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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00538018
		Study Code:	HMR3647A_4015
Generic drug name:	Telithromycin	**Date:**	03/Oct/2007

Title

A multinational multicenter randomized open-label clinical study in areas of high resistance comparing the clinical efficacy and health outcomes of outpatients with mild to moderate community-acquired pneumonia treated with either telithromycin 800 mg once daily for 7-10 days, or a usually prescribed/ locally recommended single oral antibiotic ("usual care")

Investigator(s), study site(s)

Multinational/ 43 centers, in Asia: Hong-Kong (2), Korea (8), Taiwan (7), Thailand (2); in Europe: Greece (2), Hungary (2), Spain (9); and in Africa: South Africa (5), Tunisia (6).

Coordinating investigator: Pr. Visanu Thamlikitkul, Siriraj hospital, Bangkok, Thailand

Study duration and dates	**First subject included**:	January 15, 2003	**Phase**	IIIB/IV
	Last subject included:	June 08, 2004.		

Objectives

Primary
To demonstrate the superior efficacy of telithromycin over single-agent oral antibiotics usually prescribed and/ or recommended by local guidelines ("usual care") for treating adult outpatients with mild to moderate community-acquired pneumonia (CAP) in high bacterial resistance areas, at the test-of-cure (TOC) visit (days 17-21).

Secondary
To compare the effect of telithromycin *versus* "usual care" on the total symptoms score of pneumonia and on health outcomes, in CAP adult outpatients at the end-of-therapy visit (days 8-11) and for health outcomes at the TOC visit (days 17-21). Health outcomes were defined as additional resource utilization, which were not required by the protocol: e.g. additional low respiratory tract infection-related (LRTI-related) antibiotic use, LRTI-related hospitalization with length of stay and LRTI-related office visit/ emergency room visit.

To compare the effect of telithromycin *versus* "usual care" on clinical efficacy in CAP adult outpatients at end of therapy (days 8-11).

To compare the effect of telithromycin *versus* "usual care" on clinical and bacteriological efficacy, total symptoms score and health outcomes in CAP adult outpatients with *Streptococcus pneumoniae* isolated at inclusion, at end of therapy (days 8-11) and at test of cure (days 17-21).

To compare the safety of telithromycin *versus* "usual care".

Study design

This was a multinational, multicenter, centrally-randomized (1:1), open-labeled, parallel-group (1:1) comparative study.

Participating countries were to have a minimal level of erythromycin resistance in *Streptococcus pneumoniae* of 30%.

Subjects randomly received either telithromycin (TEL; 800 mg once daily) for 7 to 10 days, or a singleagent oral antibiotic chosen by the investigator according to his/ her judgment and/ or as recommended by local guidelines ("usual care"). Following the entry/ pre-therapy visit on day 1, subjects returned for end-oftherapy (EOT) visit (days 8-11) and test-of-cure (TOC) visit (days 17-21). A phone or clinic contact was performed at on-therapy visit (days 3-5).

An independent study Steering Committee composed of 9 international experts was set up in order to review study safety and provide scientific advice in the conduct of the study. Moreover, a study Review Board was constituted, which was composed of 3 members of the study Steering Committee (2 members from France and one member from Thailand). This Review Board was devoted to: 1) the elaboration of the study design and protocol review; 2) the blinded implementation of protocol rules to the population (evaluability) prior to database lock and statistical analysis plan finalization; and 3) the review of all results and the definition of exploratory analyses. For this purpose, the Review Board: a) blinded reviewed all chest X-rays (CXR) at inclusion leading to the definition of a subgroup of CAP subjects with central CXR confirmation; b) validated *ad hoc* clinical outcome classification by applying a stringent pre-defined outcome algorithm ("experts' outcome").

Number of subjects planned

The sample size needed to demonstrate the 10% superiority of TEL over "usual care" with 80% power and 5% alpha (two-sided) was **260 treated subjects by treatment group** (520 in total).

Inclusion criteria

Adult outpatients with mild to moderate CAP. Diagnosis of CAP was based on the presence of fever and/ or hyperleucocytosis and the new and sudden onset of at least two clinical signs and symptoms of pneumonia (cough, dyspnea or tachypnea, chills, pleuritic chest pain, purulent sputum or change in sputum character, auscultatory findings). Clinical diagnosis of CAP had to be confirmed by chest X-ray findings (e.g. presence of presumably new infiltrate). Specimens for microbiological documentation had to be collected within 24 hours prior to enrollment.

Treatments

Study medication: **telithromycin 800 mg** (2 x 400mg tablets) **once daily** per os **for 7-10 days**.

Comparator: **single-agent oral antibiotic**. The choice of the antibiotic and its dose, the duration of treatment were decided by the investigator according to his/ her clinical judgment and/ or local guidelines ("usual care").

