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No clinically relevant effect of TMC125 on the pharmacokinetics of oral contraceptives

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Poster No. P277

Abstract

Background
TMC125 is an NNRTI with potent activity against wild-type HIV-1 and HIV-1 resistant to currently approved NNRTIs. TMC125 is an inducer of CYP3A4 and an inhibitor of both CYP2C9 and 2C19, all involved in the metabolism of oral contraceptives. This study assessed the effect of TMC125 on the pharmacokinetics of ethinylestradiol and norethindrone.

Methods
The oral contraceptive Ortho-Novum® 1/35 was given for three cycles of 28 days: a run-in cycle followed by two cycles with pharmacokinetic (PK) assessments. In the third cycle, 200mg TMC125 bid (Phase III formulation) was co-administered from Day 1 to Day 15. On Day 15 of Cycles 2 and 3, the 24-hour pharmacokinetics of ethinylestradiol and norethindrone were assessed. The 12-hour pharmacokinetics of TMC125 were evaluated on Day 15 of Cycle 3. PK parameters were calculated by non-compartmental methods. The pharmacokinetics of ethinylestradiol and norethindrone were analysed using a linear, mixed-effects model. Safety and tolerability were evaluated.

Results
Thirty HIV-negative female volunteers participated (median age 24 years). When combined with TMC125, ethinylestradiol AUC_{24h} was 122% (90% CI: 113–131%) compared with administration of oral contraceptives alone; C_{max} and C_{min} were 133% (90% CI: 121–146%) and 109% (90% CI: 101–118%), respectively. AUC_{24hr}, C_{max} and C_{min} of norethindrone were 95% (90% CI: 90–99%), 105% (90% CI: 98–112%) and 78% (90% CI: 68–90%), respectively, when combined with TMC125 compared with administration of oral contraceptives alone. The concomitant administration of TMC125 and oral contraceptives was generally safe and well tolerated. Ten adverse events (AEs) led to trial discontinuation: seven grade 2 rashes, one grade 2 pyrexia, one grade 3 herpes simplex and one grade 2 lymphadenopathy.

Conclusions
No clinically relevant changes in the pharmacokinetics of ethinylestradiol and norethindrone were observed when TMC125 was given concomitantly with Ortho-Novum® 1/35. No loss in the efficacy of oral contraceptives are expected when TMC125 is co-administered.

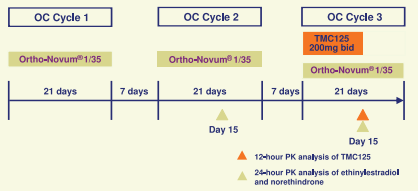
Introduction

- 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 optimised background regimen, reduced viral load at 48 weeks significantly more than active control. No dose-related effects on safety and tolerability were noted[2]
- TMC125 is predominantly metabolised by CYP3A4, CYP2C and UDP-glucuronosyl transferase (UGT); it is an inducer of CYP3A4 and an inhibitor of CYP2C
- Ortho-Novum® 1/35 is an oral contraceptive containing 0.035mg ethinylestradiol and 1mg norethindrone
- The metabolism of oral contraceptives involves both CYP3A and CYP2C subfamilies and glucuronidation by UGT. Ethinylestradiol is an inhibitor of CYP2C19[3,4]
- To assess the effect of TMC125 on the pharmacokinetics of oral contraceptives, an interaction study with Ortho-Novum® 1/35 and TMC125 (administered as Phase III formulation) was conducted

Study design

- TMC125-C166 was a Phase I, open-label, one-way, sequential, drug-drug interaction trial in 30 HIV-negative female volunteers
- The trial consisted of three consecutive full cycles of oral contraceptive treatment with Ortho-Novum® 1/35 as prescribed in the package insert (one pill daily for 21 days, no treatment on days 22–28)
- TMC125 200mg bid (Phase III formulation) was co-administered on Days 1 to 15 of the third cycle
- All doses of TMC125 were taken within 10 minutes after a meal, the morning intake concomitantly with the oral contraceptive
- 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 (cont'd)



