SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals **Trade Name**: - **Indication**: HIV-1 infection	**Drug Substance**: TMC278 **Trial no**.: TMC278-TiDP6-C152 **Clinical Phase**: I
Title: A Phase I, double-blind, double-dummy, randomized, placebo controlled and active controlled trial to evaluate the effect of TMC278 25 mg q.d. at steady-state and the effect of efavirenz (EFV) 600 mg q.d. at steady-state on the QT/QTc interval, in 2 randomized panels of healthy subjects.	
Investigator: M.-J. Allison, M.D., MDS Pharma Services, 2420 Baseline Road, Phoenix, AZ 85283, USA	**Country**: United States of America
Trial Period: Start: 03-Sep-2008 End: 03-Mar-2009	**No. of Investigators**: 1 **No. of Subjects**: 120

Objectives: The primary objective of this trial was to evaluate the effect of TMC278 25 mg once daily (q.d.) at steady-state on the QT/QTc interval in healthy subjects.

The secondary objectives were:

- to evaluate steady-state pharmacokinetics of TMC278 25 mg q.d. in healthy subjects;
- to characterize the TMC278 concentration-effect relationship for change in QTc interval in healthy subjects;
- to evaluate the effect of a single dose of moxifloxacin 400 mg q.d. on the QT/QTc interval, and thus ascertain trial sensitivity;
- to evaluate the safety and tolerability of TMC278 25 mg q.d. administered in healthy subjects;
- to evaluate the effect of steady-state concentrations of efavirenz (EFV) 600 mg q.d. on the QT/QTc interval in healthy subjects;
- to characterize the EFV concentration-effect relationship for change in QTc interval in healthy subjects;
- to evaluate the safety and tolerability of EFV 600 mg q.d. administered in healthy subjects.

Design: This was a trial to evaluate the effect of TMC278 25 mg q.d. (selected dose for further clinical development) on the QT/QTc interval in healthy subjects. TMC278 is being investigated as a treatment for HIV-1 infection. In a separate panel of healthy subjects, the effect of EFV 600 mg q.d. on the QT/QTc interval was evaluated.

In one panel, the effect of TMC278 at steady-state on the QT/QTc interval in healthy subjects was evaluated in a double-blind, double-dummy, randomized, placebo controlled, and positive controlled 3-way crossover design. In one session, one dose regimen of TMC278 was tested, i.e., 25 mg q.d. for 11 days. In a second session, a single dose of moxifloxacin 400 mg was used as a positive control to assess trial sensitivity. A placebo session was included as a reference.

In a separate panel, the effect of EFV at steady-state on the QT/QTc interval in healthy subjects was evaluated in a double-blind, randomized, placebo controlled, 2-way crossover design. In one session, one dose regimen of EFV was tested, i.e., 600 mg q.d. (therapeutic dose) for 11 days. Similar to the TMC278 panel, a placebo session was included as a reference, but no moxifloxacin session was included, since this was included in the TMC278 panel.

The overall trial population consisted of 120 healthy subjects of which 52 were female and 95 were Hispanic and 25 non-Hispanic, thereby achieving the planned targets for this trial.

Subjects were randomized in a 1:1 ratio to either the TMC278 panel or the EFV panel and within each panel subjects were randomized to a treatment sequence. The randomization between the 2 panels was stratified for

gender and ethnicity (non-Hispanic Caucasians versus Other) and the randomization within each panel was stratified for gender.

Each subject in the TMC278 panel received, in 3 sessions, a random assignment to one out of 6 possible sequences of the following treatments: TMC278 25 mg q.d. on Day 1-11 and moxifloxacin placebo q.d. on Day 11 (Treatment A), TMC278 placebo q.d. on Day 1-11 and moxifloxacin placebo q.d. on Day 11 (Treatment B), and TMC278 placebo q.d. on Day 1-11 and moxifloxacin 400 mg q.d. on Day 11 (Treatment C). All intakes of TMC278, moxifloxacin, TMC278 placebo, and moxifloxacin placebo were under fed conditions and took place under supervision in the unit. There was a wash out period of at least 21 days between consecutive treatments within the TMC278 panel.

Each subject in the EFV panel received, in 2 sessions, a random assignment to 2 possible sequences of the following treatments: EFV 600 mg q.d. for 11 days (Treatment D) or EFV placebo q.d. for 11 days (Treatment E). All intakes of EFV and EFV placebo were under fasted conditions and took place under supervision in the unit. There was a wash out period of at least 53 days between the 2 treatments within the EFV panel.

In both the TMC278 and EFV panels, electrocardiograms (ECGs) were recorded continuously for 24 hours by 12-lead Holter monitoring on Day -1 and Day 11 of all treatment sessions. Time-matched, 12-lead triplicate ECGs were extracted from the Holter recording at predefined timepoints. In addition, for real-time safety monitoring, 12-lead ECGs were performed at predefined timepoints for immediate reading.

