

Table 4: Statistical evaluation of the pharmacokinetic parameters of sildenafil, with or without co-administration of TMC125

Sildenafil	n		Least squares means				p-value		
			sildenafil+ TMC125 Test	sildenafil alone Reference	Treatment ratio, % and 90% CI*		Treatment	Period	Sequence
Parameter	Test / Ref.								
C_{max} ng/mL	14 / 15		87	158	55	40-75	0.0047	0.4502	0.4835
AUC_{last} ng.h/mL	14 / 15		248	578	43	36-51	<.0001	0.4763	0.3892
AUC_{∞} ng.h/mL	14 / 15		263	608	43	37-51	<.0001	0.5776	0.3688

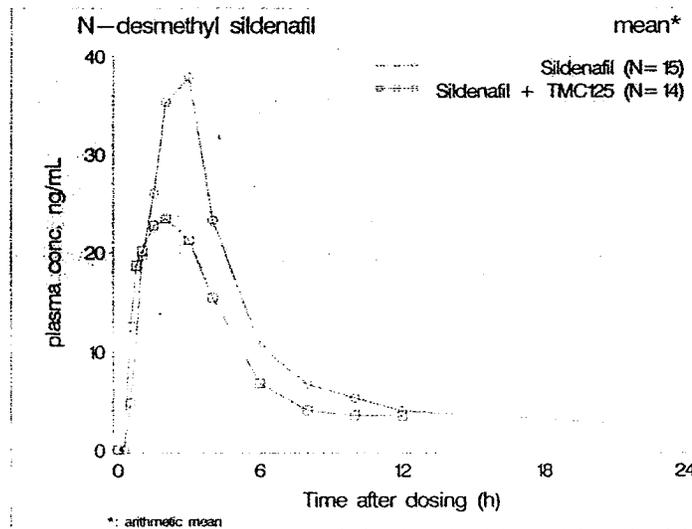
* 90% confidence interval

The LS_{means} ratios of C_{max} , AUC_{last} , and AUC_{∞} of sildenafil were decreased by 45 %, 57 %, and 57 %, respectively, when sildenafil was co-administered with TMC125 as compared to when sildenafil was administered alone.

N-Desmethyl Sildenafil

Fig 2 shows the mean plasma concentration-time profile for N-desmethyl sildenafil after a single 50 mg dose of sildenafil, with and without co-administration of TMC125 800 mg b.i.d.

Fig 2: Mean plasma concentration-time profile for N-desmethyl 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 5 shows the pharmacokinetic parameters of N-desmethyl sildenafil, after a single dose of 50 mg sildenafil, with or without co-administration of TMC125 800 mg b.i.d.

Table 5: Pharmacokinetic parameters of N-desmethyl sildenafil, after a single dose of 50 mg sildenafil, with or without co-administration of TMC125 800 mg b.i.d.

Pharmacokinetics of N-desmethyl sildenafil (mean±SD, t _{max} : median [range])	sildenafil + TMC125 Test	sildenafil alone Reference
n	14	15
t _{max} , h	1.75 [0.50-4.00]	2.00 [0.75-3.00]
C _{max} , ng/mL	43.3 ± 23.1	53.2 ± 19.8
AUC _{last} , ng.h/mL	110 ± 55	177 ± 80
AUC _∞ , ng.h/mL	121 ± 59	194 ± 83
t _{1/2term} , h	2.56 ± 0.97	3.50 ± 1.01

Table 6 shows the statistical evaluation of the pharmacokinetic parameters of N-desmethyl sildenafil, after a single dose of 50 mg sildenafil, with or without co-administration of TMC125 800 mg b.i.d.

Table 6: Statistical evaluation of the pharmacokinetic parameters of N-desmethyl sildenafil after a single dose of 50 mg sildenafil, with or without co-administration of TMC125 800 mg b.i.d.

N-desmethyl sildenafil	n		Least squares means				p-value		
	Test / Ref.		sildenafil+ TMC125 Test	sildenafil alone Reference	Treatment ratio, % and 90% CI*		Treatment	Period	Sequence
C _{max} , ng/mL	14	15	38	50	75	59-96	0.0639	0.1310	0.4033
AUC _{last} , ng.h/mL	14	15	98	164	59	52-68	<.0001	0.1824	0.3039
AUC _∞ , ng.h/mL	14	15	109	182	60	52-69	<.0001	0.3120	0.2689

* 90% confidence interval

The LS_{means} ratios of C_{max}, AUC_{last}, and AUC_∞ of N-desmethyl sildenafil (after a single 50 mg dose of sildenafil) were decreased by 25 %, 41 %, and 40 %, respectively, when sildenafil was co-administered with TMC125 as compared to when sildenafil was administered alone.

Pharmacokinetic Results Summary

- 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.
- The LS_{means} ratios of C_{max}, AUC_{last}, and AUC_∞ of sildenafil were decreased by 45 %, 57 %, and 57 %, respectively, when sildenafil was co-administered with TMC125 as compared to when sildenafil was administered alone.

- The LS_{means} ratios of C_{max} , AUC_{last} , and AUC_{∞} of N-desmethyl sildenafil (after a single 50 mg dose of sildenafil) were decreased by 25 %, 41 %, and 40 %, respectively, when sildenafil was co-administered with TMC125 as compared to when sildenafil was administered alone.

Conclusion

INTELENCE™ and sildenafil can be co-administered without dose adjustments, however, the dose of sildenafil may need to be altered based on clinical effect.

**APPEARS THIS WAY
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Study Number
TMC125-C161

Title

Phase I, open-label trial to investigate the pharmacokinetic interaction between tipranavir (TPV)/ritonavir (RTV) and TMC125 at steady-state in healthy subjects.

Objectives

The primary objective of the trial was to evaluate the effect of steady state pharmacokinetics of TPV/RTV on the steady-state pharmacokinetics of TMC125 and to evaluate the effect of steady-state pharmacokinetics of TMC125 on the steady-state pharmacokinetics of TPV/RTV.

Study Design

Phase I, open label, randomized, 2-way crossover trial. 24 subjects were randomized to 2 panels (**panel 1** and **panel 2**) in a 1:1 ratio (12 subjects in each panel). Each panel consisted of two sessions (separated by a washout period of at least 14 days): **session A** and **session B1** for **panel 1**, and **session A** and **session B2** for **panel 2**. Within each panel, the subjects were randomized equally to the two sessions.

Session A:

800 mg b.i.d. TMC125 for 7 days with an additional morning dose on **day 8**. The PK during the 12-hour dosing interval for TMC125 was assessed on **day 8**.

Session B1:

Subjects received TPV/RTV 500/200 mg b.i.d. for 15 days with an additional morning dose on day 16, co-administered with 800 mg b.i.d. TMC125 from days 9 through 15, with an additional morning dose on day 16. The steady state (12-hour) PK of TMC125 was assessed on day 16 to evaluate the effect of TPV/RTV on the PK of TMC125. The PK during the 12 hour dosing interval for TPV/RTV were determined on **day 8** and **day 16** to investigate the effect of TMC125 on the pharmacokinetics of TPV/RTV.

Session B2:

Subjects received TPV/RTV 500/200 mg b.i.d. for 15 days with an additional morning dose on day 16, co-administered with 800 mg b.i.d. TMC125 from days 1 through 7, with an additional morning dose on day 8. The steady state (12-hour) PK of TMC125 was assessed on day 8 to evaluate the effect of TPV/RTV on the PK of TMC125. The steady state (12-hour) PK of TPV/RTV was determined on **day 8** and **day 16** to investigate the potential effect of TMC125 on the pharmacokinetics of TPV/RTV.

Prior to the first intake in each session, subjects had to be fasted overnight for at least 10 hours (except for the intake of water which was allowed until 2 hours before intake of trial medication). The trial medication (TPV/RTV and TMC125) was to be taken under fed conditions, within 15 minutes after completion of a meal. The evening intake (mainly at home) of the medication(s) was to be taken within 15 minutes of completion of the meal with approximately 200 mL of water. The subjects were admitted to the testing facility the night before pharmacokinetic sampling days (day 8 of session A, session B1, or session B2 and day 16 of session B1 and session B2) and were discharged the next day.

Investigational Product(s)

TMC125 was formulated as TF035; this tablet formulation contains 200 mg TMC125, HPMC, lactose. The batch number used was D03109 (expiry date: December, 2004). TPV was supplied as a liquid-filled soft gelatin capsule containing 250 mg TPV; the batch number used was PD-2448B (expiry date: July 2005). RTV was supplied as a 100 mg capsule; the batch number used was 16238VA (expiry date: April 2006).

Assay Methods

The plasma concentrations of TMC125, TPV, 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, 1000 ng/mL for TPV, and 25 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

A total of 12 subjects per panel were included in this exploratory crossover trial. A minimum of at least 10 subjects completing all the sessions were considered sufficient to allow for relevant conclusions. Descriptive statistics were calculated for the plasma concentrations of TMC125, TPV, and RTV. The statistical analysis was performed for TMC125 by using treatment with TPV/RTV as test treatment and treatment without TPV/RTV as reference treatment. The statistical analysis was performed for TPV/RTV by using treatment with TMC125 as test treatment and treatment without TMC125 as reference treatment. The primary pharmacokinetic parameters were C_{0h} , C_{min} , C_{12h} , C_{max}

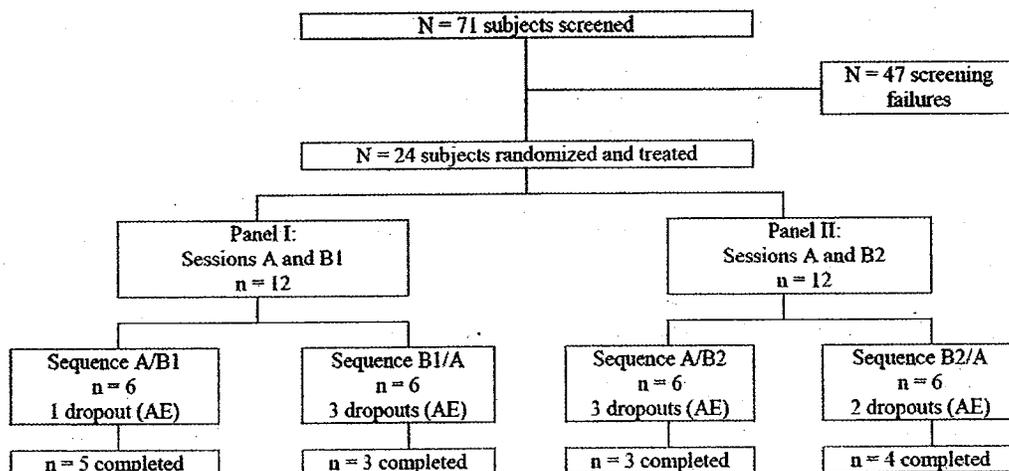
and AUC_{12h} for TMC125, TPV, and RTV on the logarithmic scale. All observations, paired or unpaired, for the test and reference were included in the statistical analysis.

RESULTS

Subject Disposition and Demographics

Out of the 71 subjects screened, 24 subjects were randomized to the two panels and started treatment. Fig 1 shows the subject disposition in the trial.

Fig 1: Subject Disposition in Trial TMC125-C161



Session A: 800 mg TMC125 b.i.d. for 7 days and once daily (q.d.) on Day 8.

Session B1: 500/200 mg TPV/RTV b.i.d. for 15 days and q.d. on Day 16; 800 mg TMC125 b.i.d. from Days 9 to 15 and q.d. on Day 16.

Session B2: 500/200 mg TPV/RTV b.i.d. for 15 days and q.d. on Day 16; 800 mg TMC125 b.i.d. from Days 1 to 7 and q.d. on Day 8.

Table 1 shows the demographics in the trial.

Table 1: Demographics in Trial TMC125-C161

Demographic Parameter	Panel I N = 12	Panel II N = 12	All Panels N = 24
Age, years Median (range)	39.0 (19-55)	31.5 (23-54)	37.5 (19-55)
Height, cm Median (range)	177.5 (165-192)	181.0 (156-194)	178.0 (156-194)
Weight, kg Median (range)	80.5 (68-103)	73.5 (50-102)	78.5 (50-103)
BMI, kg/m ² Median (range)	25.3 (19-30)	22.4 (19-30)	24.9 (19-30)
Gender, n (%)			
Male	10 (83.3)	9 (75.0)	19 (79.2)
Female	2 (16.7)	3 (25.0)	5 (20.8)
Ethnic origin, n (%)			
White/Caucasian	12 (100.0)	11 (91.7)	23 (95.8)
Oriental/Asian		1 (8.3)	1 (4.2)
Type smoker, n (%)			
Light smoker	5 (41.7)	3 (25.0)	8 (33.3)
Nonsmoker	7 (58.3)	9 (75.0)	16 (66.7)

Pharmacokinetics

Table 2 shows the subjects who dropped out of the study and the available pharmacokinetic data from those subjects.

Table 2: Drop Out Subjects from Trial TMC125-C161

CRF ID	Sequence	Last Measurement	Profile(s) TMC125 Alone	Profile(s) TPV/RTV Alone	Profile(s) TMC125 + TPV/RTV
1610002	B1/A	B1: Day 5, predose	no	no	no
1610017	B2/A	B2: Day 8, 12 h ^a	no	no	yes
1610019	B1/A	B1: Day 11, predose	no	yes	no
1610026	B1/A	B1: Day 7, predose ^b	no	yes	no
1610028	A/B1	B1: Day 7, predose	yes	no	no
1610047	A/B2	B2: Day 1, predose	yes	no	no
1610051	A/B2	B2: Day 13, predose	yes	no	yes
1610053	A/B2	B2: Day 11, predose	yes	no	yes
1610070	B2/A	B2: Day 8, 12 h ^a	no	no	yes
Number available profiles (total)			n = 19	n = 17	n = 19

^a no dropout sample taken

TMC125

Fig 2 shows the mean plasma concentration-time profile of TMC125 after 8 days of dosing with TMC125 800 mg b.i.d., with or without co-administration of TPV/RTV 500/200 mg b.i.d. (panel 1 and panel 2 combined)

Fig 2: Mean plasma concentration-time profile of TMC125 after 8 days of dosing with TMC125 800 mg b.i.d., with or without co-administration of TPV/RTV 500/200 mg b.i.d. (panel 1 and panel 2 combined)

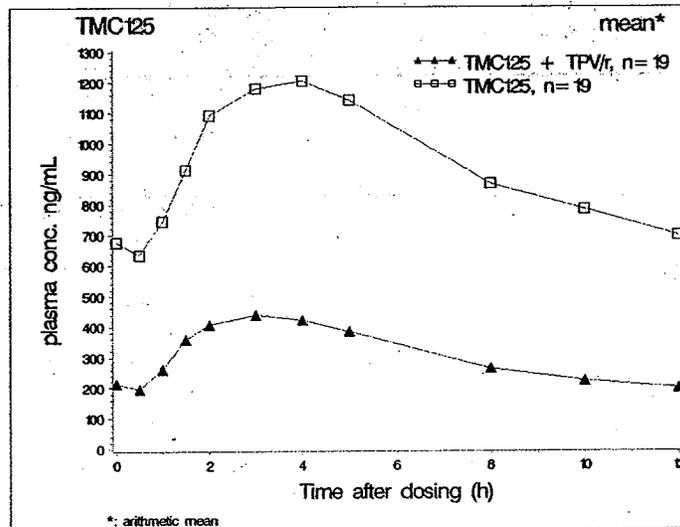


Table 3 shows the pharmacokinetic parameters of TMC125 800 mg b.i.d., with or without co-administration of TPV/RTV.

Table 3: Pharmacokinetic parameters of TMC125 800 mg b.i.d., with or without co-administration of TPV/RTV

Pharmacokinetics of TMC125 mean \pm SD, t_{max} : median (range)	TMC125 + TPV/RTV Test	TMC125 Alone Reference
n	19	19
t_{max} , h	3.0 (2.0-5.0)	4.0 (2.0-8.0)
C_{0h} , ng/mL	214 \pm 259	676 \pm 254
C_{min} , ng/mL	183 \pm 234	625 \pm 227
C_{max} , ng/mL	456 \pm 307	1263 \pm 345
AUC_{12h} , ng.h/mL	3697 \pm 3336	11236 \pm 3210
$C_{ss,av}$, ng/mL	308 \pm 278	936 \pm 267
FI, %	105.5 \pm 39.7	69.6 \pm 13.9

Table 4 shows the statistical evaluation of the pharmacokinetic parameters of TMC125 800 mg b.i.d., with or without co-administration of TPV/RTV.

Table 4: Statistical evaluation of the pharmacokinetic parameters of TMC125 800 mg b.i.d., with or without co-administration of TPV/RTV

TMC125	n		LSmeans				p-Value		
			TMC125 +TPV/RTV	TMC125 Alone	Treatment Ratio, % and 90% CI		Treatm.	Period	Sequence
Parameter	Test / Ref.	Test	Reference	Test/Reference					
C _{0h} , ng/mL	19 19	143	751	19	13 - 27	<.0001	0.2204	0.7551	
C _{min} , ng/mL	19 19	122	680	18	13 - 25	<.0001	0.1967	0.6090	
C _{max} , ng/mL	19 19	379	1288	29	22 - 40	<.0001	0.5748	0.5189	
AUC _{12h} , ng.h/mL	19 19	2863	11965	24	18 - 33	<.0001	0.3411	0.5912	
		Median		p-Value (Koch Analysis)					
Parameter	Test / Ref.	TMC125 +TPV/RTV	TMC125 Alone	Treatment	Period	Sequence			
t _{max} , h	19 19	3.0	4.0	0.2450	0.7102	1.0000			

The results of the statistical analysis showed that co-administration of TMC125 with TPV/RTV decreased the LS_{means} of C_{0h}, C_{min}, C_{max}, and AUC_{12h} of TMC125 by 81 %, 82 %, 71 %, and 76 %, respectively, as compared to when TMC125 was administered alone.

TPV

Fig 3 shows the mean plasma concentration-time profile of TPV (administered as TPV/RTV 500/200 mg b.i.d.) after 8 days of dosing with or without TMC125.

Fig 3: Mean plasma concentration-time profile of TPV (administered as TPV/RTV 500/200 mg b.i.d.) after 8 days of dosing with or without TMC125

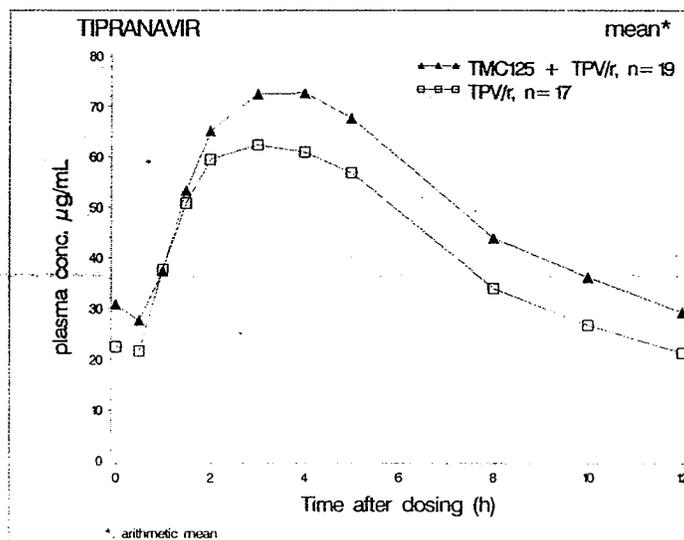


Table 5 shows the pharmacokinetic parameters of TPV (administered as 500/200 mg b.i.d. TPV/RTV) with or without co-administration of TMC125.

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Table 5: Pharmacokinetic parameters of TPV (administered as 500/200 mg b.i.d. TPV/RTV) with or without co-administration of TMC125

Pharmacokinetics of TPV mean \pm SD, t_{max} , median (range)	TPV/RTV + TMC125 Test	TPV/RTV Alone Reference
n	19	17
t_{max} , h	4.0 (2.0-5.0)	3.0 (1.5-5.0)
C_{0h} , ng/mL	30.8 \pm 26.4	22.5 \pm 13.4
C_{12h} , ng/mL	29.2 \pm 26.2	21.6 \pm 11.7
C_{min} , ng/mL	25.5 \pm 24.3	18.6 \pm 10.4
C_{max} , ng/mL	77.8 \pm 30.5	68.5 \pm 22.5
AUC _{12h} , ng.h/mL	607.4 \pm 329.1	503.1 \pm 188.3
$C_{ss,av}$, ng/mL	50.6 \pm 27.4	41.9 \pm 15.7
FI, %	117.7 \pm 37.2	126.5 \pm 28.5

Table 6 shows the statistical analysis of the pharmacokinetic parameters of TPV (administered as 500/200 mg b.i.d. TPV/RTV) with or without co-administration of TMC125.

Table 6: Statistical analysis of the pharmacokinetic parameters of TPV (administered as 500/200 mg b.i.d. TPV/RTV) with or without co-administration of TMC125.

TPV Parameter	n		LSmeans				p-Value		
	Test / Ref.		TMC125 +TPV/RTV Test	TPV/RTV Alone Reference	Treatment Ratio, % and 90% CI Test/Reference		Treatm.	Period	Sequence
C_{0h} , μ g/mL	19	17	24.6	19.3	127	101 - 161	0.0905	0.0159	0.0006
C_{12h} , μ g/mL	19	17	23.6	18.8	125	107 - 148	0.0296	0.0014	0.0012
C_{min} , μ g/mL	19	17	19.6	15.8	124	96 - 159	0.1537	0.0130	0.0012
C_{max} , μ g/mL	19	17	76.0	66.7	114	102 - 127	0.0600	0.0710	0.0042
AUC _{12h} , μ g.h/mL	19	17	569.8	481.4	118	103 - 136	0.0522	0.0815	0.0021
Parameter	n		Median		p-Value (Koch Analysis)				
	Test / Ref.		TMC125 +TPV/RTV Test	TPV/RTV Alone Reference	Treatment	Period	Sequence		
t_{max} , h	19 ^a	17	4.0	3.0	0.2350	0.6628	0.8368		

^a n= 17 for Koch analysis

For C_{0h} and C_{min} , no significant treatment effects were observed after the combined treatment compared to TPV/RTV alone. The C_{12h} increased by 25 %; however, there were significant sequence and period effects for this comparison. The C_{max} and AUC_{12h} of TPV increased 14 % and 18 %, respectively; however, there was a significant sequence effect.

RTV

Table 7 shows the pharmacokinetic parameters of RTV after administration of TPV/RTV, either alone or in combination with TMC125.

