WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT
• Owing to its potassium channel blocking properties, moxifloxacin is routinely used as a probe to confirm assay sensitivity in thorough electrocardiogram (ECG) studies.
• A meal has been shown to shorten the QT interval and in some instances it may be desirable to use moxifloxacin after a meal which may affect pharmacokinetics (PK) or pharmacodynamics (PD) or both. However there is no published data.
• There is also a paucity of data investigating ethnic differences of the effects of medicines on QTc.

WHAT THIS STUDY ADDS
• This study defined the difference in the effect of oral moxifloxacin on the QTc interval in the fed and fasted state in healthy Japanese and Caucasian subjects under the rigorous conditions of a thorough QT (TQT) study.
• The study revealed that the apparent difference in QTc effects in fed and fasted conditions is the sum of two distinct effects: (i) a meal primarily delayed and reduced the absorption of moxifloxacin and (ii) the QTc shortening effect of a meal counteracted the QTc prolonging effect of moxifloxacin.
• Subtle differences between Caucasian and Japanese subjects were observed in this study but due to the small sample size these differences were not statistically significant. Caucasians were on average heavier than Japanese subjects resulting in differences in drug exposure.

AIMS
The aims of this study were three-fold and were to (i) investigate the effect of food (fasted and fed state) on the degree of QT prolongation caused by moxifloxacin under the rigorous conditions of a TQT study, (ii) differentiate the effects on QTc, that arise from changes in PK from those arising as a result of electrophysiological changes attributable to raised levels of C-peptide [11] offsetting in part the potassium channel blocking properties of moxifloxacin and (iii) characterize the QTc profile of oral moxifloxacin (400 mg) in healthy Japanese volunteers compared with Caucasian subjects.

METHODS
The study population consisted of 32 healthy non-smoking, Caucasian (n = 13) and Japanese (n = 19), male and female subjects, aged between 20–45 years with a body mass index of between 18 to 25 kg m−2. Female volunteers were required to use an effective contraceptive method or be abstinence. Subjects with ECGs which were deemed unsuitable for evaluation in a TQT study were excluded. ECGs were recorded in triplicate with subsequent blinded manual adjudication of the automated interval measurements. Electrocardiograms in the placebo arm were recorded twice in fasted and fed condition.

RESULTS
The results demonstrated a substantial change in the typical moxifloxacin effect on the ECG. The effect on ΔΔQTc in the fed state led to a significant delay and a modest reduction compared with the fasted state correcting both conditions with the corresponding placebo data. The largest QTc change from baseline in the fed state was observed at 4 h with a peak value of 11.6 ms (two-sided 90% CI 9.1–14.1). In comparison, the largest QTcF change observed in the fasted state was 14.4 ms (90% CI 11.9, 16.8) and occurred at 2.5 h post-dose. The PK of moxifloxacin were altered by food and this change was consistent with the observed QTcF change. In the fast state plasma concentrations of moxifloxacin were considerably and consistently lower in comparison with the fasted state, and this applied to both ethnicities. The concentration–effect analysis revealed that there was no change in slope and confirmed that the difference in this analysis was caused by a change in the PK profile of moxifloxacin. Comparisons of the moxifloxacin effect in the fed state compared with fasted placebo also revealed a pharmacodynamic effect whereby a meal appears to antagonize the effects of moxifloxacin on the lengths of the QTc interval.

CONCLUSIONS
Our findings demonstrate that the food effect by itself leads to a shortening of the QTc interval offsetting in part the effects of a 400 mg single dose of oral moxifloxacin. The typical moxifloxacin PK profile is also altered by food prior to dosing reducing the Cmax and delays the peak effects on QTc, up to several hours thereby reducing the overall magnitude of the effect and delaying the peak QTc prolongation. The contribution of the two effects was clearly discernible. Given that moxifloxacin is sometimes given with food in TQT studies, consideration should be given to adequate baseline corrections and appropriate sampling time points. In this study the PK–PD relationship was similar for Japanese and Caucasian subjects in the fed and fasted conditions, thereby providing further evidence that the sensitivity to the QTc prolonging effects of fluoroquinolones was likely to be independent of ethnicity. The small differences observed between the two subpopulations were not statistically significant. However, future studies should give consideration to formal ethnic comparisons as a secondary outcome parameter as very little is known about the relationship between ethnicity and drug effects on cardiac repolarization.
Introduction