Pharmacokinetic samples were collected on Day -1, Day 9, Day 10, and Day 11, within 5 minutes after each safety ECG recording or Holter extraction timepoint, as applicable, for the determination of TMC278, moxifloxacin, or EFV plasma concentrations, as appropriate.

Safety and tolerability were monitored throughout the trial.

Subject Selection

Inclusion Criteria

1. Aged between 18 and 55 years, extremes included.
2. Nonsmoker (no tobacco products, nicotine or nicotine containing products of any kind for at least 1 year).
3. Body Mass Index: (weight in kg divided by the square of height in meters) of 18.0 to 30.0 kg/m^2, extremes included.
4. Informed Consent Form signed voluntarily before first trial-related activity.
5. Healthy on the basis of a pre-trial physical examination, medical history, ECG, vital signs, and the results of blood biochemistry and hematology tests, and a urinalysis carried out at screening.
6. Normal 12-lead ECG at screening and on Day -1 (safety ECG) of the first treatment period including:
   - normal sinus rhythm (heart rate between 40 and 99 beats per minute);
   - Fridericia corrected QT interval (QTcF) $\leq$ 440 ms for males and $\leq$ 460 ms for females;
   - QRS interval < 120 ms;
   - PR interval < 210 ms.
7. Able to comply with protocol requirements.

Exclusion Criteria

1. A positive human immunodeficiency virus (HIV)-1 or HIV-2 test at trial screening.
2. Female of childbearing potential without the use of effective birth control methods or not willing to continue practicing these birth control methods from screening onwards until at least 30 days after last intake of study medication.

   Therefore to be eligible for this trial, women of childbearing potential had to agree to use 1 of the following birth control methods:

   i. male condom in combination with diaphragm or cervical cap or male condom with spermicide*;

   ii. intrauterine device or hormonal contraceptive in combination with a barrier contraceptive (i.e., male condom, diaphragm, cervical cap, or female condom)*;

   iii. be non-heterosexually active, practiced sexual abstinence, or had a vasectomized partner. Vasectomy was to have been performed more than 6 months prior to trial initiation.

   *A male and female condom were not to be used together due to risk of breakage or damage caused by latex friction.
3. History or evidence of current use of alcohol, barbiturate, amphetamine, recreational, or narcotic drug use, which in the investigator's opinion would compromise subject's safety and/or compliance with the trial procedures.
4. A positive urine drug test at trial screening. Urine was tested for the presence of alcohol, methadone, barbiturates, amphetamines, benzodiazepines, cocaine, cannabinoids, and opioids.
5. Hepatitis A infection (confirmed by Hepatitis A IgM antibody), Hepatitis B infection (confirmed by Hepatitis B surface antigen), or Hepatitis C infection (confirmed by Hepatitis C antibody) at trial screening.
6. Currently active or underlying gastrointestinal, cardiovascular, neurologic, psychiatric, metabolic, renal, hepatic, respiratory, inflammatory, or infectious disease.
7. Any current or previous adrenal disease.
8. Currently significant diarrhea, gastric stasis, or constipation that in the investigator's opinion could influence drug absorption or bioavailability.
9. Any history of significant skin disease such as, but not limited to, rash or eruptions, drug allergies, food allergy, dermatitis, eczema, psoriasis, or urticaria.
10. Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the investigational medication administered in this trial (i.e., TMC278) as well as to moxifloxacin or EFV.
11. Use of concomitant medication, including over-the-counter products, herbal medications, and dietary supplements. Over-the-counter medication had to be discontinued at least 7 days prior to the first administration of study medication and prescribed medication had to be discontinued at least 14 days prior to the first intake of study medication, except for ibuprofen and paracetamol.
12. History of psychiatric disorders.
13. Regular reports of dizziness, headache etc. in history.
14. Having used cisapride, terfenadine, astemizole, or any psychoactive drug within 30 days prior to the first intake of study medication.
15. Participation in an investigational drug trial within 60 days prior to the first intake of study medication.
16. Donation of blood or plasma or significant blood loss within 60 days preceding the first intake of study medication.

