N-143

Pharmacokinetic Parameters of Once-Daily TMC278 Following Administration of Efavirenz in Healthy Volunteers

Herta Crauwels,[1] Johan Vingerhoets,[1] Robert Ryan,[2] James Witek[3] and David Anderson[3]

[1]Tibotec BVBA, Beerse, Belgium; [2]Tibotec Inc., Titusville, NJ, USA; [3]Tibotec Therapeutics, Titusville, NJ, USA

Herta Crauwels, PhD,
Tibotec BVBA,
Turnhoutseweg 30,
B-2340 Beerse, Belgium;
HCrauwel@its.jnj.com

Introduction

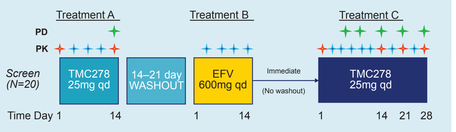
- TMC278 is an investigational nonnucleoside reverse transcriptase inhibitor (NNRTI) with in vitro activity against wild-type HIV-1 and NNRTI-resistant HIV-1
- Two large Phase III studies in antiretroviral (ARV)-naïve, HIV-1–infected subjects have demonstrated high virologic response rates and noninferiority of TMC278 25mg once daily (qd) compared with efavirenz (EFV) 600mg qd[1]
- TMC278 and EFV are both metabolized by cytochrome P450 (CYP) 3A[2]
- EFV has been shown to induce CYP3A, which could lead to increased metabolism of CYP3A substrates, such as TMC278.[2,3] At the 25mg dose, TMC278 does not induce CYP enzymes
- EFV has a long half-life of 40 to 55 hours,[4] and consequently EFV plasma concentrations remain detectable for some time after cessation of treatment
- Additionally, induction of the CYP enzymes persists based on the turnover rate of the CYP enzymes
- ARV regimens are sometimes switched during treatment due to tolerability and toxicity issues, or to simplify an ARV regimen; drug-drug interactions may occur when switching from EFV to TMC278
- This study investigated the pharmacokinetics (PK), safety, and tolerability of TMC278 in healthy adult volunteers, immediately following an EFV treatment period
- Additionally, an exploratory assay was used to determine the ex vivo antiviral activity (pharmacodynamics [PD]) in serum samples

Methods

Study design and treatment

- Phase I, open-label, single-sequence, single-center trial (**Figure 1**)
- All subjects received a fixed sequence of treatments
  - Treatment A: TMC278 25mg qd for 14 days, followed by a 14- to 21-day washout period
  - Treatment B: EFV 600mg qd for 14 days
  - Treatment C: TMC278 25mg qd for 28 days
  - There was no washout between Treatments B and C
- TMC278 was taken with a meal (breakfast) and EFV was taken in the evening, before bed, on an empty stomach

Figure 1. Study design



[a]Samples taken at predose, 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 16 and 24 hours postdose; PD, pharmacodynamic; PK, pharmacokinetic; qd, once daily; EFV, efavirenz

Study objectives

- The primary objective was to assess the PK of TMC278 25mg qd following a 2-week (steady-state) EFV 600mg qd treatment period
- Secondary objectives included
  - Evaluation of EFV plasma concentrations over time after cessation of EFV intake
  - Assessment of the safety of TMC278 25mg qd alone and after EFV intake
- The combined ex vivo antiviral activity of TMC278 and EFV, following the EFV treatment period, was measured

Study evaluations

- 24-hour PK profiles for TMC278 were determined on Days 1 and 14 of Treatment A and on Days 1, 14, 21 and 28 of Treatment C (**Figure 1**), and predose (trough, C_{tau}) samples for the determination of TMC278 plasma concentrations were obtained at regular time points in between
- EFV plasma concentrations were determined at regular time points during Treatments B and C
- Plasma concentrations of TMC278 and EFV were determined using validated liquid chromatography–tandem mass spectrometry methods
  - The lower limit of quantification was 1.0ng/mL for TMC278 and 0.100µg/mL for EFV
- Blood samples were collected under fasting conditions (10-hour) for laboratory assessments on Day 13 of Treatment A, Days 1 and 14 of Treatment B and Days 13 and 27 of Treatment C
- Safety and tolerability were evaluated throughout the trial
- Serum samples for determination of ex vivo antiviral activity were collected predose on Day 14 of Treatment A and on Days 2, 4, 7, 14, 21 and 28 of Treatment C (**Figure 1**)
  - This assay[5,6] measured the total ex vivo antiviral activity resulting from both TMC278 and EFV present in the serum samples taken during Treatment C
  - The antiviral activity is measured as an EC_{50} value, which is expressed as the percent dilution (ranging from 0.02% to 5%) of the serum sample needed to obtain 50% inhibition of viral replication
  - The limit of detection of the assay was 6ng/mL
  - Each volunteer served as his/her own control by comparing activity levels between Treatment A (at Day 14) and Treatment C (at multiple time points)
  - A twofold variation of the EC_{50} value is typically within the variability limits of this type of assay; when compared with the Treatment A (Day 14) EC_{50} value (set at 100% for each volunteer individually), the EC_{50} value determined during Treatment C can vary from 50% to 200% without being relevantly different
- No pharmacogenomic analyses were performed

