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

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Introduction

- TMC278 (Figure 1), a next-generation NNRTI, has demonstrated potent in-vitro anti-HIV-1 activity.[1]
- A Phase IIb, dose-finding trial has demonstrated the efficacy, safety and tolerability of TMC278 over 192 weeks in antiretroviral (ARV)-naïve, HIV-1-infected patients.[2]
- TMC278 is currently being evaluated at a dose of 25 mg q.d. in two Phase III trials,[3] in combination with a background regimen of two NRTIs.

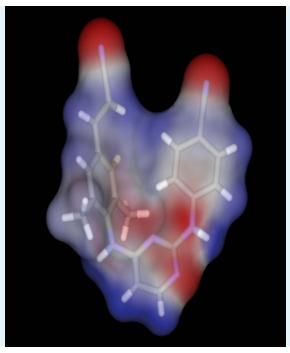

Figure 1. Chemical structure and three-dimensional model of TMC278.

- Intravenous drug use is one of the modes of HIV transmission, and a substantial number of HIV-infected patients are on methadone therapy.
- Methadone is a synthetic narcotic analgesic used for the treatment of opiate dependence.
- Methadone is usually administered as a racemic mixture of the R-isomer and the S-isomer
  - The R-isomer is mostly responsible for the therapeutic opioid effects of methadone maintenance treatment
  - Variations in the relative exposure to R- and S-methadone could potentially influence the therapeutic response.
- Substantial and clinically relevant pharmacokinetic (PK) interactions of an ARV with methadone can precipitate methadone withdrawal symptoms, warranting close monitoring of HIV-1-infected patients on methadone and the interacting ARV.
- This trial aimed to evaluate the
  - Effect of steady-state TMC278 25 mg q.d. on the steady-state pharmacokinetics of R- and S-methadone
  - Potential effect of TMC278 on the pharmacodynamics of methadone therapy
  - Steady-state pharmacokinetics of TMC278 25 mg q.d. in HIV-negative volunteers on stable methadone maintenance therapy (compared with historical controls)
  - Short-term safety and tolerability of co-administration of TMC278 and methadone in HIV-negative volunteers on stable methadone maintenance therapy.

Methods

Study design

- Open-label, single-sequence, drug-drug interaction trial in 13 HIV-negative healthy volunteers on stable methadone maintenance therapy (Figure 2).
- Methadone: individualised stable dose; range of doses: 60–100 mg q.d. (methadone dose was not to be changed during the course of the trial); TMC278: 25 mg q.d.
- Two different treatments in sequential order, there was no washout in-between treatments
  - Treatment A: methadone q.d. (individualised dose) alone: Day –14 to Day –1
  - Treatment B: methadone q.d. (individualised dose) + TMC278 25 mg q.d.: Day 1 to Day 11.
- TMC278 and (racemic) methadone were administered within 10 minutes after breakfast.

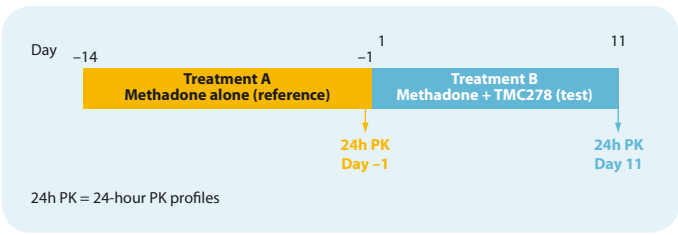

Figure 2. Study design.

Study assessments

- Venous blood samples for PK analysis were collected at regular timepoints in each treatment session, and 24h PK profiles were obtained for
  - R- and S-methadone: on Day –1 of Treatment A, and on Day 11 of Treatment B
  - TMC278: on Day 11 of Treatment B.
- Bioanalysis of TMC278, R- and S-methadone in plasma was performed using validated liquid chromatography-mass spectrometry/mass spectrometry methods, with a lower limit of quantification of 1.0 ng/mL for TMC278 and 5.0 ng/mL for R- and S-methadone.
- Pharmacodynamic assessments of the signs and symptoms of methadone withdrawal were performed on Day –7 and daily from Day –3 until Day 11, by means of Short Opiate Withdrawal Scale (SOWS), Desires for Drug Questionnaire (DDQ) and pupillometry, within 2 hours before methadone intake.
- Short-term safety and tolerability of co-administration of TMC278 and methadone were evaluated.
- The study protocol was reviewed and approved by the appropriate institutional ethics committee and health authority, and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

PK and statistical analysis

- PK parameters were calculated using non-compartmental analysis.
- Primary PK parameters for the statistical analysis were minimum plasma concentration (C_{min}), maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from time of administration to 24 hours after dosing (AUC_{24h}), on the logarithmic scale.
- Statistical analysis was performed by comparing the test treatment (methadone + TMC278) with the reference treatment (methadone alone), both for R- and S-methadone.
- All observations for test and reference, paired and unpaired, were included in the statistical analysis.
- The least square means (LSM) of the PK parameters for each treatment were estimated using a linear mixed effects model with treatment as fixed effect and subject as random effect. A 90% confidence interval (CI) was constructed around the difference in the LSM of each test compared with reference.
- Pharmacodynamic assessments and safety data were summarised using descriptive statistics and frequency tabulations.