Table 7: Pharmacokinetic parameters of RTV after administration of TPV/RTV, either alone or in combination with TMC125

Pharmacokinetics of RTV mean \pm SD, t_{max} : median (range)	TPV/RTV + TMC125 Test	TPV/RTV Alone Reference
n	19	17
t_{max} , h	4.0 (2.0-5.0)	5.0 (1.0-5.0)
C_{0h} , ng/mL	261 \pm 202	178 \pm 247
C_{12h} , ng/mL	121 \pm 109	124 \pm 90
C_{min} , ng/mL	97 \pm 87	84 \pm 85
C_{max} , ng/mL	2237 \pm 1053	1874 \pm 861
AUC _{12h} , ng.h/mL	10561 \pm 5076	8542 \pm 3952
$C_{ss,av}$, ng/mL	880 \pm 423	712 \pm 329
FI, %	247.9 \pm 43.4	255.0 \pm 45.4

Pharmacokinetic Results Summary

- Co-administration of TMC125 with TPV/RTV decreased the LS_{means} of C_{0h} , C_{min} , C_{max} , and AUC_{12h} of TMC125 by 81 %, 82 %, 71 %, and 76 %, respectively, as compared to when TMC125 was administered alone.
- Co-administration of TMC125 with TPV/RTV increased the LS_{means} of C_{0h} , C_{min} , C_{max} , and AUC_{12h} of TMC125 by 27 %, 24 %, 14 %, and 18 %, respectively, as compared to when TPV/RTV was administered alone

Conclusion

Based on the decrease in the systemic exposure of TMC125 (76 %) when TMC125 was co-administered with TPV/RTV as compared to when TMC125 was administered alone, TMC125 should not be co-administered with TPV/RTV.

**APPEARS THIS WAY
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Study Number
TMC125-C164

Title

Phase I, open-label, randomized, 2-way crossover trial to investigate the pharmacokinetic interaction of steady-state TMC125 and atorvastatin in healthy subjects.

Objectives

The primary objective of the present trial was to determine the effect of steady state plasma concentrations of TMC125 (TF035) on the pharmacokinetics of atorvastatin and atorvastatin metabolites (atorvastatin lactone and 2- and 4-hydroxy atorvastatin) and to determine the effect of steady state plasma concentrations of atorvastatin on the steady state pharmacokinetics of TMC125.

Study Design

Phase 1, open label, randomized trial. The trial was divided into two treatment sessions in which atorvastatin alone (**treatment A**) or a combination of TMC125 and atorvastatin (**treatment B**) was given. Subjects randomized to **sequence 1** started with **treatment A** and subjects randomized to **sequence 2** started with **treatment B** in **session 1**. After a washout of 14 days, subjects randomized to **treatment A** in **session 1** were administered **treatment B** in **session 2** and subjects randomized to **treatment B** in **session 1** were administered **treatment A** in **session 2**. All the medications were administered within 10 minutes after completion of breakfast.

The following two treatments were administered:

Treatment A: 40 mg atorvastatin q.d. for 4 days.

Treatment B: TMC125 800 mg b.i.d for 13 days with co-administration of 40 mg atorvastatin q.d. from **day 8** to **day 11**.

Full pharmacokinetic profiles of atorvastatin, atorvastatin lactone and 2- and 4-hydroxy-atorvastatin were determined on **day 4** of **treatment A** and on **day 11** of **treatment B**. A full pharmacokinetic profile of TMC125 was determined on **day 7** and **day 11** of **treatment B**.

Investigational Product(s)

TMC125 was provided as TF035, a tablet containing 200 mg of TMC125 —
hydroxypropylmethylcellulose (HPMC) — lactose —
The batch # was D03109 and the expiration date was
Feb 1, 2005.

Atorvastatin (Lipitor[®]) was provided as a 10 mg tablet. The batch # was 0290024NH and the expiration date was Jan 31, 2007.

Assay Methods

The plasma concentrations of TMC125, atorvastatin, atorvastatin lactone, 2-, and 4-hydroxy atorvastatin 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 0.5 ng/mL for atorvastatin, atorvastatin lactone, and 2- and 4-hydroxy atorvastatin.

Pharmacokinetics 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 derived.

Statistical Analysis

The primary pharmacokinetic parameters were C_{max} , C_{min} , and AUC_{12h} for TMC125 and C_{max} and AUC_{24h} for atorvastatin and the atorvastatin metabolites on the logarithmic scale. All the observations for test and reference were included in the statistical analyses.

RESULTS

Subject Disposition and Demographics

Out of the 33 subjects screened, 16 subjects were randomized and started treatment. 13 subjects failed the screening procedure (11 subjects did not meet the eligibility criteria and 2 subjects withdrew consent) and 4 subjects were designated as reserve subjects. All the subjects (n = 16) randomized to start treatment completed the trial.

Table 1 shows the demographic data in the trial:

Table 1: Demographics in Trial TMC125-C164

Parameter	Group I N=8	Group II N=8	All Subjects N=16
Age, years			
Median (range)	31.0 (19-51)	43.5 (24-53)	39.5 (19-53)
Height, cm			
Median (range)	173.5 (159-180)	184.0 (181-191)	180.5 (159-191)
Weight, kg			
Median (range)	67.5 (60-86)	82.0 (74-98)	76.5 (60-98)
BMI, kg/m ²			
Median (range)	23.9 (19-27)	24.8 (21-29)	24.2 (19-29)
Sex, n (%)			
Male	6 (75.0)	8 (100.0)	14 (87.5)
Female	2 (25.0)	0	2 (12.5)
Ethnic Origin, n (%)			
Caucasian/White	6 (75.0)	8 (100.0)	14 (87.5)
Black	1 (12.5)	0	1 (6.3)
Other	1 (12.5)	0	1 (6.3)
Type of Smoker, n (%)			
Nonsmoker	3 (37.5)	4 (50.0)	7 (43.8)
Light	5 (62.5)	4 (50.0)	9 (56.3)

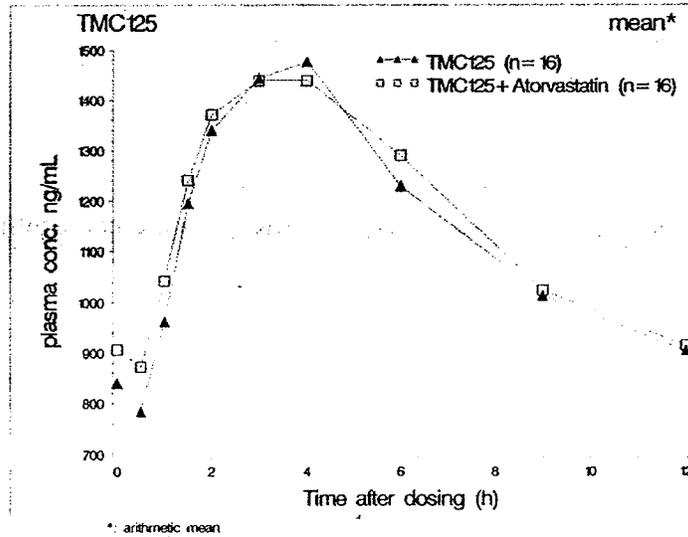
N = number of subjects

Pharmacokinetics

TMC125

Fig 1 shows the mean steady state plasma concentration-time profiles of TMC125, with and without co-administration of atorvastatin in healthy subjects.

Fig 1: Mean steady state plasma concentration-time profiles of TMC125, with and without co-administration of atorvastatin in healthy subjects



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The mean plasma concentrations of TMC125 were similar when TMC125 800 mg b.i.d. (TF035) was administered with or without atorvastatin. Table 2 shows the

pharmacokinetic parameters of 800 mg TMC125 b.i.d. (TF035) after administration with and without 40 mg q.d. atorvastatin.

Table 2: Pharmacokinetic parameters of 800 mg TMC125 b.i.d. (F035) after administration with and without 40 mg q.d. atorvastatin

Pharmacokinetics of TMC125 (mean ± SD, t _{max} : median [range])	TMC125 + Atorvastatin Test	TMC125 alone Reference
n	16	16
t _{max} , h	3.0 [2.0-6.0]	3.0 [1.5-6.0]
C _{0h} , ng/mL	907 ± 240	840 ± 167
C _{min} , ng/mL	847 ± 207	760 ± 139
C _{max} , ng/mL	1514 ± 367	1548 ± 339
AUC _{12h} , ng.h/mL	14098 ± 3290	13816 ± 3044
C _{ss, av} , ng/mL	1175 ± 274	1151 ± 254
FL, %	56.2 ± 12.5	67.9 ± 13.7

Source: Supporting Data Display 9

The C_{max} and AUC_{12h} of TMC125 were similar when TMC125 800 mg b.i.d. (TF035) was administered with and without 40 mg q.d. atorvastatin.

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

Table 3: Statistical analysis of the pharmacokinetic parameters of TMC125, with and without administration of atorvastatin

TMC125 Parameter	n		Least squares means			p-value		
	Test / Ref.		TMC125 +Atorvastatin Test	TMC125 alone Reference	Treatment ratio, % and 90% CI* Test/Reference	Treatment	Sequence	
C _{min} , ng/mL	16	16	826	749	110	102 - 119	0.0361	0.7859
C _{max} , ng/mL	16	16	1471	1511	97	93 - 102	0.3350	0.8854
AUC ₁₂ , ng.h/mL	16	16	13738	13502	102	97 - 107	0.5636	0.7918

* 90% confidence interval (CI).

Source: Appendix 7.3.6. Pharmacokinetic Data

The LS_{means} ratios of C_{min}, C_{max}, and AUC_{12h} of TMC125 were not significantly altered (all changes < 10 %) when TMC125 was administered with and without atorvastatin.

Atorvastatin

Fig 2 shows the mean plasma concentration-time profile of atorvastatin, with and without co-administration of TMC125.

Fig 2: Mean plasma concentration-time profile of atorvastatin, with and without co-administration of TMC125

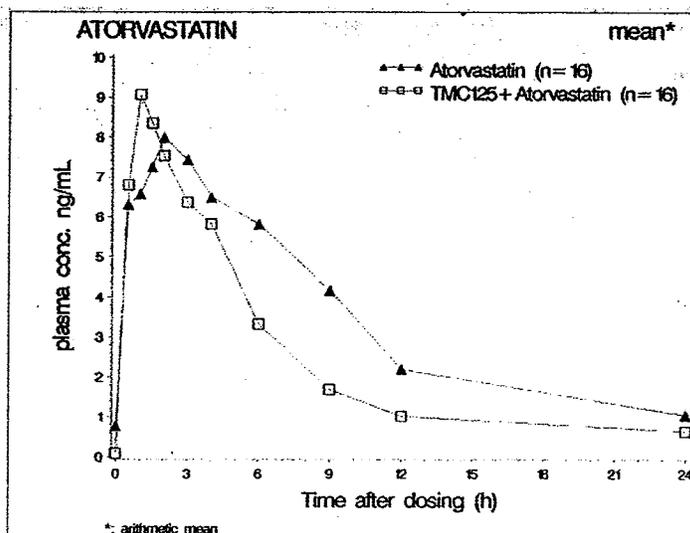


Table 4 shows the pharmacokinetic parameters of atorvastatin, with and without co-administration of TMC125.

Table 4: Pharmacokinetic parameters of atorvastatin, with and without co-administration of TMC125

Pharmacokinetics of atorvastatin (mean \pm SD, t_{max} : median [range])	TMC125 + atorvastatin Test	Atorvastatin alone Reference
N	16	16
t_{max} , h	1.5 [0.5-4.0]	2.0 [0.5-4.0]
C_{0h} , ng/mL	NQ	0.85 \pm 0.60
C_{min} , ng/mL	NQ	0.82 \pm 0.55
C_{max} , ng/mL	11.5 \pm 6.04	11.0 \pm 5.86
AUC_{24h} , ng.h/mL	52.6 \pm 29.4	82.7 \pm 40.3
$C_{ss, av}$, ng/mL	2.19 \pm 1.23	3.45 \pm 1.68
FI, %	521.2 \pm 178.3	315.2 \pm 179.4

NQ = not quantifiable

Source: Supporting Data Display 14

Table 5 shows the summary of the statistical analysis of the pharmacokinetic parameters of atorvastatin, with and without co-administration of TMC125.

Table 5: Summary of the statistical analysis of the pharmacokinetic parameters of atorvastatin, with and without co-administration of TMC125

Atorvastatin Parameter	n		Least squares means			p-value			
	Test / Ref.		TMC125 +atorvastatin Test	Atorvastatin alone Reference	Treatment ratio, % and 90% CI ^a Test/Reference	Treatm.	Period	Sequence	
C _{max} , ng/mL	16	16	10.09	9.66	104	84 - 130	0.7350	0.4910	0.1029
AUC _{24h} , ng.h/mL	16	16	47.2	74.8	63	58 - 68	<0001	0.1107	0.2984

^a 90% confidence interval

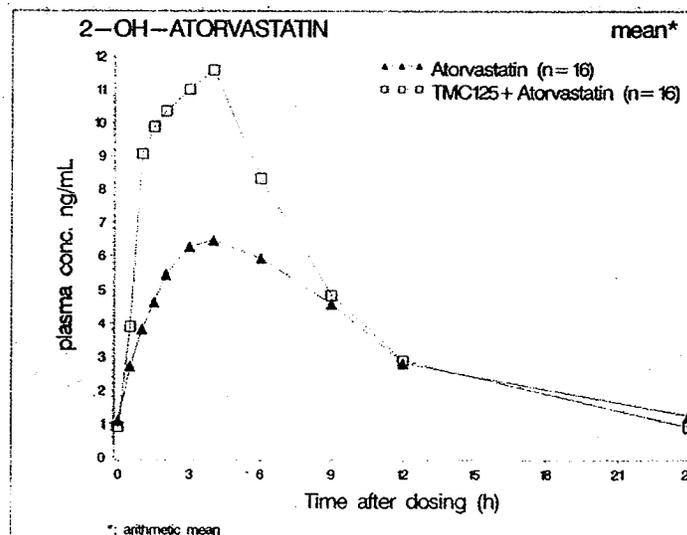
Source: Appendix 7.3.6, Pharmacokinetic Data

The LS_{means} ratios of C_{max} of atorvastatin was not significantly altered, however the LS_{means} ratios of AUC_{24h} of atorvastatin was decreased by 37 % when atorvastatin was co-administered with TMC125 as compared to when atorvastatin was administered alone.

2-hydroxy-Atorvastatin

Fig 3 shows the mean plasma concentration-time profiles of 2-hydroxy-atorvastatin when atorvastatin was dosed with and without co-administration of TMC125 800 mg b.i.d.

Fig 3: Mean plasma concentration-time profiles of 2-hydroxy-atorvastatin when atorvastatin was dosed with and without co-administration of TMC125 800 mg b.i.d.



The mean plasma concentration-time profile of 2-hydroxy-atorvastatin was higher when atorvastatin was co-administered with TMC125 as compared to when atorvastatin was administered alone.

Table 6 shows the summary of the pharmacokinetic parameters of 2-hydroxy atorvastatin after administration of atorvastatin with and without TMC125.

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Table 6: Summary of the pharmacokinetic parameters of 2-hydroxy atorvastatin after administration of atorvastatin with and without TMC125

Pharmacokinetics of 2-hydroxy-atorvastatin (mean ± SD, t _{max} : median [range])	TMC125 + atorvastatin Test	Atorvastatin alone Reference
n	16	16
t _{max} , h	4.0 [1.0-6.0]	3.0 [0.5-6.0]
C _{0h} , ng/mL	0.96 ± 0.55	1.08 ± 0.41
C _{min} , ng/mL	0.79 ± 0.47	1.05 ± 0.41
C _{max} , ng/mL	13.66 ± 6.14	7.40 ± 2.25
AUC _{24h} , ng.h/mL	109.8 ± 46.8	82.9 ± 26.4
C _{ss, av} , ng/mL	4.57 ± 1.95	3.45 ± 1.10
FI, %	282.3 ± 47.2	186.7 ± 41.9

Source: Supporting Data Display 19

Table 7 shows the summary of the statistical analysis of the pharmacokinetic parameters of 2-hydroxy-atorvastatin after administration of atorvastatin with and without TMC125.

Table 7: Summary of the statistical analysis of the pharmacokinetic parameters of 2-hydroxy-atorvastatin after administration of atorvastatin with and without TMC125

2-hydroxy-atorvastatin Parameter	n		Least squares means			p-value			
			TMC125 +atorvastatin Test	Atorvastatin alone Reference	Treatment ratio, % and 90% CI*	Treatm.	Period	Sequence	
C _{max} , ng/mL	16	16	12.45	7.05	176	160 - 194	<0001	0.0397	0.0676
AUC _{24h} , ng.h/mL	16	16	100.9	79.2	127	119 - 136	<0001	0.0053	0.2092

* 90% confidence interval

Source: Appendix 7.3.6, Pharmacokinetic Data

The LS_{means} ratios of C_{max} and AUC_{24h} of 2-hydroxy atorvastatin were increased by 76 % and 27 % respectively, when atorvastatin was administered with TMC125 as compared to when atorvastatin was administered alone.

4-hydroxy-Atorvastatin

The plasma concentrations of 4-hydroxy atorvastatin were below the LLOQ for the majority of subjects in both the treatments. Therefore, plasma concentrations times were not generated and pharmacokinetic and statistical analysis was not conducted.

Atorvastatin Lactone

Fig 4 shows the mean plasma concentration-time profiles of atorvastatin lactone when atorvastatin was administered with and without TMC125 800 mg b.i.d.

Fig 4: Mean plasma concentration-time profiles of atorvastatin lactone when atorvastatin was administered with and without TMC125 800 mg b.i.d.

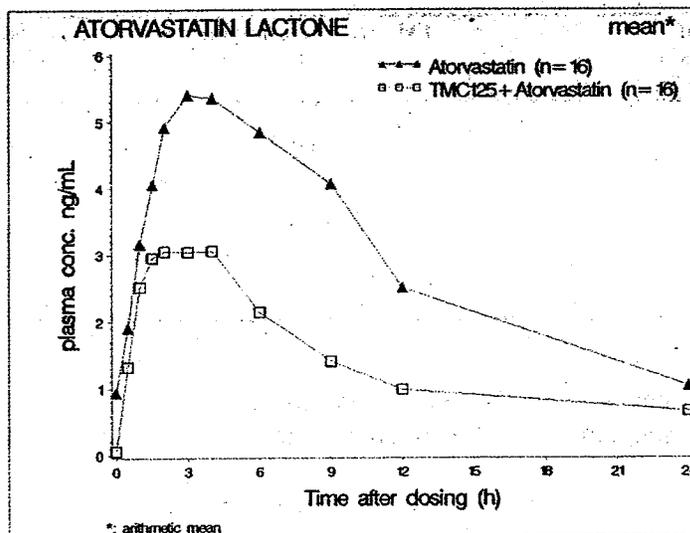


Table 8 shows the summary of the pharmacokinetic parameters of atorvastatin lactone after administration of atorvastatin with and without TMC125.

Table 8: Summary of the pharmacokinetic parameters of atorvastatin lactone after administration of atorvastatin with and without TMC125

Pharmacokinetics of atorvastatin lactone (mean \pm SD, t_{max} : median [range])	TMC125 + atorvastatin Test	Atorvastatin alone Reference
n	16	16
t_{max} , h	2.0 [1.0-4.0]	3.0 [1.0-9.0]
C_{0h} , ng/mL	NQ	0.95 \pm 0.44
C_{min} , ng/mL	NQ	0.91 \pm 0.42
C_{max} , ng/mL	3.86 \pm 2.13	6.04 \pm 2.87
AUC _{24h} , ng.h/mL	28.6 \pm 17.2	70.9 \pm 30.4
$C_{ss, av}$, ng/mL	1.19 \pm 0.72	2.95 \pm 1.27
FI, %	305.2 \pm 57.9	172.7 \pm 41.9

NQ = not quantifiable

Source: Supporting Data Display 25

The results of the pharmacokinetic analysis showed that the mean C_{max} and AUC_{24h} of atorvastatin lactone were lower when atorvastatin was combined with TMC125 as compared to when atorvastatin was administered alone.

Table 9 shows the summary of the statistical analysis of the pharmacokinetic parameters of atorvastatin lactone after administration of atorvastatin with and without TMC125.

Table 9: Summary of the statistical analysis of the pharmacokinetic parameters of atorvastatin lactone after administration of atorvastatin with and without TMC125

Atorvastatin lactone	n		Least squares means				p-value		
			TMC125 +atorvastatin Test	Atorvastatin alone Reference	Treatment ratio, % and 90% CI*		Treatm.	Period	Sequence
Parameter	Test	Ref.			Test/Reference				
C _{max} , ng/mL	16	16	3.38	5.44	62	56 - 69	<.0001	0.5865	0.7167
AUC _{24h} , ng.h/mL	16	16	24.7	65.1	38	34 - 42	<.0001	0.1230	0.9682

* 90% confidence interval

Source: Appendix 7.3.6, Pharmacokinetic Data

The LS_{means} ratios of C_{max} and AUC_{24h} of atorvastatin lactone were decreased by 38 % and 62 % respectively, when atorvastatin was administered with TMC125 as compared to when atorvastatin was administered alone.

Pharmacokinetic Results Summary

- The LS_{means} ratios of C_{min}, C_{max}, and AUC_{12h} of TMC125 were not significantly altered (all changes < 10 %) when TMC125 was administered with and without atorvastatin.
- The LS_{means} ratios of C_{max} of atorvastatin was not significantly altered, however the LS_{means} ratios of AUC_{24h} of atorvastatin was decreased by 37 % when atorvastatin was co-administered with TMC125 as compared to when atorvastatin was administered alone.
- The LS_{means} ratios of C_{max} and AUC_{24h} of 2-hydroxy atorvastatin were increased by 76 % and 27 % respectively, when atorvastatin was administered with TMC125 as compared to when atorvastatin was administered alone.
- The LS_{means} ratios of C_{max} and AUC_{24h} of atorvastatin lactone were decreased by 38 % and 62 % respectively, when atorvastatin was administered with TMC125 as compared to when atorvastatin was administered alone.

Conclusion

The combination of INTELENCE™ and atorvastatin can be given without any dose adjustments, however, the dose of atorvastatin may need to be altered based on the clinical response.

Study Number
TMC125-C165

Title

Phase I, open-label, randomized two-way crossover trial to investigate the pharmacokinetic interaction between paroxetine 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 pharmacokinetics of paroxetine and to determine the effect of steady state concentrations of paroxetine on the steady state pharmacokinetics of TMC125.

Study Design

Open label, randomized, 2-way crossover trial. 16 subjects were equally randomized to either **panel 1** or **panel 2**. Subjects randomized to **panel 1** started with **treatment A** followed by **treatment B** and subjects randomized to **panel 2** started with **treatment B** followed by **treatment A**. There was a washout period of at least 14 days between the two treatments. The following treatments were administered:

Treatment A: 7-day treatment with paroxetine 20 mg q.d.

Treatment B: 14-day treatment with TMC125 800 mg b.i.d. co-administered with 20 mg paroxetine q.d. from **day 8** through **day 14**.

A full pharmacokinetic profile of paroxetine was determined on **day 7** of **treatment A** and on **day 14** of **treatment B**. A full pharmacokinetic profile of TMC125 was determined on **day 7** and **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 D03109 (expiry date: Feb, 2005).

