Abstract

Background: TMC125, a next-generation NNRTI, has shown antiviral benefit in two large Phase III studies. In vitro, TMC125 has no effect on HERG and no relevant electrocardiogram (ECG) changes were observed in dogs administered up to 400mg/kg/day of TMC125. ECG parameters in healthy or HIV-infected volunteers have shown no clinically-relevant changes. This thorough QT study was conducted in accordance with ICH E14 guidelines to confirm the lack of QT prolongation by TMC125.

Methods: A double-blind, double-dummy, randomised, placebo- and active-controlled, four-period crossover trial was conducted in 41 HIV-negative volunteers (19 female/22 male). Volunteers received TMC125 200mg bid, TMC125 400mg qd, moxifloxacin 400mg qd (positive control), and placebo in separate sessions. Each treatment was given for 8 days followed by a washout period of ≥14 days. On Days 1–8, 1 and 8 of each session, 12-lead triplicate ECGs were collected at 11 timepoints over 12 hours.

Results: During TMC125 treatment, the upper limit of all 90% confidence intervals (CIs) of the mean time-matched differences in QTcF was below the 10ms threshold defined by the ICH E14 guidelines. The maximum mean change (90% CI) difference of the time-matched changes in QTcF versus placebo on Day 1 was +0.1ms (−6.4 to 7.6) and +0.1ms (−10.3 to 10.1). On Days 8 and 29, respectively, TMC125 400mg qd and moxifloxacin, respectively, on Day 8 these values were +0.6ms (−12.3 to 13.5), +0.1ms (−4.3 to 5.5) and +0.1ms (6.7 to 13.8), respectively. During TMC125 treatment, no QTcF values >60 ms were observed and no changes occurred on PR and QR intervals or heart rate. No gender differences were observed and results were similar when other QT correction methods were applied. Short-term administration of TMC125 was generally safe and well tolerated.

Conclusions: TMC125 does not prolong the QT interval. No clinically-relevant ECG changes were observed in healthy volunteers receiving TMC125.

Study design

The study was a double-blind, double-dummy, randomised, placebo-controlled, four-period crossover trial in healthy volunteers. Each treatment consisted of TMC125 200mg bid or TMC125 400mg qd administered with placebo or moxifloxacin 400mg qd (positive control) and placebo in separate sessions. TMC125 was administered as a single dose at 1200 hours and triplicate ECGs were collected at each timepoint.

Safety and tolerability

No volunteers receiving TMC125 had a QTcF >450ms (threshold of particular clinical concern), compared with three receiving placebo. No meaningful changes in ECG-derived parameters were observed. TMC125 dosing regimens on the QT/QTc interval in healthy, HIV-negative volunteers. Additional safety and tolerability parameters were assessed.

References

2. P9.5/03

Acknowledgements

The authors would like to express their gratitude to the volunteers. We also acknowledge:

- Tibotec/Beersel, Belgium – W Hasznai, MD, SGS LSS, Antwerp, Belgium
- Trial monitor, GCO Janssen-Cilag, Berchem, Belgium
- MP Boeck, PRD Beersel, Belgium (bioanalysis).