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Sponsor/company:	sanofi-aventis	ClinialTrials.gov Identifier:	NCT00393744
		Study Code:	PRIST_L_01683
Generic drug name:	PRISTINAMYCIN	Date:	13/Mar/2009

Rationale of the study: The increasing frequency of Group A beta-hemolytic Streptococcus (GAS) resistance to macrolides in France called for new recommendations for the treatment of tonsillitis, notably in case of contra-indications to beta-lactamins and short durations of treatments must be favoured in order to increase compliance. In this context sanofi-aventis France conducted a study in agreement with the French Health Authorities (Afssaps) in order to document the efficacy and safety of pristinamycin in tonsillitis and to propose an administration schedule (dose, duration) for both children and adults.	
Title of the study:	A phase III, multicentre, randomized, open study comparing the efficacy and safety of pristinamycin 50mg/kg/day in two daily intakes in children and 1g twice a day in adults for 4 days versus amoxicillin 50mg/kg/day in two daily intakes in children and 1g twice a day in adults for 6 days orally, in the treatment of group A beta-hemolytic streptococcal tonsillitis in patients aged 6 to 25 years.
Investigator(s):	Coordinating Investigator : Professor Joël Gaudelus, Hôpital Verdier, Bondy Planned: 95 GPs and pediatricians Active: 63 GPs and pediatricians
Study centre(s):	Private medical practice all over France
Publications (reference):	Not applicable

Study period: Date first patient enrolled: 16-OCT-2006 Date last patient completed: 13-MAR-2008	Phase of development: III

Objectives:	Primary objective: To demonstrate the non-inferiority in terms of bacteriological efficacy of pristinamycin (PRI) administered for 4 days *versus* amoxicillin (AMX) administered for 6 days, at the recovery assessment visit V3 (D10/D14), in the treatment of group A Streptococcus Tonsillitis (GAST) in patients aged 6 to 25, in the per protocol (PP) population. Secondary: ▪ To compare the bacteriological efficacy of PRI and AMX at visit V3, in the mITT population. ▪ To compare the bacteriological efficacy of PRI and AMX, 3 to 4 weeks after the end of treatment (V4 visit, D25/D34), in the PP and mITT populations. ▪ To compare the clinical efficacy of PRI and AMX at visits V3 and V4, in the PP and mITT populations. ▪ To compare the bacteriological efficacy of PRI and AMX at visits V3 and V4, in the treatment of macrolide resistant GAST, in the PP and mITT populations. ▪ To assess the safety of PRI and AMX.
Methodology:	Phase III, national, prospective, multicentre, comparative, randomized (2 PRI : 1 AMX), stratified according to the patient's age (≤ 15 years, > 15 years), open trial, comparing two parallel treatment groups, PRI (4 days) *versus* AMX (6 days) in patients aged 6 to 25, presenting a GAST confirmed by a Rapid Diagnostic Test (RDT).

