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Review

Gender Analysis of Moxifloxacin Clinical Trials

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Abstract

Purpose: To determine the inclusion of women and the sex-stratification of results in moxifloxacin Clinical Trials (CTs), and to establish whether these CTs considered issues that specifically affect women, such as pregnancy and use of hormonal therapies. Previous publications about women's inclusion in CTs have not specifically studied therapeutic drugs. Although this type of drug is taken by men and women at a similar rate, adverse effects occur more frequently in the latter.

Methods: We reviewed 158 published moxifloxacin trials on humans, retrieved from MedLine and the Cochrane Library (1998–2010), to determine whether they complied with the gender recommendations published by U.S. Food and Drug Administration Guideline.

Results: Of a total of 80,417 subjects included in the moxifloxacin CTs, only 33.7% were women in phase I, in contrast to phase II, where women accounted for 45%, phase III, where they represented 38.3% and phase IV, where 51.3% were women. About 40.9% ($n = 52$) of trials were stratified by sex and 15.3% ($n = 13$) and 9% ($n = 7$) provided data by sex on efficacy and adverse effects, respectively. We found little information about the influence of issues that specifically affect women. Only 3 of the 59 journals that published the moxifloxacin CTs stated that authors should stratify their results by sex.

Conclusions: Women are under-represented in the published moxifloxacin trials, and this trend is more marked in phase I, as they comprise a higher proportion in the other phases. Data by sex on efficacy and adverse effects are scarce in moxifloxacin trials. These facts, together with the lack of data on women-specific issues, suggest that the therapeutic drug moxifloxacin is only a partially evidence-based medicine.

Introduction

Fluoroquinolone antibiotics are surrounded by controversy due to their adverse effects, some of which occur more frequently in women, such as QT-interval prolongation, which can lead to torsades de pointes[1] or cutaneous photosensitization.[2,3] In addition, moxifloxacin has been the center of extensive debate since its authorization, mainly due to the alleged advantages it has over other drugs in its class and also due to the increased risk of cardiac disorders.[4] Interestingly, the U.S. Food and Drug Administration (FDA) approved moxifloxacin despite the objections raised by some members of the FDA advisory committee and the medical review officer.[5] Lastly, the FDA and European Medicines Agency (EMA) have approved its use in uncomplicated gynecological infections; a decision that has been criticized since authorization was based on a single randomized, double-blind controlled trial with 741 patients over 6 weeks. Thus, the potential for long-term complications such as infertility or extra-uterine pregnancy are unknown.[4]

Some fluoroquinolones have been withdrawn from the market in certain countries due to serious adverse events and safety concerns. These include temafloxacin (in 1992), which has been shown to cause hemolytic anemia, often accompanied by renal or hepatic dysfunction and/or coagulopathy[6]; trovafloxacin and alatrofloxacin (2001), which cause fatal liver damage[7]; grepafloxacin (2003), which produces adverse effects related to prolongation of the QT interval on the electrocardiogram, leading to cardiac events and sudden death—more frequently in women than men[8]; and gatifloxacin (2006), since it increases risk of diabetes, hallucinations, liver damage, and purpura.[9] Other quinolones, including moxifloxacin, have had their licensed indications restricted due to toxicity issues.[10] In 2008, alerted by the serious risks involved in the use of oral moxifloxacin, the EMA and FDA analyzed pharmacovigilance data.[7,11] The EMA decided that moxifloxacin should only be prescribed in the treatment of acute bacterial sinusitis, acute exacerbation of chronic bronchitis, and community-acquired pneumonia when other antibiotics cannot be used or have failed. Furthermore, the FDA has stated that

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moxifloxacin shows no advantages over other antibiotics and moreover has been observed to entail a higher cardiovascular risk in women than in men.

Despite the problems associated with taking fluoroquinolones, they are now the most commonly prescribed class of antibiotics in adults.[12] Nearly half of these prescriptions are to treat non-approved conditions.[12] Despite the restrictions on its use, moxifloxacin has become a bestseller for Bayer—accounting for 497 million Euros ($697.3 million) worldwide in 2010.[13]

In 1993, the FDA published its Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, aimed at promoting not only the inclusion of women in clinical trials (CTs) but also the analysis of gender differences.[14] There has been an increase in the number of studies which have since examined the inclusion of women in CTs and conducted analyses by sex. These studies found that women only represent around 20% of subjects included in CTs of drugs for specific diseases,[15] published in high impact factor journals,[16–18] or funded by public institutions.[19] Lastly it has been demonstrated that CTs of some drugs, such as antiretrovirals[20] and aripiprazol[21] have included fewer women than men. In contrast, CTs of other drugs have included more women than men, particularly in the case of anti-inflammatory drugs,[22,23] which were withdrawn from the market following fatalities. However, women were significantly under-represented in the crucial first phase,[22,23] where the objective is to evaluate the safety of the drug. It has been explained on the basis of the potential risk of fetal harm should women become pregnant during the CT.[24] Other explanations for the exclusion of women in the CTs reported in the literature include the confounding effects related to the hormonal cycle, the higher withdrawal rate of women and interactions with other hormonal treatments.[24]

Due to pressure from the U.S. FDA and National Institutes of Health (NIH), feminist movements, and other lobby groups, women are now better represented in sample sizes. Nevertheless, one form of measurement bias persists as 75% of CTs that receive federal funding from NIH,[25] and up to 95% of CT reports to the Spanish Medical Agency[26]do not include sex stratification. If analyses by sex is not considered in the design phase, it is possible that, in the subsequent analysis phase, the overall sample sizes are too small to produce valid results by sex.

The aims of this study were to determine compliance of moxifloxacin CTs with published good practice guidelines for sex and clinical trials[14] and to explore editorial policies on sex differences and women-specific issues in the journal of publication. The rationale for choosing moxifloxacin was that previous publications have not specifically studied therapeutic drugs, such as antibiotics, where the benefit–risk profile differs from that of symptomatic medications. Furthermore, this drug belongs to a group of antibiotics that is consumed by both sexes to the same degree although the adverse effects occur more frequently in women.[27,28]

Methods

We conducted a review of moxifloxacin clinical trials, using as keywords "moxifloxacin" and "avelox," and as limits "humans," in Medline and the Cochrane Library. We identified a total of 173 trials published between January 1998 and December 2010 described in 172 papers of moxifloxacin on adults, published in English (171) and Spanish (1) and excluded those that gave no information about the number or frequency of women and men in the sample (15). Consequently, we retrieved and analyzed a total of 158 CTs (Fig. 1).

In order to conduct a sex analysis of the CTs reviewed, we designed a protocol in accordance with the recommendations of the Food and Drug Administration (FDA) Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs,[14] which included the following variables:

1. Demographic characteristics: inclusion frequencies for women and men, age (range, or failing that, mean), type of patient (healthy or type of infection).
2. CT phase
   - Phase I: to test an experimental drug or treatment in a small group of people for the first time, to gather preliminary data on the agent's pharmacodynamics and pharmacokinetics, and to evaluate its safety, determine a safe dosage range, and identify side effects;
   - Phase II: the experimental treatment is given to a larger group of people to see if it is effective and to further evaluate its safety;
   - Phase III: treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely; and
   - Phase IV: post-marketing studies delineate additional information, including the treatment's risks, benefits, and optimal use.
3. Objective/s of the clinical trials.
4. Limiting omissions (from the gender perspective interest).
5. Sex differences: discussion of the results by sex. Data stratified in order to enable gender analysis of the results. Analysis by sex of efficacy, adverse effects, dose–response, blood concentration–response.
6. Women-specific issues: pregnancy as an exclusion criterion, use of contraceptive methods, use of hormonal contraceptives, and use of hormone replacement therapy (HRT).
7. Excluded from the analysis: editorial policies on sex differences and women-specific issues in the journal of publication.

We analyzed the frequencies and percentages of the variables described above. The main criterion for considering whether a clinical trial fulfilled a sex-related recommendation was any mention of the sex variable in the text. The level of inter-observer agreement (authors E.C. and M.T.R.) was calculated by means of the Kappa index, and a high level of agreement was obtained (Kappa index: 95%). Any lack of agreement (5%) was resolved by a third researcher (A.P.).

The criteria used for the inclusion of clinical trials under each analysis variables were not mutually exclusive (Fig. 1):

- ➢ Sex stratified data and discussion of results by sex: CTs that include both sexes (127 CTs), excluding those that only included one sex or the other.
- ➢ Efficacy by sex: CTs that included both sexes and gave efficacy as an objective (85 CTs).
- ➢ Adverse effects by sex: CTs that included both sexes and gave information about adverse effects (78 CTs).

