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Pharmacokinetic interaction study with TMC125 and TMC114/r in HIV-negative volunteers

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Abstract

Background
TMC125 is an NNRTI and TMC114 (darunavir) a protease inhibitor (PI); agents with potent activity against HIV. This study evaluated the pharmacokinetic (PK) interaction between TMC125 and TMC114/r.

Methods
This was an open-label, two-way crossover trial in 32 HIV-negative volunteers, randomized to two groups. All volunteers received 100mg TMC125 bid (Phase III formulation) for 8 days. After a washout period of 14 days, volunteers received TMC114/r 600/100mg bid for 16 days. From Day 9 to 16, group A received 100mg TMC125 bid; group B received 200mg bid.

Results
When 100mg TMC125 bid was combined with TMC114/r, TMC125 AUC_{12h} was 63% (90% confidence interval [CI]: 54–73%) compared to 100mg TMC125 bid alone; TMC125 C_{max} and C_{min} were 68% (57–82%) and 51% (44–61%), respectively. TMC114 PK did not show significant changes when combined with 100mg TMC125 bid. When 200mg TMC125 bid was co-administered with TMC114/r, AUC_{12h}, C_{max} and C_{min} of TMC125 were 180% (156–208%), 181% (156–211%) and 167% (138–203%), respectively, compared with 100mg TMC125 bid alone. TMC114 AUC_{12h} was increased by 15% (105–126%). The concomitant administration of TMC125 and TMC114/r was generally safe in HIV-negative volunteers; most common reason for discontinuation was rash (5/32).

Conclusions
No clinically relevant changes in TMC114 were observed with either TMC125 dose. For 100mg TMC125 bid, exposure decreased by 37% when co-administered compared to 100mg TMC125 bid alone; the magnitude is comparable with interactions observed with boosted PIs in Phase II trials. For 200mg TMC125 bid in combination with TMC114/r, exposure was 80% greater than 100mg TMC125 bid alone, and in the range observed for the selected TMC125 dose from Phase II trials. In Phase III trials, TMC125 will be used at 200mg bid combined with TMC114/r 600/100mg bid.

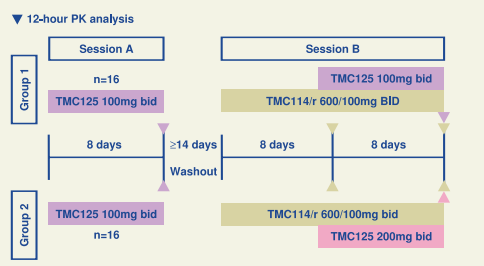
Introduction

- TMC125 is a novel 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 reduced viral load significantly greater than active control. No dose-related effects on safety and tolerability were noted[2]
- TMC114 is a novel PI, which is highly active against both wild-type HIV-1 strains and those resistant to all currently approved PIs[3]
- POWER 1 and 2 (TMC114-C213 and TMC114-C202), both Phase IIb trials, recently demonstrated that TMC114 with low-dose ritonavir (/r) provides sustained viral load reductions and CD4 gains in treatment-experienced HIV patients and was generally well tolerated[4–5]
- The combination of TMC114/r and TMC125 in treatment-experienced HIV patients is currently under evaluation in Phase III trials, DUET-1 and DUET-2 (TMC125-C206 and TMC125-C216)

TMC125-C176 study objectives and design

- Primary objective was to determine the effect of steady-state concentrations of TMC114/r on the steady-state PK of TMC125 (Phase II formulation F060) and vice versa. The short-term safety and tolerability of co-administered TMC125 and TMC114/r was also investigated
- Randomized, open-label, two-way, two-period crossover study
- Thirty-two healthy volunteers were randomized to two groups (group 1 and 2) in a 1:1 ratio. Two treatment sessions were scheduled for all volunteers, Session A and B, separated by a washout period of at least 14 days
  - groups 1 and 2 during Session A received TMC125 100mg bid for 7 days with an additional morning dose on Day 8
  - group 1 volunteers during Session B received TMC114/r 600/100mg bid for 15 days with an additional morning dose on Day 16, co-administered with TMC125 100mg bid from Day 9 until 15 with an additional morning dose on Day 16
  - group 2 volunteers during Session B received TMC114/r 600/100mg bid for 15 days with an additional morning dose on Day 16, co-administered with TMC125 200mg bid from Day 9 until 15 with an additional morning dose on Day 16
- 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

