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Moxifloxacin and Glucose Homeostasis

A Pooled-Analysis of the Evidence from Clinical and Postmarketing Studies

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Abstract

Background: Recently, clinical data has emerged suggesting that the fluoroquinolone, gatifloxacin, can affect glucose homeostasis through an unknown mechanism. In order to explore the potential effects of moxifloxacin on glucose metabolism in humans, a pooled analysis of phase II/III clinical trials and postmarketing studies was performed and compared with results from an investigation in laboratory animals.

Methods: A pooled analysis of 30 (26 controlled, 4 uncontrolled) oral and two intravenous/oral prospective, controlled phase II/III moxifloxacin studies was performed to evaluate the frequency of hyper- and hypoglycaemic episodes and glucose-related adverse events and adverse reactions (i.e. those considered to be drug related) versus comparator antimicrobials (penicillins, cephalosporins, macrolides, doxycycline, fluoroquinolones). Similar evaluations were conducted on data pooled from five postmarketing surveillance studies. In addition, potential effects of supratherapeutic doses of moxifloxacin on blood glucose and plasma insulin levels in fed and fasted rats were assessed in comparison with those of gatifloxacin, levofloxacin and glibenclamide (glyburide).

Results: The phase II/III database was comprised of 14 731 patients (8474 moxifloxacin, 6257 comparator antimicrobial). There were no drug-related hypoglycaemic adverse events reported for moxifloxacin in either the oral or intravenous/oral database. Two drug-related hypoglycaemic adverse events were reported in the oral comparator group, both following administration of levofloxacin and both of mild severity; one drug-related hypoglycaemic adverse event was reported in the intravenous/oral comparator group after trovafloxacin administration. Drug-related hyperglycaemic adverse events were reported in seven (<0.1%) moxifloxacin and 1 (<0.1%) comparator-treated patients in the oral study database, none of these cases were considered serious and six of the seven moxifloxacin cases were graded as mild and required no countermeasures. There were no cases of drug-related hyperglycaemic events in any patient enrolled in the intravenous/oral studies. Coadministration of oral antidiabetic drugs with moxifloxacin or comparator antimicrobials did not change the rate of blood glucose

increases or decreases in diabetic patients. Data from five moxifloxacin postmarketing studies (46 130 subjects) reported no episodes of hypoglycaemia and two non-drug-related hyperglycaemic episodes. Data from animal studies revealed that supratherapeutic doses of moxifloxacin and levofloxacin did not affect blood glucose or plasma insulin levels in both fed and fasted rats, whereas gatifloxacin decreased both blood glucose and plasma insulin in a dose-dependent manner in fed rats only. The reference compound glibenclamide increased insulin and decreased glucose levels as expected.

Conclusions: Hyperglycaemic or hypoglycaemic adverse reactions were reported rarely in studies with oral or sequential intravenous/oral moxifloxacin, and incidence was comparable in moxifloxacin and comparator groups. Changes in glucose metabolism were also similar in diabetic patients treated with moxifloxacin compared with those patients without diabetes mellitus. This comprehensive analysis of the datapool for moxifloxacin phase II/III clinical trials and postmarketing studies suggests that moxifloxacin administration has no clinically relevant effect on blood glucose homeostasis.

It is well established that certain drugs can alter serum glucose levels, potentially leading to clinically significant hyperglycaemic or hypoglycaemic reactions.[1] The most recognised anti-infective agents that cause elevated blood glucose levels are pentamidine and the protease inhibitors, all of which are associated with hyperglycaemia and new-onset diabetes mellitus.[1-3] At the other end of the clinical spectrum, prolonged periods of drug-induced hypoglycaemia may precipitate serious adverse reactions (e.g. loss of consciousness, encephalopathy).[1] While sulfonylurea agents are linked most often with hypoglycaemic episodes through well-known mechanisms, pentamidine has also been associated with severe episodes of low blood glucose levels.[4,5] Patients at highest risk for a drug-induced hypoglycaemic event include those who have restricted food intake, those who are older in age, and those with underlying hepatic or renal disease.[4] Clinicians must be sensitive to the unique circumstances in which a drug may cause both hyper- and hypoglycaemia in the same patient depending on the time of drug administration.[2]

While the precise mechanism of drug-induced hyper- or hypoglycaemia remains to be elucidated for many of the drugs involved, it is probably multifactorial and dependent, in part, on underlying host factors (e.g. previous pancreatic reserve, nutritional state, use of concomitant medications, or exposure to alcohol).[2] It often remains unclear whether drug-induced changes in glucose metabolism are direct effects of the drug or caused by unmasking of pre-existing diabetic disease.[6] It is also accepted that infection may stimulate an episode of hyperglycaemia possibly based on complex hormonal and associated metabolic changes.[7,8]

Moxifloxacin, a 8-methoxy fluoroquinolone, has a favourable safety profile with no clinical evidence of an effect on glucose metabolism.[9] Because of recent reports of hypo- and hyperglycaemia during treatment with gatifloxacin,[10-14] we have retrospectively analysed pooled data from all completed moxifloxacin phase II/III clinical trials and postmarketing studies taken from the Bayer database of moxifloxacin studies to determine if moxifloxacin therapy in patients with and without a medical history of diabetes mellitus is associated with any effects on glucose metabolism. In addition, supportive data have been derived from a laboratory investigation of blood glucose and insulin levels in rats that were exposed to supratherapeutic doses of moxifloxacin, gatifloxacin, levofloxacin and glibenclamide (glyburide).

Patients and Methods

Phase II/III Clinical Trial Database

Data on glucose homeostasis was collected from 28 prospective, controlled clinical trials (tablet studies n = 26; sequential intravenous/oral studies n = 2) comparing moxifloxacin at a dose of 200–400mg once daily with standard antimicrobial therapies and four uncontrolled clinical trials investigating oral moxifloxacin at a dose of 400mg. Only six of the 26 controlled oral studies (556 patients) used a low (currently not recommended) 200mg dose. All phase III studies were multicentre trials conducted primarily in Europe and North America (table I). Overall, the phase II/III database was comprised of 14 731 patients (8474 moxifloxacin, 6257 comparator antimicrobial).

Comparator antimicrobials included broad-spectrum penicillins (amoxicillin, amoxicillin/clavulanic acid), cephalosporins (cefuroxime-axetil), macrolides (azithromycin, clarithromycin), doxycycline and other fluoroquinolones (trovafloxacin, levofloxacin). For the purpose of this analysis, the safety results with the comparator drugs were pooled.

