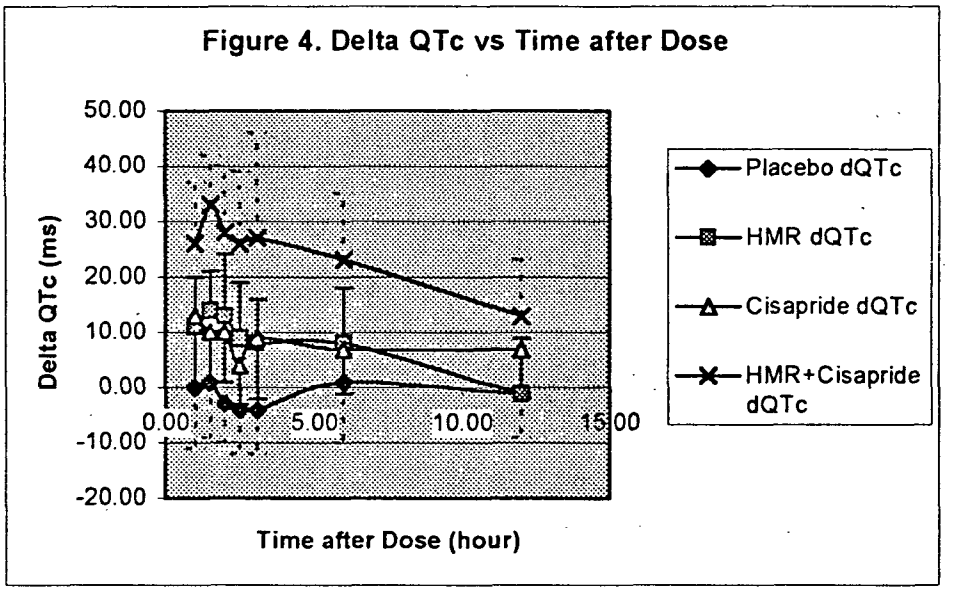
Table 2A. The regression analysis of study 1030, 1046, 1049 and population analysis

	Design		Heart rate	ΔQTc at 2 mg/L (ms)	ΔQTc at 4 mg/L (ms)	ΔQTc at 6 mg/L (ms)	Is ΔQTc ∝ HR
1030	Placebo/crossover Young: 1600/2000/2400 single dose (n=8) Elderly: 1200/1600/2000 single dose (n=8) Young: 1600 mg parallel repeated (n=6) Elderly: 1200 mg parallel repeated (n=6)	ΔQTc=-2.05+3.93*HMR maximal conc: ~ mg/mL	ΔHR=-2.10+16.51*C/(2.54+C)	6	14	22	No
1046[b]	Placebo/crossover/single dose dose 2400 mg 3200 mg	ΔQTc=-3.8+4.90*HMR maximal conc ~ mg/L	ΔHR[b]= 0.9+2.7*HMR	6	16	26	Yes
1049[b]	Placebo/crossover/single 800mg 1600 mg	ΔQTc=-3.15+3.27*HMR maximum conc ~ mg/L	No increase	3	10	17	No
PPK	Study 1030, 1031, 1032, 1037, 1041, 1045, 1046	ΔQTc=-1.30+3.90*HMR	ΔHR=-0.7+13.8*C/(1.61+C)	7	14	22	No

a: results are obtained from sponsor's analysis. b: Emax model did not fit the data.
c: PA (population analysis) was conducted on pooled data from 7 studies (Study 1030, 1031, 1032, 1037, 1041, 1045, 1046)

Table 2B. Regression analysis on delta QTf vs HMR 3647 concentrations

	Design		ΔQTf at 2 mg/L (ms)	ΔQTf at 4 mg/L (ms)	ΔQTf at 6 mg/L (ms)	ΔQTf at 10 mg/L (ms)
1030	Placebo/crossover Young: 1600/2000/2400 single dose (n=8) Elderly: 1200/1600/2000 single dose (n=8) Young: 1600 mg parallel repeated (n=6) Elderly: 1200 mg parallel repeated (n=6)	ΔQTf= -1.43+1.57*HMR maximal conc: ~ mg/mL	2	5	8	14
1046	Placebo/crossover/single dose 2400 mg 3200 mg	ΔQTf=-4.8+2.2*HMR maximal conc: ~ mg/L	0	4	8	17
1049	Placebo/crossover/single dose 800mg 1600 mg	ΔQTf= -0.515+2.7*HMR	5	10	16	26
PPK	Study 1030, 1031, 1032, 1037, 1041, 1045, 1046	ΔQTf= -1.98+1.56*HMR	1	4	7	14



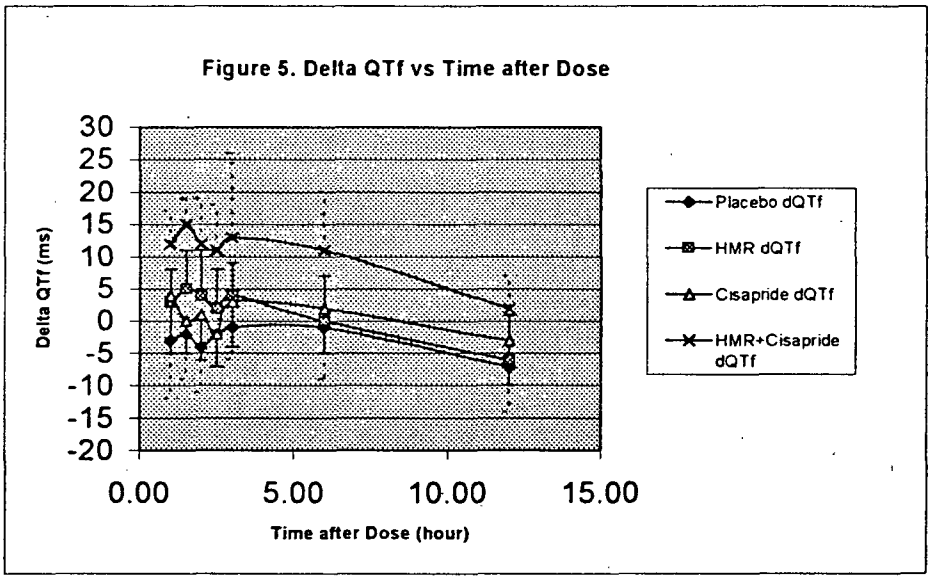


Table 3. Maximum QTc after once daily oral dosing with 800 mg HMR 3647 alone, 400 mg ketoconazole alone, 800 mg HMR 3647 concomitantly with 400 mg ketoconazole, or placebo

Parameter	Treatment	Mean	N	Comparison	Estimated difference	(90% CI) on difference	P-value
Maximum QTc (msec)	A	410.4	11	A-D	3.344	(-2.3, 9.00)	0.322
	B	413.4	14	B-D	6.388	(0.92, 11.9)	0.057
	C	417.5	11	C-D	10.493	(4.80, 16.2)	0.004
				C-A	7.149	(1.42, 12.9)	0.043
				C-B	4.105	(-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

Figure 6. The change of heart rate vs telithromycin concentration using Emax model
Data are pooled by study 1030, 1031, 1032, 1037, 1045, 1046

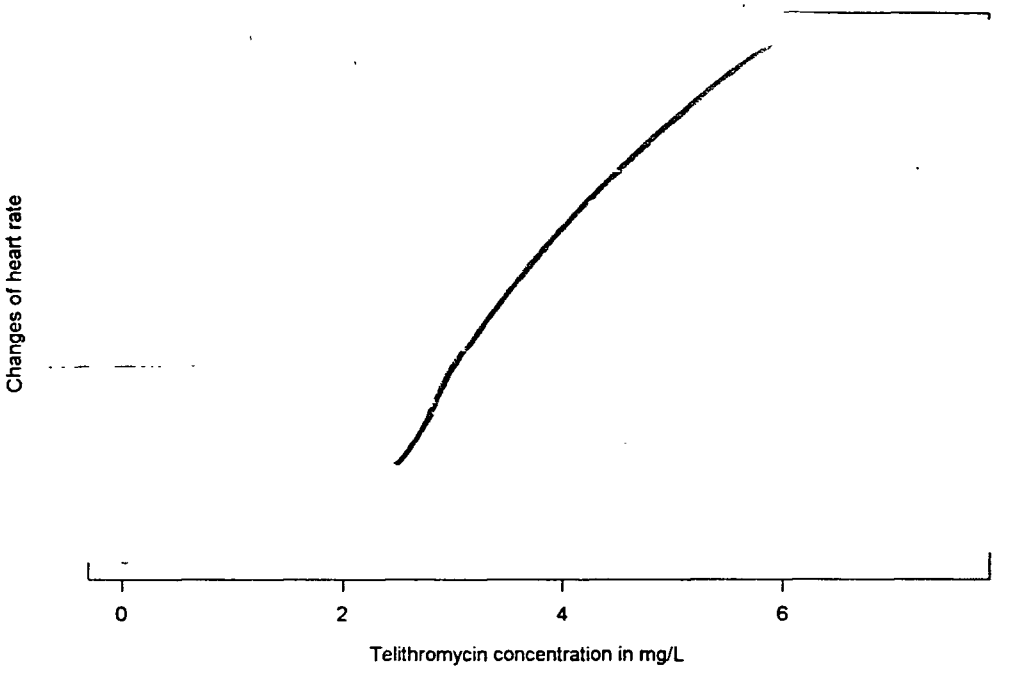
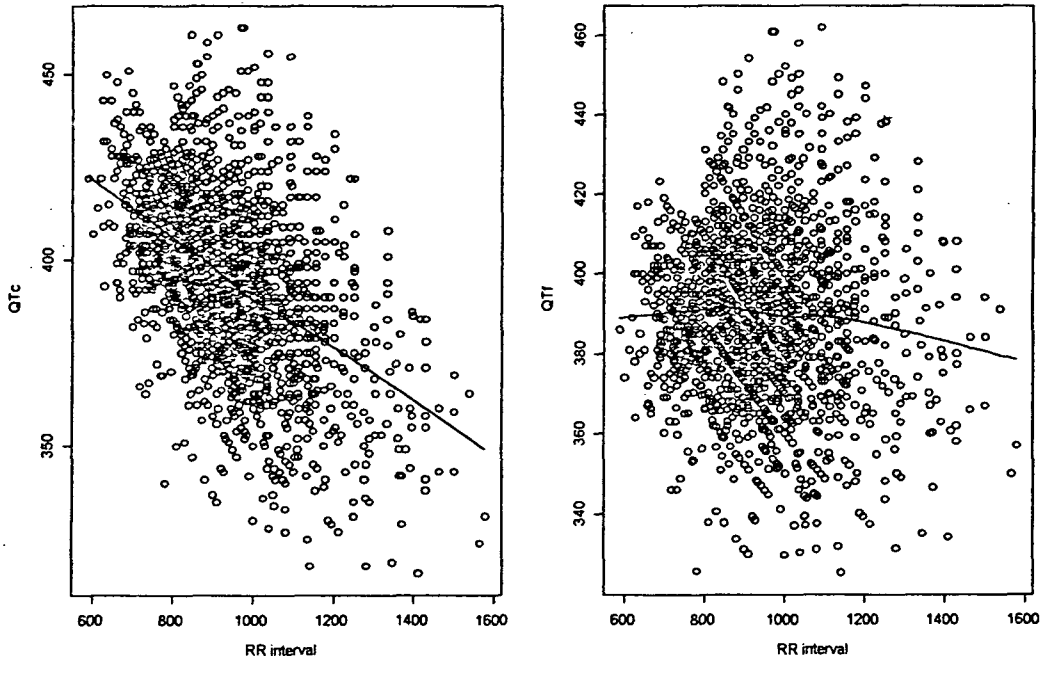


Figure 7. Comparison of two heart rate correction formula Bazett (QTc) vs Fridericia (QTf) using placebo data
Data are pooled by study 1030, 1031, 1032, 1037, 1045, 1046



Issue 2. The use of HMR 3647 in renal impaired patients

Study 1016 showed that after a single oral dose of 800 mg telithromycin, the mean C_{max} and AUC were increased by 33% and 42%, respectively in subjects with moderate renal impairment (CLcr were between 40-79 mL/min). The mean C_{max} and AUC were increased by 44% and 59%, respectively, in subjects with severe renal impairment (CLcr were between 10-39 mL/min). It was demonstrated in Study 1008 that pharmacokinetics of telithromycin is nonlinear. Therefore, more significant exposure in renal impaired subjects is expected after multiple doses. Due to the nonlinearity of the drug, an appropriate dose adjustment can not be determined The study seemed to suggest that the dose needs to be adjusted in renal impaired subjects.

Issue 3. Use of HMR 3647 in elderly:

1. It was found in study 1005 that the C_{max} and AUC in elderly subjects are 2-fold of corresponding values in young subjects after multiple oral doses.
2. It was also found in a population pharmacokinetics study (1052) that elderly tend to have higher concentrations but the difference between young patients and elderly patients was not quantitated in this study.

Although higher exposure was observed in elderly from phase 1 study, the same dose of 800 mg was given for both young and elderly subjects in phase 3 studies. No dose adjustment was recommended for elderly subjects.

Issue 4. The use of HMR 3647 in hepatic impaired patients

HMR 3647 is mainly metabolized and only about 12% and 20% of the dose are eliminated as unchanged HMR 3647 in urine and feces, respectively. However, it was found that C_{max} and AUC values in hepatic impaired subjects were <u>not</u> significantly different from C_{max} and AUC in healthy subjects after single dose study. Therefore no dose adjustment was recommended for hepatic impaired subjects by the sponsor. However, it was found from the study that the half-life of HMR 3647 was significantly increased in hepatic impaired subjects, indicating potential drug accumulation after multiple doses. The comparable AUC and C_{max} values in hepatic impaired subjects are the result of compensated renal function in hepatic impaired subjects. Renal clearance was increased in hepatic impaired subjects in this study, therefore, exposure could be higher in the subjects with impaired renal and hepatic function. Due to the concern about accumulation in hepatic impaired patients after multiple doses, the sponsor conducted a multiple dose study in hepatic impaired subjects. Although the final study report has not been submitted, the preliminary results showed that the mean Cmax and AUC in hepatic impaired patients are similar to healthy subjects even after multiple doses. The mean C_{max} are 1.82 mg/L and 1.96 mg/L in hepatic impaired patients and healthy subjects, respectively. The mean AUC are 12.34 mg•h/L and 13.82 mg•h/L in hepatic impaired patients and healthy subjects, respectively. Therefore, the concern about hepatic impaired patients become not significant.

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3. SYNOPSIS (question based)

Has PK/PD relationship been studied?

The exposure and response relationship was studied in an animal model. It was demonstrated from that study that AUC/MIC is the major determinant of in vivo activity, which was not consistent with the findings for other macrolides, where the time above MIC is the major determinant factor to correlate with activity.

The sponsor conducted two population pharmacokinetics studies.

Study 1051: Population pharmacokinetics in patients with community acquired pneumonia, CAP) (study 3000). The results of Study 1051 were considered not adequate because a wrong model was used in the analysis.

1. One compartment model was used to describe the pharmacokinetics of HMR 3647, which was not supported by phase 1 studies. The phase 1 studies clearly showed that two compartment model should be used to describe pharmacokinetics of HMR 3647.
2. In theory, the exposure would be under estimated if a one compartment model was used for two compartment drug.
3. The estimated half-life from this study was 2.2 hours, which was significantly shorter than 8 to 10 hours estimated from phase 1 studies.
4. The plot of observation vs. prediction clearly showed that concentrations of HMR 3647 were under estimated.

Due to inadequate pharmacokinetics estimation, the pharmacodynamics analysis was considered not reliable.

Study 1052: The population pharmacokinetics study was conducted in a larger population (including CAP, sinusitis, acute exacerbation of chronic bronchitis and pharyngitis/tonsillitis patients). The data set used for the analysis came from 1590 subjects. Since almost 69% of the subjects had only a single measurable plasma concentration, the remainder being below the limit of quantification, parametric population methods could not be used to analyze the data. Instead, a nonparametric population approach was used. The pharmacokinetic parameters were estimated by running a median smoother using a span of 0.10. The results showed that the decay of HMR 3647 was bi- or tri-exponential with an absorption phase. The time to maximal plasma concentrations was about 2.4 h. The population estimates for median HMR 3647 clearance, maximal plasma concentration and half-life were 99 L/h, 1.25 mg/L, and 16.7 h, respectively. The estimated clearance after single and multiple doses of 800 mg HMR 3647 are 102.3L/h and 71.1 L/h, respectively in study 1008 and 88L/h after multiple doses in study 3000.

It was found that elderly patients greater than 66 yr. old tended to have higher HMR 3647 plasma concentrations than other subjects. Male subjects were slightly under-represented in the group with the highest plasma concentrations suggesting that males may have a slightly larger volume of distribution than females, an effect probably more related to weight or BSA than sex. Patients with body surface area greater than 2.1 m^2 had lower plasma concentrations than patients with normal body surface area possibly as a result of a larger volume of distribution. Patients with decreased creatinine clearance tended to have higher HMR 3647 plasma concentrations than patients with normal renal function. Patients who were heavy smokers tended to have lower HMR 3647 plasma concentrations than moderate smokers or non-smokers. Patients rated as having severe illness at pre-dose tended to have higher plasma concentrations than patients with mild to moderate illness. However, this analysis can not quantitate the difference between populations, for example, the difference between young and elderly.

How does HMR-3647 work (Mode of Action)?

Ketolides inhibit protein synthesis by acting on the bacterial ribosome. HMR 3647 differs from available 14- and 15-membered ring macrolides in that it acts on at least four sites of the

ribosomal machinery: domains II and V of the 23S rRNA, the 50S subunit and the 30S subunit. The affinity of HMR 3647 to the 50S ribosomal subunit is higher ($>10^{-9}$) than that of erythromycin A ($>10^{-8}$). In addition, HMR 3647 also inhibits the formation of both the 30S and 50S subunits, whereas 14- and 15-membered ring macrolides inhibit the formation of the 50S subunit only.

What is the bioavailability? Does food affect the bioavailability?

