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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00273520
		Study Code:	HMR3647A_3503
Generic drug name:	Telithromycin	**Date:**	25/Sep/2007

Title

A Randomized, Double Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Telithromycin 800 mg (Once Daily for 10 Days) as a Supplement to the Standard of Care for Patients with Acute Exacerbations of Asthma

Investigator(s), study site(s)

Multinational/81 sites: Australia (4), Canada (24), France (19), Germany (16), Italy (8), New Zealand (2), and the United Kingdom (8)

Sponsor's responsible medical officer: Richard Nieman, MD, Bridgewater, New Jersey, USA

Study duration and dates	**Start of inclusion**:	January 27, 2003	**Phase**	IIIB
	End of inclusion:	March 29, 2004		

Objectives

Primary
The primary objective was to evaluate the clinical efficacy of telithromycin vs placebo as a supplement to the usual standard of care in patients with acute exacerbations of asthma.

Secondary
To evaluate the following:
• The safety of 10 days of oral telithromycin as a supplement to the standard of care for patients with an acute exacerbation of asthma,
• The antimicrobial activity of telithromycin during an acute exacerbation of asthma, and
• To assess additional efficacy variables and health outcome evaluations after 10 days of treatment with either oral telithromycin or placebo, with study medication used as a supplement to standard of care for patients with an acute exacerbation of asthma.

Study design

This was a Phase IIIB, double blind, parallel group, randomized (1:1), placebo-controlled, multi site, multinational study with a treatment phase of 10 days. Patients were randomly assigned to receive either oral telithromycin (800 mg once daily) or placebo for 10 days.

There were 4 visits: screening and randomization occurred at Visit 1 (Day 1) (Visit 1a was a telephone contact); end-of-treatment assessments occurred at Visit 2 (Day 11-14); and post-therapy follow-up visits occurred at Visits 3 and 4 (Days 28 and 42), for a total of 6 weeks of patient participation.

Number of patients planned

Approximately 280 patients (140 per treatment arm) were to be enrolled at approximately 70 study sites, with the goal of obtaining 240 clinically and microbiologically evaluable patients.

Inclusion criteria

Male and female adults 18 to 55 years of age were eligible if they had a history of asthma and were experiencing an acute exacerbation of asthma, presenting at the time of initial exacerbation or within 24 hours of initial medical care in an urgent care clinic, emergency room, or inpatient hospital setting. To qualify for enrollment, they must have presented with signs and symptoms of an acute deterioration in asthma control, with asthma symptoms and reduced peak expiratory flow rate (PEFR) (<80% predicted).

Treatments

Placebo : 2 capsules (lactose filler) once a day orally for 10 days.
Telithromycin 800 mg: two 400-mg capsules once a day orally for 10 days.

Efficacy data

Primary efficacy assessments:
• Patient's daily diary summary symptom scores
• Morning diary PEFR

Secondary efficacy assessments:
• In-clinic pulmonary function tests, including:
  o Forced expiratory volume in 1 second (FEV1)
  o Percent predicted FEV1
  o Forced vital capacity (FVC)
  o Forced expiratory flow rate at 25% to 75% of FVC (FEF25-75)
  o PEFR, and percent predicted PEFR
• Evening diary PEFR, and diary PEFR variability
• Time to symptom resolution from study entry acute exacerbation of asthma
• Health outcomes questionnaire, including the Asthma Quality-of-Life Questionnaire (AQLQ), Short Form-36 Health Survey (SF-36®)
• Need for additional medications and healthcare resource utilization
• Microbiology test results, including the patient's clinical improvement relative to initial *Chlamydophila (Chlamydia) pneumoniae* and/or *Mycoplasma pneumoniae* status and the eradication or decreased microbiological burden of *C. pneumoniae* and/or *M. pneumoniae*

Safety data

Safety assessments included adverse events (AEs) reported by the patient or noted by the investigator, laboratory test results, physical examination findings, and vital signs.

Statistical procedures

The intent-to-treat (ITT) analysis was performed on all randomized patients who received at least 1 dose of study medication and who had 1 primary efficacy endpoint value, excluding all patients who received study medication without being randomized. The bacteriologic efficacy population included all patients who had

an acceptable diagnosis for *C. pneumoniae* and/or *M. pneumoniae* at baseline (Visit 1), as a proportion of the total number of patients in the as-treated population who provided interpretable baseline microbiology samples. This definition was adjusted from the prespecified definition in which only patients testing positive for either *C. pneumoniae* and/or *M. pneumoniae* were to be included. The as-treated population included all enrolled patients who received study medication. All as-treated analyses examined patients in the treatment group to which they were actually treated. The as-treated population was only used for analyses of the primary efficacy endpoints to support the ITT analyses. The per-protocol analysis was performed on the ITT population, excluding patients with important protocol violations. The safety analysis was performed on all patients who received at least 1 dose of the study medication with post-baseline safety assessments.

