Repeated suprathreshold dosing of strontium ranelate over 15 days does not prolong QT_c interval in healthy volunteers

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Strontium ranelate 2 g (granule form) oral suspension, is an anti-osteoporotic treatment which is available in European countries.
- Repeated administration of strontium ranelate (4 g day⁻¹) was found to be clinically and biologically well tolerated by healthy post menopausal women volunteers.
- Strontium is a bivalent cation with strong affinity for bone and which in certain conditions has a metabolism similar to that of calcium. In terms of importance, calcium has a major role in the electrophysiology of cardiac muscle and ECG abnormalities are known to be due to changes in plasma calcium concentrations.
- Although no signal was observed in pre-clinical or clinical studies, the safety of strontium ranelate in accordance with the ICH – E14 guidelines needed to be assessed in order to characterize the effect on QT_c of repeated oral doses of strontium ranelate (4 g day⁻¹).

WHAT THIS STUDY ADDS

- This thorough QT/QT_c study directly compared suprathreshold repeat doses of strontium ranelate (4 g day⁻¹ for 15 days) with placebo on the largest time-matched mean QT_c variation (from baseline to under treatment values) in healthy subjects.
- The largest time-matched difference in QT_I compared with placebo was observed at 1 h post dose (mean [90% CI] 7.54 [5.17, 9.90] ms).
- Suprathreshold (4 g day⁻¹) repeated doses of strontium ranelate did not produce any clinically significant prolongation in QT_c.
- The findings of this study clearly indicate that administration of strontium ranelate at the therapeutic dose of 2 g will not cause prolongation of QT that is of any clinical concern.

AIMS

The study was performed to assess the safety of strontium ranelate in accordance with the ICH, E14 guidelines for QT/QT_c studies. Its primary objective was to compare suprathreshold repeated dosing of strontium ranelate (4 g day⁻¹ for 15 days) with placebo on the largest time-matched mean QT_c variation, from baseline to under treatment values, in healthy subjects.

METHODS

Ninety-six healthy male and female subjects (27.7 ± 7.5 years) were included to receive 1 day of placebo followed by 15 days of suprathreshold repeated dosing of strontium ranelate (4 g day⁻¹), in a 4 month, randomized, placebo (16 days) and positive-controlled (single dose of moxifloxacin 400 mg preceded by 15 days of placebo), double-blind, double dummy, crossover design. Measurement of QT interval was performed automatically on the ECGs with subsequent manual onscreen over-reading by cardiologists using electronic callipers.

RESULTS

The largest time-matched difference in QT_I (individual QT correction for heart rate) between moxifloxacin 400 mg and placebo was observed at 2 h post dose (mean [95% CI] 10.62 [7.90, 13.35] ms). For strontium ranelate (4 g day⁻¹) the largest time-matched difference in QT_I compared with placebo was observed at 1 h post dose (mean [90% CI] 7.54 [5.17, 9.90] ms). No subject had a QT_c greater than 480 ms during the study. Both moxifloxacin and strontium ranelate were well tolerated in healthy subjects.

CONCLUSIONS

The findings of this study demonstrate that the administration of suprathreshold repeated oral doses of strontium ranelate (4 g day⁻¹ for 15 days) does not lead to a prolongation of the QT/QT_c interval above the threshold of regulatory concern.

Introduction

Post menopausal osteoporosis is one of the most important medical conditions which affect women after they have reached and past their menopause. Women suffering from the condition are prone to enhanced bone fragility and are more likely to be at risk from fractures [1]. Strontium ranelate 2 g (granule form) oral suspension, is an anti-osteoporotic treatment which is available in European countries. A marketing authorization for this product was issued in September 2004 by the European Commission which is valid throughout the European Union for the following indication: 'treatment of post menopausal osteoporosis to reduce the risk of vertebral and hip fractures' [2]. Extensive non-clinical development has shown that its effects on bone remodelling are mediated both by stimulation of bone formation and inhibition of bone resorption [3, 4].

