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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00538148
		Study Code:	HMR3647A_4014
Generic drug name:	Telithromycin	**Date:**	03/Oct/2007

Title

A multicenter, multinational, randomized, double-blind controlled clinical study of the efficacy and safety of oral telithromycin 800 mg once a day for 5 days versus azithromycin (500 mg OAD day 1 then 250 mg OAD for 4 days) in the treatment of acute exacerbation of chronic bronchitis in adult outpatients with chronic obstructive pulmonary disease

Investigator(s), study site(s)

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Study duration and dates	**First subject included**:	November 19, 2002	**Phase**	IV
	Last subject included:	September 21, 2004.		

Objectives

Primary

The primary objective of this study was to demonstrate the non-inferiority of the clinical efficacy of a 5 days course of oral telithromycin 800 mg once a day compared to a 5 days course of treatment with azithromycin 500 mg once a day (Day 1) then 250 mg once a day for 4 days in the treatment of acute exacerbation of chronic bronchitis (AECB) in adults at the post-therapy/Test of Cure visit (TOC) (Days 17-21).

Secondary

The secondary objectives of the study were:

- To evaluate the bacteriological efficacy at TOC visit (Days 17-21) in population with bacteriological documentation at inclusion.
- To compare the time to next exacerbation (time to relapse) with a follow-up of 6 months.
- To examine the causative pathogens isolated during the second acute exacerbation episode in both groups of treatment (to compare them to those of the 1st acute exacerbation) and to assess the evolution of the susceptibility [minimum inhibitory concentration (MIC), molecular typing if necessary] of *S. pneumoniae, Haemophilus spp., Moraxella catarrhalis* between the inclusion, TOC and relapse.
- To examine the evolution of susceptibility of *S. viridans* in France from the oropharyngeal flora at inclusion, End-of-Treatment (EOT) visit, TOC visit, and next exacerbation or 3 months follow-up visit (if no previous exacerbation) and/or 6 months follow-up visit (if no previous exacerbation).

- To assess the following health outcomes of 5 days oral telithromycin versus 5 days of oral azithromycin for treating AECB in adults all along the study (inclusion, TOC, 3 months, 6 months).
  - >Health status assessed through the St. George's Respiratory Questionnaire (SGRQ),
  - >Days lost from work/usual activities due to AECB,
  - >AECB related unscheduled outpatient visits and number of hospitalizations with length of stay
  - >(LOS) (diagnosis, as well as discharge summary).
- To compare the safety (from Day 1 to last dose of study treatment + 14 days) in the 2 treatment groups.

Study design

This study was a multicenter, multinational, double-blind, active-controlled comparative 1/1 randomized,2-arm, parallel group study. Subject AECB status was assessed at up to 7 visits as follows:
. Visit V1: inclusion and Day 1 of treatment.
. Visit V2: EOT (Day 6 - Day 9).
. Visit V3: TOC (Day 17 - Day 21).
. Visit V4: late post-therapy visit or phone contact (Day 31 - Day 36).
. Visit V5: 3-month follow-up (Day 90 ± 15 days).
. Visit V6: 6-month follow-up (Day 180 ± 15 days).
. Visit V7: possible extemporaneous exacerbation visit.

Number of subjects planned

Planned: 690, i.e., 345 per study group.

Inclusion criteria

>Adult outpatients, either sex, aged 45 years or older.
>Patients with a documented history of chronic bronchitis with a basal FEV1 <70% and >35% made in the previous 12 months **and** who had had at least one or more AEBC in the previous year **and** with FEV1/FVC <70% (lung function tests made in the previous 12 months).
.>Patients with a clinical diagnosis of acute exacerbation of chronic bronchitis presumably due to bacterial infection based on all of the following signs and symptoms of AECB: increased sputum purulence, and at least 1 of the 2 following signs and symptoms (increased dyspnea, increased sputum volume).
.>Patients with negative chest radiography (posterior/anterior and lateral views) to rule out a pneumonia within 48 hours before initiation of study medication or at the latest 24 hours after initiation of study medication (it was necessary to not include patients with pneumonia associated with AECB).
.>Patients with sputum specimens collected at inclusion for gram stain and bacteriological culture.

Treatments

Telithromycin 800 mg once a day for 5 days.
Azithromycin 500 mg once a day (Day 1) then 250 mg once a day for 4 days.
Both treatments were taken as oral opaque capsules of identical appearance.