Thorough QTc (TQT) studies are a well-established method for testing the pro-arrhythmic propensity of drugs. The design of these studies is described in guideline documents and is widely documented in literature [1]. An indispensable part of any study designed in accordance with the current International Conference on Harmonisation (ICH) E14 guidelines is the use of a positive control that can change the QTc interval in a reproducible manner and therefore can be used to assure assay sensitivity [2, 3]. The QTc prolonging effects of the anti-bacterial fluoroquinolone, moxifloxacin, have been used in many TQT studies to demonstrate the sensitivity of the assay [4]. In most instances it is used in the fasted state but occasionally it is desirable to administer moxifloxacin in a fed condition. This may alter the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of moxifloxacin. However, there are no published reports on the effects of moxifloxacin on the QTc interval under fed conditions.

Moxifloxacin is a reversible blocker of the rapid component of the delayed rectifier, potassium current of the cardiac \( I_{Kr} \) potassium channel and causes a mean increase of the QTc interval of 10–14 ms between 2 and 4 h after an oral single dose of 400 mg [4–9]. The ICH E14 guidelines state that a positive control used in a TQT study should cause at least a 5 ms change in the QTc [3]. According to the ICH E14 Questions & Answers document [3], two approaches are suggested in which a positive control showing an effect ‘greater than 5 ms,’ or a positive control with an effect ‘close to 5 ms,’ can be used. Recently we have shown that food produces a QTc shortening effect [10] with an effect ‘close to 5 ms,’ or a positive control approaches are suggested in which a positive control the ICH E14 Questions & Answers document [3], two approaches are suggested in which a positive control showing an effect ‘greater than 5 ms,’ or a positive control with an effect ‘close to 5 ms,’ can be used. Recently we have shown that food produces a QTc shortening effect [10] correlated closely with the release of C-peptide and blood glucose concentrations [11]. The PK of moxifloxacin is altered if taken after a meal [4, 12]. However, there is controversy in the literature with some studies reporting that the PK of moxifloxacin do not change after a meal [13, 14]. It is therefore conceivable that food may alter the effect of moxifloxacin on the QTc interval in more than one way when given together. However, the interaction between moxifloxacin and the food effect on cardiac repolarization has not been formally investigated.

Methods

Study design

This study was designed as an open-label, randomized, placebo-controlled, crossover trial that evaluated the effect of a 400 mg oral dose of moxifloxacin in fed and fasted conditions to a baseline and a placebo treatment. Subjects participating in the study attended for screening, two treatment periods (periods 1 and 2) of 4 assessment days each and a follow-up visit (Table 1). Data obtained on study days 1 and 2 compared the ECG effects of different types of food and placebo. These results have been presented elsewhere [10]. Each period consisted of a baseline ECG day (day −1) and treatment days (days 1–3). Moxifloxacin was given in either the fed or fasted condition, on day 3 of each study period. The two periods were separated by at least 3 days to allow for the effects of moxifloxacin to wash-out. No wash-out was required between the other treatments investigated. The ECG and samples for PK and PD analysis on the treatment days were taken at the corresponding clock time points as on the baseline days. Each subject received all treatments and all the comparisons between treatment effects were made intra-individually reducing the anticipated variability and thereby reducing the sample size.

