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.

Webposting Clinical Trial Results Synopsis

Study Sponsor:	Bayer Healthcare AG	
Study Number:	11881	NCT00493038
Study Phase:	Phase 4	
Study Title:	Prospective, multicenter, randomized, double blind, parallel arm study to evaluate the efficacy and safety of moxifloxacin 400 mg OD for 7 days versus amoxicilline/clavulanate 1000 mg TID for 10 days in the treatment of Acute Bacterial Rhino Sinusitis (Title as per *Protocol Amendment 1*)	
Therapeutic Area:	Acute bacterial rhinosinusitis (ABRS)	
Name of Test Product:	Avelox® / Italy: Avalox®	
Active Ingredient:	Moxifloxacin (BAY 12-8039)	
Dosage:	Administered daily (OD) as single 400 mg tablet	
Reference Therapy:	Amoxicillin/clavulanate	
Dosage:	Administered as 1000 mg tablets every 8 hours (three times daily [TID])	
Placebo:	Moxifloxacin matching placebo tablets, amoxicillin/clavulanate matching placebo tablets	
Route of Administration:	Both the active drugs and the matching placebos were supplied in tablet form for oral administration.	
Treatment Duration:	10 days in total: moxifloxacin for 7 days (active), amoxicillin/clavulanate for 10 days (active)	
Study Period:	Date of first subjects' first visit:	13 February 2006
	Date of last subjects' last visit:	21 January 2008
Methodology:	• Multi-center • Randomized • Double-blind • Double-dummy • Parallel-group • Active controlled • Treatment arms: Test product: moxifloxacin 400 mg tablets OD for 7 days and amoxicillin/clavulanate 1000 mg matching placebo tablets TID for 10 days Reference therapy (comparator): amoxicillin/clavulanate 1000 mg tablets TID for 10 days and moxifloxacin 400 mg matching placebo tablets OD for 7 days (as per *Protocol Amendment 1*)	
Study Site:	34 active otorhinolaryngology centers in Italy	
Main Inclusion Criteria:	Age ≥18 years; clinical diagnosis of acute rhinosinusitis with signs and symptoms present for ≥5 to 7 days but <28 days. Two major symptoms or *one major and at least two minor symptoms (Protocol Amendment 1)* required. Major symptoms: purulent anterior or posterior nasal discharge, unilateral moderate or severe facial pain or malar tenderness, nasal obstruction or congestion. Minor symptoms: cough, headache, hyposmia/anosmia, fever oral ≥38.0°C / tympanic ≥38.5°C.	

Study Objectives:	Overall: To compare the efficacy and safety of moxifloxacin 400 mg given for 7 days with amoxicillin/clavulanate 1000 mg TID given for 10 days (as per *Protocol Amendment 1*) in the treatment of adult subjects with ABRS Primary: To determine the clinical response at the test of cure (TOC), within a time frame from Day 1 to 3 post therapy Secondary: To determine the clinical response at follow-up (FU). Objectives of a microbiological sub-study: To evaluate the microbiological efficacy of moxifloxacin and amoxicillin/clavulanate at TOC and FU in the microbiologically valid population (subgroup with positive baseline culture from middle meatus specimen), within a time frame from Day 1 to 3 post therapy and from FU Day 24 to 30 post therapy.
Evaluation Criteria:	Efficacy (Primary): • Clinical response at the TOC, within a time frame from Day 1 to 3 post therapy, in subjects valid for efficacy (Per Protocol Analysis Set), with outcome "clinical cure" defined as resolution or improvement in the signs and symptoms such that no further therapy (ie, antimicrobial, steroid or irrigation) was required. Efficacy (Secondary): • Clinical response at TOC in subjects valid for intent-to-treat analysis (Full Analysis Set) • Clinical response at FU in subjects valid for efficacy (Per Protocol Analysis Set) • Clinical response at FU in subjects valid for intent-to-treat analysis (Full Analysis Set) • Microbiological response at TOC and at FU in microbiologically valid subjects and in subjects valid for intent-to-treat analysis with causative organisms Safety: Treatment-emergent adverse events, clinical laboratory, physical examination including vital signs in subjects valid for safety analysis (Full Analysis Set).
Statistical Methods:	Efficacy (Primary): All statistical tests were 2-sided and performed at the 0.05 significance level. The primary efficacy variable was clinical response at the TOC visit, where failures were carried forward (ie, successes were defined as subjects with clinical cure at TOC; failures were subjects with failure at the TOC visit or improvement or failure at TOC). For success rates, a 95% confidence interval (CI) of the difference between the two clinical success rates (moxifloxacin minus comparator) was calculated using Mantel-Haenszel weights based on centers. If the lower limit of this 95% CI was greater than -15%, it was proven that treatment with moxifloxacin is clinically not less effective than the comparator treatment regimen. If the lower limit of this 95% CI was greater than 0, superiority of treatment with moxifloxacin was proven. Efficacy (Secondary): For secondary efficacy analyses, clinical and bacteriological responses at TOC and FU visits were analyzed exploratively in the same way as the primary efficacy variable. Safety: Treatment groups were compared with respect to incidence rates of treatment-emergent adverse events (MedDRA Version 10.1), laboratory abnormalities, and vital sign abnormalities.
Number of Subjects:	594 subjects were planned to be enrolled (as per *Protocol Amendment 1*). The study was prematurely terminated due to slow enrollment beyond the planned study timelines. 293 subjects were randomized (147 to moxifloxacin, 146 to comparator), 249 subjects completed the TOC visit (123 receiving moxifloxacin, 126 receiving comparator), and 248 subjects completed the FU visit (122 receiving moxifloxacin, 126 receiving comparator).