Number of patients:	Planned: 393 (262 in the PRI group, 131 in the AMX group), with at least 30 in the PRI group with a macrolide resistant GAS. Randomized: 395 (260 in the PRI group, 135 in the AMX group)
Evaluated:	PP: 314 201 in the PRI group: 126 ≤ 15 years, 75 > 15 years 113 in the AMX group: 73 ≤ 15 years, 40 > 15 years mITT: 353 231 in the PRI group : 145 ≤ 15 years, 86 > 15 years 122 in the AMX group : 77 ≤ 15 years; 45 > 15 years Safety: 394 260 in the PRI group: 156 ≤ 15 years, 104 > 15 years 134 in the AMX group: 82 ≤ 15 years, 52 > 15 years
Diagnosis and criteria for inclusion:	▪ Male and female outpatients. ▪ Aged 6 to 25. ▪ Body weight ≥ 20 kg. ▪ Suspicion of GAST (erythema and/or pharyngeal exudate and/or tonsil exudate with oro-pharyngeal pain and/or odynophagia, fever ≥ 38°C, sore satellite adenopathies). ▪ Confirmed by a positive RDT. ▪ With a throat swab for culture. ▪ Capable of swallowing a tablet. The written consent was to be obtained prior to the inclusion into the study, either from the patients themselves or from their legal representatives (for patients less than 18 years old).
Non inclusion criteria	▪ Related to the studied disease o Suspicion of viral infection (associated dysphonia, cough, conjunctivitis or rhinitis). o Adenophlegmon, peri-tonsil abscess. ▪ Related to the study treatments o Known or suspected allergy to beta-lactams (penicillin, cephalosporin). o Suspicion of infectious mononucleosis. o Phenylketonuria. o Congenital galactosemia, glucose and galactose malabsorbtion syndrome, lactase deficit. o Allergy to pristinamycin and/or virginiamycin. o History of pustular eruption with pristinamycin. o Hypersensitivity or intolerance to gluten. o Treatment with cyclosporin, methotrexate, colchicine, allopurinol, tacrolimus, oral anticoagulant. ▪ Related to previous treatments o Patient having been given an antibiotic treatment within one month before inclusion, except for azithromycin for which the minimum wash-out period was 3 months. o Patient on short-term corticotherapy. Subjects on stable long-term corticotherapy initiated prior to the entry into the study could be included. ▪ Related to the patient o Breast-feeding women. o Pregnant women or women likely to be pregnant. o Patient likely to be given, during the study, any forbidden treatment according to the protocol. o Treatment with any other experimental drug during the 4 weeks before inclusion in the study. o Immunodeficiency, medically relevant cardiovascular, neurological, endocrine disorders or any other relevant disorder making either the realization of the protocol or the interpretation of the study results difficult.

	○ Known hepatic failure. ○ Known renal failure (creatinine clearance < 30 mL/min.) ○ Cancer, hemopathies. ○ History of drug or alcohol abuse. ▪ Related to the protocol ○ Mental condition making the patient unable to understand the nature, the objectives and the likely consequences of the study. ○ Patient unable to comply with the constraints of the protocol (for instance, not cooperating, unable to attend the follow-up visits and likely unable to complete the study). ○ Subjects deprived of their liberty due to administrative or judicial decision. ○ Subjects not benefiting from the French health and pensions organization. ○ Patient being the investigator or any member of the study team or related to the investigator.
Investigational product: Dose: Administration:	Pristinamycin 250mg or 500mg tablets. Children: 50mg/kg/day (without exceeding 2g/day), in two intakes. Adults: 1 g, twice a day. Oral route
Duration of treatment: PRI group: 4 days	Duration of observation: 1 month
Reference therapy: Dose: Administration:	Amoxicillin 500mg capsules or 250mg sachets. Children: 50mg/kg/day (without exceeding 2g/day), in two intakes Adults: 1 g, twice a day Oral route
Duration of treatment: AMX group: 6 days	Duration of observation: 1 month
Criteria for evaluation:	
Efficacy	Primary endpoint: Bacteriological eradication rate at V3 visit (D10/D14), in the PP population Secondary endpoint: ▪ Bacteriological eradication rate at V3 visit, in the mITT population ▪ Bacteriological eradication rate at V4 visit (D25-D35) , in the PP and mITT populations ▪ Clinical success rate at visits V3 and V4, in the PP and mITT populations ▪ Bacteriological eradication rate at visits V3 and V4 on patients with a macrolide resistant GAST, in the PP and mITT populations
Safety:	▪ Adverse events reported by the patient or noted by the investigator ▪ Heart rate, systolic and diastolic blood pressure