17. Having previously participated in more than 1 trial (single or multiple dose) with TMC125, TMC120, and/or TMC278 (formerly known as R278474) or having developed a rash, erythema, or urticaria while participating in a trial with the aforementioned compounds.
18. Subjects with the following laboratory abnormalities at screening as defined by the Division of Acquired Immunodeficiency Syndrome (DAIDS) table for Grading the Severity of Adult and Pediatric Adverse Events and in accordance with the normal ranges of the clinical laboratory:
    - serum creatinine grade 1 or greater (≥ 1.1 x upper limit of normal range [ULN]);
    - lipase grade 1 or greater (≥ 1.1 x ULN);
    - hemoglobin grade 1 or greater (≤ 12.0 g/dL);
    - platelet count grade 1 or greater (≤ 124.999 x 10^9/L);
    - absolute neutrophil count grade 1 or greater (≤ 1.3 x 10^9/L);
    - aspartate aminotransferase or alanine aminotransferase grade 1 or greater (≥ 1.25 x ULN);
    - direct bilirubin grade 1 or greater (≥ 1.1 x ULN);
    - any other toxicity grade 2 or above, including proteinuria (spot urine) ≥ 2+ and microscopic hematuria (> 10 red blood cells/high power field) with the exception of low density lipoprotein cholesterol < ULN of the local laboratory. A urine retest for proteinuria and microscopic hematuria could be performed in women after the menstrual period.
19. History of clinically relevant heart rhythm disturbances.
20. Blood pressure outside of the normal range (supine systolic blood pressure < 90 or > 140 mmHg and/or diastolic blood pressure < 40 or > 90 mmHg) at screening or on Day -2 of the first treatment period.
21. Unusual T wave morphology (such as bifid T wave) at screening or on Day -1 of the first treatment period.
22. History of additional risk factors for Torsade de Pointes, such as heart failure, hypokalemia, family history of known long QT syndrome, or sudden unexplained death at a young age (≤ 40 years) in a first-degree relative (i.e., biological parent, sibling, or offspring).
23. Electrolyte abnormalities (hypokalemia, hypocalcemia, hypomagnesemia) above grade 1 at screening and Day -2.

Treatment	Treatment A	Treatment B	Treatment C	Treatment D	Treatment E
Dosage	TMC278 25 mg + moxifloxacin placebo	TMC278 placebo + moxifloxacin placebo	TMC278 placebo + moxifloxacin 400 mg	EFV 600 mg	EFV placebo
Dosage Form (F No.)	TMC278 25 mg tablet (F006) moxifloxacin placebo capsule (GFI 90000- 000-B-043X)	TMC278 placebo tablet (F013) moxifloxacin placebo capsule (GFI 90000-000- B-043X)	TMC278 placebo tablet (F013) moxifloxacin 400 mg capsule (GFI 80000- 000-B-038Y)	EFV 600 mg tablet (F343)	EFV placebo tablet (F335)
Usage	1 x TMC278 25 mg tablet q.d. orally on Days 1-11 + 1 x moxifloxacin placebo capsule q.d. orally on Day 11	1 x TMC278 placebo tablet q.d. orally on Days 1-11 + 1 x moxifloxacin placebo capsule q.d. orally on Day 11	1 x TMC278 placebo tablet q.d. orally on Days 1-11 + 1 x moxifloxacin 400 mg capsule q.d. orally on Day 11	1 x EFV 600 mg tablet q.d. orally on Days 1-11	1 x EFV placebo tablet q.d. orally on Days 1-11
Batch Number	F006: 8BL2H GFI 90000-000- B-043X: PD2776	F013: PD2806 GFI 90000-000- B-043X: PD2776	F013: PD2806 GFI 80000-000- B-038Y: PD2867	F343: JO81068	F335: PD2872
Dose Regimen	In the TMC278 panel: TMC278 25 mg q.d., moxifloxacin placebo q.d. **or** TMC278 placebo q.d., moxifloxacin placebo q.d. **or** TMC278 placebo q.d., moxifloxacin 400 mg q.d. In the EFV panel: EFV 600 mg q.d. **or** EFV placebo q.d.				
Duration of Treatment	Treatment A, B, C, D and E: 11 days each.				
Duration of Trial	TMC278 panel: 75 days excluding screening and follow-up (3 treatment periods of 11 days each with a wash out period of at least 21 days in between for Treatments A, B, and C). EFV panel: 75 days excluding screening and follow-up (2 treatment periods of 11 days each with a wash out period of at least 53 days in between for Treatments D and E).				

Disallowed Medication	All systemic over-the-counter medication had to be discontinued at least 7 days before the first administration of study medication and all prescribed medication had to be discontinued at least 14 days before the first administration of study medication, except for ibuprofen or paracetamol. Subjects were also not to use any systemic herbal medications or dietary supplements from 7 days before the first study medication intake and up to 7 days after the last study medication intake. Products containing *Hypericum perforatum* (e.g., St. John's wort) were not allowed from 14 days before the first study medication intake and up to 7 days after the last study medication intake. Ibuprofen or paracetamol could be used up to 3 days before the first drug administration in each session. After that, the clinical investigator could permit the use of ibuprofen or paracetamol from 3 days before the first intake of study medication until Day 12 at no more than 1 x 400 mg per day for ibuprofen, and at no more than 2 x 500 mg per day or no more than 2 g per week for paracetamol. Paracetamol or ibuprofen was not to be used on Days -1 and 11 of each treatment session (days with Holter monitoring). Female subjects of childbearing potential were to use birth-control methods and had to be willing to continue practicing these birth-control methods throughout the trial and for at least 30 days after the last intake of study medication. Hormone replacement therapy was allowed in postmenopausal women. In case of cutaneous reaction/rash and/or an allergic reaction, the use of cetirizine (Zyrtec®), levocetirizine (Xyzal®), topical corticosteroids, or antipruritic agents in the recommended dosing scheme was permitted. In case of nausea, the use of antiemetics was permitted. In case of diarrhea, the use of loperamide was permitted.

