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Lack of interaction between TMC125 and methadone

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Abstract

Background
TMC125 is an NNRTI with potent activity against wild-type and NNRTI-resistant HIV. The objective of this trial was to evaluate the effect of TMC125 on the pharmacokinetics (PK) and pharmacodynamics (PD) of methadone in HIV-negative volunteers.

Methods
In an open-label, add-on, one-way interaction trial, volunteers on stable methadone maintenance therapy received 100mg TMC125 bid (Phase III formulation) for 14 days. Since an interaction affecting methadone levels was possible, TMC125 was administered at 100mg bid (lower than the Phase III dose) to limit the severity of any potential opiate withdrawal. PK of methadone R(–) and S(+) isomers were determined on Days –1, 7, and 14 (24 hours) and for TMC125 on Days 7 and 14 (12 hours). PK parameters were determined by non-compartmental analysis. Safety, tolerability and symptoms of methadone withdrawal were assessed.

Results
Sixteen male volunteers participated. The least square (LS) mean ratios (90% confidence interval [CI]) for AUC_{24h}, C_{max} and C_{min} of S(+) methadone on Day 7 were 93% (86–99%), 91% (85–98%) and 94% (86–104%), respectively; on Day 14: 89% (82–96%), 89% (83–97%) and 89% (81–98%), respectively, compared with methadone alone. The LS mean ratios for AUC_{24h}, C_{max} and C_{min} of R(–) methadone on Day 7 were 108% (102–113%), 103% (97–109%) and 112% (105–119%), respectively; on Day 14: 106% (99–113%), 102% (96–109%) and 110% (102–119%), respectively, compared with methadone alone. No clinically significant withdrawal symptoms were observed and no dose adjustment of methadone was required during co-administration with TMC125 or during follow-up. The concomitant administration of TMC125 and methadone was generally safe and well tolerated.

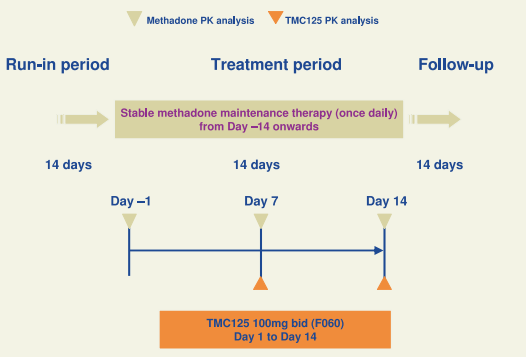
Conclusion
TMC125 has no clinically relevant effect on the PK or PD of methadone.

Introduction

- TMC125 is a novel NNRTI with potent in-vitro activity against both wild-type strains of HIV-1 and those resistant to current NNRTIs[1]
- A Phase IIb trial (TMC125-C223) in treatment-experienced HIV patients demonstrated that TMC125, with an optimized background regimen, reduced viral load significantly more than the standard of care regimen. No dose-related effects on safety and tolerability were noted[2]
- Methadone is widely used in the HIV-infected population. The drug is administered as a racemic mixture of R(–) active and S(+) inactive isomers
- Methadone is stereoselectively metabolized by cytochrome P450 3A4, 2D6, 2C9, 2C19 and 1A2. PK interactions with methadone are known for a number of drugs
- *In vitro*, TMC125 induces CYP3A4, 2B6 and 2C and inhibits 2C9 and 2C19
- This study (TMC125-C158) evaluated the effect of TMC125 (Phase III formulation F060) on the PK and PD of methadone

1. Andries K, et al. Antimicrob Agents Chemother 2004;48:4680–6
2. Cohen C, et al. 12th BHIVA 2006 (Poster 2)

Study design



Study design (cont'd)

- Open-label, add-on trial
- Sixteen HIV-negative volunteers on stable, individualized methadone therapy entered the trial
- A run-in period of stable, witnessed methadone intake was included from Day –14 to Day –1
- Volunteers received TMC125 (F060 formulation) 100mg bid from Day 1 to Day 14, in order to
  - reach steady state
  - allow the development of enzyme induction, if any
  - enable the development of withdrawal symptoms, if any
- Methadone dose adjustments were allowed from Day 8 until Day 15, if clinically justified
- Supervised methadone intake continued until Day 25, with evaluation of withdrawal symptoms, if any

Study design (cont'd)

- TMC125 was administered within 10 minutes after a meal, methadone was taken immediately after TMC125 intake
- Plasma concentrations of R(–) and S(+) methadone were determined until 24 hours after administration on Days –1, 7 and 14
- Plasma concentrations of TMC125 were determined until 12 hours after administration on Days 7 and 14
- The study protocol was reviewed and approved by the appropriate institutional ethics committee(s) and health authorities, and was conducted in accordance with the Declaration of Helsinki

PK and statistical analysis

- Plasma concentrations of R(–) methadone, S(+) methadone and TMC125 were determined using validated liquid chromatographic-tandem mass spectrometric (LC-MS/MS) methods
- PK and statistical PK analyses were performed using
  - WinNonlin Professional™ (version 4.1; Pharsight Corporation, Mountain View, California, USA)
  - Microsoft Excel® (version 2000; Microsoft, Redmond, Washington, USA)
  - SAS (version 9.1.3, SAS Institute Inc., Cary, NC, USA)
- A non-compartmental model with extravascular input was used for the PK analysis. Primary PK parameters were
  - C_{0h} (ng/mL): predose plasma concentration
  - C_{min} (ng/mL): minimum plasma concentration
  - C_{max} (ng/mL): maximum plasma concentration
  - $AUC_{12/24h}$ (ng·h/mL): area under the plasma concentration-time curve from time of administration until 12 or 24 hours post-dosing, calculated by linear trapezoidal summation
- Descriptive statistics were calculated for the PK parameters of TMC125. LS means were estimated with a linear mixed effects model

