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:	11974	NCT00402727
Study Phase:	IIIb	
Official Study Title:	A prospective, randomized, double-dummy, double-blind, multi-national, multi-center trial comparing the safety and efficacy of sequential (intravenous/oral) moxifloxacin 400 mg once daily to intravenous piperacillin/tazobactam 4.0/0.5 g every 8 hours followed by oral amoxicillin/clavulanic acid tablets 875/125 mg every 12 hours for the treatment of subjects with complicated skin and skin structure infections.	
Therapeutic Area:	Anti-Infectives	
Test Product		
Name of Test Product:	Moxifloxacin (Avelox, BAY12-8039)	
Name of Active Ingredient:	Moxifloxacin Hydrochloride	
Dose and Mode of Administration:	400 mg intravenously (IV), once daily, followed sequentially by step down therapy of moxifloxacin 400 mg orally, once daily.	
Reference Therapy/Placebo		
Reference Therapy:	Piperacillin/tazobactam and amoxicillin/clavulanic acid	
Dose and Mode of Administration:	Piperacillin/tazobactam 4.0/0.5 g administered IV. three times daily followed sequentially by step down therapy of amoxicillin/clavulanic acid 875/125 mg administered orally twice daily (PIP/TAZ-AMC group).	
Duration of Treatment:	A minimum of 7 days and a maximum of 21 days.	
Studied period:	Date of first subjects' first visit:	28 SEP 2006
	Date of last subjects' last visit:	12 JUN 2008
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 12 SEP 2006) was enacted prior to enrollment of the first subject. Additionally, a pharmacogenetic sub-study was implemented. The following changes were made: • Clinical examination was performed at the pre-treatment visit 48 hours preceding initiation of study drug therapy • The stratification of subjects was amended to include stratification by surgical intervention • The statistical and analytical plan section of the protocol was revised to account for stratification by surgical intervention. • Specimen for culture from infected area was obtained within 48 hours prior to the initiation of study drug therapy instead of 24 hours.) • Oral therapy started at Investigator´s discretion after the subject no longer had fever for a minimum of 24 hours	

	• The timing of the IV. treatments in Subgroup 1B was swapped for placebo (from "every 24 hours" to "every 8 hours") and moxifloxacin groups (from "every 8 hours" to "every 24 hours") • The timing of the IV treatments in Subgroup 2A was swapped for piperacillin/tazobactam (from "every 24 hours" to "every 8 hours") and placebo groups (from "every 8 hours" to "every 24 hours") • The sequence of administration of IV.treatments in Subgroup 2B was amended to start with moxifloxacin placebo infusion instead of the piperacillin/tazobactam infusion • Laboratory assessments were revised to include international normalized ratio (INR) determination (for subjects taking oral anti-coagulants), urinalysis and pharmacogenetic substudy analysis. • The intent-to-treat (ITT) with causative organism and microbiologically valid (MBV) analysis populations were amended to state that causative organisms Amendment no. 2 (dated 12 SEP 2006) was implemented to change the instructions regarding the intake of oral study drug to make them easier to follow, and to indicate the address change of the Co-ordinating Investigator and pharmacogeneticist.
Study Centre(s):	The study was conducted in 61 active centers in Belgium, Bulgaria, Germany, Greece, Hungary, Israel, Latvia, Lithuania, Poland, Romania, Russia, South Africa, Ukraine, Spain, and the UK.
Methodology:	The study design consisted of a pre-treatment period (within 48 hours before randomization), a during treatment period (from randomization to 7 days minimum and 21 days maximum), a Test of Cure (TOC) visit (14 to 28 days after the end of treatment [EOT]), and an alternative therapy visit (14 to 28 days after completion of alternative therapy for subjects requiring additional antimicrobial therapy). Subjects were stratified, prior to randomization, according to cSSSI subtype, surgical intervention, and the severity of their illness. Efficacy was determined by clinical and microbiological evaluations, including photographic assessments, and the use of health resources. The diagnosis of cSSSI was validated by an independent DRC, which also made an assessment of the efficacy of study drugs for all subjects. The safety of the treatment was monitored by physical examination findings, vital signs, electrocardiograms (ECGs), laboratory assessments (hematology, clinical chemistry, urinalysis, INR (for subjects receiving oral anti-coagulants), concomitant medications and by the reporting of adverse events (AEs).
Indication/ Main Inclusion Criteria:	Indication: Complicated skin and skin structure infections Main Inclusion Criteria: Men and women ≥ 18 years of age with a diagnosis of bacterial skin and skin structure infection (duration < 21 days) that required hospitalization and initial parenteral therapy for at least 48 hours, and also met at least one of the following criteria: • Involvement of deep soft tissue (e.g., fascial, muscle layers).