Breakfasts were provided 30 min prior to the scheduled dosing time and were to be consumed 10 min before dosing (time 0). Subjects were served lunch (7 h post-dose), dinner (11 h post-dose) and a snack (13.5 h post-dose). Two types of breakfasts were used, one was a continental breakfast and rich in carbohydrates (used in this publication) and the other was a calorie reduced FDA standard breakfast (data presented elsewhere [10]) which is a very weak blocker of \( I_{Kr} \) \( (I_{C50}, 915 \mu M) \) [18] and so it is also possible that that differences with regard to ethnicity on the QTc cannot be demonstrated at tolerable dose levels i.e. would only become apparent at much higher plasma concentrations. Reports on electrocardiographic and ethnic differences are sparse and largely inconclusive. These differences are not thought to be of any clinical relevance. In addition, ICH E14 states that racial effects are not to be expected and the results of a typical TQT study are not formally analyzed in terms of ethnic differences. Equally, given the lack of evidence to either support or discourage specific investigations in different ethnicities, further studies comparing ECG effects, are desirable [15]. The ICH E5 guideline provides for formal assessments of ethnic differences in drug response and safety. Notably, bridging ECG studies performed in a similar way would allow for meaningful comparisons where ethnicity would be the only variable. In this respect, this is the first study to investigate the effect of moxifloxacin on the QT interval in healthy Japanese and Caucasian subjects within the same study and site.
was low in carbohydrates and rich in fat and not given prior to the moxifloxacin administration. The study (EudraCT: 2011–002423-17, NCT01642485) was approved by a National Health Service (NHS) Research Ethics Committee (London Surrey-Borders, UK) and the Medicines and Healthcare products Regulatory Authority (MHRA) and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

**ECG assessment and QTc evaluation**

Twelve-lead ECGs were recorded using a MAC1200® (500 samples s\(^{-1}\), 4.88 \(\mu\)V amplitude resolution, GE Healthcare, Milwaukee, WI, USA) recorder connected via a fixed network connection to the MUSE® Cardiology Information System (MUSE). All ECGs recorded during the study were stored electronically on the MUSE information system. Only ECGs recorded electronically at a stable heart rate were valid for QT interval measurements. Simultaneous 12-lead Holter ECG recordings were taken from pre-dose to 6 h post-dose for later analysis (data not presented).

Twelve-lead ECG recordings were made at the following time points, pre-dose, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 and 6.0 h post-dose on days –1, 1, 2, and 3 of each period after the subjects had been resting in a supine position for at least 10 min. Clinical staff ensured that subjects were awake during all ECG recordings to avoid autonomic QTc changes occurring during sleep. The use of a semi-permanent skin marker was used to ensure consistent placement of the leads for consecutive study days. At each time point, the ECGs were recorded in triplicate, to reduce variance and improve the precision of measurement. The triplicates were performed at approximately 1 min intervals.

**ECG analysis**

Each electronic ECG data file contained the ECG data as well as the result of the automated ECG analysis performed by the Marquette® 12SL™ ECG Analysis Program (MEAP), software which handles the data within each of the ECG recorders.

All ECGs and their associated automated interval measurements were subsequently reviewed by qualified cardiologists following one of the methods listed in the ICH E14 Guidance for Industry document [2] and ICH E14 Implementation Working Group Questions and Answers document [4] before any of the ECGs were used for the subsequent statistical analyses. The manual adjudication process applied in this study is also referred to in the ICH guidance and relevant literature as ‘manual over-read’ ECG measurements. All ECGs recorded were manually adjudicated by a competent cardiologist to review and document.

The QT interval, RR interval and heart rate, PR interval and QRS duration, the presence or absence of U-waves, quantitative and qualitative ECG variations were assessed by cardiologists with extensive experience with manual on-screen over-reading using electronic callipers using the commercially available MUSE® in its latest version to correct any implausible readings presented by the automated process. For all study ECGs, the over-reading cardiologists were blinded to time, date, treatment and any data identifying the subject. All ECGs pertaining to an individual volunteer were over-read by the same cardiologist to ensure consistency across all treatments. If manual adjustments of the automated measurement became necessary, a second cardiologist confirmed the assessment. Any disagreement between first and second reader was adjudicated by a third and most senior cardiologist.

Fridericia’s heart rate correction (QTcF) was used for adjustment of heart rate changes in line with our previous publication [10], where we showed that QTcF was in good agreement with individual heart rate corrections whereas QTcB was grossly overcorrecting as a meal consistently causes heart rate increases of up to 10 beats min\(^{-1}\).

