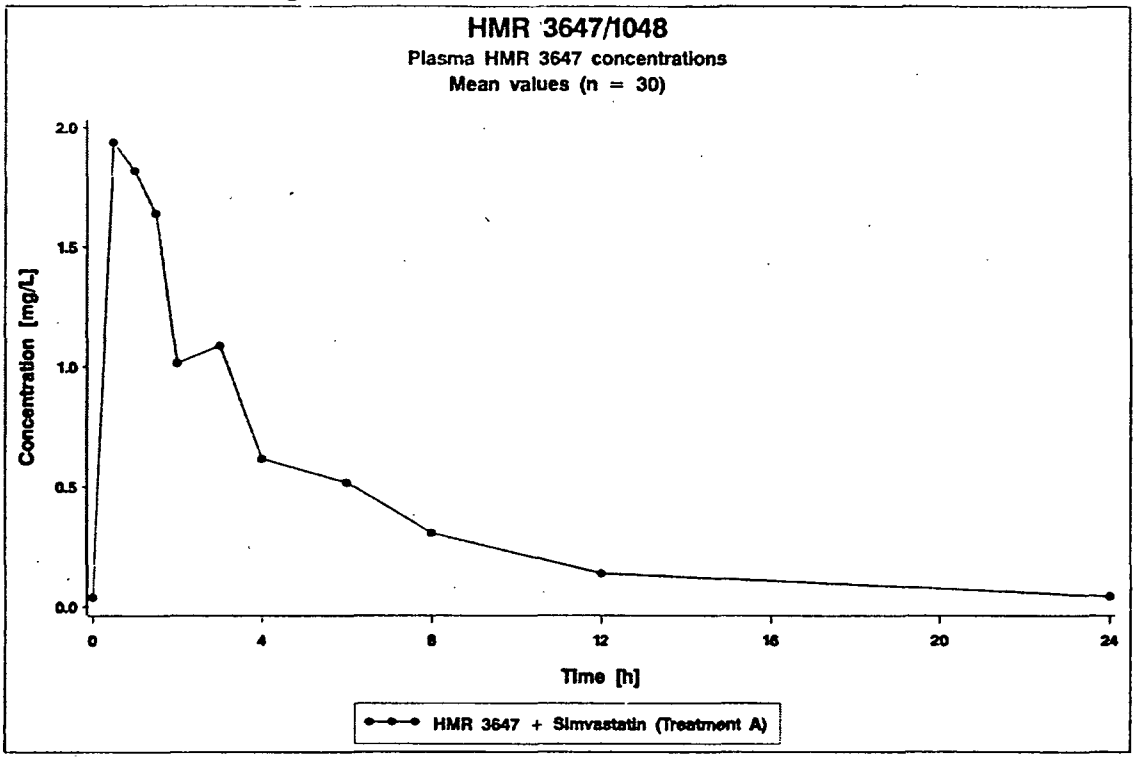


Figure 3. Mean HMR 3647 concentrations vs time



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STUDY NUMBER: 1056

TITLE: An open, randomized, crossover study to assess the effect of multiple oral doses of telithromycin (800 mg q.d.) on the pharmacokinetics of midazolam, after single intravenous infusion or single oral dose, in healthy male subjects

INVESTIGATOR(S):

OBJECTIVES:

To assess the effect of multiple oral doses of telithromycin (800 mg q.d) on the pharmacokinetics of midazolam, after single intravenous infusion or single oral dose, in healthy male subjects.

To assess the contribution of intestinal and hepatic CYP3A4 first-pass effects to the interaction of telithromycin on midazolam.

STUDY DESIGN:

Open, single center, randomized, two-treatment, two-period study with a cross-over design.

The treatments were as follows:

- Treatment A

-Day 1: single IV infusion of 2 mg midazolam over 30 minutes

-Day 2-7: multiple oral doses of telithromycin (800 mg q.d.)

-Day 6: single IV infusion of 2 mg midazolam over 30 minutes in presence of oral telithromycin

- Treatment B

-Day 1: single oral dose of 6 mg midazolam

-Day 2-7: multiple oral doses of telithromycin (800 mg q.d.)

