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:**	NCT00174694
		Study Code:	HMR3647A_4023
Generic drug name:	Telithromycin	**Date:**	21/June/2007

Title

A prospective, randomized, open-label, active-controlled study in adult subjects with acute bacterial sinusitis comparing the clinical efficacy of telithromycin (KETEK®) 800 mg once a day for 5 days versus amoxicillin-clavulanic acid (AUGMENTIN®) 875/125 mg twice a day for 10 days

Investigator(s), study site(s)

Principal Investigator: Dr Ralph Mösges, IMSIE-Medical Faculty, University of Cologne, Germany

Study duration and dates	First subject included: 24 November 2004 Last subject completed: 19 December 2005	**Phase**	4

Objectives

The primary objective of the study was to demonstrate that telithromycin (800 mg od for 5 days) is not inferior to amoxicillin/clavulanic acid (875/125 mg bid for 10 days) in clinical efficacy at post-therapy/test of cure (TOC) visit (Day 17-21) in patients with acute bacterial sinusitis (ABS).
The secondary objectives of the study were:

- to assess the time to resolution of signs and symptoms between the baseline (Day 1) and TOC (Day 17-21) visits,
- to assess the rate of clinical relapse at follow-up visit (Day 41-49),
- to compare safety of telithromycin and amoxicillin/clavulanic acid treatment,
- to assess health economic outcome (extra additional visits due to sinusitis, additional treatments taken by the patient related to the sinusitis, days lost from usual activities due the sinusitis) until follow-up visit (Day 41-49),
- to assess quality-of-life outcome using SF 36 questionnaire between baseline and follow-up (Day 41-49),
- to compare the bacteriological outcome of both treatments as observed at TOC (Day 17-21) and at follow-up visit (Day 41-49),

in patients with ABS.

Study design

This was a multinational, prospective, open-label, active-controlled non-inferiority randomized study (1:1, telithromycin: amoxicillin/clavulanic acid). Patient ABS status was assessed at up to 4 visits:

- Visit 1 (V1): inclusion and Day 1 of treatment.
- Visit 2 (V2) (Day 3-5): on-therapy visit or phone contact.
- Visit 3 (V3) (Day 17-21): TOC visit.
- Visit 4 (V4) (Day 41-49): follow-up visit.

Number of subjects planned

Planned: 298, ie, 149 per study group.

Inclusion criteria

- Male or non-pregnant female with age ≥18 years old.
- Outpatients with a clinical diagnosis of ABS, based on the presence of:
  - signs and symptoms lasting longer than 7 days and less than 28 days,
  - purulent anterior or posterior nasal discharge,
  - one additional major sign and symptom or 2 minor signs and symptoms. The major and minor signs and symptoms were defined as follows:
    - **major signs and symptoms**: facial pain/pressure/tightness over the maxillary sinuses, nasal congestion/obstruction, change in the perception of smell (hypoanosmia/ anosmia), fever defined by a temperature >38°C [100.4 F] (oral)/ >38.5°C [101.2 F] (tympanic)/ >39°C [102.2 F] (rectal).
    - **minor signs and symptoms**: headache, halitosis, dental pain, ear pressure/fullness, cough, fatigue,
- Patients with abnormal maxillary sinus X-rays (Waters views and additional views, if necessary) or limited sinus CT-scans or sinus ultrasound in the previous 48 hours before inclusion defined as the presence of at least 1 of the following homolateral radiological criteria: presence of air/fluid level, total opacification, mucosal thickening ≥10 mm.
- Written informed consent must have been obtained prior to enrollment in the study for all patients.

Treatments

- Telithromycin 800 mg (Ketek® 400 mg tablets) once a day for 5 days
- Ampicillin/clavulanic acid 875/125 mg (Augmentin® or Clavulin® tablets) twice a day for 10 days.

