These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription. Ketek is not indicated in this patient population

Sponsor/Company: sanofi-aventis **Drug substance**: Telithromycin (HMR3647)	**Study Identifier:** NCT00315003 **Study code:** EFC6132

Title of the study:

Multinational, randomized, double-blind, double-dummy, comparative study to evaluate the efficacy and safety of 5 days of telithromycin oral suspension 25 mg/kg, given once daily, versus 5 days of azithromycin oral suspension, given once as 10 mg/kg followed by 5 mg/kg given once daily for 4 days, in children with acute otitis media.

Study center(s): Multicenter study in the USA with 27 sites

Study period:

Date first subject/patient enrolled: 30-Jan-2006

Date last subject/patient completed: 18-Jul-2006

Phase of development: Phase 3

Objectives:

The prmary objective of this study was to assess the efficacy of telithromycin versus azithromycin in children with acute otitis media (AOM) with regard to superiority of time to symptom resolution in the modified intent-to-treat (mITT) population and non-inferiority of clinical outcome at the test-of-cure visit (Days 13 to 17) in the per protocol (PPc) population.

Methodology:

Multicenter, randomized, double-blind, double-dummy, comparative, 2-treatment group study.

Number of subjects/patients:

Planned: 1500; Randomized: 321 (the study was terminated on 20 September 2007 before randomization was completed)

Treated: 318; Evaluated: 317 for efficacy; 318 for safety

Diagnosis and criteria for inclusion:

Patients between 6 and 72 months of age with confirmed AOM and with the following inclusion criteria participated:

- Recent and rapid onset of AOM symptoms and signs
- Presence of middle ear fluid (MEF) on otoscopy
- Otalgia or ear tugging or touching
- At least 1 of the following clinical findings not specific to AOM: fever (>38°Celsius), vomiting, diarrhea, anorexia, sleep disturbance, or irritability
- Tympanometry exhibiting the following results: Type B curve or positive pressure peak-curves

Investigational product: Telithromycin 50 mg/mL oral suspension

Dose: 25 mg/kg once daily on Day 1 to 5

Administration: Oral

Reference therapy: Azithromycin 40 mg/mL oral suspension

Dose: 10 mg/kg once on Day 1, not exceeding 500 mg, followed by 5 mg/kg once daily on Days 2 to 5 not exceeding 250 mg/day

Administration: Oral

Placebos for telithromycin and azithromycin:

Dose: Not applicable

Administration: Oral

Duration of treatment: 5 days

Duration of observation: maximum of 28 days

Criteria for evaluation:

Efficacy:

The primary evaluation criterion was to assess the efficacy of telithromycin versus azithromycin in children with AOM using 2 co primary analyses:

- Superiority analysis of time to symptoms resolution in the mITTpopulation
- Noninferiority analysis of clinical outcome at test-of-cure visit (Day 13 to 17) in the PPc population.

Safety:

The safety assessment included adverse events reported by patients, their parents/legally authorized representative, or observed by the Investigators, specified adverse events of special interest (cardiac, hepatic, and visual) reported spontaneously or elicited, clinical laboratory parameters, and vital signs.

Health outcomes:
Quality of life variables included unscheduled office visits or emergency room visits, the number of days patients missed school, and number of days the caregiver missed work or usual activities and additional hours of child care.

Statistical methods:

Because this study was terminated after randomization of 321 of the planned 1500 patients, consequently, the type II error was not controlled as planned, and only descriptive statistics are generated. No inferential statistical tests for noninferiority or superiority were carried out.

Summaries of efficacy data were prepared for 2 analysis populations: (mITT) and (PPc) for clinical evaluation. The mITT population consists of all randomized subjects with confirmed AOM who received at least 1 dose of study medication and were analyzed as randomized. The PPc population consists of all mITT subjects except those with major protocol violations or classified as clinically indeterminate.

Analysis of safety measurements (vital signs, laboratory values and adverse events) was performed on all patients who received at least 1 dose of study medication by treatment taken. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 10.1).

Summary:

Because of the early termination of the study and limited data, no definite efficacy conclusions can be drawn.

Three hundred twenty-one patients were randomized out of the total target population of 1500 and of those, 317 (98.7%) were in the mITT population and 269 (83.8%) were in the PPc population at posttherapy (Day 13 to 17).

Efficacy results:

The primary efficacy assessment of clinical outcome at posttherapy in the PPc population showed that the clinical cure rate for telithromycin was 78.5% (102 of 130) and for azithromycin 82.7% (115 of 139).

The median time to symptom resolution in the ITT population was 3.0 days in the telithromycin group and 2.75 days in the azithromycin group. Seventy-fifth percentiles for time to symptom resolution were 5 days in both treatment groups.

Safety results:

No deaths were reported during the study.

Treatment emergent adverse events were reported by 37.6% of telithromycin and 36.6 % of azithromycin patients. Treatment emergent adverse events leading to treatment discontinuation were 1.3 % in the telithromycin and 1.2% in the azithromycin group. Vomiting was the treatment emergent adverse event that most frequently led to discontinuation in both the telithromycin and azithromycin group. The most frequently reported treatment emergent adverse event of ≥3 % in either treatment group were otitis media, diarrhea, cough, vomiting, and viral gastroenteritis in both treatment groups. Overall the incidence of treatment emergent adverse events was similar between the treatment groups.

There was 1 serious treatment emergent adverse event reported during the study in the telithromycin group. The patient developed a viral infection on Day 13 that resolved without sequelae on Day 18 of the study. The investigator judged the event was unrelated to study treatment.

No adverse events of special interest such as hepatic or cardiac events were reported in either group. There was 1 patient in the telithromycin group that reported a visual treatment emergent adverse event of special interest of blepharospasm that manifested 1 hour after the first dose of study medication and resolved without sequelae. The investigator assessed the event as nonserious, of mild intensity and possibly related to study medication.

The pattern of postbaseline hepatic enzyme levels and the majority of abnormalities in laboratory analytes were similar between the 2 treatment groups.

A total of 5 subjects had elevated postbaseline alkaline phosphatase (AP) values. Three subjects, 1 in the telithromycin group and 2 in the azithromycin group had a ≥5 ULN AP elevation at postbaseline. In addition, 1 subject in the azithromycin group had a >3, ≤5 ULN AP elevation at postbaseline. Out of the 5 total subjects with postbaseline elevated AP, 1 subject in the telithromycin group and 1 subject in the azithromycin group had normal baseline values and the remaining 3 subjects had elevated baseline values.

Eight of 130 (6.2%) patients in the telithromycin group and 2 of 132 (1.5%) in the azithromycin group had platelets ≥1.5 ULN at postbaseline.

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