Paroxetine (Deroxat®) was provided as 20 mg tablets. The batch # was 4227 and the expiry date was June 2007.

Assay Methods

The plasma concentrations of TMC125 and paroxetine 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 0.1 ng/mL for paroxetine.

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

A total of 16 subjects was considered sufficient to allow for relevant conclusions. The primary pharmacokinetic parameters were C_{0hr} , C_{min} , C_{max} , and AUC_{12hr} of TMC125, and C_{0hr} , C_{min} , C_{max} , and AUC_{24hr} of paroxetine on the logarithmic scale.

RESULTS

Subject Disposition and Demographics

Out of the 29 subjects screened, 16 subjects were randomized to two panels and started treatment. One subject (randomized to sequence A-B) dropped out of the trial due to maculopapular rash during combined TMC125/paroxetine treatment (session 2).

Table 1 shows the demographics in trial TMC125-C165.

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Table 1: Demographics in Trial TMC125-C165

Parameter	All Subjects N = 16
Age, years	
Median (range)	29.0 (21-38)
Height, cm	
Median (range)	182.0 (163-194)
Weight, kg	
Median (range)	74.5 (64-107)
BMI, kg/m ²	
Median (range)	23.7 (20-30)
Sex, n (%)	
Male	16 (100.0)
Ethnic Origin, n (%)	
White	12 (75.0)
Black	4 (25.0)
Type of Smoker, n (%)	
Light*	5 (31.3)
Nonsmoker	11 (68.8)

* No more than 10 cigarettes or 2 cigars or 2 pipes per day
Source: Supporting Data Display 4

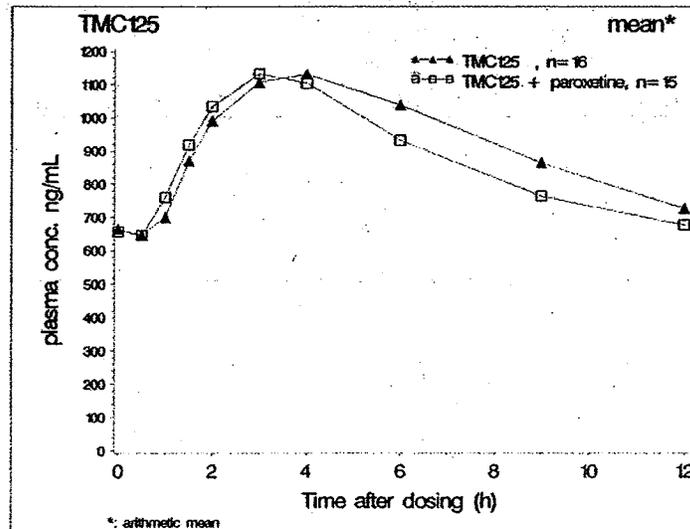
Pharmacokinetics

Due to 1 discontinuation during session 2 (subject was randomized to sequence A-B), pharmacokinetic profiles were available for 16 subjects for TMC125 alone and paroxetine alone, and for 15 subjects for the pharmacokinetic profiles of both drugs during the combined administration.

Fig 1 shows the mean plasma concentration-time profiles of TMC125 after administration of TMC125 800 mg b.i.d. (formulation TF035) with or without co-administration of paroxetine 20 mg q.d.

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Fig 1: Mean plasma concentration-time profiles of TMC125 after administration of TMC125 800 mg b.i.d. (formulation TF035) with or without co-administration of paroxetine 20 mg q.d.



The individual plasma concentration-time profiles showed that the plasma concentration-time profiles of the test treatment (co-administration of TMC125 and paroxetine) were comparable to the plasma concentrations when TMC125 was administered alone.

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

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

Pharmacokinetics of TMC125 (mean±SD, t _{max} : median [range])	TMC125 + Paroxetine Test	TMC125 alone Reference
n	15	16
t _{max} , h	3.0 [1.5-4.0]	4.0 [2.0-6.0]
C _{0h} , ng/mL	657 ± 248	665 ± 321
C _{min} , ng/mL	626 ± 241	637 ± 305
C _{max} , ng/mL	1149 ± 377	1161 ± 449
AUC _{12h} , ng.h/mL	10529 ± 3808	11099 ± 4524
C _{12h} , ng/mL	877 ± 317	925 ± 377
FI, %	61.4 ± 15.0	59.7 ± 16.1

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

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

TMC125	n		Least squares means				p-value	
			TMC125+ Paroxetine	TMC125 alone	Treatment ratio, % and 90% CI ^a		Period	Sequence
Parameter	Test / Ref.		Test	Reference	Test/Reference			
C _{0h} , ng/mL	15	16	635	588	108	98 - 119	-	0.4632
C _{min} , ng/mL	15	16	605	566	107	98 - 117	-	0.4715
C _{max} , ng/mL	15	16	1125	1073	105	96 - 115	-	0.2738
AUC _{12h} , ng.h/ml	15	16	10217	10122	101	93 - 110	-	0.3321

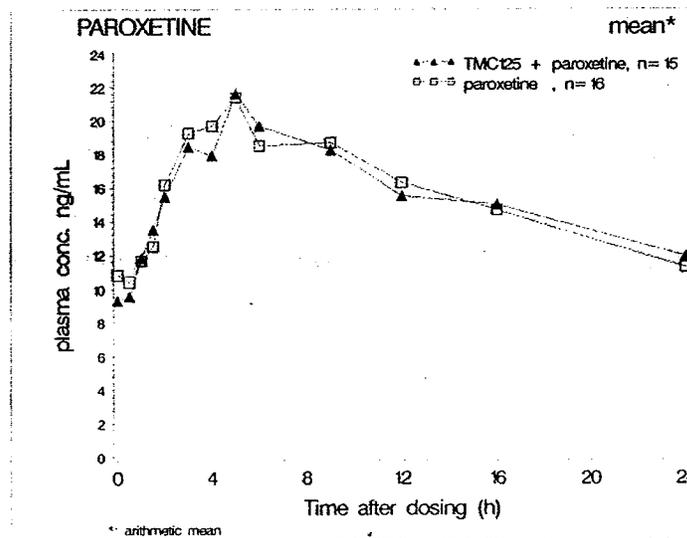
^a90% confidence interval

The LS_{means} ratio of C_{0hr}, C_{min}, C_{max}, and AUC_{12h} of TMC125 were not significantly altered (all changes were < 10 %) when TMC125 was co-administered with paroxetine, as compared to when TMC125 was administered alone.

Paroxetine

Fig 2 shows the mean plasma concentration-time profiles of paroxetine after administration of paroxetine 20 mg q.d. with or without co-administration of TMC125 800 mg b.i.d. (TF035).

Fig 2: Mean plasma concentration-time profiles of paroxetine after administration of paroxetine 20 mg q.d. with or without co-administration of TMC125 800 mg b.i.d. (TF035)



The mean plasma concentration-time profiles of paroxetine were similar when paroxetine was administered with and without TMC125.

Table 4 shows the summary of the pharmacokinetic parameters of paroxetine, with and without co-administration of TMC125.

Table 4: Summary of the pharmacokinetic parameters of paroxetine, with and without co-administration of TMC125

Pharmacokinetics of paroxetine (mean±SD, t _{max} : median [range])	TMC125 + Paroxetine Test	Paroxetine alone Reference
N	15	16
t _{max} , h	5.0 [2.0-16.0]	5.0 [3.0-16.0]
C _{0h} , ng/mL	9.34 ± 8.59	11.56 ± 10.81
C _{min} , ng/mL	8.63 ± 8.12	9.52 ± 8.47
C _{max} , ng/mL	22.83 ± 13.07	22.71 ± 16.28
AUC _{24h} , ng.h/mL	375.3 ± 252.1	375.6 ± 282.8
C _{ss, 24h} , ng/mL	15.64 ± 10.50	15.65 ± 11.78
FI, %	119 ± 60	111 ± 63

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

Table 5: Statistical evaluation of the pharmacokinetic parameters of paroxetine, with and without co-administration of TMC125

Paroxetine Parameter	n		Least squares means				p-value	
	Test / Ref.		TMC125 + Paroxetine Test	Paroxetine alone Reference	Treatment ratio, % and 90% CI* Test/Reference		Period	Sequence
C _{0h} , ng/mL	15	16	4.88	6.18	79	65 – 97	0.5068	0.4048
C _{min} , ng/mL	15	16	4.62	5.29	87	75 – 102	0.1147	0.3494
C _{max} , ng/mL	15	16	18.71	17.58	106	95 – 120	0.7934	0.3891
AUC _{24h} , ng.h/mL	15	16	279.61	272.05	103	90 – 118	0.7092	0.3806

*90% confidence interval

The LS_{means} ratio of C_{0hr} and C_{min} were decreased by 21 % and 13 % when paroxetine was administered with TMC125 as compared to when paroxetine was administered alone. The C_{max} and AUC_{12h} of paroxetine were not significantly altered (all changes were < 10 %) when paroxetine was co-administered with TMC125 as compared to when paroxetine was administered alone.

Pharmacokinetic Results Summary

- The LS_{means} estimates of $C_{0\text{hr}}$, C_{min} , C_{max} , and $AUC_{12\text{h}}$ of TMC125 were not significantly altered (all changes were $< 10\%$) when TMC125 was co-administered with paroxetine, as compared to when TMC125 was administered alone.
- The LS_{means} estimates of $C_{0\text{hr}}$ and C_{min} of paroxetine were decreased by 21 % and 13 % when paroxetine was administered with TMC125 as compared to when paroxetine was administered alone. The C_{max} and $AUC_{12\text{h}}$ of paroxetine were not significantly altered (all changes were $< 10\%$) when paroxetine was co-administered with TMC125 as compared to when paroxetine was administered alone.

Conclusion

TMC125 and paroxetine can be co-administered without any dose adjustments. Due to difference in elimination mechanisms, no drug-drug interaction was expected.

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Study Number
TMC125-C166

Title

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.

Objectives

The primary objectives of the trial were to determine the effect of TMC125 on the steady state pharmacokinetics of ethinylestradiol and to determine the effect of TMC125 on the steady-state pharmacokinetics of norethindrone.

Study Design

Phase I, open label, 1-way interaction trial in healthy female subjects. The trial population was to consist of 24 healthy women who were on stable oral contraceptive therapy, specifically, ethinyl estradiol 0.035 mg and norethindrone 1 mg (the components of Ortho-Novum[®] 1/35).

The subjects participated in the trial during 3 consecutive 28-day cycles, i.e., 3 full oral contraceptives (OC) cycles. During the run-in period, all subjects received OC alone for 1 OC cycle prior to the start of the treatment period. During the 3 OC cycles, all subjects were given a daily dose of Ortho-Novum[®] 1/35 for 21 days. There was no OC treatment on **day 22 to day 28** of each OC cycle, i.e., on **day - 8 to day -1 (1st OC cycle)**, on **day 22 to day 28** in the first treatment period (**2nd OC cycle**) and on trial **day 50 to day 56** in the second treatment period (**3rd OC cycle**). During the third OC cycle, the subjects were also given TMC125 200 mg b.i.d. (formulation **F060**) from **day 29** until **day 43**. TMC125 was administered within 10 minutes after the consumption of breakfast or dinner.

24-hour pharmacokinetic profile of ethinylestradiol and norethindrone were determined after the first two weeks of the second OC cycle (**day 15**) and after the first two weeks of the third OC cycle (**day 43**). The full 12-hour pharmacokinetic profile of TMC125 was determined on trial **day 43 (day 15 of the third OC cycle)**.

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.

Ortho-Novum® 1/35 was provided as a tablet containing ethinylestradiol 0.035 mg and norethindrone 1 mg. The batch # was 05BS079 and the expiration date was March 2008.

Assay Methods

The plasma concentrations of TMC125, ethinylestradiol, and norethindrone 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, 3 pg/mL for ethinylestradiol and 0.05 ng/mL for norethindrone.

Pharmacokinetic, Pharmacodynamic, 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 analysis was performed comparing OC alone (reference treatment, second OC cycle) versus OC and TMC125 (test treatment, third OC cycle). The primary pharmacokinetic parameters were C_{min} , C_{max} , and AUC_{24h} for ethinylestradiol and norethindrone on the logarithmic scale. All observations for test treatment (treatment period 2) and reference treatment (treatment period 1) were included in the statistical analysis.

RESULTS

Subject Disposition and Demographics

Out of the 58 subjects screened, 30 subjects were assigned to treatment. 16 of the 30 subjects completed the trial and 14 subjects dropped out of the trial before completion of the trial. 6 subjects discontinued the trial during the first treatment period (OC alone) due to withdrawal of consent (5 subjects) or due to AEs (1 subject). 8 subjects discontinued the trial during the second treatment period (OC + TMC125) due to AEs.

Table 1 shows the demographics in the trial.

Table 1: Demographics in Trial TMC125-C166

Parameter	All Subjects N = 30
Age, years	
Median (range)	24.0 (18-30)
Height, cm	
Median (range)	165.0 (157-174)
Weight, kg	
Median (range)	62.7 (50-81)
BMI, kg/m ²	
Median (range)	21.80 (19.0-29.4)
Sex, n (%)	
Female	30 (100)
Ethnic Origin, n (%)	
Caucasian	29 (96.7)
Other	1 (3.3)

N= total number of subjects

Pharmacokinetics

Full pharmacokinetic profiles of TMC125 were available for 16 subjects on **day 43**. The full pharmacokinetic profiles of ethinylestradiol and norethindrone were available for 24 subjects on **day 15** and 16 subjects on **day 43**.

TMC125

Table 2 shows the pharmacokinetic parameters of TMC125, when co-administered with Ortho Novum 1/35 (ethinyl estradiol and norethindrone).

Table 2: Pharmacokinetic parameters of TMC125, when co-administered with Ortho Novum 1/35 (ethinyl estradiol and norethindrone)

<i>Pharmacokinetics of TMC125</i> (mean ± SD, t _{max} : median [range])	Ethinylestradiol and norethindrone + TMC125 (test)
n	16
C _{0h} , ng/mL	886.5 ± 316.9
C _{min} , ng/mL	791.6 ± 186.7
C _{max} , ng/mL	1188 ± 292.8
C _{12h} , ng/mL	893.4 ± 215.0
t _{max} , h	4.0 (0.0 - 6.0)
AUC _{12h} , ng.h/mL	11820 ± 2591
C _{ss.av} , ng/mL	985.8 ± 216.0
FI, %	40.60 ± 15.17

The mean C_{min} value was lower than the mean C_{0h} and C_{12h} values because of the delay in absorption resulting in C_{min} being reached between 0.5 to 2 hours in 9 out of the 16 subjects.

The pharmacokinetic parameters of TMC125 in the current trial were compared with the pharmacokinetic parameters generated in trials TMC125-C171 and TMC125-C177. In these trials, the same formulation (F060) and same dose (200 mg b.i.d.) of TMC125 was given to healthy subjects after a standardized breakfast. Table 3 shows the comparison of the pharmacokinetic parameters of TMC125 with the historical data.

Table 3: Comparison of the pharmacokinetic parameters of TMC125 with the historical data

Pharmacokinetics of TMC125 (mean and 90% CI)	TMC125-C166: TMC125 + ethinylestradiol and norethindrone (n=16)		TMC125-C171: TMC125 alone (n=15)		TMC125-C177: TMC125 alone (n=23)	
	Mean	90% CI	Mean	90% CI	Mean	90% CI
C _{0h} , ng/mL	886.5	(747.6 - 1025)	529.1	(455.4 - 602.8)	461.3	(400.3 - 522.3)
C _{min} , ng/mL	791.6	(709.8 - 873.4)	498.1	(428.3 - 567.9)	426.1	(370.7 - 481.4)
C _{max} , ng/mL	1188	(1060 - 1316)	1015	(904.1 - 1126)	875.7	(792.3 - 959.0)
AUC _{12h} , ng.h/mL	11820	(10684 - 12956)	9008	(7920 - 10096)	7638	(6831 - 8444)

Based on cross-trial comparison, the mean estimates of C_{0hr}, C_{min}, C_{max}, and AUC_{12h} of TMC125, when co-administered with ethinyl estradiol and norethindrone (**treatment period 2** of the current trial) were higher compared to the estimates of these pharmacokinetic parameters when TMC125 200 mg b.i.d. was administered alone.

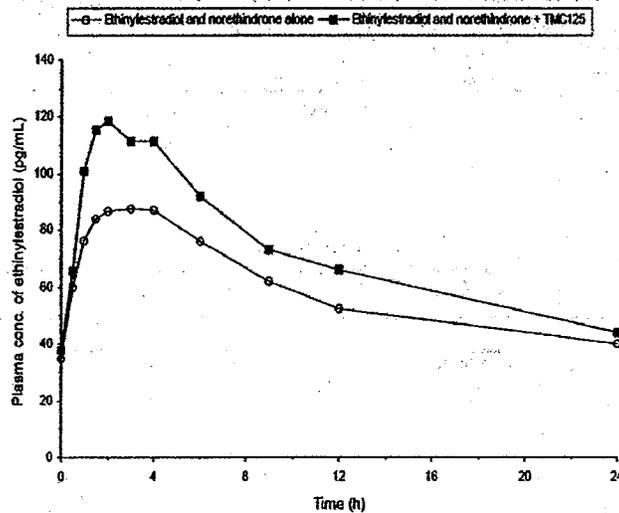
Reviewer's Note:

The cross-trial comparison of TMC125 pharmacokinetic parameters indicates that the pharmacokinetic parameters of TMC125 were higher in the current trial as compared to the pharmacokinetic parameters in trial TMC125-C171 and TMC125-C177. Trials TMC125-C171 and TMC125-C177 did not enroll any female subjects in the trial, thereby suggesting that the pharmacokinetic parameters of TMC125 are higher in female subjects as compared to male subjects. However, these "differences" should be noted in the context of cross-trial comparisons and the fact that no gender related differences in the pharmacokinetic parameters were noted in the pivotal phase III trials.

Ethinyl Estradiol

Fig 1 shows the mean plasma concentration time profiles of ethinylestradiol (administered as Ortho-Novum 1/35 q.d.) with and without co-administration of TMC125 200 mg b.i.d.

Fig 1: Mean plasma concentration time profiles of ethinylestradiol (administered as Ortho-Novum 1/35 q.d.) with and without co-administration of TMC125 200 mg b.i.d.



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The mean concentrations of ethinylestradiol were higher when Ortho-Novum (1/35 q.d.) was co-administered with TMC125 200 mg b.i.d. as compared to when Ortho-Novum (1/35 q.d.) was administered alone.

Table 4 shows the pharmacokinetic parameters of ethinylestradiol, administered as Ortho-Novum (1/35 q.d.), with and without co-administration of TMC125.

Table 4: Pharmacokinetic parameters of ethinylestradiol, administered as Ortho-Novum (1/35 q.d.), with and without co-administration of TMC125 200 mg b.i.d.

<i>Pharmacokinetics of ethinylestradiol</i> (mean ± SD, t_{max} : median [range])	Ethinylestradiol and norethindrone alone (reference)	Ethinylestradiol and norethindrone + TMC125 (test)
n	24	16
C_{0h} , pg/mL	34.90 ± 10.80	37.89 ± 10.12
C_{min} , pg/mL	34.51 ± 10.29	37.66 ± 9.727
C_{max} , pg/mL	98.30 ± 25.83	134.1 ± 44.48
C_{24h} , pg/mL	40.08 ± 13.77	43.94 ± 12.08
t_{max} , h	3.0 (1.0 - 4.0)	2.0 (1.0 - 4.0)
AUC_{24h} , pg.h/mL	1412 ± 356.9	1726 ± 382.3
$C_{ss,av}$, pg/mL	58.88 ± 14.86	71.94 ± 15.93
FI, %	109.2 ± 25.48	132.7 ± 33.51

Table 5 shows the summary of the statistical analysis of the pharmacokinetic parameters of ethinylestradiol, administered as Ortho-Novum (1/35 q.d.), with and without co-administration of TMC125 200 mg b.i.d.

Table 5: Summary of the statistical analysis of the pharmacokinetic parameters of ethinylestradiol, administered as Ortho-Novum (1/35 q.d.), with and without co-administration of TMC125 200 mg b.i.d.

Parameters of ethinylestradiol	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b
	Ethinylestradiol and norethindrone alone (reference)	Ethinylestradiol and norethindrone + TMC125 (test)		
C _{min} , pg/mL	33.12	36.17	109.2	101.0 - 118.1
C _{max} , pg/mL	94.84	125.8	132.6	120.7 - 145.7
AUC _{24hr} , pg.h/mL	1371	1666	121.5	113.0 - 130.6
Median ^c				
Parameters of ethinylestradiol	Ethinylestradiol and norethindrone alone (reference)	Ethinylestradiol and norethindrone + TMC125 (test)	Treatment difference median	90% CI, % ^b
t _{max} , h	2.5	2.0	0.00	(-0.75) - (0.50)

^a n=24 for reference and n=16 for test

^b 90% confidence intervals.

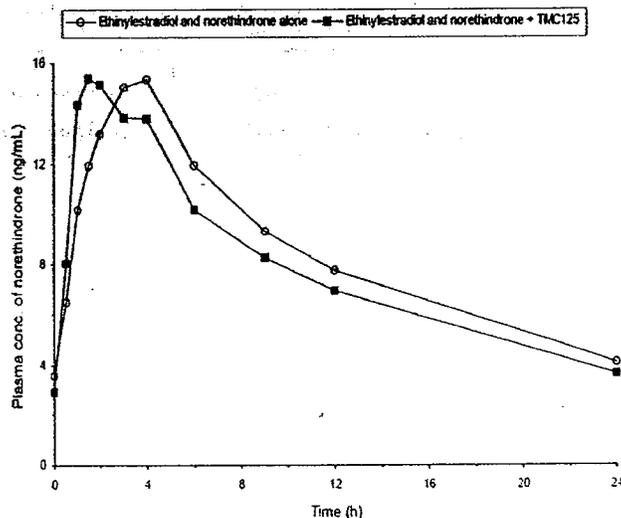
^c n=16 for reference and n=16 for test

The LS_{means} ratio of C_{min}, C_{max} and AUC_{24hr} of ethinylestradiol increased by 9 %, 33 % and 22 %, respectively, when ethinylestradiol, administered as Ortho-Novum (1/35 q.d.), was co-administered with TMC125 200 mg b.i.d as compared to when ethinylestradiol was administered (as Ortho Novum 1/35 q.d.) alone.

Norethindrone

Fig 2 shows the mean plasma concentration time profiles of norethindrone, (administered as Ortho-Novum 1/35 q.d.) with and without co-administration of TMC125 200 mg b.i.d.

Fig 2: Mean plasma concentration time profiles of norethindrone, (administered as Ortho-Novum 1/35 q.d.) with and without co-administration of TMC125 200 mg b.i.d.