The treatment allocation was centrally-randomized (1:1) by means of an interactive voicing randomization system (IVRS) using pre-established randomization lists. Randomization was balanced by centre.

Efficacy data

Pneumonia-related signs and symptoms

Chest X-ray (CXR)
Bacteriology (sputum or other respiratory secretions samples for culture, blood samples for culture and "atypical" serologies and urine sample for antigen detection of *S. pneumoniae*)
Symptoms score of pneumonia *via* a subject diary.

Safety data

Adverse Events (AE) reporting.

Statistical procedures

Study populations:
> Modified Intent-To-Treat (mITT) population (primary efficacy population): all included subjects, as treated, who received at least one dose of the study medication and with signs and symptoms of CAP and radiological findings supporting the diagnosis for CAP.
> Per Protocol (PP) population: all mITT subjects excluding those with major protocol violations.
> Safety population: all subjects who received at least one dose of the study treatment with post-baseline safety assessment.

Demographic and baseline characteristics:
Descriptive statistics, by treatment group and overall. Formal testing of homogeneity among treatment groups at Review Board request, using a Student t test or a Wilcoxon rank test for continuous data, and a Fisher's exact test for categorical data.

Primary efficacy variable:
Difference in clinical cure rate between TEL and "usual care" in the mITT population. Calculation of the two-sided 95% confidence interval (CI) of this difference. Rejection of the null hypothesis of no difference among groups whenever this CI did not include 0. Sensitivity tests: two-sided Fisher exact test, center adjusted Cochran-Mantel-Haenzel test.

Secondary efficacy variables:
- Difference in clinical cure rate between TEL and "usual care" in the PP population.
- Other secondary efficacy variables:
  - Clinical failure rates in the mITT and the PP populations: same analyses as for the primary efficacy endpoint.
  - Comparison of cure and failure rates at EOT: Fisher's exact test.
  - Difference in clinical cure rate between TEL and "usual care" in the mITT subjects with pneumococcal CAP.
  - Difference in clinical cure rate between TEL and "usual care" according to the class of antibiotics given in the "usual care" group.
  - Changes in each symptom scores and in total symptoms score: changes from day 1 at end point (last available value) analyzed using a fixed effect ANCOVA with treatment group as explicative variable, score at day 1 as co-variable. Time to resolution: median time to resolution of each symptom and of the total symptoms score was computed using the Kaplan Meier non-parametric estimate.

Exploratory analyses
In addition to the statistical analyses described in the Statistical Analysis Plan, several exploratory analyses were carried out at request of the Steering Committee or of the Review Board. Those exploratory analyses were defined and conducted after discussion on primary and secondary endpoints to better understand the difference observed and its robustness.
> In a meeting dated 30-Oct-2004, the Review Board stated that "even though the mITT population was defined in the Statistical Analysis Plan prior to data base freezing and it was similar to those in the phase III Telithromycin studies, it would be better to have results from a full ITT exploratory analysis". Accordingly,

an ITT analysis was defined, which included all patients (i.e. violation of CAP inclusion criteria) and incorporated indeterminate outcomes as failures (full ITT).

> The following analyses were based on expert outcome evaluation and/ or expert evaluation of CXR:

Efficacy by expert clinical outcome in the mITT population at TOC visit

Efficacy by expert clinical outcome in the PP population at TOC visit

Efficacy by expert clinical outcome in the "CXR expert confirmed CAP" mITT subgroup at TOC

> Efficacy was also analyzed by investigator clinical outcome population and by pathogens of interest in the bmITT population at TOC visit

> Descriptive analyses were carried out in subgroups of clinical interest to investigate the effect of some covariates based on investigator clinical outcome:

-by country in the mITT population at TOC visit

-by extrapolated Fine score at TOC visit

-adjusting for patients' weight (< 57 kg or =57 kg (corresponding to Q2 of weight), < 77 kg or =77 kg (corresponding to Q3 of weight) and adjusting for history of: diabetes, cardiac disorders, bronchospasm/ obstruction and any medical history. A logistic regression model taking into account the treatment group and the factor of interest as explicative variable was used.

>Reasons for failure were also explored including the time to antibiotic substitution/ addition.

Safety:

Descriptive statistics of incidences of AEs overall, by system organ and preferred term of the MedDRA code, broken down by treatment group and intensity. Same description for treatment related events.

Interim analysis

No interim analysis was planned for this study.

Results - Study subjects and conduct

In all, 505 subjects were included in the study from 15-Jan-2003 to 08-Jun-2004 at 43 investigating sites. Study populations are presented in the following table.

