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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00132938
		Study Code:	HMR3647A_4020
Generic drug name:	Telithromycin	**Date:**	04/Oct/2007

Title of the study:	An open-label, randomized, multicenter, clinical study to compare the effects of telithromycin, azithromycin and cefuroxime axetil on the penicillin or macrolide resistance of *Streptococcus pneumoniae* in patients with acute exacerbation of chronic bronchitis
Investigator(s), Study center(s) :	Coordinating Investigator: Dr. François Liard, 65 Grande rue, 37800 Saint Epain, France
Study period: Date first **subject** enrolled: 05-January-2004 Date last **subject** completed: 20-May-2006	**Phase of development:** Phase IV
Objectives:	The primary objective of the study was to demonstrate the superiority of telithromycin over azithromycin and over cefuroxime axetil in the reduction of *Streptococcus pneumoniae* (*Sp*) strains resistant to ß-lactams or macrolides at the test-of-cure (TOC) visit in the sputum of patients with *Sp* detected at the start of the study (Visit 1). The secondary objectives of the study were: >to demonstrate the superiority of telithromycin over azithromycin and over cefuroxime axetil in achieving clinical cure and *Sp* eradication success at the TOC visit in patients with *Sp* detected in sputum specimen at the start of the study (Visit 1), >to compare the clinical cure rates achieved by each treatment group in the penicillin or erythromycin resistant *Sp* (PER*Sp*) population with the cure rates in the sensitive *Sp* (S*Sp*) population at the end of treatment (EOT) and TOC visits, >to compare the effect of telithromycin, azithromycin and cefuroxime axetil at the EOT visit on the presence of *Sp* strains resistant to beta-lactams or macrolides in the sputum of patients with *Sp* detected at the start of the study (Visit 1), >to compare the clinical efficacy at the EOT visit and safety at the TOC visit of telithromycin, azithromycin and cefuroxime axetil in the "global" randomized population, in patients with acute exacerbation of chronic bronchitis (AECB).

Study design:	This was a multicenter, multinational, active-controlled, open, parallel-group, randomized (ratio 1.414:1:1, telithromycin, azithromycin, cefuroxime axetil), prospective study. The duration of therapy was 5 days for telithromycin and azithromycin and 10 days for cefuroxime axetil, starting at Visit 1, with an EOT visit (Visit 2) at Day 6 to Day 8 for patients treated with telithromycin or azithromycin and Day 11 to Day 13 for patients treated with cefuroxime axetil, and a TOC visit (Visit 3) at Day 17 to Day 21 for all the treated patients (office visit for patients who were *Sp* positive patients at Visit 1 and telephone contact for patients who were *Sp* negative patients at Visit 1).
Number of subjects planned:	Planned: 481 meeting protocol specified criteria of sputum Sp positive, i.e., 199 in the telithromycin group and 141 in each of the azithromycin and cefuroxime axetil groups, requiring planned enrollment of up to 5660 AECB patients.
Diagnosis and criteria for inclusion:	**Inclusion criteria** >Informed consent obtained in writing at enrollment. >Outpatients, male or female, aged 35 years or older. >Patients with a documented history of chronic bronchitis (CB), characterized by cough and excessive sputum production for most days of at least 3 months for 2 consecutive years. **And** >Patients with a clinical diagnosis of AECB, presumed due to bacterial infection based on increased sputum purulence with either increased dyspnea or sputum volume. >Patients producing spontaneous sputum. >Patients with 3 or less AECBs in the previous 12 months.

