

		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.
fosamprenavir/ritonavir*	↑ amprenavir	Due to a significant increase in the systemic exposure of amprenavir, the appropriate doses of the combination of INTELENCE™ and fosamprenavir/ritonavir have not been established. INTELENCE™ and fosamprenavir/ritonavir should not be co-administered.
lopinavir/ritonavir* (soft gel capsule)	↑ etravirine ↓ lopinavir	The mean systemic exposure (AUC) of etravirine after co-administration of INTELENCE™ with lopinavir/ritonavir is anticipated to be about 85% higher than the mean systemic exposure of etravirine observed in the Phase 3 trials. The safety profile at these increased etravirine exposures is unknown, therefore, INTELENCE™ and lopinavir/ritonavir should be co-administered with caution.
saquinavir/ritonavir*	↓ etravirine ↔ saquinavir	The mean systemic exposure (AUC) of etravirine was reduced by about 33% when INTELENCE™ was co-administered with saquinavir/ritonavir. Because the reduction in the mean systemic exposures of etravirine in the presence of saquinavir/ritonavir is similar to the reduction in mean systemic exposures of etravirine in the presence of darunavir/ritonavir, INTELENCE™ and saquinavir/ritonavir can be co-administered without any dose adjustments.
tipranavir/ritonavir*	↓ etravirine	Concomitant use of INTELENCE™ with tipranavir/ritonavir may cause a significant decrease in the plasma concentrations of etravirine. This may result in loss of therapeutic effect of INTELENCE™. It is not recommended to co-administer tipranavir/ritonavir and INTELENCE™.
Other Agents		
Antiarrhythmics: amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	↓ antiarrhythmics	Concentrations of these antiarrhythmics may be decreased when co-administered with INTELENCE™. INTELENCE™ and antiarrhythmics should be co-administered with caution. Drug concentration monitoring is recommended, if available.
Anticoagulants: warfarin	↑ Warfarin	Warfarin concentrations may be increased when co-administered with INTELENCE™. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with INTELENCE.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ etravirine	Carbamazepine, phenobarbital and phenytoin are inducers of CYP450 enzymes. INTELENCE™ should not be used in combination with carbamazepine, phenobarbital, or phenytoin as co-administration may cause significant decreases in etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE™.
Antifungals: fluconazole,	↑ etravirine ↔ fluconazole	Posaconazole is a potent inhibitor of CYP3A4 and fluconazole is a potent inhibitor of CYP2C9; both may

itraconazole, ketoconazole, posaconazole, voriconazole	↓ itraconazole ↓ ketoconazole ↔ posaconazole ↑ voriconazole	increase plasma concentrations of etravirine. Itraconazole and ketoconazole are potent inhibitors as well as substrates of CYP3A4. Concomitant systemic use of itraconazole or ketoconazole and INTELENCE™ may increase plasma concentrations of etravirine. Simultaneously, plasma concentrations of itraconazole or ketoconazole may be decreased by INTELENCE™. Voriconazole is a CYP2C19 substrate and CYP3A4, CYP2C9 and CYP2C19 inhibitor. Concomitant use of voriconazole and INTELENCE™ may increase plasma concentrations of both drugs. Dose adjustments for itraconazole, ketoconazole or voriconazole may be necessary depending on other co-administered drugs.
Antiinfectives: clarithromycin*	↑ etravirine ↓ clarithromycin ↑ 14-OH- clarithromycin	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 <i>Mycobacterium avium</i> complex (MAC), overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered for the treatment of MAC.
Antimycobacterials: rifampin, rifapentine	↓ etravirine	Rifampin and rifapentine are potent inducers of CYP450 enzymes. INTELENCE™ should not be used in combination with rifampin or rifapentine as co-administration may cause significant decrease in etravirine plasma concentrations and loss of therapeutic effect of INTELENCE™.
Antimycobacterials: rifabutin*	↓ etravirine ↓ rifabutin ↓ 25-O- desacetyl rifabutin	If INTELENCE™ is NOT part of a regimen consisting of Protease Inhibitor/ritonavir, rifabutin at a dose of 300 mg q.d. is recommended If INTELENCE™ is part of a regimen containing darunavir/ritonavir or saquinavir/ritonavir, rifabutin should not be co-administered due to the potential for significant reduction in etravirine exposure.
Benzodiazepines: diazepam	↑ diazepam	Concomitant use of INTELENCE™ with diazepam may increase plasma concentrations of diazepam. A decrease in diazepam dose may be needed.
Corticosteroids: Dexamethasone (systemic)	↓ etravirine	Systemic dexamethasone induces CYP3A4 and can decrease etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE™. Systemic dexamethasone should be used with caution or alternatives should be considered, particularly for long-term use.
Estrogen-based Contraceptives: ethinylestradiol* norethindrone*	↔ etravirine ↑ ethinylestradiol ↔ norethindrone	The combination of estrogen- and/or progesterone-based contraceptives and INTELENCE™ can be used without any dose adjustments.
Herbal Products: St. John's wort (<i>Hypericum perforatum</i>)	↓ etravirine	Concomitant use of INTELENCE™ with products containing St. John's wort may cause significant decreases in etravirine plasma concentrations and loss of therapeutic effect of INTELENCE™. INTELENCE™ and products containing St. John's wort should not be co-administered.
HMG-CoA Reductase Inhibitors:	↔ etravirine ↓ atorvastatin	The combination of INTELENCE™ and atorvastatin can be given without any dose adjustments, however, the dose of

atorvastatin* fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin	↑ 2-OH-atorvastatin ↔ etravirine ↑ fluvastatin, ↓ lovastatin, ↔ pravastatin, ↔ rosuvastatin, ↓ simvastatin	atorvastatin may need to be altered based on clinical response. No interaction between pravastatin or rosuvastatin and INTELENCE™ is expected. Lovastatin and simvastatin are CYP3A4 substrates and co-administration with INTELENCE™ may result in lower plasma concentrations of the HMG-CoA reductase inhibitor. Fluvastatin is metabolized by CYP2C9 and co-administration with INTELENCE™ may result in higher plasma concentrations of the HMG-CoA reductase inhibitor. Dose adjustments for these HMG-CoA reductase inhibitors may be necessary.
H₂-Receptor Antagonists Ranitidine* Cimetidine Famotidine	↔ etravirine	INTELENCE™ can be co-administered with H ₂ -receptor antagonists without any dose adjustments.
Immunosuppressants: cyclosporine, sirolimus, tacrolimus	↓ etravirine	Co-administration with systemic immunosuppressants should be done with caution because plasma concentrations of cyclosporine, sirolimus, or tacrolimus may be affected when co-administered with INTELENCE™.
Narcotic Analgesics: methadone*	↔ etravirine ↔ methadone	INTELENCE™ and methadone can be co-administered without dose adjustments, however, clinical monitoring for withdrawal symptoms is recommended as methadone maintenance therapy may need to be adjusted in some patients.
Phosphodiesterase Type 5 (PDE-5) Inhibitors: sildenafil*, vardenafil, tadalafil	↓ sildenafil ↓ N-desmethyl-sildenafil	INTELENCE™ and sildenafil can be co-administered without dose adjustments, however, the dose of sildenafil may need to be altered based on clinical effect.
Proton Pump Inhibitors: omeprazole*	↑ etravirine	INTELENCE™ can be co-administered with proton pump inhibitors without any dose adjustments.
↑ = increases, ↓ = decreases, ↔ = no change		

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

No

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

No

- 2.4.3. What issues related to dose, dosing regimens, or administrations are unresolved and represent significant omissions?

TMC125 was co-administered with darunavir/ritonavir in the pivotal clinical trials. Darunavir/ritonavir has been shown to reduce the systemic exposures of TMC125 by approximately 40 % and thus, the safety data generated in the pivotal trials was in the presence of reduced exposures of TMC125. Consequently, the non-availability of safety data to support co-administration of TMC125 with some ritonavir boosted protease inhibitors represents a major omission. Further, since all the subjects in the pivotal phase III trials received darunavir/ritonavir, the efficacy of the combination of TMC125 with other ritonavir boosted protease inhibitors or without ritonavir boosted protease inhibitors was not assessed.

2.5 General Biopharmaceutics

- 2.5.1. Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

TMC125 is insoluble in aqueous media (< 0.001 g/100 mL) in the pH range evaluated (1.1-12.9).

The *in vitro* permeability data suggest that TMC125 has low to intermediate permeability in Caco-2 monolayers, indicating that TMC125 would exhibit sufficient membrane permeability to obtain adequate intestinal absorption.

The sponsor indicates that TMC125 is a BCS class IV compound.

- 2.5.2. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The sponsor used formulation F060 (to-be-marketed formulation) in the pivotal clinical trials (TMC125-C206 and TMC125-C216). Therefore, no relative bioavailability study was needed. Further, the results of trial TMC125-C228 showed that the mean systemic exposures of TMC125 after oral administration of TMC125 200 mg b.i.d. as formulation F060 (F060 was used in the pivotal phase 3 trials) were significantly higher than the mean systemic exposures after oral administration of TMC125 800 mg b.i.d. as formulation TF035 (TF035 was used in phase 2b trials). However, the results of the same trial showed that the individual exposures of TMC125 after multiple dosing in HIV-1 infected subjects were in the same range between TMC125 200 mg b.i.d. as formulation F060 and TMC125 800 mg b.i.d. as formulation TF035.

- 2.5.2.1. What data support or do not support a waiver of *in vivo* BE data?

The sponsor intends to market only the 100 mg tablets, therefore, there was no biowaiver request.

2.5.2.2. What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90 % CI using equivalence limits of 80-125 %?

Not applicable to this NDA.

2.5.2.3. If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Not applicable to this NDA

2.5.3 What is the effect of food on the bioavailability (BA) of TMC125 from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effect of presence/absence of food and the effect of the type of food on the pharmacokinetics of TMC125 (administered as a single 100 mg dose using formulation F060) was evaluated in TMC125-C147. Based on the results of the study, the mean systemic exposure (AUC_{last}) of TMC125 was increased by 105 % when TMC125 was administered under fed conditions as compared to when TMC125 was administered under fasted conditions. Therefore, the proposed label recommends that TMC125 should always be taken with food.

The results from study TMC125-C147 (using treatment A as reference treatment) also showed that the “type” of the meals does not affect the systemic exposure to TMC125. Table 16 provides the description of the various meals tested in the study.

Table 16: Description of the various meals tested in the study

Treatment	Description	Results
Treatment A (Standardized Breakfast)	4 slices of bread, 2 slices of ham or cheese, butter, jelly, and 2 cups of decaffeinated coffee or tea with milk and/or sugar, if desired (486 grams, 561 kcal; 15.33 gms fat, 21.89 gms protein, 83.86 gms carbohydrates, and 8.08 gms fiber)	C_{max} increased by 77 % and AUC_{last} increased by 105 % relative to the fasting state.
Treatment C (Croissant)	Butter croissant with 1 tsp unsalted butter and 1 tsp jam, 1 cup of decaffeinated coffee/tea with milk and/or sugar as desired (213 gms, 345 kcal, 17.44 gms fat, 5.16 gms protein, 41.43 gms carbohydrates, 1.25 gms fiber)	C_{max} increased by 71 % and AUC_{last} increased by 65 % relative to the fasting state.
Treatment D (High Fiber Breakfast)	80 gms grapes with skin, 80 gms raw pineapple, 80 gms raw pears, 80 gms raw strawberries, 1 glass of orange juice (225 gms), 1 raw banana (200 gms), 2 slices of mixed grain bread, 2 tbsp (40 gms) of jam (855 gms; 685 kcal, 3.12 gms fat, 13.37 g proteins, 151.24 gms carbohydrates, 16.4 gms fiber).	C_{max} increased by 21 % and AUC_{last} increased by 34 % relative to the fasting state.
Treatment E (High Fat Breakfast)	2 large fried eggs, 2 slices of fried bacon, 1 butter croissant, 2 slices of white bread, 1 tsp unsalted butter, 1 bar of semisweet chocolate (30 gms), 1 cup of decaffeinated coffee/tea with milk and/or sugar as desired (468 gms, 1160 kcal, 70.26 gms fat, 40.36 gms protein, 91.26 gms carbohydrates, and 2.21 gms fiber).	C_{max} increased by 88 % and AUC_{last} increased by 94 % relative to the fasting state.

2.5.4 When would a fed BE study be appropriate and was one conducted?

Not applicable to this NDA.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

Please refer to the Chemistry review by Dr. Mark Seggel.

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of various strengths of the to-be-marketed product?

Not applicable to this NDA.

2.5.7 If the NDA is for a modified release formulation of an unapproved immediate product without supportive safety and efficacy studies, what dosing regimen change are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable to this NDA.

- 2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either *in vitro* or *in vivo* data to evaluate BE?

Not applicable to this NDA.

- 2.5.9. What other significant, unresolved issues related to *in vitro* dissolution or *in vivo* BA and BE need to be addressed?

There are no other significant BA and BE that need to be further addressed. For information pertaining to *in vitro* dissolution, please refer to the chemistry review by Dr. Mark Seggel.

2.6. Analytical Section

- 2.6.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The active moieties were identified and measured in the plasma by using validated LC/MS/MS methods.

- 2.6.2. Which metabolites have been selected for analysis and why?

The sponsor did not monitor the metabolites for TMC125 except in the ¹⁴C mass balance study (TMC114-C130).

- 2.6.3. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The analytical methods used measured the total concentrations of TMC125. Although measurement of free concentrations may be more clinically relevant, it is standard to measure total concentrations of non nucleoside reverse transcriptase inhibitor.

- 2.6.4 What bioanalytical methods are used to assess concentrations?

The bioanalytical method used for the determination of etravirine was developed using LC-MS/MS system. The calibration range for this assay was 2-5000 ng/mL. The accuracy and precision for etravirine quality control samples (2 ng/mL, 6 ng/mL, 250 ng/mL, and 4000 ng/mL) complied with the pre-specified criteria at all concentrations (accuracy: overall bias = 20 % for the LLOQ and 15 % for all other concentrations; precision: total and intra-run coefficients of variation = 20 % for the LLOQ and = 15 % for all other concentrations).

These analytical methods are acceptable.

11 Page(s) Withheld

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4. Appendices

4.1 Individual Study Review

BIOPHARMACEUTICS

Study Number	Description	Page #
TMC125-C141	A Phase 1, randomized, open-label, single-dose, crossover trial to evaluate the relative bioavailability of 3 dose levels of TMC125 in HIV infected subjects as a spray-dry formulation compared to the reference formulation TF035.	56
TMC125-C146	A Phase 1, open-label, randomized, single dose, 2-way crossover trial in 3 parallel panels of 12 healthy subjects each, to determine the relative bioavailability of 3 different spray-dry formulations of TMC125 compared to reference formulation TF035 (<i>Effect of TMC125 to Polymer Ratio</i>).	63
TMC125-C147	The effect of food on the relative bioavailability of a single intake of TMC125 formulated as tablet F060 (Pivotal Food Effect Study) .	66
TMC125-C150	A Phase 1, open-label, randomized, single dose, 2-way crossover multi-center trial to determine the bioavailability of TMC125 from four different formulations, relative to the reference formulation, TF035 (<i>Effect of manufacturing technology, type of solubilizing polymer, and TMC125 to polymer ratio</i>).	78
TMC125-C155	A Phase 1, open-label, randomized, three way crossover trial in 36 healthy subjects, to determine the pharmacokinetics, safety, and tolerability of a single 400 mg dose of TMC125, administered as three different formulations (2 new formulations and reference TF035) (<i>Effect of manufacturing technology</i>).	82
TMC125-C162	A Phase 1, open-label, randomized, single dose, 4-way crossover trial in healthy subjects to determine the relative oral bioavailability of TMC125 administered as formulation F016 and 3 different batches of formulation F060 (<i>Effect of Manufacturing Scale and Long-Term Tablet Storage</i>).	85
TMC125-C169	A Phase 1, randomized, open-label, single-dose, 4-period crossover trial in healthy subjects to evaluate the oral bioavailability of TMC125 produced at different scales of production.	89
TMC125-C170	A Phase 1, open-label, randomized, single-dose, 2-way crossover trial in 4 parallel panels of 12 healthy subjects each, to determine the relative bioavailability of 4 different spray dried formulations of TMC125 compared to the reference formulation TF035.	95
TMC125-C172	A Phase 1, open-label, randomized, single dose, 3- period crossover study to evaluate the relative bioavailability of TMC125 in healthy subjects using 200 mg TMC125 spray-dry product formulated as Powder 1, Powder 2, and as a tablet. (<i>Effect of Powder Manufacturing Site</i>).	102
TMC125-C173	A Phase 1, randomized, open-label, single dose, 3-period crossover trial in healthy subjects to evaluate the relative oral bioavailability of the — and the 100 mg tablets of TMC125.	105
TMC125-C228	A Phase 1, randomized, open-label, multiple-dose, crossover trial in HIV-1 infected subjects to evaluate the relative bioavailability of TMC125 as a spray-dry formulation (F060) compared to the reference formulation TF035 .	111

Study Number
TMC125-C141

Title

A Phase 1, randomized, open-label, single-dose, crossover trial to evaluate the relative bioavailability of 3 dose levels of TMC125 in HIV infected subjects as a spray-dry formulation compared to the reference formulation TF035.

Objectives

The primary objectives of the trial were to evaluate the relative oral bioavailability of the spray-dry formulation of TMC125 (**F060**) compared to the reference formulation (**TF035**; 200 mg) of TMC125 administered as a single dose at 3 dose levels in HIV-1 infected subjects. The secondary objective (clinical pharmacology related) was to assess the dose proportionality of TMC125 as spray dried formulation in HIV-1 infected subjects.

Study Design

Phase I, add-on, randomized, open-label, single-dose crossover trial. Eligible subjects had NNRTI experience for at least 3 months, a HIV-1 plasma viral load below 50 copies/mL, and an ARV regimen that included lopinavir/ritonavir (LPV/RTV) or saquinavir/ritonavir (SQV/RTV) plus a minimum of 1 nucleoside reverse transcriptase inhibitor (NRTI) with or without enfuvirtide. Subjects continued to take their existing ARV regimen throughout the treatment period without interruption.

The trial was divided in 2 stages (to allow for an earlier decision on the doses to be used with formulation **F060** in future trials with TMC125). Subjects in **Panel 1 (Stage I)** received a single dose of 100 mg TMC125 as formulation **F060** and a single dose of 800 mg TMC125 as formulation **TF035** in a crossover fashion. Subjects in **Panel 2 (Stage I)** received a single dose of 200 mg TMC125 as formulation **F060** and a single dose of 1600 mg TMC125 as formulation **TF035** in a crossover fashion. Subjects in **Panel 3 (Stage II)** received a single dose of 300 mg TMC125 as formulation **F060** and a single dose of **2400** mg TMC125 as formulation **TF035** in a crossover fashion.

Within each panel (12 subjects per panel), the subjects were randomized to start with either formulation **F060** or formulation **TF035** (1:1). The randomization was stratified for the presence of SQV/RTV in the subject's ARV regimen because of the decreased exposure of TMC125 (33 % decrease) when co-administered with SQV/RTV (**TMC125-C123**). The 2 single doses (administered within 10 minutes of completion of breakfast) were separated by a washout period of at least 14 days. A 96-hour pharmacokinetic profile (pre-dose, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, and 96 hours after single dose administration) of TMC125 was determined after each intake.

Investigational Product(s)

The reference formulation (TF035) was a tablet containing 200 mg of TMC125 in HPMC, lactose and . The batch number used was D03108.

The test formulation (F060) was a tablet containing 100 mg of TMC125 spray-dried in combination with HPMC and microcrystalline cellulose, croscarmellose sodium, magnesium stearate, lactose monohydrate and . The batch number used was 04H26.

Assay Methods

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

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

Statistical analyses were performed using formulation F060 as test formulation and TF035 as reference formulation at each dose level. The primary pharmacokinetic parameters were C_{max} , AUC_{last} and $AUC_{0-\infty}$ on the logarithmic scale. The $AUC_{0-\infty}$ was not used as a primary parameter for a treatment if more than half of the values of $AUC_{0-\infty}$ for that treatment could not be determined accurately.

The least squares means of the primary parameters for each treatment were estimated with a linear mixed effects model, controlling for treatment, sequence and period as fixed effects and subject (nested in sequence) as a random effect. A 90 % CI was constructed around the difference between the least squares means of test and reference. The difference between the least squares means and the 90 % confidence limits were back-transformed to the original scale. The period effects were considered significant at the 5 % level and sequence effects were considered significant at the 10 % level.

RESULTS

Subject Disposition and Demographics

Out of the 55 subjects screened, 41 subjects were randomized to the 3 panels. One subject was randomized but withdrew consent before the start of the treatment. Therefore, 40 subjects started treatment (15 subjects in **Panel 1**, 13 subjects in **Panel 2**, and 12 subjects in **Panel 3**).

Fig 1: Subject Disposition in Trial TMC125-C141

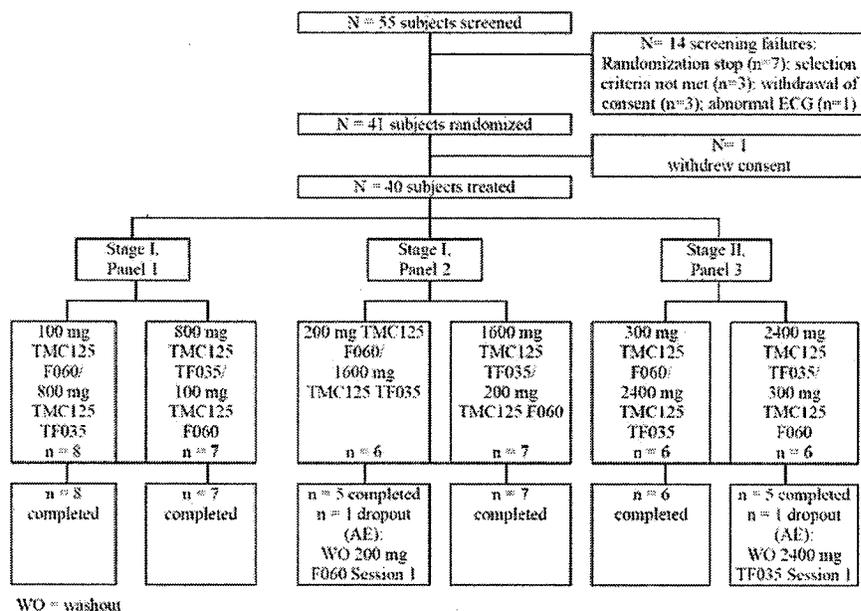


Table 1 shows the demographics in the trial.