In terms of clinical development, strontium ranelate has been studied in up to 19 clinical trials involving nearly 8000 subjects. Three randomized controlled trials, including one phase II and two phase III studies have been conducted in post menopausal women for the treatment of osteoporosis. Two randomized controlled phase III studies (SOTI and TROPOS) showed that strontium ranelate significantly decreased the risk of new vertebral or non-vertebral fracture (such as hip fractures) in post menopausal women with long term efficacy of up to 8 years. Repeated administration of strontium ranelate was found to be clinically and biologically well tolerated by healthy post menopausal women volunteers at doses up to and including 4 g day⁻¹ for 25 days [5–7]. The maximal dose of strontium ranelate tested in repeated administration is 4 g day⁻¹.

Strontium is a bivalent cation with strong affinity for bone and which in certain conditions has a metabolism similar to that of calcium. In terms of importance, calcium has a major role in the electrophysiology of the cardiac muscle and ECG abnormalities are known to be due to changes in plasma calcium concentrations. Due to these possibilities, the potential pro-arrhythmic effect of strontium ranelate and the potential QT_c interval prolongation were evaluated using the most relevant recommended approaches (*in vitro* and *in vivo*) in accordance with the EMEA's points to consider documents [8].

However, since the ICH E14 guidelines were issued [7], a specific study needed to be performed. The aim of this study was to characterize the effect on QT_c of repeated oral doses of strontium ranelate (4 g) for 15 days compared with placebo on the largest time-matched mean QT_c variation from baseline to under treatment values. A single oral dose of 400 mg moxifloxacin was used as a positive control to confirm assay sensitivity.

Methods

Subjects

The study population consisted of 96 healthy, non-smoking, male and female subjects, with a mean age of 27.7 ± 7.5 years and a body mass index ranging between 19.0 and 29.0 kg m⁻² inclusive. Subjects were excluded if they had (i) a medical history or family history of congenital long QT syndrome, (ii) a clinically significant abnormal ECG (PR consistently <120 or >230 ms, QRS consistently > or equal 120 ms, QT_cB >430 ms for males and >450 ms for females, heart rate consistently <45 beats min⁻¹ or >100 beats min⁻¹) or (iii) if they used concomitant medication that could interfere with moxifloxacin or strontium ranelate absorption or elimination. Pregnant or lactating females were excluded. Women of childbearing potential agreed to sexual abstinence or to an acceptable contraception method during the whole study. All subjects provided written informed consent prior to any study-specific procedures.

Study design

The study was designed as a single centre, randomized, placebo and positive-controlled, double-blind, double dummy, 3 × 3 crossover (Figure 1). Each subject received three treatments and all the comparisons between treatment effects were intra-individual reducing the anticipated variability and thereby reducing the sample size. Multiple dosing and the need for a sufficiently long washout period resulted in a study duration of 104 days plus the period between screening and baseline for each subject. Eligible subjects were randomized to strontium ranelate, placebo and moxifloxacin for the three treatment periods. Each treatment period (P1, P2 and P3) consisted of 16 days: 1 placebo baseline day at the centre (day 1 of each period), 14 days out of the unit with either placebo or strontium ranelate (day 2 to 15 of each period) and 1 last day at the hospital unit with either placebo or strontium ranelate or moxifloxacin (day 16 of each period). The treatment periods were separated by two 28 day washout periods allowing complete elimination of strontium ranelate or moxifloxacin. The baselines were treatment and period specific in order to provide information on possible carryover effects, which were not observed. ECG profiling was performed over 24 h on day 1 and day 16 of each treatment period after the morning dose of placebo on day 1 and each study medication on day 16. Pharmacokinetic profiling was performed for strontium and moxifloxacin analyses over 24 h on the last day of each treatment period (i.e. on day 16 of each period), at the same time points as the ECG measurements. During each treatment period subjects received, according to a double dummy procedure, two sachets per day of either strontium ranelate oral suspension 2 g (Protelos®, Les Laboratoires Servier, Neuilly-sur-Seine, France) or placebo, and one capsule per day of either placebo or moxifloxacin 400 mg

Figure 1

Summary of study design: a randomized, placebo and positive-controlled, double-blind, double dummy, 3 × 3 crossover study

(Izilox®, Bayer Pharma SAS, Puteaux, France). This was a suprathreshold dose of strontium ranelate (4 g day⁻¹ for 15 days) which was chosen since this was the maximal dose for which safety data were available. All the subjects were hospitalized on seven occasions (screening, day 1 and day 16 of each of the three treatment periods) in order to standardize the conditions of each of the ECG evaluation days. The study was approved by the local ethics committee (North London REC 3, Harrow, UK) and the Medicines and Healthcare products Regulatory Authority, and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

ECG assessments and QT_c evaluation

Twelve-lead ECGs were recorded using a MAC1200® recorder (GE Healthcare, Bucks, UK) and stored electronically on the MUSE CV® information system (GE Healthcare).