-Day 6: single oral dose of 6 mg midazolam in presence of oral telithromycin

A seven-day washout period was to separate the treatments A and B.

FORMULATION: HMR-3647 400 mg tablet (batch #: RG 9811)

SAMPLING:

Blood samples were drawn just before dosing, at 0.25h, 0.5h, 0.75h, 1h, 1.5h, 2h, 3h, 4h, 6 h, 8 h, 10h, 12h and 24 h postdose on day 1 (midazolam alone) and day 6 (midazolam + telithromycin). Two additional blood samples were drawn at 34 h and 48 h after administration of midazolam + telithromycin.

To determine plasma concentrations of midazolam after oral administration of midazolam alone (day 1) and midazolam + telithromycin (day 6), blood samples were drawn just before dosing, at 0,

0.5h, 1h, 1.5h, 2h, 3h, 4h, 6 h, 8 h, 10h, 12h and 24 h postdose. Two additional blood samples were drawn at 34 h and 48 h after administration of midazolam + telithromycin.

To determine trough plasma concentrations of telithromycin blood samples were drawn prior to dosing telithromycin, from day 4 (C24h-day 3) to day 8 (C24h-day 7) within each period.

To determine plasma concentrations of telithromycin after concomitant administration of telithromycin with midazolam (intravenous and oral) on day 6, blood samples were drawn just before dosing telithromycin, 1h, 2h, 3h, 4h, 6 h, 12h and 25h post telithromycin administration and 25 hours after the last telithromycin administration.

Urine samples were collected over the following periods: pre-dose (spot collection), 0-24 hours after intravenous and oral administration of midazolam alone (day 1) and of midazolam + telithromycin (day 6) and also 24-48 hours after intravenous and oral administration of midazolam + telithromycin (day 7) to determine 1'-hydroxymidazolam.

ASSAY:

Midazolam was assayed in blood by a validated gas chromatography/mass spectrometry (GC/MS) method. 1'-hydroxymidazolam was assayed in urine after deconjugation by a validated liquid chromatography mass spectrometry method (LC/MS). Telithromycin was assayed in plasma by a validated high performance liquid chromatography/mass spectrometric (LC/MS) method.

The performance of the assay is shown in the following:

	HMR 3647/Plasma	Midazolam	1-hydroxy-midazolam
Accuracy of QC samples	93.7-102.0%	91.3-98.0%	105.14-113.8%
Precision (CV) of QC samples	3.2-8.7%	8.16-11.39	0-5.79%
The limit of quantification			

DATA ANALYSIS:

Pharmacokinetics:

Pharmacokinetics parameters such as Cmax, AUC, MRT, Vss were calculated using non-parametric method.

E_H: Hepatic extraction ratio was calculated as $E_H=CL_b/Q_H$ and assuming non-hepatic contributions to clearance were negligible and hepatic blood flow was constant (0.0216L/min/kg).

F_H: Predicted hepatic availability after oral administration of midazolam, calculated from intravenous data of midazolam according to the following formula:

$F_H = 1 - E_H$

- **F_G**: Intestinal availability of midazolam calculated according to the following formula, assuming that the absorption of oral midazolam from the intestinal lumen into the epithelia was complete i.e.

F_A (fraction of midazolam absorbed) »1:

$F_G = F/ F_A*F_H$

- **E_G**: Intestinal extraction ratio of midazolam calculated according to the following formula:

$E_G = 1 - F_G$

Pharmacodynamics:

Sleeping time duration was determined between time of dosing and 4h post-dose after midazolam administration.

Statistics:

Descriptive statistics were calculated.

Relationship between blood to plasma concentration ratio (C_b /C) of midazolam and plasma concentration (C)

In order to assess any relationship between C_b /C and the plasma concentrations of midazolam encountered within the study, a regression analysis with C_b /C as dependent variable and C as independent variable was performed by pooling the data collected after intravenous administration of midazolam alone and midazolam + telithromycin.

