CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-976

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-976	Submission Date: December 22, 2005
Brand Name	PREZISTA
Generic Name	DARUNAVIR
Reviewer	Vikram Arya, Ph.D.
In Vitro Metabolism Reviewer	Yuanchao (Derek) Zhang, Ph.D.
Pharmacometrics Reviewer	Christine Garnett, Pharm.D.
Team Leader	Kellie S. Reynolds, Pharm.D.
Pharmacometrics Team Leader	Jogarao Gobburu, Ph.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	DAVP
Sponsor	Tibotec
Relevant IND(s)	IND 62, 477
Submission Type; Code	505 (b) (1), 1P
Formulation; Strength(s)	Tablet ; 300 mg
Dosing regimen	600 mg TMC114, co-administered with 100 mg ritonavir, b.i.d.
Indication	Treatment of HIV-1 infection in protease inhibitor-experienced adults

Table of Contents

1. Executive Summary

Darunavir (TMC114) is an inhibitor of the human immunodeficiency virus (HIV) protease. Darunavir, in combination with low dose ritonavir, is proposed for the treatment of HIV-1 infection in adults. The clinically recommended dose is 600 mg darunavir/100 mg ritonavir b.i.d.

The accelerated approval decision for darunavir is based on the 24-week data generated in pivotal Phase IIB randomized open label, controlled, efficacy and safety trials **(TMC114-C202 and TMC114-C213)**. In addition, to expand the safety database at the clinically recommended dose, safety data were collected from two additional non-randomized clinical trials (TMC114-C208 and TMC114-C215). The data from the ongoing Phase III trials were not used to support the current submission.

The sponsor conducted 35 clinical trials to characterize the biopharmaceutics (12 trials), pharmacokinetics (4 trials), potential of darunavir to prolong the QT interval (1 trial), and drug-drug interaction potential of darunavir (18 trials). In addition, the sponsor developed a population pharmacokinetic model using data from healthy and HIV-1 infected subjects. This model was used to obtain the pharmacokinetic parameters based on sparse sampling from subjects enrolled in the two phase IIb trials.

1.1 Recommendation

The Clinical Pharmacology and Biopharmaceutics Information provided by the Sponsor is acceptable.

1.2 Phase IV Commitments

The following postmarketing commitments (PMCs) will provide further information regarding the safe and effective use of darunavir/rtv in the target population. PMC # 1 and PMC # 3 were originally included by the sponsor in the list of ongoing/planned studies.

These PMCs address the pharmacokinetics and safety of darunavir/riitonavir in special population (PMC # 1), assess the inhibitory/induction potential of darunavir/rtv on various CYP enzymes (PMC # 2), and provide quantitative drug interaction information (PMC # 3, 4, and 5).

1. Evaluate the pharmacokinetics of Darunavir/rtv in HIV-negative subjects with Child-Pugh A and Child-Pugh B liver disease in order to determine dosing recommendations.

2. Please conduct a cocktail study to determine the effects of steady state Darunavir/rtv 600/100 mg b.i.d. on the metabolism of CYP450 probe substrates for the following enzymes: CYP2C9, CYP2C19, and CYP2D6.

3. Conduct an *in vivo* drug-drug interaction study between Darunavir/rtv b.i.d. and rifabutin.

4. Conduct an *in vivo* drug-drug interaction study between Darunavir/rtv b.i.d. and buprenorphine/naloxone.

5. Conduct an *in vivo* drug-drug interaction study between Darunavir/rtv b.i.d. and carbamazepine.

In addition to the PMC's listed above, the sponsor has planned to conduct a drug-drug interaction study between darunavir/rtv b.i.d. and methadone (TMC114-C127).

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Darunavir is an inhibitor of the human immunodeficiency virus (HIV) protease. It selectively inhibits the cleavage of HIV encoded Gag-Pal polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles. Darunavir, coadministered with low dose ritonavir, is proposed for the treatment of HIV-1 infection in adults. The clinically recommended dose is 600/100 mg b.i.d.

Exposure Response

- Exposure-response analyses were conducted on pooled data from two dose-ranging controlled trials (studies C202 and C213) in antiretroviral treatment-experienced HIV-infected adult patients (total number of subjects, 637). In these studies, patients were randomized to a control group (investigator-selected protease inhibitor based regimen) or to 400/100 mg QD, 800/100 mg QD, 400/100 mg BID or 600/100 mg BID dosing regimens of darunavir/ritonavir in addition to an optimized background regimen. At 24 weeks, the virologic response rate was evaluated (primary efficacy evaluation).

- The exposure-response analysis of combined phase 2b trials (C202 and C213) demonstrated that the probability of having a response to darunavir treatment (measured either by 1 log reduction in viral load or HIV-1 RNA <50 copies/ml) by week 24 is related to the patient's darunavir inhibitory quotient (IQ; ratio between the trough concentration and IC_{50}). The primary driver for response rate is the fold change (FC; measure of the fold-increase in the IC_{50} value relative to a standard IC_{50} value for a wild-type HIV-1 virus with no mutations) at baseline and response was less dependent on darunavir exposure.

- Individualized doses above 600/100 mg b.i.d. to compensate for an increased IC_{50} value is not expected to improve the response rate in HIV-1 patients because of less than dose proportional increase in plasma concentrations with increasing dose. However, it may increase the likelihood of response in some individuals.

- Analysis of safety data from all four dosing regimens showed no apparent relationship between darunavir exposure (measured by AUC_{24h}) and maximum change in cholesterol, lipids and LFT markers as well as in the incidence of adverse events.

- Based on the population pharmacokinetic analysis of darunavir, dose adjustments are not required for race, gender, renal impairment, hepatitis B or C co-infection, and age greater than 65 years.

Table 1 shows the summary of exposure parameters (based on intensive sampling in the PK sub-study) in studies TMC114-C202 and TMC14-C213 (pivotal Phase IIb studies in HIV-1 infected subjects).

Table 1: Summary of Exposure Parameters (based on intensive sampling in the PK sub-study) in studies TMC114-C202 and TMC14-C213 (pivotal Phase IIb studies in HIV-1 infected subjects).

Parameter	t_{max}: Median (Range); Mean ± SD			
	Darunavir/Ritonavir 400/100 mg q.d.	Darunavir/Ritonavir 800/100 mg q.d.	Darunavir/Ritonavir 400/100 mg b.i.d.	Darunavir/Ritonavir 600/100 mg b.i.d.
Week 24				
N	11	14	15	9
t_{max}, h	3.0 (1.0-4.0)	4.0 (2.0-6.0)	3.0 (1.0-12.0)[c]	3.0 (1.0-4.1)
C_{24h}, ng/mL	1199 ± 890	2667 ± 3048	2567 ± 994	4086 ± 1642
C_{12h}, ng/mL	-	-	2893 ± 1919	2993 ± 999
C_{12h}, ng/mL	1329 ± 785	2325 ± 2371	-	-
C_{min}, ng/mL	1083 ± 864	1956 ± 2131	2202 ± 820	3386 ± 1547
C_{max}, ng/mL	4748 ± 1855	7091 ± 4400	5309 ± 1695	6468 ± 1697
$C_{ss,av}$, ng/mL	2371 ± 1011	3812 ± 3388	3670 ± 1299	4329 ± 1104
AUC_{12h}, ng.h/mL	-	-	44042 ± 15583	51951 ± 13246
AUC_{24h}, ng.h/mL	56894 ± 24268	91485 ± 81305	-	-
PI, %	163 ± 49.6	157 ± 53.8	81.4 ± 21.5	74.3 ± 23.4

In addition, Bayesian estimates of darunavir pharmacokinetic parameters from sparse sampling in trials TMC114-C202 and TMC114-C213 suggested a less than dose proportional increase within the q.d. (400/100 mg [n = 118] and 800/100 mg [n = 118]) and the b.i.d. regimens (400/100 mg [n = 113] and 600/100 [n = 119]). Based on the analysis, a 50 % increase in dose (from 400 mg b.i.d to 600 mg b.i.d.) resulted in a 29 % increase in exposure (as compared to an increase in AUC by 18 % estimated based on the results from the intensive sampling). However, there was an increase in C_{min} by approximately 50 %.

Absorption

- Darunavir has an intermediate to high absorptive permeability in Caco-2 monolayers indicating sufficient membrane permeability to show adequate intestinal absorption. The absolute bioavailability of darunavir, in the absence and presence of ritonavir (100 mg b.i.d) is 37 % and 82 % respectively.
- In vitro results suggest that darunavir is a P-gp substrate.
- *In vitro* studies have shown that darunavir is a CYP3A substrate. This was further confirmed *in vivo* from the results of a clinical trial that showed a 14-fold increase in exposure of darunavir in the presence of 100 mg b.i.d. ritonavir, a potent

CYP3A4 inhibitor. This increase in exposure is, in part, due to an approximate 5.5 fold reduction in systemic clearance (observed after IV administration).

- The exposure to darunavir (co-administered with low-dose RTV) under fasted conditions was approximately 30 % lower than under fed conditions. Therefore, the proposed label recommends that darunavir should be taken with food. Within the range of meals studied, darunavir exposure is similar. The total caloric content of the various meals evaluated ranged from 240Kcal (12 gms fat) to 928Kcal (56 gms fat).

Distribution

- The *in vitro* plasma protein binding of darunavir is approximately 95 % in humans.
- Darunavir is mainly present in the plasma, with limited distribution to the erythrocytes, and is mostly bound to α-1 acid glycoprotein (AAG) and to a lesser extent to albumin.
- The volume of distribution of darunavir is 130 L (after intravenous administration).

Metabolism

- The results from the mass balance study showed that at 48 hours after dosing with ^{14}C-TMC114 (in the presence of ritonavir), 41.2 % and 7.7 % of the drug was recovered unchanged in the feces and urine respectively.
- Darunavir primarily undergoes oxidative metabolism. In an *in vitro* study conducted to characterize the various CYP isozymes involved in the oxidative metabolism of darunavir, only ketoconazole (predominantly CYP3A4 inhibitor) showed significant inhibition of the darunavir metabolism, and only CYP3A4 showed metabolic activity towards darunavir.

Excretion

- The results of the mass balance study showed that after a single dose administration of ^{14}C-TMC114 with ritonavir, the majority of the radioactivity was excreted in the feces. At 168 hours after dosing, 79.5 % of the radioactivity was recovered in the feces and 13.9 % of the radioactivity was recovered in the urine. The results from other Phase I studies suggested that less than 7 % of the drug is excreted unchanged in the urine. In addition, the % of absorbed drug eliminated through the renal route is < 10 %. These results suggest that renal elimination is a minor route for darunavir elimination.

Intrinsic Factors

- The intrinsic factors that have been considered for their potential effect on the pharmacokinetics of darunavir include gender, race, body weight, hepatitis B and/or C virus co-infection status, and AAG concentrations in plasma at baseline.

The subgroup analysis showed that race, gender, body weight, and hepatitis B and/or C virus co-infection status had no clinically significant effect on the exposure to darunavir.

- The exposure to darunavir was positively correlated with baseline AAG concentrations in plasma. There was a trend towards higher darunavir AUC_{24h} and C_{0h} in subjects with higher concentrations of AAG in plasma at baseline.
- In view of the limited renal excretion of darunavir (< 7 % across all studies), a study to investigate the exposure to darunavir in subjects with renal impairment was not conducted. Further, the results from population pharmacokinetic analysis and safety evaluations suggested that the slightly higher darunavir exposure in HIV-1 infected subjects with moderate renal impairment (CL_{cr} between 30-60 mL/min, n = 20) is not clinically relevant.
- A clinical study to assess the impact of hepatic impairment on the pharmacokinetics of darunavir is currently being planned.

Extrinsic Factors

Drug-Drug Interactions

- Drug-Drug interaction studies were conducted using the solution or tablet under fed conditions. When given in the presence of low-dose ritonavir (100 mg b.i.d.), darunavir doses of 300 or 400 mg b.i.d. were generally used in the drug-drug interaction studies. It is acceptable to extrapolate the drug interaction results to the commercial tablet (F016) and dose (600/100 mg b.i.d.).
- The following drugs should not be co-administered with darunavir/rtv due to serious adverse events (because of the co-administered drug) or due to potential loss of efficacy because of reduction in darunavir exposure. These conclusions are based on either clinical studies or expected drug-drug interactions based on mechanism.
    - Drugs that should not be co-administered with darunavir/ritonavir due to serious adverse events: Antihistamines (astemizole, terfenadine), Ergot Derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonavine), GI motility agent (cisapride), neuroleptic (pimozide), and sedative/hypnotics (midazolam, triazolam) and HMG-CoA reductase inhibitors (lovastatin, simvastatin)
    - Drugs that should not be co-administered with darunavir/ritonavir due to potential loss of efficacy of darunavir: Anticonvulsants (carbamazepine, phenobarbital, phenytoin), antimycobacterial (rifampin), herbal products (St. Johns. Wort), HIV protease inhibitors (Kaletra, saquinavir),

Table 2 shows the established and other potentially significant drug interactions based on which alterations in dose or regimen may be recommended. The interaction between darunavir and the drug preceding the asterisk (*) sign was evaluated in a clinical study; the interactions between darunavir and other drugs (not preceding the asterisk sign) are predicted. Further, some of the listed drug interactions are typical for ritonavir boosted PIs.

Table 2: Established and other potentially significant drug interactions: alterations in dose or regimen may be recommended based on drug interaction studies or predicted interaction.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz*	↓ darunavir ↑ efavirenz	Co-administration of darunavir/rtv and efavirenz decreased darunavir AUC by 13% and C_{min} by 31%. The clinical significance has not been established. The combination of PREZISTA/rtv and efavirenz should be used with caution.
Nevirapine*	↔ darunavir ↑ nevirapine	PREZISTA/rtv and nevirapine can be co-administered without any dose adjustments.
HIV-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Didanosine		It is recommended that didanosine be administered on an empty stomach. Therefore, didanosine should be administered one hour before or two hours after PREZISTA/rtv (which are administered with food).
Tenofovir Disoproxil Fumarate*	↔ darunavir ↑ tenofovir	PREZISTA/rtv and tenofovir disoproxil fumarate can be co-administered without any dose adjustments.
HIV-Antiviral Agents: HIV-Protease Inhibitors (PIs)		
Atazanavir* (The reference regimen for atazanavir was atazanavir/ritonavir 300/100 mg q.d.)	↔ darunavir ↔ atazanavir	PREZISTA/rtv and atazanavir (300 mg q.d.) can be co-administered.
Indinavir* (The reference regimen for indinavir was indinavir/ritonavir 800/100 mg b.i.d.)	↑ darunavir ↑ indinavir	The appropriate dose of indinavir in combination with PREZISTA/rtv has not been established. The reference regimen used in the study was not approved.
Lopinavir/ritonavir*	↓ darunavir ↑ Lopinavir	Due to decrease in the exposure (AUC) of darunavir by 53%, appropriate doses of the combination have not been

		established. Hence, it is not recommended to coadminister lopinavir/ritonavir and PREZISTA, with or without an additional low-dose of ritonavir.
Saquinavir*	↓ darunavir ↔ saquinavir	Due to a decrease in the exposure (AUC) of darunavir by 26%, appropriate doses of the combination have not been established. Hence, it is not recommended to coadminister saquinavir and PREZISTA, with or without low-dose ritonavir.
Other Agents		
Antiarrhythmics: bepridil, lidocaine (systemic), quinidine, amiodarone	↑ antiarrhythmics	Concentrations of bepridil, lidocaine, quinidine and amiodarone may be increased when coadministered with PREZISTA/rtv. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when coadministered with PREZISTA/rtv.
Anticoagulant: Warfarin	↓ warfarin ↔ darunavir	Warfarin concentrations may be affected when coadministered with PREZISTA/rtv. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with PREZISTA/rtv.
Antidepressant: Trazodone	↑ Trazodone	Concomitant use of trazodone and PREZISTA/rtv may increase concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A inhibitor such as PREZISTA/rtv, the combination should be used with caution and a lower dose of trazodone should be considered.
Anti-infective: clarithromycin*	↑ clarithromycin	No dose adjustment of darunavir or clarithromycin is required for patients with normal renal function. For patients with renal impairment, the following dose adjustments should be considered: • For subjects with CLcr of 30-60 mL/min, the dose of clarithromycin should be reduced by 50%. • For subjects with CLcr of <30 mL/min, the dose of clarithromycin should be reduced by 75%.

Antifungals: ketoconazole*, itraconazole, voriconazole	↑ ketoconazole ↑ darunavir ↑ itraconazole (not studied) ↓ voriconazole (not studied)	Ketoconazole and itraconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of ketoconazole, itraconazole, and darunavir/ritonavir may increase plasma concentration of darunavir. Plasma concentrations of ketoconazole or itraconazole may be increased in the presence of darunavir/ritonavir. When coadministration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg. Co-administration of voriconazole with darunavir/ritonavir has not been studied. Administration of voriconazole with ritonavir (100 mg twice daily) decreased the AUC of voriconazole by an average of 39%. Voriconazole should not be administered to patients receiving darunavir/ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
Antimycobacterial: Rifabutin* Note: Due to dropouts, the study results were not interpretable.	↑ rifabutin ↓ darunavir	Rifabutin is an inducer and substrate of CYP450 enzymes. Concomitant use of rifabutin and darunavir in the presence of ritonavir is expected to increase rifabutin plasma concentrations and decrease darunavir plasma concentrations. When indicated, it is recommended to administer rifabutin at a dosage of 150 mg once every other day when coadministered with PREZISTA/rtv.
Calcium Channel Blockers: felodipine, nifedipine, nicardipine	↑ calcium channel blockers	Plasma concentrations of calcium channel blockers (e.g. felodipine, nifedipine, nicardipine) may increase when PREZISTA/rtv are coadministered. Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: dexamethasone fluticasone propionate	↓ darunavir ↑ fluticasone propionate	Use with caution. Systemic dexamethasone induces CYP3A and can thereby decrease darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA. Concomitant use of inhaled fluticasone propionate and PREZISTA/rtv may increase plasma concentrations of fluticasone propionate. Alternatives should be considered, particularly for long term use.

HMG-CoA Reductase Inhibitors: Atorvastatin* Pravastatin*	↑ Atorvastatin ↑ Pravastatin	When atorvastatin and PREZISTA/rtv is co-administered, it is recommended to start with the lowest possible dose of atorvastatin with careful monitoring. A gradual dose increase of atorvastatin may be considered based on the clinical response. When PREZISTA/rtv was administered with pravastatin, the mean increase in pravastatin AUC was 81 %. However, pravastatin AUC increased by up to 5-fold in some patients. The mechanism of interaction is not known.
H2-Receptor Antagonists and Proton Pump Inhibitors: omeprazole*, ranitidine*	↔ darunavir	PREZISTA/rtv can be coadministered with H2-receptor antagonists and proton pump inhibitors without any dose adjustments.
Immunosuppressants: cyclosporine, tacrolimus, sirolimus	↑ immunosuppressants	Plasma concentrations of cyclosporine, tacrolimus or sirolimus may be increased when coadministered with PREZISTA/rtv. Therapeutic concentration monitoring of the immunosuppressive agent is recommended for immunosuppressant agents when coadministered with PREZISTA/rtv.
Narcotic Analgesic: methadone	↓ methadone	When methadone is coadministered with PREZISTA/rtv, patients should be monitored for opiate abstinence syndrome, as ritonavir is known to induce the metabolism of methadone, leading to a decrease in its plasma concentrations. An increase in methadone dosage may be considered based on the clinical response.
Oral Contraceptives/estrogen: ethinyl estradiol norethindrone (study completed; results not part of NDA submission)	↓ ethinyl estradiol ↓ norethindrone	Plasma concentrations of ethinyl estradiol may be decreased due to induction of its metabolism by ritonavir. Alternative or additional contraceptive measures should be used when estrogen-based contraceptives are coadministered with PREZISTA/rtv.
PDE-5 inhibitors: sildenafil*, vardenafil, tadalafil	↑ PDE-5 inhibitors	Concomitant use of PDE-5 inhibitors with PREZISTA/rtv should be done with caution. If concomitant use of PREZISTA/rtv with sildenafil, vardenafil, or tadalafil is required, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding

		2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours, is recommended.
Selective Serotonin Reuptake Inhibitors (SSRIs): sertraline*, paroxetine*	↔ darunavir ↓ sertraline ↓ paroxetine	If sertraline or paroxetine is coadministered with PREZISTA/rtv, the recommended approach is a careful dose titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with PREZISTA/rtv should be monitored for antidepressant response.

PIVOTAL BIOEQUIVALENC STUDY

The results of study TMC114-C116 (pivotal bioequivalence study) showed an approximately 35 % higher exposure (AUC) with the commercial tablet formulation (F016) compared to each of the clinical tablet formulations (F001 and F002). This higher exposure was not clinically relevant because:

- Population pharmacokinetic analysis showed that the relative bioavailability of the commercial formulation was 18 % higher as compared to the clinical trial formulation in HIV-1 patients.
- There was similarity in the safety profiles (incidence of adverse events) in study TMC114-C202 and TMC114-C213 before and after the switch to the commercial formulation.
- No apparent relationship was observed between exposure and safety endpoints for study TMC114-C215 (Phase IIb safety study) in which all 292 subjects were started at the clinically recommended 600/100 mg dose using the commercial formulation (F016)).

Vikram Arya, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 4

Concurrence:

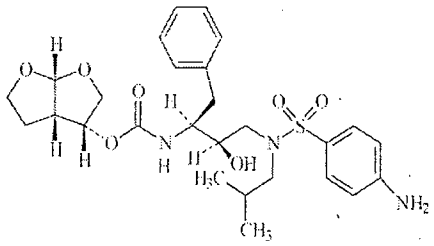
Kellie S. Reynolds, Pharm. D
Team Leader
Division of Clinical Pharmacology 4

2 Question based review (QBR)

2.1 General Attributes of The drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

Darunavir is an inhibitor of the human immunodeficiency virus (HIV) protease. The chemical name for darunavir is [(1S,2R-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester. The molecular formula is $C_{27}H_{37}N_3O_7S$ and its molecular weight is 547.66. Darunavir has the following structural formula:



The composition of the proposed to-be-marketed formulation [redacted] is shown below.

Table 1: Composition of the proposed to-be-marketed formulation [redacted]

Name	Amount Required (mg)
TMC114 Ethanolate	[redacted]
Microcrystalline cellulose and colloidal [redacted] silica	
Crospovidone	
Magnesium Stearate	
Total Core Weight	
OPADRY Orange Film Coat	
Total Tablet Weight	**650.2**

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Darunavir is an inhibitor of the HIV-1 protease. It selectively inhibits the cleavage of HIV encoded Gag-Pal polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The proposed oral dose of darunavir is 600 mg (two 300 mg tablets), co-administered with 100 mg ritonavir, twice daily.

2.2 General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor collected pivotal efficacy and safety data from the following two Phase IIb trials:

TMC114-C202 (POWER 2)

A Phase II, randomized, controlled, partially blinded trial to investigate the dose response of TMC114/RTV in 3-class-experienced HIV-infected subjects, followed by an open label period on the recommended dose of TMC114/RTV.

TMC114-C213 (POWER 1)

A Phase II, randomized, controlled, partially blinded trial to investigate the dose response of TMC114/RTV in 3-class-experienced HIV-infected subjects, followed by an open label period on the recommended dose of TMC114/RTV.

The trials were designed as two part hybrid i.e., the randomized controlled (standard of care), partially blinded dose finding part study (24 weeks) in 3-class experienced patients followed by the open label, controlled, long term efficacy and safety part (96 weeks). Four dosing regimens [total number of subjects in the two trials] (400/100 mg q.d. [n = 129], 800/100 mg q.d.[n = 127], 400/100 mg b.i.d. [n = 126], and 600/100 mg b.i.d. [n = 131]) in combination with an optimized background regimen were tested. The comparator [n = 124] was an active control group in which the subjects received an individually optimized protease inhibitor (PI) based regimen.

Due to the limited safety database at the 600/100 mg b.i.d. dose, additional subjects were enrolled in trials TMC114-C208 and TMC114-C215. These trials were originally designed to provide darunavir/RTV to subjects who previously participated in trials with darunavir (TMC114-C202, TMC114-C213, TMC114-C201, TMC114-C207) and sponsor-selected trials in HIV-infected subjects.

At the time of the current submission, 375 HIV-1 infected subjects have been treated at the recommended dose of darunavir/RTV 600/100 mg b.i.d. for 6 months (and 92 subjects for 48 weeks) which meets the specified ICH criteria of safety data in 300-600 subjects receiving the proposed dose for 6 months. Table 2 shows the efficacy results at the clinically recommended dose (600/100 mg b.i.d.).

Table 2: Outcomes of Randomized Treatment Through Week 24 of Studies TMC114-C213 and TMC114-C202 (Pooled Analysis)

	Randomized Studies TMC114-C213 and TMC114-C202	
	PREZISTA/rtv 600 mg b.i.d. + OBR N=131	Comparator PI + OBR N=124
Virologic Responders confirmed at least 1 $\log_{10}$ HIV-1 RNA below baseline through Week 24 (< 50 copies/mL at Week 24)	69.5% (45.0%)	21.0% (12.1%)
Virologic failures	26.0%	71.0%
Lack of initial response[a]	9.9%	57.3%
Rebound[b]	9.2%	9.7%
Never Suppressed[c]	6.9%	4.0%
Death or discontinuation due to adverse events	3.9%	1.6%
Discontinuation due to other reasons	0.8%	6.5%

[a]Subjects who did not achieve at least a confirmed 0.5 $\log_{10}$ HIV-1 RNA drop from baseline at Week 12
[b]Subjects with an initial response (confirmed 1 $\log_{10}$ drop in viral load), but without a confirmed 1 $\log_{10}$ drop in viral load at Week 24
[c]Subjects who never reached a confirmed 1 $\log_{10}$ drop in viral load before Week 24

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

Viral load and CD4+ cell count are accepted as surrogate markers for efficacy in trials with antiretroviral agents. The amended primary endpoint selected for trials TMC114-C202 and TMC114-C213 was confirmed virologic response at Week 24, defined as a decrease in viral load of at least 1.0 $\log_{10}$ copies/mL versus baseline (primary endpoint), without (1) introduction of any ARV not originally foreseen in the trial regimen, or (2) discontinuation from the trial. In addition, various secondary efficacy endpoints, such as full suppression (defined as viral load < 50 copies/mL), and effects on CD4+ cell count, were also assessed.

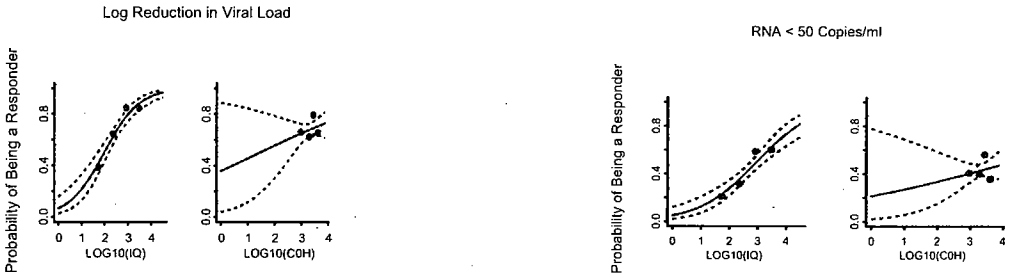
2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the sponsor quantified the appropriate moieties in all the clinical pharmacology studies. Darunavir and ritonavir were quantified using sensitive and validated HPLC/MS/MS methods. In addition, concentrations of other moities were also determined in the drug-drug interaction studies. It was not necessary to measure concentrations of darunavir metabolites, except for in the mass balance study since *in vitro* studies indicate that the metabolites were at least 90 % less active than darunavir. See Analytical section (section 2.6.4.) for more details.

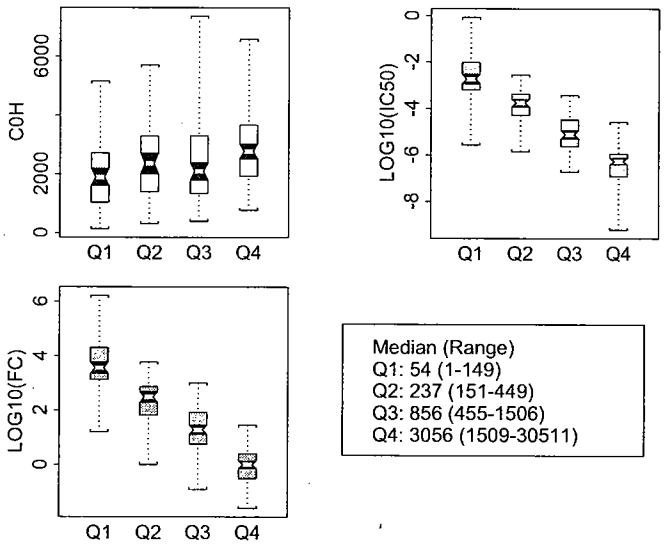
2.2.4. Exposure-Response

2.2.4.1. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

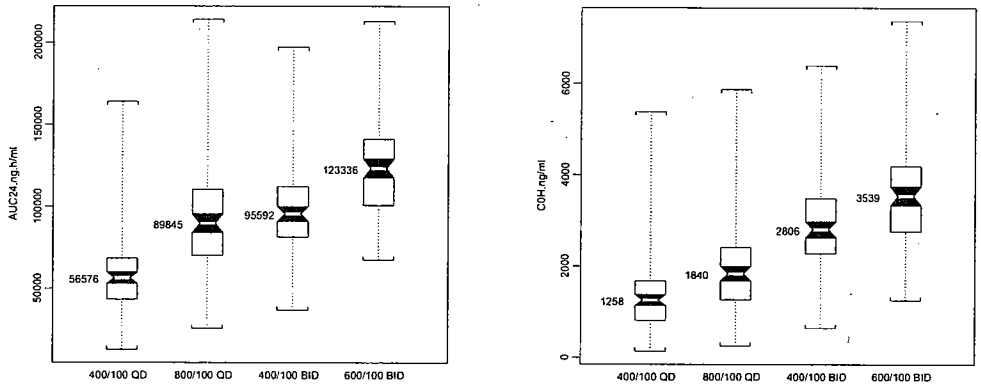
The exposure-response analysis of combined phase 2b trials (C202 and C213) demonstrated that the probability of having a response to darunavir treatment (measured either by 1 log reduction in viral load or HIV-1 RNA <50 copies/ml) by week 24 is related to the patient's darunavir inhibitory quotient. **The inhibitory quotient (IQ) is the ratio between steady-state trough concentration and the baseline IC_{50} value. Thus IQ combines the drug concentration and the susceptibility of a patient's virus to darunavir.** Larger IQ values are correlated with a higher response rates using logistic regression analysis.



The figure below summarizes darunavir exposure, IC_{50}, and fold-change values by darunavir IQ quartile. As illustrated, patients with the lowest IQ values in Q1 (and lowest response rate) have the highest IC_{50} values (increase in resistance). **Fold-change (FC) is a measure of the fold-increase in the IC_{50} value relative to a standard IC_{50} value for a wild-type HIV-1 virus with no mutations**. A higher FC indicates more resistant virus. Patients with the lowest response rate have the highest darunavir FC at baseline.



A key question is whether an individual patient's IQ can be increased by increasing trough concentrations of darunavir. Within the lowest quartile of IQ values (ranging from 1 to 149), median (95% CI) trough darunavir concentrations for the 600/100 mg BID dose group were lower than the range of values observed in higher IQ quartiles. Hypothetically, doubling of the trough concentrations would increase the IQ to a value that falls within second IQ quartile in 36 % of the patients. However, due to the less than proportional increase in exposure to darunavir with increasing doses, doubling of the trough concentrations would require a greater than doubling of dose of darunavir.



2.2.4.2. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for safety?

The exposure-toxicity analysis of combined phase 2b trials demonstrated that there is no clear relationship between darunavir exposure (measured by AUC_{24h}) and maximum change in cholesterol, lipids and LFT markers as well as in the incidence of adverse events.

2.2.4.3. Does darunavir prolong QT or QTc interval?

The sponsor conducted a definitive QT study (TMC114-C153) to assess the potential of darunavir to prolong the QT interval. The darunavir doses evaluated were 800/100 mg b.i.d. and 1600/100 mg q.d. The results of the study suggest that darunavir does not cause QT prolongation.

2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The recommended oral dose of 600/100 mg BID is consistent with the known exposure-response and exposure-toxicity relationships. The highest IQ values were observed in the 600/100 mg dose group and there are no additional toxicities observed with higher exposure to darunavir. Based on the population pharmacokinetic analysis of darunavir, dose adjustments are not required for race, gender, renal impairment, hepatitis B or C co-infection, and age greater than 65 years.

2.2.5. What are the PK characteristics of darunavir?

2.2.5.1. What are the single dose and multiple dose PK parameters?

The single and multiple dose pharmacokinetics of darunavir was assessed using the tablet formulation (TF036, also used in the pivotal Phase IIb trials) in study TMC114-C137. The results from the *in vitro* studies showed that darunavir is a substrate of CYP3A4. To achieve adequate TMC114 concentrations for efficacy, it must be administered with ritonavir, a potent CYP3A4 inhibitor. Therefore, all single and multiple dose PK parameters were determined in the presence of ritonavir. The mean concentration time curves of darunavir, administered as a tablet under fed conditions at different dosages in the presence of RTV is shown below.

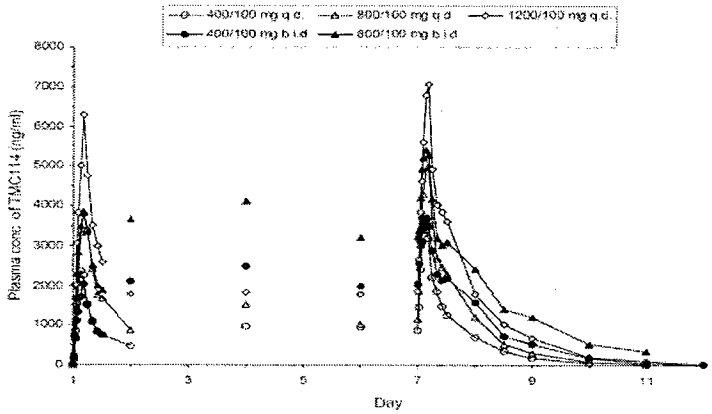


Table 3 and 4 show the PK results at the clinically recommended dose (600/100 mg b.i.d.) in healthy subjects (TMC114-C139) and HIV-1 infected subjects (integrated 24-week analysis from the PK sub-study of the two pivotal phase IIb studies) respectively.

Table 3: Summary of pharmacokinetic parameters of TMC114 at the clinically recommended dose in healthy subjects (TMC114-C139).

Parameter of TMC114	TMC114/RTV (600/100 mg b.i.d.) Reference (N = 17)	
	Mean (CV %)	Geometric Mean (min-max)
C_{0h} (ng/mL)	3154 (30.0)	3018 (1710-4680)
C_{max} (ng/mL)	5460 (22.1)	5341 (3840-8140)
C_{min} (ng/mL)	2609 (25.1)	2534 (1660-3910)
AUC_{12h} (ng*hr/mL)	46250 (20.4)	45347 (30670-66000)
$T_{1/2term}$ (h)	20.07 (54.5)	17.48 (6.26-44.68)
t_{max} (h) (median [range])	3.0 [1.5-4.0]	

Table 4: Summary of pharmacokinetic parameters of TMC114 in HIV-1 infected subjects.

Parameter	t_{max}: Median (Range); Mean ± SD			
	Darunavir/Ritonavir 400/100 mg q.d.	Darunavir/Ritonavir 800/100 mg q.d.	Darunavir/Ritonavir 400/100 mg b.i.d.	Darunavir/Ritonavir 600/100 mg b.i.d.
Week 24				
N	11	14	15	9
t_{max}, h	3.0 (1.0-4.0)	4.0 (2.0-6.0)	3.0 (1.0-12.0)[c]	3.0 (1.0-4.1)
C_{0h}, ng/mL	1199 ± 890	2667 ± 3048	2567 ± 994	4086 ± 1642
C_{12h}, ng/mL	-	-	2893 ± 1919	2993 ± 999
C_{24h}, ng/mL	1329 ± 785	2525 ± 2371	-	-
C_{min}, ng/mL	1083 ± 864	1956 ± 2131	2202 ± 820	3386 ± 1547
C_{max}, ng/mL	4748 ± 1853	7091 ± 4400	5309 ± 1695	6468 ± 1697
$C_{ss,av}$, ng/mL	2371 ± 1011	3812 ± 3388	3670 ± 1299	4329 ± 1104
AUC_{12h}, ng.h/mL	-	-	44042 ± 15583	51951 ± 13246
AUC_{24h}, ng.h/mL	56894 ± 24268	91485 ± 81305	-	-
FI, %	163 ± 49.6	157 ± 53.8	81.4 ± 21.5	74.3 ± 23.4

2.2.5.2. How does the PK of darunavir and its major active metabolites in healthy volunteers compare to that in patients?

The primary 24-week analysis of integrated data from study TMC114-C202 and TMC114-C213 (Pivotal Phase IIb studies) indicated that exposure to darunavir was positively correlated with baseline alpha-1 acid glycoprotein (AAG) concentrations in plasma.

The comparison between data obtained in HIV-1 infected subjects (TMC114-C202 and TMC114-C213) and data obtained in healthy subjects (TMC114-C137; comparison shown in table 5) showed that HIV-1 infected subjects had higher exposure for the same dose, possibly due to higher AAG concentrations.

However, these observations do not change the conclusions of studies conducted with darunavir in healthy subjects.

Table 5: Comparison between data obtained in HIV-1 infected subjects (TMC114-C202 and TMC114-C213) and data obtained in healthy subjects (TMC114-C137).

	t_{max}: Median; Mean					
	Darunavir/Ritonavir 400/100 mg q.d.		Darunavir/Ritonavir 800/100 mg q.d.		Darunavir/Ritonavir 400/100 mg b.i.d.	
Parameter	HIV-1 (TMC114-C202/213) Week 4	Healthy (TMC114-C137) Day 7	HIV-1 (TMC114-C202/213) Week 4	Healthy (TMC114-C137) Day 7	HIV-1 (TMC114-C202/213) Week 4	Healthy (TMC114-C137) Day 7
N	10	8	9	7	15	8
t_{max}, h	2.0	2.5	4.0	4.0	3.0	2.5
C_{0h}, ng/mL	1027	890	2385	1153	3683	2038
C_{min}, ng/mL	987	637	1898	1067	2748	1848
C_{max}, ng/mL	5252	3760	7534	5259	5731	3913
$C_{ss,av}$, ng/mL	2418	1610	3884	2546	4226	2793
AUC_{12h}, ng.h/mL	-	-	-	-	50714	33511
AUC_{24h}, ng.h/mL	58032	38636	93220	61106	-	-

2.2.5.3. What are the characteristics of drug absorption?

The results from the *in vitro* studies suggest that darunavir has an intermediate to high absorptive permeability in Caco-2 monolayers indicating sufficient membrane permeability to show adequate intestinal absorption. In vitro results suggest that darunavir is a P-gp substrate. In addition, *in vitro* studies have shown that darunavir is a CYP3A substrate.

The concomitant intake of ritonavir (a potent CYP3A inhibitor) with darunavir resulted in a significant increase in darunavir exposure. The results from trial TMC114-C114 (absolute BA study) showed that after oral administration of 600 mg TMC114/100 mg RTV, the systemic exposure to darunavir was increased by approximately 14-fold (net "pharmacokinetic enhancing effect" of ritonavir). In addition, the results from the same study showed a 5.5 fold decrease in the systemic clearance of darunavir in the presence of ritonavir thereby suggesting an approximate 2.2 -fold increase in absorption in the presence of ritonavir. In the absence of ritonavir, the absolute bioavailability was 37 %. When TMC114 was administered with ritonavir, the absolute bioavailability was 82 %.

2.2.5.4. What are the characteristics of drug distribution?

The *in vitro* plasma protein binding of darunavir was approximately 95 % in humans (study TMC114-N215). Darunavir was mainly present in the plasma, with limited distribution to the erythrocytes, and was mostly bound to α-1 acid glycoprotein and to a lesser extent to albumin. The volume of distribution of darunavir (determined in study TMC114-C114; absolute bioavailability study) was 130 L.

2.2.5.5. Does the mass balance study suggest renal or hepatic as the major route of elimination?

The results of the mass balance study (TMC114-C109) showed that after a single dose administration of ^{14}C-TMC114 in the presence of ritonavir, the majority of radioactivity was excreted in the feces. At 168 hours after dosing, 79.5 % of the radioactivity) was recovered in the feces and 13.9 % of the radioactivity was recovered in the urine. The radioactivity recovered in the feces and urine was comprised of the parent drug and metabolite(s).

The results from other Phase I studies suggested that less than 7 % of the administered dose is excreted unchanged in the urine. In conjunction with the results obtained from the absolute bioavailability study (TMC114-C114), the amount of the absorbed drug excreted unchanged through the renal route is < 10 %. These results suggest that renal elimination is a minor route for darunavir elimination.

2.2.5.6. What are the characteristics of drug metabolism?

In an *in vitro* study conducted to characterize the various CYP isozymes involved in the oxidative metabolism of darunavir (TMC114-NC112), only ketoconazole (predominantly CYP3A4 inhibitor) showed significant inhibition of the darunavir metabolism, and only CYP3A4 showed metabolic activity towards darunavir.

In humans, TMC114 was extensively metabolized *via* different metabolic pathways, namely aliphatic hydroxylation, aromatic hydroxylation, alicyclic hydroxylation, carbamate hydrolysis, glucuronidation and N-dealkylation. Several of the hydroxylated metabolites were further metabolized by either hydroxylation, oxidation to an acid metabolite, or carbamate hydrolysis. Several metabolites also originated from aliphatic or aromatic hydroxylation, alone or in combination with glucuronidation, of the carbamate hydrolysed metabolite of TMC114. TMC114 itself was also glucuronidated.

The results from the mass balance study (TMC114-C109) showed that at 48 hours after dosing with ^{14}C-TMC114 (in the presence of ritonavir), 41.2 % and 7.7 % of the drug was recovered unchanged in the feces and urine respectively. Based on the ratio of AUC values of unchanged drug and total radioactivity, unchanged TMC114 accounted for about 68 % of the total radioactivity in plasma of subjects administered ^{14}C-TMC114 in the presence of ritonavir.

2.2.5.7. What are the characteristics of drug excretion?

See Section 2.2.5.5.

2.2.5.8. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

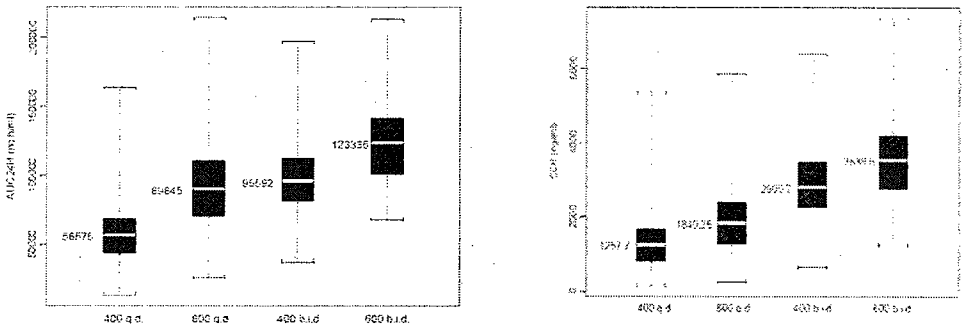
The PK parameters in studies TMC114-C202 and TMC114-C213 (pivotal Phase IIb studies in HIV-1 infected subjects) showed that there was a less than dose proportional increase in exposure (AUC) within the q.d. and the b.i.d. regimens.

Table 6: Summary of PK parameters (based on intensive sampling in the PK sub-study) in studies TMC114-C202 and TMC14-C213 (pivotal Phase IIb studies in HIV-1 infected subjects).

Parameter	t_{max}: Median (Range); Mean ± SD			
	Darunavir/Ritonavir 400/100 mg q.d.	Darunavir/Ritonavir 800/100 mg q.d.	Darunavir/Ritonavir 400/100 mg b.i.d.	Darunavir/Ritonavir 600/100 mg b.i.d.
Week 24				
N	11	14	15	9
t_{max}, h	3.0 (1.0-4.0)	4.0 (2.0-6.0)	3.0 (1.0-12.0)[5]	3.0 (1.0-4.1)
C_{0h}, ng/mL	1199 ± 890	2667 ± 3048	2567 ± 994	4086 ± 1642
C_{12h}, ng/mL	-	-	2893 ± 1919	2993 ± 999
C_{24h}, ng/mL	1329 ± 785	2325 ± 2371	-	-
C_{min}, ng/mL	1083 ± 864	1956 ± 2131	2202 ± 820	3386 ± 1547
C_{max}, ng/mL	4748 ± 1853	7091 ± 4400	5309 ± 1695	6468 ± 1697
C_{ave}, ng/mL	2371 ± 1011	3812 ± 3388	3670 ± 1299	4329 ± 1104
AUC_{12h}, ng.h/mL	-	-	44042 ± 15583	51951 ± 13240
AUC_{24h}, ng.h/mL	56894 ± 24268	91485 ± 81305	-	-
FL, %	163 ± 49.6	157 ± 53.8	81.4 ± 21.5	74.3 ± 23.4

In addition, Bayesian estimates of darunavir pharmacokinetic parameters from sparse sampling in trials TMC114-C202 and TMC114-C213 also suggested a less than dose proportional increase within the q.d. (400/100 mg [n = 118] and 800/100 mg [n = 118]) and the b.i.d. regimens (400/100 mg [n = 113] and [n = 119]), however, based on the analysis, a 50 % increase in dose (from 400 mg b.i.d to 600 mg b.i.d.) resulted in a 29 % increase in exposure (as compared to 18 % estimated based on the results from the intensive sampling in the pharmacokinetic substudy) as shown below.

Bayesian estimates of darunavir pharmacokinetic parameters from sparse sampling in trials TMC114-C202 and TMC114-C213.



2.2.5.9. How do PK parameters change with time following chronic dosing?

The pharmacokinetics of darunavir was determined in the pharmacokinetic sub-study, conducted as part of trials TMC114-C202 and TMC114-C213. The integrated pharmacokinetic parameters from the two studies estimated (based on intensive sampling) at week 4 and 24 are shown in table 7.

Table 7: Integrated pharmacokinetic parameters from the two Phase IIb studies (based on intensive sampling) at week 4 and 24.

Parameter	Mean ± SD; t_{max}: Median (Range)			
	Darunavir/Ritonavir 400/100 mg q.d.	Darunavir/Ritonavir 800/100 mg q.d.	Darunavir/Ritonavir 400/100 mg b.i.d.	Darunavir/Ritonavir 600/100 mg b.i.d.
Week 4				
N	10	9	13	8
t_{max}, h	2.0 (1.0-4.0)	4.0 (1.0-6.0)	3.0 (1.0-6.0)	3.0 (2.0-4.0)
C_{12h}, ng/mL	1027 ± 455	2385 ± 1178	3683 ± 1581	4010 ± 1635
C_{12h}, ng/mL	-	-	3204 ± 1117	2813 ± 1642
C_{24h}, ng/mL	1349 ± 659	2132 ± 861	-	-
C_{max}, ng/mL	987 ± 444	1898 ± 945	2748 ± 1369	2904 ± 1516
C_{max}, ng/mL	5252 ± 1609	7534 ± 2269	5731 ± 1836	6800 ± 1729
C_{min}, ng/mL	2418 ± 893	3884 ± 1445	4226 ± 1655	4520 ± 1864
AUC_{12h}, ng·h/mL	-	-	50714 ± 12632	54243 ± 22362
AUC_{24h}, ng·h/mL	58032 ± 21429	93220 ± 34677	-	-
FI, %	180 ± 45.7	153 ± 30.9	76.1 ± 25.9	96.0 ± 29.7
Week 24				
N	11	14	15	9
t_{max}, h	3.0 (1.0-4.0)	4.0 (2.0-6.0)	3.0 (1.0-12.0)	3.0 (1.0-4.1)
C_{12h}, ng/mL	1199 ± 890	2667 ± 3048	2567 ± 994	4086 ± 1642
C_{12h}, ng/mL	-	-	2893 ± 1919	2993 ± 909
C_{24h}, ng/mL	1329 ± 785	2325 ± 2571	-	-
C_{max}, ng/mL	1083 ± 864	1956 ± 2131	2202 ± 820	3386 ± 1547
C_{max}, ng/mL	4748 ± 1853	7091 ± 4400	5309 ± 1695	6468 ± 1697
C_{min}, ng/mL	2371 ± 1011	3812 ± 3588	3670 ± 1299	4329 ± 1104
AUC_{12h}, ng·h/mL	-	-	44042 ± 15585	51951 ± 13246
AUC_{24h}, ng·h/mL	86894 ± 24268	91485 ± 81305	-	-
FI, %	163 ± 49.6	157 ± 53.8	81.4 ± 21.5	74.3 ± 23.4

The number of subjects with data obtained from intensive sampling at Week 24 in Study TMC114-C202 was too low to enable any meaningful comparison of the exposure between Weeks 4 and 24. In Study TMC114-C213, there was no consistent trend across the treatment groups regarding changes in exposure between Weeks 4 and 24.

In addition, the mean darunavir exposure decreased by less than 15 % between Weeks 4 and 24.

2.2.5.10. What is the inter- and intra-subject variability in volunteers and patients, and what are the major causes of variability?

The data were not available to determine the intra-patient variability. The integrated pharmacokinetic data generated at Week 24 in study TMC114-C202 and TMC114-C213 suggest that the inter-subject variability in TMC114 exposure parameters was approximately 30 %.

2.3 Intrinsic Factors

2.3.1. What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The intrinsic factors that were evaluated for their potential effect on the pharmacokinetics of darunavir include gender, race, body weight, hepatitis B and/or C virus co-infection

status, and AAG concentrations in plasma at baseline. These factors were included in the subgroup analysis of the population pharmacokinetic data obtained in studies TMC114-C202 and TMC114-C213 (primary 24 week analysis) in HIV-1 infected subjects. The subgroup analysis showed that race, body weight, hepatitis B and/or C virus co-infection status had no apparent effect on the exposure to darunavir.

As described in section 2.2.5.2., the analysis suggested that exposure to darunavir was positively correlated with AAG concentrations in plasma.

2.3.2. Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1. Elderly

There was no clinical study conducted to specifically characterize the effect of age on the disposition of darunavir, however, the population pharmacokinetic analysis, based on integrated 24 week data from the two pivotal phase IIb trials suggested that the pharmacokinetics of darunavir are not considerably different across the age range (18-75 years; n = 12 $\geq$ 65 years) evaluated in HIV-1 infected subjects.

2.3.2.2. Pediatric Patients

The pharmacokinetics of darunavir in pediatric subjects is currently under investigation and the sponsor does not seek pediatric indication in this NDA.

2.3.2.3. Gender

In Study TMC114-C202, a trend towards higher AUC_{24h} and C_{0h} for darunavir in females than males was observed, which was most pronounced at the 400/100 mg q.d. and 400/100 mg b.i.d. groups. This trend was not observed in Study TMC114-C213. In the primary 24- week analysis of integrated data from studies TMC114-C202 and TMC114-C213, this effect of gender on darunavir exposure was primarily noted in the 400/100 mg q.d. group, as summarized in table 8.

Table 8: Effect of gender on the pharmacokinetics of darunavir (intergrated week 24 data from study TMC114-C202 and TMC114-C213).

Parameter	Mean ± SD; Median (Range)			
	Darunavir/Ritonavir 400/100 mg q.d.	Darunavir/Ritonavir 800/100 mg q.d.	Darunavir/Ritonavir 400/100 mg b.i.d.	Darunavir/Ritonavir 600/100 mg b.i.d.
Females				
N	11	14	16	14
$AUC_{\tau,ss}$ ng·h/mL	71413 ± 51814, 64886 (24320 – 136980)	94522 ± 22726, 92190 (59401 – 147340)	111934 ± 33734, 107100 (71170 – 197186)	127963 ± 30107, 126655 (89570 – 205360)
$C_{\tau,ss}$ ng/mL	1793 ± 1042, 1468 (496 – 4105)	1957 ± 571, 1911 (1108 – 3254)	3538 ± 1246, 3308 (2055 – 6391)	3655, 1001 3543 (2397 – 6180)
Males				
N	107	104	97	105
$AUC_{\tau,ss}$ ng·h/mL	56843 ± 21169, 54899 (13035 – 163950)	92421 ± 35003, 88803 (25828 – 214040)	97755 ± 25801 94130 (37030 – 168346	124262 ± 32676, 122306 (67714 – 212980)
$C_{\tau,ss}$ ng/mL	1295 ± 709, 1254 (140 – 5380)	1964 ± 1050, 1784 (256 – 3868)	2921 ± 993, 2787 (646 – 5707)	3567 ± 1175, 3483 (1255 – 7868)

Based on population pharmacokinetic analysis, the differences in clearance after addition of gender as a covariate was 16.8 %. This difference was not considered to be clinically relevant.

2.3.2.4. Race

Population pharmacokinetic analysis of darunavir in HIV infected subjects indicated that race had no apparent effect on the exposure to darunavir.

2.3.2.5. Renal Impairment

The pharmacokinetics of darunavir has not been studied in subjects with renal impairment. However, in view of the limited renal excretion of darunavir (< 10 % of the absorbed dose), the clearance of darunavir is not expected to be significantly altered in subjects with renal impairment. Further, the results from population pharmacokinetic analysis and safety evaluations suggested that the slightly higher darunavir exposure in HIV-1 infected subjects with moderate renal impairment (CL_{cr} between 30-60 mL/min, n = 20) is not clinically relevant.

2.3.2.6. Hepatic Impairment

The pharmacokinetics of darunavir has not been studied in subjects with hepatic impairment. Based on the information provided by the sponsor, a study to evaluate the effect of varying degree of hepatic impairment on the pharmacokinetics of darunavir is currently planned.

2.4 Extrinsic Factors:

2.4.1. What extrinsic factors influence dose-exposure and/or –response, and what is the impact of any differences in exposure on response?

The extrinsic factors that were considered for their potential effect on the pharmacokinetics of darunavir were the impact of concomitant food intake (described in section 2.5.3.), and the potential for drug-drug interactions.

The potential for drug-drug interactions has been investigated in 18 Phase I drug-drug interaction studies and the potential effect of concomitant medication was also explored in study TMC114-C215 *via* a drug-drug interaction screen. The subjects in this Phase IIb rollover study were HIV-1 positive and were administered the clinically recommended dose (600/100 mg b.i.d.) using the commercial formulation (F016).

2.4.2. Drug-Drug Interactions

2.4.2.1. Is there any *in vitro* basis to suspect *in vivo* drug-drug interactions?

Yes, CYP3A4 appears to be the CYP enzyme responsible for the oxidation of TMC114 in human liver microsomes, as evidenced by the significant inhibition of formation of all metabolites, M6, M19, M23, M27, M28 and M29 (up to 100 %) and the overall metabolism of TMC114 (up to 80 %) by CYP3A inhibitors (troleandomycin, ritonavir, ketoconazole, clarithromycin). In addition, the observation was in good agreement with correlation analysis and incubation with heterologously expressed recombinant CYP3A enzymes.

The inhibitory potential of TMC114 on the activity of human liver microsomal CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 was studied. Based on I/K_i values, the *in vivo* inhibitory potential of TMC114 on CYP3A4 enzyme is high. However its inhibitory potential on CYP2B6, CYP2C9, CYP2C19 and CYP2D6 is low. (see section 2.4.2.3)

2.4.2.2. Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Yes, darunavir is a substrate of CYP enzymes. In human liver microsomes (HLM), only ketoconazole (predominantly CYP3A inhibitor) showed significant inhibition of darunavir metabolism. In addition, out of the various human cytochrome P450 isozymes, only CYP3A4 showed metabolic activity towards darunavir. Based on these results, it was concluded that the oxidative metabolism of darunavir is almost exclusively catalyzed by CYP3A4.

