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ORIGINAL RESEARCH ARTICLE

Effect of Degarelix, a Gonadotropin-Releasing Hormone Receptor Antagonist for the Treatment of Prostate Cancer, on Cardiac Repolarisation in a Randomised, Placebo and Active Comparator Controlled Thorough QT/QTc Trial in Healthy Men

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Abstract

Background and Objectives Degarelix is a gonadotropin-releasing hormone antagonist registered for the treatment of advanced hormone-dependent prostate cancer. Treatment causing androgen deprivation is associated with QT prolongation and this study investigated whether degarelix at supratherapeutic concentrations has an intrinsic effect per se on cardiac repolarisation and the QT interval.

Methods This was a single-centre, randomised, crossover study comparing the effect of degarelix, placebo, and the positive control moxifloxacin on the QT interval. Degarelix and placebo treatments were double-blind, whereas moxifloxacin treatment was open-label. Eighty healthy men, aged 18–45 years, received single intravenous doses of degarelix 2.8 mg, and placebo, as well as a single oral dose of moxifloxacin 400 mg. Electrocardiograms were collected up to 24 h after the start of administration, with the QT interval assessed and plasma concentrations of degarelix concomitantly analysed.

Results Time-matched, one-sided 95% upper confidence boundaries for baseline-corrected average changes from placebo for the QT interval, corrected using the Fridericia method ($\Delta\Delta$QTcF), did not exceed 10 ms at any timepoint, with maximum degarelix concentrations reaching approximately threefold the concentrations seen in the treatment of prostate cancer. Furthermore, concentration-exposure analysis indicated absence of any QT prolongation effects of degarelix. No significant effect on any other cardiac parameter was observed. The lower bound of the 98.3% confidence interval for moxifloxacin $\Delta\Delta$QTcF exceeded 5 ms, thus verifying assay sensitivity.

Conclusion The results showed that the study was validated to detect a significant effect on the QT interval, and that degarelix by itself does not have any effect on the QT interval and cardiac repolarisation at supratherapeutic concentrations.

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Key Points

Degarelix does not have any effect on the QT interval and cardiac repolarisation at supratherapeutic concentrations, as demonstrated by this study, validated using moxifloxacin to detect a significant effect on the QT interval.

No difference in the safety profiles was observed between degarelix and placebo.

Since the effect on the QT interval related to androgen deprivation has caused a black-box warning on all androgen deprivation products, these results provide important clinical information relating to the use of degarelix.

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1 Introduction

Degarelix is a gonadotropin-releasing hormone (GnRH) receptor antagonist with high affinity and selectivity towards the human GnRH receptor [1]. Blockage of the GnRH receptor by degarelix results in decreased secretion of luteinizing hormone and follicle-stimulating hormone and, consequently, decreased release of testosterone [2]. In contrast to GnRH receptor agonists, which cause an initial surge of testosterone followed by subsequent testosterone suppression, the direct receptor antagonism by degarelix results in rapid testosterone suppression, without any surge, to below castration level (0.5 ng/mL), the critical level in the treatment of patients with prostate cancer in need of hormone androgen ablation therapy [2–4].

Assessment of the QT interval of the electrocardiogram (ECG) provides a measure of the effect of a drug on cardiac repolarisation, and can be used as a substitute marker for the risk of ventricular tachyarrhythmia, so-called torsade de pointes. Some drugs are associated with prolonged QT/QTc interval, and regulatory guidance for drug development therefore recommends a thorough investigation of the effect of an investigational drug on the QT/QTc interval [5].

It is well known that testosterone deprivation in men to levels below the normal age-adjusted physiological range, irrespective of cause, is associated with prolongation of the QT interval, and is thus suggested to be a risk factor for cardiovascular-related morbidity and mortality [6, 7]. Prolongation of the QT interval by approximately 10–20 ms has been associated with GnRH agonists, combined androgen blockade, and a GnRH antagonist in the treatment of prostate cancer [8], which has resulted in a 'Warnings and Precautions' label regarding the effect of GnRH analogue products on the QT interval. Indeed, several studies have shown longer QT intervals in hypogonadal men after any intervention that reduced the level of testosterone, compared with men with more normal testosterone levels [9–12].

Many drugs that prolong the QT interval also block certain cardiac ion channels, mainly the so-called human ether-a-go-go-related gene (hERG) channel [13]. Preclinical investigations showed that degarelix had no effect on these channels (Ferring Pharmaceuticals, unpublished data), which supports the hypothesis that degarelix does not have any intrinsic QT prolongation properties.