Antimicrobial treatment duration varied between 5 and 14 days, depending on the primary infection. The clinical trials were similar with regard to design, treatment regimen, and data collection standards (e.g. same 'case report form' with regard to safety information, same instructions and definitions for data entry, etc.). Data recording the effects of study drug on glucose began with the first dose of moxifloxacin or comparator antimicrobial through the 1-month post-therapy follow-up period. To describe the overall experience on glucose homeostasis, event rates (as specified below) were calculated for all treatment groups. For this analysis, controlled and uncontrolled trials were combined. Descriptive statistical methods (i.e. calculation of crude event rates) were used to analyse the data. All results are purely exploratory and cannot be interpreted as confirmatory statistical analyses.

Types and rates of glucose-related adverse events regardless of drug causality and drug-related glucose adverse events (hereafter referred to as adverse reactions) following moxifloxacin therapy were tabulated from the 32 clinical trials. Two analyses of glucose-related adverse events and reactions were performed: investigator reported and a retrospective analysis of serum glucose levels. However, direct comparison of adverse event/reaction rates should be interpreted cautiously, as these two analyses are not comprised of identical patient populations. All rates are calculated as crude rates.

The investigator categorised any abnormality in serum glucose levels as either an adverse event or adverse drug reaction. An adverse event was defined as any treatment-emergent event, as identified by the study's investigator, that occurred during therapy or in the specified follow-up period and did not suggest any relationship to moxifloxacin or the comparator antimicrobial. Adverse drug reactions were those adverse events deemed by the investigator to be possibly or probably related to moxifloxacin or comparator antimicrobial.

The search for adverse events or adverse drug reactions was performed for the entire oral/intravenous database using the COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms) terms 'hyperglycaemia', 'hypoglycaemia' or 'hypoglycaemic reaction'. In this database, the terms 'hyperglycaemia' and 'hypoglycaemia' refer to the laboratory finding of an increase or decrease in blood glucose values that an investigator in the original trial considered to be clinically significant, while the term, 'hypoglycaemic reaction', refers to a symptomatic episode of hypoglycaemia that was reported as a clinical adverse event.

In addition to investigator reported adverse events and adverse reactions, all blood glucose laboratory assessments were evaluated. Specifically, this analysis included the number of patients who had a pretreatment glucose determined within the normal range (or above the upper limit of normal for the analysis of low laboratory abnormalities and below the lower limit of normal for high laboratory abnormalities, respectively), and who had subsequently (during any time of the study) on further blood testing a serum glucose value that was below ('low

Table I. List of the 32 phase II/III/IIIb clinical studies comprising the database for moxifloxacin

Study no. (region)[a]	Phase	Indication	Design	Treatment	Duration (days)
0109 (EU)	II	Acute sinusitis	c, ol, p, r	Moxifloxacin 200mg od Moxifloxacin 400mg od Clarithromycin 500mg bid	7–14 7–14 7–14
0126 (NA)	III	Acute sinusitis	c, db, p, r	Moxifloxacin 400mg od Cefuroxime 250mg bid	7 10
0125 (NA)	III	Acute sinusitis	ol, u	Moxifloxacin 400mg od	7
0116 (EU)	III	Acute sinusitis	c, db, p, r	Moxifloxacin 400mg od Cefuroxime 250mg bid	7 10
0161 (EU)	III	Acute sinusitis	c, db, p, r	Moxifloxacin 400mg od Cefuroxime 250mg bid	10 10
100107 (NA)	IIIb	Acute sinusitis	c, db, p, r	Moxifloxacin 400 mg od Cefuroxime 250mg bid	10 10
100131 (NA)	IIIb	Acute sinusitis	ol, u	Moxifloxacin 400mg od	10
100161 (NA)	IIIb	Acute sinusitis	c, db, p, r	Moxifloxacin 400mg od Trovafloxacin 200mg od	10 10
400012 (EU)	IIIb	Acute sinusitis	c, db, p, r	Moxifloxacin 400mg od Trovafloxacin/200mg od	7 10
0106 (EU)	II	Acute exacerbations of chronic bronchitis	c, db, p, r	Moxifloxacin 200mg od Moxifloxacin 400mg od Cefixime 400mg od	6-14 6–14 6–14
0128 (NA)	III	Acute exacerbations of chronic bronchitis	c, db, p, r	Moxifloxacin 200mg od Moxifloxacin 400mg od Cefuroxime 500mg bid	10 10 10
0127 (NA)	III	Acute exacerbations of chronic bronchitis	c, db, p, r	Moxifloxacin 400mg od Moxifloxacin 400mg od Clarithromycin 500mg bid	10 5 10
84 (EU)	IIIb	Acute exacerbations of chronic bronchitis	c, ol, p, r	Moxifloxacin 400mg od Amoxicillin/clavulanic acid 500/125mg	5 7
85 (EU)	IIIb	Acute exacerbations of chronic bronchitis	ol, u	Moxifloxacin 400mg od	5
10035 (O)	IIIb	Acute exacerbations of chronic bronchitis	c, db, p, r	Moxifloxacin 400mg od Levofloxacin 500mg od	5 7
100243 (NA)	IIIb	Acute exacerbations of chronic bronchitis	c, db, p, r	Moxifloxacin 400mg od Levofloxacin 500mg od	5 7
0124 (EU)	III	Acute exacerbations of chronic bronchitis	c, db, p, r	Moxifloxacin 400mg od Clarithromycin 500mg bid	5 7
100160 (NA)	IIIb	Acute exacerbations of chronic bronchitis	c, db, p, r	Moxifloxacin 400mg od Azithromycin 250mg od	5 5
0112 (O)	II	Community-acquired pneumonia	c, db, p, r	Moxifloxacin 200mg od Moxifloxacin 400mg od Amoxicillin 500mg tid	5–14 5–14 5–14
0119 (EO)	III	Community-acquired pneumonia	c, db, p, r	Moxifloxacin 200mg od Moxifloxacin 400mg od Clarithromycin 500mg bid	10 10 10
0130 (NA)	III	Community-acquired pneumonia	c, db, p, r	Moxifloxacin 400mg od Clarithromycin 500mg bid	10 10
0129 (NA)	III	Community-acquired pneumonia	ol, u	Moxifloxacin 400mg od	10