1. The absolute bioavailability in both young and elderly subjects is 57% (Study 1044).
2. The rate of absorption of HMR 3647 tablets varied with t_{max} occurring from 1 to 4 hours postdose.
3. Food does not affect the absorption of HMR 3647 tablet (Study 1003).

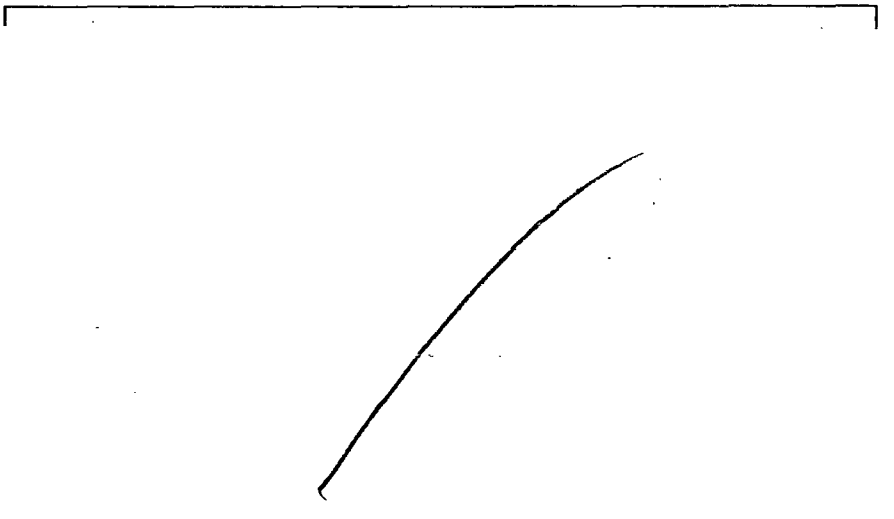
How many formulations have been used in the drug development process? Are these formulations bioequivalent?

Four formulations (21 batches) were used in phase 2/3 studies. The only difference between to-be-market formulation and the phase 3 formulation is that , which are of the composition, are added in to-be-market formulation. It was found that phase 1 formulation of the 100 mg tablet, is bioequivalent to the phase 3 formulation, 400 mg tablet (Study 1006) and the phase 3 formulation is bioequivalent to to-be-marketed formulation (Study 1017).

What is the dissolution method and specification?

Apparatus Type:
Media:
Volume:
Speed of Rotation:
Recommended Dissolution Specification: (Q = at
The dissolution profiles are shown in **Figure 8**. Based on dissolution profiles submitted, OCPB recommends the specification to be changed to (Q= at
Dissolution test was conducted at pH and no significant difference was found, therefore, was chosen be the media.

Figure 8. Dissolution profiles



Are the analytical methods used to quantitate HMR 3647 concentrations acceptable?

The sponsor developed HPLC/fluorescence, HPLC/MS, HPLC/MS/MS and microbiological methods to quantitate telithromycin concentrations in plasma, urine, feces and tissue (blister fluid, epithelial lining fluid, white blood cells and tonsil). The accuracy is within 85% to 115% and precision (CV%) of the methods is less than +/- 15% except the microbiological method. It was found that precision of microbiological method is acceptable but the accuracy was off up to 133%. This method was used to measure HMR 3647 in epithelial lining fluid (Study 1029).
The major metabolite, RU76363 was measured by HPLC/MS method. Accuracy of the method is between 85% to 115% and the precision is within 15%. The method is acceptable.
The quantitation method used to measure other drugs such as cisapride, theophylline, paroxetine, R-, S- warfarin, ehtinylestradiol/levonorgestrel, clarithromycin, 6β-hydroxycortisol, cortisol, ketoconazole, itraconazole, midazolam, and sotalol are acceptable with accuracy within 85% to 115% and precision less than 15%. The accuracy and precision of the method used to measure paroxetine, simvastatin and digoxin are between 15% to 20%.

What are the pharmacokinetic characteristics of HMR 3647? Is the dose versus exposure proportional within therapeutic range?

1. The mean C_{max} and $AUC_{0-\infty}$ were 1.90 mg/L and 8.40 mg•h/L, after a single 800 mg (2 x 400 mg tablets) dose was administered to healthy male subjects, respectively.
2. The steady state can be reached after 2 to 3 days. The mean C_{max} and AUC_{0-24} were 2.27 mg/L and 12.5 mg•h/L, after multiple 800 mg (2 x 400 mg tablets) doses were administered to healthy male subjects, respectively.
3. A mean terminal elimination half-life was approximately 7 and 10 hours after single and multiple 800 mg doses, respectively.
4. HMR 3647 exhibits a moderate deviation from linear pharmacokinetics over the single and multiple dosing range of 400 to 1600 mg. The total clearances were 174.4, 102.3 and 71.4 mg•h/L after single dose of 400, 800, and 1600 mg HMR 3647, respectively. The total clearances were 124.9, 71.1 and 54.2 mg•h/L after multiple doses of 400, 800, and 1600 mg HMR 3647, respectively (Study 1008).
5. Total clearance decreased from 102.3 L/h after single dose of 800 mg HMR 3647 to 71.1 L/h after multiple doses of 800 mg HMR 3647 (once a day for 7 days), indicating nonlinear pharmacokinetics of HMR 3647 (Study 1008).
6. A moderate accumulation was observed which was similar for the three doses (1.42). Single dose pharmacokinetics is not able to predict the steady-state pharmacokinetics due to the nonlinearity.
7. The main metabolite, RU 76363, exhibited a similar deviation from linearity indicating that a saturation of this metabolic pathway is not occurring.

How does HMR 3647 distribute in the body?

1. HMR 3647 has an apparent volume of distribution of approximately 210 L in young subjects and approximately 226 L in elderly subjects (Study 1044).
2. Protein binding: About 60 to 70% of HMR 3647 is bound to plasma proteins. The binding of HMR 3647 to albumin and AGG is approximately 49% and 30%, respectively.
3. Cells: It distributes well into whole blood, red blood cells and white blood cells.
4. Pulmonary tissue: HMR 3647 penetrates well into pulmonary tissues and bronchial secretions. In study 1043, the mean concentrations were 69.3 mg/L (ranged — . mg/L) in alveolar macrophages (AM) and 14.89 mg/L (ranged — mg/L) in epithelial lining fluid (ELF) at 2 hours post dose after repeated dosing with 800 mg once a day for 5 days. In study 1028, the mean concentrations were 65 mg/L (ranged — mg/L) in AM and 5.4

mg/L (ranged — / mg/L) in ELF at 2 hours post dose after repeated dosing with 800 mg once a day for 5 days. The mean concentration was 100 mg/L (— mg/L) and 41 mg/L in AM at 8 and 24 hours postdose after repeated dosing with 800 mg QD for 5 days, respectively. The mean concentration was 4.2 mg/L — , mg/L) and 1.17 mg/L (— mg/L) in ELF at 8 and 24 hours postdose after repeated dosing with 800 mg QD for 5 days, respectively.

5. Tonsils: The mean concentrations of HMR 3647 in tonsil tissue were 3.85 mg/kg, 0.88 mg/kg, and 0.72 mg/kg at 3, 12 and 24 hours post dose after repeated dosing of 800 mg HMR 3647. HMR 3647 concentrations were on average greater than 10 times the MIC_{50} values (MIC_{50} of group A beta-haemolytic streptococci ranged from 0.008 to 0.06 mg/L). It should be noted that the unit of tissue concentration is mg/kg instead of mg/L.
6. Saliva: Concentrations of HMR 3647 in saliva were greater than those in plasma (ratio was 1.7 on day 1 and 1.6 on day 10).
7. Blister fluid: HMR 3647 has been shown to diffuse into extracellular space as evidenced by concentrations observed in blister fluid. But the C_{max} in blister fluid was about half of C_{max} in plasma.

What do we know about metabolism of HMR 3647 *in vitro*?

It was found from an *in vitro* study that telithromycin was mainly metabolized by CYP 3A4 in human liver microsomes. On the other hand, telithromycin inhibited CYP3A with a Ki of 58 μM and CYP2D6 with a Ki of 46 μM. There were minor effects on CYP1A1 and CYP1A2 at 0.1 to 1 mM. These *in vitro* studies indicate that there is a potential for HMR 3647 to cause drug-drug interactions.

How is HMR 3647 metabolized in humans? How is HMR 3647 excreted?

1. The metabolic pathways and recovered radioactivity after a single dose of HMR 3647 are shown in **Figure 9**.
2. In feces, a total of 76% of ingested dose is recovered. The most abundant compound was HMR 3647 and its α-epimer, comprising 29% of the radioactivity recovered in feces (22% of ingested dose). The remaining characterized compounds were RU 76363 (3.86% the radioactivity recovered in the feces), RU 78849 (16.5%), RU 76584 (1.0%), and RU 72365 (2.79%). The remaining radioactivity in feces was comprised of several other metabolites, background, and individual peaks below 0.5% of dose. Therefore, only about 53% of radioactivity recovered in feces was identified, 47% of the radioactivity was not characterized.
3. In urine, 17% of ingested dose is recovered. The most abundant compound in urine was HMR 3647 and its α-epimer, comprising 69% of the radioactivity recovered in urine (11.7% of the ingested dose). The remaining characterized compounds were the same as those found in feces, RU 76363, RU 78849, RU 76584, and RU 72365 comprising 7.28%, 3.51%, 0.63%, and 0.41% of the radioactivity recovered in the urine, respectively. The remaining radioactivity in urine was comprised of several other metabolites, background, and individual peaks below 0.05% of dose. Therefore, about 81% of radioactivity recovered in urine was identified, 19% of the radioactivity was not characterized.
4. HMR 3647 and its four main metabolites were also found in plasma. The main circulating compound in plasma was HMR 3647, with its mean total AUC representing 57% of total radioactivity AUC. The next most prevalent compound was RU 76363 whose mean AUC represented 12.6% that of HMR 3647. The three other metabolites were also quantitated in plasma however each of their mean AUC's represented less than 3% the AUC of HMR 3647.
5. Metabolism is considered the principle route of elimination of HMR 3647. Only 34% of dosed HMR 3647 was recovered as unchanged compound (22% in feces, 12% in urine).

Are the metabolites active? Are the metabolites toxic?
Only HMR 3647 and RU 76363 display biological activity. The activity of RU 76363 is 4 to 16 times lower than that of HMR 3647. The toxicity of the metabolites is unknown.

Is there a difference in HMR 3647 PK between males and females?
The pharmacokinetics of HMR 3647 were similar between healthy male and female subjects for both single and multiple doses. Mean Cmax and AUC(0-24) values observed in healthy female subjects (1.08 mg/L and 5.52 mg·h/L) after a single 800 mg HMR 3647 oral dose were similar to those observed in male subjects (1.08 mg/L and 5.68 mg·h/L). Thus, the dose regimen of HMR 3647 should be the same for both genders.

How different is the PK between pediatric patients and adults?
Not been studied.

How different is the PK among various ethnic groups?
Not been studied.

Is dose adjustment needed in elderly?
It was found in study 1005 that the C_{max} and AUC values in elderly subjects are 2-fold greater compared to C_{max} and AUC values in young subjects after multiple oral doses. However, the same dose (800 mg) was used for both young and elderly subjects in clinical trials. No dose adjustment was recommended by the sponsor. A smaller difference in C_{max} and AUC was found between young subjects and elderly subjects in study 1044. The reason might be that the difference in renal function between elderly and young subjects, expressed as creatinine clearance, was different in Study 1005 and 1044. The difference in creatinine clearance between elderly and young subjects was 17% in Study 1044 but the difference was 37% in study 1005 **(Table 4)**.

Table 4. The pharmacokinetics parameters of HMR 3647 in study 1044, 1005 and 1004

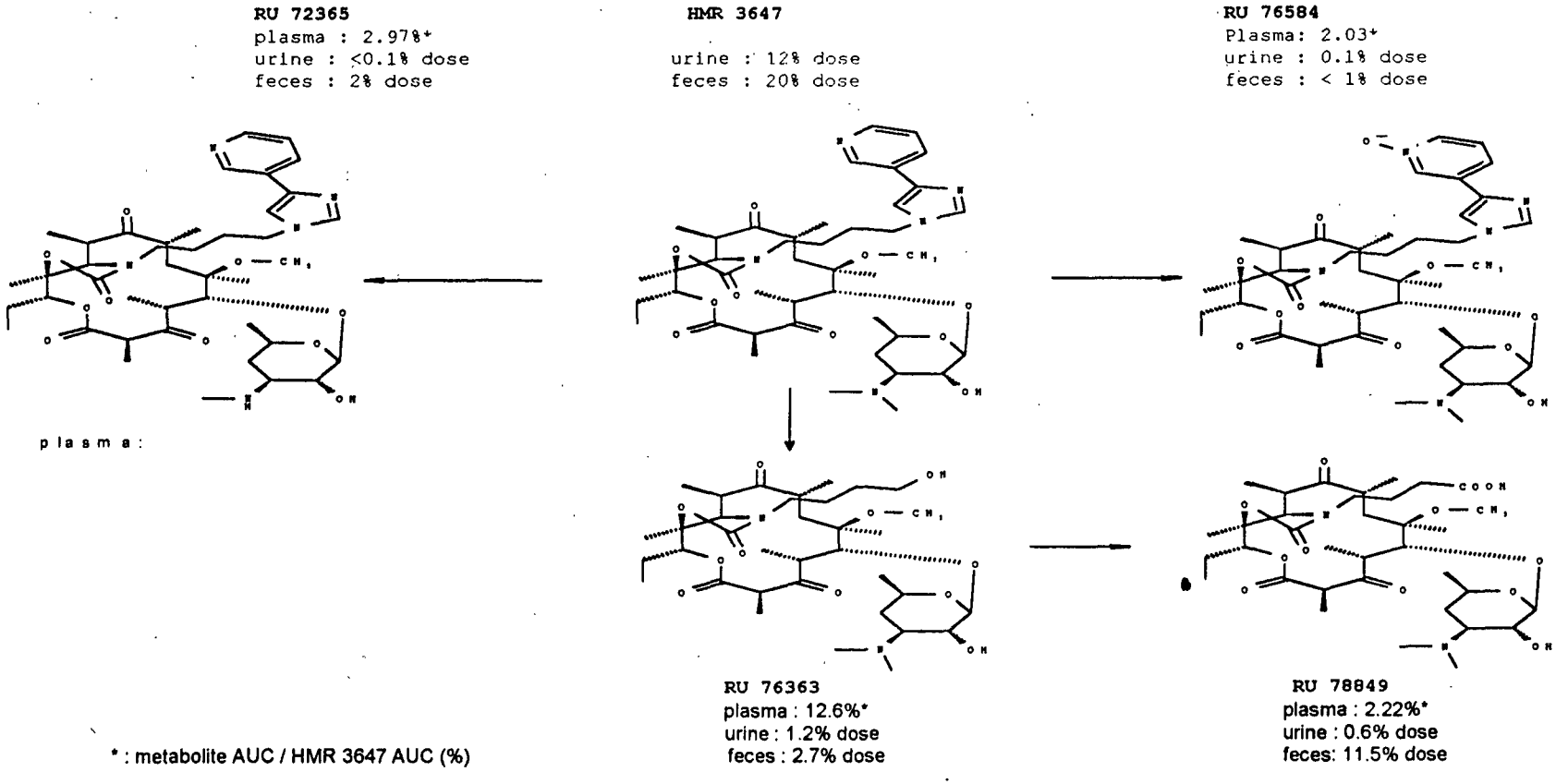
Study	1044			1005			1004		
	young	elderly	% of difference	Young	elderly	% of difference	Young	Elderly	% of difference
Gender	12 M	9M/3F		12M	10M/6F		6M	3M/3F	
CLcr(ml/min/1.73m^2)	110.9	91.5	**-17.5%**	118.7	74.5	**-37%**	105	69	**-34%**
Age	20.5	72.2		21.3	73.6		26.3	73.5	
CLr [a] (L/h)	11.42	8.50	**-25.6%**	12.91	7.11	**-44.9%**	14.88	10.54	**-29%**
Cmax (single dose)	1.64	1.91	**+16**	1.99	2.59	**+30%**	1.411	1.8	**+28%**
Cmax (steady state)	NA	NA		1.84	3.6	**+96%**	NA	NA	
AUC (single dose)	8.4	10.83	**+28%**	7.89	12.63	**+60%**	6.05	9.5	**+57%**
AUC (steady state)	NA	NA		9.42	20.3	**+115%**	NA	NA	

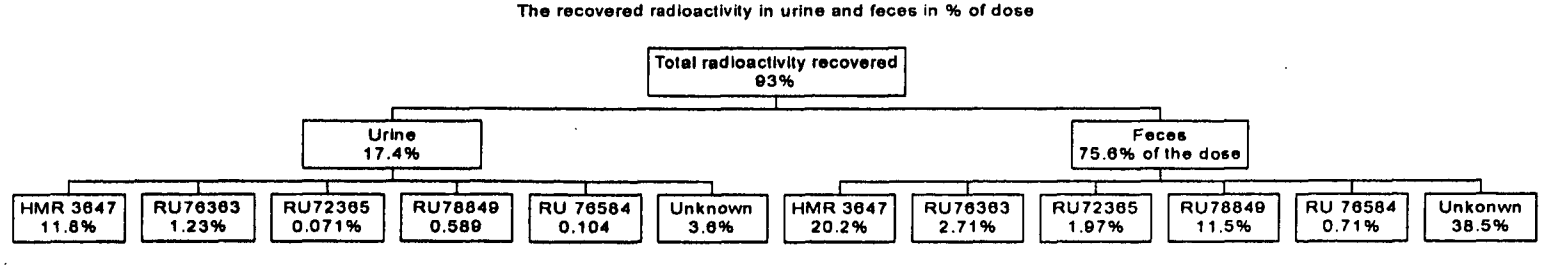
a. after single oral 800 mg dose

In addition to the studies in phase 1, it was also found in a population pharmacokinetics study (1052) that elderly tend to have higher concentrations but the difference between young patients and elderly patients was not quantitated.