Table 1: Demographics in Trial TMC125-C141

Parameter	Panel 1 N = 15	Panel 2 N = 13	Panel 3 N = 12	All Subjects N = 40
Age, years				
Median (min: max)	37.0 (30: 51)	43.0 (37: 58)	45.5 (37: 62)	42.0 (30: 62)
Height, cm				
Median (min: max)	178.0 (168: 188)	180.0 (170: 190)	180.0 (168: 196)	179.0 (168: 196)
Weight, cm				
Median (min: max)	70.0 (65: 117)	73.0 (63: 83)	77.0 (57: 95)	74.0 (57: 117)
BMI, kg/m ²				
Median (min: max)	22.5 (20: 34)	22.9 (20: 26)	24.9 (19: 27)	23.0 (19: 34)
Sex, n (%)				
Male	15 (100.0)	13 (100.0)	12 (100.0)	40 (100.0)
Ethnic Origin, n (%)				
Caucasian/White	15 (100.0)	12 (92.3)	10 (83.3)	37 (92.5)
Black	0 (-)	1 (7.7)	2 (16.7)	3 (7.5)
Type of Smoker, n (%)				
Nonsmoker	4 (26.7)	6 (46.2)	6 (50.0)	16 (40.0)
Light	1 (6.7)	3 (23.1)	3 (25.0)	7 (17.5)
Moderate	7 (46.7)	4 (30.8)	2 (16.7)	13 (32.5)
Heavy	3 (20.0)	0 (-)	1 (8.3)	4 (10.0)

Pharmacokinetics

TMC125

Fig 2 shows the mean plasma concentration-time profile of TMC125 after single dose administration of 100 mg F060 and 800 mg TF035 in Panel 1.

Fig 2: Mean plasma concentration-time profile of TMC125 after single dose administration of 100 mg F060 and 800 mg TF035 in Panel 1.

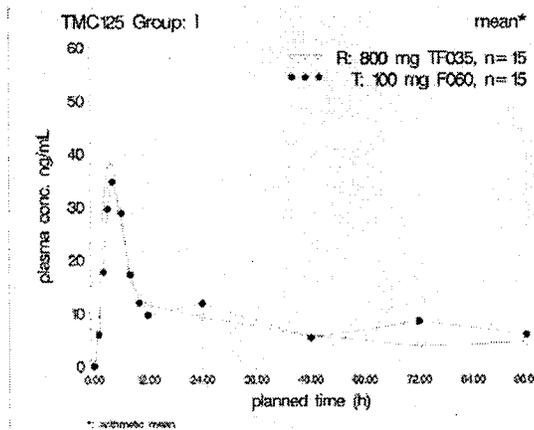


Fig 3 shows the mean plasma concentration-time profile of TMC125 after single dose administration of 200 mg F060 and 1600 mg TF035 in Panel 2.

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Fig 3: Mean plasma concentration-time profile of TMC125 after single dose administration of 200 mg F060 and 1600 mg TF035 in Panel 2.

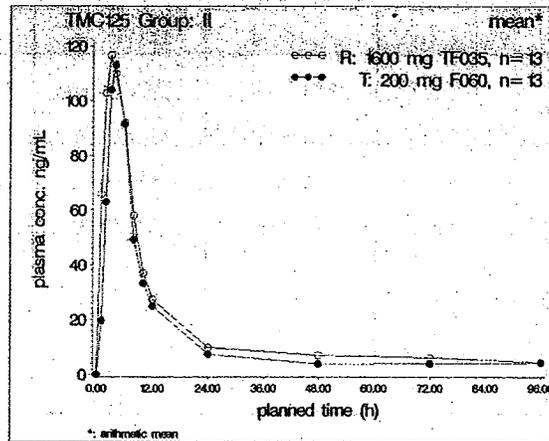


Fig 4 shows the mean plasma concentration-time profile of TMC125 after single dose administration of 300 mg F060 and 2400 mg TF035 in Panel 3.

Fig 4: Mean plasma concentration-time profile of TMC125 after single dose administration of 300 mg F060 and 2400 mg TF035 in Panel 3.

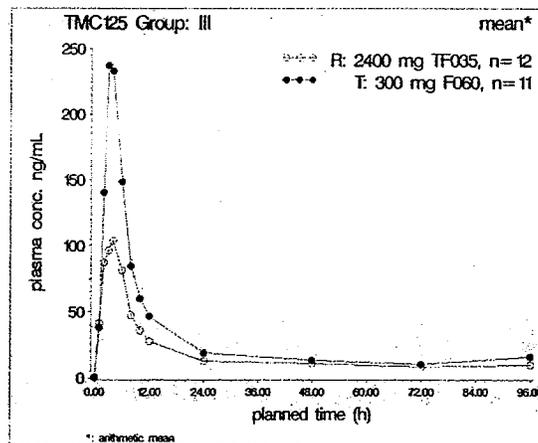


Table 2 shows the pharmacokinetic parameters of TMC125 in the various panels.

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Table 2: Pharmacokinetic parameters of TMC125 in the various panels.

Panel 1	100 mg TMC125 F060 (Test)	300 mg TMC125 TF035 (Reference)
n	15	15
C _{max} (ng/mL)	37.6 ± 33.9	44.7 ± 48.5
AUC _{last} (ng.h/mL)	360 ± 562	392 ± 508
AUC _∞ (ng.h/mL)	425 ± 641	470 ± 565
t _{max} (h)	4.00 [2.00 – 12.00]	3.00 [2.00 – 6.00]
t _{1/2} (h)	7.89 ± 8.50	9.94 ± 10.28
Panel 2	200 mg TMC125 F060 (Test)	1600 mg TMC125 TF035 (Reference)
n	13	12
C _{max} (ng/mL)	131.4 ± 125.4	132.4 ± 207.2
AUC _{last} (ng.h/mL)	1059 ± 906	1285 ± 1887
AUC _∞ (ng.h/mL)	1131 ± 955	1358 ± 1982
t _{max} (h)	4.00 [3.00 – 6.00]	5.00 [2.00 – 6.00]
t _{1/2} (h)	15.83 ± 8.86	13.55 ± 9.32
Panel 3	300 mg TMC125 F060 (Test)	2400 mg TMC125 TF035 (Reference)
n	11	12
C _{max} (ng/mL)	257.7 ± 170.8	114.8 ± 81.6
AUC _{last} (ng.h/mL)	2434 ± 2221	1348 ± 1349
AUC _∞ (ng.h/mL)	2831 ± 3090	1579 ± 1725
t _{max} (h)	3.00 [3.00 – 12.00]	4.00 [2.00 – 6.00]
t _{1/2} (h)	21.55 ± 17.31	20.58 ± 16.69

Values are mean ± SD; for t_{max}: median [range]

For Panel 1 and 2, the C_{max} and the AUC_{0-∞} were comparable for the test (F060) and the reference (TF035) formulation. For Panel 3, these parameters were higher for the test formulation (F060) compared to the reference formulation (TF035).

For the majority of the profiles in Panels 2 and 3, the λ_z and AUC_{0-∞} could be reliably determined, however, for some profiles (especially in Panel 1), the time span between the first and last concentration values used for the determination of λ_z was smaller than 2 times the elimination half life and/or the extrapolated part of AUC_{0-∞} >15 % and/or the number of data points used for determination of λ_z was 2. Therefore, the requirements for an acceptable calculation of AUC_{0-∞} were not always met, especially for Panel 1.

The test formulation F060 showed a more than dose proportional increase in the pharmacokinetic parameters with an increase in dose across the three panels. The increase in systemic exposure (AUC_{last}) was after administration of TF035 was more than dose proportional between panel 1 and panel 2, however, the increase in the PK parameters between panel 2 and panel 3 was less than dose proportional. The mean observed elimination half life was lower as compared to the half life observed in other trials. This may be due to the high inter-individual variability and the plasma concentrations being below the lower limit of quantification in this trial.

Table 3 shows the statistical evaluation of the pharmacokinetic parameters of TMC125.

Table 3: Statistical Evaluation of the Pharmacokinetics of TMC125

Panel 1								
Parameter	n Test/ Ref	Least squares means				p-value		
		100 mg F060 (Test)	800 mg TF035 (Reference)	Ratio	90% CI*	Treatment	Period	Sequence
C _{max} (ng/mL)	15/15	28	27	103	78 - 137	0.8374	0.7267	0.7282
AUC _{last} (ng.h/mL)	15/15	186	181	103	75 - 142	0.8733	0.8993	0.8853
AUC _∞ (ng.h/mL)	14/14	230	248	.93	71 - 121	0.6229	0.4986	0.6739

Panel 2								
Parameter	n Test/ Ref	Least squares means				p-value		
		200 mg F060 (Test)	1600 mg TF035 (Reference)	Ratio	90% CI*	Treatment	Period	Sequence
C _{max} (ng/mL)	13/12	102	80	127	99 - 162	0.1092	0.0163	0.7100
AUC _{last} (ng.h/mL)	13/12	820	741	111	84 - 146	0.5280	0.0102	0.7640
AUC _∞ (ng.h/mL)	13/12	882	796	111	85 - 145	0.5064	0.0089	0.7551

Panel 3								
Parameter	n Test/ Ref	Least squares means				p-value		
		300 mg F060 (Test)	2400 mg TF035 (Reference)	Ratio	90% CI*	Treatment	Period	Sequence
C _{max} (ng/mL)	11/12	195	86	227	174 - 295	0.0003	0.9555	0.8349
AUC _{last} (ng.h/mL)	11/12	1726	811	213	156 - 291	0.0017	0.6882	0.8610
AUC _∞ (ng.h/mL)	11/12	1862	918	203	149 - 276	0.0022	0.7455	0.9158

F060 = test formulation TF035 = reference formulation
 *90% confidence interval of ratio

Conclusion

- The mean systemic exposures observed after single dose administration of 100 mg and 200 mg F060 were similar to the mean systemic exposures observed after single dose administration of 800 mg and 1600 mg TF035, respectively.
- The mean systemic exposures observed after single dose administration of 300 mg F060 were approximately 100 % higher than the systemic exposures observed after single dose administration of 2400 mg TF035.

Study Number
TMC125-C146

Title

A Phase 1, open-label, randomized, single dose, 2-way crossover trial in 3 parallel panels of 12 healthy subjects each, to determine the relative bioavailability of 3 different spray-dry formulations of TMC125 compared to reference formulation TF035 (*Effect of TMC125 to Polymer Ratio*).

Study Design

Open-label, randomized, parallel group, 2-period crossover trial to investigate the relative bioavailability of 3 different tablet formulations of TMC125 (F048, F049, and F052, all manufactured by spray drying technology but with different ratios of HPMC {hydroxypropylmethylcellulose} as solubilizing polymer), compared to the reference tablet formulation of TMC125 in HPMC, manufactured using technology (TF035).

The trial population consisted of 36 healthy subjects in 3 parallel panels. In each panel, 12 subjects (randomized equally to 2 sequences; reference (TF035) formulation followed by test (F048 {for panel 1}, F049 {for panel 2}, or F052 {for panel 3}) formulation or test formulation followed by the reference formulation) received a single dose of 400 mg TMC125. The treatment groups were:

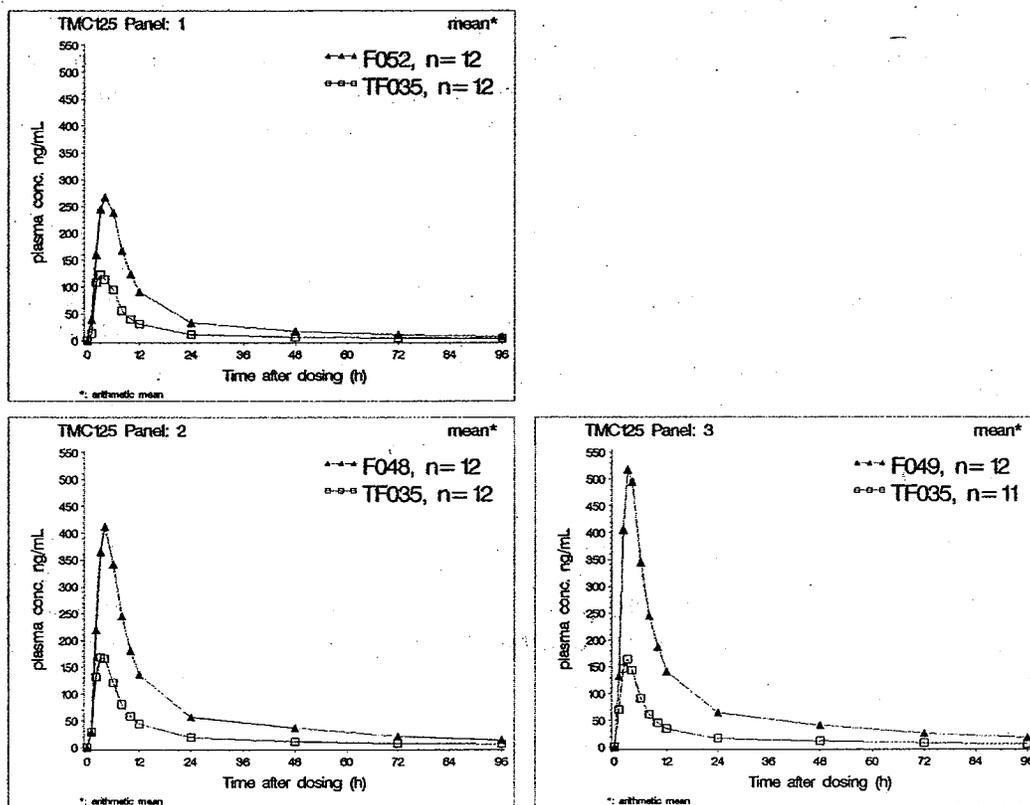
- **Treatment A (reference):** 2 tablets (TF035), each containing 200 mg TMC125 in HPMC.
- **Treatment B (test):** 2 tablets (F052), each containing 200 mg TMC125 in HPMC, spray-dried (TMC125 to HPMC ratio of —).
- **Treatment C (test):** 2 tablets (F048), each containing 200 mg TMC125 in HPMC, spray-dried (TMC125 to HPMC ratio of —).
- **Treatment D (test):** 3 tablets (F049), each containing 133 mg TMC125 in HPMC, spray-dried (TMC125 to HPMC ratio of —).

All treatments were taken under fed conditions within 10 minutes after completion of a standardized breakfast. The washout period between treatments was 14 days.

RESULTS

Fig 1 shows the mean plasma concentration-time profiles of the test tablet formulations (F048, F049, and F052) and the reference formulation (TF035).

Fig 1: Mean plasma concentration-time profiles of the test tablet formulations (F048, F049, and F052) and the reference formulation (TF035)



The mean systemic exposure of TMC125 (C_{max} and AUC) was higher for all the 3 test formulations (F048, F049, and F052) than for the reference formulation TF035, with the mean increases in exposure ranging from 130 % - 280 % higher for C_{max} and from 170 % to 340 % higher for AUC_{last} . The increases in exposure were highest for formulation F049 (TMC125 to HPMC ratio of —), and comparable for formulations F048 (TMC125 to HPMC ratio of —) and F052 (TMC125 to HPMC ratio of —). The C_{max} and AUC parameters showed considerable inter-individual variability for all treatments. The mean elimination half-life of TMC125 was similar with all treatments, in the range of approximately 30 to 40 hours.

Although the pair-wise comparisons to formulation TF035 indicated that the relative bioavailability of TMC125 with formulation F048 (TMC125 to HPMC ratio of —) was lower than with formulation F052 (TMC125 to HPMC ratio of —), the absolute values for C_{max} and AUC_{last} indicated that the exposure to TMC125 was higher with formulation F048 than with formulation F052. The reason for the lower bioavailability to TMC125 with formulation F048 when the data for formulations F048 and F052 were analyzed by comparison to reference formulation TF035 was that the exposures to TMC125 in the reference group (TF035) for formulation F052 was lower than in the reference group for

formulation F048 (and F049), hence — the ratio for the comparison between formulations TF035 and F052. Therefore, on the basis of the absolute exposure data, the results of the trial showed that the bioavailability of TMC125 increased when TMC125: HPMC ratio —

Table 1 shows the pharmacokinetics of TMC125 after administration of three test tablet formulations of TMC125 (F048, F049, and F052) and the reference tablet formulation (TF035) at a single dose of 400 mg.

Table 1: Pharmacokinetics of TMC125 after administration of three test tablet formulations of TMC125 (F048, F049, and F052) and the reference tablet formulation (TF035) at a single dose of 400 mg

Parameter	Mean ± SD; t _{max} : Median (Range)		Ratio ^a (Test:Reference)	90% CI
	Treatment A: TMC125 400 mg (TF035) (Reference)	Treatment B, C, or D: TMC125 400 mg (F052, F048, and F049) (Test)		
Treatment A (TF035) vs. Treatment B (F052)				
N	12	12	-	-
t _{max} , h	4.0 (2.0 - 6.0)	5.0 (2.0 - 6.0)	-	-
C _{max} , ng/mL	145.9 ± 136.4	326.6 ± 172.7	2.68	2.08 - 3.47
AUC _{last} , ng.h/mL	1472 ± 1076	3919 ± 2295	2.99	2.32 - 3.85
AUC _∞ ^b , ng.h/mL	1633 ± 1206	4341 ± 2770	2.94	2.30 - 3.76
t _{1/2,term} ^b , h	31.06 ± 12.92	33.27 ± 8.02	-	-
Treatment A (TF035) vs. Treatment C (F048)				
N	12	12	-	-
t _{max} , h	3.0 (2.0 - 6.0)	4.0 (3.0 - 6.0)	-	-
C _{max} , ng/mL	184.1 ± 99.6	433.7 ± 235.7	2.29	1.41 - 3.71
AUC _{last} , ng.h/mL	2234 ± 1410	6175 ± 3502	2.68	1.62 - 4.44
AUC _∞ ^b , ng.h/mL	2556 ± 1623	6911 ± 3795	2.69	1.73 - 4.16
t _{1/2,term} ^b , h	35.97 ± 17.54	33.40 ± 11.64	-	-
Treatment A (TF035) vs. Treatment D (F049)				
N	11	12	-	-
t _{max} , h	3.0 (1.0 - 6.0)	3.0 (1.0 - 4.0)	-	-
C _{max} , ng/mL	190.2 ± 130.9	580.8 ± 217.9	3.77	2.57 - 5.54
AUC _{last} , ng.h/mL	2027 ± 1816	7331 ± 4286	4.38	3.03 - 6.32
AUC _∞ ^b , ng.h/mL	2394 ± 2367	8454 ± 5562	4.29	3.01 - 6.13
t _{1/2,term} ^b , h	38.61 ± 12.86	35.77 ± 9.35	-	-

N = maximum number of subjects with data.

^a Ratio based on LS means.

^b Accurate determination not possible in all subjects.

Conclusion

- The spray-drying technology used for the manufacture of tablet formulations of TMC125 in HPMC (F052, F048, and F049) led to increase in the exposure to TMC125, compared to the reference tablet formulation of TMC125 in HPMC manufactured using — technology (TF035).
- The mean exposure to TMC125 was higher with a TMC125 to HPMC ratio of — (F049) than with a ratio of — (F048) or — (F052).

Study Number
TMC125-C147

Title

The effect of food on the relative bioavailability of a single intake of TMC125 formulated as tablet F060 (Pivotal Food Effect Study).

Objectives

The primary objective of the trial was to determine the effect of different types of meals on the relative bioavailability of TMC125 after a single oral dose of 100 mg, formulated as F060.

Study Design

Phase I, open label, randomized 3-way crossover trial in 2 panels of healthy subjects. The trial population consisted of 2 parallel panels of 12 healthy subjects each. In 3 sessions, panel 1 received treatment A, treatment B and treatment C and panel 2 received treatment A, treatment D, and treatment E. In all treatments (4 subjects assigned to each treatment), a single dose of 100 mg TMC125 (formulated as F060) was taken within 10 minutes after completion of a standardized breakfast (treatment A), under fasted conditions (treatment B), after a croissant (treatment C), and after a high fiber breakfast (treatment D), or after a high fat breakfast (treatment E). There was a washout period of at least 14 days between subsequent intakes of TMC125. In each session, full pharmacokinetic profiles of TMC125 were determined up to 96 hours post-dose. Table 1 shows the description of the various treatments:

Table 1: Description of the various treatments used in the trial

Treatment	Description
Treatment A (Standardized Breakfast)	4 slices of bread, 2 slices of ham or cheese, butter, jelly, and 2 cups of decaffeinated coffee or tea with milk and/or sugar, if desired (486 grams, 561 kcal; 15.33 gms fat, 21.89 gms protein, 83.86 gms carbohydrates, and 8.08 gms fiber)
Treatment B (Fasted Conditions)	Fasted for at least 10 hours before study medication administration, water intake was allowed for 2 hours prior to study medication administration
Treatment C (Croissant)	Butter croissant with 1 tsp unsalted butter and 1 tsp jam, 1 cup of decaffeinated coffee/tea with milk and/or sugar as desired (213 gms, 345 kcal, 17.44 gms fat, 5.16 gms protein, 41.43 gms carbohydrates, 1.25

Treatment D (High Fiber Breakfast)	gms fiber) 80 gms grapes with skin, 80 gms raw pineapple, 80 gms raw pears, 80 gms raw strawberries, 1 glass of orange juice (225 gms), 1 raw banana (200 gms), 2 slices of mixed grain bread, 2 tbsp (40 gms) of jam (855 gms; 685 kcal, 3.12 gms fat, 13.37 g proteins, 151.24 gms carbohydrates, 16.4 gms fiber).
Treatment E (High Fat Breakfast)	2 large fried eggs, 2 slices of fried bacon, 1 butter croissant, 2 slices of white bread, 1 tsp unsalted butter, 1 bar of semisweet chocolate (30 gms), 1 cup of decaffeinated coffee/tea with milk and/or sugar as desired (468 gms, 1160 kcal, 70.26 gms fat, 40.36 gms protein, 91.26 gms carbohydrates, and 2.21 gms fiber).