Continued next page

Table I. Contd

Study no. (region)[a]	Phase	Indication	Design	Treatment	Duration (days)
0140 (EO)	III	Community-acquired pneumonia	c, db, p, r	Moxifloxacin 400mg od Amoxicillin 1000mg tid	10 10
0122 (O)	II	Skin and skin structure	c, db, p, r	Moxifloxacin 200mg od Moxifloxacin 400mg od Cephalexin 500mg tid	5–14 5–14 5–14
0131 (O)	III	Skin and skin structure	c, db, p, r	Moxifloxacin 400mg od Cephalexin 500mg tid, (+) or (−) MET 400mg tid	5–14 5–14
0158 (NA)	III	Skin and skin structure	c, db, p, r	Moxifloxacin 400mg od Cephalexin 500mg tid	7 7
0114 (NA)	II	Uncomplicated urinary tract infection	c, db, p, r	Moxifloxacin 400mg od Cotrimoxazole 160/800mg bid	7 7
0121 (EO)	III	Complicated urinary tract infection	c, db, p, r	Moxifloxacin 400mg od Ofloxacin 200mg bid	7–14 7–14
0134 (EU)	IIIb	Uncomplicated pyelonephritis	c, db, p, r	Moxifloxacin 400mg od Ofloxacin 200mg od	7–10 7–10
0118 (EO)	III	Pelvic inflammatory disease	c, db, p, r	Moxifloxacin 400mg od MET 400mg tid, (+) Doxycycline 100mg bid, (+) 1× ciprofloxacin 500mg	10–14 10–14
200036 (EO)	III	Community-acquired pneumonia	c, ol, r, p	Moxifloxacin 400mg od IV/PO Amoxicillin/clavulanic acid 625mg tid IV/PO ± clarithromycin 500mg bid IV/PO	7–14
100039 (NA)	III	Community-acquired pneumonia	c, db, p, r	Moxifloxacin 400mg od IV/PO Trovafloxacin 200mg IV/PO or Levofloxacin 500 mg od IV/PO	7–14

a Geographical region where study was conducted.

bid = twice daily; **c** = controlled; **db** = double-blind; **EO** = Europe and other countries (excluding NA); **EU** = Europe; **IV** = intravenous; **MET** = metronidazole; **NA** = North America; **O** = excluding NA and EU; **od** = once daily; **ol** = open label; **p** = parallel; **PO** = oral; **r** = randomised; **tid** = three times daily; **u** = uncontrolled.

laboratory abnormality') or above ('high laboratory abnormality') the normal range as defined by the particular laboratory that performed the testing (see definitions below). These low and high laboratory abnormalities may or may not have been reported as an adverse event or an adverse drug reaction by the investigator.

'Very low' serum glucose levels were defined as <50 mg/dL; 'very high' serum glucose levels were defined as >250 mg/dL. It should be emphasised that this analysis is confounded by the fact that a significant number of hospitals only provided normal ranges for glucose values measured at the fasting state (e.g. 70–110 mg/dL). Thus, glucose levels measured in patients who were not fasting most likely fell above the upper limit of normal. For the purpose of this analysis, serum glucose was the parameter evaluated, typically with no information available on whether it was measured in the fasting or not fasting state. This mode of analysis will likely report artificially high rates of glucose values above the upper limit of the normal range, as indicated above. However, the unknown degree of bias in these glucose values should be similar between the moxifloxacin and comparator antimicrobial groups.

A secondary analysis was conducted to investigate whether there were any relevant differences in the qualitative or quantitative adverse experience profile of diabetic patients in the moxifloxacin database compared with non-diabetic patients. Patients were included in the 'diabetics' sub-population if 'diabetes mellitus' (type 1 or 2, with or

without complications, COSTART terminology) was listed as an underlying disease. If this entry was not present, a patient was classified as 'non-diabetic'.

This analysis only included controlled (i.e. comparative) studies and compares moxifloxacin 400mg versus the pooled comparators. Of 11 659 patients participating in the 26 oral trials, 801 (6.9%) were identified as having diabetes (432 moxifloxacin, 369 comparator). For the two controlled intravenous/oral phase III moxifloxacin trials, 184 of 1129 (16.3%) patients (85 moxifloxacin, 99 comparator) were identified as having a clinical diagnosis of diabetes mellitus. Both the investigator-reported and retrospective serum glucose analyses were performed on this cohort.

Postmarketing Surveillance Studies

Following the licensing of moxifloxacin in the US and Europe, five postmarketing surveillance studies were conducted (one in the US, four in Germany).[15-19] A total of 46 130 moxifloxacin-treated patients comprised this database. In these studies, within 48 hours of the patients completing the course of treatment, the investigator performed a follow-up assessment, either in person or by telephone contact. At the follow-up, the investigator collected detailed information on any adverse events. Adverse events were graded according to the investigator's assessment of the relationship to study drug ('probable', 'possible', 'unlikely', 'none', or 'not assessable'). Patients with community-acquired pneumonia (CAP) or sinusitis received once-daily oral moxifloxacin 400mg for 10 days; the majority of acute bacterial exacerbations of chronic bronchitis (AECB) patients received 5 days' treatment.

Animal Investigations

The reference compound glibenclamide was obtained from Sigma-Aldrich Chemicals (Deisenhofen, Germany). Suspensions of thoroughly ground fluoroquinolone tablets gatifloxacin 400mg, moxifloxacin 400mg, levofloxacin 500mg or glibenclamide were freshly prepared on each experimental day using Tylose (0.5%, w/v) in demineralised water.

The present animal investigation was conducted in accordance with the principles outlined in the Declaration of Helsinki and the German law governing the Care and Use of Laboratory Animals. Male rats (about 7 weeks old) were obtained from a commercial breeder (Harlan Winkelmann, Borchen, Germany) and were selected at random for the study. They were fed a standard diet, food and drinking water were available *ad libitum*. After at least 7 days of acclimatisation, the animals were used in the study. Two groups of 35 animals each were fasted over the night preceding the experiment, another two groups of the same size ('fed' rats) retained their *ad libitum* access to the food.

Gatifloxacin, moxifloxacin and levofloxacin were administered orally by gavage at doses of 30 and 100 mg/kg each, glibenclamide was administered orally at a dose of 10 mg/kg bodyweight. Control animals received the vehicle (Tylose 0.5%) in demineralised water. Each treatment group consisted of seven male rats. Approximately 60 minutes before drug/vehicle administration, and approximately 30 and 90 minutes after drug or vehicle administration, blood samples were collected by incision of the sublingual vein plexus, treated with perchloric acid and centrifuged for deproteinisation. The blood glucose level was determined by a colorimetric hexokinase enzyme test (Roche Diagnostics GmbH, Mannheim, Germany). For plasma insulin levels, blood was collected in heparinised tubes and insulin levels measured using a [^{125}I] rat insulin radioimmunoassay kit (Linco Research Inc., St. Charles, MO, USA).

The data reported are rounded group mean values and corresponding standard deviations of the mean. Possible treatment-related effects were statistically evaluated by analysis of variance followed by Dunnett's test for *post hoc* analysis. The level of statistical significance was set to $p < 0.05$.