Conclusion: Since it is known that QT prolongation is concentration dependent and elderly patients have higher exposure there is concern about using the same dose in both young and elderly patients. The safety of HMR 3647 in elderly patients should be evaluated in the phase 3 clinical trials.

Figure 9. Metabolic pathway of HMR 3647 in human





Is dosage adjustment needed in patients with renal impairment?

Although it was shown in Study 1016 that pharmacokinetics of HMR 3647 was not changed with renal function statistically significant **(Table 5)**, the variability of the parameters was high, indicating that the study might be under-powered to detect any difference. Similarly, the regression analysis of Cmax and AUC(0-∞) on CL_{CR} values showed no relationship between the parameters. However, the sponsor suggested the dose needs to be adjust to 400 mg in severe renal impairment The pharmacokinetics of telithromycin in end-stage renal failure group was similar to healthy subjects. This result might not be very reliable because the pharmacokinetic study in this group was conducted only 2 hours after the dialysis procedure. The effect of dialysis on the pharmacokinetics of HMR 3647 was not assessed.

Table 5. Pharmacokinetics parameters for healthy subjects and renal impaired subjects

	Renal						Pairwise comparisons		
Parameter					Adjusted			90% Conf.	P
(units)	Group*	N	Mean	CV (%)	mean[a]	Pair	Ratio[a] (%)	interval[a]	value
AUC(0-∞)	I	10	10.09	34.65	9.47				
(h•mg/L)	II	10	14.31	40.26	13.35	II/I	140.89	(98.16, 202.12)	0.1180
	III	10	16.00	45.72	14.36	III/I	151.61	(105.64, 217.60)	0.0597
	IV	10	10.79	57.24	9.29	IV/I	98.10	(68.35, 140.80)	0.9291
C_{max}	I	10	2.25	37.56	2.12				
(mg/L)	II	10	3.00	26.05	2.90	II/I	137.12	(99.59, 188.80)	0.1043
	III	10	3.25	43.10	2.92	III/I	137.73	(100.04, 189.64)	0.0996
	IV	10	2.13	40.79	1.94	IV/I	91.51	(66.46, 125.99)	0.6422
$t_{1/2}$	I	10	10.66	24.89	10.38				
(h)	II	10	11.41	12.63	11.33	II/I	109.11	(86.38, 137.82)	0.5328
	III	10	12.58	26.63	12.20	III/I	117.54	(93.06, 148.48)	0.2504
	IV	10	14.64	68.36	12.80	IV/I	123.36	(97.66, 155.83)	0.1380
CL_R	I	10	9.34	35.79	8.57	-	-	-	-
(L/h)	II	10	5.71	29.29	5.45	II/I	63.62	(39.14, 103.42)	0.1246
	III	10	2.63	58.20	2.16	III/I	25.25	(15.53, 41.04)	0.0001
	IV	2	0.36	117.85	0.20	IV/I	2.32	(1.00, 5.39)	0.0001

* Group I: Subjects with normal renal function (creatinine clearance >80 mL/min)
Group II: Subjects with mild to moderate renal impairment (creatinine clearance 41 to 80 mL/min)
Group III: Subjects with moderate to severe renal impairment (creatinine clearance 11 to 40 mL/min)
Group IV: Subjects with end-stage renal failure (creatinine clearance <10 mL/min) or who are anuric. 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.

Is dosage adjustment needed in patients with hepatic impairment?

In the hepatic impairment study (Study 1016), 7 out of 12 patients in the study were moderately impaired and 5 out of 12 patients with Child Pugh score of greater than 10 was severely impaired. The C_{max} and AUC are not statistically significant between healthy subjects and hepatic impaired subjects **(Table 6)**. It was found that one hepatic impaired subject had extremely low Cmax and AUC values compared to others. Therefore, calculations were made after excluding the subject from the study. The Cmax and AUC values were still comparable after excluding the "outlier". The Cmax and AUC were calculated for the severe hepatic impaired subjects. These values are also comparable with the values of healthy volunteers. It was shown that the similar exposure between healthy volunteers and hepatic impaired patients was the results of compensated renal function in hepatic impaired patients. Renal clearance of healthy subjects and moderately hepatic impaired subjects was 10.78 and 17.7 L/hr, respectively. Compared with healthy volunteers, renal clearance in hepatic impaired subjects was increased by 60%, indicating that decreased metabolic clearance was partially compensated by renal clearance. Compared with healthy subjects, renal clearance in severe hepatic impaired subjects (Child Pugh Score >10) was increased by 103%.

The elimination half-life in healthy volunteers and hepatic impaired subjects was 10.3 hour and 14.2 hours, respectively. These findings raised the concern about the accumulation of HMR 3647 after multiple doses. Due to the concern about accumulation in hepatic impaired patients after multiple doses, per requested by FDA, the sponsor conducted a multiple dose study in hepatic impaired subjects. Although the final study report has not been submitted, the preliminary results showed that the mean Cmax and AUC in hepatic impaired patients are similar to healthy subjects even after multiple doses. The mean C_{max} are 1.82 mg/L and 1.96 mg/L in hepatic impaired patients and healthy subjects, respectively. The mean AUC are 12.34 mg•h/L and 13.82 mg•h/L in hepatic impaired patients and healthy subjects, respectively. Therefore, the concern about hepatic impaired patients become not significant.

Table 6. Pharmacokinetics parameters of HMR 3647 in study 1015

	Cmax (mg/L)	$AUC_{0-\infty}$ (mL*h/L)	$t_{1/2}$ (h)	C24 (mg/L)	Ae (0-72) (%)	CLr (L/h)
Healthy	2.32	10.10	10.33	0.039	13.1	10.78
Hepatic impaired (excluding subject 12)	2.15	11.78	13.7	0.0899	22.84	16.35
Severe hepatic impaired (Child Pugh Score>10, n=5)	2.18	10.4	14.68	0.0798	26.86	21.92

Conclusion: Renal function becomes critical when hepatic function is impaired. The exposure could be increased in the patients with both renal and hepatic impairment.

What are the drug-drug interaction concerns based on the available information?

Eleven drug-drug interaction studies were conducted including interaction with CYP 3A inhibitors (ketoconazole, itraconazole), CYP3A substrate (cisapride, simvastatin), CYP2D6 substrate (paroxetine), other mixed CYP substrates (theophylline, warfarin and oral contraceptive), others (digoxin, grapefruit juice, — . The results are summarized in **Table 7**. It was shown that P450 3A inhibitors such as ketoconazole and itraconazole could significantly increase HMR 3647 concentration and HMR 3647 can also increase concentrations of other P450 3A substrates such as cisapride and simvastatin (**Table 8**). HMR 3647 increased theophylline's Cmax and AUC by 16% and 16%, respectively, and digoxin C_{max} and AUC by 37% and 73%, respectively. Grapefruit juice and ranitidine and ~ did not affect HMR 3647 plasma levels. HMR 3647 had no effect on pharmacokinetics of warfarin, an oral contraceptive and paroxetine.

Table 7. Drug drug interaction effect of other drugs on HMR 3647

Study	Drugs/dose	HMR 3647		Interacted drugs		P450	Conclusion
		AUC* [CI#]	Cmax* [CI#]	AUC [CI#]	Cmax [CI#]		
1045	Ketoconazole (400 mg/multiple doses)	95% ↑ [150-250]	52% ↑ [112-205]	20% ↓ [67-96]	20% ↓ [70-92]	3A inhibitor	Ketoconazole ↑ HMR 3647 exposure. HMR decreased ketoconazole exposure.
1037	Itraconazole (200 mg/multiple doses)	54% ↑ [135-177]	22% ↑ [103-143]	NM	NM	3A inhibitor	Intraconazole ↑ HMR exposure.
1020	Ranitidine (300mg)	9.3%↓ [75-96]	13.4%↓ [71-95]	NM	NM	NA	Not significant
	Maalow (30mL)	1.9% ↑ [88-112]	1% ↑ [87-116]	NM	NM		
1047	Grapefruit (single dose)	3.9%↑ [95-113]	0.8%↑ [90-113]	NM	NM	NA	Not significant

*: ↑ indicates percent of increase compared with given HMR 3647 alone; ↓ indicates percent of decrease compared with given HMR 3647 alone.
#: 90% confidence interval
NA: not applicable.
NM: not measured

Table 8. The drug drug interaction effect of HMR 3647 on other drugs

Study	Drugs/dose	HMR 3647		*Interacted drugs*		P450	Conclusion
		AUC mg•h/L	Cmax mg/L	AUC mg•h/L [CI*]	Cmax mg/L [CI*]		
1041	Cisapride (20 mg/multiple)	14.57 13.65	2.96 2.99	150%↑ [219-284]	95.2%↑ [154-189]	3A substrate	↑ cisapride exposure
1011	Theophylline (titration to concentration in the range of 10 μg/mL to 20 μg/mL)	NM	NM	16%↑ [110-126]	16% ↑ [107-126]	1A2/3A4 substrate	Significant increase but less than 30% of increase. C_{min} ↑ by 23% [90%: 117-131]
1012	Warfarin (25 mg/single)	NM	NM	20% ↑ (R) [114-125] 5%↑ (S) [101-109]	11%↑ (R) [104-118] 12% ↑ (S) [105-109]	2C9/3A4 substrate	Not significant
1013	Digoxin (loading dose:0.5 followed by 0.25mg bid)	9.68	1.98	37%↑ [132-142]	73%↑ [159-189]		↑ digoxin exposure
1042	Oral contraceptive (ethinyl estrdiol	10.18	1.74	2%↑ [98-107]	17%↓ [78-87]	NA	Not significant
	levonorgestrel			50%↑ [144-157]	20%↑ [115-125]	NA	Not significant
1022	Paroxetine (30mg multiple dose)	NM	NM	0.44↓ [90-110]	5.9%↑ [95-118]	2D6 substrate	Not significant
1048	Simvastatin	9.41	2.24	727%↑ [761-974]	397%↑ [434-654]	3A4 substrate	↑ simvastatin and its metabolite's exposure
	Simvastatin acid (metabolite)			982%↑ [964-1219]	1418%↑ [1307-1697]		
1056	Midazolam (iv infusion: 2 mg oral: 6 mg)	10.3 (iv) 11.4 (oral)	1.48 (iv) 1.59 (oral)	115% ↑ (iv) 511%↑ (oral)	6% ↑ (iv) 162% ↑ (oral)	3A4 substrate	↑ midazolam's exposure
1057	Sotalol (160 mg single dose)	5.80	1.24	20%↓	34%↓		↓ sotalol exposure

* 90% confidence interval

In study 1011, 1012 and 1022, only trough level of HMR 3647 were measured.

In study 1056 and 1057, confidence interval was not constructed.

How has QT prolongation been evaluated in phase I studies?

Five phase 1 studies were conducted to specifically investigate the QT prolongation of HMR 3647.

Study 1031: It was a double-blind, randomized, placebo-controlled, 3-way crossover study. During 3 different periods, each subject received the following doses, which were orally administered for 6 days: 800 mg HMR 3647 in the morning (2 x 400 mg HMR 3647 tablets) and 2 matching placebo capsules in the evening, or 2 matching placebo capsules twice a day, or 500 mg clarithromycin (2 x 250 mg) blinded into capsules twice a day.

QT prolongation was assessed by exercise tolerance test (ETT) to compare QT intervals at different heart rates after single dose and multiple doses of 800 mg HMR 3647, 500 mg

clarithromycin (bid) and placebo. This test allows the comparison of QT interval between treatments at different heart rates. With this design the bias associated with correction of the QT interval using Bazett's formula is eliminated. The ETT was conducted 2 hours after the dose. The results from this study showed that QT interval was similar between placebo, 800 mg HMR 3647 treatment and 500 mg clarithromycin treatment.

Study 1032: QT prolongation was assessed using ETT. It was a double-blind, randomized, placebo controlled, four-way cross over study. During 4 different periods each subject received a single oral administration of placebo, 800 mg, 1600 mg or 2400 mg HMR 3647. The ETT was conducted 2 hours after the dose. The results showed that the QT interval was not statistically significantly different between treatments (800 mg HMR 3647, 1600 mg HMR 3647 and 2400 mg HMR 3647) and placebo.

These two studies were not informative due to the following reasons:

1. ETT was conducted at 2 hours after treatment when the maximal HMR 3647 concentration was not achieved. The mean HMR 3647 t_{max} is 3 hour after both 800 mg HMR 3647 and 250 mg (bid) clarithromycin in Study 1031.
2. ETT conducted at 2 hours after treatment is considered an insensitive method because of the wide range of HMR 3647 t_{max}. The value of t_{max} ranged from 2 hours to 6 hours for HMR 3647 and 1 to 8 hours for clarithromycin in Study 1031.
3. In Study 1031, the mean HMR 3647 concentrations at 2 hours after the dose on day 1 and day 6 were 0.637 mg/L and 0.806 mg/L, respectively. The concentrations were relatively low compared with mean C_{max} of 1.9 mg/L after oral administration of 800 mg HMR 3647 (Study 1008). The QT prolongation assessed by ETT conducted at these low concentrations was considered not useful.
4. In Study 1032, HMR 3647 concentrations were low at 2 hours when ETT was conducted. The mean concentrations at 2 hours after 800 mg, 1600 mg and 2400 mg were 0.84 mg/L, 1.04 mg/L and 1.95 mg/L, respectively. Although doses were pushed as high as 3 times the clinical dose, the pharmacokinetic data showed that the true exposure was low.

Study 1030, 1046 and 1049 were dose escalating studies.

Study 1030: Four treatment groups were included in the study:

Group A: It was four-period, double blind, randomized, placebo-controlled study. Eight healthy young subjects received a single oral dose of HMR-3647. Each subject received 3 incremental doses of HMR 3647 (1600, 2000, 2400 mg) and 1 placebo dose. During each period, 6 subjects received active treatment (at 1 or more dose-strengths) and 2 subjects received placebo.

Group B: It was double blind, parallel randomized, placebo-controlled study. Eight healthy young subjects received HMR 3647 (1600 mg) once a day for 5 days. Each subject was randomly allocated to 1 of 2 treatments (HMR 3647: 6 subjects or placebo: 2 subjects).

Group C: Identical design to group A, except that 8 elderly (aged 60 years to 85 years) male and postmenopausal female subjects were enrolled. Each subject received 3 incremental doses of HMR 3647 (1200, 1600, 2000 mg).

Group D: Identical design to group B, except 8 elderly (aged 60 years to 85 years) male and postmenopausal female subjects were enrolled. Subjects received placebo or 1200 mg HMR-3647 once a day for 5 days.

The mean delta QTc was calculated at each sample collection time. The study showed that the mean maximum delta QTc after single doses of 1600 mg, 2000 mg and 2400 mg in young subjects occurred at 1.5 hours with values of 20 ms, 18 ms and 28 ms, respectively. The corresponding delta QTc after placebo was 4 ms. The difference between treatments and placebo was statistically different. The mean maximum delta QTc after single doses of 1200 mg, 1600 mg and 2000 mg in elderly subjects occurred at 4 hours with the values of 12 ms, 18 ms and 19 ms, respectively (**Table 9**). The corresponding delta QTc after placebo was -3 ms. The difference between treatments and placebo was statistically significant. However, no statistically significant

difference in delta QTc was found after repeated doses of 1600 mg in young and 1200 mg in elderly. It should be noted that the placebo and treatment group were parallel instead of crossover in the repeated study.

The regression analysis using pooled data showed that the delta QTc was correlated with HMR 3647 plasma concentrations. **(Table 10 and Figure 10)**.

HMR 3647 increased heart rate with the mean maximal increase of 17 bpm **(Figure 10)**

Table 9. The mean maximum change of QTc, QTf and heart rate after HMR 3647 treatments

	Group A				Group B	
Treatment	Placebo	1600 mg	2000 mg	2400 mg	Placebo	1600 mg
Number of subject	8	8	8	7	2	6
Mean maximum delta QTc [a]	4 (18)	20 (14)	18 (10)	28 (19)	0 (1)	17 (17)
Mean maximum delta QTf [a]	3 (14)	10 (11)	7 (8)	15 (11)	-1 (2)	5 (12)
Mean heart rate increase	0 (7)	9 (5)	10 (7)	13 (7)	1 (4)	11 (5)
	Group C				Group D	
Treatment	Placebo	1200 mg	1600 mg	2000 mg	Placebo	1200 mg
Number of subjects	8	8	8	8	2	6
Mean maximum delta QTc [b]	-3 (8)	12 (15)	18 (17)	19 (11)	-6 (9)	4 (14)
Mean maximum delta QTf [b]	3 (5)	13 (11)	12 (15)	12 (7)	-6 (7)	-5 (13)
Mean heart rate increase	-5 (4)	-2 (6)	5 (4)	7 (4)	1 (1)	9 (6)

a. The mean average QTc, QTf, heart rate (HR) was calculated at each observed time point. The maximum QTc/QTf was observed at 1.5 hours after single dose in treatment A. The maximum QTc/QTf was observed at 1.5 hours after last dose on day 5 for treatment B.

b. The maximum QTc/QTf was observed at 4 hours after single dose in treatment C. The maximum QTc/QTf was observed at 1.5 hours after last dose on day 5 for treatment D.