Efficacy data

- Principal efficacy criterion: clinical outcome at TOC visit (Day 17 -21).
- Main second efficacy criteria:
  - time to resolution of signs and symptoms;
  - rate of clinical relapse at follow-up visit;
  - bacteriological outcome at TOC visit;
  - bacteriological outcome at follow-up visit;

Safety data

Treatment-emergent adverse events (TEAE) and serious adverse events at each scheduled office visit.

Quality-of-life data

Health-related quality of life by SF-36 questionnaire completed by the patient.

Health economic data

Health economic data originating from patient notebook completed from V1 to V4 completed by the investigator.

Oropharyngeal flora

Oropharyngeal flora data were collected from a subgroup of German patients to describe antibiotic treatment impact.

Statistical procedures

Test of non-inferiority of the clinical efficacy of telithromycin versus amoxicillin/clavulanic acid. Non-inferiority was demonstrated if the lower limit of the 95% confidence interval (95% CI) was -15% or greater and the upper limit crossed 0.

Median times to reduction of 75% and 50% of clinical symptoms were computed using Kaplan-Meier non-parametric estimates. The 95% CI estimates and survival curves were compared using a log-rank test.

Three analysis populations were considered:

- The modified intent-to-treat (m-ITT) population which included all randomized patients who received at least 1 dose of study drug, and with signs and symptoms of ABS and radiological findings supporting diagnosis for ABS.
- The per-protocol clinical (PPc) population which included all m-ITT patients, excluding those with the major protocol violations.
- The per-protocol bacteriological (PPb) population which included all PPc patients with isolation of a causative pathogen in an adequate pretherapy specimen for culture obtained within 48 hours before the

start of therapy. The following pathogens were always considered as causative: *S. pneumoniae, S. Mitis, S. sanguis, S. pyogenes, Streptococcus Group A, H. influenzae, S. aureus* (>10^4), and *M. catarrhalis.*

- The safety population which included patients who had received at least one dose of study drug with a postbaseline safety assessment.

Interim analysis

No interim analysis was performed.

Results - Study subjects and conduct

A total of 298 patients were included, 148 in the telithromycin group and 150 in the amoxicillin/clavulanic acid group.

The m-ITT population comprised 144 patients aged (mean ± standard deviation) 40 ± 14 years in the telithromycin group, and 146 patients aged 31 ± 13 in the amoxicillin/clavulanic acid group.

The PPc population comprised 123 and 125 patients, respectively.

The PPb population comprised 54 and 49 patients, respectively.

The safety population comprised 145 and 148 patients, respectively.

Results – Efficacy

Clinical success rate at TOC visit in PPc population: primary efficacy analysis
Telithromycin group: 88.6%; amoxicillin/clavulanic acid group: 88.8%; 95% CI of difference [-8.9; 8.5] – Non-inferiority of telithromycin to amoxicillin/clavulanic acid.

Clinical success rate at TOC visit in m-ITT population:
Telithromycin group: 86.8%; amoxicillin/clavulanic acid group: 87.7%; 95% CI of difference [-9.2; 7.5].

Median time [95% CI] to reduction of 75% of baseline total symptom score (m-ITT population):
Telithromycin group: 7.0 days [6.0; 8.0]; amoxicillin/clavulanic acid group: 8.0 days [7.0; 9.0] (p = 0.115).

Median time [95% CI] to reduction of 50% of baseline total symptom score (m-ITT population):
Telithromycin group: 4.0 days [3.0; 5.0]; amoxicillin/clavulanic acid group: 5.0 days [5.0; 6.0] (p = 0.044).

Median time to resolution of individual symptoms (telithromycin versus amoxicillin/clavulanic acid - m-ITT population):

- nasal congestion: 9.0 days versus 10.0 days (p = 0.107);
- runny nose: 7.0 days versus 9.0 days (p = 0.239);
- post-nasal discharge: 8.0 days versus 10.0 days (p = 0.007);
- thick nasal discharge: 7.0 days versus 8.0 days (p = 0.341);
- facial pain/pressure: 7.0 days versus 7.0 days (p = 0.404).

Clinical success rate [95% CI] at follow-up visit (PPc population):
Telithromycin group: 84.6% [76.93; 90.44]; amoxicillin/clavulanic acid group: 84.8% [77.29; 90.59].

