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Sponsor/company:	sanofi-aventis	**Clinicaltrials.gov Identifier:**	NCT00906048
		Study Code:	LEVOF_L_03815
Generic drug name:	Levofloxacin + Rifampicin	**Date:**	03 February 2011

Title of the study:	**LEVOF_L_03815** National, multi-centre, non-comparative study to evaluate the efficacy of the combination of Levofloxacin (500 mg) and Rifampicin (600 or 900 mg depending on weight) administered orally once per day as relay treatment for intravenous probabilistic antibiotic therapy, with a total duration of antibiotic therapy of six weeks, in the treatment of Osteo-Articular Prosthetic Infections (OAPI) with two-stage revision of prosthesis.			
Coordinating Investigator:	**Prof Louis BERNARD,** Infectiology Department, CHRU Tours			
Study center(s:	France (6 active centres)			
Publication:	No			
Study period: Date first patient enrolled: 29th April 2009 Date last patient completed: 23rd April 2010		**Development phase:** Phase III		
Objectives:	Principal objective: To evaluate the microbiological success of the combination of levofloxacin and rifampicin, administered orally over 32 to 37 days, as relay treatment for intravenous probabilistic antibiotic therapy of 5 to 10 days maximum, in the treatment of OAPIs, with two-stage revision of prosthesis. The total duration of antibiotic therapy was to be 6 weeks. Microbiological success was evaluated at the time of reimplantation of a new prosthesis (15 days to 3 months after stopping the combination of antibiotics). Secondary objectives: o To evaluate the rate of clinical failure 12 months after reimplantation of the prosthesis, o To evaluate the functional joint mobility score 12 months after reimplantation of the prosthesis o To evaluate the safety of the combination of levofloxacin and rifampicin, o To research the prognostic factors for success after the end of treatment and at 12 months after prosthesis reimplantation.			
Methodology:	Phase III national, multi-centre, non-comparative study.			
Number of subjects:	***Planned***: 150		***Included***: 10*	***Treated***: 10*
	Evaluated:	Efficacy: 10	Safety: 10	
	** Premature termination of the study decided by the sponsor in January 2010.*			

Diagnosis and criteria for inclusion:	1. Man or woman aged ≥ 50 years. 2. Osteo-articular prosthetic bacterial infection (hip or knee). 3. Microbiological infection caused by *Staphylococcus aureus* and/or coagulase-negative staphylococcus (CNS), sensitive to fluoroquinolones and rifampicin with: • for *Staphylococcus aureus*, a minimum of 2 positive perioperative samples is required • for coagulase-negative staphylococcus, a minimum of 3 positive perioperative samples is required • in the event of a combination, a minimum of 2 positive perioperative samples for *Staphylococcus aureus* and a minimum of 3 positive perioperative samples for CNS. 4. Two-stage surgical treatment with: • during the first surgical stage: removal of the prosthesis, wide debridement, implantation or not of a spacer * • during the second surgical stage: implantation of a new prosthesis, cemented or not*. 5. Negative urine pregnancy test for women of child-bearing age 6. Use of barrier contraceptive device throughout the treatment and the 4 weeks following the discontinuation of rifampicin for women of childbearing age **if possible without antibiotics as recommended by Sofcot (SOciété Française de Chirurgie Orthopédique et Traumatologique = French Society for Orthopaedic Surgery and Traumatology) , otherwise, containing Gentamicin.* **Written informed consent** must be collected by the investigator for all patients participating in the study, before entering the patient into the study.
Investigational product:	"Levofloxacin/rifampicin" combination: • Film-coated scored tablet containing 500 mg of levofloxacin • capsule containing 300mg of rifampicin.
Dose:	• Weight < 70 kg: 1 tablet of levofloxacin and 2 capsules of rifampicin, • Weight ≥ 70 kg: 1 tablet of levofloxacin and 3 capsules of rifampicin.
Administration:	*Per os,* one dose per day (preferably at least 30 minutes before a meal or 2 hours after).