- Plasma concentrations of TMC125 were determined up to 12 hours on Day 15 of Cycle 3
- Plasma concentrations of ethinylestradiol and norethindrone were determined up to 24 hours on Day 15 of Cycle 2 and Cycle 3
- Safety and tolerability assessments were performed throughout the trial until 30 ± 1 days after the last trial medication intake

OC = Ortho-Novum® 1/35

Methods

- Plasma concentrations of TMC125 and ethinylestradiol were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method (LLOQ 2ng/mL and 3pg/mL, respectively)
- Plasma concentrations of norethindrone were determined using a validated gas chromatography mass spectrometry method (LLOQ 0.05ng/mL)
- 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, N.C., USA)
- A non-compartmental model with extravascular input was used for the PK analysis

PK and safety parameters and analyses

- Primary PK parameters
  - C_{max} (ng/mL): maximum plasma concentration
  - C_{min} (ng/mL): minimum plasma concentration
  - $AUC_{12 \text{ or } 24h}$ (ng-h/mL): area under the plasma concentration-time curve over 12 or 24-hour period, calculated by linear trapezoidal summation
- Safety parameters
  - AEs were evaluated throughout the study; laboratory assessments, ECG, vital signs assessment and physical examinations were performed at specific timepoints
  - severity and drug relationship of AEs to the oral contraceptive and/or TMC125 were recorded
- Pharmacodynamic assessments
  - serum progesterone, LH and FSH were assessed on Days 1 and 14 of Cycles 2 and 3
- Statistical analyses
  - descriptive statistics were calculated for the PK parameters of TMC125, ethinylestradiol and norethindrone
  - least square (LS) means were estimated with a linear mixed effects model
  - safety parameters were evaluated by descriptive statistics and frequency tabulations

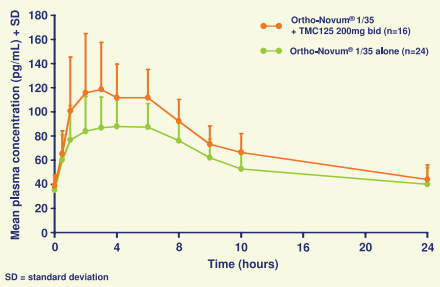
Demographics

Demographic parameter	All volunteers (n=30)*
Age, years (median [range])	24 (18–30)
Height, cm (median [range])	165 (157–174)
Weight, kg (median [range])	63 (50–81)
BMI, kg/m² (median [range])	22 (19–29)
Ethnic origin, n (%)	
Caucasian/White	29 (97)
Black	1 (3)

All volunteers were female
*Sixteen volunteers completed the trial (five volunteers withdrew consent and nine volunteers discontinued the trial prematurely due to AEs)

BMI = body mass index

PK profile of ethinylestradiol

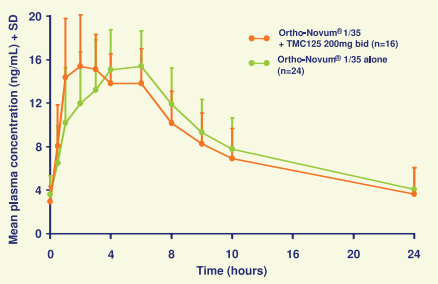


SD = standard deviation

Ethinylestradiol PK parameters (mean±SD)

PK parameter	OC alone (reference) (n=24)	OC + TMC125 (test) (n=16)	LS mean ratio (test/reference) (90% CI)
AUC_{24h} (pg·h/mL)	1,412±357	1,726±382	1.22 (1.13–1.31)
C_{max} (pg/mL)	98±26	134±44	1.33 (1.21–1.46)
C_{min} (pg/mL)	35±10	38±10	1.09 (1.01–1.18)

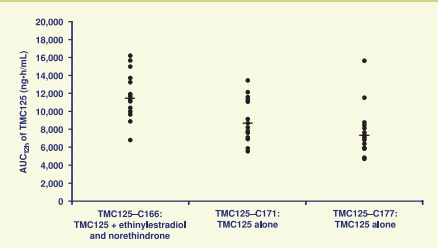
PK profile of norethindrone



Norethindrone PK parameters (mean±SD)

