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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00277511
		Study Code:	HR355_3036
Generic drug name:	Levofloxacin	**Date:**	11/Oct/2007

Title

Prospective, multinational, multicenter, non-comparative, open study with a 6 months follow-up period to demonstrate the efficacy and safety of oral Levofloxacin 500 mg once daily in the treatment of chronic bacterial prostatitis (CBP).

Investigator(s), study site(s)

21 study centers located in 8 countries: Germany (5), France (3), Greece (2), Hungary (3), Italy (1), Russia (4), Spain (2), South Africa (1).
Coordinating investigators: Prof. H. Botto, Suresnes, France, Prof. K. G. Naber, Straubing, Germany

Study duration and dates	**Start of inclusion**:	March 10, 2003	**Phase**	III
	End of inclusion:	October 05, 2005.		

Objectives

Primary
The primary objective was to investigate the microbiological efficacy, assessed as eradication rate based on microbiologically evaluable patients 1 month post treatment with oral Levofloxacin 500 mg in male adults with chronic bacterial prostatitis (CBP, Category II).

Secondary
Secondary objectives were:

1. To investigate the microbiological efficacy, assessed as eradication rate based on microbiologically evaluable patients 6 months post treatment with oral Levofloxacin 500 mg in male adults with chronic bacterial prostatitis (CBP, Category II).
2. To assess the clinical response rate based on resolution of signs and symptoms after 2 weeks of treatment; 5-12 days, one month, 3 months and 6 months post treatment with oral Levofloxacin 500 mg in male adults with chronic bacterial prostatitis (CBP, Category II).
3. To assess the safety of Levofloxacin 500 mg on the basis of adverse events (AEs), standard clinical chemistry, hematology , urinalysis and vital signs in male adults with chronic bacterial prostatitis (CBP, Category II).

Study design

Open-label, non comparative, multicenter study. Microbiologically and clinically confirmed patients with CBP entered a 4-weeks treatment period, followed by a 6-months follow-up period.

Study medication was given once daily for 28 days. Clinical signs and symptoms were evaluated after 2 weeks of treatment as well as 5-12 days, one month, 3 months and 6 months post treatment. Microbiological eradication rate was determined one month and 6 months post treatment.

Number of subjects planned

It was planned to enrol 120 evaluable patients.

Inclusion criteria

Adult men (=18 years of age) with chronic bacterial prostatitis were to be included on the basis of clinical signs and symptoms, a history of chronic prostatitis and laboratory evidence of prostatitis (Meares-Stamey method, CBP Category II).

Treatments

All subjects in the study were to receive oral Levofloxacin 500 mg (tablets) once daily for 28 days. Each dose was to be taken each morning with a full 200 ml glass of water – independent of food consumption.

Efficacy data

Primary efficacy data were determined by eradication rate based on microbiologically evaluable subjects, determined at one month follow-up.
Secondary efficacy data were determined by microbiological eradication rate at 6 months follow-up and clinical response rate based on resolution of signs and symptoms after 2 weeks of treatment and during follow-up period.

Safety data

Safety was assessed on the basis of adverse events (AEs), standard clinical chemistry, hematology, urinalysis and vital signs.

Statistical procedures

Efficacy: The evaluation of microbiological and clinical response rate was essentially descriptive and was based on point-estimates and corresponding 95%-confidence intervals.

Safety: The evaluation involved examination of severity and type of AEs reported for each patient during the study and by changes in physical findings including vital signs and clinical lab tests from admission to post-therapy. AEs were classified according to the treatment emergent AE principle and were summarized by body system and preferred term. Analysis of vital signs and clinical lab variables included determination of predefined changes abnormal and last predefined changes abnormal.

Interim analysis

No interim analyses were performed.

Results - Study subjects and conduct

204 subjects were enrolled, 117 subjects received at least one dose of study medication and were thus included into the safety population. 116 subjects received at least one dose of study medication and provided efficacy data for at least one visit post baseline (Visit 2). These subjects were included into the ITT data set. 67 subjects without major protocol violations were included into the PP data set. 85/117 subjects (72.6%) who received study medication at least once terminated the study on regular terms,

whereas 32/117 subjects (27.4%) subjects terminated the study prematurely. Most frequent reasons for premature study termination were treatment failure occurring in 22/117 subjects (18.8%) and adverse events in 6/117 subjects (5.1%).

Results – Efficacy

The table below summarizes the number of patients in the ITT data set available for efficacy analysis at Visits 4, 5, 6 and 7. Because clinical failure/relapse was carried forward to the respective visit of assessment if clinical failure/relapse was already assessed prior to the time interval, the number of reported assessments of clinical success/failure could be higher at later visits compared to Visit 4.

	Intention-to-treat analysis	
	N	%
Intention-to-treat analysis	116	100.0
Subjects with original pathogens at baseline	99	85.3
Analysis A: Microbiological assessment of response (subject level, eradication versus persistence)		
Visit 5 [a]	98	84.5
Visit 7 [a]	57	49.1
Assessment of clinical response / relapse		
Visit 4	100	86.2
Visit 5	106	91.4
Visit 6	106	91.4
Visit 7	105	90.5

N = Number of subjects assessed
[a] Assessment based on microbiology and clinical assessment

Microbiological eradication at Visit 5, one month after termination of study medication, was stated in 55/67 subjects (82.1%) (95% CI [70.8, 90.4] %) in the PP data set and 82/98 subjects (83.7%) (95% CI [74.8, 90.4] %) in the ITT data set.