Reviewer's Note:

The standard breakfast (as opposed to fasting conditions) was used as the reference treatment because TMC125 was administered with food in the pivotal Phase III trials and has been administered in the fed state throughout its development.

Investigational Product(s)

TMC125 was formulated as F060, a tablet containing 100 mg of TMC125 in a fixed ratio with hydroxypropylmethylcellulose and microcrystalline cellulose, and other excipients. The batch # of the formulation used in the study was 05A05 and the expiration date was July 2005.

Assay Methods

Plasma concentrations of TMC125 were determined by a validated liquid chromatography-tandem mass spectrometry method. The lower limit of quantification (LLOQ) was different for several samples of TMC125, because of the different dilution factors used (due to insufficient sample volume), and could be 2.00, 4.00, 6.00, or 20.00 ng/mL.

Pharmacokinetic and Statistical Data Analysis

Pharmacokinetic Analysis

Pharmacokinetic and statistical analysis was performed using WinNonlin Professional (version 4.1, Pharsight Corporation, Mountain View, California). A non-compartmental analysis model 200 (extravascular input, plasma data) was used for the pharmacokinetic analysis. The actual sampling time was checked for major aberrations. In case major

aberrations (> 10 % deviations from the scheduled times) occurred for a subject, the actual sampling times were used in the pharmacokinetic analysis for that subject and treatment.

Reviewer's Note:

For treatment B, one major aberration (> 10 % deviation between the scheduled time and actual sampling time) was identified. For one subject, the actual sampling time of the 72-hour blood sample deviated 10.37 % from the scheduled sampling time, therefore, the actual sampling time was used. However, this is not expected to have any impact on the conclusions of the trial.

Statistical Analysis

Statistical analyses were performed for TMC125 using treatments B, C, D, and E as test and treatment A as reference. The primary pharmacokinetic parameters were C_{max} , AUC_{0-last} , and $AUC_{0-\infty}$ on the logarithmic scale. $AUC_{0-\infty}$ was rejected as a primary parameter for a treatment if more than half of the subjects did not have a reliable estimate for that treatment. No relevant food effect on the bioavailability of TMC125 was concluded when the 90 % confidence intervals for the primary pharmacokinetic parameters were contained with the bioequivalence limits (80 % -125 %).

RESULTS

Subject Disposition and Demographics

Out of the 38 subjects screened, 24 subjects were randomized to 2 panels of 12 subjects each. 20 randomized subjects completed the trial; four subjects dropped out of the trial before the completion of the trial. 1 subject (randomized to panel 2) withdrew consent during the washout period after the first treatment phase (subject received **treatment E**), 2 subjects withdrew consent during the follow up period (both the subjects were randomized to **panel 1**, one subject to **treatment** sequence BCA and one subject to **treatment** sequence CAB; both subjects received all the three treatments), and 1 subject (randomized to **panel 1**, treatment sequence BCA; the subject received all the three treatments) was lost to follow up.

Table 2 shows the summary of the demographics in the trial.

Table 2: Demographics in Trial TMC114-C147

Parameter	All Subjects N = 24
Age, years	
Median (range)	27.5 (20-51)
Height, cm	
Median (range)	181.0 (171-192)
Weight, kg	
Median (range)	82.5 (62-115)
BMI, kg/m ²	
Median (range)	25.15 (20.2-31.2)
Sex, n (%)	
Male	24 (100.0%)
Ethnic Origin, n (%)	
Caucasian/White	23 (95.8%)
Black	1 (4.2%)
Smoker, n (%)	
Yes	10 (41.7%)
No	14 (58.3%)

BMI=Body Mass Index

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Pharmacokinetics

Subject 1470003 (panel 2) only completed session 1, treatment E, and discontinued the trial during the washout after treatment E. This subject was included in the descriptive statistics and statistical analysis for treatment E and was not replaced. Therefore, full pharmacokinetic profiles of TMC125 were available for 12 subjects for treatment A (panel 1), and for treatment B, treatment C, and treatment E. Full pharmacokinetic profiles were available for 11 subjects randomized to treatment A and treatment D in panel 2.

Fig 1 shows the mean plasma concentration time profiles of TMC125 after treatment A (TMC125 100 mg taken after a standardized breakfast), treatment B (TMC125 100 mg taken under fasted conditions), and treatment C (TMC125 100 mg taken after a snack {croissant}).

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Fig 1: Mean plasma concentration time profiles of TMC125 after treatment A (TMC125 100 mg taken after a standardized breakfast), treatment B (TMC125 100 mg taken under fasted conditions), and treatment C (TMC125 100 mg taken after a snack (croissant)).

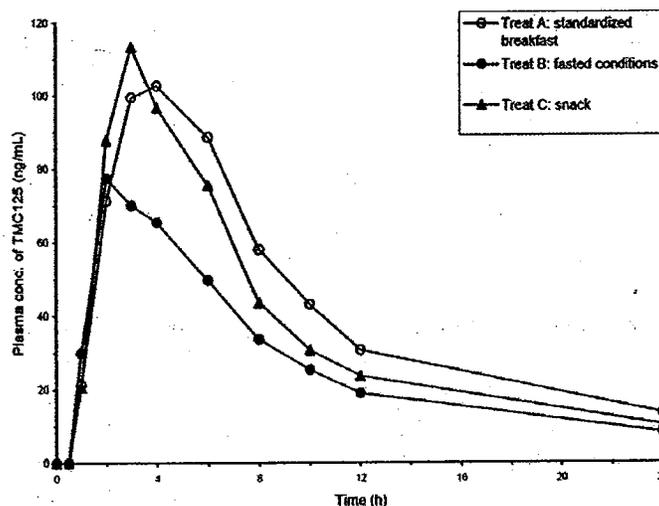


Table 3 shows the mean pharmacokinetic parameters of TMC125 for treatment A, treatment B, and treatment C (panel 1).

Table 3: Mean pharmacokinetic parameters of TMC125 for treatment A, treatment B, and treatment C (panel 1).

Pharmacokinetics of TMC125 (mean \pm SD, t_{max} and t_{lag} ; median [range])	Treatment A, Panel 1: 100 mg TMC125 standardized breakfast	Treatment B, Panel 1: 100 mg TMC125 fasted conditions	Treatment C, Panel 1: 100 mg TMC125 croissant
n	12	12	12
t_{lag} , h	0.5 (0.0 - 1.0)	0.5 (0.0 - 2.0)	0.5 (0.0 - 1.0)
t_{max} , h	4.0 (2.0 - 6.0)	2.0 (2.0 - 6.0)	3.0 (2.0 - 6.0)
C_{max} , ng/mL	128.6 \pm 63.73	88.83 \pm 67.97	127.5 \pm 73.06
AUC_{last} , ng.h/mL	1417 \pm 1140	920.5 \pm 1024	1189 \pm 1106
AUC_{inf} , ng.h/mL	1641 ^a \pm 1437 ^a	1089 ^a \pm 1314 ^a	1462 ^a \pm 1691 ^a
$t_{1/2elim}$, h	24.14 ^a \pm 12.93 ^a	19.91 ^a \pm 15.43 ^a	25.02 ^a \pm 20.88 ^a

^a Accurate determination not possible

Fig 2 shows the plots of the pharmacokinetic parameters (C_{max} , AUC_{last} , and AUC_{inf}) observed in treatment A, treatment B, and treatment C.

Fig 2: Plots of the pharmacokinetic parameters (C_{max} , AUC_{last} , and AUC_{inf}) observed in treatment A, treatment B, and treatment C

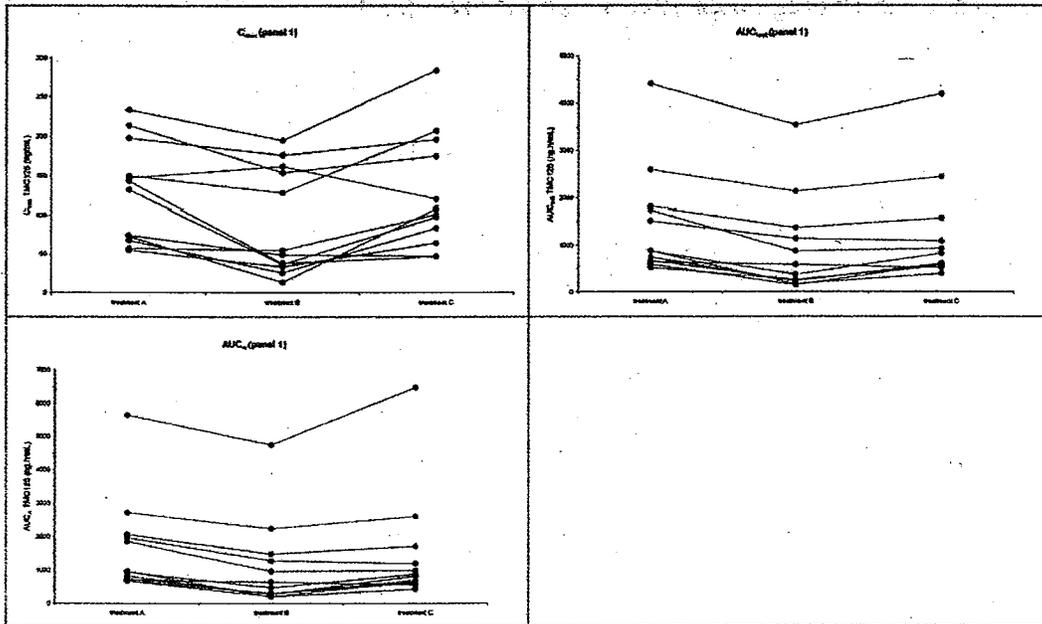


Fig 2 shows the mean plasma concentration time profiles of TMC125 after **treatment A** (TMC125 100 mg taken after a standardized breakfast), **treatment D** (TMC125 100 mg taken with a high fiber breakfast) and **treatment E** (TMC125 100 mg taken after a high fat breakfast).

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Fig 2: Mean plasma concentration time profiles of TMC125 after treatment A (TMC125 100 mg taken after a standardized breakfast), treatment D (TMC125 100 mg taken with a high fiber breakfast) and treatment E (TMC125 100 mg taken after a high fat breakfast)

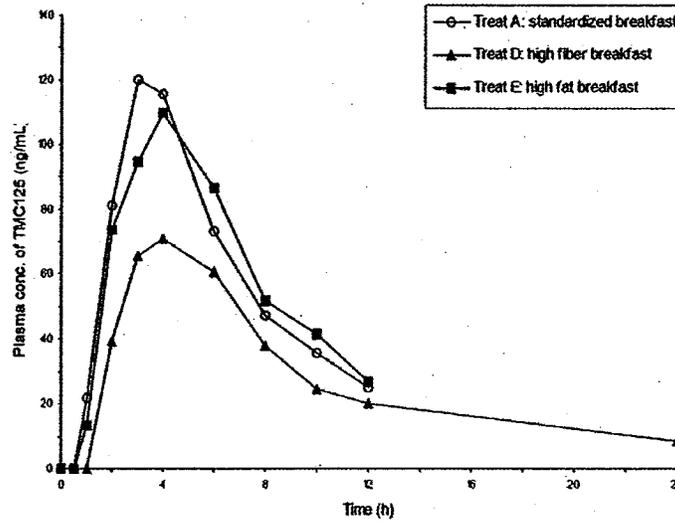


Table 4 shows the pharmacokinetic parameters of TMC125 for treatments A, D, and E (Panel 2).

Table 4: Pharmacokinetic parameters of TMC125 for treatment A, treatment D, and treatment E (Panel 2)

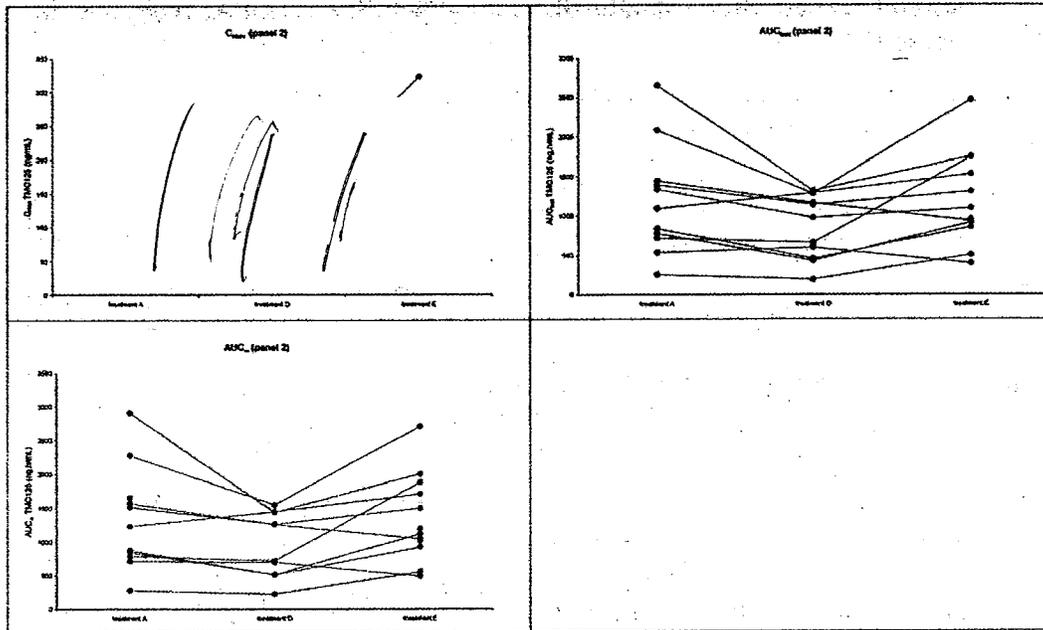
Pharmacokinetics of TMC125 (mean \pm SD, t_{max} and t_{lag} : median [range])	Treatment A, Panel 2: 100 mg TMC125 standardized breakfast	Treatment D, Panel 2: 100 mg TMC125 high fiber breakfast	Treatment E, Panel 2: 100 mg TMC125 high fat breakfast
n	11	11 ^b	12
t_{lag} , h	0.5 (0.0 - 1.0)	0.5 (0.0 - 2.0)	0.5 (0.0 - 2.0)
t_{max} , h	3.0 (2.0 - 6.0)	3.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)
C_{max} , ng/mL	138.4 \pm 61.33	85.05 \pm 40.31	129.9 \pm 64.12
AUC_{last} , ng.h/mL	1191 \pm 699.6	863.6 \pm 407.2	1202 \pm 585.7
AUC_{∞} , ng.h/mL	1330 ^a \pm 762.6 ^a	960.3 ^a \pm 479.7 ^a	1342 ^a \pm 642.4 ^a
$t_{1/2term}$, h	24.67 ^a \pm 15.23 ^a	22.39 ^a \pm 18.89 ^a	25.81 ^a \pm 12.91 ^a

^a Accurate determination not possible

^b n = 10 for AUC_{∞} and $t_{1/2term}$

Fig 4 shows the plots of the pharmacokinetic parameters (C_{max} , AUC_{last} and AUC_{inf}) observed in treatment A, treatment D, and treatment E.

Fig 4: Plots of the pharmacokinetic parameters (C_{max} , AUC_{last} , and AUC_{inf}) observed in treatments A, D, and E



For all treatments, more than 50 % of the individual values of $AUC_{0-\infty}$, λ_z , and $t_{1/2term}$ could not be determined accurately, consequently, descriptive statistics related to these parameters could also not be reported accurately. Therefore, AUC_{0-last} instead of $AUC_{0-\infty}$ was used as the primary pharmacokinetic parameter.

Table 5 shows the statistical evaluation of the pharmacokinetic parameters of TMC125 administered under fasting conditions (treatment B; test) compared to administration after a standardized breakfast (treatment A; reference) in panel 1.

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Table 5: Statistical evaluation of the pharmacokinetic parameters of TMC125 administered under fasting conditions (treatment B; test) compared to administration after a standardized breakfast (treatment A; reference) in panel 1

Parameter	Least square means		Least square means ratio, %	90% CI, % *	p-value		
	Treatment A (reference)	Treatment B (test)			Treatment	Period	Sequence
C_{max} , ng/mL	113.7	63.98	56.28	41.04 - 77.17	0.0087	0.4440	0.5941
AUC_{last} , ng.h/mL	1126	550.6	48.91	39.06 - 61.25	0.0002	0.0709	0.2979
Parameter	Median		Treatment difference median	90% CI, % *	p-value		
	Treatment A (reference)	Treatment B (test)			Treatment	Period	Sequence
t_{max} , h	4.0	2.0	-1.00	(-2.00) - (0.00)	0.0590	0.0557	0.0898
t_{lag} , h	0.5	0.5	0.00	(-0.25) - (0.75)	0.6177	0.3566	0.2759

* 90% confidence intervals.

n = 12 for all pharmacokinetic parameters and both treatments.

The LS_{means} ratio of C_{max} and AUC_{last} of TMC125 were decreased by 44 % and 51 % respectively, under fasted conditions as compared to when TMC125 was taken with a standardized breakfast.

The individual treatment ratios (B/A) for C_{max} and AUC_{last} ranged from 18.48 % to 110.2 % and from 19.24 % to 90.64 %, respectively, with a geometric mean of 56.28 % and 48.91 %, respectively.

Table 6 shows the statistical evaluation of the pharmacokinetic parameters of TMC125 administered after a croissant (treatment C; test) and after a standardized breakfast (treatment A; reference) in panel 1.

Table 6: Statistical evaluation of the pharmacokinetic parameters of TMC125 administered after a croissant (treatment C; test) and after a standardized breakfast (treatment A; reference) in panel 1

Parameter	Least square means		Least square means ratio, %	90% CI, % *	p-value		
	Treatment A (reference)	Treatment C (test)			Treatment	Period	Sequence
C_{max} , ng/mL	113.7	109.7	96.51	74.65-124.8	0.3052	0.6885	0.5016
AUC_{last} , ng.h/mL	1126	905.9	80.49	69.04-93.83	0.0290	0.9822	0.2455
Parameter	Median		Treatment difference median	90% CI, % *	p-value		
	Treatment A (reference)	Treatment C (test)			Treatment	Period	Sequence
t_{max} , h	4.0	3.0	-0.50	(-1.50)-(0.50)	0.4637	0.5704	0.5152
t_{lag} , h	0.5	0.5	0.00	(-0.25)-(0.25)	0.8586	0.1179	0.6171

* 90% confidence intervals.

n = 12 for all pharmacokinetic parameters and both treatments.

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The LS_{means} ratio of C_{max} of TMC125 was not significantly different when TMC125 was administered with a croissant or with standardized breakfast, however, the AUC_{last} of TMC125 was decreased by 20 % when TMC125 was administered with a croissant as compared to when TMC125 was administered with a standardized breakfast.

The individual treatment ratios (C/A) for C_{max} and AUC_{last} ranged from 32.73 % to 176.9 % and from 44.17 % to 106.3 %, respectively, with a geometric mean of 96.51 % and 80.49 %, respectively.

Table 7 shows the statistical evaluation of the pharmacokinetic parameters of TMC125 administered after a high fiber breakfast (treatment D; test) and after a standardized breakfast (treatment A; reference) in panel 2.

Table 7: Statistical evaluation of the pharmacokinetic parameters of TMC125 administered after a high fiber breakfast (treatment D; test) and after a standardized breakfast (treatment A; reference) in panel 2.

Parameter	Least square means		Least square means ratio, %	90% CI, % ^a	p-value		
	Treatment A (reference)	Treatment D (test)			Treatment	Period	Sequence
C _{max} , ng/mL	124.7	77.54	62.16	46.80 - 82.57	0.0143	0.4158	0.9519
AUC _{last} , ng.h/mL	978.4	736.3	75.25	63.04 - 89.83	0.0174	0.8445	0.4927
Parameter	Median		Treatment difference median	90% CI, % ^a	p-value		
	Treatment A (reference)	Treatment D (test)			Treatment	Period	Sequence
t _{max} , h	3.0	3.0	1.00	(-0.50) - (1.50)	0.3865	1.000	0.9248
t _{1/2} , h	0.5	0.5	0.25	(0.00) - (0.50)	0.1073	0.1073	0.7782

^a 90% confidence intervals.

N = 11 for all pharmacokinetic parameters and both treatments.

The LS_{means} ratio of C_{max} and AUC_{last} of TMC125 were decreased by 37 % and 25 % respectively, after a high fiber breakfast (treatment D) as compared to when TMC125 was administered with a standardized breakfast (treatment A).

The individual treatment ratios (D/A) for C_{max} and AUC_{last} ranged from 17.7 % to 97.95 % and from 49.74 % to 118.3 %, respectively, with a geometric mean of 60.51 % and 74.88 %, respectively.

Table 8 shows the statistical evaluation of the pharmacokinetic parameters of TMC125 administered after a high fat breakfast (treatment E; test) and after a standardized breakfast (treatment A; reference) in panel 2.

Table 8: Statistical evaluation of the pharmacokinetic parameters of TMC125 administered after a high fat breakfast (treatment E; test) and after a standardized breakfast (treatment A; reference) in panel 2

Parameter	Least square means		Least square means ratio, %	90% CI, % *	p-value		
	Treatment A (reference)	Treatment E (test)			Treatment	Period	Sequence
C_{max} , ng/mL	126.6	120.6	95.29	70.23 - 129.3	0.7991	0.9073	0.1980
AUC_{last} , ng.h/mL	984.3	1070	108.7	83.90 - 140.9	0.5665	0.8263	0.1404
Parameter	Median		Treatment difference median	90% CI, % *	p-value		
	Treatment A (reference)	Treatment E (test)			Treatment	Period	Sequence
t_{max} , h	3.0	4.0	1.00	(-1.00) - (1.50)	0.1601	0.7052	0.9247
$t_{1/2}$, h	0.5	0.5	0.00	(-0.25) - (0.50)	0.9155	0.2904	0.1218

* 90% confidence intervals.