In the present thorough QT/QTc study, designed according to the ICH E14 guidelines [5], the effect of the degarelix molecule by itself on the duration of the QT interval of the cardiac cycle was investigated in healthy men.

2 Methods

2.1 Study Design

This was a single-centre, randomised, placebo- and active-controlled, six-sequence, three-period, three-way crossover study comprising treatment with degarelix, placebo, and the positive control moxifloxacin. The degarelix and placebo treatments were double-blind, whereas the moxifloxacin treatment was open-label. The study documents were approved by the Yorkshire Independent Research Ethics Committee, Manchester, UK, and the study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice at Covance Clinical Research Unit Ltd, Leeds, UK. Written informed consent was obtained from all subjects prior to commencement of any study activities.

2.2 Subjects

Healthy men aged 18–45 years with a body mass index (BMI) of 18–30 kg/m^2, a body weight of 50–100 kg, and serum testosterone at or above the lower limit of normal were eligible for inclusion in the study. Subjects with risk factors for torsades de pointes, prolonged QT/QTc interval [Fridericia's corrected QT (QTcF) >450 ms], or any other important abnormality in resting ECG were excluded.

2.3 Treatments

Each subject was randomised to one of six treatment sequences (Table 1), and received three treatments interrupted by washout periods of 7–10 days. The treatments were degarelix 2.8 mg in 5% glucose, and placebo (5% glucose in water), both administered as a single intravenous infusion over 60 min, and a single oral tablet of moxifloxacin hydrochloride 400 mg (Avelox®, Bayer AG, Leverkusen, Germany) concomitant with an intravenous infusion over 60 min of placebo. Moxifloxacin is known to induce a small but consistent QT prolongation and was included as a positive control to confirm assay sensitivity [14, 15].

Table 1 Treatment sequences

Sequence no.	Period 1	Period 2	Period 3
1	Placebo	Degarelix	Moxifloxacin
2	Placebo	Moxifloxacin	Degarelix
3	Moxifloxacin	Placebo	Degarelix
4	Moxifloxacin	Degarelix	Placebo
5	Degarelix	Moxifloxacin	Placebo
6	Degarelix	Placebo	Moxifloxacin

2.4 Pharmacodynamic Assessments

ECGs were obtained digitally from 1 h prior to administration of each arm of the crossover trial using a Mortara Instrument, Inc. (Milwaukee, WI, USA) H12+ ECG continuous 12-lead digital recorder.

In each treatment period, nine 12-lead ECGs were recorded at 45, 30 and 15 min predose, and triplicate ECGs were recorded at 30, 60, 90, 120, 150, and 180 min, and 6, 12, and 24 h after the start of infusion when subjects had been resting in a supine position for at least 10 min. A semi-permanent skin marker was used to ensure consistent placement of the leads on consecutive study days. Recordings were performed 2 min apart and each ECG covered an approximate 10 s period. The timepoints for ECG recordings were chosen to ensure capturing of any direct and delayed effect on the QT interval occurring around the time of maximum concentration (C_{max}). The ECGs were stored continuously on a flash card unavailable for review, and subsequently transferred electronically to the central ECG core laboratory, eResearch Technology, Inc. (Philadelphia, PA, USA), for high-resolution measurement of the cardiac intervals and morphological assessment by a central cardiologist blinded to the study treatment. All ECGs for a given subject were analysed by the same reader.

Interval duration measurements were collected using computer-assisted caliper placements on three consecutive beats. The cardiologist then verified the interval durations and performed the morphology analysis, noting any T–U wave complex that was compatible with an effect on cardiac repolarisation.

The measured QT intervals were corrected for heart rate (HR) using the Fridericia's ($QTcF = QT/RR^{1/3}$) and Bazett's ($QTcB = QT/RR^{0.5}$) correction formulae [16], of which Fridericia's correction was defined as the primary assessment [5, 17]. The change in QTc from predose baseline was expressed as ΔQTc for each timepoint, while the time-matched difference in ΔQTc between degarelix and moxifloxacin on the one hand and placebo on the other was denoted as $\Delta\Delta$QTc.

On-screen measurements of the RR, PR, QRS, and QT interval durations were performed, and variables for QTcF, QTcB, and HR were obtained for each 10-s ECG by the mean of three measurements. Each fiducial point (onset of P wave, onset of Q wave, offset of S wave, and offset of T wave) was electronically marked.