Statistical analysis

- A linear mixed-effects model controlling for treatment (fixed effect) and subject (random effect) compared the relevant PK parameters during Treatment C with the respective reference PK parameters during Treatment A
  - All data, paired and unpaired, were included for the statistical analysis
- Safety and tolerability are reported for the intent-to-treat population

Results

Baseline characteristics and subject disposition

- 20 subjects were enrolled in the trial and received study drug
- Most subjects were male and white (**Table 1**)
- 17 subjects completed the study
- 1 subject discontinued study medication on Day 8 of Treatment B due to grade 2 erythematous rash, 1 subject was lost to follow-up on Day 22 of Treatment C and 1 subject was withdrawn from the study for medication noncompliance on Day 2 of Treatment C

Table 1. Baseline demographics and disease characteristics

Parameter	All subjects (N=20)
Sex, n (%)	
Male	18 (90)
Female	2 (10)
Ethnic origin, n (%)	
White	14 (70)
Black or African American	6 (30)
Age, median (min, max), years	26 (18, 51)
BMI, median (min, max), kg/m^2	23.9 (20.4, 29.3)

BMI, body mass index

Pharmacokinetics

- Higher mean TMC278 plasma concentrations were observed with Treatment A compared with Treatment C, particularly immediately following the switch (eg, Day 1; **Figure 2a**)
- TMC278 PK parameters at Days 1, 14 and 21 of Treatment C were lower compared with similar time points in Treatment A (**Table 2**)
- By Day 28 of Treatment C, TMC278 PK parameters were similar to those at Day 14 of Treatment A, except for C_{min} (**Table 2**)
- Steady-state conditions for TMC278 were generally reached between 7 and 12 days during Treatment A and after 19 days during Treatment C
- By 7 days after the end of Treatment B, plasma concentrations of EFV were below the 0.100µg/mL limit of quantification for half the subjects (**Figure 3**)
  - 2 subjects had quantifiable EFV plasma concentrations until 22 days after the end of Treatment B

Pharmacodynamics

- The total ex vivo antiviral activity resulting from the presence of both TMC278 and EFV during Treatment C was measured and compared with the activity of TMC278 alone (Treatment A, Day 14)
- At each time point in Treatment C, more than 80% of the subjects demonstrated ex vivo antiviral activity that was not relevantly different from that observed in Treatment A (**Table 3**)

Figure 2. Mean plasma concentration-time curves of TMC278 comparing a) Day 1 of Treatments A and C, and b) Day 14 of Treatment A with Days 14, 21 and 28 of Treatment C

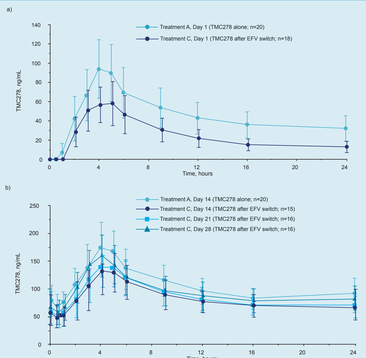


Table 2. Pharmacokinetics of TMC278 during Treatment A and Treatment C

Time point	PK parameter, mean±SD	Treatment A[a] (n=20)	Treatment C[b] (n=16)	LS means ratio (90% CI) for Treatment C vs A[c]
Day 1	C_{max}, ng/mL	99.8±28.3	64.8±20.7[d]	0.64 (0.53, 0.77)
	AUC_{24h}, ng·h/mL	1095±327	602±204[d]	0.54 (0.46, 0.64)
Day 14	C_{max}, ng/mL	67.3±20.7	47.4±18.5[e]	0.72 (0.64, 0.81)
	C_{max}, ng/mL	180.9±45.0	140.2±33.8[f]	0.81 (0.71, 0.93)
	AUC_{24h}, ng·h/mL	2528±596	1940±528[f]	0.82 (0.75, 0.89)
Day 21	C_{min}, ng/mL	-	49.7±20.7	0.72 (0.62, 0.84)
	C_{max}, ng/mL	-	153.6±30.7	0.87 (0.78, 0.98)
	AUC_{24h}, ng·h/mL	-	2089±526	0.84 (0.74, 0.94)
Day 28	C_{min}, ng/mL	-	56.3±23.0	0.75 (0.56, 1.00)
	C_{max}, ng/mL	-	165.6±41.1	0.92 (0.81, 1.05)
	AUC_{24h}, ng·h/mL	-	2298±548	0.91 (0.82, 1.01)