Effect of telithromycin on midazolam (and 1'-hydroxymidazolam) pharmacokinetics

Treatment effect on the cumulative urinary excretion of 1'-hydroxymidazolam:

In order to support the assumption that F_A »1 after oral administration of midazolam (i.e. the cumulative excretion of 1'-hydroxymidazolam (% dose) is similar after oral and intravenous administration of midazolam) treatment effect was assessed with respect to the pharmacokinetic parameter Ae (% dose) using a two way analysis of variance with treatment and subject as main effects in the model after ln transformation of the parameter. The factor treatment has four levels: IV midazolam, oral midazolam, IV midazolam + telithromycin and oral midazolam+ telithromycin.

Effect of telithromycin on the pharmacokinetic parameters of midazolam after administration of midazolam :

In order to compare the pharmacokinetic parameters of midazolam between day 1 and day 6 for assessing the effect of telithromycin on midazolam pharmacokinetics after single IV infusion or oral administration, a two way analysis of variance was used with treatment (IV midazolam alone and IV midazolam + telithromycin) and subject as main effects in the model, with respect to the following ln transformed pharmacokinetic parameters which were obtained after intravenous administration of midazolam: Cmax , AUC(0-∞), CL, CLb , $t_{1/2,\lambda z}$ and Vss .

Effect of telithromycin on F, E H , F H and F G of midazolam:
In order to compare the pharmacokinetic parameters of midazolam when it was administered alone or in the presenceof telithromycin, a two way analysis of variance was used with treatment (midazolam alone and midazolam + telithromycin) and subject as main effects in the model, after ln transformation of the following pharmacokinetic parameters: F, E_H , F_H and F_G .
Assessment of steady state:
Time at which steady state of telithromycin plasma concentrations was reached was assessed by visual inspection of the trough concentrations and by using a two way analysis of variance with subject and day (from day 3 to day 7) as main effects for each treatment period. Days' means comparison was performed using Tukey's method.
Comparison of pharmacokinetic parameters of telithromycin in the presence of intravenous or oral midazolam :
In order to check that similar telithromycin exposure was provided when telithromycin was co-administered with either intravenous or oral midazolam, a three way analysis of variance was performed with respect to the telithromycin pharmacokinetic parameters, C max and AUC(0-25h) with treatment, period and subject as main effects in the model after ln transformation of the parameters.

RESULTS:

Twelve (12) subjects were enrolled, randomized and treated with study medication, as planned. All
12 subjects completed the study and were included in the pharmacokinetic, pharmacodynamic and safety analyses.
Eight plasma samples from subject 4,5,7, and 8 were not included in the analysis because samples were believed contaminated. Three samples from subject 10 were not included in the analysis but not explainable reason for the high concentrations.
Regression analysis showed that C_b/C did not vary significantly over the plasma concentration range encountered in the present study (C ranged from — 2 ng/mL); mean C_b /C was 0.82.
Pharmacokinetics:
The pharmacokinetic parameters of midazolam after 2 mg iv, 6 mg oral administration alone and in the presence of telithromycin are shown in Table 1. Plasma concentration vs time profiles are shown in Figure 1 and 2. The bioavailability of midazolam and hepatic and intestinal extraction ratio are shown in Table 2. In the presence of telithromycin a significant 2.8-fold increase in the oral absolute availability of midazolam was observed. Telithromycin also caused the increase of both the hepatic and intestinal availability with a greater increase of the intestinal component (1.9-fold) compared to the hepatic one (1.5-fold).
Pharmacokinetic parameters of telithromycin are shown in Table 3. Concentration vs time profiles are shown in Figure 3. Pharmacokinetic parameters did not change.
Pharmacdynamics:
The sleeping time after 2 mg iv administration of midazolam, 6 mg oral administration alone or in the presence of telithromycin are shown in Table 4. It was shown that in the presence of telithromycin, a 1.7 and 1.6-fold significant increase in sleeping time was observed after intravenous and oral administration of midazolam respectively. Whatever the route of administration there was no statistically significant difference in sleeping duration after midazolam. alone. This was also true when midazolam was administered in the presence of telithromycin.