PK parameter	OC alone (reference) (n=24)	OC + TMC125 (test) (n=16)	LS mean ratio (test/reference) (90% CI)
AUC_{24h} (ng·h/mL)	203±60	189±54	0.95 (0.90–0.99)
C_{max} (ng/mL)	17±4	17±4	1.05 (0.98–1.12)
C_{min} (ng/mL)	4±2	3±1	0.78 (0.68–0.90)

Exposure to TMC125 compared to historical controls



- Trial TMC125-C171: TMC125 200mg bid 8 days in males
- Trial TMC125-C177: TMC125 200mg bid 8 days in males

TMC125 PK parameters (mean±90% CI)

All PK parameters of TMC125 were higher in this trial than in historical controls

Trial / PK parameter	TMC125-C166 with OC (n=16)	TMC125-C171 alone (n=15)	TMC125-C177 alone (n=23)
AUC_{12h} (ng·h/mL)	11,820 (10,684–12,956)	9,008 (7,920–10,096)	7,638 (6,831–8,444)
C_{max} (ng/mL)	1,188 (1,060–1,316)	1,015 (904–1,126)	876 (792–959)
C_{min} (ng/mL)	792 (710–873)	498 (428–568)	426 (371–481)

- Other possible factors than a PK interaction
  - gender effect (female vs male volunteers)
  - longer treatment duration (2 weeks in this trial vs 1 week in historical controls)

CI = confidence interval

Safety and pharmacodynamic summary

- One case of grade 3 herpes simplex was reported during treatment with oral contraceptive alone. All other AEs were mild or moderate in severity
- There were no consistent or relevant changes in laboratory or cardiovascular safety parameters or physical examinations
- No relationship was observed between the occurrence of rash and PK parameters of TMC125 and/or the components of the oral contraceptive
- No differences were observed when comparing the plasma concentrations of progesterone, LH and FSH on Days 1 or 14, during treatment with oral contraceptives alone and during combined administration of oral contraceptives and TMC125

Study discontinuations due to AEs

- One serious AE was reported: one volunteer receiving combined treatment developed grade 2 rash and was hospitalised for observation. This volunteer discontinued the trial and the rash resolved, with treatment, within 4 weeks
- Seven volunteers discontinued the trial due to grade 2 rash (as required by the protocol)
  - observed after 8–10 days of combined treatment
  - resolved within 4–40 days
  - assessed as probably related to TMC125 and doubtfully related to the oral contraceptive
- Other discontinuations
  - one due to grade 2 pyrexia during the combined treatment
  - one due to grade 3 herpes simplex and grade 2 lymphadenopathy with the oral contraceptive alone

Conclusions

- When co-administered with TMC125 200mg bid, ethinylestradiol exposure was increased by 22%, and C_{max} by 33%, without a relevant change of C_{min}. Norethindrone pharmacokinetics did not change significantly except for a decrease in C_{min} of 22%.
- Based on these results and the pharmacodynamic findings, TMC125 is unlikely to affect the contraceptive efficacy.
- TMC125 exposure was slightly higher than that observed after 8 days' administration of the same dose in male volunteers (historical controls). This increase in exposure is not believed to be clinically relevant.
- The short-term co-administration of TMC125 and oral contraceptives in HIV-negative female volunteers was generally safe and well tolerated. The most frequent AE leading to trial discontinuation was rash during the co-administration phase; the incidence of rash may be higher in HIV-negative volunteers than in HIV-1 infected patients.
- TMC125 and oestrogen-progesterone based oral contraceptives can be given concomitantly without dose modifications.

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.
- U Lorch, Richmond Pharmacology Ltd., London, UK.

Supported by Tibotec

Presented at the 8th International Congress on Drug Therapy in HIV infection, Glasgow, UK, 12–16 November 2006.

This poster is available on-line at www.tibotec.com