2.5 Statistical Analysis

The primary analysis was an analysis of covariance (ANCOVA) on QTcF adjusted for the baseline QTcF as a covariate, and period, sequence, and treatment as factors, with subject within sequence as a random effect (SAS PROC MIXED, SAS Institute Inc., Cary, NC, USA). The effect of degarelix treatment on the QTcF interval was compared with the placebo effect at all nine postdose timepoints. For each timepoint, an upper bound, one-sided 95% confidence interval (CI; type I error $\alpha = 5\%$) was computed for the treatment difference between degarelix and placebo using simulations. All nine upper bounds had to be below 10 ms in order to define the trial as 'negative', i.e. no effect of degarelix on the QTcF interval [5, 18].

In order for the results to be valid, the study had to provide evidence that it was sufficiently sensitive to detect an increase in the duration of the QTcF interval of approximately 5 ms using moxifloxacin [5]. To establish assay sensitivity, at least one of the lower limits of the one-sided 98.3% CIs for the time-matched treatment differences between moxifloxacin and placebo had to be above 5 ms [18]. Three timepoints were selected for testing this endpoint, thus the overall type I error rate of 5% was protected by using a Bonferroni-corrected nominal error rate of 1.67%.

The concentration–response effect of degarelix on the QT interval was assessed for each subject for each degarelix concentration, by calculating the individual placebo-corrected change from the baseline of QTcF, i.e. $\Delta\Delta$QTcF, and plotting the individual $\Delta\Delta$QTcF values against the degarelix concentration.

The exploratory concentration–response analysis was performed by applying a repeated measures ANCOVA, modelling ΔQTcF as being dependent on baseline QTcF, and concentration of degarelix as covariates, with time-point of assessment and treatment as factors and subject within treatment as a random effect [19]. The mean difference in ΔQTcF between degarelix and placebo and the 95% CI of the difference was calculated.

2.6 Pharmacokinetic Assessments

Blood samples for analysis of the plasma concentration of degarelix were collected predose and 30, 60, 90, 120, 150, and 180 min, and 6, 12, and 24 h after the start of infusion. Degarelix plasma concentrations were analysed by the Bioanalytical Department at Ferring Pharmaceuticals A/S, Copenhagen, Denmark, using validated automated solid-phase extraction and liquid chromatography with tandem mass spectrometric detection (LC–MS/MS). The plasma samples were applied to an Isolute carboxylic acid column for solid-phase extraction, after which they were transferred to a Zorbax Eclipse XDB 50 × 2.1 mm, 5 μm column linked to a Perkin Elmer Series 200 HPLC system, and analysed by an Applied Biosystems/MDS PE Sciex API 4000 Series triple quadrupole MS/MS system. The lower and upper limits of quantification were 0.500 and 100 ng/mL of degarelix, respectively, with the possibility to quantify up to 500 ng/mL after dilution, as determined

from quality control (QC) samples. The bias and coefficient of variation (CV) for intra- and inter-run precision and accuracy were at all concentration levels within 10%.

The pharmacokinetic parameters were calculated by noncompartmental analysis (NCA) using the WinNonlin® Pro software (Pharsight Corporation, Mountain View, CA, USA). Plasma concentration values below the lower limit of quantitation, as well as missing values, were excluded from the NCA.

2.7 Safety Assessments

Safety parameters, including clinical variables [12-lead ECG, vital signs, and adverse events (AEs)] and laboratory values (clinical chemistry, haematology, and urinalysis) were assessed throughout the study. An adverse event was any untoward medical occurrence in a subject participating in the clinical trial, i.e. any unfavourable and unintended sign, symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. With respect to intensity, any AE was graded as mild (awareness of signs or symptoms, but no disruption of usual activity), moderate (event sufficient to affect usual activity), or severe (inability to work or perform usual activities). Laboratory samples were analysed by Covance Laboratories Ltd, Harrogate, UK.

3 Results

3.1 Study Subjects

Eighty subjects were randomised to the six treatment sequences and administered at least once, of whom 74 subjects received all three study treatments. Seventy-six subjects completed treatment with degarelix 2.8 mg administered intravenously, 78 subjects completed treatment with moxifloxacin 400 mg per orally, and 78 subjects completed treatment with placebo. Two subjects were withdrawn from the study due to AEs prior to receiving all treatments, none of which was regarded by the investigator as related to the treatment. Two subjects were not completed due to noncompliance with the protocol, and two withdrew due to personal reasons.

