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Sponsor/company: sanofi-aventis	**ClinicalTrials.gov Identifier:** NCT00237445
	Study Code: HMR3647A_4027
Generic drug name: Telithromycin	**Date:** 07/Jan/2009

Title of the study:	A multinational, multicenter, randomized, double-blind study in areas of high pneumococcal resistance comparing the clinical efficacy and health outcomes of outpatients with mild to moderate community-acquired pneumonia (CAP) treated with either KETEK® (telithromycin) once daily for 7 days or ZITHROMAX® (azithromycin) once daily for 5 days: [HMR3647A/4027; COBRA II]
Investigator(s):	Multicenter
Study center(s):	43 centers were initiated in South Africa, Thailand, Tunisia, and United States. 29 centers enrolled patients

Study period: Date first patient enrolled: 21-Nov-2005 Date last patient completed: 20-Sep-2006	**Phase of development:** Phase. IV : efficacy and health outcomes

Objectives:	**Objectives:** Primary: To evaluate the clinical success rates of telithromycin versus azithromycin for treating adult outpatients (patients) with mild to moderate CAP in high pneumococcal bacterial resistance areas at the Test of Cure (TOC) visit (ie, Days 17 to 21) Secondary: (a) To compare the effect of telithromycin versus azithromycin on clinical efficacy in adult patients with mild to moderate CAP at the End of Therapy (EOT) visit (ie, Days 8 to 11); (b) to compare the effect of telithromycin versus azithromycin on bacterialogical efficacy in adult patients with mild to moderate CAP at the EOT and TOC visits; (c) to compare the effect of telithromycin versus azithromycin on the total symptoms score of pneumonia and on health outcomes in adult patients with mild to moderate CAP at the EOT visit and for health outcomes at the TOC visit [Health outcomes are defined as additional resource utilization which are not required by the clinical study protocol: eg, additional lower respiratory tract infection (LRTI)-related antibiotic use, LRTI-related hospitalization with length of stay, and LRTI-related office visit/emergency room visit.]; (d) to compare the effect of telithromycin versus azithromycin on clinical and bacteriological efficacy, total symptoms score and health outcomes in adult patients with mild to moderate CAP and *Streptococcus pneumoniae* isolated at study entry; (e) to evaluate bacterial culture positive rates of *S pneumoniae* in adult patients with mild to moderate CAP and positive urinary Binax NOW® *S pneumoniae* antigen test (Binax) results in high bacterial resistance areas; (f) to evaluate culture positive rates of susceptible and resistance *S pneumoniae* from sputum cultures; (g) to evaluate bacterial culture positive rates of the causative pathogen (*S pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*) in adult patients with mild to moderate CAP and positive Binax results at Visit 1 (baseline); and (h) to compare the safety of telithromycin versus azithromycin.
Methodology:	Multinational, multicenter, randomized, two-arm parallel group comparator (1:1) during a 7-day double-blind treatment period. Efficacy, health outcomes, and safety observations up to a 21-day observation period**.**
Number of patients:	Planned: 170 (85/treatment arm) evaluable patients. Assuming an evaluability rate of 85%, a total of approximately 200 (100/treatment arm) patients were to be enrolled Randomized: 110 patients (54 telithromycin; 56 azithromycin) Treated: 110 patients (54 telithromycin; 56 azithromycin)

Evaluated:

Analysis population	Telithromycin (n)	Azithromycin (n)	Total (N)
Randomized	54	56	110
Safety (treated)	54	56	110
Modified intent-to-treat (mITT)	54	56	110
Modified intent-to-treat bacteriological (mITTb)	30	29	59
Modified intent-to-treat bacteriological S pneumoniae (mITTbsp)	23	25	48
Per-protocol clinical (PPc)	48	47	95
Per-protocol bacteriological (PPb)	28	26	54
Per-protocol bacteriological S pneumoniae (PPbsp)	23	23	46

Diagnosis and criteria for inclusion:

