

between the 400 mg q.d. and the 800 mg q.d. group, while a less than dose proportional increase was observed between the 800 mg q.d. and 1600 mg q.d. group.

**APPEARS THIS WAY
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Study Number
TMC125-C168

Title

A Phase 1, open-label, randomized, multiple-dose, crossover trial in healthy subjects to evaluate the pharmacokinetics of TMC125 in a spray dry formulation administered once daily compared to twice daily.

Study Design

Open-label, randomized, 4-period crossover trial to determine the pharmacokinetics of TMC125 (F060), after once and twice daily dosing. The trial was divided into 2 sessions of 8 days each, with a washout period of at least 14 days between the two sessions. The subjects received 100 mg twice daily (b.i.d.) TMC125 for 7 days with an additional morning intake on day 8 (**treatment A**) and 200 mg TMC125 once daily (q.d.) for 8 days (**treatment B**) in a crossover fashion. TMC125 was administered with approximately 200 mL of water, within 10 minutes after completion of a standardized breakfast and within 10 minutes after completion of the evening meal (for b.i.d. dosing only).

In the twice daily dosing session, subjects received 100 mg TMC125 b.i.d. for 7 days with an additional morning intake on Day 8. A 12-hour PK profile was determined on day 1 and day 8. In the once daily dosing session, subjects received 200 mg TMC125 q.d. for 8 days. A 24-hour pharmacokinetic profile for TMC125 was determined on day 1 and day 8.

Fig 1 shows the mean plasma concentration-time profiles (on day 1) of TMC125 after administration as a tablet formulation F060 (TMC125 in HPMC, spray dried) at doses of 100 mg b.i.d. or 200 mg q.d. in healthy subjects.

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Fig 1: Mean plasma concentration-time profiles of TMC125 after administration as a tablet formulation F060 (TMC125 in HPMC, spray dried) at doses of 100 mg b.i.d. or 200 mg q.d. in healthy subjects (day 1).

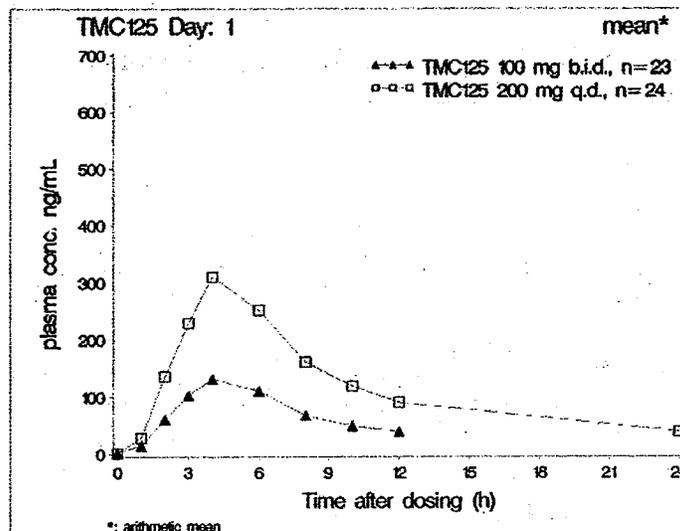


Fig 2 shows the mean plasma concentration-time profiles (on day 8) of TMC125 after administration as a tablet formulation F060 (TMC125 in HPMC, spray dried) at doses of 100 mg b.i.d. or 200 mg q.d. in healthy subjects.

Fig 2: Mean plasma concentration-time profiles of TMC125 after administration as a tablet formulation F060 (TMC125 in HPMC, spray dried) at doses of 100 mg b.i.d. or 200 mg q.d. in healthy subjects (day 8).

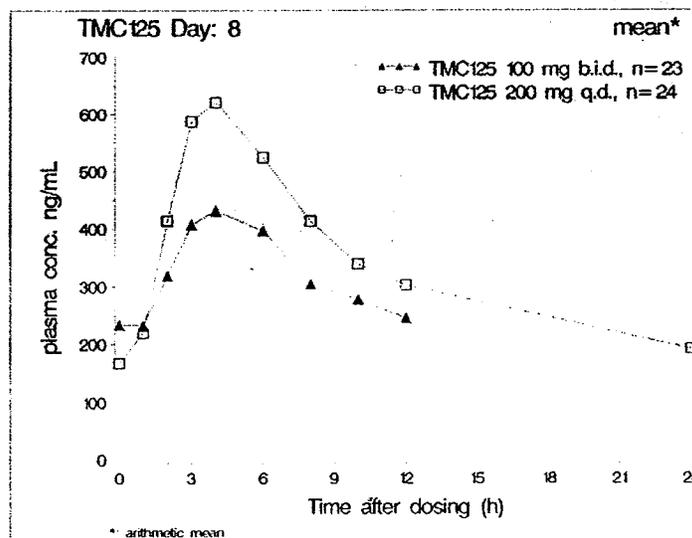


Table 1 shows the pharmacokinetic parameters of TMC125 (on day 1 and day 8) after administration as tablet formulation F060 (TMC125 in HPMC, spray dried) at doses of 100 mg b.i.d. or 200 mg q.d. in healthy subjects.

Table 1: Pharmacokinetic parameters of TMC125 (on day 1 and day 8) after administration as tablet formulation F060 (TMC125 in HPMC, spray dried) at doses of 100 mg b.i.d. or 200 mg q.d. in healthy subjects.

Parameter	Mean \pm SD; t_{max} : Median (Range)		Ratio * (Test:Reference)	90% CI
	100 mg b.i.d. (Reference)	200 mg q.d. (Test)		
Day 1				
N	23	24	-	-
t_{max} , h	4.0 (3.0 - 6.0)	4.0 (3.0 - 6.0)	-	-
C_{max} , ng/mL	143 \pm 55	326 \pm 121	2.31	2.04 - 2.62
AUC _{12h} , ng.h/mL	875 \pm 409	-	-	-
AUC _{24h} , ng.h/mL	1749 \pm 819	2797 \pm 1014	1.66	1.52 - 1.80
Day 8				
N	23	24	-	-
t_{max} , h	4.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	-	-
C_{0h} , ng/mL	234 \pm 92	167 \pm 77	-	-
C_{min} , ng/mL	215 \pm 86	163 \pm 76	0.74	0.69 - 0.80
C_{max} , ng/mL	471 \pm 141	659 \pm 177	1.42	1.34 - 1.51
$C_{ss,av}$, ng/mL	318 \pm 104	336 \pm 115	-	-
AUC _{12h} , ng.h/mL	3925 \pm 1251	-	-	-
AUC _{24h} , ng.h/mL	7628 \pm 2506	8054 \pm 2748	1.05	0.96 - 1.14
FI, %	84.9 \pm 33.6	156.0 \pm 38.5	-	-

N = maximum number of subjects with data.

* Ratio based on LS means.

Note: For 100 mg b.i.d., AUC_{24h} was calculated as 2 X AUC_{12h}.

The mean pre-dose plasma concentration-time profiles (based on pre-dose concentrations on days 6 through 8) suggested that steady state was reached after 7-8 days.

Pre-dose concentrations on Day 1 of Session II were above the LLOQ in 16 out of 24 subjects: Seven of the 11 subjects who received the 100 mg b.i.d. regimen in Session II showed measurable pre-dose concentrations of TMC125 (after dosing with 200 mg b.i.d. in session 1). In 3 of these subjects, pre-dose concentrations exceeded 5 % of the C_{max} reached after dosing (10.00 %, 6.38 %, and 7.91 %). Nine of the 12 subjects who received 200 mg q.d. in Session II had pre-dose plasma concentrations above the LLOQ (after dosing with 100 mg b.i.d. in session 1). All the pre-dose concentrations were less than 2 % of the C_{max} obtained in the same subject after a dose of 200 mg q.d.

Reviewer's Note:

Due to differences in the dosing regimen (b.i.d. vs. q.d.) in the two periods, the proportion of subjects showing pre-dose concentrations in period 2 after administration of 100 mg b.i.d. in period 1 is expected to be higher than the proportion of subjects showing pre-dose concentrations in period 2 after administration of 200 mg q.d. in period 1. However, the proportion of subjects showing a pre-dose concentration > 5 % of C_{max} is expected to be lower for subjects administered b.i.d. regimen in period 1 (since C_{max} in period 2 after a q.d regimen is expected to be higher than C_{max} in period 2 after a b.i.d. regimen). Therefore, although some subjects showed pre-dose concentrations > 5 % C_{max} in the trial, due to differences in dosing regimen used in the two periods, it cannot be fully concluded that these concentrations were indeed > 5 % of C_{max} . Further, due to

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the high intra-subject variability and long half life of the drug, these "pre-dose" concentrations are not expected to have an impact on the conclusions of the trial.

On day 1, the mean C_{max} and AUC_{24} of TMC125 were 131 % and 66 % higher, respectively, when TMC125 was administered as 200 mg q.d., compared to 100 mg b.i.d.

On day 8, the mean AUC_{24} of TMC125 was similar between the two dosing regimens, however, the mean C_{max} of TMC125 increased by 42 %, and the mean C_{min} of TMC125 decreased by 26 %, when TMC125 was administered once daily (q.d.). The 90 % confidence interval (CIs) of the LS_{means} ratios for both comparisons were outside the 80 % - 125 % range. The mean AUC values on day 8 were approximately 200-300 % higher on day 8 as compared to the estimates on day 1.

Conclusion

- The mean steady state TMC125 systemic exposure (AUC_{24h}) after administration of the tablet formulation (F060; TMC125 in HPMC, spray-dried) at a dose of 200 mg q.d. was comparable to the mean steady state TMC125 exposure after administration of 100 mg b.i.d. (F060; TMC125 in HPMC, spray-dried) in healthy subjects.
- After multiple-dose steady state administration, the mean C_{max} of TMC125 was 42 % higher, and the mean C_{min} was 26 % lower, with 200 mg once-daily dosing compared to 100 mg twice-daily dosing.

Reviewer's Note:

Based on the similarity in systemic exposures (AUC) between the q.d. and the b.i.d. regimens, a q.d. regimen could have been pursued by the sponsor in the phase III trials. However, due to safety and efficacy related concerns (because of higher C_{max} and lower C_{min}) associated with a q.d regimen, a b.i.d regimen was pursued.

DRUG-DRUG INTERACTIONS

Study Number	Description	Page #
TMC125-C117	Phase I, open-label trial to evaluate the effect of TMC125 on steady-state pharmacokinetics of fosamprenavir (fosAPV)/rtv plus NRTIs in HIV-1 infected, NNRTI experienced subjects.	136
TMC125-C120	Phase I, open-label, randomized, 3-way crossover trial in healthy subjects to investigate the effect of steady-state ranitidine and steady-state omeprazole on the pharmacokinetics of a single dose of TMC125.	141
TMC125-C122	Open label, 1-sequence trial in 2 parallel panels of 15 healthy male subjects to evaluate the potential pharmacokinetic interaction between TMC125 and lopinavir/ritonavir at steady-state.	147
TMC125-C123	Open-label, 1-sequence trial in 2 parallel panels of 15 healthy subjects to evaluate the potential pharmacokinetic interaction between TMC125 and saquinavir/ritonavir at steady state.	155
TMC125-C151	Phase I, open-label, randomized, 2-way crossover trial in two parallel groups of 16 healthy subjects each, to determine the pharmacokinetic interaction between TMC125 and atazanavir (ATV), with and without low dose ritonavir (RTV), at steady state.	168
TMC125-C156	Phase I, open-label, randomized 2-period crossover trial in 16 healthy subjects to determine the pharmacokinetic interaction between TMC125 and rifabutin at steady state.	181
TMC125-C157	Phase I, open-label trial to investigate the pharmacokinetic interaction between didanosine (ddI) and TMC125 at steady-state in healthy subjects.	189
TMC125-C158	Phase I, open-label, add on trial in subjects on stable methadone maintenance therapy to investigate the potential pharmacokinetic interaction between steady-state TMC125 and methadone.	196
TMC125-C159	Phase I, open-label trial to investigate the effect of TMC125 at steady state on sildenafil pharmacokinetics in healthy male subjects.	206
TMC125-C161	Phase I, open-label trial to investigate the pharmacokinetic interaction between tipranavir (TPV)/ritonavir (RTV) and TMC125 at steady-state in healthy subjects.	213
TMC125-C164	Phase I, open-label, randomized, 2-way crossover trial to investigate the pharmacokinetic interaction of steady-state TMC125 and atorvastatin in healthy subjects.	221
TMC125-C165	Phase I, open-label, randomized two-way crossover trial to investigate the pharmacokinetic interaction between paroxetine and TMC125 at steady-state in healthy subjects.	230
TMC125-C166	Phase I, open-label, 1-way interaction trial to investigate the effect of steady state TMC125 on the pharmacokinetic characteristics of ethinyl estradiol and norethindrone at steady-state in healthy women.	237
TMC125-C171	Phase I, randomized, open-label, crossover trial in healthy volunteers to investigate the effect of steady-state clarithromycin and its active metabolite 14-OH-clarithromycin on the pharmacokinetic characteristics of TMC125 at steady state and vice versa.	246
TMC125-C174	Phase I, open-label, 1-way, 2-period crossover trial in 14 subjects to assess the drug interaction potential of TMC125 with a drug "cocktail" representative for CYP1A2, CYP2C9, CYP2D6, CYP3A4, and CYP2C19 substrates.	256
TMC125-C176	Phase I, open-label trial to investigate the pharmacokinetic interaction between TMC114/ritonavir and TMC125 at steady-state in healthy subjects.	278
TMC125-C177	Phase I, open-label trial to investigate the pharmacokinetic interaction between tenofovir (TDF) and TMC125 at steady-state in healthy subjects.	290
TMC125-C179	An open label, 3-period, fixed sequences study to evaluate the 2-way interaction of MK-0518 and etravirine in healthy adult subjects.	298

Study Number
TMC125-C117

Title

Phase I, open-label trial to evaluate the effect of TMC125 on steady-state pharmacokinetics of fosamprenavir (fosAPV)/rtv plus NRTIs in HIV-1 infected, NNRTI experienced subjects.

Objectives

The primary objective of the present trial was to evaluate the effect of steady state co-administration of 800 mg TMC125 b.i.d. as formulation TF035 on the pharmacokinetics of amprenavir (APV; administered as FPV) and RTV at a dose of 700/100 mg b.i.d..

Study Design

Phase I, open label trial in HIV-1 infected subjects with documented NNRTI resistance. The subjects included in the trial had a HIV-1 plasma viral load < 50 copies/mL and were on antiretroviral therapy (ART) including fosAPV/rtv and at least 2 NRTIs with or without ENF. The subjects received 800 mg TMC125 b.i.d. as formulation TF035 for 13 days with a morning dose on day 14 in addition to their current ART through the treatment period without interruption. The doses of fosAPV and RTV were 700 mg b.i.d. and 100 mg b.i.d., respectively.

All the medications (NRTIs, FPV/rtv/TMC125) were taken at the same time. A 12-hour pharmacokinetic sampling was conducted on day -1 and day 14 for fosAPV/RTV and on day 14 for TMC125. At screening and on day -1, a pre-dose PK sample was drawn for APV and RTV concentrations. On day 1 and day 7, a pre-dose PK sample was drawn for fosAPV, RTV, and TMC125 concentrations.

To describe the potential effect of co-administration of fosAPV/rtv on the pharmacokinetics of TMC125, plasma concentrations of TMC125 obtained in this trial were compared with the historical data from trials conducted in HIV-1 infected subjects using comparable background medications and the same dose (800 mg b.i.d.) and formulation (TF035) of TMC125 (Trial TMC125-C223).

Investigational Product(s)

TMC125 was formulated as TF035; this formulation is tablet containing 200 mg TMC125 in HPMC lactose

The batch number used was D03168 (expiry date: July 2005).

Assay Methods

The plasma concentrations of TMC125, APV, and RTV were determined using a validated liquid chromatographic with tandem mass spectrometry (LC-MS/MS) method. The lower limit of quantification (LLOQ) was 2 ng/mL for TMC125, 50 ng/mL for APV, and 5 ng/mL for RTV.

Pharmacokinetic and Statistical Data Analysis

Pharmacokinetic Analysis

Pharmacokinetic and statistical analysis was performed using SAS System for Windows® version 8.2 (SAS Institute Inc., Cary, NC). A non-compartmental model with extravascular input was used for the pharmacokinetic analysis. Based on the individual plasma concentration-time data and using the scheduled sampling times, the standard pharmacokinetic parameters were calculated.

Statistical Analysis

The sponsor indicated that a total of 16 subjects was considered sufficient to allow for relevant conclusions. If subjects discontinued the trial before receiving their first dose of TMC125, additional subjects could be recruited to have 16 subjects receiving treatment. In more than 2 subjects were prematurely withdrawn from the trial after dosing for reasons other than drug tolerability/safety, additional subjects were to be recruited to aim for at least 14 evaluable subjects. An evaluable subject was a subject that completed the entire treatment period.

Due to slow recruitment and the difficulty to find subjects fulfilling the entry criteria despite participation of a second site, it was decided (by the sponsor) to prematurely end the trial. The results of the 8 subjects who were enrolled and treated in the trial were provided.

RESULTS

Subject Disposition and Demographics

Out of the 11 subjects screened, 8 subjects were enrolled and received trial medication. All 8 subjects completed the trial. Table 1 shows the demographic data collected during the trial.

Table 1: Demographic data collected during the trial

Demographic Parameter	All Subjects N = 8
Age, years Median (range)	42.00 (33.0-45.0)
Height, cm Median (range)	171.00 (165.0-186.0)
Weight, kg Median (range)	66.00 (54.0-110.0)
BMI, kg/m ² Median (range)	21.80 (18.6-40.4)
Gender, n (%)	
Male	7 (87.5)
Female	1 (12.5)
Ethnic Origin, n (%)	
Caucasian/White	5 (62.5)
Black	3 (37.5)
Type of Smoker, n (%)	
Nonsmoker	7 (87.5)
Light smoker	1 (12.5)

Pharmacokinetics

TMC125

Table 2 shows the pharmacokinetic parameters of TMC125 in the presence of steady state FPV/rtv.

Table 2: Pharmacokinetic parameters of TMC125

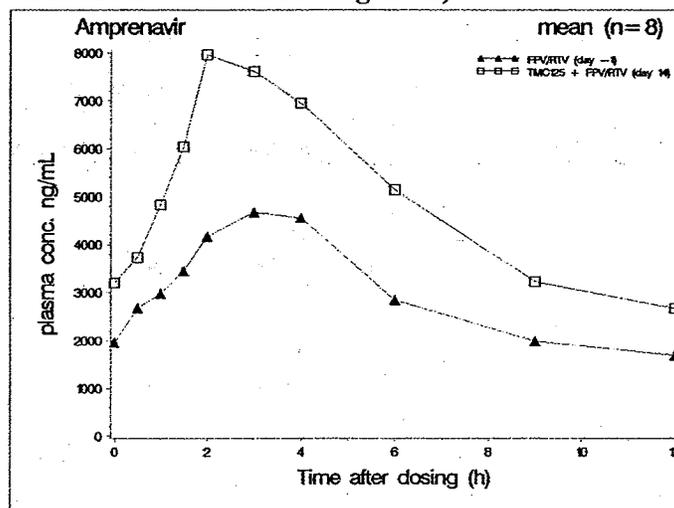
Pharmacokinetics of TMC125 mean±SD, t _{max} , median (range)	TMC125 + fosAPV/RTV Test
n	8
t _{max} , h	3.00 (3.00 - 6.00)
C _{0h} , ng/mL	495 ± 278
C _{min} , ng/mL	422 ± 227
C _{max} , ng/mL	1019 ± 723
AUC _{12h} , ng.h/mL	8633 ± 5408
C _{ss, av} , ng/mL	719 ± 451
FI, %	76.1 ± 22.5
t _{1/2α} , h	8.64 ± 2.34

The pharmacokinetic parameters of TMC125 estimated in this trial were compared with the pharmacokinetic parameters of TMC125 from trial TMC125-C223, a clinical trial in which HIV infected subjects receiving 800 mg TMC125 b.i.d. as formulation TF035 and at least 2 NRTIs with or without a PI (lopinavir/rtv) and with or without ENF. However, due to the low number of subjects (as compared to the subjects in the trials used for comparison purposes) who completed the current trial (TMC125-C117) and the variability in the pharmacokinetic parameter of TMC125, no reliable conclusions can be drawn regarding the effect of APV (administered as FPV/rtv) on the pharmacokinetics of TMC125.

APV (administered as FPV/rtv)

Fig 1 shows the mean steady state (day 14) plasma concentration-time profile of APV (administered as FPV/rtv 700/100 mg b.i.d.).

Fig 1: Mean steady state (day 14) plasma concentration-time profile of APV (administered as FPV/rtv 700/100 mg b.i.d.).



Note: FPV: fosAPV

The mean plasma concentrations of APV (administered as FPV/rtv) were higher in the presence of TMC125 as compared to the mean plasma concentrations of APV when administered alone (as FPV/rtv).

Table 3 shows the pharmacokinetic parameters of APV.

Table 3: Pharmacokinetic parameters of APV

Pharmacokinetics of APV mean \pm SD, t_{max} : median (range)	TMC125 + fosAPV/RTV Test	fosAPV/RTV Alone Reference
n	8	8
t_{max} , h	2.00 (1.50 - 4.00)	3.50 (0.50 - 4.00)
C_{0h} , ng/mL	3196 \pm 1242	1956 \pm 855
C_{min} , ng/mL	2595 \pm 1135	1538 \pm 700
C_{max} , ng/mL	8983 \pm 2369	5505 \pm 1152
AUC_{12h} , ng.h/mL	58645 \pm 17120	35270 \pm 11115
$C_{ss, av}$, ng/mL	4887 \pm 1427	2939 \pm 926
FI, %	134.5 \pm 32.5	145.1 \pm 41.9
$t_{1/2\alpha}$, h	5.91 \pm 1.60	6.03 \pm 1.79

All the mean pharmacokinetic parameters of APV (administered as FPV/rtv) were higher in the presence of TMC125 as compared to the pharmacokinetic parameters of APV when administered alone (as FPV/rtv).

Table 4 shows the results of the statistical analysis of the pharmacokinetic parameters of APV for TMC125 + APV (administered as fosAPV/rtv) and APV administered alone (fosAPV/rtv).