Further, at the clinically recommended dose, ritonavir, a potent inhibitor of the CYP3A4 enzymes, caused an approximately 14-fold increase in darunavir exposure when compared to administration of darunavir alone (TMC114-C114). Therefore, in the drug-drug interaction studies and pivotal Phase IIb trials, ritonavir was used as a "pharmacokinetic enhancer" and co-administered with darunavir.

2.4.2.3. Is the drug an inhibitor and/or inducer of CYP enzymes?

The interaction between darunavir and CYP enzymes was tested *in vitro* (TMC114-NC123) using probe substrates selective towards CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A in the presence and absence of darunavir. The results of the study (shown in table 9 below) suggested that CYP3A was most potently inhibited by darunavir (K_i = 0.4 µM). The K_i values for the other CYP enzymes were at least 60-fold higher, and the resultant I/Ki values were all <1, indicating a significantly lower affinity (as compared to darunavir) for CYP3A. However, for CYP2C9, CYP2C19, and CYP2D6, the I/K_i ratio was >0.1.

In vivo, the combined effect of TMC114/RTV is relevant. In an *in vivo* study with the sensitive CYP3A substrate sildenafil (TMC114-C128), the administration of TMC114/rtv with sildenafil resulted in a 4-fold reduction in CL/F. The inhibitory/induction effect of darunavir/rtv on CYPs 2C9, 2C19 and 2D6 will be evaluated in a cocktail study.

Table 9: Interaction between darunavir and various CYP enzymes.

P450 Enzyme	Darunavir Concentration (µM)	Type of Inhibition	Mean Inhibition Constant K_i (µM)	I/Ki		
				I=7.1 µM[a]	I=10.0 µM[b]	I=10.5 µM[c]
CYP2B6	100	Non-competitive	500	0.01	0.02	0.02
CYP2C9	100	Competitive	52	0.14	0.19	0.20
CYP2C19	50	Competitive	25	0.28	0.40	0.42
CYP2D6	50	Competitive	41	0.17	0.24	0.26
CYP3A	0.5	Competitive	0.40	17.8	25.0	26.3

I = C_{max} at the recommended dose in µM.
[a] I = 7.1 µM (3913 ng/mL) for darunavir/ritonavir 400/100 mg b.i.d. (Study TMC114-C137)
[b] I = 10.0 µM (5460 ng/mL) for darunavir/ritonavir 600/100 mg b.i.d. (Study TMC125-C139).
[c] I = 10.5 µM (5736 ng/mL) for darunavir/ritonavir 800/100 mg b.i.d. (Study TMC114-C137).

An *in vitro* study with primary hepatocytes assessing mRNA activity (TMC114-NC171) showed a slight induction of CYP3A by darunavir at a concentration of 50 µM, which is approximately 4- to 5 times the *in vivo* C_{max} value of 11.8 µM (6468 ng/mL) obtained for darunavir in plasma after administration of darunavir/RTV 600/100 mg b.i.d. in HIV-1 infected subjects (trials TMC114-C202 and TMC114-C213). However, additional studies are needed to assess the *in vivo* CYP induction potential of darunavir.

2.4.2.4. Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

In vitro permeability studies using Caco-2 monolayers demonstrated that TMC114 is a substrate of efflux pumps (e.g. P-gp) and it is an inhibitor of P-gp. The clinical relevance of these in vitro findings (inhibition of p-gp by darunavir) is currently being investigated in study TMC114-C150 (drug-drug interaction study between darunavir and digoxin).

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

No study was conducted to evaluate other metabolic/transporter pathways.

2.4.2.6. Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Yes, the label specifies co-administration of other drugs with darunavir. Refer to section 2.4.2.7 and 2.4.2.8. for further details.

2.4.2.7. What other co-medications are likely to be administered to the target patient population?

In addition to other antiretroviral drugs, other co-medications likely to be administered in the target population (for which drug-drug interaction studies were conducted) with darunavir include statins, selective serotonin reuptake inhibitors (SSRIs), antimycobacterial, drugs used to treat erectile dysfunction, anti-fungals, anti-infectives, and drugs that alter intragastric pH.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

The sponsor conducted numerous drug-drug interaction studies (DDIs) with drugs that are routinely taken by HIV-1 infected subjects. All the DDIs (with the exception of the DDI with nevirapine) were conducted in healthy volunteers under fed conditions. The sponsor generally used 300/100 mg b.i.d. or 400/100 mg b.i.d of darunavir (as solution or tablets) in drug interaction studies. As indicated on page 32, the use of a lower dose and different formulation should not alter the interpretation of most drug interaction results. The following drugs should not be co-administered with darunavir/rtv due to serious adverse events (because of the co-administered drug) or due to potential loss of efficacy because of reduction in darunavir exposures. These conclusions are based on either clinical studies or expected drug-drug interactions.

- Drugs that should not be co-administered with darunavir/ritonavir due to serious adverse events: Antihistamines (astemizole, terfenadine), Ergot Derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonavine), GI motility agent (cisapride), neuroleptic (pimozide), and sedative/hypnotics (midazolam, triazolam) and HMG-CoA reductase inhibitors (lovastatin, simvastatin).
- Drugs that should not be co-administered with darunavir/ritonavir due to potential loss of efficacy of darunavir: Anticonvulsants (carbamazepine, phenobarbital, phenytoin), antimycobacterial (rifampin), herbal products (St. Johns. Wort), HIV protease inhibitors (Kaletra, saquinavir).

Table 10 shows the pharmacokinetic parameters for darunavir in the presence of co-administered drugs.

Table 10: Drug Interactions: Pharmacokinetic Parameters for Darunavir in the Presence of Co-administered Drugs.

Co-Administered Drug	Dose/Schedule		N	PK	LS Mean Ratio % (90% CI) of Darunavir Pharmacokinetic Parameters With/Without Coadministered Drug No Effect =1.00		
	Co-Administered Drug	Darunavir/ rtv			C_{max}	AUC	C_{min}
Co-Administration With Other Protease Inhibitors							
Atazanavir	300 mg q.d.[^]	400/100 mg b.i.d.[†]	13	↔	1.02 (0.96-1.09)	1.03 (0.94-1.12)	1.01 (0.88-1.16)
Indinavir	800 mg b.i.d.	400/100 mg b.i.d.	9	↑	1.11 (0.98-1.26)	1.24 (1.09-1.42)	1.44 (1.13-1.82)
Lopinavir/ Ritonavir	400/100 mg b.i.d.	300/100 mg b.i.d.	9	↓	0.61 (0.51-0.74)	0.47 (0.40-0.55)	0.35 (0.29-0.42)
Saquinavir hard gel capsule	1000 mg b.i.d.	400/100 mg b.i.d.	14	↓	0.83 (0.75-0.92)	0.74 (0.63-0.86)	0.58 (0.47-0.72)
Co-Administration With Other Antiretrovirals							
Efavirenz	600 mg q.d.	300/100 mg b.i.d.	12	↓	0.85 (0.72-1.00)	0.87 (0.75-1.01)	0.69 (0.54-0.87)
Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	8	↑	1.40[‡] (1.14-1.73)	1.24[‡] (0.97-1.57)	1.02[‡] (0.79-1.32)
Tenofovir Disoproxil Fumarate	300 mg q.d.	300/100 mg b.i.d.	12	↑	1.16 (0.94-1.42)	1.21 (0.95-1.54)	1.24 (0.90-1.69)
Co-Administration With Other Drugs							
Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	17	↔	0.83 0.72-0.96	0.87 0.75-1.01	1.01 0.81-1.26
Ketoconazole	200 mg b.i.d.	400/100 mg b.i.d.	14	↑	1.21 (1.04-1.40)	1.42 (1.23-1.65)	1.73 (1.39-2.14)
Omeprazole	20 mg q.d.	400/100 mg b.i.d.	16	↔	1.02 (0.95-1.09)	1.04 (0.96-1.13)	1.08 (0.93-1.25)
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	↔	0.97 (0.92-1.02)	1.02 (0.95-1.10)	1.07 (0.96-1.19)
Ranitidine	150 mg b.i.d.	400/100 mg b.i.d.	16	↔	0.96 (0.89-1.05)	0.95 (0.90-1.01)	0.94 (0.90-0.99)
Sertraline	50 mg q.d.	400/100 mg b.i.d.	13	↔	1.01 (0.89-1.14)	0.98 (0.84-1.14)	0.94 (0.76-1.16)

N = number of subjects with data; - = no information available.
[^] q.d. = daily
[†] b.i.d. = twice daily
[‡] Ratio based on between-study comparison.

Table 11 shows the pharmacokinetic parameters for co-administered drugs in presence of darunavir/ritonavir.

Table 11: Pharmacokinetic parameters for co-administered drugs in presence of darunavir/ritonavir.

Table 5: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Darunavir/Ritonavir							
	Dose/Schedule				LS Mean Ratio % (90% CI) of CoAdministered Drug Pharmacokinetic Parameters With/Without Darunavir No effect =1.00		
Co-Administered Drug	Co-Administered Drug	Darunavir/ rtv	N	PK	C_{max}	AUC	C_{min}
Co-Administration With Other Protease Inhibitors							
Atazanavir	300 mg q.d.^/100 mg RTV q.d. when administered alone 300 mg q.d. when administered with darunavir/ritonavir	400/100 mg b.i.d. †	13	↔	0.89 (0.78-1.01)	1.08 (0.94-1.24)	1.52 (0.99-2.34)
Indinavir	800 mg b.i.d./100 mg RTV b.i.d. when administered alone 800 mg b.i.d. when administered with darunavir/ritonavir	400/100 mg b.i.d.	9	↑	1.08 (0.95-1.22)	1.23 (1.06-1.42)	2.25 (1.63-3.10)
Lopinavir/ Ritonavir	400/100 mg b.i.d.	300/100 mg b.i.d.	9	↑	1.22 (1.12-1.32)	1.37 (1.27-1.49)	1.72 (1.46-2.03)
Saquinavir hard gel capsule	1000 mg b.i.d./100 mg RTV b.i.d. when administered alone 1000 mg b.i.d. when administered with darunavir/ritonavir	400/100 mg b.i.d.	12	↔	0.94 (0.78-1.13)	0.94 (0.76-1.17)	0.82 (0.52-1.30)
Co-Administration With Other Antiretrovirals							
Efavirenz	600 mg q.d.	300/100 mg b.i.d.	12	↑	1.15 (0.97-1.35)	1.21 (1.08-1.36)	1.17 (1.01-1.36)
Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	8	↑	1.18 (1.02-1.37)	1.27 (1.12-1.44)	1.47 (1.20-1.82)
Tenofovir	300 mg q.d.	300/100 mg	12	↑	1.24	1.22	1.37

Disoproxil Fumarate		b.i.d.			(1.08-1.42)	(1.10-1.35)	(1.19-1.57)
Co-Administration With Other Drugs							
Atorvastatin	40 mg q.d. when administered alone 10 mg q.d. when administered with darunavir/ritonavir	300/100 mg b.i.d.	15	↑	0.56 (0.48-0.67)	0.85 (0.76-0.97)	1.81 (1.37-2.40)
Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	17	↑	1.26 (1.03-1.54)	1.57 (1.35-1.84)	2.74 (2.30-3.26)
Ketoconazole	200 mg b.i.d.	400/100 mg b.i.d.	15	↑	2.11 (1.81-2.44)	3.12 (2.65-3.68)	9.68 (6.44-14.55)
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	↓	0.64 (0.59-0.71)	0.61 (0.56-0.66)	0.63 (0.55-0.73)
Pravastatin	40 mg single dose	600/100 mg b.i.d.	14	↑	1.63 (0.95-2.82)	1.81 (1.23-2.66)	-
Sertraline	50 mg q.d.	400/100 mg b.i.d.	13	↓	0.56 (0.49-0.63)	0.51 (0.46-0.58)	0.51 (0.45-0.57)
Sildenafil	100 mg (single dose) administered alone 25 mg (single dose) when administered with darunavir/ritonavir	400/100 mg b.i.d.	16	↑	0.62 (0.55-0.70)	0.97 (0.86-1.09)	-

N = number of subjects with data;- = no information available.
^ q.d. = daily
† b.i.d. = twice daily

For tables 10 and 11, further details and discussion are available in the individual study reviews.

- Drug-drug interaction studies were conducted using the solution/tablet under fed conditions. When given in the presence of low-dose ritonavir (100 mg b.i.d.), darunavir doses of 300 or 400 mg b.i.d. were generally used in the drug-drug interaction studies.
- The results from the studies were extrapolated to the clinically recommended dose (600/100 mg b.i.d) based on the following considerations:
  - Considerable overlap in the exposure between the 400/100 mg and 600/100 mg TMC114/RTV. Therefore, if no significant interaction was observed at 400/100, the data can be extrapolated to 600/100.
  - Drug Interactions "typical" of RTV-boosting e.g. sildenafil, atorvastatin, rifabutin, ketoconazole: The results from these studies would be similar if 600/100 mg b.i.d. darunavir was used since the effect on the interacting drug is driven by ritonavir.
  - Drug Interactions observed with Saquinavir and Lopinavir- No meaningful conclusions could be drawn due to significant decrease in darunavir exposures, study discontinuation, or high variability. These drugs are disallowed and will remain disallowed until further evaluation is conducted using the clinically recommended dose.

Table 12 shows the established and other potentially significant drug interactions based on which, alterations in dose or regimen may be recommended. The interaction between darunavir and the drug preceding the asterisk (*) sign was evaluated in a clinical study; the interactions between darunavir and other drugs (not preceding the asterisk sign) are predicted. Further, some of the listed drug interactions are typical for ritonavir boosted PIs.

Table 12: Established and other potentially significant drug interactions: alterations in dose or regimen may be recommended based on drug interaction studies or predicted interaction.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz*	↓ darunavir ↑ efavirenz	Co-administration of darunavir/rtv and efavirenz decreased darunavir AUC by 13% and C_{min} by 31%. The clinical significance has not been established. The combination of PREZISTA/rtv and efavirenz should be used with caution.
Nevirapine*	↔ darunavir ↑ nevirapine	PREZISTA/rtv and nevirapine can be co-administered without any dose adjustments.
HIV-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Didanosine		It is recommended that didanosine be administered on an empty stomach. Therefore, didanosine should be administered one hour before or two hours after PREZISTA/rtv (which are administered with food).
Tenofovir Disoproxil Fumarate*	↔ darunavir ↑ tenofovir	PREZISTA/rtv and tenofovir disoproxil fumarate can be co-administered without any dose adjustments.
HIV-Antiviral Agents: HIV-Protease Inhibitors (PIs)		
Atazanavir* (The reference regimen for atazanavir was atazanavir/ritonavir 300/100 mg q.d.)	↔ darunavir ↔ atazanavir	PREZISTA/rtv and atazanavir (300 mg q.d.) can be co-administered.
Indinavir* (The reference regimen for	↑ darunavir ↑ indinavir	The appropriate dose of indinavir in combination with PREZISTA/rtv has not been established. The reference regimen

indinavir was indinavir/ritonavir 800/100 mg b.i.d.)		used in the study was not approved.
Lopinavir/ritonavir*	↓ darunavir ↑ Lopinavir	Due to decrease in the exposure (AUC) of darunavir by 53%, appropriate doses of the combination have not been established. Hence, it is not recommended to coadminister lopinavir/ritonavir and PREZISTA, with or without an additional low-dose of ritonavir.
Saquinavir*	↓ darunavir ↔ saquinavir	Due to a decrease in the exposure (AUC) of darunavir by 26%, appropriate doses of the combination have not been established. Hence, it is not recommended to coadminister saquinavir and PREZISTA, with or without low-dose ritonavir.
Other Agents		
Antiarrhythmics: bepridil, lidocaine (systemic), quinidine, amiodarone	↑ antiarrhythmics	Concentrations of bepridil, lidocaine, quinidine and amiodarone may be increased when coadministered with PREZISTA/rtv. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when coadministered with PREZISTA/rtv.
Anticoagulant: Warfarin	↓ warfarin ↔ darunavir	Warfarin concentrations may be affected when coadministered with PREZISTA/rtv. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with PREZISTA/rtv.
Anti-infective: clarithromycin*	↑ clarithromycin	No dose adjustment of darunavir or clarithromycin is required for patients with normal renal function. For patients with renal impairment, the following dose adjustments should be considered: • For subjects with CLcr of 30-60 mL/min, the dose of clarithromycin should be reduced by 50%. • For subjects with CLcr of <30 mL/min, the dose of clarithromycin should be reduced by 75%.
Antidepressant: Trazodone	↑ Trazodone	Concomitant use of trazodone and PREZISTA/rtv may increase

		concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A inhibitor such as PREZISTA/rtv, the combination should be used with caution and a lower dose of trazodone should be considered.
Antifungals: ketoconazole*, itraconazole, voriconazole	↑ ketoconazole ↑ darunavir ↑ itraconazole (not studied) ↓ voriconazole (not studied)	Ketoconazole and itraconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of ketoconazole, itraconazole, and darunavir/ritonavir may increase plasma concentration of darunavir. Plasma concentrations of ketoconazole or itraconazole may be increased in the presence of darunavir/ritonavir. When coadministration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg. Co-administration of voriconazole with darunavir/ritonavir has not been studied. Administration of voriconazole with ritonavir (100 mg twice daily) decreased the AUC of voriconazole by an average of 39%. Voriconazole should not be administered to patients receiving darunavir/ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
Antimycobacterial: Rifabutin* Note: Due to dropouts, the study results were not interpretable.	↑ rifabutin ↓ darunavir	Rifabutin is an inducer and substrate of CYP450 enzymes. Concomitant use of rifabutin and darunavir in the presence of ritonavir is expected to increase rifabutin plasma concentrations and decrease darunavir plasma concentrations. When indicated, it is recommended to administer rifabutin at a dosage of 150 mg once every other day when coadministered with PREZISTA/rtv.
Calcium Channel Blockers: felodipine, nifedipine, nicardipine	↑ calcium channel blockers	Plasma concentrations of calcium channel blockers (e.g. felodipine, nifedipine, nicardipine) may increase when PREZISTA/rtv are coadministered. Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: dexamethasone	↓ darunavir ↑ fluticasone	Use with caution. Systemic dexamethasone induces CYP3A and can

fluticasone propionate	propionate	thereby decrease darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA. Concomitant use of inhaled fluticasone propionate and PREZISTA/rtv may increase plasma concentrations of fluticasone propionate. Alternatives should be considered, particularly for long term use.
HMG-CoA Reductase Inhibitors: Atorvastatin* Pravastatin*	↑ Atorvastatin ↑ Pravastatin	When atorvastatin and PREZISTA/rtv is co-administered, it is recommended to start with the lowest possible dose of atorvastatin with careful monitoring. A gradual dose increase of atorvastatin may be considered based on the clinical response. When PREZISTA/rtv was administered with pravastatin, the mean increase in pravastatin AUC was 81 %. However, pravastatin AUC increased by up to 5-fold in some patients. The mechanism of interaction is not known.
H2-Receptor Antagonists and Proton Pump Inhibitors: omeprazole*, ranitidine*	↔ darunavir	PREZISTA/rtv can be coadministered with H2-receptor antagonists and proton pump inhibitors without any dose adjustments.
Immunosuppressants: cyclosporine, tacrolimus, sirolimus	↑ immunosuppressants	Plasma concentrations of cyclosporine, tacrolimus or sirolimus may be increased when coadministered with PREZISTA/rtv. Therapeutic concentration monitoring of the immunosuppressive agent is recommended for immunosuppressant agents when coadministered with PREZISTA/rtv.
Narcotic Analgesic: methadone	↓ methadone	When methadone is coadministered with PREZISTA/rtv, patients should be monitored for opiate abstinence syndrome, as ritonavir is known to induce the metabolism of methadone, leading to a decrease in its plasma concentrations. An increase in methadone dosage may be considered based on the clinical response.
Oral Contraceptives/estrogen: ethinyl estradiol norethindrone (study completed; results not included in the NDA	↓ ethinyl estradiol ↓ norethindrone	Plasma concentrations of ethinyl estradiol may be decreased due to induction of its metabolism by ritonavir. Alternative or additional contraceptive measures should be used when estrogen-based contraceptives are coadministered with

submission)		PREZISTA/rtv.
PDE-5 inhibitors: sildenafil*, vardenafil, tadalafil	↑ PDE-5 inhibitors	Concomitant use of PDE-5 inhibitors with PREZISTA/rtv should be done with caution. If concomitant use of PREZISTA/rtv with sildenafil, vardenafil, or tadalafil is required, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours, is recommended.
Selective Serotonin Reuptake Inhibitors (SSRIs): sertraline*, paroxetine*	↔ darunavir ↓ sertraline ↓ paroxetine	If sertraline or paroxetine is coadministered with PREZISTA/rtv, the recommended approach is a careful dose titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with PREZISTA/rtv should be monitored for antidepressant response.

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?

The assessment of the inhibitory/induction potential of darunavir/rtv on CYP2C9, CYP2C19, and CYP2D6 remains unresolved. This will be evaluated as part of the post marketing commitments.

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

As part of post marketing commitments (PMCs), the sponsor will conduct the following studies: Assessment of the inhibitory/induction potential of darunavir/rtv towards CYP2C9, CYP2C19, and CYP2D6; the effect of hepatic impairment (Child Pugh A and Child Pugh B liver disease); drug-drug interaction studies with rifabutin, buprenorphine/naloxone, and carbamazepine. In addition to these PMCs, the sponsor plans to conduct drug-drug interaction studies with methadone.

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?

The solubility of darunavir in water is 0.15 mg/mL (pH 7.6). It is very slightly soluble in aqueous solutions. The solubility increases with decreasing pH as shown in the table below.

Table 13: Effect of pH on the solubility of darunavir.

Solvent	Solubility (g/100 mL)	pH of Solution
Water	0.015	7.6
0.1 N HCl	0.096	1.0
0.01 N HCl	0.025	2.1
citrate-HCl buffer pH 2	0.025	2.0
citrate-NaOH buffer pH 5	0.013	5.0
phosphate buffer pH 7	0.014	7.0
borate-KCl-NaOH buffer pH 9	0.016	9.0
phosphate-NaOH buffer pH 12	0.014	12.0
simulated gastric fluid	0.083	1.1
simulated intestinal fluid	0.016	7.4

Darunavir remains very slightly soluble in the pH region between 1 and 12. The *in vitro* permeability data suggest intermediate to high absorptive permeability in Caco-2 monolayers, indicating that darunavir would exhibit sufficient membrane permeability to obtain adequate intestinal absorption.

The sponsor has not provided any BCS classification for darunavir.

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

The relative bioavailability of the proposed to-be-marketed formulation (F016) to the pivotal clinical trial formulations (F001 and F002) was assessed in study TMC114-C116. Table 14 provides the description of the clinical trial and commercial formulations used in the study TMC114-C116 (Pivotal Bioequivalence Trial).

Table 14: Description of the clinical trial and commercial formulations used in the study TMC114-C116.

Name	Amount Required (mg)		
	F002 eq. 200 mg Phase IIb	F001 eq. 400 mg Phase IIb	F016 eq. 300 mg Phase III/commercial
TMC114 ethanolate	[redacted]	[redacted]	[redacted]
Microcrystalline Cellulose and Colloidal [redacted] Silica [5]			
Crospovidone			
Magnesium Stearate			
Total Core Weight			
Purified Water [6]	-	-	
OPADRY®: Orange Film-coat	-	-	
Total Tablet Weight	*416.8*	*833.6*	*650.2*

[5] Quantity of TMC114 ethanolate required for delivery of 200, 400 and 500 mg of TMC114, respectively.

The results of the study showed that under fasted conditions and in the presence of a low dose of RTV, the commercial formulation (F016) failed to meet bioequivalence limits (80% to 125%) compared to the clinical trial formulations (F002 and F001). For tablet F016 versus tablet F002, point estimates (and 90 % CI) were 134 % (122.3-146.7 %) for AUC_{last}, 133.4 % (121.0-146.9 %) for C_{max} and 135.4 % (123.2-149) for AUC_{∞}. For tablet F016 versus tablet F001, point estimates (and 90% CI) were 134.4 % (123.1-146.8 %) for AUC_{last}, 122.5 % (113.0-132.8 %) for C_{max} and 137.9 % (123.4-154 %) for AUC_{∞}.

The population pharmacokinetic model was used to estimate the increase in exposure to darunavir with the commercial formulation (F016). The relative bioavailability was estimated as 1.18 (BSV, 26%) in HIV-1 patients with the commercial formulation. There were 21 patients in the 600/100 mg BID dose group who had parameter estimates for both the clinical and commercial formulations. A two-way ANOVA showed that geometric mean AUC_{tau} ratio for the commercial formulation relative to the clinical formulations was 1.09 (90% CI: 0.999, 1.18). Therefore, the increase in bioavailability of the commercial formulation has little impact on darunavir exposure in HIV-1 patients (see discussion in 2.5.2.2.).

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

The sponsor intends to market only one strength (300 mg), hence, 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 %?

The results of study TMC114-C116 showed an approximately 35 % higher exposure (AUC) with the commercial tablet formulation (F016) compared to each of the clinical tablet formulations (F001 and F002). This higher exposure is not clinically relevant because of the following reasons:

- The bioequivalence study was designed as a single-dose study under fasted conditions in healthy subjects, however, in the clinical setting, HIV-1 infected subjects will be using TMC114 at steady-state and under fed conditions (as in pivotal studies TMC114-C202 and TMC114-C213, and in the rollover study TMC114-C215). Under these conditions, the commercial and clinical trial tablet formulations were shown to have comparable bioavailability.
- There was similarity in the safety profiles (incidence of adverse events) of study TMC114-C202 and TMC114-C213 before and after the switch to the commercial formulation.
- No apparent relationship was observed between exposure and safety endpoints for study TMC114-C215 (Phase IIb safety study in which 292 subjects were started at the clinically recommended 600/100 mg dose using the commercial formulation (F016)).

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?

Refer to section 2.5.2.2.

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

When darunavir was administered with food, the relative bioavailability of darunavir (given as the 400-mg tablet formulation TF036 and coadministered with low-dose RTV) under fasted conditions was approximately 30 % lower than under fed conditions. Therefore, the proposed label recommends that darunavir should be taken with food.

The results from study TMC114-C143 showed that the type of the meals does not affect exposure to darunavir. The various meals tested were:

- Standard breakfast: 4 slices of bread, 1 slice of ham, 1 slice of cheese, butter, jelly and 2 cups of coffee or tea with milk and/or sugar, if desired. (fat: 21 g, carbohydrates: 67 g, proteins: 19 g)

- High-fat breakfast: 2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with 1 slice of cheese and 240 mL of whole milk. (fat: 56 g, carbohydrates: 65 g, proteins: 41 g)

- Nutritional drink rich in proteins: Ensure® 250 ml (fat: 8.4 g, carbohydrates: 33.4 g, proteins: 10.5 g)

- A croissant with coffee: (fat: 12 g, carbohydrates: 28 g, proteins: 5g)

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

The sponsor did not conduct a fed bioequivalence study.

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

The sponsor proposed the following dissolution recommendation for darunavir.

USP Apparatus 2 (paddle) at 75 rpm in 900 mL of 2.0 % Tween-20 in 0.05 M sodium phosphate buffer (pH = 3.0) at 37 ± 0.5 °C. The proposed specification for dissolution release and stability is [redacted] % (Q) in 30 minutes. All the batches tested over the course of

the stability studies complied with the proposed specification for release and stability as shown in the table 15.

Table 15: % darunavir released (as a function of time) of various batches.

	Dissolution (% released) mean (min-max)				
Batch	10 min	20 min	30 min	45 min	60 min
PD1352	78 ( )	93 ( )	97 ( )	97 ( )	98 ( )
PD1348	75 ( )	89 ( )	93 ( )	96 ( )	96 ( )
PD1326	72 ( )	88 ( )	93 ( )	95 ( )	96 ( )
PD1324	75 ( )	92 ( )	97 ( )	98 ( )	99 ( )
PD1322	76 ( )	93 ( )	97 ( )	98 ( )	99 ( )
PD1328	74 ( )	90 ( )	95 ( )	96 ( )	96 ( )
PD1419	67 ( )	87 ( )	94 ( )	96 ( )	97 ( )
PD1330	78 ( )	94 ( )	98 ( )	98 ( )	98 ( )
4NG4517-X	85 ( )	95 ( )	98 ( )	100 ( )	100 ( )
4NG4518-X	84 ( )	95 ( )	98 ( )	99 ( )	99 ( )
4NG4689-X	80 ( )	92 ( )	95 ( )	95 ( )	95 ( )

The dissolution results comply with the proposed specification using the proposed dissolution method and are acceptable. See individual review for further details.

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, unresolved issues related to *in vitro* dissolution or *in vivo* BA and BE that need to be further addressed.

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 moities 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 darunavir except in the ^{14}C mass balance study (TMC114-C109).

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 darunavir and ritonavir. Although measurement of free concentrations of both moieties may be more clinically relevant, it is standard to measure total concentrations of protease inhibitors.

2.6.4 What bioanalytical methods are used to assess concentrations?

The bioanalytical method used for the determination of darunavir and ritonavir was developed using the LC-MS/MS system. The calibration ranges for this assay were 10-10,000 ng/mL for darunavir and 5-5000 ng/mL for ritonavir. The sensitivity/LLOQ was set to 10 ng/mL for darunavir and 5 ng/mL for ritonavir (for processing a sample volume of 100 µL). The overall recovery was 120.9 % for darunavir and 119.8 % for ritonavir. The accuracy and precision for darunavir and ritonavir quality control samples (darunavir: 10.0 [LLOQ], 40.0, 400, 8000 and 20,000 ng/mL); ritonavir: 5.00, 20.0, 200, 4000 and 10,000 ng/mL) complied with the prespecified 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.

15 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio- 1

4. Appendices

4.1 Individual Study Review

BIOPHARMACEUTICS

The sponsor provided the pharmacokinetic data from 12 clinical studies (description provided in table 1) conducted to evaluate the bioavailability of an oral solution, tablet, powder, and capsule formulations of darunavir (TMC114) ethanolate. The initial studies were conducted using the oral solution formulation of TMC114 (TF019, 20 mg base eq/mL), but as solid dosage form is preferred for chronic therapy due to ease of administration, solid dosage forms were evaluated to determine the relative bioavailability of these formulations compared to the reference oral solution.

The proposed commercial formulation is the 300 mg film coated (Opadry®), orange, oval shaped tablet containing TMC114 ethanolate eq. 300 mg (F016). The pivotal Phase 2b efficacy studies (on which the indication is based) and the majority of drug interaction studies were conducted using the optimized tablet formulation (F001 and 002). Hence, relative bioavailability studies conducted with only the solution and/or capsule formulations (TMC114-102, TMC114-117, and TMC114-136) and studies conducted to optimize the various physiochemical characteristics of the clinical trial formulation(s) F001 (400 mg) and F002 (200 mg) (TMC114-C144, TMC114-148, TMC114-154, and TMC114-156) were not reviewed in detail; summaries of the studies have been presented. On the other hand, pivotal studies such as bioequivalence, food effect, and absolute bioavailability were reviewed in detail.

The review of biopharmaceutical studies is divided into two sections: Section A and Section B. Section A consists of summary of the studies TMC114-102, TMC114-117, and TMC114-136, TMC114-C144, TMC114-148, TMC114-154, and TMC114-156.

Section B consists of detailed reviews of studies TMC114-103, TMC114-C114, TMC114-C116, TMC114-C118, and TMC114-C143.

Table 1: Review of Biopharmaceutics Studies

	TMC114		
Study Number	**Dosage Form**	**Formulation Number**	**Dosage Form of Co-administered Drug**
Relative Bioavailability Studies-Testing of Experimental Formulations			
TMC114-C103	20 mg base eq/mL solution 400 mg oral tablet 800 mg oral powder 100 mg oral hard gelatin capsule	TF019 TF036 TF041 TF038	Not Applicable
TMC114-C118	20 mg base eq/mL oral solution 400 mg oral tablet	TF019 TF036	Ritonavir: 100 mg commercial soft gelatin capsule
Relative Bioavailability Studies- Formulations Not Developed Further			
TMC114-C117	20 mg base eq/mL solution 100 mg oral hard gelatin capsule 150 mg oral hard gelatin capsule 150 mg oral hard gelatin capsule	TF019 TF042 TF043 TF044	Ritonavir: 100 mg commercial soft gelatin capsule
TMC114-C136	20 mg base eq/mL solution 60 mg oral hard gelatin capsule 60 mg oral hard gelatin capsule	TF019 TF051 TF052	Ritonavir: 100 mg commercial soft gelatin capsule
Absolute Bioavailability Study			
TMC114-C114	5 mg base eq/mL I.V. solution 400 mg oral tablet[a] 200 mg oral tablet[a]	F008 F014 F015	Ritonavir: 100 mg commercial soft gelatin capsule
Pivotal Bioequivalence Study			
TMC114-C116	200 mg oral tablet 400 mg oral tablet 300 mg commercial oral tablet	F002 F001 F016	Ritonavir: 100 mg commercial soft gelatin capsule
Food Effect Studies			
TMC114-C102	20 mg base eq/mL oral solution	TF019	Not Applicable
TMC114-C143	400 mg oral tablet[a]	F014	Ritonavir: 100 mg commercial soft gelatin capsule

Table 1: Review of Biopharmaceutics Studies (continued)

Study Number	TMC114 Dosage Form	TMC114 Formulation Number	Dosage Form of Co-administered Drug
Relative Bioavailability Studies-Optimization of Selected Tablet Formulations			
TMC114-C144	400 mg oral tablet 400 mg oral tablet 400 mg oral tablet 400 mg oral tablet	F001 F011 F012 F013	Ritonavir: 100 mg commercial soft gelatin capsule
TMC114-C148	400 mg oral tablet 400 mg oral tablet 400 mg oral tablet 400 mg oral tablet	TF036 F036A F036B F036C	Ritonavir: 100 mg commercial soft gelatin capsule
TMC114-C154	200 mg oral tablet[b] 200 mg oral tablet[c] 200 mg oral tablet[c]	F002, Batch X F002, Batch Y F002, Batch Z	Ritonavir: 100 mg commercial soft gelatin capsule
TMC114-C156	200 mg oral tablet[b] 200 mg oral tablet[c]	F002, Batch X F009, Batch Y[d]	Ritonavir: 100 mg commercial soft gelatin capsule

a: Composition proportionally identical to commercial formulation F016
b: Darunavir drug substance supplied [redacted]
c: Darunavir drug substance supplied by Cilag, Switzerland
d: Darunavir [redacted]

Reviewer's Note
The [redacted] of TMC114 used in study TMC114-C154 were [redacted] drug substance, however, in study TMC114-C156, batch X was [redacted] batch Y [redacted].

SECTION A

TMC114-C102

Title
Effect of Food on Bioavailability of an Oral Solution of Darunavir, Without Ritonavir.

Study Design
This was an open-label, controlled, 2-way crossover study to investigate the effect of food on the bioavailability of a single dose of an oral solution of darunavir (TF019). A total of 12 healthy subjects took a single 800-mg dose of the oral solution of darunavir in 2 sessions, once under fasted conditions and once under fed conditions, immediately after a standardized breakfast.

Fig 1 shows the mean plasma concentration time profiles of a single dose of 800 mg darunavir given as an oral solution under fed and fasted conditions.

Fig 1: Mean plasma concentration time profiles of a single dose of 800 mg darunavir given as a oral solution under fed and fasted conditions.

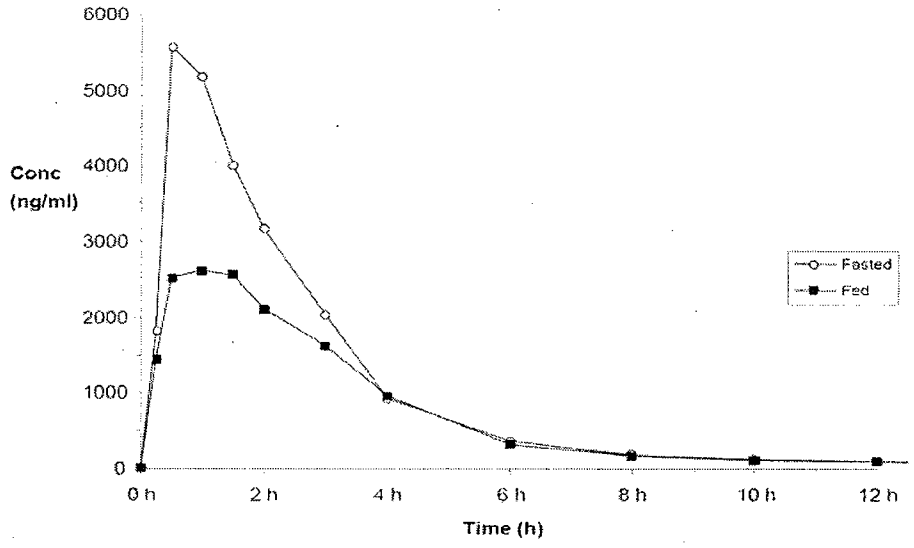


Table 1 shows the pharmacokinetic parameters of an oral solution of darunavir under fasted and fed conditions.

Table 1: Pharmacokinetic parameters of an oral solution of darunavir under fasted and fed conditions.

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio (%) [a] (Test:Reference)	90% CI
	Darunavir 800 mg Fasted Conditions (Reference)	Darunavir 800 mg Fed conditions (Test)		
N	12	12		
t_{max}, h	0.5 (0.5-1.5)	1.0 (0.5-2.0)		
C_{max}, ng/mL	6860 ± 2231	3051 ± 1442	42.21	36.2-49.2
AUC_{last}, ng.h/mL	15431 ± 5337	10684 ± 4171	67.83	61.6-74.7

N = number of subjects with data.
[a] Ratio based on geometric means.

When administered as an oral solution, under fed conditions, in the absence of ritonavir, the exposure to darunavir, as measured by AUC_{last} and C_{max}, was approximately 32 % and 58 % lower, respectively, than under fasted conditions.

Reviewer's Comment(s)

- *Due to the decrease in the bioavailability of TMC114 solution, when administered in the presence of food, the solution formulation was administered in the fasted state in the study TMC114-C201, the proof-of-principle study.*

- *The pharmacokinetic data from this study provides important information regarding the disposition of darunavir when administered as a solution formulation. However, the use of solution formulation and the absence of co-administered ritonavir renders the data to be purely exploratory in nature because the sponsor will market the 300 mg tablet formulation that will be co-administered with ritonavir.*

5 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio- 1

TMC114-C144

Title
Relative Bioavailability of Darunavir Given as the Test Tablets F011, F012, and F013 Compared to the Reference Tablet F001, With Low-Dose Ritonavir (Effect of Change in Excipients).

Study Design
This was an open-label, randomized, 4-way crossover study in 16 healthy subjects to determine the relative bioavailability of darunavir formulated as the test tablets F011, F012, and F013, as compared to the reference tablet F001 (previously termed TF036), all co-administered with low-dose ritonavir (100 mg b.i.d.). **This study investigated the effect of including varying levels of [redacted] and/or the presence or absence of crospovidone on relative bioavailability of TMC114.** During 4 sessions, each subject received single doses of 400 mg darunavir formulated as the reference tablet F001 (Treatment A) and as the test tablets F011, F012, and F013 (Treatments B, C, and D respectively). All intakes were under fed conditions. Ritonavir 100 mg b.i.d. was given from 2 days before until 2 days after administration of darunavir.

Table 1 provides the composition of the tablet formulations (400 mg) used in the trial.

Table 1: Composition of Tablet Formulations Used in the Trial

	Composition Weight (mg)
Darunavir ethanolate	
[redacted] **microcrystalline cellulose**	
Crospovidone	
[redacted]	
Magnesium stearate	
OPADRY orange film-coat	

*: equivalent in composition to TF036

Fig 1 shows the mean plasma concentration-time profiles of darunavir after single 400 mg dose of darunavir given as tablet formulation F001 (treatment A), F011 (treatment B), F012 (treatment C), or as F013 (treatment D), co-administered with low-dose ritonavir

Fig 1: Mean plasma concentration-time profiles of darunavir after single 400 mg dose of darunavir given as tablet formulation F001 (treatment A), F011 (treatment B), F012 (treatment C), or as F013 (treatment D), co-administered with low-dose ritonavir

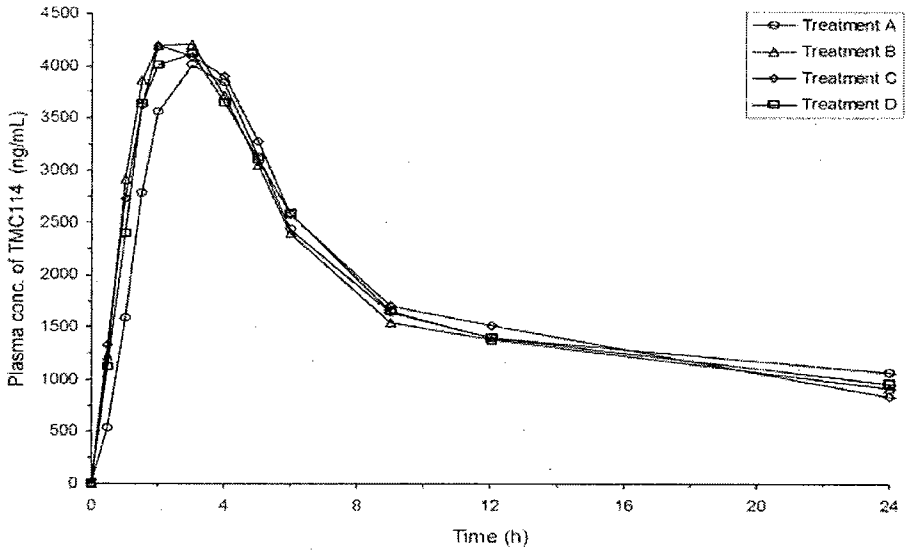


Table 2 shows the pharmacokinetic parameters of the 4 different formulations of darunavir, co-administered with low-dose ritonavir.

Table 2: Pharmacokinetic parameters of the 4 different formulations of darunavir, co-administered with low-dose ritonavir.

Parameter	N	Mean ± SD; t_{max}: Median (Range)		Ratio (%) [a] (Test:Reference)	90% CI
		Treatment A: Darunavir/Ritonavir 400/100 mg Tablets (F001) (Reference)	Treatment B, C, or D: Darunavir/Ritonavir 400/100 mg Tablets (F011, F012, or F013) (Test)		
Treatment A: Darunavir Tablets (F001) vs. Treatment B: Darunavir Tablets (F011)					
t_{max}, h	15	3.0 (1.5 - 4.0)	2.0 (1.0 - 4.0)	-	-
C_{max}, ng/mL	15	4358 ± 1516	4634 ± 1253	107.7	95.7 - 121
AUC_{last}, ng.h/mL	15	63416 ± 41551	60896 ± 18334	105.3	90.4 - 123
Treatment A: Darunavir Tablets (F001) vs. Treatment C: Darunavir Tablets (F012)					
t_{max}, h	15	3.0 (1.5 - 4.0)	2.5 (1.0 - 4.0)	-	-
C_{max}, ng/mL	15	4358 ± 1516	4527 ± 1057	107.2	95.2 - 121
AUC_{last}, ng.h/mL	15	63416 ± 41551	59974 ± 18922	103.8	84.7 - 127
Treatment A: Darunavir Tablets (F001) vs. Treatment D: Darunavir Tablets (F013)					
t_{max}, h	15	3.0 (1.5 - 4.0)	2.0 (1.0 - 4.0)	-	-
C_{max}, ng/mL	15	4358 ± 1516	4568 ± 1296	106.7	92.6 - 123
AUC_{last}, ng.h/mL	15	63416 ± 41551	60989 ± 19617	102.8	86.0 - 123

N = number of subjects with data.

[a] Ratio based on LS means.

Ritonavir 100 mg b.i.d. was given from 2 days before until 2 days after administration of darunavir.

The results of this study demonstrated that under fed conditions and in the presence of low-dose ritonavir (100 mg b.i.d.), all of the test formulations F011, F012, and F013 exhibited comparable bioavailability to the reference formulation F001 indicating that **including SLS and/or crospovidone in the tablet formulation had no effect on the bioavailability of darunavir.**

Reviewer's Note:
The results of the study showed that the bioavailability of darunavir, administered as the 3 test formulations, was comparable to the bioavailability of darunavir administered as the reference formulation F001. [redacted] because of the potential toxicity and GI side effects, formulation F012, containing [redacted] was selected for further development.

However, because of clinical and manufacturing needs, a compositionally proportional 300 mg tablet formulation (F016; commercial formulation) was developed based on the 400 mg tablet formulation F012. Compared to the formulations used in the clinical trials (F001 and F002), the following changes were incorporated in the commercial formulation (F016):

- ***Omission of*** [redacted]
- ***Addition of*** [redacted]
- ***Addition of*** [redacted]

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio- 1

TMC114-C154

Title
Relative Bioavailability of Darunavir Given as the Test Tablets F002 Batches Y and Z Compared to the Reference Tablet F002 Batch X, With Low-Dose Ritonavir (**Effect of Change in Particle Size and Drug Substance Supplier**).

Reviewer's Note Regarding Rationale for the Study

Batches of drug substance generated by the previous manufacturer, [redacted], appeared to differ in particle size distribution from batches generated by the current manufacturer, Cilag (Switzerland). This difference in [redacted] can have an impact on the bioavailability of TMC114. In this trial, the relative bioavailability of TMC114 from [redacted] of F002 tablets using drug substance produced by Cilag was determined with regard to a reference [redacted] batch using drug substance manufactured by [redacted]

Reviewer's Note Regarding Formulation Used in the Study

F002 tablets are identical to the TF036 tablets except for the dose (200 mg vs 400 mg), and differences in particle size distributions of the drug substance.

Study Design
The study population consisted of 24 healthy subjects. Each subject received 3 single doses of 400 mg darunavir, given as 2 F002 (200 mg) tablets from the reference Batch X made with drug substance supplied by [redacted] (Treatment A), 2 tablets from test Batch Y made with drug substance supplied by Cilag (Cilag II, Treatment B) and 2 tablets from test Batch Z also made with drug substance supplied by Cilag (Cilag III, Treatment C) in 3 sessions under fed conditions. Ritonavir 100 mg b.i.d. was given from 2 days before until 2 days after administration of darunavir.

Fig 1 shows the mean plasma concentration-time profiles of single doses of 400 mg darunavir given as two 200 mg F002 tablets from batch X (treatment A), batch Y (treatment B), or batch Z (treatment C), co-administered with low dose ritonavir.

Fig 1: Mean plasma concentration-time profiles of single doses of 400 mg darunavir given as two 200 mg F002 tablets from batch X (treatment A), batch Y (treatment B), or batch Z (treatment C), co-administered with low dose ritonavir.

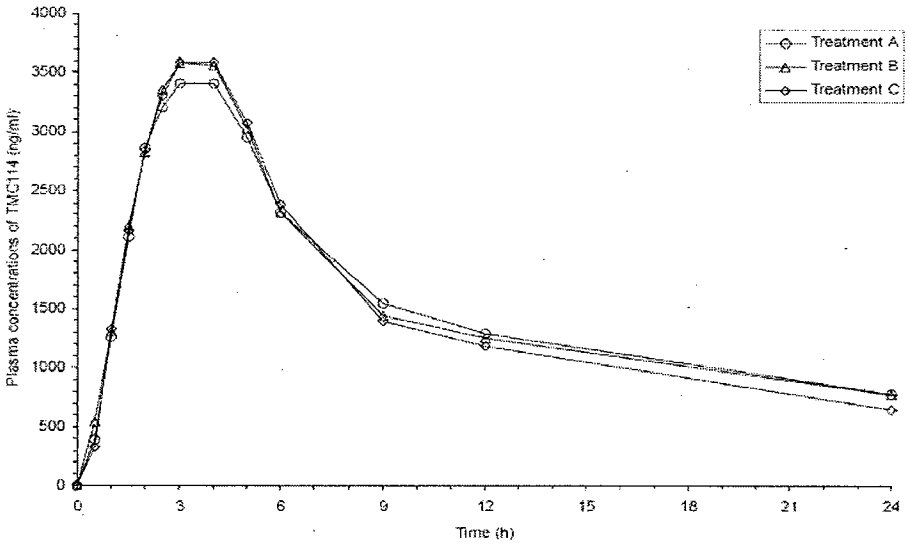


Table 1 shows the pharmacokinetic parameters of darunavir administered as 2 F002 tablets from batch X (treatment A), batch Y (treatment B), or batch Z (treatment C), co-administered with low-dose ritonavir.

Table 1: Pharmacokinetic parameters of darunavir administered as 2 F002 tablets from batch X (treatment A), batch Y (treatment B), or batch Z (treatment C), co-administered with low-dose ritonavir.

Parameter	N	Mean ± SD; t_{max}: Median (Range)		Ratio (%) [a]	90% CI
		Treatment A: Darunavir/Ritonavir 400/100 mg Tablets (F002, Batch X) (Reference)	Treatment B or C: Darunavir/Ritonavir 400/100 mg Tablets (F002, Batch Y or Z) (Test)	(Test:Reference)	
Treatment A: Darunavir Tablets (F002, Batch X) vs. Treatment B: Darunavir Tablets (F002, Batch Y)					
t_{max}, h	23	3.0 (1.5 - 5.0)	3.0 (1.0 - 5.0)	-	-
C_{max}, ng/mL	23	3840 ± 1007	4084 ± 1106	106.4	98.5-115
AUC_{last}, ng.h/mL	23	54003 ± 22400	52876 ± 17468	101.0	91.0-112
Treatment A: Darunavir Tablets (F002, Batch X) vs. Treatment C: Darunavir Tablets (F002, Batch Z)					
t_{max}, h	23	3.0 (1.5 - 5.0)	3.0 (1.5 - 5.0)	-	-
C_{max}, ng/mL	23	3840 ± 1007	4020 ± 976	105.0	96.4-115
AUC_{last}, ng.h/mL	23	54003 ± 22400	48784 ± 16820	93.19	83.9-104

N = number of subjects with data.

[a] Ratio based on LS means.

Ritonavir 100 mg b.i.d. was given from 2 days before until 2 days after administration of darunavir.

The results of this study show that the rate and extent of absorption of darunavir, formulated as the F002 tablet and co-administered with low-dose ritonavir, was not significantly affected by differences in particle size distribution between the different batches of drug substance used to produce the F002 tablets.

Reviewer's Note
The in vitro dissolution profiles of the test tablet formulation F002 batch Y and F002 batch Z were both comparable to the dissolution profile of the reference tablet formulation F002 batch X.

TMC114-C156

Title
Relative Bioavailability of Darunavir Given as the Test Tablets F009 Batches Y Compared to the Reference Tablet F002 Batch X, With Low-Dose Ritonavir **(Effect of Differing Particle Size)**.

Study Design
This was an open-label, randomized, 2-way crossover study to determine the relative bioavailability of darunavir formulated as tablets, using 2 different batches of drug substance. The study population consisted of 16 healthy subjects. In 2 sessions each subject received 2 single doses of 400 mg darunavir, formulated as the F002 Batch X (200 mg) tablet (using drug substance produced by [redacted] from a reference batch (Treatment A) and as the F009 Batch Y (200 mg) tablet (using [redacted] produced by Cilag) from a test batch (Treatment B). All treatments were given under fed conditions. Ritonavir 100 mg b.i.d. was given from 2 days before until 2 days after administration of darunavir.

Fig 1 shows the mean plasma concentration-time profiles of single 400 mg dose of darunavir given as 2 X 200 mg F002 tablets (DSM, Treatment A) or as 2 X 200 mg F009 tablets (Cilag, treatment B), co-administered with low-dose ritonavir.

Fig 1: Mean plasma concentration-time profiles of single 400 mg dose of darunavir given as 2 X 200 mg F002 tablets (DSM, Treatment A) or as 2 X 200 mg F009 tablets (Cilag, treatment B), co-administered with low-dose ritonavir.

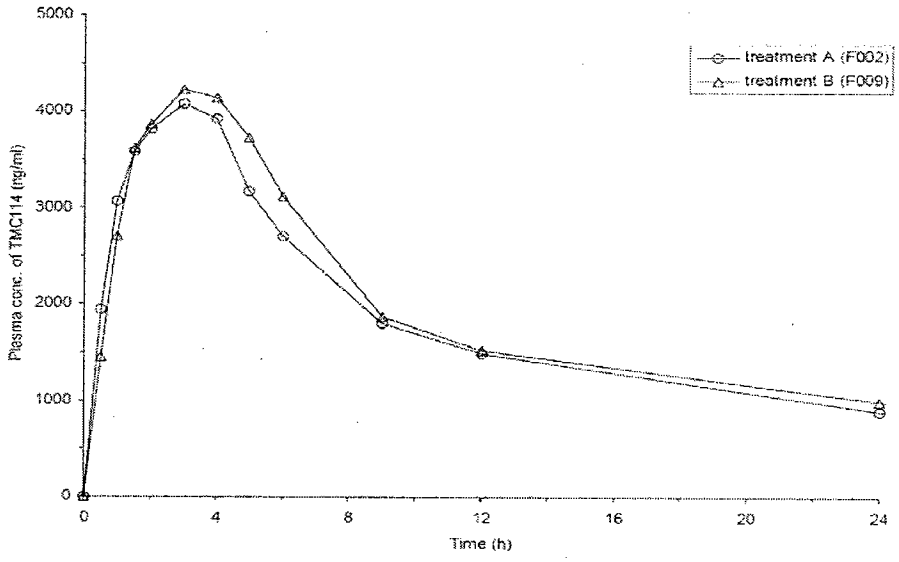


Table 1 shows the pharmacokinetic parameters of darunavir given as tablet F002 (DSM, treatment A) or as tablet F009 (Cilag, treatment B), co-administered with low-dose ritonavir.

Table 1: Pharmacokinetic parameters of darunavir given as tablet F002 (DSM, treatment A) or as tablet F009 (Cilag, treatment B), co-administered with low-dose ritonavir.

Parameter	N	Mean ± SD; t_{max}: Median (Range)		Ratio (%) [a] (Test:Reference)	90% CI
		Treatment A: Darunavir/Ritonavir 400/100 mg Tablet F002 (DSM) (Reference)	Treatment B: Darunavir/Ritonavir 400/100 mg Tablet F009 (Cilag) (Test)		
t_{max}, h	15	2.3 (0.5 - 4.0)	3.0 (1.0 - 5.0)	-	-
C_{max}, ng/mL	15	4838 ± 1053	4770 ± 1387	96.87	89.0 - 105
AUC_{last}, ng.h/mL	15	64976 ± 21550	68445 ± 21823	108.3	96.2 - 122

N = number of subjects with data.
[a] Ratio based on LS means.
Ritonavir 100 mg b.i.d. was given from 2 days before until 2 days after administration of darunavir.

No significant treatment effects on C_{max} or AUC_{last} were observed when comparing values between both treatments, indicating that formulation as tablet F002 using drug substance produced by [redacted] or as tablet F009 using milled drug substance produced by Cilag did not affect the rate and extent of darunavir absorption.

SECTION B

TMC114-C103

1. Title

The systemic exposure of TMC114 in [redacted] under fed and fasted conditions as compared to TMC114 [redacted] /PEG400 oral solution under fasted conditions.

2. Objectives

The objectives of this trial were:

- To determine the systemic exposure of TMC114 from [redacted] ; as compared to [redacted] oral solution.
- To determine the effect of food on the systemic exposure of TMC114 from the 3 experimental formulations.
- To determine the safety and tolerability of the experimental formulations.

3. Study Design

This was an open-label, randomized, controlled, 3-way crossover study in which 3 panels, consisting of 9 healthy subjects each, received 3 single-dose treatments of 800 mg TMC114 as 2 different formulations. Each subject received the reference oral [redacted] PEG400 solution (TF019) under fasted conditions (Treatment A) and one of the 3 test formulations: [redacted] tablets (TF036), a [redacted]), or [redacted] under fasted (Treatment B) and fed (Treatment C) conditions. Subsequent dose administrations were separated by a washout period of at least 6 days.

4. Investigational Drugs

TMC114 was formulated as the following formulations.