Treatments:	>**Telithromycin** (Ketek 400 mg tablets): 800 mg (2 tablets) once a day for 5 days. >**Azithromycin** (250 mg tablets): 500 mg (2 tablets) once on Day 1 and 250 mg (1 tablet) once a day on the next 4 days. >**Cefuroxime axetil** (250 mg tablets or 500 mg tablets in Spain): 250 mg (or 500 mg in Spain) twice a day, i.e., 1 tablet twice a day for 10 days.
Efficacy data:	**>Primary efficacy criterion**: PER*Sp* colonization rate at TOC visit in the telithromycin group compared to the azithromycin and the cefuroxime axetil groups in the stringent *Sp* m ITT population. **>Secondary efficacy criteria:** 1. Bacteriological (*Sp* eradication) and clinical outcome (rate of success) in patients with S.pneumoniae at inclusion at TOC visit 2. Clinical outcome at EOT and TOC visits comparison in patients with PER*Sp* and PES*Sp* *at visit 1 in each treatment group*, 3. PER*Sp* presence at EOT visit in patients with S.pneumoniae present at inclusion, 4. Clinical efficacy in the whole AECB (ITT) population at EOT.
Safety data:	Treatment-emergent adverse events (TEAE) and serious adverse events (SAE) are reported during the on treatment period (from Visit 1 through Visit 3.)

Statistical procedures:	The following populations were considered in the analyses: **Efficacy populations** Four populations were considered in the efficacy analyses: ***Intent-to-treat population*** The intent-to-treat (ITT) population of patients eligible for global efficacy analysis included all safety patients randomized through central randomization process (interactive voice response system: IVRS) who showed signs and symptoms of AECB (increased sputum purulence, dyspnea and/or sputumvolume) at Visit 1. Patients taking a treatment that was not attributed through the central randomization process were excluded from the ITT population. Note that one site was suspended following an audit. As such, all patients from this site were excluded from the ITT population and all efficacy analysis. Duplicate patients were also removed from this population. In particular, data recorded for the patient number with the earliest inclusion date was to be used for analysis. ***Sp modified intent-to-treat population*** The *Sp* modified intent-to-treat (*Sp* mITT) population was defined as all ITT patients, with documented history of chronic bronchitis, characterized by a cough and excessive sputum production for most days of at least 3 months for 2 consecutive years: >with S*p* detected from sputum sample at Visit 1; >with or without antibiotics during the protocol; and excluding: >asthmatic patients (except patients older than 35 years smoking at least 10 packs/year, reviewed by the Advisory Board); >patients with a history of: >bronchiectasis, >cystic fibrosis, >lung cancer or lung metastases, >active pulmonary tuberculosis, >suspected pneumonia, >hospitalized patients and patients from institutional care facilities. Reasons of exclusion from the S*p* mITT population were defined independently of treatment identification. If there were discrepancies between central laboratory and local laboratory results, the Central Laboratory results were taken into account for all analyses. The S*p* mITT population (confirmatory) was used to check for the consistency of the efficacy analyses based on the stringent S*p* mITT. A S*p* mITT analysis was performed for all efficacy variables.

Statistical procedures (follow):	***Stringent Sp modified intent-to-treat population*** The stringent *Sp* modified intent-to-treat population (stringent *Sp* mITT) population was a subset of the *Sp* mITT population: >with a sputum sample available at Visit 3 (or carried forward from Visit 2 in the case where antibiotics were prescribed for failure between Visit 2 and Visit 3) regardless of the date it was realized; >without antibiotics taken between Visit 1 and Visit 3 that could interfere with the study treatment, unless the antibiotics were prescribed for failure between Vis it 2 and Visit 3 and a Visit 2 sputum result was available from a sample taken before the new antibiotic was taken; in the latter case, the Visit 2 result was carried forward to Visit 3 for the efficacy analyses. The stringent *Sp* mITT population has been defined in the SAP plan as the primary analysis population instead of PP population predefined in the protocol (Advisory board of September 8th 2006). ***Sp per-protocol population*** The *Sp* per-protocol (*Sp* PP) population was a subset of the stringent *Sp* mITT population with no major protocol violations according to the exclusion criteria. **Safety population** The safety population included all patients, as treated, who received at least one dose of the study treatment. Patients withdrawing consent, patients taking commercial medication and nonrandomized patients were excluded from the safety population if they did not receive at least one dose of the study treatment. **Analysis of baseline variables** Baseline demographic, characteristics and prognostic variables were summarized by treatment group using means, standard errors, and medians (minima and maxima for continuous variables) and frequencies and percentages for categorical variables. P-values were given for information and not considered as a proof for unbalance between groups. The descriptive test was performed globally on the treatment groups using the Kruskall-Wallis test and Chi-square test. **Efficacy analyses** ***Primary efficacy analysis*** The primary efficacy analysis was to demonstrate the superiority of telithromycin compared to either azithromycin or cefuroxime axetil on the PER*Sp* colonization rates at TOC visit, assessed on Day 17 to Day 21 in the stringent *Sp* mITT patients. A similar analysis was also performed for the *Sp* PP patients. Test for comparison was carried out using an adjusted Chi-square test for continuity correction with an alpha risk of 0.025. Four sensitivity analyses were performed on the *Sp* mITT population in which: 1. Patients without a Visit 3 sputum result were considered as noncarriers of PER*Sp** 2. Patients without a Visit 3 sputum result were considered as carriers of PER*Sp**