The mean age of subjects was 29 years, mean body weight was 80.4 kg, and mean BMI was 25.2 kg/m^2 (Table 2).

3.2 Fridericia's Corrected QT (QTcF) Threshold Analysis by Timepoint

The one-sided 95% upper and lower confidence boundaries (in ms) for time-matched, placebo-corrected, average change from baseline (i.e. $\Delta\Delta$) for QTcF did not exceed 10 ms at any

Table 2 Demographic characteristics

Parameter	Value
Age, years {mean (SD) [range]}	29 (8) [18–46]
Weight, kg {mean (SD) [range]}	80.4 (9.1) [61.4–100.5]
BMI, kg/m^2 {mean (SD) [range]}	25.2 (2.6) [18.7–30.4]

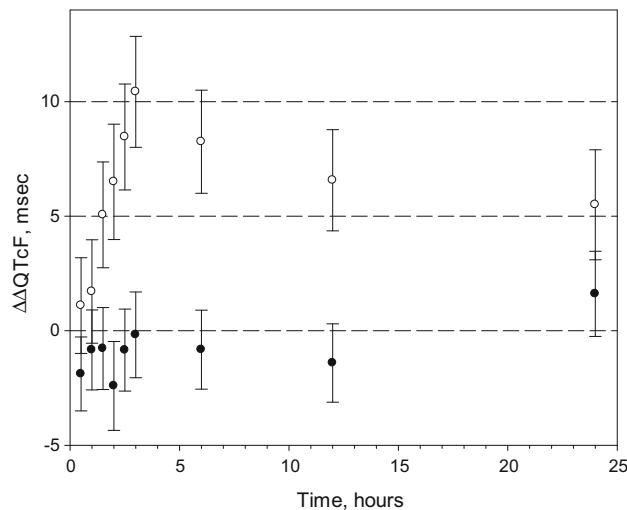*SD* standard deviation, *BMI* body mass index

Fig. 1 Adjusted least squares mean estimates of time-matched, baseline-corrected differences from placebo of QTcF (i.e. $\Delta\Delta$QTcF) from the start of administration of intravenous degarelix 2.8 mg (*closed circles* 95% CI) and oral moxifloxacin 400 mg (*open circles* 98.3% CI). *QTcF* Fridericia's corrected QT, *CI* confidence interval

of the nine timepoints during the 24-h period after the start of infusion. The maximum upper bound level was 3.5 ms, occurring at 24 h after the start of degarelix administration (Fig. 1), at which time the degarelix concentration was <10% of the C_{max} value. Thus, it was demonstrated that infusion of degarelix 2.8 mg did not increase the QT interval and had no effect on cardiac repolarisation.

The assay sensitivity was verified since the time-matched analysis of the difference between moxifloxacin and placebo for the lower bound 98.3% CI for the moxifloxacin QTcF effect exceeded 5 ms at 2.5, 3, and 6 h (Fig. 1).

3.3 Pharmacokinetics

The plasma concentration of degarelix was followed over a 24-h period (Fig. 2) in order to document the exposure. A mean maximum plasma concentration of 222 ng/mL was observed at the end of the 60-min infusion.

3.4 QTcF Concentration–Response Analysis

The dataset for the $\Delta\Delta$QTcF concentration–response analysis comprised 677 observations from 79 subjects. The
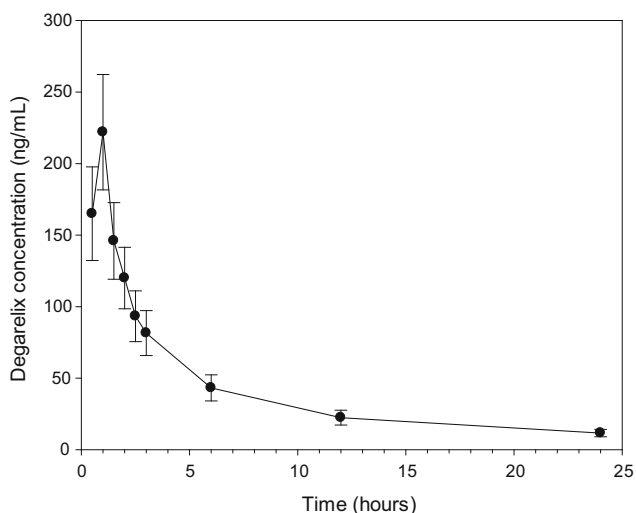
Fig. 2 Time course of mean (standard error) degarelix plasma concentration

analysis of the concentration–response effect on QTcF by degarelix compared with placebo resulted in a slightly negative slope and did not show any sign or tendency towards increased $\Delta\Delta$QTcF interval with increasing degarelix plasma concentration (Fig. 3). The mean values for $\Delta\Delta$QTcF of the plasma concentration deciles were all within ±2 ms, with the 90% CI exceeding ±3 ms for a single individual decile only.

