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Sponsor/Company:	sanofi-aventis	**Study identifier:**	
Drug substance(s):	HMR3647 (telithromycin)	**Study Code:**	EFC6370 (HMR3647B/3103)
		Date:	13 July 2006

Title of the study:	Evaluation of the Safety, Efficacy, Pharmacokinetics, and Acceptability of HMR3647 20 mg/kg qd for 5 days with Acute Otitis Media (AOM) in children (Multicenter, open label, non comparative study)
Investigator(s):	**Medical expert** Sunkichi Baba, Emeritus Professor of Nagoya City University **Coordinating investigator** Noboru Yamanaka, Professor, Department of Otolaryngology, Wakayama Medical University Rinya Sugita, Hospital Director, Sugita ENT Clinic Naoya Miyamoto, Director, Kamo Hospital
Study center(s):	9 study centers – trial performed in Japan
Publications:	No
Study period: Date first patient/subject enrolled: 17 February 2004 Date last patient/subject completed: 6 October 2004	**Phase of development:** Phase 3
Objectives:	**Primary objective** To assess the safety of telithromycin 20 mg/kg qd in children with acute otitis media (AOM) (Study EFC6370) and children with community-acquired pneumonia (CAP) (Study EFC6369) **Secondary objectives** To assess the following in children with AOM treated with telithromycin 20 mg/kg qd for 5 days: - Efficacy - Pharmacokinetics - Acceptability

Methodology:	This is a multicenter, open label, noncomparative study in children with apparent infectious symptoms of AOM. Each subject will receive 20 mg/kg once daily (qd) to a maximum of 800 mg/d of telithromycin oral fine granule for 5 days. Duration of the study is from the day of obtaining informed consent until the test of cure (TOC) visit (Day 10-12). Observation for symptoms/signs, clinical laboratory tests etc. are carried out during the pretherapy visit, on-therapy visit (Day 2-4), end of therapy (EOT) visit (EOT: Day 5-7), and TOC visit (Day 10-12). Tympanocentesis will be performed at baseline for all subjects for bacteriologic evaluation and middle ear fluid (MEF) will be collected using an aspirator. A second tympanocentesis will be performed at EOT (Day 5-7) in those subjects who present with local middle ear signs (erythema and bulging of tympanic membrane) and MEF will be collected using an aspirator. In addition, in subjects who present with perforation of the tympanic membrane and otorrhea, otorrhea will be collected from tympanum for bacteriologic evaluation using an aspirator. The blood for determining telithromycin concentrations in plasma will be collected at Day 2 (only for the subjects who have undergone collection of MEF, the blood will be collected within 30 minutes after MEF sampling.), and at Day 5 (within 24 hours after the final administration, if possible). If MEF is observed at Day 2, it will be collected using aspirator at 6-12 after administration for determining telithromycin concentrations in the MEF. In case of the occurrence of adverse events (AEs) (subjective/objective symptoms, abnormal changes in laboratory findings), the events will generally be followed until resolution (normal or pretreatment values are obtained) or until the Investigator/Subinvestigator judges that the termination of the follow-up investigation is medically valid.
Number of patients/subjects evaluated:	56 subjects / 55 subjects

Diagnosis and criteria for inclusion:	**Diagnosis** Acute otitis media presumably caused by bacterial pathogens **Inclusion criteria** Subjects whose parent or guardian has given written informed consent to participate in the study upon being provided with sufficient information on the details of the clinical study. Informed assent is to be obtained for those more than 7 years of age. 1. Subjects who are outpatients of either gender, 6 months to 16 years of age, weighing 40.0 kg or less. If female, premenarchal status is required. 2. Subject with signs of infection according to following all middle ear signs and at least 1 of the general signs or symptoms. 1) Middle ear signs i) Inflammation signs (erythema of tympanic membrane) ii) Middle ear fluid identified iii) Bulging tympanic membrane iv) Tympanic opacification (loss of normal light reflex) 2) General signs or symptoms i) Otalgia ii) Fever (defined as normal body temperature +1 °C, by infraaxillary) iii) Ear discomfort (fullness/frequent touching of the ear) iv) Sleep disturbance v) Irritability (eg, crying, ill temper) vi) Inconsolability
Investigational product: Dose: Administration: Batch number(s):	Telithromycin 20% fine granule (1 g fine granule containing 200 mg telithromycin) 20 mg/kg Oral administration of telithromycin fine granule, 20 mg/kg once daily after breakfast. The maximum daily dosage must not exceed 800 mg (based on strength). KT03T038
Duration of treatment: 5 days	**Duration of observation:** 10 days
Reference therapy: Dose: Administration: Batch number(s):	No

