Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare AG	
Study Number:	12669	NCT00717561 EudraCT: 2007-001320-12
Study Phase:	IIIb	
Official Study Title:	A national, prospective, randomized, open label study to assess the efficacy and safety of IV/PO moxifloxacin vs IV ceftriaxone + IV azithromycin followed by PO amoxicilline/clavulanate and PO clarithromycin in subjects with community-acquired pneumonia	
Therapeutic Area:	Anti-Infectives	
Test Product		
Name of Test Product:	Moxifloxacin (Avelox, BAY12-8039)	
Name of Active Ingredient:	Moxifloxacin (BAY 12-8039)	
Dose and Mode of Administration:	Sequential IV/PO monotherapy moxifloxacin 400/400 mg OD (every 24 hours), for 7 to 14 days, provided as 400 mg/250 mL of 0.16% saline in glass bottles for the intravenous doses, and as 400 mg tablets for the oral doses.	
Reference Therapy/Placebo		
Reference Therapy:	Ceftriaxone; Azithromycin; Amoxicilline/clavulunate; Clarithromycin.	
Dose and Mode of Administration:	IV ceftriaxone 2 gr OD (every 24 hours) plus IV azithromycin 500 mg OD followed by PO amoxicilline/clavulanate 1000 mg TID (every 8 hours) and PO clarithromycin 500 mg BID (every 12 hours) for 7 to 14 days. Ceftriaxone: provided as 2 g of ceftriaxone sterile powder for reconstitution in 40 mL of sodium chloride solution for injection, administered once daily as an IV infusion over 30 minutes. Azithromycin: provided as vials containing 0,5 g of azithromycin as powder for reconstitution in 4,8 ml of sterile water for injections, administered once daily as an IV infusion over 180 minutes. Sodium chloride solution (0,9% normal saline) used for the dilution. Amoxicillin/clavulanic acid oral treatment: provided as 875/125 mg tablets to be taken every 8 hours.	

	Clarithromycin oral treatment provided as 500 mg tablets to be taken every 12 hours.	
Duration of Treatment:	7 - 14 days	
Studied period:	**Date of first subjects' first visit:**	19FEB2008
	Date of last subjects' last visit:	05JUN2009
Study Center(s):	23 sites were selected in Italy; 18 sites were activated and 10 sites enrolled at least one patients.	
Methodology:	Prospective, randomized, multicentre, national, open label trial to compare the efficacy and safety of sequential intravenous /oral moxifloxacin to those of an intravenous combination therapy with ceftriaxone and azithromycin followed by oral amoxicillin/clavulanic acid and claritromycin, in patients with CAP (Community-Acquired Pneumonia) who require initial parenteral therapy and meet the study eligibility criteria.	
Indication/ Main Inclusion Criteria:	• Hospitalized non-ICU patients (age ≥18 years) • Clinical signs and symptoms of CAP, with PSI score IV or V • Radiologically confirmed evidence of a new and/or progressive infiltrate(s) • Requirement for initial parenteral therapy • At least 2 of the following conditions: o productive or non-productive cough with or without purulent or mucous or mucopurulent sputum o dyspnea and/or tachypnea (respiratory rate of > 20 breaths/min) o rigors and/or chills o pleuritic chest pain o auscultatory findings of rales and/or crackles on pulmonary examination and/or evidence of pulmonary consolidation o fever (an oral temperature of ≥ 38 °C, a rectal temperature of ≥ 39 °C, or a tympanic temperature of ≥ 38.5 °C) or hypothermia (rectal or core temperature of < 35 °C), and a WBC count of ≥ 10,000 cells/mm3 or ≥ 15% immature neutrophils bands; regardless of peripheral WBC count) or leukopenia (total WBC count of <4500 cells/mm3) • Written informed consent	
Study Objectives:	**Overall:** To assess the efficacy and safety of sequential intravenous/oral moxifloxacin monotherapy in comparison to a combination therapy with intravenous ceftriaxone plus azithromycin followed by oral	