Statistical analyses and data presentations were generated using SAS® version 8.2. Descriptive statistical summaries included the number of patients, mean, standard deviation, appropriate standard error, median, minimum, and maximum for the continuous variables, and the number and percent of patients for the categorical variables. For all inferential analyses, the standard error presented was the standard error obtained from the analysis of covariance (ANCOVA) model. For all descriptive summaries where a model was not used, the standard error presented was: (standard deviation [SD]/vn). All statistical inferential tests were 2-sided and were performed at a significance level of a = 0.05 unless otherwise specified.

Primary and secondary efficacy variables were analyzed using an ANCOVA model, with factors for treatment, study site (investigator), treatment-by-site interaction, and baseline as a covariate. The treatment-by-site interaction was to be removed from the model if found to be not significant at a level of 0.15. For between-treatment group comparisons, a 2-sided 95% confidence interval was constructed for the difference in least-squares means. Departures from the assumptions of the primary analysis ANCOVA model and the presence of outliers were examined to assess the validity of the results.

Interim analysis

No interim analysis was conducted.

Results - Study patients and conduct

Of the 278 patients enrolled, 270 patients were randomized, and 239 completed the study. Of the enrolled patients, 94.6% were included in the as-treated population, 94.6% were included in the safety population, 91.7% were included in the ITT population, 86.0% were included in the per protocol population, and 80.2% were included in the bacteriologic efficacy population. Demographics were similar between treatment groups. In the ITT population, the mean age was 39.6 years, 91.8% of patients were white, 65.1% of were female, and 34.9% were male. Overall, 16.5% were current smokers, 23.0% were former smokers, and 60.4% never smoked; mean tobacco consumption was 2.1 pack-years. The mean duration of asthma was 15.1 years. In the 3 days prior to, or 3 days after baseline, 83.3% of patients in the telithromycin group and 83.7% in the placebo group used inhaled steroids and 34.1% in the telithromycin group and 32.6% in the placebo group used oral steroids. In the bacteriologic efficacy population, 57.8% had at least 1 positive criterion for *C. pneumoniae* and 5.8% had at least 1 positive criterion for *M. pneumoniae*.

Results – Efficacy

Diary symptom scores (ITT population): Patients in the telithromycin group reported more relief from symptoms and faster improvement from their asthma exacerbation as assessed by diary symptom scores compared with patients in the placebo group. The differences between the telithromycin group and placebo group were statistically significant, as summarized in the tables below.

Mean change from baseline	Placebo	Telithromycin	*P* value
Over treatment period	-1.0	-1.3	0.004
To end of treatment	-1.3	-1.7	0.002

Peak expiratory flow rate (PEFR) morning diary values (ITT population): Patients in the telithromycin group had consistently numerically greater adjusted mean morning diary PEFR values at all study periods, compared with patients in the placebo group, although the difference between treatment groups was not significant.

Secondary efficacy assessment

In-clinic pulmonary function (ITT population): Patients in the telithromycin group demonstrated greater clinical improvement at the end of treatment as assessed by pulmonary function tests, with clinically relevant improvement in FEV1 compared with patients in the placebo group.

Mean change from baseline to end of treatment	Placebo	Telithromycin	*P* value
FEV_1	0.34 L	0.63 L	0.001
% predicted FEV_1	9.6%	16.9%	0.001
PEFR	88.9 L/min	115.8 L/min	0.036
% predicted PEFR	17.0%	21.8%	0.028
FVC	0.31 L	0.58 L	0.006
FEF_{25-75}	0.45 L/sec	0.85 L/sec	0.004

Symptom reduction (ITT population): Patients in the telithromycin group reported faster symptom reduction, as assessed by daily diary symptom summary scores, compared with patients in the placebo group.