Results

Patient disposition and baseline characteristics

- Table 1 shows the baseline demographics and methadone maintenance dose.

Table 1. Baseline demographics and methadone maintenance dose.

Characteristic	Value
N	13* (all male)
Age,‡ years	41 (31–54)
Weight,‡ kg	84 (57–112)
Body mass index,‡ kg/m²	26.4 (20.3–33.4)
Race, n (%)	
Black or African American	1 (7.7)
Asian	2 (15.4)
White	10 (76.9)
Methadone maintenance dose, n	
60 mg q.d.	3
65 mg q.d.	1
70 mg q.d.	2
75 mg q.d.	1
80 mg q.d.	3
90 mg q.d.	1
100 mg q.d.	2

*One volunteer dropped out before trial completion due to non-compliance with the protocol; ‡Median and range

Effect of TMC278 on methadone plasma concentrations

- The addition of TMC278 25 mg q.d. (steady-state) to treatment with methadone resulted in lower mean (± standard deviation [SD]) plasma concentrations of R- and S-methadone compared with administration of methadone alone (Day –1), over the entire dosing interval (Figure 3).

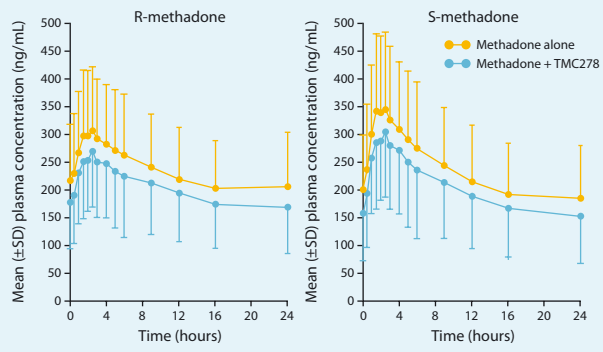

Figure 3. Mean (± SD) plasma concentration of R- and S-methadone with and without co-administration of TMC278 (steady-state).

Effect of TMC278 on methadone PK parameters

- When TMC278 25 mg qd was added to a stable methadone maintenance therapy, the methadone C_{min}, C_{max} and AUC_{24h} values decreased relative to treatment with methadone alone (Tables 2, 3 and Figure 4)
  - By 22% (LSM ratio 0.78; 90% CI: 0.67–0.91), 14% (0.86; 0.78–0.95) and 16% (0.84; 0.74–0.95), respectively, for R-methadone (Table 3)
  - By 21% (0.79; 0.67–0.92), 13% (0.87; 0.78–0.97) and 16% (0.84; 0.74–0.96), respectively, for S-methadone (Table 3).
- The $AUC_{24h,\ S\text{-}/R\text{-methadone}}$ ratio was comparable between both treatments (Tables 2 and 3).

Table 2. Comparison of PK parameters for R- and S-methadone with and without (reference) co-administration of TMC278 (steady-state).

	R-methadone		S-methadone	
	Methadone alone (reference)	Methadone + TMC278 (test)	Methadone alone (reference)	Methadone + TMC278 (test)
N	13	12	13	12
C_{min}, ng/mL	195.9 ± 86.66	159.4 ± 81.25	179.9 ± 90.59	146.1 ± 85.02
C_{max}, ng/mL	315.8 ± 122.8	279.3 ± 109.2	358.1 ± 145.2	316.1 ± 123.2
t_{max},* h	2.5 (1.5–4.0)	2.5 (1.15–6.0)	2.5 (1.5–4.0)	2.5 (1.2–6.0)
AUC_{24h}, ng•h/mL	5578 ± 2343	4811 ± 2106	5610 ± 2515	4815 ± 2275
$C_{SS,av}$, ng/mL	232.4 ± 97.61	200.5 ± 87.74	233.7 ± 104.8	200.7 ± 94.77
Ratio $AUC_{24h,\ S\text{-}/R\text{-methadone}}$			1.02 ± 0.17	1.00 ± 0.12

Data presented as mean (± SD); *Median (range); t_{max} = time-to-reach the maximum plasma concentration; $C_{SS,av}$ = average steady-state plasma concentration

Table 3. Statistical analysis comparing methadone primary PK parameters in the presence and absence of TMC278: LSM ratio (90% CI).

