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Moxifloxacin Safety
An Analysis of 14 Years of Clinical Data

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Abstract

Background: Moxifloxacin, a fluoroquinolone antibiotic, is used for the treatment of respiratory tract, pelvic inflammatory disease, skin, and intra-abdominal infections. Its safety profile is considered favorable in most reviews but has been challenged with respect to rare but potentially fatal toxicities (e.g. hepatic, cardiac, or skin reactions).

Objective: To analyze and compare the safety profile of moxifloxacin versus comparators in the entire clinical database of the manufacturer.

Setting: Data on the valid-for-safety population from phase II–IV actively controlled studies (performed between 1996 and 2010) were analyzed. Studies were either double blind (n = 22 369) or open label (n = 7635) and included patients with indications that have been approved in at least one country [acute bacterial sinusitis, acute exacerbation of chronic bronchitis, community-acquired pneumonia, uncomplicated pelvic inflammatory disease, complicated and uncomplicated skin and skin structure infections, and complicated intra-abdominal infections] (n = 27 824) and patients with other indications (n = 2180), using the recommended daily dose (400 mg) and route of administration (oral, intravenous/oral, intravenous only). The analysis included patients at risk (age ≥65 years, diabetes mellitus, renal impairment, hepatic impairment, cardiac disorders, or body mass index <18 kg/m^2). Patients with known contraindications were excluded from enrollment by study protocol design, but any patient having entered a study, even if inappropriately, was included in the analysis.

Main Outcome Measure: Crude incidences and relative risk estimates (Mantel–Haenszel analysis) of patients with any adverse event (AE), adverse drug reaction (ADR), serious AE (SAE), serious ADR (SADR), treatment discontinuation due to an AE or ADR, and fatal outcomes related to an AE or ADR.

Results: Overall incidence rates of AEs were globally similar in the moxifloxacin and comparator groups. By filtering the data for differences in disfavor of moxifloxacin (i) at ≥2.5% for events with an incidence ≥2.5% or

at ≥2-fold for events with an incidence <2.5% in one or both groups and (ii) affecting ≥10 patients in either group, we observed slightly more (i) AEs in double-blind intravenous-only and open-label oral studies, (ii) SAEs in double-blind intravenous-only studies, (iii) ADRs and SADRs in open-label oral studies, (iv) SADRs in open-label intravenous/oral studies, and (v) premature discontinuation due to AEs in open-label intravenous-only studies. The actual numbers of SADRs (in all studies) were small, with clinically relevant differences noted only in intravenous/oral studies and mainly driven by 'gastrointestinal disorders' (15 versus 7 patients) and 'changes observed during investigations' (23 versus 7 patients [asymptomatic QT prolongation: 11 versus 4 patients in double-blind studies]). Analysis by comparator (including another fluoroquinolone) did not reveal medically relevant differences, even in patients at risk. Incidence rates of hepatic disorders, tendon disorders, clinical surrogates of QT prolongation, serious cutaneous reactions, and *Clostridium difficile*-associated diarrhea were similar with moxifloxacin and comparators.

Conclusion: The safety of moxifloxacin is essentially comparable to that of standard therapies for patients receiving the currently registered dosage and for whom contraindications and precautions of use (as in the product label) are taken into account.

Introduction

Moxifloxacin is approved for oral and intravenous administration in 123 and 108 countries, respectively, as a once-daily 400 mg antibiotic for the treatment of respiratory tract infections (community-acquired pneumonia [CAP], acute exacerbations of chronic bronchitis [AECB], and acute bacterial sinusitis [ABS]) and, depending on the country, pelvic inflammatory disease [PID], complicated and uncomplicated skin and skin structure infections [cSSSIs/uSSSIs], and complicated intra-abdominal infections [cIAIs]. An estimated 140 million prescriptions have been issued for moxifloxacin worldwide, and the drug is included as an effective alternative in guidelines and/or recommendations for each of these indications.[1-10]

The clinical efficacy of moxifloxacin has been unambiguously demonstrated,[11-30] and its safety profile has been analyzed periodically on the basis of pre-marketing studies,[21,31-35] including populations with risk factors,[36,37] such as the elderly[38,39] and those with hepatic or renal insufficiency.[37,40] These data did not show significantly higher toxicity of moxifloxacin compared with commonly used antibiotics if the contraindications and precautions of use mentioned in the Summary of Product Characteristics[41-43] are taken into account. Post-marketing studies[44-53] have confirmed that moxifloxacin is generally well tolerated in medical practice, without new or unanticipated serious adverse events (SAEs) beyond those already established from controlled clinical studies.

The safety profile of moxifloxacin has nevertheless been questioned for two main reasons. First, a number of initially promising fluoroquinolones have been withdrawn (e.g. temafloxacin, trovafloxaxin, sparfloxacin, and gatifloxacin[54-58]) or not approved in Europe (e.g. garenoxacin and gemifloxacin), partly because of toxicity concerns,[59,60] creating suspicion about the whole class. Second, the safety profile of fluoroquinolones has been challenged by the regulatory authorities, triggering (i) for all approved drugs in the US, the inclusion of a 'black box warning' for

tendinitis;[41] and (ii) for moxifloxacin, the issue in European countries of 'Dear Healthcare Provider' letters[61] warning about rare but serious side effects related to hepatotoxicity and severe skin reactions, together with a statement by the European Medicines Agency that "due to safety concerns (hepatic, cardiac [in women and elderly patients], and intestinal problems), moxifloxacin should only be used when other antibiotics cannot be used or have stopped working",[62] with corresponding label changes throughout the European Union.[42,43]

The current paper presents an in-depth analysis of the safety profile of moxifloxacin, based on the manufacturer's clinical trial database comprising all actively controlled phase II–IV clinical trials. The objective of the analysis was to examine and compare the safety profile of moxifloxacin with those of the comparators that were all selected as reference therapies for the treatment of corresponding indications at the time the studies were designed.

Methods

Studies

The analysis comprised all double-blind and open-label actively controlled clinical trials included in the clinical trial database of moxifloxacin 400 mg once daily and performed by the manufacturer as part of the phase II–IV programs that were initiated and completed between 1996 and 2010, with the exception of one exploratory phase II study conducted in cirrhotic patients, most of them with Child–Pugh class C cirrhosis. All studies used the oral formulation (400 mg tablets), the 400 mg/250 mL solution for infusion formulation, or a sequence of intravenous and oral formulations. Forty-nine oral studies enrolled patients diagnosed with streptococcal pharyngitis (n = 1), ABS (n = 10), AECB (n = 17), CAP (n = 12), uSSSIs (n = 4), uncomplicated PID (uPID; n = 3), or uncomplicated (n = 3) or complicated (n = 1) urinary tract infection (UTI). Some patients could be enrolled in the same study looking at two different indications – for example, ABS and AECB, or AECB and CAP. Fifteen intravenous/oral studies enrolled patients with CAP (n = 7), cSSSIs (n = 3), cIAIs (n = 2), nosocomial pneumonia (n = 2), or lung abscess or aspiration pneumonia (n = 1). Four intravenous-only studies enrolled patients with CAP (n = 2), cIAIs (n = 2), or AECB (n = 1; this study also enrolled patients with CAP).

Patients

The studies were conducted in Europe, the Americas, the Middle East, Africa, and the Asia/Pacific region. Safety-valid patients were defined as those randomized within an actively controlled clinical trial, having received at least one dose of the study drug and having had at least one observation after initial drug intake. The following subgroups of patients with pre-existing risk factors were evaluated: elderly (age ≥65 years); diabetes mellitus (blood glucose level >200 mg/dL at baseline or at least one medical history finding coded to a preferred term [PT] with a primary path in the high-level term [HLT] diabetes [including subtypes]); renal impairment (serum creatinine ≥1.5 mg/dL for women and ≥1.8 mg/dL for men, or calculated creatinine clearance ≤89 mL/min and ≤59 mL/min for patients aged <65 and ≥65 years, respectively); hepatic impairment (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >3 × the upper limit of normal [ULN]; or alkaline phosphatase [ALP] >2 × ULN; or total bilirubin >2 × ULN and ALT or ALP >1 × ULN); cardiac disorders (at least one medical history finding coded to a cardiac PT in the Bayer MedDRA Query [BMQ] history of cardiac disease); and low body mass index (BMI) [<18 kg/m^2]. Patients with known contraindications, according to what was known or included in the labeling at the time of enrollment, were excluded from entering the study as per the study protocol design. Conversely, no patient entering a study and receiving one or more doses of moxifloxacin or a comparator was excluded from the analysis, even if found later to be among those who should have been prevented from enrollment.

Analyses

All patients valid for the safety analysis from trials with oral, intravenous, or sequential intra-

venous/oral moxifloxacin and active comparators that were available in the most recent database (data lock point: March 31, 2010) were included in the analysis. The analysis examined all treatment-emergent events (that is, any event occurring after the first dose of medication until the end of follow-up [typically 10–27 days following the last dose]). The planned treatment duration as per the protocols varied from 5 to 21 days according to the indication and/or disease severity, except in one study (treatment duration determined by the investigator).

An overall analysis of safety data was carried out to estimate differences in incidence rates of treatment-emergent adverse events (AEs), adverse drug reactions (ADRs), SAEs, serious ADRs (SADRs), premature discontinuations due to AEs, premature discontinuations due to ADRs, AEs with fatal outcome, and ADRs with fatal outcome. The Medical Dictionary for Regulatory Activities (MedDRA; http://www.meddramsso.com/ [version 13.0]) was used for coding the events. The assessment of causality and seriousness of AEs was made by the study investigators. The incidence rates for events are presented overall, by system organ class (SOC), or by PT within SOC. The analysis was extended by looking specifically for rare events known to be associated with the use of fluoroquinolones, as defined by Standard MedDRA Queries (SMQs)[63] and customized BMQs developed by medical and coding experts (see table SDC-I in the Supplemental Digital Content [SDC]; available online at http://links.adisonline.com/DRZ/A6). Descriptive statistical methods were used to analyze the demographic and safety data.[64] Incidence rates were calculated as crude rates. To compare the risk of a specific AE for moxifloxacin relative to a comparator, relative risk estimates (with corresponding 95% confidence intervals) were calculated by a Mantel–Haenszel analysis stratified by study,[65] utilizing a constant continuity correction term of 0.1 in case of zero cells. Because of the large number of comparisons (several outcome variables, various study pools, and a large number of subgroups), no detailed assessment or exploration of heterogeneity of relative risks across studies is provided. The analyses presented are exploratory in nature; confirmatory statistics were not carried out.

For the present reporting, filters were applied to highlight incidence rates and numerical differences between groups. These are explicitly stated in the titles and/or captions of each table or figure. Although somewhat arbitrary, these filters were always set at a low value and were conservative to avoid missing potentially important signals. Highlighted differences were interpreted on the basis of the actual number of patients involved in the comparison. Unless stated otherwise, data are presented overall for the double-blind and the open-label studies, but separate reporting is available in the SDC.

Results

Population and Comparator Antibiotics

Table I shows the number of patients valid for the safety analysis who received moxifloxacin (n = 14 981) or comparator treatment (n = 15 023) by the oral, intravenous, or intravenous/oral routes, stratified by study design (double blind or open label). Approximately 75% of patients were enrolled in the double-blind studies. The percentage of patients with intravenous and intravenous/oral (sequential) treatments (29%) is substantially higher than that currently seen in clinical practice but reflects the design of studies and the severity of the studied indications. The choice of comparator(s) and dosage is consistent with standard therapies for the respective indications at the time each study was conducted.

Demographics

Table II shows the demographics of the population analyzed (total = 30 004: see table SDC-II for stratification between double-blind and open-label studies). There was no meaningful difference between the patients receiving moxifloxacin and those receiving a comparator with respect to age, sex, BMI, race, indications, and pre-existing risk factors (renal or hepatic impairment, diabetes mellitus, cardiac disorders, or low BMI). Overall, the distribution of patients among the different indications mirrors the current prescribing patterns

Table I. Distribution of patients valid for the safety analysis, stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only) and by comparator

Study design and COMP	Treatment route [n]					
	PO [n = 21 298]		IV/PO [n = 6846]		IV only [n = 1860]	
	MXF [n = 10 613]	COMP [n = 10 685]	MXF [n = 3431]	COMP [n = 3415]	MXF [n = 937]	COMP [n = 923]
Double-blind studies						
β-lactam	2391	2104	1077	1034	408	390
β-lactam + macrolide	274	155	0	0	0	0
Fluoroquinolone	2246	2287[a]	444	457[b]	0	0
Macrolide	3659	2929	0	0	0	0
Other	1230	1168[c]	368	365[d]	180	181[e]
Total	*8822*[f]	*8643*	*1889*	*1856*	*588*	*571*
Open-label studies						
β-lactam	1318	1301	554	547	0	0
β-lactam + macrolide	186	190	0	0	0	0
β-lactam ± macrolide	0	0	532	549	0	0
Fluoroquinolone	263	270[g]	0	0	349	352[g]
Macrolide	287	281	0	0	0	0
Other	0	0	456	463[h]	0	0
Total	*1791*[f]	*2042*	*1542*	*1559*	*349*	*352*

a Levofloxacin, ofloxacin, trovafloxacin.

b Levofloxacin, trovafloxacin.

c Ofloxacin + metronidazole (n = 363); levofloxacin + metronidazole (n = 230); doxycycline + metronidazole + ciprofloxacin (n = 326); cephalexin + metronidazole (n = 224); trimethoprim/sulfamethoxazole (n = 25).

d Ceftriaxone + levofloxacin.

e Ceftriaxone + metronidazole.

f The total number of MXF patients is not necessarily equal to the sum of all MXF patients over all drug classes, because some trials used more than one COMP, and the COMPs came from different drug classes. In this case, the MXF patients were included in all possible COMP subpools, but only once in the total pool.

g Levofloxacin.

h Ceftriaxone + metronidazole (n = 295); ceftriaxone ± azithromycin ± metronidazole (n = 168).

COMP = comparator; **IV** = intravenous; **MXF** = moxifloxacin; **PO** = oral.

and clinical usage.[19,29] The majority of patients receiving oral moxifloxacin were treated for respiratory tract infections,[66] whereas patients receiving intravenous or intravenous/oral therapy (i) were older; (ii) were predominantly treated for CAP, cIAI and cSSSI; and (iii) had a higher incidence of pre-existing risk factors (related to the severity of their infection and their age).