	• Requirement for a significant surgical intervention including surgical drainage, drainage procedure guided by imaging and/or debridement. • Association with a significant underlying disease that could have complicated response to treatment. An underlying disease was considered significant if it included any of the following conditions that were present at the time of presentation: cancer (except basalor squamous-cell cancer of the skin), cardiac (i.e., congestive heart disease), diabetes mellitus, hepatic (i.e., cirrhosis or another form of chronic liver disease), immunologic, renal disease, respiratory, transplantation or vascular disease. • Diagnosis of one of the following skin and skin structure infections: ▪ Major abscess(es) associated with extensive cellulitis, which required antibiotic therapy in addition to surgical incision and drainage. ▪ Diabetic foot infection of mild to severe intensity (perfusion, extent/size, depth/tissue loss, infection and sensation [PEDIS] grade 2-4) in the presence or absence of osteomyelitis. Subjects with osteomyelitis could only be enrolled if the infected bone was completely removed by surgery and if residual infection requiring antibiotics was still present following surgery. ▪ Wound infection including: post-surgical (surgical incision), post-traumatic, human bite/clenched fist and animal bite wound and wound associated with injection drug abuse. Infected ischemic ulcers with at least one of the following conditions: 1) Peripheral vascular disease. 2) Conditions predisposed to pressure sores, such as paraplegia, peripheral neuropathy.
Study Objectives:	Overall: The objective of this study was to compare the efficacy and safety of two sequential (IV/oral) treatment regimens for the treatment of adult subjects with cSSSIs: • Moxifloxacin, 400 mg i.v.every 24 hours followed by moxifloxacin 400 mg orally every 24 hours. • Piperacillin/tazobactam, 4.0/0.5 g administered i.v.three times daily followed by oral amoxicillin/clavulanic acid tablets, 875/125 mg twice daily.
Evaluation Criteria:	Efficacy (Primary): The primary efficacy variable was the clinical response assessed by an independent DRC, 14 to 28 days after the completion of study drug therapy (TOC visit). Efficacy (Secondary): Secondary efficacy variables were as follows: • Clinical response assessed by the Investigator on Day 3 to 5, and at the EOT and TOC visits. • Bacteriological response assessed by culture on Day 3 to 5, and at the EOT and TOC visits.

	Subjects had a photographic assessment of their skin lesions at each assessment time-point, which was used by the DRC, together with blinded subject data, to evaluate clinical response to the study drug at the TOC visit. Safety: Safety evaluations were based on physical examinations, AEs, vital signs, electrocardiogram (ECG) findings and laboratory results.
Statistical Methods:	Efficacy (Primary): All statistical tests were two sided and performed at the 0.05 significance level. All analyses were based on subjects "as treated." Valid per-protocol (PP) analyses were performed as primary efficacy analyses. ITT analyses were performed as supportive efficacy analyses. Indeterminate and missing outcomes were considered non-successes in the ITT populations. Centers were pooled before unblinding the study. Treatment groups (moxifloxacin vs comparator) were compared using the Mantel-Haenszel (MH) point estimate and 95% confidence interval (CI) for calculating the difference in clinical success rates, as confirmed by the DRC, at TOC (14 to 28 days after the EOT, where EOT was 7 to 21 days after start of treatment). Statistical analyses were adjusted based on cSSSI subtype strata (major abscess, diabetic foot infection, wound infection, infected ischemic ulcer), severity of illness and presence or absence of a cSSSI surgical procedure prior to or planned within 48 hours after entry into the study. For moxifloxacin to be considered not less effective than the comparator, the lower limit of the 95% CI (moxifloxacin-comparator) had to be greater than -0.10 (-10%). The DerSimonian and Laird tests were used to test the homogeneity of differences across strata. Efficacy (Secondary): Secondary efficacy analyses were performed on the ITT populations. As secondary efficacy analyses, the clinical response as assessed by the Investigator at the EOT and TOC visits, and the clinical response as assessed by both the Investigator and the DRC at the EOT and TOC visits, were analyzed exploratively for subjects with bacteriologically proven cSSSI in the same way as the primary efficacy variable. The bacteriological responses at the EOT and TOC visits were analyzed in the same way as the primary efficacy variable. Other secondary variables were analyzed descriptively.

	Safety: Descriptive statistics were presented for physical examinations, AEs, vital signs, electrocardiogram (ECG) findings and laboratory results. The safety analysis included tabulation of the type (using MedDRA version 11.1) and frequency of all AEs.
Number of Subjects:	It was planned that 804 subjects would be randomized (402 per treatment group) to ensure 642 valid subjects, assuming a validity rate of 80%. A total of 834 subjects were enrolled and 813 were randomized at 61 centers; 763 subjects completed treatment and 749 subjects completed the study.

Study Results

Results Summary — Subject Disposition and Baseline

Of the 813 subjects randomized in this study, 432 were randomized to the moxifloxacin group and 381 were randomized to the PIP/TAZ-AMC group. The imbalance in the number of subjects randomized to each treatment group was due to an interactive voice reponse system (IVRS) error. Analysis of the randomized population by primary diagnosis, severity class, prior surgery and stratum revealed no major differences between treatment groups. Statistical analysis had shown that this error had no notable impact on the efficacy results of this study. The disposition of randomized subjects in each analysis population is presented in Table 1.

Table 1: Subjects included in analyses (randomized subjects)

Population	Moxifloxacin N=432		PIP/TAZ-AMC N=381		Total N=813	
	n	(%)	n	(%)	n	(%)
Randomized	432	(100)	381	(100)	813	(100)
PP	361	(83)	307	(81)	668	(82)
MBV	268	(62)	243	(64)	511	(63)
Safety/ITT	426	(99)	377	(99)	803	(99)
ITT with causative organism(s)	313	(72)	290	(76)	603	(74)

Note: an additional 21 subjects were enrolled but not randomized (11 withdrew their consent and 10 had a protocol violation).