	Placebo	Telithromycin	*P* value
Median time to 50% reduction	8 days	5 days	0.031
% symptom-free days at end of treatment	8.0%	16.0%	0.006
% patients reporting symptoms at end of treatment	41.1%	27.8%	0.025
% patients reporting being asymptomatic throughout study	56.6%	67.5%	0.043

Quality of life (ITT population): Patients in the telithromycin group had significantly improved quality of life scores compared to patients in the placebo group. The statistically significant results are summarized in the table. The emotional function domain score of the AQLQ was not significantly different between the groups.

% change from baseline	Placebo	Telithromycin	*P* value
Overall AQLQ score	0.7	0.9	0.041
AQLQ activity limitation score	0.4	0.7	0.014
AQLQ symptom domain score	0.9	1.2	0.127
SF-36 social functioning score	4.9	14.2	0.002

Need for additional medication and healthcare utilization (ITT population): There were no important differences in the use of additional medication (i.e., inhaled steroids, oral steroids, long acting bronchodilators, additional reliever medication), or healthcare utilization (i.e., hospital emergency department, intensive care, or general ward, and outpatient facility).

Efficacy results by microbiological status (Bacteriologic efficacy population):

Diary symptom scores: *Chlamydia pneumoniae*-negative telithromycin patients reported more relief from acute exacerbation of asthma symptoms than *C. pneumoniae*-negative patients treated with placebo as assessed by diary symptom scores.

Mean change from baseline was significantly different between the telithromycin- and the placebo groups over the treatment period (-1.4 and -0.8, respectively; $P = 0.040$). The sample sizes of telithromycin- and placebo patients in the *C. pneumoniae*-positive/*M. pneumoniae*-positive group (4 and 1, respectively), and

the *C. pneumoniae*-negative/*M. pneumoniae*-positive group (4 and 4, respectively) were small, and no meaningful statistical analyses were produced.

The remaining bacteriologic sample populations (*C. pneumoniae*-positive/*M. pneumoniae* negative, *C. pneumoniae*-negative/*M. pneumoniae*-negative, *C. pneumoniae*-positive and/or *M. pneumoniae*-positive, and *C. pneumoniae*-positive) did not yield significant differences between treatment groups.

FEV1*: Chlamydia pneumoniae*-positive/*M. pneumoniae*-negative patients who were treated with telithromycin demonstrated greater clinical improvement at the end of treatment than patients treated with placebo as assessed by FEV1. The mean change from baseline to the end of treatment was significantly different between the telithromycin (0.75 L) and the placebo (0.42 L) groups ($p = 0.001$). Conversely, *C. pneumoniae*-negative/*M. pneumoniae*-negative patients did not show any difference in FEV1 whether treated with telithromycin or placebo.

Microbiological activity: The effect of telithromycin on *C. pneumoniae* and *M. pneumoniae* during an acute exacerbation of asthma was unclear as assessed by serology, PCR, and culture. Possible explanations may include the fact that no standardized laboratory tests exist to accurately diagnose *C. pneumoniae* infection status; the PCR does not have standardized methods to study asthma; and rates of chronic infection may have been higher than the serology results indicated.

Results – Safety

There were no deaths or unexpected AEs.

A total of 7 patients experienced serious adverse events (SAEs); 4 SAEs were treatment-emergent adverse events (TEAEs) (constipation and asthma in the telithromycin group and 2 events of asthma in the placebo group) and 3 SAEs were reported during the follow-up period (pelvic inflammatory disease and asthma in the telithromycin group, and spontaneous abortion in the placebo group).

None of the SAEs was considered related to the study medication.

Diarrhea and nausea occurred more often in the telithromycin group (13 and 9 patients, respectively) compared with the placebo group (5 and 1 patients, respectively). Diarrhea and nausea AEs were usually considered related to study medication; most of these events were mild to moderate.

A total of 3 telithromycin-treated patients experienced eye disorders (moderate visual acuity reduced in 2 patients and mild blurred vision in 1 patient), all of which were considered related to study medication, not serious, and not unexpected. These events resolved without sequelae.

Two patients in the telithromycin group and none in the placebo group had laboratory abnormalities that were considered medically important; both patients presented with abnormal results at baseline. One patient had an elevated alkaline phosphatase level of 196 U/L and an elevated GGT level of 51 U/L at baseline. The other patient had an elevated total bilirubin level at baseline of 24 µmol/L, which increased to 32 µmol/L at Visit 2, and decreased to 18 µmol/L at retest. None of these laboratory abnormalities were considered serious and none led to discontinuation of the study medication or premature discontinuation from the study.

There were no notable changes in either treatment group with regard to vital signs or physical examination.

Date of the report: 20-Sep-2006