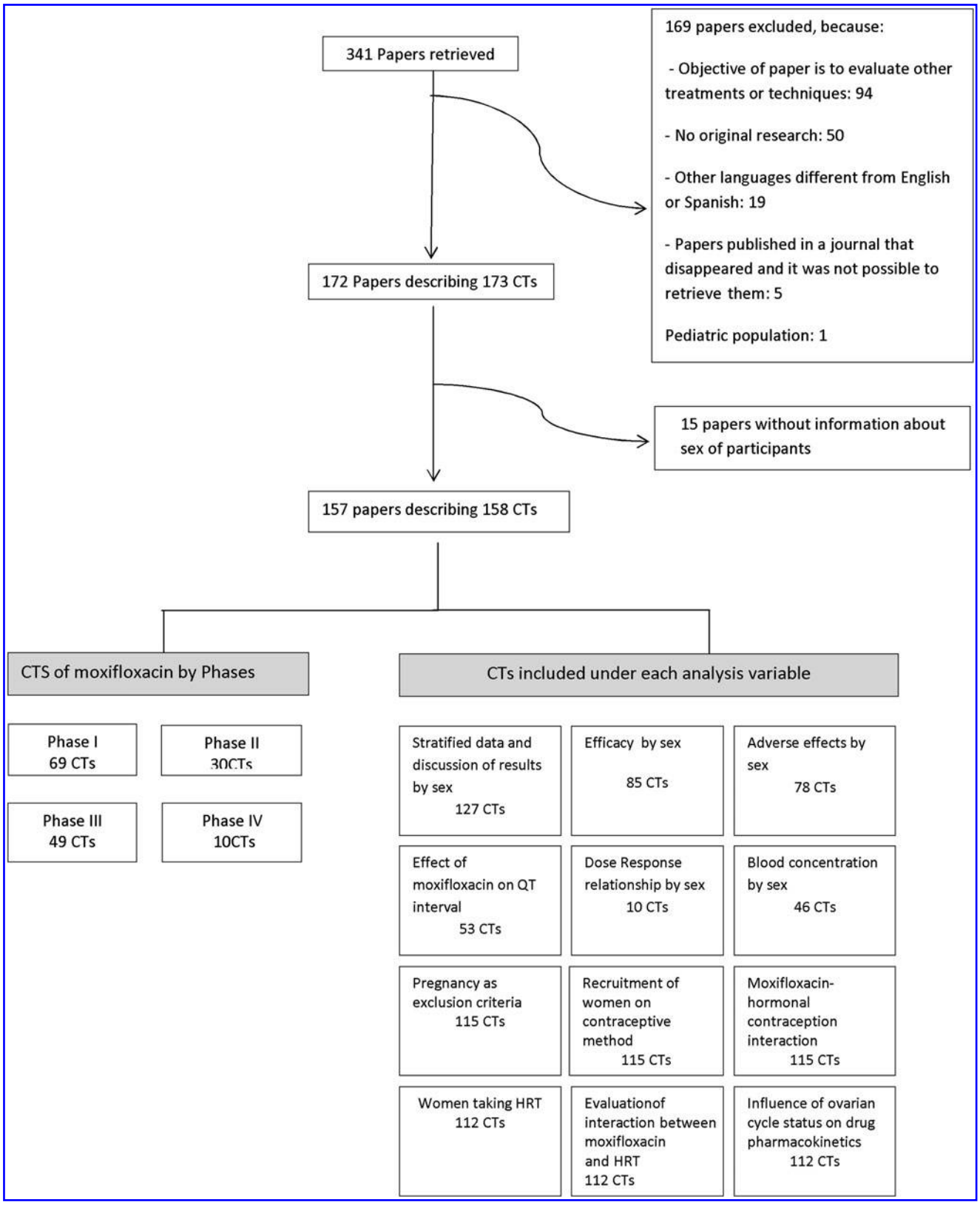

FIG. 1. Diagram illustrating the review process. CTs, clinical trials; HRT, hormone replacement therapy.

- ➢ Effect of moxifloxacin on QT interval: CTs that included both sexes and studied the QT interval after moxifloxacin administration (53 CTs).
- ➢ Dose response relationship: CTs that included both sexes and analyzed the dose-response relationship (10 CTs).
- ➢ Blood concentration by sex: CTs that included both sexes and gave an analysis of the dose-response relationship among their objectives (46 CTs).

For the following variables, only CTs that included women of childbearing age were considered in the analysis: Pregnancy as an exclusion criterion, recruitment of women using a contraceptive method or hormonal contraception, interaction between moxifloxacin and hormonal contraception.

- CTs that included women at menopausal age were included in the analysis of recruitment of women taking HRT, evaluation of interaction of the drug and HRT.
- CTs including women were considered in the analysis of the influence of ovarian cycle status on drug pharmacokinetics.

To determine whether a CT included women of childbearing age or women of menopausal age, we used the study population age data provided by the CTs.

Results

Tables 1 to 4 show the number of subjects (% women) and characteristics of study subjects for 69 phase I CTs[29–95] (Table 1), 30 phase II CTs[96–125] (Table 2), 49 phase III CTs[126–174] (Table 3), and 10 phase IVCTs[175–184] (Table 4). The titles of the journals that published the 158 CTs reviewed also appear. A total of 80,417 individuals participated in the CTs studied, 46.6% (37,474) of whom were women. The frequency of healthy subjects was 1,021 (31% women), while 68,289 had some kind of respiratory infection (46.8% women), 2,082 had eye infections (51.2% women), 1,964 had gastrointestinal infections (47.9% women) and 6,803 suffered other diseases (13.8% women).

Thirty-one CTs were conducted on one sex alone: 23 phase I CTs were performed with 436 men and 3 CTs with 99 women; 3 phase II CTs were conducted with 52 men; and 2 phase III CTs with 1,427 women.

Figure 2 shows that women made up 33.7% of the enrollment in the 69 phase I CTs, 45% of the 30 phase II CTs, 38.3% of the 49 phase III CTs, and in 51.3% of the 10 phase IV CTs.

Fifty-two (40.9%) of CTs stratified randomization by sex, accounting for 42.7% of the women ($n = 15{,}361$ women) included as study subjects in the CTs (Table 5). Only 8 CTs (5.5%) discussed the results by sex (Table 5).

Of the 85 CTs studying efficacy, 15.3% ($n = 13$) conducted an analysis by sex (Table 5). Specifically, 11% of women and 10.8% of men were included. The results of these CTs showed that 11 CTs did not detect any differences (Table 5), 1 CT detected sex differences at the time of peak serum bactericidal activity, and 1 CT found the drug to be more effective in men than in women. Nine percent ($n = 7$) of the 78 CTs that studied adverse effects conducted an analysis by sex (Table 5). These CTs included 42.7% of women, compared with 28.2% of men. However, only 3 CTs (7.4%) analyzed the QT interval by sex, accounting for 1.7% of study subjects of both sexes (269 women and 308 men): 1 CT did not detect significant differences between men and women, but 2 reported increased QT intervals in women (Table 5).

No sex differences were detected in the 3 CTs (8.7%) that analyzed blood concentration by sex (Table 5) and included 1.7% of study subjects of both sexes (25 women and 77 men). None of the CTs studied dose response by sex.

Table 5 shows the FDA recommendations related to women-specific issues. The most frequently observed recommendation was to consider pregnancy as an exclusion criterion in women of childbearing age, used in 52.1% of CTs ($n = 60$). Regarding the recommendations related to contraception, 18.3% of CTs ($n = 21$) included the recommendation to take measures to avoid pregnancy during the trial (either barrier or hormonal contraceptive methods). These CTs only included 13.5% ($n = 4{,}907$) of women participating in CTs with women of childbearing age.

Only 3 CTs mentioned the inclusion of women using hormonal contraceptives (64 women) (Table 5). Furthermore, only 2 CTs conducted a comparison of women taking hormonal contraception and those who were not and analyzed the possible interactions between hormonal contraceptives and moxifloxacin (59 women) (Table 5). None of the CTs involving women of menopausal age specified whether the women were taking HRT. One CT studied the influence of menstrual status, including a comparison between pre- and postmenopausal women (Table 5).

The 158 CTs were published in 59 journals. Of these, only 4[66,73,104,167] CTs were published in 3 journals that recommended analyzing data by sex in their instructions for authors: *Current Medical Research Review*, *Ophthalmology*, and *PLoS One*. One of the 4 provided efficacy results by sex,[167] while the other 3 stratified the study sample by sex.[66,73,104]

Discussion

The main findings of this review of published CTs on moxifloxacin were that fewer women participated in phase I trials. This is significant, as results from this initial phase are used to determine dosage in subsequent phases. The study also revealed that CTs that examined adverse effects included more women than men, and that although a considerable number of CTs stratified by sex in the design phase, only a very small proportion analyzed the results by sex. Moreover, very little attention was paid to the influence of hormones on the action of moxifloxacin. Although an increasing number of policies exist aimed at ensuring the inclusion of women in CTs and the analysis of sex differences, and organizations such as the FDA, NIH,[185] or the General Accounting Office [186] have made considerable efforts in this respect, in practice implementation of such policies is still insufficient according to the information published on CTs of therapeutic drugs such as moxifloxacin.

Since the CT is the paradigm of clinical research, and the fundamental tool for evaluating drugs, the distribution of CT patients by sex should reflect the population of patients that will use the drug once it is on the market.[14] The moxifloxacin CTs included equal numbers of men and women, coinciding with the number of users according to phase IV or postmarketing data.[147,178–186] However, women were underrepresented in phase I, which implies the loss of information necessary for the design of subsequent CT phases.[18]

Table 1. Characteristics of Published Phase-1 Clinical Trials of Moxifloxacin[a]