Criteria for evaluation:	
Efficacy/ Pharmacodynamics:	Clinical efficacy (EOT): In each individual subject, the clinical outcome at EOT was evaluated from the tympanic signs and subjective/objective findings on Day 5 or at discontinuation (EOT: Day 5-7 or the day of the last dose to 2 days after the last dose). Clinical efficacy (TOC): In each individual subject, the clinical outcome at TOC was evaluated from the tympanic signs and subjective/objective findings at TOC (TOC: Day 10-12). Bacteriologic efficacy: In each individual subject, the bacteriologic outcome was evaluated from the presence/absence of the causative pathogen after treatment with the study medication.
Safety:	The presence/absence of subjective/objective symptoms and abnormal laboratory findings (abnormal changes of parameters in general hematological tests and blood biochemical tests) was investigated in safety evaluation.
Acceptability	The acceptability was evaluated from compliance status and willingness to take medication.
Pharmacokinetics:	Plasma telithromycin concentrations on Day 2 and Day 5 and MEF telithromycin concentrations on Day 2 were determined. The rate of drug transfer to MEF (MEF concentration/plasma concentration) on Day 2 was calculated.
Pharmacokinetic sampling times and bioanalytical methods:	**Sampling time** Sparse blood samples for pharmacokinetics (PK) will be collected at following points to enable population PK analysis. Blood sampling at Day 2-4 will be carried out within 30 minutes after MEF sampling. Otorrhea at following points and determine telithromycin concentration. 1. Blood EOT (Day 5-7) in case of visit within 24 hours from final administration: 1 timepoint On-therapy visit (Day 2-4) only from subjects from whom MEF was collected at the on-therapy visit: 1 timepoint 2. Otorrhea Six to 12 hours after administration at the on-therapy visit (Day 2-4), MEF will be collected only from the subjects with otorrhea due to tympanic membrane perforation: 1 timepoint **Bioanalytical methods** Plasma concentration: LC/MS/MS (Liquid chromatography/mass spectrometry/mass spectrometry) MEF concentration: HPLC (High Performance Liquid Chromatography)

Statistical methods:	**Efficacy** 1. Clinical outcome In the primary analysis set for clinical outcome, ie, the per protocol population for analysis of clinical outcome at end of therapy (PPcEOT), the efficacy rate in clinical outcome at EOT and its 2-sided 95% confidence interval were calculated. 2. Bacteriological outcome In the primary analysis set for bacteriologic outcome, ie, the per protocol population for analysis of bacteriologic outcome (PPb), the eradication rate for the causative pathogen and its 2-sided 95% confidence interval were calculated. **Safety** In the safety analysis set, among the entire AEs and the adverse events for which a causal relationship with the study drug could not be ruled out, treatment-emergent adverse events (TEAEs) were tabulated by System Organ Class, and the incidences as well as 2-sided 95% confidence intervals thereof were calculated. With respect to laboratory parameters, basic statistics were calculated for the values at baseline, values at EOT and differences between baseline and EOT, and the incidence of abnormal value changes were calculated and tabulated for each parameter. **Acceptability** In the acceptability analysis set, the acceptability ratings and drug-taking statuses were subjected to descriptive analysis. **Pharmacokinetics** In per protocol set of pharmacokinetics (PPpk) population, the basic statistics (number of subjects, mean, standard deviation, median, minimum, maximum) were calculated for the plasma drug concentrations on Day 2 and at EOT and the MEF drug concentrations on Day 2 as well as the rates of transfer to MEF on Day 2 (MEF drug concentration on Day 2 / plasma drug concentration on Day 2).