- **Vit E-TPGS/PEG400** (TF019): an oral aqueous solution of 20 mg/ml containing [redacted] , PEG400 as main [redacted] in the formulation (batch # 01J03; expiry date: 03/01/2002)

- **TF036**: an oral tablet [redacted] , containing 400 mg TMC114 (batch # 01J08; expiry date:08/01/02)

Reviewer's Note: The test substance TMC114 used in this trial was processed under the assumption that it was 100 % TMC114. However, in the course of development, it was identified that TMC114 drug substance is a solvate (ethanolate) and it should be corrected for solvent content. As a result, the actual dose levels, expressed as TMC114 base, were [redacted] lower for [redacted] than stated in the study report. However, this is not expected to change the overall conclusions.

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Blood samples (5 mL) were collected at the following time points: pre-dose (within 1h before drug intake), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (day 2) and 48 (day 3) hrs. The lower limit of quantification for TMC114 in plasma was 2 ng/mL.

Pharmacokinetic Assessments

Non parametric analyses were performed using WinNonlin Professional. (version 4.1; [redacted] using a [redacted] .. Based on the individual plasma concentration-time data, using the scheduled sampling times, the following pharmacokinetic parameters of TMC114 were derived from every formulation and food condition: T_{max}, C_{max}, AUC_{48h}, AUC_{∞}, λ_z, and $t_{1/2term}$.

For Treatments B, 90 % CIs were calculated for the means of the ratio of AUC_{48h}, AUC_{∞} and C_{max}, relative to Treatment A, using population geometric means based on log-transformed data. The t_{max} was subjected to a non-parametric analysis. For Treatments C, 90 % CIs were calculated for the means of the ratio of AUC_{48h}, AUC_{∞} and C_{max} relative to Treatment B, using population geometric means based on log-transformed data. The t_{max} was subjected to a non-parametric analysis.

6. Results

6.1 Subject Disposition

27 subjects were equally randomized to panels 1, 2, and 3. Subjects randomized to panel 1 received the reference solution formulation (under fasted conditions) and the direct [redacted] (under fasted and fed conditions). Subjects randomized to panel 2 received the reference [redacted] (under fasted conditions) and the [redacted] (under fasted and fed conditions). Subjects randomized to panel 3 received the reference solution formulation (under fasted conditions) and the [redacted] (under fasted and fed conditions). All the subjects randomized to the three panels completed all assessments. Table 2 shows the demographic characteristics of subjects enrolled in the trial.

Table 2: Demographic Characteristics in Study TMC114-C103

Demographic characteristic	Panel 1	Panel 2	Panel 3	All subjects
Age (median, years)	28	35	44	39
Height (median, cm)	178	168	165	168
Weight (median, kg)	71	68	74	70
BMI (median, kg/m²)	24.0	24.5	24.4	24.4
Sex: M (n (%))	6 (66.7)	5 (55.6)	3 (33.3)	14 (51.9)
F (n (%))	3 (33.3)	4 (44.4)	6 (66.7)	13 (48.1)
Race: Caucasian (n (%))	9 (100)	9 (100)	9 (100)	27 (100)

6.2 Pharmacokinetic Analysis

Relative Bioavailability (Under Fasted Conditions)

Panel 1

Fig 1 shows the mean plasma concentration-time profiles of 800 mg TMC114 administered as oral [redacted] solution (TF019) and as tablet (TF036) under fasted and fed conditions (Panel 1).

Fig 1: Plasma concentration-time profiles of 800 mg TMC114 administered as oral [redacted] solution (TF019) and as tablet (TF036) under fasted and fed conditions (Panel 1).

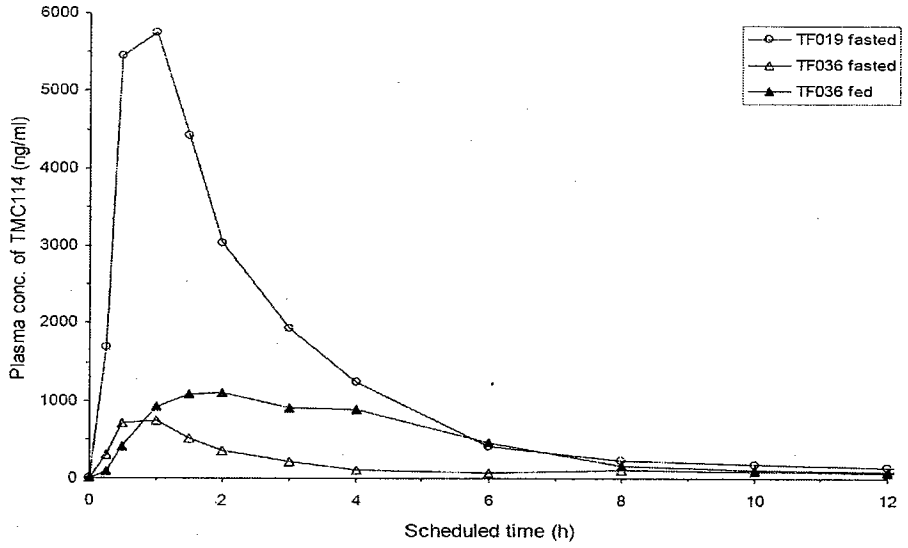


Table 3 shows the pharmacokinetic results of 800 mg TMC114 administered as a tablet (TF036) vs. reference formulation under fasted conditions (treatment B vs. A) for panel 1.

Table 3: Pharmacokinetic results of 800 mg TMC114 administered as a tablet (TF036) vs. reference formulation under fasted conditions (treatment B vs. A) for panel 1.

Pharmacokinetics of TMC114 (mean±SD)	Panel 1	
	Treatment A: [redacted] /PEG400 solution, fasted	**Treatment B:** 2 tablets (TF036), fasted
n	9	9*
t_{max}, h**	0.5 (0.5 - 1.0)	1.0 (0.5 - 3.0)
C_{max}, ng/ml	6956 ± 1683	813 ± 333
AUC_{48h}, ng.h/ml	17368 ± 6266	4234 ± 2666
AUC_{∞}, ng.h/ml	17554 ± 6258	4515 ± 2546
$t_{1/2term}$, h	9.25 ± 4.84	12.4 ± 5.20

* For parameters $t_{1/2term}$ and AUC_{∞}: n=4 for Treatment B; ** t_{max} in median (range)

Panel 2

Fig 2 shows the mean plasma concentration-time profiles of 800 mg TMC114 administered as oral [redacted] and as [redacted] under fasted and fed conditions (Panel 2).

Fig 2: Plasma concentration-time profiles of 800 mg TMC114 administered as [redacted] and as a powder dispersed in water (TF041) under fasted conditions (B) and fed conditions (C) for panel 2.

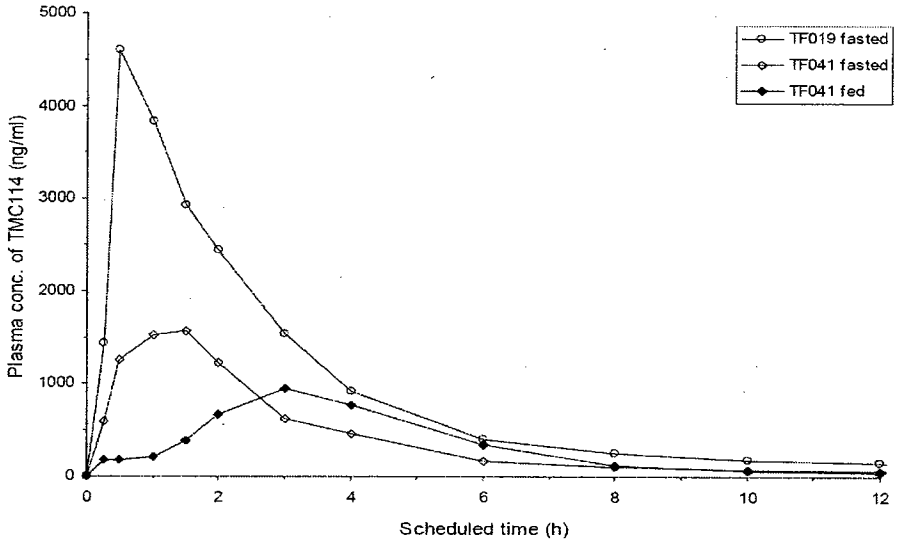


Table 4 shows the pharmacokinetic results of 800 mg TMC114 administered as [redacted] vs. reference formulation under fasted conditions (treatment B vs. A) for panel 2.

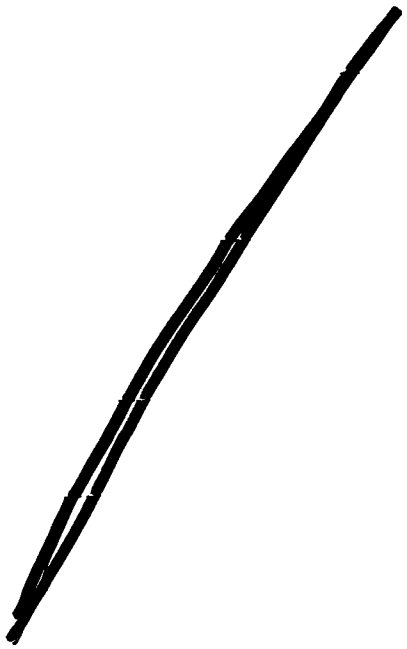
1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio-1



Statistical Analysis

Tables 6 shows the statistical evaluation of the pharmacokinetics of TMC114 under fasted conditions in tablet (TF036) vs. reference formulation (treatment B vs. A) for panel 1.

Table 6: Statistical evaluation of the pharmacokinetics of TMC114 under fasted conditions in tablet (TF036) vs. reference formulation (treatment B vs. A) for panel 1.

Parameter (log transformed)	n	Least square means		Least square means ratio, %	90% CI	p-value
		A (reference)	B (test)			Treatment
t_{max}, h*	9	0.5	1.0	-	-	0.4407
C_{max}, ng/ml	9	7017	771.3	10.99	8.26 - 14.6	0.0001
AUC_{48h}, ng.h/ml	9	16681	3620	21.70	14.1 - 33.3	0.0004
AUC_{∞}, ng.h/ml	4	20365	3712	18.23	4.08 - 81.4	0.0925

t_{max} in median

Table 7 shows the statistical evaluation of the pharmacokinetics of TMC114 under fasted conditions in [redacted] vs. reference formulation (treatment B vs. A) for panel 2.

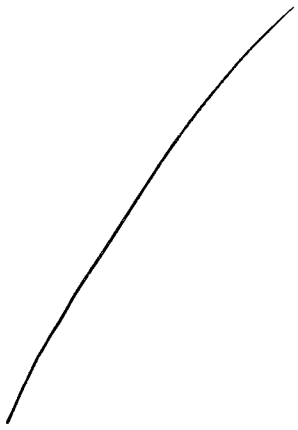
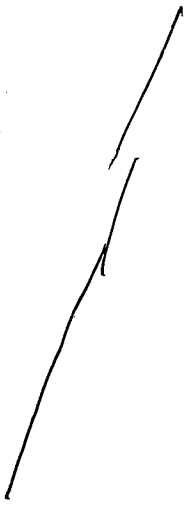


Table 8 shows the statistical evaluation of the pharmacokinetics of TMC114 under fasted conditions in [redacted] vs. reference formulation (treatment B vs. A) for panel 3.



The relative bioavailability of TMC114, under fasted conditions, and compared to the oral solution [redacted], was [redacted] and 10-20 %, for the [redacted], the [redacted], and the tablet [redacted] formulation, respectively. For the [redacted], higher t_{max} values were observed than for the corresponding reference treatment which was statistically significant. For the other test formulations, the t_{max} values were not significantly different from those of the oral reference solution.

Food Effect

Table 9 shows the pharmacokinetic results of 800 mg TMC114 administered as tablet formulation (TF036) under fed vs. fasted conditions (treatment C vs. B) for panel 1.

Table 9: Pharmacokinetic results of 800 mg TMC114 administered as tablet formulation (TF036) under fed vs. fasted conditions (treatment C vs. B) for panel 1.

Pharmacokinetics of TMC114 (mean±SD)	**Panel 1**	
	Treatment B: 2 tablets (TF036), fasted	**Treatment C:** 2 tablets (TF036), fed
n	9*	9*
t_{max}, h**	1.0 (0.5 - 3.0)	2.0 (1.0 - 6.0)
C_{max}, ng/ml	813 ± 333	1426 ± 552
AUC_{48h}, ng.h/ml	4234 ± 2666	7212 ± 2879
AUC_{∞}, ng.h/ml	4515 ± 2546	8072 ± 3086
$t_{1/2term}$, h	12.4 ± 5.20	11.7 ± 6.34

* For parameters $t_{1/2term}$ and AUC_{∞}: n=4 for Treatment B and n=8 for Treatment C

** t_{max} in median (range)

Table 10 shows the statistical evaluation of the pharmacokinetics of TMC114 in tablet formulation (TF036) under fed vs. fasted conditions (treatment C vs. B) for panel 1.

Table 10: Statistical evaluation of the pharmacokinetics of TMC114 in tablet formulation (TF036) under fed vs. fasted conditions (treatment C vs. B) for panel 1.

Parameter (log transformed)	n	Least square means		Least square means ratio, %	90% CI	p-value
		B (reference)	C (test)			Treatment
t_{max}, h*	9	1.0	2.0	-	-	0.0135
C_{max}, ng/ml	9	753.7	1346	178.6	133 - 239	0.0083
AUC_{48h}, ng.h/ml	9	3601	6714	186.5	145 - 240	0.0030
AUC_{∞}, ng.h/ml	3	4606	7346	159.5	NA	NA

NA: not assessable; * t_{max} in median

Table 11 shows the pharmacokinetic results of 800 mg TMC114 administered as — formulation under fed vs. fasted conditions (treatment C vs. B) for panel 2.

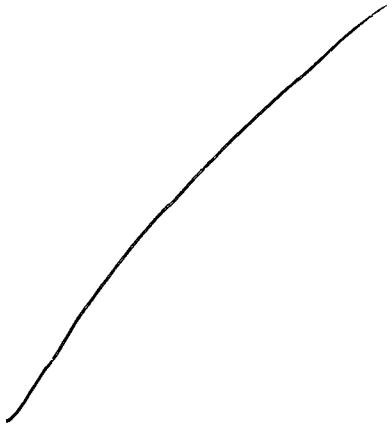
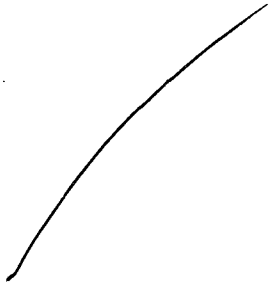


Table 12 shows the pharmacokinetic results of 800 mg TMC114 administered as — formulation (TF038) under fed vs. fasted condition (treatment C vs. B) for panel 3.

Table 12: Pharmacokinetic results of 800 mg TMC114 administered as — formulation (TF038) under fed vs. fasted conditions (treatment C vs. B) for panel 3.



7. Conclusion

- The bioavailability of TMC114 was highest for the oral — PEG400 reference solution (TF019) under fasted conditions. TMC114, administered as the oral solution, was rapidly absorbed from the GI-tract with maximum plasma

concentrations of TMC114 generally reached 0.5h post-dose. The single dose pharmacokinetics of the oral [redacted]./PEG400 reference solution (TF019) was comparable between the three panels.

- The relative bioavailability of TMC114, under fasted conditions, and compared to the [redacted] (TF019), was [redacted], and 10-20 % for the [redacted] [redacted] and the tablet formulation respectively.
- Under fed conditions, the relative bioavailability of the tablet formulation significantly increased and the relative bioavailability of the [redacted] formulations significantly decreased compared to intake under fasted conditions.

Reviewer's Note

The lower bioavailability of TMC114, when administered as the tablet formulation (when compared with the oral solution) suggested that the tablet formulation, administered alone, is unsuitable for use in clinical trials due to the potential for inadequate exposures.

TMC114-C114

1. Title

The absolute bioavailability of TMC114, formulated as a tablet, administered alone and in the presence of low dose ritonavir, in healthy subjects compared to intravenous administration, alone and in presence of low dose ritonavir.

2. Objectives

The primary objective of this trial was to determine the absolute bioavailability of TMC114 after a single 600 mg single oral dose as F014/F015 tablets, alone and in the presence of low-dose RTV. The secondary objectives were to determine the safety and tolerability of TMC114 after a single oral dose of 600 mg, formulated as the tablets F014/F015, and after intravenous administration of 150 mg TMC114 (formulation F008), alone and in the presence of low dose of RTV.

Reviewer's Note Regarding Formulations Used in the Trial.

The formulations used in this trial, F014 and F015, were manufactured from the same blend and therefore, have the same proportional composition as F016, the commercial formulation.

3. Study Design

Phase I, open-label, randomized, 4-way crossover trial in healthy subjects to investigate the pharmacokinetics of TMC114 after single oral dosing with the tablets F014/F015, as compared with the pharmacokinetics of TMC114 following intravenous administration. The absolute bioavailability of TMC114 formulated as tablets F014/F015 was determined in the presence and absence of low-dose RTV.

The trial population consisted of 8 healthy subjects. During 4 sessions each subject received the Treatments A, B, C and D. In Treatments A and C, a single 1-hour intravenous infusion of 150 mg TMC114, formulated as F008, was administered. In Treatments B and D, a single oral dose of 600 mg TMC114, formulated as tablets F014 (400 mg tablet)/F015 (200 mg tablet), was administered. All intakes were under fed conditions (standard breakfast which consisted of four slices of bread, one slice of ham, one slice of cheese, butter, jelly and two cups of decaffeinated coffee or tea with milk and/or sugar). In Treatments A and B, TMC114 was administered alone, while in Treatments C and D multiple oral doses of 100 mg RTV b.i.d. were co-administered from 2 days before until 3 days after administration of TMC114. There was a washout period of at least 7 days between consecutive treatments.

In each session, full pharmacokinetics were determined up to 96 hours after dosing for TMC114 and up to 12 hours after the morning intake on Day 3 for RTV. Safety and tolerability were also assessed throughout the trial.

3.1 Discussion of Trial Design, Including Choice of Control Group.

- In this trial, a single oral dose of 600 mg TMC114 was given as one 400 mg tablet F014 and one 200 mg tablet F015, alone or in the presence of 100 mg RTV b.i.d. This dose regimen was selected based on the results of ongoing dose finding trials in which TMC114/RTV was administered at 600/100 mg b.i.d. to 3-class-experienced, multi PI-experienced HIV-1 infected subjects for 96 weeks.
- For selection of the intravenous (IV) dose, it was assumed that the absolute bioavailability of TMC114 given alone is 5%. Therefore, after 150 mg, the exposure was expected to correspond to that after a single oral dose of 3000 mg. A single oral dose of 3200 mg has been given safely to healthy volunteers in trial TMC114-C101.

4. Investigational Drugs

Table 1 shows the investigational drugs used in the trial.

Table 1: Description of Investigational Agents.

Study Medications	Batch Number	Expiry Date
TMC114 400 mg tablet (F014)	PD1220	Aug/06
TMC114 200 mg tablet (F015)	PD1243	Aug/06
TMC114 5 mg/mL solution (F008)	04K22/F008	May/05

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Plasma samples for treatment A and C were collected at predose, and at 15 min, 30 min, 45 min, 1h, 1h 5 min, 1h 10 min, 1h 15 min, and at 1.5, 2, 2.5, 3, 4, 5, 6, 9, 12, 24, 48, 72, and 96 hours. Plasma samples for treatment B and D were collected at 15 min, 30 min, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 24, 48, 72, and 96 hours. The plasma concentrations of TMC114 and RTV were determined using a validated LC-MS/MS method. The lower limit of quantification (in plasma) was 10 ng/mL for TMC114 and 5 ng/mL for RTV.

Pharmacokinetic Assessments

Pharmacokinetic analysis was performed using WinNonlin Professional (version 4.1; and Microsoft Excel® (version 2000; Microsoft, . Noncompartmental analysis were used for the primary pharmacokinetic analysis in Treatments B and D. Model 202 was used for non-compartmental analysis of TMC114 in Treatments A and C. In addition, a secondary compartmental analysis was performed on the IV data using the standard models available in the library of WinNonlin Professional.

Statistical analyses was performed for TMC114 comparing Treatment B (test) vs. Treatment A (reference), Treatment D (test) vs. Treatment C (reference), Treatment D (test) vs. Treatment B (reference) and Treatment C (test) vs. Treatment A (reference). The primary pharmacokinetic parameters were dose-normalized C_{max}, AUC_{∞}, and AUC_{last} on the logarithmic scale.

6. Results

6.1 Demographics

8 subjects were equally randomized to the four different treatment sequences (ADBC, BACD, CBDA, and DCAB). All the subjects (except 1 subject randomized to the CBDA arm) completed all the assessments. Table 2 shows the demographics of the subjects enrolled in the trial.

Table 2: Demographics in Study TMC114-C114

Parameter	Group 1	Group 2	Group 3	Group 4	All Subjects
Age, years median (range)	20.5 (19-22)	25.0 (25-25)	30.0 (28-32)	29.5 (26-33)	25.5 (19-33)
Height, cm median (range)	184.5 (184-185)	183.0 (180-186)	175.5 (175-176)	179 (170-188)	182.0 (170-188)
Weight, kg median (range)	67.0 (64-70)	72.0 (69-75)	66.0 (64-68)	72.0 (62-82)	68.5 (62-82)

6.3 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time curve of TMC114 after a single 1-hour infusion of 150 mg TMC114 (treatment A), a single oral administration of 600 mg TMC114 (treatment B), a single 1-hour IV infusion of 150 mg TMC114 co-administered with RTV capsules 100 mg b.i.d. (treatment C) and a single oral administration of 600 mg TMC114 co-administered with RTV capsules 100 mg b.i.d. (treatment D).

Fig 1: Mean plasma concentration-time curve of TMC114 after a single 1-hour infusion of 150 mg TMC114 (treatment A), a single oral administration of 600 mg TMC114 (treatment B), a single 1-hour IV infusion of 150 mg TMC114 co-administered with RTV capsules 100 mg b.i.d. (treatment C) and a single oral administration of 600 mg TMC114 co-administered with RTV capsules 100 mg b.i.d. (treatment D).

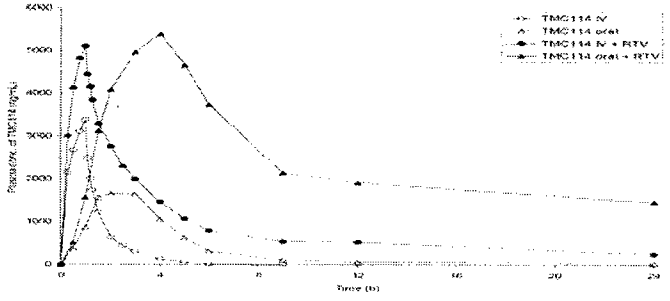


Table 3 shows the pharmacokinetic results of TMC114 for all treatments.

Table 3: Pharmacokinetic results of TMC114 for all treatments

Pharmacokinetics of TMC114 (mean ± SD, t_{max}: median (range))	Treatment A: TMC114 150 mg IV	Treatment B: TMC114 600 mg Oral	Treatment C: TMC114 150 mg IV + RTV 100 mg b.i.d.	Treatment D: TMC114 600 mg Oral + RTV 100 mg b.i.d.
	Day 1	Day 1	Day 3	Day 3
n	7	7[a]	8	7
C_{0h}, ng/mL	0[b]	0	0	0
t_{max}, h	0.98 (0.75 - 1.08)	2.00 (1.00 - 4.00)	0.98 (0.75 - 1.00)	4.00 (2.00 - 5.00)
C_{max}, ng/mL	3427 ± 512.2	2204 ± 1071	5196 ± 886.1	5627 ± 923.5
AUC_{last}, ng.h/mL	4726 ± 1059	7748 ± 4867	27220 ± 7801	91390 ± 20050
AUC_{∞}, ng.h/mL	4775 ± 1099	10990[c] ± 4601[c]	27710 ± 7943	92340 ± 20020
$t_{1/2term}$, h	2.107 ± 1.896	23.95[c] ± 21.90[c]	15.89 ± 5.398	14.19 ± 1.857
Cl. L/h	32.770 ± 6.955	-	5.911 ± 2.122	-
Vd. L	88.120 ± 58.950	-	130.800 ± 49.870	-
F	-	0.3693	-	0.8193

[a] n= 5 for AUC_{∞} and $t_{1/2term}$
[b] 0 = NQ = Not Quantifiable (<10.00 ng/mL)
[c] accurate determination not possible

After oral administration of TMC114 alone, a lower (dose-normalized) systemic exposure to TMC114 was observed for all subjects compared to IV administration of TMC114 alone. Individual B/A treatment ratios ranged from 16 % to 92 % for dose-normalized AUC_{last} and from 33 % to 94 % for dose-normalized $AUC_{0-\infty}$, with geometric means of 35 % and 52 %, respectively. However, for treatment B, more than 50 % of individual values of $AUC_{0-\infty}$ could not be determined accurately.

After IV administration, the mean systemic clearance of TMC114 was decreased by approximately 5.5-fold, from 32.8 L/h to 5.9 L/h, when TMC114 was co-administered with RTV. Mean values of volume of distribution were 88.1 and 130.8 L for TMC114 given alone or with RTV, respectively.

Table 4 shows the summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment B (oral administration of TMC114 alone) compared to treatment A (IV infusion of TMC114 alone).

Table 4: Summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment B (oral administration of TMC114 alone) compared to treatment A (IV infusion of TMC114 alone).

Parameter	n		Least square means		Least square means ratio. %	90% CI [a]	p-value		
	Treatment A (reference)	Treatment B (test)	Treatment A (reference)	Treatment B (test)			Treatment	Period	Sequence
Dose norm. C_{max}, ng/mL	7	7	23.19	3.506	15.12	8.91 - 25.7	0.0035	0.4703	0.4093
Dose norm. AUC_{last}, ng.h/mL	7	7	32.08	11.85	36.93	22.2 - 61.3	0.0190	0.3400	0.3338
Dose norm. AUC_{∞}, ng.h/mL [b]	-	-	-	-	-	-	-	-	-

[a] 90% confidence intervals.

[b] for more than half of the subjects the value for AUC_{∞} could not be assesed

Table 5 shows the summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment D (oral administration of TMC114 in the presence of RTV) compared to treatment C (IV infusion of TMC114 alone in the presence of RTV).

Table 5: Summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment D (oral administration of TMC114 in the presence of RTV) compared to treatment C (IV infusion of TMC114 in the presence of RTV).

Parameter	n		Least square means		Least square means ratio. %	90% CI [a]	p-value		
	Treatment C (reference)	Treatment D (test)	Treatment C (reference)	Treatment D (test)			Treatment	Period	Sequence
Dose norm. C_{max}, ng mL	8	7	34.19	9.135	26.72	25.2 - 28.3	<0.0001	0.0244	0.9554
Dose norm. AUC_{last}, ng.h/mL	8	7	174.2	143.9	82.59	70.2 - 97.2	0.0701	0.0898	0.8853
Dose norm. AUC_{∞}, ng.h/mL	8	7	177.4	145.3	81.93	69.8 - 96.2	0.0616	0.0927	0.8833

[a] 90% confidence intervals.

Table 6 shows the summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment C (IV infusion of TMC114 in the presence of RTV) compared to treatment A (IV infusion of TMC114 alone).

Table 6: Summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment C (IV infusion of TMC114 in the presence of RTV) compared to treatment A (IV infusion of TMC114 alone).

Parameter	n		Least square means		Least square means ratio. %	90% CI [a]	p-value		
	Treatment A (reference)	Treatment C (test)	Treatment A (reference)	Treatment C (test)			Treatment	Period	Sequence
Dose norm. C_{max}, ng/mL	7	8	22.63	34.19	151.1	132 - 173	0.0040	0.6213	0.3837
Dose norm. AUC_{last}, ng.h/mL	7	8	31.39	174.2	555.0	401 - 768	0.0019	0.3868	0.3553
Dose norm. AUC_{∞}, ng.h/mL	7	8	31.72	177.4	559.2	400 - 781	0.0023	0.4067	0.3696

[a] 90% confidence intervals

Table 7 shows the summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment D (Oral administration of TMC114 in the presence of RTV) compared to treatment A (IV infusion of TMC114 alone).

Table 7: Summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment D (oral administration of TMC114 in the presence of RTV) compared to treatment B (oral administration of TMC114 alone)

Parameter	n		Least square means		Least square means ratio, %	90% CI [a]	p-value		
	Treatment B (reference)	Treatment D (test)	Treatment B (reference)	Treatment D (test)			Treatment	Period	Sequence
Dose norm. C_{max}, ng/mL	7	7	3.375	9.813	290.8	172 - 491	0.0122	0.9772	0.4600
Dose norm. AUC_{last}, ng.h/mL	7	7	11.29	159.9	1416	768 - 2610	0.0008	0.8165	0.4667
Dose norm. AUC_{∞}, ng.h/mL [b]	-	-	-	-	-	-	-	-	-

[a] 90% confidence intervals.

[b] more than half of the subjects have a not assessable value for AUC_{∞}

Based on the ratios of the LSmeans, dose-normalized C_{max} and AUC_{last} were, respectively, 85 % and 63 % lower after oral intake of TMC114 alone compared to IV infusion of TMC114 alone (Treatment B versus Treatment A). These differences were statistically significant. **The oral bioavailability of TMC114 administered alone was approximately 37 %.**

In the presence of RTV, dose-normalized C_{max}, AUC_{last} and AUC_{∞} were, respectively, 73 %, 17 % and 18 % lower after oral intake of TMC114 compared to IV infusion (Treatment D versus Treatment C). Only the difference in C_{max} was statistically significant. **In the presence of low-dose RTV, the oral bioavailability of TMC114 was increased over 2-fold, to 82 %.**

When TMC114 was administered orally, dose-normalized C_{max} and AUC_{last} increased by 191 % and 1316 %, respectively, after coadministration with RTV, based on the ratios of the Lsmeans (Treatment D versus Treatment B). All increases were statistically significant. **Therefore, following oral administration of TMC114, an approximately 14-fold increase in TMC114 exposure was observed when low-dose RTV was coadministered.**

Reviewer's Note
The sponsor provided the summary of the results from the compartmental analysis, however, the bias of the curve fitting procedure towards higher concentrations, coupled with the error in the underlying pharmacokinetic parameters did not result in reliable estimates of the pharmacokinetic parameters. Therefore, the compartmental analysis was considered exploratory in nature.

Ritonavir

Table 8 shows the pharmacokinetic results of RTV for treatments C and D.

Table 8: Pharmacokinetic results of RTV for treatments C and D

Pharmacokinetics of Ritonavir (mean ± SD, t_{max} median (range))	Treat C: TMC114 150 mg IV + RTV 100 mg b.i.d.	Treat D: TMC114 600 mg Oral + RTV 100 mg b.i.d.
n	8	7
Day 3		
C_{0h}, ng/mL	459.8 ± 229.3	386.2 ± 385.5
t_{max}, h	5.00 (3.00 - 5.00)	5.00 (1.50 - 6.00)
C_{min}, ng/mL	270.4 ± 119.1	253.5 ± 200.8
C_{max}, ng/mL	1273 ± 452.8	1144 ± 585.0
AUC_{12h}, ng.h/mL	8039 ± 2983	7294 ± 4702
Day 4		
C_{0h}, ng/mL	510.4 ± 236.0	430.9 ± 259.1
Day 5		
C_{0h}, ng/mL	415.6 ± 115.1	441.1 ± 169.5
Day 6		
C_{0h}, ng/mL	382.9 ± 181.7	450.5 ± 308.8
Day 7		
C_{0h}, ng/mL	444.3 ± 195.3	306.3 ± 140.9

For both treatments, the mean C_{min} was lower than the mean C_{0h} after 3 days of administration. This was partly due to the delay in absorption, resulting in lower concentrations immediately after dosing compared to pre-dose.

7. Conclusion

- Mean systemic clearance of TMC114 was 32.8 L/h and 5.9 L/h, respectively, for TMC114 administered alone or in combination with RTV. **Assuming a liver flow of 90 L/h, TMC114 could be characterized as a drug with an intermediate extraction ratio (between 0.3-0.7) when given alone and with a low extraction ratio (<0.3) in the presence of RTV.**
- The mean volume of distribution of TMC114 was 88.1 L and 131 L for TMC114 administered alone or in combination with RTV, respectively. However, given the high interindividual variability, no definite conclusions could be drawn about the effect of RTV on the volume of distribution of TMC114.
- When TMC114 alone was administered orally, a lower (dose-normalized) systemic exposure to TMC114 was observed for all subjects compared to IV administration. Based on the ratios of the LSmeans, dose-normalized C_{max} and AUC_{last} values of TMC114 were statistically significantly decreased by 85% and 63%, respectively, after oral intake compared to IV infusion, indicating that the absolute bioavailability of TMC114 administered alone was approximately 37 %.
- In the presence of RTV, dose-normalized C_{max}, AUC_{last} and $AUC_{0-\infty}$ were, respectively, 73 %, 17 % and 18 % lower after oral intake of TMC114 compared to IV infusion, based on the ratios of the LSmeans. The absolute bioavailability of TMC114 was approximately 82 % when coadministered with RTV (assuming that

the systemic clearance of TMC114 is the same after oral and intravenous administration).

- In the presence of RTV, systemic exposure to TMC114, administered intravenously or orally, was higher compared to treatment with TMC114 alone in all subjects. Based on the ratios of the LS_{means}, dose-normalized C_{max}, AUC_{last} and $AUC_{0-\infty}$ were statistically significantly increased by 51 %, 455 % and 459 %, respectively, when IV infusion of TMC114 in the presence of RTV was compared to IV infusion alone. The results indicate that the systemic clearance of TMC114 was inhibited by approximately 5-fold by the addition of RTV.
- When TMC114, taken orally, was co-administered with RTV, C_{max} and AUC_{last} were statistically significantly increased by 191 % and 1316 %, respectively, based on the ratios of the LS_{means}, compared to oral administration alone. **The results indicate that after oral intake, the systemic exposure to TMC114 was increased by approximately 14-fold in the presence of RTV. This can be explained by an almost complete inhibition of the first pass metabolism of TMC114 combined with a 5-fold inhibition of its systemic clearance.**

TMC114-C116

1. Title

A Phase I, open-label, randomized, crossover study to compare the rate and extent of absorption of TMC114 following a single administration of the clinical trial and commercial tablet formulation in the presence of low-dose ritonavir **(Pivotal Bioequivalence Trial).**

2. Objectives

The primary objective of this pivotal bioequivalence trial was to compare the rate and extent of absorption of a 300 mg commercial tablet formulation (F016) of TMC114 to that of a 200 mg (F002) and 400 mg (F001) clinical trial formulation, administered as a single dose (600 mg or 1200 mg) in healthy subjects in the presence of low-dose RTV. The secondary objective was to evaluate the short-term safety and tolerability of TMC114 following administration of a 600 mg and 1200 mg single dose in the presence of low-dose RTV in the fasted state.

3. Study Design

This was a Phase I, randomized, open-label, single-dose, two-panel, two-way crossover trial to assess the rate and extent of absorption of TMC114 following administration of 3 formulation strengths (all in the presence of low-dose RTV). For each panel (1 and 2), 24 healthy volunteers were randomly assigned to one of 2 treatment sequences (n=12 each). A total of 48 healthy subjects participated in the trial.

In Panel 1, subjects received a single oral 600 mg dose (3 x 200 mg, Treatment A) of TMC114 as the 200 mg clinical trial tablet formulation (F002) in one of the trial periods, and a single oral 600 mg dose (2 x 300 mg, Treatment B) of TMC114 in a 300 mg commercial tablet formulation (F016) in the other period.

In Panel 2, subjects received a single oral 1200 mg dose (3 x 400 mg, Treatment C) of TMC114 as the 400 mg clinical trial tablet formulation (F001) in one of the trial periods, and a single oral 1200 mg dose (4 x 300 mg, Treatment D) of TMC114 in a 300 mg commercial tablet formulation (Formulation F016) in the other period.

After two days of b.i.d. dosing of 100 mg RTV, TMC114 (Treatment A, B, C or D) was administered in the fasted state as a single dose. B.i.d. dosing of RTV was continued up to Day 5. On Day 3, full pharmacokinetic profiles of TMC114 and RTV were determined up to 72 hours after administration. There was a washout period of at least 7 days between subsequent treatments. Table 1 shows the overview of the dose regimens.

Table 1: Overview of Dose Regimens

Treatment		Dose, formulation	Volume, concentration
Panel 1	A	**TMC114:** single dose of 600 mg (tablet, F002) on Day 3	TMC114 ethanolate (reference) (eq. TMC114 200 mg/tablet)
		RTV: 100 mg b.i.d. on Day 1-5	1 capsule of RTV (Norvir®) per intake
	B	**TMC114:** single dose of 600 mg (tablet, F016) on Day 3	TMC114 ethanolate (commercial) (eq. TMC114 300 mg/tablet)
		RTV: 100 mg b.i.d. on Day 1-5	1 capsule of RTV (Norvir®) per intake
Panel 2	C	**TMC114:** single dose of 1200 mg (tablet, F001) on Day 3	TMC114 ethanolate (reference) (eq. TMC114 400 mg tablet)
		RTV: 100 mg b.i.d. on Day 1-5	1 capsule of RTV (Norvir®) per intake
	D	**TMC114**: single dose of 1200 mg (tablet, F016) on Day 3	TMC114 ethanolate (commercial) (eq. TMC114 300 mg/tablet)
		RTV: 100 mg b.i.d. on Day 1-5	1 capsule of RTV (Norvir®) per intake

Reviewer's Note:

The sponsor requested the division's feedback on the design of the pivotal bioequivalence study (SN 227). The division recommended that the single oral dose of 600 mg can be administered as two treatments (300 mg of the commercial formulation X 2) and (200 mg of the clinical trial formulation (F002) X 3) and the comparative in vitro dissolution data for the 200 mg and the 400 mg clinical trial formulation can be used to "link" both the formulations as they are compositionally proportional.

However, the sponsor indicated that while the dissolution profiles of the 200 mg clinical trial tablet formulation (F002) and the 300-mg commercial tablet formulation (F016) were similar, the profiles of the 400-mg clinical tablet formulation (F001) and the 300-mg commercial tablet formulation (F016) ***were not similar****. Therefore, both the clinical trial tablet formulations were included in this pivotal bioequivalence study for assessing the bioavailability of clinical tablet formulations (F001 and F002) vs. the commercial tablet formulation (F016).*

4. Investigational Drugs

Table 2 shows the composition of the clinical trial and commercial formulations of TMC114.

Table 2: Composition of Clinical Trial and Commercial Formulations of TMC114

Name	Amount Required (mg)		
	[redacted] eq. 200 mg Phase IIb	[redacted] eq. 400 mg Phase IIb	[redacted] eq. 300 mg Phase III commercial
TMC114 ethanolate	[redacted]	[redacted]	[redacted]
Microcrystalline Cellulose and	[redacted]	[redacted]	[redacted]
Crospovidone	[redacted]	[redacted]	[redacted]
Magnesium Stearate	[redacted]	[redacted]	[redacted]
Total Core Weight	[redacted]	[redacted]	[redacted]
OPADRY® Orange Film-coat	[redacted]	[redacted]	[redacted]
Total Tablet Weight	*416.8*	*833.6*	*650.2*

[redacted] Quantity of TMC114 ethanolate required for delivery of 200, 400 and 300 mg of TMC114, respectively.
[redacted] (w/w) Microcrystalline Cellulose and [redacted]
each excipient individually complying with the Ph.Eur. and NF monographs

Compared to the Phase IIb formulations (F001 and F002), the following changes were incorporated in the commercial formulation:

- Omission of [redacted]
- Addition of [redacted]
- Addition of [redacted]

Table 3 shows the identity of the investigational products.

Table 3: Identity of the Investigational Products

	Batch Number	Expiry Date
Treatment A	PD1168	03/06
Treatment B	4NG4518-X	12/06
Treatment C	PD1175	05/06
Treatment D	4NG4518-X	12/06

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Plasma samples for all the treatments were collected at predose (immediately before drug intake), and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 9, 12 hrs on day 3. Additional samples (immediately before administration of the morning dose of ritonavir) were collected on days 4, 5, and 6. The plasma concentrations of TMC114 and RTV were determined using a validated LC-MS/MS method. The lower limit of quantification (in plasma) was 5 ng/mL for TMC114 and 5 ng/mL for RTV.

Pharmacokinetic Assessments

Pharmacokinetic analysis was performed using WinNonlin Professional. (version 4.1; [redacted] Microsoft Excel® (version 2000; Microsoft, [redacted]. Statistical analyses were performed for TMC114 comparing Treatment B (test) vs. Treatment A (reference) and Treatment D (test) vs. Treatment C (reference). The primary pharmacokinetic parameters were C_{max}, $AUC_{0-\infty}$ and AUC_{0-last} on the logarithmic scale. $AUC_{0-\infty}$ was rejected as primary parameter for a treatment if more than half of the subjects did not have a reliable value for that treatment. All observations for test and reference, paired and unpaired, were included in the statistical analysis. A 90% confidence interval was constructed around the difference between the least square means of test and reference. Both the difference between the least square means and the 90% confidence limits were retransformed to the original scale. Treatment and period effects were considered significant at the 5% level and sequence effects were considered significant at the 10% level.

6. Results

6.1 Subject Disposition

49 subjects were randomized into two panels (N=24 in panel 1 and N=25 in panel 2). For panel 1, 24 subjects were equally randomized to treatment sequences A-B and B-A. All subjects completed the assessments. For panel 2, 13 subjects were randomized to treatment sequence D-C and 12 subjects were randomized to sequence C-D. 2 subjects discontinued in sequence D-C and 1 subject discontinued in sequence C-D. Table 4 shows the demographics of the subjects enrolled in the trial.

Table 4: Demographics in Study TMC114-C116

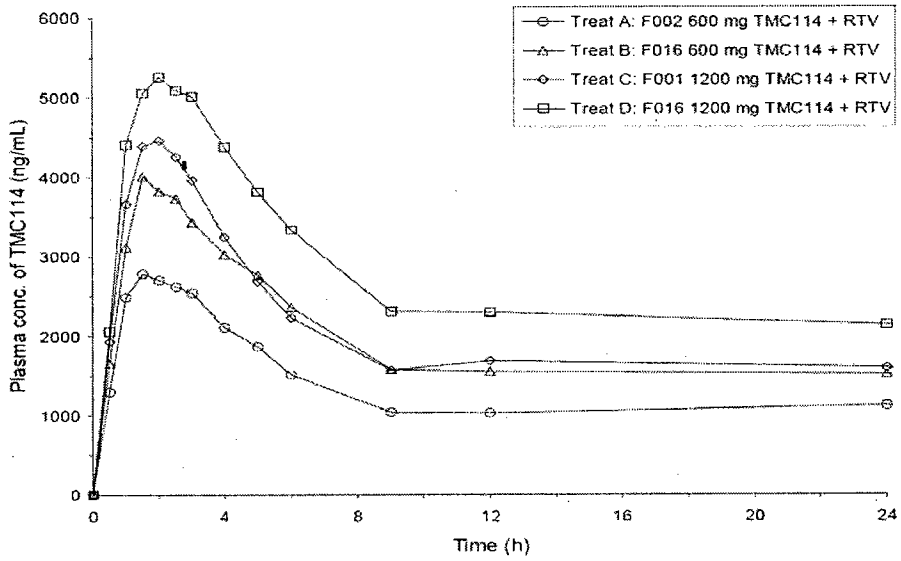
Parameter	Panel 1 N = 24	Panel 2 N = 25	All Subjects N = 49
Age, years	25.5	29.0	27.0
Median (range)	(18-52)	(18-53)	(18-53)
Height, cm	179.0	175.0	177.0
Median (range)	(158-189)	(168-195)	(158-195)
Weight, kg	70.5	73.0	73.0
Median (range)	(54-94)	(58-100)	(54-100)
BMI, kg/m^2	23.0	23.9	23.5
Median (range)	(18-29)	(19-28)	(18-29)
Ethnic Origin, n (%)			
Black	6 (25.0)	7 (28.0)	13 (26.5)
Caucasian /White	16 (66.7)	16 (64.0)	32 (65.3)
Other	2 (8.3)	2 (8.0)	4 (8.2)

N = number of subjects.

6.4 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time curve of TMC114 after oral administration of a single dose of 600 mg TMC114, formulated as a tablet F002 (treatment A) or as tablet F016 (treatment B), or after oral administration of a single dose of 1200 mg TMC114, formulated as tablet F001 (treatment C) or as tablet F016 (treatment D), all in the presence of 100 mg RTV b.i.d., under fasted conditions.

Fig 1: Mean plasma concentration-time curve of TMC114 after oral administration of a single dose of 600 mg TMC114, formulated as a tablet F002 (treatment A) or as tablet F016 (treatment B), or after oral administration of a single dose of 1200 mg TMC114, formulated as tablet F001 (treatment C) or as tablet F016 (treatment D), all in the presence of 100 mg RTV b.i.d., under fasted conditions.



Visual inspection of the mean plasma concentration-time curves of TMC114 showed that a **single oral intake of 600 mg or 1200 mg TMC114 in the presence of low-dose RTV under fasted conditions resulted in higher plasma concentrations of TMC114 when formulated as tablet F016 (2 x 300 mg or 4 x 300 mg) compared to tablet F002 (3 x 200 mg) and tablet F001 (3 x 400 mg), respectively**. Table 5 shows the pharmacokinetic results of TMC114 for all treatments.

Table 5: Pharmacokinetic results of TMC114 for all treatments

Pharmacokinetics of TMC114 (mean ± SD. t_{max}: median (range))	Treatment A: 600 mg TMC114 (F002) + RTV	Treatment B: 600 mg TMC114 (F016) + RTV	Treatment C: 1200 mg TMC114 (F001) + RTV	Treatment D: 1200 mg TMC114 (F016) + RTV
n	23[a]	24[b]	24[c]	23[d]
t_{max}, h	1.5 (1.0 - 5.0)	1.5 (1.0 - 4.0)	1.75 (1.0 - 3.0)	2.0 (1.0 - 5.0)
C_{max}, ng/mL	3284 ± 958.2	4376 ± 1133	4910 ± 1289	6020 ± 1205
AUC_{last}, ng.h/mL	59389 ± 16932	81500 ± 25040	84466 ± 37141	117900 ± 47860
AUC_{∞}, ng.h/mL	64229 ± 19530	86720 ± 27450	93630 ± 49890	119800 ± 40530
$t_{1/2term}$, h	15.88 ± 5.520	16.78 ± 5.499	15.93 ± 6.610	16.84 ± 9.255

[a] For parameters AUC_{∞} and $t_{1/2term}$: n=21

[b] For parameters AUC_{∞} and $t_{1/2term}$: n=23

[c] For parameter AUC_{last} : n=23: For parameters AUC_{∞} and $t_{1/2term}$: n=22

[d] For parameters AUC_{∞} and $t_{1/2term}$: n=22

Table 6 shows the summary of the statistical analysis of the pharmacokinetic parameters of 600 mg TMC114 of treatment B (Tablet F016) compared to treatment A (tablet F002) at a dose level of 600 mg.

Table 6: Summary of the statistical analysis of the pharmacokinetic parameters of 600 mg TMC114 of treatment B (Tablet F016) compared to treatment A (tablet F002) at a dose level of 600 mg.

Parameter	n		Least square means		Least square means ratio, %	90% CI,% [a]	p-value		
	Treatment A (reference)	Treatment B (test)	Treatment A (reference)	Treatment B (test)			Treatment	Period	Sequence
C_{max}, ng/mL	23	24	3174	4233	133.4	121.0 - 146.9	<0.0001	0.3474	0.0376
AUC_{last}, ng.h/mL	23	24	57991	77683	134.0	122.3 - 146.7	<0.0001	0.6636	0.4094
AUC_{∞}, ng.h/mL	21	23	60838	82402	135.4	123.2 - 149.0	<0.0001	0.4061	0.5684
	n		Median				p-value		
Parameter	Treatment A (reference)	Treatment B (test)	Treatment A (reference)	Treatment B (test)	Treatment difference median	90% CI,% [a]	Treatment	Period	Sequence
t_{max}, h	23	24	1.5	1.5	-0.25	(-0.75) - (0.25)	0.4379	0.4940	0.4747

[a] 90% confidence intervals.

Table 7 shows the summary of the statistical analysis of the pharmacokinetic parameters of 1200 mg TMC114 of treatment D (Tablet F016) compared to treatment C (tablet F001) at a dose level of 1200 mg.

Table 7: Summary of the statistical analysis of the pharmacokinetic parameters of 1200 mg TMC114 of treatment D (Tablet F016) compared to treatment C (tablet F001) at a dose level of 1200 mg.

Parameter	n		Least square means		Least square means ratio, %	90% CI,% [a]	p-value		
	Treatment C (reference)	Treatment D (test)	Treatment C (reference)	Treatment D (test)			Treatment	Period	Sequence
C_{max}, ng/mL	24	23	4749	5816	122.5	113.0 - 132.8	0.0004	0.8192	0.7433
AUC_{last}, ng.h/mL	23	23	79846	107306	134.4	123.1 - 146.8	<0.0001	0.9823	0.8452
AUC_{∞}, ng.h/mL	22	22	83173	114672	137.9	123.4 - 154.0	0.0001	0.7927	0.9792
	n		Median				p-value		
Parameter	Treatment C (reference)	Treatment D (test)	Treatment C (reference)	Treatment D (test)	Treatment difference median	90% CI,% [a]	Treatment	Period	Sequence
t_{max}, h	24	23	2.0	2.0	0.25	(0.00) - (0.50)	0.2972	0.0346	1.0000

[a] 90% confidence intervals

Based on the ratios of the LS_{means}, C_{max}, AUC_{last} and AUC_{∞} were, respectively, 33 %, 34 %, and 35 % higher for the commercial formulation compared to formulation as (clinical

trial) tablet F002 (Treatment B vs. Treatment A) under fasted conditions. These differences were statistically significant. Further, after a single oral intake of 1200 mg TMC114 under fasted conditions, C_{max}, AUC_{last} and AUC_{∞} were, respectively, 22 %, 34 % and 38 % higher when TMC114 was formulated as (commercial) tablet F016 compared to the clinical trial formulation F001 (Treatment D versus Treatment C), based on the ratios of the LS_{means}. These differences were statistically significant.

Ritonavir

Table 8 shows the pharmacokinetic results of RTV on day 3 for all treatments.

Table 8: Pharmacokinetic results of RTV on day 3 for all treatments.

Pharmacokinetics of ritonavir (mean ± SD, t_{max}: median (range))	**Treatment A: 600 mg TMC114 (F002) + RTV**	**Treatment B: 600 mg TMC114 (F016) + RTV**	**Treatment C: 1200 mg TMC114 (F001) + RTV**	**Treatment D: 1200 mg TMC114 (F016) + RTV**
n	23	24	24	23
C_{0h}, ng/mL	563.3 ± 340.4	561.2 ± 302.9	376.3 ± 225.1	430.0 ± 255.1
t_{max}, h	2.0 (1.0 - 4.0)	2.0 (1.5 - 4.0)	2.0 (1.0 - 4.0)	2.0 (1.0 - 4.0)
C_{min}, ng/mL	403.6 ± 253.9	436.9 ± 282.1	320.4 ± 217.3	323.5 ± 187.8
C_{max}, ng/mL	2152 ± 880.7	2504 ± 1257	1982 ± 909.7	2135 ± 916.7
AUC_{12h}, ng.h/mL	12762 ± 5344	13650 ± 6783	10740 ± 4980	11320 ± 4970

The systemic exposure to RTV did not significantly change with TMC114 dose or formulation. For all treatments, the mean C_{min} was lower than the mean C_{0h} after 3 days of administration. This was partly due to the delay in absorption, resulting in lower concentrations immediately after dosing compared to pre-dose.

7. Conclusion

- The results of this study showed that under fasted conditions and in the presence of a low dose of RTV, the TMC114 test product (F016, commercial tablet) **failed** to meet bioequivalence limits (80% to 125%) compared to the reference products (F002 and F001, clinical trial tablets).
- For tablet F016 versus tablet F002, point estimates (and 90% CI) were 134 % (122.3-146.7 %) for AUC_{last}, 133.4 % (121.0-146.9 %) for C_{max} and 135.4 % (123.2-149) for AUC_{∞}. For tablet F016 versus tablet F001, point estimates (and 90% CI) were 134.4 % (123.1-146.8 %) for AUC_{last}, 122.5 % (113.0-132.8 %) for C_{max} and 137.9 % (123.4-154 %) for AUC_{∞}.

Additional Pharmacokinetic and Safety Data to Support the Commercial Formulation.

Although the results of study TMC114-C116 showed an approximately 35% higher exposure with the commercial tablet formulation compared to each of these clinical tablet formulations, this higher exposure is not clinically relevant because of the following reasons:

- *This bioequivalence study was designed as a single-dose study under fasted conditions in healthy subjects, however, in the clinical setting, HIV-1 infected subjects will be using TMC114 at steady-state and under fed conditions (as in pivotal studies TMC114-C202 and TMC114-C213, and in the rollover study TMC114-C215). Under these conditions, the commercial and clinical trial tablet formulations were shown to have comparable bioavailability.*
- *There was similarity in the safety profiles (incidence of adverse events) of study TMC114-C202 and TMC114-C213 before and after the switch to the commercial formulation.*
- *No apparent relationship was observed between exposure and safety endpoints for study TMC114-C215.*

TMC114-C143

1. Title
The effect of food on the bioavailability of TMC114 co-administered with a low dose of ritonavir.

2. Objectives
The objectives of this trial were to determine:

- The effect of different type of meals on the bioavailability of TMC114 after a single oral dose of 400 mg, formulated as tablet F014 and administered in combination with low-dose ritonavir (RTV).
- Short term safety and tolerability of TMC114 after a single oral dose of 400 mg, formulated as tablet F014 and administered in the presence of low-dose RTV, under fasted and various fed conditions.

3. Study Design
This was a Phase I, open-label, 2-panel, randomized 3-way crossover trial in healthy subjects to investigate the effect of various types of meals on the bioavailability of a single intake of TMC114 formulated as tablet F014 and co-administered with low-dose RTV (100 mg). The trial population consisted of 24 healthy subjects, equally divided into 2 panels. In 3 sessions, Panel 1 received Treatments A, B and C and Panel 2 received Treatments A, D and E. In all treatments, a single dose of 400 mg TMC114, formulated as tablet F014 was administered, while from 2 days before until 2 days after TMC114 intake, 100 mg RTV b.i.d. was administered. TMC114 was taken immediately after a standard breakfast **(Treatment A)**, under fasted conditions **(Treatment B)**, after a high-fat breakfast **(Treatment C)**, after a nutritional drink rich in proteins **(Treatment D)** or after a croissant with coffee **(Treatment E)**.

Subsequent sessions in a panel were separated by a washout period of at least 7 days. In each session, full pharmacokinetic profiles were determined up to 72 hours after dosing for TMC114 and for one dosing interval after the morning intake on Day 3 for RTV. The following meals were administered in the trial (for fasted conditions, the subjects were fasted for 10 hours before drug administration, water intake was allowed up to 2 hours prior to drug administration).

- Standard breakfast: 4 slices of bread, 1 slice of ham, 1 slice of cheese, butter, jelly and 2 cups of coffee or tea with milk and/or sugar, if desired. (fat: 21 g, carbohydrates: 67 g, proteins: 19 g)

- High-fat breakfast: 2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with 1 slice of cheese and 240 mL of whole milk. (fat: 56 g, carbohydrates: 65 g, proteins: 41 g)

- Nutritional drink rich in proteins: Ensure® 250 ml (fat: 8.4 g, carbohydrates: 33.4 g, proteins: 10.5 g)

- A croissant with coffee: (fat: 12 g, carbohydrates: 28 g, proteins: 5g)

Table 1 shows the calorific value of different treatments.

Table 1: Calorific values of different treatments

Treatment	Total calories (Kcal)	Calories from fat (Kcal)	Calories from carbohydrates (Kcal)	Calories from proteins (Kcal)
A (standard breakfast)	533	189	268	76
B (fasted conditions)	0	0	0	0
C (high-fat breakfast)	928	504	260	164
D (protein-rich drink)	250	76	132	42
E (croissant and coffee)	240	108	112	20

Reviewer's Note:
The standard breakfast (as opposed to fasting conditions) was used as the reference treatment because TMC114/RTV was administered with food in Phase IIb efficacy studies and has been administered in the fed state throughout its development.