3.5 Categorical Analysis of QTcF

The proportion of subjects with a QTcF interval exceeding 450, 480 or 500 ms, or with a change from baseline greater than 30 or 60 ms, were recorded to identify any outliers. Three subjects, 1 (1%) after treatment with placebo and 2 (3%) after treatment with moxifloxacin, showed QTcF values above 450 ms but below 480 ms, while no such observation was made after degarelix treatment (Table 3). For several subjects, mostly after moxifloxacin treatment but occasionally after degarelix and placebo treatment, a QTcF change exceeding 30 ms from baseline was recorded; however, on no occasion was 60 ms exceeded.

Thus, no subject fulfilled the outlier criteria of QTcF >500 ms or change from baseline >60 ms. The non-specific outlier criterion of 30–60 ms increase from baseline showed no imbalance between degarelix and placebo.

3.6 Safety

Baseline and treatment ECGs, within the same treatment period, were evaluated for changes in the T and U waves, showing no development of any relevant changes in any subject during the study. Mean changes in placebo-corrected HR, PR and QRS durations for degarelix did not show any clinically relevant results.

AEs were reported by 46 of the 80 subjects. Nineteen (25%), 17 (22%), and 22 (28%) subjects reported 27, 23, and 29 AEs after treatment with degarelix, placebo, and moxifloxacin, respectively. The most commonly reported AEs were headache (in 15% of subjects), dizziness (9%), diarrhoea (6%) and contact dermatitis (5%). All AEs were of mild intensity, with the exception of five events reported after treatment with placebo and two events reported after treatment with moxifloxacin that were of moderate intensity, and all AEs resolved without sequelae. No

Fig. 3 Exposure–response analysis of the effect of degarelix on $\Delta\Delta$QTcF. The *solid line* is the mean baseline-corrected, placebo-adjusted QTcF (i.e. $\Delta\Delta$QTcF) with 95% confidence intervals (*shaded interval*). The plasma concentration observations were divided into deciles. *Circles with bars* represent the mean and standard error for the $\Delta\Delta$QTcF at the mean concentration within each degarelix plasma concentration decile. *QTcF* Fridericia's corrected QT
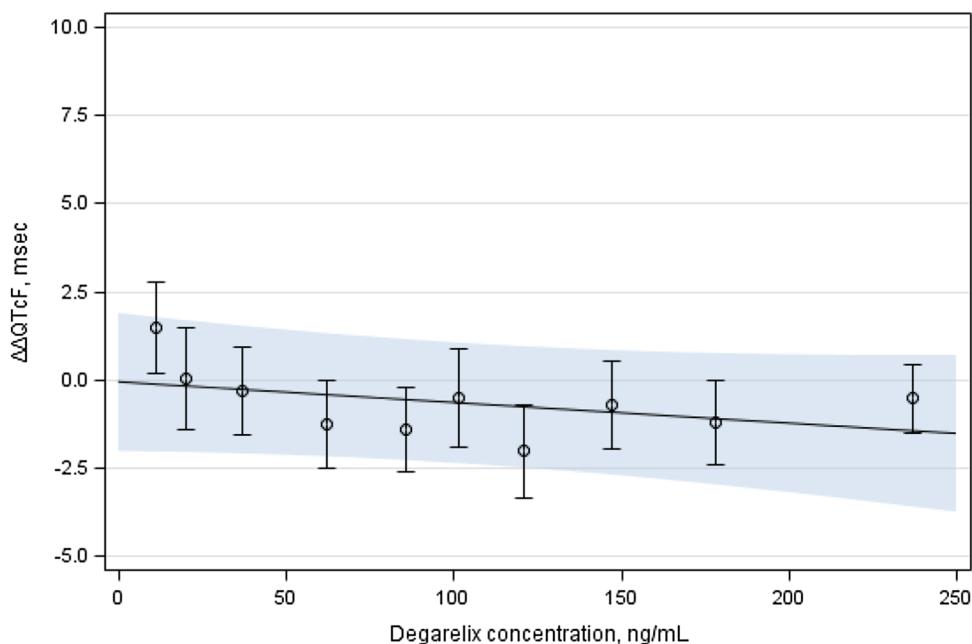
Table 3 Summary of categorical analysis of absolute QTcF and baseline-corrected QTcF (ΔQTcF) values