Study design



- Plasma concentrations of TMC125 were determined up to 12 hours on Days 8 and 16 in Session A and B, respectively
- Plasma concentrations of TMC114 and ritonavir were determined up to 12 hours on Days 8 and 16 in Session B
- The safety and tolerability of TMC125, TMC114/r, and their concomitant administration were assessed throughout the trial until at least 30 days after the last trial medication intake

Methods

- Plasma concentrations of TMC114, TMC125, and ritonavir were determined using a validated liquid chromatographic-tandem mass spectrometric (LC-MS/MS) method
- PK and statistical PK analyses were performed using
  - WinNonlin Professional™ (version 5.1; Pharsight Corporation, Mountain View, California, USA)
  - Microsoft Excel® (version 2000; Microsoft, Redmond, Washington, USA)
- A non-compartmental model with extravascular input was used for the PK analysis

PK, statistical and safety analyses

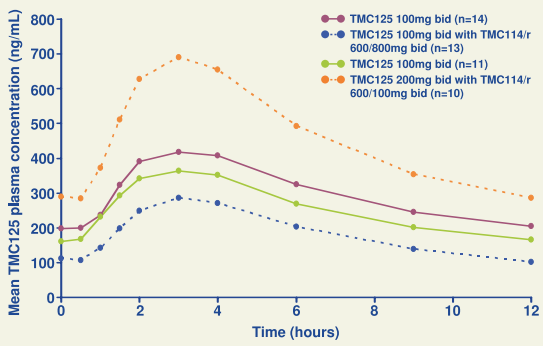
- Primary PK parameters
  - C_{max} (ng/mL): maximum plasma concentration
  - C_{min} (ng/mL): minimum plasma concentration
  - AUC_{12h} (ng•h/mL): area under the plasma concentration-time curve over 12-hour period calculated by linear trapezoidal summation
- Statistical analysis
  - descriptive statistics were calculated for the PK parameters of TMC114, TMC125, and ritonavir
  - least square (LS) means were estimated with a linear mixed effects model
- Safety analysis
  - adverse events (AEs), laboratory assessments, cardiovascular safety, and physical and skin examinations were evaluated throughout the study
  - severity and drug relationship of AEs at least possibly related to TMC114/r or TMC125 were recorded
  - post-treatment safety visits took place 7 days and 31 (±1) days after the last intake of trial medication

Participant demographics

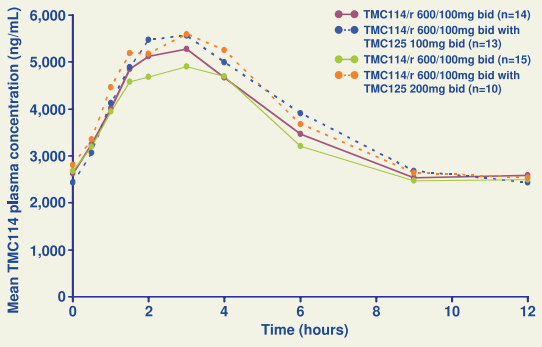
Demographic parameter	Total (n=32)
Age, years (median [range])	42 (18–55)
Height, cm (median [range])	180 (155–193)
Weight, kg (median [range])	78 (58–95)
Gender, n (%)	
Male	28 (87.5)
Female	4 (12.5)
Ethnic origin, n (%)	
Caucasian/White	30 (93.8)
Hispanic	2 (6.3)
Type of smoker, n (%)	
Non-smoker	25 (78.1)
Light smoker*	7 (21.9)

*Light smoker was defined as smoking no more than 10 cigarettes, two cigars, or two pipes per day

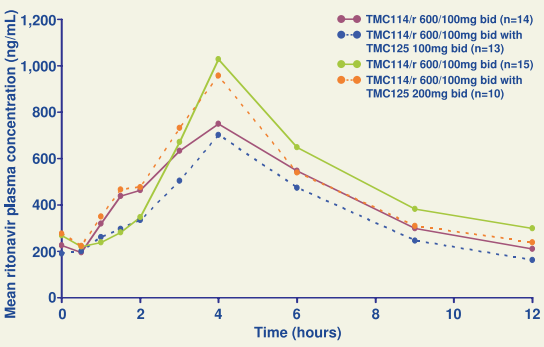
PK of TMC125 alone or co-administered with TMC114/r



PK of TMC114 with ritonavir alone or co-administered with TMC125



PK of ritonavir with TMC114 alone or co-administered with TMC125



TMC125 PK parameters (mean ± SD)

