Pharmacokinetic interaction study between TMC278, a next-generation NNRTI, and methadone

Herta M Crauwels,1,2 Katia Boven,3 Ann Vandevoorde,1 David F McNeeley,4,5 Annemie Buelens,2 Katja Boven,1 Richard MW Hoetelmans2
1Tibotec BVBA, Beerse, Belgium; 2Tibotec Inc., Titusville, NJ, USA

Methods

Study design

Open-label, single-dose, drug-drug interaction trial in 13 HIV-negative healthy volunteers on stable methadone maintenance therapy (Figure 2).

Methodology: individualised stable dose; range of doses: 60–100 mg q.d. (methadone alone).

The trial aimed to evaluate the effect of steady-state TMC278 25 mg q.d. on the steady-state pharmacokinetics of R- and S-methadone.

Translation of the mean (± standard deviation [SD]) plasma concentrations of R- and S-methadone in the presence and absence of TMC278.

Effect of TMC278 on methadone plasma concentrations

The addition of TMC278 25 mg q.d. to steady-state treatment with methadone resulted in lower mean (standard deviation) plasma concentrations of R- and S-methadone compared with administration of methadone alone (Day 1), over the entire dosing interval (Figure 4).

Results

Effect of TMC278 on methadone PK parameters

When TMC278 25 mg q.d. was added to a stable methadone maintenance therapy, the methadone Cmin, SS,av and AUC24h, S-/R-methadone values decreased relative to treatment with methadone alone (Table 2 and Figure 4).

The LSM ratio (90% CI) for R- and S-methadone PK parameters (Cmin, SS,av and AUC24h) was comparable between the two treatments (Table 2 and Figure 4).

Conclusion

Co-administration of TMC278 25 mg q.d. and methadone was generally well tolerated.

The proportion of volunteers experiencing AEs was 66.7% during co-administration of TMC278 and methadone, and 69.2% during treatment with methadone alone.

There were no notable changes in laboratory safety parameters. There were no grade 3 or grade 4 AEs, and there were no serious AEs.

References


Acknowledgements and disclosures

TMC278 pharmacokinetics in the presence of methadone

Mean (± SD) plasma concentrations of TMC278 in the presence of methadone are shown in Figure 5.

These values were obtained in previous trials in healthy volunteers, where TMC278 25 mg q.d. was administered alone (data on file).

Conclusions

Co-administration of TMC278 25 mg q.d. and methadone was generally well tolerated.

When TMC278 25 mg q.d. was added to a stable methadone maintenance therapy, the methadone Cmin, SS,av and AUC24h, S-/R- values were decreased as compared with methadone maintenance alone by:

22%, 15%, and 10%, respectively, for S-methadone.

The LSM ratio (90% CI) was comparable between both treatments, indicating the absence of a stereo-specific effect of TMC278.

The exposure to TMC278 when administered in the presence of methadone was within the range observed in previous trials in healthy volunteers.

The LSM ratio (90% CI) was comparable between both treatments, indicating the absence of a stereo-specific effect of TMC278.

During co-administration with TMC278, no clinically relevant changes in the pharmacodynamic assessments of methadone withdrawal signs and symptoms (SWiDQ, SOWDQ scores and pupal dilation) were observed.

The combination of TMC278 and methadone was generally well tolerated.

No adjustment of the methadone dosage was required when co-administered with TMC278 25 mg q.d. However, clinical monitoring for methadone withdrawal symptoms is recommended as methadone maintenance therapy may need to be adjusted in some patients.