Male or female 18 years of age or older (20 years of age or older in Tunisia) patient who had signs and symptoms of mild to moderate CAP for ≤ 7 days； positive Binax result and/or positive gram stain for diplococci; chest x-ray findings that support diagnosis of acute pneumonia with presence of a new infiltrate (patients with history of chronic obstructive pulmonary disease [COPD] required confirmation of new infiltrate versus prior chest x-ray); diagnosis of acute mild to moderate CAP defined as (a) fever (oral > 37.5°C [> 99.5°F], axillary > 37.4°C [> 99.4°F], or rectal > 38.5°C [> 101.5°F]), **or** (b) elevated total peripheral white blood cell (WBC) count > 10 000/mm3 or > 15% immature neutrophils (bands) regardless of peripheral WBC, **and** (c) new and sudden onset (defined as ≤ 48 hours) of at least two of the following signs or symptoms: cough, dyspnea or tachypnea, pleuritic chest pain, purulent sputum production or change in sputum character, or auscultatory findings (eg, rales and/or evidence of pulmonary consolidation); and sputum sample collection within 24 hours before baseline. [The sputum sample (or other respiratory secretion samples, as appropriate) was required for Gram staining, culture and pathogen identification, and susceptibility testing.]

Investigational product:

KETEK (telithromycin) capsule

Dose/ Administration:

Dose: 800 mg/day (as two capsules of 400 mg) for 7 days

Administration: orally once daily

Duration of treatment: 7 days

Duration of observation: between 17 and 21 days

Reference therapy:

ZITHROMAX (azithromycin) capsule

Dose/ Administration:

Dose: 500 mg/day (as two capsules of azithromycin 250 mg) for 1 day (Day 1). Immediately followed by 250 mg/day (as one capsule of azithromycin 250 mg and one capsule of placebo 0 mg) for 4 days (Days 2 through 5). Immediately followed by 0 mg (as two capsules of placebo) for 2 additional days (Days 6 and 7)

Administration: orally once daily

Criteria for evaluation:

Efficacy/Health Outcomes:

This study was terminated prior to achieving the target sample size. This document represents an abbreviated clinical study report (ACSR) where only the safety results are being presented in full. Only partial analyses of the efficacy evaluations were performed. No health outcomes evaluations were performed.

Efficacy: Clinical outcome and bacteriological outcome; infection-related signs and symptoms (investigator assessment); chest x-ray, microbiology (sputum or other respiratory secretions) for Gram staining, culture and pathogen identification, and susceptibility testing.

Health outcomes: Additional LRTI-related antibiotic use and associated costs; additional LRTI-related resources utilization (laboratory tests and procedures not required by the clinical study protocol) and associated costs; LRTI-related office visit/hospitalization, length of stay, and associated costs; and time to pneumonia symptoms resolution (patient diary).

Safety:	Adverse events reported by the patient or noted by the investigator. Additionally, Adverse Events of Special Interest (AESI) were pre-specified search terms which included cardiac, hepatic, visual, syncope, and Myasthenia gravis AESI types, as well as the following alert terms: jaundice, total bilirubin > 2 mg/dL (> 34 μmol/L), alanine aminotransferase > 3 times the upper limit of normal range (> 3 ULN), aspartate aminotransferase > 3 ULN, and visual disturbances. Standard biochemistry and hematology was assessed at baseline. Physical examinations including vital signs (body temperature, respiration rate, systolic and diastolic pressure, and pulse) were assessed.
Statistical methods:	The primary analysis was on the clinical success rates of telithromycin versus azithromycin at TOC visit in the modified intent-to-treat (mITT) population. The difference (telithromycin – azithromycin) in clinical success rates between telithromycin and azithromycin and a two-sided 95% confidence interval (CI) of the difference was calculated. If the difference was greater than zero, it was to be concluded that telithromycin is numerically superior over azithromycin. In the event the lower limit of the 95% CI for the difference was greater than zero, it was to be concluded that telithromycin was superior over azithromycin at a significance level $\alpha = 5\%$. Secondary analyses, clinical success rates at EOT visit and bacteriological satisfactory rates at EOT and TOC visits, were performed using the same methodology as the primary analysis in other subpopulations (mITT, modified intent-to-treat bacteriological [mITTb], modified intent-to-treat bacteriological S pneumoniae [mITTbsp], per-protocol clinical [PPc], per-protocol bacteriological [PPb], and/or per-protocol bacteriological S pneumoniae [PPbsp]). Bacteriological outcome at EOT and TOC visits were to be displayed for each causative pathogen. Concordance between clinical outcome and bacteriological outcome at TOC visit was summarized in the mITTb and PPb populations. Susceptibility testing for patients with clinical failure or bacteriological unsatisfactory at EOT and TOC visits; infection-related signs and symptoms assessed by the investigator; healthcare resource utilization from baseline to TOC visit by additional CAP-related visits, laboratory tests and procedures, additional CAP-related antibiotic use, and CAP-related hospitalization; time to symptoms resolution assessed daily by the patient; oxygen saturation levels and chest x-ray findings; and culture positive for *S pneumoniae* with correlative positive Binax results: all were provided as individual patient listings and no tabulation or analyses were performed due to the limited data and sample size. For the safety population, number and percent of patients were used to present the results for the adverse events, in particular the treatment-emergent adverse events (TEAEs). Descriptive statistics by treatment group of mean, standard deviation, median, and minimum and maximum were used to summarize vital signs. In addition, an analysis of variance model (ANOVA) was used to evaluate the differences between treatments for the changes from baseline in vital signs. Laboratory (biochemistry, hematology, and CD4+ T-lymphocytes [in HIV positive patients only]) data were listed, but not analyzed. No interim analysis was performed.