Overall Safety Data

Table III shows the summary of the safety data for all patients, subdivided between double-blind studies and open-label studies, respectively. As for any drug, a gradual decrease in the incidence of events was seen when looking from all AEs down to ADRs and further to SADRs. To help identify the highest incidence rates and imbalances between the treatment groups affecting a specific event, the data were filtered, and situations are highlighted where (i) there was a 2-fold difference between treatment arms for events with an incidence <2.5% in either of the treatment groups or a ≥2.5% difference between treatments for events with an incidence ≥2.5% in both groups and (ii) the number of patients experiencing an event was ≥10 in either treatment group. With these filters, the differences between moxifloxacin

Table II. Demographic parameters of the patients valid for the safety analysis, stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only). See table SDC-II or further stratification according to study design (double blind versus open label)

Parameter	Treatment route					
	PO [n = 21 298]		IV/PO [n = 6846]		IV [n = 1860]	
	MXF [n = 10 613]	COMP [n = 10 685]	MXF [n = 3431]	COMP [n = 3415]	MXF [n = 937]	COMP [n = 923]
Age [years]						
Mean ± SD	48.2 ± 18.0	48.0 ± 17.9	56.8 ± 19.1	56.1 ± 19.2	46.9 ± 17.1	47.1 ± 17.5
Median	47.0	47.0	58.0	58.0	47.0	47.0
Range	16.0–98.0	17.0–95.0	17.0–100.0	17.0–101.0	18.0–88.0	18.0–93.0
Sex [n (%)]						
Male	4840 (45.6)	4868 (45.6)	2082 (60.7)	2092 (61.3)	570 (60.8)	593 (64.2)
Female	5773 (54.4)	5817 (54.4)	1349 (39.3)	1323 (38.7)	367 (39.2)	330 (35.8)
BMI [kg/m^2]						
Mean ± SD	26.0 ± 5.9	25.9 ± 5.8	26.9 ± 6.6	26.7 ± 6.4	24.0 ± 4.4	23.9 ± 4.3
Median	24.9	25.0	25.8	25.7	23.4	23.4
Range	12.4–72.7	12.8–66.3	11.1–81.6	12.4–75.5	15.3–44.3	14.4–44.1
Race [n (%)]						
White	6848 (64.5)	6997 (65.5)	2281 (66.5)	2278 (66.7)	370 (39.5)	348 (37.7)
Asian	1134 (10.7)	1152 (10.8)	107 (3.1)	92 (2.7)	529 (56.5)	536 (58.1)
Black	1084 (10.2)	994 (9.3)	245 (7.1)	257 (7.5)	22 (2.3)	19 (2.1)
Others[a]	182 (1.7)	157 (1.5)	335 (9.8)	316 (9.2)	1 (0.1)	4 (0.4)
Missing[b]	1365 (12.9)	1385 (13.0)	463 (13.5)	472 (13.8)	15 (1.6)	16 (1.7)
Indications [n (%)]						
ABS	2331 (22.0)	2641 (24.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AECB	4029 (38.0)	3820 (35.8)	0 (0.0)	0 (0.0)	96 (10.2)	100 (10.8)
CAP	1790 (16.9)	1822 (17.1)	1511 (44.0)	1539 (45.1)	253 (27.0)	252 (27.3)
uPID	946 (8.9)	919 (8.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
uSSSI	587 (5.5)	582 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
cSSSI	0 (0.0)	0 (0.0)	1130 (32.9)	1077 (31.5)	0 (0.0)	0 (0.0)
cIAI	0 (0.0)	0 (0.0)	618 (18.0)	622 (18.2)	588 (62.8)	571 (61.9)
Others[c]	930 (8.8)	901 (8.4)	172 (5.0)	177 (5.2)	0 (0.0)	0 (0.0)
Pre-existing risk factors [n (%)][d]						
Age ≥65 years	2451 (23.1)	2403 (22.5)	1373 (40.0)	1334 (39.1)	170 (18.1)	191 (20.7)
Diabetes mellitus	777 (7.3)	717 (6.7)	926 (27.0)	917 (26.9)	80 (8.5)	72 (7.8)
Renal impairment	1283 (12.1)	1229 (11.5)	888 (25.9)	863 (25.3)	203 (21.7)	218 (23.6)
Hepatic impairment	146 (1.4)	163 (1.5)	183 (5.3)	196 (5.7)	46 (4.9)	46 (5.0)
Cardiac disorder	1476 (13.9)	1404 (13.1)	1167 (34.0)	1136 (33.3)	106 (11.3)	104 (11.3)
BMI <18 kg/m^2	318 (3.0)	365 (3.4)	116 (3.4)	115 (3.4)	45 (4.8)	53 (5.7)

a American Indian, Alaska native, or Hispanic.

b In some countries, for legal reasons, the patients' race was not documented.

c Complicated and uncomplicated urinary tract infection, streptococcal pharyngitis in PO studies, hospital-acquired pneumonia, aspiration pneumonia/lung abscess in IV/PO studies.

d See Methods for definition of each risk factor.

ABS = acute bacterial sinusitis; **AECB** = acute exacerbation of chronic bronchitis; **BMI** = body mass index; **CAP** = community-acquired pneumonia; **cIAI** = complicated intra-abdominal infection; **COMP** = comparator; **cSSSI** = complicated skin and skin structure infection; **IV** = intravenous; **MXF** = moxifloxacin; **PO** = oral; **SD** = standard deviation; **uPID** = uncomplicated pelvic inflammatory disease; **uSSSI** = uncomplicated skin and skin structure infection.

and comparators were related to (i) AEs and SAEs in the intravenous double-blind studies; and (ii) AEs, ADRs, and SADRs in the oral studies, SADRs in the intravenous/oral studies, and premature discontinuation due to AE in the intravenous open-label studies. Concerning SADRs reported in open-label oral and intravenous/oral studies, the numbers of patients with such events were small in each treatment group (moxifloxacin 12 [0.7%] versus comparator 5 [0.2%] in the oral studies; moxifloxacin 42 [2.7%] versus comparator 19 [1.2%] in the intravenous/oral studies). In the intravenous/oral studies, the difference in incidence rates (1.5%) was driven by gastrointestinal disorders (mostly diarrhea: 8 cases [0.5%] for moxifloxacin versus 1 case [<0.1%] for comparator) and results of investigations (10 cases [0.6%] for moxifloxacin versus 1 case [<0.1%] for comparator), including asymptomatic prolongation of the QT interval.

Table III. Summary of safety data for patients valid for the safety analysis, treated with moxifloxacin or a comparator and stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only) and by study design. An asterisk (*) indicates differences observed between treatment groups in disfavor of moxifloxacin that were ≥2.5% for events with an incidence ≥2.5% in both groups or ≥2-fold for events with an incidence <2.5% in one or both groups and for which the number of patients experiencing an event was ≥10 in either group

Study design and event	Treatment route [n (%)]					
Double-blind studies	PO [n = 17 465]		IV/PO [n = 3745]		IV [n = 1159]	
	MXF [n = 8822]	COMP [n = 8643]	MXF [n = 1889]	COMP [n = 1856]	MXF [n = 588]	COMP [n = 571]
Any AE	3782 (42.9)	3711 (42.9)	1202 (63.6)	1138 (61.3)	305 (51.9)*	253 (44.3)
Any ADR	2211 (25.1)	2026 (23.4)	455 (24.1)	439 (23.7)	85 (14.5)	83 (14.5)
SAE	318 (3.6)	316 (3.7)	315 (16.7)	282 (15.2)	74 (12.6)*	54 (9.5)
SADR	47 (0.5)	48 (0.6)	53 (2.8)	46 (2.5)	9 (1.5)	7 (1.2)
Premature discontinuation due to AE	366 (4.1)	337 (3.9)	144 (7.6)	131 (7.1)	16 (2.7)	9 (1.6)
Premature discontinuation due to ADR	261 (3.0)	251 (2.9)	74 (3.9)	63 (3.4)	4 (0.7)	4 (0.7)
AE with fatal outcome	28 (0.3)	36 (0.4)	66 (3.5)	54 (2.9)	21 (3.6)	13 (2.3)
ADR with fatal outcome[a,b,c]	3 (<0.1)	4 (<0.1)	3 (0.2)	3 (0.2)	0 (0.0)	1 (0.2)
Open-label studies	PO [n = 3833]		IV/PO [n = 3101]		IV [n = 701]	
	MXF [n = 1791]	COMP [n = 2042]	MXF [n = 1542]	COMP [n = 1559]	MXF [n = 349]	COMP [n = 352]
Any AE	764 (42.7)*	766 (37.5)	891 (57.8)	899 (57.7)	86 (24.6)	84 (23.9)
Any ADR	330 (18.4)*	325 (15.9)	348 (22.6)	315 (20.2)	49 (14.0)	50 (14.2)
SAE	104 (5.8)	96 (4.7)	280 (18.2)	245 (15.7)	0 (0.0)	1 (0.3)
SADR	12 (0.7)*	5 (0.2)	42 (2.7)*	19 (1.2)	0 (0.0)	0 (0.0)
Premature discontinuation due to AE	70 (3.9)	67 (3.3)	137 (8.9)	109 (7.0)	21 (6.0)*	11 (3.1)
Premature discontinuation due to ADR	51 (2.8)	49 (2.4)	66 (4.3)	54 (3.5)	17 (4.9)	9 (2.6)
AE with fatal outcome	10 (0.6)	15 (0.7)	64 (4.2)	80 (5.1)	0 (0.0)	0 (0.0)
ADR with fatal outcome[d]	0 (0.0)	0 (0.0)	1 (<0.1)	2 (0.1)	0 (0.0)	0 (0.0)

a In the PO studies, ADRs with fatal outcome in the MXF group were pneumonia (in 2 patients), *Clostridium difficile* colitis, and gastrointestinal hemorrhage; and ADRs with fatal outcome in the COMP group were acute renal failure, septicemia and respiratory arrest, viral pneumonia, and confusional state.

b In the IV/PO studies, ADRs with fatal outcome in the MXF group were acute renal failure and coagulopathy, multi-organ failure, and ventricular tachycardia (in the context of an acute myocardial infarction with respiratory failure); and ADRs with fatal outcome in the COMP group were cardio-respiratory arrest (in 2 patients), acute myocardial infarction, and acute respiratory failure.

c In the IV studies, ADR with fatal outcome was multi-organ failure in the COMP group.

d In the IV/PO studies, ADRs with fatal outcome in the MXF group were prothrombin time prolonged; and ADRs with fatal outcome in the COMP group were hepatitis (in the context of right ventricular failure, septic shock, and acute renal failure), and HIV infection.

ADR = adverse drug reaction; **AE** = adverse event; **COMP** = comparator; **HIV** = human immunodeficiency virus; **IV** = intravenous; **MXF** = moxifloxacin; **PO** = oral; **SADR** = serious ADR; **SAE** = serious AE.

Adverse Events (AEs)

Rates of treatment-emergent AEs (classified by MedDRA SOC and PTs) based on study design are presented in table SDC-III. Reported AEs with ≥5% incidence for patients in the double-blind studies included wound infections (moxifloxacin 11.7% versus comparator 7.4% [intravenous; corresponding mainly to patients treated for cIAIs and cSSSI]); diarrhea (moxifloxacin 6.2% versus comparator 4.9% [oral], moxifloxacin 8.1% versus comparator 7.9% [intravenous/oral], moxifloxacin 6.3% versus comparator 4.4% [intravenous]); nausea (moxifloxacin 7.9% versus comparator 6.2% [oral], moxifloxacin 7.3% versus comparator 6.3% [intravenous/oral], moxifloxacin 5.4% versus comparator 3.5% [intravenous]); headache (moxifloxacin 5.6% versus comparator 5.9% [intravenous/oral]); constipation (moxifloxacin 7.7% versus comparator 6.1% [intravenous/oral]); hypokalemia (moxifloxacin 5.1% versus comparator 5.0% [intravenous/oral]); and insomnia (moxifloxacin 7.2% versus comparator 7.2% [intravenous/oral]). Reported AEs with ≥5% incidence for patients enrolled in open-label studies included diarrhea (moxifloxacin 3.6% versus comparator 7.4% [oral], moxifloxacin 6.1% versus comparator 6.5% [intravenous/oral]) and nausea (moxifloxacin 5.1% versus comparator 2.4% [oral]).

Again limiting the description to situations where (i) there was a 2-fold difference between treatment arms for events with an incidence <2.5% in either of the treatment groups or a ≥2.5% difference between treatments for events with an incidence ≥2.5% in both groups, and (ii) the number of patients experiencing an event was ≥10 in either treatment group, the following differences were noted in disfavor of moxifloxacin in the double-blind studies: (i) for patients treated with oral therapy (moxifloxacin 8822 versus comparator 8643): hyperhidrosis (36 [0.4%] versus 16 [0.2%]), tremor (35 [0.4%] versus 15 [0.2%]), atrial fibrillation (16 [0.2%] versus 3 [<0.1%]), and pleural effusion (12 [0.1%] versus 5 [<0.1%]); (ii) for patients treated with intravenous/oral therapy (moxifloxacin 1889 versus comparator 1856): incision site pain (21 [1.1%] versus 10 [0.5%]), erythema (19 [1.0%] versus 6 [0.3%]), hypophosphatemia (16 [0.8%] versus 3 [0.2%]), depression (15 [0.8%] versus 4 [0.2%]), increase in white blood cell (WBC) count (11 [0.6%] versus 5 [0.3%]), and increase in lactate dehydrogenase (LDH; 10 [0.5%] versus 4 [0.2%]); and (iii) in patients treated by the intravenous route (moxifloxacin 588 versus comparator 571): insomnia (11 [1.9%] versus 3 [0.5%]) and abdominal pain (10 [1.7%] versus 1 [0.2%]). Conversely, and with the same double filter, the following AEs were more frequently reported in the comparator group: (i) in oral studies: dysgeusia (moxifloxacin 74 [0.8%] versus comparator 179 [2.1%]), increase in gammaglutamyl transferase (GGT; moxifloxacin 20 [0.2%] versus comparator 41 [0.5%]), muscle spasms (moxifloxacin 12 [0.1%] versus comparator 25 [0.3%]), and myocardial infarction (moxifloxacin 2 [<0.1%] versus comparator 12 [0.1%]); and (ii) in intravenous/oral studies: cough (moxifloxacin 7 [0.4%] versus comparator 15 [0.8%]), myocardial infarction (moxifloxacin 5 [0.3%] versus comparator 10 [0.5%]), musculoskeletal pain (moxifloxacin 3 [0.2%] versus comparator 10 [0.5%]), and leukocytosis (moxifloxacin 2 [0.1%] versus comparator 10 [0.5%]).