The number of subjects included in the main analysis population (PP population) is presented by primary diagnosis in Table 2.

Table 2: Number of subjects by primary diagnosis – PP population

Primary Diagnosis	Moxifloxacin N=361	PIP/TAZ-AMC N=307	Total N=668
	n (%)	n (%)	n (%)
Major abscess	167 (46)	153 (50)	320 (48)
Diabetic foot infection	110 (30)	96 (31)	206 (31)
Wound infection	62 (17)	47 (15)	109 (16)
Infected ischemic ulcer	22 (6)	11 (4)	33 (5)

In the PP population, the majority of subjects were White (660 subjects, 99%) and male (442 subjects, 66%). Subjects had a mean age of 52 years (range: 18 to 90 years), a mean weight of 82 kg (range: 42 to 180 kg), a mean height of 173 cm (range: 147 to 197 cm), and a mean BMI of 27 kg/m^2 (17 to 56 kg/m^2).

Subjects were generally well-matched in terms of demographics and other characteristics though, in the PP population, WBC and glycosylated hemoglobin (HbA_{1c}) values were significantly higher in the moxifloxacin-treated subjects (p=0.022 and 0.018, respectively).

In both treatment groups, subjects most frequently had a primary diagnosis of major abscess or diabetic foot infection. A very low number of subjects in both groups had a primary diagnosis of infected ischemic ulcer.

For the Safety/ITT population, no statistically significant differences were observed between treatment groups, except for the following parameters:

- BMI – the mean BMI of subjects was 28 kg/m^2 in the moxifloxacin group vs 27 kg/m^2 in the PIP/TAZ-AMC group (p=0.007).
- Weight – the mean weight of subjects was 84 kg in the moxifloxacin group vs 81 kg in the PIP/TAZ-AMC group (p=0.016).

These differences were not considered large enough to be clinically important as this was confirmed by the analysis of the clinical response by BMI group.

Results Summary — Efficacy

The study demonstrated that treatment with sequential (IV/oral) moxifloxacin 400 mg once daily is not less effective than treatment with the comparator, i.v. piperacillin/tazobactam 4.0/0.5 g every 8 hours followed by oral amoxicillin/clavulanic acid tablets 875/125 mg every 12 hours daily, in adults with cSSSIs. The lower limit of the 95% CI of the difference between the two clinical success rates (moxifloxacin minus comparator) at the TOC visit was greater than –10% for all analyzed populations.

Clinical success:
Clinical success rates at the TOC visit are presented by treatment group, analysis population and primary diagnosis in Table 3.

The success rate for clinical response at TOC in the PP population, the primary efficacy variable, was almost identical in both treatment groups and the statistical hypothesis of inferiority of moxifloxacin to the comparator regimen could be rejected at the 2.5% level. The results in the other populations (MBV, ITT, ITT with causative organism[s]) all supported the results from the PP analysis with none of the lower limits being lower than 10%.

Table 3: Clinical success rates at the TOC by primary diagnosis

Population Primary Diagnosis	Moxifloxacin n/N (%)	PIP/TAZ-AMC n/N (%)	Total 95% CI
PP			
Major abscess	160/167 (95.8)	147/153 (96.1)	
Diabetic foot infection	84/110 (76.4)	75/96 (78.1)	
Wound infection	59/62 (95.2)	45/47 (95.7)	
Infected ischemic ulcer	17/22 (77.3)	8/11 (72.7)	
Total	320/361 (88.6)	275/307 (89.6)	-5.3 to 3.9
MBV			
Major abscess	119/125 (95.2)	113/117 (96.6)	
Diabetic foot infection	69/92 (75.0)	64/85 (75.3)	
Wound infection	38/39 (97.4)	31/32 (96.9)	
Infected ischemic ulcer	7/12 (58.3)	7/9 (77.8)	
Total	233/268 (86.9)	215/243 (88.5)	-7.5 to 3.4
ITT			
Major abscess	163/183 (89.1)	151/169 (89.3)	
Diabetic foot infection	86/123 (69.9)	76/110 (69.1)	
Wound infection	65/72 (90.3)	48/55 (87.3)	
Infected ischemic ulcer	17/24 (70.8)	9/18 (50.0)	
cSSSI not included in protocol	3/4 (75)	3/3 (100)	
Uncomplicated SSSI	16/17 (94.1)	18/18 (100.0)	
No infection	0/3 (0)	0/4 (0)	
Total	350/426 (82.2)	305/377 (80.9)	-3.8 to 6.3
ITT with causative organism(s)			
Major abscess	122/135 (90.4)	114/125 (91.2)	
Diabetic foot infection	71/102 (69.6)	65/96 (67.7)	
Wound infection	41/45 (91.1)	34/39 (87.2)	
Infected ischemic ulcer	7/14 (50.0)	8/14 (57.1)	
cSSSI not included in protocol	2/3 (67)	2/2 (100)	
Uncomplicated SSSI	11/12 (91.7)	11/11 (100.0)	
No infection	0/2 (0)	0/3 (0)	
Total	254/313 (81.2)	234/290 (80.7)	-5.8 to 6.1

Bacteriological success

The bacteriological response rates observed at the TOC visit are presented for the MBV and ITT with causative organism(s) populations in Table 4.