Table 4: Statistical analysis of the pharmacokinetic parameters of APV for TMC125 + APV (administered as fosAPV/rtv) and APV administered alone (fosAPV/rtv)

APV Parameter	n		LSmeans				p-value Treatm.
	Test/Ref.		TMC125 + fosAPV/RTV Test	fosAPV/RTV Alone Reference	Treatment Ratio, % and 90% CI Test/Reference		
C _{0h} , ng/mL	8	8	3020	1748	173	137 - 218	0.0029
C _{min} , ng/mL	8	8	2427	1375	177	139 - 225	0.0029
C _{max} , ng/mL	8	8	8740	5397	162	147 - 179	<.0001
AUC _{12h} , ng.h/mL	8	8	56709	33598	169	153 - 186	<.0001

The C_{0h}, C_{min}, C_{max}, and AUC_{12h} of APV (administered as FPV/rtv) in the presence of TMC125 were higher by 73 %, 77 %, 62 %, 69 % as compared to when APV was administered alone (as FPV/rtv).

Pharmacokinetic Results Summary

- Due to cross study comparison and low number of subjects, no reliable conclusions can be drawn regarding the effect of APV (administered as FPV/rtv) on the pharmacokinetics of TMC125.
- The C_{0h}, C_{min}, C_{max}, and AUC_{12h} of APV (administered as FPV/rtv) in the presence of TMC125 were higher by 73 %, 77 %, 62 %, 69 % as compared to when APV was administered alone (as FPV/rtv).

Conclusion

The following language is suggested for the clinical recommendation section:

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Study Number
TMC125-C120

Title

Phase I, open-label, randomized, 3-way crossover trial in healthy subjects to investigate the effect of steady-state ranitidine and steady-state omeprazole on the pharmacokinetics of a single dose of TMC125.

Objectives

The primary objectives of the trial were to determine the effect of steady state concentrations of ranitidine on the pharmacokinetics of a single dose of TMC125 and to determine the effect of steady state concentrations of omeprazole on the pharmacokinetics of a single dose of TMC125.

Study Design

Phase 1, open label, randomized, three way crossover trial in 18 healthy subjects. In 3 sessions, each subject randomly received one of the following three treatments:

Treatment A: A single dose of 100 mg TMC125 (formulation F060).

Treatment B: Ranitidine 150 mg b.i.d. for 11 days and a single dose of 100 mg TMC125 on day 8.

Treatment C: Omeprazole 40 mg q.d. for 11 days and a single dose of 100 mg TMC125 on day 8.

Ranitidine was administered one hour before breakfast or dinner, omeprazole was administered one hour before breakfast (to be ingested within 30 minutes), and TMC125 was administered within 10 minutes after completion of the breakfast (to be ingested within 30 minutes). The three treatment sessions were separated by a washout period of at least 14 days after TMC125 intake. In each session, a full pharmacokinetic profile of TMC125 was determined up to 96 hours post dose.

Reviewer's Note

The primary objective of the trial was to investigate the effect of an increase in the intragastric pH (decreasing acidity) on the pharmacokinetics of TMC125. Therefore, use of a single dose of TMC125 (instead of multiple doses of TMC125) and the design of the trial (1-way design in which the PK of ranitidine and omeprazole was not assessed) is acceptable for meeting the objectives of the study.

Investigational Product(s)

TMC125 was provided as a tablet containing 100 mg of TMC125 — spray-dried in combination with hydroxypropylmethylcellulose (HPMC) and microcrystalline cellulose, excipients and manufacturing aids (formulation F060). The batch # was 05A05 and the expiry date was July 2005.

Ranitidine (Zantac®) was provided as a 150 mg tablet. The batch number was 04I01-A and the expiry date was September 2009.

Omeprazole (Losec MUPS 40®) was provided as a controlled release tablet containing the equivalent of 40 mg omeprazole as omeprazole magnesium. The batch number was 03LI8EM3196 and the expiry date was December, 2006.

Assay Methods

The plasma concentrations of TMC125 was determined using a validated liquid chromatographic with tandem mass spectrometry (LC-MS/MS) method. The lower limit of quantification (LLOQ) was 2 ng/mL for TMC125.

Pharmacokinetic and Statistical Data Analysis

Pharmacokinetic Analysis

Pharmacokinetic and statistical analysis was performed using Winonlin Professional™ (version 4.1, Pharsight Corporation). A non-compartmental model with extravascular input was used for the pharmacokinetic analysis. Based on the individual plasma concentration-time data and using the scheduled sampling times, the standard pharmacokinetic parameters were calculated.

Statistical Analysis

The statistical analyses were performed for TMC125 in plasma using **treatment B** and **treatment C** as test treatment and **treatment A** as reference treatment. The primary pharmacokinetic parameters were C_{max} , AUC_{last} , and $AUC_{0-\infty}$ on the logarithmic scale. $AUC_{0-\infty}$ was rejected as the primary pharmacokinetic parameter for a treatment if more than half of the subjects did not have a reliable estimate for that treatment.

RESULTS

Subject Disposition and Demographics

Out of the 43 subjects screened, 19 subjects were randomized and received treatment. 16 subjects completed the trial and 3 subjects discontinued before trial completion. Of the three subjects who discontinued, subject 1200003 randomized to **sequence A-C-B** withdrew consent after the first session and was replaced by subject 1200037; subject

120035 (randomized to sequence B-A-C) and subject 1200037 (randomized to sequence A-C-B) were discontinued from the trial on day 8 (day of TMC125 intake) of their third session (omeprazole and ranitidine session, respectively) due to a dosing error; the subjects had to take omeprazole or ranitidine in the morning 1 hour before breakfast, and a single dose of TMC125 10 minutes after completion of breakfast, however both subjects took TMC125 tablets instead of omeprazole or ranitidine before breakfast and did not take ranitidine or omeprazole.

Table 1 shows the demographics in the trial.

Table 1: Demographics in Trial TMC125-C120

Parameter	Treatment sequence						All subjects N = 19
	A/B/C n = 3	B/C/A n = 3	C/A/B n = 3	C/B/A n = 3	B/A/C n = 3	A/C/B n = 4	
Age, years Median (range)	47.0 (42-51)	42.0 (36-52)	49.0 (49-52)	43.0 (36-51)	54.0 (51-54)	49.0 (27-54)	49.0 (27-54)
Height, cm Median (range)	169.0 (163-186)	171.0 (166-186)	171.0 (170-176)	170.0 (168-182)	173.0 (173-177)	181.5 (175-194)	173.0 (163-194)
Weight, cm Median (range)	74.0 (64-75)	76.0 (58-85)	80.0 (62-81)	84.0 (73-86)	88.0 (78-94)	88.5 (82-98)	81.0 (58-98)
BMI, kg/m ² Median (range)	24.1 (22-26)	22.0 (21-29)	26.1 (22-27)	25.9 (25-30)	29.4 (26-30)	26.4 (26-28)	26.0 (21-30)
Sex, n (%)							
Female	1 (33.3)	2 (66.7)	1 (33.3)	1 (33.3)	1 (33.3)	1 (25.0)	7 (36.8)
Male	2 (66.7)	1 (33.3)	2 (66.7)	2 (66.7)	2 (66.7)	3 (75.0)	12 (63.2)
Ethnic origin, n (%)							
Black	0	0	0	0	0	1 (25.0)	1 (5.3)
Caucasian	3 (100.0)	3 (100.0)	3 (100.0)	1 (33.3)	3 (100.0)	3 (75.0)	16 (84.2)
Hispanic	0	0	0	1 (33.3)	0	0	1 (5.3)
Caucasian x Black	0	0	0	1 (33.3)	0	0	1 (5.3)

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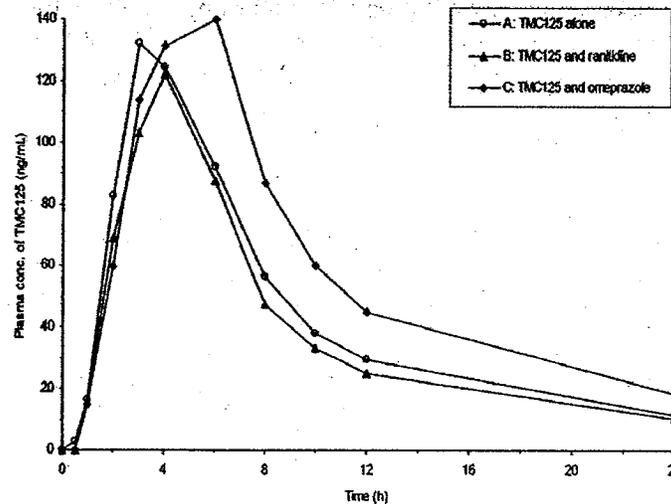
Pharmacokinetics

In addition to the discontinuations previously indicated, subject 1200029 (randomized to sequence C-B-A) took ranitidine 150 mg b.i.d. on day 1-day 4, and the morning intake on day 5. No further intakes of ranitidine were recorded, and TMC125 was not taken on day 8. After the washout, the subject completed session A. The two available plasma concentrations measured in treatment B were excluded from the descriptive statistics. Subject 1200018 did not take ranitidine 150 mg at home in the evening of day 1. Full pharmacokinetic profiles of TMC125 were available for 18 subjects for treatment A, 16 subjects for treatment B, and 17 subjects for treatment C.

TMC125

Fig 1 shows the mean plasma concentration-time profile of TMC125, with and without co-administration of ranitidine or omeprazole.

Fig 1: Mean plasma concentration-time profile of TMC125, with and without co-administration of ranitidine or omeprazole



The mean plasma concentration-time profiles of TMC125 were similar after administration of TMC125 alone or after co-administration of TMC125 and ranitidine. After co-administration of TMC125 with omeprazole, the plasma concentrations of TMC125 were increased in more than half the subjects. For all the treatments, more than 50 % of the individual estimates of $AUC_{0-\infty}$, λ_z , and $t_{1/2term}$ could not be determined accurately. Therefore, descriptive statistics related to these parameters could not be reported accurately.

Table 2 shows the mean pharmacokinetic parameters of TMC125 with and without co-administration of ranitidine and omeprazole.

Table 2: Mean pharmacokinetic parameters of TMC125 with and without co-administration of ranitidine and omeprazole

Pharmacokinetics of TMC125 mean \pm SD, t_{max} : median (range)	Treatment A: 100 mg TMC125 alone	Treatment B: 100 mg TMC125 + ranitidine	Treatment C: 100 mg TMC125 + omeprazole
N	18	16	17
t_{max} , h	3.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	4.0 (3.0 - 6.0)
C_{max} , ng/mL	146.2 \pm 69.01	140.9 \pm 77.66	165.0 \pm 50.82
AUC_{last} , ng.h/mL	1501 \pm 685.6	1257 \pm 653.2	2113 \pm 669.5
AUC_{∞} , ng.h/mL ^a	1768 \pm 861.3	1422 \pm 737.0	2505 \pm 845.5
$t_{1/2term}$, h ^a	46.01 \pm 20.25	34.65 \pm 12.79	44.62 \pm 9.554

^a accurate determination not possible

The individual ratios of C_{max} and AUC_{last} of TMC125, with and without co-administration of ranitidine, ranged from 37 % to 316 % and from 46.5 % to 130.1 % with geometric means of 96.7 % and 86 %, respectively. After co-administration with omeprazole, the mean values for all the pharmacokinetic parameters were increased. The individual ratios of C_{max} and AUC_{last} of TMC125, with and without co-administration of omeprazole

ranged from 56 % to 315 % and from 79 % to 242 % with geometric means of 116 % and 137 %, respectively.

Table 3 shows the statistical analysis of the pharmacokinetic parameters of TMC125, with and without co-administration of ranitidine.

Table 3: Statistical analysis of the pharmacokinetic parameters of TMC125, with and without co-administration of ranitidine

Parameter	Least square means		Least square means ratio, %	90% CI, % *	p-value		
	Treatment A, TMC125 alone (reference) N=18	Treatment B, TMC125 and ranitidine (test) N=16			Treatment	Period	Sequence
C _{max} , ng/mL	132.6	124.4	93.85	75.34 - 116.9	0.6153	0.0742	0.0373
AUC _{last} , ng.h/mL	1319	1133	85.92	75.92 - 97.25	0.0491	0.1089	0.0918

* 90% confidence intervals.

AUC_∞ excluded from statistics because accurate determination was not possible for more than half of the values

The LS_{means} ratio of C_{max} and AUC_{last} of TMC125 were decreased by 6 % and 14 % respectively, when TMC125 was co-administered with ranitidine as compared to when TMC125 was administered alone.

Table 4 shows the statistical analysis of the pharmacokinetic parameters of TMC125, with and without co-administration of omeprazole.

Table 4: Statistical analysis of the pharmacokinetic parameters of TMC125, with and without co-administration of omeprazole

Parameter	Least square means		Least square means ratio, %	90% CI, % *	p-value		
	Treatment A, TMC125 alone (reference) N=18	Treatment C, TMC125 and omeprazole (test) N=17			Treatment	Period	Sequence
C _{max} , ng/mL	132.6	154.9	116.8	95.77 - 142.5	0.1902	0.5114	0.3105
AUC _{last} , ng.h/mL	1319	1855	140.7	122.0 - 162.2	0.0009	0.3724	0.1558

* 90% confidence intervals.

AUC_∞ excluded for statistics because accurate determination was not possible for more than half of the values

The LS_{means} ratio of C_{max} and AUC_{last} of TMC125 were increased by 17 % and 41 % respectively, when TMC125 was co-administered with omeprazole as compared to when TMC125 was administered alone.

Reviewer's Note:

The results of the study showed that the mean systemic exposures of TMC125 increased by 41 % in the presence of omeprazole. However, there was no significant change in the systemic exposures of TMC125 in the presence of ranitidine. Although ranitidine (H₂ receptor antagonist) and omeprazole (Proton Pump Inhibitor) act by different mechanisms, the pharmacodynamic effect (increase in gastric pH) after steady state administration of omeprazole and ranitidine is expected to be the same (although the magnitude of effect on intragastric pH will be higher for proton pump inhibitors). Further, ranitidine and omeprazole were administered (to steady state) approximately 1.5 hours before administration of a single dose of TMC125, therefore, the pH is expected to be altered to highest degree (as compared to alteration in pH if ranitidine or omeprazole were co-administered with TMC125 or if TMC125 was administered after ranitidine and omeprazole) at the time of TMC125 administration. Therefore, based on the results from the TMC125-ranitidine component of the study, it can be concluded that increase in gastric pH is not expected to alter the systemic exposure of TMC125.

Omeprazole and TMC125 are substrates and inhibitors of CYP2C19. Therefore, the increase in the systemic exposure of TMC125 in the presence of omeprazole can be due to the inhibition of CYP2C19 by omeprazole. On the other hand, TMC125 may also increase the concentrations of omeprazole by inhibition of CYP2C19 and decrease the concentrations of omeprazole by induction of CYP3A4 (omeprazole has been shown to be a CYP3A4 substrate). The sponsor did not measure the plasma concentrations of omeprazole in the study, therefore, no firm conclusions regarding the effect of TMC125 on altering the pharmacokinetics of omeprazole can be drawn.

Pharmacokinetic Results Summary

- The LS_{means} ratio of C_{max} and AUC_{last} of TMC125 were decreased by 6 % and 14 % respectively, when TMC125 was co-administered with ranitidine as compared to when TMC125 was administered alone.
- The LS_{means} ratio of C_{max} and AUC_{last} of TMC125 were increased by 17 % and 41 % respectively, when TMC125 was co-administered with omeprazole as compared to when TMC125 was administered alone.

Conclusion

TMC125 can be co-administered with ranitidine or omeprazole without any dose adjustments.

Study Number
TMC125-C122

Title

Open label, 1-sequence trial in 2 parallel panels of 15 healthy male subjects to evaluate the potential pharmacokinetic interaction between TMC125 and lopinavir/ritonavir at steady-state.

Objectives

The primary objectives of the trial were to determine the effect of LPV/RTV on the steady state pharmacokinetics of TMC125 and the effect of TMC125 on the steady-state pharmacokinetics of LPV/RTV.

Study Design

This was an open label, 1-sequence trial in 2 parallel groups of 15 healthy male subjects. There were two panels (panel 1 and panel 2) in the study:

Panel 1:

All subjects received a single dose of 400/100 mg LPV/RTV in session 1. In session 2, after a washout period of at least 3 days, subjects received a 7-day treatment with TMC125 1600 mg b.i.d. (day 1 to day 7), followed by a 13-day combined treatment with 1600 mg TMC125 b.i.d. and 400/100 mg LPV/RTV b.i.d. (day 8 to day 20), and a single morning dose of 1600 mg TMC125 and 400/100 mg LPV/RTV on day 21. A 12-hour pharmacokinetic profile of TMC125 was obtained on day 7 of session 2 (to determine the PK of TMC125 in the absence of LPV/rtv) and day 21 of session 2 (to determine the PK of TMC125 in the presence of LPV/rtv) in panel 1. The pharmacokinetics of lopinavir and ritonavir were also determined on day 21 of session 2 to determine the PK of LPV/rtv in the presence of TMC125.

Panel 2:

All subjects received a single dose of 400/100 mg LPV/RTV in session 1. In session 2, subjects received a 13-day treatment with 400/100 mg LPV/RTV b.i.d., followed by a single morning dose of 400/100 mg b.i.d. on day 14. The pharmacokinetics of lopinavir and ritonavir were determined on day 14 of session 2 to determine the PK of LPV/rtv in the absence of TMC125.

The pharmacokinetics of LPV/rtv was determined on day 1 of session 1 in both panels to compare the PK of LPV/rtv between the two groups in order to validate the comparison of lopinavir and ritonavir pharmacokinetics between the two panels.

Reviewer's Comment Regarding the Dose of TMC125 Used in the Trial

The sponsor used 1600 mg b.i.d. TMC125 (as TF035) in this trial. This dose is higher than the dose used in other drug interaction trials using the same formulation (TF035) and results in higher systemic exposures as compared to the systemic exposures observed with 800 mg B.I.D. TF035 (dose that has been shown similar, in terms of systemic exposures, to TMC125 200 mg BID as F060). However, the use of higher dose of TMC125 in this trial is not expected to alter the conclusions of the study because of the following reasons:

- *LPV/rtv is a substrate and inhibitor of CYP3A4. Therefore, the magnitude of change in PK parameters of LPV/rtv in the presence of TMC125 (substrate and inducer of CYP3A) will be similar/higher than the magnitude of change in LPV/rtv PK parameters after administration of 800 mg TMC125 b.i.d. (as TF035).*
- *Due to the CYP3A inhibitory properties of LPV/rtv, the concentrations of TMC125 observed after co-administration of TMC125 (1600 mg b.i.d) with LPV/rtv are expected to be higher than the concentrations when TMC125 is administered alone. Therefore, irrespective of the dose of TMC125 (800 mg b.i.d. or 1600 mg b.i.d.) co-administered with Kaletra, the resulting concentrations will be acceptable (in terms of interpretation of the results of the drug-drug interaction study) since 800 mg b.i.d. (TF035) has been previously shown to be associated with acceptable efficacy.*

All morning doses in both the panels were taken at the testing facility after subjects consumed breakfast that was served at the testing facility. In both panels, the evening doses were taken at home after consumption of the evening meal except for the days when the subjects were admitted to the testing facility for PK and safety assessment; in these cases, the evening meal was provided at the testing facility. Subjects remained for at least 12 hours in the testing facility after the morning intake on day 7 and day 21 for panel 1 and after the morning intake on day 14 for panel 2.

Investigational Product(s)

TMC125 was supplied as 200 mg tablets (TF035) containing TMC125
HPMC _____ The batch number used was
D01177 (expiry date: June 30, 2004).

LPV/RTV was supplied as soft gelatin capsules containing 133.3 mg lopinavir and 33.3 mg ritonavir per capsule. The batch number used was 79445VA.

Assay Methods

The plasma concentrations of TMC125, LPV, and RTV were determined using a validated liquid chromatographic with tandem mass spectrometry (LC-MS/MS) method.

The lower limit of quantification (LLOQ) was 2 ng/mL for TMC125, 20 ng/mL for LPV, and 10 ng/mL for RTV.

Pharmacokinetic and Statistical Data Analysis

Pharmacokinetic Analysis

Pharmacokinetic analysis was performed using Winnonlin (Version 3.1, Pharsight Corporation) using a non-compartmental model with extravascular input, and SPLUS software. A common descriptive statistical and graphical analysis of the primary pharmacokinetic parameters of TMC125, lopinavir, and ritonavir was performed using Microsoft® Excel. Based on the individual plasma concentration-time data, and using the scheduled sampling time, the standard pharmacokinetic parameters were computed.

For **session II, panel 1**, TMC125 pre-dose plasma concentrations in the morning of days 5, 6, 7 and Days 17, 19 and 21 were compared graphically to verify the achievement of steady-state conditions for TMC125.

For **session II**, lopinavir and ritonavir pre-dose plasma concentrations in the morning of days 17, 19 and 21 for **panel 1** and days 10, 12 and 14 for **panel 2** were compared graphically to verify the achievement of steady-state conditions for lopinavir and ritonavir.

Statistical Analysis

Comparison of the pharmacokinetic parameters of TMC125 with and without concomitant LPV/RTV were performed using ANOVA with factors for subjects and treatment. The 90 % CI of the ratio of C_{min} , C_{max} and AUC_{12h} with (test) and without (reference) LPV/RTV treatment was calculated.

Comparison of the session 2 pharmacokinetic parameters of lopinavir and ritonavir with and without concomitant TMC125 treatment were performed between **panel 1** and **panel 2** using a 2-sided t-test and 95 % CI based on log-transformed data. The comparison of the session 1 pharmacokinetic parameters of lopinavir and ritonavir between **panel 1** and **panel 2** were assessed using the same methodology.

RESULTS

Subject Disposition and Demographics

Out of the 35 subjects screened, 30 subjects were assigned to treatment (15 subjects in each panel). 28 subjects completed the trial; 2 subjects in panel 1 discontinued before trial completion due to adverse events.

Table 1 shows the demographics in the trial.