4. Investigational Drugs

TMC114 was formulated as tablet F014. The batch number of TMC114 used in this trial was PD1220 (expiry date: February 2006). Ritonavir (Norvir®) was formulated as a capsule containing 100 mg ritonavir base.

Reviewer's Note:
The formulation used in this trial, F014, is compositionally similar and proportional to F016, the 300 mg commercial formulation. Therefore, this study was considered as the pivotal food-effect study.

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

For all the treatments, plasma samples were collected immediately before drug intake, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 24, 48, and 72 hours after drug intake. The plasma concentrations of TMC114 and RTV were determined using a validated LC-MS/MS method. The lower limit of quantification (in plasma) was 10 ng/mL for TMC114 and 5 ng/mL for RTV.

Pharmacokinetic Assessments

Pharmacokinetic analysis was performed using WinNonlin Professional. (version 4.1; [redacted] and Microsoft Excel® (version 2000; Microsoft, [redacted] Statistical analyses were performed for TMC114 comparing Treatment B (test) vs. Treatment A (reference), Treatment C (test) vs. Treatment A (reference), Treatment D (test) vs. Treatment A (reference) and Treatment E (test) vs. Treatment A (reference). The primary pharmacokinetic parameters were C_{max}, AUC_{∞}, and AUC_{last} on the logarithmic scale.

The treatment and period effects were considered significant at the 5 % confidence level and sequence effects were considered significant at the 10 % level. The 90 % confidence intervals and the bioequivalence limits [80%; 125%] were used to evaluate the data.

6. Results

6.1 Subject Disposition

24 subjects were equally randomized to panel 1 and panel 2. For panel 1, 2 subjects each were randomized to the following treatment sequences: ABC, BCA, CAB, CBA, BAC, and ACB. All subjects completed the assessments. For panel 2, 2 subjects were assigned to the following treatment sequences: ADE, DEA, EAD, EDA, DAE, and AED. All subjects completed assessments except 1 subject each discontinued (withdrawal of consent) in sequence ADE and EAD.

Reviewer's Note:

There was one major protocol deviation: in panel 1, one subject assigned to treatment sequence ABC received treatment CAD.

Table 2-A: Demographics in Panel 1

Parameter	Treatment A-B-C N = 2	Treatment B-C-A N = 2	Treatment C-A-B N = 2	Treatment C-B-A N = 2	Treatment B-A-C N = 2	Treatment A-C-B N = 2	All Panel 1 N = 12
Age, years Median (range)	31.5 (31-32)	40.0 (36-44)	39.0 (28-50)	35.0 (24-46)	22.0 (22-22)	35.0 (32-38)	32.0 (22-50)
Height, cm Median (range)	181.5 (176-187)	182.0 (175-189)	173.5 (173-174)	174.5 (174-175)	189.0 (188-190)	171.5 (167-176)	175.5 (167-190)
Weight, kg Median (range)	88.5 (88-89)	76.5 (75-78)	73.0 (70-76)	74.0 (62-86)	88.5 (77-100)	72.5 (69-76)	76.5 (62-100)

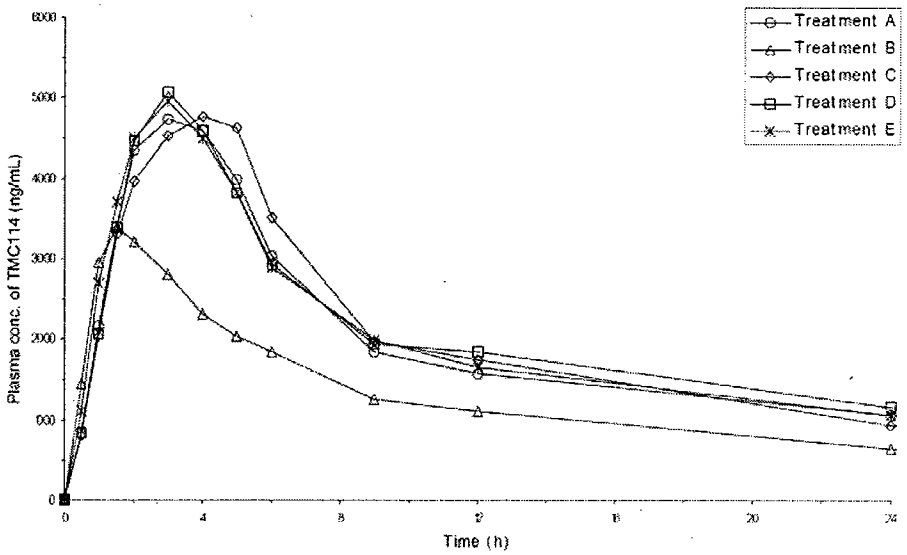
Table 2-B: Demographics in Panel 2

Parameter	Treatment A-D-E N = 2	Treatment D-E-A N = 2	Treatment E-A-D N = 2	Treatment E-D-A N = 2	Treatment D-A-E N = 2	Treatment A-E-D N = 2	All Panel 2 N = 12
Age, years Median (range)	51.0 (50-52)	54.5 (54-55)	50.5 (50-51)	39.0 (38-40)	42.0 (39-45)	41.0 (34-48)	49.0 (34-55)
Height, cm Median (range)	169.0 (168-170)	162.0 (159-165)	161.0 (159-163)	169.5 (164-175)	157.5 (153-162)	159.5 (154-165)	163.5 (153-175)
Weight, kg Median (range)	64.0 (53-75)	66.5 (65-68)	62.0 (54-70)	63.0 (59-67)	55.5 (54-57)	58.0 (53-63)	61.0 (53-75)

6.2 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time curve of TMC114 after a single oral 400 mg dose, formulated as tablet F014, administered in the presence of 100 mg RTV b.i.d. and after a standard breakfast (treatment A), under fasted conditions (treatment B), after a high fat breakfast (treatment C), after a nutritional drink rich in proteins (treatment D), or after a croissant with coffee (treatment E).

Fig 1: Mean plasma concentration-time curve of TMC114 after a single oral 400 mg dose, formulated as tablet F014, administered in the presence of 100 mg RTV b.i.d. and after a standard breakfast (treatment A), under fasted conditions (treatment B), after a high fat breakfast (treatment C), after a nutritional drink rich in proteins (treatment D), or after a croissant with coffee (treatment E).



The mean concentration-time plots of TMC114 showed that a single oral intake of 400 mg TMC114, formulated as F014 and in the presence of RTV, resulted in comparable TMC114 plasma concentration-time profiles for all administrations under fed conditions (Treatments A, C, D and E). Compared to these treatments, administration of TMC114 under fasted conditions (Treatment B) resulted in a lower mean TMC114 plasma concentration-time profile.

Reviewer's Note:
All subjects in panel 1 were male and all subjects in panel 2 were females. Since both panels received treatment A (standard breakfast), the sponsor compared the TMC114 plasma concentration time profile between subjects (males) in Panel 1 and subjects (females) in panel 2 following Treatment A. Plasma TMC114 concentrations were similar for males and females following Treatment A, suggesting that the assignment of all females to Panel 2 and all males to Panel 1 did not affect the results observed in this study.

Table 3 shows the pharmacokinetic results of TMC114 after a single oral dose of 400 mg, formulated as tablet F014, administered under different food conditions, in the presence of 100 mg RTV b.i.d.

Table 3: Pharmacokinetic results of TMC114 after a single oral dose of 400 mg, formulated as tablet F014, administered under different food conditions, in the presence of 100 mg RTV b.i.d.

Pharmacokinetics of TMC114 (mean ± SD.t_{max}: median (range))	Treat A: standard breakfast	Treat B: fasted conditions	Treat C: high-fat breakfast	Treat D: nutritional drink rich in proteins	Treat E: croissant with coffee
n	23	12	12	10	11
t_{max}, h	3.0 (1.5 - 5.0)	1.5 (1.0 - 3.0)	3.0 (1.5 - 5.0)	3.0 (1.5 - 4.0)	3.0 (1.5 - 4.0)
C_{max}, ng/mL	5326±1148	3609±775.2	5908±1687	5545±1245	5363±958.5
AUC_{last}, ng.h/mL	71929±21675	46750±11137	68675±15266	80270±28211	76732±26330
AUC_{∞}, ng.h/mL	75207±25515	48918±14468	70591±16222	89032±33703	81874±32666
$t_{1/2term}$, h	14.55±4.823	14.07±6.250	12.67±4.494	20.99±9.614	17.11±5.638

0 = NQ= Not Quantifiable (<10.0 ng/mL)

Table 4 (A, B, C, and D) shows the summary of the statistical analysis of the pharmacokinetic parameters of TMC114 after various treatments.

Table 4-A: Summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment B (fasted condition) compared to treatment A (standard breakfast).

Parameter	n		Least square means		Least square means ratio, %	90% CI [a]	p-value		
	Treatment A (reference)	Treatment B (test)	Treatment A (reference)	Treatment B (test)			Treatment	Period	Sequence
C_{max}, ng/mL	23	12	5170	3586	69.37	62.4 - 77.1	0.0001	0.0929	0.9810
AUC_{last}, ng.h/mL	23	12	68227	48025	70.39	62.6 - 79.2	0.0005	0.3197	0.9941
AUC_{∞}, ng.h/mL	23	12	70596	49796	70.54	62.1 - 80.1	0.0008	0.3230	0.9856
	n		Median				p-value		
Parameter	Treatment A (reference)	Treatment B (test)	Treatment A (reference)	Treatment B (test)	Treatment difference median	90% CI [a]	Treatment	Period	Sequence
t_{max}, h	12	12	3.0	1.5	1.375	(0.50) - (2.00)	0.0289	0.6858	0.9355

[a] 90% confidence intervals.

Table 4-B: Summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment C (high-fat breakfast) compared to treatment A (standard breakfast).

Parameter	n		Least square means		Least square means ratio, %	90% CI [a]	p-value		
	Treatment A (reference)	Treatment C (test)	Treatment A (reference)	Treatment C (test)			Treatment	Period	Sequence
C_{max}, ng/mL	23	12	5183	5710	110.2	97.9 - 124	0.1669	0.1514	0.8976
AUC_{last}, ng.h/mL	23	12	68385	71406	104.4	96.0 - 114	0.3669	0.1936	0.9701
AUC_{∞}, ng.h/mL	23	12	70746	73703	104.2	95.8 - 113	0.3943	0.1813	0.9633
	n		Median				p-value		
Parameter	Treatment A (reference)	Treatment C (test)	Treatment A (reference)	Treatment C (test)	Treatment difference median	90% CI [a]	Treatment	Period	Sequence
t_{max}, h	12	12	3.0	3.0	-0.50	(-1.00) - (0.25	0.2455	0.0213	0.0310

[a] 90% confidence intervals.

Table 4-C: Summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment D (protein-rich nutritional drink) compared to treatment A (standard breakfast).

Parameter	n		Least square means		Least square means ratio, %	90% CI [a]	p-value		
	Treatment A (reference)	Treatment D (test)	Treatment A (reference)	Treatment D (test)			Treatment	Period	Sequence
C_{max}, ng/mL	23	10	5182	5125	98.89	86.0 - 114	0.8833	0.9092	0.9929
AUC_{last}, ng.h/mL	23	10	68593	68482	99.84	88.4 - 113	0.9807	0.1170	0.9209
AUC_{∞}, ng.h/mL	23	10	70995	74004	104.2	93.7 - 116	0.4864	0.0302	0.9030
	n		Median				p-value		
Parameter	Treatment A (reference)	Treatment D (test)	Treatment A (reference)	Treatment D (test)	Treatment difference median	90% CI [a]	Treatment	Period	Sequence
t_{max}, h	10	10	3.0	3.0	0.25	(-1.25) - (1.00	0.6481	0.6481	0.0169

[a] 90% confidence intervals.

Table 4-D: Summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment E (croissant with coffee) compared to treatment A (standard breakfast).

Parameter	n		Least square means		Least square means ratio, %	90% CI [a]	p-value		
	Treatment A (reference)	Treatment E (test)	Treatment A (reference)	Treatment E (test)			Treatment	Period	Sequence
C_{max}, ng/mL	23	11	5198	5139	98.86	87.7 - 111	0.8621	0.3747	0.9605
AUC_{last}, ng.h/mL	23	11	68750	67289	97.88	86.7 - 110	0.7502	0.0677	0.8928
AUC_{∞}, ng.h/mL	23	11	71155	70048	98.44	87.4 - 111	0.8132	0.0594	0.8846
	n		Median				p-value		
Parameter	Treatment A (reference)	Treatment E (test)	Treatment A (reference)	Treatment E (test)	Treatment difference median	90% CI [a]	Treatment	Period	Sequence
t_{max}, h	11	11	3.0	3.0	0.00	(-1.00) - (1.25	1.000	0.7079	0.3086

[a] 90% confidence intervals.

For each comparison with the reference treatment, the ratios of the LS_{means} of C_{max}, AUC_{last} and AUC_{∞} were close to 100 %, except for the comparison between Treatment A and Treatment B. In this case, the systemic exposure to TMC114, expressed as C_{max}, AUC_{last} and AUC_{∞}, decreased with approximately 30 % for administration under fasted conditions (Treatment B) , when compared to administration after a standard breakfast (Treatment A).

7. Conclusion

- The results of this trial demonstrate that in the presence of low-dose RTV, the systemic exposure to TMC114 is decreased by approximately 30 % when taken in a fasted state as compared to when taken after a standard breakfast.
- The exposure to TMC114 is comparable for different types of meals (standard breakfast, high-fat breakfast, nutritional protein-rich drink or croissant with coffee). Based on the results from this study, **it is recommended that TMC114/RTV should always be taken with food. However, the type of meal does not affect the exposure to TMC114.**

TMC114-C118

1. Title

The relative bioavailability of a single intake of TMC114, after 2-days b.i.d. low dosing of ritonavir, with the experimental formulation TF036 under fed and fasted conditions as compared to the [redacted] PEG400 [redacted] under fed and fasted conditions.

2. Objectives

The objectives of this trial were to assess:

- The relative bioavailability of TMC114 with the experimental solid formulation TF036 as compared to the reference [redacted] /PEG400 (TF019) [redacted] both in the presence of a low dose RTV.
- The effect of food on the relative bioavailability of TMC114 with the experimental solid formulation TF036 and the reference [redacted] /PEG400 (TF019) oral solution, both in the presence of low dose of ritonavir.

3. Study Design

Sixteen healthy volunteers received the following four treatments in a randomized fashion (as shown in table 1).

Table 1: Various treatments in TMC114-C118

Treatment A (Fasted conditions)	Treatment B (Fed conditions)	Treatment C (Fasted conditions)	Treatment D (Fed conditions)
[redacted] PEG400 solution (TF019) 400 mg TMC114/20 ml (20 mg/ml)	[redacted] PEG400 solution (TF019) 400 mg TMC114/20 ml (20 mg/ml)	TF036 400 mg TMC114/ 1 Tablet (400 mg/tablet)	TF036 400 mg TMC114/ 1 Tablet (400 mg/tablet)

From 2 days before until 1 day after administration of TMC114, 100 mg RTV b.i.d. was administered. There was a washout period of 7 days between each dose of TMC114.

4. Investigational Drugs

[redacted] /PEG400 (TF019) formulation: Aqueous solution containing TMC114 ethanolate eq. 20 mg/ml and containing Vit E-TPGS and PEG400 as main solubilizing agents in the formulation. The solution was filled into an amber-colored flask and stored at 2-8 °C. The batch number and expiry date of the formulation were 02E22 and Nov 22, 2002 respectively.

TF036 formulation: Oral tablet at a strength of 400 mg per tablet [redacted] The tablet was packed in a [redacted] and stored at room temperature (under 25 °C). The batch number and expiry date of the formulation were 02E06 and Nov 6, 2002 respectively.

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

For all the treatments, plasma samples were collected immediately before drug intake, and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, and 48 hours after administration of TMC114. The plasma concentrations of TMC114 and RTV were determined using a validated LC-MS/MS method. The lower limit of quantification (in plasma) was 10 ng/mL for TMC114 and 5 ng/mL for RTV.

Pharmacokinetic Assessments

Non-parametric analyses were performed using WinNonlin Professional(version 3.3; [redacted] using a [redacted] Based on the individual plasma concentration-time data, using the scheduled sampling times, the following pharmacokinetic parameters of TMC114 were derived from the bioanalytical results:

Days 3, 10, 17 and 24: C_{0h}, C_{12h}, C_{24h}, C_{max}, t_{max}, AUC_{last}, AUC_{∞}, λ_z, $t_{1/2term}$
Ratio: Treatment B vs. A, C vs. A, D vs. A, D vs. B and D vs. C for C_{max} and AUC_{last}

6. Results

6.1 Subject Disposition

16 subjects were randomized to the following four treatment sequences: ADBC, BACD, CBDA, and DCAB. The subjects randomized to sequences ADBC, BACD, and CBDA completed all assessments, however, one subject randomized to sequence DCAB withdrew consent after the first session.

Table 2: Demographics in Study TMC 114-C118

Parameter	All subjects
Age, years, median (range)	44 (26-52)
Weight, kg, median (range)	74 (56-90)
Height, cms, median (range)	175.5 (156-188)

6.2 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time profiles of a single dose of 400 mg TMC114, administered as [redacted](TF019) and as tablet (TF036) under fasted and fed conditions, in the presence of a low dose of RTV (100 mg b.i.d.).

Fig 1: Mean plasma concentration-time profiles of a single dose of 400 mg TMC114, administered as [redacted]) and as tablet (TF036) under fasted and fed conditions, in the presence of a low dose of RTV (100 mg b.i.d.).

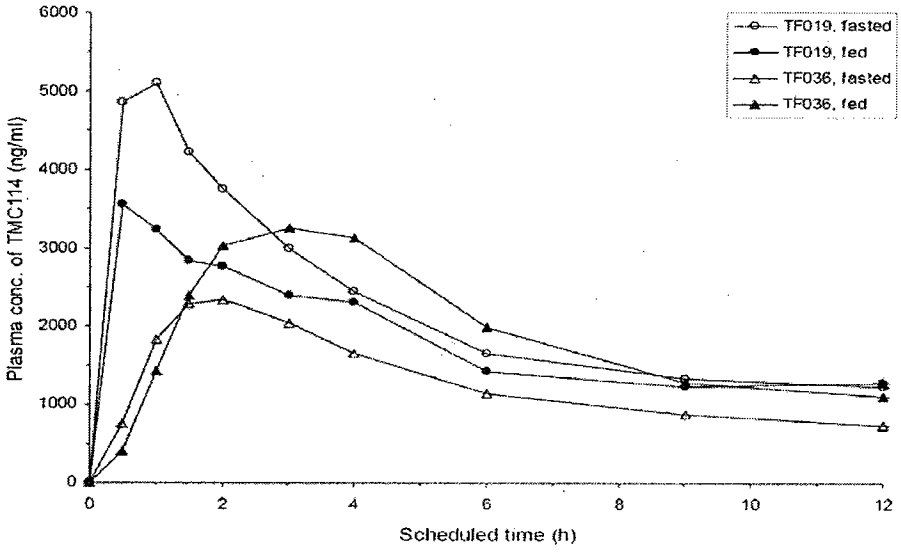


Table 3 shows the pharmacokinetic results of TMC114 after a single oral dose of 400 mg, formulated as the [redacted] and as a tablet (TF036) under fasted and fed conditions, in the presence of a low dose of RTV (100 mg b.i.d.).

Table 3: Pharmacokinetic results after a single dose of 400 mg TMC114, formulated as the [redacted]) and as a tablet (TF036) under fasted and fed conditions, in the presence of a low dose of RTV (100 mg b.i.d.).

Pharmacokinetics of TMC114 (mean±SD. t_{max}: median (range))	Treatment A: TF019 (fasted)	Treatment B: TF019 (fed)	Treatment C: TF036 (fasted)	Treatment D: TF036 (fed)
n	15[#]	15	15[#]	16[#]
t_{max}, h	1.0 (0.5 - 1.0)	0.5 (0.5 - 4.0)	1.5 (1.0 - 4.0)	3.0 (1.5 - 4.0)
C_{0h}, ng/ml	NQ	NQ	NQ	NQ
C_{12h}, ng/ml	1240 ± 371	1290 ± 550	732±274	1110±570
C_{24h}, ng/ml	828 ± 293	725 ± 308	593±257	715±390
C_{max}, ng/ml	5571 ± 1601	3701 ± 960	2769±708	3614±905
AUC_{last}, ng.h/ml	52112 ± 15923	45608 ± 14400	32452±10396	43938±20064
AUC_{∞}, ng.h/ml	59803 ± 18642	51552 ± 17802	37311±13151	53221±21098
$t_{1/2term}$, h	16.3 ± 4.54	15.2 ± 4.33	18.4±5.84	16.3±5.81

[#] n=14 for AUC_{∞} and $t_{1/2term}$ for Treatment A: n=13 for AUC_{∞} and $t_{1/2term}$ for Treatment C: n=15 for C_{24h} and n=14 for $t_{1/2term}$ and AUC_{∞} for Treatment D
NQ: not quantifiable (<10.0 ng/ml)

For the [redacted] TF019), maximum plasma concentrations of TMC114 were reached between 0.5 and 1.0h (median: 1.0h) under fasted conditions and between 0.5 and 4.0h (median: 0.5h) under fed conditions after administration with a low dose of RTV.

The rate of absorption was slower for the tablet formulation compared to the oral solution. For most subjects, the rate of absorption was slower when the tablet was given with food, resulting in a median t_{max} value of 3.0 h (range: 1.5-4.0h) compared to a median t_{max} value of 1.5 h (range: 1.0-4.0h) under fasted conditions. Under fed conditions, the mean C_{max} and AUC_{last} values were increased by 35 % and 42 %, respectively. **The highest bioavailability of TMC114 was obtained for the oral solution under fasted conditions.** Compared to the oral solution, the C_{max} and AUC_{last} of TMC114 were 50 % and 38 % lower for the tablet under fasted conditions, respectively. Under fed conditions, the bioavailability of TMC114 from the oral solution was decreased compared to fasted conditions, indicated by 33 % lower C_{max} and 13 % lower AUC_{last} values. Under fed conditions, the bioavailability of TMC114 from the tablet was increased, indicated by 35 % higher C_{max} and 42 % higher AUC_{last} values. ***The bioavailability of TMC114 was comparable when administered as a tablet or oral solution under fed conditions.*** Terminal elimination half-lives ($t_{1/2\ term}$) were comparable for the solution and tablet, but the rate and extent of absorption were different for both formulations.

Table 4A-E presents the statistical evaluation of the pharmacokinetic parameters.

Table 4-A: Statistical evaluation of the pharmacokinetics of a single dose of 400 mg TMC114 of the oral [redacted] (TF019) under fed vs. fasted conditions, in the presence of a low dose of RTV (100 mg b.i.d.).

Parameter	n	Least square means Treatment A: [redacted] fasted (reference)	Least square means Treatment B: [redacted] fed (test)	Least square means ratio, %	90% CI	p-value Treatment
C_{max}, ng/ml	15	5394	3619	67.10	59.6 - 75.6	0.0001
C_{12h}, ng/ml	15	1183	1190	100.6	84.9 - 119	0.9543
C_{24h}, ng/ml	15	776.3	655.2	84.41	68.9 - 103	0.1616
AUC_{last}, ng·h/ml	15	49726	43243	86.96	78.5 - 96.4	0.0331
		Median				p-value
Parameter	n	Treatment A: TF019, fasted (reference)	Treatment B: TF019, fed (test)	Treatment difference median	90% CI	Treatment
t_{max}, h	15	1.0	0.5	0.0	(-0.25) - (0.25)	0.6007

Table 4-B: Statistical evaluation of the pharmacokinetics of a single dose of 400 mg TMC114 of the tablet (TF036) under fed vs. fasted conditions, in the presence of a low dose of RTV (100 mg b.i.d.).

Parameter	n	Least square means Treatment C: TF036, fasted (reference)	Least square means Treatment D: TF036, fed (test)	Least square means ratio, %	90% CI	p-value Treatment
C_{max}, ng/ml	15	2697	3633	134.8	122 - 149	0.0004
C_{12h}, ng/ml	15	680.2	1081	158.9	124 - 203	0.0070
C_{24h}, ng/ml	15	520.8	622.9	119.6	94.6 - 151	0.1975
AUC_{last}, ng·h/ml	15	30799	43799	142.2	120 - 169	0.0036
		Median				p-value
Parameter	n	Treatment C: TF036, fasted (reference)	Treatment D: TF036, fed (test)	Treatment difference median	90% CI	Treatment
t_{max}, h	15	1.5	3.0	-1.125	(-1.50) - (-0.75)	0.0102

Table 4-C: Statistical evaluation of the pharmacokinetics of a single dose of 400 mg TMC114 of the tablet (TF036) vs. the oral [redacted] (TF019), in the presence of a low dose of RTV (100 mg b.i.d.) and under fasted conditions.

Parameter	n	Least square means		Least square means ratio, %	90% CI	p-value
		Treatment A: TF019, fasted (reference)	Treatment C: TF036, fasted (test)			Treatment
C_{max}, ng/ml	15	5415	2710	50.05	44.8 - 55.9	<0.0001
C_{12h}, ng/ml	15	1191	691.3	58.04	51.5 - 65.4	<0.0001
C_{24h}, ng/ml	15	780.1	524.2	67.20	52.5 - 86.0	0.0139
AUC_{last}, ng.h/ml	15	50066	31049	62.01	55.2 - 69.7	<0.0001
		Median				p-value
Parameter	n	Treatment A: TF019, fasted (reference)	Treatment C: TF036, fasted (test)	Treatment difference median	90% CI	Treatment
t_{max}, h	15	1.0	1.5	-1.0	(-1.50) - (-0.75)	0.0010

Table 4-D: Statistical evaluation of the pharmacokinetics of a single dose of 400 mg TMC114 of the tablet (TF036) administered under fed conditions vs. the oral [redacted] (TF019) administered under fasted conditions, in the presence of a low dose of RTV (100 mg b.i.d.).

Parameter	n	Least square means		Least square means ratio, %	90% CI	p-value
		Treatment A: TF019, fasted (reference)	Treatment D: TF036, fed (test)			Treatment
C_{max}, ng/ml	15	5405	3638	67.31	62.0 - 73.0	<0.0001
C_{12h}, ng/ml	15	1191	1080	90.71	77.9 - 106	0.2749
C_{24h}, ng/ml	15	773.1	628.2	81.26	64.4 - 103	0.1374
AUC_{last}, ng.h/ml	15	49816	43907	88.14	78.1 - 99.5	0.0888
		Median				p-value
Parameter	n	Treatment A: TF019, fasted (reference)	Treatment D: TF036, fed (test)	Treatment difference median	90% CI	Treatment
t_{max}, h	15	1.0	3.0	-2.25	(-2.75) - (-1.50)	0.0011

Table 4-E: Statistical evaluation of the pharmacokinetics of TMC114 of the tablet (F036) vs. the oral [redacted] (TF019), in the presence of a low dose of RTV (100 mg b.i.d.), and under fed conditions.

Parameter	n	Least square means		Least square means ratio, %	90% CI	p-value
		Treatment B: TF019, fed (reference)	Treatment D: TF036, fed (test)			Treatment
C_{max}, ng/ml	15	3623	3649	100.7	90.8 - 112	0.9042
C_{12h}, ng/ml	15	1190	1072	90.03	71.9 - 113	0.4212
C_{24h}, ng/ml	15	659.9	624.6	94.65	72.8 - 123	0.7154
AUC_{last}, ng.h/ml	15	43461	43709	100.6	86.2 - 117	0.9485
		Median				p-value
Parameter	n	Treatment B: TF019, fed (reference)	Treatment D: TF036, fed (test)	Treatment difference median	90% CI	Treatment
t_{max}, h	15	0.5	3.0	-2.25	(-2.50) - (-1.50)	0.0013

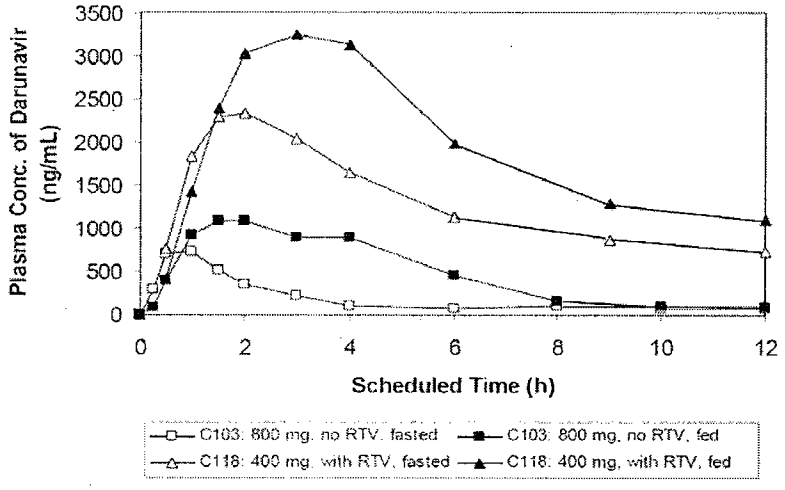
7. Conclusion

- When co-administered with RTV under **fed** conditions, the bioavailability of TMC114 formulated as a tablet (TF036) is similar to the bioavailability of the oral solution (TF019).
- Under fasted conditions and co-administered with RTV, the bioavailability of TMC114 formulated as a tablet (TF036) is lower than the bioavailability of the oral solution (TF019).
- For the tablet formulation (TF036), food intake increased the bioavailability as compared to intake under fasted conditions. However, for the oral solution, food intake decreased the bioavailability as compared to intake under fasted conditions.

Reviewer's Note

In the summary of the biopharmaceutics studies, the sponsor provided a cross study comparison of study TMC114-C103 (which included a single dose of darunavir 800 mg given as a tablet formulation TF036 under fasted and fed conditions) and study TMC114-C118. Fig 1 shows the mean concentration time profiles of darunavir given as a tablet formulation (TF036) either as a single 800-mg dose in the absence of ritonavir (study TMC114-C103) or as a single 400 mg dose co-administered with low-dose (100 mg b.i.d.) ritonavir (study TMC114-C118), with both doses given under fasted and fed conditions.

Mean concentration time profiles of darunavir given as a tablet formulation (TF036) either as a single 800-mg dose in the absence of ritonavir (study TMC114-C103) or as a single 400 mg dose co-administered with low-dose (100 mg b.i.d.) ritonavir (study TMC114-C118), with both doses given under fasted and fed conditions.



The inter study comparison (between study TMC114-C103 and TMC114-C118) showed that the exposure to darunavir can be substantially increased when co-administered with low-dose ritonavir (based on comparison between 800 mg, no RTV, fasted arm from

study TMC114-C103 and 400 mg, with RTV, fasted arm from study TMC114-C118) under fed (based on intra study comparison between the two arms in study TMC114-C118) conditions.

DISSOLUTION OF TMC114

Table 1 provides the description of the formulations used in the dissolution method development along with the proposed commercial formulation.

Table 1: Formulations Used in Method Development along with Proposed Commercial Formulation

	Formulations (mg/tablet)				
		400-mg		200-mg	300-mg
Component	C-001/F001	C-016	CA-009/F014	CA-012/F015	CA-008/F016
TMC114					
[redacted]					
[redacted]					
Magnesium Stearate					
Crospovidone					
OPADRY® II Orange					

NI = Not included

The initial dissolution method development for the phase 3/commercial formulation tablets (F016) started from the parameters used to assess the release rate of the Phase 2b formulations. The dissolution method (USP App 2, 900 mL of 1 % SLS in 0.01N HCl at 37 ± 0.5 °C) and the media selection was based on the solubility of TMC114 (table 2).

Table 2: Solubility of TMC114 in Aqueous Media as a Function of pH

Solvent	Solubility (g/100 mL)	pH of Solution
Water	0.015	7.6
0.1 N HCl	0.096	1.0
0.01 N HCl	0.025	2.1
citrate-HCl buffer pH 2	0.025	2.0
citrate-NaOH buffer pH 5	0.013	5.0
phosphate buffer pH 7	0.014	7.0
borate-KCl-NaOH buffer pH 9	0.016	9.0
phosphate-NaOH buffer pH 12	0.014	12.0
simulated gastric fluid	0.083	1.1
simulated intestinal fluid	0.016	7.4

The resulting profile for the Phase 2b tablets, which did not contain a [redacted] varied as a [redacted] (approximately 90% released in 10 minutes). In addition, the dissolution test was performed at a pH very near the pKa (2.02), resulting in variable dissolution results. Therefore, additional *in vitro* studies were conducted to determine the individual components of the dissolution methodology such as stirring speed and the type and concentration of surfactant.

Stirring speed

The stirring speed of 75 rpm was selected based on tests using the earlier 400-mg tablet formulation F001 to determine optimum stirring conditions. Paddle speeds of 50 and 60 rpm were investigated using USP (paddle) Apparatus 2; however, at these speeds it was not possible to achieve full release of the drug substance. The lack of complete release was attributed to [redacted]. A paddle speed of 75 rpm was needed to [redacted]. USP Apparatus 1 (basket) at 100 rpm was also evaluated, but [redacted] occurred under these conditions. [redacted] vessels using Apparatus 2 at 50 rpm were evaluated; equivalent profiles were obtained using Apparatus 2 at 75 rpm and the Peak vessels at 50 rpm, but the conventional dissolution vessels with a paddle speed of 75 rpm were chosen as the preferred configuration. The paddle speed experiments were repeated using the final 400-mg tablet formulation F014, which confirmed the suitability of the paddle speed of 75 rpm.

Surfactant

Using the earlier 400-mg clinical tablet formulation (F001), SLS, Tween-20, and hydroxypropyl-beta-cyclodextrin (cyclodextrin) were evaluated using USP Apparatus 2 at 75 rpm in pH 3.0 buffer at different concentrations to determine a surfactant concentration that would provide complete release as well as a defined profile. For all 3 surfactants, the rate of dissolution was a function of surfactant concentration. Cyclodextrin required over 2 hours to approach complete release. Appropriate concentrations of SLS were not able to maintain adequate solubility at ambient room temperatures. Tween-20 provided adequate solubility at ambient temperatures, with complete release in approximately one hour, and a profile with the potential to discriminate between formulations.

To test the robustness of the dissolution method, the following key dissolution parameters were varied by preplanned amounts using a Plackett-Burman design: molarity (NaH2PO4.2 H2O) and pH of the medium, percentage surfactant (Tween-20), and rotation of paddles. The results indicated that only paddle rotation was a critical parameter, which is controlled by USP requirements and must be within [redacted] of 75 rpm. The experimental design varied the rpm ± [redacted].

Based on the results of the *in vitro* assessments, the sponsor proposed the following dissolution specifications:

USP Apparatus 2 (paddle) at 75 rpm in 900 mL of 2.0 % Tween-20 in 0.05 M sodium phosphate buffer (pH = 3.0) at 37 ± 0.5 °C. The proposed specification for dissolution release and stability is [redacted] (Q) in 30 minutes.

Reviewer's Note

Based on discussions with the Chemistry Reviewer, the dissolution specifications are acceptable.

All the batches tested over the course of the stability studies complied with the proposed specification for release and stability. Table 3 provides the batch overview of the release data of TMC114 300 mg orange film coated tablet batches.

Table 3: Batch Overview of the Release Rate of TMC114 300-mg Orange Film Coated Tablet Batches.

	Dissolution (% released) mean (min-max)				
Batch	10 min	20 min	30 min	45 min	60 min
PD1352	78 (	93 (	97	97 (	98 (
PD1348	75 (	89 (	93	96 (	96 (
PD1326	72	88 (	93	95 (	96 (
PD1324	75	92 (	97	98 (	99 (
PD1322	76	93 (	97 (	98 (	99 (
PD1328	74	90 (	95 (	96 (	96 (
PD1419	67	87 (	94 (	96 (	97 (
PD1330	78	94 (	98 (	98 (	98 (
4NG4517-X	85	95 (	98 (	100 (	100 (
4NG4518-X	84	95 (	98 (	99 (	99 (
4NG4689-X	80	92 (	95 (	95 (	95 (

SINGLE AND MULTIPLE DOSE PHARMACOKINETICS

Study Number	Description	Page #
TMC114-C101	Safety, tolerability, and pharmacokinetics of increasing single oral doses of TMC114 in healthy adult subjects.	122
TMC114-C104	Randomized, placebo-controlled, double-blind, multiple dose escalation trial to examine the safety, tolerability, and pharmacokinetics of oral twice or three times daily TMC114 doses in healthy subjects.	127
TMC114-C112	The effect of repeated doses of ritonavir on the pharmacokinetics of repeated doses of TMC114 in healthy subjects.	132
TMC114-C137	The pharmacokinetics, safety and tolerability of TMC114, formulated as tablet TF036, and boosted with a low dose of ritonavir, for various multiple dose regimens.	137

1. Title

Safety, tolerability, and pharmacokinetics of increasing single oral doses of TMC114 in healthy adult subjects **(TMC114-C101).**

2. Objectives

The objectives of this trial were to assess the pharmacokinetics, safety, and tolerability of single oral doses of 100 to 4000 mg of TMC114 administered as an oral solution.

3. Study Design

Randomized, double blind, placebo controlled phase I dose escalation trial. The dose of the test drug was consecutively escalated in 2 alternating panels of 9 subjects. Subjects in **Panel A** received doses of 100, 400, and 1200 mg of TMC114. Subjects in **Panel B** received 200, 800, and 1600 mg of TMC114. If these doses were well tolerated in panels A and B, an additional panel of 9 subjects (**Panel C**) would be added to receive 2400, 3200, and 4000 mg of TMC114 subsequently. For each individual subject, there was a time interval of at least 14 days between two subsequent dose administrations. Before each treatment, subjects fasted overnight for at least 10 hours.

4. Investigational Drugs

TMC 114 was formulated as an oral aqueous solution of TMC114 20 mg/mL containing [redacted] and PEG400 as main solubilizing agents in the formulation. The batch number of TMC114 and placebo used in the trial was 01A05 and 01A04 respectively.

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Per dose level, 5 mL of blood was collected at pre-dose (immediately before drug intake) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 32, 48, and 72 hours after drug administration. In addition, a pre-dose urine sample and the complete urinary output during the intervals 0-8 hours, 8-24 hours, 24-32 hours, and 32-48 hours after each dose was collected.

The plasma and urine concentrations of TMC114 were determined using validated chromatographic methods. The lower limit of quantification (LLOQ) was 2.01 ng/mL and 20 ng/mL in plasma and urine respectively.

Pharmacokinetic Assessments

Winnonlin Professional ™ [redacted] was used for all pharmacokinetic assessments.

6. Results

6.1 Subject Disposition

27 subjects were randomized to receive the trial medication. 9 subjects (6 treatment and 3 placebo) in panel A received 100 mg, 400 mg, and 1200 mg of TMC114. Similarly, 9 subjects in panel B received 200 mg, 800 mg, and 1600 mg of TMC114. **9 subjects in panel C received 2400 mg and 3200 mg, however, the sponsor decided to stop the trial beyond 3200 mg due to AEs.** Table 2 shows the subject disposition.

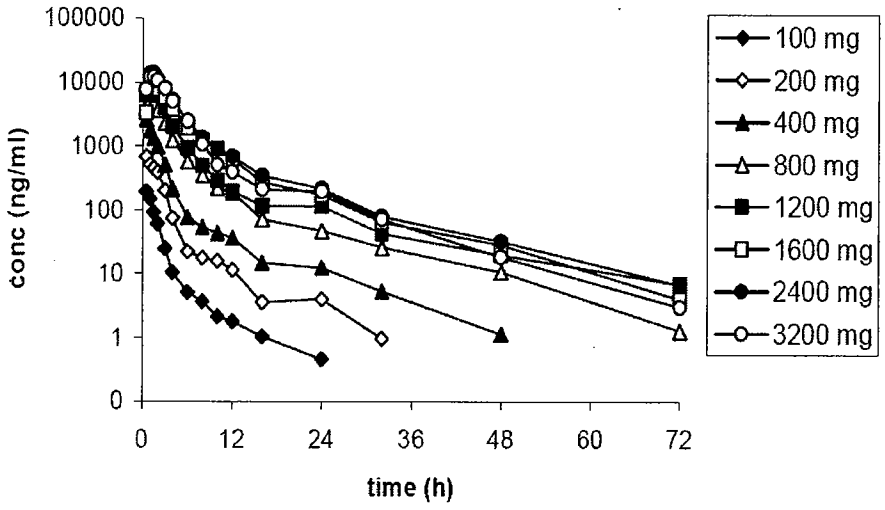
Table 2: Demographics in Study TMC 114-C101

Parameter			Panel A	Panel B	Panel C	All subjects
Age (years)	Median (range)		52.0 (34-56)	41.0 (24-52)	42.0 (19-54)	42.0 (19-56)
Weight (kg)	Median (range)		65.0 (54-90)	65.0 (62-92)	72.0 (61-90)	71.0 (54-92)
Height (cm)	Median (range)		166.0 (162-189)	171.0 (153-192)	179.0 (157-192)	171.0 (153-192)
BMI (kg/m²)	Median (range)		23.5 (20-29)	25.0 (21-31)	23.9 (19-29)	23.9 (19-31)
Race	Caucasian: n (%)		9 (100)	9 (100)	9 (100)	27 (100)
Gender	M	n (%)	5 (55.6)	4 (44.4)	7 (77.8)	16 (59.3)
	F	n (%)	4 (44.4)	5 (55.6)	2 (22.2)	11 (40.7)
Smoker	Y	n (%)	0	4 (44.4)	2 (22.2)	6 (22.2)
	N	n (%)	9 (100)	5 (55.6)	7 (77.8)	21 (77.8)

6.5 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time curve of TMC114 at different dose levels.

Fig 1: Mean plasma concentration-time profiles of TMC114 at different dose levels



At the higher dose levels, the plasma concentration-time profiles were characterized by a fast absorption phase, followed by an initial extensive distribution phase and a slower elimination phase. As most samples of the terminal elimination phase were below the LLOQ, the slower elimination phase could not be observed at the lower dose levels.

Table 3 presents the summary of the pharmacokinetic parameters of TMC114 (n = 6 per dose level).

Table 3: Summary of Pharmacokinetic Parameters of TMC114 (n = 6 per dose level)

Pharmacokinetics of TMC114 (mean±SD. t_{max}: median (range))	100 mg	200 mg	400 mg	800 mg
t_{max}, h	0.5 (0.5-1.0)	0.5 (0.5-2.0)	0.5 (0.5-1.5)	1.0 (0.5-1.5)
C_{max}, ng/ml	220.0 ± 165.9	995.3 ± 813.0	2927 ± 1443	6468 ± 2270
AUC_{last}, ng.h/ml	336 ± 321	1622 ± 1287	5087 ± 3028	18035 ± 9607
AUC_{∞}, ng.h/ml	NA	NA	5144 ± 3054	18113 ± 9606
$t_{1/2term}$, h	NA	NA	9.3 ± 2.5	11.7 ± 5.1
% unchanged in urine	0.2 ± 0.2	0.5 ± 0.3	0.9 ± 0.3	2.1 ± 0.7
Pharmacokinetics of TMC114 (mean±SD. t_{max}: median (range))	1200 mg	1600 mg	2400 mg	3200 mg
t_{max}, h	1.0 (0.5-1.5)	1.3 (1.0-2.0)	1.0 (1.0-1.5)	1.0 (0.5-3.0)
C_{max}, ng/ml	11277 ± 2991	10658 ± 3357	15300 ± 3164	14407 ± 3440
AUC_{last}, ng.h/ml	30578 ± 8502	41066 ± 25465	57823 ± 11327	51835 ± 19127
AUC_{∞}, ng.h/ml	30735 ± 9073	41163 ± 25456	57979 ± 11436	51979 ± 19213
$t_{1/2term}$, h	11.5 ± 2.8	9.8 ± 3.0	8.6 ± 3.3	9.2 ± 3.2
% unchanged in urine	2.4 ± 0.5	2.1 ± 1.3	1.8 ± 0.8	1.9 ± 1.2

At all dose levels, a fast absorption of TMC114 was observed. The median T_{max} was 1 hr at the 100 mg, 400 mg, and 800 mg doses and 1.3 hours at the 200 mg dose. At dose levels of 400 – 3200 mg, the mean terminal half-life was about 10h. Fig 2 and Fig 3 show the dose normalized plots for C_{max} and AUC_{last} respectively.

Fig 2: Dose normalized plot of C_{max}

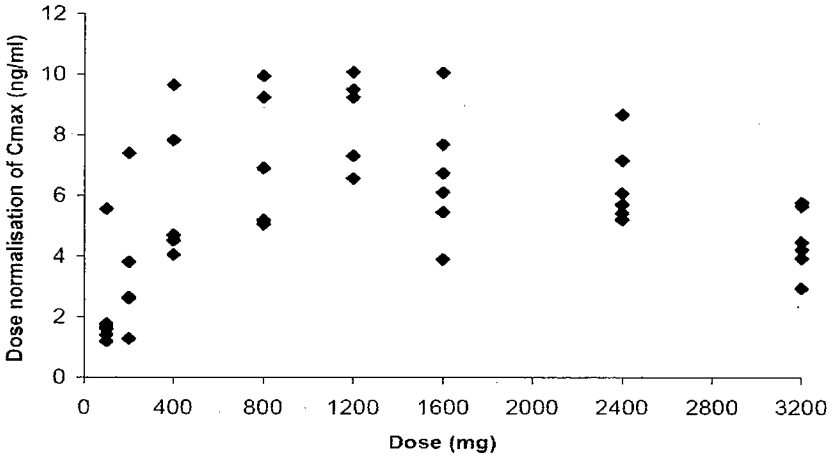
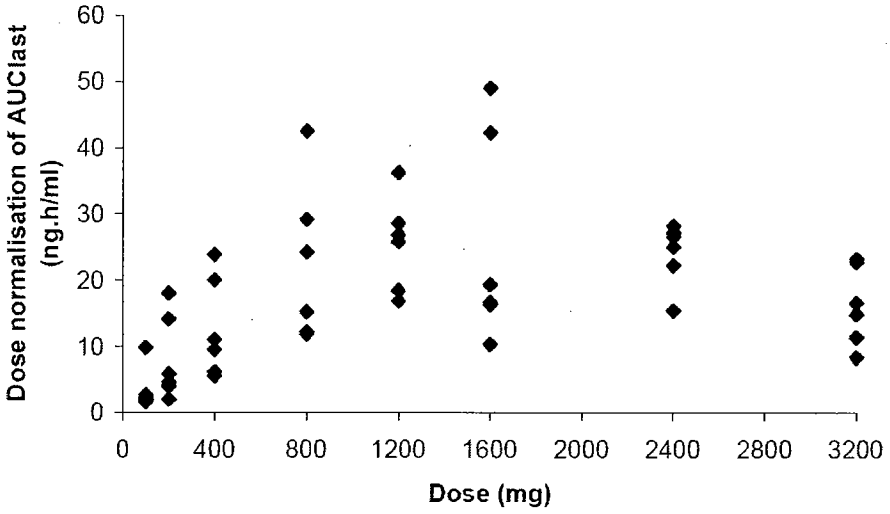


Fig 2: Dose normalized plot of AUC_{last}



The dose normalized plots suggested the following: Up to 800 mg, maximum concentrations and exposures increased more than proportional with dose. There was a dose proportional increase in C_{max} for doses between 400 mg and 2400 mg and a dose-proportional increase in AUC for doses of 800 mg and 2400 mg. At 3200 mg, no further increase in maximum concentration or exposure was found in comparison to 2400 mg.

7. Safety Assessments

Overall, 22 subjects (22/27, 81.5 %) reported at least 1 adverse event during the trial. The most frequently reported AEs were diarrhea, nausea, headache, paresthesia, and dizziness. The highest incidence of diarrhea was observed at the highest three doses (1600 mg, 2400 mg, and 3200 mg). GI events, particularly diarrhea, were the dose limiting toxicity events. Therefore, dosing beyond 3200 mg was not evaluated. GI events were likely due to large volume of PEG. CNS related events, possibly related to TMC114, were predominately observed at the highest dose group (3200 mg). None of the subjects discontinued the trial and there were no deaths or SAEs reported during the trial.

8. Conclusion

- TMC114 administered as an oral solution was absorbed with a median T_{max} of 1-1.3 hours. The pharmacokinetics of TMC114 was dose dependent for doses up to 2400 mg. No further increases in plasma levels were observed between the 2400 and 3200 mg dose.
- At the different dose levels, the inter-individual variability was large i.e., the % CV was between 15-80 % for C_{max} and 20-95 % for AUC.

- The high metabolic conversion of TMC114 is confirmed by the low urinary excretion of TMC114. The maximum amount of administered dose excreted unchanged in the urine was 2 %.

1. Title

Randomized, placebo-controlled, double-blind, multiple dose escalation trial to examine the safety, tolerability, and pharmacokinetics of oral twice or three times daily TMC114 doses in healthy subjects **(TMC114-C104).**

2. Objectives

The objectives of this trial were to assess the tolerability, cardiovascular and laboratory safety, and pharmacokinetics after repeated twice or three times daily doses of TMC114 as an oral solution.

3. Study Design

Randomized, double blind, placebo controlled multiple dose escalation trial. Four doses of TMC114 **(400 mg b.i.d., 800 mg b.i.d., 800 mg t.i.d., and 1200 mg t.i.d.)** were tested in 4 panels of 9 healthy subjects. Within each panel, 6 subjects were treated with TMC114 and 3 subjects with placebo for 13 days with a single intake in the morning of day 14. The higher doses were only tested if the previous treatment had been proven safe and tolerable for at least 7 days.

Table 1 provides the overview of the dose regimens.

Table 1: Overview of dose regimens

Session number	Subject panel	Dose (n° of volunteers)	Volume
I	A	400 mg TMC114 oral solution b.i.d. (n=6) or placebo (n=3)	20 ml of TMC114 b.i.d. (20 mg/ml) or 20 ml of placebo b.i.d.
II	B	800 mg TMC114 oral solution b.i.d. (n=6) or placebo (n=3)	2x20 ml of TMC114 b.i.d. (20 mg/ml) or 40 ml of placebo b.i.d.
III	C	800 mg TMC114 oral solution t.i.d. (n=6) or placebo (n=3)	2x20 ml of TMC114 t.i.d. (20 mg/ml) or 2x20 ml of placebo t.i.d.
IV	D	1200 mg TMC114 oral solution t.i.d. (n=6) or placebo (n=3)	2x30 ml of TMC114 t.i.d. (20 mg/ml) or 2x30 ml of placebo t.i.d.

4. Investigational Drugs

TMC 114 was formulated as an oral aqueous solution of TMC114 20 mg/mL containing [redacted] and PEG400 as main solubilizing agents in the formulation. The placebo solution contained PEG400, [redacted] and taste masking agents. The batch numbers of TMC114 and placebo used in the trial were 01D05 and 01D06 respectively.

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Plasma

For session 1 and 2 (b.i.d. treatment), pre-dose samples were collected on day 2, 3, 4, 5, 6, 9, 11, and 13. In addition, intensive PK sampling was done at pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hrs on day 1, 7, and 14. Additional blood samples were collected on day 15 (24 hr), day 16 (48 hr) and day 17 (72 hrs).

For session 3 and 4 (t.i.d. treatment), pre-dose samples were collected on day 2, 3, 4, 5, 6, 9, 11, and 13. In addition, intensive PK sampling was done at pre-dose and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 8.5, 8.75, 9, 9.5, 10, 11, 12, 14, and 16 hrs on day 1. Identical sampling schedule (up to 8 hrs on day 7 and up to 12 hrs on day 14) was also followed. Additional blood samples were collected on day 15 (24 hr), day 16 (48 hr) and day 17 (72 hrs).

Urine

Urine samples were collected at screening, day 1, 3, 7, 11, and 17. On day 14, the complete urinary output during the intervals 0-8 hrs and 8-24 hrs after intake was collected.

Assay

The plasma and urine concentrations of TMC114 were determined using validated chromatographic methods. The lower limit of quantification (LLOQ) was 2 ng/mL and 20 ng/mL in plasma and urine respectively.

Pharmacokinetic Assessments

Winnonlin Professional ™ [redacted] was used for all pharmacokinetic assessments.

6. Results

6.1 Subject Disposition

Out of the 55 subjects screened, 36 subjects (6 subjects were randomized to each treatment group and 3 subjects each were randomized to each placebo group) were enrolled in the study.

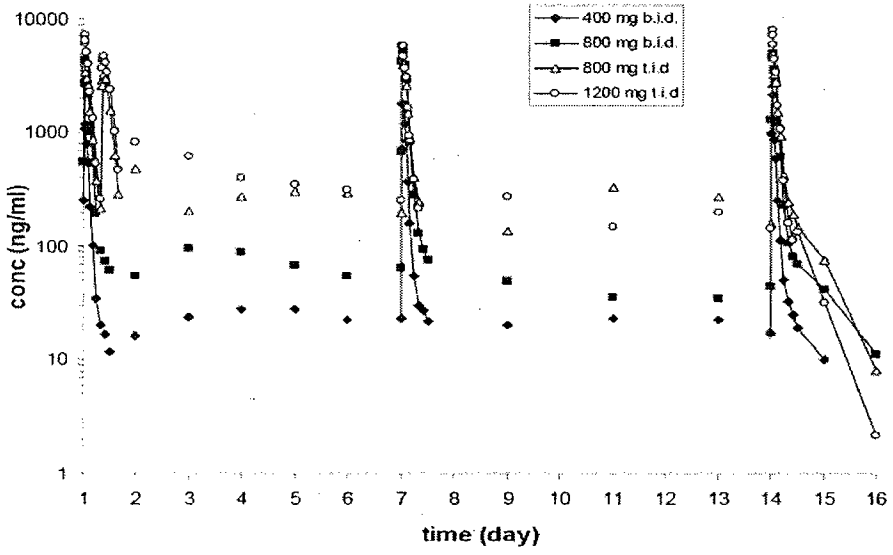
Table 2: Demographics in Study TMC114-C104

Parameter		Treatment groups				
		Placebo (N=12)	TMC114 400 mg b.i.d. (N=6)	TMC114 800 mg b.i.d. (N=6)	TMC114 800 mg t.i.d. (N=6)	TMC114 1200 mg t.i.d. (N=6)
Age, median (min-max), years		35.0 (23-47)	29.5 (21-42)	37.5 (25-55)	34.0 (25-41)	41.5 (27-55)
Weight, median (min-max), kg		80.0 (53-101)	68.5 (62-97)	65.0 (53-80)	74.5 (60-84)	72.5 (59-91)
Height, median (min-max), cm		179.0 (160-194)	176.0 (170-184)	167.5 (162-182)	172.5 (167-176)	176.5 (162-183)
BMI, median (min-max)		26.0 (20-31)	23.7 (19-29)	21.6 (20-27)	25.2 (20-29)	23.5 (21-29)
Gender, n (%)	female	5 (41.7)		5 (83.3)	2 (33.3)	1 (16.7)
	male	7 (58.3)	6 (100.0)	1 (16.7)	4 (66.7)	5 (83.3)

6.6 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time curves of TMC114 after oral administration of 400 mg b.i.d., 800 mg b.i.d., 800 mg b.i.d., and 1200 mg t.i.d. TMC114 t.i.d. for 13 days and a single TMC114 morning dose on day 14.

Fig 1: Mean plasma concentration-time curves of TMC114 after oral administration of 400 mg b.i.d., 800 mg b.i.d., 800 mg t.i.d., and 1200 mg t.i.d TMC114 for 13 days and a single TMC114 morning dose on day 14.



The full pharmacokinetic profile on day 14 showed that for all dose levels, the absorption phase was followed by an initial rapid distribution/elimination phase and a subsequent slower elimination phase. At 400 mg b.i.d., steady state was reached within 3 days.

Table 3 presents the summary of the pharmacokinetic parameters of TMC114 on day 1 (n = 6 per dose level).

