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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:**	NCT00408135
Drug substance(s):	HMR3647 (telithromycin)	**Study Code:**	EFC6371 (HMR3647B/3104)
		Date:	24 October 2006

Title of the study:	Evaluation of the Safety, Efficacy and Acceptability of HMR 3647 (20% fine granules 1 g sachet) in Children with infections. (multicenter, open label, non comparative study)
Investigator(s):	**Medical expert** Keisuke Sunagawa, Professor, Department of Infectious Diseases, School of Medicine, Kitasato University **Coordinating investigator** Naoichi Iwai, Director, Department of Pediatrics, Meitetsu Hospital Satoshi Iwata, Director, Department of Pediatrics, National Tokyo Medical Center Shinichi Watanabe, Professor, Department of Dermatology, Teikyo University School of Medicine Rinya Sugita, Hospital Director, Sugita Otolaryngology Clinic Akihiko Kaneko, Professor, Dept. of Oral Surgery, School of Medicine, Tokai University
Study center(s):	24 study centers, trial performed in Japan
Publications:	No
Study period: Date first patient/subject enrolled: 17 August 2004 Date last patient/subject completed: 2 May 2005	**Phase of development:** Phase 3
Objectives:	**Primary objective** To assess the safety of telithromycin (HMR 3647) (20% fine granules) 1g filling sachet in children with infections: respiratory tract infections, dermatological infections, otorhinolaryngological infections, or dentistry/oral surgery infections. **Secondary objectives** To assess the clinical efficacy, bacteriological efficacy and acceptability of telithromycin (20% fine granules) 1g filling sachet in children with infections in the primary objective.

Methodology:	This is a multicenter, open label, noncomparative study in children with apparent infectious symptoms of following infections: respiratory tract infections, dermatological infections, otorhinolaryngological infections, dentistry/oral surgery infections. Each subject will receive 1 to 4 sachets of telithromycin (1 g sachet: 1-g telithromycin 20% fine granule), once daily, depending on the body weight of subject. The duration of treatment with dentistry/oral surgery infections is 3 days, and that of the other disease (respiratory tract infections, dermatological infections and otorhinolaryngological infections) is 5 days. *Respiratory tract infections, Dermatological infections and Otorhinolaryngological infections* Duration of the study is from the day of obtaining informed consent until the test of cure (TOC) visit (Day 10-16). Observation for symptoms/signs, clinical laboratory tests are carried out during the pretherapy visit, on-therapy visit (Day 3-4), end of therapy (EOT) visit (Day 5-8), and TOC visit (Day 10-16). *Dentistry/Oral surgery infections* Duration of the study is from the day of obtaining informed consent until TOC visit (Day 8-12). Observation for symptoms/signs, clinical laboratory tests are carried out during the pretherapy visit, EOT visit (Day 3-4), and TOC visit (Day 8-12). In case of the occurrence of adverse events (AEs) (subjective/objective symptoms, abnormal changes in laboratory findings), the subjects were to be followed until resolution (normal or pretreatment values are obtained) or until the Investigator/Sub-investigator judged that the termination of the follow-up investigation is medically valid.
Number of patients/subjects:	111 included subjects / 109 treated and evaluated subjects
Diagnosis and criteria for inclusion:	**Diagnosis** Following Infections presumably caused by bacterial pathogens, Mycoplasma or Chlamydia. - **Respiratory tract infections**: Tonsillitis, Pharyngitis/Laryngopharyngitis, Acute Bronchitis, Scarlet Fever, Secondary Infection to Chronic Respiratory Disease - **Dermatological infections**: Simple Skin Infections, Superficial Skin Infections such as Contagious Impetigo - **Otorhinolaryngological infections**: Acute Sinusitis, Acute exacerbation of chronic sinusitis - **Dentistry/Oral surgery infections**: Periodontitis, Perimandibular Infection **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 was obtained for those more than 7 years of age.