The recordings were made during the run-in day for 24 h at each baseline (day 1 of each period) and at the maximum concentration time on day 16 of each period (Figure 1). On day 1 of period 1, ECG recordings were taken at -2, -1 and 0 h pre dose and then on 22 time points post dose (0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, 13 and 24 h), in order to evaluate the individual heart rate correction for each subject. On all other study days, ECG recordings were taken at 0 h pre dose and then at regular intervals around the C_{max} of active study drugs, including 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 h post dose. At each time point, ECGs were recorded in triplicate to reduce the variance and improve the precision of measurement. Each ECG lasted 10 s and triplicates were performed at 1 min intervals during 3 min. Before ECG recordings were made subjects maintained an undisturbed supine resting position for at least 10 min. During the ECG recordings postural

changes were avoided. During hospitalizations subjects were served the same light lunch (4 h post dose) and light dinner (10–11 h post dose). No breakfast was served and the subjects fasted until lunch.

Data analysis and statistical methods

The effect on QT/QT_c interval was analyzed using the largest time-matched mean difference from baseline to under treatment values between strontium ranelate/moxifloxacin and placebo. ECGs were taken in triplicate at each time point and the QT_c interval was expressed as the mean of these three values. Each treatment period had a baseline day (D01) and a post baseline day (D16). For each treatment the QT/QT_c interval value change at each time point was expressed as the difference between baseline and post baseline (Δ QT_c). The effect size was then determined as the time-matched, baseline adjusted QT/QT_c interval value for strontium ranelate/moxifloxacin vs. placebo ($\Delta\Delta$ QT_c). Measurement of the QT interval was performed as per ICH E14 Q&A guidelines using manual adjudication.

The following four QT correction formulae were calculated for each subject:

- Individual correction (QT_{cI}) (linear and non linear models)
- Population-based correction (QT_{cP}) optimized for all the data of the study pooled together (linear and non linear models)
- Fridericia's correction (QT_{cF} = QT/RR^{0.33})
- Bazett's correction (QT_{cB} = QT/RR^{0.5})

Among these four correction formulae, the best correction (i.e. the correction giving QT_c values that were least influenced by the heart values) was used for the primary criterion. This most accurate heart rate correction was determined by a statistician under blinded conditions based on the mean square estimate (MSE) approach. Considering the number of available ECGs per subject and the HR range in this study, it was determined that the best correction was QT_{cI}. However the same analysis as for QT_{cI} was provided for the other corrections of QT interval: QT_{cP}, QT_{cF} and QT_{cB}. All statistical analyses were performed using SAS 9.1 software (SAS Institute Inc., NC, USA).

The treatment effect of strontium ranelate 4 g and moxifloxacin 400 mg as compared with placebo on the QT_c change per time point was estimated using a mixed model taking into account the crossover design, with gender, baseline, period and carry over effect as covariates and subject as random effect. A 90% two-sided confidence interval (CI) of the difference between adjusted treatments means was derived.

Sample size was estimated on QT_c interval change in order to ensure assay-sensitivity, for a difference between moxifloxacin 400 mg vs. placebo, using the two-sided Student's *t*-test for paired samples at 5% type I error on the safety set [9]. For a 9.5 ms intra-individual variability (within subject SD), and under the hypothesis of a withdrawal rate

of 20%, 96 included subjects (of whom 77 were to complete) were necessary to reach a statistical significance in the comparison between treatments, with a power of 90%, assuming a difference of at least 5 ms. However, the difference was found to be greater and the intra-individual variability was less and therefore, the withdrawal of 26 subjects did not affect the power of the analysis.