Table 3: Summary of Pharmacokinetic Parameters of TMC114 on Day 1(n = 6 per dose level)

Parameter Mean ± s.d. (min-max)	400 mg b.i.d.	800 mg b.i.d.	800 mg t.i.d.	1200 mg t.i.d.
C_{max} (ng/mL)	1463 ± 842.9 (593-2800)	5103 ± 3131 (1830-11100)	4850 ± 1422 (3350-7110)	8122 ± 1797 (5740-10600)
T_{max} (hr)	0.75*(0.5-1.5)	1.25* (0.5-1.5)	0.75* (0.5-1.5)	0.75* (0.5-1)
AUC_{12}** (ng*hr/mL)	2380± 985.3 (1126-3634)	9234 ± 4626 (4606-17433)	10997± 3834 (4779-14600)	17771± 5165 (11543-26333)

*: median

**: AUC_8 for t.i.d. regimens

Table 4 presents the summary of the pharmacokinetic parameters of TMC114 on day 7 and 14 (n = 6 per dose level).

Table 4: Summary of Pharmacokinetic Parameters of TMC114 on day 7 and 14 (n = 6 per dose level)

Session 1, 400 mg b.i.d. (mean±SD, t_{max} median (range))	Day 7 (n=6)	Day 14 (n=6)
t_{max}, h	0.5 (0.5-1.0)	0.5 (0.5-1.0)
C_{0h}, ng/ml	23.2 ± 13.1	17.3 ± 8.14
C_{max}, ng/ml	2458 ± 944	2168 ± 759
$C_{ss,av}$, ng/ml	321 ± 115	270 ± 67.7
AUC_{24h}, ng.h/ml*	7702 ± 2754	6477 ± 1625
$t_{1/2eff}$, h		12.6** ± 6.93
Session 2, 800 mg b.i.d. (mean±SD, t_{max} median (range))	Day 7 (n=6)	Day 14 (n=4)
t_{max}, h	1.0 (0.5-1.0)	0.75 (0.5-1.5)
C_{0h}, ng/ml	64.2 ± 15.8	44.4 ± 8.56
C_{max}, ng/ml	5493 ± 965	5755 ± 1363
$C_{ss,av}$, ng/ml	1033 ± 340	951 ± 139
AUC_{24h}, ng.h/ml*	24788 ± 8166	22830 ± 3339
$t_{1/2eff}$, h		10.3 ± 4.31
Session 3, 800 mg t.i.d. (mean±SD, t_{max} median (range))	Day 7 (n=6)	Day 14 (n=3)
t_{max}, h	0.5 (0.5-1.0)	1.0 (0.75-1.0)
C_{0h}, ng/ml	197 ± 125	161 ± 127
C_{max}, ng/ml	5227 ± 1078	5143 ± 328
$C_{ss,av}$, ng/ml	1463 ± 342	1506 ± 372
AUC_{24h}, ng.h/ml*	35102 ± 8198	25656 ± 7568
$t_{1/2eff}$, h		6.02 ± 3.58
Session 4, 1200 mg t.i.d. (mean±SD, t_{max} median (range))	Day 7 (n=6)	Day 14 (n=2)
t_{max}, h	0.75 (0.5-0.75)	0.5 (0.5-0.5)
C_{0h}, ng/ml	254 ± 151	142 ± 90.4
C_{max}, ng/ml	6332 ± 1956	8040 ± 467
$C_{ss,av}$, ng/ml	1714 ± 468	2027 ± 166
AUC_{24h}, ng.h/ml*	41122 ± 11221	48639 ± 3997
$t_{1/2eff}$, h		7.84** ± 1.02

* Extrapolated AUC24h (for b.i.d. 2*AUC_{12h} for t.i.d. 3*AUC_{8h})

**Accurate determination of $t_{1/2eff}$ was not possible for session 1 and 4

The C_{0h} and AUC_{24h} decreased with time, especially for the 800 mg t.i.d. and 1200 mg t.i.d. regimens. AUC_{24h} and C_{ssave} were approximately proportional with the total daily dose (800-3600 mg). C_{max} was dose proportional with respect to the dose per intake. The mean terminal half-lives ($t_{1/2term}$) could not accurately be assessed for all volunteers, but for 400 mg b.i.d. and 800 mg b.i.d., the $t_{1/2}$ was 10-12 h, while for 800 mg t.i.d. and 1200 mg t.i.d. the half life appeared to be shorter (6-8 h).

7. Safety Assessments

No deaths or SAEs were reported during the trial. Overall, the most commonly reported AEs were GI events (diarrhea (28/36), abnormal bowel sounds (6/36) and flatulence (6/36)), skin & subcutaneous disorders (rash (13/36) and pruritus (10/36)) and CNS disorders (mainly headache (11/36)). The incidence of diarrhea was similar in the TMC114 groups compared to placebo. Skin & subcutaneous disorders were more commonly reported in the TMC114 groups compared to placebo. Nine subjects prematurely discontinued the trial due to rash. Overall, there did appear to be a relationship between the occurrence of rash and dose (See details in Medical Officer's review).

8. Conclusions

- Steady-state plasma concentrations were reached generally within 3 days, although C_{0h} and AUC_{24h} slightly decreased with time at all dose levels.
- AUC_{24h} and $C_{ss,av}$ increased approximately dose-proportionally with total daily dose. C_{max} was dose-proportional with respect to dose per intake.
- Less than 2% of unchanged TMC114 was excreted in the urine at all dose levels (data not shown).
- The most commonly reported AEs were rash, GI and CNS events. At the higher dose levels, 800 mg b.i.d., 800 mg t.i.d., and 1200 mg t.i.d., 9 subjects discontinued treatment due to the development of maculo-papular rash.
- The incidence of diarrhea and headache were similar between the placebo and TMC114 groups. The GI events, specifically diarrhea may be, at least part, due to the PEG400 component of the formulation.

1. Title

The effect of repeated doses of ritonavir on the pharmacokinetics of repeated doses of TMC114 in healthy subjects **(TMC114-C112).**

2. Objectives

The objectives of this trial were

- To assess the steady-state pharmacokinetics of TMC114 administered as an oral solution in various dosages in combination with various dosages of ritonavir.
- To assess the safety and tolerability of the co-administration of TMC114 and ritonavir in healthy subjects.

3. Study Design

Open label, parallel group, one-sequence, cross-over, multiple dose-escalating design
Four sequential panels, each comprising 8 healthy volunteers, were treated with TMC114/RTV 200/100 mg q.d., 400/100 mg q.d., 300/100 mg b.i.d., or 600/200 mg q.d. If these regimens were safe and well tolerated, an additional panel receiving 1200/200 was to be included. In all panels, TMC114 was administered alone on day 1. From day 2 to 14, TMC114 and ritonavir were co-administered; administration of ritonavir alone continued until day 16. All medications were taken within 15 minutes after a meal.

Table 1 provides the summary of the treatments administered.

Table 1: Overview of dose regimens

Panel (number of subjects)	Dose	Volume (per dose)
1 (n=8)	**TMC 114:** 200 mg q.d. on days 1-14 **ritonavir:** 100 mg q.d. on days 2-16	2x5 ml (20 mg/ml) 1 capsule of ritonavir (Norvir®)
2 (n=8)	**TMC 114:** 400 mg q.d. on days 1-14 **ritonavir:** 100 mg q.d. on days 2-16	4x5 ml (20 mg/ml) 1 capsule of ritonavir (Norvir®)
3 (n=8)	**TMC114:** 300 mg b.i.d. on days 1-13, 300 mg q.d. on day 14 **ritonavir:** 100 mg b.i.d. on days 2-16	1x15 ml (20 mg/ml) 1 capsule of ritonavir (Norvir®)
4 (n=8)	**TMC114:** 600 mg q.d. on days 1-14 **ritonavir:** 200 mg q.d. on days 2-16	3x10 ml (20 mg/ml) 2 capsules of ritonavir (Norvir®)

4. Investigational Drugs

TMC 114 was formulated as an oral aqueous solution of TMC114 20 mg/mL containing [redacted] and PEG400 as main solubilizing agents in the formulation. The batch numbers of TMC114 used in the trial was 01H01 (expiry date: Oct 31, 2001). The batch number of ritonavir used in the trial was 00K16 (Nov 30, 2001).

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Plasma

Pre-dose (within 1 hour before drug intake on day 1 and immediately before drug intake on days 7 and 14) samples were collected on day 1, 7, and 14. Blood samples were also collected immediately before drug intake on days 2, 4, 6, 10, 12 and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, and 12 hrs after drug administration on day 1, day 7, and day 14. In addition to the intensive sampling schedule on day 14, additional blood samples were collected on days 15 (24 hr), day 16 (48 hr), and day 17 (72 hr).

The plasma concentrations of ritonavir and TMC114 were determined using validated LC-MS/MS methods. The lower limit of quantification (LLOQ) of TMC114 and ritonavir in plasma was 2 ng/mL and 10 ng/mL respectively.

Pharmacokinetic Assessments

Winnonlin Professional ™ [redacted] was used for all pharmacokinetic assessments.

6. Results

6.1 Subject Disposition

Out of the 60 subjects screened, 40 subjects were equally randomized to the 5 treatment groups. 1 subject each was withdrawn from the 200/100, 300/100, and 1200/200 mg group due to adverse events. Table 2 shows the subject disposition in study TMC114-C104.

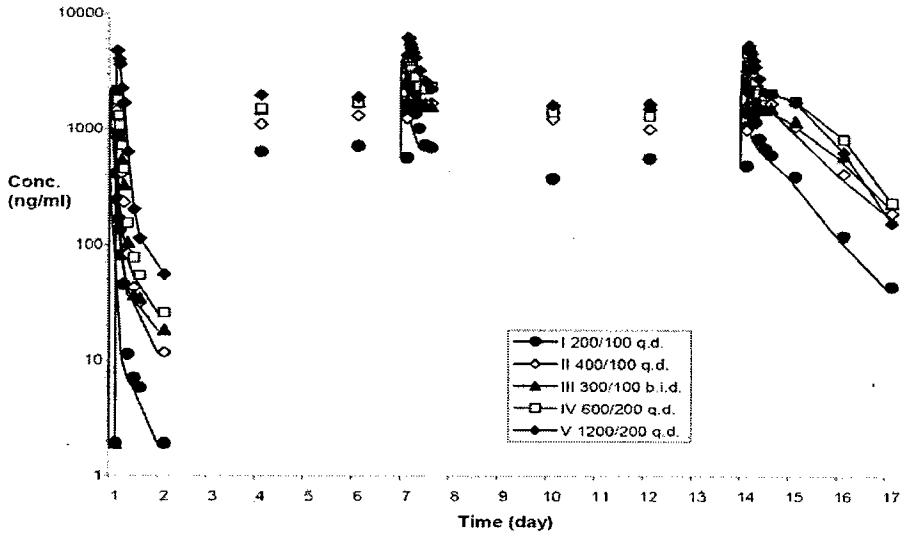
Table 2: Demographics in Study TMC 114-C112

Parameter (median)	All subjects (n=40)	Panel 1 TMC114/RTV 200/100 mg q.d. (n=8)	Panel 2 TMC114/RTV 400/100 mg q.d. (n=8)	Panel 3 TMC114/RTV 300/100 mg b.i.d. (n=8)	Panel 4 TMC114/RTV 600/200 mg q.d. (n=8)	Panel 5 TMC114/RTV 1200/200 mg q.d. (n=8)
Age (years)	34.5	31.5	31.5	33.5	40.0	36.5
BMI	24.8	23.5	26.6	23.5	25.2	24.7
Height (cm)	178.0	183.5	174.0	178.0	180.0	176.5
Weight (kg)	79.0	81.5	81.5	72	81.5	77.0

6.7 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time curves of TMC114 at different dose levels in the absence and presence of ritonavir.

Fig 1: Mean plasma concentration-time curves of TMC114 at different dose levels in the absence and presence of ritonavir



After a single intake of TMC114, a fast absorption phase was followed by a fast distribution/elimination phase, leading to low C_{0h} levels (plasma concentrations after 24 h). The C_{max} was reached between 0.25 and 3h for all dose regimens. In the presence of ritonavir, the TMC114 C_{0h} on day 14 was increased by 27-fold (for the 1200/200 mg q.d.) to at least 254-fold (for the 200/100 mg q.d.) as compared with the C_{0h} after intake of TMC114 alone (Day 1). For all dose regimens, values for C_{max} were only 2- to 4-fold higher than the corresponding values for C_{0h} and C_{min} if co-administered with ritonavir. Table 3 shows the pharmacokinetic results of TMC114.

Table 3: Pharmacokinetic results of TMC114

Parameter*	TMC114/RTV 200/100 mg q.d.	TMC114/RTV 400/100 mg q.d.	TMC114/RTV 600/100 mg q.d. (day 1), TMC114/RTV 300/100 mg b.i.d. (days 2 - 14)	TMC114/RTV 900/200 mg q.d.	TMC114/RTV 1200/200 mg q.d.
Day 1					
n	8	8	8	8	8
t_{max}, h	0.5 (0.25 - 1.0)	0.5 (0.25 - 1.0)	0.5 (0.25 - 3.0)	0.5 (0.5 - 1.0)	1.0 (0.5 - 2.0)
C_{max}, ng/ml	459 ± 290	1485 ± 583	1560 ± 585	2150 ± 866	5225 ± 1136
AUC_{24h}, ng·h/ml	808 ± 437	3757 ± 1214	4001 ± 1598	5959 ± 2327	17456 ± 5743
C_{24h}, ng/ml	NQ (1.89)[1]	11.5 ± 3.89	18.2 ± 11.9	25.5 ± 15.7	84.5 ± 42.5
Day 7					
n	7	8	8	8	8
C_{0h}, ng/ml	562 ± 396	1226 ± 418	1539 ± 427	1740 ± 821	3882 ± 846
C_{min}, ng/ml	547 ± 395	1223 ± 416	1446 ± 427	1668 ± 887	3882 ± 846
t_{max}, h	1.0 (0.25 - 3.0)	0.5 (0.5 - 2.0)	0.5 (0.25 - 1.5)	0.75 (0.25 - 1.0)	0.75 (0.5 - 1.5)
C_{max}, ng/ml	1750 ± 862	3540 ± 1086	2893 ± 492	4196 ± 963	6458 ± 1812
AUC_{24h}, ng·h/ml	20562 ± 10619	44814 ± 13162	45408 ± 11854	55839 ± 14565	66399 ± 23878
C_{av}, ng/ml	857 ± 443	1851 ± 549	1892 ± 494	2327 ± 607	2767 ± 995
F^{1}_{rel}, %	160 ± 84.7	329 ± 41.8	82.0 ± 38.4	137 ± 48.5	193 ± 88.7
Day 14					
n	7	8	7	8	7
C_{0h}, ng/ml	486 ± 236	981 ± 319	1650 ± 1242	1511 ± 708	1486 ± 1094
C_{min}, ng/ml	384 ± 245	781 ± 458	1305 ± 1051	1404 ± 752	1278 ± 908
t_{max}, h	2.0 (0.5 - 2.0)	0.75 (0.5 - 2.0)	0.5 (0.25 - 1.5)	0.5 (0.5 - 1.5)	0.5 (0.5 - 1.0)
C_{max}, ng/ml	1569 ± 588	3125 ± 884	2854 ± 1151	4628 ± 966	5453 ± 1444
AUC_{24h}, ng·h/ml	17401 ± 6675	40879 ± 18015	42499 ± 25515	52505 ± 22743	59043 ± 20455
$t_{1/2,term}$, h	13.0 ± 6.89	16.4 ± 7.03	15.4 ± 8.69	15.2 ± 6.76	12.7 ± 4.12
C_{av}, ng/ml	725 ± 278	1703 ± 751	1771 ± 1863	2188 ± 948	2460 ± 852
F^{1}_{rel}, %	173 ± 57.9	349 ± 51.2	108 ± 58.9	174 ± 82.5	184 ± 62.4

* Mean ± SD, t_{max} as median (range)
[1] Not quantifiable (value)
[2] Extrapolated AUC_{24h} calculated using the C_{0h} values of day 7 for time-point 24h for q.d. regimens. For b.i.d. doses $AUC_{24h} = AUC_{12h} \times 2$ was used

Note(s):

The pharmacokinetic data on day 1 was obtained after administration of TMC114 alone (without ritonavir).

All subjects of panel 3 (TMC114/RTV 300/100 mg b.i.d.) took 600 mg TMC114 q.d. on day 1 instead of 300 mg TMC114 b.i.d.

In the presence/absence of ritonavir, no significant differences were observed in the T_{max} estimates. The increase in C_{max} was small, while the increases in other pharmacokinetic parameters (C_{min}, C_{0h}, $C_{ss,av}$ and AUC_{24h}) were much more pronounced. The pharmacokinetics of TMC114 for the q.d. dose regimens were dose-proportional in the presence of ritonavir, except for 1200 mg TMC114/200 mg RTV q.d., which was lower than expected based on dose-proportionality. The administration of TMC114/RTV 300/100 mg b.i.d. resulted in comparable C_{min} values as after administration of TMC114/RTV 600/200 mg q.d., while AUC_{24h} and C_{max} were slightly lower. The estimates of C_{0h}, C_{min}, $C_{ss,avg}$ and C_{max} (day 14 vs. day 7) showed a slight decrease, which is probably due to the induction of CYP3A4 by ritonavir and/or TMC114.

RTV

Table 4 shows the pharmacokinetic parameters of RTV.

Table 4: Pharmacokinetic results of RTV

Parameter*	TMC114/RTV 200/100 mg q.d.	TMC114/RTV 400/100 mg q.d.	TMC114/RTV 600/100 mg q.d. (day 1), TMC114/RTV 300/100 mg b.i.d. (days 2 - 14)	TMC114/RTV 600/200 mg q.d.	TMC114/RTV 1200/200 mg q.d.
Day 7					
n	7	8	8	8	8
C_{0h}, ng/ml	85.5 ± 99.2	56.5 ± 41.7	201 ± 81.5	128 ± 67.5	109 ± 88.7
C_{min}, ng/ml	42.1 ± 41.0	34.4 ± 33.5	118 ± 56.4	72.8 ± 41.9	78.2 ± 50.2
t_{max}, h	6.0 (4.0 - 6.0)	6.0 (6.0 - 6.0)	6.0 (4.0 - 9.0)	6.0 (4.0 - 6.0)	6.0 (4.0 - 9.0)
C_{max}, ng/ml	582 ± 539	577 ± 218	514 ± 149	1488 ± 353	1017 ± 569
AUC_{12h}, ng.h/ml	3735 ± 3084	3867 ± 1644	5809 ± 1194	9357 ± 1689	7109 ± 3941
AUC_{24h}, ng.h/ml[#]	5992 ± 5244	5554 ± 2527	7612 ± 2387	13394 ± 2274	10730 ± 6331
$C_{ss,av}$, ng/ml	250 ± 219	231 ± 105	317 ± 99.5	558 ± 94.7	447 ± 264
FI, %	217 ± 40.2	244 ± 47.9	125 ± 24.2	256 ± 65.1	253 ± 72.2
Day 14					
n	7	8	7	8	7
C_{0h}, ng/ml	69.4 ± 59.7	82.6 ± 82.5	237 ± 169	166 ± 109	90.6 ± 60.0
C_{min}, ng/ml	34.2 ± 22.0	33.6 ± 34.4	106 ± 62.0	80.7 ± 27.9	57.8 ± 40.6
t_{max}, h	6.0 (4.0 - 6.0)	5.0 (1.0 - 6.0)	6.0 (4.0 - 6.0)	6.0 (4.0 - 6.0)	6.0 (2.0 - 6.0)
C_{max}, ng/ml	379 ± 221	514 ± 203	548 ± 396	1612 ± 707	825 ± 387
AUC_{12h}, ng.h/ml	2594 ± 1531	3446 ± 1645	3850 ± 2898	10612 ± 2580	5401 ± 2750
AUC_{24h}, ng.h/ml	4028 ± 2221	4916 ± 2440	7699 ± 5797	14593 ± 3888	7756 ± 4175
$C_{ss,av}$, ng/ml	168 ± 92.5	205 ± 102	321 ± 242	608 ± 162	323 ± 174
FI, %	205 ± 28.6	247 ± 42.4	138 ± 23.0	250 ± 91.0	259 ± 62.0

* Mean ± SD, t_{max} as median (range).

[#] Extrapolated AUC_{24h} calculated using the C_{0h} values of day 7 for time-point 24h for q.d. regimens. For b.i.d. doses $AUC_{24h} = AUC_{12h} \times 2$ was used.

For all regimens, AUC, $C_{ss,avg}$ and C_{max} decreased during the treatment period. For all regimens, the fluctation index (FI), representing the ratio between C_{max} and C_{min} levels,

was stable during the treatment period. At day 7, the interindividual variability of C_{min} ranged from 48 % (panel 3) to 97 % (panel 1), C_{ssavg} ranged from 31 % (panel 3) to 88 % (panel 1) and the C_{max} ranged from 24 % (panel 4) to 93 % (panel 1).

7. Safety Assessments

No deaths or serious adverse events occurred in this trial. Three subjects did not complete the trial due to AEs. One subject from panel 1 discontinued participation because of illness (diarrhea, vomiting, pyrexia, considered doubtfully related to trial medication by the investigator). One subject of panel 3 discontinued due to aggression (considered not related with trial medication by the investigator). One subject of panel 5 discontinued because of maculo-papular rash (considered probably related with trial medication by the investigator). All other subjects completed the trial. The most frequently reported AEs were diarrhea, loose stools, flatulence, nausea, headache, sore throat and pruritus. Pruritus was only reported in the highest treatment group. Two subjects in the highest treatment group developed rash, one had maculo-papular rash and the other had erythema on two separate occasions (See details in Medical Officer's review).

8. Conclusion

- Co-administration of 100 or 200 mg q.d. or 100 mg b.i.d. ritonavir, significantly increased the C_{min} and AUC values of TMC114; the effect on C_{max} was less pronounced.
- The plasma concentrations of TMC114 slightly decreased within the 2-week study period.
- For all TMC114/RTV dose regimens, values for mean C_{max} were only 2- to 4-fold higher than the corresponding values for C_{min} levels, however, without co-administration of ritonavir, the ratio between C_{max} and C_{min} ranged from 25-130.
- The pharmacokinetics of TMC114 for the q.d. dose regimens were dose-proportional, except for TMC114/RTV 1200/200 mg q.d., which was lower than expected based on dose-proportionality. Further, a decrease in ritonavir plasma concentrations in the TMC114/RTV 1200/200 mg q.d. regimen as compared to the ritonavir plasma concentrations in the TMC114/RTV 600/200 mg q.d. regimen was observed. This could indicate that a higher dose of TMC114 influenced the pharmacokinetics of ritonavir thereby leading to a reduction in the boosting effect of ritonavir.

1. Title

The pharmacokinetics, safety and tolerability of TMC114, formulated as tablet TF036, and boosted with a low dose of ritonavir, for various multiple dose regimens **(TMC114-C137).**

2. Objectives

The primary and secondary objectives of this trial were to determine:

- The plasma pharmacokinetics of various multiple oral doses of TMC114 formulated as tablet TF036 when low-dose ritonavir (100 mg) was co-administered.
- The dose-proportionality for the investigated dose range of TMC114 (400-1200 mg q.d. and 400-800 mg b.i.d.) formulated as tablet TF036 when low-dose RTV (100 mg) was co-administered.
- The percentage of unchanged TMC114 excreted in urine of various multiple oral doses of TMC114 formulated as tablet TF036 when low-dose RTV (100 mg) was co-administered.
- The safety and tolerability of various multiple oral doses of TMC114 formulated as tablet TF036 when low-dose RTV (100 mg) was co-administered.

3. Study Design

Open, parallel group, dose ranging trial. During 5 parallel sessions, 5 panels (comprised of 8 subjects each) were treated from Day 1 to 7 with the following TMC114/RTV dose regimens: **400/100 mg q.d., 800/100 mg q.d., 1200/100 mg q.d., 400/100 mg b.i.d. and 800/100 mg b.i.d.for 6 days with an additional morning dose on Day 7.** The administration of RTV continued until Day 11 in all sessions. Full pharmacokinetic profiles of TMC114 were determined for 1 dosing interval on Day 1 and up to 120h post-dosing on Day 7. Pharmacokinetic profiles of RTV were determined for 1 dosing interval on Days 1 and 7. TMC114 and RTV were administered under **fed** conditions.

Table 1 provides the summary of the treatments administered.

Table 1: Overview of dose regimens

Treatment	Dose (number of subjects)	Volume
A	**TMC114**: 400 mg q.d on Day 1-7 **RTV**: 100 mg q.d on Day 1-11 (n=8)	1 tablet of TMC114 per intake (TMC114 ethanolate eq. 400 mg /tablet) 1 capsule of ritonavir (Norvir®) per intake
B	**TMC114**: 800 mg q.d on Day 1-7 **RTV**: 100 mg q.d on Day 1-11 (n=8)	2 tablets of TMC114 per intake (TMC114 ethanolate eq. 400 mg /tablet) 1 capsule of ritonavir (Norvir®) per intake
C	**TMC114**: 1200 mg q.d on Day 1-7 **RTV**: 100 mg q.d on Day 1-11 (n=8)	3 tablets of TMC114 per intake (TMC114 ethanolate eq. 400 mg /tablet) 1 capsule of ritonavir (Norvir®) per intake
D	**TMC114**: 400 mg b.i.d. on Day 1-6, 400 mg q.d. on Day 7 **RTV**: 100 mg b.i.d. on Day 1-11 (n=8)	1 tablet of TMC114 per intake (TMC114 ethanolate eq. 400 mg /tablet) 1 capsule of ritonavir (Norvir®) per intake
E	**TMC114**: 800 mg b.i.d. on Day 1-6, 800 mg q.d. on Day 7 **RTV**: 100 mg b.i.d. on Day 1-11 (n=8)	2 tablets of TMC114 per intake (TMC114 ethanolate eq. 400 mg /tablet) 1 capsule of ritonavir (Norvir®) per intake

4. Investigational Drugs

TMC 114 was formulated as a tablet (TF036) containing TMC114 ethanolate eq. 400 mg. Ritonavir (Norvir®) was formulated as a capsule containing 100 mg RTV.

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Plasma

For all the panels, Pre-dose (within 1 hour before drug intake on day 1 and day 7 and immediately before drug intake on days 2, 4, 6, 8, 9, 10, 11,) samples were collected. In addition, intensive sampling was done on day 1 and day 7 at the following time points: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hrs. In addition, blood samples were collected on day 8 (24 hr and 36 hr), day 9 (48 hr), day 10 (72 hr), day 11 (96 hr) and day 12 (120 hr).

Urine

On day 7 of each session, the complete urinary output during the interval 0-12 hr (for treatment D and E) or during the intervals 0-12 h and 12-24 h (for treatment A, B, and C) after the morning intake of day 7 was collected.

The plasma concentrations of TMC114 and ritonavir and urinary concentrations of TMC114 were determined using validated LC-MS/MS methods. The lower limit of quantification (LLOQ) of TMC114 and ritonavir in plasma was 10 ng/mL and 5 ng/mL respectively.

Pharmacokinetic Assessments

Winnonlin Professional ™ ([redacted] was used for all pharmacokinetic and statistical assessments.

6. Results

6.1 Demographics

Out of the 52 subjects screened, 40 subjects were equally randomized to the 5 treatment groups. Only one subject (CRF ID 1371277) discontinued in the 400/100 mg q.d. group due to a grade 3 lipase increase. Table 2 shows the subject disposition in study TMC114-C104.

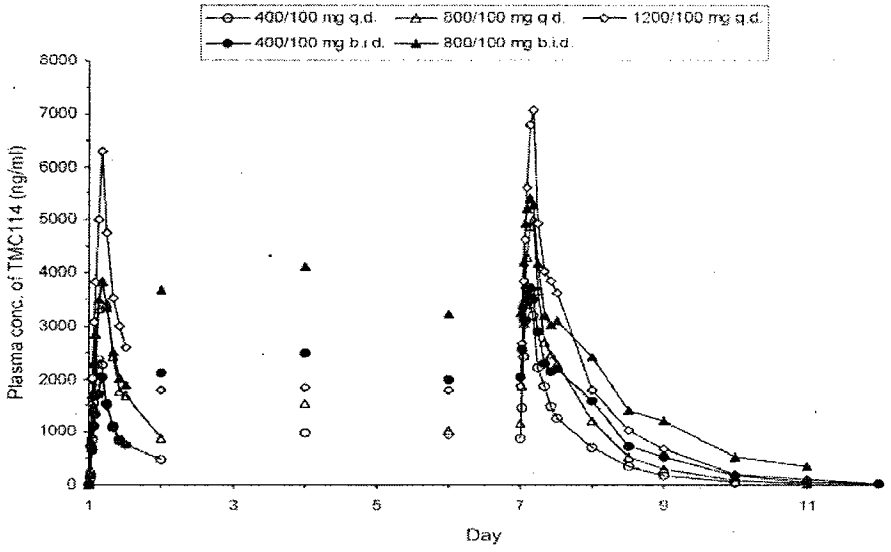
Table 2: Demographics in Study TMC114-C112

Parameter	TMC114/RTV 400/100 mg q.d. N=8	TMC114/RTV 800/100 mg q.d. N=8	TMC114/RTV 1200/100 mg q.d. N=8	TMC114/RTV 400/100 mg b.i.d. N=8	TMC114/RTV 800/100 mg b.i.d. N=8	All subjects N=40
Age (years) median (range)	35.0 (18-46)	37.0 (19-46)	44.0 (29-51)	35.5 (18-51)	44.0 (26-46)	38.0 (18-51)
Height (cm) median (range)	181.0 (172-192)	180.0 (164-191)	175.5 (151-187)	179.0 (165-184)	172.5 (160-197)	177.5 (151-197)
Weight (cm) median (range)	84.5 (69-87)	79.5 (58-93)	74.0 (71-104)	68.5 (60-100)	72.0 (50-110)	76.5 (50-110)

6.8 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time curves of TMC114, administered as a tablet (TF036) under fed conditions at different dosages in the presence of a low dose of RTV.

Fig 1: Mean plasma concentration-time curves of TMC114, administered as a tablet (TF036) under fed conditions at different dosages in the presence of a low dose of RTV.



Visual inspection of the profiles showed that TMC114 was rapidly absorbed from the GI-tract for all dose regimens of TMC114/RTV. At Day 1 and 7, median maximum concentrations were reached between 2.5 and 4.0 h post-dose for all dose regimens. After the absorption phase, an initially fast distribution/elimination phase was followed by a slower elimination phase. The elimination part of the plasma concentration-time profile was biphasic for almost all subjects. **TMC114 steady-state concentrations were generally reached within 4 days after start of dosing of TMC114/RTV**. Table 3 shows the pharmacokinetic parameters of TMC114, administered as a tablet (TF036) under fed conditions at different dosages in the presence of a low dose of RTV.

Table 3: Pharmacokinetic results of TMC114, administered as a tablet (TF036) under fed conditions at different dosages in the presence of a low dose of RTV

Pharmacokinetics of TMC114 (mean±SD, t_{max}: median (range))	Treatment A: 400 mg TMC114/ 100 mg ritonavir q.d.	Treatment B: 800 mg TMC114/ 100 mg ritonavir q.d.	Treatment C: 1200 mg TMC114/ 100 mg ritonavir q.d.	Treatment D: 400 mg TMC114/ 100 mg ritonavir b.i.d.	Treatment E: 800 mg TMC114/ 100 mg ritonavir b.i.d.
Day 1					
n	8	7*	7$	8	8
C_{0h}, ng/ml	NQ	NQ	NQ	NQ	NQ
t_{max}, h	3.5 (3.0 - 4.0)	4.0 (4.0 - 6.0)	4.0 (1.5 - 4.0)	4.0 (1.5 - 6.0)	4.0 (2.0 - 6.0)
C_{max}, ng/ml	2561 ± 1306	4113 ± 1842	6497 ± 1306	2247 ± 1356	4534 ± 1937
AUC_{12h}, ng.h/ml	-	-	-	14291 ± 8725	31443 ± 15182
AUC_{24h}, ng.h/ml	23576 ± 12544	44142 ± 22041	71598 ± 11831	-	-
Day 7					
n	8**	7*	7$	8	8
t_{max}, h	2.5 (1.5 - 4.0)	4.0 (3.0 - 4.0)	4.0 (3.0 - 10.0)	2.5 (1.0 - 3.0)	3.5 (1.5 - 6.0)
C_{0h}, ng/ml	890 ± 432	1153 ± 357	1861 ± 414	2038 ± 607	3239 ± 2297
C_{min}, ng/ml	637 ± 458	1067 ± 361	1548 ± 388	1848 ± 528	2893 ± 1965
C_{max}, ng/ml	3760 ± 937	5259 ± 1576	7320 ± 659	3913 ± 873	5736 ± 1879
AUC_{12h}, ng.h/ml	-	-	-	33511 ± 9540	48243 ± 22605
AUC_{24h}, ng.h/ml	38636 ± 14843	61106 ± 22455	89298 ± 11897	-	-
$t_{1/2term}$, h	10.9 ± 1.96	14.4 ± 5.17	15.0 ± 6.91	16.6 ± 4.25	17.2 ± 11.4
$C_{\infty,ss}$, ng/ml	1610 ± 618	2546 ± 936	3721 ± 496	2793 ± 795	4020 ± 1884
FI, %	207 ± 53.9	170 ± 28.5	157 ± 19.9	75.9 ± 8.99	82.6 ± 38.7

NQ: Not Quantifiable (< 10.0 ng/ml)

* CRF ID 1371297 is excluded from descriptive statistics

$: CRF ID 1371279 is excluded from descriptive statistics

**: For the parameter $t_{1/2term}$ for Treatment A: n = 7

Reviewer's Note regarding pharmacokinetic analysis:

CRF ID 1372279, receiving the 1200/100 mg q.d. (treatment C), was found positive for HCV antibodies at screening (major protocol deviation), therefore, this subject was excluded from all the pharmacokinetic and statistical assessments of TMC114 and RTV. CRF ID 1371297 received clarithromycin (a major protocol deviation) from days 2-6, therefore this subject was excluded from descriptive statistics and statistical analysis of

TMC114 and RTV. CRF ID 1371277 discontinued the trial before the morning intake of RTV on day 8, therefore, λ_z and $t_{1/2term}$ of TMC114 could not be calculated for this subject.

The dose normalized plots (plots not shown in the review) suggested that the systemic exposure to TMC114, in the presence of low dose of RTV, seemed to increase dose-proportionally after multiple dosing. **At steady-state, the average concentration of TMC114 after 800/100 mg q.d. (Treatment B) and 400/100 mg b.i.d. (Treatment D) was comparable, suggesting that the daily exposure to TMC114 after a total daily dose of 800 mg was independent of the dosing frequency of TMC114/RTV.** Within the once daily dosing range of TMC114/RTV, based on the ratio of LS means and the associated 90 % confidence intervals, the AUC_{24h}, C_{0h}, C_{min} and C_{max} of TMC114 seemed to increase dose-proportionally except for C_{max} between Treatment B and Treatment A and between Treatment C and Treatment A. Within the investigated twice daily dosing range of TMC114/RTV, a dose-proportional increase in C_{0h} and C_{min} and a less than dose-proportional increase in C_{max} and AUC_{12h} was observed.

RTV

Table 4 shows the pharmacokinetic parameters of RTV after multiple oral administration of RTV, in the presence of TMC114, administered as a tablet (TF036) under fed conditions.

Table 4: Pharmacokinetic parameters of RTV after multiple oral administration of dosages of TMC114 administered as a tablet (TF036) under fed conditions in the presence of a low dose of RTV.

Pharmacokinetics of ritonavir (mean±SD t_{max} median (range))	Treatment A: 400 mg TMC114/ 100 mg ritonavir q.d.	Treatment B: 800 mg TMC114/ 100 mg ritonavir q.d.	Treatment C: 1200 mg TMC114/ 100 mg ritonavir q.d.	Treatment D: 400 mg TMC114/ 100 mg ritonavir b.i.d.	Treatment E: 800 mg TMC114/ 100 mg ritonavir b.i.d.
Day 1					
n	8	7*	7$	8	8
C_{0h} ng/ml	NQ	NQ	NQ	NQ	NQ
t_{max} h	5.0 (4.0 - 6.0)	6.0 (4.0 - 6.0)	4.0 (1.5 - 6.0)	6.0 (4.0 - 6.0)	5.0 (0.5 - 8.0)
C_{max} ng/ml	344 ± 131	539 ± 133	526 ± 448	597 ± 213	595 ± 164
AUC_{12h} ng.h/ml	-	-	-	2482 ± 1370	2529 ± 1285
AUC_{24h} ng.h/ml	3637 ± 1613	3506 ± 1759	3361 ± 877	-	-
Day 7					
n	8	7*	7$	8	8
C_{0h} ng/ml	68.2 ± 44.2	40.1 ± 24.6	41.5 ± 17.1	26.3 ± 11.8	23.8 ± 11.7
C_{min} ng/ml	48.2 ± 35.7	30.8 ± 21.9	30.3 ± 11.1	19.9 ± 11.3	16.7 ± 6.80
t_{max} h	6.0 (4.0 - 6.0)	6.0 (1.0 - 6.0)	4.0 (1.0 - 10.0)	4.0 (4.0 - 6.0)	5.0 (2.0 - 6.0)
C_{max} ng/ml	540 ± 208	592 ± 226	626 ± 266	392 ± 161	392 ± 154
AUC_{12h} ng.h/ml	-	-	-	5464 ± 3037	4529 ± 1336
AUC_{24h} ng.h/ml	5134 ± 2584	4769 ± 1680	4709 ± 1042		
$C_{ss,av}$ ng/ml	214 ± 108	199 ± 66.3	196 ± 43.4	455 ± 253	382 ± 111
FL %	244 ± 37.8	284 ± 43.5	298 ± 104	129 ± 27.9	135 ± 48.4

NQ: Not Quantifiable (< 5.00 ng/ml)

* CRF ID 1371297 is excluded from descriptive statistics

$ CRF ID 1371279 is excluded from descriptive statistics

The systemic exposure to RTV, expressed as AUC_{12h} or AUC_{24h}, did not vary significantly between the 3 once daily TMC114/RTV dosing regimens and between the 2 twice daily dosing regimens. Furthermore, C_{max}, C_{0h} and C_{min} values were also comparable between the 3 once daily dosing regimens and between the 2 twice daily dosing regimens.

6.3 Urinary Excretion of TMC114

Table 5 shows the recovery of unchanged TMC114 in urine on day 7.

Table 5: Recovery of Unchanged TMC114 in Urine on Day 7*

Parameter	Mean ± SD				
	Treatment A: Darunavir/RTV 400/100 mg q.d.	Treatment B: Darunavir/RTV 800/100 mg q.d.	Treatment C: Darunavir/RTV 1200/100 mg q.d.	Treatment D: Darunavir/RTV 400/100 mg b.i.d.	Treatment E: Darunavir/RTV 800/100 mg b.i.d.
N	8	7	8	8	8
Recovery of unchanged darunavir, %	3.9 ± 1.2	4.0 ± 0.9	3.0 ± 0.4	5.0 ± 1.8	4.3 ± 1.0

*: The recovery of unchanged TMC114 in urine is for the appropriate dosing interval (q.d.: 24 hours; b.i.d.: 12 hours)

The urinary excretion of TMC114 during one dosing interval was 3-5 % of the total TMC114 dose for all different TMC114/RTV dose regimens. Further, the deconjugation of TMC114 with beta-glucoronidase prior to bioanalysis did not affect the mean urinary excretion, indicating the limited role of glucoronidation in the metabolism of TMC114 when RTV was co-administered.

7. Safety Assessments

There were no deaths or SAEs during this study. One subject with grade 3 elevated serum lipase was terminated from the study at the discretion of the investigator. Headache was the most frequently observed adverse event. Gastrointestinal symptoms with this formulation appeared relatively infrequent. There was no apparent relationship between TMC114 dose and the frequency or severity of AEs (See details in Medical Officer's review).

8. Conclusion

- **Under fed conditions and in the presence of a low dose of ritonavir, the systemic exposure (AUC) of TMC114, formulated as the tablet [redacted] (after multiple q.d. or b.i.d. dosing), seemed to increase dose-proportionally for the q.d. regimens and less than dose-proportionally for the b.i.d. regimens.**
- TMC114 C_{0h} and C_{min} seemed to increase dose-proportionally for the q.d. and b.i.d. regimens after multiple dosing.
- TMC114 C_{max} seemed to increase less than dose-proportionally after multiple dosing for the q.d. and b.i.d. dosing regimens.

- After total daily dose of 800 mg TMC114 (800 mg q.d. or 400 mg b.i.d.), the daily exposure to TMC114 was similar.
- The mean urinary excretion of unchanged TMC114 was similar for all treatments and was 3-5 % of the administered dose within a dosing interval.

DRUG-DRUG INTERACTIONS

Study Number	Description	Page #
TMC114-C105	The effect of repeated doses of ritonavir on the pharmacokinetics, safety, and tolerability of a single dose of TMC114.	145
TMC114-C107	The pharmacokinetic interaction between rifabutin and TMC114, co-administered with low-dose ritonavir, in healthy subjects.	149
TMC114-C110	The effect of repeated doses of TMC114 on the pharmacokinetics of a single dose of saquinavir in healthy subjects.	152
TMC114-C111	The pharmacokinetic interaction between TMC114, boosted with a low dose of RTV, and EFV in healthy volunteers.	157
TMC114-C119	The pharmacokinetic interaction between TMC114/RTV and nevirapine in HIV-1 infected subjects.	166
TMC114-C120	The effect of TMC114, boosted with low doses of ritonavir, on pravastatin (PRA) pharmacokinetics in healthy volunteers.	176
TMC114-C121	The pharmacokinetic interaction between paroxetine or sertraline and TMC114, co-administered with low-dose ritonavir, in healthy subjects.	181
TMC114-C122	The effect of ranitidine and of omeprazole on the pharmacokinetics of TMC114, co-administered with a low dose ritonavir, in healthy subjects.	192
TMC114-C124	The pharmacokinetic interaction between TMC114, boosted with a low dose of ritonavir, and tenofovir in healthy volunteers.	198
TMC114-C125	The pharmacokinetic interaction of various combinations of lopinavir, TMC114, and ritonavir in healthy volunteers.	206
TMC114-C128	The effect of repeated dosing of TMC114, coadministered with a low dose of ritonavir (RTV), on sildenefil pharmacokinetics in healthy male subjects.	209
TMC114-C129	The pharmacokinetic interaction between ketoconazole and TMC114, with and without co-administration of a low dose of ritonavir, in healthy subjects.	217
TMC114-C133	The effect of TMC114 boosted with a low dose of ritonavir on the pharmacokinetics of atorvastatin in healthy volunteers.	226
TMC114-C138	The pharmacokinetic interaction between boosted TMC114 and boosted saquinavir in healthy subjects.	235
TMC114-C139	A Phase I, open-label trial to investigate the pharmacokinetic interaction between TMC114/ritonavir and TMC125 at steady-state in healthy subjects.	243
TMC114-C141	The pharmacokinetic interaction between TMC114 and indinavir, both co-administered with a low dose of ritonavir, in healthy subjects.	245
TMC114-C142	The pharmacokinetic interaction between clarithromycin and TMC114, co-administered with a low dose of ritonavir, in healthy subjects.	254
TMC114-C149	The pharmacokinetic interaction between TMC114 and atazanavir, both in the presence of low dose of ritonavir, in healthy subjects.	261

1. Title

The effect of repeated doses of ritonavir on the pharmacokinetics, safety, and tolerability of a single dose of TMC114 **(TMC114-C105).**

2. Study Design

10 healthy subjects received a single dose of 800 mg TMC114 in session 1. In session 2, the subjects started an escalating dose regimen of 300-600 mg ritonavir b.i.d. for 6 days with the co-administration of a single 800 mg dose of TMC114 on day 4. If 600 mg ritonavir b.i.d. was not tolerated, the dose could be lowered to 400 mg ritonavir b.i.d. There was a washout period of at least 4 days between both sessions. The morning doses of TMC114 and RTV were taken with a standard breakfast. Table 1 provides the description of the various treatments.

Table 1: Treatment Overview

Session	Dose (number of subjects)	Volume
1	**TMC114 (oral solution):** Single dose of 800 mg on day 1 (n=10)	40 ml (20 mg/ml)
2	**RTV (oral capsules):** 300 mg b.i.d. on day 1 400 mg b.i.d. on day 2 500 mg b.i.d. on day 3 600 mg b.i.d. on days 4 – 6 **TMC114 (oral solution):** A single dose of 800 mg on day 4 (n=10)	 2x3 capsules of Norvir® 2x4 capsules of Norvir® 2x5 capsules of Norvir® 2x6 capsules of Norvir® 40 ml (20 mg/ml)

3. Drugs Used in the Trial

Table 2 shows the drugs used in the trial.

Table 2: Description of Drugs Used in the Trial

	TMC114	RTV (Norvir®)
Dosage Form	[redacted] (TF 019)	Capsule
Strength	20 mg/mL	100 mg
Batch Number	01B28	70671VA00F16
Expiry Date	05/28/2001	June 2001

4. Sample Collection , Bioanalysis, and Pharmacokinetic Assessments

For session 1, plasma samples were collected at pre-dose (within 1 hour before drug intake), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 48, and 72 hours post-dose for the determination of TMC114. For session 2, on day 4, plasma samples for the determination of TMC114 were collected at the same time points as session 1 and plasma samples for the determination of ritonavir were collected at 0, 1, 2, 3, 4, 6, 8, 10, and 12 hours.

The plasma concentrations of TMC114 and RTV were determined using validated LC-MS/MS methods. The lower limit of quantification (in plasma) was 2 ng/mL for TMC114 and 10 ng/mL for RTV.

Pharmacokinetic Assessments

Descriptive statistical and graphical analysis of the primary pharmacokinetic parameters were performed using Microsoft® Excel. Non-parametric analyses were performed using WinNonlin Pro™ [redacted]

5. Results

5.1 Subject Disposition

Out of the 15 subjects recruited for the trial, 10 subjects were assigned to treatment with TMC114 in session 1 and TMC114 and RTV in session 2. All subjects completed session 1, however, 5 subjects dropped out of the trial in session 2. Table 3 shows the demographics of the study.

Table 3: Demographics of Study TMC114 C105

	Median	Minimum	Maximum
Age (years)	40.5	30	51
Height (cm)	168.5	161	181
Weight (kg)	69.5	54	95

Reviewers Note Regarding Subject Dropout in Session 2

All the subjects (n =10) who completed session 1 entered session 2. In session 2, the subjects were administered ritonavir 300 mg b.i.d. on day 1, 400 mg b.i.d. on day 2, 500 mg b.i.d. on day 3, and 600 mg b.i.d on days 4-6. However, only 1 subject had stopped taking RTV as of the morning of day 4 (the day of TMC114 and RTV assessments after co-administration). Therefore, although 5 subjects dropped out of session 2, plasma concentrations of TMC and RTV were available from 9/10 subjects on day 4.

6.9 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time profile of a single 800 mg dose of TMC114 without (session 1) and with (session 2) co-administration of RTV.

Fig 1: Mean plasma concentration-time profile of a single 800 mg dose of TMC114 without (session 1) and with (session 2) co-administration of RTV.

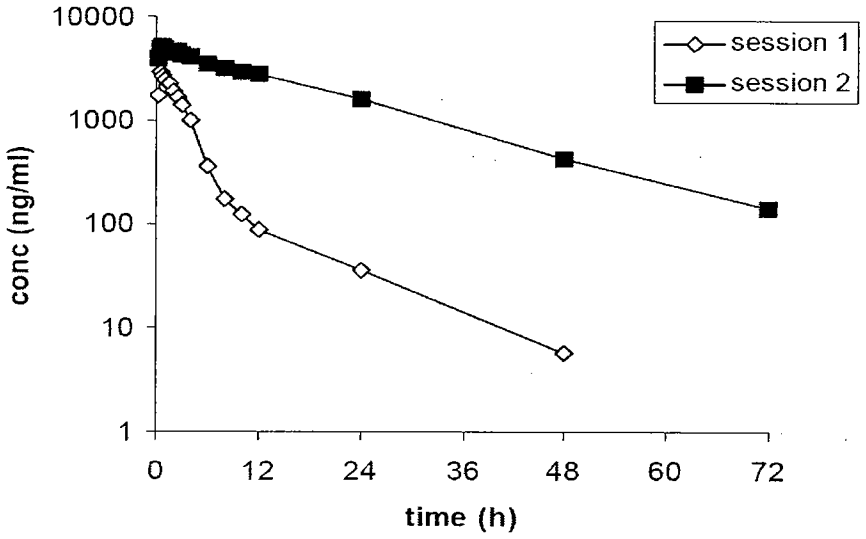


Table 4 shows the pharmacokinetic results of TMC114, with and without RTV.

Table 4: Pharmacokinetic results of TMC114, with and without RTV.

Pharmacokinetics of TMC114 (mean±SD. t_{max}: median (range))	Session 1 (n=10)	Session 2 (n=9)
t_{max}, h	0.8 (0.3-2.5)	1.0 (0.3-4.0)
C_{max}, ng/ml	3306 ± 1487	6220 ± 2826
AUC_{last}, ng.h/ml	10713 ± 3126	98729 ± 38481
AUC_{∞}, ng.h/ml	10920* ± 3100	102000 ± 41137
λ_z, 1/h	0.071* ± 0.029	0.062 ± 0.020
$t_{1/2term}$, h	11.3* ± 4.62	12.2 ± 4.03

*Accurate determination not possible for two out of ten subjects

Without RTV, the TMC114 absorption phase was followed by a rapid distribution/elimination phase and a subsequent slower elimination phase, whereas in the presence of RTV, the initial rapid distribution/elimination phase was no longer present and the absorption phase was followed by the slower elimination phase only, with a similar elimination half-life for TMC114 in the absence and presence of RTV.

Table 5 shows the pharmacokinetic parameters of RTV.

Table 5: Pharmacokinetic parameters of RTV.

Pharmacokinetics of RTV (mean±SD, t_{max}: median (range))	Session 2 (n=9)
t_{max}, h	6.0 (2.0-6.0)
C_{min}, ng/ml	4474 ± 3876
C_{max}, ng/ml	14862 ± 8753
AUC_{last}, ng.h/ml	109334 ± 59850

Table 6 shows the statistical evaluation of the pharmacokinetics of single-dose TMC114 with or without concomitant RTV treatment.

Table 6: Statistical evaluation of the pharmacokinetics of single-dose TMC114 with and without concomitant RTV treatment.

Parameter	n	Geometric mean		Ratio (test/ reference)	90% CI	p-value
		Without RTV (reference)	With RTV (test)			
C_{max}, ng/ml	9	2917	5745	197	140-277	0.0062
AUC_{last}, ng.h/ml	9	9875	91177	923	662-1288	0.0001
AUC_{∞}, ng.h/ml	9	10088	93697	929	666-1296	0.0001

6. Conclusion

- In the presence of 600 mg RTV b.i.d., exposure to TMC114 was increased as compared to the same dose of TMC114 alone. This was probably due to the inhibition of CYP3A4-mediated metabolism by RTV.
- The $t_{1/2term}$ of TMC114 were similar for the treatments with or without RTV. Since only the initial rapid distribution/elimination phase observed for TMC114 administered alone is affected by RTV co-administration, it appears that this phase represents metabolism by CYP3A4. The slower elimination phase may represent another elimination route not affected by RTV.
- The mean C_{max} and AUC_{last} estimates of single-dose TMC114 were increased 2-fold and 9-fold in the presence of RTV.

1. Title

The pharmacokinetic interaction between rifabutin and TMC114, co-administered with low-dose ritonavir, in healthy subjects **(TMC114-C107).**

2. Objectives

The objectives of this trial were to determine:

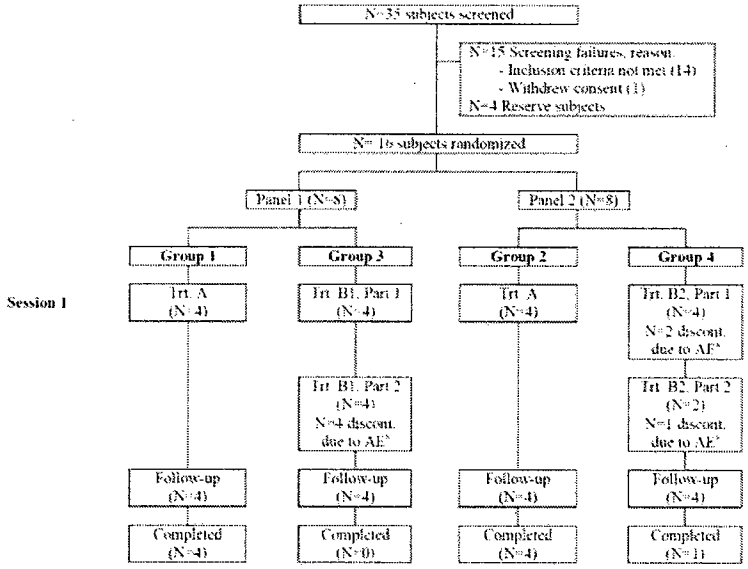
- The effect of steady-state administration of TMC114, in combination with low-dose RTV, on the steady-state pharmacokinetics of rifabutin (RFB) and its active metabolite, 25-O-desacetylrifabutin.
- The effect of steady-state administration of RFB on the steady-state pharmacokinetics of TMC114, in combination with low-dose RTV.

3. Study Design

Phase I, open-label, randomized, cross-over trial in healthy subjects. The trial population consisted of 16 healthy subjects, equally divided into two panels. In two sessions, Panel 1 was to receive treatments A and B1 in a randomized order and Panel 2 was to receive treatments A and B2 in a randomized order. In treatment A, TMC114/RTV 400/100 mg b.i.d. was administered for 9 days with an additional morning dose on day 10. In treatment B1, 300 mg RFB q.d. was administered for 10 days, immediately followed by a combined administration of 150 mg RFB q.d. and TMC114/RTV 400/100 mg b.i.d. for 10 days. In treatment B2, the combination of 150 mg RFB q.d. and TMC114/RTV 400/100 mg b.i.d. was administered for 10 days, immediately followed by the administration of 300 mg RFB q.d. alone for 10 days. All the treatments were administered under fed conditions and subsequent sessions were separated by a washout period of 14 days. Full pharmacokinetic profiles of TMC114 and RTV were determined for one dosing interval after the morning intake on day 10 of treatments A and B2, and on day 20 of treatment B1. Full pharmacokinetic profiles of RFB and its active metabolite 25-O-desacetylrifabutin were determined for one dosing interval after the intake on day 10 and day 20 of treatments B1 and B2.

4. Results

Schematic 1 shows the subject disposition in the trial. The sponsor stopped the trial after session 1, due to safety concerns.



* This figures indicates in which phase the subject discontinued the trial; this phase can be different than the phase in which the AE leading to treatment discontinuation emerged

Trt = treatment, discont = discontinued

Treatment A: TMC114/RTV 400/100 mg b.i.d. on Days 1-9 and q.d. on Day 10

Treatment B1, Part 1: RFB 300 mg q.d. on Days 1-10

Treatment B1, Part 2: TMC114/RTV 400/100 mg b.i.d. + RFB 150 mg q.d. on Days 11-20

Treatment B2, Part 1: TMC114/RTV 400/100 mg b.i.d. + RFB 150 mg q.d. on Days 1-10

Treatment B2, Part 2: RFB 300 mg q.d. on Days 11-20

Seven subjects discontinued the trial during Session 1 due to AEs during treatment phases including RFB. Overall, 15 subjects (94 %) reported 77 AEs during the trial. The most commonly reported AEs were lymphopenia and influenza like illness, both reported by 7 subjects (44 %), and leucopenia reported by 5 subjects (31 %). These events were only noted during treatments including RFB. Due to safety concerns, the sponsor decided to discontinue the trial after Session 1.

Reviewer's Note:
Please refer to the Medical Officer's review for further details regarding safety assessments.