[a]TMC278 25mg qd; [b]TMC278 25mg qd post EFV cessation; [c]Day 21 and 28 of Treatment C are each compared with Day 14 of Treatment A; [d]n=18; [e]n=15; [f]n=14; PK, pharmacokinetic; SD, standard deviation; LS, least squares; CI, confidence interval; C_{max}, maximum plasma concentration; AUC_{24h}, area under the plasma concentration-time curve over the dosing interval; C_{min}, minimum plasma concentration; qd, once daily; EFV, efavirenz

Figure 3. Mean plasma concentrations of efavirenz over time during Treatments B and C

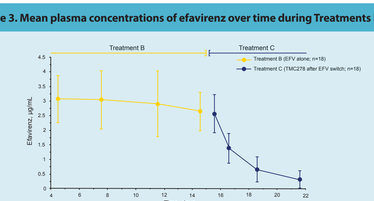


Table 3. Ex vivo antiviral activity

Treatment C	Subjects with a mean EC_{50} value that is within the subject's reference range,[a] n (%)
Day 2	17 (100)
Day 4	17 (100)
Day 7	17 (100)
Day 14	15 (88.2)
Day 21	14 (82.4)
Day 28	15 (88.2)

[a]Reference range defined from Treatment A, Day 14 EC_{50} value (set at 100%). In comparing EC_{50} values, a twofold variation (eg, 50% to 200%) of the EC_{50} value is within the variability limits of the assay; EC_{50}, 50% effective concentration

Safety

- All adverse events (AEs) were grade 1 or 2 and no serious AEs occurred (**Table 4**)
- One subject discontinued study medication on Day 8 of Treatment B due to grade 2 erythematous rash
- The most frequent AEs were dizziness, abnormal dreams, headache and upper respiratory tract infection (**Table 4**)
- Overall, the incidence of AEs was similar regardless of whether TMC278 was administered with or without a prior EFV exposure (comparing Treatments A and C)
- AEs considered at least possibly related to TMC278 were reported in 5 subjects (**Table 4**); of these, only headache (n=2, 10%) was reported in more than one subject
- AEs considered at least possibly related to EFV were reported in 14 subjects (14 subjects in Treatment B and 2 subjects in Treatment C); the most frequently reported were dizziness (n=9, 45.0%) and abnormal dreams (n=6, 30.0%)

Table 4. Incidence of all adverse events[a] by treatment

Parameter, n (%)	Treatment A[b] (n=20)	Treatment B[c] (n=20)	Treatment C[d] (n=19)	Whole study[e] (n=20)
Any AE	10 (50.0)	15 (75.0)	8 (42.1)	19 (95.0)
AEs at least possibly related to TMC278	3 (15.0)	0	2 (10.5)	5 (25.0)
Adverse events regardless of causality or severity[f]				
Dizziness	0	9 (45.0)	1 (5.3)	9 (45.0)
Headache	3 (15.0)	0	2 (10.5)	5 (25.0)
Abnormal dreams	1 (5.0)	5 (25.0)	1 (5.3)	7 (35.0)
Feeling hot	0	2 (10.0)	0	2 (10.0)
Injection site hemorrhage	2 (10.0)	0	0	2 (10.0)
Upper respiratory tract infection	2 (10.0)	0	1 (5.3)	4 (20.0)
Rhinitis	2 (10.0)	0	0	2 (10.0)
Rash	0	2 (10.0)	0	2 (10.0)
Musculoskeletal and connective tissue disorders	2 (10.0)	0	0	2 (10.0)

[a]Does not include laboratory abnormalities reported as AEs; [b]TMC278 25mg qd; [c]EFV 600mg qd; [d]TMC278 25mg qd post EFV cessation; [e]Includes screening and follow-up; [f]Occurring in >1 subject in any treatment course; AE, adverse event; qd, once daily; EFV, efavirenz

- Most graded laboratory abnormalities were grade 1 or 2 and none were grade 4
  - 3 subjects (15%) experienced treatment-emergent grade 3 laboratory abnormalities: 1 subject had increases in total cholesterol (TC; Treatment B, Day 14), 1 subject had increases in low-density lipoprotein (LDL; Treatment C, Days 13 and 14) and 1 subject had increases in both TC and LDL (Treatment B, Day 14)
- No major differences in graded laboratory abnormalities were noted between treatment phases