In the open-label studies, the most common AEs in disfavor of moxifloxacin were nausea (in oral studies: moxifloxacin 91 [5.1%] versus comparator 50 [2.4%]) and dizziness (in oral studies: moxifloxacin 45 [2.5%] versus comparator 9 [0.4%]; in intravenous/oral studies: moxifloxacin 26 [1.7%] versus comparator 13 [0.8%]), and the most common AE in disfavor of the comparator was diarrhea (in oral studies: moxifloxacin 65 [3.6%] versus comparator 152 [7.4%]).

Adverse Drug Reactions (ADRs)

ADRs occurring in at least 0.5% of patients in either treatment group are shown in table IV. In the oral population enrolled in double-blind studies, the most common ADRs were nausea (moxifloxacin 602 [6.8%] versus comparator 457 [5.3%]), diarrhea (moxifloxacin 432 [4.9%] versus comparator 334 [3.9%]), dizziness (moxifloxacin 247 [2.8%] versus comparator 198 [2.3%]), headache (moxifloxacin 165 [1.9%] versus comparator 177 [2.0%]), and vomiting (moxifloxacin 162 [1.8%] versus comparator 150 [1.7%]). Only dysgeusia

Table IV. Adverse drug reactions occurring in either treatment group in ≥0.5% of patients valid for the safety analysis, treated with moxifloxacin or a comparator and stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only) and by study design (double blind, open label). Numbers in bold italic text correspond to events with an incidence ≥5% in either treatment group. A single asterisk (*) indicates differences observed between groups that were ≥2.5% for events with an incidence ≥2.5% in both groups or ≥2-fold for events with an incidence <2.5% in one or both groups (calculations were made using the number of patients [no rounding]; in the event of a null value for one treatment, only situations where ≥2 cases were observed in the other treatment group are indicated); the symbol is placed to the right of the value observed for the drug in disfavor. A double asterisk (**) indicates differences observed between treatment groups according to the same rule and where the number of patients experiencing an event was ≥10 in either group; the symbols are placed to the right of the value observed for the drug in disfavor

Study design, system organ class, and ADR	Treatment route [n (%)]					
Double-blind studies	PO		IV/PO		IV	
	MXF [n = 8822]	COMP [n = 8643]	MXF [n = 1889]	COMP [n = 1856]	MXF [n = 588]	COMP [n = 571]
Cardiac disorders						
Atrial fibrillation	2 (<0.1)*	0 (0.0)	0 (0.0)	4 (0.2)*	0 (0.0)	4 (0.7)*
Gastrointestinal disorders						
Abdominal discomfort	59 (0.7)	44 (0.5)	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)
Abdominal pain	68 (0.8)	64 (0.7)	6 (0.3)	6 (0.3)	0 (0.0)	0 (0.0)
Abdominal pain upper	81 (0.9)	85 (1.0)	3 (0.2)	2 (0.1)	0 (0.0)	0 (0.0)
Constipation	28 (0.3)	30 (0.3)	16 (0.8)	12 (0.6)	0 (0.0)	0 (0.0)
Diarrhea	432 (4.9)	334 (3.9)	***96 (5.1)***	***95 (5.1)***	7 (1.2)	7 (1.2)
Dry mouth	56 (0.6)	49 (0.6)	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)
Dyspepsia	65 (0.7)	58 (0.7)	10 (0.5)	6 (0.3)	0 (0.0)	0 (0.0)
Nausea	***602 (6.8)***	***457 (5.3)***	46 (2.4)	42 (2.3)	12 (2.0)**	3 (0.5)
Vomiting	162 (1.8)	150 (1.7)	13 (0.7)	26 (1.4)**	4 (0.7)*	1 (0.2)
General disorders and administration site conditions						
Injection site pain	0 (0.0)	0 (0.0)	7 (0.4)	10 (0.5)	0 (0.0)	0 (0.0)
Infections and infestations						
Clostridial infection[a]	1 (<0.1)	3 (<0.1)*	9 (0.5)	13 (0.7)	1 (0.2)	1 (0.2)
Oral candidiasis	16 (0.2)	21 (0.2)	17 (0.9)	16 (0.9)	0 (0.0)	0 (0.0)
Vulvovaginal mycotic infection	36 (0.4)	37 (0.4)	7 (0.4)	11 (0.6)	0 (0.0)	0 (0.0)
Investigations						
Alanine aminotransferase increased	43 (0.5)	42 (0.5)	17 (0.9)	22 (1.2)	11 (1.9)	9 (1.6)
Aspartate aminotransferase increased	21 (0.2)	26 (0.3)	13 (0.7)	19 (1.0)	7 (1.2)	7 (1.2)
Blood alkaline phosphatase increased	8 (<0.1)	15 (0.2)	7 (0.4)	8 (0.4)	3 (0.5)	3 (0.5)
Blood amylase increased	3 (<0.1)	5 (<0.1)	4 (0.2)	2 (0.1)	6 (1.0)	8 (1.4)
ECG QT prolonged	4 (<0.1)*	1 (<0.1)	18 (1.0)	12 (0.6)	0 (0.0)	0 (0.0)
Gammaglutamyl transferase increased	11 (0.1)	30 (0.3)**	16 (0.8)	18 (1.0)	13 (2.2)	18 (3.2)
Hepatic enzyme increased	16 (0.2)	17 (0.2)	6 (0.3)*	2 (0.1)	5 (0.9)	5 (0.9)
Lipase increased	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	14 (2.4)	18 (3.2)
Nervous system disorders						
Dizziness	247 (2.8)	198 (2.3)	14 (0.7)	15 (0.8)	3 (0.5)*	0 (0.0)
Dysgeusia	66 (0.7)	171 (2.0)**	3 (0.2)	4 (0.2)	0 (0.0)	0 (0.0)
Headache	165 (1.9)	177 (2.0)	17 (0.9)	30 (1.6)	1 (0.2)	0 (0.0)
Psychiatric disorders						
Insomnia	31 (0.4)	58 (0.7)	12 (0.6)	10 (0.5)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders						
Dermatitis allergic	5 (<0.1)	6 (<0.1)	2 (0.1)	2 (0.1)	3 (0.5)*	0 (0.0)

Continued next page

Table IV. Contd

Study design, system organ class, and ADR	Treatment route [n (%)]					
Double-blind studies	PO		IV/PO		IV	
	MXF [n = 8822]	COMP [n = 8643]	MXF [n = 1889]	COMP [n = 1856]	MXF [n = 588]	COMP [n = 571]
Pruritus	32 (0.4)	43 (0.5)	11 (0.6)	15 (0.8)	0 (0.0)	0 (0.0)
Rash	33 (0.4)	41 (0.5)	13 (0.7)	16 (0.9)	0 (0.0)	3 (0.5)*
Vascular disorders						
Phlebitis	0 (0.0)	0 (0.0)	9 (0.5)	8 (0.4)	6 (1.0)	5 (0.9)
Open-label studies	PO		IV/PO		IV	
	MXF [n = 1791]	COMP [n = 2042]	MXF [n = 1542]	COMP [n = 1559]	MXF [n = 349]	COMP [n = 352]
Blood and lymphatic disorders						
Thrombocytosis	0 (0.0)	0 (0.0)	9 (0.6)	6 (0.4)	0 (0.0)	0 (0.0)
Gastrointestinal disorders						
Abdominal pain	13 (0.7)	14 (0.7)	7 (0.5)*	2 (0.1)	0 (0.0)	1 (0.3)
Abdominal pain upper	23 (1.3)	20 (1.0)	5 (0.3)	10 (0.6)	0 (0.0)	0 (0.0)
Diarrhea	54 (3.0)	***141 (6.9)*****	61 (4.0)	60 (3.8)	0 (0.0)	2 (0.6)*
Dyspepsia	9 (0.5)	8 (0.4)	3 (0.2)*	1 (<0.1)	0 (0.0)	0 (0.0)
Nausea	77 (4.3)	44 (2.2)	30 (1.9)	30 (1.9)	5 (1.4)*	2 (0.6)
Vomiting	20 (1.1)	14 (0.7)	16 (1.0)	26 (1.7)	1 (0.3)	1 (0.3)
Hepatobiliary disorders						
Hepatic function abnormal	0 (0.0)	1 (<0.1)	7 (0.5)*	2 (0.1)	7 (2.0)	4 (1.1)
Investigations						
Alanine aminotransferase increased	4 (0.2)*	2 (<0.1)	33 (2.1)	33 (2.1)	9 (2.6)	8 (2.3)
Aspartate aminotransferase increased	2 (0.1)	2 (<0.1)	26 (1.7)	22 (1.4)	4 (1.1)*	1 (0.3)
Blood alkaline phosphatase increased	3 (0.2)*	1 (<0.1)	9 (0.6)	8 (0.5)	0 (0.0)	0 (0.0)
Blood lactate dehydrogenase decreased	2 (0.1)*	1 (<0.1)	6 (0.4)	5 (0.3)	2 (0.6)*	1 (0.3)
Blood triglycerides increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	4 (1.1)*
Blood urea increased	1 (<0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	2 (0.6)*
ECG QT prolonged	0 (0.0)	0 (0.0)	19 (1.2)**	3 (0.2)	2 (0.6)*	0 (0.0)
Gammaglutamyl transferase increased	2 (0.1)*	0 (0.0)	23 (1.5)	27 (1.7)	0 (0.0)	2 (0.6)*
Hepatic enzyme increased	0 (0.0)	0 (0.0)	15 (1.0)	21 (1.3)	0 (0.0)	1 (0.3)
Transaminases increased	0 (0.0)	1 (<0.1)	7 (0.5)*	2 (0.1)	0 (0.0)	2 (0.6)*
White blood cell count decreased	2 (0.1)*	1 (<0.1)	0 (0.0)	0 (0.0)	1 (0.3)	4 (1.1)*
Nervous system disorders						
Dizziness	30 (1.7)**	4 (0.2)	10 (0.6)**	2 (0.1)	6 (1.7)	6 (1.7)
Dysgeusia	13 (0.7)**	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	15 (0.8)	15 (0.7)	12 (0.8)	10 (0.6)	1 (0.3)	2 (0.6)
Somnolence	10 (0.6)**	2 (<0.1)	2 (0.1)*	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders						
Dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)*
Erythema	0 (0.0)	0 (0.0)	4 (0.3)*	0 (0.0)	2 (0.6)*	0 (0.0)
Rash	16 (0.9)**	8 (0.4)	8 (0.5)	6 (0.4)	8 (2.3)*	3 (0.9)
Skin edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)*	0 (0.0)
Vascular disorders						
Phlebitis	0 (0.0)	1 (<0.1)	14 (0.9)	28 (1.8)	4 (1.1)*	1 (0.3)

a Includes clostridial infection, *Clostridium* colitis, and *Clostridium difficile* colitis.

ADR = adverse drug reaction; **COMP** = comparator; **ECG** = electrocardiogram; **IV** = intravenous; **MXF** = moxifloxacin; **PO** = oral.

(moxifloxacin 66 [0.7%] versus comparator 171 [2.0%]) and increased GGT (moxifloxacin 11 [0.1%] versus comparator 30 [0.3%]) met the criteria set by the double filter used in table III. In the double-blind intravenous/oral population, diarrhea was the most common ADR (moxifloxacin 96 [5.1%] versus comparator 95 [5.1%]). Differences affected fewer than 10 patients in each treatment group, except for vomiting (moxifloxacin 13 [0.7%] versus comparator 26 [1.4%]). In the double-blind intravenous population, increased lipase (moxifloxacin 14 [2.4%] versus comparator 18 [3.2%]) and increased GGT (moxifloxacin 13 [2.2%] versus comparator 18 [3.2%]) were the most common ADRs, and only nausea showed a difference in disfavor of moxifloxacin versus comparator (12 [2.0%] versus 3 [0.5%], respectively) according to the double filter. In the open-label oral studies, nausea (moxifloxacin 77 [4.3%] versus comparator 44 [2.2%]) and diarrhea (moxifloxacin 54 [3.0%] versus comparator 141 [6.9%]) were again the most common ADRs across therapy arms, followed by dizziness (moxifloxacin 30 [1.7%] versus comparator 4 [0.2%]), upper abdominal pain (moxifloxacin 23 [1.3%] versus comparator 20 [1.0%]), and vomiting (moxifloxacin 20 [1.1%] versus comparator 14 [0.7%]), all experienced by >1% of patients in the moxifloxacin arm. Application of the double filter to the open-label oral population showed that diarrhea was more frequent with comparators (moxifloxacin 54 [3.0%] versus comparator 141 [6.9%]), whereas dizziness (moxifloxacin 30 [1.7%] versus comparator 4 [0.2%]), rash (moxifloxacin 16 [0.9%] versus comparator 8 [0.4%]), dysgeusia (moxifloxacin 13 [0.7%] versus comparator 2 [<0.1%]), and somnolence (moxifloxacin 10 [0.6%] versus comparator 2 [<0.1%]) were more frequent with moxifloxacin. In the open-label intravenous/oral population, diarrhea was the most common ADR for both moxifloxacin and comparator (61 [4.0%] and 60 [3.8%], respectively). Differences in disfavor of moxifloxacin versus comparator that met the double filter criteria concerned QT prolongation (moxifloxacin 19 [1.2%] versus comparator 3 [0.2%]) and dizziness (moxifloxacin 10 [0.6%] versus comparator 2 [0.1%]). For patients treated with intravenous therapy in the open-label population, all ADRs occurred in <10 patients in both treatment groups at low incidence rates, i.e. nausea (moxifloxacin 5 [1.4%] versus comparator 2 [0.6%]), dizziness (moxifloxacin 6 [1.7%] versus comparator 6 [1.7%]), increased ALT (moxifloxacin 9 [2.6%] versus comparator 8 [2.3%]), and rash (moxifloxacin 8 [2.3%] versus comparator 3 [0.9%]).