Statistical procedures (follow):	3. Mean prevalence rate in the 3 tested arms was attributed to each patient without a Visit 3 sputum result* 4. Patients without a Visit 3 sputum result and patients taking antibiotics prescribed for failure without a Visit 3 sputum result available from a sample taken before the new antibiotic was taken were considered as carriers of PERS*p*. *Note concerning items 1 to 3: for patients taking antibiotics prescribed for failure between Visit 2 and Visit 3, if the Visit 3 sputum result was missing or the sample was taken after the new antibiotic was taken and if the Visit 2 sputum result was available from a sample taken before the new antibiotic was taken, the Visit 2 result was used. ***Secondary efficacy analyses*** Rate of success (clinical outcome and *Sp* eradication) at TOC visit was described using the same approach as primary efficacy on the stringent *Sp* mITT and *Sp* PP populations. The other secondary efficacy variables were described by frequency and percentage on the stringent *Sp* mITT and *Sp* PP populations by treatment group. The clinical cure rates achieved by each treatment group in patients with PER*Sp* and PES*Sp* at EOT and TOC were compared. The clinical efficacy was described also on the ITT population. **Safety analysis** The proportions of patients with TEAEs were compared between the 3 treatment groups overall, by system organ class (primary SOC decode), and by preferred term (PT decode), using Fisher's exact test. These p-values were not constructed as formal tests of hypothesis with associated Type I and Type II error rates, but were used to numerically assess differences between treatment groups and identify adverse events of possible interest.
Interim analysis:	No interim analysis was performed.

Results – Study subjects and conduct:	3959 patients were recruited, of whom 3946 were included in the study. The reason for non-inclusion of 13 of the recruited patients was the absence of informed consent. A total of 3946 patients were included in the study of which 4 were not randomized. The distribution in the analysis populations was as follows: **Safety population**: 3910 patients, including 1624 on telithromycin, 1146 on azithromycin and 1140 on cefuroxime axetil. 36 patients are excluded from safety population for no intake of study drug treatment (among them one patient withdrew consent). **ITT population**: 3869 patients, including 1609 on telithromycin, 1128 on azithromycin and 1132 on cefuroxime axetil. ***Sp* mITT population**: 526 patients, including 223 on telithromycin, 138 on azithromycin and 165 on cefuroxime axetil. **Stringent *Sp* mITT population**: 413, including 177 on telithromycin, 106 on azithromycin and 130 on cefuroxime axetil. ***Sp* PP population**: 405, including 175 on telithromycin, 104 on azithromycin and 126 on cefuroxime axetil.
Results – Efficacy:	**Primary efficacy endpoint:** Percentage of patients harboring a PER*Sp* at TOC visit in stringent *Sp* mITT population: A statistically significant superiority of telithromycin over azithromycin was found at TOC visit in reducing the carriage of PER*Sp*. On the other hand, no statistically significant difference in the percentage of PER*Sp* carriers was found between telithromycin and cefuroxime axetil.