Table 10. Correlation of QTc or QTf with HMR 3647 plasma concentration

	Intercept	Slope (p value)
Delta QTc ~ Concentration	-2.05	3.93 (0.0000)
Delta QTc ~ Concentration (linear mix effect)	-2.91	3.68 (0.0001)
Delta QTc ~ Concentration + Heart rate	-4.39	Conc: 3.87 (0.0000) HR: 0.03 (0.597)
Delta QTc~ Concentration (young (A & B)	-1.065	4.40 (0.0000)
Delta QTc~ Concentration (elderly (C & D)	-3.71	3.26 (0.0001)
Delta QTc ~ Maximum Concentration	-13.5	5.48 (0.0000)
Delta QTf ~ Concentration (linear)	-1.43	1.57 (0.0000)
Delta QTf ~ Concentration (linear mix effect)	-2.15	1.41 (0.001)
Delta QTf ~ maximum Concentration	-9.53	3.05 (0.0023)

Figure 10. The Relationship between Delta QTc/Delta QTf and HMR3647 concentration

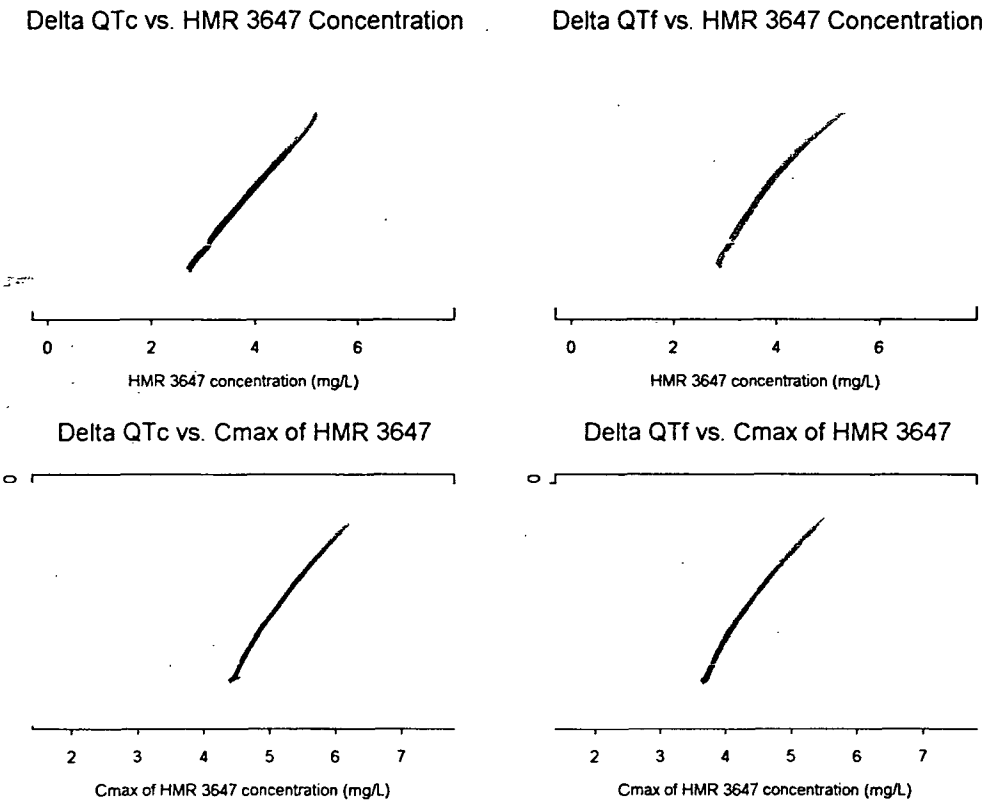
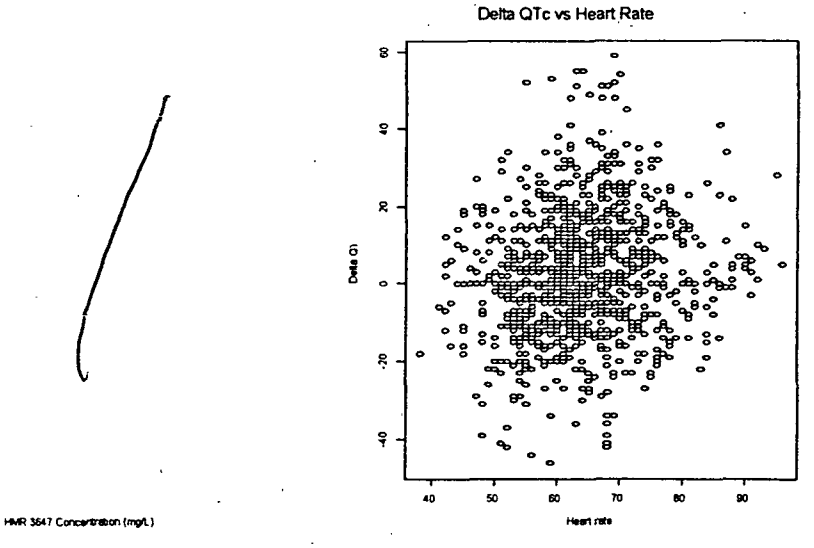


Figure 11. Heart rate vs. HMR 3647 concentration



The sponsor was requested to compare the maximal delta QTc between each treatment (1600 mg, 2000 mg and 2400 mg in young subjects and 1200 mg, 1600 mg and 2000 mg in elderly subjects) and placebo. The results showed that the mean maximal delta QTc values were 16, 24, 28 and 33 ms after oral administration of placebo or 1600 mg or 2000 mg or 2400 mg of HMR 3647, respectively, in young subjects. Significant differences in delta QTc values were found between placebo and each treatment group (1600 mg, 2000 mg, 2400 mg) in young female subjects but not in young male subjects. The mean maximal delta QTc values were 7, 18, 24 and 22 ms after oral administration of placebo or 1200 mg or 1600 mg or 2000 mg of HMR 3647, respectively, in old subjects. Similarly, significant differences in delta QTc were found between placebo and each treatment group (1200 mg, 1600 mg, 2000 mg) in older female subjects but not in older male subjects.

Study 1046: It was a double blind, randomized, placebo controlled, 3-period crossover study, with 2 escalating single oral doses of HMR3647 (2400 mg and 3200 mg) and an interspersed single placebo dose.

Twenty four subjects (12M/12F) were recruited in this study. Mean maximal delta QTc (over the time) occurred at 4 hours with the values of 17 ms and 17 ms after HMR 3647 2400 mg and 3200 mg, respectively. The corresponding delta QTc was –7 for placebo. At the same time, the maximal delta HR was 11 and 13 bpm for HMR3647 2400 mg and 3200 mg, respectively. There was a significant difference between treatments (Placebo, HMR3647 2400 and 3200 mg) for the variables delta QT, delta RR, delta QTc, and delta HR. Significant time and time-by-treatment interaction effect in delta QTc were found by ANOVA.

Regression analysis showed that the delta QTc was correlated with HMR 3647 plasma concentrations (**Table 11 and Figure 12**). The results also showed HMR 3647 increased heart rate (**Figure 13**)

The sponsor was requested to compare the maximal delta QTc between treatments (placebo, HMR 3647 2400 mg and HMR 3647 3200 mg). The results showed that the mean maximal delta QTc values were 12, 23, and 24 ms after placebo, 2400 mg HMR 3647 and 3200 mg HMR 3647 treatment, respectively. The delta QTc for each treatment was significantly different from placebo.

It should be noted that the mean C_{max} was about 3.29 mg/L after 2400 mg of HMR 3647 oral administration, which was lower than 5.98 mg/L obtained from Study 1030. The mean Cmax was only 4.41 mg/L after 3200 mg oral dose. Therefore, although the higher dose of 3200 mg was studied, the true C_{max} was not as high as expected. Therefore, this study was considered uninformative.

Table 11. Correlation between Delta QTc, Delta QTf, Delta HR and HMR 3647 concentrations

	Delta QTc	Delta QTf	Delta HR	Concentration
Delta QTc (ms)	1.00000			
Delta QTf (ms)	0.87227	1.00000		
	p = 0.0001			
Delta HR	0.72479	0.30567	1.00000	
(bpm)	p = 0.0001	p = 0.0001		
Concentration	0.55615	0.38494	0.55211	1.00000
(mg/L)	p = 0.0001	p = 0.0001	p = 0.0001	

Figure 12. Regression between delta QTc and HMR 3647 concentrations

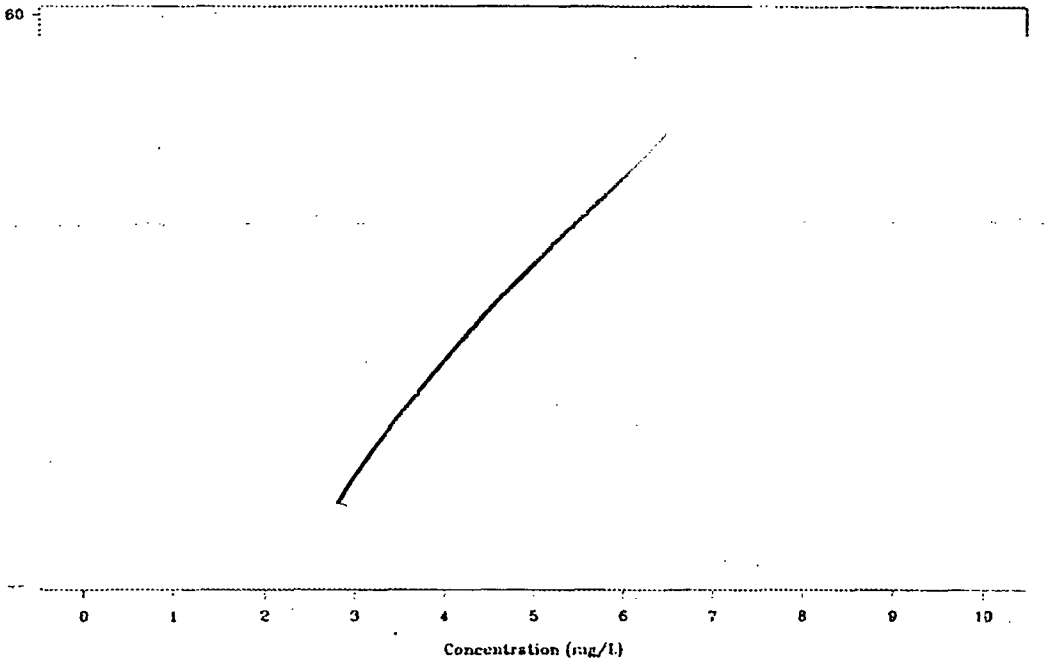
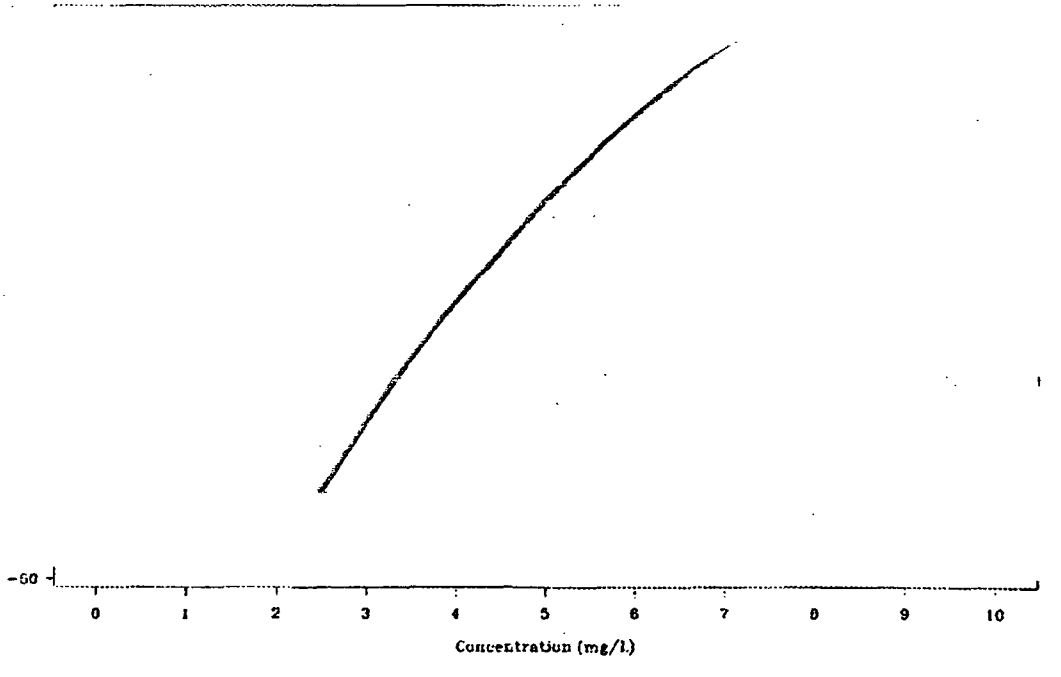


Figure 13. Regression between delta HR and HMR 3647 concentrations



Study 1049: It was a double-blind, randomized, placebo-controlled, 4-way crossover study. During 4 different study periods, subjects received HMR3647 800 mg and HMR3647 1600 mg as

single oral doses, clarithromycin 500 mg twice daily for one day, and placebo as single dose treatment. The study was conducted in patients with underlying cardiovascular diseases.
The mean delta QTc was calculated at each time point when the ECG was recorded. The maximal mean delta QTc occurred at 4 hours with the values of 2, 5, 7, and 12 ms after placebo, 800 mg HMR 3647, 2x250 mg clarithromycin and 1600 mg HMR 3647, respectively. No significant difference in delta QTc was found between placebo and 800 mg HMR or 500 mg clarithromycin, but a statistically significant difference was found in delta QTc between placebo and 1600 mg HMR 3647. Significant time and time-by-treatment interaction effect were found in delta QTc, indicating the comparison should be made between treatments at each time. The delta QTc at 2 hours after 800 mg HMR 3647 was significantly different from placebo but not the other time points.
No heart rate increase was observed in this study. The regression analysis showed that delta QTc was correlated with HMR 3647 concentrations when the data of 800 mg and 1600 mg were combined. It was also shown delta QTc was correlated with clarithromycin concentrations **(Figure 14 and 15)**.
The mean maximal delta QTc were 11, 14, 18, and 14 ms after placebo, 800 mg HMR 3647, 1600 mg HMR 3647, and 500 mg clarithromycin, respectively. Statistical analysis showed that there was a significant difference between treatments of 1600 mg HMR 3647 and placebo, but there was no significant difference between 800 mg HMR 3647 or 500 mg clarithromycin and placebo.

Figure 14. Correlation between plasma concentration and delta QTc when 800 mg and 1600 mg HMR 3647 was administered as a single dose

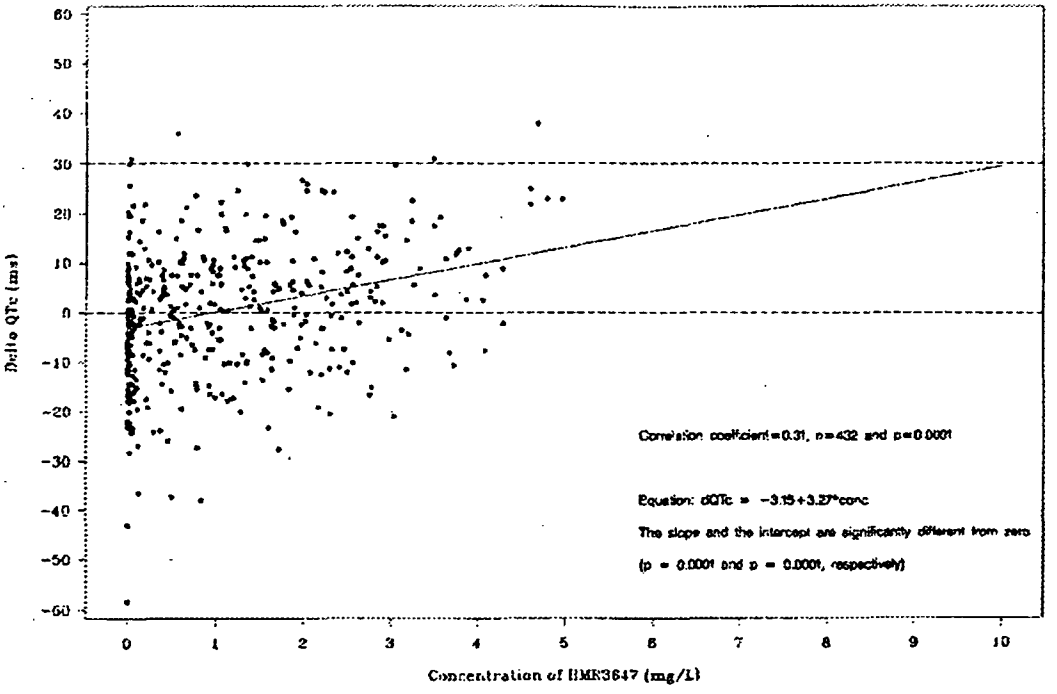
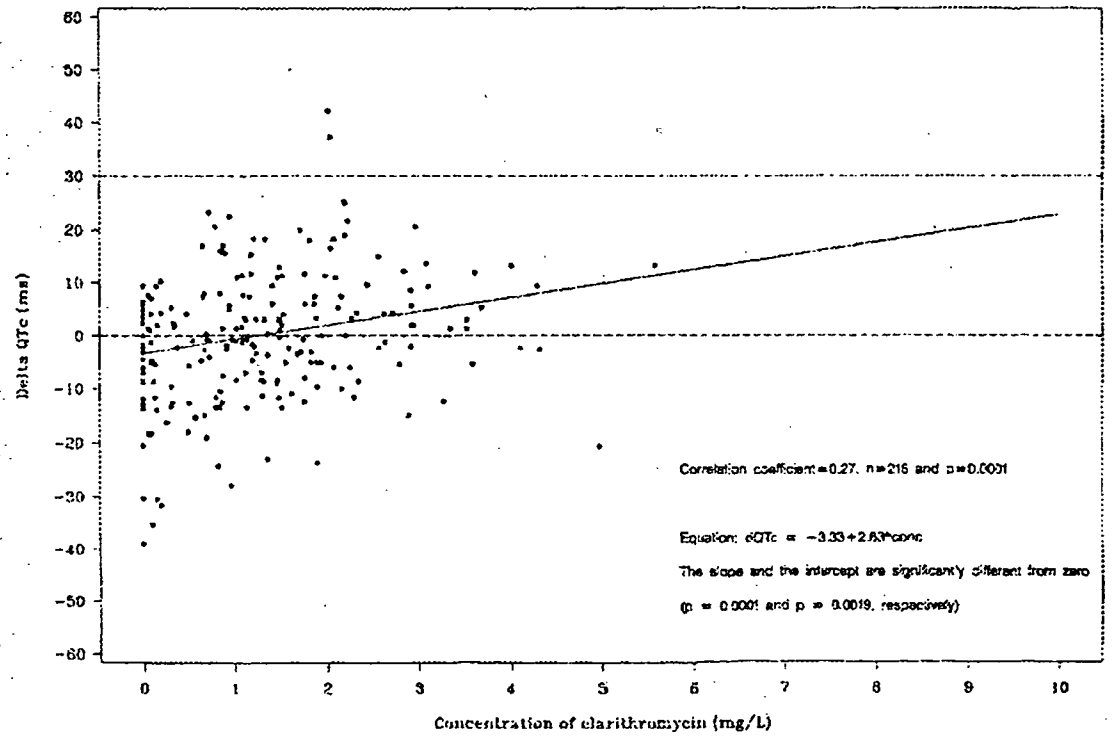