Serious AEs and Serious ADRs

Treatment-emergent SAEs are presented by SOCs for combined double-blind and open-label studies in table V. In the oral population, the overall incidence of SAEs (4.0% versus 3.9% in moxifloxacin- and comparator-treated patients) and those within the SOCs were very similar in the treatment groups. More SAEs were reported in the intravenous/oral studies in both treatment groups (moxifloxacin 595 [17.3%] versus comparator 527 [15.4%]), as expected given the increased severity of the disease. The SOCs associated with the highest incidences of events in both treatment groups, were 'infections and infestations' (moxifloxacin 219 [6.4%] versus comparator 165 [4.8%]) and 'respiratory, thoracic, and mediastinal disorders' (moxifloxacin 129 [3.8%] versus comparator 143 [4.2%]). Serious 'cardiac disorders' in the population treated by the intravenous/oral routes were reported with a similar incidence in the two groups (moxifloxacin 84 [2.4%] versus comparator 89 [2.6%]). In the intravenous-only trials, the overall rates were 7.9% and 6.0% in moxifloxacin- and comparator-treated patients, respectively, with SAEs from the SOC 'infections and infestations' being predominant (moxifloxacin 38 [4.1%] versus comparator 23 [2.5%]).

Table VI shows the incidences of SADRs in the combined double-blind and open-label studies, stratified by administration route. These were low considering the number of patients treated (oral: moxifloxacin 0.6% versus comparator 0.5%; intravenous/oral: moxifloxacin 2.8% versus comparator 1.9%; intravenous: moxifloxacin 1.0% versus comparator 0.8%). In the oral population, the incidences of SADRs within each SOC were similar between the treatment groups, with no individual SADR occurring at an incidence >0.15% in either the moxifloxacin or the comparator

Table V. Serious adverse events presented by system organ class in patients valid for the safety analysis, treated with moxifloxacin or a comparator and stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only). A single asterisk (*) indicates differences observed between groups that were ≥2.5% for events with an incidence ≥2.5% in both groups or ≥2-fold for events with an incidence <2.5% in one or both groups (calculations were made using the number of patients [no rounding]; in the event of a null value for one treatment, only situations where ≥2 cases were observed in the other treatment group are indicated); the symbol is placed to the right of the value observed for the drug in disfavor. A double asterisk (**) indicates differences observed between treatment groups according to the same rule and where the number of patients experiencing an event was ≥10 in either group; the symbols are placed to the right of the value observed for the drug in disfavor

System organ class	Treatment route [n (%)]					
	PO		IV/PO		IV	
	MXF [n = 10 613]	COMP [n = 10 685]	MXF [n = 3431]	COMP [n = 3415]	MXF [n = 937]	COMP [n = 923]
Total number of patients with events[a]	422 (4.0)	412 (3.9)	595 (17.3)	527 (15.4)	74 (7.9)	55 (6.0)
Blood and lymphatic system disorders	9 (<0.1)	9 (<0.1)	12 (0.3)	13 (0.4)	0 (0.0)	0 (0.0)
Cardiac disorders	43 (0.4)	40 (0.4)	84 (2.4)	89 (2.6)	13 (1.4)	8 (0.9)
Congenital, familial, and genetic disorders	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	1 (<0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (0.1)	0 (0.0)
Endocrine disorders	0 (0.0)	2 (<0.1)*	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Eye disorders	3 (<0.1)*	0 (0.0)	3 (<0.1)*	1 (<0.1)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	32 (0.3)	39 (0.4)	77 (2.2)	48 (1.4)	13 (1.4)	12 (1.3)
General disorders and administration site conditions	38 (0.4)	32 (0.3)	50 (1.5)	40 (1.2)	9 (1.0)	6 (0.7)
Hepatobiliary disorders	2 (<0.1)	4 (<0.1)	11 (0.3)	10 (0.3)	2 (0.2)*	0 (0.0)
Immune system disorders	6 (<0.1)*	3 (<0.1)	1 (<0.1)	3 (<0.1)*	0 (0.0)	0 (0.0)
Infections and infestations	132 (1.2)	118 (1.1)	219 (6.4)	165 (4.8)	38 (4.1)	23 (2.5)
Injury, poisoning, and procedural complications	11 (0.1)	11 (0.1)	31 (0.9)**	14 (0.4)	6 (0.6)	8 (0.9)
Investigations	11 (0.1)	15 (0.1)	33 (1.0)	18 (0.5)	3 (0.3)*	1 (0.1)
Metabolism and nutrition disorders	10 (<0.1)	7 (<0.1)	19 (0.6)	16 (0.5)	1 (0.1)	1 (0.1)
Musculoskeletal and connective tissue disorders	10 (<0.1)**	3 (<0.1)	10 (0.3)**	3 (<0.1)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	25 (0.2)	42 (0.4)	23 (0.7)	34 (1.0)	3 (0.3)	3 (0.3)
Nervous system disorders	14 (0.1)	23 (0.2)	35 (1.0)	25 (0.7)	4 (0.4)*	1 (0.1)
Pregnancy, puerperium, and perinatal conditions	9 (<0.1)	5 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	6 (<0.1)	9 (<0.1)	11 (0.3)	9 (0.3)	2 (0.2)*	0 (0.0)
Renal and urinary disorders	12 (0.1)	8 (<0.1)	26 (0.8)	26 (0.8)	5 (0.5)*	2 (0.2)
Reproductive system and breast disorders	8 (<0.1)	10 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	114 (1.1)	112 (1.0)	129 (3.8)	143 (4.2)	14 (1.5)	8 (0.9)
Skin and subcutaneous tissue disorders	9 (<0.1)	8 (<0.1)	8 (0.2)	4 (0.1)	0 (0.0)	1 (0.1)
Social circumstances	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Surgical and medical procedures	18 (0.2)	21 (0.2)	34 (1.0)	26 (0.8)	0 (0.0)	0 (0.0)
Vascular disorders	9 (<0.1)	7 (<0.1)	31 (0.9)	30 (0.9)	1 (0.1)	1 (0.1)

a Patients may have experienced more than one event.

COMP = comparator; **IV** = intravenous; **MXF** = moxifloxacin; **PO** = oral.

groups. In the intravenous/oral population, the SOCs associated with the highest incidence of events in both treatment groups were 'infections and infestations' (moxifloxacin 24 [0.7%] versus comparator 23 [0.7%]), 'investigations' (moxifloxacin 23 [0.7%] versus comparator 7 [0.2%]), and 'gastrointestinal disorders' (moxifloxacin 15 [0.4%] versus comparator 7 [0.2%]). Differences in disfavor of moxifloxacin versus comparator, using a 2-fold cut-off and events affecting at least 10 patients, were seen only for the SOCs 'gastrointestinal disorders' and 'investigations'. Of note,

'cardiac disorders' were less frequent for moxifloxacin than for comparators (moxifloxacin 5 [0.1%] versus comparator 11 [0.3%] patients). In the intravenous-only population, the numbers were all very small, limiting the meaning and accuracy of any comparison. In the moxifloxacin and comparator intravenous groups, only one and two patients, respectively, experienced a cardiac disorder.

The nature of SADRs occurring in more than two patients in the oral, intravenous/oral, and intravenous populations was examined by the double-blind versus open-label design of the studies (see table SDC-IV). This showed that the occurrences of corrected QT (QTc) interval prolongation, for the studies where ECG data were available, were few in both the double-blind studies (intravenous/oral: moxifloxacin 11 versus comparator 4) and the open-label studies (moxifloxacin 2 versus comparator 0). Diarrhea was the most frequent SADR in both the double-blind and the open-label studies, but with quite small numbers: (i) in double-blind studies: oral, moxifloxacin 3 (<0.1%) versus comparator 3 (<0.1%); intravenous/oral, moxifloxacin 2 (0.1%) versus comparator 3 (0.2%); and (ii) in open-label studies:

Table VI. Serious adverse drug reactions presented by system organ class in patients valid for the safety analysis, treated with moxifloxacin or a comparator and stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only). A single asterisk (*) indicates differences observed between groups that were ≥2.5% for events with an incidence ≥2.5% in both groups or ≥2-fold for events with an incidence <2.5% in one or both groups (calculations were made using the number of patients [no rounding]; in the event of a null value for one treatment, only situations where ≥2 cases were observed in the other treatment group are indicated); the symbol is placed to the right of the value observed for the drug in disfavor. A double asterisk (**) indicates differences observed between treatment groups according to the same rule and where the number of patients experiencing an event was ≥10 in either group; the symbols are placed to the right of the value observed for the drug in disfavor

System organ class	Treatment route [n (%)]					
	PO		IV/PO		IV	
	MXF [n = 10 613]	COMP [n = 10 685]	MXF [n = 3431]	COMP [n = 3415]	MXF [n = 937]	COMP [n = 923]
Total number of patients with events[a]	59 (0.6)	53 (0.5)	95 (2.8)	65 (1.9)	9 (1.0)	7 (0.8)
Blood and lymphatic system disorders	5 (<0.1)*	1 (<0.1)	2 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)
Cardiac disorders	6 (<0.1)*	2 (<0.1)	5 (0.1)	11 (0.3)**	1 (0.1)	2 (0.2)*
Eye disorders	1 (<0.1)	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	8 (<0.1)	13 (0.1)	15 (0.4)**	7 (0.2)	1 (0.1)	1 (0.1)
General disorders and administration site conditions	6 (<0.1)	7 (<0.1)	9 (0.3)*	4 (0.1)	0 (0.0)	1 (0.1)
Hepatobiliary disorders	1 (<0.1)	1 (<0.1)	5 (0.1)*	2 (<0.1)	1 (0.1)	0 (0.0)
Immune system disorders	2 (<0.1)	3 (<0.1)	1 (<0.1)	3 (<0.1)*	0 (0.0)	0 (0.0)
Infections and infestations	13 (0.1)	8 (<0.1)	24 (0.7)	23 (0.7)	1 (0.1)	3 (0.3)*
Injury, poisoning, and procedural complications	1 (<0.1)	0 (0.0)	2 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)
Investigations	3 (<0.1)	3 (<0.1)	23 (0.7)**	7 (0.2)	2 (0.2)*	0 (0.0)
Metabolism and nutrition disorders	1 (<0.1)	3 (<0.1)*	2 (<0.1)	2 (<0.1)	1 (0.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	2 (<0.1)*	0 (0.0)	2 (<0.1)*	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	4 (<0.1)	5 (<0.1)	3 (<0.1)*	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	0 (0.0)	2 (<0.1)*	4 (0.1)*	1 (<0.1)	0 (0.0)	0 (0.0)
Renal and urinary disorders	1 (<0.1)	2 (<0.1)	3 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	4 (<0.1)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	8 (<0.1)	6 (<0.1)	4 (0.1)	5 (0.1)	2 (0.2)*	0 (0.0)
Skin and subcutaneous tissue disorders	6 (<0.1)	5 (<0.1)	4 (0.1)	3 (<0.1)	0 (0.0)	0 (0.0)
Surgical and medical procedures	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	2 (<0.1)*	1 (<0.1)	2 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)

a Patients may have experienced more than one event.

COMP = comparator; **IV** = intravenous; **MXF** = moxifloxacin; **PO** = oral.

intravenous/oral, moxifloxacin 5 (0.3%) versus comparator 0 (0%). All other SADRs were rarely reported and with a similar incidence in the two groups, except that in the intravenous/oral double-blind studies, there were more 'cardiac disorders' with the comparator (moxifloxacin 2 [0.1%] versus comparator 10 [0.5%]) and more 'investigations' related to electrocardiographic QTc prolongation with moxifloxacin (moxifloxacin 11 [0.6%] versus comparator 4 [0.2%]), and in the intravenous/oral open-label studies, there were more 'investigations' with moxifloxacin (moxifloxacin 10 [0.6%] versus comparator 1 [<0.1%]). In the intravenous-only double-blind studies, more events related to 'infections and infestations' were reported for comparators (moxifloxacin 1 [0.2%] versus comparator 3 [0.5%]). *Clostridium difficile* colitis was reported in only one patient in each group in the oral and intravenous-only double-blind studies; in the intravenous/oral studies, it was reported in none of the moxifloxacin-treated patients but in four comparator-treated patients.

Selected AEs

The official labeling of fluoroquinolones in most countries mentions a series of AEs commonly associated with administration of these drugs. These include gastrointestinal effects, central nervous system [CNS] effects (headache, dizziness, and convulsion), cardiac effects (associated with prolongation of the QTc interval), dysglycemia, tendon disorders, phototoxicity, hypersensitivity, skin disorders, and hepatic toxicity. We therefore looked specifically for these events. The corresponding incidence rates (ranked by SMQs/BMQs and most frequent PTs [if ≥0.5%]) are presented in table VII. They are commented upon hereunder along with *C. difficile*-associated events (not organized as SMQs/BMQs), which are not displayed in the table.

Drug-Related Hepatic Disorders – Comprehensive Search (Standard MedDRA Query (SMQ))

The overall incidences of the SMQs (AEs) designated as drug-related hepatic disorders in oral, intravenous/oral, and intravenous-only studies were similar in the moxifloxacin and comparator treatment groups, though in the oral studies more cases of abnormal hepatic function were observed in the moxifloxacin-treated patients. Four cases of hepatic failure were experienced in total, of which two due to the study drug occurred in moxifloxacin-treated patients and one occurred in a comparator-treated patient: with moxifloxacin, patient #1 (treated by the intravenous/oral routes for CAP) had a medical history of hepatitis C, alcohol abuse, and intravenous drug abuse, and developed acute hepatic failure after 2 days of therapy in the context of multi-organ failure with fatal outcome; patient #2 (treated orally for CAP) had a medical history of chronic hepatitis and developed hepatic failure after 4 days of therapy, which resolved spontaneously without discontinuation of the study drug; with the comparator, the patient (treated orally with levofloxacin for uncomplicated UTI) had no relevant medical history findings and developed hepatic failure 1 day after the study drug was stopped, which resolved spontaneously.

Severe Cutaneous Adverse Reactions (SMQ)

These were very rare and were reported with similar incidences in the moxifloxacin and comparator groups, with most events being non-serious (including conjunctivitis and stomatitis cases). One case of Stevens–Johnson syndrome (an ADR) was reported in a moxifloxacin-treated patient enrolled in a PID study. Three patients (one and two in the moxifloxacin and comparator groups, respectively) had skin necrosis (AEs), but these were not considered drug related.

Convulsions (SMQ)

These were very rarely reported in either treatment group.

Psychiatric Disorders (SMQ)

Psychiatric disorders (most often agitation and depression) were more frequent in the intravenous/oral and the intravenous-only studies but with no real difference between moxifloxacin and comparator, with the exception of depression, which was slightly more frequent in the moxifloxacin group in the intravenous/oral studies.