First author of study	*Journal (year of publication)*	*No. subjects (% women)*	*Age*	*Research focus*	*Objective*	*Limiting omission*
Ober et al.[29] **Germany**	J Antimicrob Chemother (2003)	16 (50.0)	24–76	Acute cholecystitis	To determine the penetration of MXF into gallbladder tissue to evaluate its antibiotic potential in acute cholecystitis	Enough women, sex was not considered in the design or data analysis
Czock et al.[30] **Germany**	Clin J Am Soc Nephrolr (2006)	15 (13.3)	25–76	Acute renal failure	To determine the PK of two quinolone antibiotics in patients who had anuric acute renal failure and were being treated with extended daily dialysis.	Sex not considered in the design Not enough women
Fuhrmann et al.[31] **Austria**	J Antimicrob Chemother (2004)	9 (22.2)	56 ± 17	Acute renal failure	To investigate the PK of intravenous MXF in anuric critically ill patients undergoing continuous venovenous hemodiafiltration	Sex not considered in the design Not enough women No sex analysis performed
Metadillis et al.[32] **Greece**	J Chemother (2007)	14 (57.1)	61.1 ± 8.8	Arthroplasty	To study levofloxacin and MXF into cancellous and cortical bone in patients who underwent routine total hip arthroplasty	Enough women, sex was not considered in the design or data analysis
Breilh et al.[33] **USA**	J Chemother (2003)	49 (10.2)	42–75	Bronchial cancer	To examine the lung tissue diffusion of MXF at a dose of 400 mg administered intravenously or orally once daily, and the results were correlated to microbiological data to estimate the clinical efficacy of MXF in lower community-acquired respiratory infections	Sex not considered in the design Not enough women
Simon et al.[34] **France**	Clin Pharmcol Ther (2003)	16 (18.8)	27–68	Bronchopneumonia	To construct a population pharmacokinetic model for MXF disposition in plasma and bronchial secretions in patients with severe bronchopneumonia who were ventilated	Sex not included in the design Not enough women
Metadillis et al.[35] **USA**	Int J Antimicrob Agents (2006)	8 (25.0)	57.1 ± 9.1	Cardiopulmonary bypass surgery	To investigate plasma and bone concentrations of MXF following a single intravenous dose of 400 mg to consider its potential role in the treatment of osteomyelitis	Sex not included in the design Not enough women
Garcia Saenz et al.[36] **Spain**	J Cataract Refract Surg (2001)	42 (66.7)	76	Cataract surgery	To study the aqueous penetration of ciprofloxacin, levofloxacin, and MXF in patients having cataract surgery	Enough women, sex not considered in the design or data analysis
Kampougeris et al.[37] **Greece**	Br J Ophthalmol (2005)	21 (60.0)	50–87	Cataract surgery	To determine the PK of MXF in the anterior chamber of the human uninflamed eye	Enough women, sex not considered in the design or analysis
Solomon et al.[38] **USA**	Ophthalmology (2005)	52 (59.6)	64	Cataract surgery	To investigate the aqueous penetration of the topical application of three commercially available ophthalmic fluoroquinolones: gatifloxacin 0.3%, MXF 0.5%, and ciprofloxacin 0.3%, administered before cataract surgery.	Sex not included in the design Not enough women
Gehanno et al.[39] **France**	J Antimicrob Chemother (2002)	48 (21.7)	41.7 ± 13	Chronic sinusitis	To determine MXF concentrations in sinus tissue, after oral MXF 400 mg once daily for 5 days to patients with chronic sinusitis, undergoing elective sinus surgery	Sex not included in the design Not enough women

(*continued*)

Table 1. (Continued)

First author of study	*Journal (year of publication)*	*No. subjects (% women)*	*Age*	*Research focus*	*Objective*	*Limiting omission*
Capitano et al.[40] **USA**	Chest (2004)	47 (29.8)	62 ± 13	Diagnostic bronchoscopy	To determine the steady-state, extracellular, and intracellular pulmonary disposition of MXF, levofloxacin, and azithromycin relative to that of the plasma over a 24-hour dosing interval	Sex not included in the design Not enough women
Skalioti et al.[41] **Greece**	Perit Dial Int (2009)	8 (0)	67.59 ± 15.94	Dialysis	To investigate the effect of CAPD on plasma and peritoneal fluid concentration and PK of MXF after administration of one 400 mg dose orally to end-stage renal failure patients undergoing CAPD	Did not include women
Wirtz et al.[42] **Germany**	J Antimicrob Chemother (2004)	22 (27.3)	53.5 ± 15.6	Gastrointestinal tract surgery	To assess the penetration of MXF into GI mucosal tissues to evaluate its potential role as an antimicrobial drug in bacterial infections of the GI tract	Sex not included in the design Not enough women
Wise et al.[43] **United Kingdom**	Antimicrob Agents Chemother (1999)	8 (0)	26–41	Healthy	To examine the PK and penetration of MXF into an inflammatory exudate were examined following a single 400-mg dose given by the oral or i.v. route	Did not include women
Stass et al.[44] **Germany**	Br J Clin Pharmacol (2005)	9 (0)	23–45	Healthy	To evaluate the extent to which enterohepatic recycling circulation contributes to MXF bioavailability in healthy males by administration of activated charcoal and to evaluate the efficacy of activated charcoal administration in decreasing systemic concentrations of MXF in the event of overdose.	Did not include women
Ballow et al.[45] **USA**	Clin Ther (1999)	10 (0)	19–39	Healthy	To compare the pharmacokinetic characteristics of 100 mg of MXF given orally with those of 100 mg of MXF given i.v. (60-minute infusion) to determine the drug's absolute bioavailability	Did not include women
Burkhardt et al.[46] **USA**	Scand J Infect Dis (2002)	12 (0)	24–40	Healthy	To investigate the single- and multiple-dose PK of MXF and its penetration into ascitic fluid in patients with severe liver insufficiency	Did not include women
Edlund et al.[47] **USA**	Scand J Infect Dis (2000)	12 (0)	24–40	Healthy	To compare effects of MXF and clarithromycin on the normal intestinal microflora.	Did not include women
Müller et al.[48] **Austria**	Antimicrob Agents Chemother (1999)	12 (0)	24–36	Healthy	To assess the potential of MXF to penetrate peripheral target sites	Did not include women
Stass et al.[49] **Germany**	Int J Clin Pharmacol Ther (2004)	12 (0)	18–39	Healthy	To confirm preclinical data suggesting that MXF is not metabolized by cytochrome p450 isozymes	Did not include women
Stass et al.[50] **Germany**	Clin Pharmacokinetic (2001)	12 (0)	24–45	Healthy	To investigate the effect of concomitant calcium administration on the PK and tolerability of MXF.	Did not include women

(*continued*)

Table 1. (Continued)

First author of study	*Journal (year of publication)*	*No. subjects (% women)*	*Age*	*Research focus*	*Objective*	*Limiting omission*
Stass et al.[51] **Germany**	Clin Pharmacokinetic (2001)	12 (0)	21–41	Healthy	To investigate the effect of concomitant Al3+(sucralfate) administration on the PK and tolerability of MXF	Did not include women
Stass et al.[52] **Germany**	Clin Pharmacokinetic (2001)	12 (0)	33.7±5.9	Healthy	To investigate the effect of probenecid administration on the PK and tolerability of MXF	Did not include women
Stass et al.[53] **Germany**	Clin Pharmacokinetic (2001)	12 (0)	19–41	Healthy	To investigate the effect of concomitant iron supplements administration on the PK and tolerability of MXF	Did not include women
Stass et al.[54] **Germany**	Clin Pharmacokinetic (2001)	12 (0)	25–46	Healthy	To investigate the effect of concomitant administration of dairy products on the PK and tolerability of MXF	Did not include women
Stass et al.[55] **Germany**	Clin Pharmacokinetic (2001)	12 (0)	21–30	Healthy	To investigate the plasma and urinary PK, safety and tolerability of theophylline and MXF after single and repeated doses of either compound administered alone or concomitantly with the other	Did not include women
Stass et al.[56] **Germany**	J Antimicrob Chemother (1999)	12 (0)	23–41	Healthy	To describe the single-dose PK following oral administration of ascending doses of 50–800 mg as part of the clinical evaluation of MXF	Did not include women
Wagenlehner et al.[57] **USA**	Int J Antimicrob Agents (2008)	12 (0)	18–44	Healthy	To investigate plasma concentrations and the penetration of MXF into prostatic fluid and ejaculate were investigated	Did not include women Sex-specific
Stass et al.[58] **Germany**	Clin Pharmacokinetic (2001)	24 (0)	22–39	Healthy	To determine the effect of concomitant administration of the antacid Maalox 70 or the histamine H receptor antagonist ranitidine on the bioavailability of MXF	Did not include women
Modi et al.[59] **USA**	J Clin Pharmacol (2009)	44 (0)	18–45	Healthy	To evaluate the PK and electrocardiographic pharmacodynamics	Did not include women
Stass et al.[60] **Germany**	Antimicrob Agents Chemother (1998)	45 (0)	23–45	Healthy	To describe the single-dose PK following oral administration of ascending doses of 50–800 mg as part of the clinical evaluation of MXF	Did not include women
Extramiana et al.[61] **France**	Clin Pharmacol Ther (2005)	48 (0)	19–45	Healthy	To assess drug-induced QT interval changes using Holter-monitoring method	Did not include women
Morganroth et al.[62] **USA**	Am J Cardiol (2004)	58 (0)	45–60	Healthy	To evaluate the effects of vardenafil and sildenafil on QT and corrected QT	Did not include women

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Table 1. (Continued)

First author of study	*Journal (year of publication)*	*No. subjects (% women)*	*Age*	*Research focus*	*Objective*	*Limiting omission*
Sullivan et al.[63] **USA**	Antimicrob Agents Chemother (1999)	15 (25.0)	18–45	Healthy	To investigate the PK, safety, and tolerability of 400 mg of MXF given once daily for a prolonged duration (10 days) in healthy male and female volunteers. A second goal was to predict the effectiveness of MXF with PK/pharmacodynamic ratios for potential efficacy	With the small number of subjects, limited conclusions can be made about gender effects in this study
Weiner et al.[64] **USA**	Antimicrob Agents Chemother (2007)	16 (25.0)	30.5–53.0	Healthy	To compare the PK of daily MXF without and with coadministration of rifampin. A secondary objective was to characterize the effects of MDR1 C3435T polymorphisms on MXF's PK	Sex not included in the design Not enough women Sex as confounding factor
Sullivan et al.[65] **USA**	Clin Pharmacokinetic (2001)	36 (33.3)	Men: 18–45 Women: >65	Healthy	To determine the effects of age and gender on PK, surrogate pharmacodynamics, safety, and tolerability of a single dose of MXF.	NA
Barriere et al.[66] **USA**	J Clin Pharmacol (2004)	160 (41.3)	18–40	Healthy	To specifically assess the effect of telavancin on the QTc interval of two dose levels of telavancin compared to negative- and positive-control agents in healthy volunteers	Enough women, sex was not considered in the design or data analysis
Joukhadar et al.[67] **Austria**	Antimicrob Agents Chemother (2003)	12 (41.7)	23–89	Healthy	To determine the penetration characteristics of MXF in patients with soft tissue infections	Enough women, sex not considered in the design or data analysis
Demolis et al.[68] **USA**	Clin Pharmcol Ther (2000)	23 (47.8)	19–32	Healthy	To measure the actual effect of single oral doses of MXF on QT interval duration in healthy volunteers	Enough women, sex not considered in the design or data analysis
Torkildsen et al.[69] **USA**	Clin Ther (2008)	48 (48.0)	40	Healthy	To compare the pharmacokinetic parameters of zithromycin ophthalmic solution 1% and MXF ophthalmic solution 0.5%-in the conjunctiva of healthy volunteers after a single topical administration	Enough women, sex not considered in the design or data analysis
Hart et al.[70] **USA**	Diagn Microbiol Infect Dis (2007)	12 (50.0)	18–40	Healthy	To compare the serum bactericidal activity of MXF and levofloxacin against penicillin-susceptible and penicillin-resistant *Streptococcus pneumoniae*	Even sex analysis was performed, sex was not considered in the design
Lubasch et al.[71] **Germany**	Antimicrob Agents Chemother (2000)	12 (50.0)	21–35	Healthy	Evaluated and compared the PK of six fluoroquinolones after a single oral dose in the same volunteers	Even sex analysis was performed, sex was not considered in the design
Stass et al.[72a] **Germany**	Clin Infect Dis (2001)	24 (50.0)	18–45	Healthy	To address pharmacokinetic interactions with other medications that were selected on the basis of either their known interactions with fluoroquinolones or the adverse event risks associated with their narrow therapeutic range	Enough women, sex not considered in the design or data analysis