CONCLUSION:

1. Telithromycin significantly inhibited CYP3A4 dependent metabolism of midazolam, both at the intestinal and hepatic level. After intravenous administration of midazolam telithromycin caused a 2-fold increase in midazolam AUC due to a 2-fold decrease of its metabolic clearance. After oral

administration of midazolam, telithromycin caused a 6-fold increase of midazolam AUC due to a decrease of its intestinal and hepatic first pass, -as shown by a 1.9 and 1.5-fold increase in intestinal and hepatic availability-, and to the decrease of its clearance.

2. In patients receiving concomitantly telithromycin and midazolam at therapeutic dosage, increase in plasma levels of midazolam will be observed and pharmacologic effect of midazolam should be also increased. Therefore dosage should be adjusted as necessary and monitoring of the patient be undertaken especially after oral administration of midazolam.
3. The same precautions should also apply to the other benzodiazepine triazolam which is highly metabolized by CYP3A4 and which undergoes a high CYP3A4 dependent first pass.
4. For the other benzodiazepines (or similar drugs) which have a good bioavailability (no CYP3A4 first pass) and are metabolized mainly or partially by CYP3A4 (alprazolam, diazepam, zolpidem) the magnitude of the interaction after oral administration should be lower as compared to midazolam. Nevertheless precautions should be taken in case of co-administration with telithromycin.
5. For those benzodiazepines which are very slightly or not metabolized by CYP3A4 (temazepam, nitrazepam, lorazepam) any clinically significant interaction with telithromycin is unlikely.

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Table 1. PK parameters of midazolam

Parameter	Statistics	Single IV infusion of 2 mg midazolam over 30 minutes				Single oral dose of 6 mg midazolam			
		Midazolam alone (day 1)	midazolam + telithromycin (800 mg q.d.) (day 6)	PE[(c)] (CV%) [Min-Max]	ANOVA	Midazolam alone (day 1)	midazolam + telithromycin (800 mg q.d.) (day 6)	PE[(c)] (CV%) [Min-Max]	ANOVA
Cmax (ng/mL)	Mean (CV%)	33.1 (20)	35.3 (27)	1.05 (20)	NS	20.8 (28)	54.6 (29)	2.62 (28)	***
	[Min-Max]								
tmax (h)	Median	NA	NA	NA	NA	0.5	0.5	NA	NA
	[Min-Max]								
AUC(0-∞) (ng.h/mL)	Mean (CV%)	73.8 (43)	159 (36)	2.20 (29)	***	57.1 (39)	354 (41)	6.11 (31)	***
	[Min-Max]								
CL (L/h)	Mean (CV%)	31.9 (41)	14.5 (44)	0.46 (32)	***	NA	NA	NA	NA
	[Min-Max]								
CLb (L/h)	Mean (CV%)	40.1 (42)	19.3 (43)	0.49 (35)	***	NA	NA	NA	NA
	[Min-Max]								
$t_{1/2,\lambda z}$ (h)	Mean (CV%)	2.25 (27)	5.30 (39)	2.26 (37)	***	2.49 (28)	6.69 (42)	2.57 (35)	***
	[Min-Max]								
V_{ss} (L)	Mean (CV%)	85.8 (15)	86.1 (25)	0.98 (21)	NS	NA	NA	NA	NA
	[Min-Max]								
Ae (% dose)	Mean (CV%)	54.0 (25)	47.0 (28)	NA	NA	45.6 (27)	41.5 (13)	NA	NA
	[Min-Max]								

Table 2. Oral absolute bioavailability (F), hepatic and intestinal availability (F H and F G) and hepatic and intestinal extraction ratio (E H and E G) of midazolam (n = 12)

