Figure 1. The mean (±SEM) plasma concentration of telithromycin after single oral administration of 800 mg telithromycin

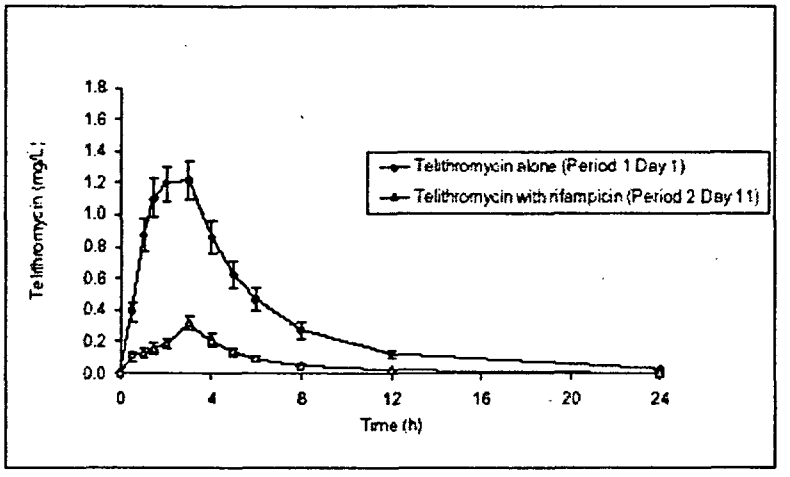


Figure 2. The mean (±SEM) plasma concentration of telithromycin after multiple oral administration of 800 mg telithromycin

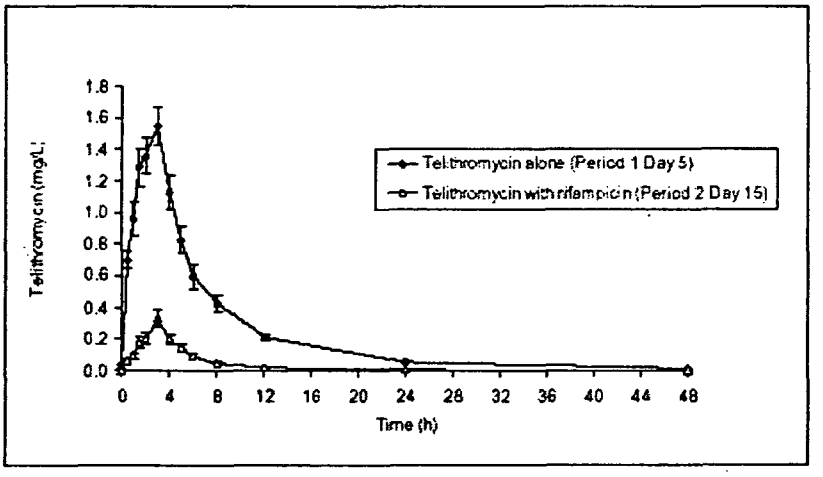


Figure 3. Individual telithromycin Cmax and AUC after single oral dose of 800 mg telithromycin with or without rifampicin

Figure 4. Individual telithromycin Cmax and AUC after repeated oral doses of 800 mg telithromycin with or without rifampicin

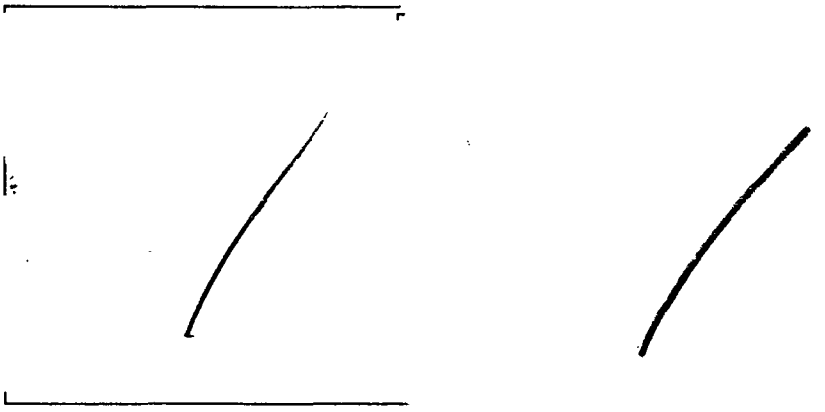


Figure 5. The mean (±SEM) plasma concentration of rifampicin after repeated oral administration of 600 mg rifampicin alone (day 10) or with telithromycin (day 15)

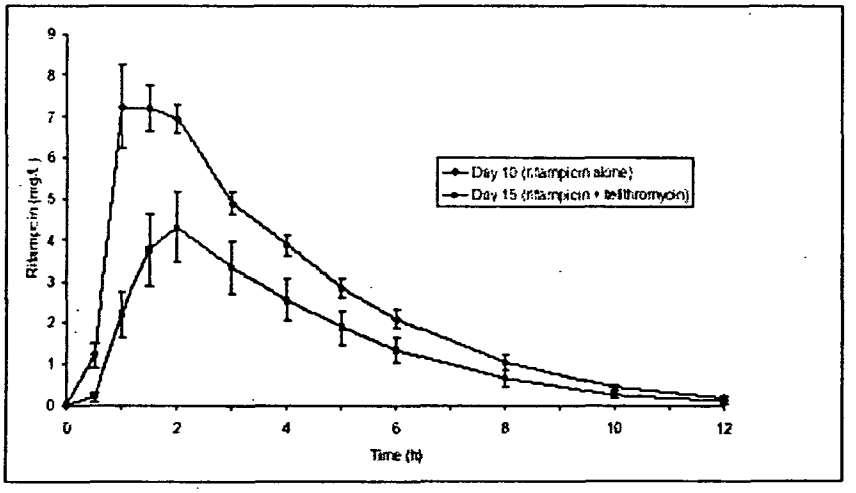


Figure 6. Individual rifampicin Cmax and AUC after repeated oral dose of 600 mg rifampicin with or without telithromycin

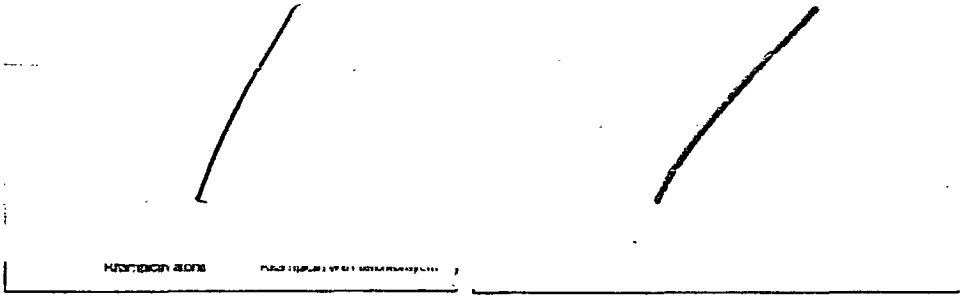
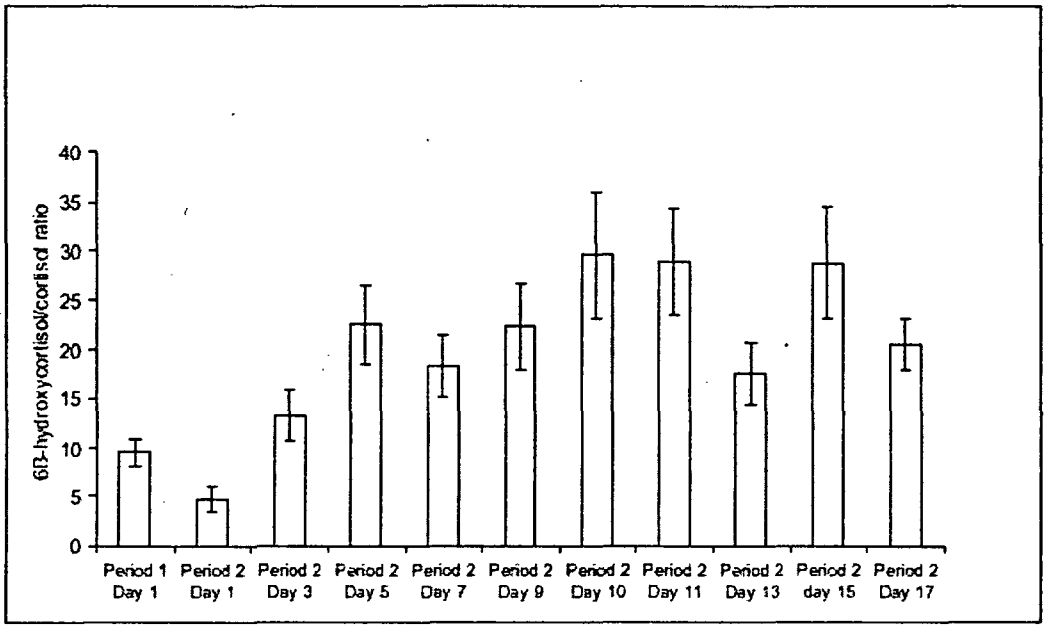


Figure 7. Mean (±SEM) 6β-hydroxycortisol/cortisol urinary ratio after multiple oral administration of rifampicin (600 mg QD for 16 days)



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STUDY NUMBER: 1059

TITLE: Mechanism of blurred vision induced by telithromycin (HMR 3647) at single supraclinical doses (2400 mg) versus a therapeutic single dose (800 mg) in a younger and older population of healthy subjects

OBJECTIVES:
- To characterize the mechanism of action of blurred vision observed in previous Phase I studies with telithromycin (HMR 3647) at supraclinical doses in young and older subjects.
- To assess the amount of telithromycin excreted in tears
- To correlate amount of telithromycin excreted in tears with the incidence of blurred vision and plasma concentrations
- To assess potential of telithromycin for treatment of ocular infections.

DESIGN: This single center study was a placebo-controlled, randomized, single dose, double blind, 3-way crossover design in two groups of subjects:
Group I: young healthy subjects male and female 18-40 years old (N=15)
Group II: older male and female subjects with presbyopia 50- <65 years old (N=15)
The female/male ratio in each group was to be approximately equivalent.
Placebo, 800 mg or 2400 mg telithromycin were given in the three periods.

FORMULATION: 400 mg telithromycin tablet (VL28095-098)

SAMPLING: Telithromycin plasma concentrations and amount excreted in tears were determined at pre-dose (0 hr), and at 1, 2, 3, 4, 6, 8, 24 hours after administration.
Tear samples were collected using a schirmer method. The paper strip was left *in situ* for exactly 120 seconds to collect approximately 5 µL tear. The part of Schirmer paper impregnated with tears were dried and stored in a polypropylene tube at –20°C.

ASSAY:
The precision and accuracy of the assay are summarized in the following table:

Analyte	Samples	Accuracy[a]	Precision[b]
Plasma			
Telithromycin	QC samples (	86.5–95.9%	6.0-9.4%
	Calibration standards (	98.8-101.1%	2.6-9.5%
Tear			
Telithromycin	QC samples	92.8-98.8 %	6.8-9.8 %
	Calibration standards	96.0-104.0%	2.4-5.5 %

[a] Accuracy, expressed as % recovery, relative to theoretical concentration.
[b] Precision, expressed as % coefficient of variation.

DATA ANALYSIS:
Pharmacokinetics:
The following plasma pharmacokinetic parameters for telithromycin were calculated using a noncompartmental analysis : Cmax, Tmax, and individual mean amount of telithromycin in tears (ng/strip).

Statistics:
Descriptive statistics were calculated.

In order to compare the amount of HMR 3647 excreted in tears of the left and right eyes, a paired t test was performed (PROC MEANS PRT) by group, dose and time point (time 0h excluded) using the difference of the amount of HMR 3647 from left and right eyes as variable.

In order to compare the mean amount of HMR 3647 excreted in tears in the [18 - 40] year group and in the [50 - 65] year group, a t test was performed by dose and time point (time 0h excluded), using group as main effect, after natural logarithmic transformation of the individual mean amount of HMR 3647 excreted in tears.

RESULTS:

Pharmacokinetics:

The plasma pharmacokinetic parameters and the amount of telithromycin excreted in tears are summarized in Table 1. The plasma concentration vs. time profiles are shown in Figure 1 and the amount of excreted in tears vs. time profiles are shown in Figure 2. The results showed that the 3-fold increase in dose of HMR 3647 resulted in 2.7 and 2.5-fold increases in mean values for Cmax in the [18 - 40] and [50 – 65] year groups, respectively. Mean plasma Cmax was slightly higher in the [50 – 65]-year group compared to the [18 - 40] year group and the time to reach Cmax was similar in both groups.

After a single telithromycin dose of 800 mg, the mean maximal amount excreted in tears was reached 3 hours after dosing in the [18 - 40] year group and 2 hours after dosing in the [50 - 65] year group with values of 108 and 54.9 ng/strip respectively. After a single 2400 mg dose, the mean maximal amount excreted in tears was reached 4 hours after dosing in the [18 - 40] group and 8 hours after dosing in the [50 - 65] group with values of 341 and 201 ng/strip respectively.

Twenty four hours after the 800 mg dose, the amount excreted in tears was quantifiable in all subjects with mean values of 5.8 and 5.2 ng/strip in the [18 - 40] and [50 - 65] groups, respectively. Twenty four hours after the 2400 mg dose, the amount excreted in tears was quantifiable in all subjects with mean values of 38 and 36.2 ng/strip in the [18 -40] and [50 - 65] groups, respectively.

From 1 to 6 hours after dosing with either 800 or 2400 mg, mean amount of telithromycin excreted in tears was higher in the [18 - 40] year group than in the [50 - 65] year group. For both doses, this difference was statistically significant from 3 to 6 hours post dose.

Blurred Vision: Four subjects (3 females and 1 male) presented with blurred vision in Group I (young subjects) and none in Group II (older subjects). All adverse events of blurred vision occurred 3 to 6 hours after administration of the 2400 mg dose, were classified as mild, and lasted from 30 minutes to 2 hours.

CONCLUSIONS:

1. No blurred vision occurred following a single dose of 800 mg of telithromycin in either the young [18-40 years] or older [50- 65 years] subjects in this study.

2. At three times the therapeutic dose (2400 mg) blurred vision was observed in 4 young subjects and was not observed in any of the older subjects.

3. The duration of blurred vision following the single 800 mg dose in the young subjects lasted from 30 minutes to 2 hours.

4. Even though the maximum plasma concentrations (Cmax) appeared to be slightly higher in the older subjects after the single doses of 800 mg or 2400mg telithromycin, the amount of telithromycin excreted in tears was higher in the younger subjects.

COMMENTS:

1. No correlation was tested between plasma concentrations and the amount of telithromycin excreted in tears.

2. The data for the amount of telithromycin excreted in tears were available and reported for only 7 younger subjects. Among these 7 subjects, only 2 were male. Therefore, the comparison between gender is not reliable. It is not clear if the amounts of telithromycin excreted in tears for the remaining 8 younger subjects are not quantifiable or has not been reported.

3. The blurred vision occurred more frequently in young subjects. It was found that telithromycin excretion in tears is higher in young subjects than that in the older subjects, but the exposure in plasma is lower in young subjects than that in elderly. Therefore, it appears that the amount of drug excreted in tears is more likely associated with the occurrence of blurred vision, instead of plasma concentrations of telithromycin.

Table 1. HMR 3647 plasma pharmacokinetic parameters and HMR 3647 amount in tears

Parameter	Statistics	[18 - 40] years (n = 15)		[50 – 65] years (n=15)	
		800 mg	2400 mg	800 mg	2400 mg
PLASMA					
C_{max} (mg/L)	Mean (CV%)	1.42 (46)	3.89 (28)	1.71 (33)	4.21 (30)
	[Min-Max]				
t_{max} (h)	Median	3.0 (39)	4.0 (35)	2.0 (48)	3.0 (36)
	[Min-Max]				
C24h (mg/L)	Mean (CV%)	0.019 (68)	0.160 (48)	0.033 (36)	0.221 (59)
	[Min-Max]				
TEARS*					
Maximal mean amount (ng/strip)	Mean (CV%)	108 (57)	341 (53)	54.9 (55)	201 (53)
	[Min-Max]				
Amount 24h post dose (ng/strip)	Mean (CV%)	5.8 (62)	38 (89)	5.2 (45)	36.2 (69)
	[Min-Max]				
Time of maximal mean amount (h)	Median	3.0	4.0	2.0	8.0

*: n=7 in the group [18-40] years

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Figure 1. Mean (± SEM) plasma concentration of Telithromycin after single oral administration of 800 and 2400 mg

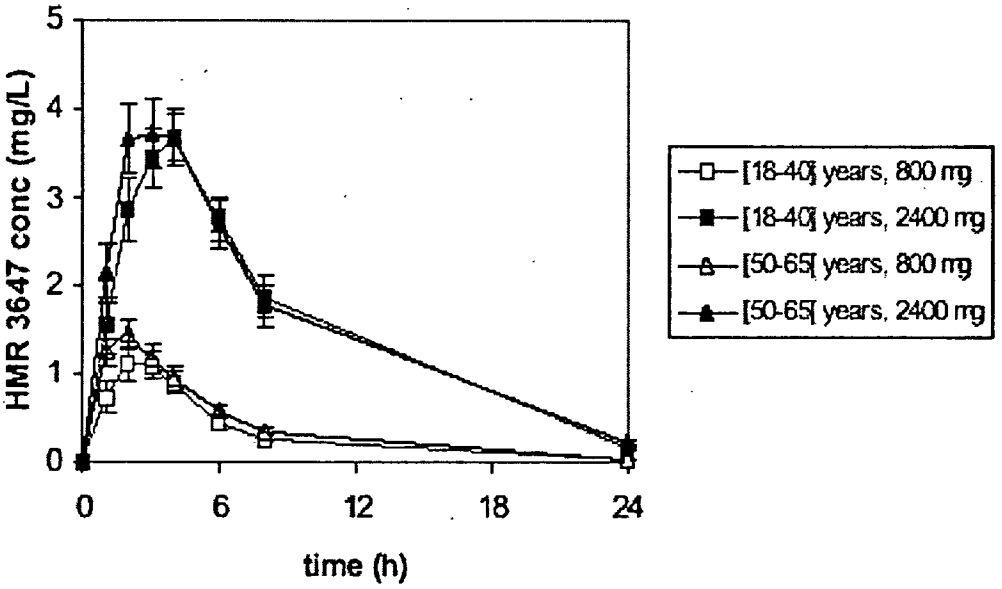
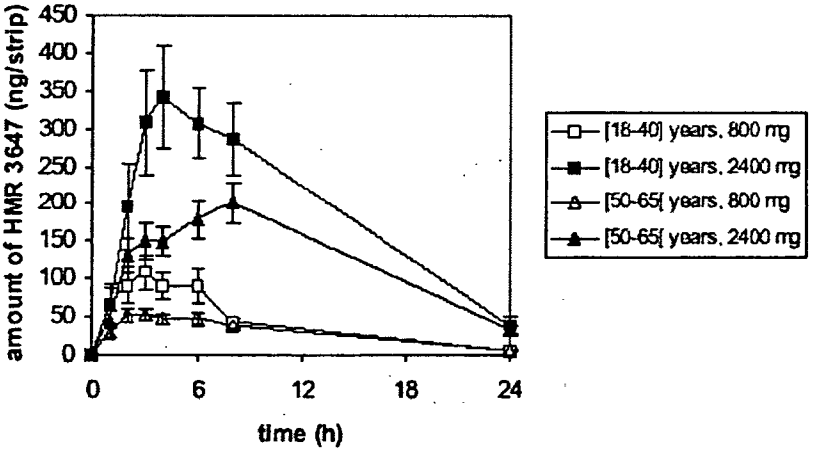


Figure 2. Mean amount of telithromycin excreted in tears after single oral administration of 800 and 2400 mg



STUDY NUMBER: 1061

TITLE: An open interaction study between multiple oral doses of telithromycin (800 mg qd) and single oral dose of metoprolol (100 mg) in healthy volunteers.