	amoxicillin/clavulanic acid and clarithromycin, in the treatment of patients admitted to hospital with CAP. **Primary:** To prove the hypothesis that therapy with moxifloxacin IV/PO 400/400 mg once daily is not less effective than the control therapy based on clinical cure rate at the Test-of-Cure (TOC) visit. **Secondary:** • To assess the clinical and bacteriological response on the day of switch from IV to oral therapy, on treatment Day 3-5 (if the day of switch is different from Day 3, 4 or 5) and at the end of treatment. • To assess the bacteriological response at TOC • To estimate the mortality attributable to pneumonia at the TOC • To evaluate the CAP-symptoms course (at the different assessment visits). Moreover an economic analysis is foreseen to assess the implications of each treatment arm on healthcare resource utilization and on overall costs associated with the treatment of CAP.
Evaluation Criteria:	**Efficacy (Primary):** Clinical response 20 days after last dose of study medication (TOC visit). **Efficacy (Secondary):** • Clinical and bacteriological response on the day of switch from IV to oral therapy, on treatment Day 3-5 (if the day of switch is different from Day 3, 4 or 5) and at the end of treatment • Bacteriological response at TOC • Mortality attributable to pneumonia at TOC visit. • CAP-symptoms at the different assessment visits. **Safety:** Adverse events (AE), vital signs, ECG findings, clinical laboratory, chest X-ray, arterial blood gases and oxigen saturation, urinary antigen and serum antibody tests.
Statistical Methods:	**Efficacy (Primary):** This is a non-inferiority trial; the primary aim of the study was to prove that 7-14 day sequential IV/PO monotherapy with moxifloxacin 400/400 mg OD is not less effective than a 7-14 day combination therapy with IV cefriaxone 2 gr OD plus IV azithromycin 500mg OD followed by oral amoxicillin/clavulanic acid 1000 mg TID plus clarithromycin 500 mg OD based on clinical success rate (= clinical cure) at the TOC visit (20 days after end of therapy), being the non-inferiority margin of clinical difference equal -15%.

Statistical Methods:	For success rate, (i.e cure rate at TOC) 95% Confidence Interval (CI) of the difference of two clinical success rates (treatment group "moxifloxacin" minus treatment group "comparator") had to be calculated. Non-inferiority of treatment with moxifloxacin would be concluded if the lower limit of this CI was greater than -15% and the CI included 0. If, and only if the lower limit of this CI was greater than 0, the superiority of treatment with moxifloxacin would be proven. All statistical tests had to be two sided and performed at the 0.05 significant level. The study enrolment was stopped prematurely on October 2009 and only 60 patients were recruited. Considering the very small size of the sample enrolled, it was agreed that only descriptive analyses on the safety population had to be done, without any statistical test. The success rate at TOC visit was calculated as proportion of safety patients with "Cure" as clinical response; 95% CIs were also computed for the difference of the success rate between the two treatment groups by means of continuity corrected Wald method. The same analyses were performed by Risk Class, age and ventilation status. **Efficacy (Secondary) :** The clinical response assessed at the day of switch from IV to oral therapy, on study Day 3-5 (only if the day of switch was not Day 3, 4 or 5 of treatment), at the end of therapy and the clinical response at TOC in patients with bacteriologically proven infection were analyzed exploratively in the same way as the primary efficacy variable. Additionally, the bacteriological responses on the day of switch, on treatment Day 3-5 (if the day of switch was different from Day 3-5), at the end of treatment, at the Test-of-Cure visit were analyzed exploratively in the same way as the primary efficacy variable based on the subgroup of microbiologically valid patients. Symptoms course and their resolution were descriptively analyzed. All other efficacy data, as well as health care resources related to CAP were analyzed with descriptive statistics. **Safety:** The treatment groups were compared with respect to the incidence of premature termination subdivided by primary reason, treatment-emerging AEs and laboratory abnormalities in a descriptive manner. The safety analysis include tabulation of the type (using MedDRA) and frequency of all treatment emergent AEs as well as events considered by the Investigator to be at least possibly drug related. All laboratory data were analyzed using descriptive statistics including identification of laboratory data outside normal ranges. All other safety data were analyzed descriptively.
Number of Subjects:	230 subjects (115 per treatment) were planned to be enrolled. The patient enrolment was prematurely terminated on October 2009 due to low recruitment rate. 60 subjects were enrolled and randomized in one of the two treatment arms: 31 (51.67%) patients in moxifloxacin arm, 29 patients (48.33%) in comparator arm. All subjects took at least one dose of

	study medication and were included in the Safety analysis population. No other analyses population were defined and no patients' validation and identification of protocol violations were done.

Study Results

Results Summary — Subject Disposition and Baseline

The study duration was in mean 29.10±10.62 days (range 2-44) in moxifloxacin group and 29.24±16.53 days (range 2-69) in comparator group; 21 patients (67.74%) under moxifloxacin therapy and 17 patients (58.62%) under comparator therapy switched from IV therapy to oral; 25 patients (80.65%) in moxifloxacin group and 20 patients (68.97%) in comparator group performed TOC visit. In moxifloxacin arm 23 patients (74.19%) completed the study; 6 patients did not complete for AEs, 1 for insufficient therapeutic effect, 1 for death. In comparator arm 16 patients (55.17%) completed the study; 6 patients did not complete for insufficient therapeutic effects, 3 for AEs, 2 for protocol violation, 1 for death and 1 was lost to follow-up.