Table 1: Demographics in Trial TMC125-C122

POPULATION: INTENT TO TREAT	N		95% C.I. <a>	S.E.	S.D.	MEDIAN	MIN	MAX
		MEAN						
AGE (years)								
PANEL 1	15	38.6	(33.36; 43.84)	2.44	9.46	40.0	23	55
PANEL 2	15	38.0	(32.90; 43.10)	2.38	9.20	41.0	23	54
OVERALL	30	38.3	(34.87; 41.73)	1.67	9.17	41.0	23	55
BMI (kg/m²)								
PANEL 1	15	25.8	(24.20; 27.34)	0.73	2.84	25.9	19	29
PANEL 2	15	25.1	(23.50; 26.65)	0.73	2.84	25.2	21	30
OVERALL	30	25.4	(24.37; 26.47)	0.51	2.81	25.7	19	30
HEIGHT (cm)								
PANEL 1	15	177.9	(174.54; 181.20)	1.55	6.01	177.0	169	190
PANEL 2	15	181.9	(176.96; 186.77)	2.29	8.85	182.0	166	199
OVERALL	30	179.9	(176.99; 182.75)	1.41	7.71	178.5	166	199
WEIGHT (kg)								
PANEL 1	15	81.7	(75.50; 87.84)	2.88	11.14	81.0	62	106
PANEL 2	15	83.5	(75.29; 91.65)	3.81	14.77	80.0	62	109
OVERALL	30	82.6	(77.75; 87.38)	2.35	12.89	81.0	62	109

Pharmacokinetics

All blood samples collected for determination of TMC125, lopinavir, and ritonavir were available for analysis. One subject in **panel 2** did not take the evening dose of LPV/RTV in the evening of **day 13** in **session 2**. This deviation was considered a major protocol deviation and the subject was excluded from the descriptive statistics in **session 2**. There was a major aberration for one subject on **day 14** of **session 2**; the 1 hour time point deviated 23 % from the scheduled time. Therefore, the actual sampling times were used for the calculation of the pharmacokinetic parameters for this subject on **day 14**. The pharmacokinetic parameters of two subjects who discontinued due to adverse events were excluded from the statistical analysis.

For **session 1**, comparison of lopinavir and ritonavir pharmacokinetics between both panels was performed using the pharmacokinetic parameters of 30 subjects. For **session 2**, the comparison of lopinavir and ritonavir pharmacokinetics was performed using the pharmacokinetic parameters of 13 subjects in **panel 1** and 14 subjects in **panel 2**.

TMC125

Fig 1 shows the mean plasma concentration-time profiles of TMC125 after oral administration of TMC125 1600 mg b.i.d. with and without LPV/RTV 400/100 mg b.i.d. (**panel 1, session 2**).

Fig 1: Mean plasma concentration-time profiles of TMC125 after oral administration of TMC125 1600 mg b.i.d. with and without LPV/RTV 400/100 mg b.i.d. (panel 1, session 2).

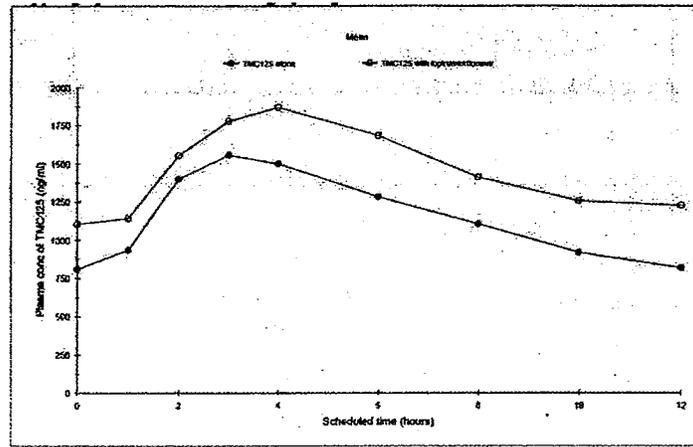


Table 2 shows the summary of the pharmacokinetic parameters of TMC125, with (day 21) or without (day 7) co-administration with LPV/RTV.

Table 2: Summary of the pharmacokinetic parameters of TMC125, with (day 21) or without (day 7) co-administration with LPV/RTV.

	Panel 1: TMC125 (Day 7)	Panel 1: TMC125 + LPV/RTV (Day 21)
n	13	13
t_{max} , h	3.0 (2.0 - 4.0)	4.0 (2.0 - 6.0)
C_{0h} , ng/ml	776 ± 362	1104 ± 791
C_{min} , ng/ml	744 ± 335	1062 ± 751
C_{max} , ng/ml	1543 ± 608	1927 ± 1041
AUC_{12h} , ng·h/ml	13456 ± 5235	17744 ± 10697

Values are mean ± SD, t_{max} , median (range)

The pre-dose concentrations on day 7 (data not shown) indicated that steady state was reached on day 7.

Table 3 shows the summary of the statistical analysis of the pharmacokinetic parameters of TMC125, with (day 21) or without (day 7) co-administration with LPV/RTV.

Table 3: Summary of the statistical analysis of the pharmacokinetic parameters of TMC125, with (day 21) or without (day 7) co-administration with LPV/RTV

Parameter	n	Geometric mean		Point Estimate, %	90% CI ⁽¹⁾	-p-value	
		Treatment (reference)	Treatment (test)			Treatment	Subject
		C_{min} , ng/ml	13				
C_{max} , ng/ml	13	1429	1640	115	93.7 - 141	0.2497	0.0021
AUC_{12h} , ng.h/ml	13	12491	14656	117	96.2 - 143	0.1760	0.0010

⁽¹⁾ 90% Confidence Intervals

Reference = TMC125 alone, test = TMC125 with LPV/RTV

The LS_{means} of C_{min} , C_{max} , and AUC_{12h} of TMC125 increased by 23 %, 15 %, and 17 % respectively, when TMC125 was co-administered with LPV/RTV.

LPV/RTV

Session 1

Table 4 shows the single dose pharmacokinetic parameters of LPV (administered as LPV/RTV) in panel 1 and panel 2 in session 1.

Table 4: Single dose pharmacokinetic parameters of LPV (administered as LPV/RTV) in panel 1 and panel 2 in session 1

	Panel 1 (Day 1)	Panel 2 (Day 1)
n	15*	15
t_{max} , h	6.0 (2.0 - 12.0)	6.0 (3.0 - 8.0)
C_{max} , ng/ml	6456 ± 2084	6345 ± 1218
AUC_{12h} , ng.h/ml	92073 ± 34515	80091 ± 26014
λ_z , 1/h	0.194 ^s ± 0.0462	0.172 ± 0.0214
$t_{1/2,term}$, h	3.77 ^s ± 0.988	4.10 ± 0.530
AUC_{∞} , ng.h/ml	98588 ^s ± 32957	81603 ± 25533

Values are mean ± SD, t_{max} : median (range)

* For parameters λ_z , $t_{1/2,term}$ and AUC_{∞} : n=11 in Panel 1

^s Accurate determination not possible

Table 5 shows the statistical analysis of the pharmacokinetic parameters of LPV (administered as LPV/RTV) in panel 1 and panel 2 in session 1.

Table 5: Statistical analysis of the pharmacokinetic parameters of LPV (administered as LPV/RTV) in panel 1 and panel 2 in session 1

Parameter	n		Geometric mean		P. Est., %	95% CI ⁽¹⁾	p-value Treatment
	single dose (panel 1)	single dose (panel 2)	single dose (panel 1)	single dose (panel 2)			
C _{max} , ng/ml	15	15	6109	6228	98	76 - 120	0.8576
AUC _{0-∞} , ng.h/ml	15	15	85474	76347	112	83 - 139	0.4127
AUC _{0-12h} , ng.h/ml	11	15	93838	78042	120	92 - 144	0.1554

⁽¹⁾ 95% confidence intervals

Session 2

Table 6 shows the pharmacokinetic parameters of LPV (administered as LPV/RTV) in panel 1 (day 21) and panel 2 (day 14).

Table 6: Pharmacokinetic parameters of LPV (administered as LPV/RTV) in panel 1 (day 21) and panel 2 (day 14)

	Panel 2: LPV/RTV (Day 14)	Panel 1: LPV/RTV + TMC125 (Day 21)
n	14	13
t _{max} , h	6.0 (2.0 - 6.0)	6.0 (2.0 - 8.0)
C _{0h} , ng/ml	4979 ± 3178	3525 ± 2097
C _{min} , ng/ml	3158 ± 2045	2656 ± 1620
C _{max} , ng/ml	8929 ± 2474	7539 ± 2193
AUC _{12h} , ng.h/ml	74858 ± 25776	60595 ± 22477

Values are mean ± SD. t_{max}: median (range)

Table 7 shows the statistical analysis of the pharmacokinetic parameters of LPV (administered as LPV/RTV) in panel 1 (day 21) and panel 2 (day 14).

Table 7: Statistical analysis of the pharmacokinetic parameters of LPV (administered as LPV/RTV) in panel 1 (day 21) and panel 2 (day 14).

Parameter	n		Geometric mean		P. Est., %	95% CI ⁽¹⁾	p-value Treatment
	with TMC125 (panel 1)	alone (panel 2)	with TMC125 (panel 1)	alone (panel 2)			
C _{min} , ng/ml	13	14	2067	2254	92	15 - 168	0.8182
C _{max} , ng/ml	13	14	7293	8605	85	62 - 105	0.1302
AUC _{12h} , ng.h/ml	13	14	56864	70848	80	49 - 107	0.1253

⁽¹⁾ 95% confidence intervals

After 14 days of co-administration of LPV/RTV with TMC125, the mean systemic exposure of LPV was 20 % lower as compared to the mean steady state exposures.

Pharmacokinetics Results Summary

- The similarity in C_{max} and AUC_∞ of lopinavir after a single dose in session 1 and session 2 suggests that it is valid to compare the pharmacokinetic parameters of lopinavir and ritonavir across the two panels.

- The LS_{means} of C_{min} , C_{max} and AUC_{12h} of TMC125 increased by 23 %, 15 %, and 17 % respectively, when TMC125 was co-administered with LPV/RTV as compared to when TMC125 was administered alone (1600 mg b.i.d.).
- The LS_{means} of C_{min} , C_{max} and AUC_{12h} of LPV (administered as LPV/rtv) decreased by 8 %, 15 %, and 20 %, when LPV/rtv was co-administered with TMC125, as compared to when LPV/rtv was administered alone.

Conclusion

The mean systemic exposure (AUC) of etravirine after co-administration of INTELENCE™ with lopinavir/ritonavir is anticipated to be about 85 % higher than the mean systemic exposure of etravirine in Phase 3 trials. The safety profiles at these increased etravirine exposures is unknown. Therefore, INTELENCE™ and lopinavir/ritonavir should be co-administered with caution.

**APPEARS THIS WAY
ON ORIGINAL**

Study Number
TMC125-C123

Title

Open-label, 1-sequence trial in 2 parallel panels of 15 healthy subjects to evaluate the potential pharmacokinetic interaction between TMC125 and saquinavir/ritonavir at steady state.

Objectives

The objectives of the present trial were to investigate the effect of steady state pharmacokinetics of TMC125 on the steady state pharmacokinetics of SQV/RTV and the effect of steady state pharmacokinetics of SQV/RTV on the steady state pharmacokinetics of TMC125.

Study Design

Open label, 1-sequence trial in 2 parallel panels; each panel consisted of 15 healthy volunteers. In **session 1**, both panels received a single dose of SQV/RTV 1000/100 mg. In **session 2** (starting at least 3 days after dosing in **session 1**), subjects in **panel 1** received 1600 mg TMC125 b.i.d. for 7 days, immediately followed by combined administration of 1600 mg TMC125 b.i.d. and 1000/100 mg SQV/RTV b.i.d. for 13 days (from **day 8** to **day 20**). An additional morning dose of 1600 mg TMC125 and 1000/100 mg SQV/RTV was administered on **day 21**. In **session 2**, the subjects in **panel 2** received 1000/100 mg SQV/RTV b.i.d. for 13 days, with an additional morning dose of 1000/100 mg SQV/RTV on **day 14**.

During **session 1**, subjects in **panel 1** and **panel 2** were administered a standardized breakfast on **day 1** and SQV/RTV was administered within 15 minutes after completion of breakfast. On **day 2**, the subjects returned to the testing facility for the 24 hour blood sample and safety assessment.

During **session 2**, for subjects in **panel 1**, a standardized breakfast was served on days 1, 3, 5, 6, 7, 8, 9, 11, 13, 15, 17, 19, and 21 at the testing facility. On **day 7** and **day 21**, the morning doses of TMC125, SQV, and RTV were administered within 15 minutes after completion of breakfast. On the other days, subjects were instructed to take the morning doses within 15 minutes after completion of breakfast and the evening doses were taken within 15 minutes after completion of the evening meal at home. The evening intake on **day 7** took place in the testing facility after a meal and after the 12 hour blood sample was collected.

During **session 2**, for subjects in **panel 2**, a standardized breakfast was served on days 1, 3, 4, 6, 8, 10, 12, and 14. On **day 14**, subjects fasted for at least 6 hours before entering the testing facility and SQV/RTV was administered within 15 minutes after completion of a standardized breakfast.

In **session 1**, intensive sampling was conducted on **day 1** and **day 2** (24 hr sample) in subjects in **panel 1** and **panel 2**. In **session 2**, intensive sampling was conducted on **day 7** and **day 21** in subjects in **panel 1** and on **day 14** in subjects in **panel 2**.

Investigational Product(s)

TMC125 was provided as a tablet containing 200 mg (formulation **TF035**) of **TMC125** hydroxypropylmethylcellulose (HPMC). The batch # was D01177 and the expiration date was October 2002.

Saquinavir was provided as soft gelatin capsules containing 200 mg **SQV** (Fortovase[®], Roche). The batch # was B1403 (01E22) and the expiry date was May 31, 2003.

Ritonavir was provided as a soft gelatin capsules containing 100 mg **RTV** (Norvir, Abbot Laboratories). The batch # (expiry date) for ritonavir used in **session 1** and **session 2** (**panel 1** and **panel 2**) was 84514VA 01J26 (October 2003) and 84553VA (Nov 1, 2003).

Assay Methods

The plasma concentrations of **TMC125**, **SQV**, and **RTV** were determined using a validated liquid chromatographic with tandem mass spectrometry (LC-MS/MS) method. The lower limit of quantification (LLOQ) was 2 ng/mL for **TMC125**, 1 ng/mL for **SQV**, and 10 ng/mL for **RTV**.

Pharmacokinetics and Statistical Data Analysis

Pharmacokinetic Analysis

Pharmacokinetic and statistical analysis was performed using Winonlin Professional[™] (version 3.3, Pharsight Corporation). A non-compartmental model with extravascular input was used for the pharmacokinetic analysis. Based on the individual plasma concentration-time data and using the scheduled sampling times, the standard pharmacokinetic parameters were calculated.

For **session 2**, **panel 1**, **TMC125** pre-dose plasma concentrations in the morning on days 5, 6, and 7 and days 17, 19, and 21 were compared graphically to verify the achievement of steady-state conditions for **TMC125**. For **session 2**, saquinavir and ritonavir pre-dose plasma concentrations in the morning of days 17, 19, and 21 for **panel 1** and days 10, 12, and 14 for **panel 2** were compared graphically to verify the achievement of steady state for saquinavir and ritonavir.

Statistical Analysis

The comparison of the pharmacokinetic parameters of TMC125 with and without concomitant ritonavir and saquinavir was performed using ANOVA with factors for subjects and treatment. The 90 % confidence intervals of the ratio of C_{min} , C_{max} , and AUC_{12h} with (test) and without (reference) were calculated. The population geometric means based on log-transformed data were used, using the ratio of means of test over reference.

The comparison of the session 2 pharmacokinetic parameters of saquinavir and ritonavir, with and without concomitant TMC125 was performed between **panel 1** and **panel 2** using a *t*-test and matching 95 % confidence intervals or other appropriate statistical tests. The comparison of the **session 1** pharmacokinetic parameters of saquinavir and ritonavir between **panel 1** and **panel 2** was assessed using the same methodology.

RESULTS

Subject Disposition and Demographics

Out of the 39 subjects screened, 30 subjects were randomized to the 2 **panels** and started treatment.

Out of the 15 subjects randomized to **panel 1**, 14 subjects completed all assessments. 1 subject discontinued on **day 17** after the morning dose (**day 14** of **session 2**) due to an adverse event (increase in transaminase). All subjects randomized to **panel 2** completed all assessments.

Table 1 shows the demographics of the trial.

Table 1: Demographics in Trial TMC125-C123

Parameter	Panel 1 N=15	Panel 2 N=15	All subjects N=30
Age: median (min-max), years	34 (19-44)	36 (22-48)	36 (19-48)
Height: median (min-max), cm	176 (162-194)	178 (162-191)	177.5 (162-194)
Weight: median (min-max), kg	80 (66-103)	74 (62-91)	78 (62-103)
BMI: median (min-max), kg/m ²	25.8 (22-30)	24.8 (19-31)	24.9 (19-31)
Gender: male (n)/female (n)	14/1	14/1	28/2

Pharmacokinetics

TMC125

One subject in **panel 1** discontinued intake of medication on **day 15** of **session 2**. A plasma sample to determine TMC125, SQV, and RTV was taken after **day 14**, however

the day and time of sampling was not recorded. Therefore, the plasma concentrations of this subject were not included in the descriptive analysis and this subject was excluded from the statistical analysis.

One subject in panel 2 reported vomiting 30 minutes after drug intake on day 11 of session 2, resulting in unusual low morning pre-dose concentration on day 12 for both SQV and RTV. These pre-dose plasma concentrations were excluded from the descriptive statistics on day 12. The plasma concentrations from day 14 onwards were within the range of other subjects.

Fig 1 shows the mean steady state plasma concentration-time curves of TMC125 administered alone (day 1-7) and with SQV/RTV (day 8-day 21)

Fig 1: Mean steady state plasma concentration-time curves of TMC125 administered alone (day 1-7) and with SQV/RTV (day 8-day 21)

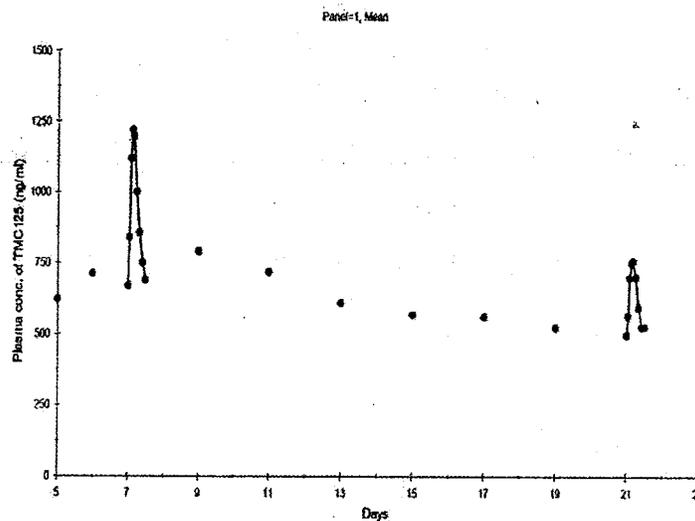


Table 2 shows the pharmacokinetic parameters of TMC125 b.i.d. on day 7 (TMC125 1600 mg b.i.d. alone) and day 21 (TMC125 1600 mg b.i.d. with SQV/RTV 1000/100 mg b.i.d.)

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Table 2: Pharmacokinetic parameters of TMC125 b.i.d. on day 7 (TMC125 1600 mg b.i.d.alone) and day 21 (TMC125 1600 mg b.i.d. with SQV/RTV 1000/100 mg b.i.d.)

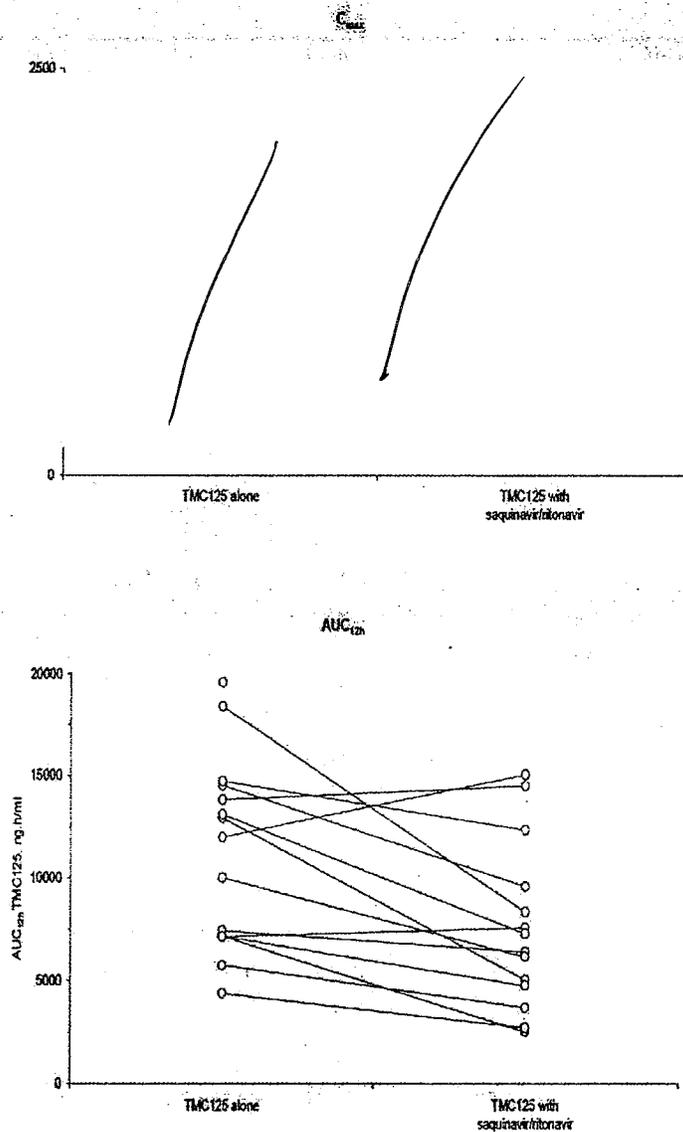
Pharmacokinetics of TMC125 (mean \pm SD, t_{max} : median (range))	Panel 1: TMC125 alone (day 7)	Panel 1: TMC125 with SQV/RTV (day 21)
n	15	14
t_{max} , h	3.0 (2.0 - 6.0)	3.5 (2.0 - 6.0)
C_{0h} , ng/ml	668 \pm 293	496 \pm 333
C_{min} , ng/ml	630 \pm 271	469 \pm 301
C_{max} , ng/ml	1291 \pm 523	809 \pm 392
AUC_{12h} , ng.h/ml	11199 \pm 4637	7555 \pm 4052

The mean estimates of C_{max} , C_{min} , and AUC_{12h} were lower when TMC125 was co-administered with SQV/RTV (day 21) as compared to when TMC125 was administered alone (day 7). The inter-individual variability in C_{0hr} , C_{min} , C_{max} , and AUC_{12h} of TMC125 was between 41 % to 44 % when TMC125 was administered alone and 48 % to 67 % when TMC125 was administered with SQV/RTV. The mean pre-dose plasma concentrations of TMC125 on day 5 (620 \pm 319 ng/mL), day 6 (712 \pm 326 ng/mL), and day 7 (668 \pm 293 ng/mL) were similar, suggesting that steady state was reached on day 7. The mean pre-dose concentrations of TMC125 on day 17 (560 \pm 317 ng/mL), day 19 (522 \pm 322 ng/mL), and day 21 (496 \pm 333 ng/mL) were similar, suggesting that steady state was reached on day 21.