Parameter	Statistics	midazolam alone	midazolam + telithromycin	PE (CV%) [Min-Max]	ANOVA
F	**Mean** (CV%)	**0.28** (40)	**0.74** (16)	**2.78** (62)	***
	[Min-Max]				
E_H	**Mean** (CV%)	**0.43** (38)	**0.21** (39)	**0.49** (35)	***
	[Min-Max]				
F_H	**Mean** (CV%)	**0.57** (29)	**0.79** (10)	**1.45** (25)	***
	[Min-Max]				
E_G	**Mean** (CV%)	**0.44** (68)	**0.066** (230)	**0.29**[(c)] (91)	ND
	[Min-Max]				
F_G	**Mean** (CV%)	**0.56** (53)	**0.93** (16)	**1.92** (87)	**
	[Min-Max]			[0.85-8.41]	

(a) PE: Point estimate = geometric mean of the individual ratios of each parameter taking into account the parameters of midazolam alone as reference;

(b) Significance of p-value from ANOVA table: NS: non significant ($p > 0.05$), * $0.01 < p \leq 0.05$, ** $0.001 < p \leq 0.01$, *** $p \leq 0.001$;

(c) n = 8;

ND: NOT DONE;

Table 3. Pharmacokinetic parameters of telithromycin

Parameter	Statistics	telithromycin (800 mg q.d.) + single IV infusion of 2 mg midazolam over 30 minutes (day 6)	telithromycin (800 mg q.d.) + single oral dose of 6 mg midazolam (day 6)
C_{max} (mg/L)	Mean(CV%)	1.48 (30)	1.59 (33)
	[Min-Max]		
tmax (h)	Median	3.0	3.0
	[Min-Max]		
AUC(0-24h) (mg.h/L)	Mean (CV%)	10.3 (40)	11.4 (36)
	[Min-Max]		

Table 4. Sleeping time duration (minutes) (n = 12)

Statistics	Single IV infusion of 2 mg midazolam over 30 minutes		Single oral dose of 6 mg midazolam		ANOVA[a] Tukey test[b]
	midazolam alone	midazolam + telithromycin	midazolam alone	midazolam + telithromycin	
	a	b	c	d	
Mean (CV%)	97.8 (45)	170.3 (23)	113.8 (33)	182.4 (12)	***
[Min-Max]					d b c a

(a) Significance of p-value from ANOVA table: NS: non significant ($p > 0.05$), * $0.01 < p \leq 0.05$, ** $0.001 < p \leq 0.01$, *** $p \leq 0.001$;

(b): Tukey test: underlined data are not statistically different

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Figure 3. Telithromycin concentration vs time profile

