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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor/Company:	sanofi-aventis	**Study identifier:**	
Drug substance(s):	HMR3647 (telithromycin)	**Study Code:**	EFC6369 (HMR3647B/3101)
		Date:	13 July 2006

Title of the study:	Evaluation of the Safety, Pharmacokinetics, Efficacy, and Acceptability of HMR3647 20 mg/kg qd for 5-7 Days with Community-Acquired Pneumonia (CAP) in Children (multicenter, open label, noncomparative study)
Investigator(s):	**Medical expert** Keisuke Sunakawa, Professor of Infectious Diseases, Kitasato University School of Medicine **Coordinating investigator** Yoshikiyo Toyonaga, Director, Department of Pediatric, Sekishinkai Sayama Hospital Hiroshi Sakata, Director, Department of Pediatric, JA Hokkaido koseiren Asahikawa Kousei Hospital Kazunobu Ouchi, Professor, Department of Pediatric, Kawasaki Medical University
Study center(s):	23 study centers – trial performed in Japan
Publications:	No
Study period: Date first patient/subject enrolled: 1 March 2004 Date last patient/subject completed: 27 October 2004	**Phase of development:** Phase 3
Objectives:	**Primary objective** To assess the safety of telithromycin (HMR3647) 20 mg/kg qd in children with community-acquired pneumonia (CAP) (Study EFC6369) and children with acute otitis media (AOM) (Study EFC6370) **Secondary objectives** To assess the following in children with CAP treated with telithromycin 20 mg/kg qd for 5-7 days: - Pharmacokinetics - Efficacy - Acceptability

Methodology:	This is a multicenter, open label, noncomparative study in children with apparent infectious symptoms of CAP. Each subject will receive 20 mg/kg once daily (qd) to a maximum of 800 mg/d of telithromycin oral fine granules for 5-7 days. Duration of the study is from the day of obtaining informed consent until the test of cure (TOC) visit (Day 15-29). Observation for symptoms/signs, clinical laboratory tests, etc. is carried out during the pretherapy visit, on-therapy visit (Day 4-6), end of therapy (EOT) visit (EOT: From the day of the last administration until 3 days after the completion of administration), and TOC visit (Day 15-29). In case of the occurrence of adverse events (AEs) (subjective/objective symptoms, abnormal changes in laboratory findings), the subjects will generally be followed until resolution (normal or pretherapy 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 / 56 subjects
Diagnosis and criteria for inclusion:	**Diagnosis** Community-acquired pneumonia (CAP) attributable to infection with typical bacteria, mycoplasma, or chlamydiae **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. • Subjects who are inpatients or outpatients of either gender, 6 months to 16 years of age, weighing 40.0 kg or less. If female, premenarchal status is required. • Subjects who are diagnosed with CAP based on chest X-ray showing the presence of a new infiltrate, clinical symptoms, and laboratory findings.
Investigational product:	Telithromycin 20% fine granule (1 g fine granule containing 200 mg telithromycin)
Dose:	20 mg/kg
Administration:	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).
Batch number(s):	KT03T037

Duration of treatment: 5-7 days	**Duration of observation:** 15 days

Reference therapy:	No
Dose:	
Administration:	
Batch number(s):	

Criteria for evaluation:	
Efficacy/ Pharmacodynamics:	Clinical efficacy (EOT): To assess clinical efficacy (EOT: From the day of the last administration until 3 days after the completion of administration) by change of following symptoms and signs: Symptoms (body temperature, cough, sputum, rales, wheezing, dyspnea, dehydration, cyanosis, lethargy) Laboratory tests (white blood cell (WBC) count, C-reactive protein [CRP]) Chest X-ray Clinical efficacy (TOC): To assess clinical efficacy (TOC: Day 14-28) by change in the following symptoms and signs: Symptoms (body temperature, cough, sputum, rales, wheezing, dyspnea, dehydration, cyanosis, lethargy) Presence or absence of supplemental use of antibiotics after the EOT Bacteriological efficacy: To assess bacteriologic efficacy by change in causative pathogen at EOT.
Safety:	Adverse events: 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 the safety evaluation.
Acceptability	The acceptability was evaluated based on compliance and willingness to take medication.
Pharmacokinetics:	Plasma concentrations of telithromycin were determined during treatment with study medication.
Pharmacokinetic sampling times and bioanalytical methods:	**Sampling time** Sparse blood samples for PK will be collected at following points (3 points totally) per patient at the on-therapy visit (Day 4-6) to enable population PK analysis. – Before telithromycin administration: 1 timepoint – 1-3 hours after telithromycin administration: 1 timepoint – 5-7 hours after telithromycin administration: 1 timepoint **Bioanalytical methods** LC/MS/MS (Liquid chromatography / mass spectrometry/ mass spectrometry)