N = 12 for C_{max} and AUC_{last} for Treatment E; n = 11 for t_{max} and $t_{1/2}$ for Treatment E and all pharmacokinetic parameters for Treatment A.

The LS_{means} ratio of C_{max} and AUC_{last} of TMC125 were not significantly altered (all changes < 10 %) when TMC125 was administered with a high fat breakfast as compared to when TMC125 was administered with a standard breakfast.

The individual treatment ratios (E/A) for C_{max} and AUC_{last} ranged from 47.67 % to 254.3 % and from 64.59 % to 242.8 %, respectively, with a geometric mean of 95.77 % and 108.2 %, respectively.

Reviewer's Comment Regarding Reduction in Systemic Exposures (AUC_{last}) with a croissant and high fiber breakfast

The results of the study showed that the mean systemic exposures of TMC125 (AUC_{last}) were decreased by 20 % and 25 % respectively, when TMC125 was administered with a croissant or high fiber breakfast, as compared to when TMC125 was administered with a standardized breakfast. However, this reduction in the mean systemic exposures of TMC125 is not expected to be clinically relevant since the decrease in the mean systemic exposures of TMC125 was greater (37 %) when co-administered with darunavir/ritonavir and food in the pivotal phase III clinical trials. As the exposures in the pivotal clinical trials were shown to be efficacious, the reduction in the mean systemic exposures of TMC125 with a croissant or high fiber breakfast is not expected to be clinically relevant.

Pharmacokinetic Results Summary

- The LS_{means} ratio of C_{max} and AUC_{last} of TMC125 were decreased by 44 % and 51 % respectively, % under fasted conditions as compared to when TMC125 was taken with a standardized breakfast.
- The LS_{means} ratio of C_{max} of TMC125 was not significantly different when TMC125 was administered with a croissant or with standardized breakfast, however, the AUC_{last} of TMC125 was decreased by 20 % when TMC125 was

administered with a croissant as compared to when TMC125 was administered with a standardized breakfast.

- The LS_{means} ratio of C_{max} and AUC_{last} of TMC125 were decreased by 37 % and 25 % respectively, after a high fiber breakfast (treatment D) as compared to when TMC125 was administered with a standardized breakfast (treatment A).
- The LS_{means} ratio of C_{max} and AUC_{last} of TMC125 were not significantly altered (all changes < 10 %) when TMC125 was administered with a high fat breakfast as compared to when TMC125 was administered with a standard breakfast.

Conclusion

Based on the results of the study, it is recommended that TMC125 should always be taken following a meal. The type of meal is not expected to have a clinically relevant effect on altering the exposures of TMC125.

**APPEARS THIS WAY
ON ORIGINAL**

Study Number
TMC125-C150

Title

A Phase 1, open-label, randomized, single dose, 2-way crossover multi-center trial to determine the bioavailability of TMC125 from four different formulations, relative to the reference formulation, TF035 (*Effect of manufacturing technology, type of solubilizing polymer, and TMC125 to polymer ratio*).

Study Design

Open-label, randomized, single dose, two-way crossover multi-center trial to investigate the relative bioavailability of 3 — tablet formulations of TMC125 in HPMC or — manufactured using spray-drying technology (F015, F016, and F017), and formulation of TMC125 in HPMC, manufactured using — technology (F039), compared to a reference tablet formulation of TMC125 in HPMC (hydroxypropylmethylcellulose), manufactured using — technology (TF035). The different formulation concepts of TMC125 investigated in this trial varied in the manufacturing technology used, the type of solubilizing polymer, and the TMC125 to polymer ratio used.

The trial population consisted of 4 parallel panels of 12 subjects each. In each panel, the subjects were randomized to one of the two sequences (n = 6 per sequence): test formulation followed by reference formulation or reference formulation followed by test formulation; treatment A and treatment B were administered to panel 1, treatment A and treatment C were administered to panel 2, treatment A and treatment D to panel 3, and treatment A and treatment E to panel 4. The various treatments were:

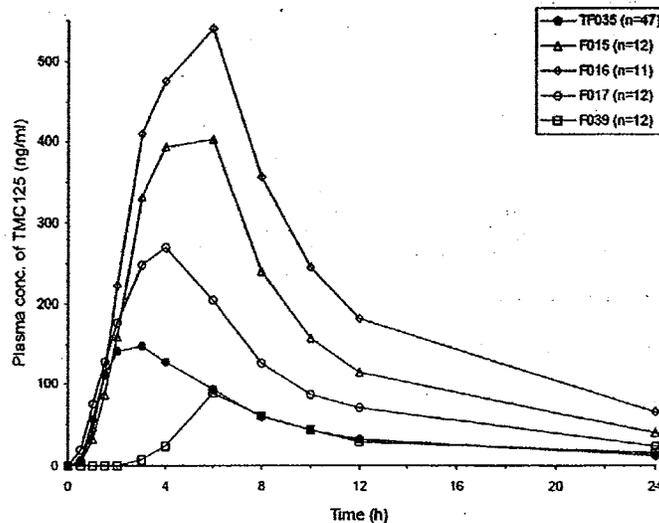
- **Treatment A (reference):** 2 tablets (TF035), each containing 200 mg TMC125 in HPMC, —
- **Treatment B (test):** 2 tablets (F015), each containing 200 mg TMC125 in HPMC, spray-dried (TMC125 to HPMC ratio of —
- **Treatment C (test):** 3 tablets (F016), each containing 133 mg TMC125 in HPMC, spray-dried (TMC125 to HPMC ratio of —
- **Treatment D (test):** 2 tablets (F017), each containing 200 mg TMC125 in — spray-dried (TMC125 to — ratio of —
- **Treatment E (test):** 2 — (F039), each containing 200 mg TMC125 in HPMC. — (TMC125 to HPMC ratio of —

All treatments were taken under fed conditions within 10 minutes after completion of a standardized breakfast. The washout period between treatments was 21 days.

RESULTS

Fig 1 shows the mean plasma concentration-time profiles of TMC125 after administration of three spray-dry tablet formulations of TMC125 (F015, F016, and F017) and a test formulation of TMC125 (F039), compared to a reference tablet formulation of TMC125 in HPMC (TF035) after a single dose of 400 mg.

Fig 1: Mean plasma concentration-time profiles of TMC125 after administration of three spray-dry tablet formulations of TMC125 (F015, F016, and F017) and a test formulation of TMC125 (F039), compared to a reference tablet formulation of TMC125 in HPMC (TF035) after a single dose of 400 mg.



The median t_{max} was shortest for the reference tablet formulation TF035 (3 hours), ranged from 4-5 hours for the test tablet formulations F015, F016, and F017 and was the longest for the test formulation F039 (6 hours).

Table 1 shows the pharmacokinetics of TMC125 after administration of three test spray-dry tablet formulations of TMC125 (F015, F016, and F017) and a test formulation of TMC125 (F039), compared to the reference tablet formulation of TMC125 in HPMC (TF035), at a single dose of 400 mg.

Table 1: Pharmacokinetics of TMC125 after administration of three test spray-dry tablet formulations of TMC125 (F015, F016, and F017) and a test formulation of TMC125 (F039), compared to the reference tablet formulation of TMC125 in HPMC (TF035), at a single dose of 400 mg

Parameter	Mean ± SD; t _{max} ; Median (Range)		Ratio ^a (Test:Reference)	90% CI
	Treatment A: TMC125 400 mg (TF035) (Reference)	Treatment B, C, D, or E: TMC125 400 mg (F015, F016, F017, F039) (Test)		
Treatment A (TF035) vs. Treatment B (F015)				
N	47	12	-	-
t _{max} , h	3.0 (1.5 - 6.0)	5.0 (3.0 - 6.0)	-	-
C _{max} , ng/mL	168 ± 145	450 ± 278	2.65	1.82 - 3.31
AUC _{last} , ng.h/mL	1665 ± 1468	5344 ± 3443	3.05	2.44 - 3.80
AUC _∞ ^b , ng.h/mL	1975 ± 1774	6089 ± 3967	-	-
t _{1/2,elim} ^b , h	42.2 ± 37.3	39.8 ± 12.9	-	-
Treatment A (TF035) vs. Treatment C (F016)				
N	47	11	-	-
t _{max} , h	3.0 (1.5 - 6.0)	4.0 (2.0 - 6.0)	-	-
C _{max} , ng/mL	168 ± 145	654 ± 228	5.82	4.09 - 8.28
AUC _{last} , ng.h/mL	1665 ± 1468	7675 ± 3677	6.24	4.45 - 8.75
AUC _∞ ^b , ng.h/mL	1975 ± 1774	8741 ± 4424	-	-
t _{1/2,elim} ^b , h	42.2 ± 37.3	40.0 ± 9.48	-	-
Treatment A (TF035) vs. Treatment D (F017)				
N	47	12	-	-
t _{max} , h	3.0 (1.5 - 6.0)	4.0 (2.0 - 6.0)	-	-
C _{max} , ng/mL	168 ± 145	288 ± 171	1.86	1.27 - 2.72
AUC _{last} , ng.h/mL	1665 ± 1468	3103 ± 2137	2.23	1.48 - 3.37
AUC _∞ ^b , ng.h/mL	1975 ± 1774	3372 ± 2249	-	-
t _{1/2,elim} ^b , h	42.2 ± 37.3	33.9 ± 14.9	-	-
Treatment A (TF035) vs. Treatment E (F039)				
N	47	12	-	-
t _{max} , h	3.0 (1.5 - 6.0)	6.0 (4.0 - 8.0)	-	-
C _{max} , ng/mL	168 ± 145	90.1 ± 65.4	0.76	0.46 - 1.23
AUC _{last} , ng.h/mL	1665 ± 1468	1297 ± 1289	0.74	0.41 - 1.35
AUC _∞ ^b , ng.h/mL	1975 ± 1774	2427 ± 3847	-	-
t _{1/2,elim} ^b , h	42.2 ± 37.3	57.2 ± 74.2	-	-

N = maximum number of subjects with data.

^a Ratio based on LS means.

^b Accurate determination not possible in all subjects.

The mean estimates of C_{max} and AUC_{last} of TMC125 were highest for F016, followed by F015, F017, TF035, and F039.

Conclusion

- The spray-drying technology used for the manufacture of tablet formulations of TMC125 in HPMC or (F015, F016, and F017) led to higher mean systemic exposure to TMC125, compared to the reference tablet formulation of TMC125 in HPMC manufactured using technology (TF035).
- The technology used for the manufacture of formulation F039 resulted in a decrease in exposure to TMC125, compared to tablet formulation TF035.
- Among the spray-dried tablet formulations, the exposure to TMC125 was higher when HPMC was used as the polymer (F015 and F016) than when was used as the polymer (F017).

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- With the — spray-dried tablet formulations of TMC125 in HPMC, the mean exposure to TMC125 was higher with a TMC125 to HPMC ratio of — (F016) than with a ratio of — F015).

**APPEARS THIS WAY
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**APPEARS THIS WAY
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Study Number
TMC125-C155

Title

A Phase 1, open-label, randomized, three way crossover trial in 36 healthy subjects, to determine the pharmacokinetics, safety, and tolerability of a single 400 mg dose of TMC125, administered as three different formulations (2 new formulations and reference TF035) (*Effect of manufacturing technology*).

Study Design

Open-label, randomized, 3-period crossover trial to determine the relative bioavailability of 2 test — tablet formulations of TMC125 (F047 [manufactured using — technology] and F046 [manufactured using spray-drying technology]), compared to a reference tablet formulation of TMC125 in HPMC (hydroxypropylmethylcellulose), manufactured using — technology (TF035).

Each subject received a single, oral, 400-mg dose of TMC125 on 3 occasions. In each of 3 sessions, the subjects received the reference formulation (**Treatment A**) and one of the 2 test formulations (**Treatments B or C**). The treatment groups were:

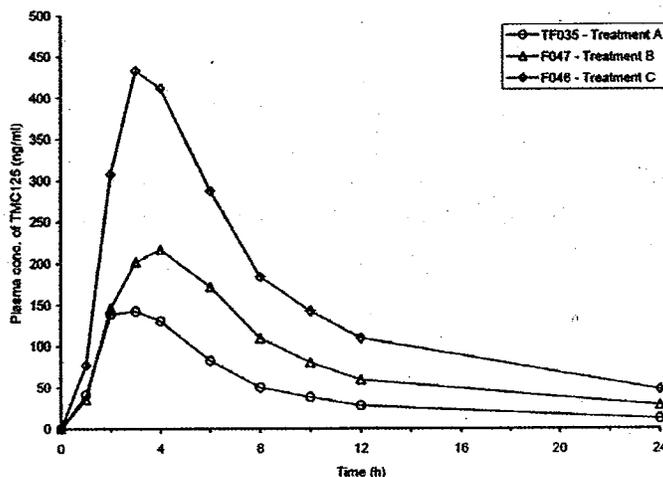
- **Treatment A (reference):** 2 tablets (TF035), each containing 200 mg TMC125 in HPMC, — (TMC125 to HPMC ratio of —)
- **Treatment B (test):** 3 tablets (F047), each containing 133 mg TMC125 in HPMC — (TMC125 to HPMC ratio of —)
- **Treatment C (test):** 2 tablets (F046), each containing 200 mg TMC125 in HPMC, spray-dried (TMC125 to HPMC ratio of —)

All treatments were taken under fed conditions within 10 minutes after completion of a standardized breakfast. The washout period between treatments was at least 21 days.

RESULTS

Fig 1 shows the mean plasma concentration-time profiles of TMC125 after administration of a single, 400 mg dose of the two test formulations (F046 and F047) and the reference formulation (TF035) of TMC125.

Fig 1: Mean plasma concentration-time profiles of TMC125 after administration of a single, 400 mg dose of the two test formulations (F046 and F047) and the reference formulation (TF035) of TMC125.



N = 30 for Treatments A and C, and N = 31 for Treatment B.

The median t_{max} was 3 hours with formulations TF035 and F046 and 4 hours with formulation F047. The C_{max} and AUC_{last} was highest for formulation F046, followed by F047, and lowest with TF035. The inter-individual variability across treatments ranged from 43 % to 59 % for C_{max} and 57 % to 88 % for AUC_{last} .

Table 1 shows the pharmacokinetics of TMC125 after administration of a single, 400 mg dose of the two test formulations (F046 and F047) and the reference formulation (TF035).

Table 1: Pharmacokinetics of TMC125 after administration of a single, 400 mg dose of the two test formulations (F046 and F047) and the reference formulation (TF035).

Parameter	Mean \pm SD; t_{max} : Median (Range)		Ratio ^a (Test:Reference)	90% CI
	Treatment A: TMC125 400 mg (TF035) (Reference)	Treatment B or C: TMC125 400 mg (F047 or F046) (Test)		
Treatment A (TF035) vs. Treatment B (F047)				
N	30	31	-	-
t_{max} , h	3.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	-	-
C_{max} , ng/mL	167 \pm 98.6	242 \pm 142	1.54	1.28 - 1.86
AUC_{last} , ng.h/mL	1545 \pm 983	3082 \pm 2701	1.96	1.64 - 2.34
AUC_e^b , ng.h/mL	1772 \pm 1179	3503 \pm 3265	-	-
$t_{1/2,obs}$, h	31.7 \pm 17.0	31.3 \pm 13.4	-	-
Treatment A (TF035) vs. Treatment C (F046)				
N	30	30	-	-
t_{max} , h	3.0 (2.0 - 6.0)	3.0 (2.0 - 6.0)	-	-
C_{max} , ng/mL	167 \pm 98.6	474 \pm 204	3.17	2.66 - 3.79
AUC_{last} , ng.h/mL	1545 \pm 983	5551 \pm 3156	3.66	3.15 - 4.26
AUC_e^b , ng.h/mL	1772 \pm 1179	6468 \pm 4345	-	-
$t_{1/2,obs}$, h	31.7 \pm 17.0	37.2 \pm 12.6	-	-

N = maximum number of subjects with data.
^a Ratio based on LS means.
^b Accurate determination not possible in all subjects.

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Both the test formulations (F046 and F047) resulted in increased exposures to TMC125, compared to the reference formulation TF035. The mean C_{max} and AUC_{last} were 220 % and 270 % higher, respectively, with formulation F046 and were 54 % and 95 % higher, respectively, with formulation F047. The 90 % CIs of the LS means ratios of C_{max} and AUC_{last} for both comparisons were outside the 80 % to 125 % range.

Conclusion

- The spray-drying technology used for the manufacture of tablet formulation F046 (TMC125 in HPMC, spray-dried, 2 X 200 mg) resulted in higher exposure to TMC125 than with the _____ technology used for the manufacture of F047 (TMC125 in HPMC, _____, 3 X 133 mg) and TF035 (TMC125 in HPMC, _____, 2 X 200 mg) formulations.

APPEARS THIS WAY
ON ORIGINAL

Study Number
TMC125-C162

Title

A Phase 1, open-label, randomized, single dose, 4-way crossover trial in healthy subjects to determine the relative oral bioavailability of TMC125 administered as formulation F016 and 3 different batches of formulation F060 (*Effect of Manufacturing Scale and Long-Term Tablet Storage*).

Study Design

Open-label, randomized, single-dose 4-way crossover trial to determine the relative bioavailability of TMC125 administered as formulation F016 and 3 different batches of formulation F060. The trial population consisted of 16 healthy subjects. Each subject received, in 4 sessions, a single oral dose of 400 mg TMC125 as treatments A, B, C, or D on 4 different occasions.

The treatment groups were:

- **Treatment A (reference):** 4 tablets (F060, Batch 04H26), each containing 100 mg TMC125 in HPMC, spray-dried (small-scale manufacture).
- **Treatment B (test):** 4 tablets (F060, Batch 05A03), each containing 100 mg TMC125 in HPMC, spray-dried (scale increase and process-variation).
- **Treatment C (test):** 4 tablets (F060, Batch 05A05), each containing 100 mg TMC125 in HPMC, spray-dried (scale increase and process variation).
- **Treatment D (test):** 3 tablets (F016, Batch 03F25, stored for approximately 2 years under un-controlled conditions), each containing 133 mg TMC125 in HPMC, spray-dried.

Reviewer's Note:

The TMC125 formulations used in treatment A, treatment B, and treatment C are identical in terms of the amount of active ingredient, the ratio of TMC125 and the polymer used — and the various excipients used, however, the formulations are different in terms of the scale of manufacturing and the differences in the manufacturing process used.

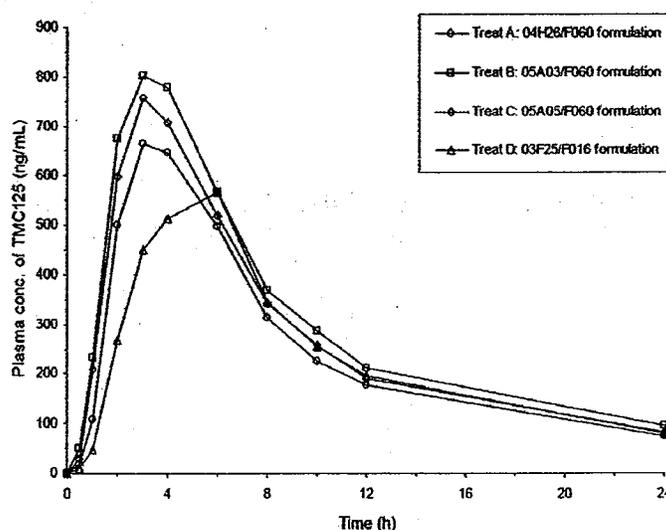
Formulation F016, batch 03F25 (treatment D) was previously used in TMC125-C150 and the tablets left over from this earlier trial were used in the current trial to assess the effect of long-term storage (storage time between trial TMC125-C150 and TMC125-C162 was approximately 2 years at room temperature) on the bioavailability of the spray-dried tablet formulation of TMC125.

All treatments were taken under fed conditions within 10 minutes after completion of a standardized breakfast (561 kilocalories, 15.3 grams of fat). The washout period between treatments was at least 14 days.

RESULTS

Fig 1 shows the mean plasma concentration-time profiles of TMC125 after administration of a single, 400 mg dose using the various batches of F060 formulation and the F016 formulation of TMC125.

Fig 1: Mean plasma concentration-time profiles of TMC125 after administration of a single, 400 mg dose using the various batches of F060 formulation and the F016 formulation of TMC125.



The median t_{max} of TMC125 was 3 hours with the 3 batches of formulation F060, and 6 hours with formulation F016. The mean C_{max} and AUC_{last} of TMC125 were 26 % and 28 % higher, respectively, with formulation F060, batch 05A03 (treatment B) compared to formulation F060, batch 04H26 (treatment A). The systemic exposures (C_{max} and AUC_{last}) were comparable when TMC125 was administered as formulation F060, batch 05A05 (treatment C) and F060, batch 04H26 (treatment A).

Similar systemic exposures (AUC_{last}) were also observed with formulations F016, Batch 03F25 (Treatment D) and F060, Batch 04H26, (Treatment A). The 90 % CI of the LS_{means} ratio of C_{max} for Treatment C vs. Treatment A were just outside the 80 % to 125 % range, while the 90 % CIs of AUC_{last} for Treatment C vs. Treatment A and Treatment D vs. Treatment A were within the 80 % to 125 % range.

For all treatments, the mean terminal elimination half-life of TMC125 was comparable, and ranged from 43.8 hours to 49.0 hours.

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Table 1 shows the pharmacokinetic parameters of TMC125 after administration of a single, 400 mg dose using the three batches of F060 formulation and the F016 formulation of TMC125.

Table 1: Pharmacokinetic parameters of TMC125 after administration of a single, 400 mg dose using the three batches of F060 formulation and the F016 formulation of TMC125.