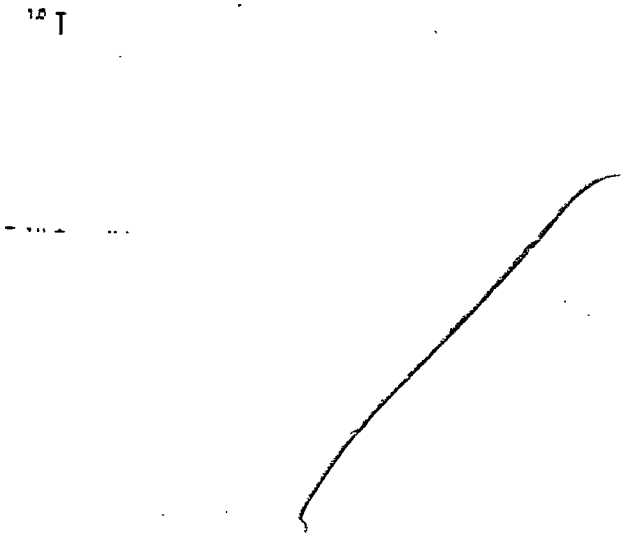
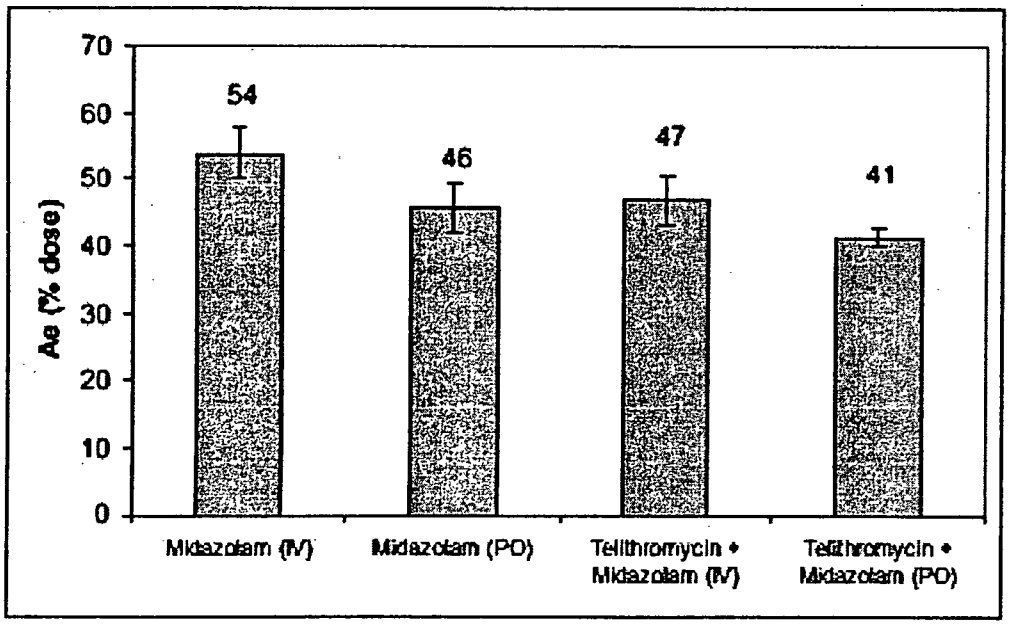


FIGURE 4. Mean(± SEM) cumulative amount of 1'- hydroxymidazolam excreted in urine after single administration of midazolam (2 mg IV infusion or 6 mg oral dose), alone or in the presence of telithromycin (800 mg q. d.)



STUDY NUMBER: 1057

TITLE: Assessment of the possible effect of a single oral dose (800 mg) of HMR 3647 on Sotalol induced prolongation of ventricular repolarization after single oral dose (160 mg) in healthy female subjects.

INVESTIGATOR(S):

OBJECTIVES:

To demonstrate the absence of amplification of maximal corrected QT interval (QTc max) lengthening induced by Sotalol following the co-administration with telithromycin.

To assess the possible effect of a single oral administration of HMR 3647 (therapeutic dose of 800 mg) on the prolongation of ventricular repolarization induced by a single oral dose of sotalol (therapeutic dose of 160 mg) at various time after administration to healthy female subjects.

To correlate the possible electrophysiologic changes induced by the study drugs to the plasma concentrations during the distribution/elimination phase.

STUDY DESIGN:

Single center, randomized, 2-way cross over, double-blind for HMR 3647 and placebo and open for sotalol.

In period I subjects received sotalol in association with either placebo or HMR 3647

In period II they received sotalol with either HMR 3647 or placebo depending on what they had already received in period I.

A wash-out of 7 days between each period had to be respected.

FORMULATION: HMR-3647 400 mg tablet (batch #: VL 28095-098)

SAMPLING:

Blood samples were drawn just before dosing, at 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 5h, 6h, 8h, 10h, 12h and 24h post dose.

ECG was recorded at the time when blood samples were collected.

ASSAY:

Sotalol Telithromycin was assayed in plasma by a validated high performance liquid chromatography/mass spectrometric (LC/MS) method.

The performance of the assay is shown in the following:

	HMR 3647/Plasma	Sotalol
Accuracy of QC samples	88.5-96.4%	99.8-111.3%
Precision (CV) of QC samples	4.8-11.8%	4.8-10.1%

DATA ANALYSIS:

Pharmacokinetics:

Pharmacokinetic parameters were calculated using a non compartmental analysis for sotalol and HMR3647.

