

Repeated dosing of strontium ranelate 4g over 15 days does not prolong QTc interval in healthy volunteers

Jorg Taubel¹, Asif Naseem¹, Yvonne Fok¹, Duolao Wang¹, Radivoj Arezina¹, Ulrike Lorch¹, and A. John Camm²

¹Richmond Pharmacology Ltd., St George's University of London, Cranmer Terrace, London, United Kingdom.

²Department of Cardiological Sciences, St George's University of London, Cranmer Terrace, London, United Kingdom.

Introduction

Postmenopausal osteoporosis is a medical disorder affecting women after their menopause. It is characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.¹

Strontium ranelate 2g (granules form) oral suspension (new anti-osteoporotic treatment) was granted a marketing authorisation in European countries (September 2004) in the indication: "Treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures".

The potential pro-arrhythmic effect of strontium ranelate and the potential QTc interval prolongation has been evaluated using relevant recommended approaches (*in vitro* and *in vivo*).

The present study was performed in accordance with the ICH E14 guidelines although no signals were detected in non-clinical and clinical studies, or in post-marketing experience.

Aims

The purpose of this study was to characterise the effect on QTc of repeated dosing of supratherapeutic strontium ranelate (4g/day over 15 days), compared to placebo on the largest time-matched mean QTc variation, using a 400mg of moxifloxacin as a positive control to confirm assay sensitivity.

Methods

Study Design

This was a 4-month, prospective, randomised, placebo-controlled, double-blind, double-dummy, single-centre, 3x3 crossover study in healthy volunteers, evaluating the effects of supratherapeutic repeated oral doses of strontium ranelate (4g/day for 15 days) on the QT/QTc interval.

During each treatment period, subjects received placebo on Day 1 for baseline assessments followed by 15 treatment days with one of the following

- Placebo (Day 2-Day 16)
- Strontium ranelate (Day 2-Day 16)
- Placebo (Day 2-15) and a single dose of Moxifloxacin (Day 16)

Electrocardiographic (ECG) profiling was performed over a 24-hour period after each dose of study medication using 10-second 12-lead triplicate bedside recording.

Data Analysis and Statistical Methods

Measurement of the QT interval was performed automatically with subsequent manual on-screen over-reading using electronic callipers (MUSE CV[®] Interval Editor; GE Healthcare). The effect on the QT/QTc interval was analysed using the largest time-matched mean difference between moxifloxacin/strontium ranelate and placebo. All on treatment values were corrected using time-matched baseline values. Under blinded conditions QTc was determined to be the best correction formula.

Safety Assessment

Adverse events were recorded from the first doses of study medication until follow-up.

Subject Disposition

192 healthy subjects were screened and 96 subjects were included and randomised onto the study. 26 subjects withdrew from the study: one due to an adverse event (see Safety Results), 22 subjects for non-medical reasons and three due to testing positive for drugs of abuse.

All 96 subjects (47 males and 49 females) randomised were Caucasians with a mean age of 27.7±7.5 years. BMI ranged between 19.0-29.0kg/m², with a mean of 24.1±2.8kg/m².

70 subjects completed the trial and all subjects completing all three periods of the trial were included in the analysis presented.

QTc Results

Effect of Moxifloxacin 400mg on QTc

Mean QTcI was prolonged in subjects receiving moxifloxacin 400mg compared with placebo (Table 1, Figure 1). This observation is consistent with previous findings at the study site^{2,3} using the same clinical and ECG core laboratory infrastructure and confirms the assay sensitivity necessary to detect an effect on cardiac repolarisation.

QTcI (Statistical analysis of change) – largest time-matched difference		
	Estimate (1)	90% CI (2)
Strontium ranelate 4g	7.54 (1.43)	(5.17, 9.90)
Strontium ranelate 4g – calcium adjustment	7.00 (1.60)	(4.36, 9.64)
	Estimate (1)	95% CI (3)
Moxifloxacin 400mg	10.62 (1.38)	(7.90, 13.35)

(1): Estimate (standard error) of the adjusted changes differences;
(2): 90% CI of the adjusted changes differences for strontium ranelate
(3): 95% CI of the adjusted changes differences for moxifloxacin

Table 1 QTcI (msec) change from P-baseline to P-post-baseline for strontium ranelate 4g and moxifloxacin 400mg.

Effect of strontium ranelate 4g on QTc

Prolonged mean QTcI was observed in subjects receiving strontium ranelate 4g compared with placebo (Table 1, Figure 1).