Parameter	Mean \pm SD; t_{max} : Median (Range)		Ratio ^a (Test:Reference)	90% CI
	Treatment A: TMC125 400 mg (F060 [04H26]) (Reference)	Treatment B, C, or D: TMC125 400 mg (F060 [05A03], F060 [05A05], or F016 [03F25]) (Test)		
Treatment A (F060 [04H26]) vs. Treatment B (F060 [05A03])				
N	16	15	-	-
t_{max} , h	3.0 (2.0 - 6.0)	3.0 (2.0 - 6.0)	-	-
C_{max} , ng/mL	720.2 \pm 275.3	885.7 \pm 294.0	1.26	1.11 - 1.42
AUC _{last} ^b , ng.h/mL	8742 \pm 3714	10890 \pm 4309	1.28	1.15 - 1.43
AUC _∞ ^b , ng.h/mL	10400 \pm 5148	13020 \pm 6056	-	-
$t_{1/2,term}$ ^b , h	46.77 \pm 17.79	48.96 \pm 15.66	-	-
Treatment A (F060 [04H26]) vs. Treatment C (F060 [05A05])				
N	16	15	-	-
t_{max} , h	3.0 (2.0 - 6.0)	3.0 (2.0 - 6.0)	-	-
C_{max} , ng/mL	720.2 \pm 275.3	804.0 \pm 280.8	1.11	0.96 - 1.28
AUC _{last} ^b , ng.h/mL	8742 \pm 3714	9670 \pm 4013	1.10	0.97 - 1.24
AUC _∞ ^b , ng.h/mL	10400 \pm 5148	11450 \pm 5787	-	-
$t_{1/2,term}$ ^b , h	46.77 \pm 17.79	45.68 \pm 12.38	-	-
Treatment A (F060 [04H26]) vs. Treatment D (F016 [03F25])				
N	16	16	-	-
t_{max} , h	3.0 (2.0 - 6.0)	6.0 (3.0 - 6.0)	-	-
C_{max} , ng/mL	720.2 \pm 275.3	647.8 \pm 260.0	0.88	0.75 - 1.03
AUC _{last} ^b , ng.h/mL	8742 \pm 3714	8726 \pm 3697	0.98	0.85 - 1.12
AUC _∞ ^b , ng.h/mL	10400 \pm 5148	10390 \pm 5272	-	-
$t_{1/2,term}$ ^b , h	46.77 \pm 17.79	43.75 \pm 16.63	-	-

N = maximum number of subjects with data.

^a Ratio based on LS means.

^b Accurate determination not possible in all subjects.

Reviewer's Note:

The treatment comparisons in table 1 are outlined in the reverse order i.e., the treatment comparisons should indicate treatment B vs. treatment A, treatment C vs. treatment A, and treatment D vs. treatment A (since treatment A is the reference treatment). However, this is not going to alter the conclusions of the trial since the ratio and 90 % confidence interval of the PK parameters were computed by using the PK parameters of treatment A as the reference treatment (PK parameters of treatment A were used as the denominator in the calculation of ratios and 90 % confidence interval).

Table 2 shows the comparison of the pharmacokinetic parameters of TMC125 after administration of the tablet formulation F016 (batch # 03F25) at a single dose of 400 mg in TMC125-C150 and in trial TMC125-C162 after long term storage at room temperature.

Table 2: Comparison of the pharmacokinetic parameters of TMC125 after administration of the tablet formulation F016 (batch # 03F25) at a single dose of 400 mg in TMC125-C150 and in trial TMC125-C162 after long term storage at room temperature.

Parameter	Mean \pm SD; t_{max} : Median (Range)		Ratio ^a (Test:Reference)	90% CI
	TMC125-C150 Treatment C: TMC125 400 mg (F016 [03F25]) (Reference)	TMC125-C162 Treatment D: TMC125 400 mg (F016 [03F25]) (Test)		
N	11	16	-	-
t_{max} , h	4.0 (2.0 - 6.0)	6.0 (3.0 - 6.0)	-	-
C_{max} , ng/mL	654.5 \pm 228.0	647.8 \pm 260.0	0.97	0.71 - 1.33
AUC _{last} , ng.h/mL	7675 \pm 3677	8726 \pm 3697	1.16	0.80 - 1.67
AUC _∞ ^b , ng.h/mL	8741 \pm 4424	10390 \pm 5272	-	-
$t_{1/2,term}$ ^b , h	40.02 \pm 9.48	43.75 \pm 16.63	-	-

N = maximum number of subjects with data.

^a Ratio based on LS means.

^b Accurate determination not possible in all subjects.

The comparison of the pharmacokinetics of TMC125 administered as formulation F016, Batch 03F25, between the current trial and the earlier trial TMC125-C150 showed that the mean C_{max} and AUC_{last} of TMC125 were comparable in the 2 trials, however, the 90 % CIs of the LS_{means} ratios of these 2 parameters were outside the pre-defined 80 % to 125 % range.

Conclusion

- The mean relative bioavailability (based on comparison of AUC_{last}) of a single dose of 400 mg TMC125 administered as formulation F060 was comparable between Batches 05A05 (large-scale) and 04H26 (small-scale) but was 28 % higher for Batch 05A03 (large-scale), compared to Batch 04H26 (small-scale).
- Long-term storage of formulation F016, Batch 03F25, had no relevant effect on the bioavailability of TMC125 (based on the comparison of exposure parameters between the current trial and trial TMC125-C150). However, due to differences in the amount of active ingredient between F016 (133 mg) and F060 (100 mg) and the differences between TMC125: polymer ratios between the two formulations – for F016 and – for F060), the long term stability data generated with formulation F016 cannot be extrapolated to formulation F060.

Study Number
TMC125-C169

Title

A Phase 1, randomized, open-label, single-dose, 4-period crossover trial in healthy subjects to evaluate the oral bioavailability of TMC125 produced at different scales of production.

Objectives

The primary objective of the trial was to compare the oral bioavailability of the F060 formulation manufactured at full scale in the commercial manufacturing sites (Tests A, B, and C) with the oral bioavailability of the F060 formulation from a batch representative for the Phase III clinical trial materials (reference).

Study Design

Phase I, open label, randomized, 4-period crossover trial in healthy subjects to evaluate the oral bioavailability of single oral doses 4 different batches of the same F060 formulation of TMC125, when administered after a standardized breakfast. 48 subjects were randomized to a sequence of 4 treatments in a 1:1:1:1 ratio, i.e., 12 subjects started with 200 mg TMC125 reference tablets, 12 subjects started with 200 mg TMC125 test A tablets, 12 subjects started with 200 mg TMC125 test B tablets, and 12 subjects started with 200 mg TMC125 test C tablets. The 4 single intakes were separated by a washout period of at least 14 days. In each session, full pharmacokinetic profiles of TMC125 were determined up to 96 hours post-dose.

The dose administered in this trial (single dose of 200 mg using the F060 formulation) was similar to the "unit dose" (200 mg) of TMC125 used in the Phase III trials (200 mg b.i.d.). The dose of 200 mg was also selected for this trial to ensure that TMC125 concentrations are higher than the lower limit of quantification for evaluation of the single dose pharmacokinetics of TMC125.

Investigational Product(s)

Reference

2 tablets of TMC125 100 mg (formulated as F060) from a batch representative of the clinical trial formulation used in the Phase III clinical trials. The tablets were manufactured in Beerse, Belgium, with spray-dried TMC125 powder from _____, and HPMC obtained from _____ manufacturing site in _____. The batch # was 05G19/F060 and the expiry date was January, 2007.

RESULTS

Subject Disposition and Demographics

Out of the 90 subjects screened, 48 subjects were randomized to one of the 24 possible treatment sequences (2 subjects per sequence). 45 subjects completed the trial. 3 subjects discontinued before trial completion; 2 subjects withdrew their consent after the second of the 4 trial sessions (one subject discontinued after receiving test treatment C and test treatment B and one subject discontinued after receiving test treatment C and the reference treatment), and 1 subject had to be withdrawn because of an adverse event in the washout period after the first session of the trial (this subject only received test treatment A).

Table 1 shows the summary of the demographics in the trial.

Table 1: Demographics in Trial TMC125-C169

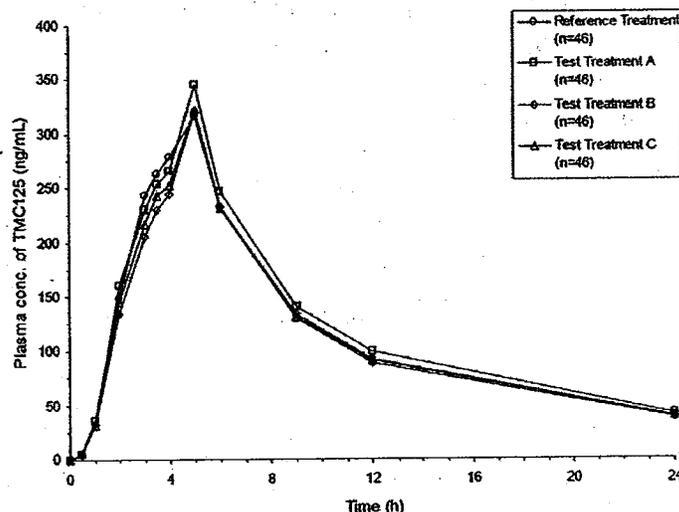
Parameter		All Subjects N = 48
Age at screening, years	Median (range)	28.0 (19-53)
Height, cm	Median (range)	175.0 (162-189)
Weight, kg	Median (range)	72.5 (58-98)
BMI, kg/m ²	Median (range)	23.9 (18-30)
Gender, n (%)	Male/Female	47 (97.9) / 1 (2.1)
Ethnic Origin, n (%)	Black	9 (18.8)
	Caucasian/White	31 (64.6)
	Other	8 (16.7)
Smoker, n (%)	Yes/No	1 / 47

Pharmacokinetics

In addition to the premature discontinuations described in the "Subject Disposition and Demographics" section, one subject vomited twice in the period between 8 and 10 hours after TMC125 intake (as test treatment C). Therefore, the plasma concentrations and pharmacokinetic parameters for this subject for test treatment C were excluded from the descriptive statistics and statistical analysis. Thus, full pharmacokinetic profiles of TMC125 were available for 46 subjects for the reference treatment, 46 subjects for test treatment A, 46 subjects for test treatment B, and 47 subjects for test treatment C (data from 46 subjects were included in the descriptive and statistical analysis).

Fig 1 shows the mean plasma concentration-time profiles of TMC125 after single dose administration of 200 mg TMC125 with food for four different batches of formulation F060.

Fig 1: Mean plasma concentration-time profiles of TMC125 after single dose administration of 200 mg TMC125 with food for four different batches of formulation F060.



The mean plasma concentration-time profiles overlapped for all the 4 treatments. The maximum plasma concentrations of TMC125 were reached 5 hours after dosing for all the 4 profiles. One to three subjects per treatment had quantifiable pre-dose plasma TMC125 concentrations with a maximum measured pre-dose plasma concentration of 3.03 ng/mL. The pre-dose concentrations were all lower than 1 % of the respective C_{max} . These low concentrations were not considered to influence the pharmacokinetic results of the trial. All subjects had quantifiable TMC125 plasma concentrations at the last sampling point of 96 hour in all treatments with a maximum value of 29.0 ng/mL.

Table 2 shows the pharmacokinetic parameters of TMC125 after single dose administration of 200 mg TMC125 with food for four different batches of formulation F060.

Table 2: Pharmacokinetic parameters of TMC125 after single dose administration of 200 mg TMC125 with food for four different batches of formulation F060

PK parameter (mean \pm SD, t_{max} and $t_{1/2}$ median [range])	Reference	Test A	Test B	Test C
n	46	46	46	46
C_{max} , ng/mL	352.5 \pm 104.8	372.2 \pm 90.43	334.7 \pm 96.73	341.5 \pm 91.69
t_{up} , h	0.0 (0.0-3.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)
t_{max} , h	5.0 (2.0-6.0)	5.0 (2.0-5.0)	5.0 (3.0-6.0)	5.0 (2.0-6.0)
AUC _{0-24h}} , ng.h/mL	4129 \pm 1463	4305 \pm 1595	3916 \pm 1614	4011 \pm 1507
AUC _{0-96h}} , ng.h/mL	4528 \pm 1699	4746 \pm 1855	4279 \pm 1848	4459 \pm 1843
$t_{1/2}$, h	32.25 \pm 7.202	33.68 \pm 10.27	31.71 \pm 6.906	33.65 \pm 9.336

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The mean estimates for C_{max} , AUC_{0-last} , and $AUC_{0-\infty}$ were similar across all the treatments. The inter-individual variability (% CV; independent of the treatment) ranged from 24.3 % to 29.7 % for C_{max} , 35.4 % to 41.2 % for AUC_{0-last} , and from 37.5 % to 43.2 % for $AUC_{0-\infty}$.

Table 3 shows the summary of the statistical evaluation of the pharmacokinetic parameters of TMC125 after single dose administration of 200 mg TMC125 (F060) (test treatment A vs. the reference treatment).

Table 3: Summary of the statistical evaluation of the pharmacokinetic parameters of TMC125 after single dose administration of 200 mg TMC125 (F060) (test treatment A vs. the reference treatment)

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI,% ^b	p-value	
	Reference	Test A			Period	Sequence
C_{max} , ng/mL	340.7	365.0	107.1	101.0-113.6	0.0583	0.3068
AUC_{last} , ng.h/mL	3897	4037	103.6	98.77-108.7	0.0068*	0.4132
AUC_{∞} , ng.h/mL	4249	4423	104.1	99.19-109.3	0.0053*	0.4551

^a n = 46 for the Reference treatment and for Test A (spray-dried powder from Geel with Plaquemine HPMC)

^b 90% confidence intervals

* Statistically significant difference

The individual test/reference treatment ratios for C_{max} , AUC_{0-last} , and $AUC_{0-\infty}$ ranged from 69-71 % to 172-180 %, with geometric means of 104 %-108 %.

Table 4 shows the summary of the statistical evaluation of the pharmacokinetic parameters of TMC125 after single dose administration of 200 mg TMC125 (F060) (test treatment B vs. the reference treatment).

Table 4: Summary of the statistical evaluation of the pharmacokinetic parameters of TMC125 after single dose administration of 200 mg TMC125 (F060) (test treatment B vs. the reference treatment)

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI,% ^b	p-value	
	Reference	Test B			Period	Sequence
C_{max} , ng/mL	340.2	323.1	94.97	88.27-102.2	0.4607	0.1915
AUC_{last} , ng.h/mL	3925	3667	93.42	87.82-99.37	0.2715	0.4263
AUC_{∞} , ng.h/mL	4282	3983	93.01	87.44-98.94	0.2342	0.4072

^a n = 46 for the Reference treatment and for Test B (spray-dried powder from Niro with Midland HPMC)

^b 90% confidence intervals

The individual test/reference treatment ratios for C_{max} , AUC_{0-last} , and $AUC_{0-\infty}$ ranged from 47-48 % to 185-213 %, with geometric means of 93 % - 95 %.

Table 5 shows the summary of the statistical evaluation of the pharmacokinetic parameters of TMC125 after single dose administration of 200 mg TMC125 (F060) (test treatment C vs. the reference treatment).

Table 5: Summary of the statistical evaluation of the pharmacokinetic parameters of TMC125 after single dose administration of 200 mg TMC125 (F060) (test treatment C vs. the reference treatment).

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b	p-value	
	Reference	Test C			Period	Sequence
C _{max} , ng/mL	338.7	332.1	98.05	92.28-104.2	0.1230	0.5024
AUC _{last} , ng.h/mL	3912	3802	97.21	91.78-103.0	0.3336	0.6038
AUC _∞ , ng.h/mL	4265	4181	98.03	92.41-104.0	0.3312	0.5974

^a n = 46 for the Reference treatment and for Test C (spray-dried powder from Geel with Midland HPMC)

^b 90% confidence intervals

The individual test/reference treatment ratios for C_{max}, AUC_{0-last} and AUC_{0-∞} ranged from 59-64 % to 171- 177 %, with geometric means of 97 % - 99 %.

For all the treatment comparisons, the 90 % confidence intervals were within the 80-125 % interval for all investigated parameters.

Conclusion

- The point estimates and the 90 % confidence intervals for test vs. reference treatment for C_{max}, AUC_{last} and AUC_{0-∞} were within the 80 % to 125 % range.
- The systemic exposures after oral administration of F060 formulation manufactured at full scale in the commercial manufacturing sites (formulations used in test treatments A, B, and C) is similar to the systemic exposures of the F060 formulation from a batch representative for the Phase III clinical trial materials.

Study Number
TMC125-C170

Title

A Phase 1, open-label, randomized, single-dose, 2-way crossover trial in 4 parallel panels of 12 healthy subjects each, to determine the relative bioavailability of 4 different spray dried formulations of TMC125 compared to the reference formulation TF035.

Objectives

The primary objective of the trial was to determine the relative bioavailability of 4 different spray-dry formulations of TMC125 compared to TMC125 formulated as TF035.

Study Design

Phase I, open label, randomized, single-dose, 2-period crossover trial to compare the bioavailability of 4 spray-dry formulations of TMC125 (**treatment B {F049}**, **treatment C {F060}**, **treatment D {F061}**, and **treatment E {F056}**) with the bioavailability of the **reference formulation (TF035; treatment A)** used in the Phase II clinical trials.

The trial was to be performed in 4 parallel panels of 12 healthy subjects each. Each subject was to receive, in randomized order, 2 single doses of 400 mg TMC125, with a washout period of at least 14 days between the 2 intakes. **Treatments A and B** were administered to **Panel 1**, **Treatments A and C** to **Panel 2**, **Treatments A and D** to **Panel 3** and **Treatments A and E** to **Panel 4**. Subjects entered the investigational site 1 day prior to the study medication intake of each session. All the subjects had fasted for at least 10 hours. In the testing facility, a standardized breakfast consisting of 4 slices of bread, 2 slices of ham or cheese, butter, jelly, and 2 cups of decaffeinated coffee or tea with milk and/or sugar, if desired, was served. The meal was ingested within 30 minutes and the medication was ingested within 10 minutes after completion of breakfast. The subjects remained in the testing facility for 24 hours after receiving each dose (i.e., until the morning of Day 2 of each session). A 96 hour pharmacokinetic profile of TMC125 was determined for each formulation.

Investigational Product(s)

The following investigational products were used in the various treatments in the trial:

Treatment A

TMC125 formulated as **TF035 (reference formulation)**; this formulation is a solid oral dosage form containing 200 mg of TMC125 in HPMC and lactose and produced on large-scale equipment. The batch # of the formulation was D03108 and the expiration date was February 2005.

Treatment B

TMC125 formulated as 'spray-dry 1' (F049); this formulation is a solid oral dosage form containing 133 mg of TMC125 — spray dried in combination with HPMC and microcrystalline cellulose (222.2 mg TMC125/g powder), colloidal anhydrous silica, croscarmellose sodium, magnesium stearate, lactose monohydrate and ———. The batch # of the formulation was 04D13 and the expiration date was November 2004.

Treatment C

TMC125 formulated as 'spray-dry 2' (F060); this formulation is a solid oral dosage form containing 100 mg of TMC125 — spray dried in a fixed ratio with HPMC and microcrystalline cellulose, excipients and manufacturing aids. The batch # of the formulation was 04H26 and the expiration date was November 2004.

Treatment D

TMC125 formulated as 'spray-dry 3' (F061); this formulation is a solid oral dosage form containing 133 mg of TMC125 — spray dried in a fixed ratio with HPMC and microcrystalline cellulose, excipients and manufacturing aids. The batch # of the formulation was 04H31 and the expiration date was November 2004.

Treatment E

TMC125 formulated as 'spray-dry 4' (F056); this formulation is a solid oral dosage form containing 100 mg of TMC125 — spray dried in a fixed ratio with HPMC and microcrystalline cellulose, excipients and manufacturing aids (coated version of F060). The batch # of the formulation was 04I02 and the expiration date was December 2004.

Assay Methods

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

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. The actual sampling time was checked for major aberrations. In case major aberrations (> 10 % deviations from the scheduled

times) occurred for a subject, the actual sampling times were used in the pharmacokinetic analysis for that subject and treatment.

Statistical Analysis

The statistical analyses were performed using treatment B, C, D, and E as test and treatment A as reference. The primary pharmacokinetic parameters were C_{max} , AUC_{last} , and $AUC_{0-\infty}$ on the logarithmic scale. $AUC_{0-\infty}$ was not used as a primary pharmacokinetic parameter if more than half of the $AUC_{0-\infty}$ estimates could not be accurately computed. The least squares means of the primary parameters for each treatment were estimated with a linear mixed effects model, controlling for treatment, sequence and period as fixed effects and subjects nested in sequence as a random effect. A 90 % confidence interval was constructed around the difference between the least squares means of the test and reference treatments. The difference between the least square means and the 90 % confidence intervals were retransformed to the original scale. The period effects were considered significant at the 5 % level and the sequence effects were considered significant at the 10 % level.

RESULTS

Subject Disposition and Demographics

Out of the 96 subjects screened, 45 subjects were randomized to the four panels. 11 subjects were randomized to panel 1; 12 subjects were randomized to panel 2, 11 subjects were randomized to panel 3, and 11 subjects were randomized to panel 4. One subject in panel 2 was withdrawn from the trial due to non-compliance with the protocol and did not receive the second single dose (using TF035); the subject only received the first dose (using F060). All the remaining subjects completed all the assessments.

Table 1 shows the summary of the demographics in the trial.