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The comparison of the mean plasma concentration-time profiles of norethindrone, when administered as Ortho-Novum 1/35 q.d., in the presence and absence of TMC125 showed that the mean plasma concentrations of norethindrone were higher in the absorption phase and lower in the elimination phase. Therefore, the median t_{max} was 1.5 hours shorter when norethindrone was co-administered (as Ortho-Novum 1/35 q.d.) with TMC125 as compared to when norethindrone was administered (as Ortho-Novum 1/35 q.d.) alone.

Table 6 shows the pharmacokinetic parameters of norethindrone, administered as Ortho-Novum (1/35 q.d.), with and without co-administration of TMC125.

Table 6: Pharmacokinetic parameters of norethindrone, administered as Ortho-Novum (1/35 q.d.), with and without co-administration of TMC125 200 mg b.i.d.

<i>Pharmacokinetics of norethindrone</i> (mean \pm SD, t_{max} : median [range])	Ethinylestradiol and norethindrone alone (reference)	Ethinylestradiol and norethindrone + TMC125 (test)
N	24	16
C_{0h} , ng/mL	3.597 \pm 1.736	2.919 \pm 1.422
C_{min} , ng/mL	3.511 \pm 1.678	2.845 \pm 1.490
C_{max} , ng/mL	16.73 \pm 3.767	17.27 \pm 4.127
C_{24h} , ng/mL	4.070 \pm 1.943	3.621 \pm 2.451
t_{max} , h	3.0 (1.0 - 6.0)	1.5 (1.0 - 4.0)
AUC _{24h} , ng.h/mL	203.3 \pm 59.63	189.2 \pm 53.92
$C_{ss,av}$, ng/mL	8.477 \pm 2.482	7.887 \pm 2.246
FI, %	163.0 \pm 41.83	193.6 \pm 67.26

The inter individual variability in the C_{min} , C_{max} , and AUC_{24h} estimates, with and without co-administration of norethindrone (as Ortho-Novum 1/35 q.d.) was 48 % and 52 %, 23 % and 24 %, 29 % and 29 %, respectively. Thus, the inter-individual variability was comparable with and without co-administration of TMC125.

Table 7 shows the summary of the statistical analysis of the pharmacokinetic parameters of norethindrone, administered as Ortho-Novum (1/35 q.d.), with and without co-administration of TMC125 200 mg b.i.d.

Table 7: Summary of the statistical analysis of the pharmacokinetic parameters of norethindrone, administered as Ortho Novum (1/35 q.d.), with and without co-administration of TMC125 200 mg b.i.d.

Parameters of norethindrone	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b
	Ethinylestradiol and norethindrone alone (reference)	Ethinylestradiol and norethindrone + TMC125 (test)		
C _{min} , ng/mL	3.162	2.479	78.37	68.12 - 90.18
C _{max} , ng/mL	16.29	17.07	104.8	97.82 - 112.2
AUC _{24hr} , ng·h/mL	195.1	184.4	94.52	90.08 - 99.18
Median ^c				
Parameters of norethindrone	Ethinylestradiol and norethindrone alone (reference)	Ethinylestradiol and norethindrone + TMC125 (test)	Treatment difference median	90% CI, % ^b
t _{max} , h	3.5	1.5	-1.25	(-2.25) - (-0.50)

^a n=24 for reference and n=16 for test

^b 90% confidence intervals.

^c n=16 for reference and n=16 for test

The LS_{means} ratio of C_{min}, and AUC_{24hr} of norethindrone decreased by 21 % and 6 %, whereas the LS_{means} ratio of C_{max} increased by 5 % when norethindrone was administered (as Ortho Novum 1/35 q.d.) with TMC125 200 mg b.i.d. as compared to when norethindrone was administered (as Ortho Novum 1/35 q.d.) alone.

Pharmacokinetic Results Summary

- Based on a cross-trial comparison, the mean estimates of C_{0hr}, C_{min}, C_{max}, and AUC_{12h} of TMC125, when co-administered with ethinylestradiol and norethindrone (Ortho-Novum 1/35 q.d.) were higher compared to the estimates of these pharmacokinetic parameters when TMC125 200 mg b.i.d. was administered alone. However, these "differences" should be noted in the context of cross-trial comparison and the fact that no gender related differences in the pharmacokinetic parameters were noted in the pivotal phase III trials.
- The LS_{means} ratio of C_{min}, C_{max} and AUC_{24hr} of ethinylestradiol increased by 9 %, 33 % and 22 %, respectively, when ethinylestradiol, administered as Ortho-Novum (1/35 q.d.), was co-administered with TMC125 200 mg b.i.d as compared to when ethinyl estradiol was administered (as Ortho Novum 1/35 q.d.) alone. The increase in ethinyl estradiol pharmacokinetic parameters is not expected to be clinically relevant since no differences were observed in the levels of luteinizing hormone (LH), follicle cell stimulating hormone (FSH), and progesterone levels between the two treatment periods.
- The LS_{means} ratio of C_{min} and AUC_{24hr} of norethindrone decreased by 21 % and 6 %, whereas the LS_{means} ratio of C_{max} increased by 5 % when norethindrone was administered (as Ortho-Novum 1/35 q.d.) with TMC125 200 mg b.i.d. as compared to when norethindrone was administered (as Ortho-Novum 1/35 q.d.) alone. The decrease in C_{min} and AUC_{24hr} of norethindrone is not expected to be

clinically relevant since no differences were observed in the levels of luteinizing hormone (LH), follicle cell stimulating hormone (FSH) and progesterone levels between the two treatment periods.

Conclusion

TMC125 and oral contraceptives can be co-administered without any dose adjustments.

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Study Number
TMC125-C171

Title

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.

Objectives

The primary objectives of the trial were to determine the effect of steady-state pharmacokinetics of clarithromycin on the steady state pharmacokinetics of TMC125 and to determine the effect of steady state pharmacokinetics of TMC125 on the steady state pharmacokinetics of clarithromycin and its active metabolite 14-OH-clarithromycin.

Study Design

Open label, randomized, 2 period crossover trial. The trial consisted of two treatment periods, **session A** and **session B**, separated by a washout period of at least 14 days. The subjects participating in the trial were randomized to two panels, **panel 1** and **panel 2**, in a 1:1 ratio (i.e. 8 subjects per panel). The subjects randomized to **panel 1** started with **session A** followed by **session B**. The subjects randomized to **panel 2** started with **session B** followed by **session A**. The following treatments were administered:

Session A:

200 mg TMC125 b.i.d. from day 1 to day 7 with an additional morning dose on day 8.

Session B:

Clarithromycin 500 mg b.i.d. from day 1 to day 12 with an additional morning dose on day 13, and 200 mg TMC125 b.i.d. from day 6 to day 12 with an additional morning dose on day 13.

The subjects entered and stayed in the testing facility the night before the start of a treatment session. In the testing facility, a standard breakfast (to be ingested within 30 minutes) was provided, and the treatments were administered within 10 minutes after completion of breakfast.

12-hour pharmacokinetic profiles of TMC125 were determined on **day 8** of **session A** and on **day 13** of **session B**. 12-hour pharmacokinetic profiles of clarithromycin and its metabolite 14-OH-clarithromycin were determined on **day 5** and **day 13** of **session B**.

Investigational Product(s)

TMC125 was formulated as **TF060**; this formulation is tablet containing 100 mg TMC125 — in hydroxypropylmethylcellulose (HPMC), microcrystalline cellulose, croscarmellose sodium, magnesium stearate, and lactose monohydrate. The batch # was 05A05/F060 and the expiry date was January 2006.

Clarithromycin (Zeclar[®]) was supplied as a 500 mg tablet. The batch # was 27338TB21 and the expiry date was March 2008.

Assay Methods

The plasma concentration of TMC125 was determined using a validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS). The plasma concentrations of clarithromycin and 14-OH-clarithromycin were determined using a validated liquid chromatography and electrochemical detection (LC-ECD) method. The lower limit of quantification was 2 ng/mL for TMC125, 50 ng/mL for clarithromycin, and 50 ng/mL for 14-OH-clarithromycin.

Pharmacokinetic and Statistical Data Analysis

Pharmacokinetic Analysis

A total of 16 subjects were included. A minimum of at least 12 subjects completing both sessions was considered sufficient to allow for relevant conclusions. An evaluable subject was a subject who had completed both sessions of the trial.

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, clarithromycin, and 14-OH-clarithromycin. The primary pharmacokinetic parameters were C_{min} , C_{0h} , C_{max} , and AUC_{12h} for TMC125, clarithromycin, and 14-OH-clarithromycin.

RESULTS

Subject Disposition and Demographics

Out of the 30 subjects screened, 16 subjects were randomized to **panel 1** (n = 8; **session A** followed by **session B**) and **panel 2** (n = 8, **session B** followed by **session A**) and started treatment. 15 subjects completed the trial. 1 subject (randomized to panel 1) dropped out before trial completion on day 6 of **session A** due to withdrawal of consent.

Table 1 shows the demographics in the trial.

Table 1: Demographics in Trial TMC125-C171

Parameter	Panel I N=8	Panel II N=8	All Panels N=16
Age, years			
Median (range)	29.0 (21-49)	26.5 (19-49)	28.5 (19-49)
Height, cm			
Median (range)	177.0 (165-181)	174.5 (162-183)	175.5 (162-183)
Weight, kg			
Median (range)	72.0 (56-74)	71.0 (52-89)	72.0 (52-89)
BMI, kg/m ²			
Median (range)	22.9 (21-25)	23.3 (20-27)	22.9 (20-27)
Sex, n (%)			
Male	8 (100)	8 (100)	16 (100)
Ethnic Origin, n (%)			
White	6 (75.0)	5 (62.5)	11 (68.75)
Black	2 (25.0)	2 (25.0)	4 (25.0)
Asian	0	1 (12.5)	1 (6.25)
Type of Smoker, n (%)			
Light smoker	3 (37.5)	3 (37.5)	6 (37.5)
Nonsmoker	5 (62.5)	5 (62.5)	10 (62.5)

Pharmacokinetics

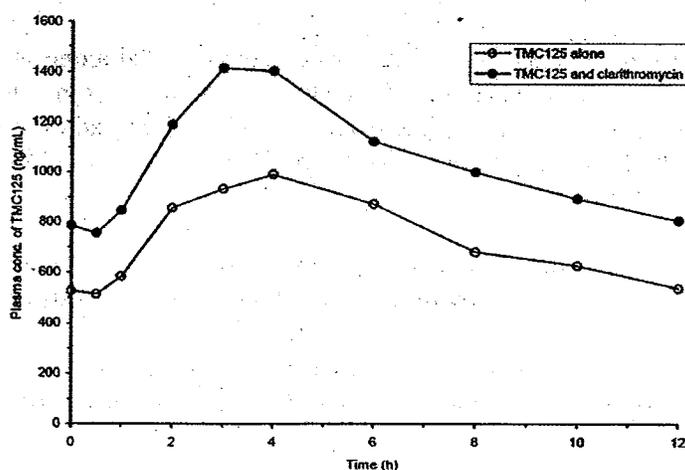
Full pharmacokinetic profiles of TMC125 were available for 15 subjects on **day 8** of session A and on **day 13** of session B. Full pharmacokinetic profiles of clarithromycin and 14-OH-clarithromycin were available for 15 subjects on **day 5** and **day 13** of session B.

TMC125

Fig 1 shows the mean plasma concentration time profile of TMC125 200 mg b.i.d., with and without co-administration of clarithromycin 500 mg b.i.d.

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Fig 1: Mean plasma concentration time profile of TMC125 200 mg b.i.d., with and without co-administration of clarithromycin 500 mg b.i.d.



TMC125 alone: n = 15
TMC125 and clarithromycin: n = 15

The mean plasma concentrations of TMC125 at steady-state were increased over the entire dosing interval when TMC125 was co-administered with clarithromycin (session B, day 13) compared with when TMC125 was administered alone (session A, day 8). The individual pre-dose plasma concentrations of TMC125 on days 6, 7, and 8 of session A and on days 11, 12, and 13 of session B (data not included in the review) suggested that steady-state conditions were achieved prior to full pharmacokinetic blood sampling for TMC125 on day 8 of session A and day 13 of session B.

Table 2 shows the pharmacokinetic parameters of TMC125 after administration of TMC125 alone (reference) or co-administration with clarithromycin.

Table 2: Pharmacokinetic parameters of TMC125 after administration of TMC125 alone (reference) or co-administration with clarithromycin

Pharmacokinetics of TMC125 (mean ± SD, t _{max} , median [range])	TMC125 alone (reference)	TMC125 and clarithromycin (test)
n	15	15
C _{0h} , ng/mL	529.1 ± 162.1	785.8 ± 253.5
C _{min} , ng/mL	498.1 ± 153.5	726.3 ± 233.0
C _{max} , ng/mL	1015 ± 243.8	1487 ± 389.7
t _{max} , h	4.0 [2.0 - 6.0]	3.0 [2.0 - 4.0]
AUC _{12h} , ng.h/mL	9008 ± 2392	12760 ± 3559
C _{ss,av} , ng/mL	750.6 ± 199.3	1064 ± 296.6
FI, %	70.39 ± 12.81	72.73 ± 15.66

The individual test/reference treatment ratios for C_{0h} , C_{min} , C_{max} and AUC_{12h} of TMC125 ranged from 111 % to 215 %, 108 % to 191 %, 120 % to 177 %, 106 % to 174 % with geometric means of 149 %, 146 %, 146 %, and 142 %, respectively.

The mean fluctuation index (FI) of TMC125, when administered alone was comparable to the mean FI of TMC125 when co-administered with clarithromycin. The inter-individual variability in C_{0h} , C_{min} , C_{max} , and AUC_{12h} of TMC125 administered alone or co-administered with clarithromycin were 31 % and 32 %; 31 % and 32 %; 24 % and 26 %; and 27 % and 28 %, respectively.

Table 3 shows the summary of the statistical analysis of the pharmacokinetic parameters of TMC125 without (reference) and with (test) co-administration of clarithromycin.

Table 3: Summary of the statistical analysis of the pharmacokinetic parameters of TMC125 without (reference) and with (test) co-administration of clarithromycin.

Parameter	LSmeans		LS means ratio, %	90% CI, %	p-value		
	TMC125 alone (reference)	TMC125 and clarithromycin (test)			Treatment	Period	Sequence
C_{0h} , ng/mL	506.9	752.8	148.5	137.1 - 160.9	<0.0001	0.4836	0.9586
C_{min} , ng/mL	476.4	697.3	146.4	135.9 - 157.6	<0.0001	0.8084	0.7098
C_{max} , ng/mL	985.8	1442	146.3	137.6 - 155.6	<0.0001	0.4234	0.9290
AUC_{12h} , ng·h/mL	8716	12366	141.9	134.1 - 150.1	<0.0001	0.4458	0.7921
	Median				p-value		
Parameter	TMC125 alone (reference)	TMC125 and clarithromycin (test)	Treatment difference median	90% CI, %	Treatment	Period	Sequence
t_{max} , h	4.0	3.0	-0.5	(-1.0) - (0.0)	0.0905	0.9035	0.7529

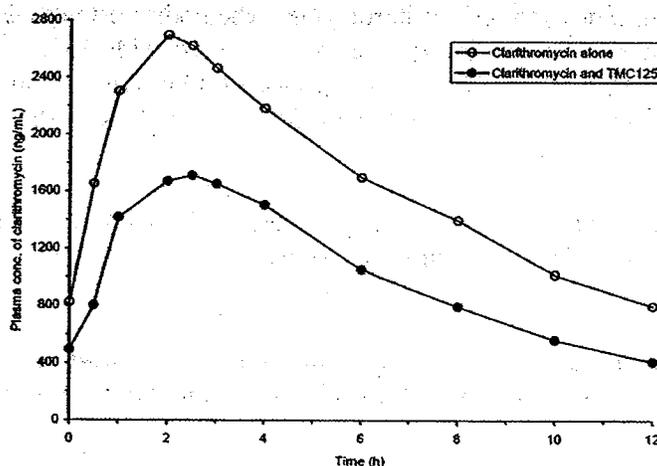
n = 15 for Session A, Day 8 (reference) and n = 15 for Session B, Day 13 (test)
CI = confidence interval

The 90 % CIs of the LS_{means} estimates of all the TMC125 pharmacokinetic parameters lay outside the 80 % -125 % interval and were higher when TMC125 was co-administered with clarithromycin as compared to when TMC125 was administered alone.

Clarithromycin

Fig 2 shows the mean plasma concentration-time profile of clarithromycin 500 mg b.i.d. with and without co-administration of TMC125.

Fig 2: Mean plasma concentration-time profile of clarithromycin 500 mg b.i.d. with and without co-administration of TMC125.



clarithromycin alone: n = 15
clarithromycin and TMC125: n = 15

The mean plasma concentration-time profile of clarithromycin showed that the mean concentrations of clarithromycin were lower when it was co-administered with TMC125, as compared to when clarithromycin was administered alone. The C_{max} of clarithromycin was reached between 0.5 hr and 8 hr post-dose when administered alone, and between 1 hr and 4 hr when co-administered with TMC125. The plasma concentrations of clarithromycin after the last dose on day 13 of session B were quantifiable in all subjects up to 12 hours post-dose.

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

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

<i>Pharmacokinetics of clarithromycin</i> (mean \pm SD, t_{max} : median [range])	clarithromycin alone (reference)	clarithromycin and TMC125 (test)
n	15	15
C_{0h} , ng/mL	823.6 \pm 391.1	492.1 \pm 374.2
C_{min} , ng/mL	734.8 \pm 362.7	370.9 \pm 288.4
C_{max} , ng/mL	3144 \pm 917.1	2088 \pm 571.6
t_{max} , h	2.0 [0.5 - 8.0]	2.0 [1.0 - 4.0]
AUC_{12h} , ng h/mL	20240 \pm 6208	12430 \pm 4248
$C_{ss,av}$, ng/mL	1687 \pm 517.4	1036 \pm 354.0
FI, %	148.3 \pm 55.18	174.5 \pm 42.51

The individual test/reference treatment ratios for C_{0h} , C_{min} , C_{max} , and AUC_{12h} ranged from 24 % to 131 %, 21 % to 117 %, 36 % to 127 %, and 32 % to 90 %, respectively, with geometric means of 55 %, 47 %, 66 %, 61 %, respectively.

The mean fluctuation index (FI) of clarithromycin, when administered alone was lower than the mean FI of clarithromycin when co-administered with TMC125. The inter-individual variability in C_{0h} , C_{min} , C_{max} , and AUC_{12h} of TMC125 administered alone or co-administered with clarithromycin were 47 % and 76 %; 49 % and 78 %; 29 % and 27 %; and 31 % and 34 %, respectively.

Table 5 shows the summary of the statistical analysis of the pharmacokinetic parameters of clarithromycin 500 mg b.i.d. administered alone and co-administered with TMC125 200 mg b.i.d.

Table 5: Summary of the statistical analysis of the pharmacokinetic parameters of clarithromycin 500 mg b.i.d. administered alone and co-administered with TMC125 200 mg b.i.d.

Parameter	LSmeans		LSmeans ratio, %	90% CI, %	p-value
	clarithromycin alone (reference)	clarithromycin and TMC125 (test)			Treatment
C_{0h} , ng/mL	735.7	402.6	54.72	44.53 - 67.23	0.0001
C_{min} , ng/mL	656.3	306.0	46.63	37.98 - 57.25	<0.0001
C_{max} , ng/mL	3024	2010	66.47	57.28 - 77.14	0.0003
AUC_{12h} , ng.h/mL	19432	11774	60.59	53.44 - 68.70	<0.0001
	Median				p-value
Parameter	clarithromycin alone (reference)	clarithromycin and TMC125 (test)	Treatment difference median	90% CI, %	Treatment
t_{max} , h	2.0	2.0	0.125	(-0.5) - (0.75)	0.6808

n = 15 for Session B, Day 5 (reference) and n = 15 for Session B, Day 13 (test)
CI = confidence interval

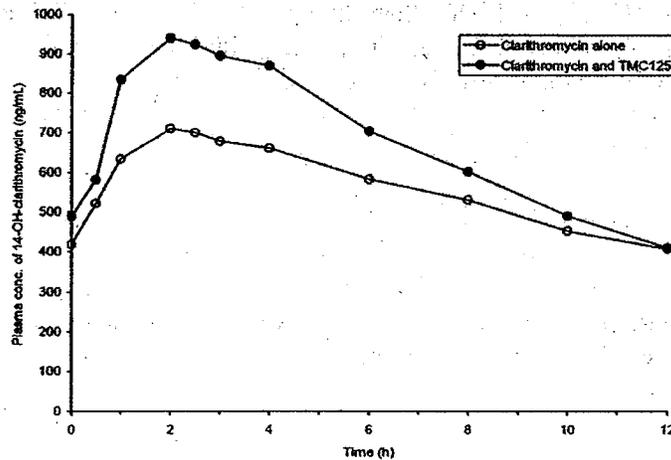
The 90 % CIs of the LS_{means} estimates of all the clarithromycin pharmacokinetic parameters lay outside the 80 % -125 % interval and were lower when clarithromycin was co-administered with TMC125 as compared to when clarithromycin was administered alone.

14-OH-Clarithromycin

Fig 3 shows the mean plasma concentration-time profile of 14-OH-clarithromycin when clarithromycin 500 mg b.i.d. was administered alone or co-administered with TMC125.

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Fig 3: Mean plasma concentration-time profile of 14-OH-clarithromycin when clarithromycin 500 mg b.i.d. was administered alone or co-administered with TMC125



clarithromycin alone: n = 15
clarithromycin and TMC125: n = 15

The mean plasma concentration-time profile of 14-OH-clarithromycin showed that the steady state mean plasma concentrations of 14-OH-clarithromycin were increased over the entire dosing interval when clarithromycin was co-administered with TMC125 (session B, day 13) compared with when clarithromycin was administered alone (session B, day 5). The plasma concentrations of 14-OH-clarithromycin after the last dose on day 13 of session B were quantifiable in all subjects up to 12 hours post dose.

Table 6 shows the pharmacokinetic parameters of 14-OH-clarithromycin when clarithromycin 500 mg b.i.d. was administered alone or co-administered with TMC125 200 mg b.i.d.

Table 6: Pharmacokinetic parameters of 14-OH-clarithromycin when clarithromycin 500 mg b.i.d. was administered alone or co-administered with TMC125 200 mg b.i.d.

Pharmacokinetics of 14-OH-clarithromycin (mean ± SD, t_{max} : median [range])	clarithromycin alone (reference)	clarithromycin and TMC125 (test)
n	15	15
C_{0h} , ng/mL	418.0 ± 165.8	488.0 ± 178.7
C_{min} , ng/mL	382.1 ± 134.3	393.8 ± 108.5
C_{max} , ng/mL	766.1 ± 205.3	1030 ± 317.9
t_{max} , h	2.0 [0.0 - 4.0]	2.0 [1.0 - 4.0]
AUC_{12h} , ng h/mL	6761 ± 1893	8183 ± 2100
$C_{ss,av}$, ng/mL	563.4 ± 157.8	681.9 ± 175.0
FI, %	68.85 ± 24.52	91.71 ± 26.28
Ratio $AUC_{12h, 14-OH-clarithromycin/clarithromycin}$ (%)	35.92 ± 12.27	72.47 ± 28.68

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The individual test/reference treatment ratios for C_{0hr} , C_{min} , C_{max} , and AUC_{12h} of 14-OH-clarithromycin ranged from 58 % to 284 %, 63 % to 198 %, 67 % to 274 %, and 80 % to 240 %, respectively, with geometric means of 116 %, 105 %, 133 %, 121 %, respectively.