Results

The incidence rate for any adverse events related to glucose metabolism disturbances was very low

Table II. Oral moxifloxacin phase II/III clinical trial database (controlled and uncontrolled trials): adverse events and adverse drug reactions related to disturbances of glucose homeostasis

	All moxifloxacin (n = 7924) [n (%)]	Moxifloxacin 200mg (n = 556) [n (%)]	Moxifloxacin 400mg (n = 7368) [n (%)]	Comparator antimicrobials (n = 5678) [n (%)]
Adverse events				
Hyperglycaemia	29 (0.4)	3 (0.5)	26 (0.4)	16 (0.3)[a]
Hypoglycaemia	1 (<0.1)	0	1 (<0.1)	3 (<0.1)[b]
Hypoglycaemic reaction	1 (<0.1)	0	1 (<0.1)	0
Adverse drug reactions (possibly or probably drug-related)				
Hyperglycaemia	7 (<0.1)	0	7 (<0.1)	1 (<0.1)[c]
Hypoglycaemia	0	0	0	2 (<0.1)[d]
Hypoglycaemic reaction	0	0	0	0

a Amoxicillin/clavulanic acid (n = 1); cefixime (1); clarithromycin (1); ofloxacin (2); cephalexin (4); cefuroxime axetil (2); amoxicillin (3); levofloxacin (2).

b Amoxicillin (n = 1); levofloxacin (2).

c Cephalexin (n = 1).

d Levofloxacin (n = 2).

for patients receiving oral or intravenous/oral moxifloxacin (table II and table III). The rate of hyperglycaemic adverse events and adverse drug reactions was somewhat higher compared with hypoglycaemic episodes (table II).

Hypoglycaemic Adverse Events and Adverse Drug Reactions

Relatively few hypoglycaemic adverse events were reported by the investigator in both the oral and intravenous/oral trial databases.

For the oral database (table II), two hypoglycaemic events occurred in patients treated with moxifloxacin 400mg (these two events occurred at 1 and 4 weeks following the discontinuation of therapy). Neither of these events was considered to be a drug-related adverse reaction. A total of three hypoglycaemic adverse events were reported from the oral comparator antimicrobial group. Two of these events, both following levofloxacin therapy, were considered to be drug-related adverse reactions and of mild severity. Both levofloxacin-treated patients were older (≥65 years) and had acute exacerbations of chronic bronchitis; each hypoglycaemic episode resolved spontaneously without medical intervention.

Similar findings were found upon examination of the intravenous/oral database (table III). Of five hypoglycaemic adverse events (four moxifloxacin, one trovafloxacin), only one was considered to be related to study drug (trovafloxacin). The trovafloxacin patient was a 77-year-old American Indian with long standing type 2 diabetes mellitus. The hypoglycaemic adverse reaction in this patient was considered to be of moderate severity and resolved following remedial therapy.

Table III. Intravenous/oral moxifloxacin phase II/III clinical trial database (controlled trials): adverse events and adverse drug reactions related to disturbances of glucose homeostasis

	Moxifloxacin 400mg (n = 550) [n (%)]	Comparator antimicrobials (n = 579) [n (%)]
Adverse events		
Hyperglycaemia	18 (3.3)	15 (2.6)[a]
Hypoglycaemia	4 (0.7)	1 (0.2)[b]
Hypoglycaemic reaction	0	0
Adverse drug reactions (possibly or probably drug-related)		
Hyperglycaemia	0	0
Hypoglycaemia	0	1 (0.2)[c]
Hypoglycaemic reaction	0	0

a Trovafloxacin/levofloxacin (n = 7); amoxicillin/clavulanic acid (8).

b Trovafloxacin (n = 1).

c Trovafloxacin (n = 1).

Table IV. Low and high serum glucose abnormalities in the oral and intravenous/oral (IV/PO) moxifloxacin studies (controlled and uncontrolled trials)

	All oral moxifloxacin (200 and 400mg) [n (%)]	All oral comparator antimicrobials [n (%)]	All IV/PO moxifloxacin (400mg) [n (%)]	All IV/PO comparator antimicrobials [n (%)]
Low laboratory abnormalities				
Serum glucose low	255/4826 (5.3)	123/3010 (4.1)	13/229 (5.7)	17/235 (7.2)
Serum glucose <50 mg/dL during or post-therapy	29/4970 (0.6)	12/3137 (0.4)	5/232 (2.2)	3/242 (1.2)
High laboratory abnormalities				
Serum glucose high	774/4052 (19.1)	470/2524 (18.6)	45/93 (48.4)	40/88 (45.5)

Hyperglycaemic Adverse Events and Adverse Drug Reactions

The adverse event incidence for hyperglycaemic findings by investigator reporting was similar between oral moxifloxacin and oral antimicrobial comparators (table II) as well as between intravenous/oral moxifloxacin and intravenous/oral antimicrobial comparators (table III). Hyperglycaemic adverse events were higher in moxifloxacin- and comparator-treated patients in the intravenous/oral studies (3.3% and 2.6%, respectively) compared with those receiving an oral only antimicrobial regimen (0.4% and 0.3%, respectively). This observation probably reflects the increased severity of infection in the intravenous/oral studies (i.e. 40% of patients suffered from severe pneumonia).

Drug-related hyperglycaemic adverse reactions were reported for seven (<0.1%) moxifloxacin- and one (<0.1%) comparator-treated (the comparator patient received cephalexin) patients in the oral study database. The majority of these patients suffered from acute exacerbations of chronic bronchitis and were on a number of concomitant medications during study drug therapy. In particular, most of these episodes occurred in patients with concomitant medications that predispose to glucose tolerance problems, such as corticosteroids. None of the eight cases of hyperglycaemia were considered serious events; in six of the seven moxifloxacin cases the severity was graded as mild, and required no countermeasures. There were no reports of hyperglycaemic adverse drug reactions in any patient enrolled in the intravenous/oral studies.

Abnormally Low and High Serum Glucose Values

The frequency of 'low' and 'high' serum glucose laboratory abnormalities was very similar between moxifloxacin and the antimicrobial comparators in the oral database (table IV). As with investigator-identified adverse events/reactions, high serum glucose laboratory abnormalities were about 4-fold more prevalent than hypoglycaemic episodes. Importantly, the incidence of 'very low' serum glucose levels (<50 mg/dL) at any time during the study period was very similar for patients treated with oral moxifloxacin or an oral antimicrobial comparator (0.6% vs 0.4%, respectively).

Rates of 'low', 'very low', and 'high' serum glucose levels also were similar between moxifloxacin and antimicrobial comparators in the intravenous/oral database (table IV). Despite the small sample size, the rates for 'very low' serum glucose levels (<50 mg/dL) were several-fold higher in the intravenous/oral database (2.2% moxifloxacin vs 1.2% comparator) compared with the oral database. In addition, rates of 'high' blood glucose levels were more than 2-fold higher for patients receiving either intravenous/oral moxifloxacin or comparator antimicrobials than those receiving an oral regimen only.

