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Thorough QT trial with TMC125 (etravirine; ETR) dosed at 200mg bid and 400mg qd in HIV-negative volunteers

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Abstract

Background: TMC125, a next-generation NNRTI, has shown antiviral benefit in two large Phase III studies. *In vitro*, TMC125 has no effect on hERG and no relevant electrocardiogram (ECG) changes were observed in dogs administered up to 400mg/kg/day of TMC125. ECG parameters in healthy or HIV-infected volunteers have shown no clinically-relevant changes. This thorough QT study was conducted in accordance with ICH E14 guidelines to confirm the lack of QT prolongation by TMC125.

Methods: A double-blind, double-dummy, randomised, placebo- and active-controlled, four-period crossover trial was conducted in 41 HIV-negative volunteers (19 female/22 male). Volunteers received TMC125 200mg bid, TMC125 400mg qd, moxifloxacin 400mg qd (positive control), and placebo in separate sessions. Each treatment was given for 8 days followed by a washout period of ≥14 days. On Days –1, 1 and 8 of each session, 12-lead triplicate ECGs were collected at 11 timepoints over 12 hours. Safety and tolerability were assessed.

Results: During TMC125 treatment, the upper limit of all 90% confidence intervals (CIs) of the mean time-matched differences in QTcF was below the 10ms threshold defined by the ICH E14 guidelines. The maximum least square means (90% CI) difference of the time-matched changes in QTcF versus placebo on Day 1 was +0.1ms (–2.64 to 2.92), –0.2ms (–2.59 to 2.10) and +10.1ms (7.33 to 12.77) for TMC125 200mg bid, TMC125 400mg qd, and moxifloxacin, respectively; on Day 8 these values were +0.6ms (–2.13 to 3.29), –1ms (–4.42 to 2.52), and +10.3ms (6.76 to 13.89), respectively. During TMC125 treatment, no QTcF values >60 ms were observed and no changes occurred on PR and QRS interval or heart rate. No gender differences were observed and results were similar when other QT correction methods were applied. Short-term administration of TMC125 was generally safe and well tolerated.

Conclusions: TMC125 does not prolong the QT interval. No clinically-relevant ECG changes were observed in healthy volunteers receiving TMC125.

Introduction

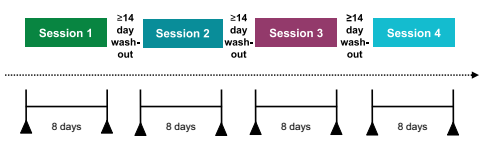
- TMC125 is a next-generation NNRTI[1] that demonstrated significant antiviral benefit in the two DUET Phase III trials in treatment-experienced patients with documented NNRTI resistance[2,3]
- Preclinical data have shown no effect of TMC125 on hERG channels or cardiac function (in-vitro data and ECG studies in dogs)[4]
- Phase II and III studies of TMC125 have shown no evidence of cardiac safety issues[2,3,5–8]
- Some antiretrovirals (including NNRTIs) have been associated with ECG changes including QT prolongation[9–11] and a thorough QT/QTc trial is a requirement from Health Authorities[12]
- The primary aim of the study was to evaluate the effect of two different TMC125 dosing regimens on the QT/QTc interval in healthy, HIV-negative volunteers. Additional safety and tolerability parameters were also assessed

Study design

- The study was a double-blind, double-dummy, randomised, controlled, four-period crossover trial in HIV-negative, healthy volunteers
- Treatments compared were TMC125 200mg bid, TMC125 400mg qd, moxifloxacin 400mg qd (positive control) and placebo
- Each treatment was given in a separate session for 8 days, followed by a washout period of ≥14 days
- ECGs (12-lead time-matched triplicate) were collected at 11 timepoints over 12 hours on Days –1, 1 and 8 of each session to cover the extent of exposure to the study drug and diurnal variation
- Pharmacokinetic (PK) samples were collected within 5 minutes of each ECG recording on Days 1 and 8 and following pre-dose ECGs on Days 5–7
- Safety and tolerability assessments were performed throughout the trial and at follow-up
- The study protocol was reviewed and approved by an independent institutional ethics committee, and the trial was conducted in accordance with the Declaration of Helsinki