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Table 1. (Continued)

First author of study	*Journal (year of publication)*	*No. subjects (% women)*	*Age*	*Research focus*	*Objective*	*Limiting omission*
Noel et al.[73] **USA**	Clin Pharmacol Ther (2003)	48 (50.0)	19–84	Healthy	To assess the effect of levofloxacin, MXF, and ciprofloxacin on the QT and QTc interval	Enough women, sex not considered in the design or data analysis
Donnenfeld et al.[74] **USA**	Curr Med ResOpin (2004)	30 (56.7)	34.4	Healthy	To compare the ocular tolerability of the commercially available ophthalmic solutions of gatifloxacin and MXF	Enough women, sex not considered in the design or data analysis
Price et al.[75] **USA**	J Cataract Refract Surg (2005)	20 (70.0)	24–59	Healthy	To determine whether gatifloxacin 0.3% ophthalmic solution or MXF 0.5% ophthalmic solutions are toxic to the corneal epithelium when used with 1 of 2 dosing regimens in healthy human eyes.	Enough women, sex not considered in the design or data analysis
Shain et al.[76] **USA**	Clin Drug Invest (2002)	30 (100)	31.1 ± 8.6	Healthy	To characterize the potential for combination oral contraceptives to negatively impact the PK of oral MXF due to some similarities in metabolic pathways.	NA
Stass et al.[72b] **Germany**	Clin Infect Dis (2001)	29 (100)	18–60	Healthy	To address pharmacokinetic interactions with other medications that were selected on the basis of the frequency of their coadministration (e.g., oral contraceptives)	NA
Stass et al.[77] **Germany**	Clin Pharmacokinet (2001)	45 (0)	23–45	Healthy and impaired renal function	To evaluate the influence of impaired renal function on the plasma and urinary PK of MXF	Did not include women
Barth et al.[78]	J Antimicrob Chemother (2008)	9 (11.1)	40–78	Hepatic impairment	To investigate the single- and multiple-dose PK of MXF and its penetration into ascitic fluid in patients with severe liver insufficiency	Sex not included in the design Not enough women
Stass et al.[79] **Germany**	Br J Clin Pharmacol (2007)	32 (62.5)	22–44	Impaired renal function	To investigate single dose and steady-state PK of MXF in eight venovenous hemodialysis patients	Enough women, sex not considered in the design or data analysis
Rink et al.[80] **Germany**	Clin Drug Invest (2008)	8 (62.5)	36–83	Intra-abdominal abscess	To examine the penetration of MXF into abdominal abscess fluid in patients with an intra-abdominal abscess	Enough women, sex not considered in the design or data analysis
Malincarne et al.[81] **Italy**	J Antimicrob Chemother (2006)	30 (76.7)	ND	Osteomyelitis	To determine plasma and bone MXF concentrations following intravenous administration of a single 400-mg dose to evaluate the potential role of MXF in the treatment of bone infections	Enough women, sex not considered in the design or data analysis
Wacke et al.[82] **USA**	J Antimicrob Chemother (2006)	60 (21.7)	25–80	Pancreas carcinoma or chronic pancreatitis	To study the penetration of MXF into pancreatic tissue in patients	Sex not included in the design Not enough women
Stass et al.[83] **Germany**	Int J Gynaecol Obstet (2008)	40 (100)	28–60	Pelvic inflammatory disease	To determine whether MXF penetrates the uterine tissue and accumulates at levels sufficient to eradicate the major pathogens causing pelvic inflammatory disease	NA

(*continued*)

Table 1. (Continued)

First author of study	*Journal (year of publication)*	*No. subjects (% women)*	*Age*	*Research focus*	*Objective*	*Limiting omission*
Pea et al.[84] **USA**	Clin Pharmacokinet (2003)	14 (57.1)	68–86	Pneumonia	PK and pharmacodynamics of intravenous levofloxacin in patients with early-onset ventilator-associated pneumonia	Enough women, sex was not considered in the design or data analysis
Stass et al.[85] **Germany**	J Antimicrob Chemother (2006)	10 (30.0)	20–78	Peritonitis	To investigate the penetration of MXF into peritoneal exudate in patients with complicated intra-abdominal infections	Sex variable not included in the design Not enough women
Leone et al.[86] **France**	Antimicrob Agents Chemother (2004)	17 (17.6)	46 ± 10	Pneumonia	To determine the MXF concentrations in bronchial secretions, compared with those in plasma, up to 24 hours after multiple 400-mg i.v. administrations of the drug to mechanically ventilated patients with pneumonia	Sex variable not included in the design Not enough women
Dinis et al.[87] **Portugal**	Ann Otol Rhinol Laryngol (2004)	20 (50.0)	51.8	Recalcitrant chronic sinusitis	To assess MXF distribution pattern into the paranasal sinuses	Enough women, sex not considered in the design or data analysis
Esposito et al.[88] **Italia**	J Antimicrob Chemother (2006)	29 (44.8)	18–58	Tonsillectomy	To determine the MXF concentrations in plasma and tonsillar tissue after the administration of three doses of MXF 400 mg to adult patients with chronic or recurrent tonsillitis undergoing tonsillectomy	Enough women, sex not considered in the design or data analysis
Alffenaar et al.[89] **Netherlands**	Clin Infect Dis (2009)	4 (0)	30–65	Tuberculosis	To measure plasma and cerebrospinal fluid concentrations of MXF over time to establish the optimal dose for treatment of tuberculosis	Did not include women
Johnson et al.[90] **USA**	Int J Tuberc Lung Dis (2006)	45 (5.0)	18–65	Tuberculosis	To evaluate the early bactericidal activity of the new fluoroquinolones levofloxacin, gatifloxacin and MXF in patients with pulmonary tuberculosis	Sex not included in the design Not enough women
Nijland et al.[91] **Indonesia**	Clin Infect Dis (2007)	19 (31.6)	18–55	Tuberculosis	To assess the interaction between rifampicin and MXF	Sex not included in the design Not enough women
Valerio et al.[92] **Italy**	J Chemother (2003)	20 (40.0)	21–81	Tuberculosis	To observe in compliant patients, the effect of 6 months of therapy with MXF, isoniazid, and rifampin	Enough women, sex not considered in the design or data analysis
Fuller et al.[93] **USA**	Am J Ophtalmol (2007)	24 (54.2)	27–83	Vitrectomy	To assess the vitreal penetration of topical, oral, and combined topical and oral MXF	Enough women, sex was not considered in the design or data analysis
Lott et al.[94] **USA**	Retina (2008)	24 (58.3)	37–88	Vitrectomy	To investigate the vitreal penetration of MXF after oral administration.	Even sex analysis was performed, sex was not considered in the design
Vedantham et al.[95] **India**	Eye (2006)	27 (11.1)	20–76	Vitrectomy	To investigate intraocular penetration of MXF hydrochloride after oral administration	Even sex analysis was performed, sex was not included in the design Not enough women

[a]Ordered by research focus and percentage of women participating in the clinical trials.
[72a]First of two clinical trials.
[72b]Second of two clinical trials.
CAPD, continuous ambulatory peritoneal dialysis; GI, gastrointestinal; i.v., intravenous; MXF, moxifloxacin; NA, not applicable; ND, no data; PK, pharmacokinetics.

Table 2. Characteristics of Published Phase-2 Clinical Trials of Moxifloxacin[a]