OBJECTIVES: To assess the effect of multiple oral doses of telithromycin (800 mg qd) on the pharmacokinetics of metoprolol after single oral dose in healthy male subjects.

DESIGN: This was an open, non randomized, sequential, single center, study. Twelve (12) healthy male subjects aged between 18 and 50 years, determined to be extensive metabolizers of CYP2D6 using the dextromethorphan test, were included in the study.

Each subject received a single oral 100 mg dose of metoprolol on two occasions (days 1 and 8) and multiple oral doses of telithromycin (800 mg qd for 7 days) from day 2 to day 8:
- Day 1: single oral dose of metoprolol (100 mg)
- Days 2 to 7: multiple oral doses of telithromycin (800 mg qd)
- Day 8: single oral dose of telithromycin (800 mg) + single oral dose of metoprolol (100 mg)

FORMULATION: 400 mg telithromycin tablet (1029668), 100 mg tablet (Lopressor®, batch no. B1004)

SAMPLING:
For metoprolol and α-OH metoprolol, the samples were collected on Day 1 and Day 8 at predose, 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, and 12 h after drug administration, on Days 2 and 9, 24 h after drug administration and on Day 10, 48h after drug administration.

For telithromycin, samples were collected at predose from Day 2 to Day 6. On Day 7 and Day 8 samples were collected at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after drug administration and on Days 9, 10, 11, and 12 at 24, 48, 72 and 96 h after drug administration, respectively.

ASSAY:
The accuracy and precision of the assays for telithromycin and metoprolol and alpha-OH-metoprolol was shown in the following table:

Analyte	Samples	Accuracy[a]	Precision[b]
	Plasma		
Telithromycin	QC samples	88.7-93.1%	7.6-22.1%
	Calibration standards	96.6–102.2%	4.1–7.5%
Metoprolol	QC samples	96.6–100.4%	2.17–9.15%
	Calibration standards	94.4–103.9%	1.34–5.72%
α-OH–Metoprolol	QC samples	93.4–97.8%	1.4–13.3%
	Calibration standards	91.4–104.6%	3.10–7.88%

[a] Accuracy, expressed as % recovery, relative to theoretical concentration.
[b] Precision, expressed as % coefficient of variation.

DATA ANALYSIS:
Pharmacokinetics:
The pharmacokinetic parameters for metoprolol and OH metoprolol on day 1 (metoprolol alone) and day 8 (metoprolol + telithromycin) and for telithromycin on day 7 (telithromycin alone) and day 8 (metoprolol + telithromycin) were calculated and analyzed. The PK parameters included:

C_{max}, Tmax, AUC(0-t) and AUC(0-infinity) for metoprolol, $AUC(0\text{-}24)_{ss}$ for telithromycin., $t_{1/2}$, λ_z and the metabolic ratio of α-OH metoprolol to metoprolol. AUC(0-t) is the area under the concentration-time curve calculated up to the last time at which the concentrations were still quantifiable.

Statistics:
Descriptive statistics [such as mean, median, standard deviation (SD), standard error of the mean (SEM) and coefficient of variation (CV)] were calculated for the pharmacokinetic parameters of metoprolol and telithromycin.

RESULTS:
Twelve (12) healthy male subjects were selected and enrolled in the study. None of them withdrew before the end of the study.

The pharmacokinetic parameters of metoprolol are shown in Table 1 and the mean plasma metoprolol concentrations are presented in Figure 1. The results indicated that when metoprolol was administered with telithromycin, Cmax, AUC(0-t) and AUC(0-infinity) of metoprolol were increased by 38.3, 36.4 and 37.0 %, respectively. The 90% upper confidence limits of Cmax, AUC(0-t) and AUC were 150.4, 155.3 and 155.3, respectively. The elimination half-life of metoprolol was not modified.

The pharmacokinetic parameters of α-OH-metoprolol are shown in Table 2 and the mean plasma α-OH-metoprolol concentrations are presented in Figure 2. It was shown that when metoprolol was administered with telithromycin, Cmax , AUC(0-t) and AUC of α-OH metoprolol were slightly increased by 12.9, 24.3 and 23.6 %, respectively. The ratio of a-OH-metoprolol to metoprolol is shown in Table 3. Ratio (Rm) for AUC(0-t) and AUC(0-infinity) decreased from 1.40 to 1.20 and from 1.56 to 1.32, respectively, after telithromycin treatment, but were not statistically different.

The pharmacokinetic parameters of telithromycin are shown in Table 4 and the mean plasma concentrations are presented in Figure 4. Scatterplots of C_{max} and AUC(0-24)ss are presented in Figure 7. It was shown that the ratio of telithromycin Cmax between co-administration with metoprolol to administration of telithromycin alone was 0.94. The ratio for AUC (0-24)ss was 0.90.

CONCLUSION:
1. Telithromycin is a weak inhibitor of cytochrome P450 2D6 as shown by a mild increase in metoprolol bioavailability (~ 38% for C_{max} and AUC) with telithromycin co-administration.

2. Telithromycin slightly increases α-OH metoprolol bioavailability (~ 24% for AUC) and also its elimination half-life.

3. Telithromycin exposure is not modified with concomitant single dose administration of metoprolol.

COMMENTS:
- α-OH-metoprolol may not be the only metabolite mediated by CYP2D6 therefore the AUC of α-OH-metoprolol was not decreased, but instead increased when telithromycin was co-administered with metoprolol.

Table 1. Mean (CV%) Metoprolol Pharmacokinetic Parameters

Treatment		T_{max}* h	C_{max} ng/mL	AUC(0-t) ng•h/mL	AUC(0-infinity) ng•h/mL	$t_{1/2}$, λz* h
Day 1 Metoprolol alone	Arithmetic Mean	1.5 (1.0-2.0)	108.6 (41)	536.0 (49)	583.9 (49)	2.99 (11)
	Geometric mean		99.1	467.5	512.3	
Day 8 Metoprolol + telithromycin	Arithmetic mean	1.5 (1.0-3.0)	150.7 (41)	699.2 (41)	771.3 (42)	3.01 (10)
	Geometric Mean		137.0	637.7	702.0	
Ratio D8/D1	Arithmetic ratio		1.40 (16)	1.40 (25)	1.40 (24)	
Ratio Day8/Day1 (90% CI)** p-value	Geometric Mean	-	1.38 (1.27-1.50) 0.0001	1.36 (1.20-1.55) 0.0015	1.37 (1.21-1.55) 0.0011	0.6662

* : median and range ** : 90% confidence interval

Table 2. Mean (CV%) α-OH-Metoprolol pharmacokinetic parameters

Treatment		T_{max}* h	C_{max} ng/mL	AUC(0-t) ng•h/mL	AUC(0-infinity) ng•h/mL	$t_{1/2}$, λz* h
Day 1 Metoprolol alone	Arithmetic Mean	1.5 (1.0-4.0)	64.2 (33)	588.1 (28)	699.8 (21)	7.23 (11)
	Geometric mean		61.5	569.0	687.1	
Day 8 Metoprolol + telithromycin	Arithmetic mean	2.0 (1.0-4.0)	73.7 (37)	734.1 (28)	869.6 (24)	8.31 (18)
	Geometric Mean		69.4	707.2	849.5	
Ratio D8/D1	Arithmetic ratio		1.17 (26)	1.26 (19)	1.25 (16)	
Day8/Day1 ratio** (90% CI)*** p-value		-	1.13 (0.98-1.31) 0.1658	124.3 (1.12-1.38) 0.0038	123.6 (1.14-1.34) 0.0010	0.0144

* : median and range ** : exp[ln(ratio)]% *** : 90% confidence interval

Table 3. Mean (CV%) a-OH metoprolol/metoprolol ratio (Rm)

Parameter	Day 1 (metoprolol alone)	Day 8 (metoprolol + telithromycin)
AUC(0-z)	1.40 (59)	1.20 (43)
AUC(0-infinity)	1.56 (61)	1.32 (43)

Table 4. Mean (CV%) telithromycin pharmacokinetic parameters

Treatment		T_{max}* h	C_{max} ng/mL	AUC(0-24) ng•h/mL	$t_{1/2}$, λz* h
Day 7 Telithromycin alone	Arithmetic Mean	3.0 (2.0-3.0)	1571 (27)	10765 (22)	-
	Geometric mean		1521	10529	
Day 8 Metoprolol + telithromycin	Arithmetic mean	2.0 (1.5-4.0)	1462 (22)	9658 (19)	8.40 (17)
	Geometric Mean		1431	9501	
Ratio D8/D7	Arithmetic ratio		0.96 (19)	0.95 (12)	
Day8/Day7 ratio** (90% CI)*** p-value		-	0.94 (0.85-1.04) 0.3151	0.90 (0.84-0.96) 0.0186	-

* : median and range ** : exp[ln(ratio)]% *** : 90% confidence interval

Figure 1. The mean metoprolol concentration vs. time profiles at Day 1 and Day 8

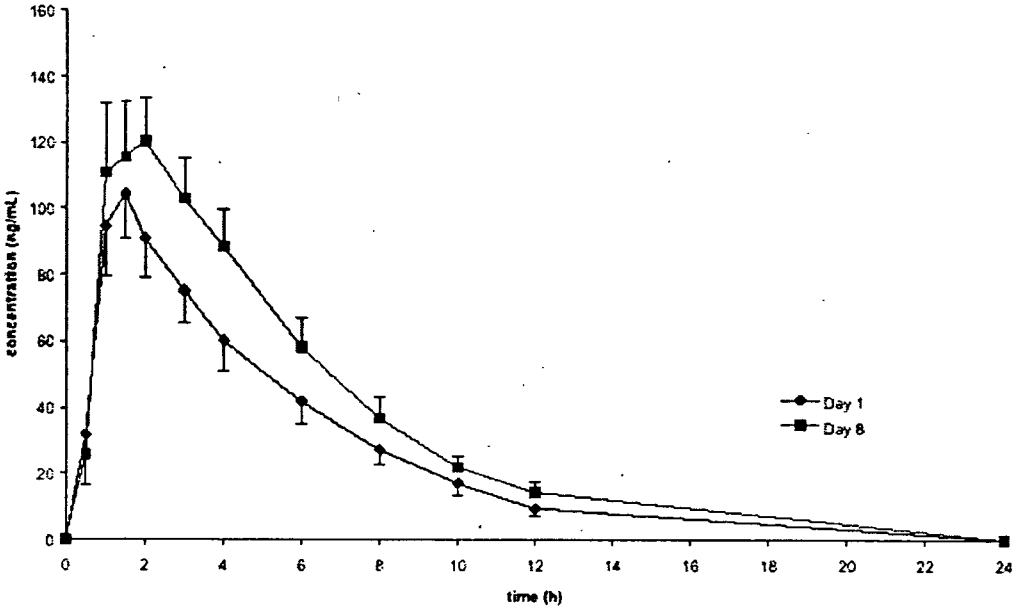


Figure 2. Mean (±SEM) plasma concentrations of α-OH metoprolol

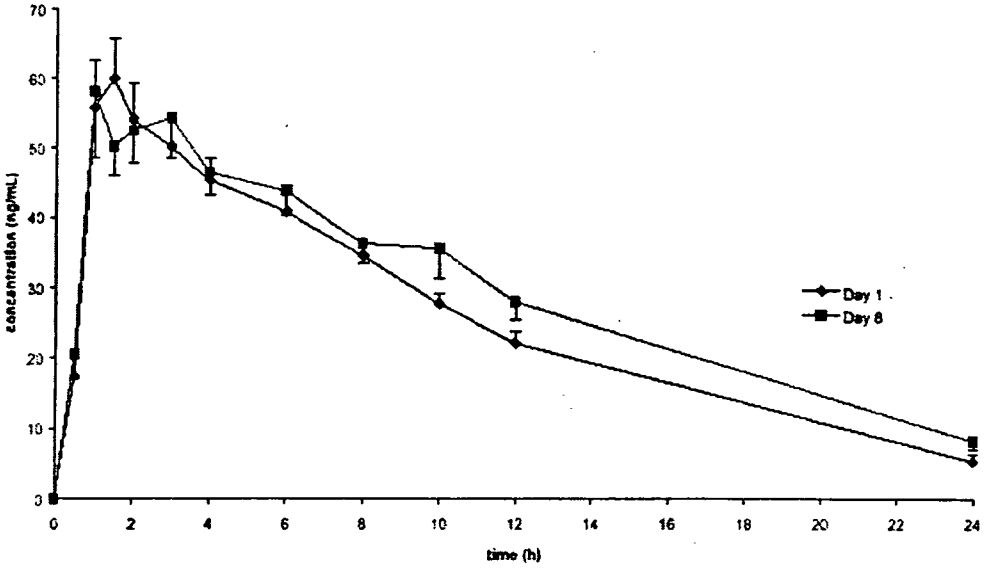


Figure 3. Mean (±SEM) plasma concentrations of telithromycin

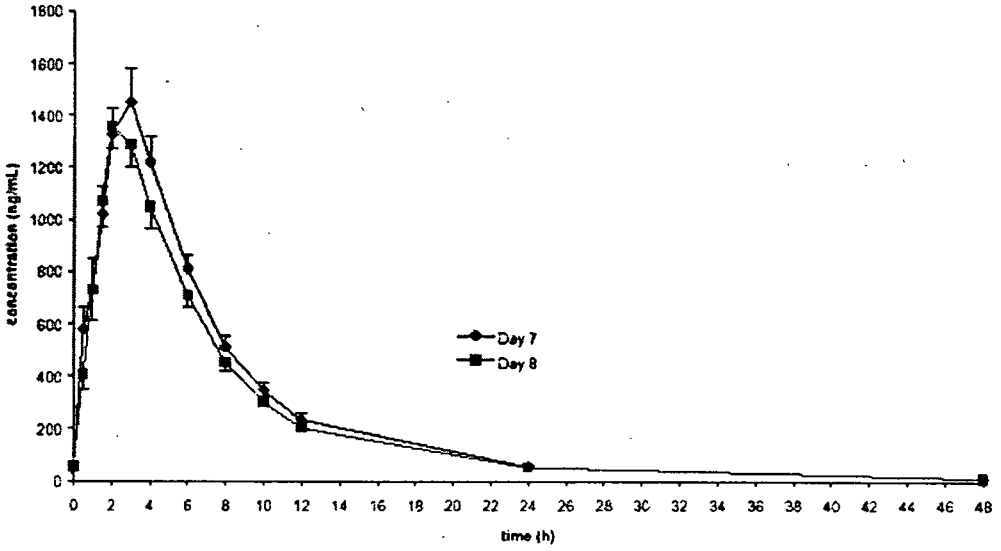
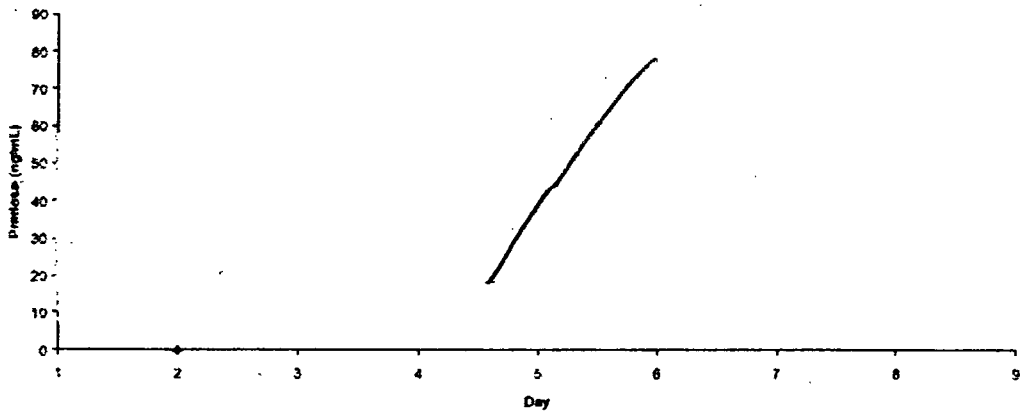


Figure 4. Individual and mean trough plasma concentration of telithromycin



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STUDY NUMBER: 1062

TITLE: Pharmacokinetics and safety of telithromycin in patients with renal impairment after multiple oral administration of 400, 600 and 800 mg once a day for 5 days.

OBJECTIVES: To assess pharmacokinetics and safety of telithromycin after multiple doses of 400, 600 and 800 mg in subjects with varying degrees of renal impairment.

