INVESTIGATING THE EFFECT OF INTRAVENOUS APD421 (AMISULPRIDE) AND THE ETHNIC DIFFERENCES BETWEEN JAPANESE AND CAUCASIANS ON CARDIAC CONDUCTION

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Introduction

Amisulpride is a substituted benzamide that acts as a selective antagonist of dopamine D2 and D3 receptors [1]. Some dopamine antagonists have been associated with prolongation of the QT interval.

Amisulpride APD421 (amisulpride) has shown promising efficacy against PONV at low doses [2]. This is the first thorough QT/QTc (TQT) to exclude an effect of i.e. APD421 on the QTc interval at the therapeutic dose proposed for PONV management.

Aim

- Characterise the effects of single intravenous (iv) doses of 5 mg and 40 mg APD421 on the QTc interval.
- Compare the PK QTc relationship in two ethnicities: Caucasian and Japanese.

Study Design:

randomised, double-blind, placebo and positive-controlled, four-way crossover study with 40 subjects (n = 17 Japanese and n = 23 Caucasian). Treatment sequences were as follows:

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Methods

Triplicate ECG recordings were performed using a MAC1200® ECG recording: Triplicate ECG recordings were performed using a MAC1200®

Statistical analysis:

The primary analysis used the change from average baseline of QTcF of the baseline day. A linear mixed effects model with sequence, period, gender and race as fixed effects and baseline as covariate was adapted, with subject (nested in sequence) as a random effect. To show assay intercept and slope but random intercepts only. Pharmacokinetics: Timings for PK blood sampling were coincident with ECG time points. Plasma samples for determination of APD421 concentration were analysed by Quotient BioAnalytical Sciences, using a validated LC/MS/MS method.

Safety Assessment: Adverse events were recorded from the date informed consent was signed until follow-up.

Results

Concentration response analysis

PK-PD relationship was linear and dose proportional.

No differences between Caucasian and Japanese. The difference between slope is not statistically significant.

PK-PD predicted that each additional increase of 10 ng/mL in plasma APD421 concentration would lead to an increase in QTcF of 0.175 ms.

No evidence of hysteresis.

Conclusions

A total of 34 adverse events (AEs) were reported in 34 of 40 subjects, 8 with moxifloxacin, 11 with placebo, 12 with 5 mg APD421 and 43 with 40 mg APD421, the majority of which were pain at the injection site. There were no SAEs, no AEs which led to withdrawal and no AEs with severe intensity. There were no clinically relevant changes in the laboratory parameters or physical examinations.

References