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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00537563
		Study Code:	HMR3647A_4017
Generic drug name:	Telithromycin	**Date:**	03/Oct/2007

Title

A prospective, randomized, double-blinded, active-controlled study for the evaluation of the efficacy, safety, and pharmacoeconomics of oral telithromycin (Ketek™) 800 mg once a day for 5 days vs moxifloxacin (Avelox®) 400 mg once a day for 10 days in the treatment of acute maxillary sinusitis (AMS) in adults

Investigators, study sites

Multicenter study: 41 sites in the US
Coordinating Investigator: Berrylin Ferguson, MD, Pittsburgh, PA

Study duration and dates	The first subject was enrolled on 24 December 2002. The last subject exited the study on 4 September 2003. Study duration was approximately 8 months.	**Phase**	IIIb/IV

Objectives

Primary

To demonstrate equivalence in clinical efficacy between telithromycin and moxifloxacin at the post-therapy/test of cure (TOC) visit (Days 17 to 24), and to assess the safety of telithromycin given once daily for 5 days vs moxifloxacin given once daily for 10 days in the treatment of subjects with AMS

Secondary

To compare clinical outcomes at the late post-therapy/follow-up (LPT) visit (Days 31 to 36) of telithromycin given for 5 days vs moxifloxacin given for 10 days. To compare the bacteriological outcome at the post-therapy/TOC (TOC) visit after 5 days treatment with telithromycin vs 10 days treatment with moxifloxacin. To determine the economic impact of the 2 study treatments assessed by cost-effectiveness analysis of healthcare resource utilization

To assess the health economic and quality of life (QOL) impact of treatment success vs treatment failure, overall, and between telithromycin and moxifloxacin

Tertiary

To characterize the time to becoming symptom-free from the start of therapy, based upon subject-reported outcome

Study design

This was a multicenter, prospective, randomized (1:1), double-blind, active-control, parallel-group study. Subjects randomized to the telithromycin treatment arm received oral telithromycin 800 mg once daily for 5 days followed by placebo for 5 days. Subjects randomized to the moxifloxacin treatment arm received oral moxifloxacin 400 mg once daily for 10 days.
Subjects completed 5 visits:
baseline/pre-therapy visit (Day 1)
on-therapy visit (Days 3 to5)
end of therapy visit (Days 11 to 13)
post-therapy/test of cure (TOC) visit (Days 17 to 24)
late post-therapy/follow-up (LPT) visit (Days 31 to 36)

Number of subjects planned

Approximately 350 subjects were to be enrolled in order to obtain a total number of approximately 280 subjects.

Inclusion criteria

Adult subjects, aged 18 years or older, AMS diagnosed (clinically and radiologically) who were willing to undergo rhinoscopic aspiration or deep nasal swab at the baseline/pre-therapy visit. Female subjects of childbearing potential were required to have a negative pregnancy test before undergoing any study procedure and to use an accepted contraceptive method during the study.

Treatments

Study medication: telithromycin 800 mg (two 400-mg tablets) orally once a day in the morning for 5 days, followed by placebo 2 tablets orally once a day in the morning for 5 days.
Moxifloxacin 400 mg plus placebo, 1 tablet, orally once a day in the morning for 10 days.
Study medication was self-administered from a treatment box that contained blister packs with 2 capsules/blister.

Efficacy data

Clinical outcome at the TOC visit and at the LPT visit was determined by the investigator's assessment of clinical and radiological signs and symptoms. Outcome was assessed as success/failure/indeterminate. Bacteriological outcome was assessed by the investigator at the TOC visit as satisfactory/unsatisfactory/indeterminate.

Safety data

Safety was evaluated by monitoring of treatment-emergent adverse events (TEAEs) from the time of informed consent through the LPT visit. Intensity and relatedness of TEAEs to study treatment was assessed by the investigator. Safety was also assessed by physical examinations, vital signs measurements, and pregnancy testing in women of childbearing potential.

Quality-of-life data

Health-related QOL was assessed using the SF-36 V2 questionnaire completed by subjects on a daily basis throughout the study.

Health economic data

Healthcare utilization, sinusitis-related healthcare utilization, associated unit cost estimates, and the value of lost productivity were assessed based on data recorded in the subject diary.
The primary objective was to demonstrate equivalence on a per-protocol basis at the TOC visit for the telithromycin treatment arm, relative to the moxifloxacin treatment arm. The null hypothesis was that the success rate of the telithromycin treatment arm minus the success rate of the moxifloxacin treatment arm was =-15%. In order to demonstrate equivalence, between-group comparisons were made in terms of a two-sided 95% CI for the difference in clinical success, with the 2 treatments considered equivalent if the lower limit of the CI was >-15%. Based upon an 85% response rate for both treatment arms and 140 subjects in each arm valid for the per-protocol analysis of clinical cure, the study had >90% power. Secondary efficacy analyses were analyzed using a similar CI approach.
The statistical analyses were performed on the SAS System for Windows, Release 8.02 TS Level 2MO.
Pharmacoeconomic and QOL data were analyzed using appropriate statistical techniques described in a separate statistical analysis plan.