Pharmacokinetic assessments

Pharmacokinetic samples were taken over 24 h on day 16 of each period, i.e. at steady-state after repeated oral administration of strontium ranelate 4 g day⁻¹ for 15 days and on the day of the single oral administration of moxifloxacin. The blood samples (5 ml) were taken at 0 h pre dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 h post dose.

Plasma samples for strontium ranelate concentrations were analyzed using inductively coupled plasma atomic emission spectrophotometry (ICP-AES) with a limit of quantification (LOQ) of 0.0125 mg l⁻¹. Moxifloxacin measurements in plasma were performed by mass spectrometry with a limit of quantification (LOQ) of 0.1 ng ml⁻¹.

Pharmacokinetic analysis was performed using WinNonlin® software version 3.3 (Pharsight Corporation, CA, USA). Non-compartmental pharmacokinetic analyses were performed on the individual plasma concentrations of strontium ranelate and moxifloxacin.

Safety assessments

All adverse events were recorded at each visit from the signature of the informed consent until the end of the study, either reported spontaneously or following direct, non-leading questions, medical examination or biological or ECG assessment. The intensity, outcome, duration and potential relationship with the study drugs of each adverse event were assessed. Body temperature, vital signs, blood pressure (systolic and diastolic) and heart rate were regularly measured during the study. Laboratory investigations including haematology, biochemistry and urinalysis were performed during the screening and follow-up periods. Any clinically relevant abnormalities in vital signs or laboratory tests were reported as adverse events.

Results

Subject demographics and disposition

A total of 192 volunteers were screened and 96 subjects were included in the study to be randomized to one of the six treatment sequences. All of them were Caucasian with a mean age of 27.7 ± 7.5 years, 49% (*n* = 47) were males and 51% (*n* = 49) were females. All the subjects had a BMI that ranged between 19.0 and 29.0 kg m⁻² inclusive, with a mean value of 24.1 ± 2.8 kg m⁻². The mean weight was 76.2 ± 9.0 kg and 65.7 ± 8.8 kg for males and females, respectively. Forty-six subjects received concomitant treatment during the study, which consisted mostly of paracetamol.

Twenty-six subjects were withdrawn, one due to an adverse event (see Safety and Tolerability), 22 subjects for non-medical reasons and three due to non-compliance with protocol requirements (testing positive for drugs of abuse). Seventy-four subjects were included in the QT_c analysis as these subjects had completed at least the placebo plus one other treatment arm.

Effect of strontium ranelate 4 g compared with placebo on QT_c

The point estimates of the difference between strontium ranelate and placebo on QT_{cI} ranged from 5.44 to 7.54 ms. The largest time-matched difference in QT_{cI} between strontium ranelate 4 g and placebo was observed at 1 h post dose, with a point estimate of the difference E (SE) = 7.54 (1.43) ms and the two-sided 90% CI 5.17, 9.90 ms (Table 1). It should be noted that the mechanism of strontium ranelate through calcium-sensing receptors leads to a mild calcium decrease [10]. An additional analysis adjusted for calcium change between baseline and post baseline values at pre dose was performed and showed that the difference between strontium and placebo was marginally

smaller (QT_{cI} estimate was found to be 6.33 (1.63) ms, 90% CI 3.63, 9.04 ms).

Similar results were obtained using other QT interval corrections. At 1 h post dose, the time-matched mean estimate difference between strontium ranelate 4 g and placebo treatments were:

QT_{cP} (Population): E (SE) = 7.24 (1.43) ms and two-sided 90% CI 4.87, 9.61 ms.

QT_{cB} (Bazett): E (SE) = 6.62 (1.51) ms and 90% CI 4.11, 9.13 ms.

QT_{cF} (Fridericia): E (SE) = 7.46 (1.43) ms and 90% CI 5.09, 9.84 ms (Table 1).

There was no effect on the heart rate which explains the similarity of results when using different heart rate correction methods.