Table VII. Incidence of selected treatment-emergent adverse events presented by Standard MedDRA Queries/Bayer MedDRA Queries and preferred terms in patients valid for the safety analysis, treated with moxifloxacin or a comparator and stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only). Data are limited to events with an incidence ≥0.5% in either group of patients. A single asterisk (*) indicates differences observed between groups that were ≥2.5% for events with an incidence ≥2.5% in both groups or ≥2-fold for events with an incidence <2.5% in one or both groups (calculations were made using the number of patients [no rounding]; in the event of a null value for one treatment, only situations where ≥2 cases were observed in the other treatment group are indicated); the symbol is placed to the right of the value observed for the drug in disfavor. A double asterisk (**) indicates differences observed between treatment groups according to the same rule and where the number of patients experiencing an event was ≥10 in either group; the symbols are placed to the right of the value observed for the drug in disfavor

SMQ/BMQ and preferred term	Treatment route [n (%)]					
	PO		IV/PO		IV	
	MXF [n = 10 613]	COMP [n = 10 685]	MXF [n = 3431]	COMP [n = 3415]	MXF [n = 937]	COMP [n = 923]
Drug-related hepatic disorders – comprehensive search	229 (2.2)	239 (2.2)	235 (6.8)	246 (7.2)	68 (7.3)	61 (6.6)
Alanine aminotransferase increased	59 (0.6)	66 (0.6)	72 (2.1)	76 (2.2)	30 (3.2)	21 (2.3)
Gammaglutamyl transferase increased	24 (0.2)	45 (0.4)	60 (1.7)	72 (2.1)	17 (1.8)	24 (2.6)
Aspartate aminotransferase increased	36 (0.3)	42 (0.4)	57 (1.7)	59 (1.7)	17 (1.8)	11 (1.2)
Blood alkaline phosphatase increased	28 (0.3)	33 (0.3)	29 (0.8)	33 (1.0)	4 (0.4)	5 (0.5)
Hepatic enzyme increased	21 (0.2)	25 (0.2)	26 (0.8)	33 (1.0)	7 (0.7)	8 (0.9)
Hepatic function abnormal	18 (0.2)**	9 (<0.1)	9 (0.3)*	4 (0.1)	10 (1.1)	6 (0.7)
Hypoalbuminemia	2 (<0.1)*	1 (<0.1)	24 (0.7)	23 (0.7)	1 (0.1)	1 (0.1)
Drug-related hepatic disorders – severe events only	19 (0.2)	18 (0.2)	17 (0.5)	9 (0.3)	5 (0.5)*	2 (0.2)
Severe cutaneous adverse reactions	25 (0.2)	33 (0.3)	23 (0.7)	17 (0.5)	1 (0.1)	2 (0.2)*
Convulsions	2 (<0.1)	5 (<0.1)*	11 (0.3)	6 (0.2)	0 (0.0)	1 (0.1)
Psychiatric disorders	85 (0.8)	49 (0.5)	91 (2.7)	64 (1.9)	14 (1.5)	8 (0.9)
Agitation	4 (<0.1)	6 (<0.1)	47 (1.4)	34 (1.0)	2 (0.2)	3 (0.3)
Depression	18 (0.2)	14 (0.1)	19 (0.6)**	6 (0.2)	0 (0.0)	0 (0.0)
AECR as clinical outcome of QTc prolongation	25 (0.2)	23 (0.2)	37 (1.1)	36 (1.1)	10 (1.1)**	2 (0.2)
Cardiac arrest	1 (<0.1)	1 (<0.1)	9 (0.3)	11 (0.3)	8 (0.9)*	2 (0.2)
Anaphylactic reactions	3 (<0.1)	3 (<0.1)	9 (0.3)	5 (0.1)	0 (0.0)	1 (0.1)
Photosensitivity reactions	5 (<0.1)	7 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tendinopathies	11 (0.1)	10 (<0.1)	3 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)
Dysglycemia	71 (0.7)	61 (0.6)	114 (3.3)	107 (3.1)	9 (1.0)*	4 (0.4)
Hyperglycemia	19 (0.2)	13 (0.1)	52 (1.5)	40 (1.2)	3 (0.3)*	0 (0.0)
Hypoglycemia	5 (<0.1)	4 (<0.1)	26 (0.8)	19 (0.6)	3 (0.3)*	0 (0.0)
Diabetes mellitus	18 (0.2)	17 (0.2)	19 (0.6)	21 (0.6)	1 (0.1)	1 (0.1)
Blood glucose increased	18 (0.2)	11 (0.1)	15 (0.4)	18 (0.5)	2 (0.2)	2 (0.2)

AECR = adverse event considered relevant; **BMQ** = Bayer MedDRA Query; **COMP** = comparator; **IV** = intravenous; **MXF** = moxifloxacin; **PO** = oral; **QTc** = corrected QT; **SMQ** = Standard MedDRA Query.

AEs Considered as Relevant Clinical Outcome of Corrected QT Interval Prolongation (Bayer MedDRA Query (BMQ))

These were reported with a similar frequency between the treatment groups in the oral studies and in the intravenous/oral studies. In the intravenous-only studies, they were slightly more frequent in the moxifloxacin group, mostly driven by a higher incidence of cardiac arrests. Only one of the eight cases of cardiac arrest reported, however, was considered to be related to the study drug (cardiac arrest in one cirrhotic patient treated with intravenous moxifloxacin for cIAI, who developed severe intra-abdominal sepsis secondary to a large intestine perforation, complicated by septic shock). Ventricular arrhythmia, tachycardia,

and fibrillation were rare events in either treatment group.

Anaphylactic Reactions (SMQ)

These were rarely reported, with circulatory collapse and shock being the most frequent AEs in the intravenous/oral studies (none being drug related in moxifloxacin-treated patients). Anaphylactic/anaphylactoid reactions were seen only in three comparator-treated patients (drug related in all cases).

Photosensitivity Reactions (BMQ)

These were rarely reported and occurred exclusively in oral studies.

Tendinopathies (BMQ)

These were equally reported in both moxifloxacin- and comparator-treated patients.

Dysglycemia (SMQ/BMQ)

Incidence rates were similar between the treatment groups, with hyperglycemia being more frequently reported than hypoglycemia.

Clostridium difficile*-Associated Diarrhea (Preferred Terms)*

Incidence rates of 'clostridial infection', '*Clostridium* colitis', '*Clostridium difficile* colitis', and 'pseudomembranous colitis' were <0.1% in the oral studies but were higher in the intravenous/oral studies, although similar in moxifloxacin- and comparator-treated patients (moxifloxacin 0.6%, comparator 0.4%). The incidence rate in the intravenous-only studies was 0.1% in each treatment group.

Analysis by Comparator Class

In order to more specifically assess the toxicity pattern of moxifloxacin independently from those of other fluoroquinolones, we conducted an analysis by classes of antibiotics for all groups with sufficient numbers of patients (oral: moxifloxacin versus a β-lactam, versus a macrolide, versus another fluoroquinolone, or versus a β-lactam with a macrolide; intravenous/oral: moxifloxacin versus a β-lactam, versus a β-lactam with or without a macrolide, or versus another fluoroquinolone; intravenous: moxifloxacin versus a β-lactam or versus another fluoroquinolone). These data are presented as table SDC-V. Concentrating on differences in disfavor of moxifloxacin, there was a near to 2-fold increased risk estimate in intravenous-only studies for (i) discontinuation due to AEs in comparison with β-lactams (moxifloxacin 11 [2.7%] versus β-lactam 6 [1.5%]); (ii) discontinuation due to AEs in comparison with another fluoroquinolone (moxifloxacin 21 [6.0%] versus other fluoroquinolone 11 [3.1%]); and (iii) discontinuation due to ADRs also in comparison with another fluoroquinolone (moxifloxacin 17 [4.9%] versus other fluoroquinolone 9 [2.6%]).

Analysis by Main Indication

Moxifloxacin is indicated for infections of different levels of severity. The data were, therefore, stratified by the main approved indications for which there were sufficient numbers of patients to draw meaningful conclusions – namely ABS, AECB, CAP, uPID, cSSSI, and cIAI. The results are presented graphically in figure 1 with substratification by administration route (oral, intravenous/oral, intravenous). A 2-fold excess in event frequencies for moxifloxacin versus comparator was only seen (i) for SADRs in cIAI patients treated by the intravenous/oral routes, and (ii) for discontinuation due to AEs or to ADRs in AECB patients treated by the intravenous route only. However, in each case, there were relatively small numbers of patients (moxifloxacin 21 [3.4%] versus comparator 9 [1.4%] in patients with cIAI; moxifloxacin 7 [7.3%] versus comparator 2 [2.0%] in patients with AECB).

Patients with Co-Morbidities

Because the safety of drugs can be adversely influenced by the patient status and may also worsen it, data were also stratified according to the main pertinent co-morbidities and elimination pathway disorders observed in the population – namely age, diabetes mellitus, renal impairment, hepatic impairment, cardiac disorders, and abnormally low BMI. First, patients were stratified by study design (double blind and open label) and administration route (oral, intravenous/oral, intravenous), and the results are presented in table VIII.

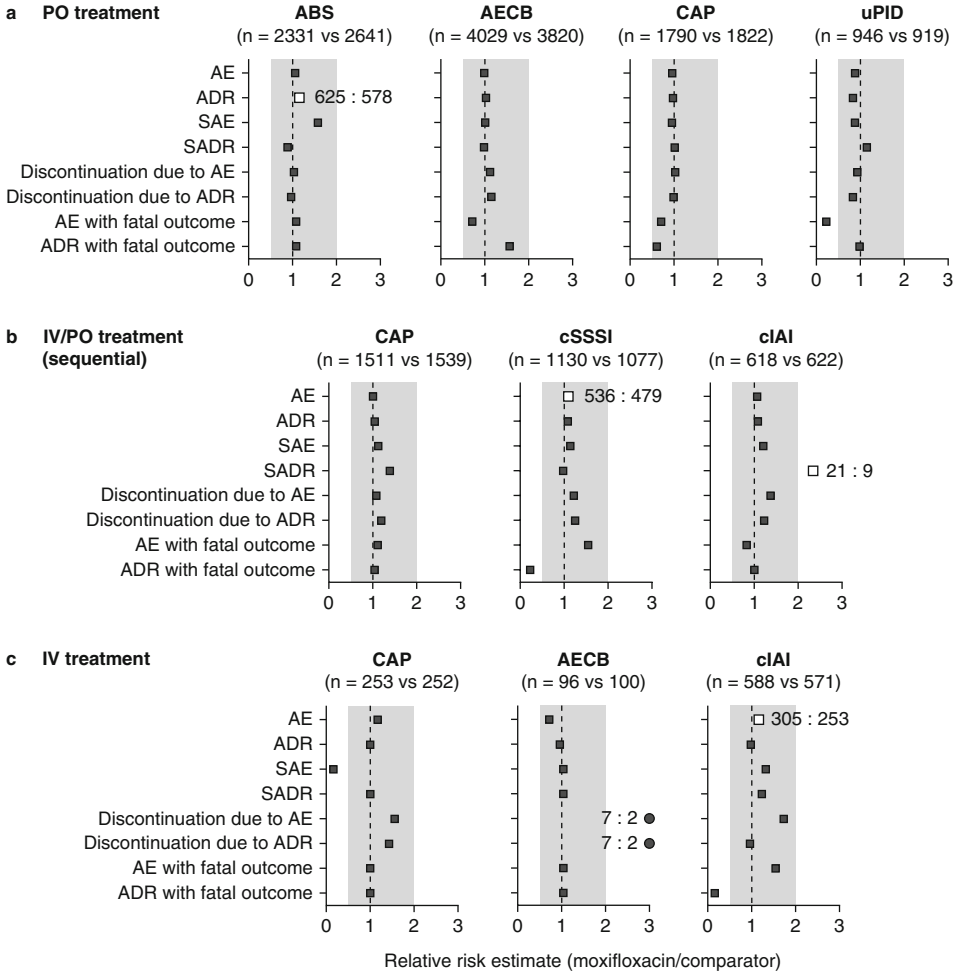

Fig. 1. Relative risk estimates (moxifloxacin versus comparator) for adverse events from pooled data stratified according to indications (the most pertinent or most frequent ones). The data are substratified according to the route of administration approved or commonly used for the corresponding indication: (**a**) oral route; (**b**) intravenous route followed by oral route [sequential]; (**c**) intravenous route. The number of patients enrolled in each cohort (moxifloxacin versus the comparator) is shown at the top of each graph. Calculations were made using the Mantel–Haenszel method stratified by study, with a continuity correction of 0.1 in the event of a null value. The relative risk estimates are presented on a 0–3 linear scale (1 denotes no difference; values <1 and >1 denote a correspondingly lower and higher risk, respectively, associated with moxifloxacin treatment relative to the comparator). Values ≤3 are displayed as squares. Circles placed at the edge of the scale indicate that the actual value is >3 (the numbers of patients who received moxifloxacin versus the comparator are shown to the left of the circle). White symbols indicate values with a lower limit of the calculated 95% confidence interval >1, indicating a nominally significantly higher risk for moxifloxacin relative to the comparator (the number of patients in each group is shown to the right of the symbol). The light gray shaded area highlights the zone where the relative risk estimate (moxifloxacin/comparator) is between 0.5 and 2. **ABS** = acute bacterial sinusitis; **ADR** = adverse drug reaction; **AE** = adverse event; **AECB** = acute exacerbation of chronic bronchitis; **CAP** = community-acquired pneumonia; **cIAI** = complicated intra-abdominal infection; **cSSSI** = complicated skin and skin structure infection; **IV** = intravenous; **PO** = oral; **SADR** = serious ADR; **SAE** = serious AE; **uPID** = uncomplicated pelvic inflammatory disease.