Interim analysis

No interim analysis was performed.

Results – Study subjects and conduct

There were 5 study populations (see @@table below):
Safety: all randomized subjects who received at least 1 dose of study treatment
mITT: randomized subjects who received at least 1 dose of study medication and had clinical and radiological findings supporting a diagnosis of AMS
bmITT: mITT subjects with a bacteriological sample obtained at baseline that contained at least 1 of the target pathogens
PPc: mITT subjects without major protocol deviations
PPb: PPc subjects with a bacteriological sample obtained at baseline that contained at least 1 of the target pathogens

Population	Telithromycin n (%)	Moxifloxacin n (%)	Total N (%)
Screened	--	--	550
Randomized	173	176	349 (63.5)
Safety	173 (100.0)	176 (100.0)	349 (100.0)
mITT	159 (91.8)	163 (92.6)	322 (92.3)
bmITT	41 (23.7)	43 (24.4)	84 (24.1)
PPc	135 (78.0)	137 (77.8)	272 (77.9)
PPb	34 (19.7)	33 (18.8)	67 (19.2)

The primary reason for subjects not being randomized was failure to satisfy the clinical and radiological criteria for a diagnosis of AMS. One subject was successfully screened, but withdrew consent before being randomized. One site was designated an incomplete site due to inability of Aventis to confirm the validity of the data and the 20 enrolled subjects were excluded from analysis. Of the 349 randomized subjects, 79.9% completed the study. The rates of completion in each treatment arm were comparable: 80.9% of telithromycin subjects and 79.0% of moxifloxacin subjects completed the study. The most common reason for early discontinuation was a subject being lost to follow-up. Adverse events accounted for 5 telithromycin subjects (2.9%) and 7 moxifloxacin subjects (4.0%) not completing the study. Two telithromycin subjects and 4 moxifloxacin subjects withdrew consent after beginning treatment.
Protocol deviations excluded 38 subjects from the telithromycin group and 39 subjects from the moxifloxacin group from the PPc population. The most common deviations were failure to satisfy inclusion/exclusion criteria, taking a prohibited medication, or failure to meet visit window criteria. Waivers were granted for 33 subjects, primarily for visits outside the specified visit window (15 subjects), mucosal thickening <10 mm (9 subjects), and an excluded prior illness (6 subjects). Mean duration of study treatment was 9.6 days in the telithromycin treatment arm and 9.4 days in the moxifloxacin treatment arm. Dosages of study treatment are described in @@treatments, above. No dosage adjustments were permitted. Compliance with the study treatment regimen was 95.5% for the telithromycin treatment arm and 93.8% for the moxifloxacin treatment arm. The treatment arms were comparable in regard to demographic and baseline characteristics. Overall, the subjects in the safety population were predominantly female (61.9%) and white (90.5%). The mean age of subjects in the telithromycin treatment arm was 44.4 years with 9.2% of the subjects being age 65 or older. The mean age in the moxifloxacin treatment arm was 45.5 years with 13.6% of subjects being age 65 or older. The median duration of AMS was 8 days for subjects in the telithromycin treatment arm and 10 days in the moxifloxacin treatment arm. Of those subjects with sinusitis over the last year, the majority of subjects required antibiotic treatment for their AMS (1 to 3 episodes) for that period (92.1% of telithromycin subjects and 88.9% of moxifloxacin subjects). There were no substantial differences between treatment arms or study populations in any of the other demographic or baseline characteristic parameter.

Results – Efficacy

Telithromycin was equivalent to moxifloxacin in clinical outcome in the PPc, and mITT populations at the TOC and LPT visits and in the PPb population at the TOC visit.

Clinical outcome TOC visit	Telithromycin n (%)	Moxifloxacin n (%)	Difference Telithromycin-moxifloxacin		
			Difference %	95% CI	P value
PPc population					
Success	118 (87.4)	119 (86.9)	0.5	-8.1;9.2	.8930
Failure	17 (12.6)	18 (13.1)			
Total subjects	135 (100.0)	137 (100.0)			
PPb population					
Success	32 (94.1)	30 (90.9)	3.2	-12.4;18.8	.6173
Failure	2 (5.9)	3 (9.1)			
Total subjects	34 (100.0)	33 (100.0)			
mITT population					
Success	128 (80.5)	125 (76.7)	3.8	-5.8;13.4	.4041
Failure	31 (19.5)	38 (23.3)			
Total subjects	159 (100.0)	163 (100.0)			
Clinical outcome LPT visit					
PPc population					
Success	101 (78.3)	104 (78.8)	-0.5	-11;10.2	.9227
Failure	28 (21.7)	28 (21.2)			
Total subjects	129 (100.0)	132 (100.0)			
mITT population					
Success	108 (67.9)	111 (68.1)	-0.2	-11;10.6	.9734
Failure	51 (32.1)	52 (31.9)			
Total subjects	159 (100.0)	163 (100.0)			