Fig 2 shows the PK parameter plots of TMC125 in the absence (panel 1, session 2, day 7) or presence (panel 1, session 2, day 21) of SQV/RTV

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Fig 2: PK parameter plots of TMC125 in the absence (panel 1, session 2, day 7) or presence (panel 1, session 2, day 21) of SQV/RTV



The comparison of the individual steady state pharmacokinetic parameters (C_{max} and AUC_{12h}) of TMC125 suggest that for most of the subjects, the steady state C_{max} and AUC_{12hr} of TMC125 in the presence of SQV/RTV was lower than the steady state C_{max} and AUC_{12hr} of TMC125 in the absence of SQV/RTV.

Table 3 shows the statistical evaluation of the pharmacokinetic parameters of TMC125, with or without co-administration of SQV/RTV.

Table 3: Statistical evaluation of the pharmacokinetic parameters of TMC125, with or without co-administration of SQV/RTV

Parameter	n	Least square means		Least square means ratio, %	90% CI ⁽¹⁾	p-value
		TMC125 alone (day 7, reference)	TMC125 with saquinavir/ritonavir (day 21, test)			
C_{min} , ng/ml	14	543.7	387.4	71.26	58.2-87.2	0.0109
C_{max} , ng/ml	14	1137	713.4	62.77	52.7-74.8	0.0004
AUC_{12h} , ng.h/ml	14	9793	6560	66.99	56.1-80.0	0.0016

⁽¹⁾ 90% confidence intervals

The LS_{means} ratios of C_{min} , C_{max} , and AUC_{12h} of TMC125 were decreased by 29 %, 37 %, and 33 % respectively, when TMC125 was co-administered with SQV/RTV (day 21) as compared to when TMC125 was administered alone (day 7).

Reviewer's Note Regarding Decrease in the Systemic Exposure of TMC125

The results of trial TMC125-C141 showed similar systemic exposures after single dose administration of 200 mg TMC125 as formulation F060 and single dose administration of 1600 mg TMC125 as formulation TF035. The same trial did not evaluate the steady state pharmacokinetics of TMC125 200 mg b.i.d (F060) and TMC125 1600 mg b.i.d. TF035, however, based on the comparison of the systemic exposures from TMC125 100 mg b.i.d. (F060) and TMC125 800 mg b.i.d. (TF035) in HIV infected subjects (TMC125-C228; the systemic exposures after administration of TMC125 100 mg b.i.d (F060) were lower than the systemic exposures after administration of TMC125 800 mg b.i.d. (TF035)), the systemic exposures of TMC125 after administration of TMC125 200 mg b.i.d. (F060) are expected to be lower than the systemic exposures of TMC125 after administration of TMC125 1600 mg b.i.d. (TF035). Consequently, the systemic exposures of TMC125 after co-administration of SQV/RTV and TMC125 (200 mg b.i.d as F060) are expected to be lower than the systemic exposures of TMC125 observed after co-administration of SQV/RTV and TMC125 1600 mg b.i.d. (TF035) in the current trial (TMC125-C123) (assuming similar magnitude of interaction).

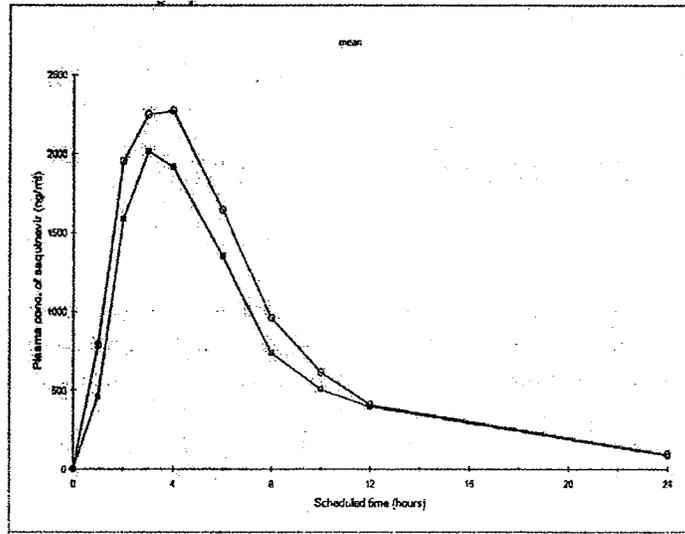
The magnitude of decrease of systemic exposures of TMC125 after co-administration of TMC125 (200 mg b.i.d., F060) and darunavir/ritonavir (TMC125-C176) is similar to the magnitude of decrease in the systemic exposures of TMC125 after co-administration of TMC125 and SQV/RTV in the current trial (TMC125-C123). Since all the HIV infected subjects in the pivotal clinical trials (DUET 1 and DUET 2) received darunavir/rtv and the exposures of TMC125 were demonstrated to be efficacious, the decrease in the systemic exposures of TMC125 in the presence of SQV/RTV as shown in the current trial (TMC125-C123) is not expected to be clinically relevant.

SQV

Session 1

Fig 3 shows the mean plasma concentration time profiles of saquinavir (administered as saquinavir/rtv) in panel 1 and panel 2.

Fig 3: Mean plasma concentration time profiles of saquinavir (administered as saquinavir/rtv) in panel 1 (○) and panel 2 (□).



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Table 4 shows the pharmacokinetic parameters of a single dose of saquinavir on day 1 in panel 1 and panel 2.

Table 4: Pharmacokinetic parameters of a single dose of saquinavir on day 1 in panel 1 and panel 2

Pharmacokinetics of saquinavir (Session I) (mean ± SD, t _{max} , median (range))	Panel 1: SQV/RTV (day 1)	Panel 2: SQV/RTV (day 1)
n	15*	15*
t _{max} , h	3.0 (1.0 - 6.0)	3.0 (2.0 - 6.0)
C _{max} , ng/ml	2687 ± 2784	2382 ± 2852
AUC _{last} , ng.h/ml	18233 ± 19676	15383 ± 21869
AUC _∞ , ng.h/ml	18992 ± 20584	16069 ± 23201
t _{1/2term} , h	6.30 ± 1.77	5.78 ± 1.05

* Both t_{1/2term} and AUC_∞ could not be accurately determined in 4 out of 15 subjects in Panel 1 and 2 out of 15 subjects in Panel 2.

Table 5 shows the statistical evaluation of the pharmacokinetic parameters of a single dose of saquinavir on day 1 in panel 1 and panel 2.

Table 5: Statistical evaluation of the pharmacokinetic parameters of a single dose of saquinavir on day 1 in panel 1 and panel 2

Parameter	n		Least square means		Least square means ratio, %	90% CI ⁽¹⁾	p-value
	Panel 1	Panel 2	Panel 1 (test)	Panel 2 (reference)			
C _{max} , ng/ml	15	15	1409	1437	98.09	46.2 - 208	0.9655
AUC _{last} , ng.h/ml	15	15	8685	8037	108.1	47.2 - 248	0.8745
AUC _{0-∞} , ng.h/ml	15	15	9099	8355	108.9	47.8 - 248	0.8614
t _{1/2elim} , h	15	15	6.080	5.691	106.8	92.3 - 124	0.4482

⁽¹⁾ 90% confidence intervals

The statistical analysis showed that the pharmacokinetic parameters of saquinavir were not statistically significantly different (all changes were < 10 % except C_{max} which was 12 % lower in panel 1) between panel 1 and panel 2. Therefore, a parallel design, as used in the study, is appropriate for comparing the pharmacokinetic parameters of SQV and RTV between the two panels.

Session 2

Fig 4 shows the mean plasma concentration time profiles of saquinavir, co-administered with ritonavir, with and without co-administration of TMC125.

Fig 4: Mean plasma concentration time profiles of saquinavir, co-administered with ritonavir, with and without co-administration of TMC125

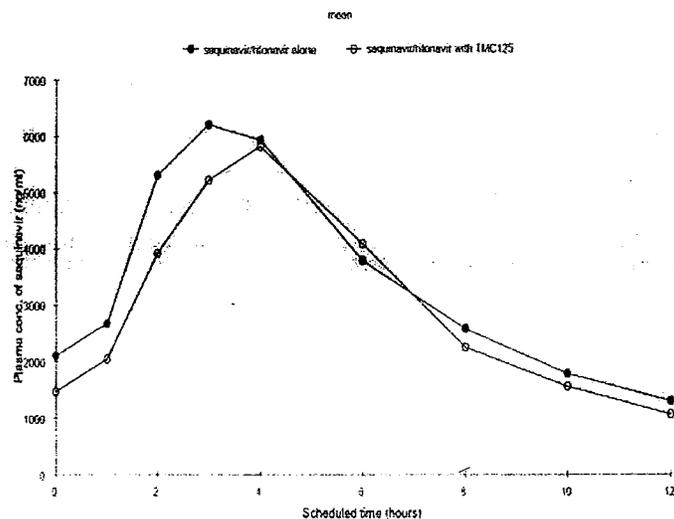


Table 6 shows the pharmacokinetic parameters of saquinavir, co-administered with ritonavir, with and without TMC125.

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Table 6: Pharmacokinetic parameters of saquinavir, co-administered with ritonavir, with and without TMC125

Pharmacokinetics of saquinavir (Session II) (mean \pm SD, t_{max} : median (range))	Panel 1: SQV/RTV with TMC125 (day 21)	Panel 2: SQV/RTV alone (day 14)
n	14	15
t_{max} , h	3.0 (2.0 - 6.0)	3.0 (2.0 - 4.0)
C_{0hr} , ng/ml	1471 \pm 1216	2106 \pm 1596
C_{min} , ng/ml	963 \pm 720	1282 \pm 1137
C_{max} , ng/ml	6212 \pm 3244	6503 \pm 3936
AUC _{12h} , ng.h/ml	37536 \pm 19103	41794 \pm 27785

Table 7 shows the statistical evaluation of the pharmacokinetic parameters of saquinavir, co-administered with ritonavir, with and without TMC125.

Table 7: Statistical evaluation of the pharmacokinetic parameters of saquinavir, co-administered with ritonavir, with and without TMC125

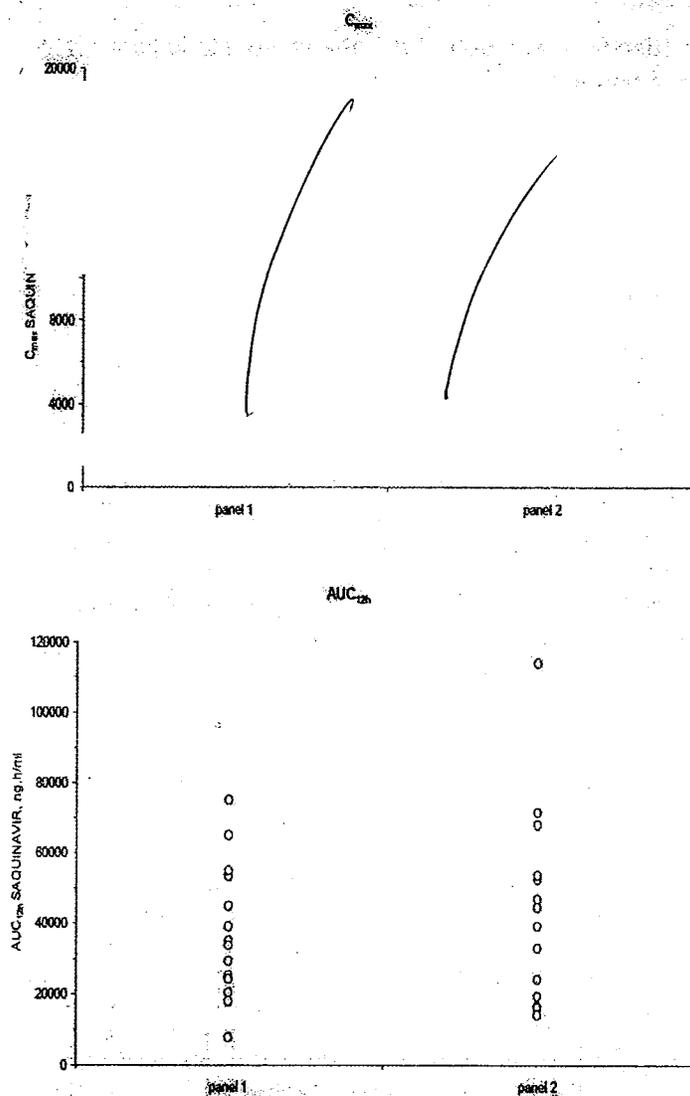
Parameter	n		Least square means		Least square means ratio, %	90% CI ⁽¹⁾	p-value
	Panel 1 Day 21	Panel 2 Day 14	SQV/RTV with TMC125 (day 21, test)	SQV/RTV alone (day 14, reference)			
C_{0hr} , ng/ml	14	15	1050	1562	67.21	38.5 - 117	0.2340
C_{min} , ng/ml	14	15	726.4	908.4	79.96	46.4 - 138	0.4895
C_{max} , ng/ml	14	15	5492	5517	99.55	69.6 - 142	0.9829
AUC _{12h} , ng.h/ml	14	15	32528	34185	95.15	63.7 - 142	0.8343

⁽¹⁾ 90% confidence intervals

The LS_{means} ratios of C_{max} and AUC_{12h} of SQV were not significantly altered when SQV/RTV was co-administered with TMC125 as compared to when SQV/RTV was administered alone. The C_{0hr} and C_{min} of SQV were decreased by 33 % and 20 % when SQV/RTV was co-administered with TMC125 as compared to when SQV/RTV was administered alone. However, due to the high inter individual variability in C_{0hr} and C_{min} (83 % and 75 %, respectively) of SQV in the presence of TMC125, no definitive conclusions can be drawn regarding the effect of TMC125 on the steady state C_{0hr} and C_{min} of SQV (administered as SQV/RTV).

Fig 5 shows the PK parameter plots of saquinavir in the absence (panel 1, session 2) or presence (panel 2, session 2) of TMC125.

Fig 5: PK parameter plots of saquinavir in the absence (panel 1, session 2) or presence (panel 2, session 2) of TMC125



The comparison of the individual steady state pharmacokinetic parameters (C_{max} and AUC_{12h}) of SQV (administered as SQV/RTV) suggest that the steady state C_{max} and AUC_{12hr} of SQV (administered as SQV/RTV) in the presence of TMC125 was in the same range as the steady state C_{max} and AUC_{12hr} of SQV (administered as SQV/RTV) in the absence of TMC125.

RTV

Session 1

Table 8 shows the statistical evaluation of the pharmacokinetic parameters of RTV in session 1, panel 1 and panel 2.

Table 8: Statistical evaluation of the pharmacokinetic parameters of RTV in session 1, panel 1 and panel 2.

Parameter	N		Least square means		Least square means ratio, %	90% CI ⁽¹⁾	p-value
	Panel 1	Panel 2	Panel 1 (test)	Panel 2 (reference)			
C _{max} , ng/ml	15	15	488.5	469.2	104.1	74.6 - 145	0.8388
AUC _{last} , ng.h/ml	15	15	3801	4348	87.43	63.2 - 121	0.4870
AUC _∞ , ng.h/ml	15	14	4033	5019	80.35	59.2 - 109	0.2325
t _{1/2term} , h	15	14	4.029	4.650	86.65	73.8 - 102	0.1409

⁽¹⁾ 90% confidence intervals

The statistical analysis of the pharmacokinetic parameters of RTV showed no statistically significant differences between panel 1 and panel 2.

Session 2

Table 9 shows the statistical evaluation of the pharmacokinetic parameters of RTV, co-administered with SQV, with and without TMC125.

Table 9: Statistical evaluation of the pharmacokinetic parameters of RTV, co-administered with SQV, with and without TMC125

Parameter	n		Least square means		Least square means ratio, %	90% CI ⁽¹⁾	p-value
	Panel 1 Day 21	Panel 2 Day 14	saquinavir/ritonavir with TMC125 (day 21, test)	saquinavir/ritonavir alone (day 14, reference)			
C _{0hr} , ng/ml	14	15	232.3	571.8	40.62	26.3 - 62.7	0.0015
C _{min} , ng/ml	14	15	144.4	289.7	49.86	33.9 - 73.3	0.0047
C _{max} , ng/ml	14	15	1092	1271	85.89	66.0 - 112	0.3346
AUC _{12h} , ng.h/ml	14	15	6499	8895	73.06	56.3 - 94.8	0.0495

⁽¹⁾ 90% confidence intervals

The LS_{means} ratios of C_{0hr}, C_{min}, C_{max}, and AUC_{12h} of RTV were decreased by 59 %, 50 %, 14 %, and 27 % when SQV/RTV was co-administered with TMC125 as compared to when SQV/RTV was administered alone.

Pharmacokinetic Results Summary

- The LS_{means} estimates of C_{min} , C_{max} , and $AUC_{12\text{h}}$ of TMC125 were decreased by 29 %, 37 %, and 33 % respectively, when TMC125 was co-administered with SQV/RTV (day 21) as compared to when TMC125 was administered alone (day 7). The decrease in the PK parameters of TMC125 in the presence of SQV/RTV is not clinically relevant since the magnitude of decrease is similar to the magnitude of decrease in the PK parameters of TMC125 in the presence of darunavir/ritonavir for which efficacy and safety data is available from the pivotal phase III trials.
- The LS_{means} estimates of C_{max} and $AUC_{12\text{h}}$ of SQV were not significantly altered when SQV/RTV was co-administered with TMC125 as compared to when SQV/RTV was administered alone.
 - The $C_{0\text{hr}}$ and C_{min} of SQV were decreased by 33 % and 20 % when SQV/RTV was co-administered with TMC125 as compared to when SQV/RTV was administered alone. However, due to the high inter individual variability in $C_{0\text{hr}}$ and C_{min} (83 % and 75 %, respectively) of SQV in the presence of TMC125, no definitive conclusions can be drawn regarding the effect of TMC125 on the steady state $C_{0\text{hr}}$ and C_{min} of SQV (administered as SQV/RTV).

Conclusion

The mean systemic exposure (AUC) of etravirine was reduced by about 33% when INTELENCE™ was co-administered with saquinavir/ritonavir. Because the reduction in the mean systemic exposures of etravirine in the presence of saquinavir/ritonavir is similar to the reduction in mean systemic exposures of etravirine in the presence of darunavir/ritonavir, INTELENCE™ and saquinavir/ritonavir can be co-administered without any dose adjustments.

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Study Number
TMC125-C151

Title

Phase I, open-label, randomized, 2-way crossover trial in two parallel groups of 16 healthy subjects each, to determine the pharmacokinetic interaction between TMC125 and atazanavir (ATV), with and without low dose ritonavir (RTV), at steady state.

Objectives

The objectives of this trial were to evaluate the effect of steady-state ATV, administered with and without RTV, on the steady-state pharmacokinetics of TMC125 and to evaluate the effect of steady-state TMC125 on the steady state pharmacokinetics of ATV, administered with and without RTV.

Study Design

This was a Phase I, open label, randomized, two-way crossover trial in two parallel groups, each consisting of 16 healthy subjects. The trial was divided into 2 sessions during which the following treatments (all treatments administered under fed conditions) were administered:

Treatment A: 400 mg ATV q.d. for 7 days

Treatment B: 800 mg TMC125 b.i.d. for 14 days with co-administration of 400 mg ATV q.d. from day 8 to day 14

Treatment C: 300 mg ATV/100 mg RTV q.d. for 7 days

Treatment D: 800 mg TMC125 b.i.d. for 14 days with co-administration of 300 mg ATV/100 mg RTV q.d. from day 8 to day 14

Treatment A and **treatment B** was administered to group 1 and **treatment C** and **treatment D** was administered to group 2. Within a group, the treatments were administered in a randomized manner with a washout period of at least 14 days between session 1 and session 2. The subjects remained in the clinical unit during the treatment periods.

For group 1, full pharmacokinetic profiles were determined for ATV on day 7 of treatment A and on day 14 of treatment B. The full pharmacokinetic profiles for TMC125 were determined on day 7 and day 14 for treatment B.

For group 2, full pharmacokinetic profiles were determined for ATV and RTV on day 7 of treatment C and day 14 of treatment D. The full pharmacokinetic profile for TMC125 was determined on day 7 and day 14 of treatment D.

Investigational Product(s)

Table 1 shows the dosage and treatment overview. TMC125, formulation TF035 (batch # D03108, expiry date Feb 2005), was used in the study.