DESIGN: This was a multicenter, multinational, open-label, repeated dose study in three strata of subjects with renal impairment in a randomized, balanced incomplete block three-treatment, two-period crossover design, and in one control stratum of healthy subjects administered only telithromycin 800 mg. Subjects were to be stratified into 4 groups based on the following creatinine clearance (CLcr) values:
Normal Renal Function: CLcr > 80 mL/min (8 subjects)
Mild Renal Impairment: CLcr 50 – 80 mL/min (12 subjects)
Moderate Renal Impairment: CLcr 30 – 49 mL/min (12 subjects)
Severe Renal Impairment: CLcr < 30 mL/min, but not requiring hemodialysis (12 subjects)

Each of the renal impairment subjects (CLcr <80 mL/min) received 2 of 3 treatments according to a balanced incomplete crossover design as follows:
Treatment A: 400 mg (1 tablet of 400 mg) once daily for 5 days
Treatment B: 600 mg (2 tablets of 300 mg) once daily for 5 days
Treatment C: 800 mg (2 tablets of 400 mg) once daily for 5 days

For healthy subjects with CLcr >80 mL/min, each subject received the 800 mg telithromycin once daily for 5 days

There was a washout of at least 7 days between the two treatment periods for the renal impairment subjects.

FORMULATION: 400 mg telithromycin tablet (L0001223) and 300 mg telithromycin tablet (KF2000005)

SAMPLING: Plasma samples were collected prior to the 1st, 3rd, 4th and 5th dose and at serial time points after the 5th dose (0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 16h and 24h post dose). The unbound plasma concentration of telithromycin at 2 hours after the 5th dose was also determined. Urine samples were collected before dosing on Day 1 and for 24 hours after the 5th dose.

ECG: 12-Lead ECG's were measured at serial timepoints over 24 hours after time zero on Day -1 and Day 5 (at timepoints: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours, which coincided with the timepoints for pharmacokinetic blood sampling on Day 5). In addition, 3 ECG's were measured at time zero on Days -1 and 1, and the respective means of the 3 measurements were used as the baseline for Day –1 and Day 5. ECG's were over-read by a central expert cardiologist who was blinded to subject number, treatment, and time of measurement.

ASSAY:

Analyte Samples	*Accuracy**	*Precision***
Telithromycin in plasma		
Telithromycin QC Samples	98.4 – 102.3%	6.1 – 18.8%
Calibration Standards	97.4 – 102.1%	4.6 – 10.4%
Telithromycin in Urine		
	91.0 – 102 %	2.1 – 5.9 %
	91.0 – 102 %	0.60 – 3.2 %
RU76363		
RU76363 QC Samples	86.0 -101.2%	4.9 – 12%
Calibration Standards	95.0 – 112 %	2.8 – 8.0%

- Accuracy, expressed as % recovery, relative to theoretical concentration
- **Precision, expressed as % coefficient of variation

DATA ANALYSIS:

Pharmacokinetics:

The following pharmacokinetic parameters for telithromycin and RU 76363, a major metabolite of telithromycin, were determined for each subject after the 5th dose using non-compartmental analysis: $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, and AUC(0-24)ss. Additional pharmacokinetic parameters, Ae (urinary recovery in % dose), CL_R , and CLss/F were calculated for telithromycin.

ECG:

QT intervals were corrected for heart rate using Bazett's formula (QTcB), Fridericia's formula (QTcF), and a population-specific formula (QTcN). The Day –1 values were evaluated for any significant, consistent circadian variation during the day.

The population-specific heart rate correction formula (QTcN) was calculated from QT and RR values measured on Day -1 (from time zero to 24 hours) as follows:

$$QTcN=QT/(RR/1000)^{*}n$$

Where n is derived from the fit of the exponential function $QT=\beta'(RR/1000)_{\alpha}$. This fit is performed using the usual regression on logarithmically transformed data for QT on RR/1000 for the drug-free time points. Under this logarithmic transformation, the function becomes $\log(QT) = \log(\beta) + \alpha^{*}\log(RR/1000)$, and n is estimated by α. All ECG data recorded up to the 24-hour time point on Day -1 were used to estimate α.

RESULTS:

A total of 45 subjects were enrolled in the study. Thirty-six subjects with renal impairment were enrolled and randomized to each treatment sequences as follows: AB, BA, AC, CA, BC, and CB.

Pharmacokinetics:

The pharmacokinetic parameters in subjects with varying degrees of renal function who received 800 mg telithromycin are shown in Table 1 and the pharmacokinetic parameters after receiving 400, 600 and 800 mg telithromycin in subjects with varying degrees of renal function are shown in Table 2. The renal route of elimination of unchanged telithromycin, expressed as % urinary recovery of dose, represented 18.2% of the total clearance in healthy subjects (n=9) at the 800 mg dose and decreased to 6% in subjects with severe renal impairment (CLcr <30 mL/min). Statistical pairwise comparisons indicated that there were no significant differences in mean Cmax,ss and AUC(0-24)ss between healthy subjects and subjects with mild to moderate renal impairment (CLcr from 30 to 80 mL/min). However, in subjects with severe renal impairment

(CLcr <30 mL/min), mean Cmax,ss and AUC(0-24)ss were increased 1.5- and 2.0-fold, respectively, compared to those in healthy control subjects ($p<0.05$).
The pharmacokinetic parameters for the metabolite, RU76363, are shown in Table 3. Following administration of the 800 mg dose of telithromycin, the mean Cmax, Tmax, and AUC(0-24) values for RU76363 were substantially increased in the subjects with severe renal impairment (CLcr <30 mL/min).

The box plots for telithromycin AUC(0-24) and Cmax at each dose and the AUC(0-24) and Cmax for the metabolite (RU76363) at the 800 mg telithromycin dose are shown in Figure 1 for each renal function group. The concentration time profile for the 800 mg treatment group by renal function is shown in Figure 2. At each dose level, subjects with severe renal impairment (CLcr <30 mL/min) tend to have higher mean AUC values, and this difference becomes more significant after 800 mg telithromycin dose, in comparison to that of the subjects with normal renal function and mild to moderate renal impairment. The systemic exposure (AUC) to the metabolite, RU76363, was also increased, the most in the severe renal impairment subjects at the 800 mg dose of telithromycin.

The relationships between Cmax, AUC(0-24), total clearance (CLss/F) and renal clearance (CLr) with the creatinine clearance (CLcr) for all subjects were examined for each dosing group and are shown in Figure 3. For all three dose groups the renal clearance (CLr) of telithromycin was significantly correlated with CLcr. A significant correlation of Cmax, AUC(0-24), and CLss/F with CLcr was only found with the 800 mg dose.

The mean trough concentrations at day 3, 4, and 5 for each renal function group and each dose group are shown in Figure 4. As shown, at doses of 400 mg and 600 mg, mean steady state plasma concentrations of telithromycin were reached at day 3 for all renal function groups. At the dose of 800 mg, it appeared that steady state was attained at day 3 for the healthy subjects with normal renal function and for the subjects with mild renal impairment (CLcr 50-80 mL/min). However, the mean trough plasma concentrations continued to increase from day 3 to day 5 for the subjects with moderate (CLcr 30-49 mL/min) and severe (CLcr <30 mL/min) renal impairment following the 800 mg dose, and suggested that steady state was not attained in these subjects.

The unbound fraction of telithromycin determined at approximately 2 hours postdose (range: 1.5 – 3 hours) was independent of dose. The unbound fraction (%) of telithromycin per renal stratum is summarized in Table 4 for all doses.

EKG:
QT correction formula evaluation: The relationships between QT interval and heart rate for the study population during the two drug-free periods (Day –1) are shown in Figure 5. These figures clearly indicate that the Bazett's formula had a significant bias in this study population, in which QTcB values were overestimated at higher heart rates. Fridericia's formula removed the dependency of QTcF on heart rate greatly. The new population-specific formula derived from the study specific population (exponent = 0.303) using Day -1 drug free data, represented the most robust correction, where there was no dependence of corrected QTc (QTcN) on heart rate.

Potentially Significant Outliers: The numbers of subjects with predefined potentially significant changes in QTc from baseline (i.e., ΔQTc of 30 to 60 ms or >60 ms) and increases in absolute QTc that are considered potentially significant (i.e., QTc ≥500 ms) are summarized below for the renal impairment and healthy subjects.

	Renal impairment Subjects			Healthy
	A (400 mg)	B (600 mg)	C(800 mg)	Subjects
QTc criterion	N=23	N=24	N=23	(800 mg) N=9
QTcB ≥500 ms	0	0	0	0
QTcB increase 30–60 ms	1	1	2	2
QTcB increase >60 ms	1	0	0	0
QTcF ≥500 ms	0	0	0	0
QTcF increase 30–60 ms	1	0	2	1
QTcF increase >60 ms	0	0	0	0
QTcN ≥500 ms	0	0	0	0
QTcN increase 30–60 ms	1	0	2	1
QTcN increase >60 ms	0	0	0	0

- One subject experienced a QTcB value of >450 ms on Day 5 at the 400 and 800 mg doses. This value was greater at the 400 than the 800 mg dose, indicating that there was no dose dependency.
- 5 male subjects reported an expert-read QTc value of >450 ms on both Day –1 and Day 5.
- No female subject reported an expert-read QTc value of >470 ms during treatment.
- One subject had heart rates of >100 bpm during treatment, although they were also high at screening and EOS.
- The greatest QTc value observed post treatment in the study was 469 ms in a male subject.
- None of the subjects had a clinically noteworthy abnormal QTc value defined as a QTc ≥500 ms.
- 14 subjects had 1 or more QTcB increases from baseline of 30 to 60 ms. Only in 6 subjects, the increase was observed on day 5 but not on day 1.
- One subject (the subject in which the greatest QTc was observed) had an increase of >60 ms.

Changes in QTc parameters at Day 5: The analysis of the change from baseline at Day 5 did not show any significant dose effect when comparing renally impaired subjects (p= 0.5191). Neither did the change from baseline at Day 5 show a significant difference when comparing renally impaired subjects treated with telithromycin 800mg to healthy subjects (p=0.4848).

Differences in observed maximum QTc parameters between Day -1 and Day 5: No change or decreases in maximum observed QTc were seen between Day –1 and Day 5 in renally impaired subjects treated with 400 and 600 mg, regardless of the severity of renal impairment. No change in maximum observed QTcB was seen between Day –1 and Day 5 at any dose or renal stratum. Slight increases in maximum observed QTc were seen in healthy subjects and in moderately renally impaired subjects treated with 800mg. However, no differences in the mild and severe renal impairment groups were observed.

ECG-pharmacokinetic evaluations: Simple linear regression was used to determine the relationship between ΔQT values and telithromycin plasma concentration on Day 5 using pooled data of treatments A (400 mg), B (600 mg) and C (800 mg) but sorted by renal stratum. The results showed no positive association between ΔQT, ΔQTcB, ΔQTcF, or ΔQTcN and telithromycin plasma concentration (p >0.05) at steady state in any of the 4 renal strata.

CONCLUSION:

1. At telithromycin doses of 400 mg and 600 mg, the relationship between Cmax or AUC(0-24) and creatinine clearance (CLcr) was not significant. However, a significant correlation between Cmax or AUC(0-24) and CLcr was detected at therapeutic dose of 800 mg.
2. No accumulation in Cmin was found from day 3 to 5 at doses of 400 and 600 mg across all four of the renal function groups. However, at the 800 mg dose, the Cmin was higher at day 5 than day 3 for the moderate (CLcr 30-49 mL/min) and severe (CLcr <30 mL/min) renal impairment subjects, and was similar between days 3 and 5 for the subjects with normal renal function (CLcr > 80 mL/min) and subjects with mild renal impairment (CLcr 50-80 mL/min).
3. In comparing the steady state AUC(0-24) in healthy subjects following the 800 mg dose of telithromycin, the steady state AUC(0-24) was increased by 100% (i.e., 2-fold) in the subjects with severe renal impairment (CLcr <30 mL/min) after administration of the same dose. No significant increases in the steady state AUC(0-24) were noted after administration of the 800 mg dose to the subjects with mild (CLcr 50-80 mL/min) and moderate (CLcr 30-49 mL/min) renal impairment
4. The analysis of the changes in QTc parameters from baseline at Day 5 did not show any significant treatment (dose) effect when comparing renally impaired subjects.
5. Slight increases in maximum observed QTc were seen in healthy subjects and in moderately renally impaired subjects treated with 800mg. However, no differences in the mild and severe renal impairment groups were observed.
6. The exposure of the metabolite, RU76363 was increased in renal impaired subjects.

COMMENTS:

1. The AUC(0-24) was increased by 100% following administration of 800 mg telithromycin for 5 days to subjects with severe renal impairment (CLcr <30 mL/min) . The sponsor proposed to reduce the dose to 400 mg for severe renal impaired subjects. However, following administration of 400 mg for 5 days to subjects with severe renal impairment , the mean AUC(0-24) and Cmax were 6.9 mg•hr /L and 1.2 mg/L, respectively, which is lower than mean AUC(0-24) and Cmax of 12.5 mg•hr /L and 2.27 mg/L, respectively, after repeated doses of 800 mg telithromycin to healthy subjects.
2. The study showed that in order to reach comparable exposure for subjects with severe renal impairment (CLcr <30 mL/min) and healthy subjects receiving the clinical regimen of 800 mg Q24 hr, a dosage regimen of 600 mg Q24 hr should be recommended for subjects with severe renal impairment. However, the commercial tablet formulation (unscored 400 mg) will not allow such dose adjustment.
3. At doses of 400 and 600 mg, renal function appears to play an insignificant role in elimination of telithromycin. Therefore, no significant correlation was observed between AUC(0-24) or Cmax and creatinine clearance at doses of 400 and 600 mg. However, renal function becomes important at the clinical dose of 800 mg. Therefore, it is speculated that in situations where telithromycin exposure is increased, e.g., telithromycin is co-administered with ketoconazole or other CYP3A4 inhibitors, renal function becomes more important.

Table 1. Pharmacokinetic parameters for telithromycin for the 800 mg treatment group with pairwise comparisons to healthy subjects (CLcr >80 mL/min)

	CLCr					Pairwise Comparisons		
Parameter	(mL/min)				Adjusted			
(Units)	Stratum	N	Mean	CV(%)	Mean[a]	Ratio[a]	90% Conf. Interval[a]	P value
$C_{max,ss}$ (mg/L)	>80	9	2.1	39.2	1.9			
	50-80	8	2.6	13.4	2.5	1.32	(0.97, 1.79)	0.1367
	30-49	8	2.2	48.2	2.0	1.04	(0.77, 1.41)	0.8293
	<30	8	3.0	39.5	2.8	1.46	(1.08, 1.99)	**0.0444**
AUC (0-24)ss (mg•hr/L)	>80	9	12.4	48.1	11.2			
	50-80	8	16.0	21.8	15.7	1.40	(1.03, 1.90)	0.0741
	30-49	8	14.8	40.7	13.7	1.22	(0.90, 1.66)	0.2819
	<30	8	23.6	29.2	22.7	2.03	(1.49, 2.75)	**0.0005**
CL_R (L/hr)	>80	9	12.7	28.4	12.3			
	50-80	8	7.3	31.0	7.0	0.58	(0.44, 0.75)	**0.0017**
	30-49	8	4.1	30.7	4.0	0.32	(0.25, 0.42)	**<0.0001**
	<30	7	2.1	40.6	2.0	0.16	(0.12, 0.21)	**<0.0001**
Urinary recovery (% of dose)	>80	9	18.2	37.3	17.2			
	50-80	8	14.4	30.6	13.8	0.80	(0.62, 1.05)	0.168
	30-49	8	7.1	35.5	6.8	0.39	(0.30, 0.51)	**<0.0001**
	<30	7	5.7	28.1	5.5	0.32	(0.24, 0.42)	**<0.0001**

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. Pharmacokinetic parameters for telithromycin in the 400, 600, and 800 mg treatment groups

Parameter (Units)	**CLcr Stratum (mL/min)**	**Treatment A (400 mg)**		**Treatment B (600 mg)**		**Treatment C (800 mg)**	
			N		**N**		**N**
Cmax,ss (mg/L)	>80					2.1 (39.2)	9
	50-80	1.0 (47.4)	8	1.7 (36.7)	8	2.6 (13.4)	8
	30-49	1.0 (69.3)	8	1.5 (40.3)	8	2.2 (48.2)	8
	<30	1.2 (49.3)	8	1.8 (32.2)	8	3.0 (39.5)	8
AUC (0-24)ss (mg•hr/L)	>80					12.4 (48.1)	9
	50-80	5.0 (43.2)	8	10.6 (51.8)	8	16.0 (21.8)	8
	30-49	5.5 (72.8)	8	10.0 (42.5)	8	14.8 (40.7)	8
	<30	6.9 (56.7)	8	14.8 (60.4)	8	23.6 (29.2)	8
CL_R (L/hr)	>80					12.7 (28.4)	9
	50-80	7.3 (50.3)	8	7.8 (19.4)	8	7.3 (31)	8
	30-49	4.3 (52.9)	8	4.4 (47.2)	8	4.1 (30.7)	8
	<30	1.6 (45)	8	1.9 (43.6)	8	2.1 (40.6)	7
Urinary recovery (% of dose)	>80					18.2 (37.3)	9
	50-80	8.6 (62.8)	8	13.2 (46.4)	8	14.4 (30.6)	8
	30-49	5.3 (59.3)	8	6.5 (33.4)	8	7.1 (35.5)	8
	<30	2.6 (52.3)	8	4.5 (70.3)	8	5.7 (28.1)	7

Table 3. Pharmacokinetic parameters of RU76363

Parameter (Units)	CLcr Stratum [mL/min]	Treatment A (400 mg)		Treatment B (600 mg)			Treatment C (800 mg)		
		Mean	CV%	Mean	CV%	N	Mean	CV%	N
AUC (0-24)ss (mg•hr/L)	> 80 (1)						1.37	(34.4)	9
	50 to 80 (2)	0.75	(45.5)	1.21	(47.0)	8	2.07	(30.2)	8
	30 to 49 (3)	0.74	(76.3)	1.43	(49.2)	8	2.16	(36.3)	8
	< 30 (4)	0.87	(49.5)	1.89	(43.8)	8	3.74	(31.4)	8
Cmax,ss (mg/L)	> 80 (1)						0.15	(23.1)	9
	50 to 80 (2)	0.09	(50.1)	0.12	(27.8)	8	0.20	(18.9)	8
	30 to 49 (3)	0.08	(61.3)	0.14	(38.5)	8	0.17	(28.0)	8
	< 30 (4)	0.09	(43.6)	0.16	(24.8)	8	0.28	(30.0)	8
tmax,ss (hr)	> 80 (1)						3.67	(40.9)	9
	50 to 80 (2)	4.25	(37.2)	4.63	(56.5)	8	4.50	(37.6)	8
	30 to 49 (3)	4.31	(45.1)	4.75	(36.9)	8	6.00	(25.2)	8
	< 30 (4)	3.63	(48.2)	5.25	(39.1)	8	6.25	(26.7)	8
% AUC(0-24)ss of RU76363 relative to AUC(0-24)ss of telithromycin	> 80 (1)						11.95	(25.4)	9
	50 to 80 (2)	15.54	(27.5)	12.05	(28.0)	8	12.82	(15.1)	8
	30 to 49 (3)	13.66	(27.8)	14.49	(21.1)	8	15.19	(26.5)	8
	< 30 (4)	13.34	(28.0)	13.73	(29.3)	8	16.41	(33.3)	8

