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Repeated supratherapeutic 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 supratherapeutic 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_cI compared with placebo was observed at 1 h post dose (mean [90% CI] 7.54 [5.17, 9.90] ms).
- Supratherapeutic (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 supratherapeutic 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 $\pm$ 7.5 years) were included to receive 1 day of placebo followed by 15 days of supratherapeutic 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_cI (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_cI 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 supratherapeutic 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.