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Sponsor/company:	sanofi-aventis	ClinicalTrials.gov Identifier:	NCT004953396
		Study Code:	LEVOF_L_00972
Generic drug name:	Levofloxacin	Date:	03/Mar/2009

Title of the study:	AN OPEN LABEL, NON COMPARATIVE CLINICAL TRIAL OF EFFICACY AND SAFETY OF 3 MONTHS TAVANIC (LEVOFLOXACIN) TREATMENT AS PART OF COMPLEX MANAGEMENT OF MULTI-DRUG RESISTANT TUBERCULOSIS (MDR TB) IN THE RF	
Investigator(s):	Prof. Aleksey Elkin, Saint-Petersburg´s Scientific-Research Institute of Ptysiopulmonology of Federal Agency on Health and Social Development	
Publications (reference):	LEVOF L 00972	
Study period: Date first **patient/subject** enrolled: June 2007 Date last **patient/subject** completed: April 2008		**Phase of development:** Phase IV
Objectives:	-To obtain data on efficacy of TAVANIC in the treatment of drug-resistant tuberculosis. -To collect data on safety of TAVANIC in the treatment of drug-resistant tuberculosis.	
Methodology:	Non-comparative, open-label	
Number of patients/subjects:	Enrolled: 100	Treated: 100
Evaluated:	Efficacy assessment : 94 (PP population)	Safety: 100 (ITT population)
Diagnosis and criteria for inclusion:	-Female and male patients, aged from 18. -Drug-resistant tuberculosis, with laboratory confirmation at the study entry (at 1Visit). Drug resistance is defined as resistance of Mycobacterium tuberculosis to the following anti-tuberculous agents of I and II choice: isoniazid, rifampicin (patients were treated previously even one of them) -Readiness of patient to fulfill protocol requirements and to comply with the dosing regimen of the study drug - Signed informed consent.	
Exclusion criteria:	-Hypersensitivity to levofloxacin or other fluoroquinolones. -Central nervous system disorders: epilepsy, history of seizures. -Pregnancy and lactation. -Tendon disorders during previous treatment with quinolones.	
Investigational product:	Tavanic (levofloxacin)	
Dosage and Administration:	Patients with body weight < 90kg take levofloxacin 500 mg/day. Patients with body weight > 90kg take levofloxacin 500 mg twice daily.	
Duration of treatment: 3 months	**Duration of observation:** NA	
Criteria for evaluation:		
Efficacy:	-Number of patients with bacterioexcretion. -Change in XR-examination picture. -Dynamics in tuberculosis clinical symptoms.	
Safety:	- All treatment emergent AE/SAE.	

Statistical methods:

All populations (ITT population- for safety evaluated and PP population- for efficacy evaluated) will be analyzed by means of descriptive statistics.
Continuous normally distributed variables will be described by the following statistics: mean, standard deviation, median, minimal and maximal values.
Categorical variables will be described by frequencies and percentages.
Two-sided statistical tests were used with a significance level of 0.05.
95% Confidence interval were constructed for % of patients without bacterioexcretion after 3 month therapy.

Summary (baseline characteristics):

Mean age of patients 34,8 (±11,0), (median 31,7).
Male 63%, female 37%.
Average BMI- 21,9 (± 2,4 kg/$m^{2)}$.
14 % patients with diagnosis disseminated tuberculosis, 55% patients- diagnosis of infiltrative tuberculosis, 23 % patients- diagnosis of caseous pneumonia, 1% patient- diagnosis of tuberculosis internal gland, 7% patients- diagnosis of fibrocavernous tuberculosis. All 100% patients discharged bacteria before the beginning of therapy. 26% patients had hectic fever, 59% patients had low grade fever.
88% patients had cough with sputum. 37% patients had purulent sputum, 37% patients had mucopurulent sputum. 14% patients had hemoptysis, 57% patients- shortness of breath, 47% patients- tachycardia.
Drug resistance MBT to Isoniazid had 100% patients, to Rifampicin- 100% patients, to Streptomycin- 69% patients, to Kanamycin- 53% patients, to Ethambutol- 50% patients, to Rifabutin- 31% patients, to Protionamide- 21% patients, to Ofloxacin- 8% patients, to Amikacin- 2 %patients, to P-Aminosalicylic acid- 1% patient, to Capreomycin- 1% patient.
Multiple lung cavities (X-ray examination) had 50% patients; single lung cavities had 43% patients.

Efficacy results:

Signs and symptoms	**At the beginning of therapy N=94**	**After 3 month of therapy N=94**
Subjects with bacterioexcrection	94 patients (100%)	22 (23,4%). 76,6% of patients, wasn`t a subject with bacteroexcrection after 3 month therapy. 95% confidence interval for % of patients without bacterioexcretion after 3 month therapy is (68%; 85,2%), p<0,00001
Body temperature	only 15 patients (15,9%) had normal body temperature. 26 patients (27,7%) had hectic fever before beginning of therapy.	83 patients (88,3%) had normal body temperature, p<0,00001. There was no patients with hectic fever, p<0,00001.
Cough with sputum	82 patients (87,2%)	33 patients (35,1%), p<0,00001.
Purulent sputum	35 patients (37,2%)	1 patient (1,06%) had purulent sputum, p<0,00001.
Mucopurulent sputum	33 patients (35,1%)	4 patient (4,3%), p<0,00001.
Hemoptysis	13 patients (13,8%)	already after 2 month therapy there was no patients with hemoptysis, p=0,00019.
Shortness of breath	54 patients (57,4%)	11 patients (11,7%), p<0,00001.
Tachycardia	42 patients (44,7%)	17 patients (18,1%), p=0,000085.
Lung cavities (clinical examination)	99 patients (99%)	74 patients (78,7%). 92 patients (97,9%) had partial resolution of inflammatory lesions, p=0,000011.
Multiple lung cavities (X-ray examination)	46 patients (48,9%)	20 patients (21,3%), p=0,000071.
Multiple or single lung cavities (X-ray examination)	87 patients (92,6%)	65 patients (69,2%), p=0,000046.
Body weight	(65,6±11,0 kg).	(69,7±10,7 kg), p<0,00001.
Heamoglobin count	(122,6±21,1 g/l).	(132,3±12,5 g/l), p<0,00001.
Leucocytes count	(9,86±2,67*10^9/l).	(7,11±1,81*10^9/l), p<0,00001.
Lymphocytes count	(23,3±8,0%).	(30,4±7,9%), p<0,00001.
ESR	(36,4±13,3 mm/hour).	(19,1±9,6 mm/hour), p<0,00001.

Safety results:	There are no serious adverse events during the trial. 4 patients had treatment withdrawn due to AEs separately: 1 patient had stable increase ALT and 3 patients had a diarrhea. 2 patients no follow-up. 29 patients had any adverse events during the therapy: -18 patients had adverse events with liver, -6 patients had adverse events with gastrointestinal tract, -3 patients had adverse events with blood system, -3 patients had adverse events with CNS. There are no adverse events concerned with cardiovascular or urogenital systems. AST: before beginning of therapy 26,8±13,5 U/l, after 3 month therapy (30,8±14,4 U/l) (P=0,034). ALT: before beginning of therapy (29,0±19,4 U/l), after 3 month therapy (33,8±14,9 U/l) (P=0,04).
Date of report:	25-Aug-2008