Study populations

	TEL	"Usual care"	Total
Randomized	256	249	505
mITT (1)	242	240	482
PP (2)	219	219	438
bmITT (3)	73	77	150
Pneumococcal CAP (4)	43	51	94
CAP with central CXR confirmation (5)	187	185	372
Safety (6)	253	245	498

(1) Of 505 randomized subjects, 23 were not eligible for entering the mITT population due to inclusion error (i.e. either 1) no diagnosis of CAP as per protocol and/ or according to the investigator and/ or according to the Review Board; 2) CAP requiring hospitalization at inclusion according to the investigator; 3) no study drug administration/ assessment).

(2) There were 44 mITT subjects not eligible for entering the PP population due to at least one major protocol violation.

(3) There were 332 mITT subjects not eligible for entering the bacteriological mITT (bmITT) population due to no bacteriological sample at inclusion or no causative pathogen and negative *S. pneumoniae* antigen result.

(4) There were 56 bmITT subjects not eligible for entering the pneumococcal CAP population due to no *S. pneumoniae* isolated at inclusion and negative *S. pneumoniae* antigen result.

(5) There were 110 mITT subjects not eligible for entering the central CXR confirmed CAP population due to no chest X-ray findings supporting the diagnosis of CAP according to the central CXR reading.

(6) There were 7 out of the 505 randomized subjects not eligible for entering the Safety population because they did not receive at least one dose of the study treatment with post-baseline safety assessment.

Demographic characteristics at entry for the mITT population are provided in the following table.

Demographics characteristics at entry _ mITT

	TEL	"Usual care"	Total
Male gender			
n (%)	138 (57.0)	135 (56.2)	273 (56.6)
Age (years)			
Mean (SD)	48.2 (17.1)	46.6 (16.9)	47.4 (17.0)
= 70 years n (%)	32 (13.3)	21 (8.8)	53 (11.0)

The two groups were comparable with respect to these characteristics apart from the percentage of subjects aged more than 70 years, which was slightly different between the two groups.

Primary disease characteristics at entry within the mITT population are provided in the table here below.

Primary disease characteristics at entry _ ITT

	TEL (n = 242)	"Usual care" (n=240)	Total (n=482)
Fever			
Mean (SD)	39.1 (0.9)	39.0 (0.9)	39.0 (0.9)
Number of symptoms*			
Mean (SD)	5.4 (1.3)	5.4 (1.3)	5.4 (1.3)
7 symptoms n (%)	58 (24.0)	56 (23.3)	114 (23.7)
Fine Score**			
Class I	122 (50.4)	108 (45.0)	230 (47.7)
Class II	77 (31.8)	87 (36.3)	164 (34.0)
Class III	41 (16.9)	44 (18.3)	85 (17.6)
Class IV	2 (0.8)	1 (0.4)	3 (0.6)

*min: 2; max: 7

**Fine score calculation was not required at inclusion. Given that some data were not collected (e.g. pulse), an explorated index was calculated retrospectively as follows: age> 65 years = + 1; pleuritic pain = - 2; temperature > 40°C = + 2; Klebsiella pneumoniae etiology = + 2; Staphylococcus aureus etiology = + 2; cancer = + 4

Causative pathogens identified at entry are provided in the table below.

Causative pathogens at entry _ bmITT

S. pneumoniae urinary AG and/ or one of the following causative pathogens n (%)	TEL (n = 73)	"Usual care" (n=77)	Total (n=150)
Positive *S. pneumoniae* isolate and/ or positive urinary Ag	43 (58.9)	51 (66.2)	94 (62.7)
Streptococcus pneumoniae isolates	22 (30.1%)	26 (33.8%)	48 (32.0%)
Positive urinary Ag	31 (42.5%)	37 (48.1%)	68 (45.3%)
Haemophilus influenzae	29 (39.7%)	24 (31.2%)	53 (35.3%)
Moraxella catarrhalis	6 (8.2%)	3 (3.9%)	9 (6.0%)
Staphylococcus aureus	4 (5.5%)	6 (7.8%)	10 (6.7%)

The telithromycin, penicillin G and erythromycin A minimum inhibitory concentrations (MICs) were centrally determined for 37 strains out of 48 *S. pneumoniae* strains isolated; 24.3% were resistant to penicillin G (MIC d1 mg/L), 27.0% resistant to erythromycin A (MIC „d0.5 mg/L) and none were resistant to telithromycin.

Classes of antibiotics prescribed in the "usual care" group within the mITT population are described in the table here below.

Antibiotic classes prescribed in the "usual care" group _ ITT population

Study comparator n (%)	"Usual care" (n= 240)
Beta-lactams: i.e. penicillins and combination of penicillins with betalactamase inhibitors	70 (29.2%)
Other beta-lactams: Cephalosporins Macrolides	36 (15.0%) 94 (39.2%)
Fluoroquinolones Total	40 (16.7%) 240 (100%)

Results – Efficacy

Primary efficacy analysis _ Clinical cure at TOC in the mITT population

The clinical cure rates at TOC visit in the mITT population (primary efficacy analysis) were 86.0% (208/242) in the TEL group vs. 78.8% (189/240) in the "usual care" group. The two -sided 95% CI was [0.4, 14] and did not include zero, indicating the clinical superiority of telithromycin over "usual care" in mild to moderate CAP outpatients.