Number and percentage of patients with PER*Sp* present at TOC - Stringent *Sp* mITT population

Telithromycin N = 177	Azithromycin N = 106	Cefuroxime axetil N = 130	p-value	
			T versus A	T versus C
23 12.99%	30 28.30%	17 13.08%	0.0024[a] 0.0142[b]	1.0000[a] 0.6117[b]

[a] adjusted Chi-square test for continuity correction
[b] test adjusted for PER*Sp* percentages at baseline
T = telithromycin ; A = azithromycin; C = cefuroxime axetil

Due to the imbalance in the frequency of PER*Sp* between telithromycin and azithromycin treatment groups at Visit 1 (54.72% for azithromycin, 39.55% for telithromycin and 50% for cefuroxime), the statistical significance of the difference between these 2 groups was further tested, taking into account PER*Sp* percentages at baseline. The superiority of telithromycin over azithromycin remained statistically significant (p = 0.0142).

Similar results were found in the *Sp* PP population.

Sensivity analyses on patients of the *Sp* mITT population with no sputum at Visit 3 confirmed the superiority of telithromycin over azithromycin. It did not show superiority over cefuroxime axetil. .

Secondary and exploratory efficacy endpoints

. **Intergroup comparisons**

>The superiority of telithromycin over azithromycin in reducing the carriage of *Sp* was also present at EOT visit

Number and percentage of patients with PER*Sp* present at EOT - Stringent *Sp* mITT population

Telithromycin N = 177	Azithromycin N = 106	Cefuroxime axetil N = 130	p-value[a]	
			T versus A	T versus C
10 6.17% [b]	34 35.42% [c]	15 12.40% [d]	<0.0001	0.1066

[a] adjusted Chi-square test for continuity correction
[b] based on 162 available values
[c] based on 96 available values
[d] based on 121 available values
PER*Sp* = penicillin or erythromycin resistant *Sp*; EOT = end of treatment; *Sp* mITT = *Streptococcus pneumoniae* modified intent-to-treat population; T = telithromycin ; A = azithromycin; C = cefuroxime axetil

>Success rate (clinical cure and *Sp* eradication) and clinical cure rate at TOC visit in the stringent *Sp* mITT population were higher in the telithromycin group but the difference was not significant with any of the treatment groups (p value = 0.025 required for significance in intergroup comparisons). Eradication of *Sp* was significantly better in the telithromycin group than in the azithromycin group but not versus cefuroxime axetil.

Success rate,clinical cure rate and Sp eradication at test of cure - Stringent *Sp* mITT population

Efficacy parameter at TOC	Telithromycin N = 177	Azithromycin N = 106	Cefuroxime axetil N = 130	p-value [a]	
				T versus A	T versus C
Success rate (clinical cure,and *Sp* eradication N/missing	177/0	106/0	130/0	0.0308	0.8096
n (%)	130 (73.45%)	64 (60.38%)	93 (71.54%)		
Clinical cure N/missing	177/0	105/1	130/0	0.0379	0.2733
n (%)	156 (88.14%)	82 (78.10%)	108 (83.08%)		
Sp eradication N/missing	177/0	106/0	130/0	0.0180	0.6485
n (%)	149 (84.2%)	76 (71.7%)	106 (81.5%)		

[a] adjusted Chi-square test for continuity correction
Sp = *Streptococcus pneumoniae*; T = telithromycin; A = azithromycin; C = cefuroxime axetil

>At EOT telithromycin was significantly better than azithromycin group; compared to the azithromycin group; difference did not reach significance between telithromycin and cefuroxime axetil.