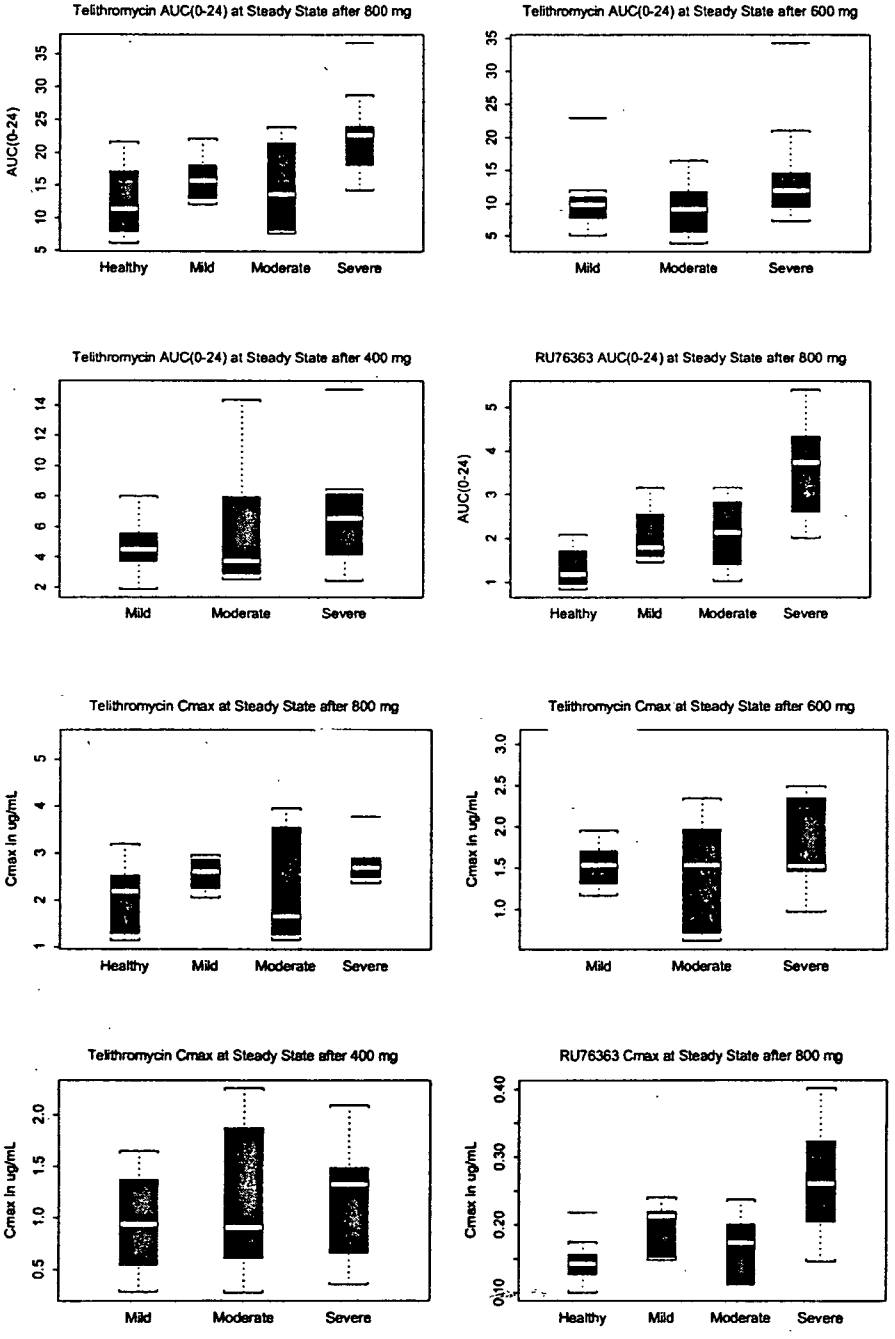
Table 4. Unbound fraction of telithromycin per CLcr stratum

CLcr Stratum (mL/min)	N	Mean % Unbound	CV (%)
>80	9	50.9	7
50 to 80	12	48.5	6
30 to 49	12	46.9	12
<30	11	41.6	17

Table 5. Difference in maximum observed QTc between Day –1 and Day 5: by creatinine clearance stratum and by treatment group

	Mild 50-80 mL/min		Moderate 30-49 ml/min		Severe <30 mL/min		Healthy >80 mL/min	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
QTcB (ms)								
A (400 mg)								
Day -1	7	434.9 (24.4)	8	418.9 (15.3)	8	434.1 (22.0)		
Day 5	7	429.4 (19.8)	8	417.9 (15.5)	8	436.6 (24.1)		
p-value		0.1821		0.7187		0.7408		
B (600 mg)								
Day -1	8	418.9 (23.9)	8	421.8 (24.7)	8	446.5 (24.0)		
Day 5	8	413.6 (23.5)	8	426.3 (22.7)	8	447.1 (25.1)		
p-value		0.1777		0.3205		0.9191		
C (800 mg)								
Day -1	7	416.0 (26.5)	8	422.4 (25.0)	8	434.5 (23.5)	9	404.0 (23.0)
Day 5	7	417.7 (22.9)	8	424.4 (20.7)	8	440.6 (27.0)	9	409.8 (29.5)
p-value		0.5675		0.4132		0.1279		0.1480
QTcF (ms)								
A (400 mg)								
Day -1	7	422.6 (21.6)	8	404.6 (13.9)	8	422.0 (20.7)		
Day 5	7	418.1(18.2)	8	403.0 (16.4)	8	423.3 (24.3)		
p-value		0.1473		0.4669		0.8331		
B (600 mg)								
Day -1	8	407.6 (19.6)	8	413.5 (24.9)	8	432.8 (24.7)		
Day 5	8	400.8 (18.0)	8	413.4 (22.1)	8	431.8 (25.4)		
p-value		0.0255		0.9683		0.8497		
C (800 mg)								
Day -1	7	410.6 (27.4)	8	412.1 (20.7)	8	422.9 (21.8)	9	396.9 (21.5)
Day 5	7	412.1 (25.7)	8	415.1 (19.7)	8	430.3 (25.5)	9	403.7 (24.8)
p-value		0.6550		0.0185		0.1335		0.0156
QTcN (ms)								
A (400 mg)								
Day -1	7	420.4 (22.0)	8	402.5 (13.8)	8	420.5 (21.8)		
Day 5	7	416.4 (18.3)	8	400.4 (16.6)	8	421.1 (25.1)		
p-value		0.2070		0.3743		0.9104		
B (600 mg)								
Day -1	8	405.6 (19.4)	8	412.1 (26.0)	8	430.5 (25.3)		
Day 5	8	398.5 (17.2)	8	411.4 (22.7)	8	428.8 (25.9)		
p-value		0.0138		0.8055		0.7325		
C (800 mg)								
Day -1	7	409.6 (27.5)	8	410.9 (20.4)	8	420.9 (21.5)	9	396.8 (21.6)
Day 5	7	411.4 (26.8)	8	413.8 (19.4)	8	428.6 (24.9)	9	402.4 (24.6)
p-value		0.5999		0.0211		0.1300		0.0547

Figure 1. Box plots of AUC and C_{max} of telithromycin and its metabolite (RU76363) for each dose and each renal function group



Horizontal Line Segments Within Black "Box" = Median (50th Percentile)
Bottom and Top Areas of Black "Box" = 1st and 3rd Quartiles (25th and 75th Percentiles)
Lower and Upper "Whiskers" = 5th and 95th Percentiles;
Horizontal Line Segments Outside of "Whiskers" = Outlier Values

Figure 2. Mean telithromycin plasma concentrations for the 800mg dose by CLcr stratum

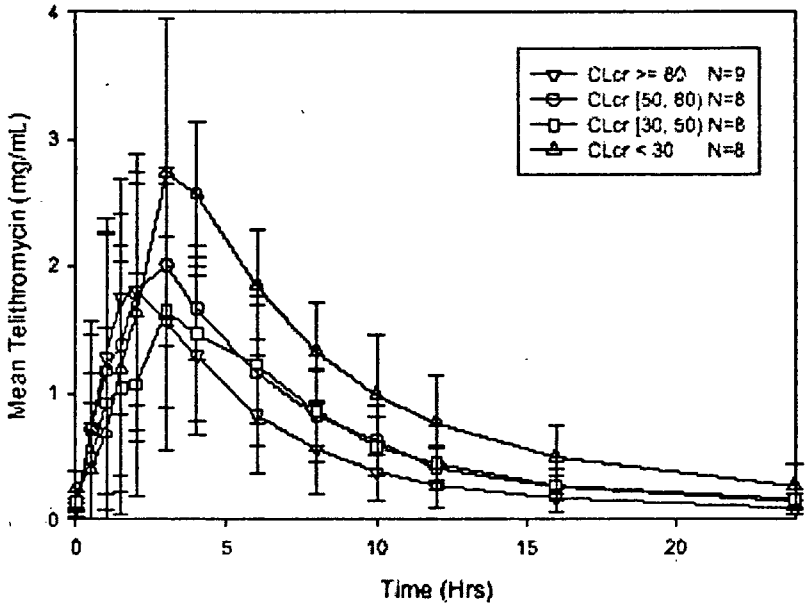


Figure 3. Correlation of Cmax, AUC(0-24), total clearance(CLss/F), and renal clearance (CLr) with creatinine clearance

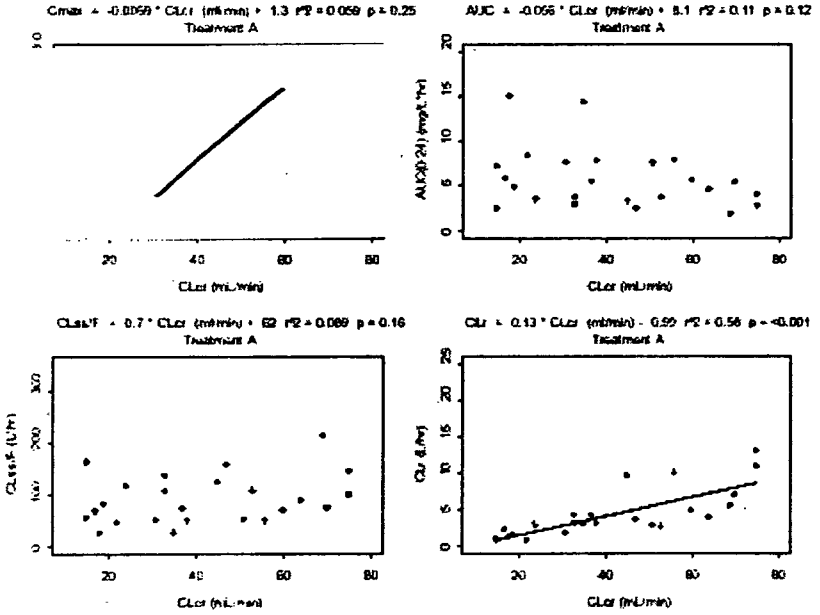
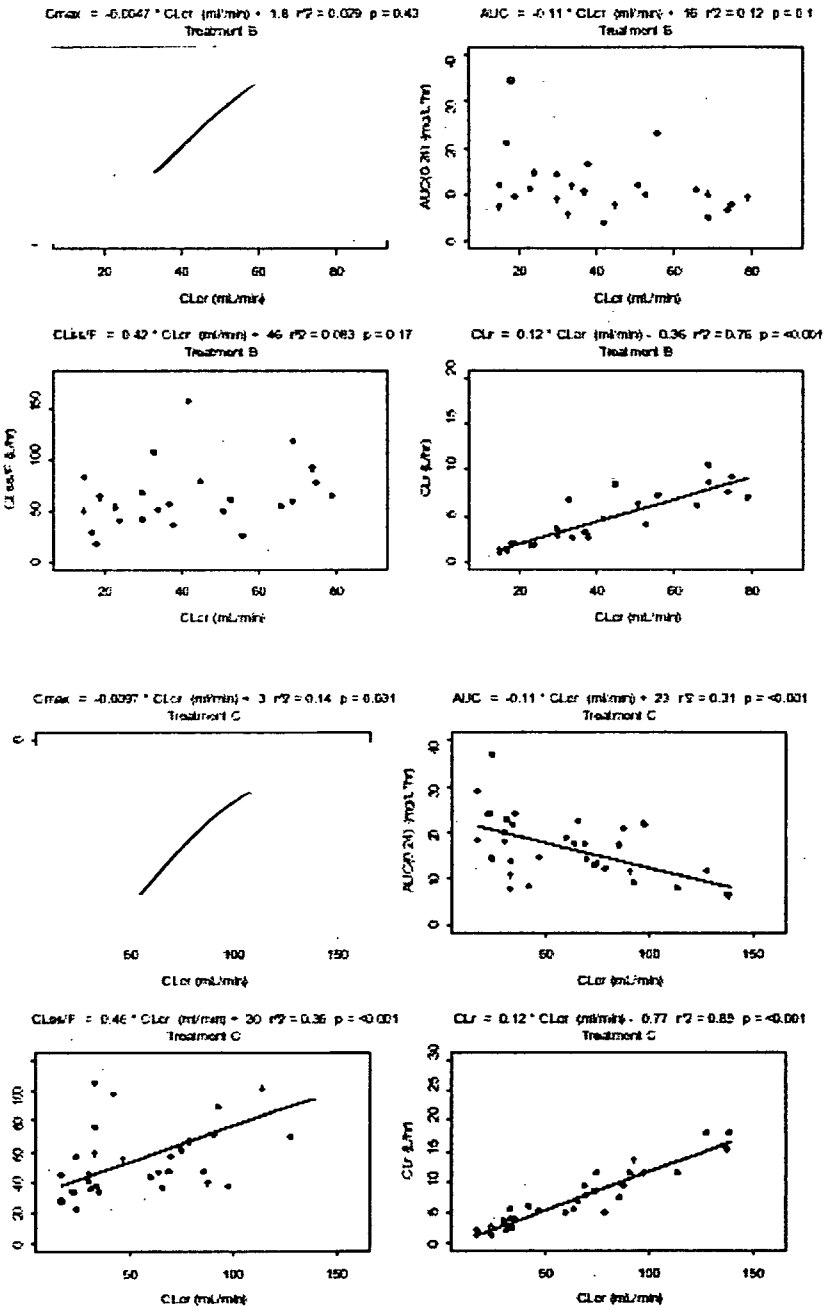
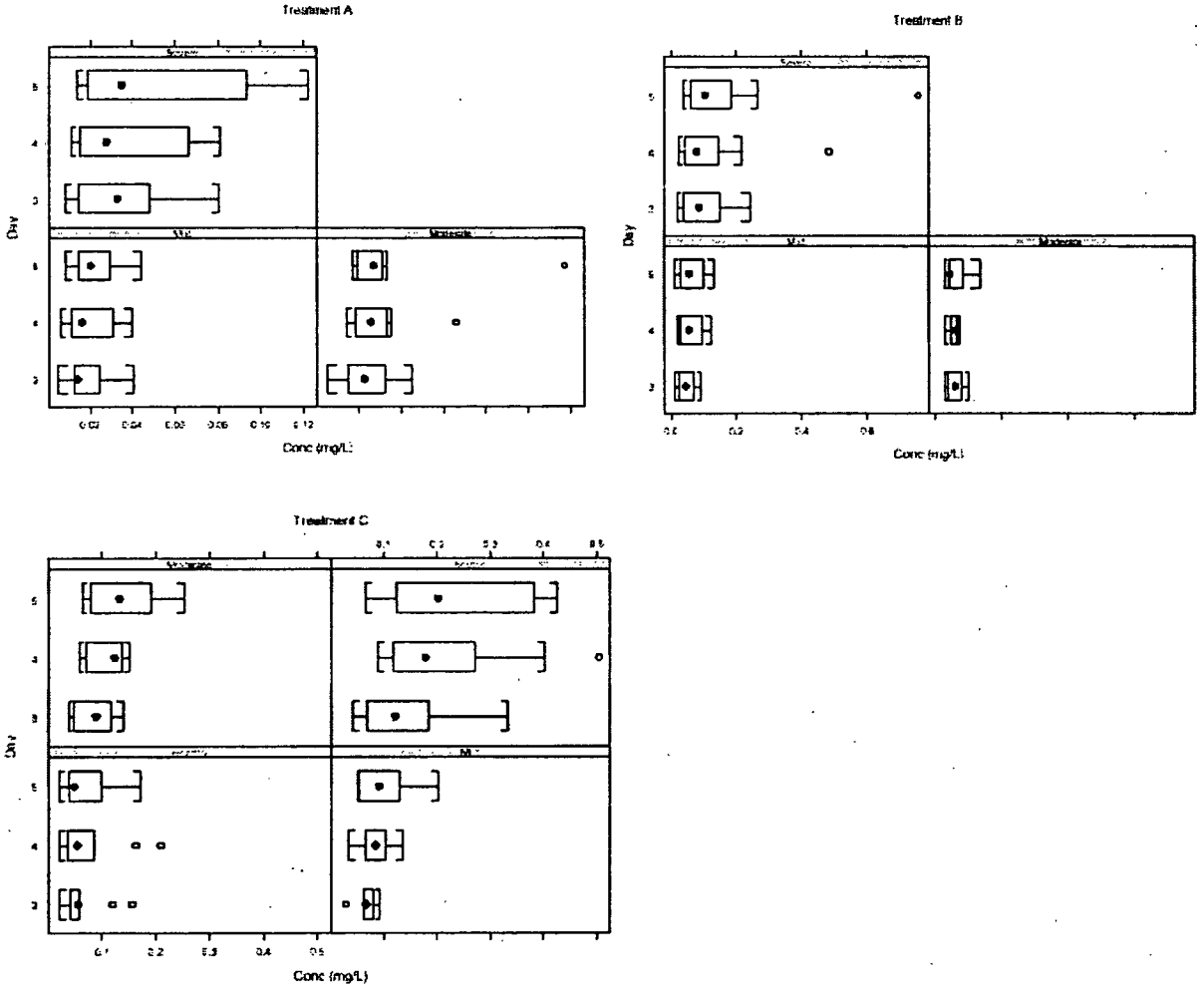


Figure 3. Continued.