Assessments	Screening[a]	Treatments A, B, and C (Session I, II, or III) and Treatments D and E (Session I or II)[b]							Follow-up
	≤ 28 days	Day -2[c]	Day -1	Day 1	Day 9	Day 10	Day 11	Day 12	Day 7 and 30, 31, or 32
Pharmacokinetics									
Blood sample[d]			X	X	X	X	X	X	
Safety									
Adverse events + concomitant medications[e]	X	X	X	X	X	X	X	X	X
Hematology + biochemistry[f]	X	X[g]	X	X			X	X	X
Urinalysis[h]	X	X[i]	X	X			X	X	X
Electrocardiogram[j]	X		X	X	X	X	X	X	X
24 hour Holter monitoring[k]			X				X		
Vital signs[l]	X	X[m]	X	X			X	X	X
Skin examination	X		X		X	X[n]		X	X
Physical examination	X		X					X	X

[a] At screening, informed consent was obtained, inclusion/exclusion criteria, subject characteristics and demographics, medical and surgical history, concomitant diseases and concomitant medication were recorded and an HIV-1 and HIV-2 test, hepatitis A, B, and C test, and urine drug screening were performed; a serum pregnancy test was also performed for females.

[b] Study medication was to be taken within 10 minutes after the end of breakfast for Treatments A, B, and C, and 2 hours prior to breakfast for Treatments D and E.

[c] Subjects were admitted to the unit on Day -2 and were to have been fasting for at least 10 hours prior to the 0 hour timepoint on Day -1. Subjects were discharged on Day 12 after breakfast.

[d] Pharmacokinetic samples for the determination of EFV or TMC278 and/or moxifloxacin plasma concentrations, as appropriate, were taken predose or at the 0 hour timepoint, as applicable, and at the following timepoints 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 9, 12, 16, and 24 hours postdose on Day -1 (predose on Day 1) and at Day 11 (predose on Day 12), and predose on Day 9 and 10. Samples were to be taken within 5 minutes after each ECG recording or Holter extraction timepoint, if applicable. Standard lunch was to be started immediately after the 5 hour sampling on Day -1 and Day 11.

[e] Adverse events and concomitant medications were monitored continuously from signing the informed consent form until the last trial-related activity.

[f] Biochemistry sample was to be taken fasted for at least 10 hours, before breakfast (for Treatments A, B, and C) or before intake of study medication, if applicable (for Treatments D and E), within 5 minutes after safety ECG recording or Holter extraction timepoint

[g] Safety sample on Day -2 was to reconfirm eligibility in Session I, only serum pregnancy test for female subjects in later sessions.

[h] On Day -1: within 2 hours before the start of Holter monitoring.

[i] Complete urine assessment in Session I, including urine drug screen, only urine drug screen in later sessions.

[j] Safety ECG was to be performed in supine position after at least 10 minutes rest, approximately 10 minutes before breakfast (for Treatments A, B, and C) or before intake of study medication, if applicable (for Treatments D and E) and was also performed at 4 hours postdose on Day 1 and Day 11; and was to be performed within 5 to 15 minutes before the Holter extraction timepoint on Days -1 and 11.

[k] Holter at ECG extraction timepoints was to be recorded in supine position after at least 10 minutes rest before breakfast (For Treatments A, B, and C) or before intake of study medication, if applicable (for Treatments D and E) and at 1, 2, 3, 3.5, 4, 4.5, 5, 6, 9, 12, 16, and 24 hours postdose (24 hours postdose = predose on Days 1 and 12). Triplicate 10 second recordings were to be collected at 60 second intervals.

[l] Blood pressure and pulse (supine after 5 minutes, standing after 1 minute) had to be measured just before the 10 minute rest period prior to the ECG recording or Holter extraction timepoint.

[m] Performed only in Session I.

[n] The subject was to be asked if any changes on the skin had occurred since examination on Day 9 and if so, a standard skin examination was to be performed.

Statistical Methods	Descriptive statistics and frequency tabulations. The primary parameter was the observed time-matched difference versus placebo in QTcF interval. At each timepoint, two-sided 90% confidence intervals (CIs) were constructed for the mean time-matched difference of this parameter between TMC278 and TMC278 placebo and similarly between EFV and EFV placebo. For each treatment and timepoint of measurement, the observed time-matched difference versus placebo and observed time-matched difference versus baseline in QT/QTc, PR, QRS and other ECG intervals were summarized using least square (LS) means estimates using mixed effects models with the observed time-matched difference versus baseline as dependent variable (mean, standard deviation [SD], 90% CI). The following other QT-correction methods were used: QTcB, QTcS, QTc ILR, QTc INLR, QTc TLR, and QTc TNLR. Per International Conference on Harmonization (ICH) E14 Guidance for Industry, a thorough QT (TQT) trial is considered negative if the upper limit of the 90% CIs of the difference versus placebo in QTc interval is less than 10 ms at all timepoints. Trial sensitivity can be claimed if the difference between the active control (moxifloxacin) and placebo is at least 5 ms for at least one timepoint. Timepoints of interest were restricted to 2, 3, 4, and 5 hours postdose. In order to account for multiple significance testing, the Bonferroni procedure was applied with an overall significance level of 10% and thus 97.5% CIs are presented for moxifloxacin. The plasma concentration-effect relationship in QTcF interval was characterized using linear mixed effects models and graphical presentations.