Summary:	This study was prematurely terminated in August 2006. [A decision was made to no longer proceed with a second identical study, which significantly impacted the value of this ongoing trial; therefore, enrollment in this study was terminated.] This document represents an ACSR where the safety results are being presented in full, as well as the primary and key secondary analyses of efficacy. No health outcomes analyses were performed.
Efficacy results:	**Primary variable**: Clinical outcome at TOC visit (mITT population): Numerical difference was not statistically significant

Clinical outcome – number of patients and rates at the TOC visit (mITT population)

Clinical outcome assessment	Telithromycin (N = 54)		Azithromycin (N = 56)		Difference (95% CI)	P value
	Number of patients (n)	Rate (%)	Number of patients (n)	Rate (%)		
Success	48	88.9	49	87.5	1.4% (−12.5%, 15.3%)	>.9999
Failure	4	7.4	5	8.9		
Indeterminate	2	3.7	2	3.6		

mITT = modified intent-to-treat
TOC = Test of Cure
95% Confidence interval (CI) based on a normal approximation.
P value based on Fisher exact test.

Secondary variables:

Clinical outcome at TOC visit (mITTbsp population): Numerical difference was not statistically significant

Clinical outcome – number of patients and rates at the TOC visit (mITTbsp population)

Clinical outcome assessment	Telithromycin (N = 23)		Azithromycin (N = 25)		Difference (95% CI)	P value
	Number of patients (n)	Rate (%)	Number of patients (n)	Rate (%)		
Success	22	95.7	22	88.0	7.7% (−11.7%, 27.0%)	.6099
Failure	1	4.3	3	12.0		
Indeterminate	0	–	0	–		

mITTbsp = modified intent-to-treat bacteriological S pneumoniae
TOC = Test of Cure
95% Confidence interval (CI) based on a normal approximation.
P value based on Fisher exact test.

Bacteriological outcome (mITTb population): Numerical differences were not statistically significant

Bacteriological outcome – total number of patients by pathogen/multiple pathogens (mITTb population)

Causative pathogen at baseline	Telithromycin (N = 30)			Azithromycin (N = 29)			P value
	Satisfactory	Unsatisfactory	Indeterminate	Satisfactory	Unsatisfactory	Indeterminate	
S pneumoniae only	20	0	0	21	0	1	1.0000
H influenzae only	6	0	1	4	0	0	1.0000
Multiple pathogens	2	1	0	2	1	0	1.0000
Total (overall per patient)	28	1	1	27	1	1	1.0000

H influenzae = *Haemophilus influenzae*; mITTb = modified intent-to-treat bacteriological; S pneumoniae = *Streptococcus pneumoniae*
Patients with clinical failure at End of Therapy visit (EOT) had bacteriological outcome assessed then; patients with clinical success at EOT, bacteriological outcome assessed at Test of Cure visit.
P value based on Fisher exact test.