Figure 15. Correlation between clarithromycin concentration and delta QTc after 500 mg bid administration for 1 day



APPEARS THIS WAY
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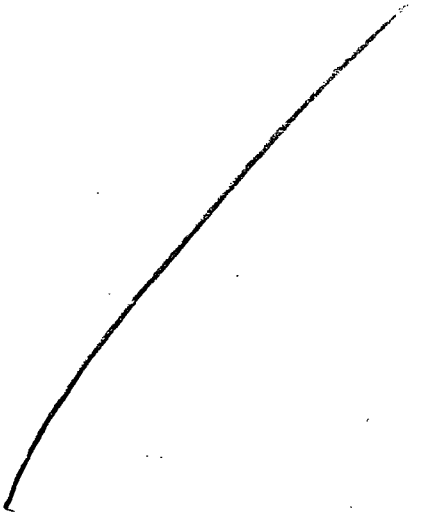
4. COMMENTS:

1. In vitro studies showed that CYP 3A is the major liver enzyme that metabolize telithromycin. However, the formation of a major metabolite identified in vivo, RU 76363, was not mediated by CYP 3A. The metabolic mechanism for forming RU76363 needs to be further explored.
2. Higher exposure in renal impaired patients suggested that dose adjustment in this population is necessary. However, the current pharmacokinetic information is not sufficient to recommend a dose for these patients because only a single dose, 800 mg, has been studied. Due to the nonlinearity of telithromycin, it is recommended that the sponsor conduct a multiple dose study in renal impaired patients at several dose levels so the information can be used to incorporate dose adjustment for renal impairment patients in the final product label.
3. When telithromycin coadministered with simvastatin, there was a 5.3-fold increase in simvastatin C_{max}, an 8.9 fold increase in simvastatin AUC, a 15-fold increase in the active metabolite C_{max} and a 12-fold increase in the active metabolite AUC. It was suggested that telithromycin should be contraindicated with simvastatin.
4. The dissolution specification should be changed from — (Q= —) at — to — (Q= —) at —

5. LABELING COMMENTS:

Three sections, CLINICAL PHARMACOLOGY section, PRECAUTION section and DOSAGE AND ADMINISTRATION section has been revised. The additions to the sponsor's draft are indicated by underline and deletions are indicated by strikeout.



7 Draft Labeling Page(s) Withheld

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jenny Zheng
5/31/01 03:32:49 PM
BIOPHARMACEUTICS

Frank Pelsor
5/31/01 04:17:24 PM
BIOPHARMACEUTICS

6. RECOMMENDATION:

NDA 21-144 was reviewed by Office of Clinical Pharmacology and Biopharmaceutics/Drug Evaluation III and found to be acceptable from clinical pharmacology point of view. Please convey the comments to the sponsor.

/S/

Jenny J Zheng, Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

RD/FT initiated by F. PELSOR, Pharm.D., Team Leader /S/

cc:
HFD-880 (Division File; F. Pelsor, TL)

STUDY NUMBER: 1011
TITLE: Effect of HMR 3647 on the Pharmacokinetics of Theophylline in Healthy Male and Female Subjects
INVESTIGATOR(S): ——
OBJECTIVES: To determine the effect of HMR 3647 on the pharmacokinetics of theophylline.
STUDY DESIGN:
This study was an open-label, non-randomized sequential design in healthy.
Phase 1 (titration phase): subjects were to report to the clinic twice daily for their theophylline doses. On days 1 to 3, subjects were to receive 125 mg theophylline b.i.d. as an immediate release tablet. On days 4 to 6, subjects were to switch to a 100 mg b.i.d. extended release tablet. On days 7 to 10, subjects were to have their dose increased to a 300 mg b.i.d. extended release tablet. On day 10, each subject's theophylline concentration was to be assessed 4 h after dosing for therapeutic drug monitoring. On day 11, each subject's theophylline dosage was adjusted to attain a steady-state theophylline concentration of 10 to 20 mg/L. The process of dose-adjustment (checking serum level and adjusting dosage appropriately) was to continue until each subject had attained a steady-state theophylline concentration within the therapeutic window or until four cycles of dose adjustment had been completed. If a subject did not achieve a steady-state theophylline concentration within the therapeutic window after four dose adjustment cycles, the sponsor had the option to drop that subject from the study.
Phase 2 (HMR 3647 treatment): once steady-state theophylline concentrations were attained and were within the therapeutic window, subjects were to be maintained on that dosing regimen and have up to 72 h to check into the clinic (day 1a). Subjects were to acclimate to the site on day 2a. The pharmacokinetics of theophylline were characterized on day 3a. By day 3a, subjects were on their final theophylline dose for a period of at least 6 days. On days 4a to 7a, subjects were given HMR 3647 800 mg (2 x 400 mg tablets) once daily. The pharmacokinetics of theophylline were characterized again on day 7a (after 4 doses). Subjects were to check out of the clinic on day 8a.
FORMULATION: HMR-3647 400 mg tablet (batch #: MD28146/055)
SAMPLING:
Blood (plasma) samples were collected for 12 h and on day 3a and 7a at pre-dose, 1, 2, 3, 4, 6, 8, 10, 12 hours after the dose for theophylline assay.
Blood (plasma) samples were collected 24, 48, and 72 h after administration of the first dose of HMR 3647 and assayed for HMR 3647 concentrations to insure that plasma concentrations were consistent with previous studies.
ASSAY: Theophylline and HMR 3647 were measured by HPLC/UV detection and HPLC/MS. The performance of the assay is shown in the following:

	HMR 3647	Theophylline
Accuracy of QC samples	-5.1 % to 10 %	3.0% - 6.0%
Precision (CV) of QC samples	2.8 % - 8.0 %	2.6% - 3.8%
The limit of quantification		

DATA ANALYSIS:
Pharmacokinetics:
Pharmacokinetic parameters such as $C_{max,ss}$, t_{max}, $AUC_{0-12,ss}$ were calculated using non-parametric method.
Statistics:
Comparisons between treatments were made using analysis of variance (ANOVA) with terms for subject and treatment. Data were dose normalized to a 300 mg dose prior to analysis to correct for differing theophylline doses being administered to subjects. 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.

Trough concentrations of HMR 3647 on days 5a, 6a, and 7a of the HMR 3647 coadministration phase were compared to determine if steady state has been reached. An analysis of variance (ANOVA) with terms for subject and day was done.

RESULTS:

Twenty-four subjects were enrolled, Nineteen subjects completed the study, 10 males and nine females with an average age and weight of 27 years old (range: 18 to 45 years) and 71 kg (range: 53 to 95 kg), respectively. To maintain theophylline concentration in the range of 10 – 20 μg/mL, twelve subjects took 300 mg and twelve subjects took 400 mg theophylline after titration phase.

HMR 3647:

The statistics of HMR 3647 trough concentration at day 4, 5, and 6 and the statistical summary are shown in Table 1. The results indicated that HMR concentration has not but near to the steady state after 4 doses.

Theophylline:

The mean pharmacokinetics parameters are shown in Table 2 and the statistical analysis is shown in Table 3. The mean plasma concentration of theophylline in both phase are shown in Figure 1. The study showed that the adjusted mean AUC (0-12)ss and Cmax,ss during theophylline administration was 119.2 mg*h/L and 11.4 mg/L, respectively, while during theophylline and HMR 3647 coadministration the adjusted mean AUC (0-12)ss and Cmax,ss was 139.8 mg*h/L and 13.3 mg/L, respectively. Theophylline AUC (0-12)ss and Cmax,ss was increased by approximately 16% ($p<0.01$) after HMR 3647 coadministration. Both average steady-state plasma concentrations and minimum plasma concentrations at steady state were also significantly higher after HMR 3647 coadministration.

CONCLUSION:

1. Maximal theophylline plasma concentrations ($C_{max,ss}$) increased 16% after coadministration of HMR 3647, an increase that was clinically insignificant.
2. Average theophylline plasma concentrations ($C_{avg,ss}$) increased by 16% after coadministration of HMR 3647, an increase that was clinically insignificant.
3. Theophylline clearance decreased by 15% after coadministration of HMR 3647.
4. Theophylline plasma concentrations tended to be higher in females than males, which may explain why females had more adverse events than males.

Table 1. HMR 3647 Trough levels comparison summary

						Pairwise Comparisons		
Treatment	Day	N	Mean	Adjusted Mean (a)	Pair	Ratio (%)	(90% CI) on Ratio	P-Value
300 mg	5a	10	0.021	0.020				
	6a	10	0.034	0.034	6a/5a	170.46	(144.2,201.6)	<0.001
	7a	10	0.048	0.045	7a/5a	226.25	(191.3,267.5)	<0.001
					7a/6a	132.72	(112.2,157.0)	0.009
400 mg	5a	9	0.026	0.025				
	6a	9	0.043	0.039	6a/5a	156.17	(129.1,188.9)	<0.001
	7a	9	0.046	0.043	7a/5a	170.99	(141.4,206.8)	<0.001
					7a/6a	109.48	(90.5,132.4)	0.418

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

Table 2. Pharmacokinetics parameters of theophylline with or without HMR3647

Theophylline alone								
Female	Variable	Unit	Mean	sd	n	CV%	minimum	maximum
	$AUC(0\text{-}12)_{ss}$	mg*h/L	136.5	35.6	11	26		
	$Cl_{po,ss}/F$	L/h/kg	0.037	0.008	11	22	0.030	0.057
	$C_{max,ss}$	mg/L	13.2	3.3	11	25		
	$C_{min,ss}$	mg/L	9.1	3.0	11	33		
	$C_{avg,ss}$	mg/L	11.4	3.0	11	26	7.1	15.5
	$T_{max,ss}$	h	3.6	2.1	11	57		
Male	$AUC(0\text{-}12)_{ss}$	mg*h/L	108.8	23.5	10	22	69.4	145.5
	$Cl_{po,ss}/F$	L/h/kg	0.036	0.011	10	29	0.022	0.053
	$C_{max,ss}$	mg/L	10.3	2.2	10	21		
	$C_{min,ss}$	mg/L	7.3	2.0	10	28		
	$C_{avg,ss}$	mg/L	9.0	1.9	10	21	5.8	12.0
	$T_{max,ss}$	h	4.2	2.3	10	54		
Theophylline with HMR 3647								
Female	$AUC(0\text{-}12)_{ss}$	mg*h/L	173.1	46.0	9	27		
	$Cl_{po,ss}/F$	L/h/kg	0.030	0.007	9	24	0.019	0.041
	$C_{max,ss}$	mg/L	16.4	5.3	9	32		
	$C_{min,ss}$	mg/L	12.3	3.6	9	29		
	$C_{avg,ss}$	mg/L	14.4	3.8	9	27	9.6	20.5
	$t_{max,ss}$	h	3.4	2.3	9	67		
Male	AUC(0-12)ss	mg*h/L	125.2	29.7	10	24		
	$Cl_{po,ss}/F$	L/h/kg	0.032	0.012	10	39	0.021	0.063
	$C_{max,ss}$	mg/L	11.9	2.9	10	25		
	$C_{min,ss}$	mg/L	8.8	2.1	10	23		
	$C_{avg,ss}$	mg/L	10.3	2.4	10	23	5.9	13.4
	$t_{max,ss}$	h	4.8	1.7	10	35		

Values were corrected for dose of theophylline administered then multiplied by 300 to correct for differing doses of theophylline administered.

STUDY NUMBER: 1012

TITLE: A study investigating a potential pharmacodynamic and pharmacokinetic interaction of HMR 3647 with racemic warfarin in healthy male subjects.

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

OBJECTIVES:

To assess whether HMR 3647 has an effect on the pharmacodynamics and pharmacokinetics of racemic warfarin.

STUDY DESIGN:

The study was double blinded, randomized, placebo controlled, two-period crossover, multiple doses study. 14-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 7 days and a single dose of warfarin (25mg) was administered on day 4.

Treatment B: Placebo was administered once a day for 7 days and a single dose of warfarin (25mg) was administered on day 4.

Since the primary objective of the study was pharmacodynamics study, a warfarin dose was given 17 days prior to the first treatment period to neutralize the greater pharmacodynamic response after the administration of the first single dose.

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

SAMPLING:

Plasma concentrations (96-hour profile) and pharmacokinetic variables of R- and S-warfarin, follow treatment with warfarin alone, and concomitantly with HMR 3647.

Trough plasma concentrations of HMR 3647 during the 7 days of administration.

Factor VII activity, prothrombin time (PT, 96-hour profiles) and pharmacodynamic variable (AUD: area under the PT and Factor VII activity-time data pairs), following treatment with warfarin alone, and concomitantly with HMR 3647.

ASSAY: Plasma concentrations of HMR 3647 were measured by a validated LC/MS method. The plasma concentrations of R- and S-warfarin were measured by validated HPLC method. The limit of quantitation level was

The performance of the assay is shown in the following:

	HMR 3647/Plasma	R-warfarin	S-warfarin
Accuracy of QC samples	-3.1 % - 10.5 %	-4.3 % - 0 %	-5.5 % - 0.6 %
Precision (CV) of QC samples	6.3 %- 8.3 %	6.1 % - 9.6%	13.8% - 15.0%
The limit of quantification			

PT and factor VII were determined with a one stage factor assay, performed on the ACL coagulation instrument. Prothrombin time (PT) reflects the *in vitro* coagulation capability of plasma, measured in seconds. A specific analyte cannot be measured, but the PT represents the result (coagulation of plasma) of the biological activity of all known factors of the extrinsic and common pathways of coagulation cascade.

Factor VII is one of the factors of the extrinsic coagulation pathway. A specific amount of analyte is not measured, but the factor level is measured as a percentage of normal activity levels.

DATA ANALYSIS:

Pharmacokinetics:

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

The pharmacodynamic variable such as area under the PT and Factor VII activity-time curve ($AUD_{(0-96)}$) were calculated using linear trapezoidal rule between 0h and 96h.

Statistics:

The calculated pharmacokinetic variables of R- and S-warfarin were subjected to analysis of variance (ANOVA) with treatment, period and subject as main effects. The analysis was performed on natural logarithmic (ln)-transformed data. 90% conventional confidence intervals were calculated for the percentage differences, expressed as ratios of the geometric means of the two treatment groups "(warfarin + HMR 3647)/(warfarin + placebo)", with respect to each variable.

t_{max} was subjected to non-parametric analysis based on the Wilcoxon signed ranks test statistic, but with the period effect also taken into account. The reported 90% confidence intervals for the median difference "(warfarin + HMR 3647) – (warfarin + placebo)" were calculated from this non-parametric analysis.

For HMR 3647, steady state of plasma concentrations was estimated by visual inspection of the plot of trough concentrations *vs* time. In addition, to confirm the visual assessment, the trough values were subjected to analysis of variance (ANOVA) with treatment day and subject as main effects. A Tukey-test was performed on the data to determine whether significant differences were present between treatment days.

For both PT and Factor VII, $AUD_{(0\text{-}96h)}$ was subjected to analysis of covariance (ANCOVA) with treatment, period and subject as main effects, and the baseline value as covariate. The analysis was performed on natural logarithmic (ln)-transformed data. 90% conventional confidence intervals were calculated for the percentage differences, expressed as ratios of the geometric means of the two treatment groups "(warfarin + HMR 3647) / (warfarin + placebo)", with respect to each variable.

A pharmacodynamic interaction of HMR 3647 with warfarin was assessed on the basis of the calculated 90% confidence intervals for the mean ratios of the pharmacodynamic variables, in relation to equivalence ranges of 95%-105% for the $AUD_{(0\text{-}96h)}$ of PT, and 90%-111% for the $AUD_{(0\text{-}96h)}$ of Factor VII activity.

RESULTS:

Twenty-four (24) healthy male subjects (mean age: 21.1) were enrolled into the study and Twenty-three (23) subjects completed the study, and were included in the pharmacokinetic and pharmacodynamic analyses.

Pharmacokinetics:

The summary of pharmacokinetic parameters for R- and S-warfarin are shown in Table 1. The median concentration vs time profiles for R- and S-warfarin are shown in Figure 1 and 2. The results showed that HMR 3647 could increased C_{max} and $AUC_{(0\text{-}\infty)}$ of R-warfarin by 9.2% and 21%, respectively.

C_{max} and $AUC_{(0\text{-}\infty)}$ of S-warfarin were increased by 10% and 4%, respectively.

The steady state levels had been reached by the fourth administration of HMR 3647 (Day 5(0h)); this was confirmed by statistical analysis of the trough levels.

The mean prothrombin time (PT) and factor VII activity are summarized in Table 2. The results showed similar profiles of PT and Factor VII activity over time were observed for warfarin + placebo and warfarin + HMR 3647 (Figure 3 and 4). The respective $AUD_{(0\text{-}96h)}$ values of PT and Factor VII compared very well for treatment with and without concomitant HMR 3647. The 90% confidence intervals for the mean ratio "(warfarin + HMR 3647)/(warfarin + placebo)" were within the pre-defined equivalence ranges of 95-105% for $AUD_{(0\text{-}96h)}$ of PT and 90-111% for $AUD_{(0\text{-}96h)}$ of Factor VII activity.

CONCLUSION:

There was no pharmacodynamic or pharmacokinetic interaction of HMR 3647 with racemic warfarin in the healthy subjects in this study.