In moxifloxacin arm 22 patients (70.97%) were male, 9 patients (29.03%) were female; mean age was of 72.68±12.98 years. In comparator arm 20 patients (68.97%) were male, 9 (31.03%) were female; mean age was of 71.21±13.72 years. With the exception of one Hispanic patient in the comparator group, all other patients were White.

Twenty patients (64.52%) in the moxifloxacin group and 18 patients (62.07%) in the comparator group were 'Past or Present' cigarettes smoker, with a mean number of pack years smoked equal to 51.40±15.84 (range 24-98) and 55.04±53.93 (range 3-240) respectively.

First signs and symptoms of CAP started in mean 5.06±5.31 (range 0-31) days before the study enrolment in the moxifloxacin group, 6.62±6.66 (range 0-36) days before the study enrolment in the comparator group.

Based on Pneumonia Severity Index, 30 patients (96.77%) in moxifloxacin group and 26 patients (89.66%) in comparator group were classified in Risk Class IV, 1 patient (3.23%) in moxifloxacin group and 2 patients (6.90%) in comparator group were classified in Risk Class V while only one patient (3.45%) in comparator group was in Risk Class II.

Glasgow coma score had the same results in two groups, with 14.93±0.25 as mean value.

Chest X-ray at baseline was done for all patients with the following results: all patients had Pulmonary consolidation, while 18 patients (30.00%) had Pleural effusion (analogues distribution in two groups).

At the study entry, all subjects reported at least on Medical History / Abnormal physical examination; the most frequent medical conditions reported by patients were: Hypertension (64.52% of patients in moxifloxacin group and 48.28% of patients in comparator group) and Chronic obstructive pulmonary disease (38.71% of patients in moxifloxacin group and 44.83% of patients in comparator group).

All patients were hospitalized when enrolled in the study: 88.33% (87.10% in moxifloxacin group and 89.66% in comparator group) were hospitalized in the Pneumology ward, 5% (3.23% in moxifloxacin group and 6.90% in comparator group) in the Emergency ward and 6.67% (9.68% in moxifloxacin group and 3.45% in comparator group) in the General medical ward; the mean duration of this hospitalization was 12.50±4.53 days with a range 6-24 in moxifloxacin group and 14.56±8.54 days with a range 6-35 in comparator group. Only two patients (one for each group) required a further hospitalization after the end of treatment.

Results Summary — Efficacy

The difference of cure rate between moxifloxacin and comparator group at TOC visit was: 0.1513 (95% CI -0.0707; 0.3732) in the overall safety population; 0.1077 (95% CI -0.1203; 0.3356) in patients classified in Risk Class IV at baseline; 0.2619 (95% CI -0.2107; 0.7345) in patients <65 years and 0.1182 (95% CI -0.1318; 0.3681) in patients >= 65 years; 0.1548 (95% CI -0.0637; 0.3732) in patients whit spontaneous ventilation. The number of patients in Risk Class V and the number of patients who required an assisted ventilation class were very small, so the results are not here reported. To be noticed that for 5 patients (2 for Moxifloxacin Group, 3 for Comparator Group) the clinical evaluation changed from 'Failure/Indeterminate' at 'End of therapy' to Cure at TOC visit, but they took alternative antibiotic therapy in the meantime.

The differences of success rates between moxifloxacin and comparator group at other visits were: 0.0089 (95% CI -0.1634; 0.1812) at Day 3-5, 0.0912 (95% CI -0.1521; 0.3345) at Day of Switch, 0.1212 (95% CI -0.1131; 0.3556) at End of therapy.

Bacteriological assessment, when performed, evidenced only a patient (comparator group) at baseline with an infecting organism; so no further analysis based on the sub-group of patients with bacteriologically proven infection at baseline was done.

Only one patient in comparator group died for pneumonia 9 days after last treatment dose.

Concerning the clinical signs and symptoms answers, the percentages of 'absent' or 'less severe' categories of each clinical sign and symptom increased during the study. The results at baseline and at TOC visit are reported below.

