CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-144

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHAMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA number:	21-144
Submission date:	10-17-2003
Generic name:	Telithromycin
Dosage Form:	400 mg Tablet
Trade name:	KETEK
Sponsor:	Aventis Pharmaceuticals Inc. Kansas City, MO
Type of submission:	Amendment to pending application
OCPB Division:	DPEIII (HFD-880)
Clinical Division:	Anti-infective Drug Product (HFD-520)
Reviewer:	Jenny J Zheng, Ph.D.

I. EXECUTIVE SUMMARY:

This application is the complete response to the approvable letter issued on January 24, 2003. Pertaining to the clinical pharmacology, the FDA requested the sponsor to submit the final study reports for the two following studies:

1. Study 1065: An open, randomized, cross-over study investigating the effect of dosing interval on the pharmacokinetic interaction of telithromycin on simvastatin in healthy male subjects.
2. Study 1067: An open study investigating the pharmacokinetic interaction of clarithromycin on simvastatin in healthy male subjects.

The results from the studies indicated that telithromycin is a strong CYP3A4 inhibitor. Simvastatin Cmax and AUC were significantly increased when simvastatin was co-administered with telithromycin. The effect of telithromycin on increasing simvastatin was reduced if the two drugs were taken 12 hours apart, as compared with when the two drugs were co-administered, but the effect was still significant. The inhibition effect of telithromycin on CYP3A4 was similar to clarithromycin.

The summaries of drug interaction between telithromycin or clarithromycin and simvastatin are shown in the following table:

Study	Design		PK	Ratio of with the drug to without the drug	
				Simvastatin	Simvastatin acid
1048	Open, double blinded, and randomized cross over trial; The effect of steady state telithromycin at 800 mg qd on single dose of 40 mg simvastatin.	Co-administration	Cmax	5.3	15
			AUC	8.9	12
1065	Open, randomized cross over trial; The effect of steady state of telithromycin at 800 mg qd on single dose of simvastatin by taking both drugs together or by 12 hours apart	Co-administration	Cmax	7.7	10
			AUC	8.5	9.4
		Administered by 12 hours apart	Cmax	3.4	3.2
			AUC	3.8	4.3
1067	Open, non randomized trial; The effect of steady state of clarithromycin at 500 mg bid on single dose of simvastatin (40 mg)	Co-administration	Cmax	8.2	14.3
			AUC	7.9	13.9

The following language with regard to the inhibition effect of telithromycin on CYP 3A4 is included in the label:

Telithromycin is a strong inhibitor of the cytochrome P450 3A4 system. Co-administration of KETEK tablets and a drug primarily metabolized by the cytochrome P450 3A4 enzyme system may result in increased plasma concentration of the drug co-administered with telithromycin that could increase or prolong both the therapeutic and adverse effects. Therefore, appropriate dosage adjustments may be necessary for the drug co-administered with telithromycin.

*In a pharmacokinetic study, simvastatin levels were increased due to CYP 3A4 inhibition by telithromycin. (See **CLINICAL PHARMACOLOGY, Other drug interactions.**) Similarly, an interaction may occur with lovastatin or atorvastatin, but not with pravastatin or fluvastatin. High levels of HMG-CoA reductase inhibitors increase the risk of myopathy. Use of simvastatin, lovastatin, or atorvastatin concomitantly with KETEK should be avoided. If KETEK is prescribed, therapy with simvastatin, lovastatin, or atorvastatin should be suspended during the course of treatment.*

Dose adjustment in severe renal impaired subjects is another issue for this application. It was found from the previous study that the AUC(0-24) was increased by approximately 100% following administration of 800 mg telithromycin for 5 days to subjects with severe renal impairment (CLcr <30 mL/min) as compared with the AUC(0-24) in subjects with normal renal function (CLcr>80 mL/min), which may warrant a dose adjustment in severe renal impaired subjects. The pharmacokinetic data suggested that, at 600 mg QD, a comparable exposure could be achieved in severe renal impaired subjects as compared with exposure in subjects with normal renal function at 800 mg QD. Based on these data, a dose of 600 mg QD should be recommended for severe renal impaired subjects. However, since only 400 mg tablet is available currently, prescribing 600 mg QD is not feasible. The sponsor proposed to give 400 mg QD in severe renal impaired subjects. This regimen was found not acceptable due to the very low exposure in some individuals. Simulations were conducted to explore other regimens such as 1) 800 mg q48h; 2) 800 mg QD for two days and followed by 800 mg q48h; and 3) alternating 800 mg and 400 mg (QOD). The simulation results showed that neither of the first two simulated regimens is acceptable because the exposures are low in the days when dose is not given in severe renal impaired subject due to the q48h regimen. The third regimen is acceptable from exposure perspective. However, it appears that the regimen is complicated, especially, in patients who need dialysis. A previous study showed that the patients who need dialysis should take 800 mg dose 2 hours after dialysis on dialysis day. Therefore, patient who needs hemodialysis should take an 800 mg dose after dialysis on the dialysis day and follow the alternating regimen on non-dialysis day. This type of dosing regimen for dialysis patients is complicated to follow

At present, the label stated that no dose has been established in this population.

RECOMMENDATION:

This application was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Drug Evaluation III and was found to be acceptable from the clinical pharmacology perspective. The labeling comments should be conveyed to the sponsor.

PHASE IV COMMITMENTS:

None.

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

RD/FT initiated by Venkat Jarugula, Ph.D., Team Leader _____

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III. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS:

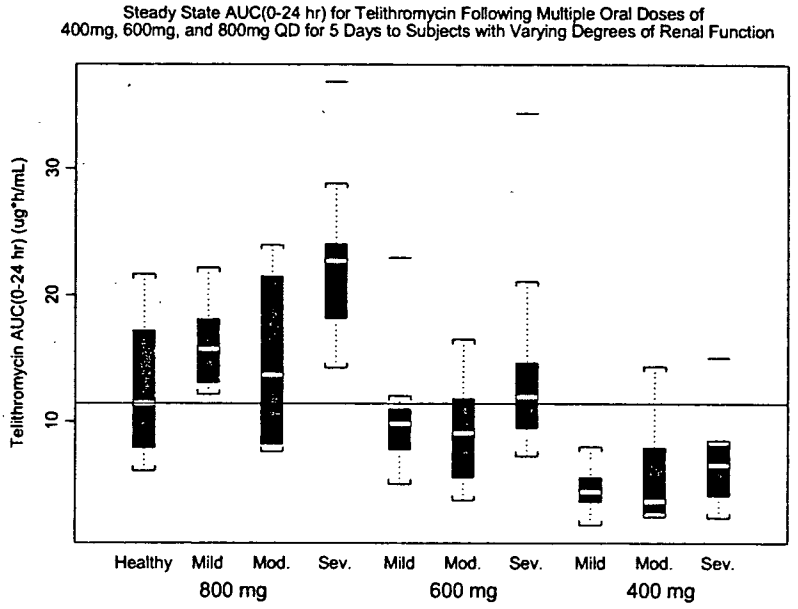
In the original application submitted on Feb 28, 2000, a drug interaction study showed that telithromycin at the clinical dose of 800 mg QD increased simvastatin maximal concentration (C_{max}) and the area under plasma concentration curve ($AUC_{0-\infty}$) by 5 and 9 folds, respectively, and more significantly increased simvastatin acid, the active metabolite of simvastatin, C_{max} and $AUC_{0-\infty}$ by 15 and 12 folds, respectively. The study indicated that telithromycin is a strong P450 3A4 inhibitor.

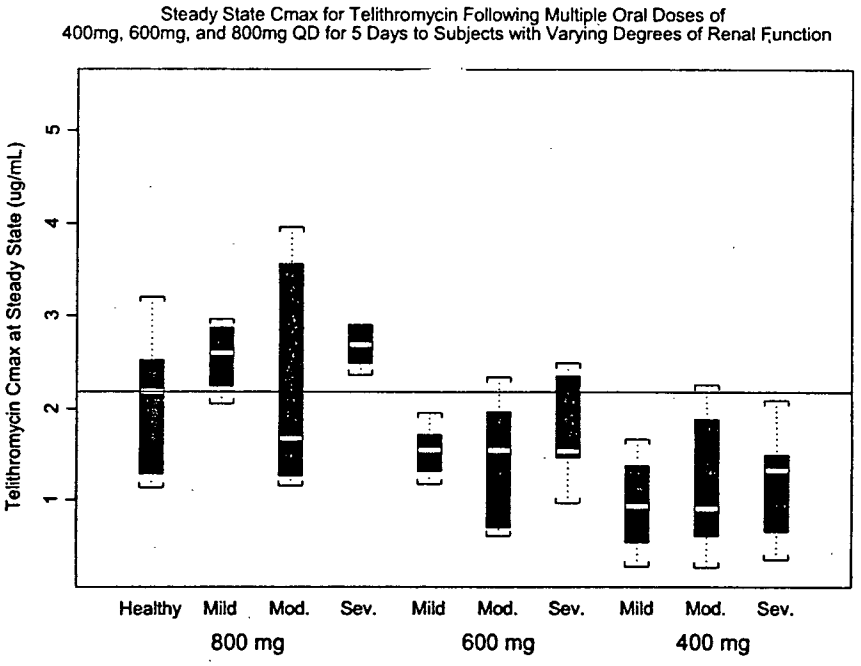
DRUG INTERACTION WITH SIMVASTATIN:
A study was conducted to evaluate if the effect of telithromycin on simvastatin/simvastatin acid could be reduced if telithromycin and simvastatin are given 12 hours apart. Giving the two drugs 12 apart is feasible in practice since the regimens for both drugs are once daily. The study results showed that by taking simvastatin and telithromycin 12 hours apart the effect on increasing simvastatin and simvastatin acid was reduced. However, the simvastatin and simvastatin acid were still significantly higher as compared with when simvastatin was given alone. Both C_{max} and $AUC_{0-\infty}$ values of simvastatin were increased by 3-folds when simvastatin and telithromycin were given 12 hours apart as compared to when simvastatin was given alone. The C_{max} and $AUC_{0-\infty}$ of simvastatin acid were increased by 4 folds when simvastatin and telithromycin were given 12 hours apart as compared to when simvastatin was given alone.

Clarithromycin, a macrolide, is also a CYP3A4 strong inhibitor. The concomitant administration of macrolide antibiotics and other hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have resulted in previous reports of rhabdomyolysis. However, to date, there are no in vivo pharmacokinetic data which assess the magnitude of the interaction between clarithromycin and simvastatin. The sponsor conducted a study to evaluate the effect of clarithromycin on simvastatin. The study showed that the effect of clarithromycin on simvastatin is similar to telithromycin. When co-administered with clarithromycin (at the dose of 500 mg bid), there was a 8-fold increase in simvastatin Cmax, and AUC, a 14-fold increase in simvastatin acid Cmax and AUC.

DOSE ADJUSTMENT IN SEVERE RENAL IMPAIRED PATIENTS:
The AUC(0-24) was increased by approximately 100% following administration of 800 mg telithromycin for 5 days to subjects with severe renal impairment (CLcr <30 mL/min) as compared with the AUC(0-24) in subjects with normal renal function (CLcr>80 mL/min). The pharmacokinetic data suggested that, at 600 mg QD, a comparable exposure could be achieved in severe renal impaired subjects as compared with exposure at 800 mg QD in normal renal subjects (Figure 1). However, only 400 mg tablet was developed for telithromycin and no appropriate dose strength is available for 600mg QD regimen. Therefore, a reduced dose of 400 mg QD was proposed by the sponsor for severe renal impaired subjects. Following administration of 400 mg QD for 5 days to subjects with severe renal impairment, the mean AUC(0-24) was 6.9 mg·hr /L which corresponded to 44% decrease in mean AUC(0-24) as compared with the values in normal renal function subjects after repeated doses of 800 mg telithromycin. The AUC at steady state at 400 mg QD in severe renal impaired patients ranged from 2.445 to 15.050 mg·hr/L.

Figure 1. The steady state AUC(0-24 hr) and Cmax for the various renal function groups at the dose levels of 400mg, 600mg, and 800 mg





Legend for "Box and Whisker" Plots:

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
Mod. = Moderate Renal Impairment; Sev. = Severe Renal Impairment

To justify the reduced exposure in severe renal impaired patients at 400 mg QD, the sponsor submitted a pharmacokinetic\pharmacodynamic (PK/PD) analysis. In the PK/PD analysis, 5 community-acquired pneumonia (CAP) studies in which the plasma samples were collected were pooled. In this analysis, forty-two of the 224 (18.8%) subjects had AUC values (mean 6.89, minimum 5.16, and maximum 8.60 mg*h/L) within AUC range observed with 400 mg in severe renal impaired subjects. Of these 42 subjects, 36 (86%) achieved clinical success and 37 (88%) achieved bacteriologic success. The bacteriologic cure rate was about 85% (154 out of 182) in the subjects with AUC>8.6 mg·h/L. It appeared that the efficacy of telithromycin observed at lower AUC values (ie, in this AUC range) was similar to that observed in subjects with higher AUC values.

An examination on the individual exposure in the patients with severe renal impairment after receiving 400 mg QD for 5 days indicated that 3 out of 8 patients (38%) had exposures less than 5.16 mg·hr/L, the observed minimal exposure in the pooled PK/PD analysis. The efficacy in those patients who had lower exposures than the minimal exposure in PK/PD analysis was of concern and could not be supported by the PK/PD analysis. Therefore, the regimen of 400 mg QD in severe renal impaired subjects was found not acceptable.