The mean fluctuation index (FI) of 14-OH-clarithromycin, when clarithromycin was co-administered with TMC125 was higher than the mean FI of 14-OH-clarithromycin when clarithromycin was administered alone. The inter-individual variability in C_{0h} , C_{min} , C_{max} , and AUC_{12h} of 14-OH-clarithromycin, when clarithromycin was administered alone or co-administered with TMC125 were 40 % and 37 %; 35 % and 28 %; 27 % and 31 %; and 28 % and 26 %, respectively.

The individual AUC_{12h} ratio of 14-OH-clarithromycin to clarithromycin ranged from 13 % to 61 % with a mean and geometric mean of 36 % and 34 %, respectively, when clarithromycin was administered alone. The individual AUC_{12h} ratio of 14-OH-clarithromycin to clarithromycin ranged from 24 % to 133 % with a mean and geometric mean of 72 % and 67 %, respectively, when clarithromycin was co-administered with TMC125.

Table 7 shows the summary of the statistical analysis of the pharmacokinetic parameters of 14-OH-clarithromycin when clarithromycin 500 mg b.i.d. was administered alone or co-administered with TMC125 200 mg b.i.d.

Table 7: Summary of the statistical analysis of the pharmacokinetic parameters of 14-OH-clarithromycin when clarithromycin 500 mg b.i.d. was administered alone or co-administered with TMC125 200 mg b.i.d.

Parameter	LSmeans			90% CI,%	p-value
	clarithromycin alone (reference)	clarithromycin and TMC125 (test)	LSmeans ratio, %		
C_{0h} , ng/mL	388.5	452.1	116.4	97.69 - 138.7	0.1491
C_{min} , ng/mL	359.9	376.4	104.6	90.09 - 121.5	0.6039
C_{max} , ng/mL	737.5	978.8	132.7	113.2 - 155.7	0.0074
AUC_{12h} , ng.h/mL	6514	7887	121.1	105.3 - 139.2	0.0300
Parameter	Median			90% CI,%	p-value
	clarithromycin alone (reference)	clarithromycin and TMC125 (test)	Treatment difference median		
t_{max} , h	2.0	2.0	0.25	(-0.25) - (1.0)	0.3073

n = 15 for Session B, Day 5 (reference) and n = 15 for Session B, Day 13 (test)
CI = confidence interval

Based on the ratio of the LSmeans, the C_{0h} , C_{min} , C_{max} , and AUC_{12h} of 14-OH-clarithromycin were increased by 16 %, 5 %, 33 %, and 21 %, respectively, when

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clarithromycin was co-administered with TMC125, as compared to when clarithromycin was administered alone. The upper limit of the 90 % CIs of the LS_{mean} ratios of C_{0h} , C_{max} , and AUC_{12h} lay outside the 80 % to 125 % interval. The 90 % CIs of C_{min} lay within the 80 % to 125 % interval.

Pharmacokinetic Results Summary

- The LS_{means} ratio of C_{0h} , C_{min} , C_{max} , and AUC_{12h} of TMC125 were **increased** by 49 %, 46 %, 46 %, and 42 %, respectively, when TMC125 was co-administered with clarithromycin, as compared to when TMC125 was administered alone.
- The LS_{means} ratio of C_{0h} , C_{min} , C_{max} , and AUC_{12h} of clarithromycin were **decreased** by 45 %, 53 %, 34 %, and 39 %, respectively, when clarithromycin was co-administered with TMC125 as compared to when clarithromycin was administered alone.
- The LS_{means} ratio of C_{0h} , C_{min} , C_{max} , and AUC_{12h} of 14-OH-clarithromycin were **increased** by 16 %, 5 %, 33 %, and 21 %, respectively, when clarithromycin was co-administered with TMC125, as compared to when clarithromycin was administered alone.

Conclusion

Clarithromycin exposure was decreased by INTELENCE™; however, concentrations of the active metabolite, 14-hydroxy-clarithromycin, were increased. Because 14-hydroxy-clarithromycin has reduced activity against Mycobacterium avium complex (MAC), overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered for the treatment of MAC.

**APPEARS THIS WAY
ON ORIGINAL**

Study Number
TMC125-C174

Title

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.

Objectives

The primary objective of the trial was to determine the induction/inhibition properties of TMC125 on the single dose pharmacokinetics of a cocktail of representative probes of CYP enzymes (CYP1A2, CYP2C9, CYP2D6, CYP3A4, and CYP2C19).

Study Design

Phase I, open label, 1-way, 2-period, cross-over trial in 14 subjects. The drug "cocktail" consisted of midazolam (0.025 mg/kg intravenously, probe CYP3A4 substrate), dextromethorphan (30 mg orally, probe CYP2D6 substrate), caffeine (150 mg orally, probe CYP1A2 substrate), omeprazole (40 mg orally, probe CYP2C19 substrate) and warfarin (10 mg orally, probe CYP2C9 substrate) supplemented with vitamin K (10 mg orally; vitamin K was co-administered to counteract the pharmacodynamic effects of warfarin).

The subjects were divided into 2 panels (7 subjects per panel). Panel 1 received treatment A in session 1 and treatment B in session 2. Panel 2 received treatment B in session 2 and treatment A in session 2.

The following two treatments were administered:

Treatment A: Subjects received a single dose of the cocktail alone.

Treatment B: Subjects received TMC125 200 mg b.i.d. (F060) for 14 days with a single dose of the cocktail on day 1 and day 14.

A 12-hour pharmacokinetic profile of TMC125 was determined on day 1 and day 14 of treatment B. The plasma concentrations of midazolam and its metabolite 1-OH-midazolam, dextromethorphan and its metabolite dextrorphan, caffeine and its metabolite paraxanthine, omeprazole and its metabolite 5-OH-omeprazole, and S-warfarin and its metabolite 7-OH-S-warfarin were determined on day 1 of treatment A and on day 1 and day 14 of treatment B.

Investigational Product(s)

TMC125 was formulated as **F060**; this tablet formulation contains 100 mg TMC125 — spray dried in combination with hydroxypropylmethylcellulose (HPMC, proportion of TMC125:HPMC = —) and microcrystalline cellulose, croscarmellose sodium, magnesium stearate, and lactose monohydrate. The batch number used was 05E18 and expiry date was May 2006.

Midazolam (probe substrate for CYP3A4) was provided as Dormicum® 1 mL vials containing 5 mg midazolam per mL.

Dextromethorphan (probe substrate for CYP2D6) was formulated as Hustenstiller-ratiopharm® capsules containing dextromethorphan hydrobromide corresponding to 30 mg dextromethorphan.

Caffeine (probe substrate for CYP1A2) was formulated as Percoffendrinol® N tablets containing 50 mg caffeine.

Omeprazole (probe substrate for CYP2C19) was formulated as Antra® MUPS tablets containing 40 mg omeprazole.

Warfarin (probe substrate for CYP2C9) was formulated as Coumadin® tablets containing 5 mg warfarin.

Vitamin K1 was formulaed as Konakion® MM ampoules containing 10 mg vitamin K1 solution per ampoule.

Assay Methods

The plasma concentrations of TMC125, caffeine, paraxanthine, S-warfarin, 7-OH-S-warfarin, dextromethorphan, dextrorphan, midazolam, 1-OH-midazolam, omeprazole, and 5-hydroxy omeprazole were determined using LC-MS/MS methods. The lower limit of quantification (LLOQ) was 2 ng/mL for TMC125, 25.0 ng/mL for caffeine and paraxanthine, 5.00 ng/mL for S-warfarin and 7-OH-S-warfarin, 0.05 ng/mL for dextromethorphan, 0.8 ng/mL for dextrorphan, 0.1 ng/mL for midazolam, 0.1 ng/mL for 1-OH-midazolam, 1 ng/mL for omeprazole, and 2 ng/mL for 5-OH-omeprazole.

Pharmacokinetic and Statistical Data Analysis

Pharmacokinetic Analysis

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

Statistical Analysis

The primary pharmacokinetic parameters were C_{max} and AUC_{last} for of the parent compounds and metabolites of the cocktail substrates. In addition, the ratio of C_{max} and AUC_{last} of each parent compound and its metabolite was also calculated.

RESULTS

Subject Disposition and Demographics

Out of the 47 screened, 14 subjects were randomized to either **panel 1** (n = 7) or **panel 2** (n = 7). Out of the 7 subjects randomized to **panel 1**, 2 subjects dropped out of the trial in **session 2** (on **day 6** and **day 9** respectively) because of an adverse event. 12 subjects completed the trial.

Table 1 shows the demographics in trial TMC125-C174.

Table 1: Demographics in Trial TMC125-C174

Parameter	Panel 1 N = 7	Panel 2 N = 7	All Subjects N = 14
Age, years Median (range)	34.0 (26-49)	35.0 (21-47)	34.0 (21-49)
Height, cm Median (range)	179.0 (176-188)	181.0 (171-193)	181.0 (171-193)
Weight, kg Median (range)	78.0 (60-95)	84.0 (75-97)	80.5 (60-97)
BMI, kg/m ² Median (range)	23.2 (19-28)	23.9 (23-30)	23.6 (19-30)
Sex, n (%) Male	7 (100)	7 (100)	14 (100)
Ethnic Origin, n (%) Caucasian	7 (100)	7 (100)	14 (100)
Type of Smoker, n (%) Nonsmoker	7 (100)	7 (100)	14 (100)

Pharmacokinetics

Full pharmacokinetic profiles of caffeine, paraxanthine, S-warfarin, 7-OH-S-warfarin, dextromethorphan, dextrorphan, midazolam, 1-OH-midazolam, omeprazole, and 5-OH-hydroxyomeprazole were available for 14 subjects for the treatment phase with drug-cocktail alone. For TMC125 and all compounds associated with the drug cocktail, full pharmacokinetic profiles for 14 subjects were available for **day 1** and for 12 subjects for **day 14** of the co-administration phase.

CYP2D6, CYP2C9, and CYP2C19 are polymorphic enzymes. In this trial, poor metabolizers were excluded from participation.

TMC125

Table 2 shows the mean pharmacokinetic parameters of TMC125 200 mg b.i.d., co-administered with a single dose of the cocktail on on day 1 and day 14.

Table 2: Mean pharmacokinetic parameters of TMC125 200 mg b.i.d., co-administered with a single dose of the cocktail on on day 1 and day 14.

<i>Pharmacokinetics of TMC125</i> (mean \pm SD, t_{max} : median [range])	TMC125 + Drug cocktail (Day 1)	TMC125 + Drug cocktail (Day 14)
n	14	12
t_{max} , h	6.00 (2.00-6.02)	4.00 (2.00-8.02)
C_{0h} , ng/mL	0	577.5 \pm 153.3
C_{min} , ng/mL	-	512.3 \pm 131.7
C_{max} , ng/mL	227.8 \pm 80.16	897.1 \pm 215.5
AUC_{12h} , ng.h/mL	1464 \pm 528.3	8517 \pm 2015

Reviewer's Note

The mean pharmacokinetic parameters of TMC125 observed in this study were similar to the mean pharmacokinetic parameters of TMC125 observed in other studies.

CYP1A2: Pharmacokinetics of Caffeine and Paraxanthine

Fig 1 shows the mean plasma concentration-time profiles of caffeine after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14).

Fig 1: Mean plasma concentration-time profiles of caffeine after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14)

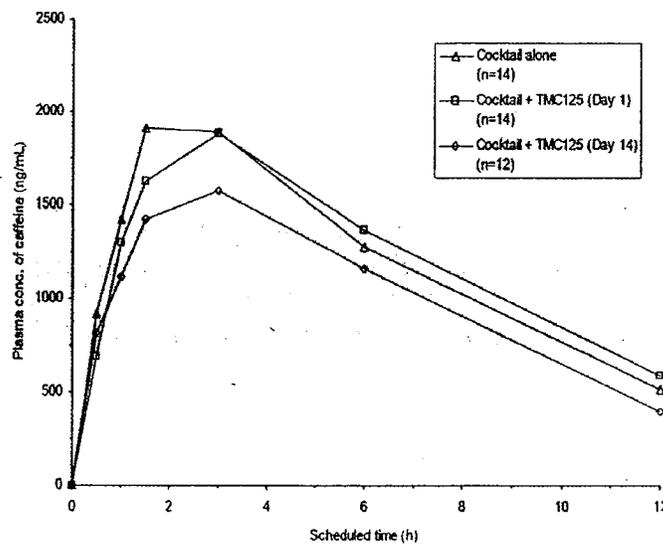
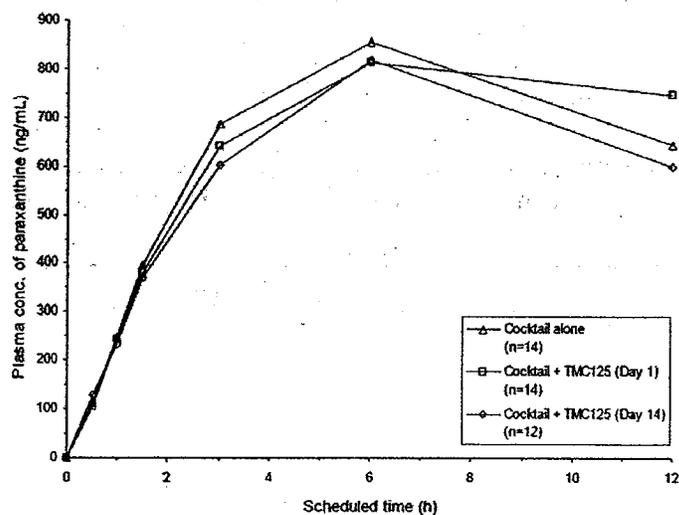


Fig 2 shows the mean plasma concentration-time profiles of paraxanthine after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14).

On day 1 of TMC125 treatment, the mean plasma concentration-time profile of caffeine was similar to the caffeine concentrations after administration of the drug cocktail alone. On day 14 of TMC125 treatment, combined intake of TMC125 and the drug cocktail resulted in lower plasma concentrations of caffeine, compared to intake of the drug cocktail alone. For 1 of the 14 subjects, the plasma concentrations of caffeine were above the LLOQ at the start of each treatment, possibly because of recent consumption of caffeine-containing food or drink. The pre-dose plasma concentrations were, respectively, 6 % and 1 % of C_{max} for treatment with drug cocktail alone and day 1 of TMC125 treatment. These low concentrations are not expected to influence the pharmacokinetic results of the trial.

Fig 2: Mean plasma concentration-time profiles of paraxanthine after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14)



For paraxanthine, the mean plasma concentration-time profiles of paraxanthine were similar between treatment with drug cocktail alone and day 1 and day 14 of TMC125 treatment.

Table 3 shows the mean pharmacokinetic parameters of caffeine, paraxanthine, and their ratios after administration of drug-cocktail alone and in combination with TMC125.

Table 3: Mean pharmacokinetic parameters of caffeine, paraxanthine, and their ratios after administration of drug-cocktail alone and in combination with TMC125

CYP1A2	Drug cocktail alone	TMC125 + Drug cocktail (Day 1)	TMC125 + Drug cocktail (Day 14)
Pharmacokinetics^a of:			
Caffeine			
n	14	14	12
C _{max} (ng/mL)	2151 ± 562.1	2091 ± 493.3	1725 ± 480.5
t _{max} (h)	1.50 (1.00-6.00)	2.19 (0.48-3.02)	2.21 (0.45-5.98)
AUC _{12h} (ng.h/mL)	14640 ± 4676	14710 ± 3985	12280 ± 3665
Paraxanthine			
n	14	14	12
C _{max} (ng/mL)	892.1 ± 129.8	856.5 ± 69.03	827.3 ± 115.4
t _{max} (h)	6.00 (2.98-12.02)	5.98 (2.77-11.93)	5.97 (5.95-11.88)
AUC _{12h} (ng.h/mL)	7912 ± 1028	7853 ± 789.2	7329 ± 898.2
Ratio caffeine/paraxanthine			
n	14	14	12
Ratio C _{max} P/M ^b (%)	243.5 ± 67.01	244.1 ± 52.56	208.2 ± 51.20
Ratio AUC _{12h} P/M ^b (%)	187.2 ± 65.95	190.0 ± 65.91	166.8 ± 42.42

^a mean ± SD, t_{max}: median [range]

^b P/M: parent/metabolite

Table 4 shows the statistical evaluation of the pharmacokinetic parameters of caffeine, paraxanthine, and their ratios after administration of drug cocktail alone and in combination with TMC125 (day 1).

Table 4: Statistical evaluation of the pharmacokinetic parameters of caffeine, paraxanthine, and their ratios after administration of drug cocktail alone and in combination with TMC125 (day 1)

CYP1A2	LSmeans ^a		LSmeans ratio (%)	90% CI (%)	p-value	
	Drug cocktail alone (reference)	TMC125 + Drug cocktail Day 1 (test)			Period	Sequence
Caffeine						
C _{max} (ng/mL)	2080	2037	97.95	86.06-111.5	0.2079	0.4869
AUC _{12h} (ng.h/mL)	14000	14230	101.6	95.58-108.1	0.1555	0.5929
Paraxanthine						
C _{max} (ng/mL)	883.7	853.9	96.63	90.98-102.6	0.8696	0.5287
AUC _{12h} (ng.h/mL)	7850	7816	99.56	93.99-105.5	0.7663	0.1229
Ratio caffeine/paraxanthine						
Ratio C _{max} P/M ^b (%)	235.4	238.6	101.4	89.78-114.5	0.2062	0.6785
Ratio AUC _{12h} P/M ^b (%)	178.4	182.1	102.1	97.00-107.4	0.0516	0.9963

^a n = 14 for drug cocktail alone (reference) and Treatment B. Day 1 (test)

^b P/M: parent/metabolite

The LS_{means} of C_{max} and AUC_{12h} of caffeine and paraxanthine were not significantly altered (all changes < 10 %) when the cocktail was co-administered with TMC125 on day 1 as compared to when the cocktail was administered alone.

Table 5. shows the statistical evaluation of the pharmacokinetic parameters of caffeine, paraxanthine, and their ratios after administration of drug cocktail alone and in combination with TMC125 (day 14).

Table 5: Statistical evaluation of the pharmacokinetic parameters of caffeine, paraxanthine, and their ratios after administration of drug cocktail alone and in combination with TMC125 (day 14)

CYP1A2 Parameter	LSmeans ^a		LSmeans ratio (%)	90% CI (%)	p-value	
	Drug cocktail alone (reference)	TMC125 + Drug cocktail, Day 14 (test)			Period	Sequence
Caffeine						
C _{max} (ng/mL)	2080	1746	83.97	75.06-93.94	0.7382	0.1832
AUC _{12h} (ng.h/mL)	14000	11840	84.57	78.20-91.46	0.5143	0.5125
Paraxanthine						
C _{max} (ng/mL)	883.7	823.4	93.18	88.04-98.63	0.9980	0.5960
AUC _{12h} (ng.h/mL)	7850	7324	93.29	88.31-98.54	0.7826	0.3173
Ratio caffeine/paraxanthine						
Ratio C _{max} P/M ^b (%)	235.4	212.1	90.13	81.17-100.1	0.7168	0.2505
Ratio AUC _{12h} P/M ^b (%)	178.4	161.5	90.55	85.44-95.97	0.5134	0.7957

^a n = 14 for drug cocktail alone (reference) and n = 12 for Treatment B, Day 14 (test)

^b P/M: parent/metabolite

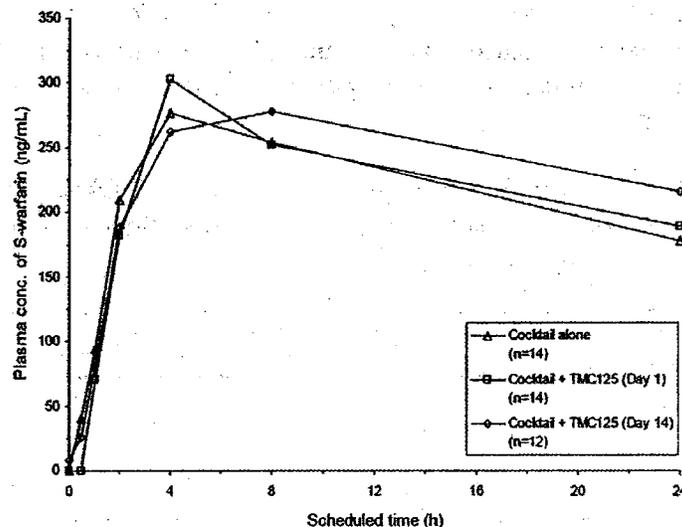
The LS_{means} of C_{max} and AUC_{12h} of caffeine were decreased by 16 % and 15 % respectively, when the cocktail was co-administered with TMC125 on day 14 as compared to when the cocktail was administered alone.

The LS_{means} of C_{max} and AUC_{12h} of paraxanthine were not significantly altered (all changes < 10 %) when the cocktail was co-administered with TMC125 on day 14 as compared to when the cocktail was administered alone.

CYP2C9: Pharmacokinetics of S-Warfarin and 7-OH-S-Warfarin

Fig 3 shows the mean plasma concentration time profiles of S-warfarin after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14).

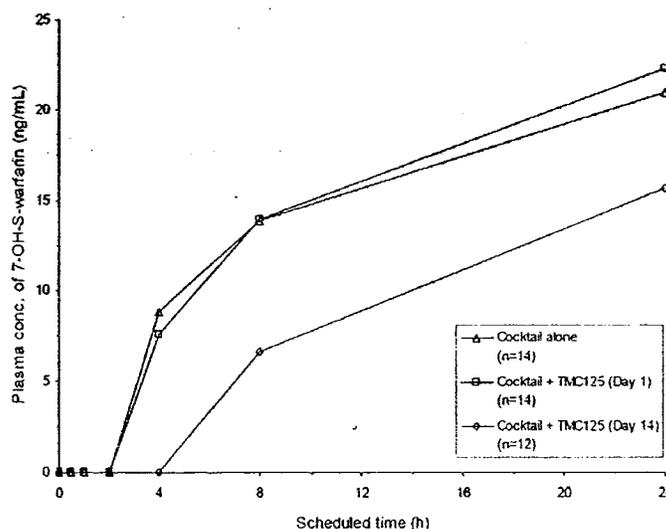
Fig 3: Mean plasma concentration time profiles of S-warfarin after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14)



The plasma concentration-time profiles of S-warfarin were similar after a single dose of cocktail on day 1 and day 14 of TMC125 treatment.

Fig 4 shows the mean plasma concentration time profiles of 7-OH-S-warfarin after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14).