### Table 1

Summary of study design

<table>
<thead>
<tr>
<th>Period 1 Day –1</th>
<th>Day 1</th>
<th>Day 2</th>
<th>*Day 3</th>
<th>Washout Minimum of 3 days</th>
<th>Period 2 Day –1</th>
<th>Day 1</th>
<th>Day 2</th>
<th>*Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>I</td>
<td>M</td>
<td></td>
<td>P</td>
<td>B</td>
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<td>M + B</td>
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<td>M</td>
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<td>F</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>F</td>
<td>M</td>
<td></td>
<td>P</td>
<td>I</td>
<td>M + B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>P</td>
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<td></td>
<td>I</td>
<td>B</td>
<td>M + B</td>
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<td>P</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>B</td>
<td>F</td>
<td>M + B</td>
<td></td>
<td>P</td>
<td>I</td>
<td>M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>P</td>
<td>M + B</td>
<td></td>
<td>I</td>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For completeness, the entire study design is presented but only *day 3 was part of this study. The data from days 1 and 2 were reported elsewhere [11]. B, high carbohydrate breakfast (>70% carbohydrates); F, calorie reduced FDA standard breakfast; I, insulin + glucose (clamp); M, moxifloxacin; P, placebo.
Statistical analysis

The primary analysis was based on the change of QTcF from the average of all baseline readings. A confirmatory analysis was based on the average of QTcF over all time points between and including 2 and 4 h. Descriptive analyses for each time point separately were also performed. The confirmatory part of the primary analysis followed a hierarchical test procedure testing the following null hypotheses in fixed order: (i) there is no difference between carbohydrate rich breakfast and placebo (test for difference), (ii) there is no difference between calorie-reduced FDA breakfast and placebo (test for difference), (iii) the prolongation under the euglycaemic hyperinsulinaemic clamp [11] at 1:30 h is ≥10 ms (test for non-inferiority), (iv) the absolute difference between the effect of moxifloxacin given in fed and fasted conditions is ≥10 ms (test for equivalence) and (v) there is no difference in the degree of QT prolongation after moxifloxacin (given in fasted state) and placebo between Caucasians and Japanese (test for difference). The results of the first three tests have been published elsewhere [11]. They are reported in this paper to assess the influence of multiplicity to the results.

A linear mixed model with sequence, day, period, gender, ethnicity and treatment as fixed effects, and baseline as covariate was adapted, with subject (nested in sequence, gender and ethnicity) as random effect. Two-sided 90% confidence intervals (CIs) for the difference between each treatment and placebo and between the two types of breakfast were derived. All subjects in the safety dataset who had valid ECG data for time points during days 1–3 of periods 1 and 2 were included in the primary analysis set. All statistical analyses were performed using R version 2.13.0 [19] or later. The descriptive per time point analysis followed the same lines.

Linear modelling of the effect of the moxifloxacin plasma concentration on the difference to placebo only or placebo plus breakfast of the change from average baseline was also performed in an exploratory way. The basic model used fed status as factor, plasma concentration and its interaction with fed status as covariates and an intercept, plasma concentration and its interaction with fed status as random effects with subject as grouping [4]. In addition, gender and ethnicity and their interaction with moxifloxacin concentration were entered as fixed effects into the model. Model fit was investigated by using normal QQ-plots of the residuals. Estimates of slopes and of the effect at a number of concentrations were given together with their 90% two-sided confidence intervals (CIs).

Results

Subject demographics

A total of 32 subjects were included in the study. Subject demographics are presented by descriptive statistics in Table 2.

Confirmatory analysis

The first three null hypotheses of the confirmatory part of the analysis could all be rejected. However, the subsequent null hypothesis of equivalence of the average effect of moxifloxacin on QTcF in fasted and fed state could not be rejected, pointing to a marked difference between the two feeding states.

Comparison of the effect of a single oral 400 mg dose of moxifloxacin on QTcF, given after a meal and given after fasting overnight

The results demonstrated a substantial delay of the effect on QTcF in the fed state compared to the fasted state. The largest QTcF change from baseline in the fed state (Figure 1) was observed at 4 h with a peak value of 11.6 ms (two-sided 90% CI 9.1, 14.1). In comparison, the largest QTcF change observed in the fasted state was 14.4 ms (90% CI 11.9, 16.8) and occurred at 2.5 h post-dose as described previously [10]. The values for each time point are presented in Table 3. The QTcF change was calculated using placebo data collected after a breakfast identical to that used prior to the moxifloxacin administration, thereby eliminating any effect the meal itself may have directly on QTcF [10]. Therefore, the QTcF change observed and