Diabetic Versus Non-Diabetic Cohort

The incidence of hyperglycaemia, regardless of relationship to study antimicrobial, was higher in diabetic patients compared with non-diabetic patients, as well as in diabetics participating in the sequential intravenous/oral studies compared with

Table V. Oral moxifloxacin phase II/III clinical trial database (controlled trials): adverse events and adverse drug reactions related to disturbances of glucose homeostasis by presence or absence of diabetes mellitus

	With diabetes (n = 801)		Without diabetes (n = 10 858)	
	moxifloxacin 400mg (n = 432) [n (%)]	comparator antimicrobials (n = 369) [n (%)]	moxifloxacin 400mg (n = 5549) [n (%)]	comparator antimicrobials (n = 5309) [n (%)]
Adverse events				
Hyperglycaemia	4 (0.9)	8 (2.2)[a]	19 (0.3)	8 (0.2)[b]
Hypoglycaemia	1 (0.2)	0	1 (<0.1)	3 (<0.1)[c]
Adverse drug reactions (possibly or probably related to study drug)				
Hyperglycaemia	1 (0.2)	0	6 (0.1)	1 (<0.1)[d]
Hypoglycaemia	0	0	0	2 (<0.1)[e]

a Cephalexin (n = 3); cefuroxime axetil (1); amoxicillin (1); ofloxacin (1); levofloxacin (1).

b Amoxicillin (n = 2); amoxicillin/clavulanic acid (1); cephalexin (1); cefuroxime axetil (1); clarithromycin (1); ofloxacin (1); levofloxacin (1).

c Levofloxacin (n = 2); amoxicillin (1).

d Cephalexin (n = 1).

e Levofloxacin (n = 2).

the oral studies (table V and table VI). The frequency of hyperglycaemic events, albeit low among diabetic patients, was higher compared with hypoglycaemic events. Only one hyperglycaemic episode (oral moxifloxacin 400mg group) and one hypoglycaemic episode (intravenous alatrofloxacin) in this diabetic cohort were considered by the investigator to be drug related.

Analyses of 'high', 'very high', 'low', and 'very low' blood glucose levels were also compared for diabetics versus non-diabetics, as well as for diabetics receiving oral antihyperglycaemic medications versus those not receiving such medications (table VII). The data show that 'high' glucose values were far more common than 'low' glucose values for all test groups, although it could not be determined for most values whether the measurements were made during the fasting or fed state. The rate of hyperglycaemia in diabetic patients was greater than the rate in non-diabetic patients, which is anticipated during an infectious disease. In addition, the rates of glucose abnormalities were higher for diabetic patients receiving intravenous/oral antimicrobials compared with diabetic patients given oral antimicrobials. Irrespective of study antimicrobial, patients without diabetes mellitus consistently had a higher frequency of 'low' glucose values (range of 5.7–8.7%) compared with patients with confirmed diabetes (range of 1–4.3%). Of note, concomitant administration of oral antidiabetic drugs did not appear to influence

Table VI. Intravenous/oral moxifloxacin clinical trial database (controlled trials): adverse events and adverse drug reactions related to disturbances of glucose homeostasis by presence or absence of diabetes mellitus

	With diabetes (n = 184)		Without diabetes (n = 945)	
	moxifloxacin 400mg (n = 85) [n (%)]	comparator antimicrobials (n = 99) [n (%)]	moxifloxacin 400mg (n = 465) [n (%)]	comparator antimicrobials (n = 480) [n (%)]
Adverse events				
Hyperglycaemia	3 (3.5)	4 (4.0)[a]	15 (3.2)	11 (2.3)[b]
Hypoglycaemia	3 (3.5)	1 (1.0)[c]	1 (0.2)	0
Adverse drug reactions (possibly or probably related to study drug)				
Hyperglycaemia	0	0	0	0
Hypoglycaemia	0	1 (1.0)[c]	0	0

a Amoxicillin/clavulanic acid (n = 3); levofloxacin (1).

b Amoxicillin/clavulanic acid (n = 5); levofloxacin (3); trovafloxacin (3).

c Trovafloxacin (n = 1).

Table VII. Low and high serum glucose abnormalities in the oral and intravenous/oral (IV/PO) moxifloxacin studies stratified by presence or absence of diabetes mellitus and oral antidiabetic drugs

	All patients with diabetes [n (%)]		All patients without diabetes [n (%)]		Patients with diabetes and oral antidiabetic drug [n (%)]		Patients with diabetes and without oral antidiabetic drug [n (%)]	
	moxifloxacin 400mg	comparator antimicrobials	moxifloxacin 400mg	comparator antimicrobials	moxifloxacin 400mg	comparator antimicrobials	moxifloxacin 400 mg	comparator antimicrobials
Oral studies								
High glucose	52/91 (57.1)	38/67 (56.7)	626/3539 (17.7)	577/3320 (17.4)	20/32 (62.5)	24/35 (68.6)	32/59 (54.2)	14/32 (43.8)
Glucose >250 mg/dL	7/91 (7.7)	4/67 (6.0)	1/3539 (<0.1)	0/3320 (0)				
Low glucose	11/360 (3.1)	3/300 (1.0)	242/4118 (5.9)	221/3851 (5.7)	7/207 (3.4)	1/176 (0.6)	4/153 (2.6)	2/124 (1.6)
Glucose <50 mg/dL	2/360 (0.6)	1/300 (0.3)	18/4118 (0.4)	15/3851 (0.4)				
IV/PO studies								
High glucose	5/5 (100.0)	7/7 (100.0)	74/210 (35.2)	81/218 (37.2)	3/3 (100.0)	7/7 (100.0)	2/2 (100.0)	0/0 (0)
Glucose >250 mg/dL	2/5 (40.0)	0/7 (0)	4/210 (1.9)	1/218 (0.5)				
Low glucose	3/78 (3.9)	4/94 (4.3)	27/428 (6.3)	38/437 (8.7)	2/47 (4.3)	4/63 (6.4)	1/31 (3.2)	0/31 (0)
Glucose <50 mg/dL	1/78 (1.3)	1/94 (1.1)	6/428 (1.4)	5/437 (1.1)				

the rate of 'high' and 'low' glucose laboratory findings, with similar results for diabetics who received moxifloxacin versus diabetics who received comparator antimicrobials.

Severe Hypo-/Hyperglycaemias

Of particular interest and concern are severe hypoglycaemias, defined as blood glucose values <50 mg/dL. Severe hypoglycaemia occurred at very low rates in all groups analysed, with slightly higher frequencies in the intravenous/oral study groups compared with the oral only study groups (table VII). The rate of blood glucose decreases to <50 mg/dL was similar between diabetic patients and non-diabetic patients. None of the moxifloxacin-treated patients with blood glucose levels <50 mg/dL was considered by the investigator as having an adverse event (i.e. clinical symptoms of hypoglycaemia were absent). Examination of 'very high' blood glucose levels (>250 mg/dL) revealed that these increases occurred at relatively low rates in all groups, but were more frequent in diabetic patients compared with non-diabetic patients following both oral moxifloxacin or comparator antimicrobial therapy (table VII). Due to small numbers of diabetic patients in the intravenous/oral database, no meaningful analysis was possible for rates of severe hyperglycaemia.