Statistical methods:	Study populations: per protocol (PP), modified Intention to Treat (mITT) and safety. Determination of sample size : the number of patients was calculated assuming a bacteriological eradication rate at V3 equal to 85% in either groups. Descriptive statistics are given by age stratum, treatment groups and overall. For quantitative data count, number of missing data, mean, median, minimum and maximum values are provided. For qualitative data count, number and percentage of missing data, frequency and percentage are provided for each level of the variable. Descriptive statistics of baseline characteristics: demographic data, medical and surgical history, concomitant diseases, prior and concomitant medications, anamnesis, clinical symptoms and clinical signs of tonsillitis. Primary endpoint (non-inferiority analysis): PP population Two-sided 95% confidence interval in the difference between groups in bacteriological eradication rate at V3 visit. Secondary endpoint: Estimation of the two-sided 95% confidence interval in the difference between groups in the eradication rate at V3 in the mITT population. Estimation of the two-sided 95% confidence interval in the difference between groups in the eradication rate at V4 (mITT and PP). Descriptive statistics of the clinical efficacy at V3 and V4, assessment of correlation between clinical and bacteriological results (mITT and PP populations). Descriptive statistics of the eradication rate at V3 and V4 on patients with macrolide resistant GAST (PP and mITT). Descriptive statistics of Safety: Incidence of Treatment Emergent Adverse Events (TEAEs) by treatment group overall and by system organ class (MedDRA 9.0). Similar incidences of drug related TEAEs and of serious TEAEs.
Summary	395 patients were included and treated (238 ≤ 15 years, 60.3%).135 were randomized to the AMX group and 260 to the PRI group. One patient was lost to follow-up after visit 1 and therefore excluded from the safety population. 42 patients were excluded from the mITT population, 13 from the AMX and 29 from the PRI group. In addition to the 42 patients excluded from the mITT population, 39 patients were excluded from the PP population because of major protocol deviations (9 from the AMX group, 30 from the PRI group). Both treatment groups were similar at baseline in terms of predominance of female patients (AMX 56.6%, PRI 53.2%), mean age (AMX 14.1±6.4 years, PRI 13.9±6.1 years), weight (mean values AMX 43.6 kg, PRI 45.8 kg), height (AMX 147 cm, PRI 149 cm) BMI (AMX 19.0 kg/m², PRI 19.5 kg/m²) (PP population). The two treatment groups were similar at baseline in terms of disease characteristics. At the time of inclusion, 2.2 days had elapsed on average since the first tonsillitis symptoms in the AMX group, 2.5 days in the PRI group. A very similar proportion of patients had a history of previous episode(s) of tonsillitis, 18.6% in the AMX group and 17.4% in the PRI group. On average, the patients had suffered from 1.3 episodes of tonsillitis in the previous 12 months in the AMX group and 1.5 episodes in the PRI group. Since the last tonsillitis episode, 6.3 months had elapsed in the AMX group and 6.4 months in the PRI group (PP). The profile of signs and symptoms of tonsillitis was similar in the 2 treatment groups: odynophagia was the most frequently reported symptom (AMX 100.0%, PRI 98.5%), followed by tonsil/pharyngeal erythema (AMX 98.2%, PRI 99.5%), fever (AMX 94.7%, PRI 94.5%), adenopathies (AMX 93.8%, PRI 92.0%) and pharyngeal exudate (AMX 63.7%, PRI 60.2%)(PP). Similar results were observed in the mITT analysis set. A total of 14 patients did not complete the study (AMX 3: AE 2, investigator's request 1 and PRI 11: investigator's request 5, promoter's request 1, lost to follow-up 1, patient refused to continue 2, other reason 2). (TEAEs) by treatment group overall and by system organ class (MedDRA 9.0). Similar incidences of drug related TEAEs and of serious TEAEs.