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics - Subject Disposition	TMC278 Panel	EFV Panel	All Subjects
Number of Subjects Entered (M/F)	60 (35/25)	60 (33/27)	120 (68/52)
Age: median (range), years	31 (19-50)	31 (18-54)	31 (18-54)
Ethnic Origin, n (%)			
Hispanic or Latino	46 (76.7)	49 (81.7)	95 (79.2)
Not Hispanic or Latino	14 (23.3)	11 (18.3)	25 (20.8)
Race, n (%)			
American Indian or Alaska native	2 (3.3)	1 (1.7)	3 (2.5)
Black or African American	1 (1.7)	0	1 (0.8)
White	57 (95.0)	59 (98.3)	116 (96.7)
Drop-Outs - Reason, n (%)			
Adverse event	2 (3.3%)	7 (11.7%)	9 (7.5%)
Non-compliance	1 (1.7%)	3 (5.0%)	4 (3.3%)
Other	1 (1.7%)	0	1 (0.8%)

Safety Results: ECG

TMC278 panel:

Table: Time-matched difference versus placebo in QTcF interval on Day 11 at the timepoint with the highest upper limit of the two-sided 90% CI for TMC278 and for moxifloxacin, the timepoint with the highest lower limit of the two-sided 97.5% CI

TMC278 25 mg (Day 11, 12 hours postdose)	Moxifloxacin (Day 11, 5 hours postdose)
Mean (SE) [90% CI]	Mean (SE) [97.5% CI]
2.0 (1.8) [-1.0;5.0]	9.5 (1.5) [6.1;13.0]

For TMC278 25 mg q.d. at steady-state (Day 11), the timepoint with the highest upper limit of the 90% CI of the time-matched difference versus placebo was at 12 hours postdose. For TMC278 25 mg q.d. at steady-state, the 90% CIs of the observed time-matched difference versus placebo in QTcF interval did not cross the 10 ms threshold at any timepoint, indicating that the TMC278 25 mg q.d. dose is not associated with a clinically relevant effect on QTcF interval. On Day 11 of TMC278 treatment, observed differences versus placebo in QTcF interval were higher for males than for females.

Considering the timepoints with the largest mean increases from baseline in QTcF interval, at steady-state (Day 11), administration of TMC278 25 mg q.d. showed small increases in QTcF interval comparable with those after administration of TMC278 placebo. The largest mean increase from baseline in QTcF interval for TMC278 25 mg q.d. and TMC278 placebo was observed predose (+0.7 ms; 90% CI [-1.3; 2.7]) and 4.5 hours postdose (+0.1 ms; 90% CI [-1.9; 2.1]) on Day 11, respectively.

Observed time-matched difference versus placebo and versus baseline in QTcF interval showed similar results.

With moxifloxacin an increase in QTcF interval compared to baseline and versus placebo was observed and the lower limit of the 97.5% CI was above 5 ms at several timepoints between 2 and 5 hours. Thus, trial sensitivity, for detecting a relevant increase in QTcF interval, was established.

EFV panel:

Table: Time-matched difference versus placebo in QTcF interval on Day 11 at the timepoint with the highest upper limit of the two-sided 90% CI for EFV

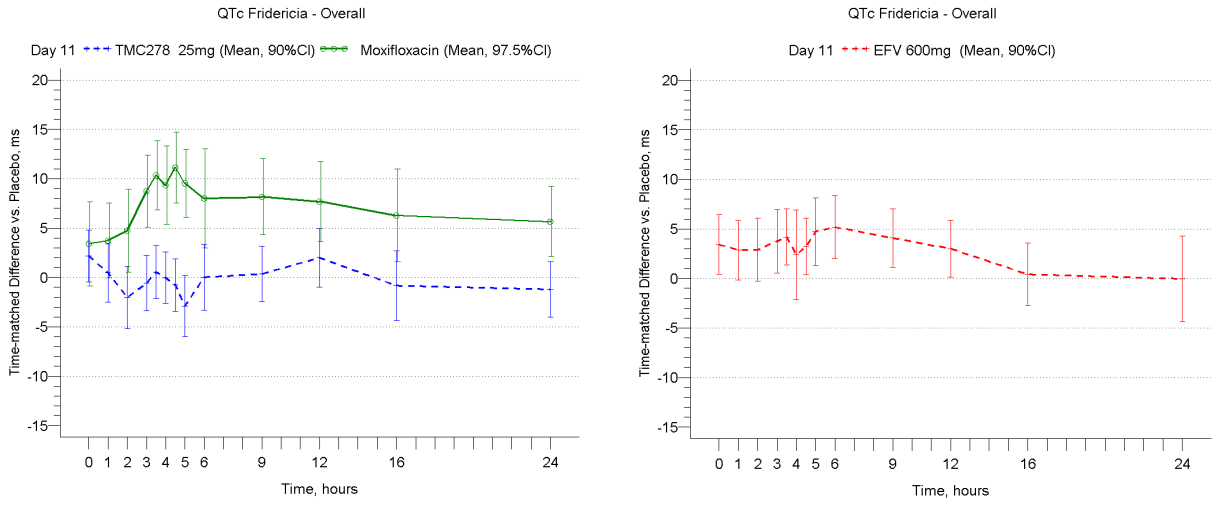
	EFV 600 mg
	Mean (SE) [90% CI]
Day 11, 6 hours postdose	5.2 (1.9) [2.0;8.4]