16/104 assessed subjects (15.4%) of the ITT data set showed persistence at Visit 5, thereof 3 with and 13 without super-infection. Super-infection was defined as the presence of a new pathogen, while at least one of the original pathogens persisted. A new infection - the detection of organisms not isolated at admission (Visit 2) causing symptoms and requiring therapy, while all original pathogens were eradicated - was diagnosed in 29/104 subjects (27.9%). Most frequent pathogen responsible for new infections was Enterococcus faecalis (15/100 patients (15.0%) with micro biological assessment.

Microbiological eradication at Visit 7, 6 months after termination of study medication, was stated in 52/57 subjects (91.2%) (95% CI [80.7, 97.1] %) in the ITT data set (eradication at Visit 7 was assessed only for subjects with microbiological eradication or suspected eradication and without new infection at Visit 5).

During the course of the study, the rate of clinical success declined continuously. At Visit 4, 92/100 subjects (92.0%) (95% CI [84.8, 96.5] %) were assessed as clinical success (i.e. cured or improved), whereas at Visit 7 clinical success was recorded in 65/105 subjects (61.9%) of the ITT data set (95% CI [51.9, 71.2] %). The relapse rate rose continuously from Visit 5 (14/86 subjects in the ITT population who were assessed as clinical success at Visit 4 (16.3%) (95% CI [9.2, 25.8] %) to Visit 7 (28/84 subjects in the ITT population (33.3%) (95% CI [23.4, 44.5] %)).

With increasing duration of the study, stratified analysis according to the WBC ratio (EPS/VB2 =10 or < 10) showed a considerably better clinical success and lower relapse rate in the stratum with the high WBC ratio compared to the stratum with low WBC ratio.

Analysis of pathogens revealed an equal share of Gram-positive and Gram-negative pathogens at baseline. In 47/94 subjects (50.0%) assessed at Visit 5 Gram-positive pathogens were detected at baseline. With 12 affected subjects, Enterococcus faecalis was the most frequent pathogen at baseline in these subjects, followed by Staphylococcus epidermidis detected in 10 subjects.
Compared to baseline, eradication for Gram-positive pathogens was stated in 39/47 subjects (83.0%) at Visit 5, whereas in 9/47 subjects (19.1%) persistent pathogens were assessed. In 51/94 subjects (54.3%) with microbiological assessment at Visit 5, Gram-negative pathogens were detected at baseline. With 34 affected subjects, Escherichia coli was the most frequent pathogen at baseline. Compared to baseline, eradication for Gram-negative pathogens was stated in 48/51 subjects (94.1%) at Visit 5, whereas in 5/51 subjects (9.8%) a pathogen persisted.
Signs and symptoms as assessed by the investigator and in the questionnaire showed a continuous improvement. At Visit 7, all signs and symptoms assessed showed an improvement or were absent in more than 90 % of the subjects.
PCR tests for genitourinary pathogens showed only few partly positive results. At Visit 7, only 3 subjects showed some results positive for Neisseria gonorrhoeae. The results of PCR testing were not considered for the microbiological analysis but treated as additional, descriptive information.

Results – Safety

The spectrum of AEs corresponded to the medical history of the subjects included in the study and the known properties of the study drug. 15/117 subjects (12.8%) experienced at least one treatment emergent AE (TEAE). This concerned mostly the SOCs gastrointestinal disorders and musculoskeletal and connective system disorders. The majority of TEAEs was of mild or moderate intensity. Two subjects experienced TEAEs of severe intensity, namely one subject each with pain in extremity and intestinal haemorrhage NOS. The latter was considered as serious TEAE.
A total of 12 AE which were considered as possibly related to the study drug occurred in 6 of the 117 patients. These 12 cases were therefore treated as suspected cases of an adverse drug reaction (ADR). Ten ADR are considered as labelled under the treatment with the study drug and 2 (dry mouth and muscle cramps) are considered as unlabeled. The ADR concerned mostly the SOCs gastrointestinal disorders (diarrhoea, abdominal pain) and musculoskeletal and connective system disorders (muscle cramps, neck pain and tendon disorder). In 4/117 subjects (3.4%) an AE led to permanent discontinuation of study drug. Additional treatment in response to an AE was required in 4 subjects (3.4%). One subject experienced an AE that required other significant intervention and one subject displayed a clinically significant abnormal laboratory value that was considered as AE. 3/117 subjects (2.6%) experienced other significant AEs affecting ear and labyrinth (one subject with dizziness), nervous system (one subject with headache and vertigo) and one subject with tendon disorders.
Safety laboratory parameters showed no systematic change during the study. There were only few last predefined changes abnormal (LPCAs) or clinically significant abnormal laboratory values.
None of these laboratory abnormalities or changes was attributed by the investigator to the study medication.

Date of the report: 15-May-2007