Efficacy results:	Primary efficacy criterion The bacteriological eradication rate at V3 in the PP analysis set was 84/201 (41.8%) in the PRI group and 102/113 (90.3 %) in the AMX group. The AMX – PRI difference in bacteriological eradication rate was 48.5%, 95% CI [40.4%; 56.5%].The upper limit of this 95% CI is greater than 10% and the non inferiority of PRI cannot be concluded compared to AMX. Secondary efficacy criteria In the mITT population the bacteriological eradication rate at V3 was 38.5% in the PRI group and 87.7% in the AMX group. The difference AMX-PRI was 49.2% with a two-sided 95% CI of [41.2%, 57.1%] . In the PP population, the bacteriological eradication rate at V4 was 36.8% in the PRI group and 73.5% in the AMX group. The difference AMX-PRI was 36.6% with two-sided 95% CI of [26.8%, 46.5%]. The results in the mITT population were very similar with an eradication rate of 33.8% in the PRI group and 72.1% in the AMX group. The difference AMX-PRI was 38.4% with a two-sided 95% CI of [29.0%, 47.8%]. The results obtained with pristinamycin may thus be explained by either a low PRI local concentration or an insufficient exposition to PRI in terms of dose and/or duration of treatment in this specific indication that requires the total eradication of GAS at the end of treatment At V3 in the PP population, the clinical success (cure or improvement) rate in the PRI group (83.6%) was lower than in the AMX group (96.5%). This was also the case at V4, with 92.0% of clinical success in the AMX group vs. 80.6% in the PRI group. The results in the mITT population were very similar with a clinical success rate at V3 of 95.1% in the AMX group and 78.4% in the PRI group, and 91.0% of clinical success rate at V4 in the AMX group vs. 75.8% in the PRI group. Except for one patient in the AMX group, all PP patients with bacteriological eradication at V3 were either clinical cures or improvements. On the other hand 7.1% of the patients of the AMX group and 43.3% of the PRI group were clinical cures or improvements but bacteriological failures. In the mITT population, 1 bacteriological success in each treatment group was a clinical failure (AMX 0.8%, PRI 0.4%) and 8.2% of the patients of the AMX group and 41.6% of the PRI group were either clinical cures or improvements but bacteriological failures. In the PP analysis set, the eradication rate at V3 in patients with macrolide resistant GAST was 8/9 (88.9%) in the AMX group and 6/11 (54.5%) in the PRI group. In the mITT analysis set, it was 8/9 (88.9%) in the AMX group and 6/11 (54.5%) in the PRI. In the PP analysis set, the eradication rate at V4 in patients with macrolide resistant GAST was 7/9 (77.8%) in the AMX group and 4/11 (36.4%) in the PRI group. In the mITT analysis it was 7/9 (77.8%) in the AMX group and 4/11 (36.4%) in the PRI group.
Safety results:	Sixteen patients from the AMX group (11.9%; ≤ 15 years 9.8%, > 15 years 15.4%) and 66 from the PRI group (25.4%, ≤ 15 years 26.3%, > 15 years 24.0%) presented at least one TEAE. They were 3 (2.2%, ≤ 15 years 2.4%, > 15 years 1.9%) in the AMX group and 32 (12.3%, ≤ 15 years 13.5%, > 15 years 10.6%) in the PRI group with at least one drug related TEAE. In the AMX group, one patient complained of diarrhoea (> 15 years), one presented with drug hypersensitivity (≤ 15 years) and one with urticaria (≤ 15 years). In the PRI group, one patient suffered from headache (> 15 years) and 31 (11.9%, ≤ 15 years 13.5%, > 15 years 9.6%) complained about gastrointestinal disorders: diarrhoea (14, 5.4%, ≤ 15 years 6.4%, > 15 years 3.8%), vomiting (9, 3.5%, ≤ 15 years 3.8%, > 15 years 2.9%), nausea (5, 1.9%, ≤ 15 years 1.3%, > 15 years 2.9%), abdominal pain (4, 1.5%, ≤ 15 years 1.3%, > 15 years 1.9%), abdominal upper pain (2, 0.8%, ≤ 15 years 1.3%, > 15 years 0.0%). Overall, the safety profile was similar in children aged 15 or less and in adults. Serious TEAEs were reported for 1 patient in the AMX group (0.7%, > 15 years) and 3

	(1.2%, ≤ 15 years 1.3%, > 15 years 1.0%) in the PRI group. None of the latter was drug related: a motorbike accident was reported for the patient in the AMX group, a phlegmon of the left tonsil, a right facial palsy and a fall while running for the 3 patients in the PRI group. No death occurred during the study. Two patients (1.5%, ≤ 15 years 2.4%, > 15 years 0.0%) from the AMX group permanently withdrew from the study medication due to adverse events (drug related). In the PRI group they were 10 (3.8%, ≤ 15 years 3.8%, > 15 years 3.8%), 8 of them (3.1%, ≤ 15 years 3.8%, > 15 years 1.9%) were drug related.
Date of report:	03-DEC-2008