Primary efficacy endpoint_ Clinical cure rate at TOC _ mITT population

Criterion	Population	TEL N (%)	"Usual care" N (%)	Two-sided 95% CI
Clinical cure rate at TOC	mITT	242 208 (86.0%)	240 189 (78.8%)	[0.4, 14.0]

Secondary efficacy analyses

The results for the main secondary efficacy analyses are provided in the table below.

Criterion	Population	TEL	"Usual care"	Two-sided 95% CI
Clinical cure rate at TOC	PP	87.2% (191/219)	79.9% (175/219)	[0.4, 14.2]
Clinical cure rate at TOC for Pneumococcal CAP	Pneumococcal CAP	90.7% (39/43)	76.5% (39/51)	[-0.5, 28.9]

-Pneumonia symptoms score at TOC visit:
The reductions in total symptoms score and in each symptom score with the exception of three (shortness of breath, fatigue and over health), were significantly greater in the TEL group vs. the "usual care" group.

Exploratory analyses

-Clinical cure at TOC visit in the ITT population:

The results of clinical cure at TOC in the full ITT population are shown here below.

Exploratory analyses_ Clinical cure rate at TOC _ ITT population

Criterion	TEL N (%)	"Usual care" N (%)	Difference	Two-sided 95% CI
N	256	249		
Clinical cure	213 (83.2)	192 (77.1)	6.1	[-0.8, 13.0]

Fisher' exact test: p=0.042

Indeterminate (ID) clinical outcomes (6 in the TEL group vs. 5 in the "usual care" group) were considered as treatment failures.

The lower and upper bounds of the two-sided 95% CI were -0.8% and 13.0%, respectively. The two-sided 95% CI included zero, the difference between groups did not reach the statistical significance.

-Experts' clinical outcome in populations of interest:

The results of the experts' clinical outcome in populations of interest are summarized here below.

Experts' clinical outcome (cure rate) in populations of interest

Population	Endpoint	TEL n/N (%)	"Usual care" n/N (%)	Two-sided 95% CI
mITT	TOC	223/242 (92.1)	206/240 (85.8)	[0.8, 11.9]
PP	TOC	206/219 (94.1)	192/219 (87.7)	[1.0, 11.8]
mITT subjects w/ central CXR confirmed CAP	TOC	170/187 (90.9)	157/185 (84.9)	[-0.6, 12.6]

These efficacy analyses according to the Review Board were consistent with the primary efficacy variable both in the mITT and the PP populations. The differences were statistically significant for the mITT and the PP populations indicating a clinical superiority over "usual care". The most stringent analysis in the subgroup of patients with a CAP radiologically confirmed did not reach the statistical significance. However, the trend was still in favour of telithromycin on this smaller sample size.

Results – Safety

During the study, 68 of 253 subjects (26.9%) treated with telithromycin, and 63 of 245 subjects (25.7%) treated with the single-agent oral antibiotic ("usual care") reported at least 1 adverse event.

The most frequently reported adverse events were diarrhea in 12 subjects (4.7%) treated with telithromycin and 8 subjects (3.3%) treated with the "usual care"; nausea and vomiting symptoms in 14 subjects (5.5%) and 5 subjects (2.0%) respectively; lower respiratory tract and lung infections in 7 subjects (2.8%) and 10 subjects (4.1%) respectively; and neurological signs and symptoms in 7 subjects (2.8%) and 4 subjects

(1.6%) respectively. The events were classified as severe in 5 (2.0%) subjects in the TEL group, and 7 (2.9%) subjects in the "usual care" group.

Twenty-nine (29) of 253 subjects (11.5%) treated with telithromycin, and 19 of 245 subjects (7.8%) treated with "usual care" reported at least 1 drug-related adverse event. The most frequently reported drug-related adverse events were nausea and vomiting symptoms in 12 subjects (4.7%) treated with telithromycin and 4 subjects (1.6%) treated with "usual care"; and diarrhea in 7 subjects (2.8%) and 6 subjects (2.4%) respectively.

Nine subjects (3.6%) discontinued the study drug for adverse event in the TEL group vs. 12 subjects (4.9%) in the "usual care" group. Of these discontinuations, 5 and 6 were considered by the investigators to be possibly related to study medication.

There were serious adverse events (SAEs) in 16 subjects (6.3%) treated with telithromycin, and 17 subjects (6.9%) treated with "usual care". No SAEs were related to the study medication, except one vomiting related to telithromycin; this expected adverse event was mild and transient.

Date of the report: 09-Jan-2007