The bacteriological success rates at the TOC visit in the MBV population were comparable in both the moxifloxacin group (84%) and the PIP/TAZ-AMC group (87%), 95% CI -9.3 to 2.2. In the ITT with causative organism(s) population, the bacteriological success rate was 79% in each treatment group, 95% CI -6.9 to 5.4. As the lower limit of the 95% CI was greater than -10% in both populations (MBV and ITT with causative organism[s]), non-inferiority was demonstrated.

Table 4: Bacteriological response rates at the TOC (MBV, ITT with causative organism populations)

MBV	Moxifloxacin N=270 n (%)	PIP/TAZ-AMC N=243 n (%)	95% CI
Bacteriological success	226 (84.3)	212 (87.2)	-9.3 to 2.2
Eradication	4 (1.5)	3 (1.2)	
Presumed eradication	222 (82.8)	209 (86.0)	
Bacteriological non-success	42 (15.6)	31 (12.8)	
Persistence	16 (6.0)	12 (4.9)	
Presumed persistence	24 (9.0)	19 (7.8)	
Eradication with superinfection	2 (0.7)	0 (0.0)	
ITT with causative organism(s)	Moxifloxacin N=313 n (%)	PIP/TAZ-AMC N=290 n (%)	95% CI
Bacteriological success	247 (78.9)	229 (79.0)	-6.9 to 5.4
Eradication	6 (1.9)	3 (1.0)	
Presumed eradication	241 (77.0)	226 (77.9)	
Bacteriological non-success	66 (21.0)	61 (21.0)	
Persistence	25 (8.0)	20 (6.9)	
Presumed persistence	25 (8.0)	19 (6.6)	
Superinfection	2 (0.6)	0 (0.0)	
Indeterminate	14 (4.5)	22 (7.6)	

Eradication without recurrence, superinfection or reinfection. Persistence includes persistence with superinfection or reinfection. For the calculation of CIs, indeterminates/missing were treated as non-successes in the ITT population.

The bacteriological response at the TOC visit is presented by causative organism isolated in at least four subjects pre-therapy in Table 5. There were no major differences in bacteriological response by bacterial grouping or species.

Table 5: Bacteriological response at TOC by causative skin organism isolated at least 4 times pre-therapy (MBV population)

Group Genus/*Species*	Bacteriological Response	Moxifloxacin 268 n/N (%)	PIP/TAZ-AMC 243 n/N (%)	Total 511 n/N (%)
Subjects	Eradication	6/268 (2)	3/243 (1)	9/511 (2)
	Presumed eradication	222/268 (83)	209/243 (86)	431/511 (84)
	Persistence	16/268 (6)	12/243 (5)	28/511 (5)
	Presumed persistence	24/268 (9)	19/243 (8)	43/511 (8)
Organisms	Eradication	22/497 (4)	10/429 (2)	32/926 (4)
	Presumed eradication	410/497 (82)	360/429 (84)	770/926 (83)
	Persistence	22/497 (4)	21/429 (5)	43/926 (5)
	Presumed persistence	43/497 (9)	38/429 (9)	81/926 (9)
Gram-positive cocci aerobic				
Subjects	Eradication	8/228 (3)	3/206 (1)	11/434 (3)
	Presumed eradication	189/228 (83)	176/206 (85)	365/434 (84)
	Persistence	10/228 (4)	10/206 (5)	20/434 (5)
	Presumed persistence	21/228 (9)	17/206 (8)	38/434 (9)
Organisms	Eradication	13/320 (4)	6/280 (2)	19/600 (3)
	Presumed eradication	263/320 (82)	234/280 (84)	497/600 (83)
	Persistence	12/320 (4)	15/280 (5)	27/600 (4)
	Presumed persistence	32/320 (10)	25/280 (9)	57/600 (9)
S. haemolyticus	Presumed eradication	0/1 (0)	3/3 (100)	3/4 (75)
	Presumed persistence	1/1 (100)	0/3 (0)	1/4 (25)
S. aureus, methicillin susceptible	Eradication	6/152 (4)	3/154 (2)	9/306 (3)
	Presumed eradication	128/152 (84)	131/154 (85)	259/306 (85)
	Persistence	3/152 (2)	9/154 (6)	12/306 (4)
	Presumed persistence	15/152 (10)	11/154 (7)	26/306 (8)
S. aureus, methicillin resistant	Presumed eradication	17/23 (74)	15/17 (88)	32/40 (80)
	Persistence	4/23 (17)	2/17 (12)	6/40 (15)
	Presumed persistence	2/23 (9)	0/17 (0)	2/40 (5)
S. agalactiae	Eradication	4/31 (13)	1/13 (8)	5/44 (11)
	Presumed eradication	22/31 (71)	11/13 (85)	33/44 (75)
	Presumed persistence	5/31 (16)	1/13 (8)	6/44 (14)
S. equisimilis	Presumed eradication	12/13 (92)	10/12 (83)	22/25 (88)
	Persistence	0/13 (0)	1/12 (8)	1/25 (4)
	Presumed persistence	1/13 (8)	1/12 (8)	2/25 (8)
S. pyogenes	Presumed eradication	34/36 (94)	22/24 (92)	58/60 (97)
	Presumed persistence	0/36 (0)	2/24 (8)	2/60 (3)
E. faecalis	Eradication	3/61 (5)	2/50 (4)	5/111 (5)
	Presumed eradication	45/61 (74)	37/50 (74)	82/111 (74)
	Persistence	5/61 (8)	3/50 (6)	8/111 (7)
	Presumed persistence	8/61 (13)	8/50 (16)	16/111 (14)
E. faecium	Presumed eradication	1/1 (100)	2/3 (67)	3/4 (75)
	Presumed persistence	0/1 (0)	1/3 (33)	1/4 (25)

Table continues on the next page.