Effect of moxifloxacin 400 mg compared with placebo on QT_c

The assay sensitivity was shown to be adequate. From 0.5 h to 24 h post dose, the point estimates of the difference

Table 1

Largest time-matched QT_{cI} and QT_{cF} (ms) change from P-baseline to P-post baseline- comparison between strontium ranelate 4 g and placebo/moxifloxacin 400 mg and placebo

QT _{cI}		Strontium ranelate 4 g (n = 74)	Placebo (n = 74)
P-Baseline	Mean ± SD	404.7 ± 13.4	405.2 ± 14.3
P-Post baseline		414.2 ± 13.5	406.9 ± 13.9
P-Post baseline – P-Baseline		9.6 ± 9.6	1.7 ± 10.6
Statistical analysis of change	Estimate (1) 90% CI (2)	7.54 (1.43) 5.17, 9.90	
		Moxifloxacin 400 mg (n = 71)	Placebo (n = 71)
P-Baseline	Mean ± SD	406.1 ± 13.8	406.9 ± 14.6
P-Post baseline		418.3 ± 16.3	407.8 ± 14.2
P-Post baseline – P-Baseline		12.2 ± 10.6	1.0 ± 7.9
Statistical analysis of change	Estimate (3) 95% CI (4)	10.62 (1.38) 7.90, 13.35	
QT _{cF}		Strontium ranelate 4g (n = 74)	Placebo (n = 74)
P-Baseline	Mean ± SD	404.2 ± 14.2	404.9 ± 14.1
P-Post baseline		413.9 ± 13.3	406.7 ± 14.0
P-Post baseline – P-Baseline		9.7 ± 10.2	1.8 ± 10.1
Statistical analysis of change	Estimate (1) 90% CI (2)	7.46 (1.43) 5.09, 9.84	
		Moxifloxacin 400 mg (n = 71)	Placebo (n = 71)
P-Baseline	Mean ± SD	405.9 ± 14.2	406.3 ± 14.4
P-Post baseline		417.6 ± 16.4	407.6 ± 14.3
P-Post baseline – P-Baseline		11.7 ± 10.4	1.3 ± 8.3
Statistical analysis of change	Estimate (3) 95% CI (4)	9.79 (1.39) 7.04, 12.54	

(1): Estimate (standard error) of the adjusted changes differences: strontium ranelate 4 g minus placebo. (2): 90% CI of the adjusted changes differences between strontium ranelate 4 g and placebo. (3): Estimate (standard error) of the adjusted changes differences: moxifloxacin 400 mg minus placebo. (4): 95% CI of the adjusted changes differences between moxifloxacin 400 mg and placebo. The '90% two-sided CI' is equivalent to a '95% one-sided CI'.

between moxifloxacin 400 mg and placebo on QT_cI ranged from 2.02 to 10.62 ms. The largest time-matched difference in QT_cI between moxifloxacin and placebo was observed at 2.0 h post dose and corresponded to the peak plasma concentration of moxifloxacin. The point estimate of the difference was $E (SE) = 10.62 (1.38)$ ms and the one-sided 95% CI had its upper bound over the 10 ms threshold: 95% CI 7.90, 13.35 ms (Table 1).

Similar results were obtained using other QT interval corrections. At 2 h post dose, the time-matched mean estimate difference between moxifloxacin 400 mg and placebo treatments were:

QT_cP (Population): $E (SE) = 10.32 (1.38)$ ms and one-sided 95% CI 7.60, 13.05 ms.

QT_cB (Bazett): $E (SE) = 11.02 (1.55)$ ms and 95% CI 7.95, 14.10 ms.

QT_cF (Fridericia): $E (SE) = 9.79 (1.39)$ ms and 95% CI 7.04, 12.54 ms (Table 1).

The difference in the median QT_cI between genders shown at baseline reinforced the adequate sensitivity of the study.

Categorical analysis

No subject at any time on any treatment had a QT_cI greater than 480 ms or a maximum QT_cI increase from baseline ≥ 60 ms. Similar results were obtained using other QT interval corrections. Seven subjects in the strontium ranelate group and seven subjects in the moxifloxacin group had changes from baseline in QT_cI between 30 and 60 ms with a mean increase of 32.6 ms (30.2–38.2 ms) or 35.7 ms (30.4–43.7 ms), respectively. Five subjects in the moxifloxacin treatment group and none in the placebo and strontium ranelate groups, had an emergent post-baseline QT_cI value between 450–480 ms (maximal value of 463.2 ms). In addition, three subjects treated with moxifloxacin with a post baseline QT_cI > 450 ms had a concomitant increase of QT_cI from baseline between 30 and 60 ms.