For EFV, the highest upper limit of the 90% CI of the observed time-matched difference versus placebo in QTcF interval was observed at 6 hours postdose. None of the 90% CIs of the observed time-matched difference versus placebo in QTcF interval crossed 10 ms. As with TMC278 at steady-state (Day 11), the upper limits of the 90% CIs of the time-matched difference versus placebo were less than the 10 ms threshold at all timepoints, indicating that the EFV 600 mg q.d. dose is not associated with a clinically relevant effect on QTcF interval. On Day 11 of EFV treatment, observed differences versus placebo in QTcF interval were higher for males than for females.

The largest mean increases from baseline for EFV 600 mg q.d. on Day 11 were observed at 6 hours (+4.8 ms; 90% CI [2.1; 7.5]) and 9 hours (+4.8 ms; 90% CI [2.8; 6.9]) postdose. The largest mean increase from baseline for EFV placebo was observed at 1 hour postdose (+0.8 ms; 90% CI [-1.3; 2.9]) on Day 11.

Observed time-matched difference versus placebo and versus baseline in QTcF interval showed similar results.

Figures: Time-matched difference versus placebo in QTcF interval (mean, 90/97.5% CI) for the TMC278 (left) and EFV (right) panels on Day 11



Other ECG Parameters: There were no consistent or clinically relevant changes over time in the ECG parameters of PR, and QRS during TMC278 or EFV treatment. A notable change (increase) over time in HR was observed during EFV treatment compared with EFV placebo. Results with other QT-correction methods were generally in line with those observed for QTcF interval for the TMC278 panel. Results for the EFV panel were also mainly in line with those observed for QTcF. The only exception was for QTcB interval: the 90% CI of the observed time-matched difference versus placebo in QTcB interval at several timepoints did cross the 10 ms threshold. This is explained by a consistent increase in HR observed on EFV, which was not observed for TMC278 or moxifloxacin.

Individual ECG Abnormalities: In the TMC278 panel, for each of the QT-corrections, the numbers of subjects with abnormalities were similar during treatment with TMC278 25 mg q.d., and TMC278 placebo. An abnormal increase versus baseline in QTcF (defined as ≥ 30 ms) was the most common ECG abnormality. For 1 male subject, a QTcF interval increase > 60 ms was reported during treatment with TMC278 25 mg q.d. This change resulted in an abnormal actual value (499 ms) for QTcF and was not noted to persist.

In the EFV panel, for QTcF, the number of subjects with abnormalities during treatment with EFV placebo was almost four times greater than that observed during treatment with EFV 600 mg q.d. (7 [12.7%] subjects versus 2 [3.8%] subjects, respectively). For QTcB, the number of subjects with abnormalities during treatment with EFV 600 mg q.d. was more than double that observed during treatment with EFV placebo (17 [32.7%] subjects versus 8 [14.5%] subjects, respectively). For each of the other QT-corrections, the number of subjects with abnormalities was similar during treatment with EFV 600 mg q.d. and EFV placebo. One (1.9%) subject was reported with a QTcF increase > 60 ms during treatment with both EFV 600 mg q.d. and EFV placebo. These changes resulted in abnormal actual values (474 ms and 489 ms, respectively) for QTcF and were not noted to persist.

In both the TMC278 and EFV panels, no subjects were reported with actual values for QTcF > 500 ms.

Pharmacokinetics of TMC278 (mean ± SD, t_{max}: median [range])	**TMC278 25 mg q.d. + moxifloxacin placebo on Day 11**
n	57
Day 11	
C_{0h}, ng/mL	132.3 ± 40.60
C_{min}, ng/mL	95.23 ± 29.07
C_{max}, ng/mL[a]	246.8 ± 74.36
t_{max}, h[a]	5.0 (4.0-24.0)
AUC_{24h}, ng.h/mL[a]	3324 ± 884.0
$C_{ss,av}$, ng/mL[a]	138.5 ± 36.83
FI, %[a]	111.1 ± 32.47