Study design scheme and analyses

- Volunteers received each of the four drug treatments in separate sessions in one of four randomly generated and allocated sequences



▲12-hour ECG and PK analysis was carried out on Day 1 and Day 8 of each session

ECGs were recorded at 0h, 0.5h, 1h, 2h, 3h, 3.5h, 4h, 4.5h, 6h, 9h and 12h on Days –1, 1 and 8 of each session and at 0h, and 4h on Days 2–7

Sequences were A/D/B/C (n=10), B/A/C/D (n=10), C/B/D/A (n=10) and D/C/A/B (n=11)
A: TMC125 200mg bid + placebo; B: TMC125 400mg qd + placebo;
C: Moxifloxacin 400mg qd + placebo; D: Placebo only

Follow-up after 7 days and 28–34 days

Parameters and analyses

Primary objective
- QT/QTc interval compared with placebo
  - QT interval corrected for heart rate using Fridericia's correction factor (QTcF; QTc = QT/RR$^{0.33}$)[13]
  - maximum mean change: change from baseline on drug for each corresponding timepoint (time-matched change) minus the corresponding change from baseline on placebo

Secondary objectives
- Other ECG parameters: heart rate; PR, RR and QRS intervals
- PK parameters
  - C_{max} (ng/mL) and C_{min} (ng/mL; bid and qd regimens), AUC_{12h} (ng•h/mL; bid regimen) and AUC_{24h} (qd regimen)
  - plasma concentration-effect relationship for QTcF
- Safety parameters
  - adverse events evaluated throughout and graded by severity
  - laboratory assessments (Days 1, 5 and 9; DAIDS toxicity grading table) and vital signs (Days –1, 1, 2 and 5–9)

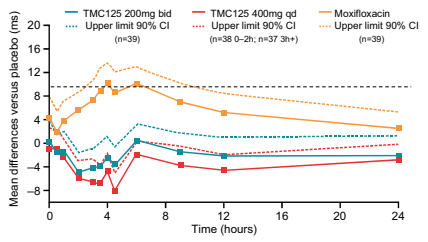
Statistical analyses (intent-to-treat)
- QTc/ECG: descriptive statistics including 90% CI, mixed-effects model and Kruskal-Wallis test for comparisons of the active treatment versus placebo
- PK analysis: linear mixed-effects model (comparison bid versus qd)
- Safety assessments: descriptive statistics

C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; $AUC_{12/24h}$ = area under the plasma concentration-time curve from time of administration to 12/24 hours after dosing

Demographics

Parameter, median (range)	All volunteers (n=41)
Age, years	44 (18–55)
Height, cm	176 (156–191)
Weight, kg	77 (47–104)
Body mass index, kg/m^2	25 (19–30)
Male/female, n	22/19
Race, n (%)	
Caucasian	39 (95)
Black	1 (2.5)
Asian	1 (2.5)

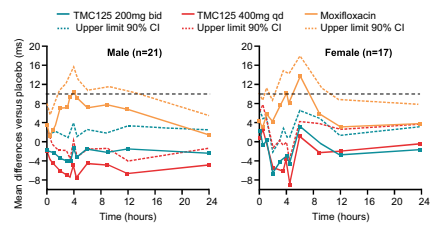
TMC125 does not prolong QTc interval



- TMC125 did not induce clinically significant changes in QTc interval at Day 8
- TMC125 changes were below the 10ms threshold for prolonged QT; moxifloxacin changes were above the 10ms threshold
- Similar findings were observed at Day 1

Values are mean time-matched differences versus placebo at Day 8;
ICH threshold = 10ms (values >10ms are defined as positive for QT prolonging effect)

TMC125 does not prolong QTcF interval, irrespective of gender



- Despite reports of increased sensitivity of women to drug induced QT effects, this study produced no evidence that TMC125 prolonged QTcF in female volunteers

Values are mean time-matched differences vs placebo at Day 8;
ICH threshold = 10ms (values >10ms are defined as positive for QT prolonging effect)