Table 5: Bacteriological response at TOC by causative skin organism isolated at least 4 times pre-therapy (MBV population) (Table continued)

Group Genus/*Species*	Bacteriological Response	Moxifloxacin 268 n/N (%)	PIP/TAZ-AMC 243 n/N (%)	Total 511 n/N (%)
Gram positive cocci anaerobic				
Subjects	Presumed eradication	5/5 (100)	6/6 (100)	11/11 (100)
Organisms	Presumed eradication	5/5 (100)	7/7 (100)	12/12 (100)
P. asaccharolyticus	Presumed eradication	2/2 (100)	3/3 (100)	5/5 (100)
P. anaerobius	Presumed eradication	2/2 (100)	2/2 (100)	4/4 (100)
Gram negative rods fermentative				
Subjects	Eradication	5/97 (5)	2/78 (3)	7/175 (4)
	Presumed eradication	75/97 (77)	63/78 (81)	138/175 (79)
	Persistence	9/97 (9)	6/78 (8)	15/175 (9)
	Presumed persistence	8/97 (8)	7/78 (9)	15/175 (9)
Organisms	Eradication	7/142 (5)	4/119 (3)	11/261 (4)
	Presumed eradication	116/142 (82)	99/119 (83)	215/261 (82)
	Persistence	10/142 (7)	6/119 (5)	16/261 (6)
	Presumed persistence	9/142 (6)	10/119 (8)	19/261 (7)
E. coli, ESBL	Presumed eradication	4/4 (100)	1/1 (100)	5/5 (100)
E. coli, non-ESBL	Eradication	3/54 (6)	1/54 (2)	4/108 (4)
	Presumed eradication	46/54 (85)	47/54 (87)	93/108 (86)
	Persistence	2/54 (4)	0/54 (0)	2/108 (2)
	Presumed persistence	3/54 (5)	6/54 (11)	9/108 (8)
K. pneumoniae, ESBL	Presumed eradication	2/4 (50)	1/4 (25)	3/8 (38)
	Persistence	1/4 (25)	2/4 (50)	3/8 (38)
	Presumed persistence	1/4 (25)	1/4 (25)	2/8 (25)
K. pneumoniae, non-ESBL	Presumed eradication	7/10 (70)	4/5 (80)	11/15 (73)
	Persistence	1/10 (10)	0/5 (0)	1/15 (7)
	Presumed persistence	2/10 (20)	1/5 (20)	3/15 (20)
K. oxytoca, non-ESBL	Presumed eradication	7/7 (100)	6/6 (100)	13/13 (100)
P. mirabilis, non-ESBL	Presumed eradication	7/8 (88)	5/7 (71)	12/15 (80)
	Persistence	0/8 (0)	2/7 (29)	2/15 (13)
	Presumed persistence	1/8 (13)	0/7 (0)	1/15 (7)
P. vulgaris, non ESBL	Presumed eradication	3/3 (100)	4/6 (67)	7/9 (78)
	Persistence	0/3 (0)	1/6 (17)	1/9 (11)
	Presumed persistence	0/3 (0)	1/6 (17)	1/9 (11)
E. cloacae	Eradication	1/22 (5)	1/19 (5)	2/41 (4)
	Presumed eradication	20/22 (91)	18/19 (95)	38/41 (93)

Table continues on the next page.

Table 5: Bacteriological response at TOC by causative skin organism isolated at least 4 times pre-therapy (MBV population) (Table continued)

Group Genus/*Species*	Bacteriological Response	Moxifloxacin 268 n/N (%)	PIP/TAZ-AMC 243 n/N (%)	Total 511 n/N (%)
M. morganii	Eradication	0/6 (0)	1/4 (25)	1/10 (10)
	Presumed eradication	3/6 (50)	3/4 (75)	6/10 (60)
	Persistence	3/6 (50)	0/4 (0)	3/10 (30)
P. aeruginosa	Eradication	1/9 (11)	0/4 (0)	1/13 (8)
	Presumed eradication	7/9 (78)	2/4 (50)	9/13 (69)
	Persistence	1/9 (11)	1/4 (25)	2/13 (15)
	Presumed persistence	0/9 (0)	1/4 (25)	1/13 (8)
A. baumannii	Eradication	1/11 (9)	1/5 (20)	2/16 (13)
	Presumed eradication	9/11 (82)	4/5 (80)	13/16 (81)
	Persistence	1/11 (9)	0/5 (0)	1/16 (6)
Gram-negative rods anaerobic				
Subjects	Eradication	2/31 (7)	0/28 (0)	2/59 (3)
	Presumed eradication	27/31 (87)	25/28 (89.3)	52/59 (88)
	Presumed persistence	2/31 (7)	3/28 (11)	5/59 (9)
Organisms	Eradication	2/35 (7)	0/30 (0)	2/65 (3)
	Presumed eradication	31/35 (89)	27/30 (90)	58/65 (89)
	Presumed persistence	2/35 (6)	3/30 (10)	5/65 (8)
B. fragilis	Eradication	2/26 (8)	0/19 (0)	2/45 (4)
	Presumed eradication	22/26 (85)	16/19 (84)	38/45 (84)
	Presumed persistence	2/26 (8)	3/19 (16)	5/45 (11)
P. bivia	Presumed eradication	3/3 (100)	3/3 (100)	6/6 (100)

