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Sponsor/company:	sanofi-aventis	ClinialTrials.gov Identifier:	NCT00253955
		Study Code:	HR355_3035
Generic drug name:	Levofloxacin	Date:	07/November/2008

Title of the study:	An open-label, multicenter, multinational, centrally randomized, two-arm parallel-group study to demonstrate the non-inferiority in clinical efficacy of levofloxacin 750mg once daily in comparison with piperacillin/tazobactam 4g/500mg every 8 hours in the treatment of adult patients with mild to moderate Hospital-Acquired Pneumonia in both the general wards and ICU Study code: HR355-3035
Coordinating Investigator:	Prof. DDr. Wolfgang GRANINGER University Hospital Vienna Department of Medicine Division of Infectious diseases & Tropical Medecine Währingergürtel 18-20 A-1090 Vienna AUSTRIA
Study center(s):	90 active centers Participating countries: Austria, Belgium, Germany, Greece, Italy, Lebanon, Netherlands, South Africa, Spain, Turkey, Latin America (Brasil, Guatemala, Mexico and Venezuela), Czech Republic, Romania, France, Ireland and Russia.
Publications (reference):	Not applicable

Study period: Date first patient enrolled: June 26th, 2003 Date last patient completed: May 11th, 2007	Phase of development: Phase IIIb

Objectives:	Primary: To demonstrate the non-inferiority in clinical efficacy at the Test of Cure (TOC) visit of levofloxacin IV/Per Os 750 mg once daily versus piperacillin/tazobactam IV 4 g/500 mg every 8 hours given for 10 to 14 days in treating adult patients with mild to moderate Hospital-Acquired Pneumonia. Secondary: - To assess the bacteriological efficacy at TOC. - To assess the clinical and bacteriological efficacy at End Of Study visit (EOS). - To assess the tolerability of both drugs.