5. Conclusion

- Based on the limited pharmacokinetic data for TMC114/rtv (8 subjects for treatment A, 2 subjects for treatment B2, no PK available for treatment B1) and for rifabutin and 25-O-desacetylrifabutin (4 subjects for day 10 of treatment B1, 2 subjects for day 10 of treatment B2, and 1 subject for day 20 of treatment B2), it is not possible to draw conclusions about the influence of RFB on the pharmacokinetics of TMC114 and RTV.

Reviewer's Note:
The sponsor indicates that based on the limited pharmacokinetic and safety data, it is recommended that subjects receiving combined TMC114/RTV + RFB treatment are monitored closely for safety. Further, dosage reduction of RFB by at least 75 % of the usual dose of 300 mg/day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). This recommendation is consistent with the dosing

recommendation for rifabutin when administered with other boosted PIs such as Aptivus® (Tipranavir), Reyataz® (Atazanavir sulfate) and Kaletra® (Lopinavir/ritonavir). A new Phase I trial will be set up to investigate the pharmacokinetic interaction between RFB and TMC114, co-administered with low-dose RTV, using a lower dose of RFB when combined with TMC114/RTV.

Labeling Recommendation

Rifabutin is an inducer and substrate of CYP450 enzymes. Concomitant use of rifabutin and darunavir in the presence of ritonavir is expected to increase rifabutin plasma concentrations and decrease darunavir plasma concentrations. When indicated, it is recommended to administer rifabutin at a dosage of 150 mg once every other day when coadministered with PREZISTA/rtv.

1. Title

The effect of repeated doses of TMC114 on the pharmacokinetics of a single dose of saquinavir in healthy subjects **(TMC114-C110)**.

2. Objectives

The objectives of this trial were to determine:

- The pharmacokinetic effect of repeated doses of TMC114 on a single 1200-mg dose of saquinavir.
- The pharmacokinetic effect of a single 1200-mg dose of saquinavir on the steady-state pharmacokinetics of TMC114.

3. Study Design

Phase I, open-label, one-sequence, cross-over trial. All subjects received a single morning dose of 1200 mg saquinavir (Fortovase®) in session 1, followed by a wash-out period of 8 days. In session 2, all subjects received twice daily (b.i.d.) treatment with 1200 mg TMC114 for 14 days. On day 14, a single morning dose of 1200 mg saquinavir was co-administered. Full pharmacokinetic profiles of TMC114 were determined on day 11 and day 14 of session 2. Full pharmacokinetic profiles of saquinavir were determined on day 1 of session 1 and on day 14 of session 2. The safety and tolerability were monitored continuously throughout the trial.

4. Drugs Used in the Trial

Table 1 shows the drugs used in the trial.

Table 1: Description of Drugs Used in the Trial

	TMC114	Saquinavir (Fortovase®)
Dosage Form	Solution (TF019)	Capsule
Strength	20 mg/mL	200 mg
Batch Number	01E31	B1212
Expiry Date	August 31, 2001	August 2001

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Plasma samples for Session 1 and 2 were collected as follows: for session 1, blood samples (5 mL) were collected at pre-dose (within 1 hour before drug intake) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, and 24 hours. For session 2, a pre-dose sample was collected on day 1. On days 3, 5, 7, 9, 11, 13, and 14, plasma samples were collected immediately before drug intake. In addition, intensive sampling was done at the following time points: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, and 12 hrs on day 11 and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, and 24 hours on day 14.

The plasma concentrations of saquinavir and TMC114 were determined using validated LC-MS/MS chromatographic methods. The lower limit of quantification (in plasma) was 1 ng/mL for saquinavir and 2 ng/mL for TMC114.

Pharmacokinetic Assessments

Non-parametric analysis were performed using Winnonlin Professional ™ [redacted] using a non-compartmental model with extravascular input.

6. Results

6.1 Subject Disposition

12 subjects entered the study in session 1. Three subjects prematurely discontinued from the trial in session 2 because of rash on days 8-10. All other subjects completed the trial.

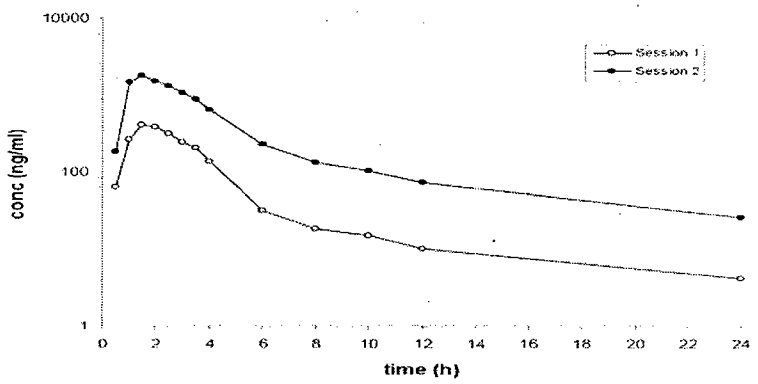
Table 2: Demographics in Study TMC 114-C110

Parameter		All subjects (N = 12)
Age (years)	Mean ± SE	42.8 ± 2.2
	Median (range)	43.0 (31 – 54)
Weight (kg)	Mean ± SE	83.6 ± 2.2
	Median (range)	82.0 (73 – 96)
Height (cm)	Mean ± SE	174.0 ± 2.3
	Median (range)	173.5 (162 – 193)
Body mass index (BMI) (kg m^{-2})	Mean ± SE	27.6 ± 0.5
	Median (range)	27.5 (25 – 31)
Gender	Male (n, %)	10 (83.3%)
	Female (n, %)	2 (16.7%)
Smoking habits	non-smoker (n, %)	9 (75.0%)

6.2 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time curves of saquinavir with and without co-administration of TMC114.

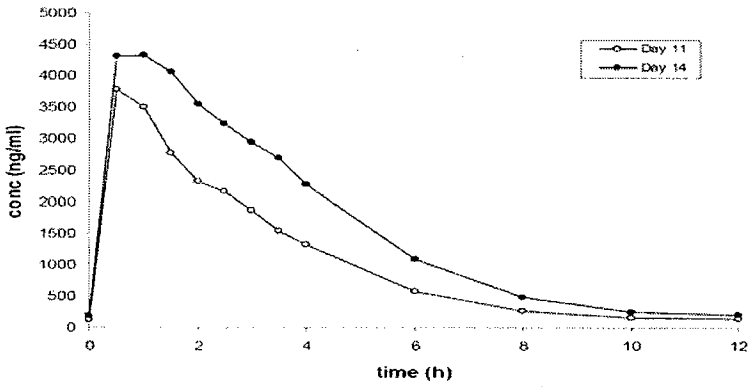
Fig 1: Mean plasma concentration-time curves of saquinavir (session 2) with and without (session 1) co- administration of TMC114.



After a single dose, saquinavir was rapidly absorbed from the gastrointestinal tract. Maximum concentrations were reached in approximately 1.5 hours. However, in the presence of steady-state concentrations of TMC114, the C_{max} of saquinavir was increased resulting in higher plasma concentrations in the fast distribution phase and a slower elimination phase.

Fig 2 shows the mean plasma concentration-time curves of TMC114 in the absence (Day 11) and presence (Day 14) of a single dose of 1200 mg saquinavir on a linear scale.

Fig 2: Mean plasma concentration-time curves of a dosing interval of TMC114 (1200 mg b.i.d.) in the absence (Day 11) and presence (Day 14) of a single dose of 1200 mg saquinavir on a linear scale.



The concentration-time profile of TMC114, when given alone, was characterized by a fast absorption phase, followed by a fast distribution/elimination phase. The final elimination phase could not be determined since TMC114 was administered as a b.i.d. regimen. In the presence of saquinavir, the duration of the absorption phase of TMC114 was increased, resulting in slightly higher maximum concentrations.

Table 3 shows the pharmacokinetic parameters of a single 1200 mg saquinavir dose with and without co-administration of steady-state concentrations of TMC114 (1200 mg b.i.d.).

Table 3: Pharmacokinetic parameters of a single 1200 mg saquinavir dose with and without co-administration of steady-state concentrations of TMC114 (1200 mg b.i.d.).

	Day 1 (saquinavir)	Day 14 (saquinavir + TMC114)
Pharmacokinetics of saquinavir (1200 mg, single dose)		
N	12	8
t_{max}, h	1.8 (1.0-3.0)	1.5 (1.0-3.0)
C_{max}, ng/ml	479 ± 192	2186 ± 872
AUC_{12h}, ng.h/ml	1337 ± 718	6526 ± 1757
$t_{1/2term}$, h	7.45 ± 1.18	6.51[5] ± 1.28
AUC_{∞}, ng.h/ml	1381 ± 735	6770 ± 1778
F_{rel} C_{max} (90%CI)	-	498 (316-783)
F_{rel} AUC_{12h} (90%CI)	-	533 (333-853)
F_{rel} AUC_{∞} (90%CI)	-	536 (336-854)

[5] Accurate determination of $t_{1/2term}$ was not possible.

Table 4 shows the pharmacokinetic parameters of TMC114 after dosing of 1200 mg b.i.d. with and without co-administration of a single 1200 mg saquinavir dose.

Table 4: Pharmacokinetic parameters of TMC114 after dosing of 1200 mg b.i.d. with and without co-administration of a single 1200 mg saquinavir dose

	Day 11 (TMC114)	Day 14 (TMC114 + saquinavir)
Pharmacokinetics of TMC114 (1200 mg, b.i.d.)		
N	9	8
t_{max}, h	0.5 (0.5-2.5)	1.5 (0.5-2.5)
C_{0h}, ng/ml	131.8 ± 68.05	187.1 ± 189.3
C_{max}, ng/ml	4187 ± 1625	4868 ± 2131
AUC_{12h}, ng.h/ml	12811 ± 3905	19298 ± 5647
F_{rel} C_{max} (90%CI)	-	121 (103-142)
F_{rel} AUC_{12h} (90%CI)	-	144 (136-153)

Results are given as mean ± SD; for t_{max} as median (range).

Table 5 shows the summary statistics of saquinavir without TMC114 (day 1) versus with TMC114 (day 14).

Table 5: Summary statistics of saquinavir without TMC114 (day 1) versus with TMC114 (day 14).

Parameter (log transformed)	n	Geometric mean		Point Estimate	90% CI	p-value	
		Day 1 (reference)	Day 14 (test)			Treatment	Subject
C_{max}, ng/ml	8	413.1	2056	497.7	316.4 - 782.7	0.0003	0.7970
AUC_{24h}, ng.h/ml	8	1185	6314	533.0	332.9 - 853.2	0.0003	0.5360
AUC_{∞}, ng.h/ml	8	1225	6561	535.8	336.3 - 853.5	0.0002	0.5348

(1) 90% CIs

Table 6 shows the summary statistics if TMC114 without saquinavir (day 11) versus with saquinavir (day 14).

Table 6: Summary statistics of TMC114 without saquinavir (day 11) versus with saquinavir (day 14).

Parameter (log transformed)	n	Geometric mean		Point Estimate	90% CI [1]	p-value	
		Day 11 (reference)	Day 14 (test)			Treatment	Subject
C_{max}, ng/ml	8	3712	4483	120.8	102.7 - 142.0	0.0630	0.0019
AUC_{12h}, ng.h/ml	8	12888	18592	144.3	136.4 - 152.5	0.0001	0.0001

(1) 90% CIs

In the presence of TMC114, C_{max} and AUC_{24hr} of saquinavir were increased by 398 % and 433 %. The t_{max} and the $t_{1/2term}$ of saquinavir were not changed in the presence of TMC114. In comparison to administration of TMC114 alone, a slight increase in C_{max} of TMC114 was observed in most subjects after co-administration with a single dose of saquinavir, however, this increase did not reach statistical significance. The AUC_{12h} for TMC114 was increased by 44 % in the presence of saquinavir and this increase was statistically significant.

7. Conclusion

- After 14 days of b.i.d. dosing with 1200 mg TMC114, C_{max} and AUC levels of a single 1200 mg dose of saquinavir were increased by about 5-fold.
- In the presence of saquinavir, AUC_{12h} of TMC114 was increased by a factor of 1.4. No significant increases were found for C_{max}.
- As both the fast distribution/elimination phase and slower elimination phase of saquinavir appear similar in the presence and absence of TMC114, the influence of TMC114 on saquinavir pharmacokinetics is likely to be at the level of absorption and/or first pass metabolism and saquinavir.

1. Title

The pharmacokinetic interaction between TMC114, boosted with a low dose of RTV, and EFV in healthy volunteers **(TMC114-C111).**

2. Objectives

The objectives of this trial were to assess:

- The pharmacokinetic effect of repeated doses of TMC114 with co-administration of a low dose of RTV on the steady-state pharmacokinetics of EFV.
- The pharmacokinetic effect of steady-state pharmacokinetics of EFV on repeated doses of TMC114 with co-administration of TMC114.
- The percentage of unchanged TMC114 excreted in urine with co-administration of a low dose of RTV.

3. Study Design

In this open, one sequence, cross-over trial, 12 healthy volunteers received 300 mg TMC114/100 mg RTV b.i.d. for 6 days, with an additional morning dose on day 7 in session 1, followed by a 7-day washout period and a second session during which the 12 subjects received 600 mg EFV q.d. for 18 days. From day 11 until day 16, 300 mg TMC114/100 mg RTV b.i.d. was co-administered, with an additional morning dose on day 17. At day 7 of session 1 and day 10 and 17 of session 2, TMC/RTV and/or EFV had to be taken within 15 minutes after completing a standard breakfast.

4. Drugs Used in the Trial

Table 1 shows the drugs used in the trial.

Table 1: Description of Drugs Used in the Trial

	TMC114	RTV	EFV
Dosage Form	Solution (TF019)	Capsule	Capsule
Strength	20 mg/mL	100 mg	200 mg
Batch Number	02C07	-	-
Expiry Date	Sep 7, 2002	-	-

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

For session 1, plasma samples (5 mL) were collected (immediately before drug intake) on day 2, 4, 6 and 7. In addition, intensive plasma sampling was done on day 7 at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 36, and 48 hours. For session 2, plasma samples were collected (immediately before drug intake) on day 4, 7, 9, 11, 12, 14, 16, and 17. In addition, serial blood sampling was done on day 10 (1, 1.5, 2, 3, 4, 5, 6, 9, 12) and on day 17 (0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 24, 36, and 48 hrs).

From day 7 to day 9 of session 1, the complete urinary output during the intervals 0 to 12h, 12-24 h, and 24-48 h after the morning intake of day 7 was collected. Within 1h after each interval, the complete urine collection volume and pH was measured and a 5 mL aliquot was retained.

The plasma concentrations of TMC114, RTV, and EFV were determined by validated LC-MS/MS methods. The lower limit of quantification was 10.1 ng/mL for TMC114, 5 ng/mL for RTV, and 50 ng/mL for EFV. The urine concentrations of TMC114 were determined by a validated LC-MS/MS method. The lower limit of quantification was 20 ng/mL.

Pharmacokinetic Assessments

Winnonlin Professional ™ ([redacted]) was used for all pharmacokinetic assessments. Comparison of the pharmacokinetic parameters C_{0h}, C_{min}, C_{max}, AUC_{12h} of TMC114/RTV with and without concomitant EFV and comparison of the pharmacokinetic parameters (C_{0h}, C_{min}, C_{max}, AUC_{24h}) of EFV with and without concomitant TMC114/RTV were performed using "linear mixed effect modeling" instead of the parametric paired test. C_{min} was determined for TMC114 on day 7 of session 1 and day 17 of session 2; for RTV on day 7 of session 1 and day 17 of session 2, and for EFV on day 10 and 17 of session 2 as C_{0h} during repeated dosing was not always the lowest observed concentration during a dosing interval. The LS mean ratio and 90 % confidence intervals around the LS mean ratio were reported with treatment of TMC114/RTV alone or treatment of EFV alone as a reference. The non-parametric t-test (Koch) instead of the non parametric Wilcoxon signed-rank test was used for t_{max}.

6. Results

6.1 Subject Disposition

12 subjects were randomized to session 1. After a washout period, the same 12 subjects completed session 2 and were followed up for 14 days. Table 2 shows the demographics of the study.

Table 2: Demographics in Study TMC114-C111

Parameter		Randomization group N = 12
Age (years) median (range)		42.0 (20-54)
Weight (kg) median (range)		71.5 (64-90)
Height (cm) median (range)		172.0 (154-181)
BMI (kg/m²) median (range)		24.6 (20-29)
Gender N (%)	Female	4 (33.3)
	Male	8 (66.7)

6.2 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time curve of TMC114, administered as a 300 mg TMC114/100 mg RTV b.i.d. in the absence or presence of steady-state concentrations of EFV, administered as 600 mg q.d. (session 1, day 7 and session 2, day 17).

Fig 1: Mean plasma concentration-time profiles of TMC114, administered as a 300 mg TMC114/100 mg RTV b.i.d. in the absence or presence of steady-state concentrations of EFV, administered as 600 mg q.d. (session 1, day 7 and session 2, day 17).

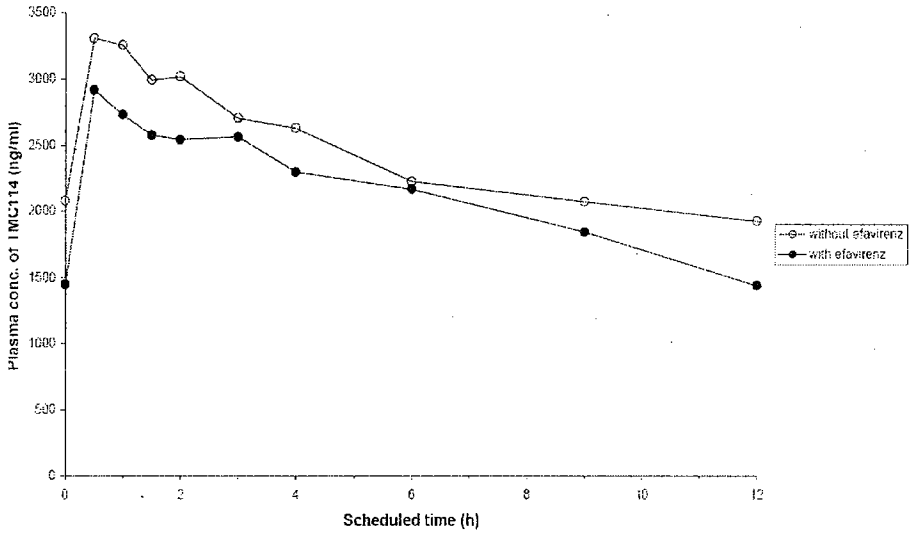


Table 3 shows the pharmacokinetic results of TMC114, administered as 300 mg TMC114/100 mg RTV b.i.d. with or without co-administration of EFV, administered as 600 mg q.d. (Session 1, day 7 and session 2, day 17).

Table 3: Pharmacokinetic results of TMC114, administered as 300 mg TMC114/100 mg RTV b.i.d. with or without co-administration of EFV, administered as 600 mg q.d. (Session 1, day 7 and session 2, day 17)

Pharmacokinetics of TMC114 (mean±SD, t_{max} median (range))	Session 1, Day 7: TMC114/RTV alone	Session 2, Day 17: TMC114/RTV + EFV
N	12	12
t_{max}, h	0.75 (0.0 - 2.0)	0.5 (0.5 – 3.0)
C_{0h}, ng/ml	2079 ± 1020	1447 ± 638
C_{min}, ng/ml	1772 ± 708	1250 ± 511
C_{max}, ng/ml	3460 ± 943	2998 ± 938
AUC_{12h}, ng.h/ml	28865 ± 8360	25485 ± 7844
$t_{1/2terminal}$, h	12.5 ± 4.76	4.97 ± 1.05
$C_{ss,av}$, ng/ml	2405 ± 697	2124 ± 654
Fl, %	72.5 ± 29.4	83.9 ± 26.7

In the presence of EFV, the mean C_{max} and AUC_{12h} were decreased by 15 %, and the mean C_{0h} and C_{min} were decreased by approximately 35 %. The mean terminal half-life of TMC114 was decreased after co-administration of EFV.

Table 4 shows the statistical evaluation of the pharmacokinetics of TMC114 administered as 300 mg TMC114/100 mg RTV b.i.d. with co-administration of 600 mg EFV q.d. (test) versus without co-administration of 600 mg EFV q.d. (reference).

Table 4: Statistical evaluation of the pharmacokinetics of TMC114 administered as 300 mg TMC114/100 mg RTV b.i.d. with co-administration of 600 mg EFV q.d. (test) versus without co-administration of 600 mg EFV q.d. (reference).

Parameter	n	Least square means		Least square means ratio, %	90% CI[1]	p-value
		Treatment (reference)	Treatment (test)			Treatment
C_{0h}, ng/ml	12	1882	1276	67.78	49.6 – 92.6	0.0471
C_{min}, ng/ml	12	1640	1127	68.72	54.2 – 87.2	0.0165
C_{max}, ng/ml	12	3343	2827	84.59	71.8 – 99.6	0.0937
AUC_{12h}, ng.h/ml	12	27771	24040	86.57	74.5 – 101	0.1128
		Median				p-value
Parameter	n	Treatment (reference)	Treatment (test)	Treatment difference median	90% CI[1]	Treatment
t_{max}, h	12	0.75	0.5	-0.25	(-1.0) – (0.25)	0.2850

[1] 90% confidence intervals

RTV

Fig 2 shows the mean plasma concentration-time profiles of RTV, administered as 300 mg TMC114/100 mg RTV b.i.d. in the absence or presence of steady-state concentration of EFV, administered as 600 mg q.d. (session 1, day 7 and session 2, day 17).

Fig 2: Mean plasma concentration-time profiles of RTV, administered as 300 mg TMC114/100 mg RTV b.i.d. in the absence or presence of steady-state concentration of EFV, administered as 600 mg q.d. (session 1, day 7 and session 2, day 17).

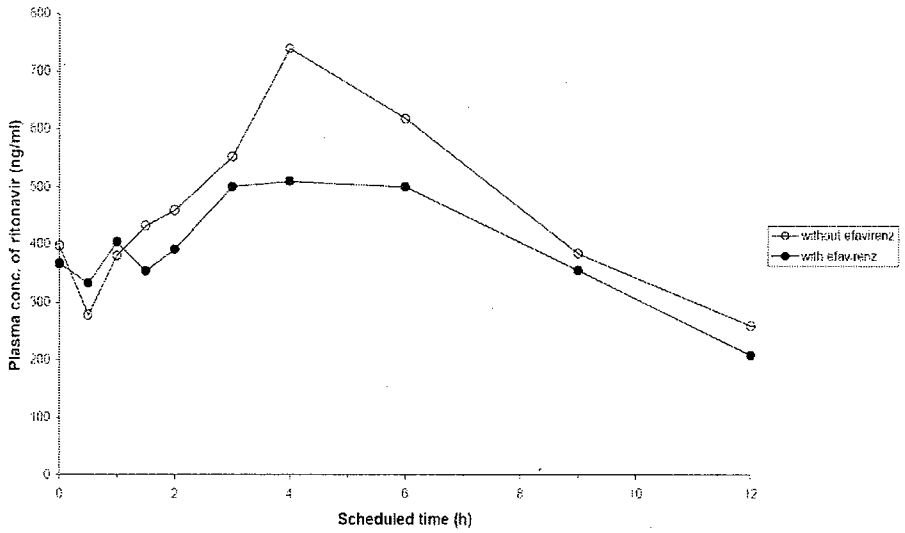


Table 5 shows the pharmacokinetic results of RTV, administered as 300 mg TMC114/100 mg RTV b.i.d. with or without co-administration of EFV, administered as 600 mg q.d. (session 1, day 7, and session 2, day 17).

Table 5: Pharmacokinetic results of RTV, administered as 300 mg TMC114/100 mg RTV b.i.d. with or without co-administration of EFV, administered as 600 mg q.d. (session 1, day 7, and session 2, day 17).

Pharmacokinetics of RTV (mean±SD; t_{max} median (range))	Session 1, Day 7: TMC114/RTV alone	Session 2, Day 17: TMC114/RTV + EFV
N	12	12
t_{max}, h	4.0 (0.5 - 6.0)	5.0 (1.0 - 9.0)
C_{0h}, ng/ml	397 ± 255	367 ± 400
C_{min}, ng/ml	211 ± 142	164 ± 154
C_{max}, ng/ml	861 ± 624	707 ± 858
AUC_{12h}, ng.h/ml	5733 ± 3499	4820 ± 4788
$t_{1/2term}$, h	8.47 ± 4.55	4.74 ± 0.775
$C_{ss,av}$, ng/ml	478 ± 292	402 ± 399
FI, %	127 ± 35.6	121 ± 38.5

After 7 days of treatment, the mean C_{min} was lower than C_{0h} in both treatments. The lower minimum plasma concentrations were caused by a lag time in absorption, resulting in lower concentrations 0.5-4h post-dose compared to pre-dose concentrations.

Table 6 shows the statistical evaluation of the pharmacokinetics of RTV administered as 300 mg TMC114/100 mg RTV b.i.d with co-administration of 600 mg EFV q.d. (test) versus without co-administration of 600 mg EFV q.d. (reference).

Table 6: Statistical evaluation of the pharmacokinetics of RTV administered as 300 mg TMC114/100 mg RTV b.i.d with co-administration of 600 mg EFV q.d. (test) versus without co-administration of 600 mg EFV q.d. (reference).

Parameter	n	Least square means		Least square means ratio, %	90% CI[1]	p-value
		Treatment (reference)	Treatment (test)			Treatment
C_{0h}, ng/ml	12	310.1	224.2	72.31	57.8 – 90.5	0.0250
C_{min}, ng/ml	12	53.56	32.18	60.07	46.7 – 77.3	0.0040
C_{max}, ng/ml	12	697.6	476.4	68.29	57.8 – 80.6	0.0017
AUC_{12h}, ng.h/ml	12	4925	3536	71.79	61.3 – 84.0	0.0031
		Median				p-value
Parameter	n	Treatment (reference)	Treatment (test)	Treatment difference median	90% CI[1]	Treatment
t_{max}, h	15	4.0	5.0	0.0	(-2.5) - (0.75)	0.6775

[1] 90% confidence intervals

Based on the ratio of the LS means, C_{0h}, C_{min}, C_{max}, and AUC_{12h} were decreased by 28 %, 40 %, 32 % and 28 % respectively when TMC114/RTV was co-administered with EFV.

EFV

Fig 3 shows the mean plasma concentration-time profiles of EFV, administered as 600 mg q.d. in the absence or presence of 300 mg TMC114/100 mg RTV b.i.d. (session 2, day 10, and day 17).

Fig 3: Mean plasma concentration-time profiles of EFV, administered as 600 mg q.d. in the absence or presence of 300 mg TMC114?100 mg RTV b.i.d. (session 2, day 10, and day 17).

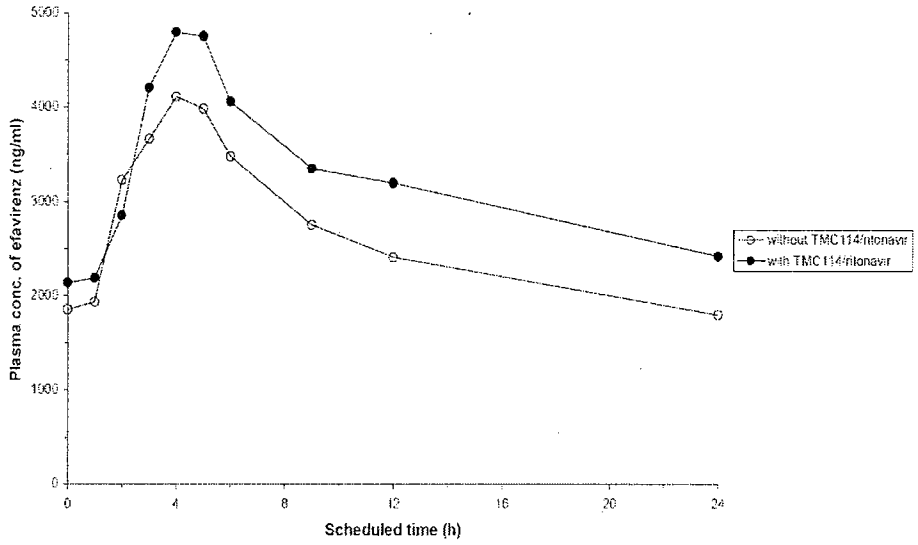


Table 7 shows the pharmacokinetic parameters of EFV, administered as 600 mg q.d. with or without co-administration of 300 mg TMC114/100 mg RTV b.i.d. (session 2, day 10 and day 17).

Table 7: Pharmacokinetic parameters of EFV, administered as 600 mg q.d. with or without co-administration of 300 mg TMC114/100 mg RTV b.i.d. (session 2, day 10 and day 17).

Pharmacokinetics of EFV (mean ± SD. t_{max}: median (range))	Session 2, Day 10: EFV alone	Session 2, Day 17: EFV + TMC114/RTV
N	12	12
t_{max}, h	4.0 (2.0 - 5.0)	4.0 (3.0 - 5.0)
C_{0h}, ng/ml	1850 ± 1023	2136 ± 1612
C_{min}, ng/ml	1647 ± 1078	1989 ± 1621
C_{max}, ng/ml	4595 ± 1480	5297 ± 1889
AUC_{24h}, ng.h/ml	61800 ± 30350	76429 ± 45527
$C_{ss,av}$, ng/ml	2575 ± 1265	3185 ± 1897
FI, %	127 ± 38.0	119 ± 34.7

The exposure to EFV was increased after co-administration with TMC114/RTV. The mean C_{0h}, C_{min}, and C_{max} were increased by 12-17 %, while the AUC_{24h} was increased by 21 %.

Table 8 shows the statistical evaluation of the pharmacokinetics of EFV administered as 600 mg q.d. with co-administration of 300 mg TMC114/100 mg RTV b.i.d. (test) versus without co-administration of 300 mg TMC114/100 mg RTV b.i.d. (reference).

Table 8: Statistical evaluation of the pharmacokinetics of EFV administered as 600 mg q.d. with co-administration of 300 mg TMC114/100 mg RTV b.i.d. (test) versus without co-administration of 300 mg TMC114/100 mg RTV b.i.d. (reference).

Parameter	n	Least square means		Least square means ratio, %	90% CI[1]	p-value
		Treatment (reference)	Treatment (test)			Treatment
C_{0h}, ng/ml	12	1659	1854	111.7	99.5 - 125	0.1138
C_{min}, ng/ml	12	1436	1680	117.0	101 - 136	0.0878
C_{max}, ng/ml	12	4396	5042	114.7	97.3 - 135	0.1630
AUC_{24h}, ng.h/ml	12	56976	68924	121.0	108 - 136	0.0126
		Median				p-value
Parameter	n	Treatment (reference)	Treatment (test)	Treatment difference median	90% CI[1]	Treatment
t_{max}, h	15	4.0	4.0	-0.25	(-1.0) - (0.50)	0.3965

[1] 90% confidence intervals

When compared to administration of EFV alone, a slight increase in C_{0h}, C_{min}, and C_{max} of EFV was observed in most volunteers after co-administration with TMC114/RTV. Based on the ratio of the LSmean, the AUC_{24h} was statistically increased by 21 %.

Urinary Excretion Analysis

The urinary excretion was measured only in the absence of EFV. Before de-conjugation, the amount of TMC114 excreted in the urine was approximately 25 mg (8 % of the total dose). The values were similar after de-conjugation.

7. Safety Assessments

No grade 4 abnormalities were reported in this trial. The most commonly reported treatment-emergent abnormalities were increases in cholesterol and in ALT. No abnormalities in vital signs or ECG leading to AE's were reported (See details in Medical Officer's review).

8. Conclusion

- The results of this trial demonstrated that concomitant treatment of TMC114, administered with a low dose RTV, and EFV resulted in approximately 13 % lower TMC114 exposure (AUC) and approximately 30 % lower RTV exposure compared to treatment without EFV. In the presence of EFV, a statistically

significant decrease of 31 % and 40 % for C_{min} was observed for TMC114 and RTV, respectively.

- The exposure to EFV was approximately 20 % increased when administered in combination with TMC114/RTV.
- **Based on the results of the study (C_{min} decrease by 31 %), it is not currently recommended to combine TMC114/RTV and EFV in HIV-1 infected subjects. This magnitude of the decrease in C_{min} may be clinically significant.**

Labeling Recommendation

Co-administration of darunavir/rtv and efavirenz decreased darunavir AUC by 13 % and C_{min} by 31 %. The AUC of efavirenz increased by 21 % and C_{min} increased by 17 %. The clinical significance of the reduction in C_{min} is [redacted] the combination of PREZISTA/rtv and efavirenz should be used with caution.

1. Title

The pharmacokinetic interaction between TMC114/RTV and nevirapine in HIV-1 infected subjects **(TMC114-C119).**

2. Objectives

The objectives of this trial were:

- To determine the effect of TMC114, in combination with a low dose of RTV, on the pharmacokinetics of NVP.
- To determine the effect of NVP on the pharmacokinetics of TMC114 and a low dose of RTV, based on historical data.

3. Study Design

This was an open label, randomized, cross-over trial to investigate the pharmacokinetic interaction between TMC114/RTV and NVP. The study population consisted of two panels of 8 HIV-1 infected subjects each, who were on stable therapy of NVP, 200 mg b.i.d. for at least 16 weeks. A third and fourth panel, each consisting of 4 other HIV infected subjects who were on stable therapy of NVP, were added to the trial.

The trial was divided into two sessions of 14 days, in which treatment A and treatment B or treatment B2 were administered in a randomized manner. There was no washout period between the sessions. In treatment A, subjects continued their usual HIV therapy consisting of NVP and at least 2 NRTIs. Treatment B consisted of TMC114 (TF019)/RTV at a dose regimen of 300/100 mg b.i.d. in addition to the usual NVP/NRTI therapy. Treatment B2 consisted of TMC114 (F001)/RTV at a dose regimen of 400/100 mg b.i.d. in addition to the usual NVP/NRTI therapy. All subjects received treatment A in one session and treatment B (n =11) or B2 (n = 8) in the other session. All treatments were administered for 13 days b.i.d., with an additional morning dose on day 14. On day 14 of each session, full pharmacokinetic profiles of NVP (all treatments), TMC114 and RTV (treatments B and B2) were assessed up to 12 hours post dose. TMC114, RTV, and NVP were taken with food.

4. Drugs Used in the Trial

Table 1 shows the drugs used in the trial.

Table 1: Description of Drugs used in the Trial

	Treatment A	Treatment B		Treatment B2	
Trial Med.	-	TMC114	RTV	TMC114	RTV
Strength	-	20 mg/mL	100 mg	400 mg	100 mg
Dosage Form	-	[redacted] (TF019)		Tablet	Capsule
Usage	-	Oral	Oral	Oral	Oral
Batch Number	-	CT 1816/1		PD1060	
Expiry Date	-	Sep 9, 2003		October 2004	

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Pre-dose plasma samples (within 15 minutes before drug intake) for treatment A (NVP) were collected on day 1, 7, 12 and 13. On day 14, in addition to the pre-dose sample, intensive sampling was done at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, and 12 hrs. For treatments B and B2 (TMC114/RTV and NVP), pre-dose samples were collected on day 1, 7, 12 and 13. On day 14, in addition to the pre-dose sample, intensive sampling was done at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, and 12 hrs. During treatment B2, an additional sample was collected at 2 hours for protein binding assessment.

The plasma concentrations of TMC114, RTV, and nevirapine were determined using LC-MS/MS methods. The free TMC114 concentration in plasma was determined using centrifugal filtration method with a [redacted] filter. The lower limit of quantification (in plasma) was 10 ng/mL for (total) TMC114, 2 ng/mL for free TMC114, 5 or 5.05 ng/mL for RTV and 10.1 ng/mL (mean LLOQ) for nevirapine.

Pharmacokinetic Assessments

The pharmacokinetic and statistical analyses were done using Winnonlin Professional ™ [redacted]) using a non-compartmental model with [redacted] Non-compartmental analysis [redacted] was used for the pharmacokinetic analysis. Descriptive statistics were calculated for the plasma concentrations of TMC114, nevirapine, and RTV at each time point and for the derived pharmacokinetic parameters. The statistical analyses were performed to compare treatments B (test) and B2 (test) versus treatment A (reference) for nevirapine (cross-over comparison) and comparing treatment B (test) for TMC114 and RTV versus data from the TMC114-C207 trial (300/100 mg b.i.d., reference) (cross-study comparison). Treatment B2 (test) for TMC114 and RTV was compared to data from the TMC114-C137 trial (TMC114/RTV 400/100 mg b.i.d., reference) (cross study comparison). The primary pharmacokinetic parameters were C_{min}, C_{max}, and AUC_{12hr} on the logarithmic scale.

6. Results

6.1 Subject Disposition

19 subjects were randomized to panel 1 (7 subjects, sequence A-B), panel 2 (4 subjects, sequence B-A), panel 3 (4 subjects, sequence A-B2) and panel 4 (4 subjects, sequence B2-A). 15 of the 19 randomized subjects completed the trial. One subject dropped out before trial completion due to an AE. Two subjects withdrew consent and 1 subject discontinued trial due to noncompliance.

Table 2: Demographics in Study TMC114-C119

Parameter	Panel 1 A-B (N = 7)	Panel 2 B-A (N = 4)	Panel 3 A-B2 (N = 4)	Panel 4 B2-A (N = 4)	All Subjects (N = 19)
Age, years	44.0	38.5	39.5	42.5	43.0
Median (range)	(33-50)	(33-45)	(34-46)	(34-56)	(33-56)
Height, cm	175.0	175.5	174.0	177.5	175.0
Median (range)	(160-189)	(169-178)	(167-185)	(173-179)	(160-189)
Weight, kg	79.0	76.5	67.0	72.0	72.0
Median (range)	(61-121)	(61-92)	(64-75)	(63-101)	(61-121)
BMI, kg/m^2	25.5	24.5	22.3	22.9	23.8
Median (range)	(24-34)	(20-32)	(20-25)	(21-32)	(20-34)
Female	2 (28.6)	1 (25.0)	1 (25.0)	1 (25.0)	5 (26.3)
Male, n (%)	5 (71.4)	3 (75.0)	3 (75.0)	3 (75.0)	14 (73.7)

6.2 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time curve of nevirapine after oral administration of treatments A (per panel), B, and B2.

Fig 1: Mean plasma concentration-time curve of nevirapine after oral administration of treatments A (per panel), B, and B2.

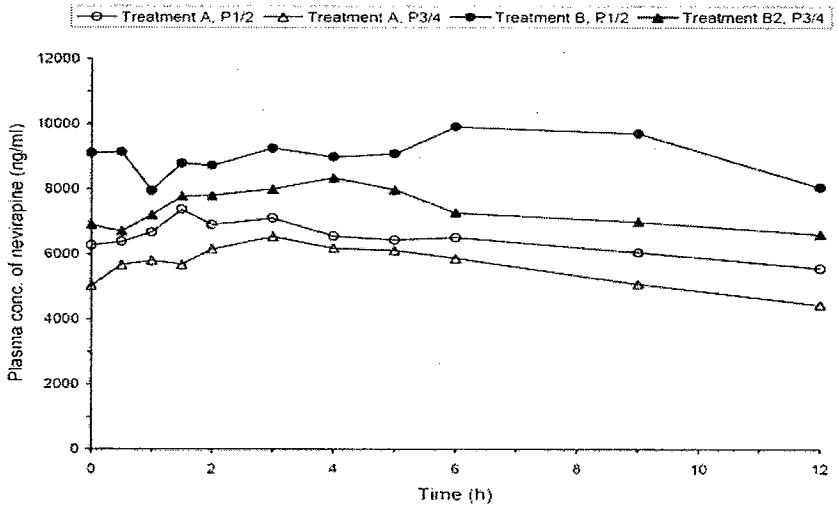


Table 3 shows the pharmacokinetic results of nevirapine for all treatments.

Table 3: Pharmacokinetic results of nevirapine for all treatments.

Pharmacokinetics of nevirapine (mean±SD, t_{max}: median (range))	Treatment A Panel 1/2: nevirapine	Treatment B Panel 1/2: TMC114/RTV/ nevirapine	Treatment A Panel 3/4: nevirapine	Treatment B2 Panel 3/4: TMC114/RTV/ nevirapine
N	9	8	8	8
t_{max}, h	1.5 (0.0 - 12.0)	4.5 (0.5 - 9.0)	3.0 (0.5 - 6.0)	4.0 (2.0 - 5.0)
C_{0h}, ng/mL	6273 ± 3005	9106 ± 5557	5031 ± 1520	6895 ± 3020
C_{min}, ng/mL	5192 ± 2137	7031 ± 4804	4273 ± 1614	6220 ± 2589
C_{max}, ng/mL	8064 ± 2531	10670 ± 6579	7005 ± 1348	8560 ± 3178
AUC_{12h}, ng.h/mL	76570 ± 29948	109749 ± 68732	66933 ± 14441	88148 ± 33335
$C_{ss,av}$, ng/mL	6381 ± 2496	9146 ± 5728	5578 ± 1203	7346 ± 2778
FI, %	48.8 ± 19.9	41.2 ± 16.5	52.6 ± 26.3	33.8 ± 10.7

For all treatments, the mean C_{min} values were lower than the mean C_{0h} values at steady-state. For treatments A (panel 1/2) and B2, this was partly due to a delay in absorption of nevirapine in a few subjects, but mostly because several subjects had a concentration during or at the end of the dosing interval that was lower than the predose plasma concentration.

Table 4 shows the statistical evaluation of the pharmacokinetics of nevirapine for treatments A and B (Panel 1/2).

Table 4: Statistical evaluation of the pharmacokinetics of nevirapine for treatments A and B (Panel 1/2).

Parameter	n	Least square means		Least square means ratio, %	90% CI[1]	p-value		
		Treatment A (reference)	Treatment B (test)			Treatment	Period	Sequence
C_{min}, ng/mL	8	5042	5948	118.0	92.6 - 150	0.2375	-	-
C_{max}, ng/mL	8	8136	9282	114.1	91.7 - 142	0.2902	-	-
AUC_{12h}, ng.h/mL	8	75178	95276	126.7	106 - 151	0.0378	-	-
		Median				p-value		
Parameter	n	Treatment A (reference)	Treatment B (test)	Treatment difference median	90% CI[1]	Treatment	Period	Sequence
t_{max}, h	8	1.5	4.5	-2.38	(-5.00) - (1.00)	0.1313	0.3173	0.4018

[1] 90% confidence intervals
- : excluded from final model

When nevirapine was co-administered with TMC114 as an oral solution and RTV (treatment B), the mean AUC_{12h} of nevirapine was increased by 27 % but the mean C_{min} and C_{max} were not significantly changed compared to treatment with nevirapine alone

(treatment A). Table 5 shows the statistical evaluation of the pharmacokinetics of nevirapine for treatments A and B2 (panel 3/4).

Table 5: Statistical Evaluation of the pharmacokinetics of nevirapine for treatments A and B2 (panel 3/4)

Parameter	n	Least square means		Least square means ratio, %	90% CI[1]	p-value		
		Treatment A (reference)	Treatment B2 (test)			Treatment	Period	Sequence
C_{min}, ng/mL	8	3938	5806	147.4	120 - 182	0.0098	-	-
C_{max}, ng/mL	8	6892	8151	118.3	102 - 137	0.0644	-	-
AUC_{12h}, ng.h/mL	8	65538	83438	127.3	112 - 144	0.0080	-	-
		Median				p-value		
Parameter	n	Treatment A (reference)	Treatment B2 (test)	Treatment difference median	90% CI[1]	Treatment	Period	Sequence
t_{max}, h	8	3.0	4.0	-1.00	(-2.50) - (1.00)	0.2338	0.7584	0.6446

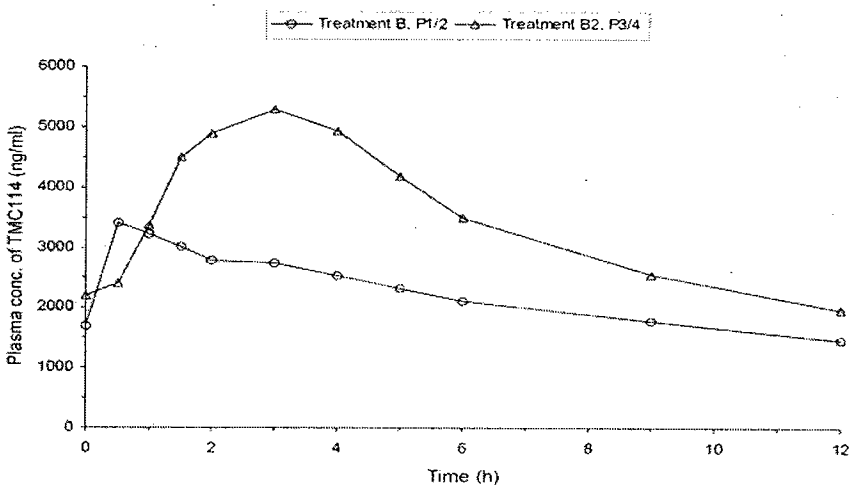
[1] 90% confidence intervals
- : excluded from final model

When nevirapine was co-administered with TMC114 and RTV (treatment B2), the mean C_{min}, AUC_{12h}, and C_{max} of nevirapine was increased by 47 % , 27 %, and 18 % respectively as compared to treatment with nevirapine alone (treatment A).

TMC114

Fig 2 shows the mean plasma concentration-time curves of TMC114 after oral administration of treatments B and B2.

Fig 2: Mean plasma concentration-time curves of TMC114 after oral administration of treatments B and B2.



The absorption after intake of TMC114 as an oral solution and with co-administration of RTV and nevirapine (treatment B) was faster than after intake of TMC114 as a tablet and

with co-administration of RTV and nevirapine (treatment B2). The C_{max} of the mean curve of treatment B was reached about 0.5 hour postdose, while the C_{max} of the mean curve of treatment B2 was reached about 3 hours post dose. The C_{max} and AUC_{12h} after intake of TMC114 as a tablet were higher than after intake of TMC114 as an oral solution. This can partly be explained by the higher dose of TMC114 administered as a tablet (400 mg b.i.d) compared to the oral solution (300 mg b.i.d.).

Table 6 shows the pharmacokinetic results of TMC114 for different treatments.

Table 6: Pharmacokinetic results of TMC114 for different treatments

Pharmacokinetics of TMC114 (mean±SD, t_{max} median (range))	Treatment B TMC114-C119: TMC114/RTV/ nevirapine	TMC114-C207: TMC114/RTV	Treatment B2 TMC114-C119: TMC114/RTV/ nevirapine	TMC114-C137 TMC114/RTV
n	8	13[S]	8	8
t_{max}, h	0.5 (0.5 - 3.0)	0.50 (0.25 - 1.00)	3.0 (2.0 - 4.0)	2.5 (1.0 - 3.0)
C_{0h}, ng/mL	1698 ± 428	1382 ± 416	2198 ± 579	2038 ± 607
C_{min}, ng/mL	1400 ± 282	1175 ± 371	1894 ± 524	1848 ± 528
C_{max}, ng/mL	3534 ± 741	4440 ± 2112	5530 ± 1357	3913 ± 873
AUC_{12h}, ng.h/mL	26588 ± 4533	25030 ± 7044	41361 ± 10625	33511 ± 9540
$C_{tr,av}$, ng/mL	2216 ± 378	2086 ± 587	3447 ± 885	2793 ± 795
FI, %	96.9 ± 35.7	152 ± 52.7	107 ± 21.3	75.9 ± 8.99

S for AUC_{12h}, $C_{tr,av}$ and FI of TMC114-C207: n = 12

In order to compare the pharmacokinetic parameters of TMC114 when co-administered with RTV and nevirapine with those when co-administered with RTV alone, data from the trials TMC114-C207 and TMC114-C137 were used. In trial TMC114-C207, TMC114 and RTV were administered at the same dose regimens as in Treatment B and for TMC114 the same [redacted] (TF019) was used.

However, in trial TMC114-C137, TMC114 and RTV were administered at the same dose as treatment B2, but only for 7 days. The difference in the duration of dosing of TMC114/RTV (14 days in this trial *vs* 7 days in trial TMC114-C137) is acceptable because previous studies have shown that steady state of TMC114/RTV is achieved by Day 4. Furthermore, the tablet of TMC114 used in study TMC114-C137 (TF036) was later renamed as F001; this tablet was used in treatment B2.

The mean value of the fraction of TMC114 not bound to protein, measured 2 hours after TMC114/RTV/NVP intake on Day 14 of Treatment B2, was 5.1 % (min-max: 2.3%-10.0%). This is comparable to the unbound fraction when TMC114 is administered without nevirapine

Table 7 shows the statistical evaluation of the pharmacokinetics of TMC114 for treatment B and data from study TMC114-C207.

Table 7: Statistical evaluation of the pharmacokinetics of TMC114 for treatment B and data from TMC114-C207.

Parameter	Least square means		Least square means ratio, %	90% CI[1]	p-value
	TMC114-C207 (reference) n=13[3]	Treatment B TMC114-C119 (test) n=8			Treatment
C_{min}, ng/mL	1119	1375	123.0	98.0 - 154	0.1311
C_{max}, ng/mL	4101	3454	84.22	64.5 - 110	0.2790
AUC_{12h}, ng.h/mL	24124	26213	108.7	89.0 - 133	0.4806

[3] for AUC_{12h} of TMC114-C207: n = 12
[1] 90% confidence intervals

Compared to when TMC114 was administered as oral solution and co-administered with RTV alone (TMC114-C207), the mean C_{min}, C_{max} and AUC_{12h} of TMC114 did not change in the presence of nevirapine (Treatment B). Based on the LS_{means}, TMC114 C_{min} and AUC_{12h} increased by 23% and 9%, respectively, and TMC114 C_{max} decreased by 16% when TMC114 and RTV were co-administered with nevirapine.

Table 8 shows the statistical evaluation of the pharmacokinetics of TMC114 for treatment B2 and data from study TMC114-C137.

Table 8: Statistical evaluation of the pharmacokinetics of TMC114 for treatment B2 and data from study TMC114-C137.

Parameter	Least square means		Least square means ratio, %	90% CI[1]	p-value
	TMC114-C137 (reference) n=8	Treatment B2 TMC114-C119 (test) n=8			Treatment
C_{min}, ng/mL	1784	1821	102.1	78.7 - 132	0.8909
C_{max}, ng/mL	3833	5379	140.3	114 - 173	0.0120
AUC_{12h}, ng.h/mL	32438	40061	123.5	97.2 - 157	0.1435

[1] 90% confidence intervals

Compared to when TMC114 was administered as tablet and co-administered with RTV alone (TMC114-C137; tablet TF036), only the mean C_{max} of TMC114 increased by approximately 40 %; mean C_{min} and AUC_{12h} did not significantly change in the presence of nevirapine (Treatment B2; tablet F001). Based on the LS_{means}, C_{min}, C_{max}, and AUC_{12h} increased with 2%, 40%, and 23%, respectively, when TMC114 and RTV were coadministered with nevirapine.

RTV

Fig 3 shows the mean plasma concentration-time curves of ritonavir after oral administration of treatments B and B2.

Fig 3: Mean plasma concentration-time curves of ritonavir after oral administration of treatments B and B2.

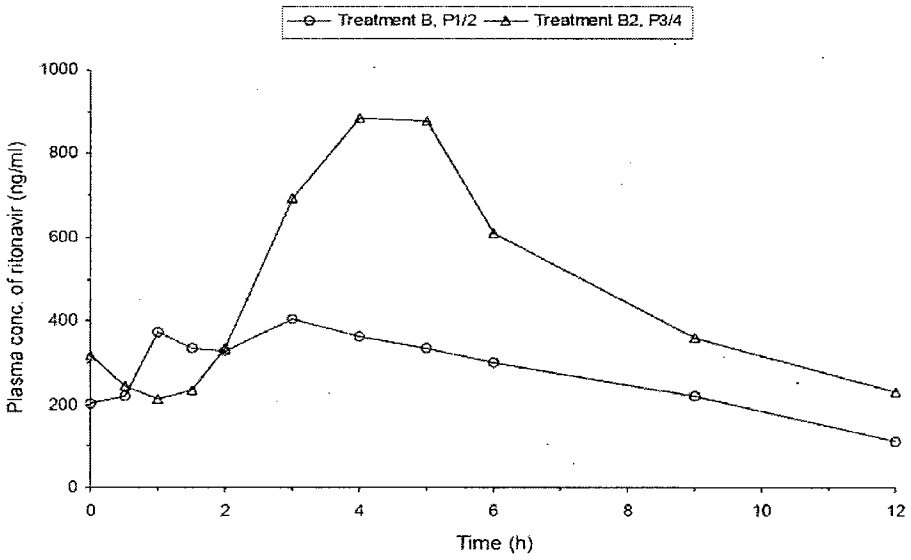


Table 9 shows the pharmacokinetic results of RTV for different treatments.

Table 9: Pharmacokinetic results of RTV for different treatments.

Pharmacokinetics of ritonavir (mean±SD, t_{max} median (range))	Treatment B TMC114-C119: TMC114/RTV/ nevirapine	TMC114-C207: TMC114/RTV	Treatment B2 TMC114-C119: TMC114/RTV/ nevirapine	TMC114-C137: TMC114/RTV
n	8	13[S]	8	8
t_{max}, h	3.0 (0.0 - 5.0)	3.00 (0.50 - 6.00)	5.0 (4.0 - 5.0)	4.0 (4.0 - 6.0)
C_{6h}, ng/mL	201 ± 116	195 ± 94.9	316 ± 196	263 ± 118
C_{min}, ng/mL	103 ± 51.7	127 ± 63.1	189 ± 95.1	199 ± 113
C_{max}, ng/mL	569 ± 370	667 ± 430	967 ± 601	792 ± 461
AUC_{12h}, ng.h/mL	3280 ± 1449	3786 ± 1401	5781 ± 3011	5464 ± 3037
$C_{ss,av}$, ng/mL	273 ± 121	315 ± 117	482 ± 251	455 ± 253
FL %	163 ± 83.8	143 ± 73.2	158 ± 48.6	129 ± 27.9

S for AUC_{12h}, $C_{ss,av}$ and FL of TMC114-C207: n = 12

Table 10 shows the statistical evaluation of the pharmacokinetics of RTV for treatment B and data from TMC114-C207.

Table 10: Statistical evaluation of the pharmacokinetics of RTV for treatment B and data from TMC114-C207.

Parameter	Least square means		Least square means ratio, %	90% CI[1]	p-value
	TMC114-**C207** (reference) n=13[$]	Treatment B TMC114-**C119** (test) n=8			Treatment
C_{min}, ng/mL	113.9	94.24	82.75	57.6 - 119	0.3769
C_{max}, ng/mL	557.1	480.1	86.19	53.2 - 140	0.6004
AUC_{12h}, ng.h/mL	3534	2969	84.02	59.2 - 119	0.3995

$ for AUC_{12h} of TMC114-C207: n = 12
[1] 90% confidence intervals

The statistical evaluation shows that, based on the LS_{means}, C_{min}, C_{max} and AUC_{12h} of RTV decreased by 17%, 14%, and 16%, respectively, when TMC114 as an oral solution and in the presence of low-dose RTV was co-administered with nevirapine compared to TMC114/RTV alone. These differences were not statistically significant.

Table 11 shows the statistical evaluation of the pharmacokinetics of RTV for treatment B2 and data from TMC114-C137.

Table 11: Statistical evaluation of the pharmacokinetics of RTV for treatment B2 and data from TMC114-C137.

Parameter	Least square means		Least square means ratio, %	90% CI[1]	p-value
	TMC114-**C137** (reference) n=8	Treatment B2 TMC114-**C119** (test) n=8			Treatment
C_{min}, ng/mL	172.8	169.5	98.06	61.2 - 157	0.9425
C_{max}, ng/mL	685.6	845.1	123.3	75.6 - 201	0.4630
AUC_{12h}, ng.h/mL	4792	5257	109.7	70.9 - 170	0.7141

[1] 90% confidence intervals

The statistical evaluation shows that, based on the LSmeans, Cmax and AUC12h increased by 23% and 10%, respectively, and Cmin decreased by 2% when TMC114 as a tablet and in the presence of low-dose RTV was co-administered with nevirapine compared to TMC114/RTV alone. These differences were not statistically significant.