The most frequently isolated pre-therapy skin pathogen in both treatment groups was methicillin-susceptible *S. aureus*. This pathogen, which was isolated pre-therapy in 152 cases in the moxifloxacin group and 154 cases in the PIP/TAZ-AMC group, was eradicated (or presumed eradicated) in 88% and 87% of these cases, respectively. Methicillin-resistant *S. aureus*, which was isolated pre-therapy in 23 cases in the moxifloxacin group and 17 cases in the PIP/TAZ-AMC group, was presumed eradicated in 74% and 88% of these cases, respectively.

E. faecalis, which was isolated in 61 cases in the moxifloxacin group and 50 cases in the PIP/TAZ-AMC group, was eradicated (or presumed eradicated) in 79% and 78% of these cases, respectively.

Non-extended-spectrum beta-lactamase (ESBL) producing *E. coli*, which was isolated pre-therapy in 54 cases in each treatment group, was eradicated (or presumed eradicated) from 91% and 89% of subjects in the moxifloxacin and PIP/TAZ-AMC group, respectively.

ESBL-producing *E.coli*, which was isolated pre-therapy in 4 cases in the moxifloxacin group and one case in the PIP/TAZ-AMC group, was eradicated in 100% of these cases.

Results Summary — Safety

In the valid for safety population (moxifloxacin, 426 subjects; piperacillin plus tazobactam followed by amoxicillin plus clavulanic acid, 377 subjects), treatment emergent AEs, and treatment-emergent drug-related AEs were experienced by a similar proportion of subjects in the moxifloxacin and PIP/TAZ-AMC groups (23% versus 19%, p=0.143 and 9% versus 7%, p=0.605, respectively).

The three system organ classes (SOCs) in which the highest rates of AEs occurred were gastrointestinal disorders (5% moxifloxacin versus 5% PIP/TAZ-AMC), infections and infestations (5% moxifloxacin versus 4% PIP/TAZ-AMC), and investigations (4% moxifloxacin versus 5% PIP/TAZ-AMC). The most commonly reported treatment-emergent AE was diarrhea, which was reported in 2% of subjects in both treatment groups. The only AE reported in more than 2% of subjects in either treatment group was hypertension (reported in 3% of the moxifloxacin and 1% of PIP/TAZ-AMC subjects).

Four deaths were reported during the study; three in the moxifloxacin group (cardiopulmonary failure, renal failure and shock, and pulmonary embolism), and one in the PIP/TAZ-AMC group (pulmonary embolism). None of them was assessed as drug-related. Thirty-five subjects experienced treatment-emergent SAEs, 21 subjects (5%) in the moxifloxacin group and 14 subjects (4%) in the PIP/TAZ-AMC group. Six of these subjects had six SAEs that were considered drug-related; four subjects (1%) in the moxifloxacin group (two events of ECG QT prolonged [one event per subject], one event of increased blood alkaline phosphatase and one event of wound infection), and two subjects (1%) in the PIP/TAZ-AMC group (one event of impaired healing and one event of wound infection).

Most AEs reported in both treatment groups were mild or moderate in severity. Nineteen subjects experienced an AE of severe intensity; 11 subjects in the moxifloxacin group (one subject had a drug-related AE of dizziness) and eight subjects in the PIP/TAZ-AMC group (no subject had a drug-related AE).

Most AEs resolved or had an improved outcome irrespective of whether they were assessed as drug-related or not. Only 15 (4%) subjects in the moxifloxacin group reported an AE with outcome unchanged and none had an outcome of worsened. In the PIP/TAZ-AMC group, 12 subjects (3%) experienced an AE that was unchanged and none had worsening as an outcome.

There was no clear treatment effect on the incidence of diarrhea and hepatic events. Three subjects in the moxifloxacin group were diagnosed with a drug-related clostridial infection (two subjects from the same center) or a drug-related *C. difficile* colitis (one subject). These events were non-serious and mild in intensity; two resolved and the third (one event of clostridial infection) had insufficient follow-up. An additional subject had a non drug-related event of pseudomembranous colitis. No subject in the PIP/TAZ-AMC group had such events. No subject in either treatment group had an AE that could be considered as a surrogate of cardiac arrhythmia.

New ECG findings were reported during treatment in 43% of moxifloxacin subjects and 42% of PIP/TAZ-AMC subjects. In subjects with paired valid ECGs, the mean QTcB change from baseline to Day 1 was greater in the moxifloxacin group than the PIP/TAZ-AMC group (10 ± 15 msec vs 1 ± 12 msec). The QTcB interval was slightly more prolonged in female subjects than in male subjects. Similar findings were observed for the mean QTcF change. QTc prolongations under therapy (≥ 450 to 500 msec for males, ≥ 470 to 500 msec for females) were more frequent in the moxifloxacin group (24

subjects, 9%) than the PIP/TAZ-AMC group (nine subjects, 4%). In addition, shifts in QT intervals from normal or borderline at baseline to borderline or prolonged under therapy (Day 1) occurred more frequently in the moxifloxacin group than the PIP/TAZ-AMC group (48 subjects, 18% vs 14 subjects 6%). However, the QTc prolongation observed in the moxifloxacin group did not translate into clinical AEs. No subjects in either treatment group had an AE that could be considered as a surrogate of cardiac arrhythmia.