Treatment A: 400 mg
Treatment B: 600 mg
Treatment C: 800 mg

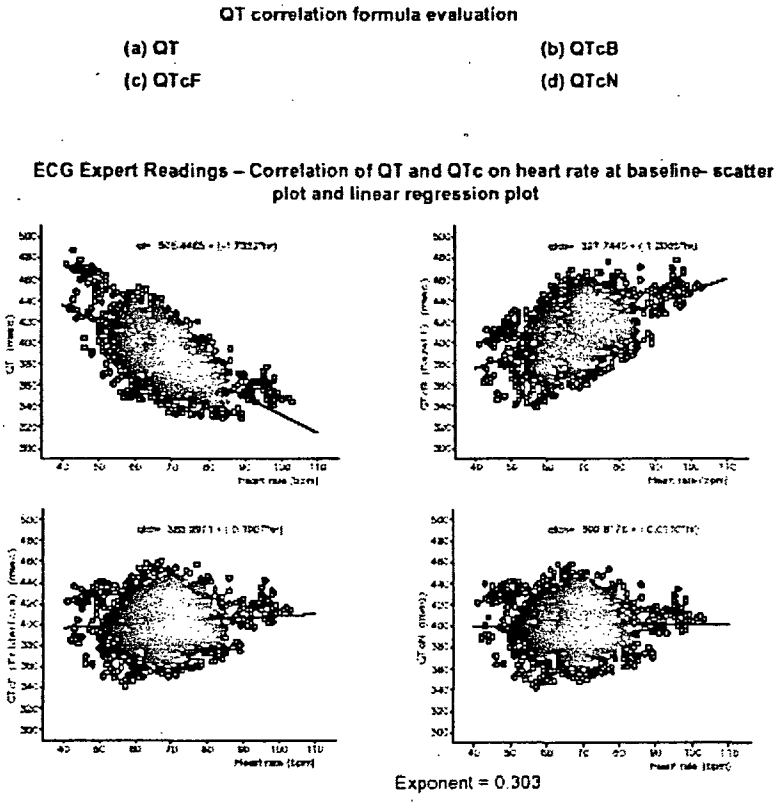
Figure 4. Mean trough concentrations of telithromycin at day 3, 4, and 5 for each dose group and each renal function group



Treatment A: 400 mg
Treatment B: 600 mg
Treatment C: 800 mg

The point Within the "Box" = Median (50th Percentile)
Left and Right Areas of the "Box" = 1st and 3rd Quartiles (25th and 75th Percentiles)
Left and Right "Whiskers" = 5th and 95th Percentiles
Points Outside of "Whiskers" = Outlier Values

Figure 5. Correlation of QT and QTc on heart rate at baseline



(a) QT (uncorrected)
(b) QT corrected by Bazett's formula (QTcB)
(c) QT corrected by Fridericia's formula (QTcF)
(d) QT corrected by the new population-specific formula (QTcN).

STUDY NUMBER: 1063

TITLE: Effects of ketoconazole on the pharmacokinetics of telithromycin after multiple oral doses of 800 mg once a day for 5 days in subjects 60 years of age and older with diminished renal function.

OBJECTIVES: To determine the effect of cytochrome P450 3A4 (CYP3A4) inhibition by ketoconazole on the pharmacokinetics of telithromycin in elderly subjects with diminished renal function.

DESIGN: This was a multicenter, multinational, open-label, 3-treatment parallel group, multiple oral dose study.

The three treatments were:
Treatment A: Ketoconazole 400 mg once daily for 5 days
Treatment B: Telithromycin 800 mg once daily plus ketoconazole 400 mg once daily for 5 days
Treatment C: Clarithromycin 500 mg twice daily plus ketoconazole 400 mg once daily for 5 days

A total of 36 elderly subjects (>60 years of age) were to be recruited (12 in each treatment group). Subjects were to have diminished renal function (planned creatinine clearance [CLcr] range 30 to 80 mL/min), and were to be hemodynamically and medically stable with no major diseases other than renal impairment, hypertension, or diabetes. Subjects were to be excluded if they had a family or congenital history of long QT syndrome or known acquired QT interval prolongation.

FORMULATION: 400 mg telithromycin tablet (MD28146/057), 500 mg clarithromycin tablet (76166AF21), and 200 mg ketoconazole (91P0649)

SAMPLING: Plasma samples were collected prior to the 1st, 3rd, 4th and 5th dose and at serial time points after the 5th dose (0h30, 1h, 1h30, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 16h and 24h post dose). Urine samples were obtained before dosing on Day 1 and at specified intervals up to 24 hours after dosing on Day 5.

ECG: 12-Lead ECG's were measured at serial timepoints over the 24 hours after time zero on Day -1 and Day 5 (at timepoints: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours, which coincided with the timepoints for pharmacokinetic blood sampling on Day 5), and at 2 and 4 hours after time zero on Days 1 to 4.

In addition, 3 ECG's were measured at time zero on Days -1 and 1, and the respective means of the 3 measurements were used as the baseline for Day -1 and Day 5. ECG's were over-read by a central expert cardiologist who was blinded to subject number, treatment, and time of measurement. QT intervals were corrected for heart rate using Bazett's formula (QTcB), Fridericia's formula (QTcF), and a population-specific formula (QTcN). The Day –1 values were evaluated for any significant, consistent circadian variation during the day.

ASSAY: Telithromycin and its main metabolite (RU 76363), clarithromycin and its main metabolite (14-OH-clarithromycin), and ketoconazole were determined in plasma using validated methods. Telithromycin and clarithromycin were also determined in urine using validated methods. The summaries of method performance are shown in the following table.

Analyte	Sample Matrix	Accuracy[a]	Precision[b]
Plasma			
Telithromycin	QC samples	91.2–97.8%	5.3–11.4%
	Calibration standards	98.3–101.7%	3.8–9.1%
RU 76363	QC samples	99.3–101.7%	4.5–9.8%
	Calibration standards	94.5–112.0%	2.1–8.0%
Clarithromycin	QC samples	102.7–105.5%	7.0–11.2%
	Calibration standards	97.1–101.9%	3.6–10.9%
14-OH–clarithromycin	QC samples	101.7–108.6%	7.5–11.7%
	Calibration standards	97.4–102.3%	2.8–9.9%
Ketoconazole	QC samples	94.4–106.1%	1.7–3.8%
	Calibration standards	91.9–105.3%	0.8–9.0%
Urine			
Telithromycin	QC samples	91.9-102.0 %	1.6-5.3 %
	Calibration standards	90.7-117.0%	0.4-4.0 %
Clarithromycin	QC samples	107.7-112.1 %	4.6-11.8 %
	Calibration standards	94.3-105.6 %	2.6-17.2 %

[a] Accuracy, expressed as % recovery, relative to theoretical concentration.
[b] Precision, expressed as % coefficient of variation.

DATA ANALYSIS:

Pharmacokinetics:

Pharmacokinetic parameters were estimated using noncompartmental methods for telithromycin, clarithromycin, and their main metabolites (as appropriate). The following pharmacokinetic parameters for telithromycin and RU 76363 were determined for each subject after the 5th dose using non-compartmental analysis: $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, and AUC(0-24)ss. Additional pharmacokinetic parameters, Ae (urinary recovery in % dose), CL_R , and CLss/F were calculated for telithromycin.

ECG:

QT intervals were corrected for heart rate using Bazett's formula (QTcB), Fridericia's formula (QTcF), and a population-specific formula (QTcN). The Day –1 values were evaluated for any significant, consistent circadian variation during the day.

A population-specific formula was calculated from QT and RR values measured on Day -1 (from time zero to 24 hours) (QTcN), where:

QTcN=QT/(RR/1000)n**

Where n is derived from the fit of the exponential function $QT=\beta'(RR/1000)^{\alpha}$. This fit is performed using the usual regression on logarithmically transformed data for QT on RR/1000 for the drug-free time points. Under this logarithmic transformation, the function becomes $\log(QT) = \log(\beta) + \alpha^*\log(RR/1000)$, and n is estimated by α. All ECG data recorded up to the 24-hour time point on Day -1 were used to estimate α. The n equals 0.5 and 0.33 for Bazett and Fredericia formula, respectively.

Statistics:
Descriptive statistics for pharmacokinetic parameters were presented for telithromycin, clarithromycin, and their main metabolites. Pharmacokinetic parameters were compared with corresponding historical pharmacokinetic data for telithromycin or clarithromycin administered alone. Descriptive statistics for ketoconazole plasma concentrations at 2 and 3 hours after the Day 5 (final) dose were presented by treatment group.

Descriptive statistics were presented for ECG parameters. The frequency of clinically noteworthy abnormal QTcB values (defined according to the CPMP guideline) was presented by treatment group. Differences in observed maximum QTc intervals between Day –1 and Day 5 were compared within treatment groups using the paired t-test. Linear or nonlinear regression was used to evaluate the relationship between changes in QTc intervals as dependent variables and plasma concentrations as independent variables.

RESULTS:
The demographics of the study are shown in Table 1. Subjects in this study were aged 59 to 84 years (mean 71.4±6.3 years, median 70 years), and most subjects were white and/or male. This study enrolled elderly subjects with varying degrees of renal impairment. The mean screening CL_{CR} (calculated using the Cockcroft and Gault formula) for the population as a whole was 49.1±15.6 mL/min. Although it was planned that only older subjects with mild to moderate renal impairment (i.e., CLcr from 30 to 80 mL/min) were to be studied, two subjects with severe renal impairment (i.e., Subject 1008 – CLcr 28 mL/min; Subject 1006 – CLcr 24 mL/min) were included in Treatment B (telithromycin + ketoconazole). In addition, one subject with CLcr 15 mL/min was also included in Treatment A (ketoconazole alone).

PHARMACOKINETICS:
The mean and individual steady state pharmacokinetic parameters of telithromycin and its metabolite, RU76363, are shown in Table 2 and Table 3, respectively, following administration of Treatment B (telithromycin + ketoconazole). The plasma concentration vs. time profiles for telithromycin in the study are shown in Figure 1.

The results of this study indicated that following co-administration of telithromycin with ketoconazole (Treatment B), the mean $C_{max,ss}$ and $AUC(0–24)_{ss}$ values obtained in the 10 subjects with mild to moderate renal impairment (i.e., CL_{CR} 30-80 mL/min were slightly higher than those obtained in an earlier telithromycin + ketoconazole interaction study conducted in healthy subjects with normal renal function (Study 1045) ($C_{max,ss}$: 3.6 versus 3.1 mg/L, and $AUC(0–24)_{ss}$: 33.4 versus 28.6 mg/L•h). These findings are consistent with the findings that the systemic exposure in mild or moderate renal impaired subjects is not significantly different from the exposure in healthy subjects.

Comparing the pharmacokinetic data in healthy subjects who received multiple 800 mg telithromycin alone, $C_{min,ss}$ in this study was on average 0.53 mg/L (n=12) following co-administration of telithromycin with ketoconazole, which represented a 7-fold increase. The mean steady state Cmax and AUC(0-24) estimates, including those values from the two severe renal impairment subjects (n=12), were increased by 1.8 fold (4.1 mg/L vs. 2.27 mg/L) and 3.0 fold (37.4 vs. 12.5 mg/L•h), respectively, as compared to healthy subjects receiving telithromycin alone.

Following co-administration of telithromycin + ketoconazole (Treatment B), the systemic exposure to telithromycin in the two subjects with severe renal impairment (i.e., CLcr 28 and 24

mL/min, respectively) was substantially higher than healthy subjects with normal renal function receiving telithromycin alone, with AUC(0-24) estimates increased by 4.1- and 4.9-fold, respectively; Cmax increased by 2.4- and 3.9-fold, respectively.

There was a statistically significant inverse linear association between $C_{max,ss}$ and CL_{CR} ($p=0.02$) and between $AUC(0–24)_{ss}$ and CL_{CR} ($p=0.02$), but no apparent linear relationship between $C_{min,ss}$ and CL_{CR} ($p >0.05$). In Figure 2, the mean AUC(0-24) and Cmax estimates after multiple doses of 800 mg telithromycin are compared in the following groups: (i) in healthy subjects with normal renal function, (ii) subjects with renal impairment, (iii) healthy subjects after co-administration with ketoconazole , and (iv) elderly subjects with renal impairment after co-administration with ketoconazole from this present study.

The mean and individual pharmacokinetic parameters of RU76363 are shown in Table 3. Ketoconazole concentrations were measured at 2 and 3 hours after the dose at steady state. Linear regression analysis was applied to the relationship between the AUC ratio of RU 76363/ telithromycin and ketoconazole plasma concentration (higher of the 2 concentrations). The results, shown in Figure 3, indicated that there was no correlation between the AUC ratio for the major metabolite of telithromycin and ketoconazole plasma concentration ($p >0.05$).

The mean and individual pharmacokinetic parameters of clarithromycin and 14-OH-clarithromycin following repeated co-administration of clarithromycin + ketoconazole (Treatment C) are shown in Tables 4 and 5, respectively. At the 500-mg clarithromycin dose level in healthy subjects, mean Cmax,ss values have been reported to range from 2.41 to 3.27 mg/L, and mean AUC(0–12) values have been reported to range from 17.6 to 26.0 mg/L×h. In the present study in of elderly subjects with renal impairment receiving concomitant ketoconazole, plasma concentrations peaked at around 4.5 hours after dosing, with an average Cmax,ss of 6.2 mg/L. The mean AUC(0–12) of clarithromycin was 56.1 mg/L×h. This represented a 2.2-fold increase in mean Cmax,ss and 2.7-fold increase in AUC compared with those values cited above from studies reported in the literature. The mean AUC and Cmax after multiple doses of 500 mg clarithromycin are compared in Figure 4 between those reported in healthy subjects from the literature and after co-administration with ketoconazole in the elderly renal impairment subjects from this present study.

Linear regression analysis was applied to the relationship between the AUC ratio of 14-OH–clarithromycin/clarithromycin and ketoconazole plasma concentration. There was a statistically significant inverse linear correlation between the AUC ratio for 14-OH–clarithromycin and ketoconazole plasma concentration ($p <0.05$) (Figure 3).

ECG:

QT correction formula evaluation: The dependency of QT and corrected QT intervals on the heart rate are shown in Figure 5. The correction formulae include Bazett, Fridericia, and created by the studied population. These figures clearly indicate that the Bazett's formula had a significant bias in this study population, in which QTc values were overestimated at higher heart rates. Fridericia's formula removed the dependency of QTcF on heart rate greatly, but not entirely. The new population-specific formula derived from the study specific population (exponent = 0.341) using Day -1 drug free data represented the most robust correction.

Clinically noteworthy ECG findings: The normal ranges, predefined changes, and clinically significant criteria for corrected QTc intervals are presented in the table below:

Variable	Unit	Sex	ULN[a]	Predefined increase[a]	Clinically noteworthy abnormal criterion
QTcB/F/N	ms	Men	450	30–60, >60	>500
	ms	Women	470	30–60, >60	>500

[a]Defined according to the European CPMP guideline.

The incidence of predefined increases in QTc from baseline from 30 to 60 ms and >60 ms are summarized in the table below by treatment group and study day for Days -1 or 5.

	No. predefined increases for QTcB/F/N		
Study day	Ketoconazole 400mg QD N=10	Ketoconazole 400mg QD +Telithromycin 800mg QD N=9	Ketoconazole 400mg QD+ Clarithromycin 500mg BID N=8
ΔQTc increase 30–60 ms			
Day -1	1/0/1	0/0/0	0/0/0
Day 5	0/0/0	5/2/2	0/2/2
ΔQTc increase >60 ms			
Day -1	0/0/0	0/0/0	0/0/0
Day 5	0/0/0	0/0/0	2/0/0

- Two males in this study had 1 or more expert-read QTcB values above 450 ms. Both subjects received clarithromycin + ketoconazole.
- There were no females in this study with QTcB values above 470 ms.
- There were 5 telithromycin + ketoconazole subjects and 2 clarithromycin + ketoconazole subjects with 1 or more ΔQTcB increases from baseline of >30 ms to Day 5.
- Using Fridericia or study-specific correction formulae, there were 2 telithromycin + ketoconazole subjects with ΔQTcF from baseline of >30 ms to Day 5. The two clarithromycin + ketoconazole subjects with increases of >60 ms by Bazett formula had increases of >30 ms by Fridericia and study-specific correction formulae.
- There were no QTc values >500 ms.

Differences in observed maximum QTc parameters between Days -1 and 5: Differences in the maximum observed QTc intervals between Days -1 and 5, and the results of statistical testing within treatment groups (paired p-test), are summarized in Table 6. There was a significant change between Day –1 and Day 5 in maximum observed QTcB for telithromycin + ketoconazole group but there were no significant differences for Max QTcF, or Max QTcN.

ECG-pharmacokinetic evaluations: Simple linear regression was used to determine the relationship between QT values and drug plasma concentration (telithromycin, clarithromycin, or ketoconazole). The dependent variable in this evaluation was ΔQT, ΔQTcB, ΔQTcF, or ΔQTcN. The independent variable was telithromycin, clarithromycin, or ketoconazole plasma concentration. The regression analysis is shown in Table 7 and Figure 6. A similar analysis was conducted for clarithromycin and the results are shown in Figure 7. The results showed that for both telithromycin and clarithromycin, there is a weak linear correlation between ΔQTcB/ ΔQTcF/ΔQTcN and the plasma concentration.

CONCLUSION:

1. The maximum plasma concentrations observed in the study population were consistent with the highest concentrations observed in Phase III trials.

2. Formation of the major metabolite (RU76363) of telithromycin was not affected by ketoconazole inhibition.
3. The sponsor concluded that in subjects with a CL_{CR} <30 mL/min, the observed Cmax,ss of telithromycin warrants a dosage adjustment when metabolic impairment is present.
4. There were no QTc intervals >450 ms for men or >470 ms for women in the telithromycin plus ketoconazole group, and no telithromycin plus ketoconazole subjects with a change from baseline in QTcB >60 ms.
5. There was a weak and comparable correlation between ΔQTcB/ ΔQTcF/ΔQTcN and telithromycin or clarithromycin plasma concentration at steady state.