<table>
<tr><td>Methodology:</td><td colspan="3">Open, multinational, multicenter, centrally randomized, two-arm parallel-group (1:1) study. Randomization was to be stratified on the presence or absence of mechanical ventilation at inclusion and on the Apache II score (≤ 15 or >15). Levofloxacin, 750 mg once daily, was to be administered as a 90 min IV infusion. Subjects could be switched to oral levofloxacin, at the investigator's discretion, after at least one day, if improvement – including defervescence – occurred. Piperacillin/tazobactam, 4 g/500 mg every 8 hours, was to be administered as a 30 min IV infusion. Duration of treatment was to be 10 to 14 days. Following a pre-therapy visit, visits were to be scheduled for on-therapy (D3-5), Test of Cure (TOC) 3 to 8 days after the end of study treatment and End of Study (EOS) 21 to 35 days after the end of therapy.</td></tr>
<tr><td>Number of patients:</td><td>Planned: 460</td><td>Randomized: 460</td><td>Treated: 457</td></tr>
<tr><td>Evaluated:</td><td colspan="3"><table>
<tr><th></th><th>Levofloxacin (N=228)</th><th>Pipe. / Tazo (N=232)</th><th>All (N=460)</th></tr>
<tr><td>Number of randomized patients*</td><td>228 (100.0%)</td><td>232 (100.0%)</td><td>460 (100.0%)</td></tr>
<tr><td>Number of patients in ITT</td><td>227 (99.6%)</td><td>230 (99.1%)</td><td>457 (99.3%)</td></tr>
<tr><td>Number of patients in m-ITT</td><td>211 (92.5%)</td><td>209 (90.1%)</td><td>420 (91.3%)</td></tr>
<tr><td>Number of patients in c-PP</td><td>127 (55.7%)</td><td>129 (55.6%)</td><td>256 (55.7%)</td></tr>
<tr><td>Number of patients in bm-ITT</td><td>97 (42.5%)</td><td>114 (49.1%)</td><td>211 (45.9%)</td></tr>
<tr><td>Number of patients in b-PP</td><td>57 (25.0%)</td><td>71 (30.6%)</td><td>128 (27.8%)</td></tr>
<tr><td>Number of patients in safety**</td><td>228 (99.6%)</td><td>229 (99.1%)</td><td>457 (99.3%)</td></tr>
<tr><td colspan="4">* one patient was randomized Pipe/Tazo but was treated by Levofloxacin
** % calculated on 229 levofloxacin-treated patients and 231 pipe/tazo-treated patients (1 patient was randomized pipe/tazo but was treated by levofloxacin)</td></tr>
</table></td></tr>
<tr><td>Diagnosis and criteria for inclusion:</td><td colspan="3">Hospitalized male or female in the general ward or Intensive Care Unit aged 18 or greater with a diagnosis of Hospital-Acquired-Pneumonia (HAP) of presumed bacterial origin based upon:
- Infection developing after at least 72 hours following hospital admission
and
- At least three of the four following signs:
- Fever (oral or tympanic temperature = > 38°C or rectal temperature = > 38.5°C)
- Purulent tracheal sputum production/secretion or change in sputum character
- Total peripheral WBC count >12 G/L or < 4.5G/L or ≥15% immature neutrophils (bands), regardless of total peripheral WBC count
- Increased plasma or serum C Reactive Protein (CRP) level as shown by a level of at least twice the upper boundary of the hospital normal range
and
- Chest X-ray findings (anterior-posterior or posterior-anterior, if possible lateral view) in agreement with the clinical diagnosis of bacterial pneumonia</td></tr>
<tr><td>Investigational product:
Dose:
Administration:</td><td colspan="3">Levofloxacin
750 mg once daily
Slow IV infusion over at least 90 min (switch to oral levofloxacin, at the discretion of the investigator, after at least one day if improvement – including defervescence – occurred).</td></tr>
<tr><td colspan="2">Duration of treatment: 10-14 days</td><td colspan="2">Duration of observation: 32-46 days</td></tr>
<tr><td>Reference therapy:
Dose:
Administration:</td><td colspan="3">Piperacillin/tazobactam
4 g/500 mg every 8 hours for 10-14 days
IV infusion over 30 min</td></tr>
<tr><td>Criteria for evaluation:
Efficacy:
Safety:</td><td colspan="3">- Clinical outcome at TOC and EOS
- Bacteriological outcome per patient and per causative pathogen at TOC and EOS
- Adverse events observed by the investigator or reported by the patient
- Vital signs
- Standard hematology and blood chemistry.</td></tr>
</table>

Statistical methods:	Efficacy: The primary efficacy analysis was to demonstrate non-inferiority of levofloxacin in comparison to piperacillin/tazobactam for the clinical cure rates at the TOC visit 3-8 days after end of treatment in the clinically evaluable (c-PP) population. The two-sided 95% CI was constructed for the difference (levofloxacin-comparator) in the primary outcome. The two treatments were considered as therapeutically equivalent (i.e. non-inferiority of levofloxacin in comparison to piperacillin/tazobactam) if the lower limit of this 95% confidence interval is -15 percentage points or greater and the upper limit is above zero. All secondary analysis variables for efficacy were analyzed using the confidence interval approach similar to the primary analysis variable. Safety: All patients, as treated, who received at least one dose of the study medication, were eligible for the safety analysis. Frequencies of subjects with treatment-emergent adverse events, and sorted by system organ class and preferred term were summarized by treatment group, relationship to the study drug and intensity. Frequencies of subjects with possibly related treatment-emergent adverse events sorted by system organ class and preferred term were summarized by treatment group and intensity. Frequencies of subjects with serious treatment-emergent adverse events including those leading to death, prolonged hospitalization and study drugs discontinuation were summarized likewise. Laboratory variables and vital signs were summarized for baseline, endpoint, and for the change from baseline using descriptive statistics.