In order to find an appropriate regimen for severe renal impaired patients, simulation was considered. The goal of the simulation is to find a regimen which could provide comparable exposure as compared with the exposures in subjects with normal renal function who received 800 mg QD considering the fact that only 400 mg strength is available currently. The sponsor was asked to simulate three regimens for severe renal impaired patients: 1) 800 mg q48h; 2) 800 mg QD for two days and followed by 800 mg q48h; and 3) alternating 800 mg and 400 mg. The rationales of proposing 800 mg dose regimens are as follows: 1) 800 mg telithromycin would provide higher concentration than 400 mg. Since the pharmacokinetic of the drug is non-linear, the elimination rate at the higher concentration would be slower than at lower concentration. It is expected that the effect of two factors, higher concentration and slower elimination rate, maybe able to provide a better profile as compared with the one by 400 mg QD regimen; 2) the animal study showed that telithromycin is a concentration dependent drug, indicating that the higher the concentration is, the better the bacterial killing might be; 3) higher concentration would result in better post-antibiotic effect.

The simulation results showed that the first two regimens are not acceptable because the exposure is low in severe renal impaired subjects at the days when no dose is given due to the q48h regimen. Alternating regimen (800 mg and 400 mg) is acceptable from exposure perspective.

25 Draft Labeling Page(s) Withheld

VI. APPENDICES:

A. Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

APPENDIX :

INDIVIDUAL STUDY REVIEWS

STUDY NUMBER: 1065

TITLE: An open, randomized, cross-over study investigating the effect of dosing interval on the pharmacokinetic interaction of telithromycin on simvastatin in healthy male subjects.

OBJECTIVES:
To assess the effect of a 12-hour dosing interval on the pharmacokinetic interaction of telithromycin on simvastatin in healthy male subjects.

DESIGN:
This was an open, randomized, cross-over, single center study. Fourteen (14) healthy male subjects aged between 18 and 45 years were planned to be included.
Each subject received one single oral dose (40 mg) of simvastatin on two occasions (Day 1 and Day 5 or 6) and multiple oral doses of telithromycin (800 mg once daily for 5 days) from Day 2 to 6:

Treatment 1:

- Day 1: simvastatin 40 mg in the morning
- Day 2 to Day 4: telithromycin 800 mg once daily in the morning
- Day 5: simvastatin 40 mg concomitantly with telithromycin 800 mg in the morning
- Day 6: telithromycin 800 mg once daily in the morning

Treatment 2:

- Day 1: simvastatin 40 mg in the morning
- Day 2 to Day 5: telithromycin 800 mg once daily in the evening,
- Day 6: simvastatin 40 mg in the morning and telithromycin 800 mg in the evening, 12 hours after administration of simvastatin

Each treatment was separated by at least a one-week wash-out period.

FORMULATION:
Simvastatin: 20 mg tablet (Zocor®, batch no. 220172);
Telithromycin: 400 mg tablet (HMR3647, batch no. 1029668)

SAMPLING:
Simvastatin blood samples were colleced for assay of simvastatin and its active metabolite (simvastatin hydroxyacid) on Days 1 and 5 for treatment 1 and Days 1 and 6 for treatment 2 (profile days) at the following sampling times : pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16 and 24 hours post administration.
Blood samples were collected for assay of telithromycin at pre-dose and 3 h post-dose on days 4, 5 and 6 for each treatment.

ASSAY:
Telithomycin was measured by validated LC/MS method and simvastatin was measured by validated LC-MS-MS method.
The accuracy and precision of the assays for telithromycin and simvastatin were shown in as the followings:

Analyte	Samples	Accuracy[a]	Precision[b]
Telithromycin	QC samples	90.8-95.4%	6.9-24.0%
	Calibration standards	97.9-104.0%	1.3-13.3%
Simvastatin	QC samples	103.5-105.3%	4.67-5.88

Simvastatin acid	Calibration standards (0.05-1 mg/L)	99.2-101.5%	2.76-4.51%
	QC samples (0.05,0.1,0.25,1 mg/L)	96.3-98.0%	5.32-5.76%
	Calibration standards (0.05-1 mg/L)	98.0-102%	2.88-4.57%

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

DATA ANALYSIS:

Pharmacokinetics:

The pharmacokinetic parameters including C_{max}, t_{max}, AUC (0-z). AUC (0-infinity), $t_{1/2}$ were determined using a non compartmental analysis on days 1 and day 5 or 6 for simvastatin and simvastatin acid.

Plasma concentrations of telithromycin observed at pre-dose and 3 hours post-dose on Days 4, 5 and 6 were compared to those obtained in previous studies.

RESULTS:

Telithromycin: The pre-dose concentration and the concentration at 3 hours after the dose of telithromycin at day 4, 5, and 6 in both treatments are summarized in Table 1. The results showed that telithromycin concentrations reached steady state at day 4 and the administration time of simvastatin did not affect the telithromycin concentrations.

Simvastatin and simvastatin acid: The pharmacokinetic parameters of simvastatin and its metabolite, simvastatin acid, and the statistical analysis on the parameters are presented in Table 2-5. These results showed that when simvastatin was taken concomitantly with telithromycin, the mean peak serum concentration (Cmax) and the mean area under the serum concentration-time curve (AUC(0-z)) of simvastatin were increased 7.7-fold and 8.5-fold, respectively, compared with control. The mean peak serum concentration (Cmax) and the mean area under the serum concentration-time curve (AUC (0-z)) of simvastatin acid were increased 10.0-fold and 9.4-fold, respectively, compared with control.

When simvastatin was administered 12 hours after administration of the last dose of telithromycin, the Cmax and AUC (0-z) were increased 3.4-fold and 4.0-fold, respectively, compared with control. The mean peak serum concentration (Cmax) and the mean area under the serum concentration-time curve (AUC (0-z)) of simvastatin acid were increased 3.2-fold and 4.3-fold, respectively, compared with control. The interaction results are summarized in the following table:

		Study 1048 Concomitantly	Study 1065 concomitantly	Study 1065 12 hr apart
Simvastatin	Cmax	5.3-fold	7.7-fold	3.4-fold
40 mg	AUC(0-z)	8.9-fold	8.5-fold	4.0-fold
Simvastatin acid	Cmax	15-fold	10.0-fold	3.2-fold
	AUC(0-z)	12-fold	9.4-fold	4.3-fold

CONCLUSIONS:

- When simvastatin and telithromycin was co-administered, the mean Cmax and AUC of simvastatin was increased by 5.3 and 8.9 fold, respectively, in Study 1048 and by 7.7 and 8.5 fold in Study 1065. The mean Cmax and AUC of simvastatin acid was increased by 15 and 12 fold, respectively, in Study 1048 and by 10.0 and 9.4 fold in Study 1065.
- With a 12-hour interval between simvastatin and telithromycin administration, the extent of bioavailability of simvastatin and simvastatin acid increases by a factor of 4 and 4.3, respectively.

- By taking simvastatin and telithromycin in 12 hours apart, the extents of increase in simvastatin and simvastatin acid were reduced but they are still quite significant.

Table 1. Mean (CV%) plasma concentration (ng/μL) of telithromycin at day 4, 5, and 6

Treatment	Day 4		Day 5		Day 6	
	C0h	C3h	C0h	C3h	C0h	C3h
Treatment 1	67.0 (70)	1670 (40)	69.2 (65)	1851 (30)	116 (109)	1684 (30)
Treatment 2	49.5 (62)	1555 (32)	56.2 (47)	1642 (35)	77.0 (46)	1792 (35)

Table 2. Mean (CV%) pharmacokinetic parameters of simvastatin when it was given alone, concomitantly with telithromycin, with telithromycin 12 hours apart

Treatment – Day	Cmax (ng/mL)	Tmax# (h)	AUC(0-z) (h.ng/mL)	AUC (h.ng/mL)	t1/2λz (h)
Simvastatin alone Treatment 1, Day 1	7.58 (48)	1.5	39.9 (67)	39.4 (71)	4.07 (54)
Simvastatin + HMR3647 Treatment 1, Day 5 (concomitant adm.)	60.1 (52)	2.75	307 (50)	317 (50)	4.99 (25)
Simvastatin alone Treatment 2, Day 1	7.56 (51)	1.5	28.8 (67)	33.7 (64)	6.70 (62)
Simvastatin + HMR3647 Treatment 2, Day 6 (12-hr dosing interval)	24.8 (50)	1.5	113 (66)	128 (62)	7.22 (57)

Table 3. Statistic analysis on simvastatin pharmacokinetic parameters between treatments

Treatment – Day	Cmax	AUC(0-z)	AUC
Treatment2/treatment1 – Day 1			
Simvastatin alone/simvastatin alone			
Mean ratio*	0.966	0.742	0.826
(90% CI)**	(0.785; 1.19)	(0.578; 0.953)	(0.578; 1.18)
p-value	0.7786	0.0514	0.3701
Treatment2/treatment1 – Day 5 or 6			
Simva+HMR (12-hr apart)/Simva+HMR (concomitant)			
Mean ratio*	0.427	0.347	0.374
(90% CI)**	(0.348; 0.526)	(0.270; 0.446)	(0.279; 0.502)
p-value	0.0001	0.0001	0.0001
Day 5/Day 1 – Treatment1			
Simva+HMR (concomitant)/simvastatin alone			
Mean ratio*	7.72	8.51	8.35
(90% CI)**	(6.27; 9.49)	(6.62; 10.93)	(5.89; 11.85)
p-value	0.0001	0.0001	0.0001
Day 6/Day 1 – Treatment2			
Simva+HMR (12-hr apart)/simvastatin alone			
Mean ratio*	3.41	3.98	3.79
(90% CI)**	(2.78; 4.20)	(3.10; 5.12)	(2.79; 5.14)
p-value	0.0001	0.0001	0.0001

* : Point estimate of "Treatment 2/Treatment 1, Day 1; Treatment 2/Treatment 1, Day 5 or 6; Day 5/Day 1, Treatment 1; Day 6/Day 1, Treatment 2" mean ratio of log-transformed data.

** : 90% Conventional confidence interval for the mean ratio of log-transformed data.

Table 4. Pharmacokinetic parameters of simvastatin acid when it was given alone, concomitantly with telithromycin, with telithromycin 12 hours apart

Treatment – Day	Cmax (ng/mL)	Tmax# (h)	AUC(0-z) (h.ng/mL)	AUC (h.ng/mL)	$T_{1/2\lambda z}$ (h)
Simvastatin alone, mean (CV) Treatment 1, Day 1	2.46 (80)	5.0	24.3 (103)	-	-
Simvastatin + HMR3647, mean (CV) Treatment 1, Day 5, min-max (concomitant adm.)	25.0 (83)	4.0	192 (79)	209 (81)	5.54 (32)
Simvastatin alone, mean (CV) Treatment 2, Day 1, min-max	1.65 (58)	5.0	15.0 (74)	-	-
Simvastatin + HMR3647 mean (CV) min-max Treatment 2, Day 6 (12-hr dosing interval)	5.46 (65)	5.0	55.0 (61)	71.0 (54)	5.93 (27)

- : not calculated (due to very low concentrations compared to the limit of quantification of the method (0.25 ng/mL) AUC and t1/2λz could not be estimated accurately)

Table 5. Statistic analysis on simvastatin acid pharmacokinetic parameters between treatments

Treatment – Day	Cmax	AUC(0-z)	AUC
Treatment2/treatment1 – Day 1 Simvastatin alone/simvastatin alone			
Mean ratio*	0.751	0.676	-
(90% CI)**	(0.620; 0.910)	(0.533; 0.859)	-
p-value	0.0162	0.0089	-
Treatment2/treatment1 – Day 5 or 6 Simva+HMR (12-hr apart)/Simva+HMR (concomitant)			
Mean ratio*	0.237	0.306	0.316
(90% CI)**	(0.196; 0.288)	(0.241; 0.388)	(0.251; 0.398)
p-value	0.0001	0.0001	0.0001
Day 5/Day 1 – Treatment1 Simva+HMR (concomitant)/simvastatin alone			
Mean ratio*	9.99	9.40	-
(90% CI)**	(8.25; 12.10)	(7.40; 11.94)	-
p-value	0.0001	0.0001	-
Day 6/Day 1 – Treatment2 Simva+HMR (12-hr apart)/simvastatin alone			
Mean ratio*	3.16	4.25	-
(90% CI)**	(2.61; 3.83)	(3.34; 5.39)	-
p-value	0.0001	0.0001	-

* : Point estimate of "Treatment 2/Treatment 1, Day 1; Treatment 2/Treatment 1, Day 5 or 6; Day 5/Day 1, Treatment 1; Day 6/Day 1, Treatment 2" mean ratio of log-transformed data.
** : 90% Conventional confidence interval for the mean ratio of log-transformed data.
# : Medians, ranges
- : not calculated

TUDY NUMBER: 1067

TITLE: An open study investigating the pharmacokinetic interaction of clarithromycin on simvastatin in healthy male subjects.

OBJECTIVES:
To assess the effect of clarithromycin on the pharmacokinetics of simvastatin in healthy male subjects.