Fig 4: Mean plasma concentration time profiles of 7-OH-S-warfarin after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14).



For 7-OH-S-warfarin, the mean plasma concentration-time profiles were similar between treatment with drug cocktail alone and day 1 of TMC125 treatment. On day 14 of TMC125 treatment, mean plasma concentration-time profiles of 7-OH-S-warfarin were decreased.

Table 6 shows the mean pharmacokinetic parameters of S-warfarin, 7-OH-S-warfarin, and their ratios after administration of drug-cocktail alone and in combination with TMC125 (day 1 and day 14).

Table 6: Mean pharmacokinetic parameters of S-warfarin, 7-OH-S-warfarin, and their ratios after administration of drug-cocktail alone and in combination with TMC125 (day 1 and day 14)

CYP2C9	Drug cocktail alone	TMC125 + Drug cocktail (Day 1)	TMC125 + Drug cocktail (Day 14)
<i>Pharmacokinetics^a of:</i>			
<i>S-warfarin</i>			
n	14	14	12
C _{max} (ng/mL)	309.9 ± 50.86	310.2 ± 38.62	307.8 ± 51.09
t _{max} (h)	4.00 (1.00-8.00)	3.97 (0.98-8.82)	3.97 (0.97-7.98)
AUC _{24h} (ng.h/mL)	5222 ± 593.4	5296 ± 695.3	5598 ± 1133
<i>7-OH-S-warfarin^b</i>			
n	14	14	12
C _{max} (ng/mL)	21.42 ± 5.822	22.27 ± 5.296	15.65 ± 3.451
t _{max} (h)	24.02 (8.02-24.38)	23.92 (23.77-24.15)	23.95 (23.52-24.00)
AUC _{24h} (ng.h/mL)	336.6 ± 101.2	339.0 ± 76.53	197.9 ± 65.33
<i>Ratio S-warfarin/7-OH-S-warfarin</i>			
n	14	14	12
Ratio C _{max} P/M ^c (%)	1588 ± 624.4	1477 ± 420.0	2057 ± 561.5
Ratio AUC _{24h} P/M ^c (%)	1929 ± 1573	1684 ± 673.5	3154 ± 1292

^a mean ± SD, t_{max}: median [range]

^b C_{max} and t_{max} may not have been reached

^c P/M: parent/metabolite

Table 7 shows the statistical evaluation of the pharmacokinetic parameters of S-warfarin, 7-OH-S-warfarin, and their ratios after administration of drug cocktail alone and in combination with TMC125 (day 1).

Table 7: Statistical evaluation of the pharmacokinetic parameters of S-warfarin, 7-OH-S-warfarin, and their ratios after administration of drug cocktail alone and in combination with TMC125 (day 1).

CYP2C9 Parameter	LSmeans ^a		LSmeans ratio (%)	90% CI (%)	p-value	
	Drug cocktail alone (reference)	TMC125 + Drug cocktail Day 1 (test)			Period	Sequence
S-warfarin						
C _{max} (ng/mL)	306.3	308.1	100.6	93.82-107.9	0.4639	0.6427
AUC _{24h} (ng.h/mL)	5191	5254	101.2	98.26-104.2	0.0807	0.4970
7-OH-S-warfarin^b						
C _{max} (ng/mL)	20.56	21.64	105.3	94.39-117.4	0.5832	0.8924
AUC _{24h} (ng.h/mL)	312.8	329.6	105.3	91.57-121.2	0.3543	0.5574
Ratio S-warfarin/7-OH-S-warfarin						
Ratio C _{max P/M} ^c (%)	1490	1424	95.56	83.22-109.7	0.9489	0.9460
Ratio AUC _{24h P/M} ^c (%)	1659	1594	96.07	85.09-108.5	0.5285	0.4647

^a n = 14 for drug cocktail alone (reference) and n = 12 for Treatment B, Day 14 (test)

^b C_{max} and t_{max} may not have been reached.

^c P/M: parent/metabolite

On day 1, the LS_{means} of C_{max} and AUC_{24h} of S-warfarin and 7-OH-S-warfarin were not significantly altered when the cocktail was co-administered with TMC125 as compared to when the cocktail was administered alone.

Table 8 shows the statistical evaluation of the pharmacokinetic parameters of S-warfarin, 7-OH-S-warfarin, and their ratios after administration of drug cocktail alone and in combination with TMC125 (day 14).

Table 8: Statistical evaluation of the pharmacokinetic parameters of S-warfarin, 7-OH-S-warfarin, and their ratios after administration of drug cocktail alone and in combination with TMC125 (day 14).

CYP2C9 Parameter	LSmeans ^a		LSmeans ratio (%)	90% CI (%)	p-value	
	Drug cocktail alone (reference)	TMC125 + Drug cocktail Day 14 (test)			Period	Sequence
S-warfarin						
C _{max} (ng/mL)	306.3	303.7	99.17	88.14-111.6	0.6727	0.7353
AUC _{24h} (ng.h/mL)	5191	5462	105.2	93.43-118.5	0.6100	0.7835
7-OH-S-warfarin^b						
C _{max} (ng/mL)	20.56	14.98	72.89	60.43-87.93	0.3333	0.3371
AUC _{24h} (ng.h/mL)	312.8	180.2	57.61	44.01-75.41	0.5305	0.1587
Ratio S-warfarin/7-OH-S-warfarin						
Ratio C _{max P/M} ^c (%)	1490	2057	138.1	116.7-163.4	0.3427	0.5110
Ratio AUC _{24h P/M} ^c (%)	1659	3013	181.6	150.7-218.7	0.5942	0.2263

^a n = 14 for drug cocktail alone (reference) and n = 12 for Treatment B, Day 14 (test)

^b C_{max} and t_{max} may not have been reached.

^c P/M: parent/metabolite

On day 14, the LS_{means} of C_{max} and AUC_{24h} of S-warfarin were not significantly altered when the cocktail was co-administered with TMC125 as compared to when the cocktail was administered alone.

On day 14, the LS_{means} ratio of C_{max} and $AUC_{24\text{h}}$ of 7-OH-S-warfarin were decreased by 27 % and 42 % respectively, when the cocktail was co-administered with TMC125 as compared to when the cocktail was administered alone.

CYP2D6: Pharmacokinetics of Dextromethorphan and Dextropropriofen

Fig 5 shows the mean plasma concentration time profiles of dextromethorphan after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14).

Fig 5: Mean plasma concentration time profiles of dextromethorphan after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14)

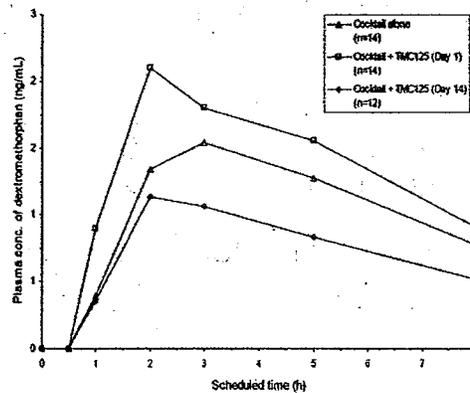


Fig 6 shows the mean plasma concentration time profiles of dextropropriofen after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14).

Fig 6: Mean plasma concentration time profiles of dextropropriofen after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14)

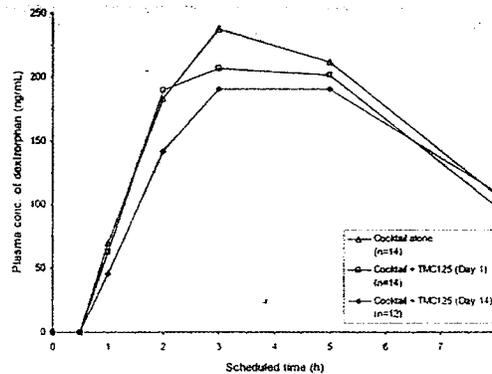


Table 9 shows the mean pharmacokinetic parameters of dextromethorphan, dextrorphan, and their ratios after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14).

Table 9: Mean pharmacokinetic parameters of dextromethorphan, dextrorphan, and their ratios after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14).

CYP2D6	Drug cocktail alone	TMC125 + Drug cocktail (Day 1)	TMC125 + Drug cocktail (Day 14)
<i>Pharmacokinetics^a of:</i>			
Dextromethorphan			
n	14	14	12
C _{max} (ng/mL)	1.890 ± 1.620	2.445 ± 2.382	1.292 ± 0.9701
t _{max} (h)	3.00 (1.00-5.00)	2.40 (0.98-4.98)	2.97 (1.95-7.98)
AUC _{0-8h} (ng.h/mL)	8.339 ± 7.648	11.12 ± 9.728	5.865 ± 4.143
Dextrorphan			
N	14	14	12
C _{max} (ng/mL)	297.9 ± 84.15	266.4 ± 69.48	236.1 ± 52.36
t _{max} (h)	3.99 (2.00-5.00)	4.85 (0.98-4.98)	2.97 (1.97-7.98)
AUC _{0-8h} (ng.h/mL)	1283 ± 235.2	1263 ± 206.4	1101 ± 239.7
Ratio dextromethorphan/dextrorphan			
n	14	14	12
Ratio C _{max} P/M ^b (%)	0.6872 ± 0.7151	0.9198 ± 0.8818	0.5284 ± 0.3622
Ratio AUC _{0-8h} P/M ^b (%)	0.6811 ± 0.7143	0.9076 ± 0.8629	0.5181 ± 0.3535

^a mean ± SD, t_{max}: median [range]

^b P/M: parent/metabolite

Table 10 shows the statistical evaluation of the pharmacokinetic parameters of dextromethorphan, dextrorphan, and their ratios after administration of drug cocktail alone and in combination with TMC125 (day 1).

Table 10: Statistical evaluation of the pharmacokinetic parameters of dextromethorphan, dextrorphan, and their ratios after administration of drug cocktail alone and in combination with TMC125 (day 1).

CYP2D6	LSmeans ^a		LSmeans ratio (%)	90% CI (%)	p-value	
	Drug cocktail alone (reference)	TMC125 + Drug cocktail, Day 1 (test)			Period	Sequence
Dextromethorphan						
C _{max} (ng/mL)	1.363	1.577	115.7	91.07-147.0	0.4911	0.2554
AUC _{0-8h} (ng.h/mL)	6.003	7.613	126.8	102.7-156.6	0.9327	0.2148
Dextrorphan						
C _{max} (ng/mL)	286.8	258.9	90.27	81.92-99.47	0.0726	0.3382
AUC _{0-8h} (ng.h/mL)	1262	1247	98.78	93.35-104.5	0.8610	0.0693*
Ratio dextromethorphan/dextrorphan						
Ratio C _{max} P/M ^b (%)	0.4751	0.6091	128.2	105.6-155.6	0.9157	0.1483
Ratio AUC _{0-8h} P/M ^b (%)	0.4756	0.6107	128.4	106.6-154.7	0.9661	0.1051

* Statistically significant difference

^a n = 14 for Treatment A (reference) and Treatment B, Day 1 (test)

^b P/M: parent/metabolite

On day 1, the LS_{means} ratio of C_{max} and AUC_{8h} of dextromethorphan increased by 16 % and 27 % respectively, when the cocktail was co-administered with TMC125 as compared to when the cocktail was administered alone.

On day 1, the LS_{means} ratio of C_{max} and AUC_{8h} of dextrophan were not significantly altered when the cocktail was co-administered with TMC125 as compared to when the cocktail was administered alone.

Table 11 shows the statistical evaluation of the pharmacokinetic parameters of dextromethorphan, dextrophan, and their ratios after administration of drug cocktail alone and in combination with TMC125 (day 14).

Table 11: Statistical evaluation of the pharmacokinetic parameters of dextromethorphan, dextrophan, and their ratios after administration of drug cocktail alone and in combination with TMC125 (day 14).

CYP2D6 Parameter	LSmeans ^a		LSmeans ratio (%)	90% CI (%)	p-value	
	Drug cocktail alone (reference)	TMC125 + Drug cocktail, Day 14 (test)			Period	Sequence
Dextromethorphan						
C_{max} (ng/mL)	1.363	1.163	85.30	59.31-122.7	0.0856	0.0535*
AUC_{8h} (ng.h/mL)	6.003	5.648	94.08	71.98-123.0	0.0523	0.0522*
Dextrophan						
C_{max} (ng/mL)	286.8	231.2	80.60	69.08-94.04	0.1094	0.4341
AUC_{8h} (ng.h/mL)	1262	1078	85.38	77.57-93.97	0.1172	0.4106
Ratio dextromethorphan/dextrophan						
Ratio C_{max} ^b (%)	0.4751	0.5285	111.2	85.93-144.0	0.0754	0.0286*
Ratio AUC_{8h} ^b (%)	0.4756	0.5306	111.6	90.17-138.0	0.0618	0.0262*

^a Statistically significant difference

^a n = 14 for Treatment A (reference) and Treatment B, Day 1 (test)

^b P/M: parent/metabolite

On day 14, the LS_{means} ratio of C_{max} and AUC_{8h} of dextromethorphan was decreased by 15 % and 6 % respectively, when the cocktail was co-administered with TMC125 as compared to when the cocktail was administered alone.

On day 14, the LS_{means} ratio of C_{max} and AUC_{8h} of dextrophan were decreased by 20 % and 15 % respectively, when the cocktail was co-administered with TMC125 as compared to when the cocktail was administered alone.

CYP3A4: Pharmacokinetics of Midazolam and 1-OH-Midazolam

Fig 7 shows the mean plasma concentration-time profiles of midazolam after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14).

Fig 7: Mean plasma concentration-time profiles of midazolam after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14)

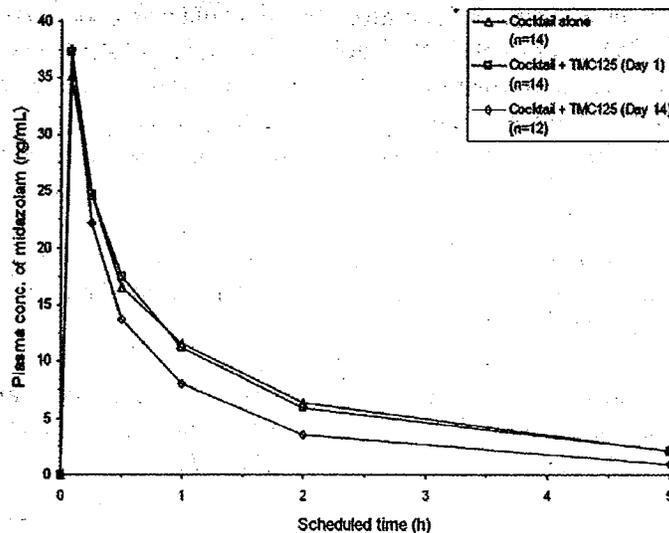
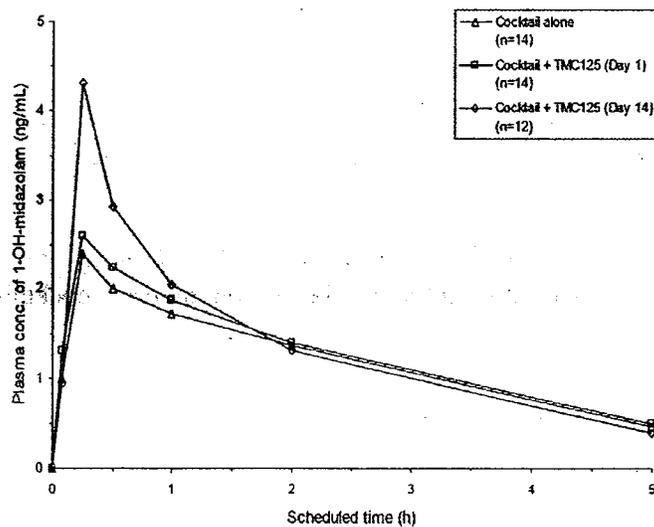


Fig 8 shows the mean plasma concentration-time profiles of 1-OH-midazolam after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14).

Fig 8: Mean plasma concentration-time profiles of 1-OH-midazolam after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14)



The mean plasma concentration-time profiles of midazolam were similar after a single intake of the drug cocktail alone and after co-administration with a single dose of TMC125 (day 1). On day 14 of treatment B, combined intake of TMC125 and the drug cocktail resulted in lower plasma concentrations of midazolam, compared to the reference treatment (treatment A). For 1-OH-midazolam, the mean plasma concentration-time profiles were similar after administration of drug cocktail alone and after single dose administration of TMC125 on day 1 of treatment B. On day 14 of treatment B, the mean plasma concentration-time profiles of 1-OH-midazolam were higher, compared to reference treatment A.

Table 12 shows the pharmacokinetic parameters of midazolam, 1-OH-midazolam, and their ratios after administration of drug-cocktail alone and in combination with TMC125 200 mg b.i.d. (day 1 and day 14).

Table 12: Pharmacokinetic parameters of midazolam, 1-OH-midazolam, and their ratios after administration of drug-cocktail alone and in combination with TMC125 200 mg b.i.d. (day 1 and day 14)

CYP3A4	Drug cocktail alone	TMC125 + Drug Cocktail (Day 1)	TMC125 + Drug Cocktail (Day 14)
<i>Pharmacokinetics^a of:</i>			
<i>Midazolam</i>			
n	14	14	12
C _{max} (ng/mL)	35.95 ± 7.755	36.26 ± 9.837	39.58 ± 14.43
t _{max} (h)	0.08 (0.07-0.25)	0.08 (0.07-0.37)	0.07 (0.05-0.23)
AUC _{0-2h} (ng.h/mL)	38.65 ± 6.626	37.33 ± 6.825	27.48 ± 5.216
<i>1-OH-midazolam</i>			
n	14	14	12
C _{max} (ng/mL)	2.582 ± 0.8024	2.989 ± 0.9204	4.310 ± 1.770
t _{max} (h)	0.25 (0.23-2.00)	0.23 (0.12-0.50)	0.23 (0.22-0.48)
AUC _{0-2h} (ng.h/mL)	5.852 ± 1.271	6.221 ± 1.081	6.531 ± 1.633
<i>Ratio midazolam/1-OH-midazolam</i>			
n	14	14	12
Ratio C _{max P/M} ^b (%)	1495 ± 472.8	1316 ± 544.0	970.7 ± 366.6
Ratio AUC _{0-2h P/M} ^b (%)	685.1 ± 167.0	608.8 ± 116.1	430.2 ± 71.76

^a mean ± SD, t_{max}: median [range]

^b P/M: parent/metabolite

Table 13 shows the statistical analysis of the pharmacokinetic parameters of midazolam, 1-OH-midazolam, and their ratios after administration of drug cocktail alone and in combination with 200 mg TMC125 b.i.d. (day 1).

Table 13: Statistical analysis of the pharmacokinetic parameters of midazolam, 1-OH-midazolam, and their ratios after administration of drug cocktail alone and in combination with 200 mg TMC125 b.i.d. (day 1)

CYP3A4 Parameter	LSmeans ^a		LSmeans ratio (%)	90% CI (%)	p-value	
	Drug cocktail alone (reference)	TMC125 + Drug cocktail Day 1 (test)			Period	Sequence
Midazolam						
C _{max} (ng/mL)	35.13	34.98	99.56	88.74-111.7	0.3454	0.8761
AUC ₀₋₂₄ (ng.h/mL)	38.11	36.74	96.42	90.01-103.3	0.0958	0.6461
1-OH-midazolam						
C _{max} (ng/mL)	2.471	2.859	115.7	95.72-139.8	0.9151	0.2984
AUC ₀₋₂₄ (ng.h/mL)	5.722	6.142	107.3	101.6-113.4	0.0114*	0.1785
Ratio midazolam/1-OH-midazolam						
Ratio C _{max P/M} ^b (%)	1422	1223	86.06	67.66-109.5	0.7077	0.2839
Ratio AUC _{0-24 P/M} ^b (%)	666.0	598.3	89.83	80.65-100.1	0.7178	0.4124

^a Statistically significant difference

^b n = 14 for Treatment A (reference) and Treatment B, Day 1 (test)

^c P/M: parent/metabolite

Table 14 shows the statistical analysis of the pharmacokinetic parameters of midazolam, 1-OH-midazolam, and their ratios after administration of drug cocktail alone and in combination with 200 mg TMC125 b.i.d. (day 14).

Table 14: Statistical analysis of the pharmacokinetic parameters of midazolam, 1-OH-midazolam, and their ratios after administration of drug cocktail alone and in combination with 200 mg TMC125 b.i.d. (day 14)

CYP3A4 Parameter	LSmeans ^a		LSmeans ratio (%)	90% CI (%)	p-value	
	Drug cocktail alone (reference)	TMC125 + Drug cocktail Day 14 (test)			Period	Sequence
Midazolam						
C _{max} (ng/mL)	35.13	35.07	99.83	78.46 - 127.0	0.1349	0.0389*
AUC ₀₋₂₄ (ng.h/mL)	38.11	26.16	68.65	64.04 - 73.59	0.2359	0.1112
1-OH-midazolam						
C _{max} (ng/mL)	2.471	3.880	157.0	130.2 - 189.3	0.3096	0.1117
AUC ₀₋₂₄ (ng.h/mL)	5.722	6.238	109.0	100.4 - 118.3	0.1920	0.1690
Ratio midazolam/1-OH-midazolam						
Ratio C _{max P/M} ^b (%)	1422	904.2	63.60	48.88 - 82.74	0.4900	0.9759
Ratio AUC _{0-24 P/M} ^b (%)	666.0	419.8	63.04	56.65 - 70.15	0.0898	0.9889

^a Statistically significant difference

^b n = 14 for Treatment A (reference) and Treatment B, Day 1 (test)

^c P/M: parent/metabolite

On day 1, The LS_{means} of C_{max} and AUC_{last} values of midazolam were similar after administration of a single dose of the drug cocktail and single dose administration the drug cocktail and TMC125. For 1-OH-midazolam, the C_{max} and AUC_{last} were increased by 16 % and 7 %, respectively, after single dose TMC125. The LS_{mean} of the parent/metabolite ratios of C_{max} and AUC_{last} were decreased on day 1 by 14 % and 10 %, respectively.

On day 14, LS_{mean} of midazolam C_{max} was similar and the AUC_{last} was decreased by 31 %. The LS_{mean} of C_{max} and AUC_{last} for 1-OH-midazolam were increased by 57 % and 9 %, respectively. The LS_{means} of the parent/metabolite ratios of C_{max} and AUC_{last} of midazolam and 1-OH midazolam decreased by 36 % and 37 %, respectively.

The plasma concentrations and the AUC_{last} of midazolam on day 1 were similar for the 2 treatment sequences (panel 1 starting with treatment A versus panel 2 starting with treatment B), suggesting the 14-day washout period was sufficient for CYP3A4 to return to its baseline activity after 14 days of induction.

Reviewer's Comment

Midazolam was not administered orally in the current trial (it was only administered intravenously), hence, the extent of CYP3A4 induction by TMC125 in the gastrointestinal tract cannot be determined. Therefore, the "true" magnitude of CYP3A induction by CYP3A4 may have been underestimated in the trial.