PK parameter	TMC125 100mg bid alone (n=14)	TMC125 100mg bid + TMC114/r 600/100mg bid (n=13)	LS mean ratio (test/reference) (90% CI)
AUC_{12h} (ng•h/mL)	3,607±1,394	2,204±952	0.63 (0.54–0.73)*
C_{max} (ng/mL)	452±122	313±118	0.68 (0.57–0.82)*
C_{min} (ng/mL)	189±95	94±49	0.51 (0.44–0.61)*

*p<0.05

SD = standard deviation

TMC125 PK parameters (mean ± SD)

PK parameter	TMC125 100mg bid alone (n=11)	TMC125 200mg bid + TMC114/r 600/100mg bid (n=10)	LS mean ratio (test/reference) (90% CI)
AUC_{12h} (ng•h/mL)	3,062±816	5,519±2,452	1.80 (1.56–2.08)*
C_{max} (ng/mL)	405±118	734±305	1.81 (1.56–2.11)*
C_{min} (ng/mL)	156±50	268±151	1.67 (1.38–2.03)*

*p<0.05

TMC114 PK parameters (mean ± SD)

PK parameter	TMC114/r 600/100mg bid alone (n=14)	TMC125 100mg bid + TMC114/r 600/100mg bid (n=13)	LS mean ratio (test/reference) (90% CI)
AUC_{12h} (ng•h/mL)	42,982±12,666	45,199±11,583	1.06 (1.00–1.13)
C_{max} (ng/mL)	5,599±1,104	5,804±1,269	1.03 (0.98–1.09)
C_{min} (ng/mL)	2,254±834	2,217±541	1.02 (0.89–1.17)

TMC114 PK parameters (mean ± SD)

PK parameter	TMC114/r 600/100mg bid alone (n=15)	TMC125 200mg bid + TMC114/r 600/100mg bid (n=10)	LS mean ratio (test/reference) (90% CI)
AUC_{12h} (ng•h/mL)	41,135±9,579	45,449±10,864	1.15 (1.05–1.26)*
C_{max} (ng/mL)	5,234±1,060	5,746±1,232	1.11 (1.01–1.22)
C_{min} (ng/mL)	2,337±631	2,301±738	1.02 (0.90–1.17)

*p<0.05

Safety summary

- Six volunteers (19.8%) prematurely discontinued due to AEs possibly or probably related to TMC114/r and TMC125
  - five due to morbilliform rash (four grade 2 and one grade 1)
  - one due to headache (grade 3)
- No serious AEs or deaths were reported
- Two volunteers developed one grade 3 AE each
  - headache and increased LDL
- Fifteen volunteers (46.9%) experienced one or more skin events of interest all of which were grade 1 or 2 in severity
  - two of 25 (8.0%) volunteers receiving TMC125 100mg bid
  - two of 31 (6.5%) volunteers receiving TMC114/r 600/100mg bid
  - six of 14 (42.9%) volunteers receiving TMC125 100mg bid with TMC114/r 600/100mg bid
  - four of 14 (28.6%) volunteers receiving TMC125 200mg bid with TMC114/r 600/100mg bid
  - onset and duration of these rashes ranged from 1 to 8 days and 3 to 31 days, respectively

Conclusions

- Concomitant administration of TMC125 and TMC114/r had no clinically significant effect on TMC114 or ritonavir PK.
- TMC125 100mg bid exposure was decreased by 37% with similar decreases in C_{max} and C_{min} (32% and 49%, respectively). These decreases are comparable to those observed in Phase IIb trials when TMC125 was co-administered with other boosted PIs and is clinically not relevant.[2]
- PK parameters for TMC125 observed after co-administration of TMC125 200mg bid with TMC114/r were slightly lower than historical control for healthy volunteers given the same dose and formulation (AUC_{12h} 7,638±2254; C_{max} 876±233).[6]
- Overall, the safety profile for TMC125, TMC114/r, and their co-administration was similar, apart from rash, which was seen more frequently during co-administration. The short-term co-administration of TMC125 with TMC114/r in healthy volunteers was generally safe and well tolerated.
- The higher incidence of skin events in the TMC125 100mg versus 200mg arm and the interaction with TMC114/r suggests no relationship with TMC125 dose or exposure.
- TMC125 200mg bid (formulation F060) is the dose and formulation selected for further clinical development, including the on-going Phase III trials DUET-1 and DUET-2.
- Preliminary efficacy, safety, and tolerability of TMC125 with TMC114/r in HIV treatment-experienced patients is reported elsewhere.[7]
- TMC125 can be co-administered with TMC114/r without dose adjustments.

References

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