	No. of subjects in each category		
	Degarelix ($n = 76$)	Moxifloxacin ($n = 78$)	Placebo ($n = 78$)
QTcF, ms			
≤450	76 (100%)	76 (97%)	77 (99%)
>450	0	2 (3%)	1 (1%)
>480	0	0	0
>500	0	0	0
ΔQTcF, ms			
≤30	73 (96%)	63 (81%)	76 (97%)
>30	3 (4%)	15 (19%)	2 (3%)
>60	0	0	0

Data are expressed as n (%)

QTcF Fridericia's corrected QT

cardiovascular AEs were reported, and assessment of laboratory parameters and vital signs did not cause any safety concerns.

4 Discussion

Treatment with GnRH agonists and antagonists have been associated with prolongation of the QT interval [8–10, 20] but is assumed to be secondary to androgen deprivation rather than a direct effect of the administered treatment on the QT interval [21].

The present thorough QT/QTc study investigated the intrinsic effect of degarelix on cardiac repolarisation by means of prolongation of the QT interval in healthy men. The time-matched effect of degarelix on the QT interval, as adjusted for HR effects by Fridericia's correction equation, did not indicate any signs of QT interval prolongation, with the mean maximum baseline-corrected difference versus placebo being <4 ms, well below the limit of 10 ms as defined by ICH E14 to constitute a QT-prolonging effect. Furthermore, the exploratory concentration–response analysis did not show any sign of increased QTcF interval when the degarelix concentration increased. The assay validity was corroborated by the positive control moxifloxacin, which produced the expected QTc prolongation of ≥5 ms.

The guidance on thorough QT/QTc studies requires supratherapeutic doses to be tested [5]. The median peak concentration of degarelix after a single subcutaneous administration of 240 mg of the clinical dose regimen in the treatment of prostate cancer was 66 ng/mL [21]. Based on nonlinear mixed-effects modelling of the pharmacokinetics of intravenously administered degarelix, and the intended clinical dose in the treatment of prostate cancer, i.e. 240 mg at 40 mg/mL followed by monthly maintenance doses of 80 mg at 20 mg/mL, the steady-state median peak value during the maintenance phase of the marketed 1-month depot was estimated to be 70 ng/mL, with the 95th percentile at 115 ng/mL (using population pharmacokinetic modelling). In the present study, degarelix was administered as a single dose of 2.8 mg infused intravenously over 60 min at a constant rate, which resulted in a median maximal degarelix plasma concentration of approximately 220 ng/mL. This was approximately three-fold the median maximal concentration observed in the clinical settings with prostate cancer, covering at least 95% of the observed C_{max} values in the respective treatment regimens. This high degarelix concentration was well tolerated and did not cause any safety concerns in the healthy men.

Administration of degarelix by the intravenous route was chosen in this trial since this is the only way to achieve concentrations that are multiples of the maximal concentrations seen in the clinical setting with subcutaneous injections. Degarelix forms a depot after subcutaneous injection, from which the drug is released into the circulation in two phases [22, 23]. This biphasic pattern of disposition comprises a short initial fast-release phase followed by a second slow-release phase, the latter in which plasma levels display a half-life of several weeks [24, 25]. Due to these physicochemical properties of degarelix, it would be practically impossible to reach prostate cancer supratherapeutic plasma levels of degarelix by the subcutaneous route. In the clinical setting, a starting dose of 240 mg is administered in a total volume of 6 mL. Since increasing the concentration of the injection suspension was not possible due to the gel formation, an unacceptable large volume would have to be administered subcutaneously in order to achieve substantial multiples of the anticipated maximum therapeutic exposure. Moreover, the half-life of subcutaneously administered degarelix is several weeks due to its slow release from the in situ depot, rendering subcutaneous administration unsuitable for a crossover study.

5 Conclusions

In this validated study, the maximum change of the time-matched ΔΔQTcF interval by a supratherapeutic exposure of degarelix was well below the limit for 'no effect' as defined by the ICH E14 guideline, and neither were there any signs of concentration–response effect on the QT interval of increasing degarelix concentrations. Thus, it can be established that degarelix by itself does not cause any clinically significant substance-related prolongation of the QT interval, and is unlikely to contribute to the QT prolongation observed by androgen deprivation.

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