Table 1. Plasma R- and S-warfarin pharmacokinetic variables, Mean (CV%) and range (n=23)

Variable	Warfarin + placebo	Warfarin + HMR 3647	Point estimate (90% CI)*	Intra-individual CV
R-warfarin				
C_{max}	1.431 (25)	1.563 (18)	111%	12%
[µg/mL]			(104; 117%)	
t_{max}	0.50#	0.50#	-0.25 h**	-
[h]				
$AUC_{(0-\infty)}$	82.0 (25)	98.9 (30)	120%	9%
[µg.h/mL]				
$t_{½:z}$	45.5 (19)	54.3 (21)	119%	11%
[h]				
S-warfarin				
C_{max}	1.490 (27)	1.639 (18)	112%	13%
[µg/mL]			(105; 119%)	
t_{max}	0.50#	0.50#	-0.25 h**	-
[h]				
$AUC_{(0-\infty)}$	50.4 (44)	52.3 (38)	105%	8%
[µg.h/mL]	27.9 - 113.0	31.2 - 104.0	(101; 109%)	
$t_{½:z}$	31.0 (34)	32.0 (28)	104%	10%
[h]				

Median value

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

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

Table 2. Prothrombin time (PT) and Factor VII activity: $AUD_{(0-96h)}$ Mean (CV%) and range (n=23)

Variable	Warfarin + placebo	Warfarin + HMR 3647	Point estimate (90% CI)*	Intra-individual CV
PT:				
$AUD_{(0-96h)}$	1680 (9)	1708 (10)	101%	3%
[sec.h]	1459 - 2100	1504 – 2195	(99.8; 102.9%)	
Factor VII:				
$AUD_{(0-96h)}$	4234 (25)	4100 (28)	95.4%	6%
[%.h]	2462 - 6816	2091 - 7308	(92.6; 98.4%)	

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

Figure 1. Median R-Warfarin concentration-time profiles with and without HMR 3647

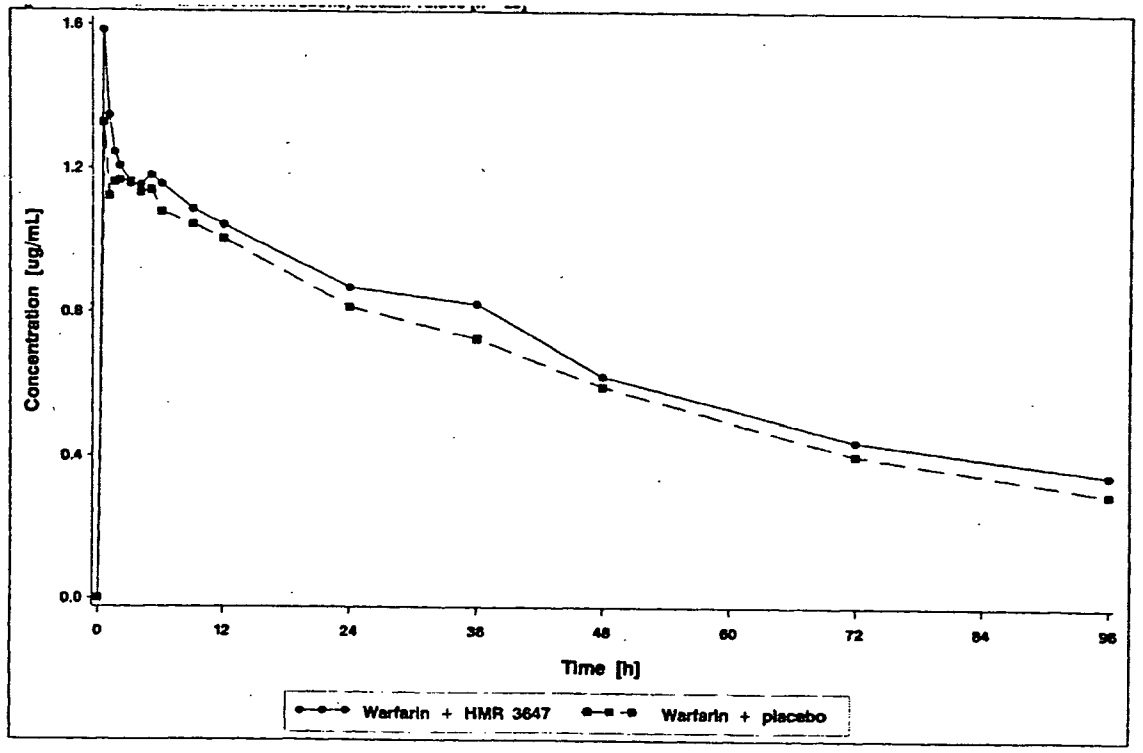


Figure 2. Median S-Warfarin concentration-time profiles with and without HMR 3647

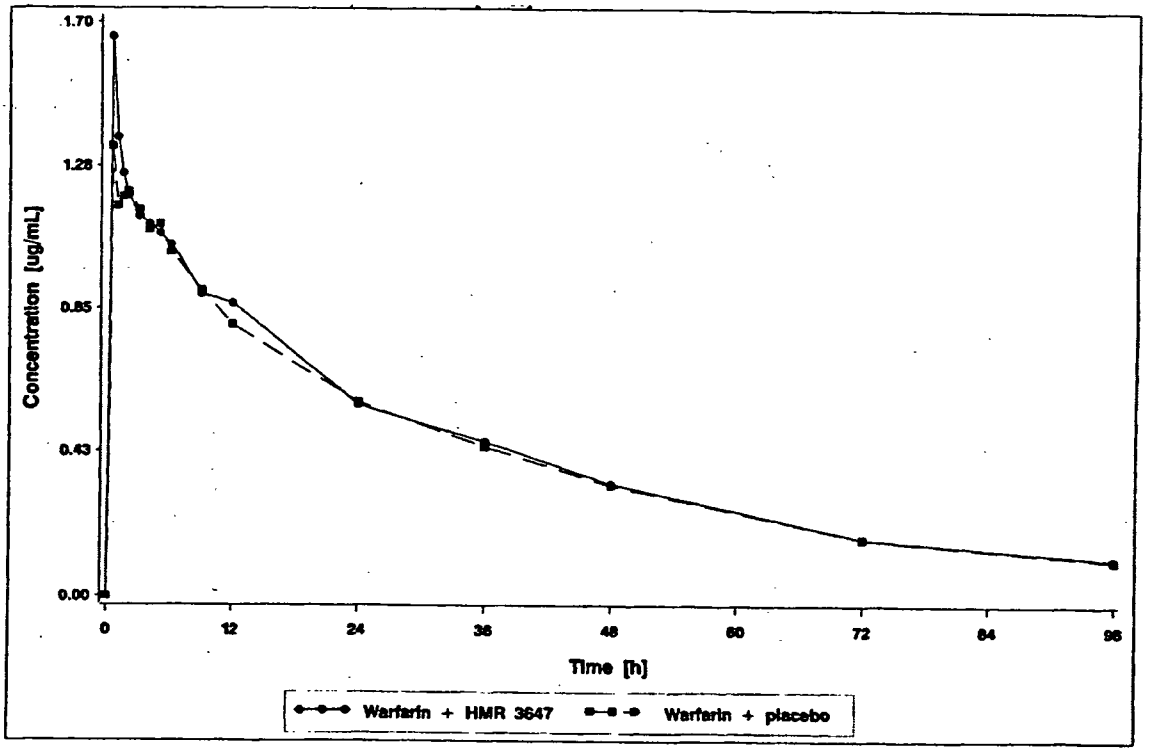


Figure 3. The median Prothrombin Time vs time after warfarin treatment with and without HMR 3647

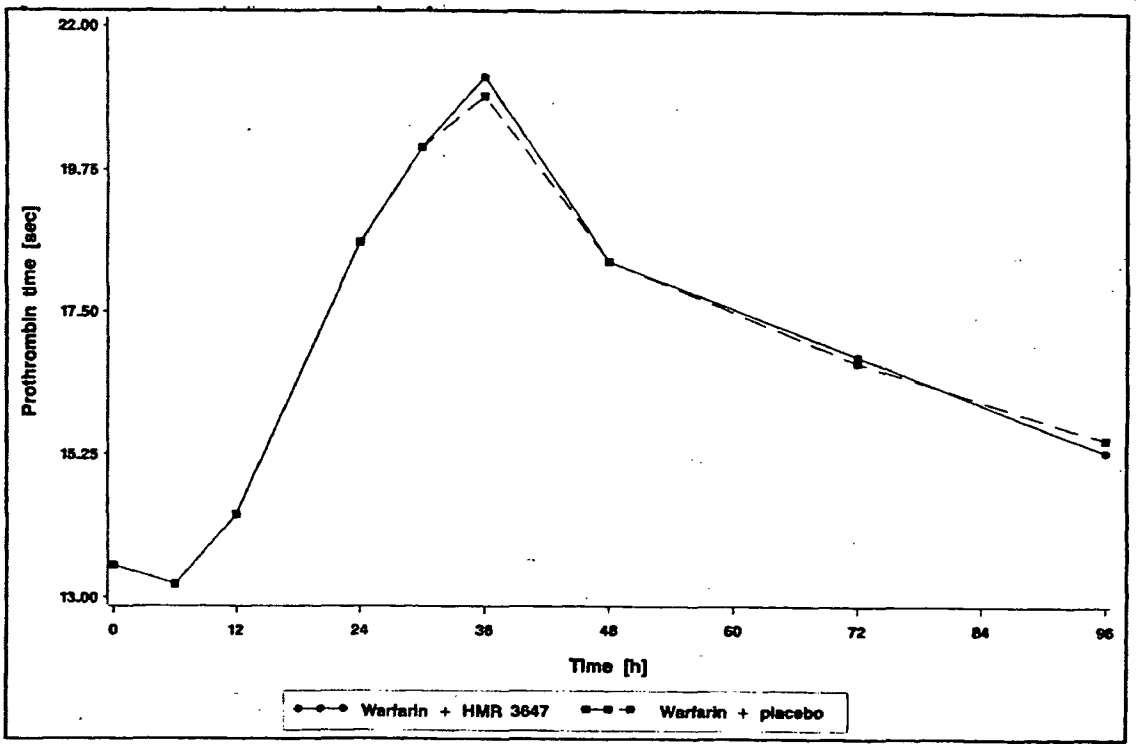


Figure 4. The median Factor VII activity vs time after warfarin treatment with or without HMR3647

APPEARS THIS WAY
ON ORIGINAL

STUDY NUMBER: 1013

TITLE: A study of the potential effects of HMR 3647 on the pharmacokinetics of digoxin in healthy male subjects.

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

OBJECTIVES:

To investigate whether the pharmacokinetics of digoxin is affected by the concomitant administration of HMR 3647.

STUDY DESIGN:

It was an open-label, non-randomized, multiple doses with two consecutive treatment periods:

Period 1 (digoxin alone): loading oral dose of digoxin (0.5 mg) on Day 1, followed by 0.25 mg b.i.d. of digoxin from Day 2 to Day 6 (first profile day on Day 6).

Period 2 (digoxin with HMR 3647): oral doses of digoxin (0.25 mg b.i.d.) and HMR 3647 (800 mg q.d.) from Day 7 to Day 11 (second profile day on Day 11).

FORMULATION: HMR-3647 400 mg tablet (batch #: VL 27095-136)

SAMPLING:

Blood samples for the determination of digoxin, HMR 3647 were taken at the following times:

Days 1 to 6 before the morning dose and on Day 6, 0.5, 1, 2, 4, 6, 8 and 12 hours after the morning dose.

Days 7 to 11 before the morning dose; on Day 11, 0.5, 1, 2, 4, 6, 8 and 12 hours after the last dose; on Days 12, 13 and 14 (respectively 24, 48 and 72 hours after the last dose).

Urine samples were collected on day 6 and 11 at 2 period: 0-12 and 12-24 hours after the morning dose and day 13 and 14: 24-48 and 48-72 hours.

ASSAY: Plasma concentrations of HMR 3647 were measured by a validated LC/MS method. Digoxin was analyzed in plasma and urine using a radioimmunoassay (RIA) kit.

The performance of the assay is shown in the following:

	HMR 3647/Plasma	Digoxin in plasma	Digoxin in urine
Accuracy of QC samples	-7.2 % - 5.0 %	-9.0 % 5 %	-1.3 % - 9 %
Precision (CV) of QC samples	7.5 %- 14 %	8.3 % - 13.1 %	4.1 % - 6.9 %
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:

Analyses of variance with treatment and subject as main effects were performed on ln-transformed digoxin pharmacokinetic parameters. Point estimates were calculated as the geometric mean of the individual ratios of each parameter for the test treatment (Digoxin + HMR 3647) relative to the reference treatment (Digoxin alone) and expressed as a percentage. The 90 % confidence interval of the point estimates was calculated using the mean square error of the analysis of variance. Similarity between the two conditions was concluded if the 90% confidence limits for the ratio of mean parameters values of digoxin administered with HMR 3647, relative to those of digoxin alone, was within 80-125%.

RESULTS: Twenty-six (26) healthy male subjects were included in the study. All of them were of Caucasian origin. Their mean age was 22.3 years [18-42] and mean weight 80.7 kg [62.9-100.0].

PHARMACOKINETICS:

The pharmacokinetic parameters for digoxin and HMR 3647 are summarized in Table 1 and 2. The mean digoxin plasma concentration vs time profiles after digoxin alone and with HMR 3647 is shown in Figure 1. After repeated administration of digoxin (0.25mg b.i.d) with HMR 3647 (800 mg q.d.) for 5 days, a marked increase in digoxin plasma concentrations was observed. Compared with digoxin treatment alone, maximal plasma concentration (Cmax) and AUC(0-12h) were increased by 73% and 37% respectively, when digoxin and HMR 3647 were coadministered.

CONCLUSION:

1. HMR 3647 can significantly increase digoxin plasma concentrations. Maximal plasma concentration (Cmax) and AUC(0-12h) were increased by 73% and 37% respectively.
2. Caution should be taken when HMR3647 coadministered with digoxin.

COMMENTS:

The increase in Cmax and AUC may be explained by an increase of bioavailability of digoxin when co-administered with HMR 3647 rather than by a slower elimination because renal clearance (CLr), which represents the main part of the total clearance, was not decreased but slightly increase after co-administration the two drugs. This increase of bioavailability could be explained by two mechanisms:

i) alteration of the gut flora, which metabolizes digoxin. Approximately 10% of the patients who receive digoxin metabolize about 40% of the digoxin dose to cardio-inactive compound such as dihydrodigoxin and dihydrodigoxigenin. This metabolism is probably due to one bacteria present in their gastrointestinal flora: *Eubacterium Lentum*. Macrolides, probably by destroying a part of the bacterial flora, reduce the formation of digoxin metabolites, enhancing thereby digoxin plasma concentrations)

ii) competition at the intestinal level with P-glycoprotein. It was demonstrated in vitro study using Caco-2/TC7 cell line that absorption of HMR 3647 was limited by p-glycoprotein.

Table 1. Digoxin pharmacokinetic parameters (N=26)

		Digoxin alone Day 6	Digoxin + HMR 3647 Day 11	PE[a] (%)	90% CI
C_{max} (mg/L)	Mean (CV%) [min-max]	**1.97** (27)	**3.44** (29)	173	159-189
t_{max} (h)	Median [min-max]	**0.50**	**0.50**	NC	NC
C12h (mg/L)	Mean (CV%) [min-max]	**1.033** (27)	**1.244** (25)	121	114 – 129
AUC(0-12h) (mg.h/L)	Mean (CV%) [min-max]	**13.83** (24) [9.19 – 24.26]	**18.76** (20) [14.17 – 27.57]	137	132 – 142
Ae(0-12h) (%dose)	Mean (CV%) [min-max]	**36.4** (36)	**60.0** (19)	174	153-197
CL_R(0-12h) (L/h)	Mean (CV%) [min-max]	**6.72** (36)	**8.26** (25)	127	112-144
$t_{1/2,\lambda z}$ [b] (h)	Mean (CV%) [min-max]	NC	**38.8** (19)		

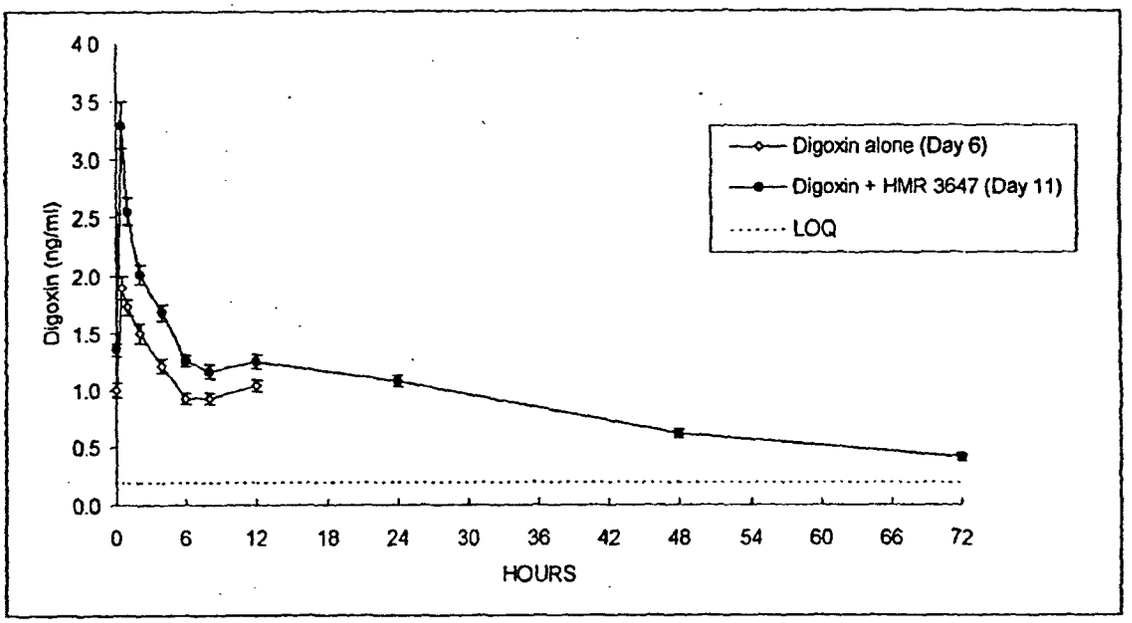
a: PE: point estimate : Geometric mean of the individual ratios of each parameter for the test treatment (Digoxin + HMR 3647) relative to the reference treatment (Digoxin alone)

b: Half-lives calculated using a non-compartmental model NC: Not calculated

Table 2. HMR 3647 pharmacokinetic parameters (N=26)

Parameter		Digoxin + HMR 3647 Day 11
C_{max} (mg/L)	Mean (CV%) [min-max]	**1.98** (45)
t_{max} (h)	Median [min-max]	**1.00** [0.43 – 4.00]
C24h (mg/L)	Mean (CV%) [min-max]	**0.043** (32)
AUC(0-24h) (mg.h/L)	Mean (CV%) [min-max]	**8.95** (27)
AUC(0-z) (mg.h/L)	Mean (CV%) [min-max]	**9.68** (28)

Figure 1. Mean (SEM) plasma concentrations of digoxin during repeated administrationof digoxin alone (0.25 mg bid for 5 days) or with HMR 3647 (800 mg qd for 5 days) to healthy young subjects (n=26)



STUDY NUMBER: 1020

TITLE: An Open-Label, Randomized Crossover Study to Determine the Effect of Intra-Gastric pH Altering Agents Ranitidine (—) on the Pharmacokinetics of HMR 3647 in Healthy Male Subjects.