[a] n=56

Pharmacokinetics of EFV (mean ± SD, t_{max}: median [range])	**EFV 600 mg q.d. on Day 11**
n	52
Day 11	
C_{0h}, µg/mL	2.344 ± 0.9683
C_{min}, µg/mL	2.249 ± 0.9566
C_{max}, µg/mL	4.975 ± 1.717
t_{max}, h	3.0 (1.0-4.5)
AUC_{24h}, µg.h/mL	72.78 ± 27.79
$C_{ss,av}$, µg/mL	3.033 ± 1.159
FI, %	94.24 ± 26.58

Pharmacokinetics of moxifloxacin (mean ± SD, t_{max}: median [range])	**TMC278 placebo q.d. + moxifloxacin 400 mg on Day 11**
n	54[a]
Day 11	
C_{max}, ng/mL	2796 ± 507.7
t_{max}, h	4.0 (2.0-5.07)
AUC_{last}, ng.h/mL	33570 ± 5386
AUC_{∞}, ng.h/mL[b]	46780 ± 8607
$t_{1/2term}$, h[b]	12.94 ± 2.582

[a] n=52 for AUC_{last} and n=55 for $t_{1/2term}$
[b] Accurate determination not possible

Pharmacokinetic/pharmacodynamic analysis for TMC278:

No relationship between TMC278 plasma concentration and change in QTcF interval was observed.

Safety: TMC278 panel (N = number of subjects with data)	**TMC278 25 mg q.d. N = 58**	**TMC278 placebo N = 59**
With 1 or more AE, n (%)	**25 (43.1)**	**27 (45.8)**
Most frequently reported treatment-emergent AEs (reported in ≥ 2 subjects during treatment with TMC278 25 mg q.d.), n (%)		
Headache	8 (13.8)	10 (16.9)
Constipation	4 (6.9)	4 (6.8)
Abdominal pain	3 (5.2)	2 (3.4)
Pruritus	3 (5.2)	2 (3.4)
Alopecia	3 (5.2)	0
Upper respiratory tract infection	2 (3.4)	2 (3.4)
Somnolence	2 (3.4)	1 (1.7)
Rash papular	2 (3.4)	1 (1.7)
Abdominal discomfort	2 (3.4)	0
Erythema	2 (3.4)	2 (3.4)
Nasal congestion	2 (3.4)	0
Insomnia	2 (3.4)	1 (1.7)
Syncope vasovagal	2 (3.4)	0
n (%) of deaths	**0**	**0**
n (%) with 1 or more other serious AEs	**0**	**0**
n (%) of treatment stopped due to AEs	**0**	**2 (3.4)**
Rash erythematous	0	1 (1.7)
Vomiting	0	1 (1.7)
n (%) with 1 or more grade 3 or 4 AEs	**0**	**0**

There were no notable differences between TMC278 and TMC278 placebo treatments in terms of the incidence of AEs. The most commonly reported AEs were headache, constipation, abdominal pain, pruritus and alopecia. One subject was reported with a grade 3 SAE of abscess of the jaw during follow-up. This event was considered by the investigator to be not related to TMC278 and was not noted to resolve at the end of the trial. Two subjects treated with TMC278 placebo had AEs that led to discontinuation from the trial. During the trial, skin events of interest were reported in a similar number of subjects when treated with TMC278 25 mg q.d. (6 [10.3%] subjects) and TMC278 placebo (5 [8.5%] subjects). No event was reported in more than 2 subjects and the types of events were similar between both treatments. Cardiac events were only reported in females and never in more than 1 subject. Cardiac events included palpitations, ECG QT prolonged, and chest pain during treatment with TMC278 25 mg q.d. and chest pain during treatment with TMC278 placebo.

Safety: EFV panel (n = number of subjects with data)	**EFV 600 mg q.d. N = 57**	**EFV Placebo N=55**
With 1 or more adverse event (AE)	42 (73.7)	26 (47.3)
Most frequently reported treatment-emergent AEs (reported in ≥ 2 subjects during treatment with EFV 600 mg q.d.), n (%)		
Dizziness	30 (52.6)	1 (1.8)
Headache	9 (15.8)	16 (29.1)
Nausea	9 (15.8)	4 (7.3)
Somnolence	8 (14.0)	8 (14.5)
Dyspepsia	6 (10.5)	3 (5.5)
Feeling hot	5 (8.8)	2 (3.6)
Vision blurred	5 (8.8)	0
Constipation	4 (7.0)	6 (10.9)
Rash maculo-papular	4 (7.0)	0
Hypoaesthesia	4 (7.0)	0
Hot flush	4 (7.0)	0
Insomnia	3 (5.3)	1 (1.8)
Dry mouth	3 (5.3)	0
Paraesthesia	3 (5.3)	0
Asthenia	3 (5.3)	0
Erythema	2 (3.5)	2 (3.6)
Pruritus	2 (3.5)	2 (3.6)
Upper respiratory tract infection	2 (3.5)	2 (3.6)
Decreased appetite	2 (3.5)	1 (1.8)
Dry throat	2 (3.5)	1 (1.8)
Head discomfort	2 (3.5)	0
Abdominal pain upper	2 (3.5)	0
Blood triglycerides increased	2 (3.5)	0
n (%) of deaths	**0**	**0**
n (%) with 1 or more other serious AEs	**0**	**1 (1.8)**
Appendicitis	0	1 (1.8)
n (%) of treatment stopped due to AEs	**4 (7.0)**	**1 (1.8)**
Rash maculo-papular	3 (5.3)	0
Drug eruption	1 (1.7)	0
Pruritus	1 (1.7)	
Eczema	0	1 (1.8)
Erythema	0	1 (1.8)
Rash erythematous	0	1 (1.8)
n (%) with 1 or more grade 3 or 4 AEs	**0**	**1 (1.8)**
Appendicitis	0	1 (1.8)