DESIGN:
This was an open, non randomized, repeated dose, single center study.
Twelve (12) healthy male subjects aged between 18 and 45 years received one single oral dose (40 mg) of simvastatin on two occasions at day 1 and day 8 and multiple oral doses of clarithromycin at 500 mg twice daily for 7 days from day 2 to day 8. The comparison of simvastatin levels between day 1 and day 8 reflected the effect of clarithromycin on simvastatin.

FORMULATION:
Simvastatin: 20 mg tablet (Zocor®, batch no. 220172);
Clarithromycin: 500 mg tablet (Zeclar, Batch no. 867175B23)

SAMPLING:
For simvastatin, the blood samples were collected on days 1 and 8 at the following sampling times: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16 and 24 hours post administration.
For clarithromycin, blood samples were collected at pre-dose, 3h and 12 h post-dose on days 6, 7, and 8.

ASSAY:
Clarithromycin, simvastatin and its metabolite were measured by validated LC/MS/MS method. The accuracy and precision of the assays for telithromycin and simvastatin were shown in as the followings:

Analyte	Samples	Accuracy[a]	Precision[b]
Clarithromycin	QC samples	87.9-100.0%	NSV
	Calibration standards	NSV	NSV
Simvastatin	QC samples	99.3-101.0%	5.41-6.73%
	Calibration standards	98.4-102.0%	3.49-5.77%
Simvastatin acid	QC samples	94.8-96.0%	4.66-6.15%
	Calibration standards	98.0-101%	2.62-4.29%

[a] Accuracy, expressed as % recovery, relative to theoretical concentration.
[b] Precision, expressed as % coefficient of variation.
NSV: no statistically valid

DATA ANALYSIS:
Pharmacokinetics:
The following pharmacokinetic parameters for simvastatin and its metabolite (Days 1 and 8): C_{max}, t_{max}, AUC(0-z), AUC and $t_{½\lambda z}$ were calculated by non-compartmental analysis.
Plasma concentration of clarithromycin observed at pre-dose, 3 and 12 hours post-dose were compared to those obtained in previous studies.

Statistics:

An analysis of variance with subject and day as main effects in the model was performed on the following natural log-transformed parameters: AUC, AUC(0-z), C_{max} and non transformed $t_{½}\lambda z$ values for simvastatin and simvastatin acid. Point estimates were calculated for each parameter as the geometric mean of the individual ratio of test Day (simvastatin + clarithromycin at day 8) relative to the reference Day (simvastatin alone at day 1).

As tmax is a discrete variable dependent on selected blood sampling times, Day effect was assessed using a Wilcoxon's test.

RESULTS:

Clarithromycin:
Plasma concentrations of clarithromycin are summarized in Table 1.
The results indicate that clarithromycin exposure was in agreement with published data and that steady-state levels were achieved.

Simvastatin and simvastatin acid:
Plasma simvastatin pharmacokinetic variables and the statistical analysis are summarized in Tables 2 and 3. The plasma simvastatin acid pharmacokinetic variables and the statistical analysis are summarized in Tables 4 and 5. The results showed that when co-administered with clarithromycin, the Cmax and AUC of simvastatin were increased by about 8.1-fold and 7.6-fold, respectively. Similarly to the effect of telithromycin, clarithromycin increased the Cmax and AUC of simvastatin acid by about 14-fold and 9.4-fold, respectively.

CONCLUSIONS:

A regimen of 500 mg bid of clarithromycin increases markedly simvastatin and simvastatin acid bioavailability (Cmax and AUC(0-z)) by about 8-fold and 14-fold, respectively, but does not change significantly their apparent elimination half-life.

Table 1. The mean (CV%) plasma concentration of Clarithromycin at Days 6, 7, and 8

	Day 6			Day 7			Day 8		
	C0h	C3h	C12h	C0h	C3h	C12h	C0h	C3h	C12h
Mean (ng/mL)	1156	2823	1125	1235	2950	1136	1160	2865	1122
CV (%)	22	25	32	33	29	31	27	20	23

Table 2. The Plasma Pharmacokinetics Parameters of Simvastatin

Treatment – Day	Cmax	Tmax#	AUC(0-z)	AUC	t½λz
	(ng/mL)	(h)	(h.ng/mL)	(h.ng/mL)	(h)
Simvastatin alone, mean (CV)	8.10 (66)	1.5	33.0 (55)	36.3 (49)*	5.35 (73)*
Day 1 [min-max]	[redacted]				
Simvastatin + clarithromycin, mean (CV)	57.7 (37)	1.75	230 (38)	244 (39)	6.61 (48)
Day 8 [min-max]	[redacted]				

Table 3. The Statistical Analysis of Plasma Pharmacokinetics Parameters of Simvastatin

Day 8 / Day 1	Cmax	AUC(0-z)	AUC***
Mean ratio*	8.18	7.90	7.55
(90% CI)**	(5.71 – 11.72)	(6.05 – 10.32)	(5.76 – 9.90)
p-value	<0.0001	<0.0001	<0.0001

*: Point estimate of "Day 8 / Day 1" mean ratio of log-transformed data.
**: 90% Conventional confidence interval for the mean ratio of log-transformed data.
***: mean ratio and confidence intervals were estimated with only 21 values.

Table 4. The Plasma Pharmacokinetics Parameters of Simvastatin Acid

Treatment – Day	Cmax	Tmax#	AUC(0-z)	AUC	t½λz
	(ng/mL)	(h)	(h.ng/mL)	(h.ng/mL)	(h)
Simvastatin alone, mean (CV)	1.47 (47)	5.0	12.0 (46)	15.7 (35)*	4.38 (44)*
Day 1 [min-max]	[redacted]				
Simvastatin + clarithromycin, mean (CV)	21.6 (55)	2.75	146 (44)	154 (42)	5.09 (28)
Day 8 [min-max]	[redacted]				

#: Medians, ranges
*: n=8 (Due to very low plasma concentrations of simvastatin acid, t½λz and AUC could not be estimated accurately in four subjects)

Table 5. The Statistical Analysis of Plasma Pharmacokinetics Parameters of Simvastatin Acid

Day 8 / Day 1	Cmax	AUC(0-z)	AUC***
Mean ratio*	14.26	13.85	9.44
(90% CI)**	(9.57 – 21.26)	(8.72 – 22.01)	(6.22 – 14.32)
p-value	<0.0001	<0.0001	<0.0001

*: Point estimate of "Day 8 / Day 1" mean ratio of log-transformed data.
**: 90% Conventional confidence interval for the mean ratio of log-transformed data.
***: mean ratio and confidence intervals were estimated with only 20 values.

EVALUATIONS OF SIMULATIONS FOR DOSE REGIMEN IN SEVERE RENAL IMPAIRED SUBJECTS:

It was found from the previous study that the AUC(0-24) was increased by approximately 100% following administration of 800 mg telithromycin for 5 days to subjects with severe renal impairment (CLcr <30 mL/min) as compared with the AUC(0-24) in subjects with normal renal function (CLcr>80 mL/min), which may warrant a dose adjustment in severe renal impaired subjects. The pharmacokinetic data suggested that, at 600 mg QD, a comparable exposure could be achieved in severe renal impaired subjects as compared with exposure in normal renal subjects at 800 mg QD. Based on these data, a dose of 600 mg QD is recommended for severe renal impaired subjects. However, since only 400 mg tablet is available currently, the 600 mg QD is not feasible in practice. The sponsor proposed to give 400 mg QD in severe renal impaired subjects. This regimen was found not acceptable due to the very low exposure in some individuals.

Simulations were conducted to explore other regimens such as 1) 800 mg q48h; 2) 800 mg QD for two days and followed by 800 mg q48h; and 3) alternating 800 mg and 400 mg. To conduct the simulations, population PK model was built with the data from 5 studies. The Study 1004, 1005 and 1008 were the pharmacokinetic studies conducted in healthy subjects after single or multiple doses of telithromycin at doses ranging from 400 to 1600 mg. Study 1016 and 1062 are pharmacokinetic studies in renal impaired subjects after a single dose of 800 mg (Study 1016) or multiple doses of 400 mg, 600 mg or 800 mg in Study 1062.

Model applied was a two compartment model with a first order input and a Michealis Menton kinetics for clearance. Model was qualified according to standard identity plots, residual plots and profile plots.

Simulation was conducted for the subjects with severe renal impairment (CLcr < 30 mL/min, n=12) and the subjects with normal renal function (n=9) from study 1062. Pharmacokinetic profiles of telithromycin were simulated based on the individual POSTHOC PK parameter estimates.

Results:

1. The goodness of fit:

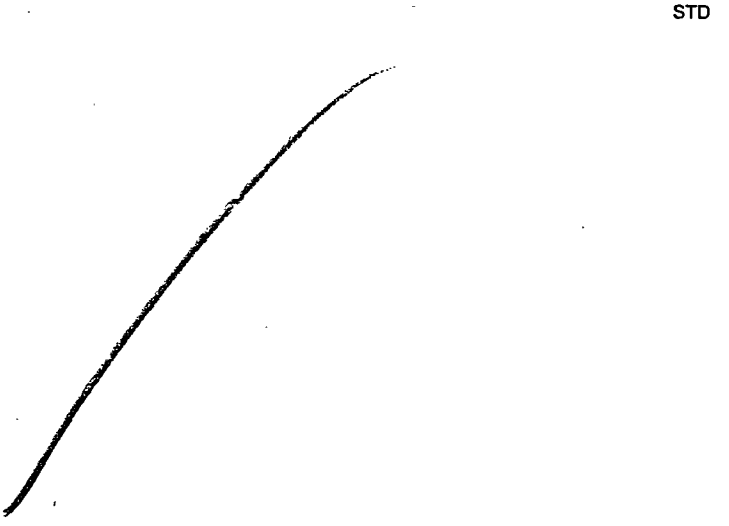
The model was evaluated by the visual examination of the plots of goodness of fit, as presented in Figure 1 and 2.

Figure 1.

On the left panel, the observed concentrations vs predicted population concentrations are presented and on the right panel, the observed concentrations vs predicted individual concentrations are presented. The red line represents the unit line and the black line represents the regression line. In general, the model reasonably described the data especially for the individual data, which is more important for this simulation because the simulations were conducted on the individual POSTHOC parameters.

Figure 2 presents the residual plots. As shown in the plots, the observations are distributed around the zero line, indicating that the model reasonably described data.

Figure 2: Residual Plots



Since the simulation was conducted only for the healthy subjects and severe renal impaired subjects in Study 1062, the observed and predicted concentrations for those subjects in the study are presented in Figure 3 and 4. The open circles represent the observed concentrations and the solid dots represent the predicted individual concentrations. As shown in Figure 3 and 4, the population prediction is about in the middle of observations, indicating that model adequately described the data. It is acceptable to use the model to simulate the regimens of interest. The concentration vs time profiles were simulated for three regimens for subjects with severe renal impairment: a) 800 mg q48h; b) 800 mg QD for two days and followed by 800 mg q48h subsequently; and c) alternating 800 mg and 400 mg.

1 Page(s) Withheld

Regimen a) 800 mg q48h

The pharmacokinetic parameters, Cmax, C24, and AUC(0-24), in subjects with normal renal function and in subjects with severe renal impairment in the first two days are presented in Table 1 and 2, respectively.

Table 1. Pharmacokinetic parameters in subjects with normal renal function

	Day 1			Day 2		
	C_{max} (ng/mL)	C_{24} (ng/mL)	AUC_{24} (ng•h/mL)	C_{max} (ng/mL)	C_{48} (ng/mL)	AUC_{48}* (ng•h/mL)
N	9	9	9	9	9	9
min						
Max						
range						
median	1481.9	35.7	8990.26	1531.6	47.27	19428.03
mean	1642.59	43.94	9829.08	1715.66	66.27	21107.13
SD	639.59	22.32	3744.02	666.09	39.94	8384.25
CV	0.39	0.51	0.38	0.39	0.6	0.4

* the sum of AUC in day 1 and day 2.

Table 2. Pharmacokinetic parameters in subjects with severe renal impaired function

	Day 1			Day 2		
	C_{max} (ng/mL)	C_{24} (ng/mL)	$AUC_{(0-24)}$ (ng•h/mL)	C_{max} (ng/mL)	C_{48} (ng/mL)	$AUC_{(0-48)}$* (ng•h/mL)
n	12	12	12	12	12	12
Min						
Max						
Range						
Median	1909.9	67.78	15690.7	NA	22.67	16392.03
Mean	1872.36	90	15236.4	NA	29.21	16479.6
SD	693.7	64.44	4677.08	NA	21.37	5303.51
C.V.	0.37	0.72	0.31	NA	0.73	0.32

* the sum of AUC in day 1 and day 2.

The pharmacokinetic parameters in subjects with normal renal function and in subjects with severe renal impairment in day 5 and 6 when steady state has achieved are presented in Table 3 and 4, respectively.