Summary:

Efficacy results:

A total of 256 patients were included in the c-PP population (primary efficacy analysis population) including 163 (63.7%) male and 93 (36.3%) female patients. Mean age was 65.6 ± 17.1 years, mean weight 71.74 ± 12.00 kg; Mean Apache II score was 11.8 ± 5.4 and 10.9% of patients were mechanically ventilated at inclusion, 39% started the study treatment in intensive care unit. 50% of the patients had at least one causative pathogen at V1 (31.3% with one different causative organism, 13.7% with 2 and 5.1% with 3); 38.7% of patients had at least one causative Gram negative pathogen (5.1% with *Acinetobacter* n=13, 27.3% of *Enterobacteriacae* n=70, 5.9% of *Haemophilus influenzae* n=15, 3.9% of *Pseudomonas aeruginosa* n=10) and 21.5% of patients had causative Gram positive pathogen at V1 (15.2% of *Staphylococcus aureus* n=39, 7% of *Streptococcus pneumoniae* n= 18 and 0.8% with other *Streptococcus* n=2)

Primary efficacy variable:

The primary efficacy analysis was to demonstrate non-inferiority of levofloxacin in comparison to piperacillin/tazobactam with regard to clinical cure rate at the TOC visit 3-8 days after the end of treatment in the c-PP population.

Clinical cure rate at TOC was similar in both treatment groups: 102/127 (80.3%) in the levofloxacin group and 105/129 (81.4%) in the piperacillin/tazobactam group.

The difference between both treatment groups regarding clinical cure rate at TOC was -1.08%. The lower limit of the 95% CI [-11.5, 9.3%] for this difference was superior to the pre-defined non-inferiority margin (-15%) . Therefore, it can be concluded that levofloxacin is not inferior to piperacillin/tazobactam with respect to the clinical cure rate at TOC in the c-PP population.

Similar results were observed in the other populations (m-ITT, bm-ITT and b-PP).

Clinical cure at TOC	Levofloxacin	Pipe. / Tazo.	Delta between Levofloxacin & Pipe. / Tazo.	95% CI of Difference
c-PP population				
N	127	129		
Yes (%)	80.3	81.4	-1.08	[-11.5 , 9.3]
m-ITT population				
N	211	209		
Yes (%)	65.9	69.4	-3.50	[-12.9 , 5.9]
bm-ITT population				
N	97	114		
Yes (%)	66.0	64.9	1.07	[-12.8 , 14.9]
b-PP population				
N	57	71		
Yes (%)	75.4	73.2	2.20	[-14.6 , 19.0]

Secondary efficacy variables:

Clinical cure at EOS	Levofloxacin	Pipe. / Tazo.	Delta between Levofloxacin & Pipe. / Tazo.	95% CI of Difference
c-PP population				
N	83	90		
Yes (%)	65.4	69.8	-4.41	[-16.7 , 7.8]
m-ITT population				
N	111	117		
Yes (%)	52.6	56.0	-3.37	[-13.4 , 6.6]
bm-ITT population				
N	50	57		
Yes (%)	51.5	50.0	1.55	[-12.9 , 16.0]
b-PP population				
N	35	45		
Yes (%)	61.4	63.4	-1.98	[-20.4 , 16.5]

Satisfactory bacteriological outcome at TOC	Levofloxacin	Pipe. / Tazo.	Delta between Levofloxacin & Pipe. / Tazo.	95% CI of Difference
bm-ITT population				
N	58	57		
Yes (%)	59.8	50.0	9.79	[-4.2 , 24.1]
b-PP population				
N	42	41		
Yes (%)	73.7	57.7	15.94	[-1.9 , 33.7]

Satisfactory bacteriological outcome at EOS	Levofloxacin	Pipe. / Tazo.	Delta between Levofloxacin & Pipe. / Tazo.	95% CI of Difference
bm-ITT population				
N	44	43		
Yes (%)	45.4	37.7	7.64	[-6.6 , 21.9]
b-PP population				
N	34	33		
Yes (%)	59.6	46.5	13.17	[-5.6 , 32.0]