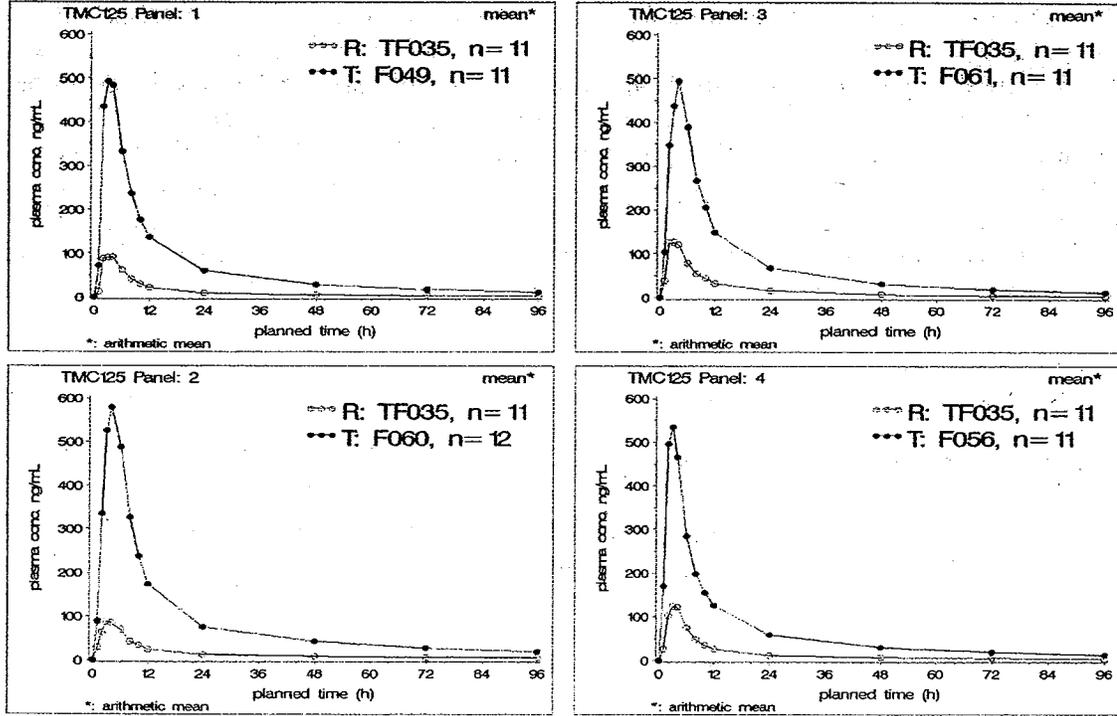
Table 1: Demographics in Trial TMC125-C170

Parameter	Panel 1 N = 11	Panel 2 N = 12	Panel 3 N = 11	Panel 4 N = 11	All Subjects N = 45
Age, years					
Median (range)	45.0 (21 - 55)	40.5 (18 - 55)	31.0 (19 - 54)	39.0 (18 - 55)	39.0 (18 - 55)
Height, cm					
Median (range)	179 (168 - 194)	179 (159 - 195)	176 (169 - 199)	179 (158 - 191)	179 (158 - 199)
Weight, kg					
Median (range)	77.0 (60 - 104)	74.5 (62 - 90)	70.0 (64 - 105)	75.0 (64 - 99)	74.0 (60 - 105)
BMI, kg/m ²					
Median (range)	22.9 (21 - 31)	23.8 (19 - 28)	22.6 (21 - 27)	25.5 (19 - 30)	23.4 (19 - 31)
Sex, n (%)					
Male	10 (90.9)	7 (58.3)	9 (81.8)	8 (72.7)	34 (75.6)
Ethnic Origin, n (%)					
White	11 (100.0)	12 (100.0)	11 (100.0)	9 (81.8)	43 (95.6)
Type of Smoker, n (%)					
Light smoker	0 (-)	2 (16.7)	4 (36.4)	4 (36.4)	10 (22.2)

Pharmacokinetics

Fig 1 shows the mean concentration-time profile of TMC125 in various panels.

Fig 1: Mean concentration-time profile of TMC125 in various panels.



Visual inspection of the mean plasma concentration of the test formulations (treatments B, C, D, and E) were higher than the mean plasma concentrations of the reference formulation (Treatment A).

Table 2 shows the pharmacokinetic parameters of TMC125 across different treatments and panels.

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Table 2: Pharmacokinetic parameters of TMC125 across different treatments and panels.

Panel 1	Treatment B (F049)	Treatment A (TF035)
n	11	11
C _{max} (ng/mL)	530 ± 254	103 ± 49
AUC _{last} (ng.h/mL)	6535 ± 3283	1080 ± 598
AUC _∞ (ng.h/mL)	7132 ± 3967	1198 ± 659
t _{max} (h)	3.0 [2.0-4.0]	3.0 [2.0-4.0]
t _{1/2} (h)	29.6 ± 8.3	25.3 ± 12.9
Panel 2	Treatment C (F060)	Treatment A (TF035)
n	12	11
C _{max} (ng/mL)	638 ± 213	100 ± 77
AUC _{last} (ng.h/mL)	8482 ± 2823	1270 ± 1056
AUC _∞ (ng.h/mL)	9936 ± 4531	1540 ± 1346
t _{max} (h)	4.0 [2.0-6.0]	4.0 [2.0-8.0]
t _{1/2} (h)	39.3 ± 16.9	31.2 ± 22.8
Panel 3	Treatment D (F061)	Treatment A (TF035)
n	11	11
C _{max} (ng/mL)	512 ± 140	146 ± 108
AUC _{last} (ng.h/mL)	6953 ± 2184	1506 ± 1380
AUC _∞ (ng.h/mL)	7571 ± 2676	1606 ± 1427
t _{max} (h)	4.0 [2.0-6.0]	3.0 [2.0-6.0]
t _{1/2} (h)	29.8 ± 10.7	19.5 ± 8.1
Panel 4	Treatment E (F056)	Treatment A (TF035)
n	11	11
C _{max} (ng/mL)	560 ± 213	135 ± 60
AUC _{last} (ng.h/mL)	6458 ± 3536	1388 ± 830
AUC _∞ (ng.h/mL)	7177 ± 4321	1549 ± 950
t _{max} (h)	2.0 [2.0-4.0]	3.0 [2.0-4.0]
t _{1/2} (h)	32.5 ± 8.9	27.9 ± 15.1

For all the test formulations (**treatments B, C, D, and E**), the mean C_{max}, AUC_{0-t}, and AUC_{0-∞} were higher compared to the reference formulation (**treatment A**). The t_{max} and t_{1/2} were approximately the same across all the formulations. The PK parameters showed considerable inter subject variability for all the treatments. The coefficient of variation for the AUC_{0-∞} across the four panels ranged from 55 % to 89 % for the reference formulation versus 35 % to 61 % for the test formulations.

An exploratory analysis of the individual data (fig 2) showed that subjects with relatively low concentrations of TMC125 after administration of the reference formulation (TF035) obtained relatively high estimates for the ratio of TMC125 C_{max} and AUC_{last} for the test/reference formulation. In other words, the plasma concentrations of TMC125 were improved with the test formulations if the plasma concentrations obtained with the reference formulation were low in any given individual.

Fig 2: Ratio of AUC_{last} of TMC125 after administration of the test formulation (F049, F060, F061, or F056) and reference formulation TF035 as a function of the AUC_{last} for TMC125 when administered as reference formulation TF035.

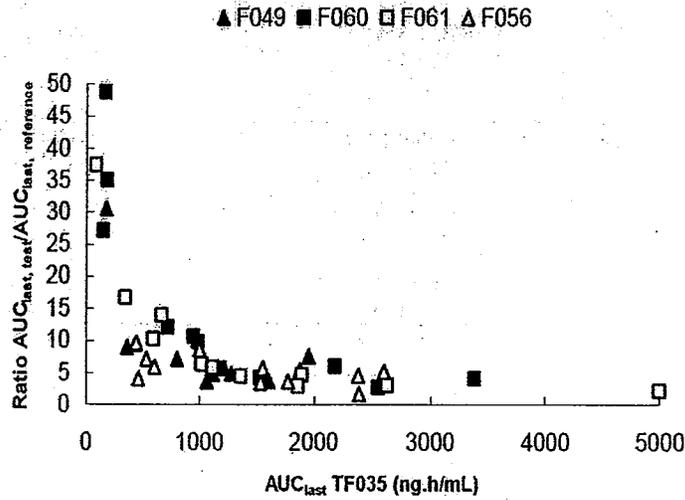


Table 3 shows the results of the statistical comparison of the pharmacokinetic parameters of TMC125 between treatments B, C, D, and E (test treatments) and treatment A (reference treatment).

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Table 3: Statistical comparison of the pharmacokinetic parameters of TMC125 between treatments B, C, D, and E (test treatments) and treatment A (reference treatment).

Panel 1								
Parameter	n	Least squares means				p-value		
		Treatment B	Treatment A	Ratio B/A	90% CI*	Treatment	Period	Sequence
C_{max} (ng/mL)	11/11	484	90	539	376 - 772	<.0001	0.8001	0.7710
AUC_{0-24} (ng·h/mL)	11/11	5981	882	678	479 - 959	<.0001	0.9314	0.8121
$AUC_{0-\infty}$ (ng·h/mL)	11/11	6420	985	652	471 - 903	<.0001	0.8518	0.8944
Panel 2								
Parameter	n	Least squares means				p-value		
		Treatment C	Treatment A	Ratio C/A	90% CI*	Treatment	Period	Sequence
C_{max} (ng/mL)	12/11	606	72	847	533 - 1348	<.0001	0.1121	0.0760
AUC_{0-24} (ng·h/mL)	12/11	8054	860	937	603 - 1455	<.0001	0.0550	0.0351
$AUC_{0-\infty}$ (ng·h/mL)	12/11	9172	1027	893	579 - 1376	<.0001	0.0558	0.0265
Panel 3								
Parameter	n	Least squares means				p-value		
		Treatment D	Treatment A	Ratio D/A	90% CI*	Treatment	Period	Sequence
C_{max} (ng/mL)	11/11	490	103	475	317 - 714	<.0001	0.2207	0.2569
AUC_{0-24} (ng·h/mL)	11/11	6566	943	696	440 - 1101	<.0001	0.2088	0.2222
$AUC_{0-\infty}$ (ng·h/mL)	11/11	7054	1054	669	438 - 1022	<.0001	0.2332	0.1862
Panel 4								
Parameter	n	Least squares means				p-value		
		Treatment E	Treatment A	Ratio E/A	90% CI*	Treatment	Period	Sequence
C_{max} (ng/mL)	11/11	517	123	418	328 - 534	<.0001	0.7812	0.8650
AUC_{0-24} (ng·h/mL)	11/11	5576	1133	492	371 - 653	<.0001	0.9830	0.8416
$AUC_{0-\infty}$ (ng·h/mL)	11/11	6068	1264	480	364 - 633	<.0001	0.9672	0.8932

*90% confidence interval of ratio

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Statistically significant treatment effects were found for all parameters in all panels, i.e., between all test formulations and the reference formulation. In addition, statistically significant sequence effects (at the 10 % level) were seen only in Panel 2 (i.e. for Treatments C and A) for AUC_{0-24} , $AUC_{0-\infty}$, and C_{max} . This sequence effect might indicate a carry-over effect, as some pre-dose concentrations above the LLOQ were observed in the second period after the first period with Treatment C. In 2 subjects, pre-dose concentrations were below 5 % of the C_{max} and in 1 subject, the pre-dose concentration was 7.6 % of the C_{max} . This carry-over is not expected to alter the conclusions of the trial. There were no other pre-dose concentrations above the LLOQ.

Conclusion

- The test formulations, manufactured by spray-drying technology (F049, F060, F061, and F056) showed higher oral bioavailability relative to the reference formulation (TF035).
- Based on the results of this trial, formulation F060 was chosen for further use in trials with healthy and HIV-1 infected subjects.

Fig 1: Mean plasma concentration-time profiles of TMC125 after administration of a single, 200 mg dose of TMC125 using the two test batches of the powder formulation and the reference tablet formulation.

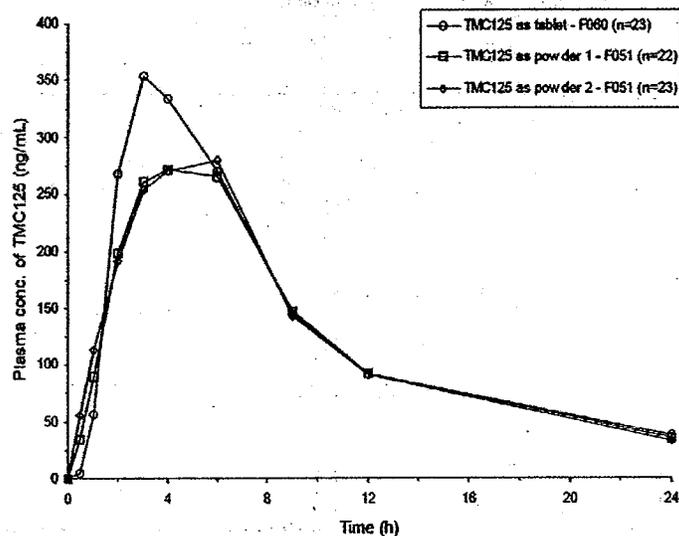


Table 1 shows the pharmacokinetic parameters of TMC125 after administration of the two test batches of the powder formulation F051 (TMC125 in HPMC, spray dried) and the reference tablet formulation F060 (TMC125 in HPMC, spray dried) as a single 200 mg dose.

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Study Number
TMC125-C173

Title

A Phase 1, randomized, open-label, single dose, 3-period crossover trial in healthy subjects to evaluate the relative oral bioavailability of the — and the 100 mg tablets of TMC125.

Objective

The secondary objective of the trial was to compare the oral bioavailability of a single dose of 100 mg TMC125 administered as a 100 mg tablet (formulation F060) in solid form, or a 100 mg tablet (formulation F060) dispersed in water before administration.

Study Design

Phase 1, open-label, randomized, 3-period crossover trial in healthy subjects. All subjects were to receive 100 mg TMC125 on three separate occasions as one of the following three treatments:

Treatment A (reference): 1 tablet of TMC125 100 mg, formulation F060.

Treatment B (test 1): _____

Treatment C (test 2): 1 tablet of TMC125 100 mg, formulation F060, dispersed in 100 mL water.

The subjects entered and stayed in the testing facility the night before each dosing and stayed in the testing facility for at least 24 hours after receiving TMC125. The three single dose intakes were separated by a washout period of at least 14 days. In each session, full pharmacokinetic profiles of TMC125 were determined up to 96 hours post dose. All intakes of TMC125 were under fed conditions (standard breakfast).

The tablets for **treatment A** and **treatment B** were taken with approximately 240 mL of water. The tablet for **treatment C** was dispersed in 100 mL of water by stirring until a homogenous suspension was obtained. After drinking the entire solution, the container had to be rinsed twice with 70 mL of water each time. In total, approximately 240 mL of water needed to be consumed.

Investigational Product(s)

TMC125 was formulated as 100 mg tablets (formulation F060) and for oral administration.

The tablets were composed of, respectively, 100 mg TMC125 spray dried in a fixed ratio with hydroxypropylmethylcellulose and microcrystalline cellulose, croscarmellose sodium, magnesium stearate, and lactose monohydrate. The batch # of reference formulation, test 1 formulation, and test 2 formulation were 6FL6Z, 6GL41, and 6FL6Z respectively.

Assay Methods

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

Pharmacokinetics and Statistical Data Analysis

Pharmacokinetic Analysis

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

Statistical Analysis

The statistical analysis was performed by comparing test 1 treatment versus reference treatment and test 2 treatment versus reference treatment. The primary pharmacokinetic parameters were C_{max} , AUC_{last} , and AUC_{∞} on the logarithmic scale. The AUC_{∞} was to be rejected as a primary pharmacokinetic parameter for a treatment if more than half the subjects did not have a reliable value for the treatment.

RESULTS

Subject Disposition and Demographics

Out of the 83 subjects screened, 37 subjects were randomized to one of the 6 possible treatment sequences. 4 subjects discontinued before trial completion (2 subjects withdrew their consent after session 1 (treatment A), 1 subject was non-compliant and was withdrawn after session 2 (treatment A) and 1 subject had to be withdrawn before of an adverse event after session 2 (treatment B).

Table 1 shows the demographics in the trial.

Table 1: Demographics in trial TMC125-C173

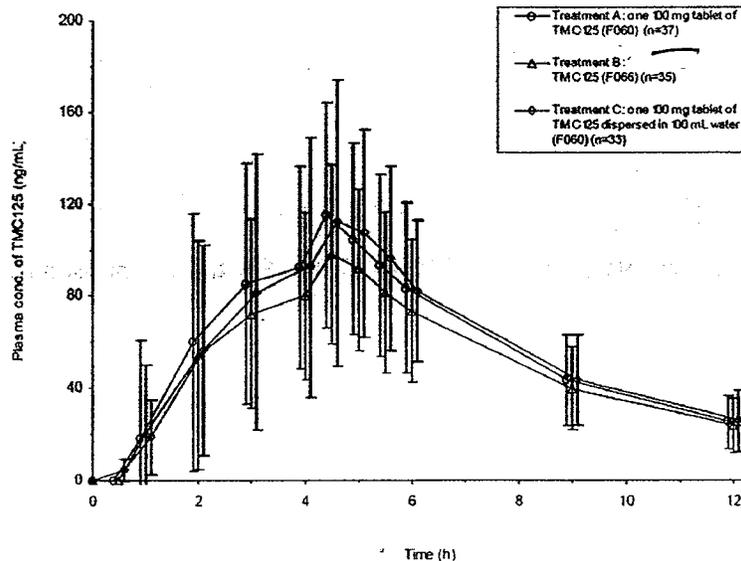
Parameter	All Subjects N = 37
Age, years	39.0
Median (range)	(22-56)
Height, cm	177.0
Median (range)	(160-194)
Weight, kg	80.0
Median (range)	(55-105)
BMI, kg/m ²	25.8
Median (range)	(19.7-29.7)
Sex, n (%)	
Male	30 (81.1)
Female	7 (18.9)
Ethnic Origin, n (%)	
White	35 (94.6)
Hispanic	1 (2.7)
Other	1 (2.7)

Pharmacokinetics

Full pharmacokinetic profiles were available from 37 subjects who completed **treatment A**, 35 subjects who completed **treatment B**, and 33 subjects who completed **treatment C**.

Fig 1 shows the mean plasma concentration-time profiles of TMC125 after administration as tablet F060 or F066 and as tablet F060 dispersed in 100 mL water.

Fig 1: Mean plasma concentration-time profiles of TMC125 after administration as tablet F060 or F066 and as tablet F060 dispersed in 100 mL water



After intake of a single 100 mg dose, the mean plasma concentration-time profiles of TMC125 were comparable between the tablet formulations **F060** and **F066**, and between administration of **F060** in the solid form and dispersed form. At 96 hours after dosing,

the plasma concentrations were above the LLOQ for 18/36 subjects who received tablet F060, 18/34 subjects having received tablet F066, and 14/33 subjects who received dispersed tablet F060. The inter-subject variability (% CV) was high (231 % at 1 hour and 157 % at 96 hours) when plasma concentrations were low (at the beginning and end of the plasma concentration-time profiles).

Table 2 shows the mean pharmacokinetic parameters of TMC125 after administration as as tablet F060 or F066 in solid form and as a tablet F060 dispersed in 100 mL water.

Table 2: Mean pharmacokinetic parameters of TMC125 after administration as as tablet F060 or F066 in solid form and as a tablet F060 dispersed in 100 mL water

Pharmacokinetics of TMC125 (mean ± SD, t_{max} : median [range])	Treatment A: one 100 mg tablet of TMC125 (F060) (Reference)	Treatment B: of TMC125 (F066) (Test 1)	Treatment C: one 100 mg tablet of TMC125 dispersed in 100 mL water (F060) (Test 2)
n	37	35	33
t_{lag} , h	0.5 (0.0 - 2.0)	0.5 (0.0 - 2.0)	0.0 (0.0 - 2.0)
t_{max} , h	4.5 (1.0 - 9.0)	4.5 (2.0 - 6.0)	4.5 (2.0 - 5.5)
C_{max} , ng/mL	130.3 ± 50.13	112.6 ± 43.86	130.7 ± 61.69
AUC _{last} , ng.h/mL	1241 ± 641.5	1126 ± 542.1	1219 ± 712.2
AUC _∞ , ng.h/mL	1412 ± 885.0	1286 ± 751.3	1409 ^a ± 1109 ^a
$t_{1/2term}$, h	27.92 ± 15.23	29.17 ± 18.09	27.94 ^a ± 16.72 ^a

^a Accurate determination not possible

For test treatment 2 (tablet F060 dispersed in water), more than 50 % of the individual values of AUC_∞, λ_z , and $t_{1/2,term}$ could not be determined accurately. Therefore, AUC_{last} (instead of AUC_∞) was used as the primary pharmacokinetic parameter. The dispersion of the tablet F060 in 100 mL water prior to oral administration did not alter the extent of exposure to TMC125. The maximum concentrations of TMC125 were reached 4.5 hours after dosing, irrespective of the mode of administration for formulation F060.

The geometric means (and range) of the individual C_{max} and AUC_{last} treatment ratios between tablet F066 (test 1) and tablet F060 (reference) were, respectively, 85.20 % (34.54 to 133.1 %), and 91.08 % (52.01 to 165.7 %). For the comparison between tablet F060 in dispersed (test 2) and F060 as solid form (reference) these values were, respectively, 95.12 % (48.48 % to 148.3 %) and 96.48 % (55 % to 153.1 %).

Table 3 shows the summary of the statistical analysis of the single dose pharmacokinetic parameters of TMC125 administered as tablet formulation F060 (1X 100 mg) and F066

Table 3: Summary of the statistical analysis of the single dose pharmacokinetic parameters of TMC125 administered as tablet formulation F060 (1 X 100 mg) and F066 / —

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI,% ^b	—	
	one 100 mg tablet of TMC125 (F060) (Reference)	of TMC125 (F066) (Test 1)			Period	Sequence
C _{max} , ng/mL	121.2	103.5	85.40	78.08 - 93.40	0.7978	0.2330
AUC _{last} , ng.h/mL	1101	1004	91.18	84.88 - 97.95	0.6757	0.1386
AUC _∞ , ng.h/mL	1226	1124	91.73	84.93 - 99.06	0.6411	0.1456

^a n=37 for Reference and n=35 for Test 1

^b 90% confidence intervals.

The LS_{means} of C_{max}, AUC_{last}, and AUC_∞ of TMC125 decreased by 15 %, 9 %, and 8 %, respectively, when TMC125 was administered as — (as formulation F066; test treatment) as compared to when TMC125 was administered as 1 X 100 mg tablet (as formulation F060; reference treatment).

Table 4 shows the summary of the statistical analysis of the single dose pharmacokinetic parameters of TMC125 administered either as solid form (as formulation F060; reference treatment) or as a tablet dispersed in water (as formulation F060; test treatment).