COMMENTS:

1. Only mild or moderate renal impaired subjects were included in this study due to the safety concern. It was found in the renal impairment Study 1062 that a significant increase in telithromycin concentration was found only in severe renal impaired subjects but not in mild and moderate renal impaired subjects. Therefore, by this design, the study results represent mostly ketoconazole effect on telithromycin concentration but little information on the additive effect of ketoconazole and severe renal impairment. The exposures in two subjects whose renal function was severely impaired tended to be higher in comparison with the rest of subjects whose renal function was mildly or moderately impaired.
2. The trough level of ketoconazole instead of concentration at 2 or 3 hours should be a better index for ketoconazole exposure if the AUC is not available.
3. Following administration of telithromycin with ketoconazole in mild or moderate renal impaired subjects, mean AUC and Cmax were increased 2.7 fold and 1.6 fold respectively, as compared with AUC and Cmax in healthy subjects receiving telithromycin alone. A reduction in the telithromycin dose might be necessary in this situation.

Table 1. Summary of subject demographics and baseline characteristics by treatment

Parameter	A (N=11)	B (N=12)	C (N=9)	All subjects (N=32)
Age (mean ± SD) [years]	70.5 (7.6)	74.2 (5.8)	68.8 (3.9)	71.4 (6.3)
Range [years]	59–84	65–81	64–78	59–84
Sex [n (%)]				
Men	5 (45.5)	9 (75.0)	4 (44.4)	18 (56.3)
Women	6 (54.6)	3 (25.0)	5 (55.6)	14 (43.8)
Race [n(%)]				
Black	3 (27.3)	4 (33.3)	4 (44.4)	11 (34.4)
White	8 (72.7)	8 (66.7)	5 (55.6)	21 (65.6)
Body weight (mean ± SD) [kg]	77.2 (15.4)	72.5 (17.2)	70.9 (16.6)	73.6 (16.2)
Range [kg]	55.6–108.1	55.6–109.7	56.8–110.3	55.6–110.3
Creatinine CL Mean (SD) [mL/min]	49.2 (17.8)[a]	45.7 (14.5)	53.5 (14.9)	49.1 (15.6)[a]
Median	49.0[a]	47.5	52.0	49.0[a]
Range	15–79[a]	24–66	35–76	15–79[a]

Treatment A : ketoconazole 400 mg once daily;
Treatment B: telithromycin 800 mg once daily + ketoconazole 400 mg once daily;
Treatment C: clarithromycin 500 mg twice daily + ketoconazole 400 mg once daily.
Screening CL_{CR} calculated from the Cockcroft and Gault formula.
[a] Includes value of 15 mL/min for Subject 1013.

Table 2. Telithromycin pharmacokinetic parameters at steady state following oral dosing with telithromycin 800 mg + ketoconazole 400 mg (Treatment B)

Subject	CL_{CR}[a] (mL/min)	$AUC_{(0-24)ss}$ (mg/L·h)	$C_{max,ss}$ (mg/L)	$t_{max,ss}$ (h)	$C_{min,ss}$ (mg/L)	CL/F (L/h)	% Recovered in urine	CL_R (L/h)	Ketoconazole Conc.ss[b] (mg/L)
3									
4									
7									
104									
110									
1012									
105									
1014									
1016									
1003									
1008									
1006									
N	12	12	12	12	12	12	12	12	12
Mean	45.7	37.4	4.1	2.6	0.53	23.6	23.7	5.6	9.1
SD	14.5	13.1	1.7	1.5	0.24	7.1	6.1	2.1	4.0
CV	63.5	70.0	83.5	115.3	89.9	60.0	51.6	73.9	88.3
Min									
Median	47.5	32.8	3.7	2.5	0.48	24.5	22.4	5.7	9.3
Max									

[a] CL_{CR} was calculated on data at screening using the Cockcroft and Gault formula.
[b] Greater of C-2 hour versus C-3 hour ketoconazole plasma concentration on Day 5.

Table 3. RU 76363 pharmacokinetic parameters at steady state following oral dosing with telithromycin 800 mg + ketoconazole 400 mg (Treatment B)

Subject	CL_{CR}[a] (mL/min)	$AUC_{(0-24)ss}$ (mg/L·h)	$C_{max,ss}$ (mg/L)	$T_{max,ss}$ (h)	% $AUC_{(0-24)ss}$ relative to $AUC_{(0-24)ss}$ of tel	Ketoconazole $conc_{ss}$[b] (mg/L)
0003					10.8	
0004					3.5	
0007					9.2	
0104					7.2	
0110					3.5	
1012					6.7	
0105					5.7	
1014					6.1	
1016					8.6	
1003					8.8	
1008					7.5	
1006					6.1	
N	12	12	12	12	12	12
Mean	45.6	2.6	0.2	6.0	7.0	9.1
SD	14.4	1.0	0.1	0.9	2.2	4.0
CV	63.5	80.0	69.8	28.4	63.1	88.3
Min					3.5	
Median	47.5	2.7	0.2	6.0	7.0	9.3
Max					10.8	

[a] CL_{CR} was calculated on data at screening using the Cockcroft and Gault formula.
[b] Greater of C-2 hour versus C-3 hour ketoconazole plasma concentration on Day 5.

Table 4. Clarithromycin pharmacokinetic parameters at steady state following oral dosing with clarithromycin 500 mg twice daily + ketoconazole 400 mg (Treatment C)

Subject	CL_{CR}[a] (mL/min)	$AUC_{(0-12)ss}$ (mg/L·h)	$C_{max,s}$ (mg/L)	$t_{max,ss}$ (h)	$C_{min,ss}$ (mg/L)	CL/F (L/h)	% Recovered in urine	CL_R (L/h)	Ketoconazole $conc_{,ss}$[b] (mg/L)
2									
5									
10									
107									
108									
102									
1007									
1002									
157									
N	6	6	6	6	6	6	6	6	6
Mean	56.8	56.1	6.2	3.2	3.3	10.1	63.9	6.4	8.4
SD	16.1	22.9	2.3	1.7	2.1	3.7	18.7	3.1	3.0
CV	28.3	40.8	36.4	54.4	64.2	36.8	29.2	47.9	35.7
Min									
Median	56.5	51.2	5.8	3.0	2.7	9.8	72.5	5.7	8.6
Max									

*C0h value on Day 3 from dropout subject was excluded from descriptive statistics.
** Data for Subject 0102 are excluded because steady state was not reached due to dosing issues.
[a] CL_{CR} was calculated on data at screening using the Cockcroft and Gault formula.
[b] Greater of C-2 hour versus C-3 hour ketoconazole plasma concentration on Day 5.

Table 5. 14-OH–clarithromycin pharmacokinetic parameters at steady state following oral dosing with clarithromycin 500 mg twice daily + ketoconazole 400 mg (Treatment C)

Subject	CL_{CR}[a] (mL/min)	$AUC_{(0-12)ss}$ (mg/L·h)	$C_{max,ss}$ (mg/L)	$t_{max,ss}$ (h)	% $AUC_{(0-12)ss}$ /$AUC_{(0-12)ss}$ of CLA	Ketoconazole $conc._{ss}$[b] (mg/L)
0002					12.7	
0005					17.2	
0010					24.6	
0108					16.7	
0102					5.7	
1007					16.2	
0157					22.1	
N	6	6	6	6	6	6
Mean	56.8	10.4	1.2	3.0	18.3	8.2
SD	16.1	4.8	0.7	3.8	4.3	2.8
CV	28.3	46.2	59.1	126.1	23.7	34.5
Min					12.7	
Median	56.5	8.8	0.9	1.8	17.0	8.3
Max					24.6	

Table 6. Difference in maximum observed QTc between Day –1 and Day 5: within treatment-group analysis

		A		B		C
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD) *a*
QTcB (ms)						
Day -1	11	426.5 (18.1)	12	410.4 (22.5)	6	421.2 (26.0)
Day 5	11	419.7 (17.5)	12	424.4 (19.0)	6	436.2 (26.8)
p-Value		0.0881		0.0142		0.0847
QTcF (ms)						
Day -1	11	410.9 (21.2)	12	414.3 (15.8)	6	410.2 (18.1)
Day 5	11	406.6 (19.7)	12	420.4 (11.8)	6	421.7 (19.4)
p-Value		0.1636		0.1194		0.0681
QTcN (ms)						
Day -1	11	411.5 (21.0)	12	414.0 (16.2)	6	410.5 (18.5)
Day 5	11	407.0 (19.5)	12	420.5 (11.9)	6	422.2 (19.6)
p-Value		0.1283		0.1198		0.0736

Table 7. Relationship between ΔQT/ΔQTc and telithromycin plasma concentration (Treatment B), Day 5 data only (N=12)

Dependent variables	Intercept	Slope	r^2	p-value
ΔQT	-11.0	2.4	0.021	0.10
ΔQTcB	4.4	2.1	0.037	0.03
ΔQTcF	-0.7	2.2	0.042	0.021
ΔQTcN	-0.79	2.3	0.046	0.016

Figure 1. Telithromycin plasma concentrations following oral dosing with telithromycin 800 mg + ketoconazole 400 mg on Day 5 for subjects in this study

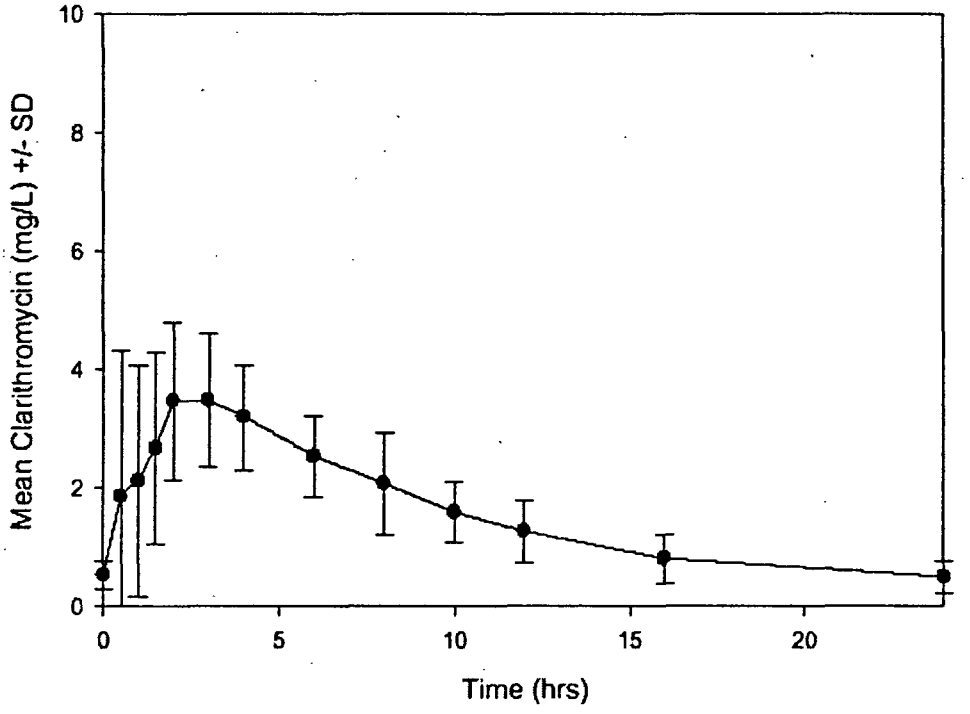


Figure 2. Comparison of Telithromycin Exposure from Various Studies

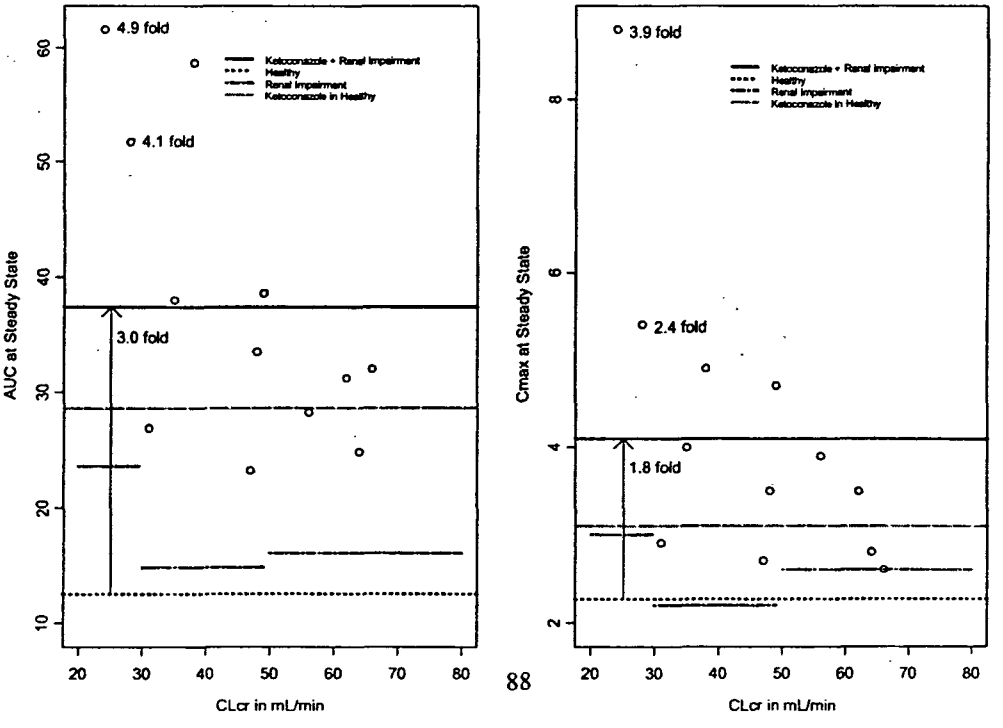


Figure 3. Regression analysis for AUC ratio RU76363 to telithromycin, versus ketoconazole plasma concentration and AUC ratio of 14-OH-clarithromycin to clarithromycin, versus ketoconazole plasma concentration

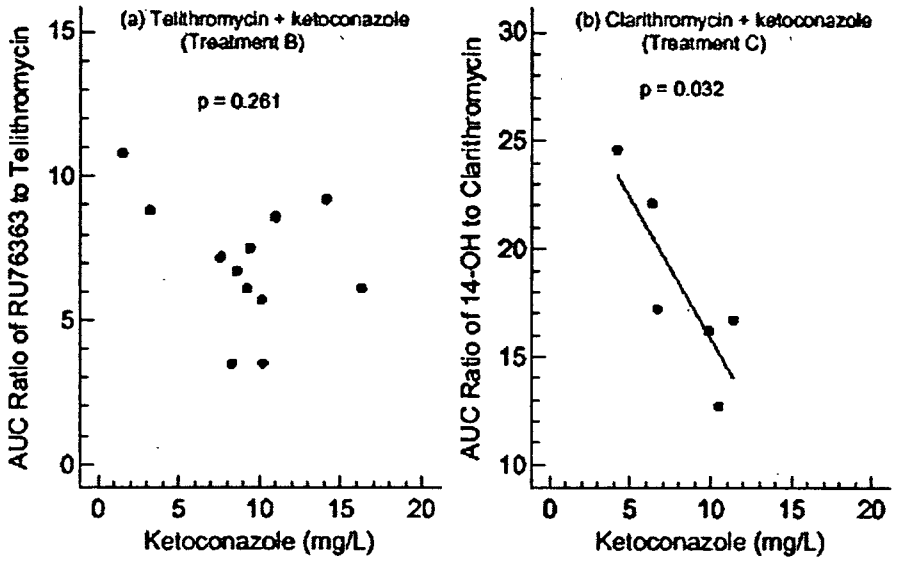


Figure 4. Comparison of Clarithromycin Exposure in Healthy Subjects from the Literature and the Present Study 1063