Table 3. Pharmacokinetic parameters in subjects with normal renal function

	Day 5			Day 6		
	C_{max} (ng/mL)	C_{120} (ng/mL)	$AUC_{(96-120)}$ (ng•h/mL)	C_{max} (ng/mL)	C_{144} (ng/mL)	$AUC_{(96-144)}$ (ng•h/mL)
N	9	9	9	9	9	9
min						
Max						
range						
median	1557	52.65	11590.05	1557.1	52.66	23182.57
mean	1785.49	91.92	12729.6	1787.23	92.66	25496.19
SD	708.22	69.3	6021.97	709.69	70.39	12091.58
CV	0.4	0.75	0.47	0.4	0.76	0.47

Table 4. Pharmacokinetic parameters in subjects with severe renal impaired function

	Day 5			Day 6		
	C_{max} (ng/mL)	C_{120} (ng/mL)	$AUC_{(96-120)}$ (ng•h/mL)	C_{max} (ng/mL)	C_{144} (ng/mL)	$AUC_{(96-144)}$ (ng•h/mL)
n	12	12	12	12	12	12
Min						
Max						
Range						
Median	1992.05	99.21	17057.43	NA	29.54	18165.3
Mean	1953.75	147.85	17263.26	NA	56.91	19515.6
SD	731.77	155.63	6527.61	NA	67.7	8890.85
C.V.	0.38	1.05	0.38	NA	1.19	0.46

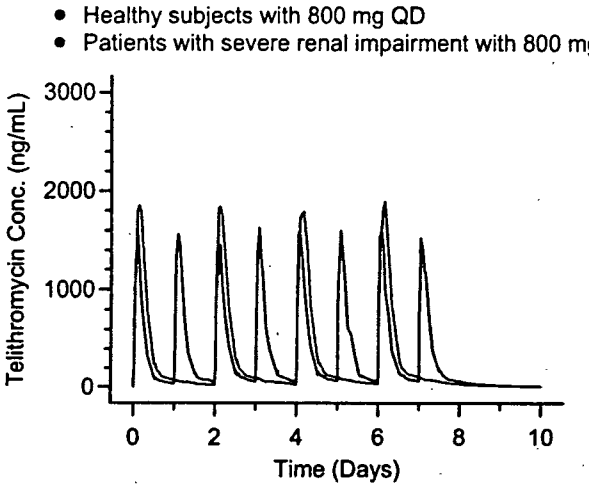
The ratios in mean parameters including Cmax, Ctrough, and AUC(0-24) in day 1, day 2, average of day 1 and day 2, day 5, day 6, and average of day 5 and day 6 between subjects with severe renal impairment who receive 800 mg q48h and subjects with normal renal function who receive 800 mg QD are summarized in Table 5. The ratios in Cmax between populations were only calculated at day 1 and day 5 since no dose is given in severe renal impaired subjects at day 2 and day 6. The ratios in mean AUC at day 1 or day 5 was calculated as ratio of AUC_{0-24} (AUC from 0 to 24 hours) or AUC_{96-120} (AUC from 96 to120 hours) values in subjects with severe renal impairment and subjects with normal renal function. The ratios in mean AUC at day 2 and day 6 was calculated as ratios of AUC_{24-48} (AUC from 24 to 48 hours) and $AUC_{120-144}$ (AUC from 120 to 144 hours) values in subjects with severe renal impairment and subjects with normal renal function. As shown in table 5, by the proposed regimen, the mean Cmax is similar between subjects with severe renal impairment and subjects with normal renal function but the mean Ctrogh is about 20-55% lower in severe renal impaired subjects. Even though the average exposure from day 1 to day 2 and from day 5 to day 6 were about 22% lower in severe renal impaired subjects, the exposures at day 2 and day 6 in subjects with severe renal impairment who would not receive the dose were about 90% and 88% lower as compared with exposure in subjects with normal renal function, indicating that the exposure was significantly increased in the first day but the exposure was low on the second day when no dose is given in subjects with

severe renal impairment. The simulated concentration vs time profiles are shown in Figure 1. Due to the low exposure in severe renal impaired subjects on the day when no dose is given, the regimen is considered not acceptable.

Table 5. The summaries in PK parameters between severe renal impaired subjects and normal renal subjects

Day	Ratio in mean parameters between subjects with severe renal impairment and subjects with normal renal function		
	Cmax	Ctrough (C48/C24)	AUC
Day 1	1.13	NA	1.56
Day 2	NA	0.44	0.10
Average in day 1+ day2	NA	NA	0.78
Day 5	1.09	NA	1.34
Day 6	NA	0.81	0.18
Average in day 5 + day 6	NA	NA	0.77

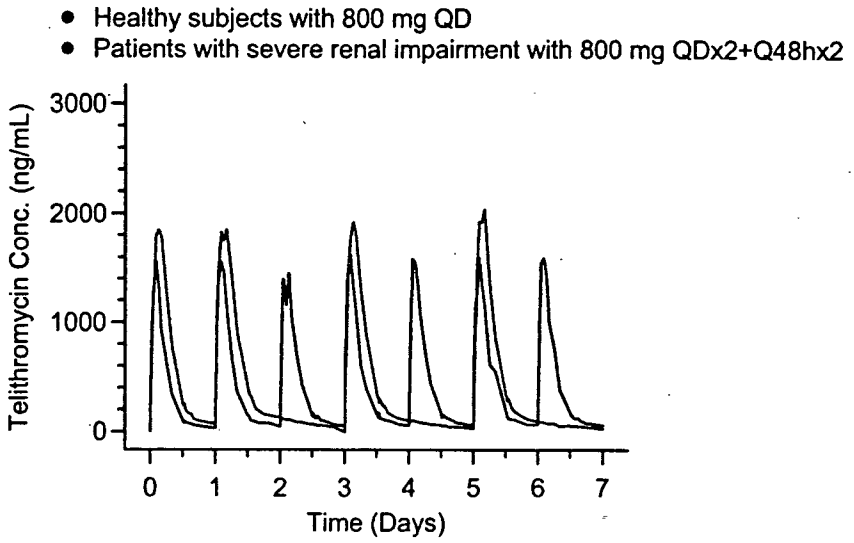
Figure 1. Concentration vs time profiles in subjects with severe renal impairment and subjects with normal renal function



b) 800 mg QD for first two days followed by 800 mg q48h

Using the same model, the concentration vs time profiles were generated and the pharmacokinetic parameters were calculated for the regimen of 800 mg QD followed by 800 mg q48h. For this regimen, the sponsor calculated average AUC from day 1 to 6 between subjects with severe renal impairment and subjects with normal renal function. The ratio in mean AUC(0-144) between two groups is 0.92, indicating that the average exposures are comparable. However, as shown in the Figure 2, similar to the first regimen, the exposures are low in subjects with severe renal impairment on the day when no dose is given. For that reason, this regimen is not acceptable.

Figure 2. Concentration vs time profiles in subjects with severe renal impairment and subjects with normal renal function



c) Alternating 800 mg and 400 mg (QOD)

The PK profiles were simulated for subjects with normal renal function who receive 800 mg QD and for subjects with severe renal impairment who receive 800 mg and 400mg in alternative days. The PK parameters were calculated for the two groups on day 1, day 2, day 7 and day 8 and presented in Table 7. The results on the comparisons between these two groups after different regimens are presented in Table 8. The mean concentration profiles are shown in Figure 4.

The results showed that the mean Cmax values in subjects with severe renal impairment was about 7% and 13% higher at day 1 and 7 when those subjects took 800 mg dose and was about 47% and 38% lower at day 2 and 8 when those subjects took 400 mg dose as compared with mean Cmax values in subjects with normal renal function. C_{trough} was higher in subjects with severe renal impairment, which related to the longer half-life in those subjects as compared with subjects with normal renal function. The mean AUC values in subjects with severe renal impairment was about 51% and 61% higher at day 1 and 7 when subjects took 800 mg dose and was about 30% and 6% lower at day 2 and 8 when subjects took 400 mg dose as compared with mean AUC values in subjects with normal renal function. The overall exposure, measured as average AUC in day 1 and day 2 or AUC in day 7 and day 8, was comparable. In the first two days, the ratios in mean Cmax, Cmin, and AUC between severe renal impaired subjects and normal renal subjects were 1.03, 1.16, and 1.08, respectively. At day 6 and 7 when steady state has achieved the ratios in mean Cmax, Cmin, and AUC between severe renal impaired subjects and normal renal subjects were 1.12, 2.31, and 1.27, respectively. Therefore, from exposure perspective, the alternating regimen is acceptable. However, a previous study showed that the patients who need dialysis should take 800 mg dose after dialysis on dialysis day. Therefore, the dialysis may change the dose pattern. For example, after Ketek treatment starts, the patient who needs to take a 400 mg dose according to the alternating regimen should take a 800 mg dose after dialysis due the dialysis event. Therefore, for dialysis patients, the alternating regimen will be too complicated to follow. Sponsor has stated that the 600 mg strength will be proposed for severe renal impaired patients (including those who need dialysis) in a supplemental application.

Table 7. Pharmacokinetic parameters in subjects with severe renal impairment and subjects with normal renal function at day 1, 2, 7, and 8

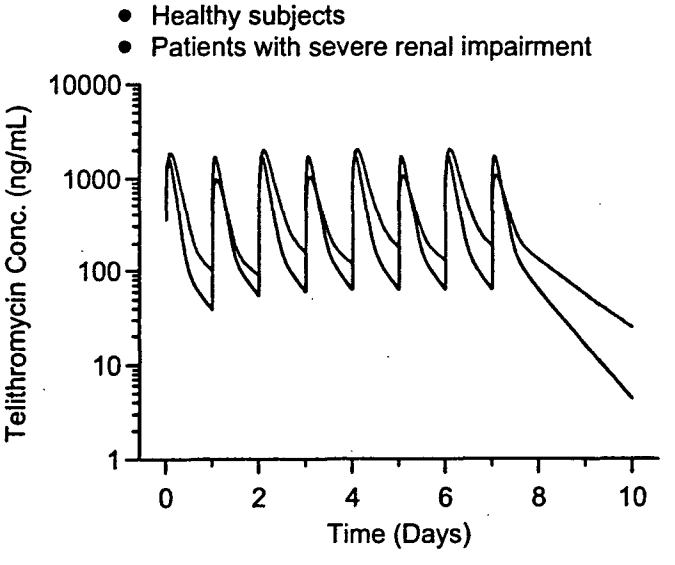
	Subjects with severe renal impairment			Subjects with normal renal function		
	Day 1 (800 mg)			Day 1 (800 mg)		
	Cmax	C24	AUC(0-24)	Cmax	C24	AUC(0-24)
n	12	12	12	9	9	9
Min						
Max						
Range						
Median	1774.75	68.53	15227.93	1481.40	35.79	9029.84
Mean	1763.03	92.41	14903.23	1644.03	44.64	9889.98
SD	618.49	66.51	4497.22	639.29	22.74	3762.46
C.V.	0.35	0.72	0.30	0.39	0.51	0.38
	Day 2 (400 mg)			Day 2 (800 mg)		
	Cmax	C48	AUC(24-48)	Cmax	C48	AUC(24-48)
n	12	12	12	9	9	9
Min						
Max						
Range						
Median	899.32	50.61	6934.46	1529.90	47.17	10474.49
Mean	915.16	77.77	7961.84	1717.04	66.83	11327.13
SD	338.68	67.04	3587.40	666.53	40.37	4668.51
C.V.	0.37	0.86	0.45	0.39	0.60	0.41
	Average in day 1 and day 2			Average in day 1 and day 2		
	Cmax	C24	AUC(0-48)	Cmax	C24	AUC(0-48)
n	12	12	12	9	9	9
Min						
Max						
Range						
Median	1774.75	50.61	22162.39	1529.90	47.17	19504.33
Mean	1763.03	77.77	22865.07	1717.04	66.83	21217.12
SD	618.49	67.04	7975.14	666.53	40.37	8429.67
C.V.	0.35	0.86	0.35	0.39	0.60	0.40
	Day 7 (800 mg)			Day 7 (800mg)		
	Cmax,ss	C24ss	AUC(0-24)ss	Cmax,ss	C24ss	AUC(0-24)ss
n	12	12	12	9	9	9
Min						
Max						
Range						
Median	2014.30	131.99	17964.03	1554.40	52.96	11583.04
Mean	2008.09	259.56	20427.06	1784.47	91.23	12714.31
SD	813.15	403.58	11694.31	707.44	68.67	5999.39
C.V.	0.41	1.56	0.57	0.40	0.75	0.47
	Day 8 (400 mg)			Day 8 (800mg)		
	Cmax,ss	C24ss	AUC(24-48)ss	Cmax,ss	C24ss	AUC(24-48)ss
n	12	12	12	9	9	9
Min						
Max						
Range						
Median	1025.05	89.38	8313.81	1554.50	52.99	11585.13
Mean	1104.07	211.92	12004.18	1786.03	91.88	12747.06
SD	624.35	413.29	11626.98	708.76	69.65	6042.39

C.V.	0.57	1.95	0.97		0.40	0.76	0.47
	Average in day 7 and 8				Average in day 7 and 8		
	Cmax,ss	C48ss	AUC(0-48)ss		Cmax,ss	C48ss	AUC(0-48)ss
n	12	12	12		9	9	9
Min							
Max							
Range							
Median	2014.30	89.38	26277.84		1554.50	52.99	23168.17
Mean	2008.09	211.92	32431.24		1786.03	91.88	25461.37
SD	813.15	413.29	23222.53		708.76	69.65	12041.76
C.V.	0.41	1.95	0.72		0.40	0.76	0.47

Table 8. The summaries of comparison in exposures between subjects with severe renal impairment and subjects with normal renal function

Day	Ratio between subjects with severe renal impairment and subjects with normal renal function		
	Cmax	Cmin	AUC
Day 1	1.07	2.07	1.51
Day 2	0.53	1.16	0.70
Average in day 1+ day2	1.03	1.16	1.08
Day 6	1.13	2.85	1.61
Day 7	0.62	2.31	0.94
Average in day 6 + day 7	1.12	2.31	1.27

Figure 3. The concentration vs time profiles in subjects with severe renal impairment at regimen of 800 mg and 400 mg and subjects with normal renal function at regimen of 800 mg QD



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/s/

Jenny Zheng
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BIOPHARMACEUTICS

Venkateswar Jarugula
3/31/04 05:45:27 PM
BIOPHARMACEUTICS

CLINICAL PHAMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA number:	21-144
Submission date:	July 24, 2002,
Generic name:	Telithromycin
Dosage Form:	400 mg Tablet
Trade name:	KETEK
Sponsor:	Aventis Pharmaceuticals Inc. Kansas City, MO
Type of submission:	Amendment to pending application
OCPB Division:	DPEIII (HFD-880)
Clinical Division:	Anti-infective Drug Product (HFD-520)
Reviewer:	Jenny J Zheng, Ph.D.