First author of study	*Journal*	*No subjects (% women)*	*Age*	*Research focus*	*Objective*	*Limiting omission*
Bozkurt et al.[96] **Turkey**	Allergol Immunopathol (2005)	20 (85.0)	38.05 ± 14.1	Antibiotic hypersensitivity	To investigate whether MXF can be among the safe alternative antibiotics determined by oral provocation tests for antibiotic intolerant patients	Enough women, sex was not considered in the design or data analysis
Constantinou et al.[97] **Austalia**	Ophthalmology (2007)	229 (41.5)	12.5–98.8	Bacterial keratitis	To determine the clinical efficacy and safety of MXF (1.0%) in patients with bacterial keratitis compared with patients treated with ofloxacin (0.3%) or fortified tobramycin (1.33%)/cephazolin (5%)	Enough women, sex was not considered in the design or data analysis
Vasavada et al.[98] **India**	J Cataract Refract Surg (2008)	145 (40.7)	55–85	Cataract surgery	To evaluate the aqueous concentration of MXF following two dosing regimens of topically administered MXF hydrochloride ophthalmic solution 0.5%	Enough women, sex was not considered in the design or data analysis
Katz et al.[99] **USA**	Cornea (2005)	61 (50)	48–85	Cataract surgery	To investigate the absorption of MXF into human aqueous humor after administration of MXF hydrochloride ophthalmic solution, 0.5% as base	Enough women, sex was not considered in the design or data analysis
Lane et al.[100] **USA**	J Cataract Refract Surg	47 (59.6)	51–88	Cataract surgery	To evaluate posterior and anterior segment safety of an intracameral injection of MXF 0.5% ophthalmic solution as prophylaxis for endophthalmitis in patients having cataract surgery	Enough women, sex was not considered in the design or data analysis
Ong-Tone et al.[101] **Canadá**	J Cataract Refract Surg (2007)	100 (65)	49–90	Cataract surgery	To determine whether the penetration into the aqueous humor of gatifloxacin and MXF eye drops was affected by altering their concentrations in the dilating mixture in which the wick used to dilate the pupil before cataract surgery was soaked	Enough women, sex was not considered in the design or data analysis
Diz Dios et al.[102] **Spain**	Antimicrob Agents Chemother (2006)	221 (43)	18–57	Dental extraction	To investigate the efficacies of the prophylactic administration of amoxicillin, clindamycin, and MXF for the prevention of bacteremia following dental extractions	Enough women, sex was not considered in the design or data analysis
DeRamo et al.[103] **USA**	Am J Ophthalmol (2006)	42 (57)	49–93	Endophthalmitis	To study the use of gatifloxacin and MXF, and bacterial sensitivity in cases of acute postoperative endophthalmitis following cataract surgery	Enough women, sex was not considered in the design or data analysis
Beyer et al.[104] **USA**	Eur J Clin Microbiol Infect Dis (2000)	12 (0)	24–40	Healthy	To investigate the effect of a 7-day treatment with MXF (400 mg orally, once daily) versus clarithromycin (500 mg orally, twice daily) on the normal oropharyngeal microflora	Did not include women
Man et al.[105] **United Kingdom**	J Antimicrob Chemother (1999)	32 (0)	18–45	Healthy	To assess the potential of MXF to induce phototoxicity when compared with lomefloxacin and placebo	Did not include women

(*continued*)

Table 2. (Continued)

First author of study	Journal	No subjects (% women)	Age	Research focus	Objective	Limiting omission
He et al.[106] **USA**	J Cataract Refract Surg (2009)	120 (50)	24–93	Healthy	To compare selection for fluoroquinolone-resistant bacteria between 1-day and 3-day application of topical MXF 0.5%	Enough women, sex was not considered in the design or data analysis
Sebban et al.[107] **France**	Support Care Cancer (2008)	90 (68.9)	21–80	Healthy	To evaluate MXF use in cancer patients with febrile neutropenia	Enough women, sex was not considered in the design or data analysis
Cheon et al.[108] **Korea**	Helicobacter (2006)	85 (44.7)	54.3 ± 11.7	*H. pylori* infection	To evaluate the efficacy and tolerability of MXF-based triple therapy as an alternative second-line treatment for *H. pylori* infection	Enough women, sex was not considered in the design or data analysis
Kilic et al.[109] **Turkey**	Dig Dis Sci (2008)	120 (47.5)	> 18	*H. pylori* infection	To evaluate the efficacy of MXF-containing regimens in the first-line treatment of *H. pylori*.	Enough women, sex was not considered in the design or data analysis
Bago et al.[110] **Croatia**	Wien Klin Wochenschr (2007)	276 (48.2)	48 ± 13	*H. pylori* infection	To prove the efficacy and tolerability of MXF-based treatment of *H. pylori* infection and to compare it with standard clarithromycin-based treatments	Enough women, sex was not considered in the design or data analysis
Miehlke et al.[111] **Germany**	Helicobacter (2008)	103 (65)	21–79	*H. pylori* infection	To investigate a 1-week once-daily triple therapy with esomeprazole, MXF, and rifabutin for rescue therapy of *H. pylori* infection	Even though there are enough women, sex was not included in the design or analysis
Ta et al.[112] **USA**	J Ocul Pharmacol (2008)	60 (31.7)	69.3	Intraocular surgery	To compare the efficacy of a 1-hour versus 1-day application of topical MXF in eliminating conjunctival bacterial flora	Sex not included in the design Not enough women
Pardillo et al.[113] **Philippines**	Antimicrob Agents Chemother (2008)	8 (0)	22–49	Leprosy	To evaluate bactericidal activity of MXF in human leprosy	Did not include women
Schwab et al.[114] **Germany**	Aliment Pharmacol Ther (2005)	20 (25.0)	53.9 ± 12.5	Obstructive cholangitis and the non-obstructed biliary tract	To establish the secretion of MXF into obstructed and non-obstructed bile	Sex not included in the design Not enough women
Hollan et al.[115] **USA**	Cornea (2008)	50 (56.0)	20–87	Penetrating keratoplasty	To examine the ocular penetration of MXF	Enough women, sex was not considered in the design or data analysis
Guentsch et al.[116] **Germany**	J Periodontol (2008)	92 (52.2)	49.6 ± 9.4	Periodontitis	To evaluate the impact of adjunctive systemic MXF compared to the use of adjunctive systemic doxycycline, well-established regimen, and scaling and root planning alone on the success of periodontitis treatment	Enough women, sex was not considered in the design or data analysis
Burka et al.[117] **USA**	Am J Ophthalmol (2005)	40 (45.0)	21–47	Photorefractive keratectomy	To compare the rate of epithelial healing following photorefractive keratectomy with gatifloxacin and MXF	Enough women, sex was not considered in the design or data analysis

(*continued*)

Table 2. (Continued)

First author of study	*Journal*	*No subjects (% women)*	*Age*	*Research focus*	*Objective*	*Limiting omission*
Moshirfar et al.[118] **USA**	Cornea (2005)	46 (50.0)	12–86	Photorefractive keratectomy	To compare the effects of topical MXF and gatifloxacin on corneal reepithelialization after penetrating keratoplasty	Enough women, sex was not considered in the design or data analysis
Jardim et al.[119] **Mexico, Chile, Brazil, Argentina, Uruguay**	Arch Bronconeumol (2003)	84 (48.8)	>18	Pneumonia	To evaluate the efficacy and safety of treatment with either MXF or amoxicillin administered for 10 days to patients suspected of having CAP caused by a pneumococcal infection	Even though there are enough women, sex was not included in the design or analysis
Ott et al.[120] **Germany**	Infection (2008)	96 (27.1)	37±14	Pneumonia and primary lung abscess	To compare MXF and ampicillin/sulbactam concerning efficacy and safety in the treatment of aspiration pneumonia and primary lung abscess	Sex variable not included in the design Not enough women
Campos et al.[121] **Brazil**	Clin Ophthalmol (2008)	61 (72.1)	29.1	Prophylaxis after LASIK	To compare the efficacy and tolerability of a fixed-dose combination of 0.5% MXF and 0.1% dexamethasone formulation versus conventional dosing with both agents dosed separately for prophylaxis after laser-assisted *in situ* keratomileusis	Women are majority, sex was not included in the design and the analysis
Gosling et al.[122] **Tanzania**	J Respir Crit Care Med (2003)	43 (14.0)	18–70	Tuberculosis	To compare the relative activity of the drugs with control regimens examined at the same time and with historic controls. In this paper, the results of a trial comparing MXF with rifampin and isoniazid are reported	Sex not included in the design Not enough women
Pletz et al.[123] **Germany**	Antimicrob Agents Chemother (2004)	17 (29.4)	50.4±8.7	Tuberculosis	To assess the potency of new antituberculous drugs in clinical studies	Sex not included in the design Not enough women
Burman et al.[124] **USA**	Am J Respir Crit Care Med (2006)	277 (32.9)	24–40	Tuberculosis	To compare the impact of MXF versus ethambutol, both in combination with isoniazid, rifampin, and pyrazinamide, on sputum culture conversion at 2 months as a measure of the potential sterilizing activity of alternate induction regimens	Even sex analysis was performed, sex not included in the design
Conde et al.[125] **Brazil**	Lancet (2009)	146 (38.4)	32.5 (11.7)	Tuberculosis	To assess the activity and safety of MXF in the initial stage of tuberculosis treatment	Even sex analysis was performed, sex not included in the design

[a]Ordered by research focus and percentage of women participating in the clinical trials.
Objective of phase-2 clinical trials: the experimental treatment is given to a larger group of people to see if it is effective and to further evaluate its safety. CAP, community acquired pneumonia.

Table 3. Characteristics of Published Phase-3 Clinical Trials of Moxifloxacin[a]