Bacteriological satisfactory outcome at TOC visit (PPb population):
Telithromycin group: 96.3%; amoxicillin/clavulanic acid group: 89.8%.

Bacteriological satisfactory outcome at follow-up visit (PPb population):

Telithromycin group: 87.0%; amoxicillin/clavulanic acid group: 81.6%

Results – Safety

Patients with at least 1 TEAE (safety population):
Telithromycin group: 20.7%; amoxicillin/clavulanic acid group: 31.8% (p = 0.034).

Most frequent TEAEs were reported in the following system organ classes (telithromycin versus amoxcillin/clavulanic acid, >1% in either group): gastrointestinal disorders (7.6% versus 15.5%); infections and infestations (4.1% versus 6.1%); nervous system disorders (3.4% versus 3.4%); cardiac disorders (1.4% versus 0.0%); general disorders and administration site conditions (1.4% versus 0.0%); skin and subcutaneous tissue disorders (0.7% versus 6.1%); respiratory, thoracic and mediastinal disorders (0.7% versus 4.7%), ear and labytinth disorders (0.7% versus 3.4%); muskuloskeletal and connective tissue disorders (0.0% versus 2.0%).

Most frequent TEAEs (>1% of patients) were diarrhea (6.2% versus 9.5%), nausea (2.1% versus 0.7%), dizziness (2.1% versus 0.7%), headache (2.1% versus 2.0%), vaginal mycosis (0.7% versus 2.0%), rash (0.7% versus 2.0%), vertigo (0.7% versus 1.4%), upper abdominal pain (0.7% versus 1.4%).
The following TEAEs were reported only in the amoxicillin/clavulanic acid group (2 patients or 1.4 % each): ear pain, loose stools, back pain, epistaxis, dermatitis allergic, and urticaria.

Most TEAEs were of mild-to-moderate intensity. Severe TEAEs were experienced by 1.4% of patients of the telithromycin group and 4.1% of the amoxicillin/clavulanic acid group.

Patients with at least 1 TEAE possibly related to study drug:
Telithromycin group: 14.5%; amoxicillin/clavulanic acid group: 21.6%.

Most frequent study drug related TEAEs were diarrhea (5.5% versus 9.5%), nausea (2.1% versus 0.7%), dizziness (2.1% versus 0.7%), vertigo (0.7% versus 1.4%), upper abdominal pain (0.7% versus 1.4%), vaginal mycosis (0.7% versus 2.0%), rash (0.7% versus 2.0%).

The following TEA Es were considered study drug related only in the amoxicillin/clavulanic acid group: loose stools, allergic dermatitis, and urticaria (2 patients or 1.4% each).

Patient with at least 1 serious TEAE:
One patient of the telithromycin group experienced meningitis of moderate severity considered not related to study drug.

Deaths:
There were no deaths reported during the study.

Patients with permanent discontinuation due to a TEAE:
Telithromycin group: 3.4%; amoxicillin/clavulanic acid group: 6.1%

Results - Quality-of-life

Change from baseline in SF-36 transformed physical component (QOL population):
Telithromycin group: baseline score (mean ± standard deviation) of 41 ± 9; change from baseline of 13 ± 11 at follow-up visit.

Amoxicillin/clavulanic acid group: baseline score of 40 ± 9; change from baseline of 15 ± 11 at follow-up visit (p = 0.601 versus telithromycin).

Change from baseline in SF-36 transformed mental component (QOL population):
Telithromycin group: baseline score (mean ± standard deviation) of 43 ± 12; change from baseline of 11 ± 13 at follow-up visit.

Amoxicillin/clavulanic acid group: baseline score of 43 ± 12; change from baseline of 10 ± 13 at follow-up visit (p = 0.298 versus telithromycin).

Results - Health economics

Results to be presented in a separate report.

Results – Oropharyngeal flora

Results to be presented in a separate report.

Date of the report: 23-Oct-2006