I. EXECUTIVE SUMMARY:

A. RECOMMENDATION:

This application was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Drug Evaluation III and was found to be acceptable from the clinical pharmacology perspective. The comments below should be conveyed to the reviewing Medical Officer. The labeling comments and Comment 3 below should be conveyed to the sponsor.

COMMENTS:

1. The multiple dose study in renal impaired subjects suggested that 600 mg should be given in severe renal impaired subjects. However, only 400mg tablet is available for this product.

2. When CYP3A4 inhibitor was co-administered with telithromycin in mild or moderate renal impaired subjects, AUC and Cmax were increased by 169% and 59%, respectively, as compared with AUC and Cmax in healthy subjects taken telithromycin alone. A dose reduction in telithromycin might be necessary in this situation.

3. The dissolution specification for the 400 mg telithromycin tablet should be changed from [redacted] (Q= [redacted], at [redacted] to [redacted], (Q= [redacted], at [redacted]

B. PHASE IV COMMITMENTS:

None.

/S/

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

RD/FT initiated by P. Colangelo, Ph.D., Pharm.D., Team Leader _____

II. TABLE OF CONTENTS

III. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS:

- Even though only 13% of unchanged telithromycin was found in the urine, renal function has an important role in eliminating the drug especially in the situation where telithromycin systemic exposure is increased by other factors such as CYP450 based metabolic drug interactions.
  i. The multiple dose renal impairment study (Study 1062) showed that the mean steady state Cmax and AUC(0-24) after 5 days of 800 mg QD telithromycin were not significantly different between subjects with mild (CLcr 50-80 mL/min) or moderate (CLcr 30-49 mL/min) renal impairment and healthy subjects with no renal impairment (CLcr >80 mL/min). However, the mean steady state AUC(0-24) and Cmax in subjects with severe renal impairment (CLcr <30 mL/min) were increased 1.9 and 1.4 fold, respectively, following 800 mg QD for 5 days. These results indicated that a dose adjustment (i.e., reduction) is needed for subjects/patients with severe renal impairment.

     Lower telithromycin dosage regimens of 400 mg and 600 mg QD for 5 days were also evaluated in the renal impairment subjects enrolled in Study 1062. The pharmacokinetic results from these lower doses suggested that a 600-mg QD dosage regimen should be given to those individuals with severe renal impairment in order to obtain comparable AUC(0-24) as healthy subjects receiving 800 mg QD. However, a potential difficulty arises with the administration of a 600-mg QD dosage regimen in that only an unscored 400-mg tablet strength of telithromycin is currently available in the United States.

  ii. When the CYP3A4 inhibitor, ketoconazole, was co-administered with 800 mg telithromycin QD in elderly subjects with mild to moderate renal impairment (CLcr 30-80 mL/min), mean AUC(0-24) and Cmax were increased 2.7 fold and 1.6 fold respectively, as compared to the AUC(0-24) and Cmax in healthy subjects receiving telithromycin 800 mg QD alone (Study 1063). A reduction in the dose of telithromycin appears to be warranted in this situation.

- Telithromycin is a CYP3A4 substrate.
  i. In a study from the original NDA submission, the CYP3A4 inhibitor, ketoconazole, increased telithromycin exposure when co-administered with telithromycin. Telithromycin mean steady state AUC(0-24) and Cmax were increased 2 and 1.5 fold, respectively, following ketoconazole co-administration to healthy young subjects.

  ii. Co-administration of the potent CYP3A4 inducer, rifampin, with telithromycin significantly decreased telithromycin systemic exposure in healthy young subjects (Study 1058). During repeated dose co-administration of rifampin with telithromycin, the mean AUC(0-24) and Cmax of telithromycin were decreased 86% and 79%, respectively.

- Telithromycin is a CYP3A4 inhibitor.
  i. In a study from the original NDA submission, co-administration of telithromycin with intravenous midazolam resulted in an increase in midazolam AUC of 2 fold and no significant change in Cmax. Co-administration of telithromycin with oral midazolam

resulted in more substantial increases in midazolam AUC and Cmax of 6- and 2.6 fold, respectively.

ii. Preliminary data from a draft study report (Study 1065) showed that co-administration of simvastatin with telithromycin increased the mean AUC and Cmax values for simvastatin 8.9 and 5.3 fold, respectively. For simvastatin acid, the mean AUC and Cmax values were increased 12 and 15 fold, respectively (final study report to be submitted at a later date).

- Telithromycin is a weak CYP 2D6 inhibitor.
  i. Co-administration of telithromycin increased the bioavailability of metoprolol (CYP2D6 substrate), resulting in approximately a 1.4 fold increase in both AUC and Cmax.

- The phase I studies showed that telithromycin can cause QT prolongation. Detailed information can be found in the review by Dr. Jenny J Zheng for the original application submitted on February 28, 2000.

IV. QUESTION BASED REVIEW:

Please refer to the review of the original application submitted on February 28, 2000 for the general pharmacokinetic characteristics of telithromycin. This review is focused on the studies in this resubmission.

The applicant, Aventis Pharmaceuticals Inc., submitted this amendment to the new drug application to the FDA on July 24, 2002 to provide a complete response to the FDA approvable letter. The original NDA was submitted on February 28, 2000 and an approvable letter was issued by the FDA on June 1, 2001. As part of the approvable letter, the FDA recommended the applicant to perform two clinical pharmacology studies:

Study 1062: Multiple dose pharmacokinetic study in renal impairment subjects
It was found from the original application 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 range 40-79 mL/min). The mean C_{max} and AUC were increased by 44% and 59%, respectively, in subjects with severe renal impairment (CLcr range 10-39 mL/min). The higher exposure in renal impaired subjects following single dose administration suggested that the dosage regimen of telithromycin might need to be adjusted for this subgroup of patients. Since the PK of telithromycin exhibits non-linear characteristics, systemic exposure in renally impaired subjects may be greater than expected after multiple dose administration, as compared to single dose administration. Thus, it was recommended that the applicant investigate the steady state pharmacokinetics of telithromycin following repeat dose administration of 400 mg, 600 mg, and 800 mg once daily to patients with mild, moderate, and severe renal impairment in order to provide adequate dose adjustment recommendations for the product label.

Study 1063: Pharmacokinetic study to investigate the effect of co-administration of ketoconazole on the steady- state pharmacokinetics of telithromycin following administration of 800 mg once daily to elderly patients with mild to moderate renal impairment
In the original NDA submission the Phase 1 studies showed that factors, such as renal impairment and drug interactions (i.e., metabolism-based inhibition) with telithromycin, can increase the systemic exposure / plasma concentrations of telithromycin. Study 1063 was designed to examine the PK of telithromycin in the situation where these two factors mentioned above are simultaneously invoked, i.e., renal impairment and co-administration of the CYP3A4 inhibitor, ketoconazole. The rationale for this study is to characterize telithromycin systemic exposure in patients that are potentially at greater risk (e.g., taking concurrent interacting drugs, elderly, renal impairment) due to multiple perturbations of the elimination pathways for telithromycin, namely renal and hepatic.

Six additional clinical pharmacology studies were included in this submission by the applicant:

1. Study 1060: A phase 1 study designed to assess the pharmacokinetics of safety of telithromycin following multiple doses in subjects with hepatic impairment.
2. Study 1058: An open, cross-over study to assess the effect of multiple dose of rifampicin (600 mg qd) on the single dose and multiple dose pharmacokinetics of telithromycin (800 mg QD) in healthy male subjects.
3. Study 1061: An open interaction study between multiple oral doses of telithromycin (800 mg qd.) and single oral dose of metoprolol (100 mg) in healthy volunteers.
4. Study 1050: An investigation of the effective permeability of HMR 3647 in the human jejunum.

5. Study1059: Mechanism of blurred vision induced by HMR 3647 at a single supraclinical doses (2400 mg) versus a therapeutic single dose (800 mg) in a younger and older population of healthy subjects.
6. Study 1064: Assessment of ophthalmological safety of telithromycin at a supraclinical single dose (2400 mg) in healthy subjects.

Dr. Jenny J Zheng evaluated Study 1060 in the original NDA submission. In addition, the dissolution of telithromycin tablets was reviewed in the original NDA submission and the comment regarding the dissolution specification is included with this review. The evaluation of the seven other studies comprises this review.

Dose the dosage regimen of telithromycin need to be adjusted in renal impairment (Study 1062)?

The effect of renal impairment on telithromycin PK was evaluated following single oral dose administration of 800mg in the original NDA submission. The mean C_{max} and AUC of telithromycin were increased by 33% and 42%, respectively, in subjects with moderate renal impairment (Creatinine Clearance (CLcr) range: 40-79 mL/min). In subjects with severe renal impairment (CLcr range: 10-39 mL/min), the mean C_{max} and AUC were increased by 44% and 59%, respectively.

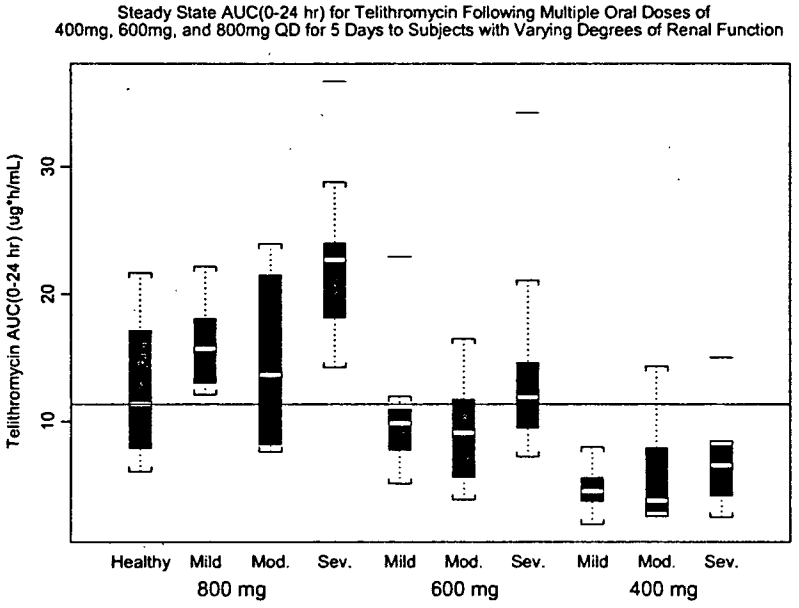
The higher systemic exposure in subjects with renal impairment following single dose administration suggested that dose adjustment may be needed for this sub-group of patients. Since the PK of telithromycin exhibits non-linear characteristics, systemic exposure in renally impaired subjects may be greater than expected after multiple dose administration, as compared to single dose administration. Thus, for a drug that exhibits non-linear PK, a single dose study will not be able to accurately predict the PK following multiple doses.

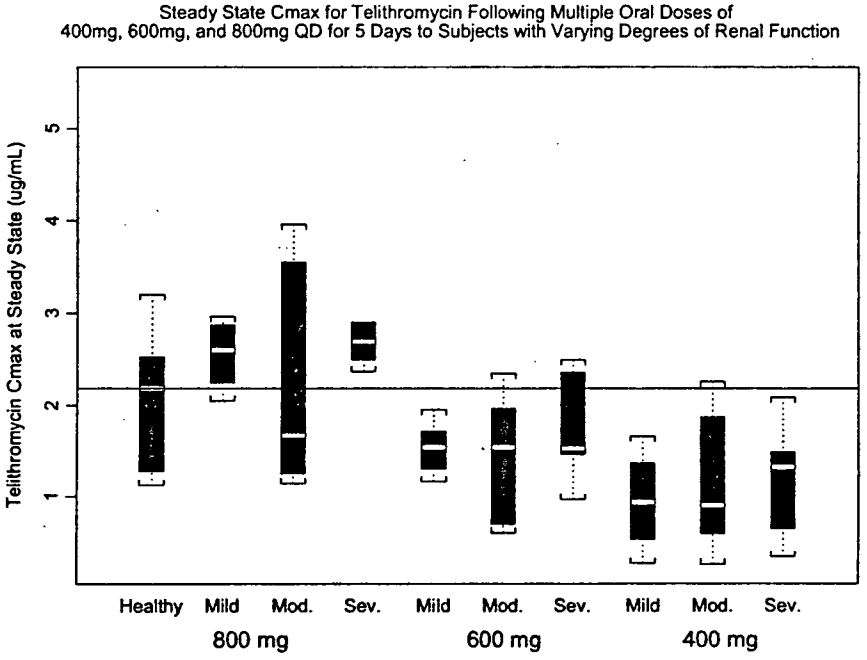
In order to adequately determine if dose adjustment in individuals with renal impairment is needed, a multiple dose pharmacokinetic study in renal impairment subjects was conducted. Study 1062 was an open-label crossover trial employing multiple oral doses of 400mg, 600mg, and 800mg telithromycin given daily for 5 days to the following 3 groups of renally impaired subjects:

Mild Impairment:	CLcr* 50 to 80 mL/min
Moderate Impairment:	CLcr 30 to 49 mL/min
Severe Impairment:	CLcr <30 mL/min

A fourth group of healthy subjects (CLcr >80 mL/min) also received multiple oral doses of 800mg telithromycin given daily for 5 days.