Statistical:

Effect of HMR3647 on sotalol pharmacokinetics:

The comparison of the pharmacokinetic parameters of sotalol when it was administered with HMR3647 versus when administered with placebo was done using a three way analysis of variance with treatment (sotalol + placebo and sotalol + HMR3647), period and subject as main effects in the model, with respect to the following ln transformed sotalol pharmacokinetic parameters: C_{max}, AUC(0-z), C_{max}/AUC(0-z),AUC(0-∞) and $t_{1/2,\lambda z}$.

As tmax is a discrete variable depending of blood sampling times, a Wilcoxon non parametric test was used for the comparison of sotalol + HMR3647 versus sotalol + placebo in order to assess the effect of HMR3647 on sotalol tmax.

The main pharmacodynamic parameter was the maximum corrected QT (QTcmax using Bazett's formula) obtained between 1 and 4 hours after drug administration in 24 evaluable subjects. QTc maximum was compared between treatments. ANCOVA was used to compare QTc maximum and ANOVA was used to compare QTc maximum change from baseline. The model used for ANOVA contains the factors subject, treatment and period. Adjusted means and the difference between treatments were calculated and reported.

RESULTS:

Twenty-four subjects completed the study.

Pharmacokinetics:

Pharmacokinetic parameters of sotalol and telithromycin are shown in Table 1. Mean plasma concentration-time curves of sotalol and telithromycin are shown in Figure 1 and Figure 2.
The results showed that

Pharmacdynamics:

Adjusted means and the differences between the adjusted means are shown in Table 2. QTc max (adjusted mean) was 469 ms with placebo + sotalol, i.e. an increase of 74 ms from baseline and 453 ms with HMR 3647 + sotalol, ie an increase of 59 ms from baseline. Similar results were obtained with QTf max. These parameters were statistically lower with treatment with HMR3647 + sotalol than with placebo + sotalol, in relation with decreased sotalol plasma concentrations.
Individual relations between sotalol plasma concentrations and QTc intervals were studied for the 24 subjects receiving placebo + sotalol. A mild hysteresis was observed only in 3 subjects, the phenomenon was taken into account and the relation between QTc and concentration was studied during the distribution phase (i.e. after Cmax was reached).
The relation between sotalol concentrations and QTc or QTf was studied using a regression analysis for each subject after treatment with placebo + sotalol or after treatment with HMR3647 + sotalol.
Except for 2 subjects, no statistically significant differences between the slopes within each subject were shown but for all subjects the QTc or QTf values observed with treatment HMR3647 + sotalol were within the 95% confidence interval for individual values of treatment placebo + sotalol.
The analysis showed that the relationship between sotalol plasma concentration and corrected QT was not modified by HMR 3647.

CONCLUSION:

1. In the presence of HMR3647 a moderate 20% decrease of sotalol bioavailability was observed: AUC and C_{max} were decreased by 20% and 34% respectively. This interaction is due to a decrease of sotalol absorption in the presence of HMR 3647.
2. Due to the decrease in sotalol concentration the mean QTc as well as the mean maximum QTc was lower in presence of HMR3647.
3. The relationship between sotalol plasma concentration and QTc was not overtly modified by HMR3647.

Table 1. PK parameters of sotalol and telithromycin

	Sotalol pharmacokinetic parameters			PE[a] (CV%)	ANOVA[b]	HMR 3647 pharmacokinetic parameters		
Parameter	Statistics	sotalol + placebo	sotalol + HMR 3647			Parameter	Statistics	HMR 3647 + sotalol
		(n = 25)	(n=24)	(n=24)				(n=24)
C_{max} (ng/mL)	Mean (CV%)	1487 (17)	996 (23)	0.66 (20)	***	C_{max}	Mean (CV%)	1.239 (28)
	[Min-Max]			[0.31-0.95]		(mg/L)	[Min-Max]	
t_{max} (h)	Median	3.0 (31)	2.0 (46)	-	**	t_{max}	Median	2.0 (43)
	[Min-Max]					(h)	[Min-Max]	
AUC(0-z) (mg.h/L)	Mean (CV%)	0.1054 (12)	0.0953 (16)	0.89 (14)	**	AUC(0-z) (mg.h/L)	Mean (CV%)	5.80 (37)
	[Min-Max]						[Min-Max]	
AUC(0-z) (ng.h/mL)	Mean (CV%)	14150 (13)	10410 (14)	0.73 (14)	***			
	[Min-Max]							
AUC(0-∞) (ng.h/mL)	Mean (CV%)	15940 (13)	12780 (13)	0.80 (11)	***			
	[Min-Max]							
$t_{1/2,\lambda z}$ (h)	Mean (CV%)	7.32 (8.2)	9.80 (15)	1.33 (17)	***			
	[Min-Max]							