Postmarketing Data

No episodes of hypoglycaemia were reported from the five postmarketing studies enrolling 46 130 patients.[15-19] Two episodes of hyperglycaemia occurred (both Germany-based trials); neither case was drug related.

Animal Investigation

In fasted vehicle-treated rats, blood glucose levels tended to increase by approximately 0.6 mmol/L over the time of the experiment, while concomitantly plasma insulin levels approximately doubled (figure 1d). These effects can be interpreted as reaction of the animals to the stress of repeated handling and blood sampling.[20] The antidiabetic reference drug glibenclamide significantly de-

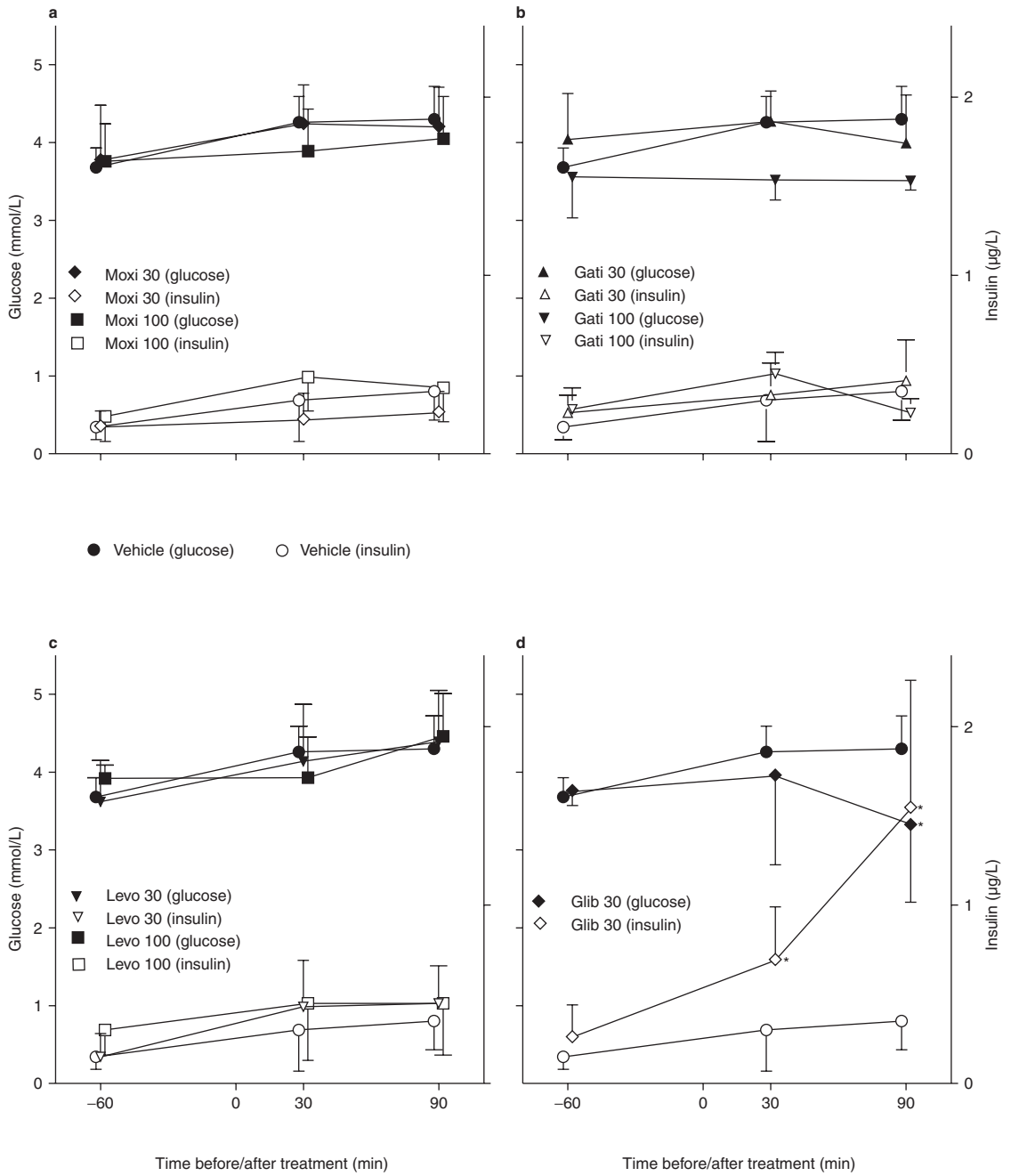

Fig. 1. Blood glucose levels (in mmol/L, filled symbols, left ordinate) and plasma insulin levels (in µg/L, unfilled symbols, right ordinate) in fasted rats 60 minutes before and 30 and 90 minutes following treatment with: (**a**) moxifloxacin (moxi) 30 mg/kg and 100 mg/kg; (**b**) gatifloxacin (gati) 30 mg/kg and 100 mg/kg; (**c**) levofloxacin (levo) 30 mg/kg and 100 mg/kg and; (**d**) the positive reference compound glibenclamide (glib)10 mg/kg. The respective values of vehicle-treated controls are repeated in all four panels. Mean values ± SD of seven animals each; asterisks denote statistically significant differences ($p < 0.05$) versus time-matched vehicle-treated controls. Note that for reasons of improved readability symbols were plotted with a horizontal offset.

creased blood glucose levels in fasted rats (figure 1d). Relative to time-matched vehicle-treated controls, a decrease of approximately 24% occurred 90 minutes after administration of glibenclamide. This decrease was preceded by a significant increase in plasma insulin levels as expected by its insulinotropic mechanism of action (figure 1d).[21]

In comparison, blood glucose levels in fasted rats were differentially affected by the fluoroquinolones tested (figure 1a–c). Within the biological variation, blood glucose level was not affected by levofloxacin or moxifloxacin, whereas, relative to time-matched vehicle-treated controls, it decreased by about 8% and 18% 90 minutes after administration of 30 mg/kg and 100 mg/kg of gatifloxacin, respectively ($p > 0.05$). It should be emphasised that plasma insulin levels in fluoroquinolone-treated animals did not differ from those of vehicle-treated controls (figure 1d).