A higher incidence of AEs was observed during treatment with EFV 600 mg q.d. than during treatment with EFV placebo. The most commonly reported AEs during treatment with EFV 600 mg q.d. were dizziness, headache, nausea, somnolence, and dyspepsia. One subject was reported with a grade 3 SAE of appendicitis during washout after treatment with EFV placebo which was preceded by an event of grade 3 abdominal pain. Five subjects discontinued the trial due to AEs during the treatment period; 4 subjects in the EFV 600 mg q.d. group and 1 subject in the EFV placebo group. In addition, 2 subjects discontinued during follow-up (1 subject was reported with blood human chorionic gonadotropin positive and 1 subject was reported with increased blood human chorionoc gonadotropin). During the trial, skin events of interest were reported in a higher proportion of subjects treated with EFV 600 mg q.d. (8 [14.0%] subjects) than with EFV placebo (5 [9.1%] subjects). The most frequently observed was rash maculo-papular in 4 subjects (none treated with EFV placebo). All other skin events of interest were reported in at most 2 subjects. Cardiac events were reported in both males and females and included ECG QT prolonged and palpitations during treatment with EFV 600 mg q.d and syncope during treatment with EFV placebo and none were reported in more than 1 subject.

Clinical laboratory tests

The incidence and type of of treatment-emergent laboratory abnormalities was similar during treatment with TMC278 25 mg q.d. and TMC278 placebo. There were no consistent or clinically relevant treatment-emergent changes over time in laboratory parameters. No grade 4 laboratory abnormalities were observed in any treatment session. Grade 3 laboratory abnormalities of decreased phosphorus and increased triglycerides were observed for 1 subject each during treatment with TMC278 25 mg q.d. Grade 2 laboratory abnormalities were observed in 6 subjects during treatment with TMC278 25 mg q.d., of which the most commonly reported were increased lipase (2 subjects) and increased LDL cholesterol (3 subjects).

The incidence and type of treatment-emergent laboratory abnormalities was similar during treatment with EFV 600 mg q.d. and EFV placebo. There were no consistent or clinically relevant treatment-emergent changes over time in laboratory parameters. No grade 4 laboratory abnormalities were observed. Grade 3 laboratory abnormalities were observed in 4 subjects during treatment with 600 mg EFV q.d (all increased LDL cholesterol). Grade 2 laboratory abnormalities were observed in 14 subjects during treatment with EFV 600 mg q.d., of which the most commonly reported were increased LDL cholesterol (7 subjects).

Vital signs

Minor changes were observed for vital sign parameters in the TMC278 and EFV panels. None of the changes were considered to be clinically relevant. No trends or relationship to study medication were apparent.

Physical examination

New findings in physical examinations were observed in both the TMC278 and EFV panels, none of which were reported as AEs, except for the following in the TMC278 panel: tender submandibular gland on the left mid jaw area and a tender right posterior shoulder and trapezius area along with tender right ribs; nausea and vomiting, loss of appetite and a soft, non-tender abdomen, and in the EFV panel: red morbilliform rash on the scalp, face, neck, chest, abdomen, upper back and anterior thigh. Each of these AEs was reported in 1 subject.

Conclusions

The change at steady-state in the QTcF interval on TMC278 at a dose of 25 mg q.d. does not exceed the threshold as defined by ICH E14, indicating that the TMC278 25 mg q.d. dose is not associated with a clinically relevant effect on QTcF interval.

QTc results

For TMC278 25 mg q.d. at steady-state (Day 11), the 90% CIs of the observed time-matched difference versus placebo in QTcF interval did not cross the 10 ms threshold at any timepoint. At steady-state, administration of TMC278 25 mg q.d. showed small changes in QTcF interval comparable to those after administration of TMC278 placebo.

In the EFV panel, none of the 90% CIs of the observed time-matched difference versus placebo in QTcF interval crossed the 10 ms threshold.

Pharmacokinetic and pharmacokinetic/pharmacodynamic

At steady-state administration of TMC278 25 mg q.d., no relationship was observed between TMC278 plasma concentration and change in QTcF interval, i.e., higher plasma concentrations did not result in higher changes in the QTcF interval.

Other relevant safety data

No safety signals for AEs, hematology and biochemistry parameters, or vital signs were observed.

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