Success rate, clinical cure rate and Sp eradication at EOT - Stringent *Sp* mITT population

Efficacy parameter at EOT visit	Telithromycin N = 177	Azithromycin N = 106	Cefuroxime axetil N = 130	p-value [a]	
				T versus A	T versus C
Success rate (clinical cure,and *Sp* eradication N/missing	162/15	96/10	121/9	<0.0001	0.0897
n (%)	135 (83.33%)	50 (52.08%)	90 (74.38%)		
Clinical cure N/missing	177/0	106/0	130/0	0.0007	0.3462
n (%)	161 (90.96%)	80 (75.47%)	113 (86.92%)		
Sp eradication N/missing	162/15	96/10	121/9	<0.0001	0.0436
n (%)	149 (92%)	59 (61.5%)	101 (83.5%)		

[a] adjusted Chi-square test for continuity correction
T = telithromycin; A = azithromycin; C = cefuroxime axetil

>In the overall population of patients (ITT population) the clinical cure rate at EOT visit showed that telithromycin was also superior to azithromycin with a cure rate difference of 3.7%. Similar cure rates were observed with telithromycin and cefuroxime axetil. Clinical cure data for the entire ITT population is only relevant for the EOT visit since efficacy data were collected at TOC only in patients with *S. pneumoniae* (*Sp*) at V1. Patients without *Sp* at V1 were followed up by a phone contact at V3 to assess their safety.

Clinical cure rate end of treatment - ITT population

Visit	Telithromycin (N = 1609)	Azithromycin (N = 1128)	Cefuroxime axetil (N = 1132)	p-value[a]	
				T versus A	T versus C
End of treatment visit					
N/missing	1603/6	1127/1	1130/2	0.0016	0.5236
n (%)	1472 (91.83)	993 (88.11)	1029 (91.06)		

[a] adjusted Chi-square test for continuity correction
T = telithromycin; A = azithromycin; C = cefuroxime axetil

Intragroup comparisons

>In the telithromycin group, at both TOC and EOT visits, clinical cure rate was slightly higher in patients with PES*Sp* present at Visit 1 compared to patients with PER*Sp* but the difference was not statistically significant at either time points. The same pattern was observed with azithromycin and cefuroxime axetil, however, in the azithromycin group, the difference was statistically significant at the EOT visit (p = 0.0021), indicating a lower efficacy of this antibiotic on PER*Sp* at TOC; in the cefuroxime axetil group, the lower clinical cure rate at TOC visit when PERS*p* was present compared to PES*Sp* present reaching borderline significance.

Intra-group comparison : Clinical cure rate at end of treatment and at test of cure by susceptibility status at Visit 1 - Stringent *Sp* mITT population

Treatment group		PER*Sp*	PES*Sp*	p-values
Telithromycin				
EOT	N/missing	70/0	107/0	
	n (%)	61 (87.14)	100 (93.46)	P = 0.1520
TOC	N/missing	70/0	107/0	P = 0.4204
	n (%)	60 (85.71)	96 (89.72)	
Azithromycin				
EOT	N/missing	58/0	48/0	
	n (%)	37 (63.79)	43 (89.58)	P = 0.0021
TOC	N/missing	58/0	47/1	P = 0.2761
	n (%)	43 (74.14)	39 (82.98)	
Cefuroxime axetil				
EOT	N/missing	65/0	65/0	
	n (%)	55 (84.62)	58 (89.23)	P = 0.4351
TOC	N/missing	65/0	65/0	P = 0.0613
	n (%)	50 (76.92)	58 (89.23)	

PER*Sp* = penicillin or erythromycin resistant *Sp*. PES*Sp* = penicillin or erythromycin susceptible *Sp*; EOT = end of treatment; TOC = test of cure

>Exploratory analysis

For telithromycin, clinical success rates were similar for erythromycin susceptible and resistant strains. Eradication of erythromycin resistant strains was reduced in comparison of susceptible ones but reached significance only at TOC visit. Azithromycin was strongly associated with a lower eradication of erythromycin resistant strains particularly at EOT visit (34%). Azithromycin clinical cure rates were also lower on resistant strains than on susceptible ones, the difference reaching significance at EOT.