In fed, vehicle-treated rats, blood glucose and plasma insulin levels remained fairly stable throughout the experiment (figure 2). Glibenclamide increased plasma insulin levels and significantly decreased blood glucose levels by approximately 40% (90 minutes after administration vs time-matched vehicle-treated controls, figure 2d). Similar to fasted rats, levofloxacin and moxifloxacin did not affect blood glucose nor plasma insulin levels in fed rats in the dose range tested (figure 2a and 2c), whereas gatifloxacin decreased both these parameters in a dose-dependent manner (figure 2b). Relative to time-matched vehicle-treated controls, 90 minutes after administration, blood glucose levels were significantly decreased by about 17% and 26% following 30 mg/kg and 100 mg/kg of gatifloxacin, respectively. The decreases in blood glucose were paralleled by decreases in plasma insulin levels (statistically significant 30 minutes after administration of 100 mg/kg; figure 2b).

Discussion

The available preclinical data presented here suggest that moxifloxacin does not significantly affect glucose homeostasis. Single oral administrations of supratherapeutic doses of the fluoroquinolones gatifloxacin, moxifloxacin and levofloxacin differentially altered blood glucose and plasma insulin levels in fasted and in fed rats. Levofloxacin and moxifloxacin were without any effect even at high doses, whereas in fed rats gatifloxacin significantly decreased both blood glucose and plasma insulin levels in an apparently dose-dependent manner. In contrast, the decrease in blood glucose levels following glibenclamide administration was preceded by an increase in plasma insulin levels. Therefore, these data suggest that gatifloxacin causes hypoglycaemia by an insulin-independent mechanism of action. A putative inhibitory action on the hepatic gluconeogenesis and/or glycogenolysis could explain, at least in part, the hypoglycaemic effect of gatifloxacin.

The pooled analysis of data from the 32 moxifloxacin clinical trials summarised in this report is consistent with the results of the preclinical studies also presented in this report. The key findings of this analysis were that the adverse events of hyperglycaemia or hypoglycaemia during oral or sequential intravenous/oral moxifloxacin therapy were rare and occurred at a similar rate to comparator-treated patients. The frequency of hyperglycaemia and hypoglycaemia by investigator-reporting were relatively similar in diabetic and non-diabetic patients who received moxifloxacin, and the frequency of hyperglycaemic and hypoglycaemic episodes was comparable between diabetic patients who were treated with moxifloxacin and diabetic patients who were treated with comparator antimicrobials. These results suggest that moxifloxacin did not place this patient population at increased risk for clinically relevant elevations or reductions in blood glucose.

A thorough analysis of all blood glucose increases (i.e. those above the upper normal limit) and decreases (i.e. those below the upper normal limit), including some events possibly not recognised by the investigator as adverse events, also revealed very similar rates for moxifloxacin and comparator antimicrobials. Hyperglycaemic episodes were observed more frequently than hypoglycaemia, regardless of the specific antimicrobial therapy administered and the causality. However, the frequency of

hyperglycaemic adverse events tended to be somewhat higher in patients receiving intravenous/oral antimicrobials versus oral regimens and in diabetics versus nondiabetic patients. This higher rate of hyperglycaemia in the intravenous/oral antimicrobial group is partially attributable to the higher rate of

