Poster No. 1059

Pharmacokinetic interaction between TMC125 and rifabutin

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Abstract

Background
TMC125 is an NNRTI with potent activity against both wild-type HIV and viruses resistant to currently approved NNRTIs. TMC125 and rifabutin are substrates and inducers of CYP3A4. To support concomitant administration, an interaction study was conducted.

Methods
TMC125-C156 was an open-label, randomized, two-period, crossover trial. In Treatment A, 300mg rifabutin qd was administered for 14 days. After a washout period of 14 days, 800mg TMC125 bid (Phase II formulation) was given for 21 days, co-administered with 300mg rifabutin qd on Days 8–21 (Treatment B). The 12-hour pharmacokinetic (PK) profile of TMC125 was assessed on Day 7 and Day 21 of Treatment B. The 24-hour PK profiles of rifabutin and its active metabolite 25-*O*-desacetyl rifabutin were determined on Day 14 of Treatment A and Day 21 of Treatment B. PK parameters were analyzed using a linear mixed effect model for crossover design. Safety and tolerability were assessed.

Results
Sixteen HIV-negative volunteers (15 male, median age 34 years) participated. When combined with rifabutin, TMC125 AUC_{12h} was 63% (90% CI: 54–74%) compared with administration of TMC125 alone. TMC125 C_{max} and C_{min} were 63% (90% CI: 53–74%) and 65% (90% CI: 56–74%), respectively. AUC_{24h}, C_{max} and C_{min} of rifabutin were 83% (90% CI: 75–94%), 90% (90% CI: 78–103%) and 76% (90% CI: 66–87%), respectively, when combined with TMC125 compared with administration alone. AUC_{24h}, C_{max} and C_{min} of 25-*O*-desacetyl rifabutin were 83% (90% CI: 74–92%), 85% (90% CI: 72–100%) and 78% (90% CI: 70–87%), respectively, when given in combination with TMC125. The short-term co-administration of TMC125 and rifabutin was generally safe and well tolerated.

Conclusions
The decrease of rifabutin and 25-*O*-desacetyl rifabutin exposures by 17% is not clinically relevant. The decrease in TMC125 exposure by 37% is comparable with interactions observed with boosted PIs in Phase II trials. Rifabutin can be combined with TMC125 without dose adjustments. The effect of all co-administered drugs should be taken into account.

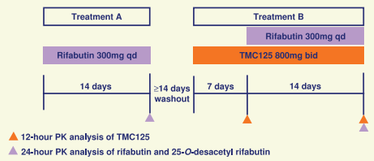
Introduction

- TMC125 is a next generation NNRTI with potent in-vitro activity against both wild-type HIV-1 and HIV-1 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 at 48 weeks significantly more than active control. No dose-related effects on safety and tolerability were noted[2,3]
- TMC125 is predominantly metabolized by CYP3A4, CYP2C and glucuronidation; it is an inducer of CYP3A4 and an inhibitor of CYP2C
- Rifabutin is indicated for the prevention of *Mycobacterium avium* complex disease in patients with advanced HIV infection
- Rifabutin is converted by CYP3A4 to its active metabolite 25-*O*-desacetyl rifabutin and is an inducer of the CYP3A sub-family[4]
- To support concomitant administration, an interaction study with rifabutin and TMC125 (Phase II formulation) was conducted

Study design

- TMC125-C156 was a Phase I, open-label, two-way, two-period, crossover trial in 16 HIV-negative volunteers
- Two treatment sessions (A and B) were scheduled for all volunteers, separated by a washout period of at least 14 days. Half of the volunteers were randomized to start with Treatment A and half were randomized to start with Treatment B
- All doses were taken concomitantly within 10 minutes after a standardized meal
- Post-treatment safety visits took place 7 days and 31 (±1) days after the last intake of trial medication
- 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

Study design



- Plasma concentrations of TMC125 were determined for 12 hours on Day 7 and Day 21 of Treatment B
- Plasma concentrations of rifabutin and 25-*O*-desacetyl rifabutin were determined for 24 hours on Day 14 of Treatment A and Day 21 of Treatment B
- Safety and tolerability assessments were performed throughout the trial until at least 30 days after the last trial medication intake

Methods

- Plasma concentrations of TMC125, rifabutin and 25-*O*-desacetyl rifabutin were determined using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods (LLOQ 2ng/mL for all compounds)
- PK and statistical PK analyses were performed using
  - WinNonlin Professional™ (Pharsight Corporation, Mountain View, CA, USA)
  - Microsoft Excel® (version 2000; Microsoft, Redmond, WA, USA)
- A non-compartmental model with extravascular input was used for the PK analysis

LLOQ = lower limit of quantification

PK and safety parameters and analyses

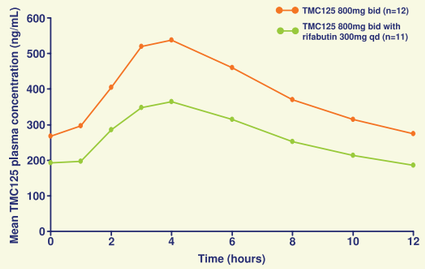
- Primary PK parameters
  - C_{max} (ng/mL): maximum plasma concentration
  - C_{min} (ng/mL): minimum plasma concentration
  - AUC_{12h} and AUC_{24h} (ng•h/mL): area under the plasma concentration-time curve over a 12- and 24-hour period, respectively, calculated by linear trapezoidal summation
- Safety parameters
  - adverse events (AEs), laboratory assessments, ECG, vital signs and physical examinations were evaluated throughout the study
  - severity and drug relationship of AEs to rifabutin or TMC125 were recorded
- Statistical analyses
  - descriptive statistics were calculated for the PK parameters of TMC125, rifabutin and 25-*O*-desacetyl rifabutin
  - least square (LS) means were estimated with a linear mixed effects model
  - safety parameters were evaluated by descriptive statistics and frequency tabulations