CYP2C19: Pharmacokinetics of Omeprazole and 5-OH-Omeprazole

Fig 9 shows the mean plasma concentration-time profiles of omeprazole after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14).

Fig 9: Mean plasma concentration-time profiles of omeprazole after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14)

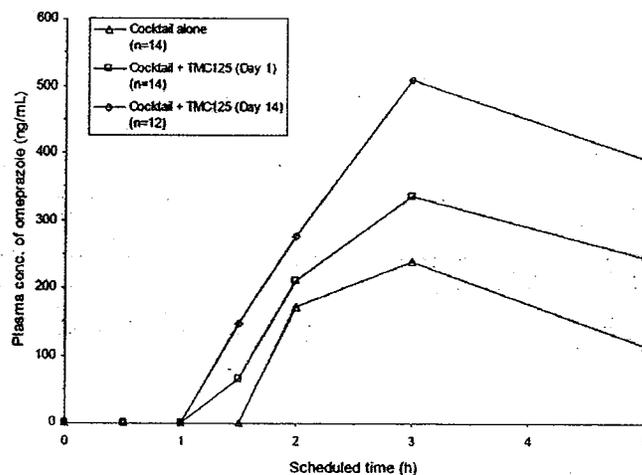
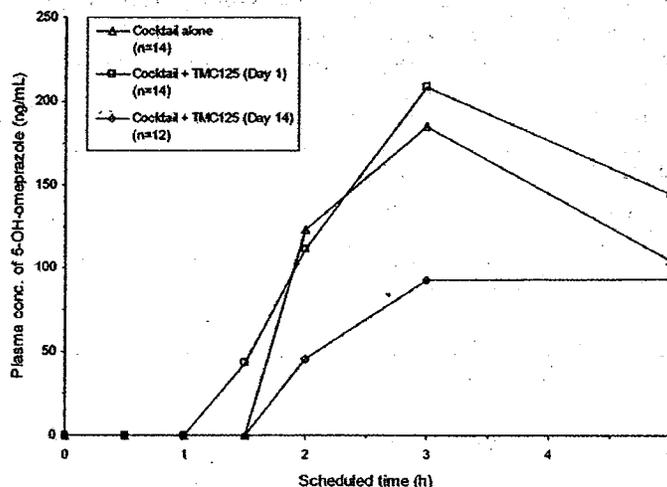


Fig 10 shows the mean plasma concentration-time profiles of 5-OH-omeprazole after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14).

Fig 10: Mean plasma concentration-time profiles of 5-OH-omeprazole after administration of drug cocktail alone and in combination with TMC125 (day 1 and day 14).



The mean plasma concentration-time profiles of omeprazole were increased after intake of the drug cocktail with a single dose of TMC125 (**day 1**) or at steady-state conditions of TMC125 (**day 14**), with the highest increase in omeprazole concentrations on **day 14**. The mean plasma concentration-time profiles of 5-OH-omeprazole were increased and decreased, respectively, after intake of the drug cocktail with a single dose of TMC125 (**day 1**), or at steady-state conditions of TMC125 (**day 14**). The maximum plasma concentrations of 5-OH-omeprazole were reached 3 h after intake of omeprazole after **treatment A**, or on day 1 of **treatment B**. On day 14 of **treatment B**, the plasma concentrations were still increasing at the end of the sampling period. It is therefore possible that the maximum plasma concentration of 5-OH-omeprazole had not yet been reached within the 5-h sampling period.

Table 15 shows the mean pharmacokinetic parameters of omeprazole, 5-OH-omeprazole, and their ratios after administration of drug cocktail alone and in combination with TMC125 200 mg b.i.d. (**day 1** and **day 14**).

Table 15: Mean pharmacokinetic parameters of omeprazole, 5-OH-omeprazole, and their ratios after administration of drug cocktail alone and in combination with TMC125 200 mg b.i.d. (day 1 and day 14).

CYP2C19 Pharmacokinetics ^a of:	Drug cocktail alone	TMC125 + Drug cocktail (Day 1)	TMC125 + Drug cocktail (Day 14)
Omeprazole			
n	14	14	12
C _{max} (ng/mL)	364.8 ± 237.3	429.4 ± 214.9	662.9 ± 356.7
t _{max} (h)	2.99 (1.00-5.00)	2.97 (1.50-4.98)	2.98 (1.97-4.97)
AUC ₀₋₂₄ (ng.h/mL)	729.4 ± 527.1	947.3 ± 502.0	1437 ± 945.0
5-OH-omeprazole			
n	14	14	12
C _{max} (ng/mL)	244.2 ± 101.0	243.0 ± 86.92	123.6 ± 66.10
t _{max} (h)	2.99 (1.00-5.00)	2.98 (1.28-4.98)	4.95 (1.97-4.97)
AUC ₀₋₂₄ (ng.h/mL)	548.2 ± 285.6	568.2 ± 199.1	279.7 ± 187.5
Ratio omeprazole/5-OH-omeprazole			
n	14	14	12
Ratio C _{max} P/M ^b (%)	146.5 ± 64.57	178.4 ± 72.14	538.3 ± 82.59
Ratio AUC ₀₋₂₄ P/M ^b (%)	133.4 ± 60.87	171.5 ± 70.48	529.0 ± 89.54

^a mean ± SD, t_{max}: median [range]
^b P/M: parent/metabolite

Table 16 shows the statistical analysis of the pharmacokinetic parameters of omeprazole, 5-OH-omeprazole, and their ratios after administration of drug cocktail alone and in combination with TMC125 200 mg b.i.d. (day 1).

Table 16: Statistical analysis of the pharmacokinetic parameters of omeprazole, 5-OH-omeprazole, and their ratios after administration of drug cocktail alone and in combination with TMC125 200 mg b.i.d. (day 1)

CYP2C19 Parameter	LSmeans ^a		LSmeans ratio (%)	90% CI (%)	p-value	
	Drug cocktail alone (reference)	TMC125 + drug cocktail, Day 1 (test)			Period	Sequence
Omeprazole						
C _{max} (ng/mL)	287.4	383.2	133.3	90.36-196.8	0.2458	0.5768
AUC ₀₋₂₄ (ng.h/mL)	516.1	837.9	162.4	100.2-262.9	0.7258	0.6446
5-OH-omeprazole						
C _{max} (ng/mL)	214.8	231.0	107.5	78.48-147.3	0.6153	0.7604
AUC ₀₋₂₄ (ng.h/mL)	423.7	528.2	124.7	75.85-204.9	0.7139	0.7918
Ratio omeprazole/5-OH-omeprazole						
Ratio C _{max} P/M ^b (%)	133.8	165.9	124.0	104.4-147.3	0.0948	0.2644
Ratio AUC ₀₋₂₄ P/M ^b (%)	121.8	158.6	130.2	112.2-151.2	0.0330*	0.2494

* Statistically significant difference
^a n = 14 for Treatment A (reference) and Treatment B, Day 1 (test)
^b P/M: parent/metabolite

Table 17 shows the statistical analysis of the pharmacokinetic parameters of omeprazole, 5-OH-omeprazole, and their ratios after administration of drug cocktail alone and in combination with TMC125 200 mg b.i.d. (day 1).

Table 17: Statistical analysis of the pharmacokinetic parameters of omeprazole, 5-OH-omeprazole, and their ratios after administration of drug cocktail alone and in combination with TMC125 200 mg b.i.d. (day 1)

Parameter	LSmeans ^a		LSmeans ratio (%)	90% CI (%)	p-value	
	Drug cocktail alone (reference)	TMC125 + drug cocktail, Day 14 (test)			Period	Sequence
Omeprazole						
C _{max} (ng/mL)	287.4	515.8	179.5	91.97-350.3	0.1502	0.7107
AUC ₀₋₂₄ (ng·h/mL)	516.1	945.1	183.1	78.25-428.6	0.2517	0.5446
5-OH-omeprazole						
C _{max} (ng/mL)	214.8	98.17	45.70	25.77-81.04	0.2138	0.2883
AUC ₀₋₂₄ (ng·h/mL)	423.7	184.0	43.44	19.74-95.60	0.3699	0.2522
Ratio omeprazole/5-OH-omeprazole						
Ratio C _{max P/M} ^b (%)	133.8	541.2	404.5	340.1-481.1	0.0832	0.1626
Ratio AUC _{0-24 P/M} ^b (%)	121.8	526.7	432.4	373.7-500.4	0.0414*	0.1047

* Statistically significant difference

^a n = 14 for Treatment A (reference) and Treatment B, Day 1 (test)

^b P/M: parent/metabolite

Compared to treatment with drug cocktail alone, the LS_{means} of C_{max} and AUC_{last} of omeprazole were increased by 33 % and 62 %, and increased by 79 % and 83 %, on day 1 and day 14 of TMC125 treatment, respectively. The LS_{means} of 5-OH-omeprazole were increased by 8 % and 25 % on day 1, and decreased by 54 % and 57 % on day 14.

Pharmacokinetic Results Summary

CYP1A2

- The LS_{means} of C_{max} and AUC_{12h} of caffeine and paraxanthine were not significantly altered (all changes < 10 %) when the cocktail was co-administered with TMC125 on day 1 as compared to when the cocktail was administered alone.
- The LS_{means} of C_{max} and AUC_{12h} of caffeine were decreased by 16 % and 15 % respectively, when the cocktail was co-administered with TMC125 on day 14 as compared to when the cocktail was administered alone.
- The LS_{means} of C_{max} and AUC_{12h} of paraxanthine were not significantly altered (all changes < 10 %) when the cocktail was co-administered with TMC125 on day 14 as compared to when the cocktail was administered alone.

CYP2C9

- On day 1, the LS_{means} of C_{max} and AUC_{24h} of warfarin and 7-OH-S-warfarin were not significantly altered when the cocktail was co-administered with TMC125 as compared to when the cocktail was administered alone.

- On day 14, the LS_{means} of C_{max} and $AUC_{24\text{h}}$ of warfarin were not significantly altered when the cocktail was co-administered with TMC125 as compared to when the cocktail was administered alone.
- On day 14, the LS_{means} ratio of C_{max} and $AUC_{24\text{h}}$ of 7-OH-S-warfarin were decreased by 27 % and 42 % respectively, when the cocktail was co-administered with TMC125 as compared to when the cocktail was administered alone.

CYP2D6

- On day 1, the LS_{means} ratio of C_{max} and $AUC_{8\text{h}}$ of dextromethorphan increased by 16 % and 27 % respectively, when the cocktail was co-administered with TMC125 as compared to when the cocktail was administered alone.
- On day 1, the LS_{means} ratio of C_{max} and $AUC_{8\text{h}}$ of dextropran were not significantly altered when the cocktail was co-administered with TMC125 as compared to when the cocktail was administered alone.
- On day 14, the LS_{means} ratio of C_{max} and $AUC_{8\text{h}}$ of dextromethorphan was decreased by 15 % and 6 % respectively, when the cocktail was co-administered with TMC125 as compared to when the cocktail was administered alone.
- On day 14, the LS_{means} ratio of C_{max} and $AUC_{8\text{h}}$ of dextropran were decreased by 20 % and 15 % respectively, when the cocktail was co-administered with TMC125 as compared to when the cocktail was administered alone.

CYP3A4

- On day 1, The LS_{means} of C_{max} and AUC_{last} values of midazolam were similar after administration of a single dose of the drug cocktail and single dose administration the drug cocktail and TMC125. For 1-OH-midazolam, the C_{max} and AUC_{last} were increased by 16 % and 7 %, respectively, after single dose TMC125. The LS_{mean} of the parent/metabolite ratios of C_{max} and AUC_{last} were decreased on day 1 by 14 % and 10 %, respectively.
- On day 14, LS_{mean} of midazolam C_{max} was similar and the AUC_{last} was decreased by 31 %. The LS_{mean} of C_{max} and AUC_{last} for 1-OH-midazolam were increased by 57 % and 9 %, respectively. The LS_{means} of the parent/metabolite ratios of C_{max} and AUC_{last} of midazolam and 1-OH midazolam decreased by 36 % and 37 %, respectively.

CYP2C19

- Compared to treatment with drug cocktail alone, the LS_{means} of C_{max} and AUC_{last} of omeprazole were increased by 33 % and 62 %, and increased by 79 % and 83 %, on day 1 and day 14 of TMC125 treatment, respectively. The LS_{means} of 5-

OH-omeprazole were increased by 8 % and 25 % on day 1, and decreased by 54 % and 57 % on day 14.

Conclusion

TMC125 is not an inducer or inhibitor of CYP1A2 and CYP2D6.

TMC125 is an inducer of CYP3A4.

TMC125 is an inhibitor of CYP2C9 and CYP2C19.

**APPEARS THIS WAY
ON ORIGINAL**

Study Number
TMC125-C176

Title

Phase I, open-label trial to investigate the pharmacokinetic interaction between TMC114 (darunavir)/ritonavir and TMC125 at steady-state in healthy subjects.

Objectives

- To determine the effect of steady-state concentrations of TMC114/rtv on the steady-state pharmacokinetics of TMC125.
- To determine the effect of steady-state concentrations of TMC125 on the steady-state pharmacokinetics of TMC114 and rtv.

Study Design

Phase I, open-label, randomized, 2 period crossover trial. The trial consisted of two treatment sessions separated by a washout period of at least 14 days. 32 subjects were randomized to 2 panels (**panel 1** and **panel 2**) in a 1:1 ratio (16 subjects per panel). In **panel 1**, subjects were randomized to either **treatment A** or **treatment B1** and in **panel 2**, the subjects were randomized to either **treatment A** or **treatment B2**. The following treatments were administered:

Treatment A:

100 mg TMC125 b.i.d for 7 days and a single dose on day 8.

Treatment B1:

TMC114/rtv 600/100 mg b.i.d. for 15 days and a single dose on day 16 + 100 mg TMC125 b.i.d from day 9 to day 15 and a single dose on day 16.

Treatment B2:

TMC114/rtv 600/100 mg b.i.d. for 15 days and a single dose on day 16 + 200 mg TMC125 b.i.d from day 9 to day 15 and a single dose on day 16.

Subjects entered the testing facilities on day -1 of each session and were discharged the following morning when all evaluations of day 1 of that session were completed. Prior to the first drug intake in each session, subjects had to fast overnight for at least 10 hours, except for the intake of water (allowed until 2 hours before trial medication intake). The trial medication (TMC114/rtv and TMC125) was taken under fed conditions within 15 minutes after completion of a meal.

In treatment A, the 12-hour pharmacokinetics of TMC125 was determined on day 8. In treatment B1, the 12-hour pharmacokinetics of TMC125 was determined on day 16 and the 12 hour pharmacokinetics of TMC114/rtv was determined on day 8 and day 16. In treatment B2, the 12 hour pharmacokinetics of TMC125 was assessed on day 16 and the 12 hour pharmacokinetics of TMC114/rtv was determined on day 8 and day 16.

Investigational Product(s)

TMC114 was provided as F001 (400 mg) or F002 (200 mg), and the inactive ingredients microcrystalline cellulose, colloidal silicon dioxide, _____ and magnesium stearate. The batch #s were PD1175 (F002) and PD1168 (F001) and the expiration date was March 2006 for both the formulations

Reviewer's Note Regarding TMC114 Formulation Used in the Trial

The sponsor used F001 (400 mg) and F002 (200 mg) formulations in the trial. These formulations were the "clinical trial formulations" of TMC114 and the results of a previously conducted single dose (administered under fasted conditions) BE study (submitted with TMC114 NDA; NDA 21-976) showed that the approved commercial formulation of TMC114 (F016) had approximately 35 % higher AUC as compared to the clinical trial formulations (F001 and F002). However, under steady state fed conditions, the systemic exposures of TMC114 from the clinical trial formulations and commercial formulation were similar. Since the PK parameters of TMC114 (after administration of the "clinical trial formulations" of TMC114) in this trial were determined under steady state fed conditions, the use of "clinical trial formulations" in this trial (instead of the commercial formulation) is not going to alter the conclusions of the trial.

TMC125 was formulated as a tablet (F060) containing 100 mg TMC125 _____ spray dried in a fixed ratio with hydroxypropylmethylcellulose and microcrystalline cellulose, _____ croscarmellose sodium, magnesium stearate, lactose monohydrate, and _____. The batch # was 05A05 and the expiration date was July 2005.

Ritonavir (Norvir®) was provided as a 100 mg capsule. The batch # was 17614A and the expiry date was April 2006.

Assay Methods

The plasma concentrations of TMC125, darunavir, and ritonavir were determined using validated liquid chromatographic-tandem mass spectrometry methods (LC-MS/MS). The lower limit of quantification for TMC125, darunavir, and ritonavir was 2 ng/mL, 5 ng/mL and 5 ng/mL, respectively.

Pharmacokinetic and Statistical Data Analysis

Pharmacokinetic Analysis

A total of 32 subjects were to be included. A minimum of at least 12 subjects completing all sessions was considered sufficient to allow for relevant conclusions. The pharmacokinetics and statistical analysis was performed using SAS system for Windows version 8.2. 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 time, the standard pharmacokinetic parameters were computed.

Statistical Analysis

Descriptive statistics were calculated for the plasma concentrations of TMC125, TMC114, and ritonavir at each time point and their derived pharmacokinetic parameters. The primary pharmacokinetic parameters used in the statistical analysis were C_{min} , C_{max} , and AUC_{12h} for TMC125, TMC114, and ritonavir on the logarithmic scale.

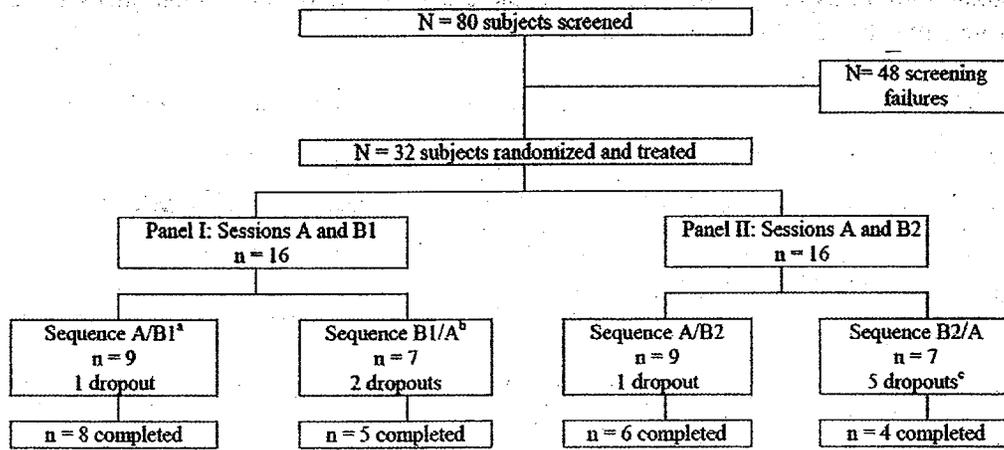
RESULTS

Subject Disposition and Demographics

Out of the 80 subjects screened, 32 subjects were randomized to the two panels and started treatment. 23 subjects completed the trial (8 subjects randomized to sequence A-B1, 5 subjects randomized to sequence B1-A, 6 subjects randomized to sequence A-B2, and 4 subjects randomized to sequence B2-A). Fig 1 shows the subject disposition.

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Fig 1: Subject Disposition in Trial TMC125-C176



^a Includes CRF ID 1760011 who was randomized to sequence B1/A, but received treatment according to sequence A/B1

^b Includes CRF ID 1760008 who was randomized to sequence A/B1, but received treatment according to sequence B1/A

^c Includes CRF IDs 1760027 & 1760028 who were randomized to sequence A/B2, but received treatment according to sequence B2/A.

9 subjects dropped out before trial completion; 6 of these subjects were withdrawn because of AEs (5 due to skin events and 1 due to headache), one subject (CRF ID 1760007) was withdrawn from sequence A/B1 (during session A treatment with TMC125) because of non-compliance (positive drug screen), and 2 subjects withdrew their consent (CRF ID 1760012 during Session B1 in sequence B1/A; and CRF ID 1760029 during session B2 in sequence B2/A).

Table 1 shows the demographic data collected in the trial.

Table 1: Demographic data collected in trial TMC125-C176

Parameter	Panel I N = 16	Panel II N = 16	All Panels N = 32
Age, years Median (range)	44.0 (18-53)	34.5 (18-55)	42.0 (18-55)
Height, cm Median (range)	180.0 (155-193)	179.5 (160-191)	180.0 (155-193)
Weight, kg Median (range)	78.5 (58-95)	78.0 (62-93)	78.0 (58-95)
BMI, kg/m ² Median (range)	23.5 (19-28)	23.7 (19-29)	23.6 (19-29)
Gender, n (%)			
Male	15 (93.8)	13 (81.3)	28 (87.5)
Female	1 (6.3)	3 (18.8)	4 (12.5)
Ethnic origin, n (%)			
Hispanic	1 (6.3)	1 (6.3)	2 (6.3)
White/Caucasian	15 (93.8)	15 (93.8)	30 (93.8)
Type smoker, n (%)			
Light smoker	6 (37.5)	1 (6.3)	7 (21.9)
Nonsmoker	10 (62.5)	15 (93.8)	25 (78.1)

Pharmacokinetics

All blood samples collected to determine plasma concentrations of TMC125, TMC114, and ritonavir were available for analysis. Table 2 shows the available pharmacokinetic data from subjects who discontinued the trial.

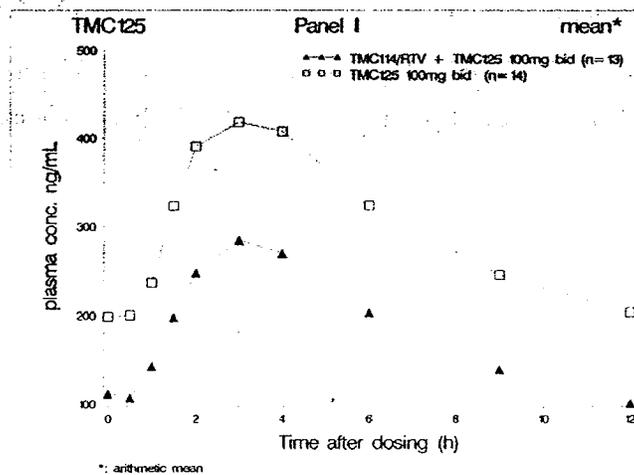
Table 2: Available pharmacokinetic data from subjects who discontinued the trial

CRF ID	Panel sequence	Final measurement	TMC125 alone profile(s)	TMC114/rtv alone profile(s)	TMC114/rtv + TMC125 profile(s)
Panel I					
1760007	A - B1	B1 Day 1	A Day 8	no	no
1760010	B1 - A	B1 Day 8, 12h	no	B1 Day 8	no
1760012	B1 - A	B1 Day 5	no	no	no
number of available profiles			n=14	n=14	n=13
Panel II					
1760022	A - B2	B2 Day 13	A Day 8	B2 Day 8	no
1760027	B2 - A	B2 Day 8, 12h	no	B2 Day 8	no
1760028	B2 - A	B2 Day 11	no	B2 Day 8	no
1760029	B2 - A	B2 Day 5	no	no	no
1760033	B2 - A	B2 Day 8, 12h	no	B2 Day 8	no
1760035	B2 - A	B2 Day 8, 12h	no	B2 Day 8	no
number of available profiles			n=11	n=15	n=10

TMC125

Fig 2 shows the mean steady state plasma concentration time profile of TMC125 after administration of TMC125 100 mg b.i.d. with or without concomitant administration of TMC114/rtv 600/100 mg b.i.d.

