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Pharmacokinetics of TMC125 in once- and twice-daily regimens in HIV-1-negative volunteers

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Abstract

Background: TMC125 (etravirine; ETR) is a next-generation nonnucleoside reverse transcriptase inhibitor (NNRTI) with potent activity against both wild-type HIV-1 and viruses resistant to currently approved NNRTIs. The pharmacokinetics of TMC125 (Phase III formulation) administered in once- (qd) or twice-daily (bid) regimens, was evaluated in two Phase I trials C168 and C178.

Methods: In these randomized crossover trials, TMC125 was administered following a meal for 7 days with a morning dose on Day 8. Dose regimens in trial C168 were 100mg bid and 200mg qd; in trial C178 200mg bid and 400mg qd. Pharmacokinetics of TMC125 were assessed on Day 1 and Day 8 over 12 or 24 hours. Pharmacokinetic (PK) parameters were calculated using noncompartmental methods. Safety and tolerability were assessed.

Results: Twenty-four (23 males) and 41 (22 males) volunteers participated in C168 and C178, respectively. Day 8 PK results are shown below.

C168

PK parameter (mean ± SD)	100mg bid (n=23)	200mg qd (n=24)	LS mean ratio qd/bid (90% CI)
C_{min} (ng/mL)	215 ± 86	163 ± 76	0.74 (0.69–0.80)
C_{max} (ng/mL)	471 ± 141	659 ± 177	1.42 (1.34–1.51)
AUC_{tau} (ng•h/mL)	3925 ± 1251	8054 ± 2748	1.05 (0.96–1.14)*

C178

PK parameter (mean ± SD)	200mg bid (n=39)	400mg qd (n=37)	LS mean ratio qd/bid (90% CI)
C_{min} (ng/mL)	469 ± 149	364 ± 133	0.75 (0.72–0.79)
C_{max} (ng/mL)	959 ± 278	1393 ± 386	1.44 (1.37–1.50)
AUC_{tau} (ng•h/mL)	8195 ± 2428	17220 ± 5009	1.03 (1.00–1.07)*

*$AUC_{24h}/2$ x AUC_{12h}
SD = standard deviation; n = number of volunteers; LS = least square; CI = confidence interval; C_{min} = minimum plasma concentration; C_{max} = maximum plasma concentration; AUC_{tau} = area under the plasma concentration-time curve from time of administration to tau (12 or 24 hours) after dosing

In C168, no volunteers discontinued due to adverse events (AEs). In C178, two volunteers discontinued due to rash. All AEs were grade 1 or 2. The most common AEs were back pain, nasopharyngitis (C168), headache and contact dermatitis (C178).

Conclusions: Equal daily doses of TMC125 result in similar daily exposures, regardless of whether given in a qd or bid regimen. The pharmacokinetics of TMC125 administered in HIV-1-negative volunteers as 100mg bid vs 200mg bid and 200mg qd vs 400mg qd are dose proportional. TMC125 was generally safe and well tolerated.

Introduction

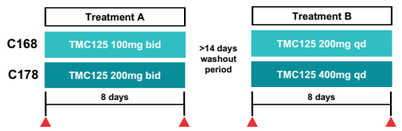
- TMC125 is a next-generation NNRTI with potent activity against both wild-type HIV-1 and HIV-1 resistant to currently available NNRTIs.[1] The protein-binding adjusted EC_{50} for wild-type HIV-1 is 4ng/mL[2]
- Two Phase III trials (DUET-1 and DUET-2) demonstrated significant antiviral benefit after 24 weeks of treatment with 200mg bid TMC125 in treatment-experienced patients with NNRTI resistance. Except for a higher incidence of rash, patients treated with TMC125 had a side effect profile similar to placebo[3,4]
- TMC125 has a terminal elimination half-life of 35–40 hours and therefore has the potential for qd dosing
- Two phase I studies (C168 and C178) were conducted to compare the pharmacokinetics of TMC125 when dosed qd versus bid

EC_{50} = 50% effective concentration

Study design

- Both studies were Phase I, randomized, crossover, multiple dose PK trials in HIV-negative volunteers (trial C168 was open-label and C178 double-blind)
- Treatment was given in both studies for 7 days with a morning dose on Day 8 in two treatment sessions, separated by a washout period of 14 days
- In study C168 all volunteers received TMC125 200mg per day (given as 100mg bid and as 200mg qd) and in trial C178 400mg per day (given as 200mg bid and as 400mg qd)
- All doses were administered following a meal in both studies
- Safety and tolerability assessments were performed throughout the trial. Post-treatment safety visits took place 1 week and 1 month after the last intake of trial medication
- The trial protocols were reviewed and approved by the appropriate institutional ethics committee and health authorities; the trials were conducted in accordance with the Declaration of Helsinki

Study design scheme and PK analyses



▲ 12- or 24-hour PK analysis of TMC125, determined on Day 1 (data not shown) and Day 8 in bid or qd regimens, respectively