Table 4: Summary of the statistical analysis of the single dose pharmacokinetic parameters of TMC125 administered either as solid form (as formulation F060; reference treatment) or as a tablet dispersed in water (as formulation F060; test treatment)

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI,% ^b	p-value		
	one 100 mg tablet of TMC125 (F060) (Reference)	one 100 mg tablet of TMC125 dispersed in 100 mL water (F060) (Test 2)			Treatment	Period	Sequence
C _{max} , ng/mL	121.2	115.5	95.33	87.78 - 103.5	0.3328	0.6649	0.4391
AUC _{last} , ng.h/mL	1100	1062	96.54	90.48 - 103.0	0.3632	0.2744	0.3298

^a n=37 for reference and n=33 for test 2

^b 90% confidence intervals.

The ratio of the LS_{means} of C_{max} and AUC_{last} were not significantly altered (all changes < 10 %) when TMC125 was administered as a tablet dispersed in water (as formulation F060; test treatment) or as a solid form (as formulation F060; reference treatment).

Pharmacokinetics Results Summary

- The ratio of the LS_{means} of C_{max}, AUC_{last}, and AUC_∞ of TMC125 decreased by 15 %, 9 %, and 8 %, respectively, when TMC125 was administered as —

— as formulation **F066; test treatment**) as compared to when TMC125 was administered as 1 X 100 mg tablet (as formulation **F060; reference treatment**).

- The ratio of the LS_{means} of C_{max} and AUC_{last} were not significantly altered (all changes < 10 %) when TMC125 was administered as a tablet dispersed in water (as formulation **F060; test treatment**) or as a solid form (as formulation **F060; reference treatment**).

Conclusion

TMC125, dispersed in water, is expected to provide similar systemic exposures as TMC125, swallowed as a tablet.

**APPEARS THIS WAY
ON ORIGINAL**

Study Number
TMC125-C228

Title

A Phase 1, randomized, open-label, multiple-dose, crossover trial in HIV-1 infected subjects to evaluate the relative bioavailability of TMC125 as a spray-dry formulation (F060) compared to the reference formulation TF035.

Objectives

The primary objective of the trial was to evaluate the oral bioavailability of TMC125 administered as formulation F060 and formulation TF035 after multiple dosing in HIV-1 infected subjects.

Study Design

Phase I, randomized, open label, crossover trial. 32 HIV-1 infected subjects (randomized in a 1:1 ratio to start with either F060 or TF035) were to be included in the trial. To be eligible for the trial, the subjects had to have at least 3 months of documented NNRTI experience, a confirmed plasma viral load of < 50 HIV-1 RNA copies/mL, and a current ARV regimen that included LPV/rtv, SQV/rtv or SQV/LPV/rtv and at least 1 NRTI with or without ENF. The subjects received 100 mg TMC125 b.i.d. as formulation F060 for 7 days with an additional morning intake on day 8 in one session, and 800 mg TMC125 b.i.d. as formulation TF035 for 7 days with an additional morning intake on day 8 in the other session. The two sessions were separated by a washout period of 14 days.

On day 1 and day 8 of each session, a standardized breakfast was served at the testing unit, consisting of 4 slices of bread, 2 slices of ham or cheese, butter, jelly and 2 cups of decaffeinated coffee or tea with milk and/or sugar. This meal was to be ingested within 30 minutes and the study medication was to be ingested within 10 minutes after completion of the standardized breakfast.

After having completed the first two sessions, the subjects were offered to participate in session 3 of the trial. In session 3, all subjects received 200 mg TMC125 mg b.i.d. as formulation F060 for 7 days with an additional morning intake on day 8.

A 12-hour pharmacokinetic profile was determined on day 1 and day 8 of session 1 and session 2. A 12-hour pharmacokinetic profile was determined on day 1 of session 3 and a 96-hour pharmacokinetic profile was determined on day 8 of session 3.

Discussion of Trial Design and Selection of Dose(s) in the Trial

Based on the results of trial TMC125-C141, a 9-fold higher systemic exposure (after administration of F060 as compared to TF035 when the same dose of each formulation was used) was anticipated. Therefore, a dosing regimen of 100 mg b.i.d. using

formulation **F060** was selected as test treatment in order to obtain comparable exposures between the two formulations (100 mg b.i.d. **F060** and 800 mg b.i.d. **TF035**). However, preliminary pharmacokinetic parameters from **session 1** and **session 2** showed that after 8 days of treatment with TMC125 **F060** and **TF035** formulations, the ratio of $AUC_{12\text{hour}}$ after administration of 100 mg b.i.d. as **F060** compared to administration of 800 mg b.i.d. **TF035** was 54 %. Assuming dose proportionality between systemic exposures after administration of 100 mg b.i.d. and 200 mg b.i.d. as **F060**, the applicant amended the protocol to add **session 3** in which all subjects received 200 mg TMC125 mg b.i.d. as formulation **F060** for 7 days with an additional morning intake on **day 8**. Further, by adding this session, the same subjects received TMC125 800 mg b.i.d. as formulation **TF035**, TMC125 100 mg b.i.d. as formulation **F060**, and TMC125 200 mg b.i.d. as formulation **F060**, thereby enabling intra subject comparisons between the three treatment arms.

TMC125 was dosed for 7 days, with a morning administration on **day 8** since previous multiple dose pharmacokinetic trials have shown that steady-state was reached within 7 days. Based on TMC125 elimination half life of 30-40 hours, a washout period of 14 days between the various sessions was considered sufficient to avoid carry over effects.

Investigational Product(s)

Reference Formulation

The reference formulation, **TF035**, was a tablet containing 200 mg TMC125 in hydroxypropylmethylcellulose — lactose —
The batch # of the formulation was D03108 and the expiry date was July 2005.

Test Formulation

The test formulation, **F060**, was a tablet containing 100 mg TMC125 — spray-dried in a fixed ratio with hydroxypropylmethylcellulose and microcrystalline cellulose, excipients, and manufacturing aids. The batch # of the formulation was 05A05/F060 and the expiry date was July 2005 (January 2006 for **session 3**).

Assay Methods

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

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. Statistical analysis for demographic data, safety, and tolerability was done using SAS® version 8.2. Based on the individual plasma concentration-time data and using the scheduled sampling times, the standard pharmacokinetic parameters were calculated. The actual sampling time was checked for major aberrations. In case major aberrations (> 10 % deviations from the scheduled times) occurred for a subject, the actual sampling times were used in the pharmacokinetic analysis for that subject and treatment.

Statistical Analysis

The statistical analyses were performed using formulation **F060** as the test formulation and **TF035** as the reference formulation. The primary pharmacokinetic parameters were C_{max} , C_{min} (on day 8 only), and AUC_{12h} . All available observations for the various treatments were included in the statistical analysis. The LS_{means} of the primary parameters for each treatment were estimated with a linear mixed effects model, controlling for period and randomization group as fixed effects and subject (nested in treatment group) as a random effect. A 90 % CI was constructed around the difference between the LS_{means} of the test treatment and reference treatment.

RESULTS

Subject Disposition and Demographics

Out of the 42 subjects screened, 33 subjects were randomized to the two panels and started treatment. 9 subjects were not randomized for the following reasons: back-up subjects (n = 6), did not meet the selection criteria (n = 2), and withdrawal of consent (n = 1).

Table 1 shows the summary of the demographics in the trial.

Table 1: Demographics in Trial TMC125-C228

Demographic Parameter	Panel I N=15	Panel II N=18	All Subjects N=33
Age, years	43.0	41.0	42.0
Median (range)	(30 - 55)	(32 - 55)	(30 - 55)
Height, cm	178.0	179.0	178.0
Median (range)	(170 - 191)	(168 - 188)	(168 - 191)
Weight, kg	71.0	74.0	72.0
Median (range)	(62 - 112)	(62 - 102)	(62 - 112)
BMI, kg/m ²	22.4	23.4	23.1
Median (range)	(20 - 33)	(19 - 29)	(19 - 33)
Gender, n (%)			
Male	15 (100)	18 (100)	33 (100)
Ethnic origin, n (%)			
White/Caucasian	15 (100.0)	17 (94.4)	32 (97.0)
Black	0	1 (5.6)	1 (3.0)
Type smoker, n (%)			
Nonsmoker	5 (33.3)	9 (50.0)	14 (42.4)
Light smoker	3 (20.0)	2 (11.1)	5 (15.2)
Moderate smoker	5 (33.3)	5 (27.8)	10 (30.3)
Heavy smoker	2 (13.3)	2 (11.1)	4 (12.1)

Pharmacokinetics

Out of the 33 subjects randomized, 31 subjects completed the trial and 2 subjects (1 subject in each panel) discontinued before trial completion. 1 subject dropped out in the washout period after session 1 (100 mg b.i.d. F060) due to an SAE {asthma} and 1 subject was unable to continue due to work commitments and discontinued participation in the trial in the washout period of session 2 (after receiving 100 mg b.i.d. F060 and 800 mg b.i.d. TF035). Therefore, full pharmacokinetic profiles were available from 33 subjects who received the test treatment (100 mg TMC125 b.i.d. on days 1 through 7 and a single morning intake on day 8 as F060) and 32 subjects who received the reference treatment (800 mg TMC125 b.i.d. on days 1 through 7 and a single morning intake on day 8 as TF035).

27 subjects participated in the optional session 3 (13 subjects in panel 1 and 14 subjects in panel 2). 6 subjects (5 subjects who participated in session 1 and session 2 and 1 subject who discontinued in the washout period of session 1) did not participate in session 3 of the trial. All subjects entering session 3 completed the trial.

Fig 1 shows the mean plasma concentration-time profiles on day 1 after oral administration of TMC125 as 800 mg b.i.d. TF035 (reference treatment) and 100 mg b.i.d. F060 (test treatment).

Fig 1: Mean plasma concentration-time profiles on day 1 after oral administration of TMC125 as 800 mg b.i.d. TF035 (reference treatment) and 100 mg b.i.d. F060 (test treatment)

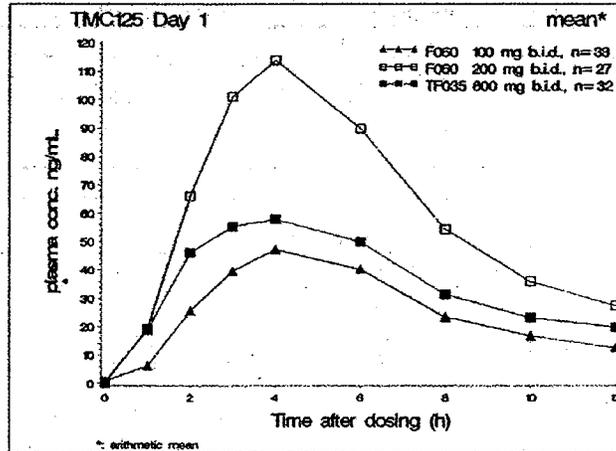
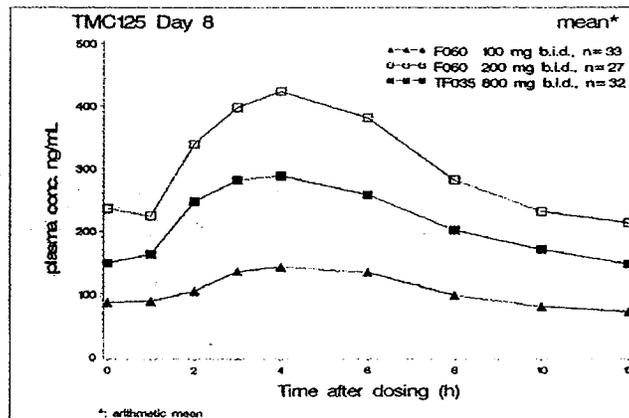


Fig 2 shows the mean plasma concentration-time profiles on day 8 after oral administration of TMC125 as 800 mg b.i.d. TF035 (reference treatment) and 100 mg b.i.d. F060 (test treatment).

Fig 2: Mean plasma concentration-time profiles on day 8 after oral administration of TMC125 as 800 mg b.i.d. TF035 (reference treatment) and 100 mg b.i.d. F060 (test treatment)



The mean plasma concentrations of TMC125 were lower after administration of the 100 mg b.i.d. TMC125 as formulation F060 and higher after administration of the 200 mg TMC125 formulation as formulation F060 compared to 800 mg b.i.d. TMC125 administered as formulation TF035 (reference treatment). The mean pre-dose concentrations (data not shown) increased from day 6 through day 8, however, this may be in part, due to the high inter-individual variability in the pre-dose concentrations and is not reflective of non-achievement of steady state.

Table 2 shows the pharmacokinetic parameters of TMC125 across various treatments.

Table 2: Pharmacokinetic parameters of TMC125 across various treatments

Pharmacokinetics of TMC125 mean \pm SD, t_{max} : median (range)	100 mg TMC125 Test (F060)	800 mg TMC125 Reference (TF035)	200 mg TMC125 Test (F060)
Day 1			
N	33	32	27
t_{max} , h	4.00 (2.00-6.00)	4.00 (2.00-8.00)	4.00 (3.00-8.00)
C_{max} , ng/mL	54.9 \pm 54.0	70.6 \pm 72.7	125.9 \pm 109.6
AUC_{12h} , ng.h/mL	312 \pm 331	434 \pm 437	745 \pm 660
Day 8			
N	33	32	27
t_{max} , h	4.00 (0.00-6.00)	4.00 (0.00-6.00)	4.00 (2.00-8.00)
C_{0h} , ng/mL	86.3 \pm 84.5	148.8 \pm 119.3	235.9 \pm 163.1
C_{min} , ng/mL	59.9 \pm 63.8	125.8 \pm 116.4	184.7 \pm 128.1
C_{max} , ng/mL	170.9 \pm 99.9	318.8 \pm 245.8	451.3 \pm 232.3
AUC_{12h} , ng.h/mL	1284 \pm 958	2607 \pm 2135	3713 \pm 2069
$C_{ss,av}$, ng/mL	107.0 \pm 79.8	217.3 \pm 177.9	309.5 \pm 172.4
FI, %	125.2 \pm 47.7	94.9 \pm 35.5	95.3 \pm 31.4

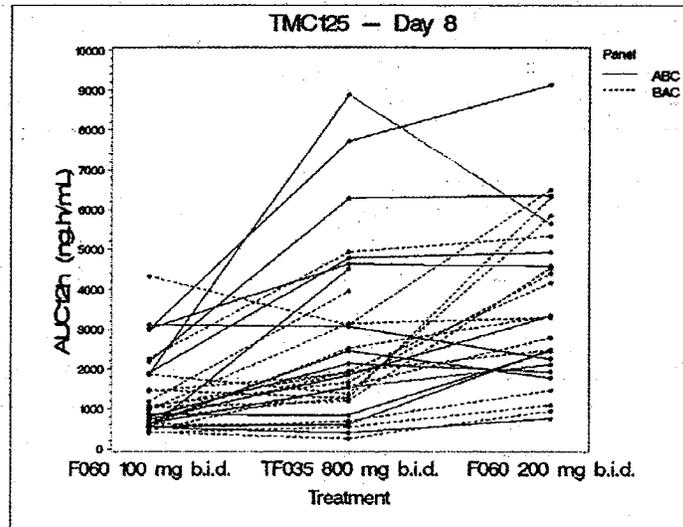
FI (%): Percent Fluctuation (variation between maximum and minimum concentrations at steady state), calculated as $100 \times [(C_{max} - C_{min}) / C_{ss,ave}]$

All pharmacokinetic parameters of TMC125 after single and multiple dose administration were lower for the 100 mg TMC125 (F060) treatment compared to the 800 mg TMC125 (TF035) treatment, and all pharmacokinetic parameters were higher for the 200 mg TMC125 (F060) treatment compared to the 800 mg TMC125 (TF035) treatment. The median t_{max} was 4 hours for all treatments. The FI was the highest for 100 mg TMC125 (F060) treatment and comparable for the 2 other treatments.

There was significant variability (higher with formulation TF035 as compared to F060) in the pharmacokinetics of TMC125. The % CV for AUC_{12h} on day 8 after administration of 800 mg b.i.d. TF035, 100 mg b.i.d. F060, and 200 mg b.i.d. F060 was 82 %, 75 %, and 56 %, respectively.

Fig 3 shows the comparison of AUC_{12h} on day 8 after administration of TMC125 800 mg b.i.d. (using TF035), TMC125 100 mg b.i.d. (using F060), and TMC125 200 mg b.i.d. (using F060).

Fig 3: Comparison of AUC_{12h} on day 8 after administration of TMC125 800 mg b.i.d. (using TF035), TMC125 100 mg b.i.d. (using F060), and TMC125 200 mg b.i.d. (using F060)



Exploratory Analysis (Conducted by Applicant)

An exploratory analysis showed a trend for higher individual ratios of AUC_{12h} for formulation F060 versus formulation TF035 in subjects with lower values of AUC_{12h} for formulation TF035, i.e., relatively higher plasma concentrations of TMC125 were achieved when administered as formulation F060 in subjects where low plasma concentrations of TMC125 were found after the administration of formulation TF035.

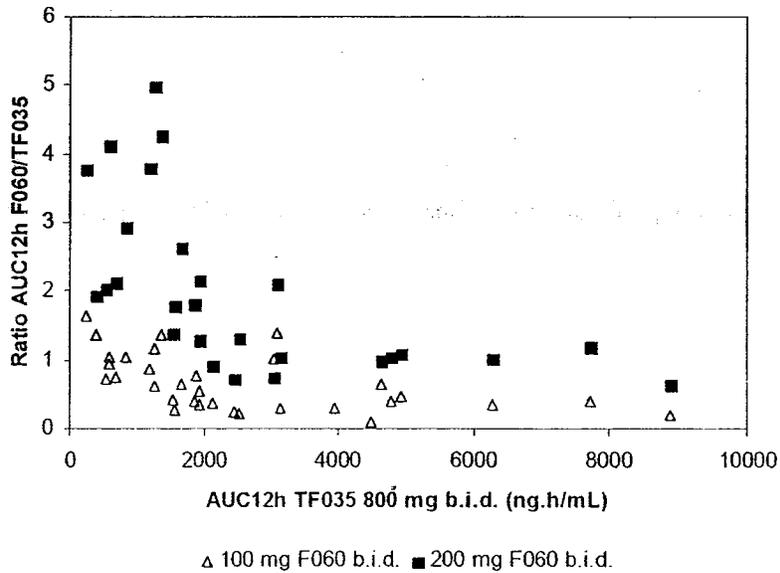


Table 3 shows the statistical evaluation of the pharmacokinetics of TMC125.

Table 3: Statistical evaluation of the pharmacokinetics of TMC125

Session 1-2	n		Least Squares Means				P-Value		
			100 mg TMC125 (F060) Test	800 mg TMC125 (TF035) Reference	Treatment Ratio, % and 90% CI Test/Reference		Treatm.	Period	Sequence
TMC125 Parameter	Test/Ref.								
Day 1									
C_{max} , ng/mL	33	32	38	47	81	65 - 100	0.1045	0.0690	0.1987
AUC_{12h} , ng.h/mL	33	32	207	286	72	59 - 88	0.0105	0.1777	0.2553
Day 8									
C_{min} , ng/mL	33	32	41	88	47	38 - 59	< 0.0001	0.4939	0.2941
C_{max} , ng/mL	33	32	148	241	61	50 - 75	0.0003	0.1799	0.1216
AUC_{12h} , ng.h/mL	33	32	1034	1928	54	44 - 65	< 0.0001	0.1558	0.1540
Session 1-2+3	n		Least Squares Means				P-Value		
TMC125 Parameter	Test / Ref.		200 mg TMC125 (F060) Test	800 mg TMC125 (TF035) Reference	Treatment Ratio, % and 90% CI Test/Reference		Treatm.	Period	Sequence
Day 1									
C_{max} , ng/mL	27	32	92	47	197	159 - 245	< 0.0001	-	0.1422
AUC_{12h} , ng.h/mL	27	32	543	285	191	154 - 236	< 0.0001	-	0.2464
Day 8									
C_{min} , ng/mL	27	32	145	87	167	137 - 204	0.0002	-	0.4701
C_{max} , ng/mL	27	32	397	237	167	137 - 204	0.0002	-	0.3117
AUC_{12h} , ng.h/mL	27	32	3176	1902	167	138 - 202	0.0001	-	0.2831

The LS_{means} ratio of C_{min} , C_{max} , and AUC_{12hr} of TMC125 on day 8 decreased by 53 %, 39 %, and 46 % respectively, when TMC125 was administered as 100 mg b.i.d. F060 as compared to when TMC125 was administered as 800 mg b.i.d. TF035.

The LS_{means} ratio of C_{min} , C_{max} , and AUC_{12hr} of TMC125 on day 8 increased by 67 % when TMC125 was administered as 200 mg b.i.d. F060 as compared to when TMC125 was administered as 800 mg b.i.d. TF035.

Significant treatment effects were found for all pharmacokinetic parameters, except for C_{max} on day 1 when comparing 800 mg TMC125 reference formulation TF035 and 100 mg TMC125 test formulation F060.

Pharmacokinetic Results Summary

- The LS_{means} ratio of C_{min} , C_{max} , and AUC_{12hr} of TMC125 on day 8 decreased by 53 %, 39 %, and 46 % respectively, when TMC125 was administered as 100 mg b.i.d. F060 as compared to when TMC125 was administered as 800 mg b.i.d. TF035.
- The LS_{means} ratio of C_{min} , C_{max} , and AUC_{12hr} of TMC125 on day 8 increased by 67 % when TMC125 was administered as 200 mg b.i.d. F060 as compared to when TMC125 was administered as 800 mg b.i.d. TF035.

Conclusion

The mean systemic exposures of TMC125 after oral administration of TMC125 100 mg b.i.d. as formulation F060 were significantly lower as compared to the mean systemic exposures after administration of TMC125 800 mg b.i.d. as formulation TF035.

The mean systemic exposures of TMC125 after oral administration of TMC125 200 mg b.i.d. as formulation F060 were significantly higher as compared to the mean systemic exposures after administration of TMC125 800 mg b.i.d. as formulation TF035. Therefore, the sponsor decided to use formulation F060 at a dose of 200 mg b.i.d. in the pivotal phase III clinical trials.