Table 1: Dosages and Treatment Overview

Group	Treatment	Number of subjects	Dose	Volume
1	A	16	ATV: 400 mg q.d. on Days 1-7	2 capsules of ATV (Reyataz TM) per intake (ATV eq. 200 mg/capsule)
1	B	16	TMC125: 800 mg b.i.d. on Days 1-14 ATV: 400 mg q.d. on Days 8-14	4 tablets of TMC125 per intake (TMC125 eq. 200 mg/tablet) 2 capsules of ATV (Reyataz TM) per intake (ATV eq. 200 mg/capsule)
2	C	16	ATV: 300 mg q.d. on Days 1-7 RTV: 100 mg q.d. on Days 1-7	2 capsules of ATV (Reyataz TM) per intake (ATV eq. 150 mg/capsule) 1 capsule of RTV (Norvir [®]) per intake (RTV eq. 100 mg/capsule)
2	D	16	TMC125: 800 mg b.i.d. on Days 1-14 ATV: 300 mg q.d. on Days 8-14 RTV: 100 mg q.d. on Days 8-14	4 tablets of TMC125 per intake (TMC125 eq. 200 mg/tablet) 2 capsules of ATV (Reyataz TM) per intake (ATV eq. 150 mg/capsule) 1 capsule of RTV (Norvir [®]) per intake (RTV eq. 100 mg/capsule)

q.d. = once daily; eq. = equivalent to; b.i.d. = twice daily; RTV = ritonavir.

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Assay Methods

The plasma concentrations of TMC125, ATV, and RTV were determined using a validated liquid chromatographic with tandem mass spectrometry (LC-MS/MS) method. The lower limit of quantification (LLOQ) was 2 ng/mL for TMC125, 1 ng/mL for ATV, and 5 ng/mL for RTV.

Pharmacokinetic and Statistical Data Analysis

Pharmacokinetic Analysis

Pharmacokinetic and statistical analysis was performed using Winnonlin ProfessionalTM (version 4.1; Pharsight Corporation, Mountain View, California), and Microsoft Excel (version 2000, Microsoft, Redmond, Washington). A non-compartmental model with extravascular input was used for the pharmacokinetic analysis. Based on the individual plasma concentration-time data and using the scheduled sampling times, the standard pharmacokinetic parameters were calculated. The actual sampling times were checked for major aberrations. In case major aberrations (> 10 % deviations from the scheduled time) occurred for a subject, the actual sampling times were used in the pharmacokinetic analysis for that subjects and treatment.

Statistical Analysis

Descriptive statistics were calculated based on the plasma concentrations of TMC125, ATV, and RTV at each time point and for the derived pharmacokinetic parameters. The statistical analyses for TMC125 were performed using day 14 of treatment B or treatment D as test and day 7 of treatment B or treatment D as reference. The statistical analysis for ATV and RTV were performed using day 14 of treatment B or treatment D as test and day 7 of treatment A or treatment C as reference. The primary pharmacokinetic parameters were C_{min} , C_{max} , and AUC (AUC_{12h} for TMC125 and AUC_{24h} for ATV and RTV) on the logarithmic scale. Only the paired observations were included in the statistical analysis.

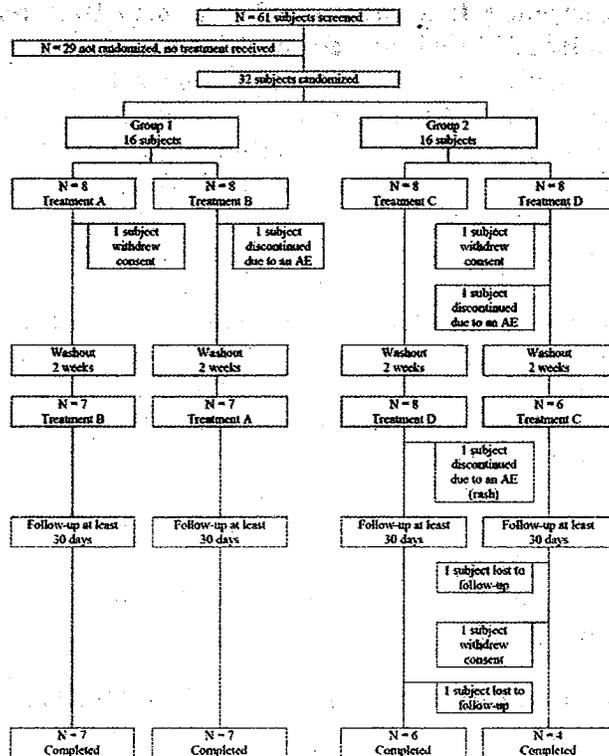
RESULTS

Subject Disposition and Demographics

Out of the 61 subjects screened, 32 subjects were randomized to 2 groups, each consisting of 16 subjects. 24 randomized subjects completed the trial and 8 subjects dropped out before trial completion. The reasons for drop out were consent withdrawal (3 subjects; 1 subject during administration of ATV, 1 subject after administration of ATV/RTV, and 1 subject during administration of TMC125 + ATV/RTV), adverse events (2 subjects during administration of TMC125), rash (1 subject during administration of TMC125), and lost to follow up (1 subject after administration of ATV/RTV and 1 subject after administration of TMC125 + ATV/RTV). Fig 1 shows the subject disposition in the trial.

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Fig 1: Subject Disposition in Trial TMC125-C151



Treatment A: 400 mg ATV q.d. on Days 1-7; Treatment B: 800 mg TMC125 b.i.d. on Days 1-14 with 400 mg ATV q.d. on Days 8-14; Treatment C: 300 mg ATV/100 mg RTV q.d. on Days 1-7; Treatment D: 800 mg TMC125 b.i.d. on Days 1-14 with 300 mg ATV/100 mg RTV q.d. on Days 8-14. Source: Supporting Data Display 1 and Supporting Data Display 2

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Table 2 shows the demographics in the trial:

Table 2: Demographics in Trial TMC125-C151

Parameter	Group 1 N = 16	Group 2 N = 16	All Subjects N = 32
Age, years			
Median	28.0	27.0	28.0
(range)	(18 - 45)	(18 - 42)	(18 - 45)
Height, cm			
Median	176.0	179.0	178.0
(range)	(153 - 191)	(164 - 188)	(153 - 191)
Weight, kg			
Median	77.0	83.5	81.0
(range)	(59 - 112)	(56 - 100)	(56 - 112)
Body Mass Index, kg/m ²			
Median	25.3	26.3	26.0
(range)	(23 - 31)	(21 - 29)	(21 - 31)
Sex, n (%)			
Male	15 (93.8)	15 (93.8)	30 (93.8)
Female	1 (6.3)	1 (6.3)	2 (6.3)
Ethnic Origin, n (%)			
Caucasian/White	6 (37.5)	10 (62.5)	16 (50.0)
Hispanic	7 (43.8)	3 (18.8)	10 (31.3)
Black	3 (18.8)	3 (18.8)	6 (18.8)
Smoker, n (%)			
No	16 (100.0)	16 (100.0)	32 (100.0)
Yes	0	0	0
Hepatitis A, n (%)			
Negative	15 (93.8)	16 (100.0)	31 (96.9)
Missing	1 (6.3)	0	1 (3.1)

Pharmacokinetics

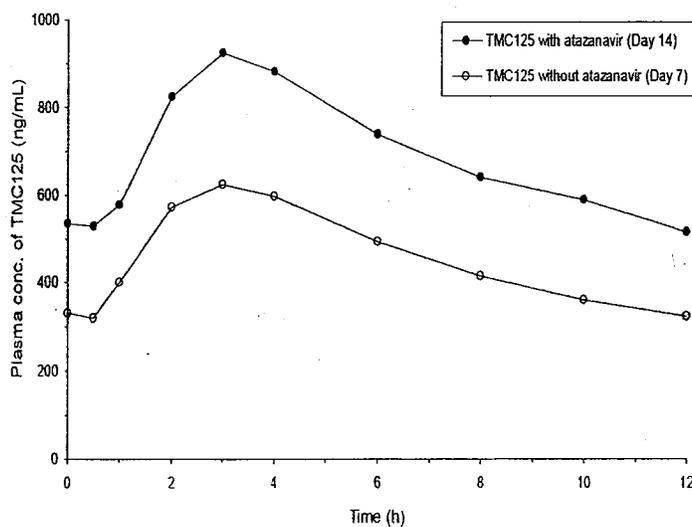
Two subjects did not complete **treatment A** and **treatment B**, therefore, full plasma concentration time profiles of 14 subjects were available for **treatment A** and **treatment B**. One subject did not complete **treatment C** and **treatment D**; one subject discontinued **treatment D** after day 7 and did not receive **treatment C**. One subject completed **treatment C** but discontinued the trial during **treatment D** on day 4. Consequently, full pharmacokinetic profiles of 14 subjects were available for **treatment C** and for **treatment D**, day 7, and full pharmacokinetic profiles of 13 subjects were available for **treatment D**, day 14.

A total of 14 deviations were noted for difference in the actual and scheduled sampling times exceeding 10 % (10 deviations were related to the 0.5 hour time point, 3 deviations were related to the 1 hour time point, and 1 deviation was related to the 2 hour time point). In subjects in whom these deviations were noted, the actual sampling time was used for all pharmacokinetic assessments.

TMC125

Fig 2 shows the mean plasma concentration time profiles of TMC125 with and without ATV (group 1, treatment B).

Fig 2: Mean plasma concentration time profiles of TMC125 with and without ATV (group 1, treatment B)



The mean plasma concentrations of TMC125 on day 14 (when co-administered with ATV) were higher than the mean plasma concentrations of TMC125 when administered alone.

Table 3 shows the pharmacokinetic parameters of TMC125 administered alone (day 7) or co-administered with ATV (day 14) [Group 1, treatment B].

Table 3: Pharmacokinetic parameters of TMC125 administered alone (day 7) or co-administered with ATV (day 14) [Group 1, treatment B]

Pharmacokinetics of TMC125 (Group 1) (mean ± SD, t _{max} , median (range))	TMC125 without ATV (Day 7)	TMC125 with ATV (Day 14)
n	14	14
C _{0h} , ng/mL	331.3 ± 166.7	534.7 ± 297.0
C _{12h} , ng/mL	322.6 ± 162.3	515.1 ± 314.6
C _{min} , ng/mL	299.5 ± 158.0	492.9 ± 298.7
C _{max} , ng/mL	627.5 ± 301.0	926.9 ± 453.9
t _{max} , h	3.0 (2.0 - 4.0)	3.00 (3.00 - 4.12)
AUC _{12h} , ng.h/mL	5496 ± 2707	8341 ± 4353

Table 4 shows the statistical analysis of the pharmacokinetic parameters of TMC125 administered alone (day 7) or co-administered with ATV (day 14) [Group 1, treatment B].

Table 4: Summary of the statistical analysis of the pharmacokinetic parameters of TMC125 administered alone (day 7) or co-administered with ATV (day 14) [Group 1, treatment B]

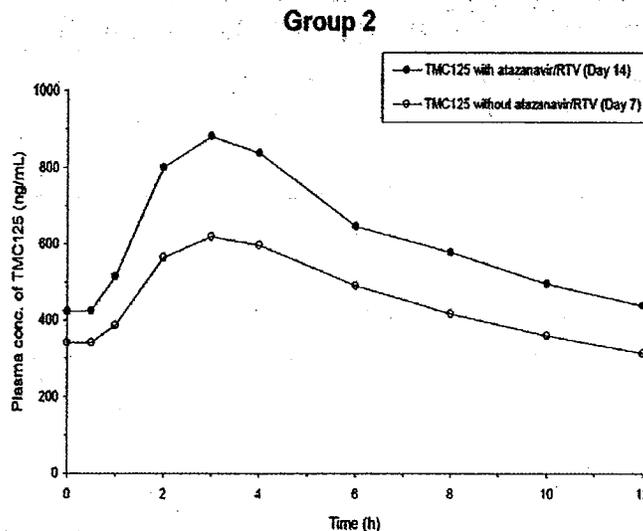
Group 1	n	Least square means		Least square means ratio, %	90% CI ^a , %	p-value
		TMC125 without ATV (Day 7) (reference)	TMC125 with ATV (Day 14) (test)			Treatment
Parameter						
C _{min} , ng/mL	14	262.2	413.7	157.8	146 - 170	<0.0001
C _{max} , ng/mL	14	553.3	814.4	147.2	136 - 159	<0.0001
AUC _{12h} , ng.h/mL	14	4822	7226	149.8	141 - 159	<0.0001

^a 90% confidence intervals.

The LS_{mean} estimates of C_{min}, C_{max}, and AUC of TMC125 increased by 47 %, 58 %, and 50 % in the presence of ATV as compared to when TMC125 was administered alone. The increase in all the TMC125 pharmacokinetic parameters was statistically significant.

Fig 2 shows the mean plasma concentration time profiles of TMC125 with and without ATV, co-administered with ritonavir (group 2, treatment D).

Fig 2: Mean plasma concentration time profiles of TMC125 with and without ATV co-administered with ritonavir (group 2, treatment D)



The plasma concentrations of TMC125 were quantifiable at the start of **treatment A** in those subjects who received **treatment B** before **treatment A**. The plasma concentrations of TMC125 were quantifiable at the start of **treatment C** in 3 of the 6 subjects who received **treatment D** before **treatment C**.

Reviewer's Note:

All the pre-dose concentrations of TMC125 were observed in subjects who were administered either treatment B or treatment D. The reason for these pre-dose concentrations could be the higher systemic exposures of TMC125 in the presence of ATV (in the case of treatment B) or ATV/rtv (in the case of treatment D). However, these pre-dose concentrations at the beginning of treatment A or treatment C will not alter the conclusions of the study since all PK and statistical assessments were based on steady state concentrations of TMC125 which will not be impacted by these pre-dose concentrations.

Table 5 shows the pharmacokinetic parameters of TMC125 administered alone (day 7) or co-administered with ATV/RTV (day 14) [group 2, treatment D].

Table 5: Pharmacokinetic parameters of TMC125 administered alone (day 7) or co-administered with ATV/RTV (day 14) [group 2, treatment D]

Pharmacokinetics of TMC125 (Group 2) (mean ± SD, t _{max} , median (range))	TMC125 without ATV/RTV (Day 7)	TMC125 with ATV/RTV (Day 14)
n	14	13
C _{0h} , ng/mL	341.6 ± 164.1	422.8 ± 178.9
C _{12h} , ng/mL	313.1 ± 132.7	439.0 ± 202.3
C _{min} , ng/mL	307.9 ± 130.9	405.8 ± 181.4
C _{max} , ng/mL	643.3 ± 216.1	888.2 ± 366.8
t _{max} , h	3.00 (2.00 - 4.33)	3.00 (2.00 - 4.00)
AUC _{12h} , ng.h/mL	5457 ± 1999	7527 ± 3241

Table 6 shows the summary of the statistical analysis of the pharmacokinetic parameters of TMC125 administered alone (day 7) or co-administered with ATV (day 14) [Group 2, treatment D].

Table 6: Summary of the statistical analysis of the pharmacokinetic parameters of TMC125 administered alone (day 7) or co-administered with ATV (day 14) [Group 2, treatment D]

Group 2	n	Least square means		Least square means ratio, %	90% CI*, %	p-value
		TMC125 without ATV/RTV (Day 7) (reference)	TMC125 with ATV/RTV (Day 14) (test)			Treatment
Parameter						
C _{min} , ng/mL	13	295.2	371.9	126.0	112 - 142	0.0046
C _{max} , ng/mL	13	635.0	823.6	129.7	117 - 144	0.0009
AUC _{12h} , ng.h/mL	13	5331	6946	130.3	118 - 144	0.0005

*90% confidence intervals

The LS_{mean} ratios of C_{min}, C_{max}, and AUC_{12h} of TMC125 increased by 26 %, 30 %, and 30 %, respectively, when TMC125 was co-administered with ATV/rtv as compared to when TMC125 was administered alone.

Atazanavir

Group 1, treatment A and treatment B

Fig 3 shows the mean plasma concentration time profiles of atazanavir, with and without co-administration of TMC125 (Group 1, treatment A and treatment B).

Fig 3: Mean plasma concentration time profiles of atazanavir, with and without co-administration of TMC125 (Group 1, treatment A and treatment B)

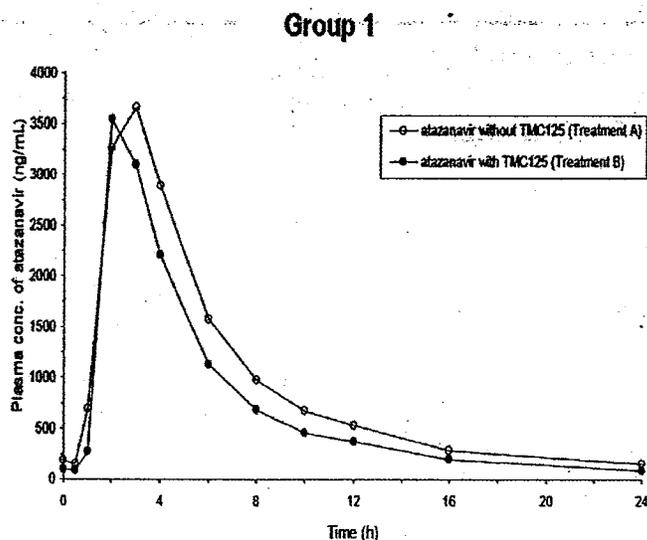


Table 7 shows the pharmacokinetic parameters of ATV, with and without TMC125 (Group 1, treatment A and treatment B).

Table 7: Pharmacokinetic parameters of ATV, with and without TMC125 (Group 1, treatment A and treatment B)

Pharmacokinetics of ATV (Group 1) (mean \pm SD, t_{max} median (range))	Treatment A: ATV without TMC125 (Day 7)	Treatment B: ATV with TMC125 (Day 14)
n	14	14
C_{0h} , ng/mL	182.8 \pm 118.2	99.80 \pm 94.66
C_{min} , ng/mL	136.8 \pm 103.7	78.67 \pm 76.59
C_{max} , ng/mL	4188 \pm 1709	3790 \pm 1588
t_{max} , h	2.50 (1.00 - 3.10)	2.00 (2.00 - 3.00)
AUC_{24h} , ng h/mL	22289 \pm 9471	17350 \pm 7985

Table 8 shows the summary of the statistical analysis of the pharmacokinetic parameters of ATV, with or without co-administration of TMC125 (Group 1, treatment A and treatment B).

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Table 8: Summary of the statistical analysis of the pharmacokinetic parameters of ATV, with or without co-administration of TMC125 (Group 1, treatment A and treatment B).

Group 1	n	Least square means		Least square means ratio, %	90% CI*, %	p-value		
		ATV without TMC125 (Day 7, TRT A) (reference)	ATV with TMC125 (Day 14, TRT B) (test)			Treatment	Period	Sequence
C_{min} , ng/mL	14	103.9	54.56	52.53	38.0 - 72.6	0.0038	-	-
C_{max} , ng/mL	14	3516	3399	96.69	72.7 - 129	0.8375	-	-
AUC_{24h} , ng·h/mL	14	18648	15439	82.79	62.6 - 109	0.2518	-	-

*90% confidence intervals
 -: excluded from final model

The LS_{mean} ratios of C_{min} , C_{max} , and AUC_{12h} of ATV decreased by 48 %, 3 %, and 17 %, respectively, when ATV was co-administered with TMC125 as compared to when ATV was administered alone.

Group 2, treatment C and treatment D

Fig 4 shows the mean plasma concentration time profiles of atazanavir, co-administered with ritonavir, with and without TMC125 (Group 1, treatment C and treatment D)

Fig 4: Mean plasma concentration time profiles of atazanavir, co-administered with ritonavir, with and without TMC125 (Group 1, treatment C and treatment D)

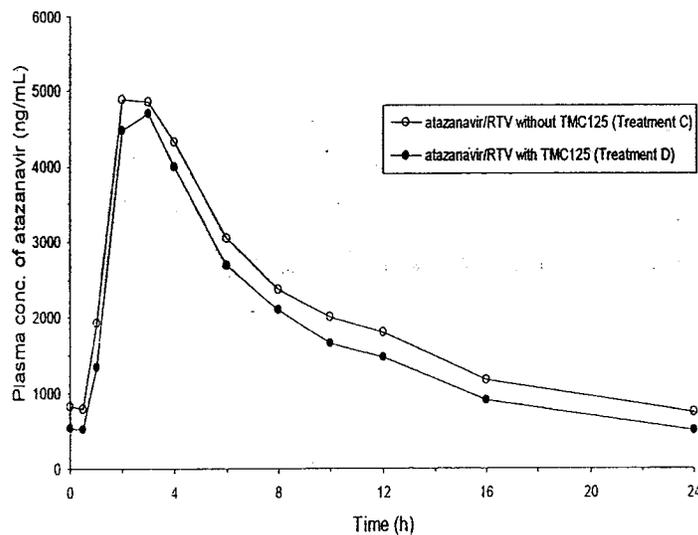


Table 9 shows the pharmacokinetic parameters of ATV, co-administered with RTV, administered with and without TMC125 (group 2, treatment C and treatment D).

Table 9: Pharmacokinetic parameters of ATV, co-administered with RTV, with and without TMC125 (Group 2, treatment C and treatment D)

Pharmacokinetics of ATV (Group 2) (mean ± SD, t _{max} , median (range))	Treatment C: ATV/RTV without TMC125 (Day 7)	Treatment D: ATV/RTV with TMC125 (Day 14)
n	14	13
C _{0h} , ng/mL	816.6 ± 299.2	533.5 ± 197.3
C _{min} , ng/mL	719.6 ± 295.6	455.3 ± 219.2
C _{max} , ng/mL	5230 ± 1102	5006 ± 785.7
t _{max} , h	2.00 (2.00 - 3.00)	2.00 (2.00 - 3.23)
AUC _{24h} , ng.h/mL	48528 ± 10996	41246 ± 7044

The mean AUC_{24h} of ATV co-administered with RTV was more than 100 % higher compared to the AUC of ATV without RTV. The within-subject variability (% CV) for AUC in treatment A and treatment B was 42 % and 46 %, respectively whereas the within-subject variability (% CV) for AUC in treatment C and treatment D was 23 % and 17 %, respectively. The higher variability in group 1 may be related to relatively low plasma concentrations of ATV in some subjects in this group.

For both the groups, co-administration with TMC125 caused a decrease in the mean pharmacokinetic parameters of ATV. The individual day 14/day 7 treatment ratios for AUC_{24h} ranged from 32.71 % to 347.2 % for group 1 (ATV without ritonavir) and from 70.46 % to 124.8 % for group 2 (ATV with ritonavir).

Table 10 shows the summary of the statistical analysis of ATV, co-administered with RTV, with and without TMC125.