Summary:

Subject accounting	Subjects registered (randomized): 56 subjects Subjects administered the investigational drug: 56 subjects Subjects in whom the study was completed: 56 subjects Subjects in whom the study medication was discontinued: 7 subjects (Three subjects were discontinued for the reason of "advese event", 3 for the reason of "protocol violation" and 1 for "withdrawal of consent by guardian") Population of subjects evaluable for safety analysis: 55 subjects Population of subjects eligible for the acceptability analysis (Acceptability): 55 subjects PPcEOT: 43 subjects PPcTOC: 43 subjects PPb: 37 subjects Full Analysis Set for Analysis of Pharmacokinetics (FASpk): 28 subjects PPpk: 28 subjects Note: Subjects in whom the study was completed: subject who completed protocol study visits even of they discontinued study medication Acceptability analysis: analysis of taste and acceptance of study medication by subjects FASpk: The population remaining, excluding the subjects who did not take the investigational drug, in whom no PK determination was performed and in whom the PK parameters could not be analyzed from the entire registered subjects. PPpk: The population remaining, excluding the subjects who were not included in the PK evaluation from FASpk.
Efficacy/ Pharmacodynamic results:	In the primary analysis set for clinical outcome, PPcEOT, the cure rate at EOT was 86.0% (37/43) and its 2-sided 95% confidence interval was [72.1, 94.7]. In the analysis set for clinical outcome at TOC, PPcTOC, the cure rate at TOC was 80.5% (33/41) and its 2-sided 95% confidence interval was [65.1, 91.2]. In the analysis set for bacteriologic outcome, PPb, the eradication rate at EOT was 86.5% (32/37) and its 2-sided 95% confidence interval was [71.2, 95.5]. Among the 9 *Streptococcus pneumoniae* strains isolated, 5 strains were penicillin-resistant (PISP: 4 strains, PRSP: 1 strain) and 6 strains were erythromycin-resistant (ERSP), but the cure rate at EOT was 5/5 (100.0%) in the subjects with the former and 6/6 (100.0%) in the subjects with the latter.

Safety results:	In the 55 subjects included in the safety analysis set, AEs were noted in 14 subjects (25.5%, 17 episodes), and the 2-sided confidence interval of the incidence was [14.7, 39.0]. All the events were mild or moderate and recovered without any sequelae. The TEAEs for which a causal relationship with the study medication could not be ruled out (adverse drug reactions [ADRs]) were noted in 11 subjects (20.0%, 11 episodes), and the 2-sided 95% confidence interval of the incidence was [10.4, 33.0]. The ADR seen most frequently was "Vomiting" (classified as "Gastrointestinal disorders") noted in 8 subjects (14.5%), and the 2-sided 95% confidence interval of the incidence was [6.5, 26.7]. In addition, "Blood uric acid increased" was noted in 1 subject (1.8%), "Liver function tests raised" in 1 subject (1.8%) and "Rash" in 1 subject (1.8%). These AEs were not markedly different from the events noted in the clinical studies conducted in adults. The combined safety results with Study EFC6369 are presented in the study synopsis for Study EFC6369.
Acceptability	In the acceptability analysis set, the subjects meeting the definition of "sufficient drug-taking status" accounted for 42, and the rate was 76.4% (42/55). The rate of subjects for whom drug-taking was judged as "Easy drug-taking rate" was 80.0% (44/55).
Pharmacokinetic results:	In 28 subjects included in FASpk and PPpk, the plasma drug concentration (mean [min-max]) on combining the data on Day 2 and Day 5 was 0.468 [0.021-2.588] µg/mL at 7.36 [0.67-28.83] (mean [min-max]) hours after administration of telithromycin. The plasma drug concentration obtained in 12 subjects on Day 2 was 0.492 [0.069-1.419] µg/mL at 8.72 [5.67-11.50] hours after administration of telithromycin, and the plasma drug concentration obtained in 21 subjects on Day 5 was 0.454 [0.021-2.588] µg/mL at 6.58 [0.67-23.83] hours after administration of telithromycin. The MEF drug concentration on Day 2 was 7.36 [1.10-17.00] ng/mL at 8.57 [5.50 – 11.42] hours after administration of telithromycin, and the rate of transfer to MEF (MEF concentration/plasma concentration on Day 2) was 37.28 [2.44-159.72]%).
Date of report:	11 October 2005