These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	ClinialTrials.gov Identifier:	NCT00132951
		Study Code:	HMR3647A_4019
Generic drug name:	Telithromycin	Date:	21/Aug/2009

Title of the study: A randomized, double-blind, parallel-group, multicenter study to compare clinical health outcomes of telithromycin versus azithromycin in outpatients with community-acquired lower respiratory tract infections (LRTIs) [HMR3647A/4019: KEYS]

Investigators: multicenter

Study centers: 439 centers were initiated in the United States and Canada. 281 centers enrolled subjects.

Publications (reference): not applicable

Study period:
Date first subject enrolled: 21 October 2004
Date last subject completed: 27 September 2006

Phase of development: IV: Efficacy, health outcomes, and safety

Objectives:

Primary: To determine if one course of antibiotic treatment with telithromycin is superior to azithromycin in the treatment of LRTIs of community-acquired pneumonia (CAP) and acute exacerbation of chronic bronchitis (AECB) in the community setting as measured by healthcare resource utilization.

Secondary: (a) to compare the efficacy and safety of telithromycin and azithromycin for the treatment of subjects with LRTIs; (b) to assess various patient-reported outcomes as follows: time to symptom resolution, days lost from work and days lost from usual activities, and health status (AECB subjects only); and (c) to assess additional healthcare resource utilization after treatment with telithromycin and azithromycin as follows: LRTI-related hospitalization with length of stay (days hospitalized post-randomization), referrals to specialists for LRTI-related concerns, antibiotic prescription for LRTI in addition to investigational product, other non-antibiotic prescriptions for LRTI symptoms, additional LRTI-related procedures (eg, clinical laboratory tests, x-rays, cultures).

Methodology: randomized, active-controlled, double-blind, parallel-group (1:1), multicenter study, stratified by diagnosis (CAP or AECB), with a 5-day (AECB) or 7-day (CAP) double-blind treatment period. Efficacy, health outcomes, and safety observations collected up to a 36 days following initiation of study treatment.

Number of subjects: Planned: 3720 (1452 [CAP] and 2268 [AECB]) evaluable subjects. Assuming a 10% attrition rate, a total of approximately 4100 (1600 [CAP] and 2500 [AECB]) subjects were to be enrolled

Randomized: 2051 subjects (1282 [CAP] and 769 [AECB])

Treated: 2042 subjects (1274 [CAP] and 768 [AECB])

Evaluated:

Analysis population	Telithromycin (n)	Azithromycin (n)	Total (N)
Randomized (via Interactive Voice Response System [IVRS])	1027	1024	2051
Safety (treated)	1022	1020	2042
Intent-to-treat (ITT)	941	934	1875
Modified intent-to-treat community-acquired pneumonia (mITT-CAP)	411	427	838
Per-protocol (PP)	Not performed		

Diagnosis and criteria for inclusion: male or female 18 years of age or older (CAP subject only) or 35 years of age or older (AECB subject only) who had confirmed clinical diagnosis (all subjects) and documented history of COPD (AECB subjects only). Confirmed clinical diagnosis in CAP subjects only included: postero-anterior or lateral chest x-ray that supported bacterial pneumonia (eg, presence of presumed new infiltrate(s); signs and symptoms of mild to moderate CAP defined as one of the following symptom of (a) fever (oral > 38°C [> 100.4°F], tympanic > 38.5°C [> 101.2°F], or rectal > 39°C [> 102.2°F]), (b) chills, or (c) pleuritic chest pain and one of the following symptom of (a) cough, (b) spontaneous product of purulent sputum or change in sputum character, or (c) auscultatory findings (eg, rales [crepitations] and/or evidence of pulmonary consolidation [dullness on percussion, bronchial breath sounds, egophony]); and dyspnea or tachypnea. Confirmed clinical diagnosis in AECB subjects only included increased sputum purulence with dyspnea or sputum. Documented history of COPD in AECB subjects only included: (a) basal forced expiratory volume in one second (FEV_1) < 70% and > 35% of predicted in the prior 12 months, (b) at least one AECB episode in the prior year, and (c) FEV_1/forced vital capacity (FVC) < 70% in the prior 12 months. Additional inclusion criteria in AECB subjects only included: spontaneous sputum and ≥ 10-year pack history of cigarette smoking.