If Clinical Signs and Symptoms collected		Pre therapy				Test of cure			
		Moxifloxacin Group N=31		Comparator Group N=29		Moxifloxacin Group N=25		Comparator Group N=20	
		N	%	N	%	N	%	N	%
Signs and Symptoms	**Evaluation**								
Rigors	**Absent**	29	93.55	19	65.52	25	100.00	20	100.00
	Present	2	6.45	10	34.48	-	-	-	-
Chills	**Absent**	25	80.65	17	58.62	24	96.00	20	100.00
	Present	6	19.35	12	41.38	1	4.00	-	-
Pleuritic Chest pain	**Absent**	24	77.42	19	65.52	24	96.00	19	95.00
	Present	7	22.58	10	34.48	1	4.00	1	5.00
Rales (Crackles)	**Absent**	1	3.23	2	6.90	23	92.00	19	95.00
	Present	30	96.77	27	93.10	2	8.00	1	5.00
Dullness to percussion	**Absent**	13	41.94	10	34.48	25	100.00	19	95.00
	Present	18	58.06	19	65.52	-	-	1	5.00
Cough	**None**	2	6.45	1	3.45	19	76.00	18	90.00
	Mild	10	32.26	2	6.90	6	24.00	2	10.00
	Moderate	14	45.16	18	62.07	-	-	-	-
	Severe	5	16.13	8	27.59	-	-	-	-
Dyspnea	**None**	5	16.13	4	13.79	19	76.00	16	80.00
	Mild	2	6.45	6	20.69	6	24.00	3	15.00
	Moderate	17	54.84	16	55.17	-	-	1	5.00
	Severe	7	22.58	3	10.34	-	-	-	-
Sputum Production	**None**	11	35.48	14	48.28	22	88.00	19	95.00

		Mild	6	19.35	5	17.24	3	12.00	1	5.00
		Moderate	10	32.26	6	20.69	-	-	-	-
		Severe	4	12.90	4	13.79	-	-	-	-

In addition, the total score of CAP symptom questionnaire progressively decreased during the study in both groups: in moxifloxacin group the mean total score at baseline was 15.90±8.66 and at Test of Cure 2.54±3.73; in comparator group the mean total score at baseline was 19.17±9.20 and at Test of Cure 1.85±2.70.

Results Summary — Safety

As to drug exposure, in moxifloxacin arm 31 patients (100.00%) assumed moxifloxacin IV for an average of 6.77±3.51 days (range 1-14) and 21 patients (67.74%) assumed moxifloxacin PO for an average of 6.00±2.93 days (range 2-14). In comparator arm 29 patients (100.00%) assumed ceftriaxone and azithromicin IV for an average of 6.90±2.92 days (range 1-14) and 17 patients (58.62%) assumed amoxicilline/clavulanate and clarithromycin PO for an average of 6.41±1.91 days (range 3-9). Compliance was high in all groups and route of administration.

Safety results on adverse events show that patients with treatment emergent adverse events were more in the comparator arm (68.97%) than in the moxifloxacin arm (58.06%). Four patients (12.90%) receiving moxifloxacin and 5 patients (17.24%) receiving comparator had at least one event considered drug-related. Six patients (19.35%) in the moxifloxacin arm and 9 patients (31.03%) in the comparator arm experienced severe treatment emergent adverse events.

Serious treatment emergent adverse events were reported for 9 subjects (29.03%) in moxifloxacin arm and for 10 subjects (34.48%) in comparator arm.

Three patients experienced serious treatment emergent adverse events considered drug-related as follows:

A patient in moxifloxacin arm experienced enteritis with a moderate grade of severity, leading to permanent discontinuation of study drug.

A patient in moxifloxacin arm was diagnosed with mild vertigo; study drug was permanently discontinued.

A patient in comparator arm experienced severe acute renal failure; remedial drug therapy was consequently administered.

Four patients died due to serious treatment emergent adverse events (all not drug related): in comparator arm a fatal cardiac failure, a death for pneumonia and a death for general physical health deterioration were recorded; in moxifloxacin arm a patient experienced cerebral ischaemia and cardiac failure.

Conclusion(s)

Considering that the enrolment was prematurely interrupted and only 60 patients over the 230 planned were recruited, and that the analyses were performed on the safety population without having performing any patient's validation, the efficacy results should be read only in a descriptive way. The cure rate results at TOC visit calculated on the safety population were: 0.8065 in moxifloxacin group and 0.6552 in comparator group with a difference value of 0.1513 (95% CI -0.0707, 0.3732). Only one patient in the comparator group died for pneumonia 9 days after last dose of study therapy. The CAP signs and symptoms progressively improved during the study in both groups.

Safety results on adverse events treatment emergent show that IV/PO moxifloxacin

monotherapy is better tolerated than IV/PO combination therapy with IV ceftriaxone+ azithromycin followed by PO amoxicillin/clavulanic acid and clarithromycin, as far as total number of events is concerned as well as relative frequencies of adverse events, of serious and of severe adverse events. Discontinuation due to adverse events is almost double in moxifloxacin arm (19.35%) compared to comparator group (10.34%).	
Publication(s):	none
Date Created or Date Last Updated:	08.10.2012

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Avelox [*Oral formulation*]
Brand/Trade Name(s) ex-US	Avelon® Avelox® Avalox® Actira® Octegra® Izilox® Megaxin® Proflox® Promira®
Generic Name	Moxifloxacin
Main Product Company Code	BAY12-8039
Other Company Code(s)	n/a
Chemical Description	1-Cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride.
Other Product Aliases	n/a

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