The steady state AUC(0-24 hr) and Cmax for the various renal function groups at the dose levels of 400mg, 600mg, and 800 mg are shown in the following figures.





Legend for "Box and Whisker" Plots:

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
Mod. = Moderate Renal Impairment; Sev. = Severe Renal Impairment

There were no significant changes in the Cmax estimates for telithromycin for all three renal impairment groups when compared to the healthy subjects following 800mg QD for 5 days. The steady-state AUC(0-24 hr) estimates following multiple 800mg doses were not significantly increased in the mild and moderate renal impairment subjects as compared to healthy subjects. However, steady state AUC(0-24 hr) was increased approximately 2-fold in the severe renal impairment subjects as compared to the healthy subjects following 800mg QD for 5 Days.

Following multiple 400mg doses of telithromycin, steady-state AUC(0-24 hr) estimates were reduced by approximately 40% to 60% in all three groups of renally impaired subjects.

The results from this study indicate that in order to obtain comparable exposure (i.e., AUC) to healthy subjects given the clinical regimen of 800mg QD, a regimen of 600mg QD should be administered to individuals with severe renal impairment (CLcr <30 mL/min). No dose adjustment is necessary in individuals with mild to moderate renal impairment (CLcr 30 to 80 mL/min, inclusive).

The results from this study also indicate that a telithromycin dosage regimen of 400mg QD in individuals with severe renal impairment, as suggested by the applicant, may result in lower systemic exposure to telithromycin that may be sub-therapeutic in this subgroup.

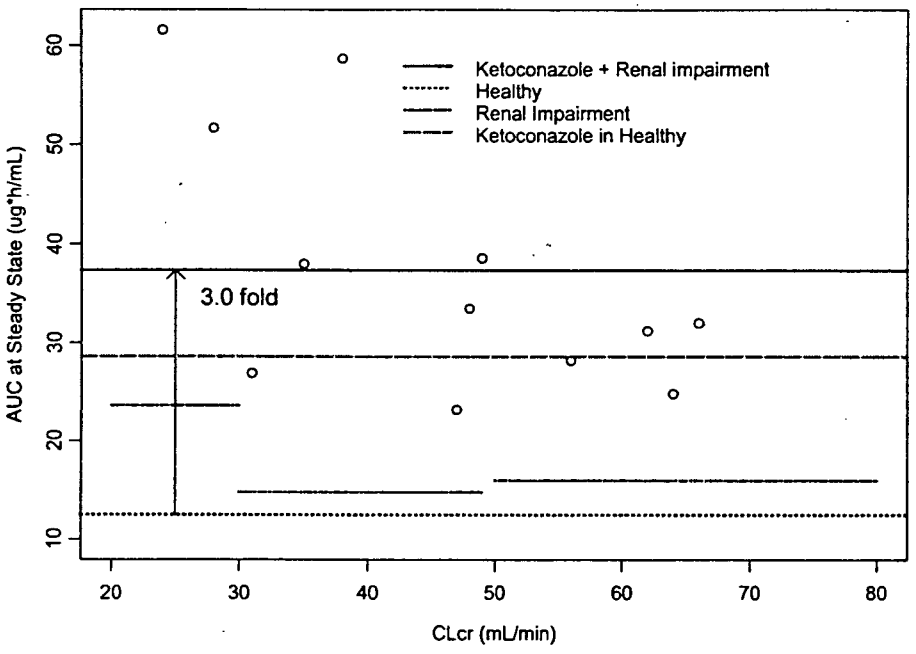
What are the effects of simultaneous CYP3A4 inhibition and renal impairment on the systemic exposure to telithromycin (Study 1063)?

In the original NDA submission the Phase 1 studies showed that factors, such as renal impairment and drug interactions with telithromycin, can increase the systemic exposure / plasma concentrations of telithromycin. In the ketoconazole drug interaction study in the original NDA, ketoconazole increased telithromycin mean C_{max} and AUC by 52% and 95%, respectively, in healthy subjects. The mechanism for this interaction is inhibition of CYP3A4-mediated metabolism of telithromycin by ketoconazole.

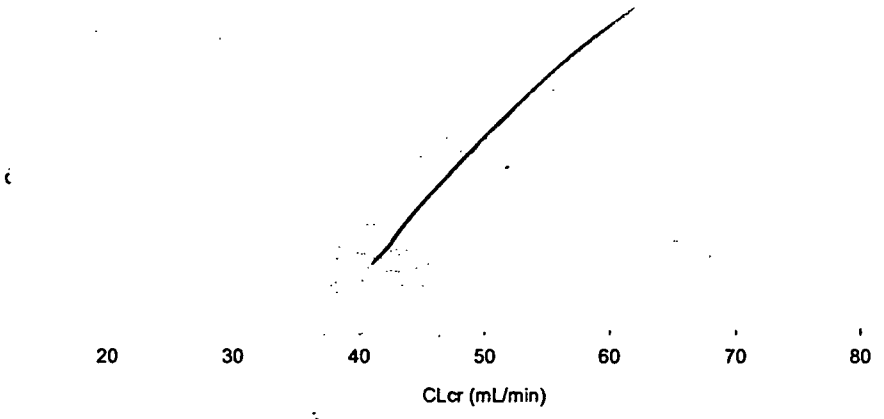
Study 1063 was designed to examine the PK of telithromycin in the situation where the two factors mentioned above are simultaneously invoked, i.e., renal impairment and co-administration of the CYP3A4 inhibitor, ketoconazole. The rationale for this study is to characterize drug exposure in patients that are potentially at greater risk (e.g., taking concurrent interacting drugs, elderly, renal impairment) due to multiple perturbations of the elimination pathways for telithromycin, namely renal and hepatic. Due to the concern about unacceptable adverse events potentially resulting from high telithromycin plasma exposure in individuals with severe renal impairment, only subjects with mild (CLcr 50-80 mL/min) and moderate (CLcr 30-49 mL/min) renal impairment were to be included in this study (N = 10). Although subjects with severe renal impairment (CLcr <30 mL/min) were to be excluded, two subjects each with CLcr <30 mL/min were studied (i.e., CLcr 24 and 28 mL/min). This study also only included subjects 60 years of age and older.

In the figures below the steady state Cmax and AUC(0-24 hr) estimates are compared across the following groups of subjects from several Phase 1 studies: (1) ≥60 years of age with mild to moderate renal impairment and ketoconazole co-administration (Study 1063); (2) healthy young subjects; (3) renal impairment (Study 1062); (4) ketoconazole co-administration to healthy young subjects.

Telithromycin Steady State AUC Estimates following Multiple Oral Dose Administration to Subjects from Various Phase 1 Studies



Telithromycin Steady State Cmax following Multiple Oral Dose Administration to Subjects from Various Phase 1 Studies



Open Circles represent individual data from Study 1063; Horizontal Lines represent mean values of each subject group described in plots

The results of these comparisons indicate the following:

- In healthy young subjects, the mean steady state AUC and C_{max} estimates after multiple doses of 800mg telithromycin are 12.4 µg•h/mL and 2.27 µg/mL, respectively.

- In healthy young subjects co-administered ketoconazole, the telithromycin mean AUC and C_{max} estimates were 28.6 µg•h/mL and 3.31 µg/mL, respectively, which represented increases of 2-fold and 1.4-fold, respectively, as compared with administration of telithromycin alone.

- In the 10 older subjects ≥60 years of age with mild to moderate renal impairment and ketoconazole co-administration (Study 1063), the mean steady state AUC and C_{max} estimates of telithromycin were increased 2.7-fold and 1.6-fold, respectively, as compared to the healthy young subjects given telithromycin alone.

- From limited data in the 2 subjects included in Study 1063 with severe renal impairment (CLcr 24 and 28 mL/min), the steady state telithromycin AUC estimates were increased 4-fold and 5-fold, and the telithromycin C_{max} estimates were increased 2.4-fold and 4-fold, as compared to the healthy young subjects given telithromycin alone.

Overall, the results from Study 1063 indicated that the systemic plasma exposure to telithromycin is increased to a greater extent in older individuals with renal impairment who are concomitantly taking the CYP3A4 inhibitor, ketoconazole, with telithromycin, as compared to the effect of either factor alone (i.e., renal impairment or co-administration with ketoconazole). A reduction in the telithromycin daily dosage is recommended in patients with severe renal impairment (CLcr <30 mL/min). Dosage reduction may be needed with co-administration of ketoconazole with telithromycin in patients with normal renal function. In addition, the telithromycin dosage may also need to be reduced in patients with both renal impairment and taking a CYP3A4 inhibitor, such as ketoconazole.

Does hepatic function affect the systemic exposure to telithromycin (Study 1060)?
In the original NDA submission, the AUC and C_{max} of telithromycin following a single oral dose of 800mg to subjects with hepatic impairment (Child-Pugh scores 5-12; median score 9) and healthy subjects were similar between the two groups. However, the half-life ($t_{1/2}$) was increased from 10 hours in healthy subjects to 14 hours in the hepatic impairment subjects. There was concern that a longer half-life in the hepatic impairment subjects could result in more significant accumulation of telithromycin in plasma after multiple doses as compared to healthy subjects.

Therefore, Study 1060 was a multiple-dose study conducted in 13 subjects with varying degrees of hepatic impairment (Child-Pugh score 5-11; median score 7) and 13 healthy subjects. The results showed that the mean C_{max}, AUC, $t_{1/2}$, and plasma accumulation of telithromycin were comparable for the hepatically impaired and healthy subjects after multiple doses. The mean renal clearance of telithromycin was 27% higher in the hepatic impairment subjects as compared to healthy subjects, indicating that renal elimination becomes a compensatory pathway when liver function is impaired.

How does rifampin affect telithromycin systemic exposure (Study 1058)?
Telithromycin has been shown to be a CYP3A4 substrate and inhibitor. The interaction of multiple doses of telithromycin 800mg QD with rifampicin 600mg QD, a potent CYP3A4 inducer, was assessed in this crossover study conducted in 12 healthy young men. The study

showed that co-administration with rifampicin decreased telithromycin C_{max} and AUC by 5- and 7-fold, respectively, as compared to when telithromycin was given without rifampicin. As suggested by the sponsor, rifampicin should be contraindicated with telithromycin.

How does telithromycin affect metoprolol systemic exposure (Study 1061)?
In vitro studies in the original NDA submission suggested that telithromycin was an inhibitor of hepatic CYP2D6. In Study 1061, the effect of telithromycin on the PK of metoprolol, a CYP 2D6 substrate, was assessed in healthy subjects. Co-administration of repeated 800mg doses of telithromycin increased metoprolol C_{max} and AUC after a single 100 mg dose by approximately 40%. No adjustment of the metoprolol dosage is needed.

What is the mechanism of blurred vision associated with telithromycin?
Two studies, Study 1064 and Study 1059, were conducted to investigate the mechanism of blurred vision associated with telithromycin administration. Please refer to the Medical Officer's review for a more detailed discussion of the ophthalmologic findings and the safety data generated from these two studies. Only the relevant clinical pharmacology / PK data will be discussed in this section.

In Study 1064 telithromycin concentrations in plasma and the amount of drug excreted in tears were to be determined following single oral dose administration of 2400mg to 24 healthy young subjects from pre-dose to 6 hr postdose. However, only plasma concentration data were reported and no data for telithromycin in tears was provided. Since the PK of telithromycin in plasma has already been characterized at this dose in previous NDA studies, no discussion of this data will be presented here.

Study 1059 was a randomized, double blind, placebo controlled, 3-period cross over design in 15 young (18-40 years) and 15 older (50- <65 years) male and female subjects. All subjects received a single dose of placebo, 800mg telithromycin, and 2400mg telithromycin. Plasma concentrations of telithromycin and the amount of drug excreted in tears were determined at pre-dose to 24 hr postdose. The results showed a proportional increase in telithromycin mean Cmax in plasma with the increase in dose within the two age groups. The maximal amount of drug excreted in tears was also proportional to the increase in dose within the two age groups. After both doses the plasma Cmax was slightly higher in the older group compared to the younger subjects. However, although plasma exposure was higher in the older subjects, the mean maximal amount of telithromycin excreted in tears was lower by approximately 40% to 50% in the older subjects compared to the younger group following administration of both doses. The clinical implication of the differences in the amount of drug excreted in tears in older vs. younger adults is not known.

V. LABELING COMMENTS:

Due to the Division of Anti-infective Drug Products action of approvable for this NDA amendment, labeling comments will be addressed at a later date.