Table 2
Subject demographics

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Gender</th>
<th>n</th>
<th>Age (years)</th>
<th>SD</th>
<th>Height (cm)</th>
<th>SD</th>
<th>Body weight (kg)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>All</td>
<td>13</td>
<td>25.6</td>
<td>4.7</td>
<td>172.8</td>
<td>9.7</td>
<td>65.1</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>7</td>
<td>25.0</td>
<td>4.5</td>
<td>178.4</td>
<td>6.2</td>
<td>68.3</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>6</td>
<td>26.3</td>
<td>5.2</td>
<td>166.3</td>
<td>9.1</td>
<td>61.4</td>
<td>6.4</td>
</tr>
<tr>
<td>Japanese</td>
<td>All</td>
<td>19</td>
<td>27.6</td>
<td>3.3</td>
<td>167.2</td>
<td>7.2</td>
<td>58.0</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>11</td>
<td>26.6</td>
<td>3.3</td>
<td>171.2</td>
<td>5.2</td>
<td>59.8</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>8</td>
<td>29.0</td>
<td>3.1</td>
<td>161.6</td>
<td>5.8</td>
<td>55.5</td>
<td>5.4</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>32</td>
<td>26.8</td>
<td>4.0</td>
<td>169.5</td>
<td>8.6</td>
<td>60.9</td>
<td>7.3</td>
</tr>
</tbody>
</table>
displayed in Figure 1 represents a change in QTcF caused by the altered PK of moxifloxacin in blood if administered after a meal.

**Moxifloxacin plasma concentration and changes in QTcF in fed and fasted condition**

The moxifloxacin plasma concentration time course (Figure 2) revealed that the PK of moxifloxacin were altered by food and this change in PK is consistent with the observed QTcF change. In the fasted state plasma concentrations of moxifloxacin were considerably and consistently lower in comparison with the fasted state, and this applied to both ethnicities. The concentration effect analysis

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**Table 3**

Changes in QTcF by time point after a single dose of 400 mg moxifloxacin in the fed and fasted state

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Fasted estimate (ms) (90% CI)</th>
<th>Fed estimate (ms) (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:00</td>
<td>0.7 (-1.7, 3.2)</td>
<td>0.8 (-1.6, 3.3)</td>
</tr>
<tr>
<td>0:25</td>
<td>1.7 (-0.8, 4.2)</td>
<td>1 (-1.5, 3.6)</td>
</tr>
<tr>
<td>0:50</td>
<td>9.3 (3.3, 12.3)</td>
<td>-0.1 (-3.1, 2.8)</td>
</tr>
<tr>
<td>0:75</td>
<td>11.9 (9, 14.7)</td>
<td>1.2 (-1.6, 4.4)</td>
</tr>
<tr>
<td>1:00</td>
<td>12.1 (8.4, 14.9)</td>
<td>3.8 (1, 6.5)</td>
</tr>
<tr>
<td>1:50</td>
<td>12.6 (9.9, 15.3)</td>
<td>1.8 (-1, 4.5)</td>
</tr>
<tr>
<td>2:00</td>
<td>13.2 (10.5, 15.8)</td>
<td>5.8 (3.2, 8.4)</td>
</tr>
<tr>
<td>2:50</td>
<td>14.4 (11.9, 16.8)</td>
<td>5.8 (3.3, 8.3)</td>
</tr>
<tr>
<td>3:00</td>
<td>13 (10.6, 15.5)</td>
<td>7.4 (5, 9.9)</td>
</tr>
<tr>
<td>3:50</td>
<td>12.2 (9.8, 14.7)</td>
<td>10.1 (7.7, 12.6)</td>
</tr>
<tr>
<td>4:00</td>
<td>13.6 (11.2, 16.1)</td>
<td>11.6 (9.1, 14.1)</td>
</tr>
<tr>
<td>6:00</td>
<td>11.9 (9.6, 14.2)</td>
<td>10.6 (8.3, 12.9)</td>
</tr>
</tbody>
</table>
Pharmacokinetics of 400 mg oral moxifloxacin in the fed and fasted state in TQT studies

The primary purpose of this study was to characterize the QTcF effect curve of a single oral dose of moxifloxacin in Japanese and Caucasian subjects. Both ethnicities showed prolongation in the mean QTcF interval after a single oral 400 mg moxifloxacin dose in the fasted state compared with placebo (Figure 4A).