Table 10: Summary of the statistical analysis of the pharmacokinetic parameters of ATV, co-administered with RTV, with and without TMC125.

Group 2	n	Least square means		Least square means ratio, %	90% CI*, %	p-value		
		ATV/RTV without TMC125 (Day 7, TRT C) (reference)	ATV/RTV with TMC125 (Day 14, TRT D) (test)			Treatment	Period	Sequence
C _{min} , ng/mL	13	673.4	418.8	62.19	54.6 - 70.8	<0.0001	-	-
C _{max} , ng/mL	13	5112	4950	96.84	88.9 - 105	0.5161	-	-
AUC _{24h} , ng.h/mL	13	47453	40654	85.67	78.9 - 93.0	0.0057	-	-

* 90% confidence intervals

- : excluded from final model

The LS_{mean} ratios of C_{min}, C_{max}, and AUC_{12h} of ATV decreased by 37 %, 3 %, and 14 %, respectively, when ATV (co-administered with low dose ritonavir) was co-administered with TMC125 as compared to when ATV/rtv was administered alone.

RTV

Table 11 shows the pharmacokinetic parameters of RTV, combined with ATV, with and without TMC125.

Table 11: Pharmacokinetic parameters of RTV, combined with ATV, with and without TMC125

Pharmacokinetics of RTV (Group 2) (mean ± SD, t _{max} , median (range))	Treatment C: RTV/ATV without TMC125 (Day 7)	Treatment D: RTV/ATV with TMC125 (Day 14)
n	14	13
C _{0h} , ng/mL	48.21 ± 34.63	34.38 ± 27.90
C _{min} , ng/mL	40.36 ± 29.33	29.58 ± 23.59
C _{max} , ng/mL	1949 ± 533.0	1952 ± 751.6
t _{max} , h	4.00 (3.00 - 6.00)	4.00 (3.00 - 6.00)
AUC _{24h} , ng.h/mL	11180 ± 2990	10415 ± 3317

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Pharmacokinetic Results Summary

TMC125

- The LS_{mean} ratio of C_{min}, C_{max}, and AUC of TMC125 increased by 47 %, 58 %, and 50 % in the presence of ATV as compared to when TMC125 was administered alone.
- The LS_{mean} ratios of C_{min}, C_{max}, and AUC_{12h} of TMC125 increased by 26 %, 30 %, and 30 %, respectively, when TMC125 was co-administered with ATV/rtv as compared to when TMC125 was administered alone.

ATV

- The LS_{mean} ratios of C_{min}, C_{max}, and AUC_{12h} of ATV decreased by 48 %, 3 %, and 17 %, respectively, when ATV was co-administered with TMC125 as compared to when ATV was administered alone.
- The LS_{mean} ratios of C_{min}, C_{max}, and AUC_{12h} of ATV decreased by 37 %, 3 %, and 14 %, respectively, when ATV (co-administered with low dose ritonavir) was co-administered with TMC125 as compared to when ATV/rtv was administered alone.

Conclusion

Concomitant use of INTELENCE™ with atazanavir/ritonavir may cause a significant decrease in atazanavir mean C_{min} and loss of therapeutic effect of atazanavir. In addition, the mean systemic exposure (AUC) of atazanavir after co-administration of INTELENCE™ with atazanavir/ritonavir is anticipated to be about 100 % higher than the mean systemic exposure of etravirine observed in the Phase 3 trials. INTELENCE™ and atazanavir/ritonavir should not be co-administered.

**APPEARS THIS WAY
ON ORIGINAL**

Study Number
TMC125-C156

Title

Phase I, open-label, randomized 2-period crossover trial in 16 healthy subjects to determine the pharmacokinetic interaction between TMC125 and rifabutin at steady state.

Objectives

The primary objectives of the trial were:

- To evaluate the effect of rifabutin, when co-administered at steady-state, on the pharmacokinetics of TMC125.
- To evaluate the effect of TMC125 on the steady-state pharmacokinetics of rifabutin and its metabolite 25-*O*-desacetyl-rifabutin.

Study Design

Phase I, open label, randomized, 2-period crossover trial in healthy subjects. 16 subjects were randomized to 2 groups (**group 1** and **group 2**). In two sessions, **treatment A** and **treatment B** were administered to the two groups in a crossover manner (**group 1** started with **treatment A** in the first session and **group 2** started with **treatment B** in the first session). There was a washout period of 14 days between the two sessions.

Treatment A:

300 mg rifabutin q.d. for 14 days.

Treatment B:

800 mg TMC125 b.i.d. for 7 days, immediately followed by a combined administration of 800 mg TMC125 b.i.d. and 300 mg rifabutin q.d. for 14 days (**day 8 to day 21**).

All the subjects entered the trial unit on day -1 of each treatment period (session) and remained in the unit for the duration of each treatment. All doses of TMC125 and rifabutin were taken within 10 minutes after completion of a meal.

Full pharmacokinetic profiles of rifabutin and its metabolite 25-*O*-desacetyl-rifabutin were determined on day 14 of **treatment A** and on day 21 of **treatment B**. A full pharmacokinetic profile of TMC125 was determined on day 7 and day 21 of **treatment B**.

Discussion of Trial Design

Rifabutin was administered for 14 days and TMC125 was administered for 7 days before a pharmacokinetic profile was determined, to ensure achievement of steady-state. The effect of TMC125 on the PK of rifabutin was determined in 2-period crossover design.

The effect of rifabutin on the PK of TMC125 was studied in a 1-sequence crossover design. Due to the slow decline of the inductive effect after discontinuation of the inducer, a 2-sequence design was not used.

Investigational Product(s)

TMC125 was formulated as TF035; this tablet formulation contains 200 mg TMC125 in hydroxypropylmethylcellulose (HPMC) lactose. The batch number was D03108 and the expiry date was Feb 2005. Mycobutin (rifabutin) was provided as a capsule containing 150 mg of rifabutin. The batch number was 1GPG66 and the expiry date was July 2005.

Assay Methods

The plasma concentrations of TMC125, rifabutin, and 25-*O*-deacetyl rifabutin were determined using a validated liquid chromatographic with tandem mass spectrometry (LC-MS/MS) method. The lower limit of quantification (LLOQ) was 2 ng/mL for all the three compounds.

Pharmacokinetic and Statistical Data Analysis

Pharmacokinetic Analysis

Pharmacokinetic and statistical analysis was performed using Winnonlin Professional™ and Microsoft Excel®. Based on the individual plasma concentration-time data and using the scheduled sampling times, the standard pharmacokinetic parameters were calculated.

Statistical Analysis

Descriptive statistics were calculated for the plasma concentrations of TMC125, rifabutin, and 25-*O*-desacetyl rifabutin at each time point and for the derived pharmacokinetic parameters. For TMC125, statistical analyses were performed using day 21 of treatment B as test treatment and day 7 of treatment B as reference treatment. For rifabutin and 25-*O*-desacetyl rifabutin, statistical analyses were performed using day 21 of treatment B as test treatment and day 14 of treatment A as reference treatment. The primary pharmacokinetic parameters were C_{min} , C_{max} , and AUC_{12h} (AUC_{24h} for rifabutin and 25-*O*-desacetyl rifabutin) on the logarithmic scale.

RESULTS

Subject Disposition and Demographics

Out of the 52 subjects screened, 16 subjects were assigned to one of the two groups (group 1 received treatment A followed by treatment B and group 2 received treatment B followed by treatment A) and started study treatment. 10 subjects completed the trial and 6 subjects dropped out before trial completion: 2 subjects discontinued due to adverse events (1 subject in group 1 due to atrial flutter that occurred during rifabutin alone treatment in session 1 and 1 subject in group 2 as a result of elevated pancreatic amylase, an AE with onset during rifabutin alone treatment in session 2), 2 subjects withdrew consent, and 2 subjects discontinued for other reasons (1 subject was unable to participate in session 2 and for 1 subject, no further information was available). Therefore, out of the 8 subjects randomized to sequence A-B, 5 subjects completed all assessments for both the treatments. Out of the 8 subjects randomized to sequence B-A, 6 subjects completed all assessments for treatment B and 5 subjects completed all assessments after treatment A.

Table 1 shows the demographics in the trial:

Table 1: Demographics in Trial TMC125-C156

Parameter	Group 1 N=8	Group 2 N=8	All Subjects N=16
Age, years Median (range)	33.0 (22-55)	34.5 (23-52)	34.0 (22-55)
Height, cm Median (range)	170.0 (155-180)	169.5 (159-191)	169.5 (155-191)
Weight, kg Median (range)	73.0 (62-88)	70.0 (56-103)	70.5 (56-103)
BMI, kg/m ² Median (range)	25.2 (23-28)	24.2 (22-28)	24.9 (22-28)
Sex, n (%)			
Female	1 (12.5)	0	1 (6.3)
Male	7 (87.5)	8 (100)	15 (93.8)
Ethnic Origin, n (%)			
Black	3 (37.5)	1 (12.5)	4 (25.0)
White	3 (37.5)	5 (62.5)	8 (50.0)
Hispanic	2 (25.0)	2 (25.0)	4 (25.0)

BMI=body mass index

Pharmacokinetics

Full pharmacokinetic profiles for rifabutin and 25-*O*-desacetylrifabutin were available on Day 14, Treatment A for 12 subjects. Full pharmacokinetic profiles of TMC125 were available for 12 subjects on Day 7, treatment B and full pharmacokinetic profiles of TMC125, rifabutin and 25-*O*-desacetylrifabutin were available for 11 subjects on Day 21, treatment B. The statistical analysis using paired data could be performed for 11 subjects for TMC125 and for 10 subjects for rifabutin and 25-*O*-desacetylrifabutin.

TMC125

Fig 1 shows the mean plasma concentration-time profile of TMC125 with (day 21) and without (day 7) co-administration of rifabutin.

Fig 1: Mean plasma concentration-time profile of TMC125 with (day 21) and without (day 7) co-administration of rifabutin

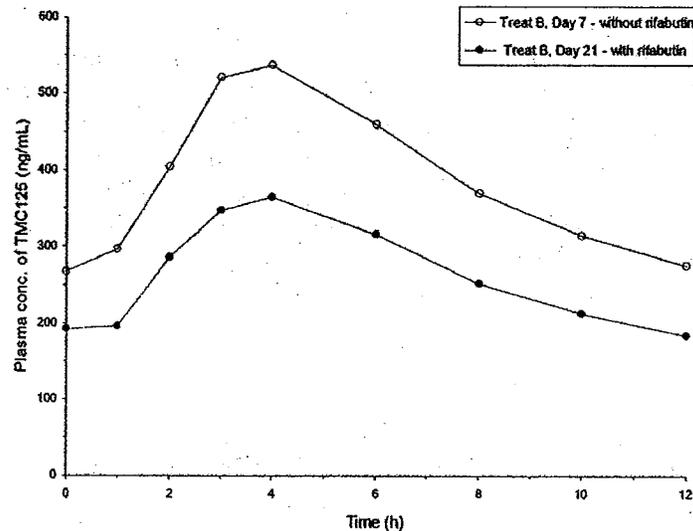


Table 2 shows the pharmacokinetic parameters of TMC125 with (day 21) and without (day 7) co-administration of rifabutin.

Table 2: Pharmacokinetic parameters of TMC125 with (day 21) and without (day 7) co-administration of rifabutin

Pharmacokinetics of TMC125 mean \pm SD t_{max} : median (range)	Treatment B, Part 1 TMC125 Without Rifabutin Day 7	Treatment B, Part 2 TMC125 With Rifabutin Day 21
N	12	11
C_{0h} , ng/mL	267.0 \pm 118.9	192.4 \pm 130.7
t_{max} , h	4.0 (3.0 - 4.0)	4.0 (3.0 - 6.0)
C_{min} , ng/mL	256.9 \pm 117.9	178.3 \pm 129.1
C_{max} , ng/mL	546.7 \pm 234.2	371.4 \pm 258.9
AUC_{12h} , ng.h/mL	4722 \pm 1949	3220 \pm 2196

The mean estimates of all the TMC125 pharmacokinetic parameters (except t_{max}) were lower on day 21 (treatment B, part 2), when TMC125 was co-administered with rifabutin compared to when TMC125 was administered alone (treatment B, part 1). The inter-individual variability for C_{min} , C_{max} , and AUC_{12h} on day 21 was higher (68 % - 72 %) compared to the inter-individual variability on day 7 (41 %-46 %).

Table 3 shows the statistical evaluation of the pharmacokinetic parameters of TMC125 with (day 21) and without (day 7) co-administration of rifabutin.

Table 3: Statistical evaluation of the pharmacokinetic parameters of TMC125 with (day 21) and without (day 7) co-administration of rifabutin.

Parameter	N	Least square means		Least square means ratio, %	90% CI *	p-value
		Treatment B, Part 1 Day 7 (reference)	Treatment B, Part 2 Day 21 (test)			Treatment
C_{min} , ng/mL	11	233.2	150.8	64.69	56.3 - 74.3	0.0002
C_{max} , ng/mL	11	509.2	319.7	62.79	53.2 - 74.1	0.0005
AUC_{12h} , ng h/mL	11	4380	2771	63.26	54.0 - 74.1	0.0004

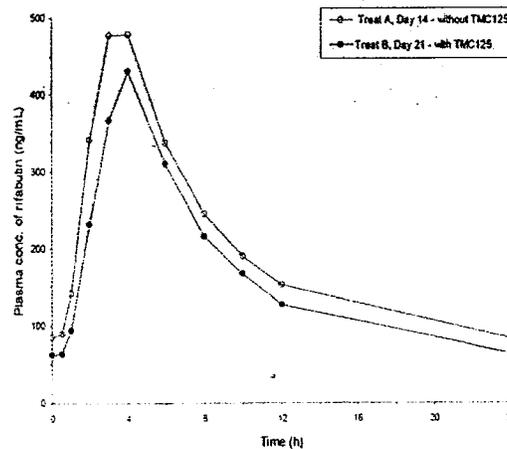
* 90% confidence intervals.

The LS_{mean} estimates of C_{min} , C_{max} , and AUC_{12h} of TMC125 decreased by 35 %, 37 %, and 37 % respectively when TMC125 was combined with rifabutin, as compared to when TMC125 was administered alone. The individual ratios for C_{min} , C_{max} , and AUC_{12h} ranged from 35 % to 102 %, 32 % to 97 %, and 32 % to 100 % with geometric means of 65 %, 63 %, and 63 %, respectively. The design of the trial did not support the analysis of period and sequence effects for TMC125.

Rifabutin

Fig 2 shows the mean plasma concentration-time profiles of rifabutin, with or without co-administration of TMC125.

Fig 2: Mean plasma concentration-time profiles of rifabutin, with or without co-administration of TMC125



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Table 4 shows the pharmacokinetic parameters of rifabutin, with or without co-administration of TMC125.

Table 4: Pharmacokinetic parameters of rifabutin, with or without co-administration of TMC125

Pharmacokinetics of Rifabutin mean \pm SD, t_{max} : median (range)	Rifabutin Without TMC125 Day 14, Treatment A	Rifabutin With TMC125 Day 21, Treatment B
N	12	11
C_{0h} , ng/mL	84.26 \pm 28.36	62.94 \pm 22.46
t_{max} , h	3.0 (2.0 - 4.0)	4.0 (2.0 - 6.0)
C_{min} , ng/mL	78.71 \pm 27.45	58.80 \pm 19.59
C_{max} , ng/mL	500.1 \pm 148.3	447.9 \pm 141.0
AUC_{24h} , ng.h/mL	4815 \pm 1374	4012 \pm 1123

The mean estimates of the pharmacokinetic parameters of rifabutin (except for t_{max}), were lower when combined with TMC125, as compared to when rifabutin was given alone.

Table 5 shows the statistical evaluation of the pharmacokinetic parameters of rifabutin, with or without co-administration of TMC125.

Table 5: Statistical evaluation of the pharmacokinetic parameters of rifabutin, with or without co-administration of TMC125.

Parameter	N	Least square means		Least square means ratio, %	90% CI*	p-value
		Treatment A, Day 14 (reference)	Treatment B, Day 21 (test)			Treatment
C_{min} , ng/mL	10	76.70	58.02	75.65	66.1 - 86.6	0.0044
C_{max} , ng/mL	10	490.5	439.2	89.55	78.1 - 103	0.1733
AUC_{24h} , ng.h/mL	10	4781	3991	83.47	74.5 - 93.5	0.0169

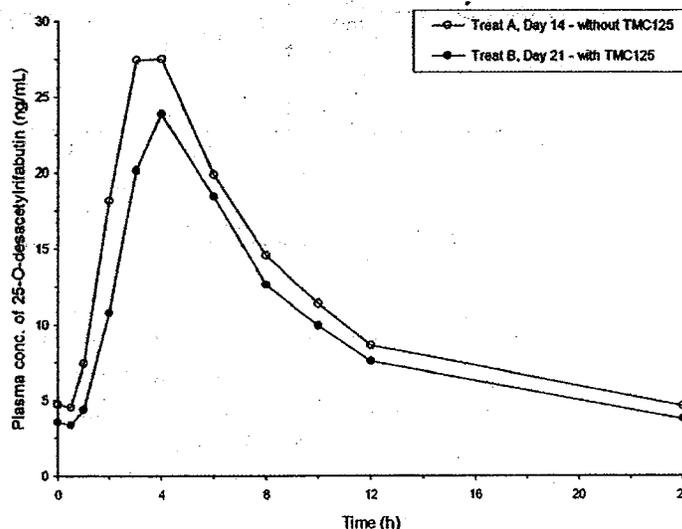
* 90% confidence intervals.

The LS_{means} of C_{min} , C_{max} , and AUC_{24h} of rifabutin decreased by 24 %, 10 %, and 16 %, when rifabutin was co-administered with TMC125 as compared to when rifabutin was administered alone. The individual ratios of C_{min} , C_{max} , and AUC_{24h} ranged from 48 % to 114 %, 52 % to 123 %, and 55 % to 114 % with geometric means of 76 %, 90 %, and 84 % respectively.

25-O-Desacetylriofabutin

Fig 3 shows the mean plasma concentration time profiles of 25-O-desacetylriofabutin with or without co-administration of TMC125.

Fig 3: Mean plasma concentration time profiles of 25-O-desacetylriofabutin with or without co-administration of TMC125.



The plasma concentration-time profiles of 25-O-desacetylriofabutin were characterized by a rapid increase in plasma concentrations after intake of rifabutin. There was a small decline in plasma concentration shortly after drug intake (0.5 hour) in most of the subjects.

Table 6 shows the pharmacokinetic parameters of 25-O-deacetylriofabutin with or without co-administration of TMC125.

Table 6: Pharmacokinetic parameters of 25-O-deacetylriofabutin with or without co-administration of TMC125

Pharmacokinetics of 25-O-desacetylriofabutin mean \pm SD, t_{max} , median (range)	25-O-desacetylriofabutin without TMC125 Day 14, Treatment A	25-O-desacetylriofabutin with TMC125 Day 21, Treatment B
N	12	11
C_{0h} , ng/mL	4.363 \pm 2.440	3.391 \pm 1.888
t_{max} , h	4.0 (3.0 - 4.0)	4.0 (3.0 - 6.0)
C_{min} , ng/mL	4.072 \pm 2.375	3.218 \pm 1.881
C_{max} , ng/mL	28.67 \pm 8.981	24.37 \pm 7.553
AUC _{24h} , ng.h/mL	272.1 \pm 102.7	229.8 \pm 92.66
Ratio AUC _{24h, desacetyl-RFB-RFB} (%)	5.741 \pm 1.754	5.834 \pm 1.840

Table 7 shows the statistical analysis of the pharmacokinetic parameters of 25-O-deacetylriofabutin with or without co-administration of TMC125.

Table 7: Statistical analysis of the pharmacokinetic parameters of 25-O-deacetylriofabutin with or without co-administration of TMC125

Parameter	n	Least square means		Least square means ratio, %	90% CI *	p-value	
		Treatment A, Day 14 (reference)	Treatment B, Day 21 (test)			Treatment	Sequence
C_{min} , ng/mL	10	3.728	2.902	77.84	69.5 - 87.1	0.0028	0.0430
C_{max} , ng/mL	10	27.50	23.35	84.89	72.1 - 99.9	0.0987	0.0238
AUC_{24h} , ng.h/mL	10	260.5	215.0	82.53	74.0 - 92.0	0.0103	0.0178

* 90% confidence intervals.

The effect of TMC125 on the pharmacokinetics of 25-*O*-deacetylriofabutin was similar (in terms of the magnitude of change in the pharmacokinetic parameters) to the effect of TMC125 on the pharmacokinetics of rifabutin. The LSmeans of C_{min} , C_{max} , and AUC_{24h} of 25-*O*-deacetylriofabutin decreased by 22 %, 15 %, and 17 %, respectively when rifabutin was co-administered with TMC125 as compared to when rifabutin was administered alone. The individual ratios for C_{min} , C_{max} , and AUC_{24h} of 25-*O*-deacetylriofabutin ranged from 54 % to 100 %, 49 % to 153 %, and 57 % to 118 % with geometric means of 76 %, 85 %, and 83 %.

Pharmacokinetic Results Summary

- The LS_{mean} estimates of C_{min} , C_{max} , and AUC_{12h} of TMC125 decreased by 35 %, 37 %, and 37 % respectively when TMC125 was combined with rifabutin, as compared to when TMC125 was administered alone.
- The LS_{means} estimates of C_{min} , C_{max} , and AUC_{24h} of rifabutin decreased by 24 %, 10 %, and 16 %, when rifabutin was co-administered with TMC125 as compared to when rifabutin was administered alone.
- The LS_{means} estimates of C_{min} , C_{max} , and AUC_{24h} of 25-*O*-deacetylriofabutin decreased by 22 %, 15 %, and 17 %, respectively when rifabutin was co-administered with TMC125 as compared to when rifabutin was administered alone.

Conclusion

If INTELENCE™ is NOT co-administered with a protease inhibitor/ritonavir, then rifabutin at a dose of 300 mg q.d. is recommended. If INTELENCE™ is co-administered with darunavir/ritonavir or saquinavir/ritonavir, then rifabutin should not be co-administered due to the potential for significant reduction in etravirine exposures.

Study Number
TMC125-C157

Title

Phase I, open-label trial to investigate the pharmacokinetic interaction between didanosine (ddI) and TMC125 at steady-state in healthy subjects.