The evaluation of significant changes in laboratory parameters did not reveal any relevant difference between treatments. No relevant treatment-related differences were detected in the analysis of vital signs.

Conclusion(s)

In this study, the results provide evidence that moxifloxacin 400 mg (orally/IV) dosed once daily for 7 to 21 days is not clinically inferior in terms of clinical response rate to piperacillin plus tazobactam (IV) possibly followed by oral amoxicillin plus clavulanic acid for the treatment of cSSSIs. The bacteriological response rates were consistent with the clinical response rates for all analysis populations. Moxifloxacin was effective in treating the four cSSSI diagnoses studied in the present trial. In addition, the AE profile of moxifloxacin (i.v.followed by oral) was similar to that of i.v.piperacillin plus tazobactam followed by oral amoxicillin plus clavulanic acid.

Publication(s):	Gyssens IC, Dryden M, Kujath P, Nathwani D, Schaper N, Hampel B, Reimnitz P, Alder J, Arvis P. A randomized trial of the efficacy and safety of sequential intravenous/oral moxifloxacin monotherapy versus intravenous piperacillin/tazobactam followed by oral amoxicillin/clavulanate for complicated skin and skin structure infections. J Antimicrob Chemother. 2011 Nov;66(11):2632-42. Epub 2011 Sep 6.

Date Created or Date Last Updated:	14 MAY 2012	Date of Clinical Study Report:	21 JUL 2009

Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Vital GmbH
Postal Address	D-51368 Leverkusen, Germany
Sponsor in Germany (if applicable)	
Legal Entity Name	Bayer HealthCare AG
Postal Address	D-51368 Leverkusen, Germany

List of Investigational Sites

No	Facility Name	Street	ZIP Code	City	Country
1	Hôpital Erasme/Erasmus Ziekenhuis	Service des maladies infectieuses/Dienst infectieuze ziekten Route de Lennik 808 Lenniksebaan	1070	BRUXELLES - BRUSSEL	BELGIUM
2	Sint-Jozefkliniek	Research Centre - Diabetic Centre Kasteelstraat 23	2880	BORNEM	BELGIUM
3	UZ Antwerpen	Wilrijkstraat 10	2650	EDEGEM	BELGIUM
4	UZ Brussel	Laarbeeklaan 101	1090	BRUXELLES - BRUSSEL	BELGIUM
5	MHAT Russe	Medical Intensive Care Unit Nezavisimosti str. 2	7002	Ruse	BULGARIA

6	Military Medical Academy	Clinic of Dermatology and venerology 3 Georgi Sofiiski str.	1431	Sofia	BULGARIA
7	UMHAT Dr. Georgi Stranski	First Surgery Clinic G. Kotchev str. 8 A	5800	Pleven	BULGARIA
8	Kliniken der Medizinischen Hochschule Hannover	Allgemein-, Viszeral- und Transplantationschirurgie Carl-Neuberg-Str. 1	30625	Hannover	GERMANY
9	Ruhr-Universität-Bochum Medizinische Einrichtungen	Klinik für Dermatologie und Allergologie Gudrunstraße 56	44791	Bochum	GERMANY
10	Universitätsklinikum Münster	Klinik und Poliklinik für Hautkrankheiten Allgemeine Dermatologie und Venerologie Von-Esmarch-Straße 58	48149	Münster	GERMANY
11	Universitätsklinikum Otto-von Guericke - Magdeburg	Klinik und Poliklinik für Dermatologie und Venerologie Leipziger Strasse 44	39120	Magdeburg	GERMANY
12	Evangelismos General Hospital of Athens	45-47, Ipsilantou Str.	106 76	Athens	GREECE
13	Budai Irgalmasrendi Hospital	Frankel Leo street 17-19	1027	Budapest	HUNGARY
14	Csolnoky Ferenc Veszprem County Hospital	Korhaz utca 1	8200	Veszprem	HUNGARY

15	Fejer megyei Szent Gyorgy Korhaz	Seregelyesi ut 3	8000	Szekesfehervar	HUNGARY
16	Petz Aladar Megyei Korhaz	Zrinyi u. 13.	9024	Györ	HUNGARY
17	Somogy County Hospital "Kaposi Mor"	Tallian, Gyula U. 20-32	7400	Kaposvar	HUNGARY
18	University of Debrecen Medical&Health Science Center	Nagyerdei krt. 98.	4032	Debrecen	HUNGARY
19	Chaim Sheba Medical Center	Tel-Aviv University Tel Hashomer 52621	52621	Tel Hashomer	ISRAEL
20	Infectious Dis. & Travel Clinic	Bnai Zion Medical Center		Haifa	ISRAEL
21	Infectious Diseases Unit Ha'emek Medical Center		18101	Afula	ISRAEL
22	Pediatrics Ward A Meyer Hospital Rambam Medical Center		31096	Haifa	ISRAEL
23	Central Hospital of Liepaja	Slimnicas street 25	LV 3400	Liepaja	LATVIA
24	Daugavpils Regional Hospital	Vasarnicas 20	LV-5417	Daugavpils	LATVIA
25	Latvian Maritime Medicine Center	Patversmes 23	1005	Riga	LATVIA
26	Paula Stradina Kliniskas Universitates slimnica	Pilsonu iela 13	1002	Riga	LATVIA