7. Safety Assessments

Of the 19 subjects enrolled in the study, 14 subjects (74 %) reported an AE during the whole trial. 18 % (3 out of 17 subjects) reported at least one AE during treatment A, while 64 % (7 out of 11 subjects) reported at least AE during treatment B and 88 % (7 out of 8 subjects) reported at least one AE during treatment B2. The most commonly reported AEs were GI (diarrhea; reported for 5 subject during treatment B and 2 subjects

during treatment B2) and nervous system (similar incidence for all treatment groups) disorders. The most commonly reported treatment-emergent abnormalities in biochemistry were related to lipid/glucose metabolism.

For 1 subject, an SAE was reported. This SAE (subarachnoid hemorrage) occurred during follow up period and the subject permanently discontinued the trial due to this SAE. This SAE was judged grade 3 and not related to trial medication by the investigator (See details in Medical Officer's review).

8. Conclusion

- The results of this study demonstrate that the steady-state exposure (AUC_{12hr}) of nevirapine increased by 27 % when TMC114, either as a tablet or an oral solution, and in the presence of low-dose RTV, was co-administered. This change was not considered clinically relevant.
- C_{min} of nevirapine was increased by 18 % and 47 % following co-administration with TMC114/RTV.
- C_{max} of nevirapine was increased by 14 % and 18 % for the oral solution and tablet of TMC114, respectively.
- The co-administration of nevirapine with TMC114/RTV generally resulted in similar exposures to TMC114 and RTV when compared with historical data with TMC114/RTV alone.

Labeling Recommendation

PREZISTA/rtv and nevirapine can be co-administered without any dose adjustments.

1. Title

The effect of TMC114, boosted with low doses of ritonavir, on pravastatin (PRA) pharmacokinetics in healthy volunteers **(TMC114-C120).**

2. Objectives

The objectives of this trial were to assess:

- The pharmacokinetic effect of repeated doses of TMC-114 boosted with low dose of ritonavir on the pharmacokinetics of a single dose of pravastatin.
- To determine the effect of a single dose of PRA on the steady state PK of TMC114 boosted with a low dose of RTV.

3. Study Design

Open label, randomized, cross over trial to investigate the effect of TMC 114, formulated as an oral solution and co-administered with ritonavir, on the pharmacokinetics of pravastatin. 14 healthy volunteers were randomized into two groups.

Group 1: A single dose of 40 mg pravastatin **(Treatment A)** in session 1, followed by wash-out period of at least 6 days. In session 2, 600/100 TMC114/RTV b.i.d was administered for 7 days. On Day 7, a single dose of 40 mg pravastatin was co-administered **(Treatment B)**.

Group 2: Subjects in group 2 received treatment B in session 1, followed by a washout period of at least 13 days. Thereafter, they received treatment A in session 2.

4. Drugs Used in the Trial

Table 1 shows the drugs used in the trial.

Table 1: Description of Drugs Used in the Trial

	TMC 114	RTV	PRA
Dosage Form	[redacted]	[redacted]	Tablet
Strength	20 mg/mL	100 mg	40 mg
Batch Number	02C07/1	80338VA	01H27A181
Expiry Date	07/Sep/2002	30/AUG/2002	30/AUG/2002

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

For treatment A (session 1 for group 1 and session 2 for group 2), plasma samples (5 mL) were collected at pre-dose (within 2 hours before drug intake) and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, and 24 hours. For treatment B (session 2 for group 1 and session 1 for group 2), the plasma samples were collected at pre-dose (immediately before drug intake) on

days 4, 6, 7, and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, and 24hrs (day 8). The plasma concentrations of TMC114, RTV, and PRA were determined using LC/MS/MS. The lower limit of quantification was 10, 5, and 1 ng/mL for TMC114, RTV, and PRA respectively.

Pharmacokinetic Assessments

Non-parametric analysis was performed using Winnonlin [redacted] to compute the standard pharmacokinetic parameters.

6. Results

6.1 Demographics

14 subjects were randomized and completed the study.

Table 2: Demographics in Study TMC 114-C120

Parameter		Group 1 N = 7	Group 2 N = 7	All subjects N = 14
Age, median (min-max), years		36.0 (25-48)	40.0 (24-53)	38.0 (24-53)
Weight, median (min-max), kg		78.0 (67-93)	76.0 (67-98)	77.0 (67-98)
Height, median (min-max), cm		174.0 (164-189)	175.0 (160-188)	173.5 (160-189)
BMI, median (min-max), kg/m²		25.8 (23-28)	26.2 (20-28)	26.0 (20-28)
Gender, n (%)	female	0	2 (29)	2 (14)
	male	7 (100)	5 (71)	12 (86)
Smoking habits, n (%)	None	3 (43)	7 (100)	10 (71)
	Light	4 (57)	0	4 (29)
Ethnic origin, n (%)	Caucasian	7 (100)	7 (100)	14 (100)

6.2 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time profile of a single dose of 40 mg PRA with or without co-administration of 600/100 TMC 114/RTV b.i.d.

Fig1: Mean plasma concentration time profile of a single dose of 40 mg PRA with or without co-administration of 600/100 TMC 114/RTV b.i.d.

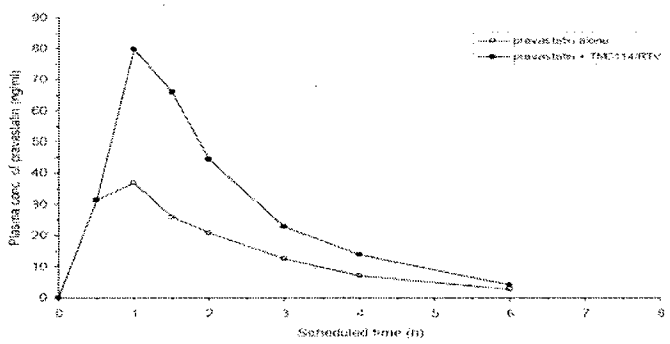


Table 3 shows the pharmacokinetic parameters obtained after a single dose of 40 mg PRA with or without co-administration of 600/100 mg TMC114/RTV b.i.d.

Table 3: Pharmacokinetic results of a single dose of 40 mg PRA with or without co-administration of 600/100 TMC114/RTV b.i.d.

Pharmacokinetics of pravastatin (mean±SD, t_{max}: median (range))	Treatment A: PRA	Treatment B: TMC114/RTV + PRA
n	14	14*
t_{max}, h	1.0 (0.5 - 3.0)	1.5 (1.0 - 3.0)
C_{max}, ng/ml	50.9 ± 67.6	86.9 ± 88.4
AUC_{last}, ng.h/ml	92.0 ± 86.4	175 ± 159
$t_{1/2term}$, h	1.79 ± 0.757	1.30 ± 0.296

* For parameter $t_{1/2term}$: n = 12

The pharmacokinetics of PRA alone, observed in this study was in good agreement with values previously reported in the literature. High interindividual variability was observed for PRA when administered alone and in combination with TMC114/RTV. For C_{max}, the % CV was 133 % and 102 % and for AUC_{last}, the % CV was 94 % and 91 % without and with co-administration of TMC114/RTV. The terminal half- lives were comparable for both treatments.

Table 4 shows the statistical evaluation of the effect of TMC114 on the PK of a single dose of PRA.

Table 4: Statistical evaluation of the pharmacokinetics of PRA (single 40 mg dose) with or without co-administration of 600/100 TMC114/RTV b.i.d.

Parameter	n	Least square means: Treatment A (reference)	Least square means: Treatment B (test)	Least square means ratio, %	90% CI	p-value Treatment
C_{max}, ng/ml	14	31.40	51.32	163.4	94.9 - 282	0.1333
AUC_{last}, ng.h/ml	14	65.75	119.0	181.0	123 - 266	0.0174
		Median				p-value
Parameter	n	Treatment A (reference)	Treatment B (test)	Treatment difference median	90% CI	Treatment
t_{max}, h	14	1.0	1.5	-0.25	(-0.75) - (0.25)	0.3575

Based on the ratio of least square means, C_{max} increased by 63 % and AUC_{last} increased by 81 %. **The wide confidence interval around the LSM ratio indicate a variable effect of TMC114/RTV on PRA pharmacokinetics between individuals. The individual ratios for C_{max}, comparing PRA co-administered with TMC 114/RTV to treatment alone, ranged from 44 %-1044 %.** Three subjects had extreme high ratios of 760, 870 and 1044%, while in 5 subjects plasma concentrations of PRA were 20% or more lower with co-administration of TMC114/RTV.

The individual ratios for AUC_{last} ranged from 57 % to 679 %. No statistically significant difference was observed for t_{max} between the two treatments. Two subjects

had high ratios of 553 % and 679 % while in one subject the plasma concentrations of PRA were 20 % or more lower during co-administration of TMC114/RTV.

Reviewer's Comment:

The metabolism of pravastatin involves multiple oxidation pathways, however CYP3A4 is not involved. Therefore, changes in systemic exposure of pravastatin in the presence or absence of TMC114/RTV were not expected.

Table 5 shows the pharmacokinetic parameters of TMC114 alone and after coadministration with pravastatin.

Table 5: Pharmacokinetic parameters of TMC114 alone and after coadministration with pravastatin.

Pharmacokinetics of TMC114 (mean±SD, t_{max}: median (range))	TMC114/RTV + PRA (TMC114-C120, 600/100 mg b.i.d., Treatment B, Day 7)	TMC114/RTV (TMC114-C207, 600/100 mg b.i.d. group, Day 14)
	healthy volunteers	HIV-1 patients
n	14	11
C_{0h}, ng/ml	2679 ± 953	2260 ± 1228
C_{max}, ng/ml	2393 ± 988	1928 ± 1223
t_{max}, h	0.5 (0.5 - 4.0)	0.5 (0.5 - 1.0)
C_{ave}, ng/ml	5447 ± 1703	6008 ± 1617
AUC_{12h}, ng.h/ml	40355 ± 13559	36986 ± 16444

To assess the effect of PRA on the pharmacokinetics of TMC114, the pharmacokinetic parameters of TMC 114 from the current study were compared with those from study TMC114-C207 in which one of the groups received 600/100 b.i.d. TMC114/RTV treatment. The comparison of data indicated that co-administration of a single dose PRA had no major impact on the pharmacokinetics of TMC/RTV.

Reviewer Comment
Although the PK parameters of TMC114 generated across the various studies show similarity, the sponsor acknowledges that this cross study comparison has two inherent limitations. First, currently, no healthy volunteer study has been conducted where 600 mg TMC 114/RTV 100 mg b.i.d. has been administered, therefore, a direct comparison of PK determined after 7 days of 600/100 b.i.d. TMC/RTV treatment cannot be made. Secondly, study C207 was conducted in HIV infected subjects and the current study was in healthy volunteers, therefore, no definitive conclusions can be drawn since it has been shown that for the same dose, exposures in HIV-1 infected subjects tend to be higher possibly due to higher protein binding.

Table 6 shows the comparison of pharmacokinetic parameters of ritonavir observed in this study and two previous studies; TMC 114-C207 (performed in HIV-1 infected subjects, PK determined on day 14) in which one of the groups also received a 600/100 bid TMC 114/RTV treatment, and TMC 114-C112 (performed in healthy volunteers, PK determined on day 7) in which one of the groups received 300/100 b.i.d. There was no

indication that co-administration of a single dose PRA had a major impact on the PK of RTV, co-administered with TMC114.

Table 6: Pharmacokinetic Results of Ritonavir

Pharmacokinetics of ritonavir (mean±SD, t_{max} median (range))	TMC114 RTV + PRA (TMC114-C120, 600/100 mg b.i.d., Treatment B, Day 7)	TMC114 RTV (TMC114-C207, 600/100 mg b.i.d. group, Day 14)	TMC114 RTV (TMC114-C112, 300/100 mg b.i.d. group, Day 7)
N	14	11	8
C_{tau}, ng/ml	217 ± 166	204 ± 122	201 ± 81.5
C_{max}, ng/ml	157 ± 103	113 ± 43.7	118 ± 56.4
t_{max}, h	6.0 (1.5 - 6.0)	3.0 (0.5 - 8.0)	6.0 (4.0 - 9.0)
C_{max}, ng/ml	582 ± 354	423 ± 275	514 ± 149
AUC_{tau}, ng·h/ml	3894 ± 2156	3113 ± 1377	3806 ± 1194

7. Safety Assessments

There were no consistent changes in the laboratory parameters from reference noted in this trial. No subject discontinued the trial due to AEs (See details in Medical Officer's review).

8. Conclusion

- Mean systemic exposure (AUC) of PRA, co-administered as a single dose (on Day 7) with TMC/RTV 600/100 b.i.d., increased by 81 % as compared to PRA administered alone.
- There was high intersubject variability in PRA exposure after co-administration with TMC/RTV.
- The pilot oral solution of TMC 114 together with a low dose of RTV, with or without PRA was well tolerated.

Labeling Recommendation

When PREZISTA/rtv was administered with pravastatin, the mean increase in pravastatin AUC was 81 %. However, pravastatin AUC increased by up to 5-fold in some patients. The mechanism of interaction is not known.

1. Title

The pharmacokinetic interaction between paroxetine or sertraline and TMC114, co-administered with low-dose ritonavir, in healthy subjects **(TMC114-C121).**

2. Objectives

- To determine the effect of steady-state concentrations of TMC114, in combination with low-dose RTV, on the steady-state pharmacokinetics of paroxetine.
- To determine the effect of steady-state concentrations of paroxetine on the steady state pharmacokinetics of TMC114, in combination with low dose RTV.
- To determine the effect of steady-state concentrations of TMC114, in combination with low dose RTV, on the steady state pharmacokinetics of sertraline.
- To determine the effect of steady-state concentrations of sertraline on the steady-state pharmacokinetics of TMC114, in combination with low-dose RTV.

3. Study Design

Phase I, open-label, randomized, cross-over trial to investigate the effect of TMC114, formulated as a 400 mg tablet (F001) and coadministered with ritonavir, on the pharmacokinetics of paroxetine and sertraline. 36 healthy volunteers were randomized into two panels:

Panel 1: Subjects in panel 1 received 400 mg TMC114/100 mg RTV b.i.d., (treatment A), 20 mg paroxetine q.d. (treatment B), and 20 mg paroxetine q.d. and 400 mg TMC114/100 mg RTV b.i.d. (treatment C) in three sessions.

Panel 2: Subjects in panel 2 received 400 mg TMC114/100 mg RTV b.i.d., (treatment A), 50 mg sertraline q.d. (treatment D), and 50 mg sertraline q.d. and 400 mg TMC114/100 mg RTV b.i.d. (treatment E) in three sessions.

Within each panel, 3 subjects were randomized to one of the 6 predefined randomization sequences. The randomization sequences for panel 1were ABC, BCA, CAB, CBA, BAC, and ACB. Similarly, for panel 2, the randomization sequences were ADE, DEA, EAD, EDA, DAE, and AED. Treatment A was administered for 6 days with an additional morning dose on Day 7. Treatments B, C, D, and E were administered for 7 days. All the treatments were administered under fed conditions. Subsequent sessions within a panel were separated with a washout period of at least 7 days.

4. Drugs Used in the Trial

Table 1 shows the drugs used in the trial.

Table 1: Description of Drugs Used in the Trial.

	TMC 114	RTV	PAR	SER
Dosage Form	Tablet (F001)	Capsule	Tablet	Tablet
Strength	400 mg	100 mg	20 mg	50 mg
Batch Number	PD 1098	097772E21	3643B11	3JT194A
Expiry Date	April 2005	Sep 2005	July 2005	Dec 2006

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

For pharmacokinetic assessments, plasma samples for treatment A were collected at pre-dose (within two hours before drug intake) on day 1, immediately before drug intake on day 5, 6, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, and 12 hrs post dose on day 7. For treatments B and D, plasma samples were collected at pre-dose (within two hours before drug intake) on day 1, immediately before drug intake on day 5, 6, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, and 16 hrs post dose. For treatment C and E, plasma samples were collected at pre-dose (within two hours before drug intake) on day 1, immediately before drug intake on day 5, 6, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16, and 24 hrs post dose (the 16 and 24 hr post dose sample was used only for the determination of paroxetine (treatment C) or sertraline (treatment E) on day 7. The plasma concentrations of TMC114, RTV, SER and PAR were determined using validated LC/MS/MS methods. The lower limit of quantification was 10 ng/mL for TMC114, 5 ng/mL for RTV, and 0.1 ng/mL for SER and PAR.

Pharmacokinetic Assessments

Non parametric analysis was performed using Winnonlin [redacted] to compute the standard pharmacokinetic parameters.

6. Results

6.1 Subject Disposition

36 subjects were randomized into two panels. In panel 1, all subjects except one subject in sequence BAC completed all assessments. In panel 2, one subject discontinued in sequence DEA, one subject discontinued in sequence EAD, and 2 subjects discontinued in sequence EDA.

Table 2: Demographics in Study TMC114-C121

Parameter	Treatment A-B-C N = 3	Treatment B-C-A N = 3	Treatment C-A-B N = 3	Treatment C-B-A N = 3	Treatment B-A-C N = 3	Treatment A-C-B N = 3	All panel 1 N = 18
Age, years	38.0	24.0	22.0	45.0	20.0	23.0	25.5
Median (range)	(31-39)	(19-39)	(20-27)	(20-47)	(18-37)	(21-29)	(18-47)
Height, cm	175.0	185.0	165.0	168.0	168.0	185.0	178.0
Median (range)	(168-178)	(180-198)	(157-178)	(155-180)	(163-185)	(178-191)	(155-198)
Weight, cm	80.0	75.0	71.0	73.0	81.0	82.0	75.0
Median (range)	(73-88)	(75-82)	(65-74)	(71-79)	(56-90)	(62-85)	(56-90)
BMI, kg/m^2	26.1	23.1	26.1	25.9	26.3	23.3	25.9
Median (range)	(26-28)	(19-24)	(23-26)	(24-30)	(21-29)	(18-26)	(18-30)
Sex, n (%)							
Male	3 (100)	3 (100)	1 (33)	2 (67)	1 (33)	3 (100)	13 (72)
Female	0	0	2 (67)	1 (33)	2 (67)	0	5 (28)

6.2 Pharmacokinetic Analysis

TMC 114

Fig 1 shows the mean plasma concentration-time curves of TMC 114 after oral administration of 400 mg TMC 114/100 mg RTV b.i.d (treatment A), 20 mg paroxetine q.d. and 400 mg TMC114/100 mg RTV b.i.d (treatment C), and 50 mg sertraline q.d. and 400 mg TMC 114/100 mg RTV b.i.d (treatment E).

Fig1: Mean plasma concentration-time curves of TMC 114 after oral administration of 400 mg TMC 114/100 mg RTV b.i.d (treatment A), 20 mg paroxetine q.d. and 400 mg TMC114/100 mg RTV b.i.d (treatment C), and 50 mg sertraline q.d. and 400 mg TMC 114/100 mg RTV b.i.d (treatment E).

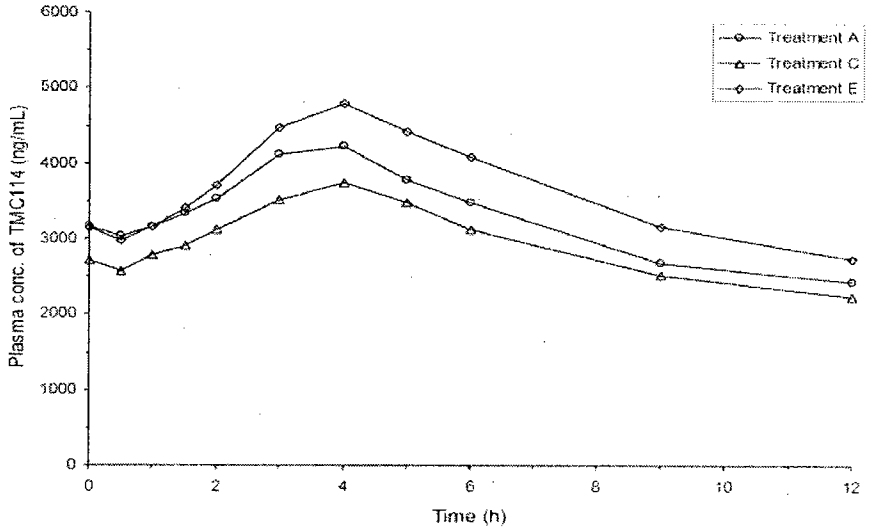


Table 3 shows the pharmacokinetic parameters obtained after oral administration of 400 mg TMC 114/100 mg RTV b.i.d. (treatment A), 20 mg paroxetine q.d. and 400 mg TMC

114/100 mg RTV b.i.d. (treatment C), and 50 mg sertraline q.d. and 400 mg TMC 114/100 mg RTV b.i.d. (treatment E).

Table 3: Pharmacokinetic results of TMC 114 after oral administration of 400 mg TMC 114/100 mg RTV b.i.d. (treatment A), 20 mg paroxetine q.d., and 400 mg TMC 114/100 mg RTV b.i.d. (treatment C), and 50 mg sertraline q.d. and 400 mg TMC 114/100 mg RTV b.i.d. (treatment E).

Pharmacokinetics of TMC 114 (mean ± SD, t_{max} median (range))	Treatment A: TMC114/RTV	Treatment C: TMC114/RTV/PAR	Treatment E: TMC114/RTV/SER
n	31[a]	16[b]	16[c]
Day 1			
C_{0h}, ng/mL	0	0	0
Day 5			
C_{0h}, ng/mL	2911 ± 1208	2998 ± 832.4	3588 ± 1205
Day 6			
C_{0h}, ng/mL	2921 ± 1533	2878 ± 914.8	3364 ± 1127
Day 7			
C_{0h}, ng/mL	3163 ± 1277	2714 ± 756.3	3149 ± 898.6
C_{tau}, ng/mL	2324 ± 1174	2091 ± 681.5	2527 ± 903.5
C_{max}, ng/mL	4479 ± 1543	3958 ± 699.0	5099 ± 1455
t_{max}, h	4.0 (0.0 - 5.0)	4.0 (2.0 - 9.0)	4.0 (0.0 - 5.0)
AUC_{12h}, ng.h/mL	39038 ± 16211	35127 ± 7368	45780 ± 13932
$C_{av,12h}$, ng/mL	3253 ± 1351	2927 ± 614.0	3648 ± 1161
FI, %	71.37 ± 22.39	66.01 ± 20.87	72.21 ± 17.90

[a] n= 33 for Day 1 C_{0h}
[b] n= 17 for Day 1 C_{0h}
[c] n=17 for Day 1, 5 and 6 C_{0h}

The plasma concentrations of TMC 114 in predose samples (C_{0h}) of Day 1 of the different treatments were all below the LLOQ, indicating that a washout period of 7 days between consecutive treatments was sufficient.

Tables 4 and 5 show the statistical comparison of the pharmacokinetics of TMC114 between treatment A and C and between treatment A and E respectively.

Table 4: Summary of statistical analysis of the pharmacokinetic parameters of TMC114 of treatment C (TMC 114/RTV/PAR) compared to treatment A (TMC 114/RTV).

Parameter	n	LS means		LS means ratio, %	90% CI	p-value		
		Treatment A (reference)	Treatment C (test)			Treatment	Period	Sequence
C_{0h}, ng/mL	16	2767	2621	94.72	84.3 - 106	0.4281	-	-
C_{tau}, ng/mL	16	1883	2008	106.6	95.7 - 119	0.3155	-	-
C_{max}, ng/mL	16	4031	3905	96.89	91.9 - 102	0.3116	-	-
AUC_{12h}, ng.h/mL	16	33862	34482	101.8	94.6 - 110	0.6732	-	-
Parameter		Median		Treatment difference median	90% CI	p-value		
	n	Treatment A (reference)	Treatment C (test)			Treatment	Period	Sequence
t_{max}, h	16	4.0	4.0	-0.5	(-1.5 ; 0.0)	0.2085	0.5462	0.5135

- : excluded from final model

Table 5: Summary of statistical analysis of the pharmacokinetic parameters of TMC114 of treatment E (TMC 114/RTV/PAR) compared to treatment A (TMC 114/RTV).

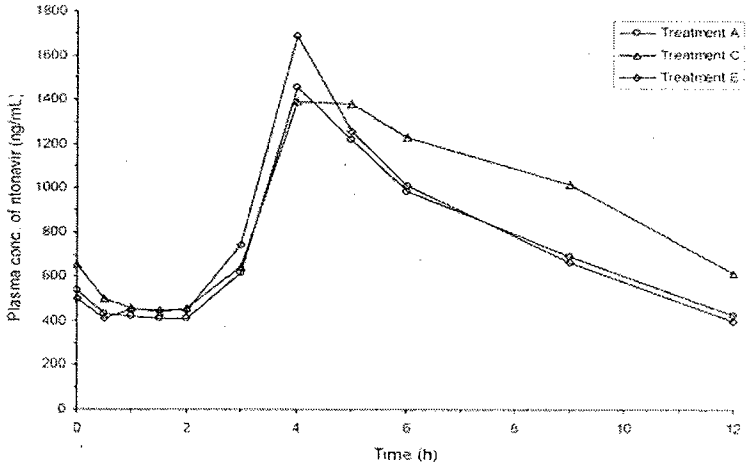
Parameter	n	LS means		LS means ratio, %	90% CI	p-value		
		Treatment A (reference)	Treatment E (test)			Treatment	Period	Sequence
C_{24}, ng/mL	13	3261	2904	89.07	72.8 - 109	0.3272	-	-
C_{max}, ng/mL	13	2436	2293	94.11	76.4 - 116	0.6123	-	-
C_{max2}, ng/mL	13	4678	4713	100.8	89.3 - 114	0.9131	-	-
AUC_{12}, ng.h/mL	13	40876	40051	97.98	83.9 - 114	0.8194	-	-
Parameter	**n**	**Median**		**Treatment difference median**	**90% CI**	**p-value**		
		Treatment A (reference)	Treatment E (test)			Treatment	Period	Sequence
t_{max}, h	13	4.0	4.0	0.0	(-0.5) - (1.0)	0.4343	0.2438	0.5498

- : excluded from final model

RTV

Fig 2 shows the mean plasma concentration-time curves of RTV after oral administration of 400 mg TMC114/100 mg RTV b.i.d (treatment A), 20 mg paroxetine q.d. and 400 mg TMC114/100 mg RTV b.i.d (treatment C), and 50 mg sertraline q.d. and 400 mg TMC 114/100 mg RTV b.i.d (treatment E).

Fig 2: Mean plasma concentration-time curves of RTV after oral administration of 400 mg TMC 114/100 mg RTV b.i.d (treatment A), 20 mg paroxetine q.d. and 400 mg TMC114/100 mg RTV b.i.d (treatment C), and 50 mg sertraline q.d. and 400 mg TMC 114/100 mg RTV b.i.d (treatment E).



Visual inspection of the mean plasma concentration-time data at steady state reveals a similar shape of the curves. However, when RTV and TMC 114 were administered with paroxetine, concentrations in the 5 to 12 hr period were higher compared to the other treatments.

Table 6 shows the pharmacokinetic parameters of RTV obtained after oral administration of 400 mg TMC114/100 mg RTV b.i.d. (treatment A), 20 mg paroxetine q.d., and 400 mg TMC114/100 mg RTV b.i.d. (treatment C), and 50 mg sertraline q.d. and 400 mg TMC 114/100 mg RTV b.i.d. (treatment E).

Table 6: Pharmacokinetic parameters of RTV obtained after oral administration of 400 mg TMC 114/100 mg RTV b.i.d. (treatment A), 20 mg paroxetine q.d., and 400 mg TMC 114/100 mg RTV b.i.d. (treatment C), and 50 mg sertraline q.d. and 400 mg TMC 114/100 mg RTV b.i.d. (treatment E).

Pharmacokinetics of ritonavir (mean ± SD, t_{max}: median (range))	Treatment A: TMC114/RTV	Treatment C: TMC114/RTV/PAR	Treatment E: TMC114/RTV/SER
n	31[a]	16[b]	16[c]
Day 1			
C_{tau}, ng/mL	0	0	0
Day 5			
C_{tau}, ng/mL	504.5 ± 287.2	670.3 ± 480.3	471.2 ± 208.1
Day 6			
C_{tau}, ng/mL	575.5 ± 325.9	692.9 ± 399.9	476.4 ± 195.0
Day 7			
C_{tau}, ng/mL	538.1 ± 273.5	655.9 ± 383.7	498.4 ± 225.0
C_{max2}, ng/mL	318.7 ± 157.9	407.2 ± 183.5	315.2 ± 171.9
C_{max}, ng/mL	1591 ± 802.2	1689 ± 741.7	1770 ± 813.7
t_{max}, h	4.0 (3.0 - 9.0)	4.5 (4.0 - 9.0)	4.0 (3.5 - 5.0)
AUC_{tau}, ng.h/mL	9059 ± 3666	11071 ± 5546	9434 ± 3657
$C_{x\,h}$, ng/ml	754.9 ± 305.5	922.5 ± 462.2	786.2 ± 304.7
FL, %	165.8 ± 56.75	143.9 ± 34.00	183.2 ± 39.39

[a] n=33 for Day 1 C_{tau}
[b] n=17 for Day 1 C_{tau}
[c] n=17 for Day 1, 5 and 6 C_{tau}

Tables 7 and 8 show the statistical comparison of the pharmacokinetics of RTV between treatment A and C and between treatment A and E respectively.

Table 7: Summary of statistical analysis of the pharmacokinetic parameters of RTV of treatment C (TMC 114/RTV/PAR) compared to treatment A (TMC 114/RTV).

Parameter	n	LS means		LS means ratio, %	90% CI	p-value		
		Treatment A (reference)	Treatment C (test)			Treatment	Period	Sequence
C_{tau}, ng/mL	16	429.2	575.3	134.0	118 - 153	0.0013	-	-
C_{max2}, ng/mL	16	248.0	373.5	152.5	134 - 174	<0.0001	-	-
C_{max}, ng/mL	16	1345	1578	117.3	100 - 137	0.0960	-	-
AUC_{tau}, ng.h/mL	16	7584	10182	134.5	122 - 147	0.0001	-	-
Parameter	**n**	**Median**		**Treatment difference median**	**90% CI**	**p-value**		
		Treatment A (reference)	Treatment C (test)			Treatment	Period	Sequence
t_{max}, h	16	4.0	4.5	0.0	(-0.5) - (0.0)	0.3127	0.0772	0.4333

- excluded from final model

Table 8: Summary of statistical analysis of the pharmacokinetic parameters of RTV of treatment E (TMC 114/RTV/SER) compared to treatment A (TMC 114/RTV).

Parameter	n	LS means		LS means ratio, %	90% CI	p-value		
		Treatment A (reference)	Treatment E (test)			Treatment	Period	Sequence
C_{ss}, ng/mL	13	496.2	425.5	85.75	75.3 - 97.7	0.0576	-	-
C_{max}, ng/mL	13	331.8	268.7	80.99	71.3 - 91.7	0.0107	-	-
C_{trough}, ng/mL	13	1464	1478	100.9	80.0 - 127	0.9444	-	-
AUC_{tau}, ng.h/mL	13	9261	8249	89.07	75.1 - 106	0.2502	-	-
Parameter	**n**	**Median**		**Treatment difference median**	**90% CI**	**p-value**		
		Treatment A (reference)	Treatment E (test)			Treatment	Period	Sequence
t_{max}, h	13	4.0	4.0	0.5	(0.0) - (0.5)	0.0233	0.7353	0.7595

- : excluded from final model

Sertraline

Fig 3 shows the mean plasma concentration time curves of Sertraline after oral administration of 50 mg sertraline q.d. (treatment D) and 50 mg sertraline q.d. and 400 mg TMC 114/100 mg RTV b.i.d. (Treatment E).

Fig 3: Mean plasma oncentration time curves of Sertraline after oral Administration of 50 mg sertraline q.d. (treatment D) and 50 mg sertraline q.d. and 400 mg TMC 114/100 mg RTV b.i.d. (Treatment E)

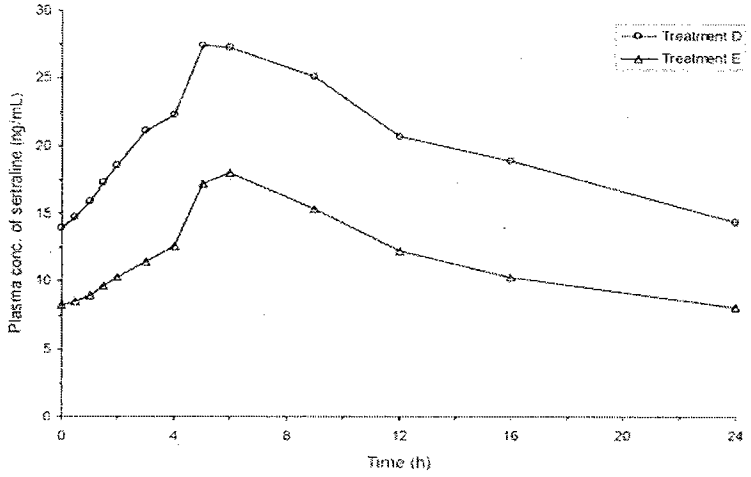


Table 9 shows the pharmacokinetic results of sertraline after oral administration of 50 mg sertraline q.d. (treatment D) and 50 mg sertraline q.d. and 400 mg TMC114/100 mg RTV b.i.d. (treatment E).

Table 9: Pharmacokinetic results of sertraline after oral administration of 50 mg sertraline q.d. (treatment D) and 50 mg sertraline q.d. and 400 mg TMC114/100 mg RTV b.i.d. (treatment E).

Pharmacokinetics of sertraline (mean ± SD, t_{max} median (range))	Treatment D: Sertraline	Treatment E: TMC114/RTV/SER
n	15	17[a]
Day 1		
C_{0h}, ng/mL	0	0
Day 5		
C_{0h}, ng/mL	12.24 ± 4.706	10.15 ± 4.521
Day 6		
C_{0h}, ng/mL	13.90 ± 5.927	9.398 ± 4.443
Day 7		
C_{0h}, ng/mL	13.96 ± 5.535	8.244 ± 3.342
C_{min}, ng/mL	12.83 ± 4.798	7.369 ± 3.276
C_{max}, ng/mL	28.86 ± 8.398	18.69 ± 7.441
t_{max}, h	6.0 (4.0 - 9.0)	6.0 (0.0 - 9.0)
AUC_{24h}, ng.h/mL	485.0 ± 167.2	284.1 ± 115.4
$C_{av,ss}$, ng/mL	20.21 ± 6.969	11.84 ± 4.809
FL %	82.70 ± 20.20	97.68 ± 25.31

[a] n=16 for Day 7

Table 10 shows the statistical results of the final model comparing the pharmacokinetics of sertraline between treatment D and E.

Table 10: Summary of the statistical analysis of the pharmacokinetic parameters of sertraline of treatment D (sertraline) compared to treatment E (TMC114/RTV/SER)

Parameter	n	LS means		LS means ratio, %	90% CI	p-value		
		Treatment D (reference)	Treatment E (test)			Treatment	Period	Sequence
C_{0h}, ng/mL	15	12.62	6.969	55.22	50.5 - 60.4	<0.0001	-	-
C_{max}, ng/mL	15	11.72	5.940	50.69	45.3 - 56.7	<0.0001	-	-
C_{max}, ng/mL	15	27.18	15.09	55.54	48.7 - 63.3	<0.0001	-	-
AUC_{24h}, ng/h/mL	15	450.2	230.5	51.20	45.6 - 57.5	<0.0001	-	-
Parameter	**n**	**Median**		**Treatment difference median**	**90% CI**	**p-value**		
		Treatment D (reference)	**Treatment E (test)**			**Treatment**	**Period**	**Sequence**
t_{max}, h	15	6.0	6.0	0.5	[-1.0 ; 1.5]	0.5595	0.4236	0.3409

- : excluded from final model

The mechanism for the decrease in sertraline (mainly metabolized through CYP3A4) exposure by approximately 50 % is currently unknown. One hypothesis (provided by the sponsor) can be that both TMC114 and sertraline are highly bound (> 95 %) to plasma α-1-acid glycoprotein (AAG). Therefore, the decrease in exposures can be due to the interaction at the AAG sites, resulting in decreased total concentration of sertraline in the presence of TMC114/RTV. However, free drug concentrations would not be expected to be altered. Although the hypothesis is reasonable, the sponsor did not provide sufficient data to support the hypothesis.

Paroxetine

Fig 4 shows the mean plasma concentration-time curves of paroxetine after oral administration of 20 mg paroxetine q.d. (treatment B) and 20 mg paroxetine q.d. and 400 mg TMC114/100 mg RTV b.i.d (treatment C).

Fig 4: Mean plasma concentration-time curves for paroxetine after oral administration of 20 mg paroxetine q.d. (treatment B) and 20 mg paroxetine q.d. and 400 mg TMC114/100 mg RTV b.i.d. (treatment C)

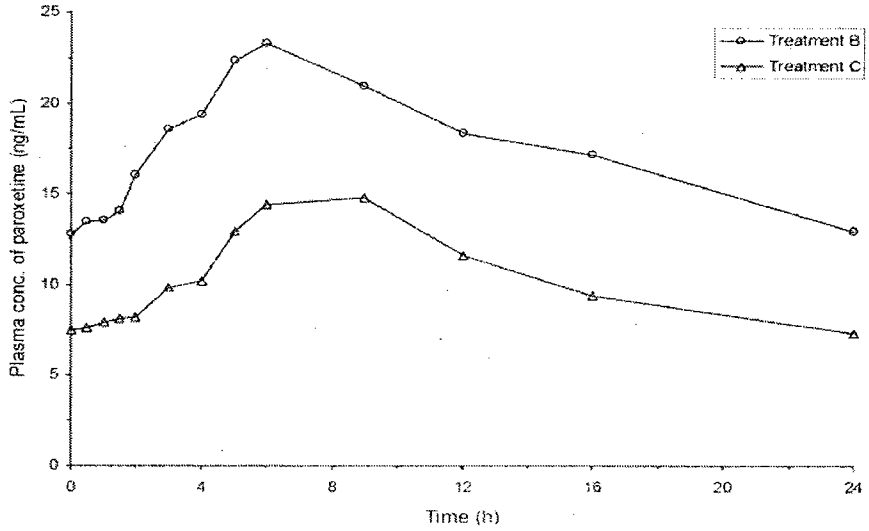
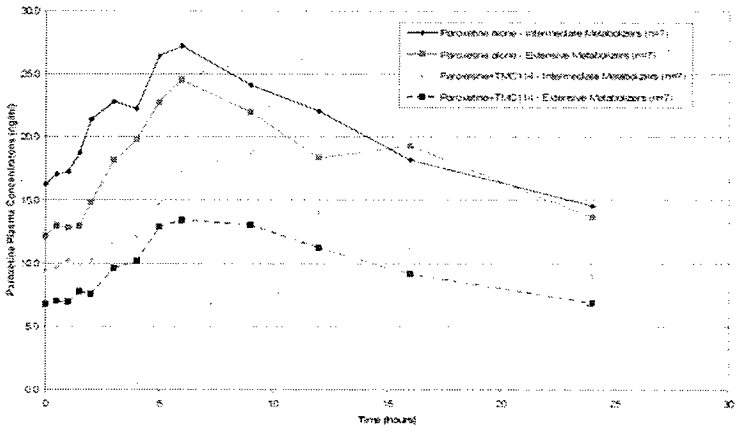


Fig 5 shows the plasma paroxetine (a substrate of CYP2D6) concentration versus time plots for intermediate and extensive metabolizers

Fig 5: Mean paroxetine plasma concentrations versus time in intermediate and extensive metabolisers.



Co-administration of paroxetine and TMC114/RTV led to a decrease in plasma concentration of paroxetine as compared to administration of paroxetine alone. Further, the magnitude of decrease in paroxetine (a CYP2D6 substrate) plasma concentrations was similar for intermediate and extensive metabolisers.

Table 11 shows the pharmacokinetic parameters of paroxetine after oral administration of 20 mg paroxetine q.d. (treatment B) and 20 mg paroxetine q.d. and 400 mg TMC114/RTV b.i.d. (treatment C).

Table 11: Pharmacokinetic parameters of paroxetine after oral administration of 20 mg paroxetine q.d. (treatment B) and 20 mg paroxetine q.d. and 400 mg TMC114/RTV b.i.d. (treatment C).

Pharmacokinetics of paroxetine (mean ± SD, t_{max} median (range))	Treatment B: PAR	Treatment C: TMC114/RTV/PAR
n	18	16[a]
Day 1		
C_{0h}, ng/mL	0	0
Day 5		
C_{0h}, ng/mL	9.016 ± 6.304	6.454 ± 4.253
Day 6		
C_{0h}, ng/mL	11.02 ± 6.732	7.526 ± 4.413
Day 7		
C_{0h}, ng/mL	12.82 ± 8.357	7.467 ± 3.915
C_{min}, ng/mL	11.42 ± 7.225	6.763 ± 3.778
C_{max}, ng/mL	24.04 ± 11.53	15.56 ± 8.111
t_{max}, h	6.0 (5.0 - 9.0)	6.0 (3.0 - 12.0)
AUC_{24h}, ng.h/mL	433.0 ± 233.6	252.5 ± 122.3
$C_{ss,av}$, ng/mL	18.04 ± 9.734	10.52 ± 5.097
FI, %	87.28 ± 49.37	91.33 ± 39.10

[a] n=17 for Day 1 C_{0h}

Table 12 shows the summary of the statistical analysis of the pharmacokinetic parameters of paroxetine of treatment B (paroxetine) compared to treatment C TMC114/RTV/PAR).

Table 12: Summary of the statistical analysis of the pharmacokinetic parameters of paroxetine of treatment B (paroxetine) compared to treatment C (TMC114/RTV+ Paroxetine).

Parameter	n	LS means		LS means ratio, %	90% CI[a]	p-value		
		Treatment B (reference)	Treatment C (test)			Treatment	Period	Sequence
C_{0h}, ng/mL	16	9.399	5.989	63.71	56.5 - 71.9	0.0001	-	-
C_{min}, ng/mL	16	8.441	5.335	63.20	55.1 - 72.5	0.0001	-	-
C_{max}, ng/mL	16	21.08	13.60	64.49	58.8 - 70.7	0.0001	-	-
AUC_{24h}, ng.h/mL	16	358.7	217.6	60.68	55.5 - 66.3	0.0001	-	-
Parameter	**n**	**Median**		**Treatment difference median**	**90% CI**	**p-value**		
		Treatment B (reference)	Treatment C (test)			Treatment	Period	Sequence
t_{max}, h	16	6.0	6.0	0.0	-1.5 ; +0.5	0.7028	0.5127	0.2862

[a] 90% confidence intervals.
- excluded from final model

7. Safety Assessments

No death or SAE's were reported in this trial. Two subjects, one in each panel, discontinued the trial due to increased blood pressure, reported during the washout period after treatment with paroxetine or TMC114/RTV/SER. In addition, three subjects in panel 2 discontinued due to laboratory-related AEs reported during treatment with TMC114/RTV/SER (2 subjects) or sertraline (1 subject). (See details in Medical Officer's review).

8. Conclusion

- The primary pharmacokinetic parameters of TMC114 were not significantly affected in the presence of sertraline or paroxetine.
- Approximately 50 and 40 % decrease in exposure for sertraline and paroxetine respectively, was observed when co-administered with TMC114.
- Co-administration of paroxetine or sertraline was generally safe and well tolerated.
- Based on the results of this trial, co-administration of sertraline or paroxetine with TMC114/RTV is acceptable. Previous studies have failed to show a correlation between plasma concentration of SSRIs and antidepressant response. Therefore, the recommended approach is a careful dose titration of SSRI based on clinical assessment of the response.

Labeling Recommendation

If sertraline or paroxetine is coadministered with PREZISTA/rtv, the recommended approach is a careful dose titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with PREZISTA/rtv should be monitored for antidepressant response.

1. Title

The effect of ranitidine and of omeprazole on the pharmacokinetics of TMC114, co-administered with a low dose ritonavir, in healthy subjects **(TMC114-C122).**

2. Objectives

Primary:

- To determine the effect of ranitidine on the steady-state pharmacokinetics of TMC114, in combination with low-dose RTV.
- To determine the effect of omeprazole on the steady-state pharmacokinetics of TMC114, in combination with low-dose RTV.

3. Study Design

Phase I, open-label, randomized, three-way crossover trial in healthy subjects to investigate the effect of ranitidine and of omeprazole on the pharmacokinetics of TMC114, co-administered with a low dose (100 mg) of ritonavir (RTV), after repeated dosing. The study population consisted of 18 healthy subjects randomized to the following three treatment groups.

Treatment A: 400 mg TMC114/100 mg RTV, b.i.d. on Day 1-4, q.d. on Day 5.

Treatment B: 400 mg TMC114/100 mg RTV, b.i.d. on Day 1-4, q.d. on Day 5 + ranitidine 150 mg b.i.d. on Day 1-4, q.d. on Day 5.

Treatment C: 400 mg TMC114/100 mg RTV, b.i.d. on Day 1-4, q.d. on Day 5 + omeprazole 20 mg q.d. on Day 1-5.

Within each treatment (A, B, or C), there were two randomization sequences. The randomization sequences for treatment A were ABC, ACB; for treatment B were BAC, BCA, and for treatment C were CAB, CBA. All the treatments were administered for 4 days with an additional morning dose on Day 5. The subsequent sessions were separated by a washout period of at least 7 days. TMC/RTV was administered in the fed state and omeprazole and ranitidine were administered in the fasted state. Subsequent sessions within a panel were separated with a washout period of at least 7 days.

3.1 Discussion of Trial Design, Including Choice of Control Group.

- Ranitidine tablet (150 mg of ranitidine as ranitidine hydrocholoride, Zantac®) and omeprazole (containing 20 mg of omeprazole, Prilosec®) as delayed release capsule were used in this trial. Ranitidine was administered at a dose regimen of 150 mg b.i.d. within 15 minutes before breakfast and dinner (treatment B) and omeprazole was administered at 20 mg q.d. within 15 minutes before breakfast (treatment C). These are recommended oral dose regimens for ranitidine and

omeprazole in patients. TMC114/RTV had to be taken within 15 minutes after completing the breakfast or dinner.

- Ranitidine, omeprazole, and TMC114, co-administered with a low dose ritonavir, were administered for 5 days to allow plasma drug concentrations to reach steady state.
- The objective of this trial was to investigate the effect of increasing intragastric pH on the pharmacokinetics of TMC114/RTV. Therefore, this trial was conducted as a 1-way design and pharmacokinetics of ranitidine and omeprazole was not determined.
- A washout period of at least 7 days between subsequent sessions was considered to be sufficient to avoid carry-over from one session to the next, considering terminal elimination half-lives of about 3, 1, 4, and 16 hours for ranitidine, omeprazole, RTV, and TMC114 respectively.

4. Drugs Used in the Trial

Table 1 shows the drugs used in the trial.

Table 1: Description of Drugs Used in the Trial

	TMC 114	RTV	Ranitidine	Omeprazole
Dosage Form	Tablet (F001)	Capsule	Tablet	Capsule
Strength	400 mg	100 mg	150 mg	20 mg
Batch Number	4322PD1098	097772E21	3ZP0701	M7902
Expiry Date	April 2005	Sep 2005	Jan 2005	Dec 2004

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

For pharmacokinetic assessments, plasma samples were collected at pre-dose (within two hours before TMC114/RTV intake) on day 1, immediately before TMC114/RTV intake on days 3 and 4, and pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, and 12 hrs post dose on day 5. The plasma concentrations of TMC114 and RTV were determined simultaneously using a validated LS-MS/MS method.

Pharmacokinetic Assessments

Pharmacokinetic (non compartmental) and statistical analysis was performed using Winnonlin [redacted] to compute the standard pharmacokinetic parameters. Descriptive statistics were calculated for the plasma concentrations of TMC114 and RTV at each time point and for the derived pharmacokinetic parameters. The primary pharmacokinetic parameters were C_{0h}, C_{min}, C_{max}, and AUC_{12h}. The least square means of the primary parameters for each treatment group were estimated with a

linear mixed effects model, controlling for treatment, sequence, and period as fixed effects and subject as random effect.

6. Results

6.1 Subject Disposition

18 subjects were randomized into three treatment groups. 16 subjects were administered all the three treatments (1 subject discontinued after treatment C in session 1 due to an adverse event and 1 subject was randomized but did not receive any treatment).

Table 2: Demographics in Study TMC114-C122

	All subjects N = 17
Age, yrs Median (range)	26 (19-53)
Height, cm Median (range)	169 (150-183)
Weight, kg Median (range)	69 (46-101)
Sex, n (%) Female Male	9 (53 %) 8 (47 %)

6.2 Pharmacokinetic Analysis

TMC 114

Fig 1 shows the mean plasma concentration-time curves of TMC 114 on Day 5, after oral administration of TMC114/RTV (treatment A), TMC114/RTV/Ranitidine (treatment B) and TMC114/RTV/Omeprazole (Treatment C).

Fig 1: Mean plasma concentration-time curves of TMC 114 on Day 5, after oral administration of TMC114/RTV (treatment A), TMC114/RTV/Ranitidine (treatment B) and TMC114/RTV/Omeprazole (Treatment C).

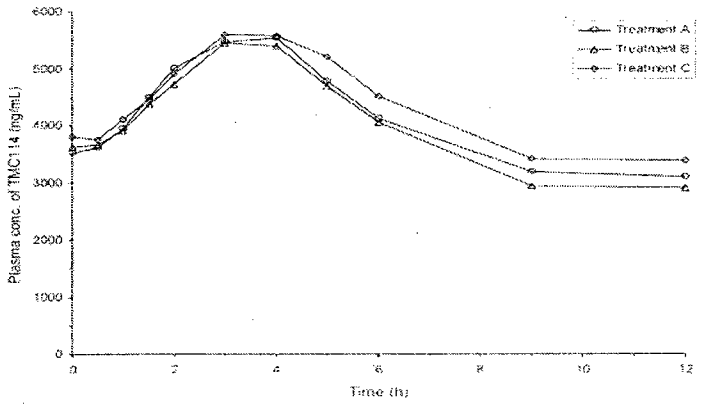


Table 3 shows the pharmacokinetic parameters of TMC114 obtained after oral administration of TMC114/RTV (Treatment A), TMC114/RTV/Ranitidine (Treatment B) and TMC/RTV/Omeprazole (Treatment C).

Table 3: Pharmacokinetic results of TMC 114 after oral administration of TMC114/RTV (Treatment A), TMC114/RTV/Ranitidine (Treatment B) And TMC/RTV/Omeprazole (Treatment C).

Pharmacokinetics of TMC 114 (mean ± SD (t_{max}: median (range))	Treatment A: TMC114/RTV 400/100 mg b.i.d.	Treatment B: TMC114/RTV 400/100 mg b.i.d. and ranitidine 150 mg b.i.d.	Treatment C: TMC114/RTV 400/100 mg b.i.d. and omeprazole 20 mg q.d.
n	16	16	15
Day 1			
C_{0h} ng/ml	0	0	0
Day 3			
C_{0h} ng/ml	3550 ± 1266	3594 ± 1575	5838 ± 1295
Day 4			
C_{0h} ng/ml	3331 ± 1348	3479 ± 1691	3749 ± 1696
Day 5			
C_{0h} ng/ml	3624 ± 1388	3636 ± 1643	3812 ± 1600
C_{max} ng/ml	2894 ± 1172	2996 ± 1593	3121 ± 1416
C_{max} ng/ml	5834 ± 1415	5733 ± 1878	6099 ± 1844
t_{max} h	4.0 (1.5 - 4.0)	3.5 (3.0 - 5.0)	4.0 (2.0 - 5.0)
AUC_{12h} ng.h/ml	45805 ± 14352	47258 ± 16340	53505 ± 18930
C_{trough} ng/ml	4075 ± 1396	3938 ± 1562	4292 ± 1578
FL %	77.8 ± 10.7	80.8 ± 22.8	71.8 ± 23.4

0 = BQL = Not Quantifiable (< 10.0 ng/ml)

Plasma concentrations of TMC114 in predose samples (C_{0h}) of Day 1 of the different treatments were all below the LLOQ, indicating that a washout period between consecutive treatments was sufficient.

Table 4 and 5 show the statistical comparison of the pharmacokinetics of TMC114 between treatment A and treatments B and C.

Table 4: Summary of statistical analysis of the pharmacokinetic parameters of TMC114 of treatment B (TMC 114/RTV/Ranitidine) compared to treatment A (TMC 114/RTV).

Parameter	n	Least square means: Treatment A (reference)	Least square means: Treatment B (test)	Least square means ratio, %	90% CI [a]	p-value: Treatment	p-value: Period	p-value: Sequence
C_{0h}, ng/mL	16	3282	3321	101.2	91.6 - 112	0.8374	-	-
C_{12h}, ng/mL	16	2639	2486	94.20	89.6 - 99.1	0.0551	-	-
C_{max}, ng/mL	16	5674	5474	96.48	89.1 - 105	0.4446	-	-
AUC_{12h}, ng.h/mL	16	46940	44806	95.45	90.4 - 101	0.1553	-	-
		Median				p-value		
Parameter	n	Treatment A (reference)	Treatment B (test)	Treatment difference median	90% CI [a]	Treatment	Period	Sequence
T_{max}, h	16	4.0	3.5	0.00	(-0.50) - (0.50)	0.5980	0.5980	0.1727

[a] 90% confidence intervals
- : excluded from final model

Table 5: Summary of statistical analysis of the pharmacokinetic parameters of TMC114 of treatment C (TMC 114/RTV/Omeprazole) compared to treatment A (TMC 114/RTV).

Parameter	n	Least square means		Least square means ratio, %	90% CI [a]	p-value		
		Treatment A (reference)	Treatment C (test)			Treatment	Period	Sequence
C_{0h}, ng/mL	16	3233	3458	107.0	95.4 - 120	0.3197	-	0.0613
C_{min}, ng/mL	16	2657	2861	107.7	92.8 - 125	0.3981	-	0.0358
C_{max}, ng/mL	16	5674	5756	101.5	94.9 - 109	0.7121	-	-
AUC_{12h}, ng.h/mL	16	47288	49072	103.8	95.7 - 113	0.4360	-	0.0884
		Median				p-value		
Parameter	n	Treatment A (reference)	Treatment C (test)	Treatment difference median	90% CI [a]	Treatment	Period	Sequence
T_{max}, h	16	4.0	3.5	0.00	(-0.75) - (0.50)	0.5316	0.3771	0.0905

[a] 90% confidence intervals.
- : excluded from final model

No significant treatment effects on C_{0h}, C_{min}, C_{max}, and AUC_{12h} of TMC114 were observed when comparing values between treatment A (TMC114/RTV) and treatment B (TMC114/RTV/ranitidine) or treatment C ((TMC114/RTV/omeprazole).

RTV

Table 6 shows the pharmacokinetic parameters of RTV obtained after oral administration of TMC114/RTV (Treatment A), TMC114/RTV/Ranitidine (Treatment B), and TMC114/RTV/Omeprazole (Treatment C).

Table 6: Pharmacokinetic parameters of RTV obtained after oral administration of TMC114/RTV (Treatment A), TMC114/RTV/Ranitidine (Treatment B), and TMC114/RTV/Omeprazole (Treatment C).