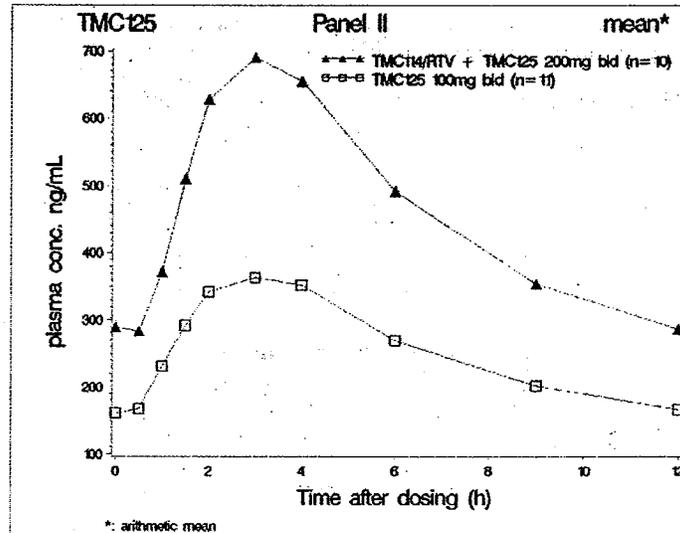
Fig 2: Mean steady state plasma concentration time profile of TMC125 after administration of TMC125 100 mg b.i.d. with or without concomitant administration of TMC114/rtv 600/100 mg b.i.d.



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Fig 3 shows the mean steady state plasma concentration time profile of TMC125 after administration of TMC125 alone (100 mg b.i.d.) or when co-administered with TMC114/rtv (TMC125 200 mg b.i.d.+ TMC114/rtv 600/100 mg b.i.d.)

Fig 3: Mean steady state plasma concentration time profile of TMC125 after administration of TMC125 alone (100 mg b.i.d.) or when co-administered with TMC114/rtv (TMC125 200 mg b.i.d.+ TMC114/rtv 600/100 mg b.i.d.)



The mean plasma concentrations of TMC125 were decreased when TMC125 (100 mg b.i.d.) was co-administered with 600/100 mg TMC114/rtv b.i.d (panel 1). When TMC125 was administered as 200 mg b.i.d. in combination with 600/100 mg b.i.d. TMC114/rtv (panel 2), the mean steady-state plasma concentrations of TMC125 were higher compared to administration of 100 mg b.i.d. TMC125 alone.

Table 3 shows the pharmacokinetic parameters of TMC125, with or without co-administration of TMC114/rtv in panel 1 and panel 2.

Table 3: Pharmacokinetic parameters of TMC125, with or without co-administration of TMC114/rtv in panel 1 and panel 2.

Panel I		
Pharmacokinetics of TMC125: mean ± SD (n _{test} : median [range])	600/100 mg TMC114/rtv + 100 mg TMC125 b.i.d. Test	100 mg TMC125 alone b.i.d. Reference
n	13	14
t _{max} , h	3.00 [2.00 - 4.00]	3.00 [1.50 - 6.00]
C _{max} , ng/mL	313 ± 118	452 ± 122
C _{min} , ng/mL	112 ± 67	198 ± 101
C _{min} , ng/mL	94 ± 49	189 ± 95
AUC ₀₋₂₄ , ng h/mL	2204 ± 952	3592 ± 1388
C _{12h} , ng/mL	101 ± 55	204 ± 108
FI, %	125 ± 35.4	96.9 ± 32.7
Panel II		
Pharmacokinetics of TMC125: mean ± SD (n _{test} : median [range])	600/100 mg TMC114/rtv + 200 mg TMC125 b.i.d. Test	100 mg TMC125 b.i.d. Reference
n	10	11
t _{max} , h	3.00 [1.50 - 4.00]	3.00 [1.50 - 6.00]
C _{max} , ng/mL	734 ± 305	405 ± 118
C _{min} , ng/mL	289 ± 157	161 ± 48
C _{min} , ng/mL	268 ± 151	156 ± 50
AUC ₀₋₂₄ , ng h/mL	5519 ± 2432	3062 ± 816
C _{12h} , ng/mL	286 ± 164	166 ± 56
FI, %	107.3 ± 30.6	98.8 ± 24.7

Table 4 shows the statistical evaluation of the pharmacokinetic parameters of TMC125.

Table 4: Statistical evaluation of the pharmacokinetic parameters of TMC125

Panel I									
TMC125	n		Least squares means				p-value		
Parameter	Test / Reference		TMC114/rtv + 100 mg TMC125 b.i.d. Test	100 mg TMC125 alone b.i.d. Reference	Treatment ratio, % and 90% CI* Test/Reference		Treatment	Period	Sequence
C _{max} (ng/mL)	13 / 14		302	444	0.68	0.57 - 0.82	0.0029	0.6187	0.4011
C _{min} (ng/mL)	13 / 14		86	167	0.51	0.44 - 0.61	<0.0001	0.9462	0.8646
AUC ₀₋₂₄ (ng h/mL)	13 / 14		2108	3352	0.63	0.54 - 0.73	0.0001	0.5790	0.9426
		n	median		p-value (Koch analysis)				
Parameter	Test / Reference		TMC114/rtv + 100 mg TMC125 b.i.d. Test	100 mg TMC125 alone b.i.d. Reference	Treatment	Period	Sequence		
t _{max} , h	13 / 13		3.0	3.0	0.6216	0.6216			0.1500
Panel II									
TMC125	n		Least squares means				p-value		
Parameter	Test / Reference		TMC114/rtv + 200 mg TMC125 b.i.d. Test	100 mg TMC125 alone b.i.d. Reference	Treatment ratio, % and 90% CI* Test/Reference		Treatment	Period	Sequence
C _{max} (ng/mL)	10 / 11		733	494	1.81	1.56 - 2.11	<0.0001	0.1767	0.0487
C _{min} (ng/mL)	10 / 11		260	155	1.67	1.38 - 2.03	0.0011	0.0444	0.0122
AUC ₀₋₂₄ (ng h/mL)	10 / 11		5538	3078	1.80	1.56 - 2.08	<0.0001	0.0883	0.0250
		n	median		p-value (Koch analysis)				
Parameter	Test / Reference		TMC114/rtv + 200 mg TMC125 b.i.d. Test	100 mg TMC125 alone b.i.d. Reference	Treatment	Period	Sequence		
t _{max} , h	10 / 10		3.0	3.0	0.6381	0.6381			0.8095

* 90% confidence interval

After concomitant steady state administration of TMC125 100 mg b.i.d. and TMC114/rtv 600/100 mg b.i.d. (panel 1), the C_{max}, C_{min}, and AUC decreased by 32 %, 49 %, and 37 %, respectively.

Reviewer's Comment:

The statistical analysis indicates higher exposures (AUC) of TMC125 after steady state co-administration of TMC125 200 mg b.i.d. and TMC114/rtv 600/100 mg b.i.d. The sponsor did not evaluate the pharmacokinetics of TMC125 after administration of 200

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mg b.i.d. TMC125 alone and used the PK parameters of TMC125 after steady state administration of 100 mg b.i.d. TMC125 alone as the reference regimen in the statistical analysis. Therefore, the "higher" TMC125 exposure, in the presence of DRV/r, should be interpreted in the context of a different dose of the reference regimen (TMC125 100 mg b.i.d.).

The results of trial TMC125-C139 (trial designed to evaluate the effect of steady state concentrations of TMC114/r, 600/100 mg b.i.d. on the steady state pharmacokinetics of 800 mg b.i.d. TMC125 (TF035) and vice versa) showed that the AUC, C_{max}, and C_{min} of TMC125 decreased by 33 %, 34 %, and 44 %, respectively, when TMC125 was combined with 600/100 mg b.i.d. TMC114/r. Further, AUC, C_{max}, and C_{min} of TMC114 (administered as TMC114/r) increased by 23 %, 26 %, and 13 %, respectively, when combined with TMC125.

Reviewer's Comment:

The results of trial TMC125-C139 showed that the systemic exposures of TMC125 (when administered as formulation TF035) decreased when TMC125 800 mg b.i.d. (as formulation TF035) was co-administered with TMC114/r, 600/100 mg b.i.d. In order to determine the magnitude of change in the pharmacokinetic parameters of 200 mg b.i.d. TMC125 (proposed dose; administered as F060) when co-administered with TMC114/r, 600/100 mg b.i.d., this reviewer compiled the data from two other studies in which TMC125 200 mg b.i.d. was administered (as formulation F060) alone as one of the regimens. Table 5 shows the comparison.

Table 5: Comparison of PK Parameters of TMC125 200 mg b.i.d (F060) across Various Studies

PK Parameters of TMC125	Mean ± SD		
	TMC125-C171*	TMC125-C177**	TMC125-C176 (Current Trial)
N	15	23	10
C _{0hr} (ng/mL)	529.1 ± 162.1	461.3 ± 170.5	289 ± 157
C _{min} (ng/mL)	498.1 ± 153.5	426.1 ± 154.6	268 ± 151
C _{max} (ng/mL)	1015 ± 243.8	875.7 ± 232.8	734 ± 305
AUC _{12hr} (ng*hr/mL)	9008 ± 2392	7638 ± 2254	5519 ± 2452

*: Drug-Drug Interaction Trial between TMC125 and Clarithromycin

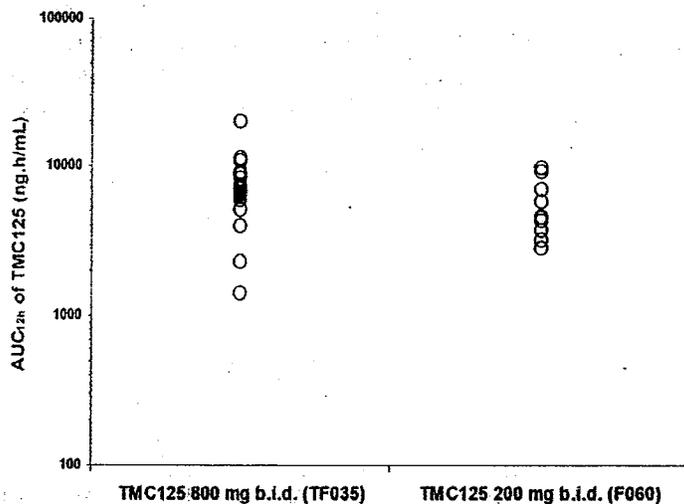
** : Drug-Drug Interaction Trial between TMC125 and Tenofovir

The comparison of PK parameters of TMC125 200 mg b.i.d. (F060; table 6) suggests that the pharmacokinetic parameters of TMC125 decreased when TMC125 200 mg b.i.d. was co-administered with TMC114/r, 600/100 mg b.i.d. in the current trial (TMC125-C176). The magnitude of the mean decrease in the PK parameters of TMC125 200 mg b.i.d. (F060; when co-administered with TMC114/r, 600/100 mg b.i.d.) as compared to administration of TMC125 200 mg b.i.d. alone (F060) is similar to the magnitude of the mean decrease in the PK parameters of TMC125 800 mg b.i.d. (TF035; when co-

administered with TMC114/rt 600/100 mg b.i.d.) as compared to administration of TMC125 800 mg alone (TF035). Further, the magnitude of the mean decrease in the PK parameters of TMC125 200 mg b.i.d (F060; when co-administered with TMC114/rtv 600/100 mg b.i.d.) as compared to administration of TMC125 200 mg b.i.d. alone (F060) is similar to the magnitude of the mean decrease in the PK parameters of TMC125 100 mg b.i.d. (F060; when co-administered with TMC114/rtv 600/100 mg b.i.d.) as compared to administration of TMC125 100 mg b.i.d. alone.

Fig 4 shows the graphical comparison of the exposure (expressed as AUC_{12h}) of TMC125 (co-administered with TMC114/rtv 600/100 mg b.i.d.) as 800 mg b.i.d. using formulation TF035 (data from trial TMC125-C139) or as TMC125 200 mg b.i.d using formulation F060 (data from TMC125-C176; current trial).

Fig 4: Graphical comparison of the exposure (expressed as AUC_{12h}) to TMC125 (co-administered with TMC114/rtv 600/100 mg b.i.d.) as 800 mg b.i.d. using formulation TF035 (data from trial TMC125-C139) or as 200 mg b.i.d using formulation F060 (data from TMC125-C176; current trial).



The graphical comparison shows a comparable range of TMC125 exposures (AUC_{12hr}) obtained after administration of TMC125 800 mg b.i.d TF035 and TMC125 200 mg b.i.d as F060. Furthermore, a decreased inter-subject variability was observed for formulation F060 compared to formulation TF035.

TMC114

Fig 5 shows the mean steady state plasma concentration-time profile of TMC114 (administered as 600 mg b.i.d. TMC114/rtv) with or without concomitant administration of TMC125 100 mg b.i.d.

Fig 5: Mean steady state plasma concentration-time profile of TMC114 (administered as 600 mg b.i.d. TMC114/rtv) with or without concomitant administration of TMC125 100 mg b.i.d.

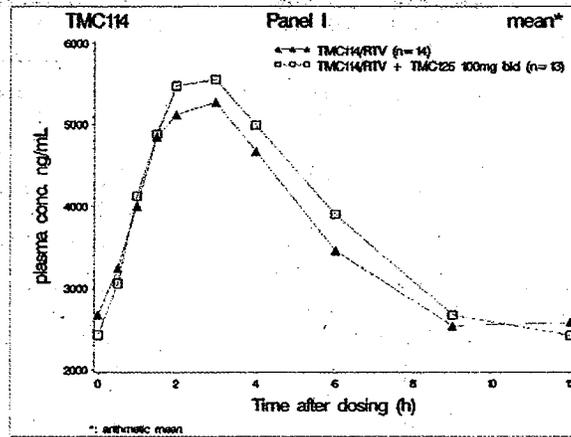


Fig 6 shows the mean steady state plasma concentration-time profile of TMC114 (administered as 600 mg b.i.d. TMC114/rtv) with or without concomitant administration of TMC125 200 mg b.i.d.

Fig 6: Mean steady state plasma concentration-time profile of TMC114 (administered as 600 mg b.i.d. TMC114/rtv) with or without concomitant administration of TMC125 200 mg b.i.d.

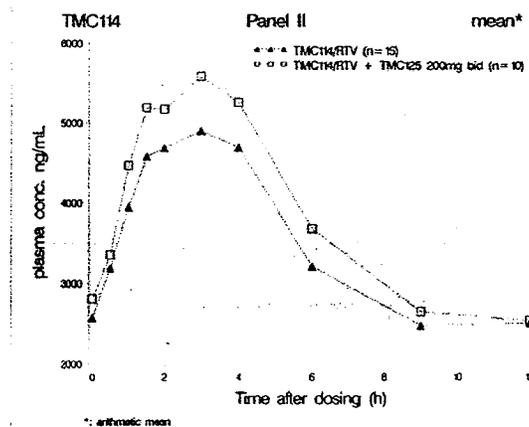


Table 6 shows the pharmacokinetic parameters of TMC114 (administered as TMC114/rtv) with or without co-administration of TMC125.

Table 6: Pharmacokinetic parameters of TMC114 (administered as TMC114/rtv) with or without co-administration of TMC125

Panel I		
Pharmacokinetics of TMC114: mean ± SD (<i>t</i> _{max} : median [range])	600/100 mg TMC114/rtv + 100 mg TMC125 b.i.d. Test	TMC114/rtv alone b.i.d. Reference
n	13	14
<i>t</i> _{max} , h	3.00 [1.00 - 4.00]	2.00 [1.50 - 4.00]
<i>C</i> _{max} , ng/mL	5804 ± 1269	5599 ± 1104
<i>C</i> _{0h} , ng/mL	2429 ± 631	2625 ± 934
<i>C</i> _{min} , ng/mL	2217 ± 541	2254 ± 834
AUC _{12h} , ng.h/mL	45199 ± 11583	42982 ± 12666
<i>C</i> _{12h} , ng/mL	2425 ± 641	2586 ± 912
FI, %	96.5 ± 20.2	99.5 ± 31.5
Panel II		
Pharmacokinetics of TMC114: mean ± SD (<i>t</i> _{max} : median [range])	600/100 mg TMC114/rtv + 200 mg TMC125 b.i.d. Test	TMC114/rtv alone b.i.d. Reference
n	10	15
<i>t</i> _{max} , h	3.00 [1.00 - 3.00]	3.00 [1.00 - 4.00]
<i>C</i> _{max} , ng/mL	5746 ± 1232	5234 ± 1060
<i>C</i> _{0h} , ng/mL	2805 ± 758	2683 ± 820
<i>C</i> _{min} , ng/mL	2301 ± 738	2337 ± 631
AUC _{12h} , ng.h/mL	45449 ± 10864	41135 ± 9579
<i>C</i> _{12h} , ng/mL	2529 ± 801	2497 ± 724
FI, %	93 ± 15.7	86.6 ± 16.1

The results of the statistical comparison of the pharmacokinetic parameters of TMC114 between the treatments with TMC114/rtv + TMC125 (test) and TMC114/rtv alone (reference) are shown in table 7.

Table 7: Statistical Evaluation of the Pharmacokinetics of TMC114

Panel I							
TMC114		Least squares means				p-value	
Parameter	Test / Reference	TMC114/rtv + 100 mg TMC125 b.i.d.		TMC114/rtv alone b.i.d.		Treatment ratio, % and 90% CI*	Treatment Sequence
		Test	Reference	Test	Reference		
<i>C</i> _{max} (ng/mL)	13 / 14	5818	5453	1.03	0.98 - 1.08	0.3019	0.1150
<i>C</i> _{0h} (ng/mL)	13 / 14	2107	2025	1.02	0.89 - 1.17	0.7865	0.1612
AUC _{12h} (ng.h/mL)	13 / 14	43049	40589	1.06	1.00 - 1.12	0.1263	0.0732
n		median		p-value (Wilcoxon analysis)			
Parameter	Test / Reference	Test	Reference	Treatment	Sequence		
<i>t</i> _{max} , h	13 / 13	3.0	2.0	0.7188	-		
Panel II							
TMC114		Least squares means				p-value	
Parameter	Test / Reference	TMC114/rtv + 200 mg TMC125 b.i.d.		TMC114/rtv alone b.i.d.		Treatment ratio, % and 90% CI*	Treatment Sequence
		Test	Reference	Test	Reference		
<i>C</i> _{max} (ng/mL)	10 / 15	5719	5142	1.11	1.01 - 1.22	0.0709	0.5246
<i>C</i> _{min} (ng/mL)	10 / 15	2315	2260	1.02	0.90 - 1.17	0.7443	0.5823
AUC _{12h} (ng.h/mL)	10 / 15	46219	40161	1.15	1.05 - 1.26	0.0174	0.6154
n		median		p-value (Wilcoxon analysis)			
Parameter	Test / Reference	Test	Reference	Treatment	Sequence		
<i>t</i> _{max} , h	10 / 10	3.0	3.0	0.9065	-		

*90% confidence interval

No significant treatment effects were observed in panel I in any of the primary pharmacokinetic parameters of TMC114. In panel 2, a statistically significant mean increase of 15 % was noted for AUC, however, no differences were observed for *C*_{max} and *C*_{min} of TMC114 when TMC114/rtv was co-administered with TMC125.

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RTV

Table 8 shows the pharmacokinetic parameters of ritonavir in the two panels.

Table 8: Pharmacokinetic parameters of ritonavir in the two panels

Panel I		
Pharmacokinetics of ritonavir: mean ± SD (C_{min} : median [range])	600/100 mg TMC114/rtv + 100 mg TMC125 b.i.d. Test	TMC114/rtv alone b.i.d. Reference
n	13	14
t_{max} , h	4.00 [1.00 - 6.00]	4.00 [1.50 - 6.00]
C_{max} , ng/mL	766 ± 184	830 ± 239
C_{0h} , ng/mL	190 ± 70	226 ± 135
C_{min} , ng/mL	142 ± 56	163 ± 86
AUC _{12h} , ng.h/mL	4396 ± 1087	5217 ± 1763
C_{12h} , ng/mL	161 ± 66	211 ± 95
FI, %	172.4 ± 24.1	157.7 ± 31.5
Panel II		
Pharmacokinetics of ritonavir: mean ± SD (C_{min} : median [range])	600/100 mg TMC114/rtv + 200 mg TMC125 b.i.d. Test	TMC114/rtv alone b.i.d. Reference
n	10	15
t_{max} , h	4.00 [3.00 - 4.00]	4.00 [3.00 - 6.00]
C_{max} , ng/mL	974 ± 351	1061 ± 461
C_{0h} , ng/mL	275 ± 130	269 ± 120
C_{min} , ng/mL	206 ± 85	192 ± 85
AUC _{12h} , ng.h/mL	5742 ± 1970	6129 ± 2218
C_{12h} , ng/mL	238 ± 97	300 ± 126
FI, %	161.3 ± 20.2	169.2 ± 53

Pharmacokinetic Results Summary

- Concomitant, steady state administration of TMC125 100 mg b.i.d. and TMC114/rtv 600/100 mg b.i.d lead to a decrease in the LS_{mean} estimates of C_{max} , C_{min} , and AUC of TMC125 by 32 %, 49 %, and 37 %, respectively.
- The decrease in the pharmacokinetic parameters of TMC125 after co-administration of TMC125 200 mg b.i.d. and TMC114/rtv 600/100 mg b.i.d. as compared to TMC125 200 mg b.i.d. administered alone (based on data from other trials) was similar to the magnitude of decrease in the TMC125 pharmacokinetic parameters when TMC125 100 mg b.i.d. was co-administered with TMC114/rtv 600/100 mg b.i.d. as compared to when TMC125 100 mg b.i.d. was administered alone.
- There was no significant change (all changes < 15 %) in the pharmacokinetic parameters of TMC114 when TMC125 100 mg b.i.d or 200 mg b.i.d. was co-administered with TMC114/rtv 600/100 mg b.i.d.

Conclusion

The mean systemic exposure (AUC) of etravirine was reduced by about 37% when INTELENCE™ was co-administered with darunavir/ritonavir. Because all subjects in the Phase 3 trials received darunavir/ritonavir as part of the background regimen and etravirine exposures from these trials were determined to be safe and effective, INTELENCE™ and darunavir/ritonavir can be co-administered without any dose adjustments.