First author of study	*Journal (year)*	*No. subjects (% women)*	*Age*	*Research focus*	*Objective*	*Limiting omissions*
Ferguson et al.[126] **USA**	Otolaryngol Head Neck Surg (2004)	322 (61.8)	19–84	Acute bacterial rhinosinusitis	To compare the clinical and bacteriologic efficacy and safety of short-duration treatment with telithromycin given for 5 days with MXF given for 10 days in adults with acute bacterial rhinosinusitis	Enough women, sex was not considered in the design or data analysis
Siegert et al.[127] **Finland, France, Spain, Sweden Germany, Greece, Israel**	Respir Med (2000)	493 (55.4)	40.4 ± 14.6	Acute bacterial sinusitis	To compare the efficacy and safety of MXF with that of cefuroxime axetil for the treatment of acute bacterial sinusitis in adults.	Enough women, sex was not considered in the design or data analysis
Rakkar et al.[128] **USA**	Int J Clin Pract (2001)	475 (48.8)	18–67	Acute maxillary sinusitis	To evaluate MXF versus amoxicillin clavulanate in the treatment of acute maxillary sinusitis	Enough women, sex was not considered in the design or data analysis
Gehanno et al.[129] **France**	J Int Med Research (2003)	216 (60.6)	18–80	Acute maxillary sinusitis	To evaluate the efficacy and safety of 7-day oral MXF (400 mg/day) for treatment of acute maxillary sinusitis after first-line treatment failure, and acute sinusitis with high risk of complications.	Enough women, sex was not considered in the design or data analysis
Burke et al.[130] **USA**	Clin Ther (1999)	457 (61.1)	18–78	Acute maxillary sinusitis	To compare the efficacy and safety of MXF with those of cefuroxime axetil for the treatment of community acquired acute sinusitis	Even sex analysis was performed, sex not included in the design
Klossek et al.[131] **France, Spain, Greece, United Kingdom Germany, Sweden, Belgium, Lithuania,**	J Laryngol Otol (2003)	347 (66.6)	38.8 ± 13.9	Acute maxillary sinusitis	To compare of the efficacy and safety of MXF and trovafloxacin for the treatment of acute, bacterial maxillary sinusitis in adults.	Enough women, sex was not considered in the design or data analysis
Miratvilles et al.[132] **USA**	Respir Med (2005)	1147 (19.0)	68.7 ± 9.4	AECB	To identify risk factors for late recovery and failure after ambulatory treatment of exacerbations of chronic bronchitis and COPD.	Sex not included in the design Not enough women
Chodosh et al.[133] **USA**	Respir Med (2000)	936 (22.0)	18–90	AECB	to compare the safety and efficacy of moxifloxacin with clarithromycin for the treatment of patients with AECB	Even sex analysis was performed, sex not considered in the design
Wilson et al.[134] **Austria, Spain, France, Germany, Greece, United Kingdom, Switzerland,**	Chest (2004)	1935 (36.0)	63.2 ± 9.8	AECB	To compare the effectiveness of oral MXF with standard antibiotic therapy in AECB	Sex not included in the design Not enough women
Starakis et al.[135] **USA**	Int J Antimicrob Agents (2004)	162 (36.4)	61.3 ± 13.5	AECB	To compare the efficacy and safety of a 5 day course of MXF 400 mg orally with that of a 7-day course of clarithromycin 500 mg orally in 750 patients with AECB	Sex not included in the design Not enough women
Niederman et al.[136] **USA**	Respir Med (2006)	441 (37.2)	19–90	AECB	To determine the rate of bacterial eradication of *Haemophilus influenzae* during AECB treated with either macrolides or MXF	Enough women, sex was not considered in the design or data analysis

(*continued*)

Table 3. (Continued)

First author of study	Journal (year)	No. subjects (% women)	Age	Research focus	Objective	Limiting omissions
Shaberg et al.[137] **USA**	J Int Med Res (2001)	575 (39.3)	61.3 ± 13.5	AECB	To compare the efficacy and safety of once daily dosing with MXF with that of co-amoxiclav given three times daily for the treatment of AECB	Enough women, sex was not considered in the design or data analysis
Wilson et al.[138] **USA**	Chest (1999)	649 (41.1)	60 ± 14	AECB	To compare the efficacy and safety of MXF and levofloxacin for the treatment of patients with AECB	Enough women, sex was not considered in the design or data analysis
DeAbate et al.[139] **USA**	Respir Med (2000)	464 (45.0)	19–88	AECB	To compare the safety and efficacy of MXF to azithromycin for the treatment of patients with AECB of suspected bacterial origin	Even sex analysis was performed, sex not considered in the design
Urueta-Robledo et al.[140] **Argentina, Peru, Brazil, Mexico, Colombia**	Respir Med (2006)	437 (49.7)	59 ± 15	AECB	To compare the efficacy and safety of MXF and levofloxacin for the treatment of patients with AECB	Enough women, sex was not considered in the design or data analysis
Portier et al.[141] **France**	Eur J Clin Microbiol Infect Dis (2005)	346 (27.5)	59.3 ± 17.9	CAP	To assess the efficacy and safety of MXF versus amoxicillin/clavulanate plus roxithromycin in adult CAP patients with risk factors.	Sex not include in the design Not enough women
Lode et al.[142] **Europe, Israel South Africa, USA**	Respir Med (2003)	479 (33.8)	18–93	CAP	To evaluate IV/PO MXF in the treatment of hospitalized patients with severe CAP	Sex not include in the design Not enough women
Petitprezt et al.[143] **Argentina, Brazil, Czech Republic, Spain, Estonia, France, Hong Kong, Hungary, Lithuania, México, Portugal, Chile, Russia, Slovenia, South Africa, Turkey, Ukrania United Kingdom, Uruguay.**	Chest (2001)	200 (38.0)	52.0 ± 20.5	CAP	To compare of the efficacy and safety of MXF vs amoxicillin for treatment of mild-to-moderate, suspected pneumococcal CAP in adult patients	Enough women, sex was not considered in the design or data analysis
Welte et al.[144] **Germany**	Clin Infect Dis (2005)	397 (37.5)	≥18	CAP	To compare the efficacy, safety, and speed and quality of defervescence of sequential intravenous or oral MXF and high-dose ceftriaxone with or without erythromycin for patients with CAP requiring parenteral therapy	Sex analysis performed sex not considered in the design
Hoefken et al.[145] **Austria, Australia, Germany, Great Britain, Greece, Hong Kong, Israel, Indonesia, New Zealand, Norway, Philippines, Taiwan, South Africa, Sweden, Switzerland**	Respir Med (2001)	675 (38.2)	48.4 ± 20.6	CAP	To compare oral MXF (200 mg or 400 mg once daily for 10 days) with oral clarithromycin (500 mg, twice daily for 10 days) in the treatment of CAP	Enough women, sex was not considered in the design or data analysis

(*continued*)

Table 3. (Continued)

First author of study	*Journal (year)*	*No. subjects (% women)*	*Age*	*Research focus*	*Objective*	*Limiting omissions*
Patel et al.[146] **USA**	Respir Med (2000)	196 (42.3)	18–85	CAP	To evaluate the safety and efficacy of MXF in the treatment of patients with CAP	Enough women, sex was not considered in the design or data analysis
Katz et al.[147] **Germany**	J Emerg Med (2004)	235 (47.2)	18–89	CAP	To evaluate in the treatment of hospitalized patients with severe CAP	Enough women, sex was not considered in the design or data analysis
Marrie et al.[148] **Canada**	J Infect (2004)	399 (48.0)	45.7 ± 15.8	CAP	To describe the resolution of five symptoms commonly associated with CAP	Enough women, sex was not considered in the design or data analysis
Morganroth et al.[149] **USA**	Chest (2005)	394 (49.0)	78	CAP	To assess the cardiac rhythm safety of MXF versus levofloxacin in elderly patients hospitalized with CAP	Sex analysis performed Sex not considered in the design
Anzueto et al.[150] **USA**	Clin Infect Dis (2006)	281 (50.2)	77.4 ± 7.7	CAP	To determine the efficacy and safety of MXF versus that of levofloxacin for the treatment of CAP in hospitalized elderly patients	Sex was included in the design as confounding factor
Torres et al.[151] **Spain**	Eur Respir J (2003)	553 (51.2)	52.7 ± 18.7	CAP	To evaluate the effectiveness of a MXF compared with standard antimicrobial regimens, in conditions relating as closely as possible to the real world setting.	Enough women, sex was not considered in the design or data analysis
Marrie et al.[152] **Canada**	Can Respir J (2004)	76 (60.5)	38.1 ± 14.4	CAP	To determine the time course of the resolution of symptoms in *Mycoplasma pneumoniae* pneumonia	Enough women, sex was not considered in the design or data analysis
McDonald et al.[153] **USA**	Ophthalmology (2009)	533 (53.3)	1–100	Conjunctivitis	To compare the clinical and antimicrobial efficacy of besifloxacin ophthalmic suspension 0.6% with that of MXF ophthalmic solution 0.5% for the treatment of bacterial conjunctivitis	Enough women, sex was not considered in the design or data analysis
Lipsky et al.[154] **USA**	J Antimicrob (2007)	127 (28.4)	57.0 ± 11.8	Diabetic foot infections	To assess the efficacy of MXF for treating diabetic foot infections	Sex variable not included in the design Not enough women
Malangoni et al.[155] **USA, Canada, Israel**	Ann Surg (2006)	379 (35.4)	47.4 ± 16.7	Intraabdominal infections	To compare the safety and efficacy of sequential i.v. to p.o. MXF against a standard antimicrobial regimen of intravenous piperacillin– tazobactam followed by oral amoxicillin– clavulanate for the treatment of adults with complicated intra-abdominal infections	Sex variable not include in the design Not enough women
Kang et al.[156] **Korea**	Helicobacter (2007)	192 (45.3)	22–80	*H. pylori* infection	To test the efficacy of 10-day MXF-based triple therapy versus 2-week quadruple therapy for the second-line treatment of H. pylori infection.	Enough women, sex was not considered in the design or data analysis
Nista et al.[157] **Italy**	Aliment Pharmacol Ther (2005)	320 (45.6)	18–65	*H. pylori* infection	To compare the efficacy of two 1-week MXF-based *H. pylori* eradication regimens with two standard treatments	Enough women, sex was not considered in the design or data analysis
Höffken et al.[158] **USA**	Respir Med (2007)	161 (46)	18–95	Hospital-acquired pneumonia	To evaluate the efficacy and safety of MXF versus ceftriaxone in patients with HAP without risk of infections with *Pseudomonas aeruginosa* and other nonfermentative gram-negative bacteria.	Enough women, sex was not considered in the design or data analysis

(*continued*)

Table 3. (Continued)