Results Summary — Subject Disposition and Baseline

In the Per Protocol Analysis Set, there were 126 (50.2%) women (66 receiving moxifloxacin, 60 receiving comparator) and 125 (49.8%) men (55 receiving moxifloxacin, 70 receiving comparator) at baseline. Mean age was 40.9 years (41.6 years in the

moxifloxacin group, 40.2 years in the comparator group). 66 subjects (26.3%) had a history of prior episodes of ABRS, 36 (29.8%) receiving moxifloxacin and 30 (23.1%) receiving comparator.

Results Summary — Efficacy

Primary efficacy:

In the Per Protocol Analysis Set, the clinical response at TOC was assessed as a clinical cure in 119 of 121 subjects receiving moxifloxacin and in 125 of 130 subjects receiving amoxicillin/clavulanate. The rates of clinical cure were thus 98.3% for moxifloxacin and 96.2% for comparator regimen. The statistical hypothesis of inferiority of moxifloxacin to the comparator regimen could be rejected at the 2.5% level (Table 1).

Table 1: Summary statistics [n (%)] on clinical response (Per Protocol Analysis Set)

Clinical response	Moxifloxacin	Amoxicillin/ clavulanate	Difference	
			Estimate	[95% CI]
Clinical cure at TOC (primary endpoint)	119/121 (98.3)	125/130 (96.2)	+2.1%	[-1.9%; +6.2%]

TOC: test of cure on Day +1 to +3 post therapy (corresponding to 11 to 13 days after the start of therapy)

Secondary efficacy:

At the TOC, in the Full Analysis Set, the rates of clinical cure were 88.3% for moxifloxacin and 89.4% for comparator treatment. At the FU, the rates of continued clinical cure in the Per Protocol Analysis Set were 95.8% for moxifloxacin and 94.4% for comparator treatment (Table 2).

Table 2: Summary statistics [n (%)] on clinical response

Clinical response	Moxifloxacin	Amoxicillin/ clavulanate	Difference	
			Estimate	[95% CI]
Clinical cure at TOC (Full Analysis Set)	128/145 (88.3)	127/142 (89.1)	-0.5%	[-7.9%; +6.8%]
Continued clinical cure at FU (Per Protocol Analysis Set)	108/113 (95.8)	117/124 (94.4)	+1.7%	[-3.8%; +7.1%]
Continued clinical cure at FU (Full Analysis Set)	117/145 (80.7)	119/142 (83.8)	-1.8%	[-10.7%; +7.1%]

TOC: test of cure on Day +1 to +3 post therapy (corresponding to 11 to 13 days after the start of therapy);

FU: follow-up on Day +24 to +30 post therapy; CI: confidence interval

Missing/indeterminates treated as non-successes in the Full Analysis Set, omitted in the Per Protocol Analysis Set.