Safety results

	Levofloxacin (N= 228)	Pipe. / Tazo. (N= 229)	
MedDRA Term (SOC Term)	N (%)	N (%)	P*
Subjects with TEAEs	115 (50.4)	117 (51.1)	
Gastrointestinal disorders	30 (13.2)	30 (13.1)	>0.999
Infections and infestations	29 (12.7)	30 (13.1)	>0.999
Respiratory, thoracic and mediastinal disorders	22 (9.6)	19 (8.3)	0.628
Cardiac disorders	21 (9.2)	22 (9.6)	>0.999
General disorders and administration site conditions	18 (7.9)	16 (7.0)	0.726
Investigations	11 (4.8)	19 (8.3)	0.185
Vascular disorders	10 (4.4)	7 (3.1)	0.472
Psychiatric disorders	9 (3.9)	12 (5.2)	0.656
Metabolism and nutrition disorders	8 (3.5)	11 (4.8)	0.640
Injury, poisoning and procedural complications	6 (2.6)	4 (1.7)	0.544
Nervous system disorders	6 (2.6)	9 (3.9)	0.601
Surgical and medical procedures	5 (2.2)	3 (1.3)	0.503
Renal and urinary disorders	5 (2.2)	8 (3.5)	0.575
Skin and subcutaneous tissue disorders	4 (1.8)	7 (3.1)	0.544
Blood and lymphatic system disorders	3 (1.3)	13 (5.7)	0.019
Musculoskeletal and connective tissue disorders	3 (1.3)	3 (1.3)	>0.999
Ear and labyrinth disorders		1 (0.4)	N/A
Endocrine disorders		3 (1.3)	N/A
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		1 (0.4)	N/A
Reproductive system and breast disorders		1 (0.4)	N/A

Safety results	A total of 555 AEs were reported during the study; among them, 493 were TEAEs (223 in the levofloxacin group; 270 in the piperacillin/tazobactam group). 232 patients presented at least one TEAE (115 in the levofloxacin group; 117 in the piperacillin/tazobactam group). 81 subjects presented at least one serious TEAEs (43 in the levofloxacin group; 38 in the piperacillin/tazobactam group) and 52 of these patients had a fatal outcome (28 in the levofloxacin group; 24 in the piperacillin/tazobactam group). Four possibly related serious TEAEs were observed, all in the levofloxacin group. There was one patient with possibly related TEAE with fatal outcome (MRSA infection). Incidence of all TEAEs, categorized according to treatment group and system organ class is summarized in the table below: The most frequently reported AE (reported by more than 2% of patients) was: – Diarrhea: 10/228 (4.4%) of patients in the levofloxacin group and 16/229 (7.0%) in the piperacillin/tazobactam group There was no statistically significant difference between treatment groups regarding the number of patients with at least one TEAE [115 (50.4%) in the levofloxacin group; 117 (51.1%) in the piperacillin/tazobactam group], the number of patients with at least one serious TEAE [43 (18.9%) in the levofloxacin group; 38 (16.6%) in the piperacillin/tazobactam group], the number of patients with at least one TEAE with fatal outcome [28 (12.3%) in the levofloxacin group; 24 (10.5%) in the piperacillin/tazobactam group] and the number of patients with at least one TEAE leading to treatment discontinuation [14 (6.1%) in the levofloxacin group; 21 (9.2%) in the piperacillin/tazobactam group]. <u>Laboratory data and vital signs:</u> Treatment groups were comparable for haematological (blood cell counts) and biochemical (liver and renal function, glycemia and CRP) laboratory parameters and vital signs, except for alkaline phosphatases at EOS for which a higher percentage of patients with an abnormal increase was observed in the piperacillin/tazobactam group (40.9%) compared to the levofloxacin group (21.4%) (p=0.048).
Date of Report	23-May-2008