Objectives

The primary objectives of the trial were to determine the effect of steady state concentrations of TMC125 on the steady state concentrations of ddI and to determine the effect of steady state concentrations of ddI on the steady-state concentrations of TMC125 in healthy subjects.

Study Design

Open label, randomized, crossover design. 16 subjects were equally randomized to 2 groups (n = 8 per group). During **session 1**, both groups received TMC125 800 mg b.i.d. (TF035) from **day 1** to **day 7**, followed by a single dose of TMC125 800 mg b.i.d. on **day 8**. In **session 2**, subjects in **group 1** received ddI 400 mg q.d. from **day 1** to **day 16** and TMC125 800 mg b.i.d. from **day 9** to **day 16**; subjects randomized to **group 2** received ddI 400 mg q.d. from **day 1** to **day 16** and TMC125 800 mg b.i.d. from **day 1** to **day 8**. There was a washout period of 2 weeks between the two sessions.

ddI had to be taken on an empty stomach with 200 mL of water. The standardized breakfast had to be taken 1.5 hours after ddI intake. TMC125 was administered 30 minutes after breakfast had started on days when TMC125 and ddI were co-administered (i.e., 2 hours after ddI intake). On days when TMC125 was administered alone, TMC125 was administered within 10 minutes after completion of a standardized breakfast.

The steady state pharmacokinetics of TMC125 was assessed on **day 8** of **session 1** and on **day 8 (group 2)** and **day 16 (group 1)** of **session 2**. The pharmacokinetics of ddI was assessed on **day 8 (group 1)** and **day 16 (group 2)** of **session 2**.

Investigational Product(s)

TMC125 was provided as TF035, a tablet containing 200 mg of TMC125 ——— hydroxypropylmethylcellulose (HPMC) ——— lactose ———
The batch # was D03108 and the expiration date was July 31, 2004.

ddI (Videx® EC) was provided as 400 mg enteric coated delayed release capsule. The batch # was 0086 and the expiry date was September, 2005.

Assay Methods

The plasma concentrations of TMC125 and ddI were determined using a validated liquid chromatographic with tandem mass spectrometry (LC-MS/MS) method. The lower limit of quantification (LLOQ) was 2 ng/mL for TMC125 and 10 ng/mL for ddI.

Pharmacokinetic and Statistical Data Analysis

Pharmacokinetic Analysis

Pharmacokinetic and statistical analysis was performed using SAS for Windows® version 8.2. Based on the individual plasma concentration-time data and using the scheduled sampling times, the standard pharmacokinetic parameters were calculated.

Statistical Analysis

A total of 16 subjects were to be enrolled. If more than 4 subjects were prematurely withdrawn from the trial for reasons other than drug tolerability/safety, additional subjects were to be recruited to aim for at least 12 evaluable subjects (an evaluable subject is a subject who has completed all sessions of the trial).

The primary plasma pharmacokinetic parameters were C_{0h} , C_{min} , C_{max} and AUC_{12h} for TMC125 and C_{0h} , C_{min} , C_{max} and AUC_{24h} for ddI.

RESULTS

Subject Disposition and Demographics

Out of the 35 subjects screened, 18 subjects failed screening (13 subjects did not meet the eligibility criteria and 5 subjects withdrew consent). Out of the 17 subjects eligible for trial after screening, 16 subjects were randomized to either **group 1** or **group 2**, and 1 subject was identified as reserve subject. 14 subjects completed the trial and 2 subjects discontinued the trial due to adverse events; one subject randomized to **group 1** (during washout period) one subject randomized to **group 2** (on day 2 of session 1).

Table 1 shows the demographics in the trial.

Table 1: Demographics in Trial TMC125-C157

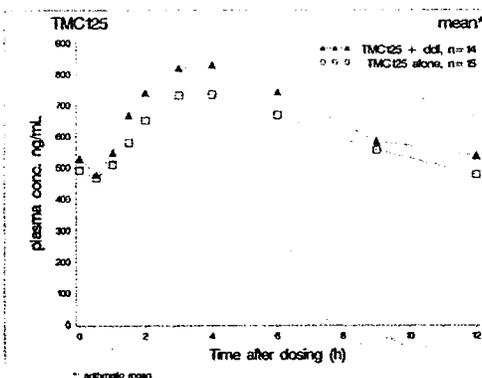
Parameter	Group 1 N=8	Group 2 N=8	All Subjects N=16
Age, years Median (range)	32.0 (22-47)	26.0 (21-41)	29.0 (21-47)
Height, cm Median (range)	179.0 (175-185)	183.0 (168-185)	182.0 (168-185)
Weight, kg Median (range)	74.0 (65-87)	75.5 (63-93)	74.0 (63-93)
BMI, kg/m ² Median (range)	22.3 (20-28)	22.7 (19-29)	22.3 (19-29)
Sex, n (%)			
Male	8 (100.0)	8 (100.0)	16 (100.0)
Ethnic Origin, n (%)			
White	7 (87.5)	6 (75.0)	13 (81.3)
Black	1 (12.5)	1 (12.5)	2 (12.5)
Hispanic	0	1 (12.5)	1 (6.3)
Type of Smoker, n (%)			
Nonsmoker	3 (37.5)	7 (87.5)	10 (62.5)
Light	5 (62.5)	1 (12.5)	6 (37.5)

Pharmacokinetics

TMC125

Fig 1 shows the mean steady state plasma concentration time profiles after administration of TMC125 800 mg b.i.d., with or without the concomitant administration of ddI 400 mg q.d.

Fig 1: Mean steady state plasma concentration time profiles after administration of TMC125 800 mg b.i.d., with or without the concomitant administration of ddI 400 mg q.d.



In 50 % of the subjects, TMC125 plasma concentrations were higher when TMC125 was co-administered with ddI (n = 7), whereas for other subjects, either no significant differences were observed (n = 5) or TMC125 exposure was lower when combined with ddI (n = 2).

Table 2 shows the mean steady state pharmacokinetic parameters of TMC125, with or without concomitant administration of ddI.

Table 2: Mean steady state pharmacokinetic parameters of TMC125, with or without concomitant administration of ddi

Pharmacokinetics of TMC125 (mean ± SD, t _{max} , median [range])	TMC125 + ddi	TMC125 alone
	Test	Reference
n	14	15
t _{max} , h	3.0 [1.5-6.0]	4.0 [2.0-6.0]
C _{0h} , ng/mL	527 ± 206	489 ± 206
C _{min} , ng/mL	468 ± 196	450 ± 212
C _{max} , ng/mL	860 ± 371	759 ± 376
AUC _{12h} , ng.h/mL	8000 ± 3328	7262 ± 3371
C _{50, 4h} , ng/mL	667 ± 277	605 ± 281
FL, %	58.7 ± 15.0	49.5 ± 16.3

All the mean pharmacokinetic parameters of TMC125 were higher when co-administered with ddi as compared to when TMC125 was administered alone.

Table 3 shows the statistical analysis of the pharmacokinetic parameters of TMC125, with or without concomitant administration of ddi.

Table 3: Statistical analysis of the pharmacokinetic parameters of TMC125, with or without concomitant administration of ddi

TMC125	n		Least squares means				p-value	
	Test / Ref.	Test / Ref.	TMC125 + ddi Test	TMC125 alone Reference	Treatment ratio, % and 90% CI ^a Test/Reference		Treatment	Sequence
C _{0h} , ng/mL	14	15	472	438	108	99 - 118	0.1516	0.3416
C _{min} , ng/mL	14	15	411	393	105	93 - 118	0.5058	0.5985
C _{max} , ng/mL	14	15	760	634	116	102 - 132	0.0609	0.3862
AUC _{12h} , ng.h/mL	14	15	7035	6341	111	99 - 125	0.1386	0.4411
Parameter	n		median		p-value (Wilcoxon signed rank test)			
	Test / Ref.	Test / Ref.	TMC125 + ddi Test	TMC125 alone Reference	Treatment		Sequence	
t _{max} , h	14	15 ^a	3.0	4.0	0.1875		-	

^a90% confidence interval; ^bn= 14 for Wilcoxon signed rank test

The LS_{means} ratio of all the pharmacokinetic parameters (except AUC_{12hr}) of TMC125 were not significantly altered (all changes < 10 %; AUC_{12hr} increased by 11 %) when TMC125 was co-administered with ddi as compared to when TMC125 was administered alone.

ddi

Fig 2 shows the mean steady state plasma concentration time profiles after administration of ddi 400 mg q.d., with or without the concomitant administration of TMC125 800 mg b.i.d.

Fig 2: Mean steady state plasma concentration time profiles after administration of ddI 400 mg q.d., with or without the concomitant administration of TMC125 800 mg b.i.d.

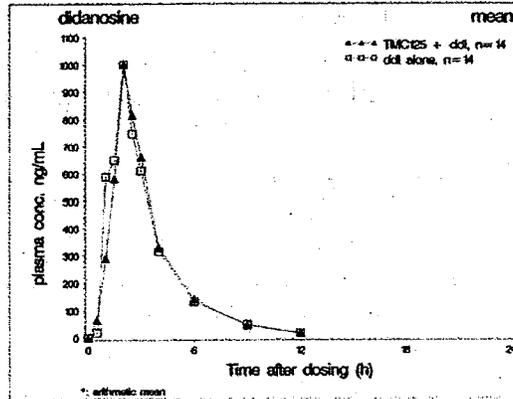


Table 4 shows the mean steady state pharmacokinetic parameters of ddI, with or without concomitant administration of TMC125.

Table 4: Mean steady state pharmacokinetic parameters of ddI, with or without concomitant administration of TMC125

Pharmacokinetics of didanosine (mean ± SD, t _{max} ; median [range])	TMC125 + ddI Test	ddI alone Reference
n	14	14
t _{max} , h	2.0 [1.0-9.0]	2.0 [1.0-3.0]
C _{0h} , ng/mL	NQ	NQ
C _{min} , ng/mL	NQ	NQ
C _{max} , ng/mL	1210 ± 623	1323 ± 741
AUC _{24h} , ng.h/mL	2899 ± 877	2883 ± 941
C _{tr,ss} , ng/mL	121 ± 37	120 ± 38
FI, %	951 ± 344	1022 ± 305

NQ: Not Quantifiable

The pre-dose concentrations and the 24-hour concentrations of ddI were below the LLOQ for all subjects, therefore, both C_{min} and C_{0h} were not quantifiable. Hence, the descriptive statistics for C_{min} and C_{0h} were not available for these parameters.

Table 5 shows the statistical analysis of the pharmacokinetic parameters of ddI, with or without concomitant administration of TMC125.

Table 5: Statistical analysis of the pharmacokinetic parameters of ddI, with or without concomitant administration of TMC125

Parameter	n		Least squares means				p-value		
	Test / Ref.		TMC125 +ddI Test	ddI alone Reference	Treatment ratio, % and 90% CI* Test/Reference		Treatm.	Period	Sequence
C _{max} , ng/mL	14	14	1028	1132	91	58 - 142	0.7090	0.8868	0.9339
AUC _{24hr} , ng.h/mL	14	14	2730	2746	99	79 - 125	0.9638	0.7767	0.5919
Parameter	n		median		p-value (Koch analysis)				
	Test / Ref.		TMC125 +ddI Test	ddI alone Reference	Treatment	Period	Sequence		
t _{max} , h	14	14	2.0	2.0	0.3427	0.3427	0.1049		

*90% confidence interval

The LS_{means} ratio of C_{max} and AUC_{24hr} of ddI were not significantly altered (all changes < 10 %) when ddI was co-administered with TMC125 as compared to when ddI was administered alone.

Pharmacokinetic Results Summary

- The LS_{means} ratio of all the pharmacokinetic parameters (except AUC_{12hr}) of TMC125 were not significantly altered (all changes < 10 %; AUC_{12hr} increased by 11 %) when TMC125 was co-administered with ddI as compared to when TMC125 was administered alone.
- The LS_{means} ratio of C_{max} and AUC_{24hr} of ddI were not significantly altered (all changes < 10 %) when ddI was co-administered with TMC125 as compared to when ddI was administered alone.

Reviewer's Note:

Videx (Enteric coated ddI) contains an antacid buffer that can neutralize the acid in the stomach. This neutralization of the stomach acid can reduce the rate and extent of systemic absorption of drugs that require acidic conditions for optimal absorption e.g. atazanavir.

The sponsor used formulation TF035 in the current study. Although studies have shown the similarity in systemic exposure after administration of TMC125 800 mg b.i.d. TF035 and TMC125 200 mg b.i.d. F060 (to-be-marketed formulation), the major effect of ddI on altering the PK of TMC125 (if any) is expected to be due to the alteration in pH of the gastrointestinal tract. The results of study TMC125-C120 (drug-drug interaction study between TMC125 and ranitidine and omeprazole) showed that decrease in gastric pH did not alter the systemic exposure of a single 100 mg dose of TMC125 (administered as F060). This suggests that the increase in gastric pH due to ddI may not have a significant impact on altering the systemic exposures of TMC125 when administered as F060. Further, due to the opposite effect of food on the

pharmacokinetics of ddI (food reduces the systemic exposure of ddI) and TMC125 (food increases the systemic exposure of TMC125), the effect of alteration in the pH due to ddI on the PK of TMC125 (if any) will be offset by the "staggered" administration of ddI and TMC125 (administered as F060).

Conclusion

The combination of didanosine (ddI) and TMC125 can be used without any dose adjustments, however, ddI should be administered on an empty stomach (2 hours before or 2 hours after a meal) and TMC125 should be administered following a meal.

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Study Number
TMC125-C158

Title

Phase I, open-label, add on trial in subjects on stable methadone maintenance therapy to investigate the potential pharmacokinetic interaction between steady-state TMC125 and methadone.

Objectives

The primary objective of the present trial was to investigate the potential effect of steady state pharmacokinetics of TMC125 on the steady state pharmacokinetics of methadone.

Study Design

16 subjects received TMC125 100 mg b.i.d. (F060) for 14 days (day 1 to day 14) added to their individualized methadone therapy. TMC125 and methadone were administered within 10 minutes after completion of a standardized breakfast. Full pharmacokinetic profiles of R(-) and S(+) methadone were determined on day -1, day 7, and day 14 up to 24 hours post dose. Full pharmacokinetic profiles of TMC125 were determined on day 7 and on day 14 up to 12 hours post dose.

Methadone was administered at the individualized dose used for maintenance therapy for each subject. The intra-subject differences in pharmacokinetics of methadone between day -1, day 7, and day 14 was used to evaluate the effect of TMC125 on the pharmacokinetics of methadone.

Investigational Product(s)

TMC125 was provided as a tablet containing 100 mg of TMC125 — spray-dried in combination with hydroxypropylmethylcellulose (HPMC) and microcrystalline cellulose, —, croscarmellose sodium, magnesium stearate, and lactose monohydrate (formulation F060). The batch # was 05A05 and the expiration date was January 2006.

Methadone was provided as Symorön® tablets.

Assay Methods

The plasma concentrations of TMC125, S(+) methadone, and R(-) methadone were determined using a validated liquid chromatographic with tandem mass spectrometry (LC-MS/MS) method. The lower limit of quantification (LLOQ) was 2 ng/mL for TMC125 and 5 ng/mL for S(+) methadone, and 5 ng/mL for R(-) methadone.

Pharmacokinetics and Statistical Data Analysis

Pharmacokinetic Analysis

Pharmacokinetic and statistical analysis was performed using Winonlin Professional™ (version 4.1, Pharsight Corporation). A non-compartmental model with extravascular input was used for the pharmacokinetic analysis. Based on the individual plasma concentration-time data and using the scheduled sampling times, the standard pharmacokinetic parameters were calculated.

The pharmacokinetic parameters of TMC125 were compared with the results obtained for the same dosing regimen (100 mg b.i.d.) of TMC125 in trial TMC125-C168. The subjects in trial TMC125-C168 did not use any medication other than TMC125, therefore, the pharmacokinetic parameters from trial TMC125-C168 can be used to assess the pharmacokinetics of TMC125 in subjects on a stable methadone regimen.

Statistical Analysis

The statistical analyses were performed for R(-) and S(+) methadone using the methadone administration on day 7 and day 14 as test treatment and methadone administration on day -1 as reference treatment. The primary pharmacokinetic parameters were C_{min} , C_{max} , C_{0h} and AUC_{24h} on the logarithmic scale.

RESULTS

Subject Disposition and Demographics

Out of the 21 subjects screened, 16 subjects started treatment. 5 subjects were not treated; 4 subjects did not meet all the selection criteria and 1 subject withdrew consent.

All 16 subjects completed the trial. Table 1 shows the demographics of the trial.

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Table 1: Demographics in Trial TMC125-C158

Parameter	All Subjects N= 16
Age, years Median (range)	41.5 (36-55)
Height, cm Median (range)	175.0 (169-189)
Weight, kg Median (range)	69.5 (54-106)
BMI, kg/m ² Median (range)	22.8 (18-30)
Ethnic Origin, n (%)	
Caucasian/White	14 (87.5)
Oriental/ Asian	1 (6.3)
Other	1 (6.3)
Type of Smoker, n (%)	
Heavy	1 (6.3)
Moderate	12 (75.0)
Light	2 (12.5)
Non-smoker	1 (6.3)

N = total number of subjects; n = number of subjects with specific parameter

Source: Supporting Data Display 3

Pharmacokinetics

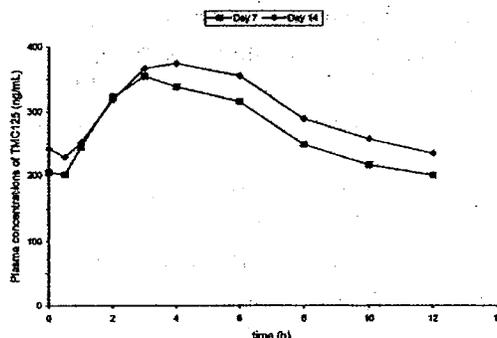
TMC125

The plasma samples were not collected at 5 time points on day 14 in one subject due to difficulty with venipuncture. Therefore, the pharmacokinetic parameters of TMC125 for this subject were not determined on day 14 and full pharmacokinetic profiles of TMC125 were available for 16 subjects on day 7 and for 15 subjects on day 14.

Fig 1 shows the mean plasma concentration-time curves of TMC125 100 mg b.i.d. on day 7 and day 14 in subjects on a stable methadone therapy.

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Fig 1: Mean plasma concentration-time curves of TMC125 100 mg b.i.d. on day 7 and day 14 in subjects on a stable methadone therapy



Note: n = 16 on Day 7, n = 15 on Day 14

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The mean concentration time profiles of TMC125 on day 7 and day 14 indicated that the mean concentrations of TMC125 on day 14 were higher than the mean concentrations of TMC125 on day 7. The mean C_{max} was reached at 3 hours post-dose on day 7 and at 4 hours on day 14.

Table 2 shows the pharmacokinetic parameters of 100 mg TMC125 b.i.d. on day 7 and day 14, with and without co-administration of methadone (historical controls).

Table 2: Pharmacokinetic parameters of 100 mg TMC125 b.i.d. on day 7 and day 14, with and without co-administration of methadone (historical controls)

Pharmacokinetics of TMC125 (mean \pm SD, t_{max} : median [range])	TMC125-C158		TMC125-C168
	Day 7 TMC125 + Methadone	Day 14 TMC125 + Methadone	Day 8 TMC125
n	16	15	23
C_{0h} , ng/mL	204.9 \pm 94.59	242.0 \pm 73.84	234 \pm 92
C_{min} , ng/mL	187.8 \pm 84.04	214.3 \pm 60.90	215 \pm 86
C_{max} , ng/mL	375.0 \pm 119.5	401.4 \pm 87.58	471 \pm 141
t_{max} , h	3.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)
AUC _{12h} , ng·h/mL	3282 \pm 1200	3567 \pm 858.5	3925 \pm 1251
$C_{ss,av}$, ng/mL	272.8 \pm 100.0	297.3 \pm 71.54	318 \pm 104
FI, %	72.51 \pm 21.71	64.72 \pm 18.32	84.9 \pm 33.6

The same dose (TMC125 100 mg b.i.d.) was used in the TMC125-C168 trial.

The pharmacokinetic parameters of TMC125 in subjects on a stable individualized methadone maintenance therapy on day 14 were in the range of the pharmacokinetic parameters previously observed after steady state administration of TMC125 100 mg b.i.d. (TMC125-C168).

Methadone

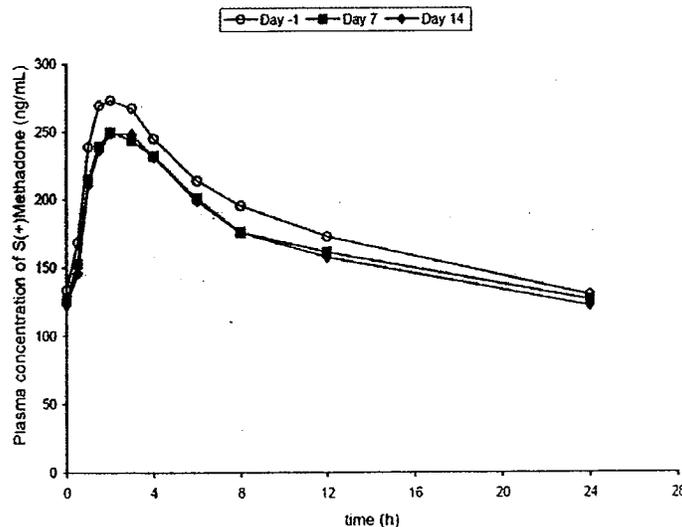
Two subjects took methadone as 60 mg and 70 mg suspension (instead of the tablets). The concentration-time profiles of these two subjects were within the range of the concentration-time profiles of the remaining subjects, therefore, these two subjects were included in the analysis. As previously indicated, for one subject, plasma samples could not be collected at some time points on day 14 due to difficulties with venipuncture. Therefore, the PK parameters of methadone were not determined in this subject. Full pharmacokinetic profiles of S(+) methadone and R(-) methadone were available for 16 subjects on day -1 and day 7 and for 15 subjects on day 14.