Table 2. **Statistical comparison between treatments for corrected QTmax parameters (n=24)**

Parameter / Treatment	Adjusted mean ± SEM (ms)	Difference between means (ms)	95% CI for difference	P-value
QTc max				
Placebo + sotalol	468.70 ± 4.69			
HMR3647 + sotalol	453.26 ± 4.69	-15.45	-27.73; -3.16	0.0162
ΔQTc max				
Placebo + sotalol	74.29 ± 5.06			
HMR3647 + sotalol	58.62 ± 5.06	-15.67	-26.23; -5.11	0.0055
QTf max				
Placebo + sotalol	422.27 ± 4.05			
HMR3647 + sotalol	448.82 ± 4.05	-23.45	-34.85; -12.05	0.0003
ΔQTf max				
Placebo + sotalol	78.54 ± 5.00			
HMR3647 + sotalol	56.29 ± 5.00	-22.25	-31.50; -13.00	0.0001

Figure 1. Mean (± SEM) plasma concentration of sotalol after single oral dose of 160 mg sotalol, administered with placebo or with a single oral dose of 800 HMR3647 (telithromycin)

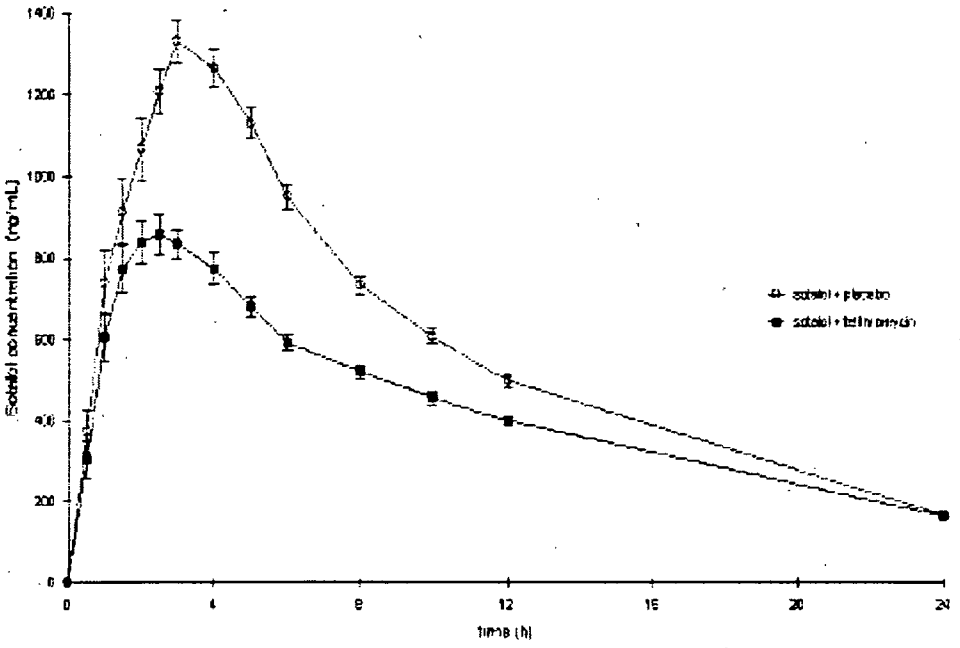


Figure 2. Mean (± SEM) plasma concentration of telithromycin after single oral dose of 800 mg telithromycin administered with a single oral dose of 160 mg sotalol