INVESTIGATOR(S) —

OBJECTIVES:

To determine the effect of intra-gastric pH altering agents on the pharmacokinetics of a single oral dose of HMR 3647 in healthy male subjects.

STUDY DESIGN:

This study was an open-label, randomized, three period, complete crossover design in healthy, male subjects. There were 7 drug free days between periods.

Treatment A: A single 800 mg (2 x 400 mg) oral dose of HMR 3647 tablets.

Treatment B: A single 300 mg oral dose of ranitidine (—), followed 1 hour later by a single 800 mg (2 x 400 mg) oral dose of HMR 3647 tablets.

Treatment C: A single 20 mL oral dose of — , followed 15 minutes later by a single 800 mg (2 x 400 mg) oral dose of HMR 3647 tablets.

FORMULATION: HMR-3647 400 mg tablet (batch #: MD28146/057)

SAMPLING:

Blood samples were collected at predose, 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 30, 36, and 48 hours HMR 3647 postdose.

ASSAY: Plasma concentrations of HMR 3647 were measured by a validated LC/MS method. The performance of the assay is shown in the following:

	HMR 3647
Accuracy of QC samples	-6.9 % to -3.1 %
Precision (CV) of QC samples	4.6 %- 16.7 %
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:

Comparisons of HMR 3647 pharmacokinetic parameters 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. Treatments B and C were compared to treatment A, 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%. The primary comparisons were based on AUC(0-∞) and Cmax .

RESULTS:

A total of 15 healthy male subjects were enrolled in this study and 14 subjects completed the study.

Pharmacokinetics:

The pharmacokinetic parameters of HMR 3647 at different treatments are summarized in Table 1. The mean HMR 3647 plasma concentration vs time is shown in Figure 1. Cmax and AUC(0-∞) were 1.34 mg/L and 8.61 mg•h/L, respectively, after single oral dose of HMR 3647 at 800 mg. Co-administration HMR 3647 with Maalox® would not affect the absorption of HMR 3647. However, Zantac® decreased the absorption of HMR 3647. Compared with the treatment of HMR 3647 alone, The Cmax and AUC was decreased by 13% and 9% when Zantac® was given with HMR 3647.

CONCLUSION:

1. Co-administration of Maalox® did not change the pharmacokinetics of HMR 3647.

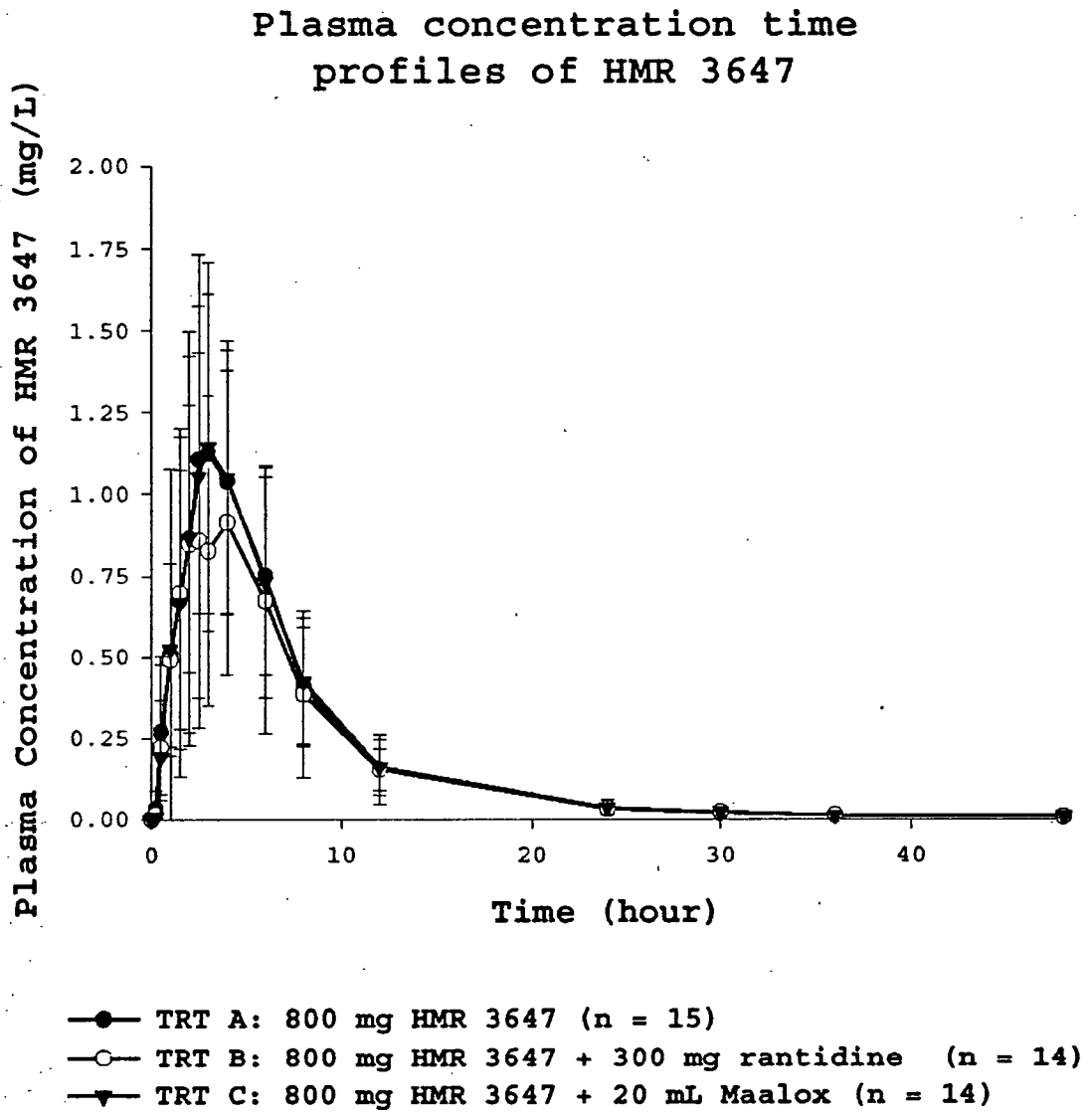
2. Coadministration of Zantac® with HMR 3647 significantly decrease absorption of HMR 3647. C_{max} and AUC were decreased by 13% and 9%, respectively.

Table 1. HMR 3647 pharmacokinetic parameters after three treatments

Parameter	Treatment	n	Mean	CV%	Adjusted Mean	Pair	Ratio (%)	90% confidence intervals on ratio
AUC(0-∞) (mg x h/L)	A	15	8.61	33.72	8.52			
	B	14	7.81	48.80	7.21	B/A	84.60	(74.70, 95.90)
	C	14	8.78	44.75	8.46	C/A	99.21	(87.60, 112.40)
C_{max} (mg/L)	A	15	1.34	29.67	1.34			
	B	14	1.16	41.56	1.10	B/A	81.96	(71.0, 94.70)
	C	14	1.42	41.21	1.35	C/A	100.78	(87.30, 116.40)

Treatment A: A single 800 mg (2 x 400 mg) oral dose of HMR 3647 tablets.
Treatment B: A single 300 mg oral dose of ranitidine (Zantac®) and a single 800 mg (2 x 400 mg) oral dose of HMR 3647 (administered 1 h after ranitidine dose).
Treatment C: A single 20 mL oral dose of Maalox® oral suspension and a single 800 mg (2 x 400 mg) oral dose of HMR 3647 (administered 15 minutes after Maalox® dose).

Figure 1.


Plasma concentration time profiles of HMR 3647
Plasma Concentration of HMR 3647 (mg/L)
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
0
10
20
30
40
Time (hour)
TRT A: 800 mg HMR 3647 (n = 15)
TRT B: 800 mg HMR 3647 + 300 mg rantidine (n = 14)
TRT C: 800 mg HMR 3647 + 20 mL Maalox (n = 14)

STUDY NUMBER: 1022

TITLE: An Open-label, Randomized Two-Period Crossover, Multiple-Dose Pharmacokinetic Interaction Study of 800 mg HMR 3647 Daily Orally and 30 mg Paroxetine Daily Orally in Healthy Adult Males.

INVESTIGATOR(S): [redacted]

OBJECTIVES:

To determine the pharmacokinetics of paroxetine when co-administered with HMR 3647.

STUDY DESIGN:

This study was an open-label, randomized, two period crossover and multiple doses design in healthy, male subjects. There were 2 weeks between period.

Treatment A: Paroxetine 30 mg orally Q24h for 10 days.

Treatment B: Paroxetine 30 mg orally Q24h for 10 days and HMR 3647 800 mg (2 x 400 mg tablets) Q24h for 5 days (days 6 through 10).

FORMULATION: HMR-3647 400 mg tablet (batch #: VE28095/021)

SAMPLING:

Blood samples for paroxetine determination were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 (day 11), 48 (day 12), 72 (day 13), and 96 hours after dosing on days 10. In addition, HMR 3647 and paroxetine trough samples were collected on days 1, 8, 9 and 10 immediately prior to dosing.

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

	HMR 3647	Paroxetine
Accuracy of QC samples	-9.8 % to –7.0 %	-1.2% - 4.4%
Precision (CV) of QC samples	0.3 % - 9.4 %	3.0% - 12.4%
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:

Comparisons between treatments were made for paroxetine parameters. An analysis of variance (ANOVA), with terms for subject, 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.

Trough concentrations of paroxetine and HMR3647 on days 8, 9, and 10 were compared to determine if steady state had been reached. In each case, an ANOVA with terms for subject and day was done.

From this ANOVA, least squares means for each day, estimated differences between days, and 90% confidence intervals for differences between days were calculated. These log-transformed results were transformed to the original scale by exponentiation to obtain adjusted means, day ratios, and 90% confidence intervals for these ratios. Later days were compared to earlier days with the earlier day as the reference.

RESULTS:

Twelve healthy male subjects (age range 19 to 44 years old) were enrolled but 9 subjects completed the study.

Pharmacokinetics:

The pharmacokinetic parameters of paroxetine in the present and absent of HMR 3647 are shown in Table 1. The mean paroxetine plasma concentration vs time profiles are shown in Figure 1. It

was shown that coadministration of HMR 3647 with paroxetine did not affect the Cmax and AUC of paroxetine. The trough levels of paroxetine and HMR 3647 at day 8, 9, and 10 are shown in Table 2 and 3. The results showed that HMR 3647 are continued increased over the time but paroxetine has reached steady state at day 8 in both treatments.

CONCLUSION:

HMR 3647 and paroxetine administered concomitantly did not alter the pharmacokinetics of paroxetine. The ratios of the mean paroxetine AUC(0-24)ss and Cmax,ss values for the co-administration of paroxetine with HMR 3647 (treatment B) compared to paroxetine alone (treatment A) were both within 99% to 106%. In addition, the 90% confidence intervals for these ratios were both within 90% to 119%.

Table 1. Pharmacokinetic parameters of paroxetine with or without HMR 3647 administration

Parameter (Units)	Treatment	N	Mean	CV(%)	Adjusted mean [a]	Pair	Ratio (%) [a]	(90% CI) on ratio [a]
$AUC_{(0\text{-}24)ss}$ (h•mg/L)	A	10	1.34	28.94	1.26			
	B	10	1.22	21.32	1.25	B/A	99.56	(90.4, 109.6)
$C_{max,ss}$ (mg/L)	A	10	0.07	26.52	0.07			
	B	10	0.07	20.03	0.08	B/A	105.88	(94.9, 118.1)
$C_{min,ss}$ (mg/L)	A	10	0.04	29.99	0.04			
	B	10	0.03	26.67	0.03	B/A	96.89	(89.6, 104.7)
$t_{1/2,ss}$ (h)	A	10	22.14	33.89	20.19			
	B	10	20.28	45.81	19.08	B/A	94.50	(86.2, 103.6)

Treatment A – Paroxetine 30 mg daily for 10 days
Treatment B – Paroxetine 30 mg daily for 10 days co-administered with HRM 3647 800 mg for 5 days (days 6 through 10)
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 2. Paroxetine trough concentrations (mg/L)

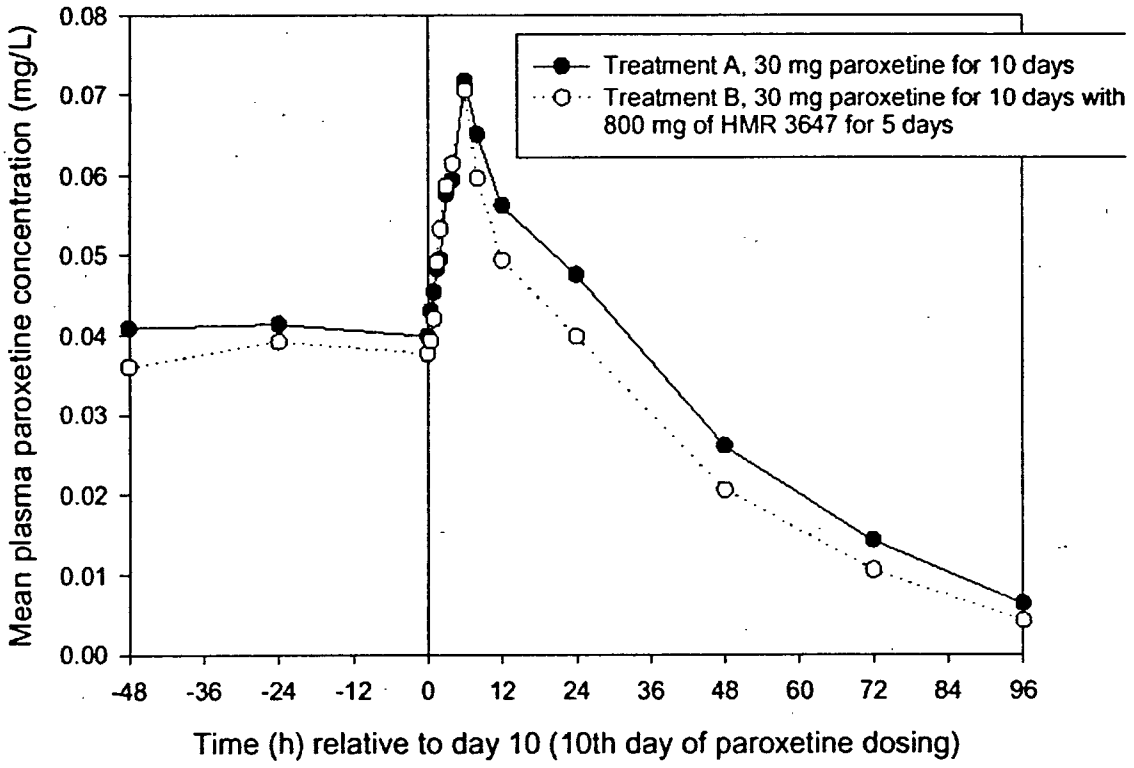
Parameter	Treatment	Day	N	Mean	CV (%)	Adjusted mean [a]	Pair	Ratio [a]	90% CI on ratio [a]	P value
Trough	A	8	10	0.041	47.60	0.037				
		9	10	0.041	42.13	0.038	9/8	102.30	(92.3, 113.4)	0.705
		10	10	0.040	29.97	0.038	10/8	103.61	(93.5, 114.8)	0.557
							10/9	101.28	(91.4, 112.3)	0.833
	B	8	10	0.036	36.74	0.033				
		9	10	0.039	34.91	0.037	9/8	110.75	(103.5, 118.5)	0.017
		10	10	0.038	29.38	0.036	10/8	108.12	(101.1, 115.6)	0.059
							10/9	97.63	(91.3, 104.4)	0.543

Treatment A – Paroxetine 30 mg daily for 10 days
Treatment B – Paroxetine 30 mg daily for 10 days co-administered with HRM 3647 800 mg for 5 days (days 6 through 10)
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. HMR 3647 trough concentrations (mg/L)

								Pairwise comparisons		
Parameter	Treatment	Day	N	Mean	CV(%)	Adjusted mean [a]	Pair	Ratio [a]	90% CI on ratio [a]	P value
Trough	B	8	10	0.054	67.37	0.045				
		9	10	0.059	63.58	0.050	9/8	109.81	(98.3, 122.6)	0.159
		10	10	0.063	60.11	0.055	10/8	120.83	(108.2, 134.9)	0.008
							10/9	110.04	(98.5, 122.9)	0.150

Figure 1.



