Electrocardiographic Effects of WCK 2349

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INTRODUCTION AND PURPOSE

WCK 2349 is a novel L-alanine ester prodrug of levonadifloxacin being developed as an oral fluoroquinolone antibacterial agent that displays excellent coverage for methicillin-resistant Staphylococcus aureus (MRSA). This agent is being developed for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and hospital-acquired bacterial pneumonia (HABP) caused by MRSA.

The primary objective of the study was to determine the effect of a supratherapeutic dose of WCK 2349 on the heart-rate-corrected QT interval (QTc) in healthy adult male and female subjects, in accordance with the ICH E14 Guidance on The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.

METHODS

- This was a randomized, double-dummy, placebo and positive-controlled, 3-way crossover study. 48 subjects were randomized in a crossover design to receive orally 2600 mg (supratherapeutic dose) of WCK 2349, 400 mg of moxifloxacin or placebo.
- Moxifloxacin was included as an active control to demonstrate the capability of the study design to detect small changes in QTc.
- Three 10-second, 12-lead electrocardiograms (ECGs) spaced on minute intervals were obtained at 4, 6, 8, 10, 16, 24 and 36 after dosing.
- Plasma samples for pharmacokinetic analysis were obtained at each time point.
- The primary analysis was a mixed effects model of change over baseline of QTcF in the WCK 2349 compared to the placebo arm, the difference of WCK 2349 termed ddQTcF. Subject was included as a random effect and treatment, hour, treatment*hour, and treatment sequence were included as fixed effects.
- Secondary analysis included ddHR (heart rate), ddPR (PR interval) and ddQRS (QRS interval), concentration-effect modelling of ddQTcF versus plasma concentration, and assessment of assay sensitivity based on the moxifloxacin response. 2 hour time-point was only for PK.

RESULTS

- Exposure: A mean Cmax of levonadifloxacin of 40.6 µg/ml was achieved at 3 hours (Tmax) and the mean plasma AUC was 412.29 h·µg/mL following administration of 2600 mg of WCK 2349. These values exceed the usual Cmax and AUC during clinical treatment by approximately 2-fold.
- QTcF: Figure 1 shows the unadjusted change in ddQTcF in the WCK 2349 and moxifloxacin arms and Table 1 shows the hourly group mean ddQTcF and its 90% 2-sided confidence band from the mixed effects model.

CONCLUSIONS

- The thorough QT study of WCK 2349 was successful.
- WCK 2349 was shown to have no clinically or statistically significant effect on QTc, PR or QRS.
- WCK caused a transient increase in HR. HR increase associated with antibiotics of several classes is well known, but usually obscured in clinical practice due to treatment-related defervescence.

REFERENCES

2. Proarrhythmic Potential for Non-Antiarrhythmic Drugs.
3. This study was sponsored by Wockhardt Bio AG, Switzerland.

DISCLOSURES

This study was sponsored by Wockhardt Bio AG, Switzerland. www.wockhardt.com

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