The largest time-matched difference in QTcI for strontium ranelate 4g compared with placebo was observed at 1 hour post-dose (mean [90%]: 7.54 [5.17, 9.90] msec) (Table 1).

After 15 days of dosing a mean change of QTcI was observed compared to baseline. Following dosing a 2 msec change from pre-dose levels had occurred

The upper 90% CI was within the regulatory guidelines for a negative QTc study.

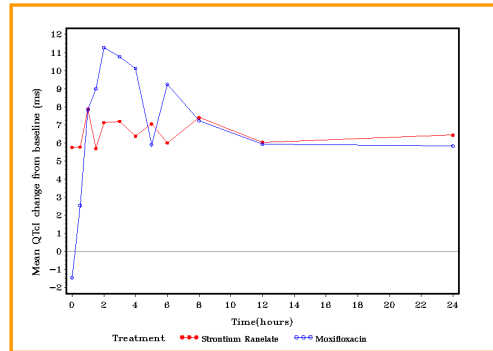


Figure 1 QTcI change from baseline against time for strontium ranelate 4g and moxifloxacin 400 mg.

Effect of strontium ranelate 4g on QTc - adjusted for calcium

Serum calcium concentration and QT/QTc interval duration is thought to be related.⁴ In addition, strontium ranelate's mechanism of action results in decreased calcium concentration (Table 2).

Therefore, the most relevant analysis allows for the calcium change in order to see the drug effect.

The largest time-matched difference in QTcI for strontium ranelate 4g adjusted for calcium compared with placebo was observed at 1 hour post-dose (mean [90% CI]: 7.00 [4.36, 9.64] msec) (Table 1)

Mean (SD) change in calcium concentration mmol/L		
	Strontium ranelate 4g	Placebo
Baseline	2.36 ± 0.09	2.36 ± 0.11
Post-baseline	2.17 ± 0.09	2.29 ± 0.09
Change from baseline	-0.18 ± 0.09	-0.07 ± 0.09

Table 2 Mean change in calcium concentration (mmol/L) from baseline to post-baseline

QTc vs PK Analysis

The relationship between QTcI and strontium ranelate and moxifloxacin plasma concentration was analysed (Figure 2).

An increase in moxifloxacin plasma concentration was associated with a moderate increase in QTcI (Figure 2). At C_{max} (2.5 ng/L) an increase of approximately 12.5 msec in QTcI was observed.

QTcI was increased following an increase in strontium ranelate plasma concentration (Figure 2). At C_{max} (25 ng/L) an increase of approximately 7.5 msec in QTcI was observed.

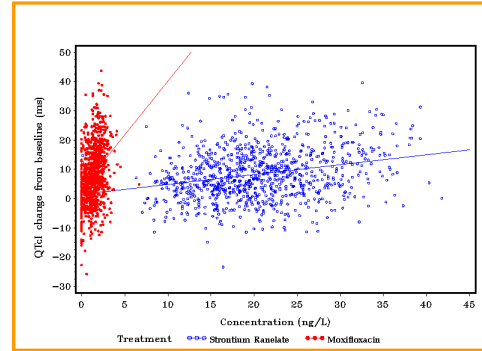


Figure 2 QTcI change from baseline against plasma concentration for strontium ranelate 4g and moxifloxacin 400 mg

Safety Results

Safety and Tolerability

Moxifloxacin and strontium ranelate were well-tolerated by healthy subjects in the study. The majority of subjects reported adverse events which were considered to be mild (92%) or moderate (8%).

No severe adverse events were reported by any subject.

One subject had flu-like symptoms and increased heart rate (up to 100bpm [5-hour post-dose]) after receiving moxifloxacin 400mg. This could have affected QTc evaluation and the subject was withdrawn as advised by the consultant cardiologist.

Conclusions

This thorough QTc study was designed to investigate strontium ranelate 4g using 400mg moxifloxacin as a positive control confirming assay sensitivity.

The administration of supratherapeutic repeated oral doses of strontium ranelate (4g/day for 15 days) do not lead to a prolongation of the QT/QTc interval above the threshold of regulatory concern.

When adjusted for calcium levels a slight reduction of the effect on QTc was observed with strontium ranelate.

The findings of the study clearly indicate that administration of strontium ranelate at the therapeutic dose of 2g will not cause prolongation of QT that is of any clinical concern.

The administration of supratherapeutic repeated oral doses of strontium ranelate (4g/day for 15 days) was well tolerated in healthy volunteers.

References

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