**Greatest change from baseline in the fasted state** The greatest change from baseline (20 ms; two-sided 90% CI 14.9, 25.1) was observed in the fasted state for Japanese subjects at 3 h (Figure 4A).

**Greatest change from baseline in the fed state** The greatest change from baseline (13.7 ms; two-sided 90% CI 9.9, 17.5) was observed in the fed state for Caucasian subjects at the 4 h time-point (Figure 4B).

**PK-ΔΔQTcF relationship (fed/fasted) for Japanese and Caucasian subjects**

The relationship between QTcF and the moxifloxacin plasma concentration in Japanese and Caucasian subjects in the fed and fasted state is shown in Figure 5. An increase in plasma moxifloxacin concentration was associated with QTcF prolongation in both the Japanese and Caucasian subjects. This relationship was similar for both ethnicities. More specifically, the intercept was below 1 ms in magnitude for both ethnicities and the slopes differed by less than 10%. Neither the difference between slopes nor that between intercepts for the two groups was statistically significant and the 95% CI for the difference in slopes was below 2 ms µg⁻¹ ml⁻¹, i.e. below 40% of the slope. The predicted difference between ethnicities at the geometric mean Cmax was 1.4 ms, with a 95% two-sided confidence interval of (−2.5, 5.5). Overall, in statistical terms the slopes did not differ between the fed and fasted state.

**Cmax, tmax and corresponding ΔΔQTcF effect at tmax of moxifloxacin**

Values of Cmax, ΔΔQTcF, and tmax of moxifloxacin in the fed and fasted condition are shown in Table 4. These findings together with the PK data displayed in Figure 2, reveal that in the fasting condition, the moxifloxacin plasma concentrations and effects on QTcF for Caucasians do not change much over the time interval 1–4 h post-dosing, indicating that no clear systematic effect on tmax can be seen in this condition. Caution should be applied to the interpretation of these results because of the wide confidence intervals, particularly in the subgroups.

**Discussion**

**The effect of a meal on QTcF and the interaction of moxifloxacin**

The primary purpose of this study was to characterize the QTcF effect curve of a single oral dose of moxifloxacin.
when given with food to the well characterized QTcF effects in the fasting condition. A further important purpose of the study was to ascertain whether and if so, how, the effect of a meal with a corresponding rise in C-peptide on the QTcF interval may interact with the effects of an I\textsubscript{Kr} channel blocker such as moxifloxacin. In a study by Bloomfield et al. [12] a transient decrease in the change in QTc from baseline at 5 and 6 h post-dose in both the moxifloxacin and placebo treatment groups was observed, suggesting that food may be responsible

Figure 4
\(\Delta QTc_F\) in fasted and fed state in healthy Japanese and Caucasian subjects. The difference between the two curves represents the effect of the moxifloxacin on QTcF in Japanese and Caucasian. A) shows the time course relationship in the fasting condition and B) after breakfast (fed). (A) –, fasted Japanese; –, fasted Caucasian; (B) –, fed Japanese; –, fed Caucasian

Figure 5
PK-\(\Delta QTc_F\) relationship (fed/fasted) for Japanese and Caucasian subjects. The PK-PD relationship by ethnicity: Japanese volunteers show a slightly steeper dose-response curve than Caucasian volunteers in the fasted state (A). However, this is reversed in the fed state (B). In this study, the sample size was small and the effect was likely to have been caused by random effect owing to the small sample size. *, female; †, male; –, Japanese; –, Caucasian