Additional effects on ECG parameters

- No volunteers receiving TMC125 had a QTcF >450ms (threshold of particular clinical concern),[12] compared with three receiving moxifloxacin (8%) and one on placebo (3%)
- No QTcF increases >60ms (threshold of particular clinical concern)[12] from baseline were observed with either dose of TMC125
- There were no consistent or clinically relevant changes over time in any of the other ECG parameters during TMC125 treatment
- Low heart rate (≤50bpm) was the most common treatment-emergent abnormal ECG effect, observed in 15 volunteers (37%) across the four treatment groups
  - the trial was performed in young healthy volunteers (54% men), so this finding is not unexpected

bpm = beats per minute

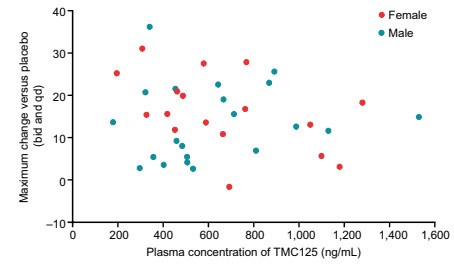
PK parameters for TMC125 (mean ± SD)

PK parameter		TMC125 200mg bid* (n=39)	TMC125 400mg qd (n=37)	Least squares mean ratio (90% CI)
Day 1	C_{max} (ng/mL)	370 ± 149	715 ± 264	–
	AUC_{tau}‡ (ng•h/mL)	2,281 ± 1,005	6,688 ± 2,749	–
Day 8	C_{min} (ng/mL)	469 ± 149	364 ± 133	0.75 (0.72–0.79)
	C_{max} (ng/mL)	959 ± 278	1,393 ± 386	1.44 (1.37–1.50)
	AUC‡ (ng•h/mL)	8,195 ± 2,428	17,220 ± 5,009	1.03 (1.00–1.07)

- Daily exposure to TMC125 was similar for bid and qd dosing
- When dosed qd TMC125 displayed a higher C_{max}
- PK data for moxifloxacin was comparable to that reported in literature

*TMC125 200mg bid was used as reference and 400mg qd as test;
‡AUC_{12h} (bid dosing) or AUC_{24h} (qd dosing)
SD = standard deviation

Lack of correlation between TMC125 plasma concentration and maximum QTcF increase



- At Day 8 there was no correlation between TMC125 time-matched plasma concentration and corresponding maximum individual increase in QTcF in volunteers

Safety and tolerability

Parameter, n (%)	TMC125 200mg bid (n=39)	TMC125 400mg qd (n=39)	Moxifloxacin 400mg qd (n=39)	Placebo (n=39)
Any adverse event	33 (85)	30 (77)	31 (80)	29 (74)
Grade 3/4	0	0	0	0
Serious AEs	0	0	1 (3)	0
Discontinuation for AE*	1 (3)	1 (3)	0	0
Most common AEs‡				
Contact dermatitis§	12 (31)	12 (31)	8 (21)	7 (18)
Headache	12 (31)	10 (26)	6 (15)	8 (21)
Erythema	6 (15)	7 (18)	2 (5)	6 (15)
Pharyngolaryngeal pain	3 (8)	6 (15)	4 (10)	0
Pruritus	1 (3)	5 (13)	0	1 (3)
Abdominal pain	1 (3)	4 (10)	2 (5)	5 (13)

- No clinically meaningful changes in laboratory parameters or vital signs were observed

*Two volunteers discontinued due to rash; ‡Occurring at frequency of ≥10% in either TMC125 arm, regardless of severity or cause; §All but one case of dermatitis was caused by the use of ECG electrodes

Conclusions

- The administration of TMC125 did not prolong QTcF.
- A lack of effect of TMC125 on QTcF was demonstrated irrespective of gender.
- There were no clinically consistent or relevant changes in any other ECG parameters with TMC125.
- Daily exposure to TMC125 was similar for bid and qd dosing.
- No correlation was observed between TMC125 plasma concentrations and QTcF. A 44% increase in C_{max} of TMC125 when administered qd did not cause QTcF prolongation.
- Safety and tolerability were similar for both TMC125 regimens despite a higher C_{max} for qd TMC125; no new safety issues were identified.
- The results of the thorough QT study demonstrate that TMC125 can be safely administered without the need for ECG monitoring.

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