Efficacy results (cont'd):	Bacteriological outcome (mITTbsp population): Numerical differences were not statistically significant

Bacteriological outcome – total number of patients by pathogen/multiple pathogens (mITTbsp population)

Causative pathogen at baseline	Telithromycin (N = 23)			Azithromycin (N = 25)			P value
	Satisfactory	Unsatisfactory	Indeterminate	Satisfactory	Unsatisfactory	Indeterminate	
S pneumoniae only	20	0	0	21	0	1	1.0000
Multiple pathogens	2	1	0	2	1	0	1.0000
Total (overall per patient)	22	1	0	23	1	1	1.0000

mITTbsp = modified intent-to-treat bacteriological S pneumoniae; S pneumoniae = *Streptococcus pneumoniae*
Patients with clinical failure at End of Therapy visit (EOT) had bacteriological outcome assessed then; patients with clinical success at EOT, bacteriological outcome assessed at Test of Cure visit.
P value based on Fisher exact test.

Clinical and bacteriological outcomes analyses at EOT and/or TOC visits in other subpopulations were consistent with the primary analysis.

Health outcomes results: No tabulation or analyses were performed due to the limited data and sample size.

Safety results:	Safety results : Number of patients with at least one adverse event during the study (safety population)

Event type	Telithromycin (n = 54)		Azithromycin (n = 56)		Total (N = 110)	
	Number of patients (n)	Rate (%)	Number of patients (n)	Rate (%)	Number of patients (N)	Rate (%)
Patient with TEAE[a]	4	7.4	12	21.4	16	14.5
Patient with possibly related TEAE	1	1.9	2	3.6	3	2.7
Patient with any treatment-emergent SAE	2	3.7	7	12.5	9	8.2
Patient with any possibly related treatment-emergent SAE	0	–	1	1.8	1	0.9
Death only	0	–	1[b]	1.8	1	0.9
Patient with alert term[c]	0	–	0	–	0	–
Patient with AESI[d]	0	–	0	–	0	–
Patient with significant overdose	0	–	0	–	0	–
Patient with permanent withdrawal from treatment due to TEAE	1	1.9	2	3.6	3	2.7

[a] Treatment-emergent adverse event was defined as any adverse event that occurred from the time the patient received first dose until 7 days after the last dose of investigational product; or, any adverse event that was considered possibly related to investigational product during the post-treatment period

[b] Death was not considered possibly related to investigational product as assessed by investigator

[c] Alert terms were specified in the clinical trial protocol

[d] Adverse Events of Special Interest (AESI) search criteria were specified in the statistical analysis plan

SAE = serious adverse event

Coding dictionary for adverse events is Medical Dictionary for Regulatory Activities terminology (MedDRA) Version 10.0.

Number of treatment-emergent adverse events[a] by overall system organ class frequency reported during the study (safety population)

System Organ Class	Telithromycin (n = 54)		Azithromycin (n = 56)		Total (N = 110)	
	Number of patients (n)	Rate (%)	Number of patients (n)	Rate (%)	Number of patients (N)	Rate (%)
Infections and Infestations	1	1.9	4	7.1	5	4.5
Gastrointestinal Disorders	1	1.9	2	3.6	3	2.7
Metabolism and Nutrition Disorders	1	1.9	1	1.8	2	1.8
Neoplasms Benign, Malignant, and Unspecified (incl cysts and polyps)	0	–	2	3.6	2	1.8
Respiratory, Thoracic and Mediastinal Disorders	0	–	2	3.6	2	1.8
Investigations	1	1.9	0	–	1	0.9
Renal and Urinary Disorders	1	1.9	0	–	1	0.9
Vascular Disorders	1	1.9	0	–	1	0.9
Musculoskeletal and Connective Tissue Disorders	0	–	1	1.8	1	0.9
Skin and Subcutaneous Tissue Disorders	0	–	1	1.8	1	0.9

[a] Treatment-emergent adverse event was defined as any adverse event that occurred from the time the patient received first dose until 7 days after the last dose of investigational product; or, any adverse event that was considered possibly related to investigational product during the post-treatment period

Coding dictionary for adverse events is Medical Dictionary for Regulatory Activities terminology (MedDRA) Version 10.0.

There were no clinically meaningful changes or observations in mean changes from baseline for any vital sign (heart rate, respiration rate, systolic and diastolic pressure, body temperature) when comparing telithromycin versus azithromycin at the EOT or TOC visit. Individual patients with clinical deterioration or lack of efficacy with hematology results at EOT visit were not remarkable.

Date of report:	15-April- 2008
Date of report and re-inssuance of report:	12-December- 2008