Efficacy data

Principal efficacy criterion: clinical outcome at TOC visit (Day 17-Day 21).
Main secondary efficacy criteria:
- Bacteriological response at TOC visit;
- Time to relapse up to 6 months after inclusion.

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Safety data

Treatment emergent adverse events (TEAE).

Interim analysis

No interim analysis was conducted.

Results - Study subjects and conduct

Number of subjects randomized:	telithromycin group: 331; azithromycin group: 337; total 668.
Safety population:	telithromycin group: 329; azithromycin group: 337; total 666.
Modified ITT (mITT) population:	telithromycin group: 326; azithromycin group: 332; total 658.
Bacteriological mITT (mITTb) population:	telithromycin group: 123; azithromycin group: 116; total 239.
Clinical per protocol (PPc) population:	telithromycin group: 272; azithromycin group: 274; total 546
Bacteriological PP (PPb) population:	telithromycin group: 96; azithromycin group: 96; total 192
Demographic data (mITT population):	
Mean age ± SD :	telithromycin group: 67.5 ± 10.00 years: azithromycin group: 66.7± 9.75 years.
Sex (male/female):	telithromycin group: 219/107; azithromycin group: 221/111.
Mean BMI ± SD :	telithromycin group: 26.2 ± 5.04 kg/m²; azithromycin group: 26.0 ± 5.17 kg/m².

Results – Efficacy

Cure rate at test of cure in PPc population: primary efficacy analysis
Telithromycin group: 89.3%; azithromycin group: 89.8%; 95% CI of difference: [-5.9; 5.1].

Cure rate at test of cure in mITT population:
Telithromycin group: 86.5%; azithromycin group: 86.8%; 95% CI of difference: [-5.7; 5.3]

Cure rate according to severity of obstruction (PPc population):
30% = FEV1 <50% - telithromycin group: 88.1%; azithromycin group: 85.8%;
50% = FEV1 =80% - telithromycin group: 90.3%; azithromycin group: 93.6%.

Cure rate according to the number of AECBs in the previous 12 months (PPc population):
0-2 episodes - telithromycin group: 91.1%, azithromycin group: 92.8%
>2 episodes - telithromycin group: 85.0%; azithromycin group: 83.9%.

Bacteriological efficacy as % satisfactory responses in PPb population per central lab:
Telithromycin group: 72.2%; azithromycin group: 82.7%.

AECB relapse rate in 6-month follow-up (PPc population):
Telithromycin group: 101/272 (37.1%); azithromycin group: 96/274 (35.0%).

Time to relapse in 6-month follow-up - first quartile (PPc population):
Telithromycin group: 52 days; azithromycin group: 58 days (logrank test, p = 0.791).

Subjects with at least 1 TEAE:
Telithromycin group: 83/329 (25.2%); azithromycin group: 76/337 (22.6%).

Most frequent TEAEs (present in >1% of subjects in either treatment group) were headache (4.6%, versus 4.5%), diarrhea (3.7% versus 4.2%), nausea (2.1% versus 3.0%), dyspepsia (2.4% versus 0.6%), back pain

(1.8% versus 0.6%), oral candidiasis (1.2% versus 0.9%), dizziness (0.6% versus 1.2%), and fatigue (0% versus 1.2 %).

Most TEAEs were of mild or moderate intensity. Severe TEAEs were experienced by 2.4% of subjects in the telithromycin group and 3.0% in the azithromycin group.

Subjects with at least 1 TEAE possibly study drug-related:
Telithromycin group: 41/329 (12.5%); azithromycin group: 30/337 (8.9%).

Most frequent possibly drug-related TEAEs in the telithromycin group and azithromycin group: diarrhea (3.3% and 3.6%, respectively); nausea (1.8% in both groups); headache (1.8% and 1.2% respectively); oral candidiasis (1.2% and 0.6%, respectively); dyspepsia (1.2% and 0.3%, respectively).

Subjects with at least 1 serious TEAE:
Telithromycin group: 6/329 (1.8%): azithromycin group: 9/337 (2.7%).
Most serious TEAEs were related to the health status of the subjects and not related to study drug.

Deaths:
Telithromycin group: 1 death on treatment (not study drug related) and 6 deaths post-treatment.
Azithromycin group: 1 death on treatment (not study drug related) and 3 deaths post-treatment.

Subjects with permanent discontinuation of study drug due to TEAEs:
Telithromycin group: 2/329 (0.6%); azithromycin group: 4/337 (1.2%).

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