STUDY NUMBER: 1037
TITLE: Effect of Itraconazole on the Pharmacokinetics of HMR 3647 in Healthy Male Subjects
INVESTIGATOR(S):

OBJECTIVES:
To examine the pharmacokinetics of HMR 3647 when administered alone and in combination with steady-state itraconazole administration.
To investigate the safety when HMR 3647 and itraconazole are coadministered.
STUDY DESIGN: The study was conducted as an open-label, nonrandomized, sequential design.
Treatment A (HMR 3647): Subjects received placebo on day -1, then 800 mg (2 x 400 mg tablets) HMR 3647 once daily for 4 days (days 1 to 4). No drug was administered on days 5 and 6.
Treatment B (Itraconazole): From days 7 to 24, each subject received 200 mg (2 x 100 mg capsules) itraconazole once daily for 18 days.
Treatment C (HMR 3647+Itraconazole): On days 21 through 24, subjects continued to receive itraconazole plus 800 mg (2 x 400 mg tablets) HMR 3647 once daily for 4 days.
FORMULATION: HMR-3647 400 mg tablet (batch #: MMG27931-081)
SAMPLING:
Blood samples were collected on day 2, 3, 4 at pre-dose and day 4 at 1,1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, and 24 after 800 mg of HMR 3647 for HMR 3647 measurements.
Blood samples were collected on day 24 at pre-dose, 1,1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, and 24 after last dose of HMR 3647 for HMR 3647 measurements.
ECG was recorded on day –1 at 1,2,3,6 hours after placebo and on day 4 at 0,1,2,3,and 6 hours after HMR 3647.
ECG was also recorded on day 18-25 prior dose and on day 20 and 24 at 0, 3, 4, 5, 8 hours after itraconazole or HMR 3647 administration.
On day –1, placebo effect was observed and on day 4, HMR 3647 effect was observed and on day 20, itraconazole effect was observed and on day 24, the combination effect of HMR 3647 and itraconazole was observed.
ASSAY: The performance of the assay is shown in the following:

	HMR 3647
Accuracy of QC samples	-0.5 % to 2.5 %
Precision (CV) of QC samples	4.6 % - 11.3 %
The limit of quantification	—

DATA ANALYSIS:
Pharmacokinetics:
Pharmacokinetic parameters such as $C_{max,ss}$, t_{max}, $AUC_{0-24,ss}$, $AUC_{0-\infty}$ were calculated using non-parametric method.
Statistics:
An analysis of variance (ANOVA), with terms for subject and treatment was done. From this ANOVA, least squares means for each treatment, estimated treatment differences, and 90% confidence intervals for treatment differences were calculated.
Steady-state HMR 3647 alone (Treatment A) was compared to HMR 3647 in the presence of steady-state itraconazole (Treatment C), with HMR 3647 alone 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%.
Trough concentrations of HMR 3647 for days 2, 3, 4 and 5 were compared to determine if steady state had been reached. An ANOVA, with terms for subject and day, were done. Later days were compared to earlier days with the earlier day as the reference.

RESULTS:

The 18 healthy normal adult male non-smoking subjects had a mean age of 28 years (range 19 to 41 years) and weight averaged 81 kg (range 60 to 96 kg). A total of 16 (89%) subjects were classified as Caucasian, 1 (6%) as Black and 1 (6%) as Asian/Oriental.

Pharmacokinetics:

Steady state after 4 doses of HMR 3647 were evaluated and the results is shown in Table 1. The analysis indicated no evidence to support that steady state was reached.

Pharmacokinetic parameter estimates for Treatments A and C are shown in Table 2. The mean plasma concentration vs time profiles are shown in Figure 1. When HMR 3647 was given with itraconazole, Cmax and AUC were increased by 20.5%, 61.7%, respectively.

Pharmacodynamics:

Administration of 800 mg HMR 3647 (alone) on day 4 was associated with a maximum mean heart rate increase of +7 bpm at 2 hour postdose when compared to day -1. Pronounced decreases in heart rate were observed after itraconazole administration (day 20), with a maximum heart rate decrease of -10 bpm, 1 hour after receiving itraconazole. When HMR 3647 was administered concomitantly with itraconazole, there were no identifiable changes in heart rate.

Descriptive statistics of QTc and QTf are shown in Table 3 and 4. Since ECG record time for itraconazole were different after the dose from the ECG record time for HMR 3647 and for HMR 3647 +itraconazole, the comparison could be made between HMR 3647 alone (day 4) and HMR 3647+itraconazole (day 24). As shown in Figure 2 and 3, QTc and delta QTc from the base line with time are not significantly different between treatments (HMR 3647 alone vs HME 3647+Itraconazole).

Table 5 displays the occurring frequency of QTc and delta QTc at specified criterion. Two alert terms (QTc >450 msec) reported during this study based on machine-read ECG data. The machine-read QTc intervals indicated that subject 007 (a 24-year old male) had a QTc interval value of 460 msec at 1 hour postdose after coadministration of itraconazole and HMR 3647 [representing a 49 msec increase from day 20 (itraconazole alone)], and subject 015 (a 41-year old male) had a QTc interval value of 461 msec at 1 hour postdose after coadministration of itraconazole and HMR 3647 [representing a 70 msec increase from day 20 (itraconazole alone)]. Based on manual measurement of the ECG tracings by the expert, an isolated QTc value of 451 msec recorded on day 4, 1 hour after administration of 800 mg of HMR 3647 was detected in subject 012 (25 year-old male). This was the only subject who reported a QTc interval change of ≥60 msec (62 msec) in the study

CONCLUSION:

1. Coadministration of multiple doses of itraconazole resulted in moderately increased systemic exposure to HMR 3647, as demonstrated by an increase in AUC(0-24)ss of approximately 54%.
2. An increase in $C_{max,ss}$ of 22% following coadministration was observed but the 90% confidence interval was only slightly outside the 70% to 143% interval, indicating similarity of $C_{max,ss}$ following itraconazole coadministration compared to HMR 3647 alone.
3. The maximum mean QTc interval prolongation following the administration of HMR 3647 alone and in combination with itraconazole was similar (+12 and +10 msec, respectively). None of the subjects had a QTc ≥500 msec.

COMMENTS:

1. Subject 12 had an QTc value of 451 msec recorded on day 4, 1 hour after administration of 800 mg of HMR 3647. This was the only subject who reported a QTc interval change of ≥60 msec (62 msec) in the study. The concentration of the subject at the time was [redacted] mg/L. The highest concentration observed from this study was [redacted] mg/L.

2. The $C_{max,ss}$ and AUC_{0-24} of HMR 3647 were 2.53 mg/L and 13.4 mg•h/L, respectively, which are similar to the observation from cisapride drug drug interaction study (Cmax: 2.96 mg/L and AUC 14.57 mg•h/L) but higher than Cmax and AUC from digoxin study (Cmax:1.98 mg/L and AUC:9.68 mg•h/L), oral contraceptive interaction study (Cmax:1.74 mg/L and AUC 10.18 mg•h/L), simvastatin study (Cmax: 2.24 mg/L and AUC: 9.41 mg•h/L).

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Table 1. Trough HMR 3647 concentrations at day 2, 3, 4, 5 and 22, 23, 24,and 25.

								Pairwise comparisons		
Parameter					CV	Adjusted		Ratio [b]		
(units)	Treatment	Day	N	Mean	(%)	Mean	Pair	(%)	Conf.Interval [b]	P value
Trough	A	2	17	0.019	59.87	0.016				
(mg/L)		3	17	0.036	64.20	0.031	3/2	187.08	(158.75, 220.47)	<0.0001
		4	17	0.043	57.89	0.037	4/2	224.90	(190.84, 265.04)	<0.0001
							4/3	120.22	(102.01, 141.67)	0.0661
		5	17	0.060	49.92	0.054	5/2	327.79	(278.15, 386.29)	<0.0001
							5/3	175.21	(148.68, 206.48)	<0.0001
							5/4	145.75	(123.68, 171.76)	0.0004
	C	22	17	0.076	53.60	0.065				
		23	17	0.097	53.40	0.084	23/22	129.02	(104.35, 159.52)	0.0496
		24	17	0.119	61.60	0.100	24/22	154.37	(124.86, 190.86)	0.0012
							24/23	119.65	(96.77, 147.93)	0.1627
		25	17	0.164	66.14	0.129	25/22	198.79	(160.78, 245.78)	<0.0001
							25/23	154.07	(124.62, 190.50)	0.0013
							25/24	128.77	(104.15, 159.21)	0.0513

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. Pharmacokinetics parameters for Treatment A (HMR 3647 alone) and C (HMR 3647+Itraconazole)

							Pairwise comparisons		
Parameter				CV	Adjusted		Ratio [b]	90%	
(Units)	Treatment [a]	N	Mean	(%)	Mean [b]	Pair	(%)	Conf.interval [b]	P value
AUC(0-24)ss	A	17	13.40	36.00	12.65				
(hr•mg/L)	C	17	20.56	34.32	19.46	C/A	153.82	(135.64, 174.44)	<0.0001
AUC(0-∞)ss	A	17	14.37	36.09	13.57				
(hr•mg/L)	C	17	23.24	38.99	21.69	C/A	159.86	(140.97, 181.27)	<0.0001
$C_{ma.ss}$	A	17	2.53	29.72	2.42				
(mg/L)	C	17	3.05	25.74	2.95	C/A	121.71	(103.37, 143.30)	0.0520
$C_{min.ss}$	A	17	0.04	57.89	0.04				
(mg/L)	C	17	0.10	72.16	0.08	C/A	219.30	(168.73, 285.02)	<0.0001
$t_{1/2.ss}$	A	17	13.32	42.53	11.25				
(hr)	C	17	14.13	65.70	11.30	C/A	100.39	(88.90, 113.36)	0.9566

a Treatment A - HMR3647 alone (days 2, 3, 4 and 5)
Treatment C - HMR3647 and itraconazole together (days 22, 23, 24 and 25)
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. Descriptive statistics of QTc

		HMR 3647 (day 4)		Itraconazole (Day 20)		HMR 3647 + Itraconazole (day 24)	
ECG*		QTc	Delta QTc	QTc	Delta QTc	QTc	Delta QTc
First	N	17	17	17	17	17	17
	Mean (SD)	367 (21)	-11 (18)	368 (19)	-10 (25)	369 (22)	-9 (21)
	Median	373	-12	369	-11	370	-16
	Range	325 - 414	-47 - 18	342 - 399	-49 - 33	329 - 404	-37 - 38
Second	N	17	17	17	17	17	17
	Mean (SD)	390 (29)	12 (19)	361 (18)	-17 (23)	388 (22)	10 (12)
	Median	387	8	366	-16	392	11
	Range	346 - 451	-19 - 53	328 - 388	-62 - 18	348 - 425	-18 - 31
Third	N	17	17	17	17	17	17
	Mean (SD)	385 (17)	7 (19)	364 (21)	-14 (18)	383 (17)	5 (16)
	Median	380	7	364	-10	384	4
	Range	361 - 415	-25 - 45	316 - 395	-60 - 12	358 - 409	-19 - 35
Fourth	N	17	17	17	17	17	17
	Mean (SD)	377 (19)	-1 (14)	380 (23)	2 (17)	376 (15)	-2 (15)
	Median	382	0	377	2	381	-6
	Range	344 - 405	-24 - 32	342 - 421	-28 - 25	345 - 395	-22 - 27
Fifth	N	17	17	17	17	17	17
	Mean (SD)	390 (19)	12 (19)	363 (19)	-15 (20)	388 (22)	10 (13)
	Median	386	9	364	-14	384	14
	Range	346 - 420	-23 - 52	322 - 395	-43 - 34	365 - 436	-25 - 26
Sixth	N	17	17	17	17	17	17
	Mean (SD)	363 (14)	-15 (17)	369 (25)	-9 (27)	368 (18)	-10 (22)
	Median	360	-10	376	-10	371	-11
	Range	333 - 386	-50 - 7	318 - 406	-54 - 36	335 - 398	-40 - 31

* First ECG is 07:00 predose. Second through fifth ECGs are 08:00, 09:00, 10:00, 13:00, except for itraconazole (Day 20) where they are 11:00, 12:00, 13:00, 16:00. Sixth ECG is 07:00 next day.
** Change from Day -1 average of 08:00, 09:00, 10:00, and 13:00 ECGs.

Table 4. Descriptive statistics of QTf

		HMR 3647 (day 4)		Itraconazole (Day 20)		HMR 3647 + Itraconazole (day 24)	
ECG*		QTf	Delta QTf	QTf	Delta QTf	QTf	Delta QTf
First	N	17	17	17	17	17	17
	Mean (SD)	368 (21)	-4 (16)	373 (19)	2 (21)	375 (22)	3 (20)
	Median	373	-4	378	-2	373	-5
	Range	326 - 417	-37 - 26	342 - 404	-29 - 38	343 - 421	-20 - 55
Second	N	17	17	17	17	17	17
	Mean (SD)	380 (24)	9 (15)	365 (14)	-6 (16)	383 (17)	12 (9)
	Median	373	5	370	-5	384	8
	Range	351 - 423	-15 - 38	341 - 386	-39 - 21	358 - 421	-5 - 28
Third	N	17	17	17	17	17	17
	Mean (SD)	372 (15)	0 (14)	367 (20)	-5 (13)	376 (16)	5 (15)
	Median	371	2	371	-6	376	6
	Range	349 - 404	-28 - 25	326 - 405	-31 - 20	352 - 405	-23 - 39
Fourth	N	17	17	17	17	17	17
	Mean (SD)	368 (17)	-3 (11)	373 (21)	2 (13)	371 (13)	-0 (12)
	Median	366	-4	378	3	371	-4
	Range	345 - 398	-22 - 16	340 - 406	-21 - 25	347 - 390	-24 - 21
Fifth	N	17	17	17	17	17	17
	Mean (SD)	379 (16)	8 (13)	363 (17)	-9 (13)	382 (20)	10 (11)
	Median	376	9	364	-9	377	12
	Range	349 - 408	-18 - 30	330 - 390	-30 - 14	360 - 420	-13 - 27
Sixth	N	17	17	17	17	17	17
	Mean (SD)	364 (13)	-7 (14)	370 (21)	-2 (22)	370 (17)	-2 (21)
	Median	365	-3	372	-2	373	-6
	Range	338 - 382	-39 - 12	329 - 402	-35 - 36	338 - 405	-31 - 49

* First ECG is 07:00 predose. Second through fifth ECGs are 08:00, 09:00, 10:00, 13:00, except for itraconazole (Day 20) where they are 11:00, 12:00, 13:00, 16:00. Sixth ECG is 07:00 next day.
** Change from Day -1 average of 08:00, 09:00, 10:00, and 13:00 ECGs.

Table 5. Frequency of subjects with expert-read QTc at specified criteria

	HMR 3647	Itraconazole	Combined drugs
Criteria	Day 4	Day 20	Day 24
	n/N (%)	n/N (%)	n/N (%)
QTc >= 450	1/17 (5.9)	0/17 (0.0)	0/17 (0.0)
30 =< Change in QTc < 60	6/17 (35.3)	3/17 (17.6)	3/17 (17.6)
Change in QTc >= 60	0/17 (0.0)	0/17 (0.0)	0/17 (0.0)
30 =< Change in QTc < 60	1/17 (5.9)	0/17 (0.0)	0/17 (0.0)

Figure 1. Mean HMR 3647 plasma concentration vs time after 800 mg HMR alone and 800 HMR 3647 with 200 mg Itraconazole

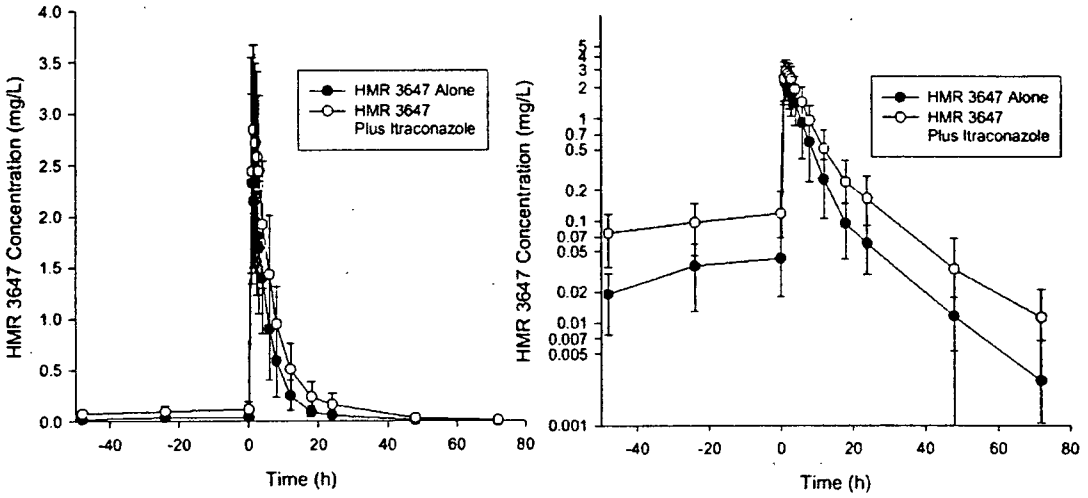

Figure 2. QTC vs Time after Dose

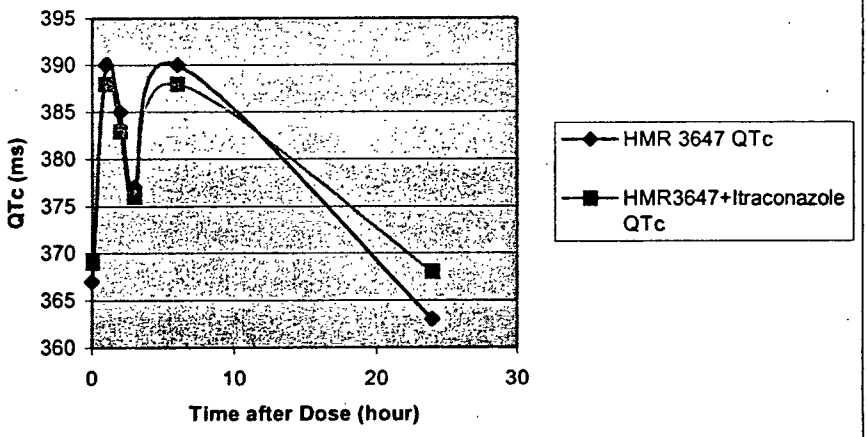

Figure 3. Delta QTc vs Time after dose