Forty-seven (47) subjects were microbiologically valid. At TOC, all moxifloxacin subjects (21/21, 100%) were bacteriological successes; the bacteriological success rate in the amoxicillin/clavulanate group was 96.2% (25/26) as one subject with a *Moraxella catarrhalis* isolate was a failure. Bacteriological success rates at FU were 90.5% (19/21) and 88.5% (23/26) in the moxifloxacin and amoxicillin/clavulanate groups, respectively.

Fifty-three (53) subjects comprised the intent-to-treat population with causative organisms. Bacteriological success rates at TOC in this population were 92.3% (24/26) and 92.6% (25/27) in moxifloxacin- and amoxicillin/clavulanate-treated subjects, respectively. Rates at FU were 84.6% (22/26) for moxifloxacin-treated subjects and 85.2% (23/27) for subjects in the amoxicillin/clavulanate group.

To summarize the primary results, moxifloxacin 400 mg OD was no less effective than amoxicillin/clavulanate 1000 mg TID in achieving clinical cure of ABRS.

Results Summary — Safety

Exposure to study drug is given for the Full Analysis Set. The mean (median) number of days on study medication was 9.3 (10) days in the moxifloxacin group and 9.6 (10) days in the amoxicillin/clavulanate group. The mean (± SD) number of doses taken was 34.3 (± 7.7) in the moxifloxacin group and 35.3 (± 6.8) in the amoxicillin/clavulanate group.

Treatment emergent adverse events appeared to be more frequent in the moxifloxacin group (18.6% of subjects) than in the amoxicillin/clavulanate group (12.7%) and were considered drug-related in more subjects receiving moxifloxacin (16.6%) than in those receiving amoxicillin/clavulanate (7.0%) (Table 3). The most common treatment emergent adverse events (MedDRA preferred term) were nausea (moxifloxacin 7 subjects [4.8%], comparator 2 subjects [1.4%]) and diarrhea (moxifloxacin 6 subjects [4.1%], comparator 4 subjects [2.8%]). Both nausea and diarrhea were considered to be drug-related in each of these subjects.

Serious adverse events were reported for 2 subjects (Table 3). Subject 11881-018-008 treated with moxifloxacin was hospitalized for moderate chest pain, which resolved within less than a week. The event had started 12 days after end of treatment and was considered not related to study drug. Subject 11881-028-001 treated with amoxicillin/clavulanate was hospitalized for severe sinusitis and underwent surgery. The event was considered not related to study drug.

Table 3: Incidence rates of adverse events (Full Analysis Set)

Number (%) of subjects with event	Moxifloxacin (N = 145)	Amoxicillin/clavulanate (N = 142)
Treatment emergent adverse events	27 (18.6)	18 (12.7)
Drug-related treatment emergent adverse events	24 (16.6)	10 (7.0)
Treatment emergent adverse events leading to discontinuation	8 (5.5)	4 (2.8)
Treatment emergent serious adverse events	1 (0.7)	1 (0.7)
Drug-related treatment emergent serious adverse events	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)

There were two types of adverse events that required premature discontinuation in more than 1% of subjects per treatment, notably diarrhea in 2 subjects (1.4%) receiving moxifloxacin and vertigo also in 2 subjects (1.4%) receiving moxifloxacin.

There were no clinically important observations regarding laboratory parameters or vital signs at any time point.

Conclusion(s)

The results of the study provide evidence that moxifloxacin 400 mg PO od for 7 days is not clinically inferior to amoxicillin/clavulanate 1000 mg TID for 10 days in terms of clinical response in the treatment of acute bacterial rhinosinusitis (ABRS). One subject in each treatment group experienced a serious adverse event considered not related to study drug. The adverse event profile of moxifloxacin, based on this study, is consistent with that currently presented in the Core Company Data Sheet.

Publication(s)

None

Updated: 13 July 2011

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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