- Plasma concentrations were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for TMC125 (lower limit of quantification 2ng/mL)

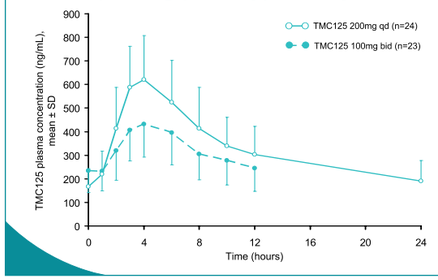
Parameters and analyses

- Primary PK parameters
  - C_{min} (ng/mL)
  - C_{max} (ng/mL)
  - $AUC_{12h/24h}$ (ng•h/mL), calculated by linear trapezoidal summation
- Safety parameters
  - AEs, laboratory assessments, electrocardiograms, vital signs assessments and physical examinations were evaluated throughout the study
  - severity and drug relationship of AEs to TMC125 were recorded
- PK and statistical analyses
  - a noncompartmental model with extravascular input was used for PK analyses; PK and statistical analyses were performed using WinNonLin Professional™ 4.1 (Pharsight Corporation, Mountain View, CA, USA) and Microsoft Excel® (version 2000; Microsoft, Redmond, WA, USA), and/or SAS (version 8.2 or 9.1.3; SAS Institute Inc., Cary, NC, USA)
  - descriptive statistics were calculated for the PK parameters of TMC125, LS means for PK parameters obtained with bid and qd regimens were estimated with a linear mixed effects model
  - safety parameters were evaluated by descriptive statistics and frequency tabulations

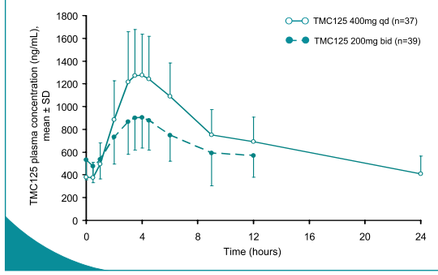
Demographics

Demographic parameter, median (range) unless indicated	Trial C168 (N=24)	Trial C178 (N=41)
Age, years	31 (22–51)	44 (18–55)
Height, cm	178 (162–198)	176 (156–191)
Weight, kg	77 (63–115)	77 (47–104)
Body mass index, kg/m²	26 (20–30)	25 (19–30)
Male/female, n	23/1	22/19
Ethnic origin, n (%)		
Caucasian	16 (67)	39 (95)
Black	4 (17)	1 (2)
Asian	0	1 (2)
Other	4 (17)	0

TMC125 plasma PK profile (200mg per day) on Day 8



TMC125 plasma PK profile (400mg per day) on Day 8



TMC125 PK parameters (mean ± SD) on Day 8

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Trial C178	**200mg bid**	**400mg qd**	**LS mean ratio qd/bid (90% CI)**
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*$AUC_{24h}/2$ x AUC_{12h}

Safety summary

- All AEs reported were mild or moderate (grade 1 and 2) in severity, there were no serious AEs reported
- The incidence of AEs and laboratory abnormalities was similar between the dose regimens in both trials
- One volunteer discontinued trial C168 (withdrew consent)
- Two volunteers discontinued trial C178 due to rash (one grade 2 during 200mg bid treatment and one grade 1 during 400mg qd treatment); one volunteer was withdrawn due to noncompliance and one withdrew consent
- The most frequently reported AEs in trial C168 were nasopharyngitis and back pain (each in two volunteers); and contact dermatitis in trial C178 (in 12 volunteers in each regimen due to electrocardiogram electrodes in all but one volunteer)
- No grade 4 laboratory abnormalities were reported; four volunteers each had one grade 3 abnormality (amylase, platelet count, low-density lipoprotein and total cholesterol abnormalities)
- There were no consistent or relevant changes in laboratory or cardiovascular safety parameters or the results of physical examinations

Conclusions

- The daily systemic exposure to TMC125 obtained with qd administration is the same as that obtained by bid administration of an equivalent dose per day.
- The minimum plasma concentration of TMC125 is 25–26% lower with a qd regimen compared with a bid regimen of the same daily dose.
- The maximum plasma concentration is approximately 42–44% higher when given qd, compared with bid administration of the same daily dose.
- The pharmacokinetics of TMC125 in HIV-negative volunteers in the range of 200–400mg per day appear to be dose proportional.
- Short-term qd and bid administration of TMC125 in HIV-negative volunteers was generally safe and well tolerated.
- Further assessment of the efficacy and safety of TMC125 in a qd regimen is warranted.

References

1. Vingerhoets J, et al. J Virol 2005;79:12773–82.
2. Andries K, et al. Antimicrob Agents Chemother 2004;48:4680–6.
3. Madruga JV, et al. Lancet 2007;370:29–38.
4. Lazzarin A, et al. Lancet 2007;370:39–48.

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