Clinical cure rate and *Sp* eradication at TOC and EOT by erythromycin susceptibility status at Visit 1 in the stringent *Sp* mITT population:

Treatment group		Ery S	Ery R	p-values
Telithromycin : clinical cure				
EOT	N/missing	111/0	66/0	
	n (%)	102 (91.9)	59 (89.4)	P = 0.5752
TOC	N/missing	111/0	66/0	P = 0.9351
	n (%)	98 (88.3)	58 (87.9)	
Telithromycin : *SP* eradication				
EOT	N/missing	101/10	61/5	
	n (%)	96 (95.0)	53 (86.9)	P = 0.0638
TOC	N/missing	111/0	66/0	P = 0.0179
	n (%)	99 (89.4)	50 (75.8)	
Azithromycin : clinical cure				
EOT	N/missing	50/0	56/0	
	n (%)	44 (88.0)	36 (64.3)	P = 0.0046
TOC	N/missing	49/1	56/0	
	n (%)	41 (83.7)	41 (73.2)	P = 0.1961
Azithromycin : *SP* eradication				
EOT	N/missing	46/4	50/6	
	n (%)	42 (91.3)	17 (34.0)	P < 0.0001
TOC	N/missing	50/0	56/0	
	n (%)	47 (94.0)	29 (51.8)	P < 0.0001

EOT = end of treatment; TOC = test of cure

> The clinical cure rate of cefuroxime axetil was lower on penicillin resistant than on penicillin susceptible strains, the difference being significant at TOC. Eradication of penicillin resistant strains was reduced in comparison of susceptible ones but reached significance only at EOT visit.

Clinical cure rate and *Sp* eradication at TOC and EOT by penicillin susceptibility status at Visit 1 in the stringent *Sp* mITT population:

Treatment group		Peni I/S	Peni R	p-values
Cefuroxime : clinical cure				
EOT	N/missing	111/0	19/0	
	n (%)	99 (89.2)	14 (73.7)	P = 0.0640
TOC	N/missing	111/0	19/0	
	n (%)	96 (86.5)	12 (63.2)	P = 0.0122
Cefuroxime : *SP* eradication				
EOT	N/missing	104/7	17/0	
	n (%)	90 (86.5)	11 (64.7)	P = 0.0247
TOC	N/missing	111/0	19/0	
	n (%)	92 (82.9)	14 (73.7)	P = 0.3396

Results – Safety:	Gastrointestinal disorders were the most frequent TEAEs in all 3 treatment groups. They were also the most frequent TEAEs leading to discontinuation of study drug in all 3 treatments groups. In this open study, the TEAE percentage with telithromycin was slightly above the one of comparators. In addition to the trend for higher rate of gastrointestinal disorders the rates of events was higher than 0.3% and tend to be different between treatments groups for: blurred vision, vertigo, dizziness and asthenia in telithromycin group, and for rash, pruritus and dyspnea in cefuroxime axetil group. Three deaths occurred during the period of observation: 2 in the telithromycin group (respiratory failure and sudden death, respectively) and 1 in the cefuroxime axetil group (small cell lung cancer with pneumonia). None of the deaths was considered as possibly related to study drug. There were only 2 SAEs deemed possibly related to study drug: 1 case of acute bronchitis in the cefuroxime axetil group and 1 case of intrauterine death 4 month after treatment completion in the telithromycin group in a women 40 years old, with several courses of antibiotics. No causal assessment was provided by the investigator. The company considers this event as related, by default. Two types of TEAEs had been identified as AE of special interest in the protocol and are described below: - Eight cases of visual disturbance (mostly blurred vision), 2 of them leading to study drug discontinuation were reported in the telithromycin group versus 1 in each of the azithromycin and cefuroxime axetil groups. In all cases, recovery without sequelae was observed. - No hepatic disorders occurred during the study.
Date of report:	21-May-2007