Discussion

- This study showed that although TMC278 exposure was initially lower when TMC278 was administered after EFV treatment (Treatment C) than when administered before EFV treatment (Treatment A), the AUC_{24h} was similar to reference levels (Treatment A) by 28 days post EFV treatment
  - The C_{max} ratio at 28 days after the switch was 0.75. In general, the variability for C_{max} is larger than that for AUC_{24h}, and AUC_{24h} is considered a more insightful PK parameter within the setting of intensive PK evaluations
  - For the NNRTI class, there is no general consensus on which PK parameter is best associated with response
- In general, TMC278 PK parameters in treatment-naïve, HIV-1–infected adults receiving TMC278 25mg qd in the ECHO and THRIVE trials were in a similar range as those observed in the current trial, across treatments[7]
- In the exploratory PD analysis, the ex vivo antiviral activity measured in the samples from Treatment C was not different from that in the reference sample (Treatment A, Day 14) in over 80% of subjects at all time points tested, suggesting that the PK interaction between EFV and TMC278 during the first weeks after the switch did not greatly affect the total combined antiviral activity during this period
  - In a clinical setting, subjects who were to switch from EFV to TMC278 would continue to have the benefit of an active ARV backbone, which could negate any transient decrease in NNRTI exposure after the treatment switch
  - It should be noted, however, that this ex vivo antiviral activity assay has not been fully validated and that clinical correlates for efficacy have not been investigated
- 2 subjects had detectable EFV plasma concentrations until Day 22, demonstrating the intersubject variability of ARV PK parameters
  - In these 2 subjects, when comparing Treatment C to Treatment A, the AUC_{24h} ratio was above the mean and close to 100% as of Day 14 after the switch from EFV, and the measured antiviral activity was greater than 100% of reference at all time points
- A pilot study is currently recruiting subjects to evaluate the efficacy and safety of a treatment switch from EFV/emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) to TMC278/FTC/TDF (single tablet regimen) in treatment-experienced, HIV-1–infected subjects (Clinicaltrials.gov identifier: NCT01286740)
- The incidence of AEs was low and similar between Treatments A and C and no clinically relevant changes in mean laboratory parameters were observed, suggesting that administration of TMC278 after an EFV treatment period is generally safe and well tolerated
  - A dose-finding trial in treatment-naïve, HIV-1–infected adults and the Phase III ECHO and THRIVE trials also reported low incidences of TMC278-related AEs, similar to those seen in Treatments A and C of this trial[1,8,9]
- The most common AEs at least possibly related to EFV, dizziness (n=9, 45.0%) and abnormal dreams (n=6, 30.0%), are common side effects of EFV[4]
  - In contrast, of the AEs at least possibly related to TMC278, only one patient (5.3%) reported abnormal dreams and no patients reported dizziness

Conclusions

- TMC278 exposure was initially lower after a switch from EFV, but by 4 weeks after the switch, the TMC278 exposure was similar to the steady-state exposure of TMC278 in the absence of EFV treatment
- These data provide useful information that are supportive to a clinical study evaluating HIV-1–positive subjects who are switched from EFV to TMC278

References

1. Cohen C, et al. Presented at the XVIIIth International AIDS Conference; Vienna, Austria; July 18–23, 2010. Abstract THLBB206.
2. Ward BA, et al. *J Pharmacol Exp Ther*. 2003;306(1):287-300.
3. Hariparsad N, et al. *J Clin Pharmacol*. 2004;44(11):1273-1281.
4. SUSTIVA® (efavirenz). Package insert. http://packageinserts.bms.com/pi/pi_sustiva.pdf. Accessed January 11, 2011.
5. Hertogs K, et al. *Antimicrob Agents Chemother*. 1998;42(2):269-276.
6. Pauwels R, et al. Presented at the 2nd International Workshop on HIV Drug Resistance and Treatment Strategies; Lake Maggiore, Italy; June 24–27, 1998. Abstract 51.
7. Crauwels HM, et al. Presented at the 10th International Congress on Drug Therapy in HIV Infection; Glasgow, UK; November 7–11, 2010. Poster P186.
8. Wilkin A, et al. Presented at the19th Annual Canadian Conference on HIV/AIDS Research (CAHR); Saskatoon, Canada; May 13–16, 2010. Abstract 7214.
9. Pozniak AL, et al. *AIDS*. 2010;24(1):55-65.

Acknowledgments

The authors would like to thank the subjects, Quintiles study site and D. Mathews (coordinating investigator) for their participation in the trial. The authors would additionally like to acknowledge internal study support staff, as well as Cali Howitt, PhD, Medicus International New York, for her editorial assistance. Funding for the study and for editorial support was provided by Tibotec Therapeutics, Janssen-Cilag and Janssen Inc. Canada.

Presented at the 18th Conference on Retroviruses and Opportunistic Infections (CROI), Boston, MA, USA, February 27–March 2, 2011. If you have any additional questions or would like a copy of this poster, call +1-877-REACH-TT (+1-877-732-2488) or go to www.ttmedicalinformation.com.