VI. APPENDICES:

A. Product Labeling proposed by the applicant.

B. Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

1. Study 1050: An investigation of the effective permeability of telithromycin (HMR 3647) in the human jejunum.
2. Study 1058: An open, cross-over study to assess the effect of multiple dose of rifampicin (600 mg qd) on the single dose and multiple dose pharmacokinetics of telithromycin (800 mg QD) in healthy male subjects
3. Study 1059: 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
4. Study 1061: An open interaction study between multiple oral doses of telithromycin (800 mg q.d.) and single oral dose of metoprolol (100 mg) in healthy volunteers.
5. Study 1062: 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.
6. Study 1063: 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.
7. Study 1064: Assessment of ophthalmological safety of telithromycin at a supraclinical single dose (2400 mg) in healthy subjects.

C. OCPB Filing Form

APPENDIX A

PROPOSED TELITHROMYCIN LABELING
(Applicant Version 1/14/03)

APPEARS THIS WAY
ON ORIGINAL

28 Draft Labeling Page(s) Withheld

APPENDIX B:

INDIVIDUAL STUDY REVIEWS

STUDY NUMBER: 1050

TITLE: An investigation of the effective permeability of telithromycin (HMR 3647) in the human jejunum

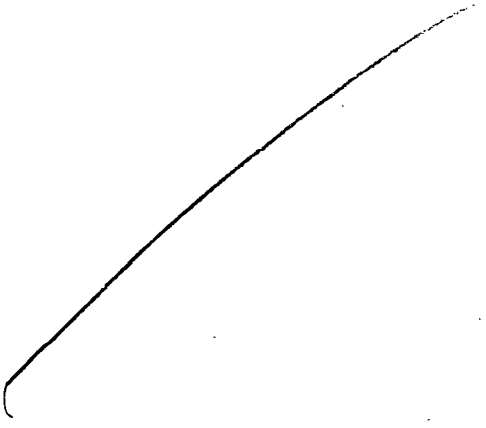
OBJECTIVES: The objective was to determine the effective intestinal permeability (Peff) of telithromycin by measuring the transport rate from the intestinal lumen with the jejunal perfusion technique [redacted].

DESIGN: This was an open labeled, non-randomized, non-controlled, single dose, single center study. Six healthy male adult subjects aged between 18 and 40 years old were recruited.
A single dose of 800 mg telithromycin as a solution (800 mg in 240 mL; 3.333 mg/mL) was administered in the jejunum using an oro-jejunal tube [redacted]. This solution also contained 2.4 mg of antipyrine (administered as a positive control) and trace amounts (2.5 µCi /L) ^{14}C-PEG 4000 (as a non absorbable marker).

FORMULATION: Telithromycin powder (GG27961-156).

SAMPLING: Concentrations of telithromycin, antipyrine and ^{14}C-PEG 4000 were determined in perfusate samples at the following times after jejunal perfusion: 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110 and 120 minutes.

Procedure:



Stability of telithromycin in jejunal fluid:
The stability of HMR 3647 in human jejunal contents was investigated by incubation of 1 ml of mixture of perfusion solution, containing HMR 3647 (c=3333 mg.l^{-1}) with 1 ml of human jejunal fluid at 37°C. The jejunal fluid was acquired previously in two human subjects using the [redacted] technique. Samples (100 µl) were taken after 0, 1, 5, 15, 20, 30, 60, 90 and 120 minutes of incubation and added to 150 µl of cold acetonitrile.

Peff of telithromycin was 0.54 x 10^{-4} cm/s (43%). The results indicate that the jejunal permeability of telithromycin was intermediate.

The jejunal absorption of antipyrine (a marker for passive transcellular absorption and mesenteric blood flow) was stable over time which indicates that no escalating viability changes occurred in the perfused segment. The mean recovery of the non-absorbable volume marker ^{14}C-PEG 4000 in the outlet jejunal perfusate was 86%. The mean (CV%) values of pH were 7.0 (9%) and the osmolality was 280.5 mOsm/L (2%) in the outlet perfusate. From the Peff values determined in this study, one can predict that the absorption of telithromycin from the human intestine would be in the range from 45 to 80% (Figure 1).

CONCLUSIONS:

1. The mean (CV%) jejunal Peff of telithromycin was 0.54 x 10^{-4} cm/s (43%). Based on these results, the sponsor concluded that the jejunal permeability of telithromycin was intermediate.
2. The measured the fraction of absorption (fa) in this study was in the range of 8%-22% with mean of 14% (n=6). However, the sponsor showed that the predicted fraction of absorption (fa) using the individual Peff values was in the range of 45% to 80%. Thus, the results from the study are inconsistent with the predicted values.
3. Telithromycin is stable in jejunal fluid at 37 °C for 2 hours.

COMMENTS:

1. According to the FDA guidance, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, telithromycin is a high solubility drug. According to the guidance, a drug substance is considered *highly soluble* when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5. The solubility of telithromycin was determined to be [redacted] ng/ml in water at pH 1, [redacted] ng/ml at pH 2 and [redacted] ml at pH 7. The Sponsor concluded that telithromycin is a high solubility drug, which is consistent with the criteria from the guidance document.

2. The sponsor concluded that telithromycin is also a highly permeable drug based on the fact that 90% of the drug was absorbed from results from two Phase 1 studies. In Study 1004, it was found that after IV administration, 12% of the dose was excreted unchanged in the feces. In the mass balance study, 20% of unchanged drug was found in the feces after oral administration of 800 mg telithromycin tablet. Even though an *in vitro* study showed that telithromycin was a PGP substrate, the *in vivo* absorption (i.e., 90%) is high, indicating that there might be active transporters involved in the absorption of telithromycin. Thus, the high absorption quoted from these two studies does not necessarily indicate that telithromycin is a high permeability drug. According to the guidance mentioned above, the stability of the drug should be studied in gastric fluid for 1 hour and in intestinal fluid for 3 hours. The stability of telithromycin in this present study was established for only 2 hours in jejunal fluid and was not evaluated in gastric fluid over any time period. Thus, the estimation of 90% *in vivo* absorption by the sponsor is only true if telithromycin is stable in the GI contents over time.

3. Even though the *in vivo* data from the two studies above may suggest that telithromycin is a high permeability drug, the mean Peff from this present study is only 0.54x10^{-4} cm/s, which is substantially lower than Peff values of other highly permeable drugs. For example, Peff values for metolprolol and antipyrine were about 2x10^{-4} cm/s, 3x10^{-4} cm/s, respectively.

ASSAY:

The accuracy and precision of the assay for telithromycin and was shown in as the followings:

Analyte	Samples	Accuracy[a]	Precision[b]
Telithromycin	QC samples (0.05,0.1,0.25,1 mg/L)	96.8-104.8%	0.4-7.6%
	Calibration standards (0.05-1 mg/L)	99.0–102.4%	0.4–5.0%

[a] Accuracy, expressed as % recovery, relative to theoretical concentration.

[b] Precision, expressed as % coefficient of variation.

DATA ANALYSIS:

Pharmacokinetics:

All calculations of the effective intestinal permeability (Peff), the net water flux (NWF) and the fraction absorbed (fa) during the single-pass perfusion were made from seven steady-state concentrations in the outlet perfusate (60-120 min) Each sample represents the mean concentration of the aliquots collected for each 10 min interval.

The net water flux (NWF) per cm in the isolated jejunal segment was calculated for each sample:

$$\text{Net water flux} = \frac{(1 - PEGout/PEGin)Qin}{L}$$

Where, PEGin and PEGout are the concentrations of ^{14}C-PEG 4000 (dpm/mL) entering and leaving the segment, respectively. Qin is the flow rate of the perfusion solution and L is the length of the perfused jejunal segment (10 cm). The concentration of each compound in the perfusate leaving the intestine was corrected for water flux before any other calculations.

The amount of each drug (telithromycin or antipyrine) that disappeared during the single-passage through the jejunal segment was assumed to have been absorbed (fa):

$$Fa=1-(Cout \bullet PEGin/Cin \bullet PEGout)$$

Where, Cin and Cout are the inlet and outlet concentrations of each compound, respectively.

The jejunal effective permeability (Peff) was calculated according to a well mixed tank model as Follows:

$$Peff = \frac{(Cin - Cout) * Qin}{Cout * 2\pi rL}$$

Where, the surface of the cylinder ($2\pi rL$) of the jejunal segment was calculated using the intestinal radius (r=1.75 cm) and length (L=10 cm) of the segment.

Statistics:

Descriptive statistics were calculated for all these parameters.

RESULTS:

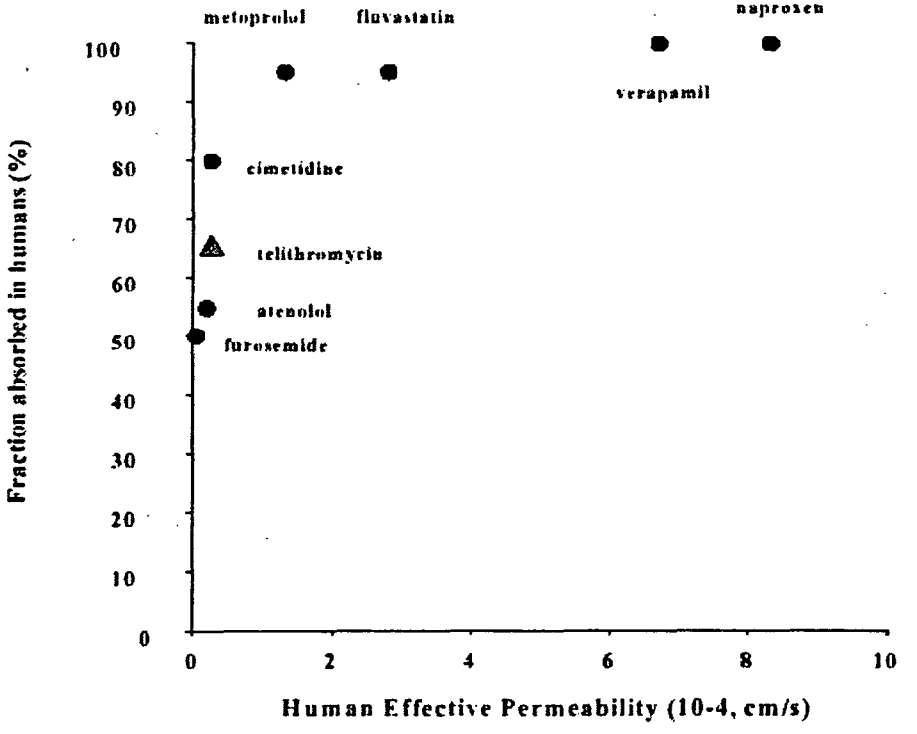
Before the start of this study, an vitro stability study in jejunal fluid and an in vitro adsorption study on the ——— tube were performed and showed that telithromycin was stable in the jejunal fluid and did not adsorb on the tube. Compared to the initial concentrations, the deviations observed after 120 minutes of incubation at 37°C were between –13.6 and 10.2%. HMR 3647 was stable in perfusion solution.

The calculated parameters are shown in Table 1. The mean (CV%) of the fraction absorbed (fa) of telithromycin from the perfused jejunal segment was 14% (33%). The mean (CV%) jejunal

Table 1. Jejunal effective permeability, absorption at the level of the jejunal segment of telithromycin, antipyrine, PEG recovery, net water flux Qout osmolality and pH

	HMR3647		Antipyrine						
	Peff	fa	Peff	fa	PEG recovery	NWF	Qout	Osm	pH
Subject	(10^{-4} cm/s)	(%)	(10^{-4} cm/s)	(%)	(%)	(mL/hxcm)	(mL/min)	(mOsm/L)	
1									
2									
3									
4									
5									
6									
N	6	6	6	6	6	6	6	6	6
MEAN	0.54	14	3.20	50	86	3.5	2.46	280.5	7.04
95% CI	0.34-0.74	10-18	2.63-3.77	45-55	69-103	2.3-4.7	2.12-2.80	276-286	6.51-7.57
MIN									
MAX									
SD	0.23	5.0	0.65	6.0	20	1.4	0.39	5.9	0.61
CV	43	33	20	11	23	40	16	2.0	9.0
SEM	0.19	4.0	0.54	5.0	17	1.0	0.29	4.8	0.45

Figure 1. Fraction absorbed in human versus human effective permeability



STUDY NUMBER: 1058

TITLE: An open, cross-over study to assess the effect of multiple dose of rifampicin (600 mg QD) on the single dose and multiple dose pharmacokinetics of telithromycin (800 mg QD) in healthy male subjects

OBJECTIVES:

1) To assess the effect of multiple dose rifampicin (600 mg QD) on the single dose and multiple dose pharmacokinetics of telithromycin (800 mg QD) in healthy male subjects
2) 2) To assess the effect of multiple dose telithromycin on multiple dose pharmacokinetics of rifampicin and to assess the safety of the co-administration of telithromycin and rifampicin

DESIGN: This study was an open, single center, non-randomized, two period cross-over study. The two treatment periods were the following:

- Treatment period 1: multiple dose administration of 800 mg telithromycin QD for 5 days (Days 1 to 5)
- Treatment period 2: multiple dose administration of 600 mg rifampicin for 10 days (Days 1 to 10 –induction period) immediately followed by co-administration of multiple dose of 600 mg rifampicin QD and multiple dose of 800 mg telithromycin for 5 days (Days 11 to 15), immediately followed by a last dose of 600 mg rifampicin alone (Day 16) in order to maintain the induction during the whole elimination phase of telithromycin.