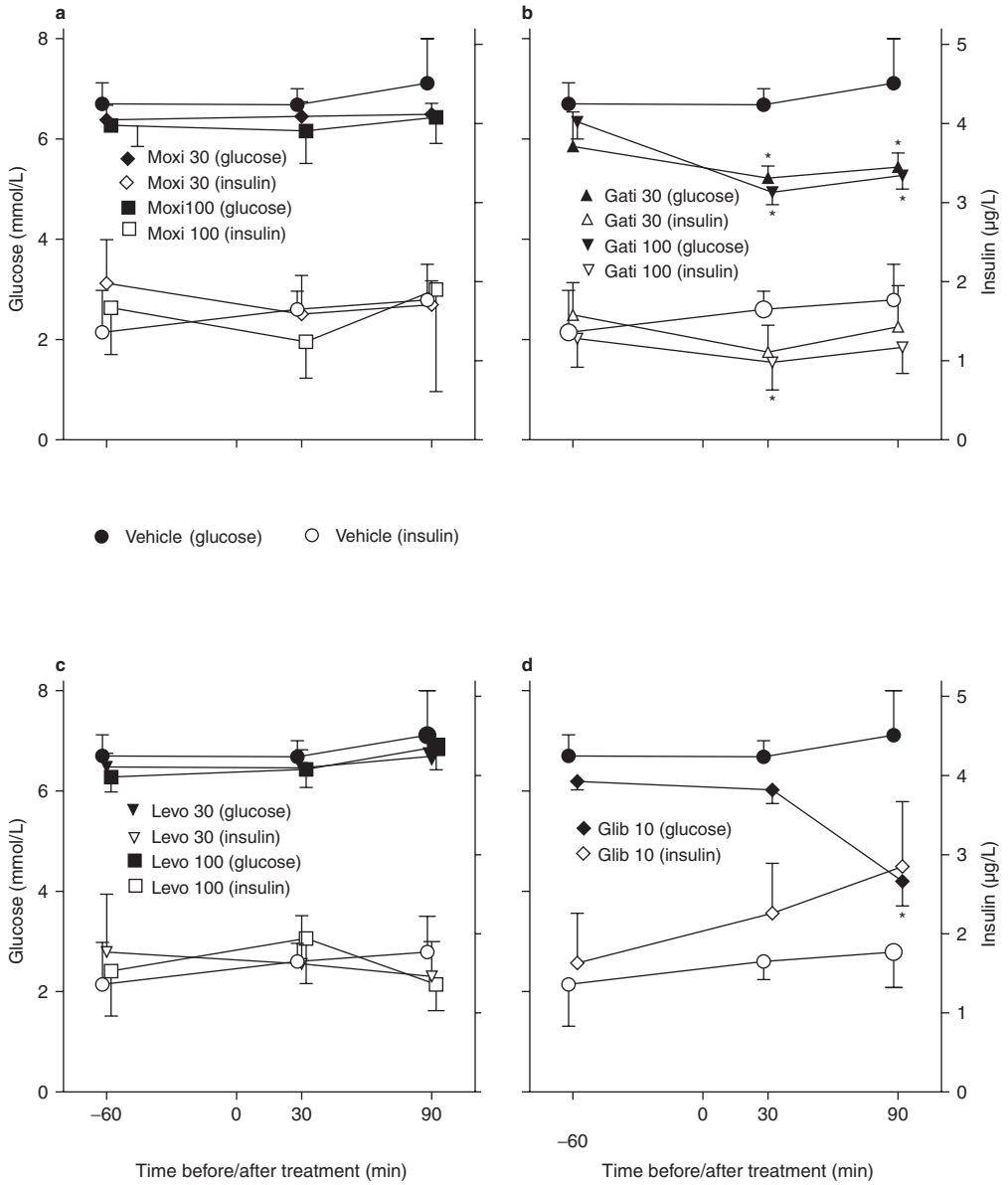

Fig. 2. Blood glucose levels (in mmol/L, filled symbols, left ordinate) and plasma insulin levels (in µg/L, unfilled symbols, right ordinate) in fed rats 60 minutes before and 30 and 90 minutes following treatment with: (**a**) moxifloxacin (moxi) 30 mg/kg and 100 mg/kg; (**b**) gatifloxacin (gati) 30 mg/kg and 100 mg/kg; (**c**) levofloxacin (levo) 30 mg/kg and 100 mg/kg and; (**d**) the positive reference compound glibenclamide (glib) 10 mg/kg. The respective values of vehicle-treated controls are repeated in all four panels (circles). Mean values ± S.D. of six to seven animals each; asterisks denote statistically significant differences ($p < 0.05$) versus time-matched vehicle-treated controls. Note that for reasons of improved readability symbols were plotted with a horizontal offset.

severe infection in this cohort (i.e. a large proportion [40%] had severe community-acquired pneumonia). It is a known phenomenon that an infection, dependent on its severity, may trigger metabolic changes in a patient, leading to hyperglycaemia much more likely than to hypoglycaemia.[7,8] Likewise, a relatively higher rate of hyperglycaemia is also expected for diabetic patients and for those with glucose intolerance who are experiencing a severe infection.

Another contributing factor for the relatively higher rates of hyperglycaemia in the database overall is the fact that many patients were receiving concomitant medications that predispose to glucose intolerance, such as corticosteroids, β-adrenoceptor antagonists, and thiazide diuretics.[6] In contrast, the coadministration of oral antidiabetic drugs (e.g. glibenclamide) with moxifloxacin or comparator antimicrobials did not appear to change the rate of blood glucose level increases or decreases in diabetic patients. It is important to stress that < 0.1% of 14 731 patients receiving moxifloxacin or a comparator antimicrobial experienced a drug-related hyperglycaemic adverse reaction in the controlled and uncontrolled phase II/III trials.

While drug-induced hyperglycaemia is bothersome, episodes of hypoglycaemia especially severe cases (<50 mg/dL) can be a significant medical concern. Hypoglycaemia events considered to be possibly or probably drug-related by the investigator was reported for only three patients in the entire database, none of whom received moxifloxacin therapy. Two patients administered oral levofloxacin and one patient given intravenous alatrofloxacin experienced mild to moderate hypoglycaemia with all episodes resolving uneventfully. Of note, the alatrofloxacin patient had a long-standing history of type 2 diabetes mellitus. Importantly, the incidence of severe blood glucose level decreases (<50 mg/dL) was very low (~0.5%) in moxifloxacin-treated patients.

It is also noteworthy that moxifloxacin has not been associated with clinically significant episodes of hyper- or hypoglycaemia in phase IV/postmarketing observational studies conducted in the US and Germany.[15-19] In the 46 130 patients participating in these observational moxifloxacin trials, no episodes of hypoglycaemia were reported.

Assessment of hyper- and hypoglycaemic adverse events in the phase II/III and phase IV/postmarketing studies is hampered by several limitations. Because all of the pooled analyses were retrospective in nature, there is always the possibility that a clinically significant change in a glucose level might have been detected in a controlled trial designed to specifically evaluate glucose changes. For example, specific definitions of low and high glucose values were not predefined in the original protocols, nor were glucose measurements conducted uniformly under fasting conditions. Patients in this pooled analysis also received moxifloxacin for varying periods of time, had varying underlying comorbid conditions, and were receiving other agents that may have affected glucose measurement. Regardless of these limitations, the degree of bias that may have been introduced by this retrospective analysis should be similar between the moxifloxacin and comparator groups. Most importantly, the investigator-driven analysis rarely identified any clinically significant hypo- or hyperglycaemic adverse reactions that were attributable to moxifloxacin. This observation is further supported by the rare reports of significant low or high glucose events following administration of oral or intravenous moxifloxacin to the general population.

The fluoroquinolone class of antimicrobials is regarded as generally safe and well-tolerated. However, there is concern that certain agents in this class (e.g. gatifloxacin) may place some patients at risk for developing hyperglycaemia, new-onset diabetes mellitus, and/or hypoglycaemia, especially those who are receiving hypoglycaemic agents or insulin.[10] Gatifloxacin has been reported to induce occasional episodes of symptomatic hyperglycaemia and hypoglycaemia based on both premarketing studies and postmarketing surveillance data.[10] The majority of these patients had type 2 diabetes mellitus. To date, five published cases of hypoglycaemia have been reported in the literature following administration of gatifloxacin 400 mg/day (three oral, two intravenous).[11-13] All five patients had

type 2 diabetes and were receiving oral antidiabetic agents; all episodes of hypoglycaemia were reversible following discontinuation of gatifloxacin and administration of intravenous dextrose. A recent report by Ambrose et al. describes ten episodes of serious hyperglycaemia following gatifloxacin administration.[14] All affected patients were aged >65 years; the high glucose levels appear attributable to a high gatifloxacin area under the concentration versus time curve (AUC) secondary to age-related reductions in creatinine clearance. Another study, comprising patients with type 2 diabetes mellitus, maintained on diet and exercise alone, explored the influence of gatifloxacin on blood glucose levels via several mechanisms.[22] Administration of oral gatifloxacin for 10 days was shown to transiently increase serum insulin levels, although no significant effect on long-term fasting serum glucose levels was apparent.[22] Long-term administration with gatifloxacin did not appear to have a significant effect on glucose tolerance and pancreatic β-cell function, as measured by oral glucose tolerance tests and insulin and C-peptide levels.[22] Nonetheless, patients at higher risk for alterations in glucose metabolism (i.e. those with diabetes who are receiving oral hypoglycaemic agents with or without insulin) are advised to closely monitor their glucose levels while on gatifloxacin treatment.[10] Furthermore, elderly patients are at greater risk for potentially serious hyperglycaemia because they may have unrecognised diabetes, age-related decrease in renal function, underlying medical problems, and/or are taking concomitant medications associated with hyperglycaemia.[10]

In summary, this comprehensive analysis of the data pooled from moxifloxacin phase II/III clinical studies, including 14 731 patients, failed to reveal any findings suggestive of a moxifloxacin-induced effect on glucose metabolism. Postmarketing data with moxifloxacin in 46 130 patients provides additional evidence that this quinolone does not induce clinically important changes in glucose metabolism. These clinical data are consistent with the lack of effect evidenced in preclinical studies. Moxifloxacin appears to have a low potential to induce clinically relevant effects on blood glucose homeostasis, even in patients with a clinical diagnosis of diabetes mellitus.

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