Safety and PD assessments

- Adverse events (AEs), laboratory assessments, cardiovascular safety, and physical and skin examinations were evaluated throughout the trial
- Severity of AEs and drug relationship towards methadone and/or TMC125 were recorded
- PD assessments of withdrawal symptoms were performed daily from Day –1 to Day 14 at 2 hours post-dose
  - Short Opiate Withdrawal Scale (SOWS)
  - Desires for Drugs Questionnaire (DDQ)
  - pupillometry
- Semiquantitative analysis of urine methadone concentration was performed daily (from Day –3 to Day 15) for real-time support of the clinical assessment of withdrawal symptoms
- Daily clinical assessments occurred up to 10 days after the last intake of TMC125

Volunteer demographics

Demographic parameter	Total (n=16)
Age, years (median [range])	42 (36–55)
Height, cm (median [range])	175 (169–189)
Weight, kg (median [range])	70 (54–106)
BMI, kg/m² (median [range])	23 (18–30)
Ethnic origin	
Caucasian/White, n (%)	14 (88)
Oriental/Asian, n (%)	1 (6)
Other, n (%)	1 (6)

- Study population: 16 HIV-negative men on stable individualized methadone treatment were randomized
- The range of individualized methadone dose was 60–130mg/day

BMI = body mass index

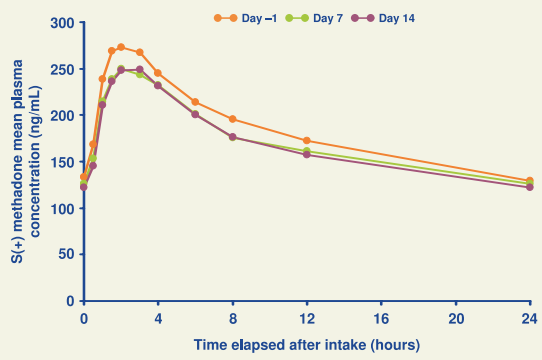
Summary of PK results for TMC125

	TMC125 + methadone (mean ± SD)		TMC125 alone* (mean ± SD)
PK parameter	Day 7 (n=16)	Day 14 (n=15)	Day 8 (n=23)
C_{0h} (ng/mL)	205±95	242±74	234±92
C_{min} (ng/mL)	188±84	214±61	215±86
C_{max} (ng/mL)	375±120	401±88	471±141
AUC_{12h} (ng·h/mL)	3,282±1,200	3,567±859	3,925±1,251

*Historical controls (trial TMC125-C168)

SD = standard deviation

PK profiles of S(+) methadone alone (Day –1) and with TMC125 (Day 7 and Day 14)

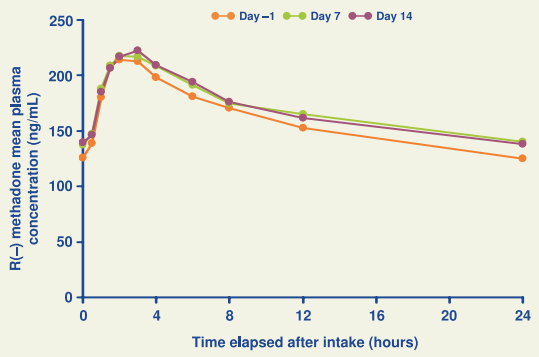


Changes in S(+) methadone PK parameters when given with TMC125

	With TMC125 versus alone LS mean ratio, % (90% CI)	
PK parameter	Day 7 (n=16)	Day 14 (n=15)
C_{0h} (ng/mL)	90 (81–101)	87 (79–96)*
C_{min} (ng/mL)	94 (86–104)	89 (81–98)*
C_{max} (ng/mL)	91 (85–98)*	89 (83–97)*
AUC_{24h} (ng·h/mL)	93 (86–99)	89 (82–96)*

*p<0.05

PK profiles of R(–) methadone alone (Day –1) and with TMC125 (Day 7 and Day 14)



Changes in R(–) methadone PK parameters when given with TMC125

	With TMC125 versus alone LS mean ratio, % (90% CI)	
PK parameter	Day 7 (n=16)	Day 14 (n=15)
C_{0h} (ng/mL)	108 (101–116)	110 (102–118)*
C_{min} (ng/mL)	112 (105–119)*	110 (102–119)*
C_{max} (ng/mL)	103 (97–109)	102 (96–109)
AUC_{24h} (ng·h/mL)	108 (102–113)*	106 (99–113)

*p<0.05

Methadone dose and PD effects

- No clinically relevant changes in SOWS and/or DDQ were observed
- No statistically significant changes in pupil diameter were noted
- No clinically relevant methadone withdrawal symptoms were observed
- No methadone dose adjustments were required during the trial

Summary of the safety results

- No serious AEs were reported
- No volunteers discontinued due to AEs
- No grade 3 or 4 AEs were reported
- The most frequently reported AEs were headache and nausea (25% and 19%, respectively). All were grade 1, except for one case of grade 2 nausea possibly related to TMC125
- The concomitant administration of methadone and TMC125 was generally safe and well tolerated

Conclusions

- TMC125 has no clinically relevant effect on the PK or PD of methadone.
- The PK of TMC125 when co-administered with methadone is comparable to historical controls.
- The co-administration of TMC125 with methadone is generally safe and well tolerated.
- TMC125 can be co-administered with methadone without dose adjustments.

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