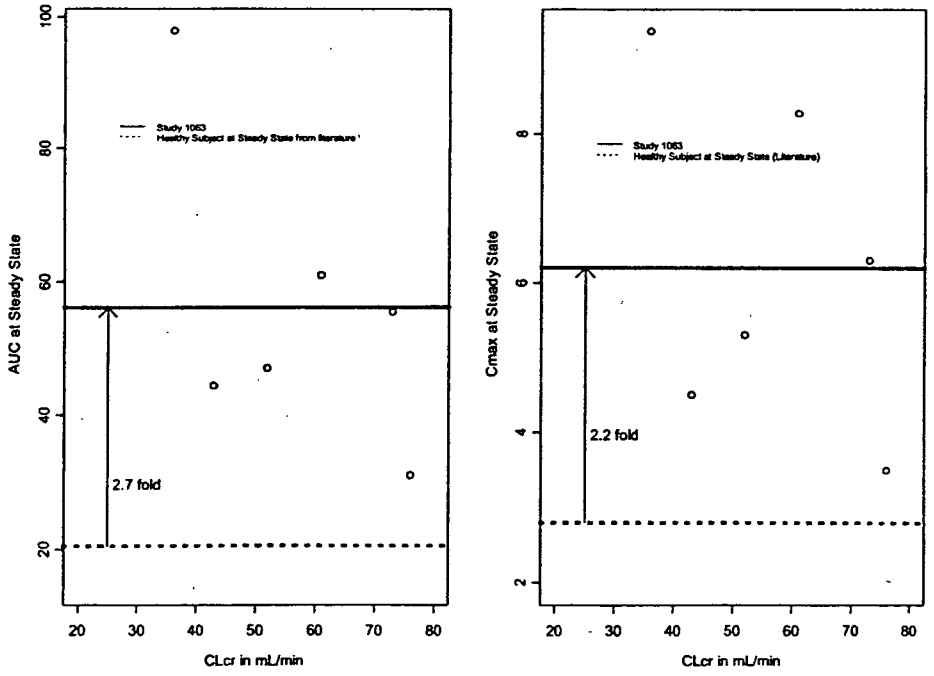


Figure 5. QT correlation formula evaluation

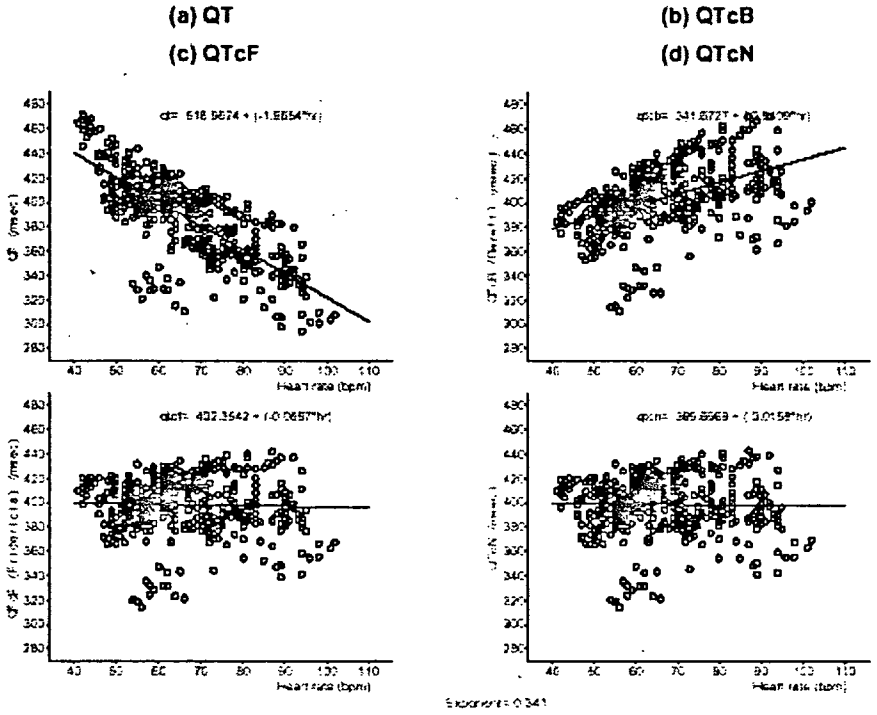


Figure 6. Correlation of delta QT or delta QTc with telithromycin concentration

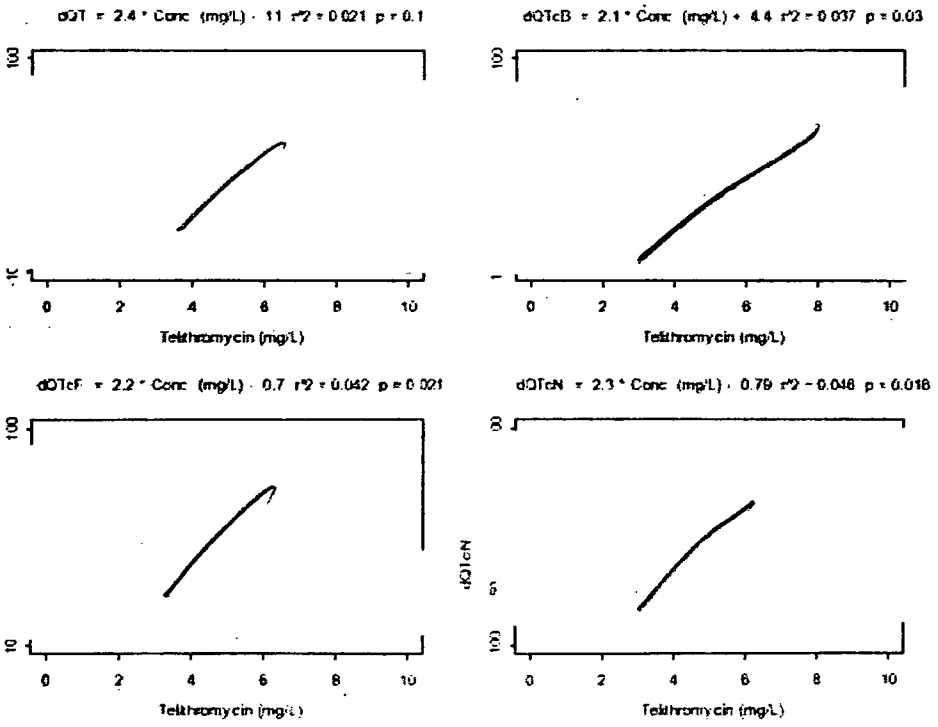
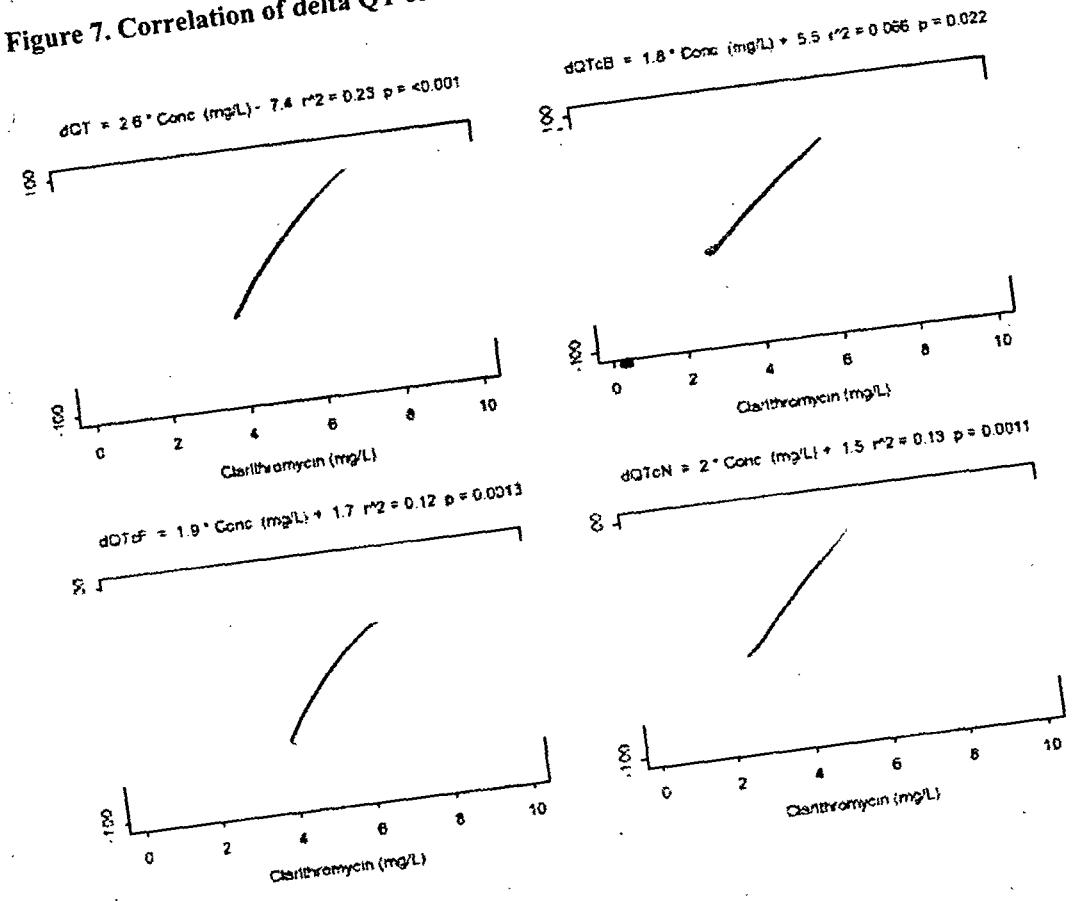


Figure 7. Correlation of delta QT or delta QTc with clarithromycin concentration



STUDY NUMBER: 1064

TITLE: Assessment of ophthalmological safety of telithromycin at a supraclinical single dose (2400 mg) in healthy subjects.

OBJECTIVES:

- To assess the risk for angle closure glaucoma by measuring intraocular pressure and anterior chamber angle, and the risk for retinal toxicity by performing visual field and color vision assessments.
- To assess the ophthalmological safety of telithromycin further by performing a complete evaluation of the visual function with measurements of visual acuity, refraction and tear film stability, and by investigating accommodation using a dynamic approach.

DESIGN: Single-center, double-blind, randomized, placebo controlled, 2-way crossover, single-dose study with a 7-day-washout period. The treatments were placebo and 2400 mg telithromycin.

The eye examination include tearscope, color vision, Pelli-Robson test, refraction — autorefractor after lens insertion for far vision (if necessary), visual acuity, visual field examination, slit lamp examination, and intraocular pressure.

Twelve-lead ECGs at screening, before dosing, and at 1, 2, 3, 6, and 24 hours after dosing on Day 1 of each treatment period, and at 7 days after dosing in Period II.

FORMULATION: 400 mg telithromycin tablet (KN 2000029)

SAMPLING: Telithromycin plasma concentration and amount excreted in tears were determined before and at 1, 2, 3, 4, 6 hours after administration.

ASSAY:

The precision and accuracy of the assay are summarized in the following table:

Analyte	Samples	Accuracy[a]	Precision[b]
Plasma			
Telithromycin	QC samples —	96.2–104.6%	3.8-15.6%
	Calibration standards —	98.1-102.7%	2.4-7.8%

[a] Accuracy, expressed as % recovery, relative to theoretical concentration.
[b] Precision, expressed as % coefficient of variation.

DATA ANALYSIS:

Pharmacokinetics:

The following plasma pharmacokinetic parameters were calculated using a noncompartmental analysis for HMR 3647: Cmax, Tmax.

Statistics:

Descriptive statistics were calculated.

RESULTS:

Pharmacokinetics:

The plasma Cmax values are summarized in Table 1. The mean concentration vs. time profile is shown in Figure 1.

Blurred vision:
Twelve subjects (7 women and 5 men) presented with blurred vision. The summary of the blurred vision is shown in Table 2.

ECG findings:
At the dose of 2400 mg, telithromycin increases the heart rate in healthy volunteers. Since changes in heart rate have a major influence on corrected QT, several correction formulae were used: Bazett's formula [$QTcB = QT/(RR/1000)^{0.5}$], Fridericia's formula $QTcF(QT/(RR/1000)^{0.33}$], which provides an improved compensation for increase in heart rate, and a study population-adapted formula based on data measured at baseline (QTcN). In this population, $QTcN = QT/(RR/1000)^{0.236}$. Figure 2 shows the correlation between the corrected QT and heart rate. The mean changes in QTcB, QTcF, and QTcN from baseline to Day 1 by treatment are shown in Figure 3.

Using Bazett's formula, 1 subject showed an increase in QTcB of more than 60 msec and 1 subject presented with a QTc above 470 msec following 2400 mg of telithromycin:

- Subject 2, a 20-year-old woman, presented with an increase in QTcB of 62 msec, 3 hours after telithromycin administration. The corresponding QTcB was 444 msec. This increase in QTcB was accompanied by an increase in heart rate of 16 bpm (69 bpm vs 53 bpm at baseline).

  Using Fridericia's formula the increase was 45 msec and using the N formula the increase was 35 msec.

- Subject 23, a 27-year old woman, presented a QTcB of 472 msec, 3 hours after telithromycin administration. This value was an increase of 46 msec from baseline. The heart rate was concomitantly increased by 19 bpm (76 bpm vs. 57 bpm at baseline). Using Fridericia's formula the QTcF was 454 msec and using the N formula the QTcN was 443 msec, with only a 13 msec increase from baseline.

Using Fridericia's formula or the N formula, none of the subjects had a QTc increase of more than 60 msec and none of the subjects had a QTc value above 450 msec (male) or 470 msec (female).

None of the subjects had a QTc value >500 msec using any of the correction formulae.

CONCLUSION:
After single oral administration of 2400 mg telithromycin, plasma pharmacokinetic parameters were in the range of those obtained in previous studies at the same dose, with a mean C_{max} of 5.11 mg/L and a median t_{max} of 3h.

COMMENTS:
1. The study was mainly designed to examine the mechanism of the blurred vision. Plasma samples were collected only up to 6 hours.
2. No amount of telithromycin excreted in tears was reported in the study even though samples were planned to be collected.

Table 1. Individual Cmax and Tmax values after a single dose of 2400 mg telithromycin

		Cmax (mg/L)	Tmax (h)
Subject No. 1			
	2		
	3		
	4		
	5		
	6		
	7		
	8		
	9		
	10		
	11		
	12		
	13		
	14		
	15		
	16		
	17		
	18		
	19		
	20		
	21		
	22		
	23		
	24		
Statistics	N	24	24
	MEAN	**5.11**	2.8
	MIN		
	MAX		
	SD	1.48	0.9
	CV	29	31

Table 2. Subjects with blurred vision during the study

Subj. No	Age/sex	Period	Treatment	Time after dosing	Duration	Intensity
1	55/M	I	TEL	1h10	2h50	Moderate
2	20/F	I	TEL	3h20	18h29	Moderate
5	21/M	II	TEL	1h18	4h27	Mild
6	19/M	I	TEL	5h	0h53	Mild
10	30/F	I	Placebo	3h	18h55	Mild
10	30/F	II	TEL	2h50	3h15	Moderate
13	34/M	II	TEL	3h06	1h14	Mild
15	40/F	I	TEL	3h07	2h43	Mild
17	54/F	I	TEL	3h05	2h25	Mild
18	22/M	I	TEL	1h25	20h20	Mild
21	47/F	I	TEL	2h	5h30	Moderate
23	27/F	II	TEL	2h55	3h55	Mild
24	41/F	II	TEL	2h35	2h40	Mild

Figure 1. The mean concentration time profile after single dose of 2400 mg telithromycin

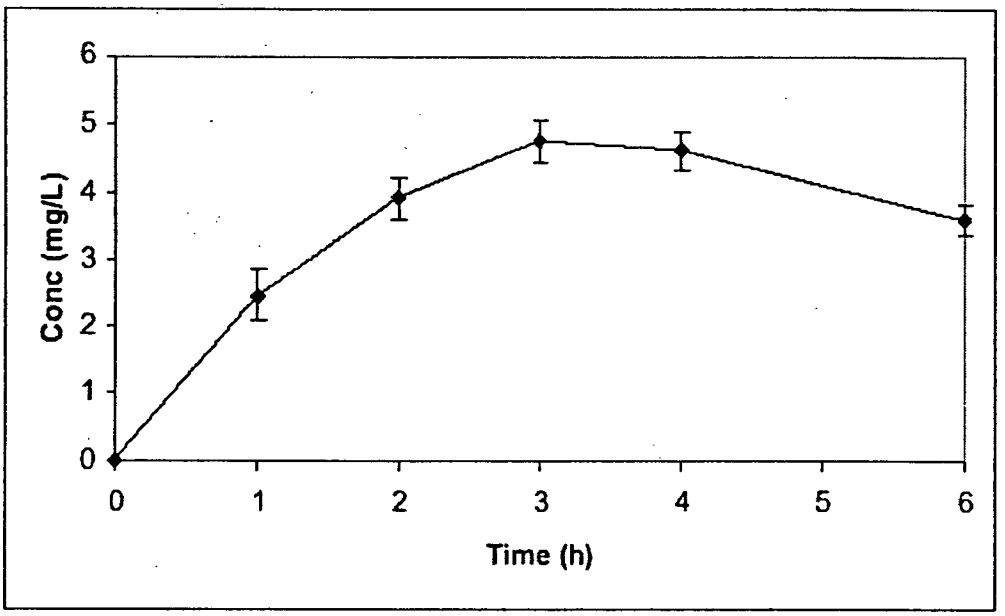


Figure 2. Correlation of QT and QTc on heart rate at baseline

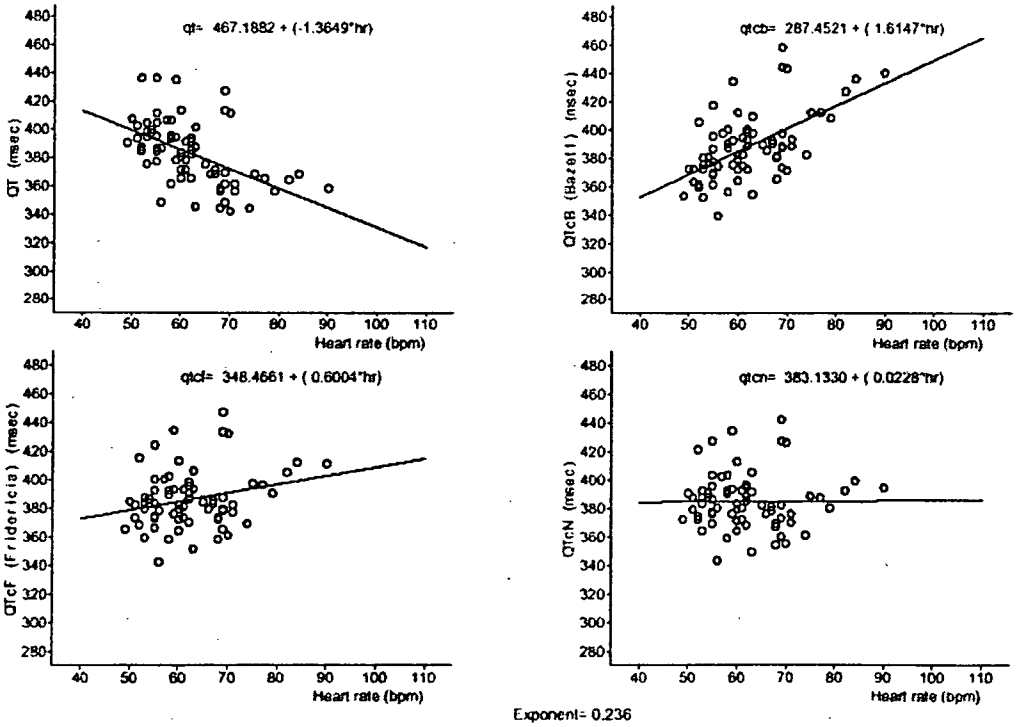
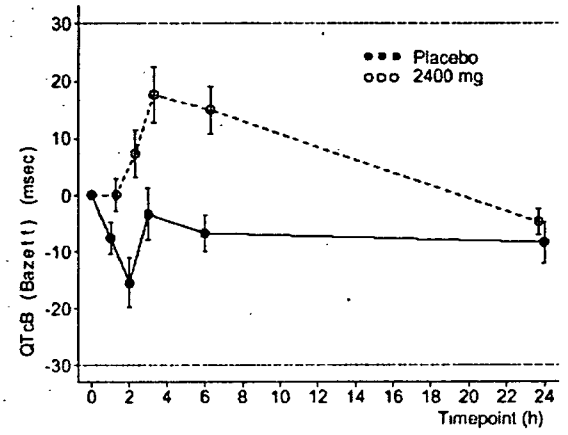
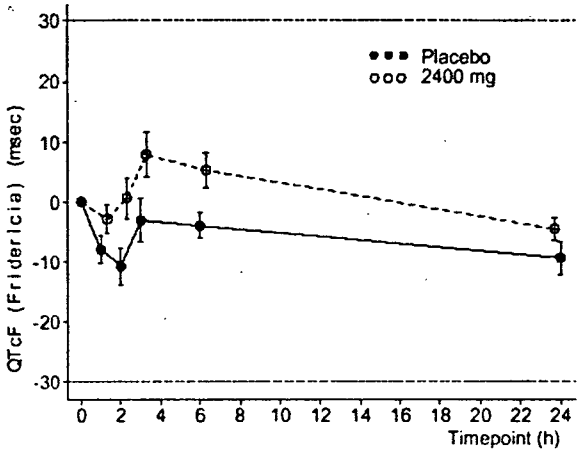
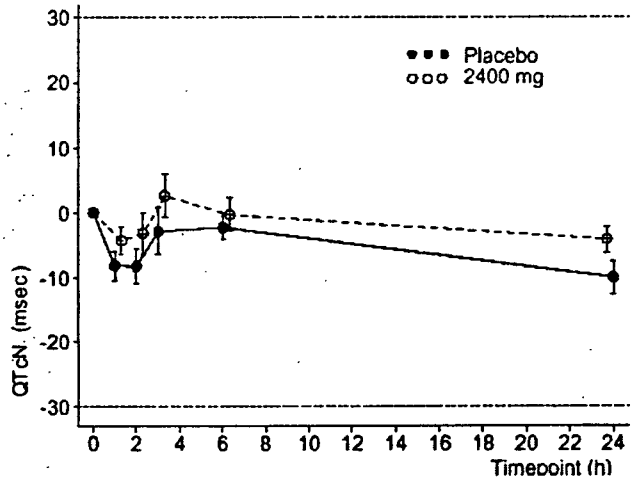