Investigational product: KETEK® (telithromycin) capsule

Dose: 800 mg/day (as two capsules of 400 mg) for 7 days (CAP subjects only) or 5 days (AECB subjects only)

Administration: orally once daily

Duration of treatment: 5 or 7 days

Duration of observation: between 31 and 36 days

Reference therapy: ZITHROMAX® (azithromycin) capsule

Dose:

All subjects: 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).

CAP subjects only: 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: 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. Most health outcomes evaluations were not performed.

Efficacy: Overall clinical outcome, disease-specific infection-related signs and symptoms, daily symptoms, time to symptom resolution.

Health outcomes: Healthcare Resource Utilization, LRTI-related hospitalization length of stay, any non-protocol non-antibiotic prescription, costs associated with utilization of healthcare resources, health status, time lost from work or usual activities.

Safety: Adverse events reported by the patient or noted by the investigator. One Alert Term, "vision blurred", was specified for this study. Additionally, Adverse Events of Special Interest (AESI) were analyzed in this study that included: cardiac preferred terms (loss of consciousness, syncope, syncope vasovagal, cardiac arrest, death, electrocardiogram QT prolonged, torsade de pointes, sudden death, ventricular fibrillation, ventricular tachycardia, electrocardiogram QT corrected interval prolonged, cardiopulmonary failure, cardio-respiratory arrest, electrocardiogram QT interval abnormal, electrocardiogram repolarization abnormality, or long QT syndrome); Hepatobiliary Disorders System Organ Class (SOC), hepatic high level group term (Hepatobiliary investigations), hepatic high level term (hepatic therapeutic procedures), and hepatic preferred terms (blood alkaline phosphatase increased or blood lactate dehydrogenase increases); visual preferred terms (vision blurred, visual disturbance, diplopia, accommodation disorder, visual acuity reduced, photopsia, visual brightness, colour blindness, hallucination, photophobia, visual field defect, visual hallucination, blindness, amaurosis fugax, blindness transient, vitreous floaters, glare, tunnel vision, altered visual depth perception, chromatopsia, hypermetropia, retinal disorder, retinal oedema, scotoma, halo vision, myopia, papilloedema, presbyopia, amaurosis, anisometropia, astigmatism, blindness unilateral, cataract, colour vision tests abnormal, corrective lens user, cycloplegia, hemianopia, iritis, macular degeneration, macular oedema, ophthalmological examination abnormal, optic neuritis retrobulbar, retinal vein occlusion, retinopathy, staring, or uveitis); syncope preferred terms (any preferred term containing syncope, loss of consciousness, or depressed level of consciousness); and myasthenia gravis high level terms (neuromuscular junction dysfunction or neuromuscular dysfunction) and generic or tradename concomitant medications (any containing pyridostigmine or neostigmine).

[The sponsor defined a treatment-emergent adverse event (TEAE) as any adverse event that occurred during the on-treatment period (time after first dose of double-blind investigational product treatment until 7 days after the last dose) or an adverse event that was possibly related to the investigational product during the post-treatment period.]

Physical examinations including vital signs (body temperature, respiration rate, blood pressure, and pulse) were assessed.

Statistical methods: The primary analysis was the percentage of subjects with Healthcare Resource Utilization that are related to the current infection as reported by the investigator, in the intent-to-treat (ITT) population. Healthcare Resource Utilization is a composite endpoint of any unscheduled non-protocol return office visit, emergency room (ER) visit, hospitalization (visit), or issuance of additional non-protocol antibiotic prescription as reported in the case report form (CRF) at Visit 3 (up to Days 31 to 36 after initiation of study treatment). Statistical comparison between investigational product treatment groups was not performed.

Secondary analyses included: percentage of subjects with individual components of the Healthcare Resource Utilization, mean comparisons in the number of times (occurrence) of the Healthcare Resource Utilization (both composite endpoint and individual components), and percentage of subjects by clinical outcome (Cure, Failure, Indeterminate); all in the ITT population.

All remaining secondary endpoints were listed and not summarized; or, the secondary endpoints were not collected in the database.

For the safety population, number and percent of patients were used to present the results for the adverse events, in particular the TEAEs. Descriptive statistics by treatment group of mean, standard deviation, median, and minimum and maximum were used to summarize vital signs.

