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Title: Glycopyrronium does not affect QT interval in healthy subjects: A randomized, 3-period cross-over, placebo- and positive-controlled study

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Body: Introduction Glycopyrronium (NVA237), a once-daily long-acting muscarinic antagonist, has recently been approved for the treatment of patients with COPD. This study evaluated the effect of glycopyrronium on the QT interval and other cardiac parameters in healthy subjects. Methods This randomized, partially-blinded, single-dose, placebo and positive (moxifloxacin) controlled, 3-way cross-over study, investigated the effect of a single inhaled supratherapeutic dose (8-fold clinical dose in COPD patients) of 400µg glycopyrronium on the QTcF interval (primary objective), QTcB, heart rate, blood pressure, pharmacokinetics, safety and tolerability. Results 73 healthy male (N=35) and female (N=38) subjects, aged 18 to 45 years, were randomized. Glycopyrronium did not cause significant QTcF prolongation compared to placebo. The largest time-matched mean difference to placebo was 2.97 ms at 5 min with the upper limit of the two sided 90% CI of 4.80 ms, excluding a relevant QT-effect as defined by the ICH E14 guideline. Glycopyrronium had a slight bradycardic effect with a mean change of -2.88 (90% CI: -3.78, -1.99) beats per min (bpm) over whole time range and a maximum of -5.87 (90% CI: -7.82, -3.92) bpm at 5 h post inhalation. No clinically relevant effects were seen on QTcB, other ECG intervals or blood pressure. Peak plasma concentration of glycopyrronium was achieved shortly after inhalation (median Tmax=7 min). All the treatments were well tolerated with no serious adverse events. Conclusion A supratherapeutic dose of glycopyrronium had a favorable cardiovascular safety profile with no clinically relevant effect on QT interval.