The Breslow-Day test for homogeneity across sites and center in the PPc population indicated no evidence of heterogeneity in the treatment effect at the TOC visit (P>.5).
Telithromycin was equivalent to moxifloxacin in bacteriological outcome in the PPb and bmITT populations at the TOC visit.

Population	Telithromycin N (%)	Moxifloxacin N (%)	Difference Telithromycin-moxifloxacin		
			Difference %	95% CI	P value
Bacteriological outcome TOC visit					
PPb population					
Satisfactory	32 (94.1)	31 (93.9)	0.2	-14.2;14.5	.9754
Unsatisfactory	2 (5.9)	2 (6.1)			
Total subjects	34 (100.0)	33 (100.0)			
bmITT population					
Satisfactory	36 (87.8)	31 (72.1)	15.7	-3.4;34.8	.0732
Unsatisfactory	5 (12.2)	12 (27.9)			
Total subjects	41 (100.0)	43 (100.0)			

Both telithromycin and moxifloxacin demonstrated effectiveness against the target pathogens at the TOC visit. Rates of satisfactory outcome were higher in the PPb population than in the bmITT population. In the telithromycin treatment arm (PPb population), 100% of subjects with *H influenzae, M catarrhalis*, or *S aureus* had a satisfactory bacteriological outcome. In the moxifloxacin treatment arm (PPb population), 100% of subjects with *H influenzae* and *M catarrhalis* had a satisfactory bacteriological outcome. In the bmITT population, the highest rate of success in the telithromycin treatment arm was against *S pneumoniae* (95.0%); in the moxifloxacin treatment arm, the highest rate of success was against *H influenzae* (87.5%).

Target pathogen Single or multiple	Telithromycin			Moxifloxacin		
PPb population	**N**	**Satisfactory Outcome n (%)**	**Unsatisfactory Outcome n (%)**	**N**	**Satisfactory Outcome n (%)**	**Unsatisfactory Outcome n (%)**
S pneumoniae	17	16 (94.1)	1 (5.9)	8	7 (87.5)	1 (12.5)
H influenzae	11	11 (100.0)	0 (0.0)	14	14 (100.0)	0 (0.0)
M catarrhalis	2	2 (100.0)	0 (0.0)	6	6 (100.0)	0 (0.0)
S aureus	3	3 (100.0)	0 (0.0)	6	5 (83.3)	1 (16.7)
S pyogenes	2	1 (50.0)	1 (50.0)	1	0 (0.0)	1 (100.0)
Total	34	32 (94.1)	2 (5.9)	33	31 (93.9)	2 (6.1)
bmITT population						
S pneumoniae	20	19 (95.0)	1 (5.0)	10	7 (70.0)	3 (30.0)
H influenzae	13	12 (92.3)	1 (7.7)	16	14 (87.5)	2 (12.5)
M catarrhalis	4	3 (75.0)	1 (25.0)	7	6 (85.7)	1 (14.3)
S aureus	4	3 (75.0)	1 (25.0)	10	5 (50.0)	5 (50.0)
S pyogenes	2	1 (50.0)	1 (50.0)	2	0 (0.0)	2 (100.0)
Total	41	36 (87.8)	5 (12.2)	43	31 (72.1)	12 (27.9)

None of the target pathogens were resistant to telithromycin or moxifloxacin. *S pneumoniae* isolates that were resistant to penicillin or erythromycin were susceptible to both study treatments. All *H influenzae* isolates from subjects in the PPb population were tested for ampicillin susceptibility and ß-lactamase production; both study treatments were 100% effective against the ampicillin resistant and ß-lactamase producing isolates.

One telithromycin subject did not have a target pathogen isolated at study entry but at the TOC visit, *Enterobacter gergoviae* was identified. The subject was assessed as having a superinfection, clinical outcome of treatment failure, and an unsatisfactory bacteriological outcome. Two subjects (1 in each treatment arm) were assessed as having an eradication of the causative pathogen and a reinfection: both subjects had *S pneumoniae* at study entry and developed *H influenzae* at the TOC visit. No subjects had a reinfection with the causative pathogen in the PPb population.