<table>
<tr><td>Diagnosis and criteria for inclusion (cont'd):</td><td>Inclusion criteria applying to all indications:
Subjects who are outpatients of either gender, 6 months to 16 years of age, and weigh from 7.0 kg.
If female, premenarchal status is required.
Inclusion criteria applying to specific infections:
For respiratory tract infections:
Subjects who are diagnosed with mild or moderate respiratory tract infection (excluding pneumonia) based on a fever (≥ 38°C) or C-Reactive Protein positive, clinical symptoms/signs, and laboratory findings.
For dermatological infections:
Subjects who are diagnosed with mild or moderate dermatological infection in terms of clinical symptoms/signs and laboratory findings.
For otorhinolaryngological infections:
Subjects who are confirmed to have purulent / mucopurulent rhinorrhea and postrhinorrhea. Subjects who are diagnosed with mild or moderate otorhinolaryngological infection in terms of clinical symptoms/signs and laboratory findings
For dental / oral surgical infections:
Subjects who have formed obstructive abscess and are diagnosed with mild or moderate dental / oral surgical infection</td></tr>
<tr><td colspan="2">Investigational product:
Dose:
1 to 4 sachets of telithromycin (1 g sachet: 1-g telithromycin 20% fine granule* packets) depending on the body weight of subject (14.3-28.6 mg/kg)
* telithromycin 20% fine granule: 1 g fine granule containing 200 mg telithromycin
body weight (kg) — Sachets (telithromycin potency)
≥ 7.0 and < 14.0 — 1sachet (200 mg potency) : 14.3< - ≤28.6 mg/kg
≥ 14.0 and < 25.0 — 2 sachets (400 mg potency): 16.0< - ≤28.6 mg/kg
≥ 25.0 and < 35.0 — 3 sachets(600 mg potency) : 17.1< - ≤24.0 mg/kg
≥ 35.0 — 4 sachets(800 mg potency) : - ≤22.9 mg/kg
The maximum daily dosage must not exceed 800 mg (based on potency).

Administration: One to four 1-g divided packets of telithromycin were to be orally administered once daily after breakfast depending on body weight of each pediatric patient.</td></tr>
<tr><td>Duration of treatment:
5 days: Respiratory tract infections,
Dermatological infections,
Otorhinolaryngological infections
3 days: Dental / oral surgical infections</td><td>Duration of observation:
10 days: Respiratory tract infections,
Dermatological infections,
Otorhinolaryngological infections
8 days: Dental / oral surgical infections</td></tr>
<tr><td colspan="2">Reference therapy: None
Dose:
Administration:</td></tr>
</table>

Criteria for evaluation:	
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 the safety evaluation.
Efficacy:	Clinical efficacy (EOT): Respiratory tract infections, Dermatological infections and Otorhinolaryngological infections: to assess clinical efficacy (EOT: Day 5-8 or the day of the last dose to 3 days after the last dose) by change in the symptoms and signs. Dentistry/Oral surgery infections: to assess clinical efficacy (EOT: Day 3-4 or the day of the last dose to 1 days after the last dose) by change in the symptoms and signs. Clinical efficacy (TOC): Respiratory tract infections, Dermatological infections and Otorhinolaryngological infections: to assess clinical efficacy (TOC: Day 10-16) by change in the symptoms and signs. Dentistry/Oral surgery infections: to assess clinical efficacy (TOC: Day 8-12) by change in the symptoms and signs. Bacteriologic efficacy: to assess bacteriologic efficacy by change in causative pathogen at EOT.
Acceptability:	The acceptability was evaluated based on compliance status and willingness to take medication.
Statistical methods:	
Safety:	For the safety analysis set, among the entire AEs and the AEs 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.
Efficacy:	1. Clinical outcome: in the primary analysis set for clinical outcome, ie, the per protocol population for analysis of clinical outcome at EOT (PPcEOT), the efficacy rate in clinical outcome at EOT and its 2-sided 95% confidence interval were calculated. In addition, as the secondary analysis, in the "Per protocol set for analysis of clinical outcome at TOC (PPcTOC)", the efficacy rate and its 2-sided 95% confidence interval were calculated similarly. 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.
Acceptability:	In the acceptability analysis set, the acceptability ratings and drug-taking statuses were subjected to descriptive analysis.

Summary:

Subject accounting:	Included subjects: 111 subjects Treated subjects: 109 subjects Subjects in whom the study was completed*: 109 subjects Subjects in whom the study medication was discontinued: 10 subjects (Seven subjects were discontinued for the reason of "adverse event", 1 for the reason of "protocol violation", 1 for "subject was wish to discontinue study medication" and 1 for "difficulty in taking the drug") Population of subjects evaluable for safety analysis: 109 subjects Population of subjects eligible for the acceptability analysis*: 110 subjects PPcEOT: 86 subjects (Respiratory tract infections: 56 subjects, Dermatological infections: 12 subjects, Otorhinolaryngological infections: 12 subjects, Dentistry/Oral Dentistry/Oral surgery infections: 6 subjects) PPcTOC: 86 subjects (Respiratory tract infections: 55 subjects, Dermatological infections: 12 subjects, Otorhinolaryngological infections: 12 subjects, Dentistry/Oral surgery infections: 7 subjects) PPb: 61 subjects (Respiratory tract infections: 32 subjects, Dermatological infections: 12 subjects, Otorhinolaryngological infections: 12 subjects, Dentistry/Oral surgery infections: 5 subjects) *Note: Subjects in whom the study was completed: subject who completed protocol study visits even if they discontinued study medication Acceptability analysis: analysis of taste and acceptance of study medication by subjects
Safety results:	In the 109 subjects included in the safety analysis set, AEs until TOC were noted in 56 subjects (51.4%) and the 2-sided 95% confidence interval of the incidence was [41.6, 61.1]. The AEs for which a causal relationship with the study medication could not be ruled out (adverse drug reactions [ADRs]) were noted in 36 subjects (33.0%) and the 2-sided 95% confidence interval of the incidence was [24.3, 42.7]. As ADRs, "Diarrhoea" and "Vomiting" classified as "Gastrointestinal disorders" were noted most frequently in 11 subjects (10.1%) each and the 2-sided 95% confidence interval of the incidence was [5.1, 17.3]. The ADRs noted with the second highest incidence was "Loose stools" noted in 4 subjects (3.7%). The other events were LDH increased (2 subjects, 1.8%), Eosinophil count increased (2 subjects, 1.8%) and Abdominal pain, Upper abdominal pain, Feeling abnormal, ALT (GPT) increased, AST (GOT) increased, Liver function test abnormal, Neutrophil count decreased, Platelet count increased, Urinary occult blood positive, White blood cell count decreased, Somnolence, Pharynx discomfort and Rash noted each 1 subject (0.9%). These events were also noted in the clinical studies conducted in adults, and the results were similar to those obtained in the preceding studies conducted in pediatric patients with community-acquired pneumonia (Study EFC6369) and pediatric patients with acute otitis media (Study EFC6370). Serious adverse events (SAEs) were noted in 3 subjects (3 episodes). The noted SAEs were "Worsening of adenovirus infection", "Infectious mononucleosis" and "Worsening of RS virus infection" noted in 1 subject each. All of those were judged as SAEs since hospitalization was necessary for treatment, but all were viral infections and the causal relationship with the investigational drug was ruled out.

Safety results (cont'd):	As Alert Term, "ALT (GPT) increased" was reported in 1 subject, but this event disappeared without any symptomatic treatments and was not clinically problematic. After the investigational drug was administered for 5 days, the ALT (GPT) level increased from 30 IU/L to 89 IU/L and the AST (GOT) level increased from 37 IU/L to 106 IU/L at Day 6. The ALT (GPT) level increased further to 109 IU/L exceeding 3 times the upper limit of the normal range (5 to 35 IU/L) at Day 8. On the other hand, the AST (GOT) level at Day 8 was 76 IU/L (normal range: 5 to 50 IU/L). Thereafter, at Day 15, the ALT (GPT) level was 35 IU/L and the AST (GOT) level 20 IU/L showing recovery to the normal range.
Efficacy/ Pharmacodynamic results:	In the PPcEOT, the efficacy rate in clinical outcome at EOT and its 2-sided 95% confidence interval were 100.0% (56/56) and [93.6, 100.0], respectively, for the respiratory infections, 81.8% (9/11) and [48.2, 97.7], respectively, for the dermatological infections, 100.0% (12/12) and [73.5, 100.0], respectively, for the otorhinolaryngological infections and 83.3% (5/6) and [35.9, 99.6], respectively, for the dental / oral surgical infections. In the PPcTOC, the cure rate at TOC and its 2-sided 95% confidence interval were 94.5% (52/55) and [84.9, 98.9], respectively, for the respiratory infections, 83.3% (10/12) and [51.6, 97.9], respectively, for the dermatological infections, 75.0% (9/12) and [42.8, 94.5], respectively, for the otorhinolaryngological infections and 85.7% (6/7) and [42.1, 99.6], respectively, for the dental / oral surgical infections. In the PPb, those in which 5 or more strains were isolated were *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Haemophilus influenzae* from the Respiratory tract infections, *Staphylococcus aureus* in the Dermatological infections and *S. pneumoniae*, *H. influenzae* and *Moraxella catarrhalis* from the Otorhinolaryngological infections. In the Dental / Oral surgical field, there were no species in which 5 or more strains were isolated, and 3 strains of *Staphylococcus mitis* were isolated as the most frequent case. In the PPb, the eradication rate at EOT for the entire pretreatment causative pathogens and its 2-sided 95% confidence interval were 65.6% (21/32) and [46.8, 81.4], respectively, for the Respiratory tract infections, 75.0% (9/12) and [42.8, 94.5], respectively, for the Dermatological infections, 50.0% (6/7) and [21.1, 78.9], respectively, for the Otorhinolaryngological infections and 80.0% (4/5) and [28.4, 99.5], respectively, for the Dental / Oral surgical infections.
Acceptability results:	Among the 110 subjects included in the acceptability analysis set, 90 subjects (81.8%) met the definition of "Sufficient drug-taking status", and the rate of easy drug taking, i.e., the rate of subjects who were assessed as "Took willingly" or "Took without problems", was 75.5% (83/110).
Date of full report:	26 June 2006