**APPEARS THIS WAY
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SINGLE AND MULTIPLE DOSE PHARMACOKINETICS

Study Number	Description	Page #
TMC125-C143	A Phase I, multi-center, open label, randomized, multiple dose ranging trial in 3 parallel panels of 12 healthy subjects each, to determine the pharmacokinetics, safety, and tolerability, of twice daily dosing of TMC125 formulated as 200 mg tablets (TF035) containing Hydroxypropylmethylcellulose (HPMC).	121
TMC125-C153	A Phase I, multi-center, open label, partly randomized, multiple dose ranging trial in 2 parallel and 1 sequential panel of 12 healthy subjects each, to determine the pharmacokinetics, safety, and tolerability of once daily dosing of TMC125 formulated as 200 mg tablets (TF035) containing Hydroxypropylmethylcellulose (HPMC).	126
TMC125-C168	A Phase I, open-label, randomized, multiple-dose, crossover trial in healthy subjects to evaluate the pharmacokinetics of TMC125 in a spray dry formulation administered once daily compared to twice daily.	131

**APPEARS THIS WAY
ON ORIGINAL**

Study Number
TMC125-C143

Title

A Phase I, multi-center, open label, randomized, multiple dose ranging trial in 3 parallel panels of 12 healthy subjects each, to determine the pharmacokinetics, safety, and tolerability, of twice daily dosing of TMC125 formulated as 200 mg tablets (TF035) containing Hydroxypropylmethylcellulose (HPMC).

Objectives

The primary objectives of the trial was to evaluate the single dose and steady-state pharmacokinetics of TMC125 after oral b.i.d. doses of TMC125 formulated as 200 mg tablets (TF035) containing HPMC.

Study Design

This was a Phase I, multicenter, open label, multiple dose ranging trial. 36 healthy subjects were to be randomized in 3 parallel groups (**Group 1, Group 2, and Group 3**) of 12 subjects each. In each group, TMC125 was administered as a single morning dose on Day 1, twice daily from Day 2 until Day 7 and as an additional morning dose on Day 8. Group 1, 2 and 3 received 200 mg b.i.d (**Treatment A**), 400 mg b.i.d. (**Treatment B**), and 800 mg b.i.d. (**Treatment C**) TMC125, respectively. Full pharmacokinetic profiles of TMC125 were determined for 24 hours on **Day 1** and up to 216 hours on **Day 8**. Additional morning pre-dose concentrations of TMC125 were determined on Day 6 and 7.

TMC125 was either taken at the clinic with a standardized breakfast (caloric value > 500 kcal) or at home with a meal (caloric value > 500 kcal).

Investigational Product(s)

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

— The batch number used was D03107 (expiry date: June 30, 2004).

Assay Methods

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

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

Descriptive statistics were calculated for the plasma concentrations of TMC125 at each time point and for the derived pharmacokinetic parameters. Graphical evaluation for dose-proportionality after a single dose (**Day 1**) was performed by comparing dose-normalized C_{max} , and AUC_{12h} of the three treatments. Graphical evaluation for dose-proportionality after multiple dose (**Day 8**) was performed by comparing dose-normalized C_{0h} , C_{min} , C_{max} and AUC_{12h} of the three treatments. The pre-dose plasma concentrations in the morning of days 6, 7, and 8 were compared graphically to verify the achievement of steady state.

RESULTS

Subject Disposition and Demographics

Out of the 74 subjects screened, 35 subjects were assigned to 3 groups of 11-12 subjects each. All randomized subjects completed the trial. Table 1 shows the demographics in the trial:

Table 1: Demographics in Trial TMC125-C143

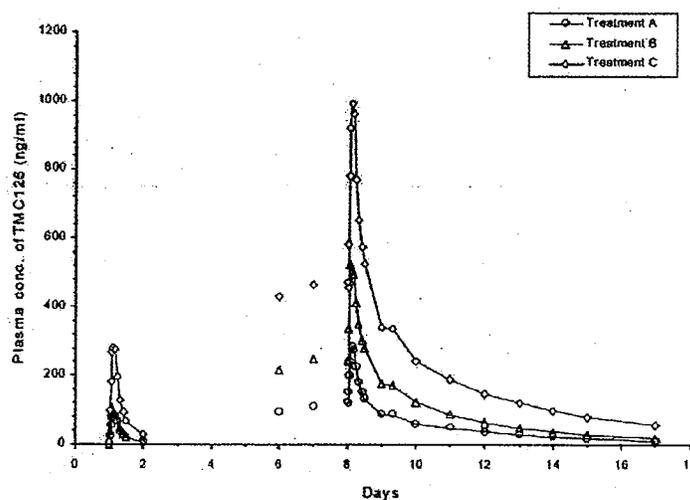
Parameter	Group 1 N=12	Group 2 N=11	Group 3 N=12	All groups N=35
Age (years), median (range)	45.0 (22-55)	25.0 (19-51)	34.5 (23-49)	39.0 (19-55)
Height (cm), median (range)	179.0 (159-194)	184.0 (165-196)	182.5 (159-196)	182.0 (159-196)
Weight (kg), median (range)	79.0 (67-97)	78.0 (59-106)	80.5 (52-98)	79.0 (52-106)
BMI (kg/m ²), median (range)	26.6 (21-29)	24.4 (18-28)	24.5 (20-28)	24.8 (18-29)
Male/female, n (%)	9 (75)/3 (25)	11 (100)/0	10 (83)/2 (17)	30 (86)/5 (14)
Smoker no, n (%)	7 (58)	10 (91)	8 (67)	25 (71)
yes (light), n (%)	5 (42)	1 (9)	4 (33)	10 (29)
Ethnic origin, n (%)				
- Caucasian	11 (92)	10 (91)	11 (92)	32 (91)
- Black	1 (8)	0	1 (8)	2 (6)
- Oriental/Asian	0	1 (9)	0	1 (3)

Pharmacokinetics

Full pharmacokinetic profiles of TMC125 were available for 12 subjects in treatment A (200 mg TMC125 b.i.d.), 11 subjects in treatment B (400 mg TMC125 b.i.d.), and 12 subjects in treatment C (800 mg TMC125 b.i.d.).

Fig 1 shows the mean plasma concentration-time profile of TMC125 after oral administration of 200 mg TMC125 b.i.d. (Treatment A), 400 mg TMC125 b.i.d. (Treatment B), and 800 mg TMC125 b.i.d. (Treatment C) on day 1 and day 8.

Fig 1: Mean plasma concentration-time profile of TMC125 after oral administration of 200 mg TMC125 b.i.d. (Treatment A), 400 mg TMC125 b.i.d. (Treatment B), and 800 mg TMC125 b.i.d. (Treatment C) on day 1 and day 8.



The plasma concentrations of TMC125 increased with increasing total daily dose. A rapid absorption phase was followed by an initially fast distribution/elimination phase and a slower terminal elimination phase.

Based on the plots (not included in the review) of the individual pre-dose plasma concentrations of TMC125 determined on days 6, 7, and 8, it appeared that steady state concentrations were reached prior to the full pharmacokinetic blood sampling on day 8.

Table 2 shows the pharmacokinetic parameters of TMC125 in treatment after oral administration of 200 mg TMC125 b.i.d. (Treatment A), 400 mg TMC125 b.i.d. (Treatment B), and 800 mg TMC125 b.i.d. (Treatment C) on day 1 and day 8.

Table 2: Pharmacokinetic parameters of TMC125 in treatment after oral administration of 200 mg TMC125 b.i.d. (Treatment A), 400 mg TMC125 b.i.d. (Treatment B), and 800 mg TMC125 b.i.d. (Treatment C) on day 1 and day 8.

Pharmacokinetics of TMC125 (mean±SD, t_{max} , median (range))	Treatment A 200 mg b.i.d.	Treatment B 400 mg b.i.d.	Treatment C 800 mg b.i.d.
Day 1			
n	12	11	12
t_{max} , h	3.0 (2.0 - 6.0)	2.0 (1.5 - 6.0)	3.0 (1.5 - 4.0)
C_{max} , ng/ml	95.1 ± 66.2	142 ± 129	319 ± 165
AUC _{12h} , ng.h/ml	581 ± 407	684 ± 459	1940 ± 1048
AUC _{24h} , ng.h/ml	731 ± 513	871 ± 579	2533 ± 1411
Day 6			
C_{0h} , ng/ml	94.2 ± 33.0	216 ± 97.4	429 ± 177
Day 7			
C_{0h} , ng/ml	111 ± 46.1	250 ± 106	463 ± 194
Day 8			
n	12	11	12
t_{max} , h	3.5 (2.0 - 6.0)	3.0 (1.5 - 4.0)	3.0 (2.0 - 6.0)
C_{0h} , ng/ml	126 ± 56.2	247 ± 111	472 ± 191
C_{min} , ng/ml	115 ± 55.3	237 ± 112	446 ± 180
C_{max} , ng/ml	294 ± 180	546 ± 269	1042 ± 423
AUC _{12h} , ng.h/ml	2389 ± 1228	4628 ± 2205	8674 ± 3152
$t_{1/2elim}$, h	62.3 ± 20.3	58.4 ± 23.2	72.8 ± 18.1
$C_{12,av}$, ng/ml	199 ± 102	386 ± 184	723 ± 263
FI, %	82.0 ± 24.5	80.5 ± 19.6	82.2 ± 30.0
Ratio AUC _{12h} (Day 8/Day 1), %	570 ± 498	862 ± 371	490 ± 116

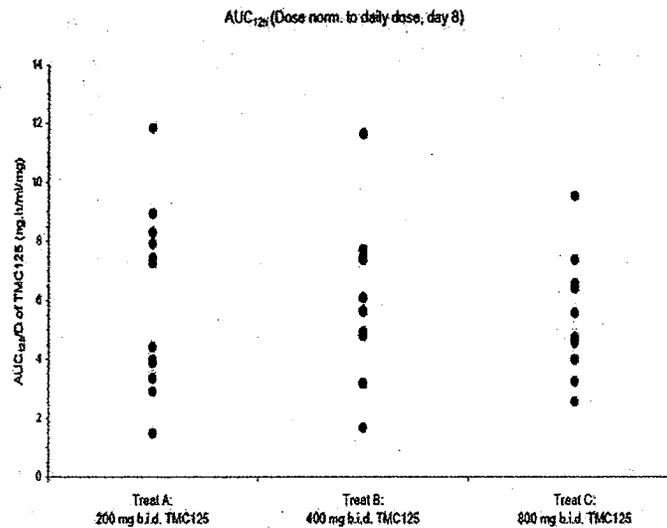
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On day 8, the maximum concentrations of TMC125 were reached between 3-3.5 hours post-dose. The steady-state PK parameters (C_{0h} , C_{max} , and AUC_{12hr}) increased with increasing dose, suggesting proportionality of the steady-state PK of TMC125 across the dose range evaluated.

Fig 2 shows the AUC_{0-12hr} of TMC125 dose-normalized to daily dose (day 8) after oral administration of TMC125 administered as 200 mg TMC125 b.i.d. (Treatment A), 400 mg TMC125 b.i.d. (Treatment B), and 800 mg TMC125 b.i.d. (Treatment C).

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Fig 2: AUC_{0-12hr} of TMC125 dose-normalized to daily dose (day 8) after oral administration of TMC125 administered as 200 mg TMC125 b.i.d. (Treatment A), 400 mg TMC125 b.i.d. (treatment B), and 800 mg TMC125 b.i.d. (treatment C).



On Day 8, the C_{max} values were 200-300 % higher than the C_{max} estimates on Day 1 for each dose level. Further, compared to day 1, the AUC_{0-12h} values were almost 500 % higher on day 8 for the 200 TMC125 b.i.d., dose about 700 % higher for the 400 mg b.i.d dose and almost 400 % higher for the 800 mg b.i.d dose. The high accumulation ratio on Day 8 for the 400 mg b.i.d. group was probably a consequence of the relatively low exposures (compared to the AUC₀₋₁₂ exposures a single dose of 200 mg and 800 mg on day 1) observed after a single dose of TMC125 on Day 1 in this group.

The individual C_{0h} , C_{min} , C_{max} , and AUC values overlapped considerably between the different dosing regimens. The % CV ranged from 40.43 % to 44.59 % for C_{0h} , from 40.36 % to 47.93 % for C_{min} , from 40.65 % to 61.17 % for C_{max} , and from 36.64 % to 51.4 % for AUC_{12hr} on day 8. The comparison of the range of dose-normalized AUC indicated proportional increase in exposures across the dose range, thereby suggesting that inter-subject variability in exposure (AUC) is similar across the three treatment groups.

Conclusion

TMC125, when administered as a b.i.d regimen using formulation TF035, showed an approximate dose proportional increase in the steady state pharmacokinetic parameters (C_{maxss} and AUC_{12hrss}) across the evaluated dose range (200 mg b.i.d to 800 mg b.i.d).

Study Number
TMC125-C153

Title

A Phase 1, multi-center, open label, partly randomized, multiple dose ranging trial in 2 parallel and 1 sequential panel of 12 healthy subjects each, to determine the pharmacokinetics, safety, and tolerability of once daily dosing of TMC125 formulated as 200 mg tablets (TF035) containing Hydroxypropylmethylcellulose (HPMC).

Objectives

The primary objectives of the trial were to evaluate the single dose and steady-state pharmacokinetics of TMC125 after once daily oral doses of TMC125 formulated as 200 mg tablets (TF035) containing HPMC.

Study Design

Phase I, multicenter, open-label, multiple-dose-ranging study. 24 healthy subjects were randomized into 2 parallel panels (Panel 1 and Panel 2) of 12 healthy subjects each. A sequential panel (Panel 3) of 12 healthy subjects, started after the assessment of safety data from Panel 1 and Panel 2. Panel 1, Panel 2, and Panel 3 received 400 mg (Treatment A), 800 mg (Treatment B) and 1600 mg (Treatment C) TMC125, respectively, as a once-daily (q.d.) oral dose under fed conditions from Day 1 until Day 8. Full pharmacokinetic profiles of TMC125 were determined on Day 1 up to 24 hours, and on Day 8 up to 216 hours. Additional pre-dose concentrations of TMC125 were determined on Day 3 through Day 7.

Investigational Product(s)

TMC125 was formulated as TF035; a tablet containing 200 mg TMC125 in HPMC lactose. The batch number used was D03107 (expiry date: June 30, 2004).

Assay Methods

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

Pharmacokinetic and Statistical Data Analysis

Pharmacokinetic Analysis

Pharmacokinetic and statistical analysis was performed using WinnonLin Professional™ (version 3.3, Pharsight Corporation, Mountain View, California).

A non-compartmental model with extra-vascular 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.

On **Day 1**, sampling was done up to 24 hours to allow investigation of dose proportionality after a single dose. AUC_{12h} on **Day 1** was also determined to enable comparison with previous studies with twice-daily dosing using formulation **TF035**. After dosing on **Day 8**, sampling was done up to 216 hours after intake to characterize the terminal elimination phase of TMC125.

Statistical Analysis

Descriptive statistics were calculated for the plasma concentrations of TMC125 at each time point and for the derived pharmacokinetic parameters. Graphical evaluation for dose proportionality after a single dose (day 1) was performed by comparing dose-normalized C_{max} and AUC_{24h} of the three treatments. The pre-dose plasma concentrations in the morning of days 3, 4, 5, 6, 7, and 8 were compared graphically to verify the achievement of steady-state conditions for TMC125 on day 8.

RESULTS

Subject Disposition and Demographics

Out of the 67 subjects screened, 36 subjects were randomized; 24 subjects were randomized to 2 panels of 12 subjects each (400 mg q.d. group and 800 mg q.d. group), and 12 subjects were randomized to the third panel (1600 mg q.d. group). 1 subject (randomized to the 400 mg q.d. group) discontinued the study prematurely due to an adverse event (dyspepsia) after 4 days of treatment with TMC125. This subject used simethicone during treatment with TMC125; due the potential effect of simethicone on the absorption of TMC125, the data from this subject was excluded from the descriptive statistics. All other subjects completed the study.

Table 1 shows the demographics in the trial.

Table 1: Demographics in Trial TMC125-C153

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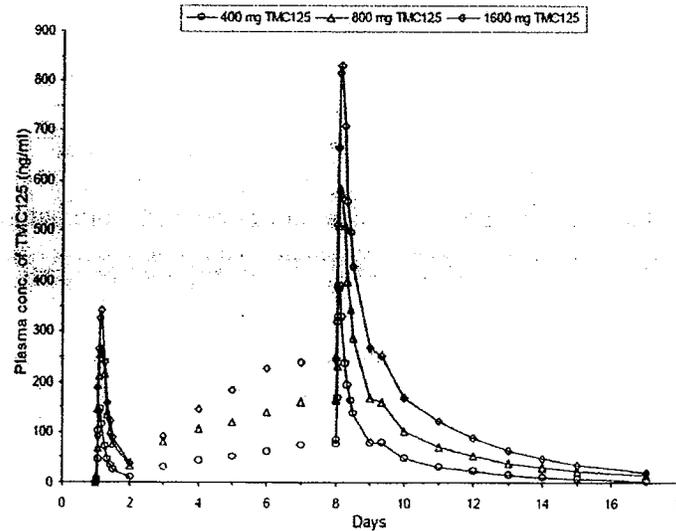
Parameter	TMC125 400 mg q.d. N=12	TMC125 800 mg q.d. N=12	TMC125 1600 mg q.d. N=12	TMC125 All Subjects N=36
Age, years median (range)	30.0 (19-50)	26.5 (19-54)	26.0 (21-55)	27.5 (19-55)
Height, cm median (range)	183.0 (170-199)	180.5 (172-195)	185.5 (166-198)	182.0 (166-199)
Weight, kg median (range)	77.0 (66-96)	74.5 (64-93)	75.0 (64-104)	75.0 (64-104)
BMI, kg/m ² median (range)	22.7 (21-27)	22.1 (19-28)	22.1 (17-28)	22.3 (17-28)
Sex, n (%)				
female	1 (8.3)	0	1 (8.3)	2 (5.6)
male	11 (91.7)	12 (100.0)	11 (91.7)	34 (94.4)
Ethnic origin, n (%)				
black	0	1 (8.3)	0	1 (2.8)
white	12 (100.0)	10 (83.3)	12 (100.0)	34 (94.4)
other	0	1 (8.3)	0	1 (2.8)
Type of smoker, n (%)				
light	6 (50.0)	4 (33.3)	5 (41.7)	15 (41.7)
nonsmoker	6 (50.0)	8 (66.7)	7 (58.3)	21 (58.3)

Pharmacokinetics

Full pharmacokinetic profiles were available for 11 subjects from treatment A (400 mg q.d.), 12 subjects from treatment B (800 mg q.d.), and 12 subjects from treatment C (1600 mg q.d.).

Fig 1 shows the mean plasma concentration-time profile of TMC125 after oral administration of 400 mg q.d, 800 mg q.d., and 1600 mg q. d. on day 1 and day 8.

Fig 1: Mean plasma concentration-time profile of TMC125 after oral administration of 400 mg q.d, 800 mg q.d., and 1600 mg q. d. on day 1 and day 8.



The plasma concentrations of TMC125 increased with increasing total daily dose. A rapid absorption phase was followed by an initially fast distribution and elimination

phase, and then a slower terminal phase. After the last drug intake on Day 8, the terminal part of the plasma concentration-time profile was biphasic for most subjects.

The plots (not included in the review) of the individual pre-dose TMC125 plasma concentrations on days 3, 4, 5, 6, 7, and 8 show that steady-state concentrations were reached prior to full pharmacokinetic blood sampling on day 8. On day 8, maximum concentrations of TMC125 were reached approximately 3.0 to 4.0 hours after dosing for the three treatment groups.

Table 2 shows the pharmacokinetic parameters of TMC125 across all the treatment groups.

Table 2: Pharmacokinetic parameters of TMC125 across all the treatment groups.

Pharmacokinetic Parameter mean \pm SD, t_{max} : median (range)	TMC125 400 mg q.d.	TMC125 800 mg q.d.	TMC125 1600 mg q.d.
Day 1			
n	11	12	12
t_{max} , h	3.0 (1.5 - 6.0)	3.5 (1.5 - 6.0)	3.5 (2.0 - 6.0)
C_{max} , ng/mL	158 \pm 89.4	283 \pm 163	364 \pm 202
AUC _{12h} , ng.h/mL	824 \pm 410	1904 \pm 1136	2307 \pm 1317
AUC _{24h} , ng.h/mL	1033 \pm 501	2575 \pm 1657	3071 \pm 1735
Day 8			
n	11	12	12
C_{0h} , ng/mL	75.9 \pm 26.5	164 \pm 93.3	245 \pm 101
C_{min} , ng/mL	72.2 \pm 25.1	155 \pm 94.0	232 \pm 89.4
C_{max} , ng/mL	422 \pm 181	620 \pm 319	895 \pm 300
t_{max} , h	3.0 (1.5 - 6.0)	3.0 (1.5 - 6.0)	4.0 (2.0 - 6.0)
AUC _{24h} , ng.h/mL	4113 \pm 1251	7787 \pm 4072	11300 \pm 3786
$t_{1/2,term}$, h	48.0 \pm 14.6	53.3 \pm 26.1	55.7 \pm 13.8
$C_{ss,av}$, ng/mL	171 \pm 52.1	324 \pm 170	471 \pm 158
FI, %	198 \pm 51.8	146 \pm 31.2	146 \pm 39.1
Ratio AUC _{24h} (Day 8/Day 1)	4.95 \pm 2.75	3.81 \pm 2.00	4.70 \pm 2.30

The individual C_{0h} , C_{min} , C_{max} , and AUC estimates overlapped between the different treatments. On day 8, the % CV ranged from 34.88 % to 56.84 % for C_{0hr} , 34.83 % to 60.51 % for C_{min} , 33.48 % to 51.55 % for C_{max} , and from 30.41 % to 52.30 % for AUC_{24hr}. After the last drug intake, the mean terminal elimination half-lives of TMC125 were 48.0 hr, 53.3 hr, and 55.7 hours for treatment A, treatment B, and treatment C, respectively.

Conclusion

- On Day 1, the mean C_{max} increased less than dose proportionally in the investigated dose range (400 mg q.d. to 1600 mg q.d.). The mean AUC_{24h} increased dose proportionally between the 400 mg q.d. and the 800 mg q.d. group, while a less than dose proportional increase was observed between the 800 mg q.d. and 1600 mg q.d. group.
- On Day 8, the increase in mean C_{max} was less than dose proportional across the dose range, however, the mean steady state AUC_{24h} increased dose proportionally

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