To better apprehend potentially meaningful differences, relative risk estimates (moxifloxacin versus comparator) were then calculated for each patient group stratified according to the administration route. The results are presented graphically in figures 2 and 3. On the basis of a threshold of a 2–fold increase in risk estimates, the only difference seen in patients receiving oral treatment was

in those with underlying cardiac disorders (more AEs with fatal outcome for comparator) [figure 3b]; and the only differences seen in those receiving intravenous treatment were in those with (i) age ≥65 years (more ADRs with fatal outcome for comparator [figure 2a]); (ii) diabetes mellitus (more discontinuations due to ADRs for comparator [figure 2b]); (iii) hepatic impairment (more SADRs, discontinuation due to ADRs, and AEs with fatal outcome for moxifloxacin [figure 3a]); (iv) cardiac disorders (more discontinuations due to AEs for moxifloxacin and more ADRs with fatal outcome for comparator [figure 3b]); and (v) BMI <18 kg/m^2 (more discontinuations due to AEs or ADRs, and more AEs with fatal outcome for moxifloxacin [figure 3c]). However, numbers in the intravenous-only studies were small in all cases (1–7 patients). Lastly, the relative risk estimates (moxifloxacin versus comparator) were calculated after substratifying each group according to the comparator used, concentrating for each comparator on patients treated by the most frequent route of administration (if versus a β-lactam: oral, intravenous/oral and intravenous; if versus a macrolide alone: oral; if versus a β-lactam alone or a beta-lactam combined with a macrolide: intravenous/oral; if versus fluoroquinolone: intravenous only). The results are shown graphically in figures 4–6. Concentrating again on differences in disfavor of moxifloxacin, a >2-fold difference in disfavor of moxifloxacin in at least one safety variable was observed for patients with (i) age ≥65 years (intravenous/oral versus β-lactam alone or versus β-lactam ± macrolide [figure 5a or 5b]); (ii) diabetes mellitus (intravenous/oral versus β-lactam alone or versus β-lactam ± macrolide [figure 5a or 5b]); (iii) renal impairment (intravenous/oral versus β-lactam ± macrolide [figure 5b], and intravenous versus β-lactam [figure 6a]); (iv) hepatic impairment (oral versus β-lactam [figure 4a], and intravenous versus β-lactam or versus another fluoroquinolone [figure 6a or 6b]); (v) cardiac disorders (intravenous versus β-lactam [figure 6a]); and (vi) BMI <18 kg/m^2 (oral versus β-lactam [figure 4a] and intravenous versus β-lactam or versus another fluoroquinolone [figure 6a or 6b]). However, the numbers of patients with events were very small in all cases (1–24).

Discussion and Conclusion

By using the data on all valid-for-safety populations in the phase II–IV randomized actively controlled clinical trials, with stratification by study design (double blind or open label), route of administration (oral, intravenous with or without a subsequent switch to oral therapy), preexisting risk factors, main indications, and types of comparator, the present paper may represent a new standard in the public reporting of adverse effects for a drug marketed over the past several years. Such data are usually communicated to regulatory authorities only (as part of registration applications, Periodic Safety Update Reports, and Risk Management Plans) and remain, therefore, largely unknown to the clinician. The benefit of using pooled randomized active-controlled clinical trial data, as has been done here, is that risks associated with the study drug can be directly compared with those of clinically valid comparators. This approach also allows estimation of the incidence of relatively rare effects with a fair degree of certainty. Since the data are from randomized studies, patients should be equally balanced with respect to known as well as unknown factors associated with the outcome variables, making comparisons between treatment groups as fair as possible.[64]

A first key observation is that moxifloxacin does not show a markedly different safety profile compared with comparator therapies. The filters used highlight situations where moxifloxacin caused more untoward effects than the comparator, but either the actual numbers of affected patients were close to those seen with the comparator or the differences were small. For ADRs, there were actually several situations where the comparator showed more untoward effects, especially in the double-blind studies. In the open-label studies, most moxifloxacin ADRs concerned nervous system disorders that are listed in the labeling, which may lead to over-reporting. Concentrating on SADRs, differences in the open-label studies mainly concerned gastrointestinal effects and the need for biological investigations. Here, also, the moxifloxacin labeling lists these effects; no difference in SADRs was seen between moxifloxacin and comparator when considering the double-

Table VIII. Incidence of adverse events, adverse drug reactions, serious adverse events, serious adverse drug reactions, discontinuation due to adverse events, discontinuation due to adverse drug reactions, adverse events with fatal outcome, and adverse drug reactions with fatal outcome in patients with risk factors (age, diabetes mellitus, renal or hepatic impairment, cardiac disorder, low body mass index) treated with moxifloxacin or a comparator and stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only) and by study design

Study design and risk factor[a]	Patients [n]		Events [n (%)]															
			AE		ADR		SAE		SADR		Discontinuation due to AE		Discontinuation due to ADR		AE with fatal outcome		ADR with fatal outcome	
	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP
Double-blind studies																		
PO administration																		
Age ≥65 years	1904	1833	801 (42.1)	797 (43.5)	368 (19.3)	376 (20.5)	139 (7.3)	117 (6.4)	13 (0.7)	15 (0.8)	93 (4.9)	93 (5.1)	64 (3.4)	63 (3.4)	21 (1.1)	19 (1.0)	3 (0.2)	1 (0.1)
Diabetes mellitus	615	565	294 (47.8)	254 (45.0)	141 (22.9)	106 (18.8)	57 (9.3)	43 (7.6)	9 (1.5)	2 (0.4)	30 (4.9)	20 (3.5)	20 (3.3)	10 (1.8)	6 (1.0)	5 (0.9)	0 (0.0)	0 (0.0)
Renal impairment	1086	1020	451 (41.5)	440 (43.1)	235 (21.6)	206 (20.2)	73 (6.7)	62 (6.1)	8 (0.7)	8 (0.8)	44 (4.1)	48 (4.7)	25 (2.3)	30 (2.9)	11 (1.0)	11 (1.1)	0 (0.0)	3 (0.3)
Hepatic impairment	133	144	64 (48.1)	63 (43.8)	35 (26.3)	29 (20.1)	3 (2.3)	7 (4.9)	1 (0.8)	1 (0.7)	6 (4.5)	6 (4.2)	6 (4.5)	3 (2.1)	1 (0.8)	4 (2.8)	0 (0.0)	1 (0.7)
Cardiac disorder	1182	1142	567 (48.0)	545 (47.8)	284 (24.0)	255 (22.3)	101 (8.5)	80 (7.0)	9 (0.8)	8 (0.7)	56 (4.7)	56 (4.9)	34 (2.9)	39 (3.4)	9 (0.8)	16 (1.4)	0 (0.0)	2 (0.2)
Low BMI	288	307	101 (35.1)	140 (45.6)	63 (21.9)	86 (28.0)	10 (3.5)	18 (5.9)	0 (0.0)	4 (1.3)	13 (4.5)	26 (8.5)	11 (3.8)	20 (6.5)	2 (0.7)	3 (1.0)	0 (0.0)	0 (0.0)
IV/PO administration																		
Age ≥65 years	800	769	558 (69.8)	521 (67.8)	216 (27.0)	197 (25.6)	161 (20.1)	150 (19.5)	29 (3.6)	23 (3.0)	70 (8.8)	60 (7.8)	37 (4.6)	24 (3.1)	49 (6.1)	41 (5.3)	1 (0.1)	3 (0.4)
Diabetes mellitus	590	558	380 (64.4)	342 (61.3)	138 (23.4)	117 (21.0)	113 (19.2)	100 (17.9)	14 (2.4)	10 (1.8)	47 (8.0)	38 (6.8)	24 (4.1)	11 (2.0)	23 (3.9)	19 (3.4)	1 (0.2)	2 (0.4)
Renal impairment	458	460	309 (67.5)	289 (62.8)	102 (22.3)	103 (22.4)	99 (21.6)	90 (19.6)	13 (2.8)	17 (3.7)	35 (7.6)	37 (8.0)	13 (2.8)	13 (2.8)	32 (7.0)	30 (6.5)	2 (0.4)	2 (0.4)
Hepatic impairment	82	89	62 (75.6)	64 (71.9)	21 (25.6)	23 (25.8)	35 (42.7)	20 (22.5)	9 (11.0)	3 (3.4)	14 (17.1)	10 (11.2)	8 (9.8)	2 (2.3)	7 (8.5)	6 (6.7)	1 (1.2)	0 (0.0)
Cardiac disorder	740	737	536 (72.4)	525 (71.2)	211 (28.5)	214 (29.0)	161 (21.8)	147 (20.0)	28 (3.8)	27 (3.7)	68 (9.2)	62 (8.4)	34 (4.6)	29 (3.9)	39 (5.3)	36 (4.9)	2 (0.3)	3 (0.4)
Low BMI	56	55	47 (83.9)	47 (85.5)	11 (19.6)	14 (25.5)	20 (35.7)	16 (29.1)	2 (3.6)	1 (1.8)	4 (7.1)	5 (9.1)	2 (3.6)	4 (7.3)	10 (17.9)	7 (12.7)	0 (0.0)	0 (0.0)

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Table VIII. Contd

Study design and risk factor[a]	Patients [n]		Events [n (%)]															
			AE		ADR		SAE		SADR		Discontinuation due to AE		Discontinuation due to ADR		AE with fatal outcome		ADR with fatal outcome	
	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP
IV administration																		
Age ≥65 years	110	117	73 (66.4)	64 (54.7)	22 (20.0)	22 (18.8)	32 (29.1)	24 (20.5)	4 (3.6)	6 (5.1)	7 (6.4)	8 (6.8)	1 (0.9)	4 (3.4)	13 (11.8)	10 (8.6)	0 (0.0)	1 (0.9)
Diabetes mellitus	53	42	36 (67.9)	29 (69.1)	10 (18.9)	10 (23.8)	16 (30.2)	11 (26.2)	2 (3.8)	2 (4.8)	4 (7.6)	4 (9.5)	0 (0.0)	2 (4.8)	9 (17.0)	4 (9.5)	0 (0.0)	0 (0.0)
Renal impairment	126	132	84 (66.7)	71 (53.8)	23 (18.3)	23 (17.4)	26 (20.6)	22 (16.7)	2 (1.6)	1 (0.8)	10 (7.9)	4 (3.0)	1 (0.8)	1 (0.8)	10 (7.9)	7 (5.3)	0 (0.0)	0 (0.0)
Hepatic impairment	39	41	22 (56.4)	18 (43.9)	6 (15.4)	6 (14.6)	7 (18.0)	7 (17.1)	1 (2.6)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorder	74	66	54 (73.0)	37 (56.1)	12 (16.2)	17 (25.8)	23 (31.1)	11 (16.7)	3 (4.1)	2 (3.0)	5 (6.8)	1 (1.5)	0 (0.0)	0 (0.0)	11 (14.9)	8 (12.1)	0 (0.0)	1 (1.5)
BMI <18 kg/m^2	19	16	12 (63.2)	6 (37.5)	2 (10.5)	0 (0.0)	3 (15.8)	3 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Open-label studies																		
PO administration																		
Age ≥65 years	547	570	249 (45.5)	224 (39.3)	72 (13.2)	72 (12.6)	68 (12.4)	67 (11.8)	3 (0.6)	3 (0.5)	23 (4.2)	16 (2.8)	14 (2.6)	11 (1.9)	8 (1.5)	13 (2.3)	0 (0.0)	0 (0.0)
Diabetes mellitus	162	152	61 (37.7)	56 (36.8)	17 (10.5)	20 (13.2)	21 (13.0)	13 (8.6)	2 (1.2)	1 (0.7)	4 (2.5)	6 (4.0)	2 (1.2)	4 (2.6)	4 (2.5)	1 (0.7)	0 (0.0)	0 (0.0)
Renal impairment	197	209	87 (44.2)	75 (35.9)	24 (12.2)	23 (11.0)	21 (10.7)	18 (8.6)	1 (0.5)	1 (0.5)	5 (2.5)	5 (2.4)	2 (1.0)	3 (1.4)	1 (0.5)	3 (1.4)	0 (0.0)	0 (0.0)
Hepatic impairment	13	19	6 (46.2)	6 (31.6)	2 (15.4)	3 (15.8)	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorder	294	262	140 (47.6)	110 (42.0)	56 (19.1)	42 (16.0)	31 (10.5)	30 (11.5)	5 (1.7)	0 (0.0)	14 (4.8)	8 (3.1)	9 (3.1)	6 (2.3)	2 (0.7)	9 (3.4)	0 (0.0)	0 (0.0)
BMI <18 kg/m^2	30	58	12 (40.0)	31 (53.5)	7 (23.3)	10 (17.2)	1 (3.3)	10 (17.2)	0 (0.0)	1 (1.7)	1 (3.3)	1 (1.7)	1 (3.3)	0 (0.0)	1 (3.3)	2 (3.5)	0 (0.0)	0 (0.0)

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Table VIII. Contd

Study design and risk factor[a]	Patients [n]		Events [n (%)]															
			AE		ADR		SAE		SADR		Discontinuation due to AE		Discontinuation due to ADR		AE with fatal outcome		ADR with fatal outcome	
	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP	MXF	COMP
IV/PO administration																		
Age ≥65 years	573	565	371 (64.8)	379 (67.1)	132 (23.0)	110 (19.5)	137 (23.9)	140 (24.8)	20 (3.5)	7 (1.2)	61 (10.7)	44 (7.8)	31 (5.4)	18 (3.2)	51 (8.9)	57 (10.1)	1 (0.2)	0 (0.0)
Diabetes mellitus	336	359	207 (61.6)	223 (62.1)	58 (17.3)	57 (15.9)	85 (25.3)	82 (22.8)	8 (2.4)	1 (0.3)	31 (9.2)	26 (7.2)	14 (4.2)	9 (2.5)	23 (6.9)	24 (6.7)	1 (0.3)	0 (0.0)
Renal impairment	430	403	263 (61.2)	260 (64.5)	94 (21.9)	78 (19.4)	103 (24.0)	90 (22.3)	17 (4.0)	6 (1.5)	40 (9.3)	41 (10.2)	15 (3.5)	12 (3.0)	26 (6.1)	37 (9.2)	1 (0.2)	1 (0.3)
Hepatic impairment	101	107	71 (70.3)	64 (59.8)	22 (21.8)	20 (18.7)	25 (24.8)	33 (30.8)	1 (1.0)	4 (3.7)	10 (9.9)	14 (13.1)	3 (3.0)	5 (4.7)	7 (6.9)	18 (16.8)	0 (0.0)	2 (1.9)
Cardiac disorder	427	399	268 (62.8)	279 (69.9)	104 (24.4)	79 (19.8)	90 (21.1)	99 (24.8)	15 (3.5)	8 (2.0)	51 (11.9)	34 (8.5)	25 (5.9)	14 (3.5)	30 (7.0)	39 (9.8)	1 (0.2)	1 (0.3)
BMI <18 kg/m^2	60	60	42 (70.0)	36 (60.0)	15 (25.0)	13 (21.7)	16 (26.7)	14 (23.3)	3 (5.0)	3 (5.0)	6 (10.0)	6 (10.0)	4 (6.7)	5 (8.3)	5 (8.3)	8 (13.3)	0 (0.0)	0 (0.0)
IV administration																		
Age ≥65 years	60	74	10 (16.7)	17 (23.0)	5 (8.3)	9 (12.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.0)	2 (2.7)	3 (5.0)	2 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetes mellitus	27	30	6 (22.2)	7 (23.3)	3 (11.1)	4 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.4)	2 (6.7)	1 (3.7)	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal impairment	77	86	18 (23.4)	21 (24.4)	8 (10.4)	9 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	3 (3.5)	1 (1.3)	2 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic impairment	7	0	1 (14.3)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorder	32	38	9 (28.1)	20 (52.6)	4 (12.5)	8 (21.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.3)	2 (5.3)	1 (3.1)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
BMI <18 kg/m^2	26	37	5 (19.2)	4 (10.8)	3 (11.5)	3 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.9)	0 (0.0)	1 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

a See Methods for definition of each risk factor.

