The pharmacokinetic interaction between isoniazid/pyrazinamide and TMC207, an investigational antimycobacterial agent

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Introduction
- TMC207 (also known as R207910) is an investigational anti-tuberculosis agent specifically directed against mycobacterial ATP-synthase.

- TMC207 has shown potent in vitro activity against M tuberculosis (MTB) including strains resistant to all first line agents and fluoroquinolones.

- TMC207 has shown significant short-term activity in treatment naïve patients with smear-positive tuberculosis.

Background and Objective

Background
- Treatment of tuberculosis requires a combination of several antimycobacterial agents, often including agents such as isoniazid and pyrazinamide.

- The effect of TMC207 on isoniazid/pyrazinamide and vice versa is unknown.

Objective
- To investigate the drug-drug interaction between TMC207 and isoniazid/pyrazinamide (H/Z) after multiple dosing in healthy subjects.

Study design
- One-way cross-over study in 24 healthy male subjects

Study methods
- TMC207 was administered at a dose of 400 mg q.d.

- Isoniazid/pyrazinamide (H/Z) were simultaneously co-administered at a standard 300/2000 mg q.d. dose.

- All drugs were administered with food.

- Non-compartmental PK analysis was performed (Cmax, Cmin, C0h and AUC).

- Bioanalysis of all drugs as well as M2, an active metabolite of TMC207, was carried out by validated LC-MS/MS methods.

- Statistical analyses of pharmacokinetic parameters were performed by linear mixed effects modeling (LSM ratio and 90% confidence intervals).

Study population

- 23 Caucasian and 1 Hispanic subjects were included in the study.

- Age range: 20-30 years

- Body weight range: 49-106 kg

- BMI range: 18.4-26.4 kg/m2

- No subject had a significant illness or active disease.

- The study protocol was reviewed and approved by the appropriate institutional ethical committee and health authorities, and was conducted in accordance with the Declaration of Helsinki.

M2* mean (SD) PK profiles

Isoniazid mean (SD) PK profiles and individual AUCs

Pyrazinamide mean (SD) PK profiles

Conclusions

- TMC207 did not have a clinically relevant effect on either isoniazid or pyrazinamide pharmacokinetics.

- The combination of isoniazid and pyrazinamide did not have a clinically relevant effect on TMC207 or M2 pharmacokinetics.

- These results support further evaluation of TMC207 in combination with isoniazid and/or pyrazinamide in patients with tuberculosis.

Acknowledgements

- We would like to express gratitude to the study volunteers, all the TMC207 team members at Tibotec, T Verhaeghe (J&J Pharmaceutical Research and Development, Beerse, Belgium), and the investigator: U Lorsh, MD, Richmond Pharmacology Ltd., London, UK.

*M2 is the monodesmethyl metabolite of TMC207.