Demographics

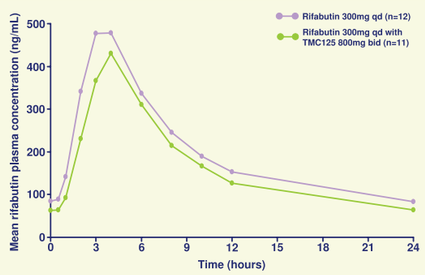
Demographic parameter	All volunteers (N=16)*
Age, years (median [range])	34 (22–55)
Height, cm (median [range])	170 (155–191)
Weight, kg (median [range])	71 (56–103)
BMI, kg/m^2 (median [range])	25 (22–28)
Ethnic origin, n (%)	
Caucasian/White	8 (50)
Black	4 (25)
Hispanic	4 (25)
Gender, n (%)	
Male	15 (94)
Female	1 (6)

*Ten volunteers completed the trial (four volunteer withdrew consent and two were withdrawn due to AEs)
BMI = body mass index

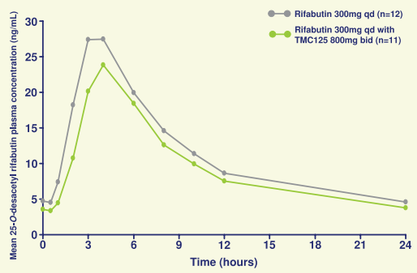
PK profiles of TMC125



PK profiles of rifabutin



PK profiles of 25-*O*-desacetyl rifabutin



TMC125 PK parameters (mean ± SD)

PK parameter	TMC125 alone (reference) (n=12)	TMC125 + rifabutin (test) (n=11)	LS mean ratio (test/reference) (90% CI)
AUC_{12h} (ng•h/mL)	4,722±1,949	3,220±2,196	0.63 (0.54–0.74)
C_{max} (ng/mL)	547±234	371±259	0.63 (0.53–0.74)
C_{min} (ng/mL)	257±118	178±129	0.65 (0.56–0.74)

SD = standard deviation

Rifabutin PK parameters (mean ± SD)

PK parameter	Rifabutin alone (reference) (n=12)	Rifabutin + TMC125 (test) (n=11)	LS mean ratio (test/reference) (90% CI)
AUC_{24h} (ng•h/mL)	4,815±1,374	4,012±1,123	0.83 (0.75–0.94)
C_{max} (ng/mL)	500±148	448±141	0.90 (0.78–1.03)
C_{min} (ng/mL)	79±27	59±20	0.76 (0.66–0.87)

25-*O*-desacetyl rifabutin PK parameters (mean ± SD)

PK parameter	Rifabutin alone (reference) (n=12)	Rifabutin + TMC125 (test) (n=11)	LS mean ratio (test/reference) (90% CI)
AUC_{24h} (ng•h/mL)	272±103	230±92.7	0.83 (0.74–0.92)
C_{max} (ng/mL)	28.7±8.98	24.4±7.55	0.85 (0.72–1.00)
C_{min} (ng/mL)	4.07±2.38	3.22±1.88	0.78 (0.70–0.87)

Safety summary

- No serious AEs or grade 4 AEs were reported
- One volunteer discontinued the trial during the rifabutin alone treatment due to atrial flutter (grade 1)
- One grade 3 event (increased serum amylase) during rifabutin alone treatment was reported, leading to premature discontinuation
- All other AEs were mild to moderate in severity
- The most frequent AEs were chromaturia, a known side effect of rifabutin use (seven volunteers, all associated with rifabutin) and headache (five volunteers), all of grade 1 severity
- No cases of rash were reported
- No consistent or relevant changes were found in laboratory or cardiovascular safety parameters, or physical examinations

Conclusions

- When co-administered with rifabutin 300mg qd, TMC125 exposure was decreased by 37% with similar decreases in C_{max} and C_{min}. This is comparable with the decrease in exposure to TMC125 when combined with boosted PIs, as observed in Phase II trials; these effects are not considered to be clinically relevant.
- The decrease of rifabutin and 25-*O*-desacetyl rifabutin exposures by 17% when co-administered with TMC125 are not clinically relevant.
- Short-term co-administration of TMC125 with rifabutin in HIV-negative volunteers was generally safe and well tolerated.
- Rifabutin can be co-administered with TMC125 without dose adjustments. The effects of co-administered drugs should be taken into account.

References

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Acknowledgements

The authors would like to express their gratitude to the volunteers. We also acknowledge:

- MP Bouche, J&J Pharmaceutical Research and Development, Beerse, Belgium
- D Hoelscher, PPD Development, Austin, Texas, USA.

Presented at the 44th Annual Meeting of the Infectious Diseases Society of America, October 12–15, 2006, Toronto, Canada. This poster is available on-line at www.tibotec.com.