First author of study	Journal (year)	No. subjects (% women)	Age	Research focus	Objective	Limiting omissions
Bago et al.[159] **Croacia**	Wien Klin Wochenschr (2009)	160 (48.1)	48 ± 15	*H. pylori* infection	To test the efficacy of 10-day MXF-based triple therapy versus 2-week quadruple therapy for the second-line treatment of *H. pylori* infection.	Enough women, sex was not considered in the design or data analysis
Yoo et al.[160] **Korea**	Helicobacter (2009)	361 (49.0)	55.3	*H. pylori* infection	To evaluate the efficacy of a MXF-containing triple therapy as second-line treatment for *H. pylori* infection. We also investigated the effect of treatment duration and antibiotic resistance on the eradication rate of this therapy	Enough women, sex was not considered in the design or data analysis
Di Caro et al.[161] **Italy**	Aliment Pharmacol Ther (2002)	120 (58.3)	18–65	*H. Pylori* infection	To compare the efficacy of different 1-week MXF-based *H. pylori* eradication regimens	Enough women, sex was not considered in the design or data analysis
Sezguin et al.[162] **Turkey**	Helicobacter (2007)	71 (62.0)	17–65	*H. pylori* infection	To investigate the effectiveness of a new second-generation fluoroquinolone, MXF-containing triple therapy in *H. pylori* eradication	Enough women, sex was not considered in the design or data analysis
Arrieta et al.[163] **Argentina, Brazil, Chile, México**	Am J Otolaryngol (2007)	459 (62.5)	37 ± 14	*H. pylori* infection	To compare the efficacy and safety of MXF with that of amoxicillin/ clavulanate for the treatment of acute bacterial sinusitis in adult	Enough women, sex was not considered in the design or data analysis
Solomkin et al.[164] **China, Indonesia, South Korea, Malaysia, Hong Kong**	Int J Antimicrob Agents (2009)	361 (30.7)	40.3 ± 16.0	Intraabdominal infections	To compare the efficacy and safety of MXF monotherapy and ceftriaxone/metronidazole combination therapy in adults with confirmed or suspected complicated intra-abdominal infections. Patients received surgical intervention and either i.v. MXF 400mg once daily or i.v. ceftriaxone 2 grams once daily plus i.v. metronidazole 500 mg twice daily.	Sex not included in the design Not enough women
Weiss et al.[165] **Germany**	J Chemother (2009)	511 (40.3)	17–94	Intraabdominal infections	To compare the efficacy and safety of sequential i.v. to p.o. MXF 400 mg once daily, with that of i.v. ceftriaxone 2 g once daily, plus metronidazole 500 mg three times daily, followed by p.o. amoxicillin/clavulanate 625 mg three times daily	Enough women, sex was not considered in the design or data analysis
Halachimi-Eyal et al.[166] **Israel**	J Cataract Refract Surg (2009)	464 (51.1)	18–91	Intraocular surgery	To assess the effectiveness of adding topical MXF 0.5% to topical povidone-iodine 5.0% for preoperative reduction of bacterial recovery from the conjunctiva	Enough women, sex was not considered in the design or data analysis
Bradshaw et al.[167] **Australia**	Plos One (2008)	313 (16.9)	ND	Mycoplasma genitalium	To determine clinical outcomes and cure rates for *Mycoplasma genitalium* genital infection in men and women following azithromycin 1 gram.	Sex analysis was performed, sex was not considered in the design
Ross et al.[168] **Denmark, Finland, France, Sweden Rusia Germany, Greece, Hungary, Lithuania, Poland, South Africa, United Kingdom, Italy,**	Sex Transm Infect (2006)	741 (100)	30.1 ± 8.4	Pelvic Inflammatory disease	To compare the efficacy and safety of MXF monotherapy with ofloxacin plus metronidazole in women with uncomplicated pelvic inflammatory disease	Sex specific

(*continued*)

Table 3. (Continued)

First author of study	*Journal (year)*	*No. subjects (% women)*	*Age*	*Research focus*	*Objective*	*Limiting omissions*
Heystek et al.[169] **USA**	Int J STD AIDS (2009)	686 (100)	29.0±7.3	Pelvis inflammatory disease	To demonstrate non-inferiority of once-daily oral MXF compared with combination therapy in the management of acute, uncomplicated pelvic inflammatory disease	Sex specific
Wenisch et al.[170] **USA**	Infection (2006)	63 (69.8)	69±15	Pneumonia	To compare standard therapy with MXF regarding clinical cure/failure rates after start of intrahospital therapy and cure/failure rates of intrahospital therapy 28 days after initiation of intrahospital therapy	Enough women, sex was not considered in the design or data analysis
Morovic et al.[171] **Croatia**	Am J Trop Med Hyg (2005)	77 (14.3)	11–66	Q fever pneumonia	To compare efficacy of clarithromycin, MXF, and doxycycline in the treatment of Q fever pneumonia	Sex not included in the design Not enough women
Giordano et al.[172] **USA**	Int J Antimicrob Agents (2005)	617 (34.6)	18–90	Skin infection	To evaluate the clinical and bacteriological efficacy and tolerability of sequential i.v./p.o. MXF compared with a control regimen of i.v. piperacillin-tazobactam followed by p.o. amoxicillin/clavulanate for the treatment of hospitalized patients with complicated skin and skin structure infections	Sex analysis performed Sex was not considered in the design
Vick- Fragoso et al.[173] **Philippines, Taiwan, Germany, Hungary, Spain, Chile, Israel, Argentina,**	Infection (2009)	804 (39.4)	51.8	Skin infection	To compare sequential intravenous/oral (i.v./p.o.) MXF, 400 mg once daily, and i.v. amoxicillin/clavulanate, 1,000 mg/200 mg three times daily followed by p.o. amoxicillin/clavulanate, 500 mg/125 mg three times daily, for 7–21 days in hospitalized patients	Enough women, sex was not considered in the design or data analysis
Parish et al.[174] **USA**	Int J Clin Pract (2000)	351 (51.6)	44	Skin infections	To compare the efficacy and safety of oral MXF (400 mg once daily, 7 days) versus cephalexin (500 mg three times daily, 7 days) in uncomplicated skin infections	Sex analysis performed Sex not considered in the design

[a]Ordered by research focus and percentage of women participating in the clinical trials.

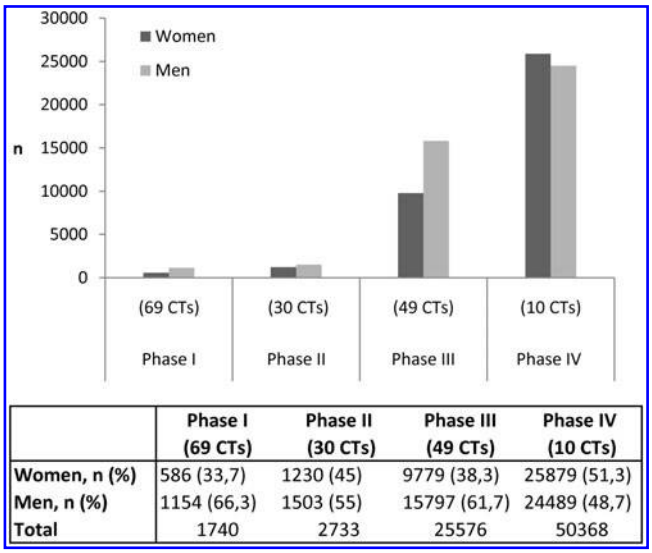
Objective of phase 3: treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it with commonly used treatments, and collect information that will allow it to be used safely.

AECB, Acute exacerbation of chronic bronchitis; COPD, chronic obstructive pulmonary disease; HAP, hospital acquired pneumonia; i.v., intravenous; p.o., oral.

Table 4. Characteristics of Published Phase-4 Clinical Trials of Moxifloxacin[a]

First author	Journal	No. subjects (% women)	Age	Research focus	Objective	Limiting omission
Grassi et al.[175] **USA**	J Chemother (2002)	423 (21.3)	69.3 ± 8.4	AECB	To compare the efficacy and tolerability of a 5-day treatment course with oral MXF vs a 7-day course with intramuscular ceftriaxone in 476 patients with acute exacerbations of chronic bronchitis, and to conduct a cost minimization analysis of the two treatments from the perspectives of both the Italian National Health Service and society	Sex not included in the design Not enough women
Miratvilles et al.[176] **Spain**	Int J Clin Pract (2001)	5,736 (35.4)	66	AECB	To examine the clinical effect of oral MXF on patients' signs and symptoms of AECB	Sex not included in the design Not enough women
Lorenz et al.[177] **USA**	J Int Med Res (2001)	332 (46.1)	16–93	AECB	To compare with the macrolides azithromycin, clarithromycin and roxithromycin in a cohort study to assess clinical, safety, and health-related outcomes of these antimicrobials in general practice settings	Enough women, sex was not considered in the design or data analysis
Koch et al.[178] **USA**	Clin Drug Investig (2004)	1,146 (47.3)	54.3 ± 18.2	CAP	To assess the efficacy, safety and tolerability of oral MXF in outpatients with respiratory tract infections treated in general practices in Germany with the focus on CAP	Sex analysis was performed Sex not considered in the design
Landen et al.[179] **Germany**	J Int Med Res (2001)	15,959 (48.7)	14–60	CAP	To study of the speed, efficacy and tolerability of MXF when used in clinical practice for the treatment of CAP or AECB	Enough women, sex was not considered in the design or data analysis
Barth et al.[180] **Germany**	Clinical Drug Investigation (2005)	1,749 (43.5)	43.4 ± 14.3	Pneumonia	To investigate the efficacy, safety, and tolerability of sequential i.v./o.p. therapy with MXF in pneumonia under general hospital treatment conditions.	Enough women, sex was not considered in the design or data analysis
Liu et al.[181] **China**	Int J Clin Pract (2007)	3,184 (41.0)	20–79	Respiratory tract infections	To assess the efficacy and tolerability of MXF post marketing	Sex analysis performed Sex not considered in the design.
Chen et al.[182] **China**	Clin Drug Investig (2006)	855 (41.1)	50.4 ± 18.5	Respiratory tract infections	To assess the efficacy, safety and tolerability of oral MXF in patients with respiratory tract infections treated by attending physicians in routine clinical practice in China	Sex analysis performed Sex not considered in the design
Faich et al.[183] **USA**	Ann Pharmacother (2004)	18,299 (61.9)	6–97	Respiratory tract infections	To further investigate MXF's general and cardiac safety and evaluate its efficacy in the community practice setting in a large surveillance study	Enough women, sex was not considered in the design or data analysis
Elies et al.[184] **Germany**	Clin Drug Investig (2004)	2,405 (56.8)	43.4 ± 14.3	Sinusitis	To assess the efficacy, safety and tolerability of MXF in patients with respiratory tract infections treated in general practice in Germany	Enough women, sex was not considered in the design or data analysis

[a]Ordered by research focus and percentage of women participating in the clinical trials.
Phase 4: postmarketing studies delineate additional information, including the treatment's risks, benefits, and optimal use.