27	Riga Clinical Hospital "Gailezers"	2, Hipokrata Str.	LV-1038	Riga	LATVIA
28	Valmiera Hospital	Jumaras street 195	LV-4201	Valmiera	LATVIA
29	Kaunas Medical University Hospital	Endocrinology Clinic Eiveniu 2	LT-3007	Kaunas	LITHUANIA
30	Siauliai County Hospital	Departement of Surgery	LT-76231	Siauliai	LITHUANIA
31	Ukmerge Hospital	Department of Surgery	LT-20184	Ukmerge	LITHUANIA
32	University Hospital of Vilnus City	Antakalnio 57	10207	Vilnius	LITHUANIA
33	Centralny Szpital Kliniczny AM	Klinika Gastroenterologii i Chorob Przemiany Materii ul. Banacha 1	02-097	Warszawa	POLAND
34	Samodzielny Publiczny Szpital Kliniczny nr 4	Oddzial Chirurgii Naczyn ul. Jaczewskiego 8	20-954	Lublin	POLAND
35	SPSK nr 1	Katedra i Klinika Chirurgii Naczyn i Angiologii ul. Staszica 11	20-081	Lublin	POLAND
36	Wojewodzki Szpital Specjalistyczny im. S. Wyszynskiego SPZOZ	Oddzial Chirurgii Naczyniowej al. Krasnicka 100	20-718	Lublin	POLAND
37	Clinical Emergency County Hospital	Diabetes Center and Clinic Clinicilor str. 2-4	400006	Cluj-Napoca	ROMANIA
38	Clinical Emergency County Hospital	Dermatology Clinic Clinicilor str. 3-5	400006	Cluj-Napoca	ROMANIA

39	Fundeni Clinical Institute	General Surgery and Hepatic Transplantation Clinic 258 Fundeni Street, District 2	022328	Bucharest	ROMANIA
40	"Sfantul Spiridon" Emergency Clinical County Hospital	Diabetes Center and Clinic 1, Independentei blvd	700106	Iasi	ROMANIA
41	Spitatul Universitar de Urgenta Bucaresti	III Internal Medicine Clinic Diabetes Dept. Splaiul Independentei str. 169 District 5	050099	Bucharest	ROMANIA
42	Bureau of Medical Social Expertise	Dept. of Infected Surgery and Infected Diabetic Foot Susanina str. 3	127486	Moscow	RUSSIA
43	Central Clinical Hospital no 1 OAO RZD	Surgery Dept. Volokolamskoe Shosse 84	123567	Moscow	RUSSIA
44	City Hospital No 14	Dept. of Infected Surgery Kosinova str.19	198099	St. Petersburg	RUSSIA
45	City Hospital No 14	Dept. of Infected Surgery Kosinova str.19	198099	St. Petersburg	RUSSIA
46	Clinical Hospital for Emergency Care n.a. N.V.Solovyov	Surgery Dept. Zagorodny Sad str. 11	150003	Yaroslavl	RUSSIA
47	Municipal Clinical Hospital N50	Surgery Department Voucheticha 21	125206	Moscow	RUSSIA

48	Smolensk Medical Academy	Surgery Dept. Krupskay str. 28	214019	Smolensk	RUSSIA
49	Clinical Projects Research SA	42 Russell Street	6850	Worcester	SOUTH AFRICA
50	Pretoria Academic Hospital Ethics Committee	H.W. Snyman Building Level 2/34 Prinshof / Gazena	0084	Pretoria	SOUTH AFRICA
51	Sunninghill Hospital	c/o Nanuke & Witkoppen Drive Sunninghill	2157	Johannesburg	SOUTH AFRICA
52	Tiervlei Trial Centre	Karl-Bremer Hospital Ward A1 Mike Pienaar Blvd Belville	7531	Cape Town	SOUTH AFRICA
53	University of Cape Town	Anzio Road Observatory	7925	Cape Town	SOUTH AFRICA
54	Hospital General Universitario Gregorio Marañón	Servicio de Cirugía, Area 2200 C/ Dr. Esquerdo, 46	28007	Madrid	SPAIN
55	Central City Clinical Hospital	Dept. of Hospital Surgery No 2 Shelkovichnaya str. 39/1	01023	Kiev	UKRAINE
56	City Hospital no 12	Podvysotskogo str. 4a	01103	Kiev	UKRAINE
57	Lviv Emergency Hospital	Mykolaychuka str. 9	79659	Lviv	UKRAINE
58	Main Military Clinical Hospital	Gospitalna str. 18	01133	Kiev	UKRAINE
59	Regional Clinical Hospital	Zabolotnogo str. 26	65065	Odessa	UKRAINE
60	Regional Clinical Hospital	Dept of General Surgery Fedkovyvha str 91	76000	Ivano-Frankivsk	UKRAINE
61	Raigmore Hospital	Perth Road	IV2 3UJ	Inverness	UNITED KINGDOM

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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