FORMULATION: 400 mg telithromycin tablet (1012056), 300 mg Rifadine® tablet (1A0015)

SAMPLING:

To determine single dose plasma concentration of telithromycin, blood samples were taken just before dosing, at 0.5h, 1h, 1.5h, 2h, 3h, 4h, 5h, 6h, 8h, 10h and 12 hours postdose at day 1 (period 1, telithromycin alone), and day 11 (period 2, telithromycin+rifampicin).

To determine multiple dose plasma concentration of telithromycin, blood samples were collected before dosing, at 0.5h, 1h, 1.5h, 2h, 3h, 4h, 5h, 6h, 8h, 12h, 24h and 48 hours postdose at day 5 (period 1) and day 14 (period 2). Additional blood samples were drawn before dosing from day 2 to day 4 and day 12 to day 14.

To determine multiple dose plasma concentrations of rifampicin after both treatments [rifampicin alone (Day 10) and telithromycin + rifampicin (Day 15)], blood samples were drawn just before dosing, at 0.5h, 1h, 1.5h, 2h, 3h, 4h, 5h, 6h, 8h, 10h and 12 hours postdose. In addition, blood samples were taken at 24h and 48 hours postdose at day 15.

Urine samples were collected at Day 1, Day 3, Day 5, Day 7, Day 9, Day 10 during rifampicin treatment alone, and at Day 11, Day 13, Day 15 and Day 17 during telithromycin + rifampicin treatment.

ASSAY:

The accuracy and precision of the plasma assays for telithromycin and rifampin and for urinary cortisol and 6-beta-OH-cortisol are summarized below:

Analyte	Samples	Accuracy[a]	Precision[b]
	Plasma		
Telithromycin	QC samples	95.2-100.0%	4.1-14.2%
	Calibration standards	98.0–102.7%	1.6–6.8%
Rifampicin	QC samples	95.25–98.43%	1.84–3.65%
	Calibration standards	97.24–102.8%	1.34–4.40%

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

Analyte	Samples	Accuracy[a]	Precision[b]
	Urine		
Cortisol	QC samples	93.90–98.90%	10.54–18.75%
	Calibration standards	99.99–100.03%	0.00 %
6β-OH-cortisol	QC samples	90.0–107.54%	11.11–13.18%
	Calibration standards	91.7–114.0%	3.60–10.48%

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

DATA ANALYSIS:

Pharmacokinetics:

The pharmacokinetic parameters for telithromycin at first treatment period on day 1 (telithromycin single dose) and day 5 (telithromycin at steady state) were calculated. For rifampicin, the pharmacokinetic parameters at second treatment period on day 10 (rifampicin alone) and day 15 (rifampicin+telithromycin) were calculated using conventional method. The parameters include: C_{max}, Tmax, AUC(0- 24), AUC(0-infinity), $t_{1/2}$, λ_z, and Cmax/AUC(0- 24). The ratio of the 6β-hydroxycortisol to cortisol in urinary was calculated at each day.

Statistics:

Descriptive statistics for plasma concentrations and pharmacokinetic parameters of telithromycin were calculated after administration of telithromycin alone and telithromycin + rifampicin. Point estimates of telithromycin parameters were calculated as the geometric mean of the individual ratios of each parameter taking into account the parameters of telithromycin alone as reference. The effect of rifampicin on telithromycin pharmacokinetics was assessed using an analysis of variance comparing the single dose pharmacokinetic parameters of telithromycin between treatments (telithromycin + rifampicin versus telithromycin) and comparing the multiple dose pharmacokinetic parameters of telithromycin between treatments.

RESULTS:

Twelve (12) subjects were enrolled and completed the study. They were aged between 20 and 35 years old (mean 25.9 years) and weighing between 59.5 and 82.1 kg (mean 69.7 kg).

The pharmacokinetic parameters of telithromycin and the results of ANOVA analysis were shown in Table 1 and the concentration profiles of telithromycin after single and repeated doses of telithromycin with or without rifampicin are shown in Figures 1 and 2. After single dose, mean maximal plasma concentrations were reached 3 hours after dosing, with mean Cmax values of 1.22 mg/L after administration of telithromycin alone (Day 1) and 0.316 mg/L after administration of telithromycin with rifampicin (Day 11). Twenty-four hours after dosing, telithromycin was still quantifiable in all subjects after telithromycin alone with a mean C_{24hr} value of 0.0260 mg/L (day 2) and was no longer quantifiable in seven out of twelve subjects after telithromycin with rifampicin (day 12).

After repeat dose administration for 5 days, mean maximal plasma concentrations of telithromycin were reached 3 hours after dosing, with mean Cmax values of 1.55 mg/L after administration of telithromycin alone (day 5) and 0.328 mg/L after administration of telithromycin with rifampicin (day 15). Forty-eight hours after repeated dosing, telithromycin was still quantifiable after telithromycin alone (mean value of 0.0110 mg/L) and was no longer quantifiable in all subjects after telithromycin with rifampicin.

Co-administration of rifampin with telithromycin significantly decreased the single dose AUC(0-24) and Cmax of telithromycin by 81% and 73%, respectively. Co-administration of rifampin with telithromycin following repeat dose administration significantly decreased the steady state AUC(0-24) and Cmax of telithromycin by 86% and 78%, respectively. The Tmax of telithromycin was not significantly affected by rifampin co-administration following either single or repeat dose administration. The mean half-life of telithromycin was reduced by approximately 50% with rifampin co-administration. The individual C_{max} and AUC values after single dose or at steady state with and without rifampicin are shown in Figures 3 and 4.

The pharmacokinetic parameters of rifampicin are shown in Table 2 and the concentration vs time profile is shown in Figure 5. The mean maximal plasma concentrations of rifampicin were reached at 1 hour after administration of rifampicin alone (day 10) and at 2 hours after administration of rifampicin + telithromycin (day 15) with mean Cmax values of 7.2 mg/L and 4.30 mg/L, respectively. Mean C_{max} and AUC(0-12h) of rifampin were both reduced by 42% following co-administration with telithromycin. A small, but statistically significant reduction in the half-life of rifampin was detected following co-administration with telithromycin ($p \leq 0.05$). The individual Cmax and AUC of rifampicin with or without telithromycin co-administration are shown in Figure 6.

The ratio of 6β-hydroxycortisol to cortisol in urine, which is believed to reflect CYP3A4 activity, was monitored on Days 1, 3, 5, 7, 9, 11, 13, 15, and 17 of rifampicin treatment and the results are shown in Table 3 and Figure 7. These results indicated that the urinary cortisol ratio appeared to increase from Day 1 to Day 5 and then remained relatively constant after Day 5.

CONCLUSIONS:

1. When rifampicin was co-administered with telithromycin, the mean C_{max} and AUC of telithromycin were decreased by 73% and 81%, respectively, after the first dose of telithromycin.

2. When rifampicin was co-administered with telithromycin, the mean steady state C_{max} and AUC of telithromycin were decreased by 78% and 86%, respectively, after repeated doses of telithromycin.

3. The elimination half-life of telithromycin was reduced by 50%.

4. Telithromycin should be contraindicated with rifampicin, and should also not be co-administered with rifampicin within 2 weeks after discontinuation of rifampicin therapy. .

COMMENTS:

Since telithromycin is CYP3A substrate and inhibitor, it is difficult to explain why rifampicin exposure was decreased when co-administered with telithromycin. The sponsor speculated that repeated administration of rifampicin induced the metabolism of itself to result in a lower rifampicin exposure.

Table 1. Telithromycin pharmacokinetic parameters (n = 12)

Parameter	Statistics	Single oral dose of 800 mg telithromycin			
		Telithromycin Alone (day 1)	Telithromycin + Rifampicin (600 mg QD) (day 11)	PE[a] (CV%) [min-max] {90%CI}	ANOVA
C_{max} (mg/L)	Mean (CV%) [Min-Max]	1.35 (28)	0.365 (29)	0.27 (26) [0.14-0.55] {0.22, 0.32}	***
t_{max} (h)	Median [Min-Max]	2.50 [1.00-3.00]	3.00 [1.00-3.00]	NA	NS[b]
AUC(0-24h) (mg.h/L)	Mean (CV%) [Min-Max]	7.44 (42)	1.38 (42)	0.19 (33) [0.096-0.34] {0.15-0.23}	***
$C_{max}/AUC_{(0-24h)}$ (1/h)	Mean (CV%) [Min-Max]	0.1900 (17) [0.1410-0.2680]	0.277 (18) [0.214-0.366]	1.45 (16) [1.04-1.93] {1.30-1.63}	***
C_{24h} (mg/L)	Mean (CV%) [Min-Max]	0.0259 (45)	LOQ	0.26 (20) [0-0.33] {0.20-0.34}	***
$t_{1/2,\lambda 1}$ (h)	Mean (CV%) [Min-Max]	1.81 (42)	1.11 (34)[c]	0.58 (42) [0.28-1.47]	*
$t_{1/2,\lambda 2}$ (h)	Mean (CV%) [Min-Max]	NC	NC	NA	NA
		Multiple oral dose of 800 mg telithromycin			
		Telithromycin Alone (day 5)	Telithromycin + Rifampicin (600 mg QD) (day 15)	PE[a] (CV%) [min-max] {90%CI}	ANOVA
C_{max} (mg/L)	Mean (CV%) [Min-Max]	1.76 (27)	0.388 (41)	0.21 (23) [0.10-0.37] {0.18-0.25}	***
t_{max} (h)	Median [Min-Max]	3.00 [0.50-3.00]	2.50 [1.00-4.00]	NA	NS
AUC(0-24h) (mg.h/L)	Mean (CV%) [Min-Max]	10.2 (44)	1.44 (37)	0.14 (31) [0.083-0.31] {0.12-0.18}	***
$C_{max}/AUC_{(0-24h)}$ (1/h)	Mean (CV%) [Min-Max]	0.1820 (17) [0.1210-0.2310]	0.273 (24) [0.189-0.417]	1.48 (20) [0.82-2.02] {1.28-1.71}	***
C_{24h} (mg/L)	Mean (CV%) [Min-Max]	0.0542 (48)	0.0050 (79)	0.12 (37) [0-0.37] {0.089-0.18}	***
$t_{1/2,\lambda 1}$ (h)	Mean (CV%) [Min-Max]	1.80 (43)	1.15 (53)[d]	0.59 (35) [0.24-1.03]	**
$t_{1/2,\lambda 2}$ (h)	Mean (CV%) [Min-Max]	9.40 (21)	5.42 (50)[e]	0.52 (37) [0.22-0.87]	**

(a) PE: Point estimate = geometric mean of the individual ratios of each parameter taking into account the parameters of telithromycin alone as reference; (b) Non parametric test for tmax; (c) N=9; (d) N=10; (e) N=11; NA: not applicable; NC: Not calculated; LOQ: limit of quantification; ANOVA: NS: non significant ($p > 0.05$); * $0.01 < p \leq 0.05$; ** $0.001 < p \leq 0.01$; *** $p \leq 0.001$

Table 2. Rifampicin pharmacokinetic parameters (n=12)

Parameter	Statistics	Rifampicin alone (600 mg QD) at day 10	Rifampicin (600 mg QD) + Telithromycin (800 mg QD) at day 15	PE[a] (CV) [min-max]	ANOVA
C_{max} (mg/L)	Mean (CV%) [Min-Max]	8.28 (34)	4.77 (65)	0.42 (77) [0.046-1.29]	**
t_{max} (h)	Median [Min-Max]	1.50	1.75	NA	NS[b]
AUC(0-12h) (mg•h/L)	Mean (CV%) [Min-Max]	30.8 (26)	17.8 (70)	0.38 (96) [0.031-1.07]	*
C_{max}/$AUC_{(0-12h)}$	Mean (CV%) [Min-Max]	0.270 (21) [0.196-0.399]	0.300 (23) [0.190-0.398]	1.11 (21) [0.70-1.54]	NS
$t_{1/2,\lambda 2}$ (h)	Mean (CV%) [Min-Max]	1.857 (15)	1.693 (17)	0.91 (9) [0.70-1.05]	*

(a) PE: Point estimate: geometric mean of the individual ratios of each parameter taking into account the parameters of rifampicin alone as reference; (b) Non parametric test for t max ANOVA: NS: non significant ($p > 0.05$); * $0.01 < p \leq 0.05$; ** $0.001 < p \leq 0.01$; *** $p \leq 0.001$
NA: not applicable

Table 3. 6β-hydroxycortisol/cortisol urinary ratio

DAY	1	1	3	5	7	9	10	11	13	15	17	ANOVA [b]
Mean	9.6	4.7 [a]	13.3	22.5	18.4	22.4	29.6	28.9	17.6	28.9	20.6	***
(CV%)	(49)	(95)	(70)	(61)	(60)	(67)	(74)	(65)	(61)	(67)	(43)	

(a): N=11
(b): Significance of p value from ANOVA table: NS: Non significant (p>0.05), *: 0.01<π£0.05, **: 0.001<π£0.01, ***: π£0.001

APPEARS THIS WAY
ON ORIGINAL