Other ECG changes from baseline

The mean changes from baseline to post baseline value pooled by period at each measurement time point for HR, RR, PR interval and QRS duration were analyzed. No clinically significant changes in RR values were seen. Similar levels of changes were seen in males and females. Very few abnormalities of P wave, QRS complex, T wave and U wave were observed regardless of the treatment period and treatment group. None of these abnormalities was considered to be clinically significant and reported as an adverse event by the investigator.

Pharmacokinetics of strontium ranelate and moxifloxacin

Following daily oral administration of strontium ranelate 4 g for 15 days, the mean maximum serum concentration ($C_{\max}$) at steady-state was reached at around 3 h (25 mg l⁻¹)

Table 2

Pharmacokinetic parameters for plasma concentration of strontium ranelate and moxifloxacin

	Strontium ranelate (4 g)	Moxifloxacin (400 mg)
<i>n</i>	79	76
$C_{\max}$ (mg l ⁻¹) (all)	25 ± 6.7 (24)	2.7 ± 0.82 (2.6)
$C_{\max}$ (mg l ⁻¹) (female)	28 ± 6.3	
$C_{\max}$ (mg l ⁻¹) (male)	22 ± 5.9	
$t_{\max}$ (h)	3.1 [2.1–5.1]	2.1 (0.58–4.2)
AUC(0, t_{last}) (mg l ⁻¹ h)	460 ± 128 (454)	25 ± 5.1 (25)

Mean ± SD (median). $t_{\max}$ expressed as median (range).

and mean exposure (AUC) was approximately 460 mg l⁻¹ h (Table 2). The $C_{\max}$ values were higher in females compared with males (Table 2). The mean exposure of women in this study after oral administration of 4 g of strontium ranelate for 15 days was higher ($AUC(0,24 \text{ h}) = 517 \pm 116$ mg l⁻¹ h) than the exposure obtained in post menopausal women receiving the therapeutic dose of 2 g day⁻¹ of strontium ranelate for 28 days ($AUC(0,24 \text{ h}) = 337 \pm 102$ mg l⁻¹ h). Following a single oral administration of moxifloxacin 400 mg, the mean maximum plasma concentration ($C_{\max}$) was 2.7 mg l⁻¹ and occurred at around 2 h. Mean exposure (AUC) was approximately 25 mg l⁻¹ h (Table 2). The moxifloxacin pharmacokinetic parameters observed in this study were similar to those presented previously in the literature under the same conditions of administration [11–14].

Safety and tolerability

There were no serious or severe adverse events in this study. Both strontium ranelate and moxifloxacin were well tolerated by healthy subjects. A total of 114 emergent adverse events were reported, the majority of which were considered to be mild (92%) or moderate (8%). Adverse events considered related to study treatment by the investigator were experienced by 15.6% subjects in the strontium ranelate group, 10.4% subjects in the moxifloxacin group and 11.5% subjects in the placebo group. The most frequent treatment-related adverse events reported in the strontium ranelate and moxifloxacin groups were headache and nausea which are both expected known drug reactions mentioned in the Summary of Product Characteristics of both treatments. The distribution of emergent adverse events was similar between the three treatment groups with no unexpected adverse events. Headache was reported by nine (9.4%) subjects (12 instances) under strontium ranelate treatment, seven (7.3%) subjects (seven instances) under moxifloxacin treatment and five (5.2%) subjects (seven instances) under placebo treatment. Nausea was reported by four (4.2%) subjects (four instances) under strontium ranelate treatment, one (1%) subject (one instance) under moxifloxacin treatment and

four (4.2%) subjects (five instances) under placebo treatment. No clinically significant changes were seen in laboratory parameters or in vital signs. One subject was withdrawn due to adverse event after receiving moxifloxacin 400 mg on P1D16. She experienced flu-like symptoms and was found pyrexial. Concomitantly her heart rate increased from 73 beats min⁻¹ at pre dose to 100 beats min⁻¹ at 5 h post dose, remained at 101 beats min⁻¹ until 12 h post dose and returned to 71 beats min⁻¹ at 24 h post dose. Since this adverse event could affect the QT_c evaluation, the subject was withdrawn from the study.