	Phase I (69 CTs)	Phase II (30 CTs)	Phase III (49 CTs)	Phase IV (10 CTs)
Women, n (%)	586 (33,7)	1230 (45)	9779 (38,3)	25879 (51,3)
Men, n (%)	1154 (66,3)	1503 (55)	15797 (61,7)	24489 (48,7)
Total	1740	2733	25576	50368

FIG. 2. Participation of men and women in published moxifloxacin CTs.

Few CTs conducted an analysis of efficacy by sex, and these included only a small proportion of men and women with respect to the total number of efficacy CTs. This raises the question of whether failure to take sex into account in the design of the sample size reduces a CT's power to detect differences between the two sexes in the subsequent sex-stratified analysis. The case of the adverse effects of moxifloxacin is different. Although few CTs were aimed at identifying adverse effects by sex, these did include a high proportion of both men and women. The results of these CTs were heterogeneous and thus no specific conclusions can be drawn. The variability of results for the occurrence of adverse effects is important, since women have been reported to experience adverse effects with greater frequency.[187] Specifically, four CTs found no sex differences.[47, 65,181,183] In contrast, one CT identified being male as a risk factor,[142] whereas another reported better tolerance in men.[182] One CT[178] reported the possibility of paralytic ileus in one woman, and six women and three men presented mild-to-moderate effects on their central nervous system in another.[27] The Summary of Product Characteristics (SPC)[3] for moxifloxacin indicates that women may be more sensitive to drugs that prolong the QT interval; however, only a few trials have studied differences by sex for this effect. This may be because the effect is already known.[188] The SPC for moxifloxacin indicates that plasma concentration may be higher in women,[3] although the published moxifloxacin CTs did not give pharmacokinetic data by sex.

As regards women-related issues, the use of moxifloxacin is contraindicated in pregnancy, since reversible joint damage has been described in children who had absorbed quinolones.[3] Furthermore, although the reproductive toxicity of moxifloxacin in humans is unknown, other fluoroquinolones have been associated with an increased frequency of miscarriage in pregnant women.[189] According to this information, all CTs that include women of childbearing age should specify pregnancy as an exclusion criterion. However, nearly half did not provide information on whether pregnancy was used as an exclusion criterion, let alone whether subjects were required to take steps to avoid pregnancy during the CT.

The possible influence of hormones on the results of the published moxifloxacin CTs is barely addressed, and thus there is a clear lack of information on the concomitant use of this drug and HRT. When reporting data about interactions between hormone levels and moxifloxacin, the information was sometimes incomplete. This was the case with one CT, which indicated that the use of oral contraceptives was permitted but did not report whether any of the women subjects were taking them nor analyzed the possible effect.[63] According to the study by Stass, moxifloxacin does not interfere with hormonal contraception[72]; however, another study found that hormonal contraceptives lowered the plasma concentration of moxifloxacin, which is an important consideration when treating for pathogens with "borderline susceptibility" to moxifloxacin.[76] Interestingly, the SPC does not mention the interaction between moxifloxacin and hormones.[3]

The pharmaceutical industry has made valuable contributions to the effective treatment of certain diseases and should therefore be an authority on the subject. Consequently, it is difficult to understand why it would risk losing credibility by not complying with recommendations such as considering an analysis by sex in the discussion sections of related articles. This information is easy to include but was only provided in a handful of articles on moxifloxacin. Two of these articles acknowledged that although sex-related differences had been detected, the results were of limited value due to the insufficient number of women included in the trial.[68] In one CT, the authors reported being unable to explain the significance of the sex difference detected in time of peak serum bactericidal activity.[70] Another reported an already well-known difference, namely that being male is a risk factor for mortality in community-acquired pneumonia.[142] A further three CTs mentioned in their discussion sections that no sex-related differences had been detected.[72,65,144]

Regulatory bodies and funding agencies should devise new programs or strategies to improve representation of both sexes in CTs and should oblige researchers to consider sex differences during data analysis. Together with public health authorities, the pharmaceutical industry is facing the new challenge of protecting health by implementing actions that comply with the codes of good scientific practice. As the Canadian Medical Research Council's Advisory Committee on Women in Clinical Trials has suggested, if information is provided by sex for each clinical trial, it would be possible to conduct meta-analyses to determine how women respond to a particular drug.[190] Furthermore, Paula A. Rochon has proposed the publication of subgroup analyses of men and women to facilitate meta-analysis.[15] The recently published CONSORT statement[191] has missed the opportunity to include recommendations from a gender perspective, which would have been decisive in preventing methodological biases in study designs and analyses that limit the accuracy and extrapolation of the findings.[192] In the case of moxifloxacin CTs, only three journals (*Current Medical Research Review*, *Ophthalmology*, *PLoS One*) mentioned this requirement. Although it is possible that many CTs are well designed, based on an adequate number of patients, and include an analysis by sex of the data, this information is not published, perhaps because the researchers did not consider the information to be relevant when they detected no differences. We could improve this situation if scientific journals were to recommend (or oblige) authors to present such data

Table 5. Moxifloxacin Clinical Trial Compliance with Variables Related to Sex Analysis and Women-Specific Issues

Moxifloxacin CT	*CT with sex analysis* n *(%)*	*Women/men in the CT with sex analysis* n *(%)*	*Bibliographic reference*
Stratification 127 CTs 42,471 men 35.948 women	52 (40.9)	15,361 (36.2)/ 18507 (43.6)	[40,66,69,73,79,87,88,93,94,97,98,100–102,108–110,120,121,124,125,132,133,135,136,142–145,150,151,153–156,159,160,164–166,168,170,172,173,177,179,182,184]
Discussion 127 CTs 42,471 men 35,948 women	8	356 (1.0)/ 627 (1.5)	[63,65,68,70,72,84,142,144]
Analysis of efficacy 85 CTs 41,703 men 35,344 women	13 (15.3)	2,304 (11.0)/ 4,501 (10.8)	11 CTs did not detect any differences[70,124,125,128,130,133,139,144,147,167,172,174,182] 1 CT detected sex differences at the time of peak serum bactericidal activity[70] 1 CT found the drug to be more effective in men than in women[182]
Analysis of adverse effects 78 CTs 37,785 men 33,651 women	7 (9.0)	14,055 (42.7)/ 10,648 (28.2)	4 CTs found no sex differences[47,65,181,183] 1 CT identified being male as a risk factor[142] 1 CT reported better tolerance in men[182] 1 CT reported the possibility of paralytic ileus in 1 woman[178] 1 CT and 6 women and 3 men presented mild-to-moderate effects on their central nervous system in another[27]
Analysis of moxifloxacin effect on QT interval 53 CTs 17, 774 men 15,697 women	3 (7.4)	269 (1.7)/ 308 (1.7)	No sex difference[94,29,65]
Analysis of dose-response 10 CTs 5,964 men 2,808 women	0	0	NA
Analysis of blood concentration response 46 CTs 4,528 men 2,762 women	3 (8.7)	25 (1.7)/ 77 (1.7)	[29,65,94]
Pregnancy as exclusion criterion[a] 115 CTs 35,828 subjects	60 (52.1)	21,298 (59.4)/ NA	[38,40,63,64,66,67,69,70,72,76,78,82,83,86,91,94,95,97,108,110,114–116,118–121,124,125,129,130,131,134,135,138–141,144–148,151,152,155,157–159,161,164,172,173,178,180–184]
Recruitment of women using a contraceptive method*,[a] 115 CTs 35,828 subjects	21 (18.3)	4,907 (13.7)/ NA	[39,63,64,66,68,71,72,76,127,128,130,131,137,143,145,169,174,175,177,182]
Recruitment of women using hormonal contraception[a] 115 CTs 35,828 subjects	3 (2.6)	64 (0.2)/ NA	[63,72,76]
Drug and hormonal contraception interaction[a] 115 CTs 35,828 subjects	2 (1.7)	59 (0.2)/ NA	1 CT Hormonal contraceptives lowered the plasma concentration of MXF[76] 1 CT MXF does not interfere with hormonal contraception[72]
Recruitment of women taking HRT[b] 112 CTs 35,327 subjects	0	0/ NA	NA
Interaction of the drug and HRT is evaluated[b] 112 CTs 35,327 subjects	0	0/ NA	NA
Influence of ovarian cycle status on pharmacokinetics of the drug†,[c] 132 CTs 36,651 subjects	1 (1.5)	30 (0.1)/ NA	NA

Adopted from the FDA Guideline for the study and evaluation of gender differences in the clinical evaluation of drugs.[14]
*Either oral or barrier contraception.
†Including comparison between pre and postmenopausal patients.
[a]CTs including women of childbearing age.
[b]CTs including women of menopause age.
[c]CTs including women.
CT, clinical trial; HRT, hormone replacement therapy.

in their editorial instructions, or if the authors were at least to state whether they had conducted (or not) an analysis by sex, and if so, that the results would be made available on request. Knowing that CT results reveal no sex-related differences is also important. Nevertheless, it would be useful to provide incentives to researchers to publish these results separately, and to train junior researchers and students in the skills necessary to analyze CT results, identify the omissions that have occurred (or can occur) and recognize exemplary studies.

The study did have some limitations. As the study was based on the sex differences and gender analyses reported in published clinical trials of moxifloxacin indexed in Medline and the Cochrane Library, it has not covered other relevant characteristics that are worthy of investigation, such as age and ethnicity. In addition, we cannot be totally sure that data by sex is not held by the regulatory authorities or pharmaceutical companies concerned. However, previous studies on reports submitted by pharmaceutical companies to regulatory authorities have indicated that this information does not exist,[26,193] and the main regulatory agencies have no authority (legal means) to compel disclosure of drug effects by gender.

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