LSM ratio (90% CI)			
Parameter	N/N	R-methadone	S-methadone
C_{min}	12/13	0.78 (0.67–0.91)	0.79 (0.67–0.92)
C_{max}	12/13	0.86 (0.78–0.95)	0.87 (0.78–0.97)
AUC_{24h}	12/13	0.84 (0.74–0.95)	0.84 (0.74–0.96)
Ratio $AUC_{24h,\ S\text{-}/R\text{-methadone}}$	12/13	1.01 (0.96–1.05)	

LSM ratio calculated as test/reference: (methadone + TMC278)/methadone alone

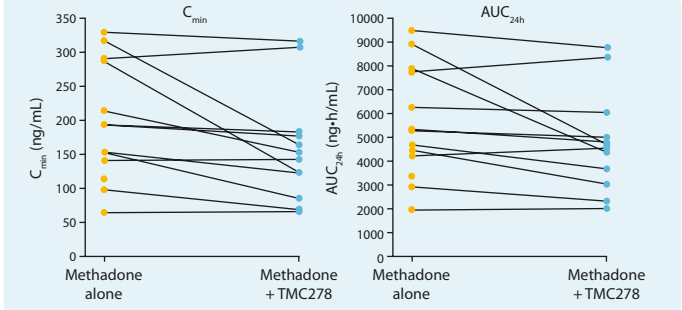

Figure 4. Effect of co-administration of TMC278 (steady-state) on individual R-methadone PK parameters (C_{min}, AUC_{24h}).

TMC278 pharmacokinetics in the presence of methadone

- Mean (± SD) plasma concentrations of TMC278 in the presence of methadone are shown in Figure 5.
- The mean (± SD) C_{min}, C_{max} and AUC_{24h} were 67.63 ± 25.08 ng/mL, 156.3 ± 65.20 ng/mL and 2174 ± 759.2 ng•h/mL, respectively.
- These values are within the range of those observed in previous trials in healthy volunteers, where TMC278 25 mg q.d. was administered alone (data on file).

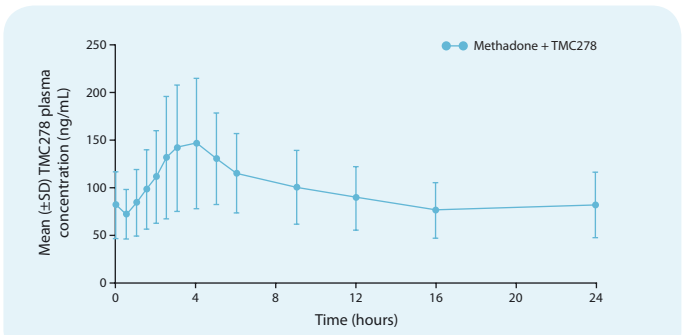

Figure 5. Mean (± SD) plasma concentration of TMC278 25 mg q.d. in the presence of methadone.

Pharmacodynamics

- There were no clinically relevant changes over time in SOWS scores, DDQ scores and pupil dilation.

Safety and tolerability

- Co-administration of TMC278 25 mg q.d. and methadone was generally well tolerated
  - Nine volunteers experienced adverse events (AEs) considered possibly or probably related to TMC278, and four volunteers experienced AEs considered possibly related to methadone
  - The proportion of volunteers experiencing AEs was 92.3% during co-administration of TMC278 and methadone, and 69.2% during treatment with methadone alone
  - No rashes were seen
  - There were no notable variations in electrocardiogram (ECG) parameters over time and no AEs related to ECGs
  - No consistent or clinically relevant changes in mean laboratory parameters were observed.
- There were no grade 3 or grade 4 AEs, and there were no serious AEs.
- No discontinuations due to AEs were observed.

Conclusions

- When TMC278 25 mg q.d. was added to a stable methadone maintenance therapy, the methadone C_{min}, C_{max} and AUC_{24h} values were decreased as compared with methadone treatment alone by
  - 22%, 14% and 16%, respectively, for R-methadone
  - 21%, 13% and 16%, respectively, for S-methadone
- The $AUC_{24h,\ S\text{-}/R\text{-methadone}}$ ratio 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.
- During co-administration with TMC278, no clinically relevant changes in the pharmacodynamic assessments of methadone withdrawal signs and symptoms (SOWS, DDQ scores and pupil dilation) were observed.
- The combination of TMC278 and methadone was generally well tolerated.
- No adjustment of the methadone dosage is required when initiating co-administration 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.

References

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3. Cohen C, et al. XVIII International AIDS Conference, Vienna, Austria, 18–23 July 2010. Abstract THLBB206.

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