Figure 3. Plot of mean change in QTcB, QTc, and QTcN from baseline to Day 1 by treatment

QTcB: Corrected QT by Bazett formula (0.5)
QTcF: corrected QT by Fredericia formula (0.33)
QTcN: corrected QT by formulaa generated by this study (0.236)







APPENDIX C:

OCPB FILING FORM

APPEARS THIS WAY
ON ORIGINAL

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-144	Brand Name	Ketek
OCPB Division (I, II, III)	III	Generic Name	Telithromycin
Medical Division	HFD-520	Drug Class	Ketolides
OCPB Reviewer	Jenny J Zheng	Indication(s)	Community acquired pneumonia; acute bacterial exacerbation of chronic bronchitis and acute sinusitis
OCPB Team Leader	Phil Colangelo	Dosage Form	Tablet
		Dosing Regimen	800 mg QD
Date of Submission	July 24, 2002	Route of Administration	Oral
Estimated Due Date of OCPB Review	January 15, 2003	Sponsor	Aventis
PDUFA Due Date	January 24, 2003	Priority Classification	priority
Division Due Date			

II. CLIN. PHARM. AND BIOPHARM. INFORMATION

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	1	1	
In-vivo effects of primary drug:	x	1	1	
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	x	2	2	
hepatic impairment:	x	1		Reviewed in original NDA
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				

Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class	x	1	1	
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Phase 1 study for side effect (blurred vision)	x	2		
Total Number of Studies		8	7	

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	Dose the dosage regimen of telithromycin need to be adjusted in renal impairment? What are the effects of simultaneous CYP3A4 inhibition and renal impairment on the systemic exposure to telithromycin? Does hepatic function affect the systemic exposure to telithromycin? How does rifampin affect telithromycin systemic exposure? How does telithromycin affect metoprolol systemic exposure? What is the mechanism of blurred vision associated with telithromycin?	
Other comments or information not included above		
Primary reviewer Signature and Date	**Jenny J Zheng,**	
Secondary reviewer Signature and Date	**Phil Colangelo,**	

CC: NDA 21--144, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-520(CSO), HFD-880(P. Colangelo, J. Lazor, A. Selen), CDR

CLINICAL PHAMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA number:	21-144
Submission date:	February 28, 2000, 1S
Product:	Telithromycin (HMR 3647)
Dosage Form:	400 mg Tablet
Trade name:	KETEK
Sponsor:	Aventis Pharmaceuticals Inc. Kansas City, MO
Type of submission:	Original New Drug Application
Reviewer:	Jenny J Zheng, Ph.D.

1. INTRODUCTION

The sponsor submitted NDA 21-144 to seek approval of telithromycin (HMR 3647) as an oral tablet for treatment of community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, acute sinusitis and tonsillitis/pharyngitis. The proposed dose regimen is 800 mg QD for 5 or 7-10 days depending on the indication.

HMR 3647 is the first ketolide developed for treatment of infections. Ketolides belong to a new class of semisynthetic 14-membered ring antibacterial compounds within the macrolide family. Ketolides are characterized by a ketone function at position 3 on the macrolactone ring instead of the α L-cladinose moiety—a sugar long thought essential for antibacteriologic activity. The chemical structure is shown in **Figure 1**.

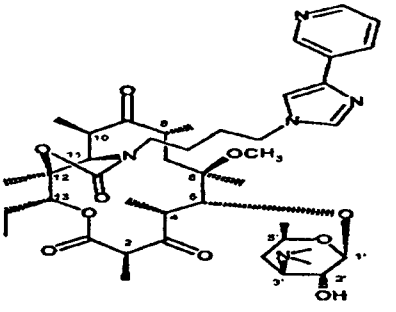


Figure 1.

2. EXECUTIVE SUMMARY:

Forty phase 1/2 studies were conducted to characterize the pharmacokinetics of HMR 3647. Among these 40 studies, 33 were submitted in original submission, 4 were submitted in 120-day safety update, and 3 submitted in the major amendment. Two population pharmacokinetic study was conducted in phase 3 trials. Three *in vitro* studies on protein binding, *in vitro* metabolism from section 5 were reviewed. Pharmacokinetics of HMR 3647 are briefly summarized in **Table 1** and the detailed information can be found in the synopsis (question based) and Appendix (summary of each study).

The sponsor has conducted adequate studies to understand pharmacokinetics of telithromycin but several issues need further discussion:

i. QT prolongation.
ii. Use of HMR 3647 in renal impaired patients.
iii. Use of HMR 3647 in elderly subjects.
iv. Use of HMR 3647 in hepatic impaired patients.

Table 1. Summary of pharmacokinetics of telithromycin

PK Assessments in Healthy Subjects	PK Parameters After 800 mg QD (Unless Noted) Expressed as Mean (CV)
Absorption and Systemic Bioavailability (Study 1044)	Tablet Absolute Bioavailability: Young: 57.3 (31); Elderly 56.6 (20) T_{max}: 2.5 –3 hours
Food Effects (Study 1003)	None
Distribution	Protein Binding: 60% – 70% Bound V_{ss} (L): Young subjects:210 (27); elderly subjects: 226 (21) Penetration into tissues: Blister fluid/tonsil secretion/pulmonary tissue/saliva
Metabolism (Study 1009)	Mainly metabolized (22% and 12% unchanged in feces and urine) CYP3A substrate Four metabolites have been identified.
Excretion (Study 1009)	Urine: 12% recovered as unchanged telithromycin Feces: 22% recovered as unchanged telithromycin
Elimination Kinetics (Study 1008)	Single dose: C_{max} (mg/L)= 1.90 (42); range:0.964-3.252 $AUC_{0-\infty}$(mg*h/L)= 8.25 (31) $t_{1/2}$ (h): 7.16 (19) CL/F (L/h): 102.3 (31) range: 53.5-184.8 CLr/F_{0-24}: (L/h): 12.32 (17) Multiple doses: C_{max} (mg/L)= 2.27(31); range:1.40-3.77 mg/L $AUC_{0-\infty}$(mg*h/L)= 12.5 (43); range: 7.08-31.53 $t_{1/2}$ (h): 9.81 (20) CL/F (L/h): 71.1 (29) range: 25.4-85.2 CLr/F: (L/h): 12.5 (34)
Disposition Kinetics	Nonlinear pharmacokinetics Slightly more than dose proportional Increases in AUC and C_{max} after 400 mg, 800 mg and 1600 mg. Accumulation was about 1.5 after multiple doses.
Significant Interactions	CYP3A4 inhibitor: ↑ telithromycin by ketoconazole/intraconazole ↔ telithromycin by grapefruit juice CYP3A4 substrate: ↑ cisapride /↑ simvastatin/↑ midazolam CYP2D6 substrate: ↔paroxetine CYP1A2 substrate: ↑ theophylline CYP2C9 substrate: ↔ warfarin Others: ↑ digoxin / ↔ oral contraceptive (ethinylestradiol)/ ↓ sotalol Gastric pH: telithromycin not changed by ranitidine and Maalox
Renal impairment	AUC and C_{max} not significantly changed after single dose.
Hepatic Impairment	AUC and C_{max} are comparable but $t_{1/2}$ ↑ significantly. No dose adjustment recommended by the sponsor.
Effects of Age on PK	AUC and C_{max} increased by 100% after repeat dose but no dose adjustment recommended by the sponsor.
Effects of Gender on PK	None

Issue 1. QT prolongation

Phase 1 studies showed that telithromycin caused QT prolongation which may not be clinically significant after 800 mg oral dose. However, the QT prolongation effect needs to be evaluated in the context of concentration variation of telithromycin. It was shown that HMR 3647 concentration is variable and the concentrations are affected by age, renal function and coadministration of P450 3A inhibitor. If these factors are combined, QT prolongation might become problematic. Risk can not be excluded although it might be minor.

Five phase 1 studies were conducted to specifically investigate the QT prolongation of HMR 3647. The findings are the following:

1. Delta QTc, which is the change of the QT interval corrected by Bazett's formula from the baseline, was dose dependent. Although no statistical difference in delta QTc was found between placebo and 800 mg HMR 3647, the difference was statically significant between placebo and 1600 mg HMR 3647 (Study 1049).
2. Delta QTc was associated with HMR 3647 concentrations. The results of regression analysis from Study 1030, 1046, 1049 and a population analysis which conducted on pooled data from 7 phase 1 studies (Study 1030, 1031, 1032, 1037, 1041, 1045, 1046) are shown in **Table 2A and Figure 2**. Delta QTc values can be predicted at concentrations of 2 mg/L, 4 mg/L and 6 mg/L using the results of regression analysis in each study. The data show that mean delta QTc is less than 10 ms when the concentration is 2 mg/L and increased in the range of 10 ms to 16 ms at 4 mg/L and in the range of 17 ms to 22 ms at 6 mg/L.
3. Delta QTf, which is the change of QT interval corrected by Fridericia formula from baseline, was associated with HMR 3647 concentrations (**Figure 3**). The regression analysis was also shown in **Table 2B**. Delta QTf values can be predicted at concentrations of 2 mg/L, 4 mg/L and 6 mg/L using the results of regression analysis in each study. The data show that mean delta QTf is about 1-2 ms when the concentration is 2 mg/L and increased to about 4 ms at 4 mg/L and 8 ms at 6 mg/L.
4. HMR 3647 has a similar QT prolongation effect to cisapride. Coadministration of HMR 3647 with cisapride will increase QT prolongation (**Figure 4 and 5**).
5. It was found that HMR 3647 increased the heart rate in two studies (Study 1030 and 1046) but not in Study 1049. The population analysis showed the maximal heart rate increase was about 14 bpm (**Figure 6**) but only 7 bpm at 2 mg.L which is the mean maximal plasma concentration after single dose of 800 mg telithromycin.
6. It was shown that coadministration of ketoconazole, a CYP3A inhibitor, with HMR 3647 significantly increased delta QTc (**Table 3**).
7. Loess function is applied on pooled placebo and baseline data (drug free), it is shown in **Figure 7** that QT interval corrected by Bazett formula was somewhat over estimated. QTf may be more appropriate for telithromycin because it was shown that heart rate was increased by telithromycin.

Since the regression analysis showed that delta QTc is associated with plasma concentration, it is important to understand the variability of pharmacokinetics of HMR 3647 and the factors which affect HMR 3647 concentrations.

1. The mean C_{max} was 1.99 mg/L after single oral dose of 800 mg HMR 3647 among 232 subjects out of 11 phase 1 studies (Study 1003, 1006, 1004, 1044, 1008, 1009, 1005, 1015, 1016, 1031, 1014). The maximal C_{max}, observed in renal impaired study, was — ng/L.
2. The mean C_{max} after multiples oral doses of 800 mg telithromycin was 2.07 mg/L (n=41, range: — mg/L) in young subjects but 3.6 mg/L (n=14, range: — mg/L) in elderly. The maximal C_{max}, observed in elderly, was 6.66 mg/L.
3. It was observed from the phase 3 study that the HMR 3647 concentration could be as high as — mg/L (Study 1051) and —mg/L (Study 1052). Using the equations obtained from phase

l studies (**Table 2A and 2B**), the predicted mean delta QTc is in the range of 36 ms to 49 ms at . The predicted delta QTf is about 11 ms and 16 ms at respectively. It needs to be pointed out that the prediction was made using regression analysis in healthy subjects instead of infected patients.

4. The results from study 1005 showed that the C_{max} and AUC in elderly increased approximately 2-fold when compared to young subjects after multiple doses of 800 mg HMR 3647.
5. HMR 3647 is a CYP 3A substrate. Ketoconazole, a potent CYP 3A inhibitor, increased the mean C_{max} and AUC of HMR 3647 after multiple doses by 52% and 95%, respectively.
6. It was shown that in Study 1016 that 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) and by 44% and 59%, respectively, in subjects with severe renal impairment (CLcr were between 10-39 mL/min). However, pharmacokinetic of telithromycin after multiple dose has not been studied.
7. It was shown in study 1015 that C_{max} and AUC were similar between healthy subjects and hepatic impaired patients after a single oral dose of 800 mg HMR 3647. However, $t_{1/2}$ was significantly increased from about 10 hours to 14 hours in hepatic impaired patients, indicating potential accumulation after multiple doses. The study also showed that renal function was increased to compensate for impaired hepatic function so similar C_{max} and AUC were observed in healthy subjects and hepatic impaired patients. It could be problematic for hepatic impaired patients with decreased renal 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.

Figure 2. Regression analysis of delta QTc vs Concentration by liner and linear mix effect model Data are from 7 phase I studies (1030,1031,1032,1037,1041,1045,1046)

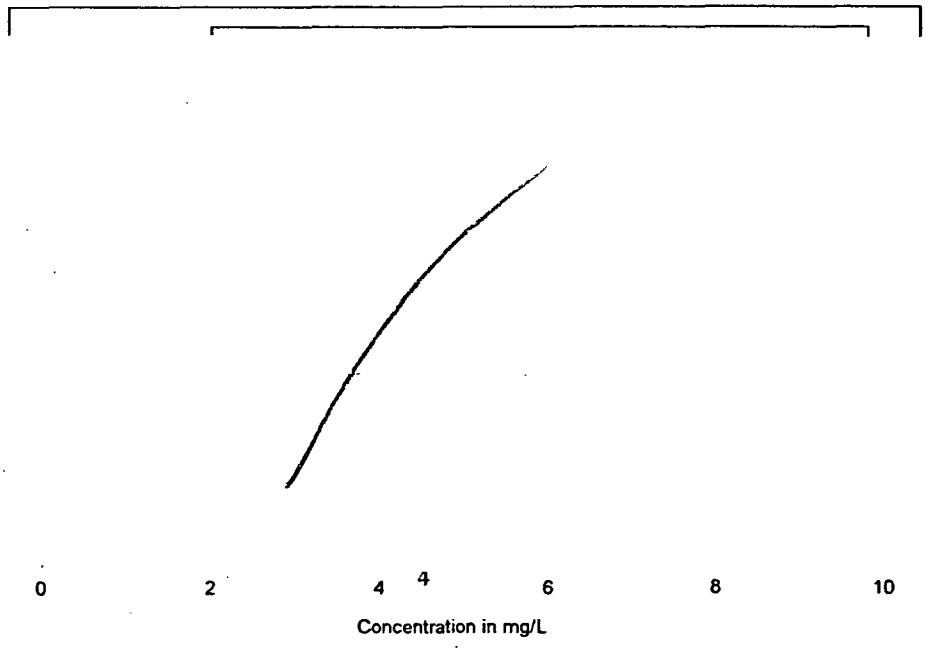
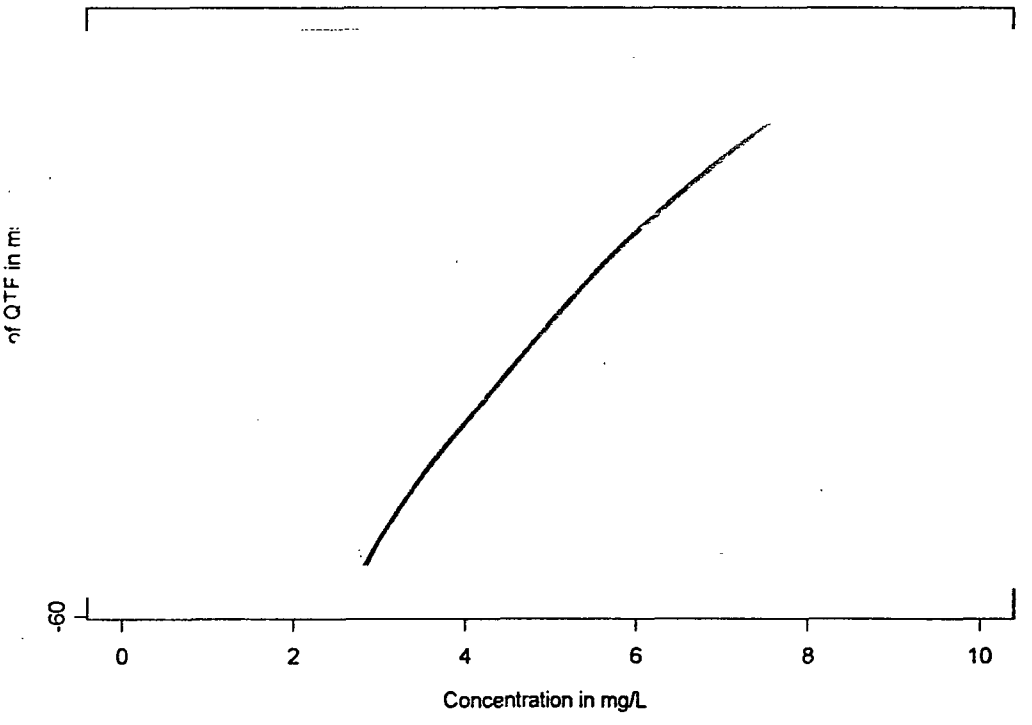


Figure 3. Regression analysis of delta QTf vs Concentration by liner and linear mix effect model Data are from 7 phase I studies (1030,1031,1032,1037,1041,1045,1046)



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