Duration of treatment: Levofloxacin/rifampicin combination for 32 to 37 days, depending on the duration of initial probabilistic antibiotic therapy at the discretion of the investigator (5 to 10 days maximum), so that the total duration of antibiotic therapy should be 6 weeks.	**Duration of observation initially planned per patient:** 14 to 16.5 months maximum. **Duration of observation carried out per patient:** 1.5 to 8 months.

Criteria for evaluation:	
Efficacy	**Principal criterion:** ***Percentage of patients with microbiological success with the combination of levofloxacin and rifampicin*****,** evaluated during reimplantation of a new prosthesis (15 days to 3 months after discontinuation of the antibiotic combination).

Microbiological success	**Eradication** of the bacteria responsible for the infection AND Absence of clinical, biological or radiological signs of osteoarticular infection AND Absence of antibiotic treatment(s) for osteoarticular infection other than those authorised by the study.
Microbiological failure	**Isolation** of the strain of *Staphylococcus aureus* responsible for the infection in at least one sample and/or the strain of CNS responsible for the infection in 3 samples Clinical, biological or radiological signs may be present or absent.
Indeterminate	All other cases will be reviewed by the Scientific Committee and/or the Independent Committee for Data Evaluation, in particular if there are 1 or 2 samples which are positive for CNS (strain responsible for the infection) or another strain of staphylococcus than that isolated at inclusion or other bacteria.

Secondary criteria:

- Rate of clinical failure 12 months after reimplantation of a new prosthesis,
- Functional joint mobility score (Merle d'Aubigné score for the hip and Knee Society score for the knee).

Safety

- Adverse events (AEs) reported by the patient or detected by the investigator,
- Changes in the biological parameters (CBC, platelets, hepatic assessment, creatinine).

Statistical methods:

The Simon optimal two-stage design was used to test the null hypothesis of a microbiological success rate of 80% and the alternative hypothesis of a success rate of 90% with an alpha risk of 0.05 and power of 95%.

The study was to include in total a maximum of 117 evaluable per-protocol patients (150 inclusions with a level of around 20% of patients who were not evaluable or who had a major violation to the protocol), with an intermediate evaluation of the first 40 patients included (to give 32 evaluable per-protocol patients). Recruitment had to be continued during the first stage of analysis. If insufficient efficacy was observed after the first stage of analysis, the study was to be stopped.

As a result of the decision to stop the study early, only the descriptive analyses were carried out.

Summary of results	
Efficacy results	In total, 10 patients were included and evaluated until visit V5 or until visit V99 (anticipated end of study from the study before or after reimplantation). No patient was monitored 12 months after reimplantation as initially planned due to the premature termination of the study. At the time of removal of the prosthesis, 6 patients presented with coagulase-negative staphylococcus and 4 patients with *Staphylococcus aureus*. At the time of reimplantation, 7 patients out of 10 presented with negative perioperative samples. None of the 7 patients presented with clinical, biological or radiological signs of infection. They were therefore considered to have microbiological success. However, one patient presented with a new prosthesis infection 2 months after reimplantation. Coagulase-negative staphylococcus resistant to methicillin, rifampicin and fluoroquinolones was identified in one patient. The antibiogram showed that this was a new infection. For 2 patients reimplantation was not carried out, due respectively to a new *Staphylococcus aureus* infection and death not attributable to the study.
Safety results	Among the 7 patients having presented with at least one adverse event during treatment, the most frequent adverse events were gastro-intestinal problems (5/10 patients) such as diarrhoea (1 patient), nausea (2 patients), nausea and vomiting (1 patient), haemorrhoids (1 patient). In the investigator's opinion: 4 patients presented with at least one adverse event linked to levofloxacin, and 5 patients presented with at least one adverse event linked to rifampicin. These adverse events are in line with the safety profile for the study products. One patient presented with a skin allergy to rifampicin, leading to termination of the latter on the third day and its replacement with another antibiotic authorised by the protocol. Two patients out of 10 presented with a total of 5 Serious Adverse Events/SAE (of which 3 were Treatment Emergent Adverse Events/TEAEs). One of these SAEs (non-TEAE) resulted in the death of one of the two patients. Another SAE (loss of weight, TEAE) was an unexpected SAE. No adverse event related to variations in the biological safety parameters was reported in this study, notably in the patient who died of pneumonia.
Date of report:	7 December 2010