for attenuating the QTcF prolongation caused by moxifloxacin. This could suggest that food might have an effect which would go beyond the alterations of PK by the modification of absorption of moxifloxacin as the meal was given 4 h after moxifloxacin. Our findings show that the typical moxifloxacin profile is changed significantly if given after a meal. When comparing the effect of the fed and fasted states, it is apparent that it is not so much the size of the maximum effect that differs between the two states but rather that there is a
significant delay of the peak effect in the fed state. The differences in plasma concentrations of moxifloxacin in the fed and fasted condition infer that food reduces the plasma concentration of moxifloxacin, which in turn alters its effect on the QTcF interval. This finding is consistent with that reported by Florian et al. [4], whereby significantly higher mean Cmax values of 3085 ng ml$^{-1}$ were observed when moxifloxacin was administered in the fasted state compared with Cmax in subjects who received a meal within 3 h of moxifloxacin administration (2668 ng ml$^{-1}$), indicating a decreased rate of absorption when moxifloxacin is ingested with food. It has been reported that the effects of moxifloxacin on the QTc interval are proportional to plasma concentrations and these are influenced by the dose, gender and the body weight of the person receiving the dose. This is consistent with our findings (Table 4) and shows that females have a higher ΔΔQTcF in the fed and fasted state in comparison with males. This difference was small and would only become statistically significant when several hundred subjects are used [4].

In this study, the concentration–response analysis revealed that the differences seen in QTcF in Japanese and Caucasian subjects can be fully explained by differences in moxifloxacin PK due to the demographics of the population. Indeed, Japanese subjects have slightly higher plasma concentrations of moxifloxacin in the fed state and therefore a greater QTcF prolongation. We have reported previously [20] that the effect of moxifloxacin on the QTcF interval is greater in females. However this apparent difference is due to a lower body weight, resulting in higher plasma concentrations of moxifloxacin. The concentration–effect slope (or sensitivity) for both genders is also almost identical suggesting that the sensitivity to the I$_{Na}$ blocking properties of moxifloxacin is the same in both genders.

A study by Lettieri et al. [13] which investigated the effect of food using moxifloxacin has demonstrated that the PK of 400 mg oral moxifloxacin was unchanged by food. In their study, the area under the concentration–time curve was almost identical in the fed and fasted conditions (37.7 and 38.5 mg l$^{-1}$ h, respectively), and only a 10% decrease was observed in the Cmax. In addition, another study has shown that moxifloxacin PK only marginally changed when 400 mg oral dose was administered after eating a standard American breakfast with high fat and calorie content [14]. The authors described a slightly lower peak concentration and unchanged area under the curve. It could be reasoned that in these studies [13, 14] meals of a different composition were used and, therefore, salient observations might not have been observed. Florian et al. [4], have suggested that it takes approximately 30 min for the changes in QTcF values to equilibrate with changes in plasma concentrations of moxifloxacin. This finding is consistent with the earlier observation where the maximum effect is typically within the time interval of maximum moxifloxacin plasma concentration [21], and only one study has reported that peak plasma moxifloxacin concentrations are poorly correlated with peak changes in QTcF prolongation [22]. In summary, our findings show that the typical moxifloxacin PK profile is altered by food prior to dosing and delays the peak effects on QTc up to several hours thereby reducing the overall magnitude of the effect.

When calculating the changes in QTcF using placebo data obtained in a baseline condition, then a clear addition of the two important effects emerge:

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**Table 4**

<table>
<thead>
<tr>
<th>Group</th>
<th>Cmax (Mean (95% CI))</th>
<th>tmax (h)</th>
<th>ΔΔQTcF at tmax (Mean (95% CI))</th>
<th>Fed Concentration Mean (95% CI)</th>
<th>tmax (h)</th>
<th>ΔΔQTcF at tmax (Mean (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>2.46 (2.26 2.66)</td>
<td>4 h</td>
<td>13.70 (10.90 16.50)</td>
<td>2.02 (1.81 2.23)</td>
<td>4 h</td>
<td>11.50 (8.00 15.10)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>2.28 (1.59 2.97)</td>
<td>1 h</td>
<td>9.00 (3.20 14.70)</td>
<td>2.05 (1.76 2.34)</td>
<td>4 h</td>
<td>13.70 (8.20 19.20)</td>
</tr>
<tr>
<td>Japanese</td>
<td>2.62 (2.33 2.91)</td>
<td>4 h</td>
<td>17.30 (13.90 20.60)</td>
<td>2.00 (1.69 2.31)</td>
<td>4 h</td>
<td>10.10 (5.10 15.10)</td>
</tr>
<tr>
<td>Male</td>
<td>2.40 (2.24 2.57)</td>
<td>3 h</td>
<td>10.80 (6.80 14.70)</td>
<td>1.89 (1.62 2.16)</td>
<td>4 h</td>
<td>9.70 (6.10 13.30)</td>
</tr>
<tr>
<td>Female</td>
<td>2.66 (2.26 3.06)</td>
<td>4 h</td>
<td>15.70 (10.60 20.70)</td>
<td>2.19 (1.85 2.53)</td>
<td>4 h</td>
<td>13.90 (6.80 21.10)</td>
</tr>
</tbody>
</table>

