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

A-780

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Introduction

- TMC207 (also known as R207910) is an investigational anti-tuberculosis agent specifically directed against mycobacterial ATP-synthase[1].
- 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[2].

[1]*Andries, K et al. Science 2005; 307:223-7.*
[2]*Diacon AH et al. IUATLD Conference, October 31-November 4, 2006*

Background and Objective

Background

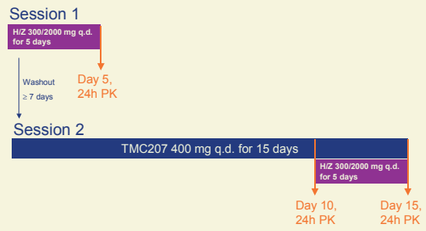
- Treatment of tuberculosis requires a combination of several antimycobacterial agents,often including agents such as isoniazid and pyrazinamide.
- The effect of TMC207 on isoniazid/pyrazinamide and *vice versa* is unknown.

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 dose of 300/2000 mg q.d.
- All drugs were administered with food
- Bioanalysis of all drugs as well as M2, an active metabolite of TMC207, was carried out by validated LC-MS/MS methods
- Non-compartmental PK analysis was performed (C_{max}, C_{min}, C_{0h} and AUC_{24h})
- Statistical analysis of pharmacokinetic parameters was performed by linear mixed effects modeling (LSM ratio and 90% confidence intervals)
- The study protocol was reviewed and approved by the appropriate institutional ethics committee and health authorities, and was conducted in accordance with the Declaration of Helsinki

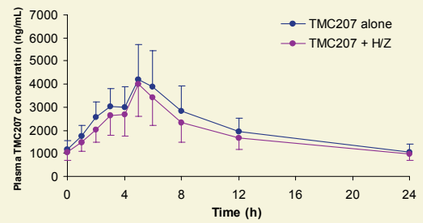
LC-MS/MS = liquid chromatography-mass spectrometry/mass spectrometry
C_{max} = maximum concentration; C_{min} = minimum concentration; C_{0h} = predose concentration; AUC = area under the concentration-time curve; LSM = Least Square Means

Study population

Characteristic	Value
N	24 (all male)
Age* (years)	24 (18-38)
Weight* (kg)	79.5 (60-101)
BMI* (kg/m²)	24.4 (20-30)
Ethnic origin (n)	
Caucasian	23
Hispanic	1

*Median and range

TMC207 mean (SD) PK profiles

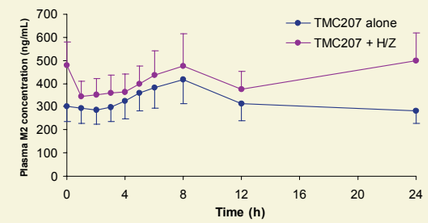


TMC207 PK parameters (mean and SD) and statistical results

	TMC207 alone	TMC207 + H/Z*	LSM ratio	90% CI
n	22	22		
C_{min} (ng/mL)	1062 ± 342	971 ± 290	0.92	0.88-0.96
C_{max} (ng/mL)	4408 ± 1532	4115 ± 1316	0.94	0.89-1.00
AUC_{24h} (ng*h/mL)	51360 ± 15750	44790 ± 13690	0.87	0.84-0.91

*H/Z = isoniazid/pyrazinamide

M2* mean (SD) PK profiles



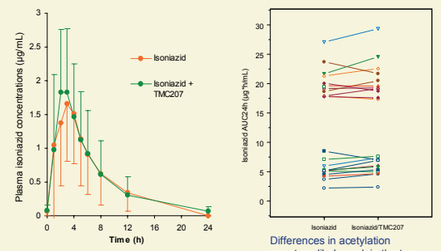
*M2 is the *N*-monodesmethyl metabolite of TMC207

M2* PK parameters and statistical results

	TMC207 alone	TMC207 + H/Z	LSM ratio	90% CI
n	22	22		
C_{min} (ng/mL)	269 ± 58	334 ± 69	1.24	1.20-1.29
C_{max} (ng/mL)	427 ± 101	546 ± 122	1.28	1.21-1.35
AUC_{24h} (ng*h/mL)	7858 ± 1840	10130 ± 2063	1.30	1.25-1.34

*M2 is the *N*-monodesmethyl metabolite of TMC207

Isoniazid mean (SD) PK profiles and individual AUCs



Differences in acetylation genotype likely explain the two clusters of exposure to isoniazid

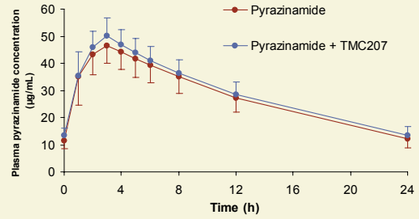
Isoniazid PK parameters (mean and SD) and statistical results

	Isoniazid alone*	Isoniazid + TMC207	LSM ratio	90% CI
n	23	22		
C_{0h} (µg/mL)	0.068 ± 0.072	0.076 ± 0.085	1.20	1.08-1.32
C_{max} (µg/mL)	2.03 ± 0.93	2.35 ± 0.93	1.20	1.09-1.33
AUC_{24h} (µg*h/mL)	13.1 ± 8.08	13.3 ± 8.24	1.07	1.02-1.11

C_{0h} (predose concentration) was used as C_{min} was not quantifiable (<0.05 µg/mL) after administration of isoniazid/pyrazinamide alone

*Isoniazid was always co-administered with pyrazinamide.

Pyrazinamide mean (SD) PK profiles



Pyrazinamide PK parameters (mean and SD) and statistical results

	Pyrazinamide alone*	Pyrazinamide + TMC207	LSM ratio	90% CI
n	23	22		
C_{min} (µg/mL)	11.5 ± 3.19	13.2 ± 2.79	1.18	1.12-1.25
C_{max} (µg/mL)	47.4 ± 6.80	51.4 ± 5.84	1.10	1.07-1.14
AUC_{24h} (µg*h/mL)	673 ± 120	710 ± 94.5	1.08	1.06-1.11

*Pyrazinamide was always co-administered with isoniazid.

Safety and tolerability

- TMC207 alone or in combination with H/Z was generally well tolerated.
- No deaths or serious Adverse Events (AEs) were reported during this trial.
- The most common AE was G3/4 hyperuricemia during treatment with H/Z alone or in combination with TMC207 (reported in 10 subjects). Hyperuricemia is a well-known effect of pyrazinamide.
- Other AEs reported in more than 2 subjects included headache (n=5), erythema (n=5), pharyngolaryngeal pain (n=3).
- One subject discontinued the trial due to G3 pyrexia during treatment with TMC207.

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

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