Statistical methods:	**Efficacy** 1. Clinical outcome Efficacy rate and its 2-sided confidence interval were calculated, using PPc EOT (per protocol population for analysis of clinical outcome at end of therapy), which was the main analysis population for clinical effect. 2. Bacteriological outcome Eradication rates of causative pathogens and the 2-sided 95% confidence interval were calculated, using PPb (per protocol population for analysis of bacteriologic outcome), the main analysis population for bacteriologic effect. **Safety** The safety analysis population of this study and the combined safety analysis population of this study and Study EFC6370 in AOM were analyzed as follows: For the safety analysis population, all AEs and the AEs for which a causal relationship could not be ruled out were classified by System Organ Class and TEAE (treatment-emergent adverse event), and the incidence and its 2-sided 95% confidence interval were calculated. For laboratory parameters, descriptive statistics were calculated each for the baseline and EOT values and the difference between baseline and EOT values. The incidence of abnormal change was compiled and tabulated by parameter. **Acceptability** In the acceptability analysis set, the acceptability ratings and drug-taking statuses were subjected to descriptive analysis. **Pharmacokinetics** For PPpk (per protocol population for analysis of pharmacokinetics), descriptive statistics (number of subjects, mean, standard deviation, median, minimum, maximum) were calculated for plasma drug concentrations during study medication.

Summary:

Subject accounting	Subjects registered (randomized): 56 subjects Subjects administered the investigational drug: 56 subjects Subjects in whom the study was completed: 55 subjects Subjects in whom the study medication was discontinued: 6 subjects (Two subjects were discontinued for the reason of "protocol violation", 2 for the reason of "withdrawal of consent by guardian", 1 for "difficulty in taking the investigational drug" and 1 for "inability to take the investigational drug") Population of subjects evaluable for safety analysis: 56 subjects Population of subjects eligible for the acceptability analysis (Acceptability): 56 subjects PPcEOT: 39 subjects PPcTOC: 39 subjects PPb: 16 subjects Note: Subjects in whom the study was completed: patient who completed protocol study visits even of they discontinued study medication Acceptability analysis: analysis of taste and acceptance of study medication by the subjects
Efficacy/ Pharmacodynamic results:	The efficacy rate at EOT, ie, the primary efficacy variable, and its 2-sided 95% confidence interval were 94.9% (37/39) and [82.7, 99.4], respectively, in the PPcEOT population, and the cure rate at TOC and its 2-sided 95% confidence interval were 97.4% (37/38) and [86.2, 99.9], respectively, in the PPcTOC population. Among the subjects who were assessed as "Effective" at EOT in clinical outcome, none were assessed as "Failure" in clinical outcome at TOC. These results were comparable with the cure rate of telithromycin at TOC in the comparative study conducted in adults with CAP (91.5 % [97/106]) and that in the overseas pediatric study (93.0 % [40/43]). The efficacy rate in 17 subjects who did not respond to other antibacterial agents was 100.0% (17/17). The eradication rate for the entire pretreatment causative pathogens was 68.8% (11/16). The eradication rate was 4/4 for *Streptococcus pneumoniae*, 37.5% (3/8) for *Haemophilus influenzae*, 1/1 for *Moraxella catarrhalis* and 3/3 for *Mycoplasma pneumoniae*. In case of *S. pneumoniae*, 3 strains resistant to penicillin and erythromycin were isolated, and the efficacy rate at EOT was 3/3, demonstrating efficacy in all the subjects infected with such antibiotic-resistant strains.

Safety results:	The main objective of this study was to investigate the safety of telithromycin in pediatric subjects with CAP. The results were analyzed in combination with the results of Study EFC6370. The safety results were as follows: In the 111 subjects included in the safety analysis set, AEs were noted in 51 subjects (45.9%, 78 episodes), and the 2-sided confidence interval of the incidence was [36.4, 55.7]. The AEs for which a causal relationship with the study medication could not be ruled out (adverse drug reactions [ADRs]) were noted in 30 subjects (27.0%, 35 episodes), and the 2-sided 95% confidence interval of the incidence was [19.0, 36.3]. The ADRs noted with an incidence of ≥3 % were "Vomiting" (15 subjects, 13.5%) and "Diarrhoea" (5 subjects, 4.5%), and the other major ADRs noted with an incidence of ≥1 % were "Loose stools" (2 subjects, 1.8%), "Liver function tests abnormal" (2 subjects, 1.8%) and "Neutrophil count decreased" (2 subjects, 1.8%). All of these AEs were mild or moderate and recovered without sequelae. These AEs were within the range observed in the adult clinical studies and were not considered to be specific to children. As serious adverse events (SAEs), "Asthma" and "Bronchitis" were noted in 1 subject each, but the causal relationship with the study drug was ruled out, so no serious ADRs were noted. The noted SAEs recovered without any sequelae. On the other hand, in 56 subjects enrolled in Study EFC6369, AEs were noted in 37 subjects (66.1 %, 61 episodes) and the 2-sided 95% confidence interval of incidence was [52.2, 78.2]. Twenty-four AEs for which causality could not be denied (ADRs) occurred in 19 subjects (33.9%), and 2-sided 95% confidence interval for the incidence was [21.8, 47.8]. Main ADRs were vomiting (7, 12.5%) and diarrhea (5, 8.9%). The gastrointestinal AEs were most frequent, showing the same trend as in the combined analysis.
Acceptability	In the acceptability analysis set, the subjects meeting the definition of "sufficient drug-taking status" accounted for 44, and the rate was 78.6% (44/56). The rate of subjects in whom drug-taking was judged as "Easy drug-taking rate" was 75.0% (42/56).
Date of report:	5 December 2005