No interim analysis was performed.

Summary: The sponsor decided to terminate the study on 23 August 2006, since the study was not achieving its target enrollment over the planned two seasons and a changing external regulatory environment regarding KETEK further reduced the likelihood of adequate recruitment. This document represents an ACSR where the safety results are being presented in full, as well as the primary and few secondary analyses of efficacy. Most secondary efficacy analyses were not performed.

Efficacy results: Primary efficacy variable: Subjects with Healthcare Resource Utilization

Healthcare Resource Utilization as reported by the investigator at Visit 3 (ITT population)

Health outcomes assessment	Telithromycin (N = 941)		Azithromycin (N = 934)	
	Number of subjects (n)	Percent of subjects (%)	Number of subjects (n)	Percent of subjects (%)
Overall Healthcare Resource Utilization				
Composite endpoint	228	24.2	226	24.2
CAP (N = 573, telithromcyin; N = 578, azithromcyin)				
Composite endpoint	129	22.5	137	23.7
AECB (N = 368, telithromcyin; N = 356, azithromcyin)				
Composite endpoint	99	26.9	89	25.0

ITT = Intent-to-treat

As reported by the investigator (in the case report form at Visit 3) from initiation of investigational product until Visit 3. If the data at Visit 3 were missing, then from initiation of investigational product until Day 36.

Secondary efficacy variable:

Clinical outcome at each visit (ITT population)

Clinical outcome assessment	Telithromycin (N = 941)		Azithromycin (N = 934)	
	Number of subjects (n)	Percent of subjects (%)	Number of subjects (n)	Percent of subjects (%)
Overall (N = 1875)				
Visit 3[a]				
Cure	672	71.4	681	72.9
Failure	190	20.2	186	19.9
Indeterminate	79	8.4	67	7.2
CAP (N = 573, telithromcyin; N = 578, azithromcyin)				
Visit 2				
Cure	454	79.2	459	79.4
Failure	76	13.3	80	13.8
Indeterminate	43	7.5	39	6.7
Visit 3				
Cure	415	72.4	431	74.6
Failure	106	18.5	102	17.6
Indeterminate	52	9.1	45	7.8
AECB (N = 368, telithromcyin; N = 356, azithromcyin)				
Visit 3				
Cure	257	69.8	250	70.2
Failure	84	22.8	84	23.6
Indeterminate	27	7.3	22	6.2

[a] If a subject was a failure at a visit (scheduled or unscheduled), the clinical outcome assessment at all subsequent visits was imputed as failure(s). If there was no clinical failure at any prior visit, a missing clinical outcome was imputed as indeterminate.
AECB = Acute exacerbation of chronic bronchitis
CAP = Community-acquired pneumonia
ITT = Intent-to-treat
Visit 3 was defined as Days 31 through 36.

Health outcomes: In general, tabulation or analyses were not performed due to the limited data and sample size.

Safety results: In this study, a 7-day treatment course in adult subjects with mild to moderate CAP or a 5-day treatment course in adult subjects with AECB, both with KETEK 800 mg/day, was associated with the known overall safety profile of KETEK® (telithromycin) tablets described in the February 2007 version of the US prescribing information.

Overall, incidence of TEAE reporting was comparable between treatment groups, including deaths and other SAEs. However, more telithromycin subjects reported TEAEs leading to withdrawal of investigational product, the Alert Term “vision blurred”, and AESIs, as compared with that in azithromycin subjects.

The overall TEAE incidence was 21.8% in the safety population. The most frequently reported TEAE was diarrhoea in 45 subjects occurring more often on telithromycin than on azithromycin (26 telithromycin, 19 azithromycin), following (in decreasing order) by nausea (40 subjects), pneumonia (29 subjects), vomiting (28 subjects), cough (25 subjects), productive cough (21 subjects), dizziness (16 subjects), and headache (15 subjects). The remaining TEAEs reported were observed at a rate < 1%. Trends in TEAE intensity were not observed. TEAEs with a possible relationship to blinded investigational product were observed more frequently with telithromycin (40.4%) than with azithromycin (31.2%) among subjects who experienced TEAE(s). The TEAEs at a prevalence of ≥ 1% which were deemed possibly related to investigational product were (in decreasing order of proportion of subjects with TEAE possibly related to telithromycin): diarrhoea, vomiting, nausea, productive cough, cough, and pneumonia.