Illustration of the results of the concentration–effect analysis: The maximum of the mean concentrations of moxifloxacin and the time of its occurrence are given by subgroup together with the effect of moxifloxacin on QTcF (ΔΔQTcF) at this timepoint and a descriptive 95% CI for both the fed and fasted conditions. There is good alignment between concentrations and effects across the two conditions. The only exception is for Caucasians in fasted state. It should be noted that this is the only maximum that occurs already at 1 h.
The alteration of the plasma PK with subsequent reduction in the QT,F effect and:

1. The QT,F shortening effects of C-peptide following a meal.

The cause for the reduction of QT,F is not well understood. There is no indication that a meal itself alters the \( h_K \) channel inhibition induced by moxifloxacin. We have described that a relationship exists between raised C-peptide concentrations and a carbohydrate rich meal [11], but it remains unclear whether this is due to the stimulation of Na\(^+\)/K\(^+\) ATPase by C-peptide by the activation of the protein kinase C (PKC) and mitogen activated protein (MAP) kinase pathway as recently observed in primary human renal tubular cells [23] or whether this effect is an indirect one through mechanisms as yet unknown. However, this paper shows that the two effects are distinguishable and that a meal by itself will reduce the QT,F prolonging effects of moxifloxacin even after taking into account the effect of a meal on PK.

**PK–PD relationship between Japanese and Caucasian subjects**

The sub-population analysis in this study revealed subtle differences but overall give no indication for statistically significant differences in QT,F prolonging effect between Japanese and Caucasian subjects. In fact, the CI for the predicted difference at mean \( C_{\text{max}} \) makes it unlikely that there is a large difference which would be of clinical relevance. As shown in Figure 5, the Japanese subjects showed a greater apparent sensitivity to the QT,F prolonging effects of moxifloxacin in the fasted state but the effect was reversed in the fed state. The PK concentrations for Japanese subjects shown in Figure 2 are marginally higher in both the fasted and fed state. However, the QT,F effect following 400 mg moxifloxacin was clearly greater in the Japanese subjects compared with Caucasians in the fasted state and again reversed in the fed state as shown in Figure 4. A possible explanation for this finding could be that the Japanese subjects are more susceptible to the attenuating effects of C-peptide after a meal.

We reiterate that we found no statistically significant difference in the change in QT,F between ethnicities. Furthermore, it is important to note that the change in the QT,F for a single dose of moxifloxacin in this study was slightly higher than previously reported [24]. Our concentration–response data are in agreement with the observations made by Sugiyama et al. [17] i.e. the QT,F and PK relationship suggests that there is no statistically significant difference in the slopes between Japanese and Caucasian subjects. The sample size used in this study was small and therefore any differences between Japanese and Caucasian subjects presented in this paper should be treated as exploratory as a much larger data set involving several hundred subjects would be required to obtain a definitive result pertaining to ethnic differences. Our findings based on the confirmatory and concentration–effect analysis show that any difference between ethnicities is largely and quite possibly only attributable to differences in plasma concentrations and not differences in sensitivity to the \( h_K \) blocking properties of moxifloxacin, i.e. comparable with the apparent gender differences in QT,F response as reported in the literature [20].

**Competing Interests**

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

The authors made the following contributions: Jorg Taubel designed the study and drafted the manuscript for this publication, Georg Ferber performed all statistical analyses, Ulrike Lorch was the Principal Investigator and conducted the clinical part of the study, Velislav Batchvarov and Irina Savelieva manually adjudicated all ECG data and A. John Camm led the peer review. All authors reviewed the paper and provided their input. We thank D. Djumanov for his contribution to manage the ECG data and J. Singh for re-editing.

**REFERENCES**