ADR = adverse drug reaction; **AE** = adverse event; **BMI** = body mass index; **COMP** = comparator; **IV** = intravenous; **MXF** = moxifloxacin; **PO** = oral; **SADR** = serious ADR; **SAE** = serious AE.

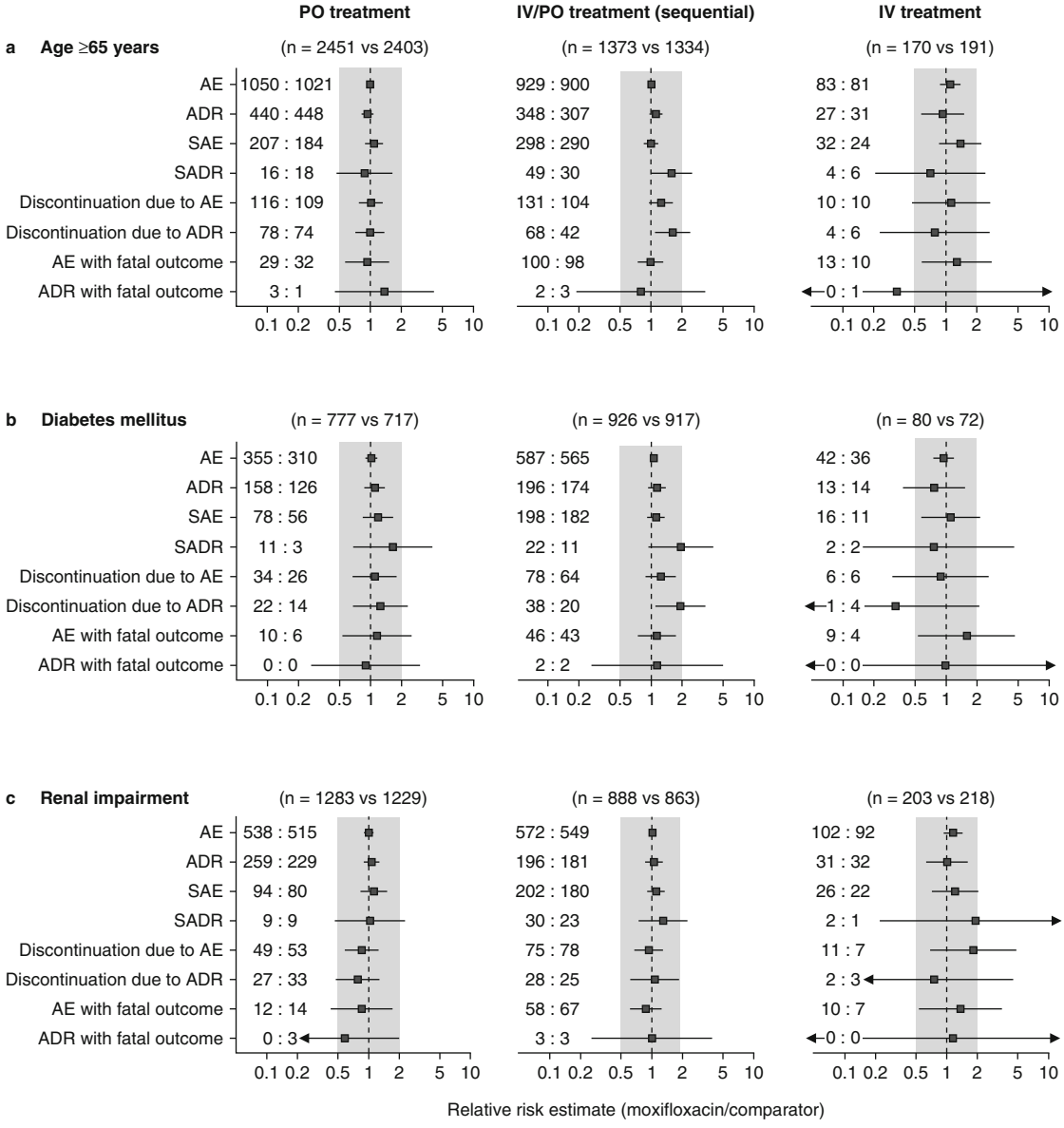

Fig. 2. Relative risk estimates (moxifloxacin versus the comparator) for adverse events from pooled data on (**a**) elderly patients, (**b**) patients with diabetes mellitus, and (**c**) patients with renal impairment. The data are stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only).The number of patients enrolled in each subgroup (moxifloxacin versus the comparator) is shown at the top of each graph, and the numbers of patients with each of the recorded events are shown to the left of the corresponding symbol. Calculations were made using the Mantel–Haenszel method (with the 95% confidence interval) stratified by study, with a continuity correction of 0.1 in the event of a null value. The relative risk estimates are presented as black squares on a (0.1–10) logarithmic scale (1 denotes no difference; values <1 and >1 denote a correspondingly lower and higher risk, respectively, associated with moxifloxacin treatment relative to the comparator), and the horizontal lines denote the confidence interval (limited to a maximum of 0.1 to 10 for reasons of legibility; lines that extend beyond these limits [or where the limits are masked by text] have an arrowhead symbol; when not visible, the lines is shorter than the corresponding symbol size). The light gray shaded area highlights the zone where the relative risk estimate (moxifloxacin/comparator) is between 0.5 and 2. **ADR** = adverse drug reaction; **AE** = adverse event; **IV** = intravenous; **PO** = oral; **SADR** = serious ADR; **SAE** = serious AE.

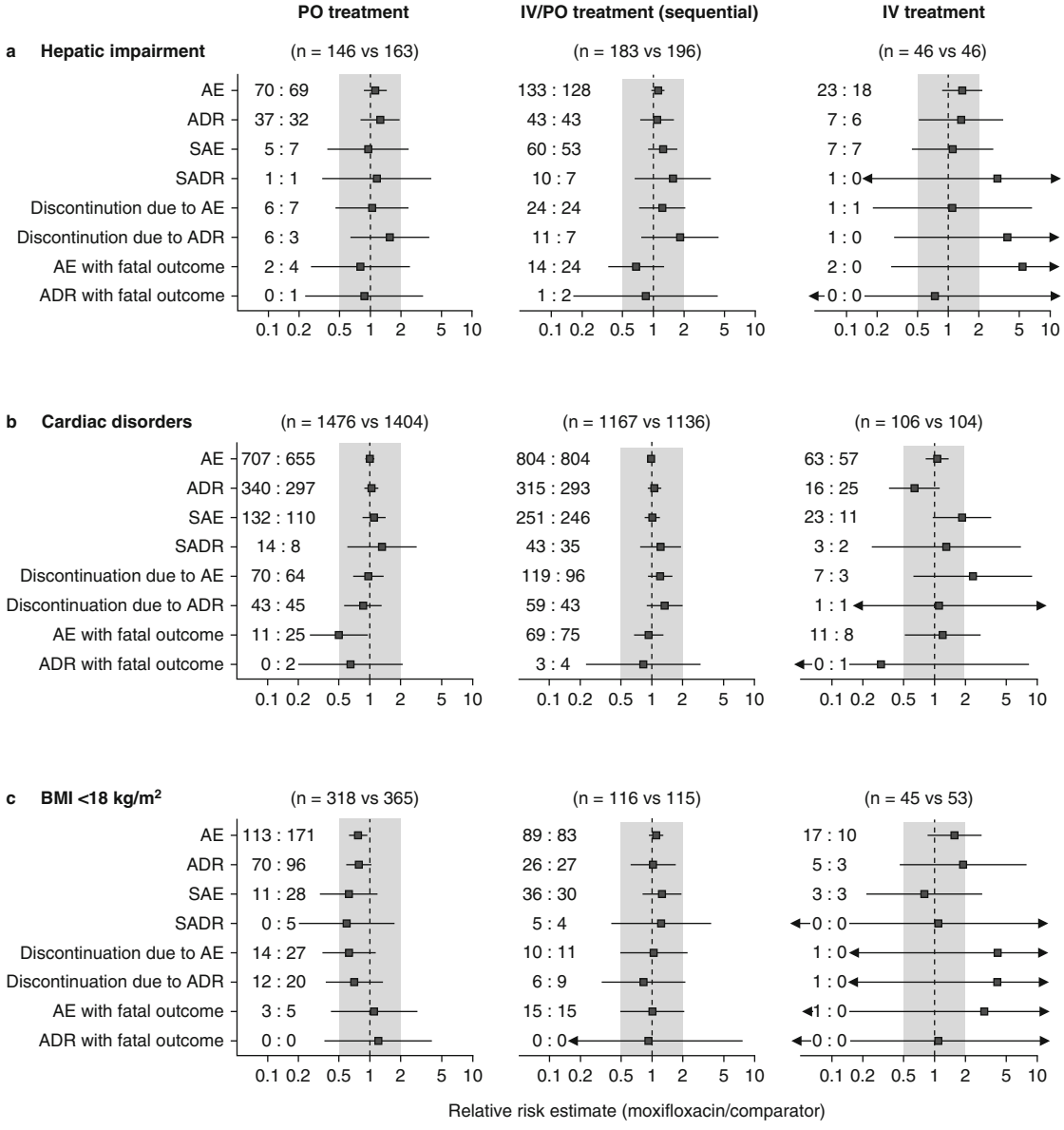

Fig. 3. Relative risk estimates (moxifloxacin versus the comparator) for adverse events from pooled data on (**a**) patients with hepatic impairment, (**b**) patients with a cardiac disorder, and (**c**) patients with a body mass index <18 kg/m^2. The data are stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only).The number of patients enrolled in each subgroup (moxifloxacin versus the comparator) is shown at the top of each graph, and the numbers of patients with each of the recorded events are shown to the left of the corresponding symbol. Calculations were made using the Mantel–Haenszel method (with the 95% confidence interval) stratified by study, with a continuity correction of 0.1 in the event of a null value. The relative risk estimates are presented as black squares on a (0.1–10) logarithmic scale (1 denotes no difference; values <1 and >1 denote a correspondingly lower and higher risk, respectively, associated with moxifloxacin treatment relative to the comparator), and the horizontal lines denote the confidence interval (limited to a maximum of 0.1 to 10 for reasons of legibility; lines that extend beyond these limits [or where the limits are masked by text] have an arrowhead symbol; when not visible, the lines is shorter than the corresponding symbol). The light gray shaded area highlights the zone where the relative risk estimate (moxifloxacin/comparator) is between 0.5 and 2. **ADR** = adverse drug reaction; **AE** = adverse event; **BMI** = body mass index; **IV** = intravenous; **PO** = oral; **SADR** = serious ADR; **SAE** = serious AE.

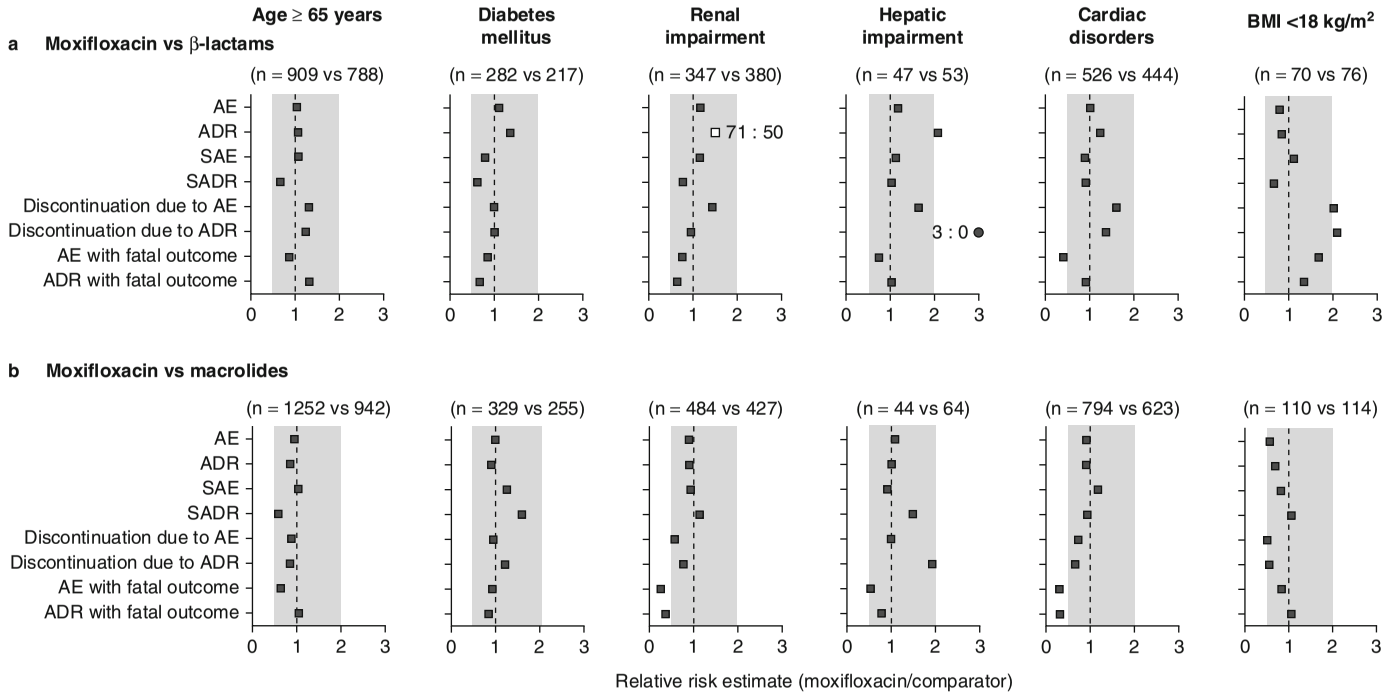

Fig. 4. Relative risk estimates (moxifloxacin versus the comparator) for adverse events from pooled data on patients treated by the oral route with the most frequent or meaningful comparator antibiotic: (**a**) β-lactam or (**b**) a macrolide. The data are stratified according to risk factors (age ≥65 years, diabetes mellitus, renal impairment, hepatic impairment, cardiac disorders, body mass index <18 kg/m^2). The number of patients enrolled in each subgroup (moxifloxacin versus the comparator) is shown at the top of each graph. Calculations were made using the Mantel–Haenszel method stratified by study, with a continuity correction of 0.1 in the event of a null value. The relative risk estimates are presented on a 0–3 linear scale (1 denotes no difference; values <1 and >1 denote a correspondingly lower and higher risk, respectively, associated with moxifloxacin treatment relative to the comparator). Values ≤3 are displayed by squares. Circles placed at the edge of the scale indicate that the actual value is >3 (the numbers of patients who received moxifloxacin versus the comparator are shown to the left of the circle). White symbols indicate values with a lower limit of the calculated 95% confidence interval >1, indicating a nominally significantly higher risk for moxifloxacin relative to the comparator (the numbers of patients in each group are shown to the right or left of the corresponding symbol). The light gray shaded area highlights the zone where the relative risk estimate (moxifloxacin/comparator) is between 0.5 and 2. **ADR** = adverse drug reaction; **AE** = adverse event; **BMI** = body mass index; **SADR** = serious ADR; **SAE** = serious AE.