Subanalyses examining demographic-, infection-, and AMS-related prognostic factors on the primary efficacy variable were performed. Subjects aged 65 years and older who were treated with telithromycin revealed more elderly (=65 years of age) telithromycin subjects (92.9%), compared with elderly moxifloxacin subjects (68.4%) who experienced a clinical success. Telithromycin subjects who smoke experienced more clinical success (88.9%), compared with those moxifloxacin subjects who smoke (83.3%). Other demographic factors such as: sex, race, age (<65 years of age), or smoking status (ex-smoker or non-smoker) did not reveal trends that were clinically meaningful.

Lastly, clinical success reflected bacteriological satisfaction (satisfactory) in 62 out of 63 subjects in the PPb population. Clinical failure reflected bacteriological dissatisfaction (unsatisfactory) in 4 out of 4 subjects. One out of 67 subjects was assessed as a clinical failure with bacteriological satisfaction (satisfactory).

Results – Safety

High compliance scores signified that subjects received their scheduled study medication over the course of the 10-day treatment period.

Alert terms were not specified and overdose was not observed with telithromycin or moxifloxacin treatment. There were no deaths; 1 subject experienced a serious adverse event. This event, a nonspecific small intestinal obstruction, was observed in a 75-year old moxifloxacin subject, with a history of gastrointestinal disorders, including small bowel obstruction. This event was not related to moxifloxacin (as assessed by the investigator) and she recovered without sequelae; it did not led to study medication discontinuation. Eleven (11) subjects discontinued study medication due to TEAEs; comparable rates of discontinuation were observed between telithromycin and moxifloxacin. Of these, 16 types of events were observed and included (in alphabetical order): blurred vision, choking sensation, diarrhea, dizziness, dry mouth, dysuria, feeling hot, glossodynia, headache, mixed connective tissue disease, nausea, oropharyngeal swelling, otitis media, tendonitis, tremor, and vomiting. There were no observable trends in treatment groups, relationship to study medication, counteractive measures, onset or duration of TEAE, intensity, or the type of TEAE. Onset of these 16 types of TEAE ranged from 1 day to 9 days and durations were <7 days, with the exception of otitis media that lasted for 16 days in duration.

Over the course of the study, there were a total of 109 subjects (31.2%) with 187 events of TEAE in the total population (N=349). The TEAE rates were comparable between treatment groups as a total of 60 subjects (34.7%) with 99 events or a total of 49 subjects (27.8%) with 88 events were observed in the telithromycin and moxifloxacin groups, respectively. Adverse events observed in the MedDRA system/organ/class were comparable between the two treatment groups, with the exception of the gastrointestinal disorders and infections and infestation systems. Telithromycin treatment resulted in higher rates in both the gastrointestinal-type in 34 subjects (19.7%) for telithromycin vs 25 subjects (14.2%) for moxifloxacin and the infection and infestation-type system in 15 subjects (8.7%) for telithromycin vs 3 subjects (1.7%) for moxifloxacin. The most frequently reported TEAEs were nausea and diarrhea; nausea rates were comparable between the two treatment groups. Nausea events considered related to telithromycin treatment were observed in 10 of 11 subjects vs 8 of 9 subjects observed with moxifloxacin.

Particular adverse events included: blurred vision, diarrhea, dizziness, nausea, palpitations, rash, tendonitis, and vomiting. Comparable rates were observed between telithromycin and moxifloxacin, with the exception of diarrhea and dizziness. Diarrhea was considered related to telithromycin treatment and observed at a higher rate (as previously stated); dizziness was considered related to moxifloxacin treatment and also observed at a higher rate. Palpitation was observed in 1 moxifloxacin-treated subject and was considered not related to study medication as evidenced by the investigator stopping guaifenisn treatment. Blurred vision was observed in 3 telithromycin-treated subjects and 2 moxifloxacin-treated subjects during the on-therapy and post-therapy periods. Of these 5 subjects, 1 event was considered moderate or resulted in discontinuation of study medication. Time of onset of these events was 1 to 2 days from start of study medication, with one exception: a moxifloxacin-treated subject whose onset was 20 days after start of study medication (event occurred during post-therapy period). Of these 5 subjects, 1 required an action (the subject changed the time of taking their study medication). No subject required an intervention or counteractive measure. Of these 5 subjects, 2 were considered related to telithromycin treatment (as assessed by the investigator) or 4 recovered without sequelae; 1 moxifloxacin-treated subject discontinued their study medication due to this event and recovered without sequelae.

Vital signs and physical examinations were not remarkable.

In summary, telithromycin was well tolerated and the overall safety profile was consistent with the underlying disease and the known adverse events reported in the proposed product label. The safety profile of telithromycin was comparable to that observed with moxifloxacin.

Date of Report

22 April 2004