During the treatment phase with TMC125 and methadone, all subjects were 100 % compliant and took the study medication as planned i.e., 100 mg TMC125 b.i.d. for 14 days added on the subject's stable methadone therapy. The dose of methadone ranged from 60 mg to 130 mg. No adjustments in methadone dose were made for any subject.

S(+) Methadone

Fig 2 shows the mean plasma concentration time profile of S (+) methadone without (day -1) and with (day 7 and day 14) co-administration of TMC125 100 mg b.i.d. in subjects on a stable methadone therapy.

Fig 2: Mean plasma concentration time profile of S (+) methadone without (day -1) and with (day 7 and day 14) co-administration of TMC125 100 mg b.i.d. in subjects on a stable methadone therapy.



The mean concentrations of methadone on day 7 and day 14 were similar and were lower than the mean concentrations of methadone on day -1. The individual plasma concentration-time curves of S(+) methadone showed that for more than half the subjects,

the plasma concentrations on day -1 were similar or higher than the plasma concentrations on day 7 and day 14.

Table 3 shows the pharmacokinetic parameters of S(+) methadone without (day -1) and with (day 7 and day 14) co-administration of TMC125 100 mg b.i.d. in subjects on a stable methadone therapy.

Table 3: Pharmacokinetic parameters of S(+) methadone without (day -1) and with (day 7 and day 14) co-administration of TMC125 100 mg b.i.d. in subjects on a stable methadone therapy.

Pharmacokinetics of S(+)/Methadone (mean \pm SD, t_{max} : median [range])	Day -1 Methadone alone (reference)	Day 7 Methadone + TMC125 (test)	Day 14 Methadone + TMC125 (test)
n	16	16	15
C_{0h} , ng/mL	133.6 \pm 58.85	126.0 \pm 64.51	122.2 \pm 62.87
C_{min} , ng/mL	125.6 \pm 57.17	123.2 \pm 62.18	117.7 \pm 61.63
C_{max} , ng/mL	284.6 \pm 103.0	259.1 \pm 92.97	263.5 \pm 106.6
t_{max} , h	2.0 (1.0 - 3.0)	2.5 (1.5 - 4.05)	2.0 (1.5 - 4.0)
AUC_{24h} , ng.h/mL	4378 \pm 1809	4088 \pm 1705	4029 \pm 1834
$C_{ss,av}$, ng/mL	182.6 \pm 75.64	170.3 \pm 70.95	167.9 \pm 76.50
FI, %	91.44 \pm 24.91	87.59 \pm 31.05	93.48 \pm 26.81

Note: no dose adjustments for methadone were made during the trial.

The mean estimates of C_{0h} , C_{min} , C_{max} , AUC_{24h} , and $C_{ss,av}$ of S(+) methadone were slightly decreased on day 7 and day 14 (with co-administration of TMC125) compared to day -1 (methadone alone). The individual day 7/day -1 treatment ratios for C_{0h} , C_{min} , C_{max} , and AUC_{24h} ranged from, respectively, 49 % to 131 %, 59 % to 125 %, 65 % to 121 %, and 69 % to 122 % with geometric means of 90 %, 94 %, 91 %, and 93 %. The individual day 14/day -1 treatment ratios for C_{0h} , C_{min} , C_{max} , and AUC_{24h} ranged from, respectively, 55 % to 118 %, 62 % to 123 %, 67 % to 118 %, and 69 % to 121 % with geometric means of 87 %, 89 %, 89 %, and 89 %. The inter-individual variability, in part, can be due to the differences in the individualized maintenance dose of methadone in the subjects enrolled in the trial.

Table 4 shows the statistical evaluation of the pharmacokinetics of S (+) methadone on day 7 and day -1.

Table 4: Statistical evaluation of the pharmacokinetics of S (+) methadone on day 7 and day -1

Parameters of S(+) Methadone	LSmeans ^a		LSmeans ratio, %	90% CI,% ^b	p-value
	Day -1 Methadone alone (reference)	Day 7 Methadone + TMC125 (test)			Treatment
C _{0h} , ng/mL	121.6	109.7	90.21	80.63 - 100.9	0.1283
C _{min} , ng/mL	114.1	107.8	94.44	85.60 - 104.2	0.3236
C _{max} , ng/mL	266.9	243.4	91.21	84.77 - 98.15	0.0439
AUC _{24h} , ng.h/mL	4049	3749	92.59	86.38 - 99.24	0.0708

^a n=16 for Day -1 (reference) and n=16 for Day 7 (test)

^b 90% confidence intervals.

Table 5 shows the statistical evaluation of the pharmacokinetics of S(+) methadone on day 14 and day -1.

Table 5: Statistical evaluation of the pharmacokinetics of S(+) methadone on day 14 and day -1

Parameters of S(+) Methadone	LSmeans ^a		LSmeans ratio, %	90% CI,% ^b	p-value
	Day -1 Methadone alone (reference)	Day 14 Methadone + TMC125 (test)			Treatment
C _{0h} , ng/mL	121.6	105.6	86.86	78.63 - 95.96	0.0258
C _{min} , ng/mL	114.1	101.4	88.84	80.76 - 97.72	0.0460
C _{max} , ng/mL	266.9	238.5	89.36	82.50 - 96.79	0.0263
AUC _{24h} , ng.h/mL	4049	3604	89.02	82.45 - 96.11	0.0181

^a n=16 for Day -1 (reference) and n=15 for Day 14 (test)

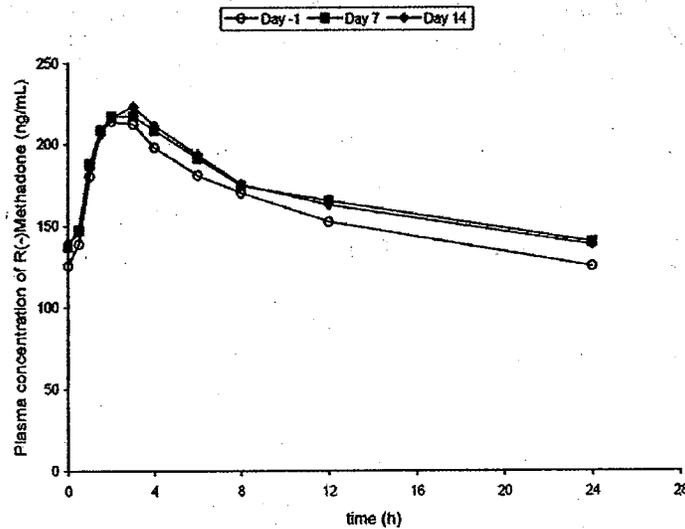
^b 90% confidence intervals.

The LS_{means} ratios of C_{0h}, C_{min}, C_{max}, AUC_{24h} of S (+) methadone were decreased by 10 %, 6 %, 9 %, and 7 % on day 7 and 13 %, 11 %, 11 %, and 11 % on day 14 when methadone was co-administered with TMC125 as compared to when methadone was administered alone.

R(-) Methadone (pharmacologically active isomer)

Fig 3 shows the mean plasma concentration time profile of R (-) methadone without (day -1) and with (day 7 and day 14) co-administration of TMC125 100 mg b.i.d. in subjects on a stable methadone therapy.

Fig 3: Mean plasma concentration time profile of R (-) methadone without (day -1) and with (day 7 and day 14) co-administration of TMC125 100 mg b.i.d. in subjects on a stable methadone therapy



The mean steady state plasma concentration-time profiles of R(-) methadone were higher when combined with TMC125 as compared to when methadone was administered alone. The individual plasma concentration-time curves of R(-) methadone showed that for more than half of the subjects, the plasma concentrations of R(-) methadone on day -1 were similar or lower than the plasma concentrations of methadone on day 7 and day 14. Further, for more than half the subjects, the plasma concentrations of methadone on day 14 were similar or lower than the plasma concentrations on day 7.

Table 6 shows the pharmacokinetic parameters of R(-) methadone without (day-1) and with (day 7 and day 14) co-administration of TMC125 100 mg b.i.d.

Table 6: Pharmacokinetic parameters of R(-) methadone without (day-1) and with (day 7 and day 14) co-administration of TMC125 100 mg b.i.d.

Pharmacokinetics of R(-)Methadone (mean \pm SD, t_{max} : median [range])	Day -1 Methadone alone (reference)	Day 7 Methadone + TMC125 (test)	Day 14 Methadone + TMC125 (test)
n	16	16	15
C_{0h} , ng/mL	125.4 \pm 39.26	137.2 \pm 47.32	139.6 \pm 49.17
C_{min} , ng/mL	120.4 \pm 38.73	135.3 \pm 44.65	134.0 \pm 44.99
C_{max} , ng/mL	222.0 \pm 73.55	225.8 \pm 68.87	228.2 \pm 74.53
t_{max} , h	2.0 (1.5 - 4.0)	3.0 (1.5 - 6.0)	3.0 (1.5 - 4.0)
AUC_{24h} , ng h/mL	3807 \pm 1301	4070 \pm 1229	4038 \pm 1309
$C_{ss,av}$, ng/mL	158.7 \pm 54.36	169.5 \pm 51.18	168.3 \pm 54.58
FL, %	64.47 \pm 15.03	54.64 \pm 13.94	56.69 \pm 10.95

Note: No dose adjustments for methadone were made during the trial.

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The mean estimates of C_{0h} , C_{min} , C_{max} , AUC_{24h} , and $C_{ss,av}$ of R(-) methadone were slightly increased on day 7 and day 14 (with co-administration of TMC125) compared to day -1 (methadone alone). The individual day 7/day -1 treatment ratios for C_{0h} , C_{min} , C_{max} , and AUC_{24h} ranged from, respectively, 75 % to 134 %, 80 % to 138 %, 81 % to 128 %, and 88 % to 131 % with geometric means of 108 %, 112 %, 103 %, and 108 %. The individual day 14/day -1 treatment ratios for C_{0h} , C_{min} , C_{max} , and AUC_{24h} ranged from, respectively, 81 % to 140 %, 84 % to 139 %, 82 % to 132 %, and 87 % to 133 % with geometric means of 110 %, 110 %, 102 %, and 106 %. The inter-individual variability of the ratios, in part, can be due to the differences in the individualized maintenance dose of methadone in the subjects enrolled in the trial.

Table 7 shows the statistical evaluation of the pharmacokinetics of R(-) methadone on day 7 and day -1.

Table 7: Statistical evaluation of the pharmacokinetics of R(-) methadone on day 7 and day -1

Parameters of R(-) Methadone	LSmeans ^a		LSmeans ratio, %	90% CI,% ^b	p-value
	Day -1 Methadone alone (reference)	Day 7 Methadone + TMC125 (test)			Treatment
C_{0h} , ng/mL	119.7	129.4	108.1	100.7 - 116.1	0.0738
C_{min} , ng/mL	114.8	128.1	111.6	104.5 - 119.1	0.0102
C_{max} , ng/mL	211.2	216.5	102.5	96.81 - 108.5	0.4599
AUC_{24h} , ng.h/mL	3619	3894	107.6	102.2 - 113.2	0.0242

^a n=16 for Day -1 (reference) and n=16 for Day 7 (test)

^b 90% confidence intervals.

Table 8 shows the statistical evaluation of the pharmacokinetics of R(-) methadone on day 14 and day -1.

Table 8: Statistical evaluation of the pharmacokinetics of R(-) methadone on day 14 and day -1

Parameters of R(-) Methadone	LSmeans ^a		LSmeans ratio, %	90% CI,% ^b	p-value
	Day -1 Methadone alone (reference)	Day 14 Methadone + TMC125 (test)			Treatment
C_{0h} , ng/mL	119.7	131.4	109.8	102.2 - 117.9	0.0379
C_{min} , ng/mL	114.8	126.4	110.1	102.3 - 118.5	0.0366
C_{max} , ng/mL	211.2	215.2	101.9	95.66 - 108.5	0.6125
AUC_{24h} , ng.h/mL	3619	3835	106.0	99.33 - 113.0	0.1370

^a n=16 for Day -1 (reference) and n=15 for Day 14 (test)

^b 90% confidence intervals.

The LSmeans ratios of C_{0h} , C_{min} , C_{max} , AUC_{24h} of R(-) methadone were increased by 8 %, 12 %, 3 %, and 8 % on day 7 and 10 %, 10 %, 2 %, and 6 % on day 14 when methadone

was co-administered with TMC125 as compared to when methadone was administered alone.

Reviewer's Comment Regarding Dose of TMC125 used in the Trial

The dose of TMC125 administered in the current trial (100 mg b.i.d. using F060) was lower than the proposed clinical dose of 200 mg b.i.d (using F060). The within study and cross study comparison of TMC125 pharmacokinetic parameters suggests a significantly higher steady state plasma concentrations of TMC125 after administration of 200 mg b.i.d. (using F060) as compared to steady state plasma concentrations of TMC125 after 100 mg b.i.d (using F060).

TMC125 is a substrate and inducer of CYP3A4 and methadone is a substrate of CYP3A4 therefore, the degree of CYP3A4 induction (and consequently methadone metabolism) by TMC125 maybe higher after administration of TMC125 200 mg b.i.d. as compared to TMC125 100 mg b.i.d.

Pharmacokinetic Results Summary

- The LS_{means} ratios of C_{0h}, C_{min}, C_{max}, AUC_{24h} of S (+) methadone were decreased by 10 %, 6 %, 9 %, and 7 % on day 7 and 13 %, 11 %, 11 %, and 11 % on day 14 when methadone was co-administered with TMC125 as compared to when methadone was administered alone.
- The LS_{means} ratios of C_{0h}, C_{min}, C_{max}, AUC_{24h} of R (-) methadone were increased by 8 %, 12 %, 3 %, and 8 % on day 7 and 10 %, 10 %, 2 %, and 6 % on day 14 when methadone was co-administered with TMC125 as compared to when methadone was administered alone.
- The pharmacokinetic parameters of TMC125 in subjects on a stable individualized methadone maintenance therapy on day 14 were in the range of the pharmacokinetic parameters previously observed after steady state administration of TMC125 100 mg b.i.d. (TMC125-C168).

Conclusion

INTELENCE™ and methadone can be co-administered without dose adjustments, however, clinical monitoring for withdrawal symptoms is recommended as methadone maintenance therapy may need to be adjusted in some patients.

Study Number
TMC125-C159

Title

Phase I, open-label trial to investigate the effect of TMC125 at steady state on sildenafil pharmacokinetics in healthy male subjects.

Objectives

The primary objective of the trial was to determine the effect of steady state concentrations of TMC125 on single dose pharmacokinetics of sildenafil and its active metabolite N-desmethyl sildenafil.

Study Design

Open label, randomized, 2-way crossover trial in 16 healthy male subjects. The following two treatments were administered:

Treatment A: Single dose of 50 mg sildenafil.

Treatment B: 13 days of treatment with TMC125 800 mg b.i.d. followed by a single 800 mg dose of TMC125 co-administered with a single dose of 50 mg sildenafil on day 14.

Subjects randomized to **group 1** received **treatment A** in **session 1** and **treatment B** in **session 2**; subjects randomized to **group 2** received **treatment B** in **session 1** and **treatment A** in **session 2**. All treatments were given under fed conditions and the two sessions were separated by a washout period of at least 14 days. Full pharmacokinetic profiles of sildenafil and N-desmethyl sildenafil were determined up to 48 hours after sildenafil intake on **day 1** in **treatment A** and **day 14** on **treatment B**. A full pharmacokinetic profile of TMC125 up to 12 hours was determined after the morning dose on **day 14** of **treatment B**.

Investigational Product(s)

TMC125 was formulated as TF035; this tablet formulation contains 200 mg TMC125 HPMC, lactose. The batch number used was D03108 (expiry date: February, 2005).

Sildenafil (Viagra®; Pfizer) was provided as a tablet containing 50 mg sildenafil as sildenafil citrate. The batch # was 3097103 (expiry date: September, 2008).

Assay Methods

The plasma concentrations of TMC125, sildenafil, and N-desmethyl sildenafil were determined using a validated liquid chromatographic with tandem mass spectrometry (LC-MS/MS) method. The lower limit of quantification (LLOQ) was 2 ng/mL for all the compounds.

Pharmacokinetic and Statistical Data Analysis

Pharmacokinetic Analysis

Pharmacokinetic and statistical analysis was performed using SAS System for Windows® version 8.2 (SAS Institute Inc., Cary, NC). A non-compartmental model with extravascular input was used for the pharmacokinetic analysis. Based on the individual plasma concentration-time data and using the scheduled sampling times, the standard pharmacokinetic parameters were calculated.

Statistical Analysis

The primary pharmacokinetic parameters were C_{max} , AUC_{last} , and AUC_{∞} for sildenafil and its metabolite on the logarithmic scale.

RESULTS

Subject Disposition and Demographics

Out of the 33 subjects screened, 15 subjects were randomized to one of the two groups of 7 subjects and 8 subjects, respectively. One subject randomized to treatment sequence A-B withdrew consent after the first day of session 2. This subject completed treatment A (sildenafil alone) and was included in the analysis of treatment A.

Table 1 shows the demographics in trial TMC125-C159.

Table 1: Demographics in Trial TMC125-C159

Parameter	sildenafil / TMC125 + sildenafil N = 7	TMC125 + sildenafil / sildenafil N = 8	All Subjects N = 15
Gender, n(%)			
male	7 (100)	8 (100)	15 (100)
Age, years			
median (range)	30.0 (23.0-39.0)	32.5 (25.0-50.0)	32.0 (23.0-50.0)
Height, cm			
median (range)	181 (170-187)	183 (169-190)	181 (169-190)
Weight, kg			
median (range)	82.3 (58-94)	79.5 (61-111)	82.3 (58-111)
BMI, kg/m ²			
median (range)	24.7 (20-29)	24.0 (20-32)	24.2 (20-32)
Type of smoker, n (%)			
Nonsmoker	5 (71)	5 (63)	10 (67)
Light smoker	2 (29)	3 (38)	5 (33)

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Pharmacokinetics

Due to the withdrawal of consent by 1 subject randomized to treatment sequence A-B, 15 subjects provided complete concentration-time profiles for sildenafil alone (treatment A) and 14 subjects provided complete concentration-time profiles for sildenafil + TMC125 (treatment B).

For one subject randomized to treatment sequence B-A, the 10 hour sample on day 14 after co-administration of TMC125 and sildenafil showed an unexpectedly low concentration of TMC125 (— ng/mL). The wash-out sample for this subject showed an unexpectedly higher concentration of TMC125 (— ng/mL), suggesting a possible switch of the samples. Therefore, this sample was excluded from the descriptive statistics and pharmacokinetic parameter calculation for TMC125.

TMC125

Table 2 shows the pharmacokinetic parameters of TMC125, with or without co-administration of sildenafil.

Table 2: Pharmacokinetic parameters of TMC125, with or without co-administration of sildenafil.

Pharmacokinetics of TMC125 ¹ (mean±SD, t _{max} , median [range])	sildenafil + TMC125 Test	TMC125 alone (range of means from other studies ²)
n	14	15-19
t _{max} , h	3.50 [2.00-6.00]	3.00 - 4.00
C _{0h} , ng/mL	501 ± 195	439 - 840
C _{min} , ng/mL	464 ± 195	428 - 760
C _{max} , ng/mL	795 ± 266	759 - 1548
AUC _{12h} , ng.h/mL	7538 ± 2663	7262 - 13816
C _{ss, av} , ng/mL	628 ± 222	713 - 1151
FI, %	54.5 ± 24.1	49.5 - 75.6

¹ Pharmacokinetic parameters on Day 8 after the administration of 800 mg TMC125 b.i.d. formulation TF035 in healthy subjects

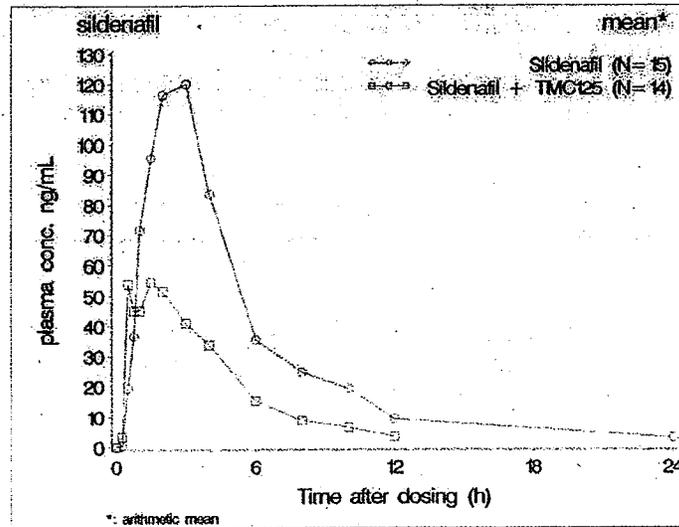
² Studies: TMC125-C138, TMC125-C157, TMC125-C161, TMC125-C164, TMC125-C165 (reports in preparation at the time of reporting), and TMC125-C139

Based on the cross-study comparison, the mean estimates of all the steady state pharmacokinetic parameters of TMC125 after co-administration with sildenafil were similar to the mean estimates of steady state pharmacokinetic parameters of TMC125 when administered alone.

Sildenafil

Fig 1 shows the mean plasma concentration-time profile for sildenafil after a single 50 mg dose of sildenafil, with and without co-administration of TMC125 800 mg b.i.d.

Fig 1: Mean plasma concentration-time profile for sildenafil after a single 50 mg dose of sildenafil, with and without co-administration of TMC125 800 mg b.i.d.



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Table 3 shows the pharmacokinetic parameters of sildenafil, with or without co-administration of TMC125.

Table 3: Pharmacokinetic parameters of sildenafil, with or without co-administration of TMC125.

Pharmacokinetics of sildenafil (mean±SD, t _{max} , median [range])	sildenafil + TMC125 Test	sildenafil alone Reference
n	14	15
t _{max} , h	1.50 [0.50-4.00]	2.00 [0.50-3.00]
C _{max} , ng/mL	110.6 ± 90.7	163.3 ± 47.7
AUC _{last} , ng.h/mL	264 ± 97	612 ± 236
AUC _∞ , ng.h/mL	277 ± 99	640 ± 232
t _{1/2term} , h	2.61 ± 0.27	2.98 ± 0.69

Table 4 shows the statistical evaluation of the pharmacokinetic parameters of sildenafil, with or without co-administration of TMC125.