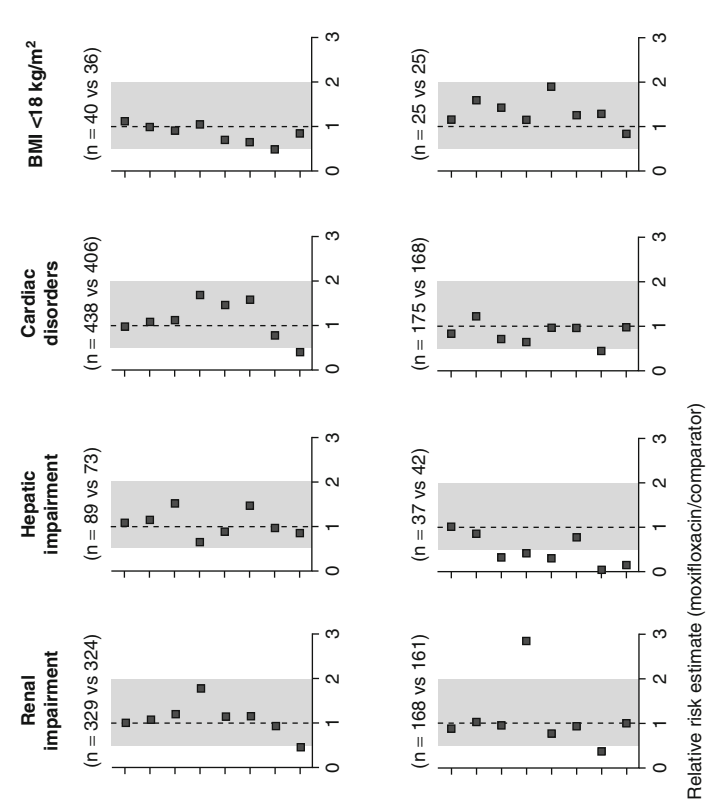

Fig. 5. Relative risk estimates (moxifloxacin versus the comparator) for adverse events from pooled data on patients treated by the intravenous route followed by the oral route (sequential) with the most frequent or meaningful comparator antibiotic(s): (**a**) β-lactam or (**b**) β-lactam ± macrolide (the design of the study did not allow differentiation between patients receiving only a β-lactam and those receiving the combination of a β-lactam and a macrolide). The data are stratified according to risk factors (age ≥65 years, diabetes mellitus, renal impairment, hepatic impairment, cardiac disorder, body mass index <18 kg/m^2). The number of patients enrolled in each subgroup (moxifloxacin versus the comparator) is shown at the top of each graph. Calculations were made using the Mantel–Haenszel method stratified by study, with a continuity correction of 0.1 in the event of a null value. The relative risk estimates are presented on a 0–3 linear scale (1 denotes no difference; values <1 and >1 denote a correspondingly lower and higher risk, respectively, associated with moxifloxacin treatment relative to the comparator). Values ≤3 are displayed by squares. Circles placed at the edge of the scale indicate that the actual value is >3 (the numbers of patients who received moxifloxacin versus the comparator are shown to the left of the circle). White symbols indicate values with a lower limit of the calculated 95% confidence interval >1, indicating a nominally significantly higher risk for moxifloxacin relative to the comparator (the numbers of patients in each group are shown to the right or left of the corresponding symbol). The light gray shaded area highlights the zone where the relative risk estimate (moxifloxacin/comparator) is between 0.5 and 2. **ADR** = adverse drug reaction; **AE** = adverse event; **BMI** = body mass index; **SADR** = serious ADR; **SAE** = serious AE.

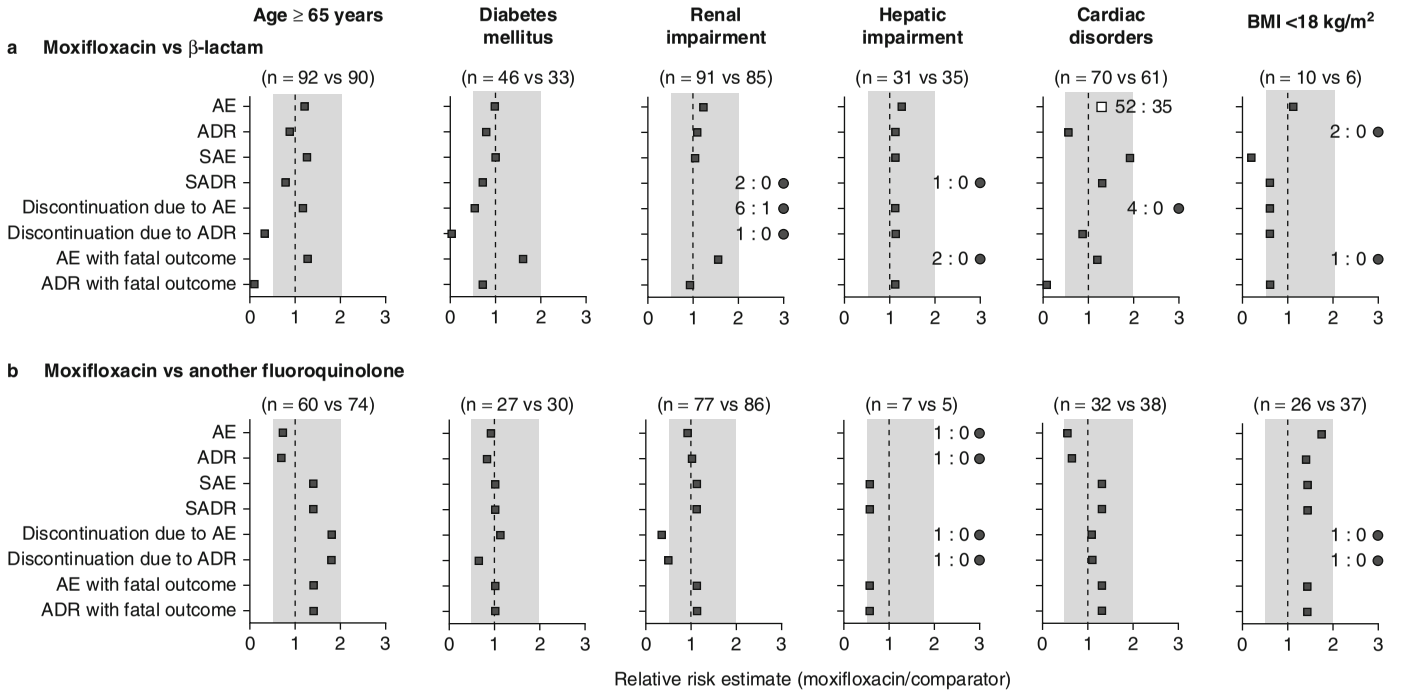

Fig. 6. Relative risk estimates (moxifloxacin versus the comparator) for adverse events from pooled data on patients treated by the intravenous route with the most frequent or meaningful comparator antibiotic: (**a**) β-lactam or (**b**) another fluoroquinolone. The data are stratified according to risk factors (age ≥65 years, diabetes mellitus, renal impairment, hepatic impairment, cardiac disorder, body mass index <18 kg/m^2). The number of patients enrolled in each subgroup (moxifloxacin versus the comparator) is shown at the top of each graph. Calculations were made using the Mantel–Haenszel method stratified by study, with a continuity correction of 0.1 in the event of a null value. The relative risk estimates are presented on a 0–3 linear scale (1 denotes no difference; values <1 and >1 denote a correspondingly lower and higher risk, respectively, associated with moxifloxacin treatment relative to the comparator). Values ≤3 are displayed by squares. Circles placed at the edge of the scale indicate that the actual value is >3 (the numbers of patients who received moxifloxacin versus the comparator are shown to the left of the circle). White symbols indicate values with a lower limit of the calculated 95% confidence interval >1, indicating a nominally significantly higher risk for moxifloxacin relative to the comparator (the numbers of patients in each group are shown to the right or left of the corresponding symbols). The light gray shaded area highlights the zone where the relative risk estimate (moxifloxacin/comparator) is between 0.5 and 2. **ADR** = adverse drug reaction; **AE** = adverse event; **BMI** = body mass index; **SADR** = serious ADR; **SAE** = serious AE.

blind studies. A higher incidence of AEs was also seen in patients receiving the intravenous formulation in double-blind studies. However, this was not seen for ADRs (except for nausea). The other global indicators of toxicity – ADRs, treatment discontinuation due to ADRs, or ADRs with fatal outcome – showed no clinically meaningful difference in frequency between moxifloxacin and comparator.

The second key observation is that the incidence of ADRs across the treatment groups was low. This may be explained by at least two factors – namely (i) patients with known contraindications were systematically excluded from participation in the studies; and (ii) all patients were closely monitored throughout the observation period, which may have prevented AEs developing into recognizable ADRs. While this could suggest that the patients analyzed do not correspond to those seen in routine clinical practice, excluding patients on the basis of contraindications and following them for occurrence of side effects should be the rule in actual prescribing situations. Excluding patients with risk factors that commonly occur alongside the primary pathology (e.g. CAP, cSSSI) but are not clear contraindications could confound results of large retrospective analyses such as that conducted in the current study. Yet, patients with risk factors were actually included in the studies, consistent with trials conducted during the whole phase II–IV development program. The impact of close monitoring of patients considered to be at high risk did not introduce bias to the reporting, since in none of these subgroups was early drug discontinuation reported more frequently (an increased frequency would, indeed, have prompted the investigators' intervention to address the corresponding safety concern and to discontinue therapy). Thus, in the context of clinical trials involving about 15 000 patients treated with moxifloxacin, no clear differentiation could be made with respect to tolerance versus the comparators used, either as a group or individually. As all of the comparators were accepted standards of care at the time at which each study was designed, it is reasonable to consider that moxifloxacin has a safety profile that is comparable to that of the comparators.

The labeling of fluoroquinolones, and of moxifloxacin in particular, includes multiple side effects (e.g. tendon, cardiac, CNS, cutaneous, and hepatic effects, and *C. difficile* infections) that were not seen in substantial frequencies in the current analysis, despite careful investigation. When detected, the incidence of cardiac and hepatic AEs was slightly higher in patients receiving moxifloxacin treatment than in those receiving comparator treatment, but this related only to 'hepatic function abnormal' in oral and 'cardiac arrest' in intravenous studies, respectively. These events were no different in frequency when examining ADRs. The incidences of SADRs related to CNS, cutaneous, cardiac, or hepatic toxicity were similar in moxifloxacin- and comparator-treated patients. Although it has been suggested that patients with pre-existing risk factors or co-morbidities may be at particular risk of experiencing an AE, our data did not reveal any clinically relevant differences compared with the comparators in this context. This holds true not only for comparisons with other fluoroquinolones, but also for comparisons with other antibiotic classes.

All but one of the studies used in the present analysis had the evaluation of the clinical efficacy of moxifloxacin in the target indications as a primary goal, and the majority of the studies have been published in peer-reviewed journals (see references[26,27,29] for recent review papers). Most studies concluded that moxifloxacin was clinically as effective as the comparators or superior to them, which implies that moxifloxacin was not underdosed (all patients received the standard registered dose that has proven to be efficacious in all registered indications to date). This contrasts with some of the comparators (including those proposed as first-line therapies in applicable guidelines), for which higher dosages than those used in the studies pooled for the current analysis are now proposed. For β-lactams[67-69] and levofloxacin,[70] this reflects the progressive decrease in bacterial susceptibility over time and the corresponding attempts by clinicians to maintain sufficient treatment efficacy based on pharmacokinetic/dynamic principles and to avoid failures[71] and/or emergence of resistance.[72,73]

As with all meta-analyses, the present study and its conclusions have several limitations. Although we looked at specific risks, we did not reanalyze the original investigators' statements or medical assessment of the corresponding cases, nor made any attempt at further adjudication of specific events. No exploration of heterogeneity of results across studies was done, because of the large number of comparisons. Lastly, although a large number of patients were included in the analysis, it may not be sufficient for detecting very rare side effects. These are usually captured from post-marketing spontaneous reports and larger non-interventional studies, but such reports are subject to other limitations relating to the quality of reporting, difficulties in ensuring unbiased data collection, and lack of detailed information on the patient characteristics. Moreover, while the population at risk is known for non-interventional studies, the actual number of exposed persons is difficult to determine for spontaneous reports. Thus, other approaches need to be followed to further define the safety profile of drugs when they are administered in a real-life setting. This has already been carried out for hepatotoxicity using a registry approach to compare telithromycin and several fluoroquinolones, including moxifloxacin[74] (that study did not reveal significant differences between moxifloxacin and the other fluoroquinolones marketed at that time in this context). It is important to stress that such studies should be applied to comparators as well, in order to correctly define their true safety profile. Centralization and cross-checking of product safety update reports and their publication by independent bodies would also be of significant interest. In the meantime, clinicians will need to rely on analyses such as those presented here for making informed choices on treatment options.

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