Safety results (cont'd.): There were 50 subjects who experienced a TEAE leading to permanent discontinuation of investigational product, which also lead to withdrawal from the study in 33 subjects (21 telithromycin, 12 azithromycin). At least twice as many telithromycin subjects (34) reported TEAEs leading to permanent discontinuation of investigational product, as compared with azithromycin subjects (16). The most frequently reported SOCs at ≥ 1% were Respiratory, Thoracic, and Mediastinal Disorders (1.1%) and Infections and Infestations (1.0%) in the telithromycin treatment group only. Overall, the most frequently reported TEAE leading to permanent discontinuation of investigational product was pneumonia (0.5%).

There were 71 (3.5%) subjects with TEAE-SAE in this study. The most frequently reported TEAE-SAE was pneumonia (19 subjects). More subjects 60 years of age and older reported a TEAE-SAE, compared with those younger than 60 years of age. Of these 71, 24 subjects permanently discontinued their investigational product due to SAE (14 telithromycin, 10 azithromycin).

In this study there were 12 cases of death, 7 deaths (4 telithromycin, 3 azithromycin) were TEAE-SAE and 5 deaths (2 telithomycin, 3 azithromycin) occurred post-treatment. Cardiac arrest was the most the frequent TEAE and cause of death observed. Most subjects (10 out of 12) who reported SAEs leading to death were older than 55 years of age. No death was considered by the investigator to be associated with the investigational product. The sponsor agreed with the investigator's assessment in all cases.

There were 5 subjects who reported the Alert Term of "vision blurred". The details were as follows:

· Four (4) subjects received telithromycin (0.4%). Two (2) of these 4 subjects also permanently discontinued investigational product due to this TEAE type. One of these 4 subjects reported this TEAE type as an SAE. Finally, 1 subject received azithromycin (0.1%).

· Onset was early and duration was less than 13 days. Of these 5, all subjects recovered without sequelae. Three (3) of the 5 subjects were younger than 50 years of age.

· The investigator stated there was a reasonable possibility all TEAEs of this type were associated with investigational product.

AESIs were reported in 15 subjects (10 telithromycin, 5 azithromycin). The most frequently reported MedDRA SOC was Eye Disorders (6 telithromycin, 1 azithromycin); the most frequently reported preferred term was "vision blurred" (4 telithromycin, 1 azithromycin; all possibly related to investigational product). Preferred terms belonging to the Hepatobiliary Disorders SOC was not reported in telithromycin subjects; however, 3 azithromycin subjects reported a preferred term belonging to this SOC. Onset of AESI was generally during the on-treatment period and short-lived at < 7 days in duration. Most AESIs resolved without sequelae excluding 2 subjects who died from cardiac arrest or cardio-respiratory arrest, 2 telithromycin subjects who permanently discontinued investigational produce due to "vision blurred", and 1 telithromycin subjects whose iritis had an unknown outcome at the end of the study. The investigator stated there was a reasonable possibility the AESI was associated with investigational product in half of these subjects.

By diagnosis, trends were generally not observed, excluding the following exceptions:

· Higher TEAE rates were reported in subjects diagnosed with CAP.

· Higher rates of TEAEs leading to permanent discontinuation of investigational product was reported in subjects diagnosed with CAP.

· The 4 subjects on telithromycin who reported the Alert Term "vision blurred" were all diagnosed with CAP.

· Of the 15 subjects who reported an AESI; 12 subjects (0.9% of total CAP) were diagnosed with CAP and 3 subjects (0.4% of total AECB) with AECB.

There were 2 azithromycin subjects who reported an overdose with a substance other than the investigational product; one was accidental (TEAE-SAE), and one was intentional (a post-treatment SAE). There was 1 telithromycin subject who reported a suicide attempt (TEAE-SAE). None of these 3 events were deemed related to the investigational product.

There were no clinically meaningful changes or observations in mean changes from baseline for any vital sign (body temperature, respiration rate, systolic and diastolic pressure, or pulse) when comparing subjects who received telithromycin versus azithromycin at Visit 3 or the final visit.

Date of ACSR: 30-Jul-2009