Discussion

The potential of a drug to impact on cardiac repolarization is determined in 'thorough QT/QT_c studies', usually carried out during the early stages of clinical development. It is important to perform them in order to detect any delays in repolarization which can lead to the development of critical cardiac arrhythmias such as torsades de pointes.

In 2004 strontium ranelate 2 g was granted a marketing authorization for the indication 'treatment of post menopausal osteoporosis to reduce the risk of vertebral and hip fractures' in the European Union and further in more than 95 countries. Overall, no signal for a pro-arrhythmic effect with strontium ranelate was observed either in preclinical studies or during clinical development or during the post-marketing phase. Despite this absence of signal, a specific thorough QT/QT_c study was performed in healthy subjects to assess the potential of strontium ranelate to prolong the QT interval.

The use of a concurrent positive control group is to establish assay sensitivity. The sensitivity target of a thorough QT/QT_c study is currently defined by the International Conference on Harmonization (ICH) guideline as a mean increase in the QT_c interval of 5 ms with the lower bound 95% CI excluding 5 ms on one or more time points. Detecting the effect this positive control establishes the ability of the study to detect small QT prolongation effects of the study drug near the threshold of regulatory concern.

Moxifloxacin is a well-characterized QT prolonging agent. There is some evidence that it can influence ventricular repolarization events [15, 16] and warnings about this effect have been included on its label. Moxifloxacin has very little effect on heart rate but does inhibit IKr, producing an average QT prolongation between 6 and 10 ms at a dose of 400 mg and approximately double the increase at a dose of 800 mg [17–19]. It is the most commonly used reference to confirm assay sensitivity [19–22].

The largest time-matched mean effect between moxifloxacin and placebo was E (SE) = 10.62 (1.38) ms and the two-sided 95% CI 7.90, 13.35 ms. These findings were consistent with the results obtained in the mentioned recent thorough QT studies. The ICH E14 guidelines state that a negative 'thorough QT/QT_c study' is one in which the upper

limit of the one-sided 95% CI interval for the largest time-matched mean QT_c variation between the drug and the placebo excludes 10 ms. In this study supratherapeutic repeated doses of strontium ranelate 4 g day⁻¹ for 15 days produced a maximal effect on mean QT_c compared with placebo of 7.54 ms with an upper limit of the 90% two-sided (equivalent to 95% one-sided) CI of 9.90 ms. This post registration study with supratherapeutic doses of strontium ranelate (4 g) performed in accordance with the guideline ICH E14, is therefore considered negative.

No subjects had QT_c values greater than 480 ms or had a QT_c change from baseline greater or equal to 60 ms. Only seven subjects in the strontium ranelate group and seven subjects in the moxifloxacin group had maximum QT_c changes from baseline between 30–60 ms.

Overall, both strontium ranelate and moxifloxacin were generally well tolerated in this study in healthy subjects. The most frequently reported adverse events were headache [reported by 9.4% subjects (strontium ranelate), 7.3% subjects (moxifloxacin) and 5.2% subjects (placebo)] and nausea [reported by 4.2% subjects (strontium ranelate), 1.0% subjects (moxifloxacin) and 4.2% subjects (placebo)]. Adverse events considered related to study treatments were reported by 15.6% subjects in the strontium ranelate group, 10.4% subjects in the moxifloxacin group and 11.5% subjects in the placebo group.

In summary, this post registration study with supratherapeutic doses of strontium ranelate (4 g), performed in accordance with the guideline ICH E14, and for which the sensitivity of the assay was confirmed by a moxifloxacin effect consistent with the description in the literature, is considered negative. No potential pro-arrhythmic effect was observed with strontium ranelate 4 g day⁻¹. No clinically relevant prolongation of the QT interval is therefore to be expected in the population prescribed strontium ranelate 2 g day⁻¹.

Competing Interests

There are no competing interests to declare.

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