Pharmacokinetics of RTV (mean±SD, t_{max}: median (range))	Treatment A: TMC114/RTV 400/100 mg b.i.d.	Treatment B: TMC114/RTV 400/100 mg b.i.d. and ranitidine 150 mg b.i.d.	Treatment C: TMC114/RTV 400/100 mg b.i.d. and omeprazole 20 mg q.d.
n	16	16	17
Day 1			
C_{0h}, ng/mL	0	0	0
Day 3			
C_{0h}, ng/mL	788 ± 300	785 ± 414	723 ± 264
Day 4			
C_{0h}, ng/mL	650 ± 256	725 ± 422	554 ± 239
Day 5			
C_{0h}, ng/mL	675 ± 288	760 ± 364	590 ± 277
C_{min}, ng/mL	437 ± 184	442 ± 209	351 ± 199
C_{max}, ng/mL	1906 ± 560	2395 ± 1040	2031 ± 987
t_{max}, h	4.0 (1.0 - 5.0)	4.0 (3.0 - 6.0)	4.0 (4.0 - 6.0)
AUC_{12h}, ng.h/mL	11670 ± 3039	12922 ± 4439	10945 ± 4009
C_{trough}, ng/mL	973 ± 253	1077 ± 370	932 ± 354
FI, %	152 ± 42.5	178 ± 64.4	182 ± 63.0

0 = NQ = Not Quantifiable (< 5.00 ng/mL)

No significant treatment effects on C_{0h}, C_{max} and AUC_{12h} of RTV were observed when comparing values between Treatment A (TMC114/RTV) and Treatment B (TMC114/RTV/ranitidine) or Treatment C (TMC114/RTV/omeprazole).
In the presence of omeprazole (Treatment C), C_{min} values of RTV were statistically significantly lower compared to TMC114/RTV given alone (Treatment A). Based on the ratio of the LSmeans, C_{min} decreased by 26% when TMC114/RTV was co-administered with omeprazole, however, in the presence of ranitidine (Treatment B), no statistically significant differences in C_{min} of RTV were observed compared to treatment with TMC114/RTV alone.

7. Safety Assessments

Fifteen subjects (88%) reported an AE during this trial. Apart from 2 grade 3 events in one subject during the follow-up period, all other 69 AEs were grade 1 or grade 2 in severity. Six grade 2 events were noted for 4 subjects (24%). No deaths or SAEs were reported in this trial. AEs leading to withdrawal were reported for 1 subject, i.e., maculopapular rash. This subject discontinued the trial on Day 3 of the washout period after Treatment C (Session I). (See details in Medical Officer's review).

8. Conclusion

- The systemic exposure to TMC114 and RTV was not significantly affected when ranitidine or omeprazole were added to treatment with TMC114/RTV.
- Based on the results of this trial, no dose adjustments are necessary when TMC114/ritonavir is combined with ranitidine or omeprazole.

Reviewers Note

Although the study evaluated the lower, over-the-counter, dose of omeprazole, there is no mechanistic reason to expect an interaction with higher doses of omeprazole.

Labeling Recommendation

PREZISTA/rtv can be coadministered with H2-receptor antagonists and proton pump inhibitors without any dose adjustments.

Phase IV Commitment

Since the plasma concentrations of omeprazole (a sensitive CYP2C19 substrate) were not measured, the sponsor has been asked to conduct a cocktail study to assess the inhibitory/induction potential of darunavir/rtv on CYP2C19.

1. Title

The pharmacokinetic interaction between TMC114, boosted with a low dose of ritonavir, and tenofovir in healthy volunteers **(TMC114-C124).**

2. Objectives

The objectives of this trial were:

- To determine the effect of steady-state concentrations of TMC114, boosted with a low dose of RTV, on the steady-state pharmacokinetics of TFV (provided as tenofovir disoproxil fumarate).
- To determine the effect of steady state concentrations of TFV on the steady state pharmacokinetics of TMC114, boosted with a low dose of RTV.
- To determine the effect of steady-state concentrations of TFV on the steady-state pharmacokinetics of RTV, when RTV is administered at a low dose to boost TMC114 exposure.
- To determine the effect of steady-state concentrations of TMC114, boosted with a low dose of RTV, on the percentage of unchanged TFV excreted in the urine.
- To determine the effect of steady-state concentrations of TFV on the percentage of unchanged TMC114 excreted in urine during boosting with low dose of RTV.

3. Study Design

Open label, one-sequence, cross-over trial in which 13 subjects were randomized into two groups. In session 1, both groups received 300 mg TMC114/100 mg ritonavir b.i.d. for 6 days, with an additional morning dose on day 7, followed by a wash-out period of at least 6 days. In session 2, both groups received 300 mg tenofovir disoproxil fumarate (prodrug of tenofovir) q.d. for 14 days. In addition to tenofovir, group 1 received 300 mg TMC114/RTV mg ritonavir b.i.d. from day 8 until day 14 and group 2 received 300 mg TMC114/100 mg ritonavir b.i.d. from day 1 until day 7. All the medications were administered with food. On Day 7 of session 1 and at day 7 and 14 of session 2, TMC114/RTV and/or TDF was taken within 15 minutes after completing a standard breakfast.

The complete pharmacokinetic profiles of TMC114 and RTV were determined on Day 7 of session 1 and on Day 14 of session 2 for group 1 and on day 7 of session 2 for group 2. Similarly, complete pharmacokinetic profiles of TFV were determined on Day 7 and 14 of session 2 for both the groups.

4. Drugs Used in the Trial

Table 1 shows the drugs used in the trial.

Table 1: Description of Drugs Used in the Trial

	TMC114	RTV	TDF (Viread®)
Dosage Form	[redacted] (TF 019)	Capsule	Tablet
Strength	20 mg/mL	100 mg	300 mg
Batch Number	02E22	85387VA	J148B1
Expiry Date	11/22/2002	11/30/2003	12/31/2003

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Plasma samples for pharmacokinetic analysis were collected in all the sessions. In session 1, plasma samples (5 mL) were collected at pre-dose (immediately before drug intake) on Days 4 and 6, and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, and 12 hours on Day 7. In session 2, for group 1, pre-dose plasma samples were collected on Days 4, 6, 7, 8, 11, 13, and 14 and plasma samples for completed pharmacokinetic profile were collected on Day 7 and Day 14 at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 (for determination of TDF only) hours. In session 2, for group 2, pre-dose plasma samples were collected on Days 4, 6, 7, 8 (for TDF only), 11, 13, and 14 and plasma samples for completed pharmacokinetic profile were collected on Day 7 and Day 14 at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 hours.

On Day 7 of session 1, the complete urinary output during the interval 0-12 hours after the morning intake on day 7 was collected. On day 7 and 14 of session 2 for both the groups, the complete urinary output during the intervals 0-12 hrs and 12-24 hrs after the morning intake on day 7 or 14 was collected.

The plasma concentrations of TMC114, RTV, and TFV and urinary concentrations of TMC114 and TFV were determined using validated LC-MS/MS methods. The lower limit of quantification (in plasma) was 10 ng/mL for TMC114, 5 ng/mL for RTV, and 20 ng/mL for TFV. The lower limit of quantification (in urine) was 20 ng/mL for TMC114 and 1 µg/mL for TFV. No beta-glucuronidase treatment was performed on the urine samples.

Pharmacokinetic Assessments

Non-parametric analysis were performed using Winnonlin Professional ™ [redacted] using a [redacted] with [redacted] To calculate the percentage of the dose excreted in the urine, the dose of tenofovir instead of tenofovir disoproxil fumarate administered was used by correcting for the molecular weight.

6. Results

6.1 Subject Disposition

13 subjects were randomized to group 1 (n = 7) and group 2 (n = 6) in session 1, however, only 12 subjects completed session 1 and session 2 (one subject withdrew his consent after the morning dose on day 2 in session 1).

Table 2: Demographics in Study TMC 114-C124

Parameter		Group 1 N = 7	Group 2 N = 6
Age, median (min-max), years		38.0 (30-48)	45.0 (20-52)
Weight, median (min-max), kg		80.2 (74-91)	74.6 (66-87)
Height, median (min-max), cm		171.0 (165-189)	178.5 (160-187)
BMI, median (min-max), kg/m²		26.1 (25-31)	25.0 (20-28)
Gender, n (%)	female	0	2 (33.3)
	male	7 (100.0)	4 (66.7)

6.2 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time profiles of TMC114 on day 7 of administration, administered as 300 mg TMC114/100 mg RTV b.i.d. in the absence and presence of steady state concentration of TFV, administered as 300 mg TDF q.d. (session 1 and session 2).

Fig 1: Mean plasma concentration-time profiles of TMC114 on day 7 of administration, administered as 300 mg TMC114/100 mg RTV b.i.d. in the absence and presence of steady state concentration of TFV, administered as 300 mg TDF q.d. (session 1 and session 2).

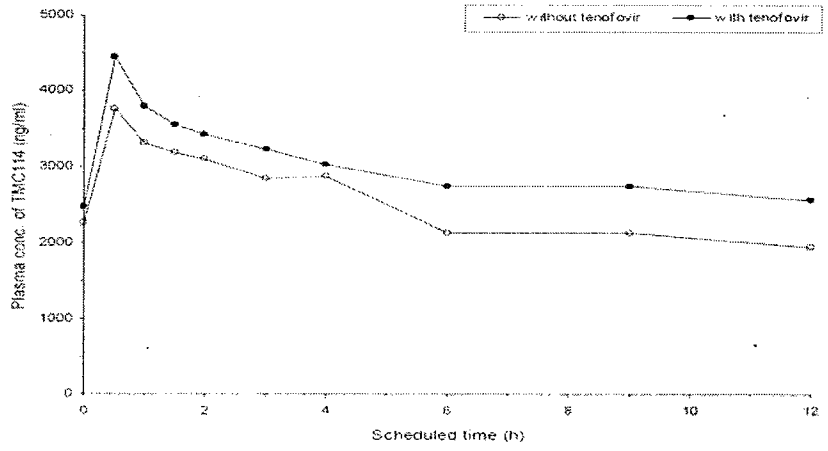


Table 3 shows the pharmacokinetic results of TMC114, administered as 300 mg TMC114/RTV b.i.d with or without co-administration of TDF, administered as 300 mg TDF q.d. (session 1 and session 2)

Table 3: Pharmacokinetic results of TMC114, administered as 300 mg TMC114/RTV b.i.d with or without co-administration of TDF, administered as 300 mg TDF q.d. (session 1 and session 2)

Pharmacokinetics of TMC114 (mean±SD; t_{max} median (range))	Session 1, day 7 without TDF	Session 2, day 7 or day 14 with TDF
n	12	12
t_{max}, h	0.5 (0.5 - 4.0)	0.5 (0.5 - 0.5)
C_{12h}, ng/ml	2262 ± 998	2473 ± 991
C_{min}, ng/ml	1845 ± 842	2220 ± 1051
C_{max}, ng/ml	3971 ± 1585	4448 ± 1008
AUC_{12h}, ng.h/ml	29837 ± 10345	35755 ± 12582
C_{0h}, ng/ml	2486 ± 862	2980 ± 1049
F1, %	90.6 ± 31.5	81.9 ± 30.4

The mean plasma concentrations of TMC114 were comparable between days 4, 6, and 7 of session 1 and between days 4, 6, and 7 (for group 1) and days 11, 13, and 14 (for group 2) of session 2 indicating the achievement of steady state.

Table 4 shows the statistical evaluation of the pharmacokinetics of TMC114 administered as 300 mg TMC114/100 mg RTV b.i.d. with co-administration of 300 mg TDF q.d. (test) versus without co-administration of 300 mg TDF q.d. (reference).

Table 4: Statistical evaluation of the pharmacokinetics of TMC114 administered as 300 mg TMC114/100 mg RTV b.i.d. with co-administration of 300 mg TDF q.d. (test) versus without co-administration of 300 mg TDF q.d. (reference)

Parameter	n	Least square means		Least square means ratio, %	90% CI[1]	p-value
		Treatment (reference)	Treatment (test)			Treatment
C_{0h}, ng/ml	12	2083	2326	111.7	84.6 - 147	0.5019
C_{max}, ng/ml	12	1658	2049	123.6	90.4 - 169	0.2580
C_{min}, ng/ml	12	3759	4343	115.5	94.1 - 142	0.2408
AUC_{12h}, ng.h/ml	12	28146	34009	120.8	95.1 - 154	0.1886
Parameter	n	Median				p-value
		Treatment (reference)	Treatment (test)	Treatment difference median	90% CI[1]	Treatment
t_{max}, h	12	0.5	0.5	0.00	0.00 - 1.25	0.0927

[1] 90% confidence intervals

As compared to administration of TMC114/RTV alone, AUC_{12h}, C_{max}, t_{max}, C_{min}, and C_{0h} of TMC114 were not statistically significantly changed during co-administration of TDF.

RTV

Fig 2 shows the mean plasma concentration-time profiles of RTV on Day 7 of administration, administered as 300 mg TMC114/100 mg RTV b.i.d. in the absence or presence of steady-state concentration of TFV, administered as 300 mg TDF q.d. (session 1 and session 2).

Fig 2: Mean plasma concentration-time profiles of RTV on day 7 of administration, administered as 300 mg TMC114/100 mg RTV b.i.d. in the absence or presence of steady-state concentration of TFV, administered as 300 mg TDF q.d. (session 1 and session 2).

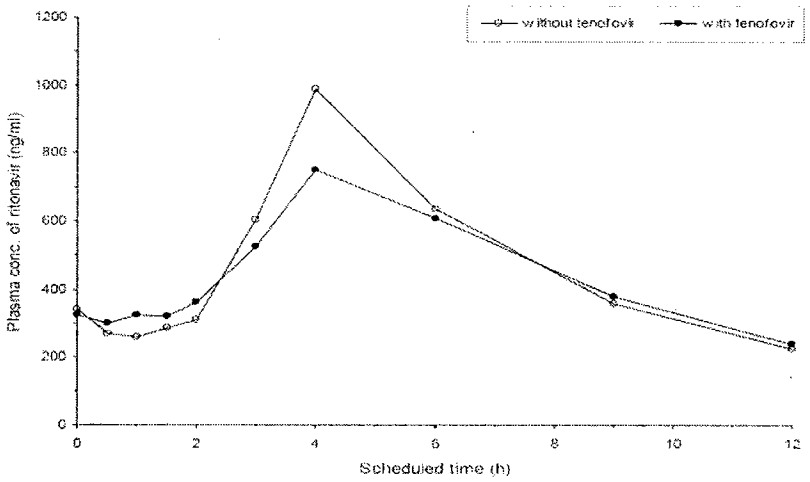


Table 5 shows the pharmacokinetic results of RTV, administered as 300 mg TMC114/100 mg RTV b.i.d. with or without co-administration of TDF, administered as 300 mg TDF q.d. (session 1 and session 2).

Table 5: Pharmacokinetic results of RTV, administered as 300 mg TMC114/100 mg RTV b.i.d. with or without co-administration of TDF, administered as 300 mg TDF q.d. (session 1 and session 2).

Pharmacokinetics of RTV (mean±SD t_{max} median (range))	Session 1: without TDF	Session 2: with TDF
n	12	12
t_{max}, h	4.0 (2.0 - 6.0)	4.0 (1.0 - 6.0)
C_{0h}, ng/ml	340 ± 181	323 ± 161
C_{min}, ng/ml	174 ± 84.6	169 ± 99.1
C_{max}, ng/ml	1030 ± 343	916 ± 356
AUC_{12h}, ng.h/ml	5811 ± 1960	5488 ± 1738
C_{av}, ng/ml	484 ± 163	457 ± 145
$FI_{\%}$	181 ± 42.2	163 ± 46.5

The mean plasma concentrations of RTV were comparable between days 4, 6, and 7 of session 1 and between days 4, 6, and 7 (for group 1) and days 11, 13, and 14 (for group 2) of session 2. In the presence of TDF, individual ratios for AUC_{12h} ranged from 70 %-133 % and the individual ratio for C_{max} ranged from 57 %-153 %.

TFV

Fig 3 shows the mean plasma concentration-time profiles of TFV on day 7 of administration, administered as 300 mg TDF q.d. in the absence or presence of 300 mg TMC114/100 mg RTV b.i.d.

Fig 3: Mean plasma concentration-time profiles of TFV on day 7 of administration, administered as 300 mg TDF q.d. in the absence or presence of 300 mg TMC114/100 mg RTV b.i.d.

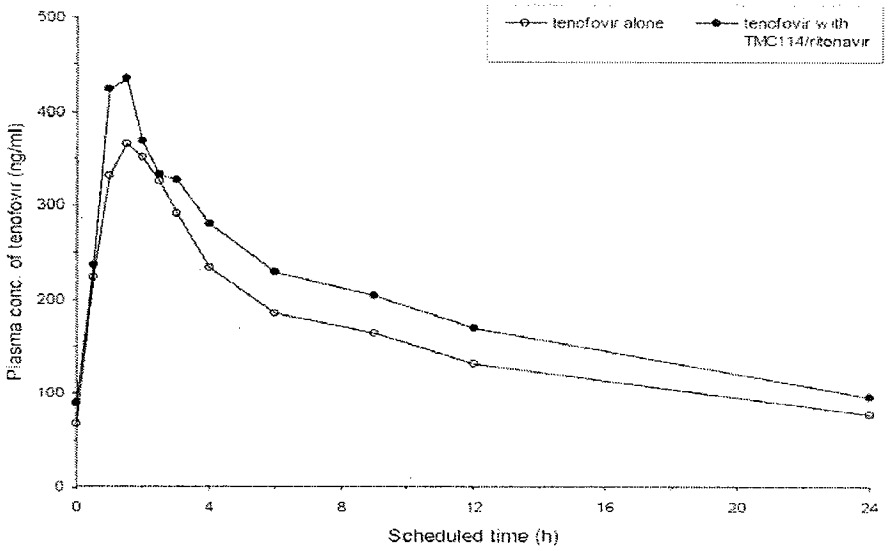


Table 6 shows the pharmacokinetic results of TFV; administered as 300 mg TDF q.d. with or without co-administration of 300 mg TMC114/100 mg RTV b.i.d. (session 2).

Table 6: Pharmacokinetic results of TFV, administered as 300 mg TDF q.d. with or without co-administration of 300 mg TMC114/100 mg RTV b.i.d. (session 2).

Pharmacokinetics of TDF (mean±SD, t_{max} median (range))	Session 2 TDF alone	Session 2 TDF + TMC114/RTV
N	12	12*
t_{max}, h	1.5 (0.5 - 2.5)	1.0 (1.0 - 4.0)
C_{24h}, ng/ml	67.4 ± 14.3	88.9 ± 17.0
C_{min}, ng/ml	65.6 ± 13.4	86.8 ± 15.7
C_{max}, ng/ml	423 ± 75.2	528 ± 106
AUC_{24h}, ng.h/ml	3789 ± 499	4633 ± 735
C_{12h}, ng/ml	158 ± 20.8	193 ± 30.6
FL, %	230 ± 54.1	230 ± 47.8

*For the parameters C_{24h} and C_{max}: n=11 for TFV with TMC114/RTV

The exposure to TFV generally increased after co-administration with TMC114/RTV. In the presence of TMC114/RTV, individual ratios for AUC24h ranged from 95 % to 151 %, with 10 out of the 12 subjects with a ratio higher than 100 %.

Table 7 shows the statistical evaluation of the pharmacokinetics of TFV administered as 300 mg TDF q.d. with co-administration of 300 mg TMC114/100 mg RTV b.i.d. (test) versus without co-administration of 300 mg TMC114/100 mg RTV b.i.d. (reference).

Table 7: Statistical evaluation of the pharmacokinetics of TFV administered as 300 mg TDF q.d. with co-administration of 300 mg TMC114/100 mg RTV b.i.d. (test) versus without co-administration of 300 mg TMC114/100 mg RTV b.i.d. (reference).

Parameter	n	Least square means		Least square means ratio, %	90% CI [1]	p-value
		Treatment (reference)	Treatment (test)			Treatment
C_{0h}, ng/ml	11	64.31	87.41	135.9	117 - 158	0.0025
C_{min}, ng/ml	11	62.61	85.53	136.6	119 - 157	0.0011
C_{max}, ng/ml	12	417.6	517.5	123.9	108 - 142	0.0146
AUC_{24h}, ng.h/ml	12	3760	4581	121.8	110 - 135	0.0026
Parameter	n	Median		Treatment difference median	90% CI [1]	p-value
		Treatment (reference)	Treatment (test)			Treatment
t_{max}, h	12	1.5	1.0	0.125	(-1.0 - 0.50)	0.7449

[1] 90% confidence intervals

Based on the ratio of LS means, statistically significant increases were observed for the pharmacokinetic parameters C_{0h}, C_{min}, C_{max}, and AUC_{24h} during co-administration of TMC114/RTV.

Urinary Excretion

TMC114

Table 8 shows the statistical evaluation of the urinary excretion of TMC114 administered as 300 mg TMC114/RTV b.i.d. with co-administration of 300 mg TDF q.d. (test) versus without co-administration of 300 mg TDF q.d. (reference).

Table 8: Statistical evaluation of the urinary excretion of TMC114 administered as 300 mg TMC114/RTV b.i.d. with co-administration of 300 mg TDF q.d. (test) versus without co-administration of 300 mg TDF q.d. (reference).

Parameter	n	Least square means		Least square means ratio, %	90% CI [1]	p-value
		Treatment (reference)	Treatment (test)			Treatment
$D_{urine,\ 0\text{-}12h}$, %	12	6.818	6.319	92.68	71.3 - 120	0.6229

[1] 90% confidence intervals

Based on the LS mean ratio, no statistically significant difference was observed for $D_{urine0\text{-}12h}$ between the two treatments.

TFV

Table 9 shows the statistical evaluation of the urinary excretion of TFV administered as TDF q.d. with co-administration of 300 mg TMC114/100 mg RTV b.i.d. (test) versus without co-administration of 300 mg TMC114/100 mg RTV b.i.d. (reference).

Table 9: Statistical evaluation of the urinary excretion of TFV administered as TDF q.d. with co-administration of 300 mg TMC114/100 mg RTV b.i.d. (test) versus without co-administration of 300 mg TMC114/100 mg RTV b.i.d. (reference).

Parameter	n	Least square means		Least square means ratio, %	90% CI [1]	p-value
		Treatment (reference)	Treatment (test)			Treatment
$D_{urine,\ 0\text{-}12h,\ }$ %	12	6.818	6.319	92.68	71.3 - 120	0.6229

[1] 90% confidence intervals

Based on the LS mean ratio, no statistically significant difference was observed for $D_{urine0\text{-}12h}$ between the two treatments.

7. Safety Assessments

The administration of 300 mg TMC114 and 100 mg RTV in healthy subjects with or without co-administration of TDF appeared to be well tolerated. There were no deaths or SAEs reported in the study. The most common reported AEs during the trial were gastrointestinal (diarrhea, flatulence, and loose stools) and headache. No subject discontinued the trial due to AEs (See details in Medical Officer's review).

8. Conclusion

- Co-administration of TMC114/RTV and TFV for 7 days resulted in an increase in plasma concentrations of TFV (C_{max}, AUC_{24h}, C_{0h}, C_{min} were increased by 24 %, 22 %, 36 %, and 37 % respectively). This interaction is similar as observed with lopinavir/RTV (32 % increase in AUC of tenofovir in the presence of lopinavir/ritonavir) for which, no dose adjustment is recommended.
- Co-administration of TDF for 7 days with TMC114/RTV resulted in an increase in TMC114 concentrations, however, these increases were not considered clinically significant.
- The urinary excretion of unchanged TMC114 and unchanged TFV was approximately 7 % and 36 % respectively, of the administered dose during one dosing interval. Co-administration did not change the urinary excretion of these compounds.

Labeling Recommendation

PREZISTA/rtv and tenofovir disoproxil fumarate can be co-administered without any dose adjustments.

1. Title

The pharmacokinetic interaction of various combinations of lopinavir, TMC114, and ritonavir in healthy volunteers **(TMC114-C125)**.

2. Objectives

The objectives of this trial were to determine:

- The effect of steady-state concentrations of TMC114, alone or with a low dose of RTV, on the steady-state pharmacokinetics of LPV, given as Kaletra® (LPV/RTV).
- The effect of steady state concentrations of Kaletra® (LPV/RTV) on the steady-state pharmacokinetics of TMC114, alone or with a low dose of RTV.
- Whether in the presence of Kaletra® (containing 100 mg ritonavir) an additional dose of RTV (100 mg) has an effect on the pharmacokinetics of TMC114.
- The difference in effect of 100 mg RTV b.i.d. (RTV was administered as Kaletra®) and 200 mg b.i.d. (RTV was administered as Kaletra® (100 mg) and an additional dose of RTV) on the steady-state pharmacokinetics of LPV in the presence of TMC114.

3. Study Design

The study population consisted of 16 healthy volunteers. The trial was divided into four sessions, separated by a washout period of at least 12 days, in which treatment A, B, C, and D were administered for 6 days b.i.d. with a single dose on day 7.

Treatment A: Kaletra® (400 mg LPV/100 mg RTV).

Treatment B: 300 mg TMC114/100 mg RTV

Treatment C: 300 mg TMC114/100 mg RTV and Kaletra®.

Treatment D: 300 mg TMC114 and Kaletra®.

All the treatments were administered under fed conditions. Subsequent sessions were separated by a washout period of 12 days. In every session, full pharmacokinetic profiles were determined for each compound on day 7 up to 12 hours after the last intake of study medication on that day.

4. Drugs Used in the Trial

Table 1 shows the drugs used in the trial.

Table 1: Dose Regimens Administered During Study TMC114-C125.

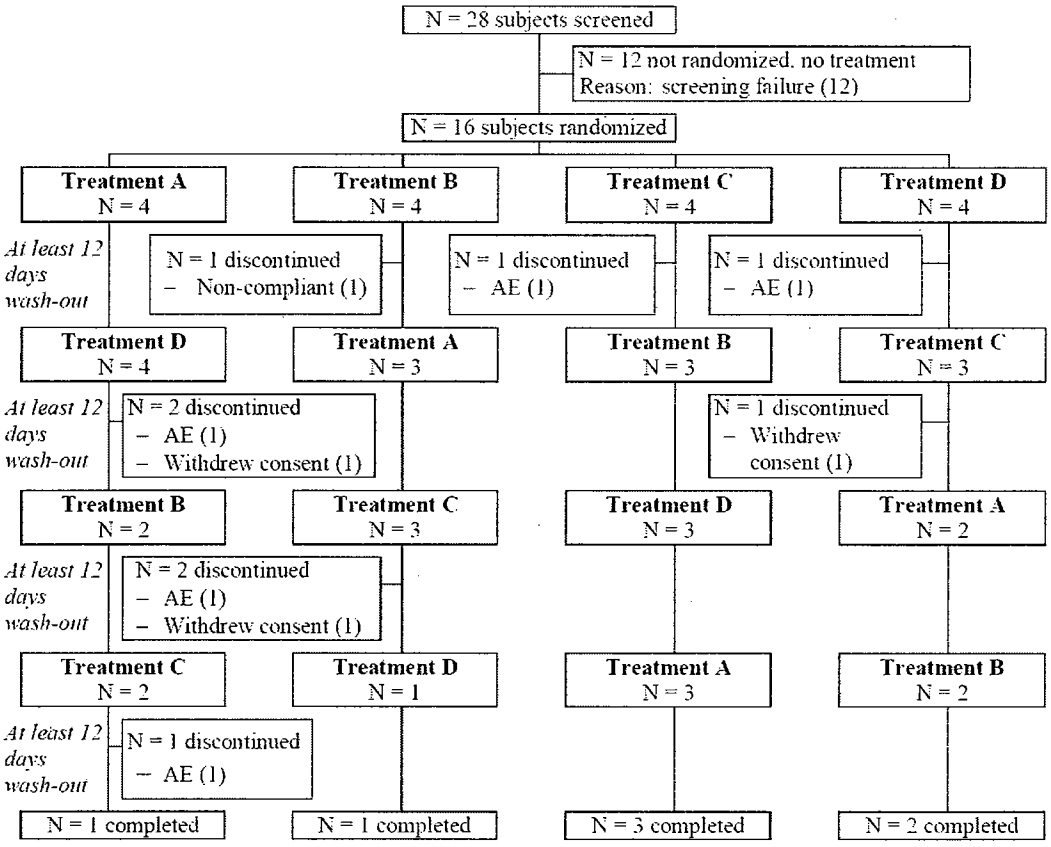
Treatment	Dose (number of subjects)	Volume
A	**Kaletra® (LPV/RTV):** 400 mg/100 mg b.i.d. on Day 1-6 400 mg/100 mg on Day 7 (n=16)	3 capsules of LPV/RTV (Kaletra®) per intake
B	**TMC114/RTV:** 300 mg/100 mg b.i.d. on Day 1-6 300 mg/100 mg on Day 7 (n=16)	15 ml TMC114 ethanolate (eq.20 mg/ml) and 1 capsule of RTV (Norvir®) per intake
C	**Kaletra® (LPV/RTV):** 400 mg/100 mg b.i.d. on Day 1-6 400 mg/100 mg on Day 7 **TMC114/RTV:** 300 mg/100 mg b.i.d. on Day 1-6 300 mg/100 mg on Day 7 (n=16)	3 capsules of LPV/RTV (Kaletra®) per intake 15 ml TMC114 ethanolate (eq.20 mg/ml) and 1 capsule of RTV (Norvir®) per intake
D	**Kaletra® (LPV/RTV):** 400 mg/100 mg b.i.d. on Day 1-6 400 mg/100 mg on Day 7 **TMC114:** 300 mg b.i.d. on Day 1-6 300 mg on Day 7 (n=16)	3 capsules of LPV/RTV (Kaletra®) per intake 15 ml TMC114 ethanolate (eq.20 mg/ml) per intake

5. Results

5.1 Subject Disposition

Fig 1 shows the schematic of the subject disposition in trial TMC114-C125.

Fig 1: Subject Disposition in Trial TMC114-C125.



6. Conclusion

The sponsor indicated that due to discontinuation of 9 out of 16 subjects, the results of the trial remain explorative and no final conclusions regarding the pharmacokinetic interaction can be drawn. **Based on the results of this trial, it is currently recommended not to combine Kaletra® and TMC114 (with or without additional RTV).**

1. Title

The effect of repeated dosing of TMC114, coadministered with a low dose of ritonavir (RTV), on sildenefil pharmacokinetics in healthy male subjects **(TMC114-C128).**

2. Objectives

The objectives of this trial were:

- To determine the effect of steady-state concentrations of TMC114, co-administered with a low dose of RTV, on the pharmacokinetics of a single dose of sildenafil and its active metabolite N-desmethyl sildenafil.
- To determine the short-term safety and tolerability of co-administered TMC114, low-dose RTV, and sildenafil.

3. Study Design

Phase I, open-label, randomized, 2-way cross-over trial to investigate the effect of repeated dosing of TMC114 combined with low-dose RTV on the pharmacokinetics of sildenafil and its active metabolite N-desmethyl sildenafil. The study population consisted of 16 healthy male subjects. In 2 sessions, each subject received treatments A and B. In treatment A, a single dose of 100 mg sildenafil was administered. In treatment B, the subjects received TMC114/RTV 400/100 mg b.i.d. for 8 days, while on Day 7, a 25 mg single dose of sildenafil was administered. All the treatments were given under fed conditions. Subsequent sessions were separated by a washout period of at least 7 days. Full pharmacokinetic profiles of sildenafil and N-desmethyl sildenafil were determined up to 48 hours after sildenafil intake on Day 1 of treatment A, and on Day 7 of treatment B. Full pharmacokinetic profiles of TMC114 and RTV were determined up to 12 hours after the morning dose of Day 7 of treatment B. The safety and tolerability was assessed continuously.

3.1 Discussion of Trial Design, Including Choice of Control Group.

- Sildenafil has not been found to affect the steady-state pharmacokinetics of the PIs SQV and RTV, therefore, it was not expected that sildenafil would affect TMC114/RTV pharmacokinetics.
- Sildenafil alone was administered as a 100 mg single dose. Due to the expected drug interaction, a 25 mg single dose of sildenafil was administered in combination with TMC114/RTV. These are consistent with the currently recommended doses for sildenafil alone and for sildenafil in combination with ritonavir boosted PIs.

4. Drugs Used in the Trial

Table 1 shows the drugs used in the trial.

Table 1: Description of Drugs Used in the Trial

	TMC114	RTV	Sildenafil*
Dosage Form	Tablet (F001)	Capsule	Tablet
Strength	400 mg	100 mg	100 mg **
Batch Number	PD 1098	R12478	R12479
Expiry Date	April, 2005	September, 2005	July 2005

*: the batch number and the expiry date are identical for the 25 and 100 mg tablet

**: 25 mg for Treatment B

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Plasma samples for full pharmacokinetic profiles of sildenafil and N-desmethyl sildenafil (Day 1 of treatment A, Day 7 of treatment B), and TMC114 and RTV (Day 7 of treatment B) were collected as follows: for treatment A, the samples were collected at pre-dose (within 2 hours before drug intake) and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, and 48 hrs. For treatment B, the samples were collected at pre-dose on day 1, immediately before drug intake on days 5, 6, 7, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12 (immediately before drug intake), 16, 24, and 48 hrs. The sample at 16, 24, and 48 hrs was collected only for the determination of sildenafil.

The plasma concentrations of TMC114, RTV, and sildenafil were determined using validated LC-MS/MS methods. The lower limit of quantification was 10 ng/mL for TMC114, 5 ng/mL for RTV, and 2 ng/mL for sildenafil and N-desmethyl sildenafil.

Pharmacokinetic Assessments

Non-parametric analyses were performed using Winnonlin Professional ™ [redacted] using a [redacted]

6. Results

6.1 Subject Disposition

13 subjects were randomized to group 1 (n = 7) and group 2 (n = 6) in session 1; however, only 12 subjects completed session 1 and session 2 (one subject withdrew his consent after the morning dose on day 2 in session 1).

Table 2: Demographics in Study TMC 114-C128

Parameter	Treatment Sequence A - B	Treatment Sequence B - A	All Subjects
Age, years	26.5	27.0	27.0
median (range)	(18 – 54)	(22 – 35)	(18 – 54)
Height, cm	178.5	168.5	177.0
median (range)	(173 – 188)	(166 – 180)	(166 – 188)
Weight, kg	79.0	72.0	77.0
median (range)	(61 – 97)	(55 – 85)	(55 – 97)
BMI, kg/m²	25.2	24.4	25.0
median (range)	(20 – 27)	(20 – 28)	(20 – 28)
Sex, n (%)			
male	8 (100.0)	8 (100.0)	8 (100.0)
Ethnic origin, n (%)			
black	0	2 (25.0)	2 (12.5)
Caucasian/white	8 (100.0)	4 (50.0)	12 (75.0)
Hispanic	0	1 (12.5)	1 (6.3)
Oriental Asian	0	1 (12.5)	1 (6.3)
Type of smoker, n (%)			
nonsmoker	8 (100.0)	8 (100.0)	8 (100.0)

6.2 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time curve of TMC114 on day 7 after oral administration of TMC114/RTV b.i.d. for 8 days, co-administered with a single dose of sildenafil on Day 7 (treatment B).

Fig 1: Mean plasma concentration-time profiles of TMC114 on day 7 after oral administration of TMC114/RTV b.i.d. for 8 days, co-administered with a single dose of sildenafil on Day 7 (treatment B).

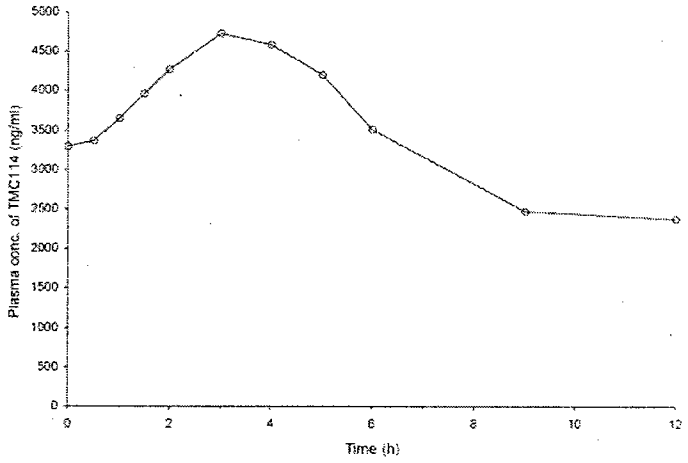


Table 3 shows the pharmacokinetic results of TMC114 after oral administration of TMC114/RTV b.i.d. for 8 days co-administered with a single dose of sildenafil on Day 7.

Table 3: Pharmacokinetic results of TMC114 after oral administration of TMC114/RTV b.i.d. for 8 days co-administered with a single dose of sildenafil on Day 7.

Pharmacokinetic Parameter mean ± SD (t_{max}: median [range])	TMC114
n	16
Day 5	
C_{08}, ng/mL	3431 ± 1316
Day 6	
C_{08}, ng/mL	3435 ± 1455
Day 7	
t_{max}, h	3.0 (1.0 - 5.0)
C_{08}, ng/mL	3291 ± 1358
C_{min}, ng/mL	2271 ± 1062
C_{max}, ng/mL	5053 ± 1255
AUC_{12}, ng.h/mL	41033 ± 13944
$C_{ss,av}$, ng/mL	3419 ± 1162
FL, %	90.0 ± 35.1

RTV

Fig 2 shows the mean plasma concentration-time curve of RTV on day 7 after oral administration of TMC114/RTV b.i.d. for 8 days, co-administered with a single dose of sildenafil on Day 7 (treatment B).

Fig 2: Mean plasma concentration-time profiles of RTV on day 7 after oral administration of TMC114/RTV b.i.d. for 8 days, co-administered with a single dose of sildenafil on Day 7 (treatment B).

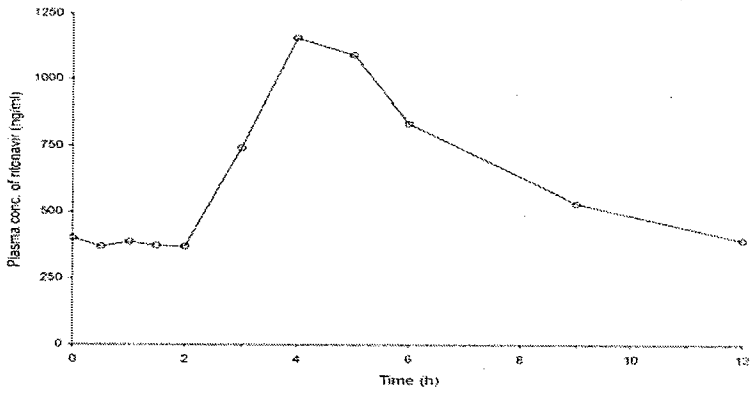


Table 4 shows the pharmacokinetic results of RTV after oral administration of TMC114/RTV b.i.d. for 8 days co-administered with a single dose of sildenafil on Day 7.

Table 4: Pharmacokinetic results of RTV after oral administration of TMC114/RTV b.i.d. for 8 days co-administered with a single dose of sildenafil on Day 7.

Pharmacokinetic Parameter mean ± SD (t_{max}: median [range])	RTV
n	16
Day 5	
C_{0h}, ng/mL	518 ± 233
Day 6	
C0h, ng/mL	479 ± 181
Day 7	
t_{max}, h	5.0 (1.0 - 5.0)
C_{0h}, ng/mL	400 ± 176
C_{12h}, ng/mL	287 ± 127
C_{max}, ng/mL	1386 ± 883
AUC_{12h}, ng.h/mL	7789 ± 3188
$C_{ss,av}$, ng/mL	649 ± 266
FI, %	160 ± 56.7

Sildenafil

Fig 3 shows the mean plasma concentration-time curves of sildenafil and N-desmethyl sildenafil after a single dose of 100 mg sildenafil alone (treatment A) and after a single dose of 25 mg sildenafil in the presence of TMC114/RTV (treatment B).

Fig 3: Mean plasma concentration-time curves of sildenafil and N-desmethyl sildenafil after a single dose of 100 mg sildenafil alone (treatment A) and after a single dose of 25 mg sildenafil in the presence of TMC114/RTV (treatment B).

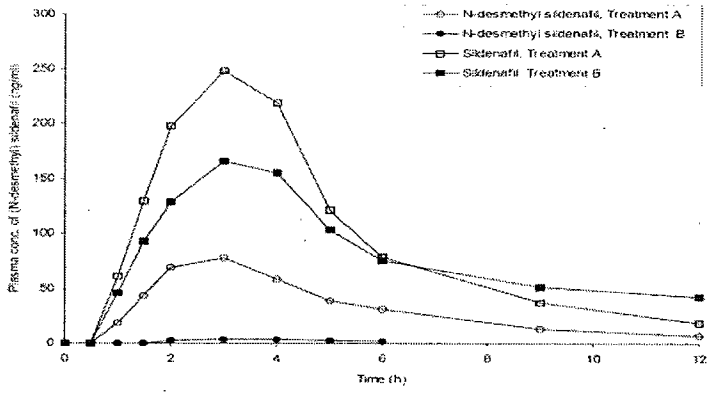


Table 5 shows the pharmacokinetic results for sildenafil after a single dose of 100 mg sildenafil alone (treatment A) and after a single dose of 25 mg sildenafil in the presence of TMC114/RTV (treatment B).

Table 5: Pharmacokinetic results for sildenafil after a single dose of 100 mg sildenafil alone (treatment A) and after a single dose of 25 mg sildenafil in the presence of TMC114/RTV (treatment B).

Pharmacokinetic Parameter Mean ± SD (t_{max}: median [range])	Sildenafil (Treatment A)	Sildenafil (Treatment B)
n	16[a]	16[b]
t_{max}, h	3.0 (1.0 - 4.0)	3.0 (1.5 - 4.0)
C_{max}, ng/mL	283 ± 84.0	181 ± 90.5
AUC_{last}, ng.h/mL	1197 ± 377	1173 ± 481
AUC_{∞}, ng.h/mL	1287 ± 378	1106 ± 274
$t_{1/2term}$, h	3.10 ± 0.759	4.36 ± 0.955

a n = 13 for AUC_{∞} and $t_{1/2term}$
b n = 15 for AUC_{∞} and $t_{1/2term}$

Table 6 shows the summary of the statistical analysis of the pharmacokinetic parameters of sildenafil after a single dose of 100 mg sildenafil alone (treatment A) and after a single dose of 25 mg sildenafil in the presence of TMC114/RTV (treatment B).

Table 6: Summary of the statistical analysis of the pharmacokinetic parameters of sildenafil after a single dose of 100 mg sildenafil alone (treatment A) and after a single dose of 25 mg sildenafil in the presence of TMC114/RTV (treatment B).

		LS mean		LS mean ratio (%)	90% CI[a]	p-value		
Parameter	n	Treatment A (reference)	Treatment B (test)			Treatment	Period	Sequence
C_{max}, ng/mL	16	270.4	167.9	62.08	54.8 - 70.3	< 0.0001	0.0294	-
AUC_{last}, ng.h/mL	16	1142	1109	97.10	86.4 - 109	0.6645	0.0021	-
AUC_{∞}, ng.h/mL	12	1144	1131	98.91	84.0 - 116	0.9052	0.0236	-
		Median				p-value		
Parameter	n	Treatment A (reference)	Treatment B (test)	Treatment difference (median)	90% CI[a]	Treatment	Period	Sequence
t_{max}, h	16	3.0	3.0	-0.50	(-0.75) - (0.00)	0.1480	0.0770	0.2178

a 90% confidence intervals
- : excluded from final model

In the presence of TMC114/RTV, the C_{max} values of sildenafil (25 mg) were lower compared to when sildenafil (100 mg) was administered alone. **Despite the lower dose of 25 mg compared to 100 mg, the LS mean ratio was close to 100 % for both $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$.** After dose normalization, the C_{max} and AUC_{∞} of sildenafil, in the presence of TMC114/RTV, increased by approximately 150 % and 300 % respectively.

N-Desmethyl Sildenafil

Table 7 shows the pharmacokinetic results for N-desmethyl sildenafil after a single dose of 100 mg sildenafil alone (treatment A) and after a single dose of 25 mg sildenafil in the presence of TMC114/RTV (treatment B).

Table 7: Pharmacokinetic results for N-desmethyl sildenafil after a single dose of 100 mg sildenafil alone (treatment A) and after a single dose of 25 mg sildenafil in the presence of TMC114/RTV (treatment B).

Pharmacokinetic Parameter Mean ± SD (t_{max}: median [range])	N-Desmethyl Sildenafil (Treatment A)	N-Desmethyl Sildenafil (Treatment B)
n	16[a]	16
t_{max}, h	2.5 (1.0 - 4.0)	4.0 (2.0 - 16.0)
C_{max}, ng/mL	95.8 ± 49.0	4.32 ± 2.39
AUC_{last}, ng.h/mL	401 ± 195	31.7 ± 27.4
AUC_{∞}, ng.h/mL	447 ± 206	NA
$t_{1/2term}$, h	4.06 ± 1.11	NA

Table 8 shows the summary of the statistical analysis of the pharmacokinetic parameters of N-desmethyl sildenafil after a single dose of 100 mg sildenafil alone (treatment A) and after a single dose of 25 mg sildenafil in the presence of TMC114/RTV (treatment B).

Table 8: Summary of the statistical analysis of the pharmacokinetic parameters of N- desmethyl sildenafil after a single dose of 100 mg sildenafil alone (treatment A) and after a single dose of 25 mg sildenafil in the presence of TMC114/RTV (treatment B).

		LS mean		LS mean ratio (%)	90% CI[a]	p-value		
Parameter	n	Treatment A (reference)	Treatment B (test)			Treatment	Period	Sequence
C_{max}, ng/mL	16	85.67	3.916	4.570	3.87 - 5.40	0.0001	0.0067	-
AUC_{last}, ng.h/mL	16	364.6	19.77	5.421	3.50 - 8.40	0.0001	0.0463	-
		Median				p-value		
Parameter	n	Treatment A (reference)	Treatment B (test)	Treatment difference (median)	90% CI[a]	Treatment	Period	Sequence
t_{max}, h	16	2.5	4.0	-1.00	(-1.50) - (-0.50)	0.0019	0.4098	0.1165

a 90% confidence intervals
- : excluded from final model

7. Safety Assessments

Overall, 5 subjects (31.3 %) experienced at least one adverse event. The adverse event observed in more than one subject during the treatment periods were insomnia and dizziness. There were no relevant differences in the type or frequency of adverse events reported when subjects received sildenafil alone compared with when subjects received TMC114/RTV /sildenafil, or TMC114/RTV. No subject discontinued the trial due to AEs (See details in Medical Officer's review).

8. Conclusion

- Systemic exposure (AUC_{last} and $AUC_{0-\infty}$) to sildenafil was comparable for treatment with sildenafil alone (100 mg) and when co-administered (25 mg) with TMC114/RTV. Sildenafil is mainly metabolized by CYP3A4 and this pathway is inhibited by TMC114 and RTV, resulting in comparable exposure when a 4 times

lower dose of sildenafil is administered in the presence of TMC114/RTV. Therefore, 25 mg sildenafil over 48-hour duration can be used as a starting dose.

Reviewer's Note

The results of the study showed an approximately 4-fold increase in the concentrations of sildenafil, a sensitive CYP3A4 substrate. This suggests the inhibitory potential of TMC114/ritonavir towards CYP3A4.

Labeling Recommendation

Concomitant use of PDE-5 inhibitors with PREZISTA/rtv should be done with caution. If concomitant use of PREZISTA/rtv with sildenafil, vardenafil, or tadalafil is required, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours, is recommended.

1. Title

The pharmacokinetic interaction between ketoconazole and TMC114, with and without co-administration of a low dose of ritonavir, in healthy subjects **(TMC114-C129)**.

2. Objectives

The objectives of this trial were to determine:

- The effect of steady-state concentrations of ketoconazole on the steady-state pharmacokinetics of TMC114 (administered alone).
- The effect of steady-state concentrations of ketoconazole on the steady-state pharmacokinetics of TMC114, in combination with a low dose of ritonavir.
- The effect of steady-state concentrations of TMC114, in combination with a low dose of ritonavir, on the steady-state pharmacokinetics of ketoconazole.
- *In vivo* protein binding of TMC114, with and without co-administration of a low dose of ritonavir, in healthy subjects.

3. Study Design

Phase I, open-label, controlled, randomized, cross-over trial to investigate the pharmacokinetic interaction between repeated dosing of TMC114, with and without co-administration of a low-dose RTV, and ketoconazole. **TMC114 was formulated as an experimental tablet F002.** The study population consisted of 26 healthy subjects, divided into two panels of 8 (panel 1) and 18 (panel 2) subjects.

Panel 1

Panel 1 received 400 mg TMC114 b.i.d. (Treatment A) and 400 mg TMC114/200 mg ketoconazole b.i.d. (Treatment B) in 2 sessions.

Panel 2

Panel 2 received 400 mg TMC114/100 mg RTV b.i.d. (treatment C), 200 mg ketoconazole b.i.d. (treatment D) and 200 mg ketoconazole/400 mg TMC114/100 mg RTV b.i.d. (Treatment E) in 3 sessions.

All treatments were administered for 6 days b.i.d. with an additional single dose on day 7. The subsequent sessions in the panel were separated by a wash-out period of 7 days. In every session, full pharmacokinetic profiles were determined for each compound on day 7 up to 12 h after the intake of study medication for that day.

3.1 Discussion of Trial Design, Including Choice of Control Group.

- Ketoconazole and TMC114, whether or not co-administered with a low dose of RTV, were administered for 7 days to allow plasma drug concentrations to reach steady state. To ensure achievement of steady state on day 7, C_{0h} levels of TMC114, ketoconazole, and RTV were determined during treatment.

- A washout period of at least 7 days between subsequent sessions was considered sufficient to avoid carry over from one session to the next, considering the elimination half lives of about 8, 4, and 16 hours for ketoconazole, RTV, and TMC114, respectively.
- A secondary objective in this trial was the determination of the *in vivo* protein binding of TMC114, with or without co-administration of a low dose of RTV since the *in vivo* protein binding of TMC114 might be different with or without co-administration of RTV and might also differ between healthy volunteers and HIV-1 infected subjects.

4. Investigational Drugs

Table 1 shows the investigational drugs used in the trial.

Table 1: Description of Investigational Agents.

	TMC114	RTV	Ketoconazole (Nizoral©)
Dosage Form	Tablet (F002)	Capsule	Tablet
Strength	200 mg	100 mg	200 mg
Batch Number(s)	PD 1059/PD 1095/2	95118VA	OOK8/287 and OOK16/287
Expiry Date	04/2004 and 26/03/2005	18/10/2004	16/11/2005

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Plasma samples for full pharmacokinetic profiles in all the treatments were collected as follows: On day 1, 5, and 6, the samples were collected at pre-dose (within 2 hours before drug intake on day 1 and immediately before drug intake on days 5 and 6). On day 7, plasma samples were collected at pre-dose and at 1, 2, 3, 4, 5, 6, 9, and 12 hrs. For treatment A and C only, the plasma sample for protein binding was collected at 3 hours post-dose on day 7.

The plasma concentrations of TMC114, RTV, and ketoconazole were determined using validated LC-MS/MS chromatographic methods. The free TMC114 concentrations in plasma were determined using a validated centrifugal filtration method with a 10,000 [redacted] The lower limit of quantification was 10.0 ng/mL for (total) TMC114, 2 ng/mL for free TMC114, 5 ng/mL for RTV, and 20 ng/mL for ketoconazole.

Pharmacokinetic Assessments

Non-parametric analyses were performed using Winnonlin Professional ™ [redacted] using a [redacted]

The statistical analyses were performed comparing treatment B (test) versus A (reference) and comparing treatment E (test) vs. C (reference) for TMC114 and comparing treatment E (test) vs. treatment D (reference) for ketoconazole. The primary pharmacokinetic parameters were C_{0h}, C_{min}, C_{max}, and AUC_{0-12} on the logarithmic scale. The least square means of the primary parameters for each treatment were estimated with a linear mixed-effect model, controlling for treatment, sequence, and period as fixed effects, and subject as a random effect. A 90 % confidence interval was constructed about the difference between the LS means of the test and reference and the difference and the 90 % confidence limits were retransformed to the original scale.

6. Results

6.1 Subject Disposition and Demographics

26 subjects were randomized into the trial (8 subjects to panel 1 and 18 subjects to panel 2). 2 subjects discontinued in panel 1 and 1 subject discontinued in panel 2. In addition, 1 subjects in panel 2 withdrew consent. Therefore, 22 subjects completed all assessments.

Table 2 shows the demographics in the study

Table 2: Demographics in Study TMC 114-C129

Parameter		Panel 1 N=8	Panel 2 N=18	All subjets N=26
Age (years), median (range)		44.5 (27-49)	38.5 (29-55)	40.5 (27-55)
Height (cm), median (range)		173.5 (157-181)	176.5 (160-186)	176.0 (157-186)
Weight (kg), median (range)		71.5 (61-77)	78.0 (60-90)	74.0 (60-90)
BMI (kg/m^2), median (range)		24.4 (19-25)	24.8 (23-29)	24.5 (19-29)
Male/female, n(%)		6 (75)/2 (25)	13 (72.2)/5 (27.8)	19 (73.1)/7 (26.9)
Smoker	No, n (%)	5 (62.5)	14 (77.8)	19 (73.1)
	Yes (light), n (%)	3 (37.5)	4 (22.2)	7 (26.9)

6.2 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time curve of TMC114 on day 7 after oral administration of 400 mg TMC114 (treatment A), 400 mg TMC114/200 mg ketoconazole b.i.d. (treatment B), 400 mg TMC114/100 mg RTV b.i.d (treatment C) and 400 mg TMC114/100 mg RTV/200 mg ketoconazole b.i.d. (treatment E).

Fig 1: Mean plasma concentration-time curve of TMC114 on day 7 after oral administration of 400 mg TMC114 (treatment A), 400 mg TMC114/200 mg ketoconazole b.i.d. (treatment B), 400 mg TMC114/100 mg RTV b.i.d (treatment C) and 400 mg TMC114/100 mg RTV/200 mg ketoconazole b.i.d. (treatment E).

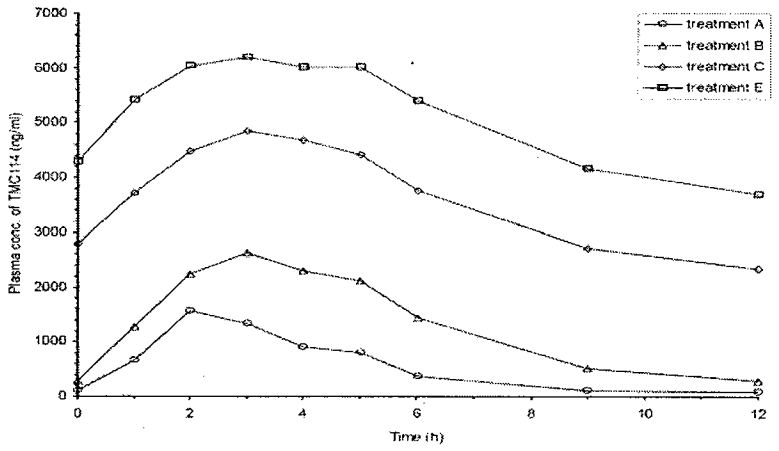


Table 3 shows the pharmacokinetic results of TMC114 on Days 5-7.

Table 3: Pharmacokinetic results of TMC114 on Days 5-7

Pharmacokinetics of TMC114 (mean±SD, t_{max} median (range))	Treatment A: TMC114 400 mg b.i.d.	Treatment B: TMC114 400 mg b.i.d. and ketoconazole 200 mg b.i.d.	Treatment C: TMC114/RTV 400/100 mg b.i.d.	Treatment E: TMC114/RTV 400/100 mg b.i.d. and ketoconazole 200 mg b.i.d.
n	7	6	14	17
Day 5				
C_{0h}, ng/ml	81.9 ± 27.7	369 ± 386	2585 ± 1048	4282 ± 1333
Day 6				
C_{0h}, ng/ml	88.5 ± 27.7	323 ± 176	2538 ± 1175	4498 ± 1048
Day 7				
C_{0h}, ng/ml	96.1 ± 29.3	281 ± 177	2801 ± 1532	4283 ± 1305
C_{max}, ng/ml	1808 ± 871	2788 ± 912	5209 ± 1625	6394 ± 1445
t_{max}, h	2.0 (2.0 - 5.0)	3.0 (2.0 - 4.0)	2.5 (1.0 - 5.0)	3.0 (0.0 - 6.0)
C_{min}, ng/ml	68.2 ± 26.8	235 ± 154	2209 ± 1143	3582 ± 966
AUC_{12h}, ng.h/ml	6478 ± 3341	15505 ± 7589	42707 ± 16234	60690 ± 14174
C_{av}, ng/ml	540 ± 278	1292 ± 632	3559 ± 1353	5058 ± 1183
FL %$_{a}$	329 ± 61.0	217 ± 56.9	89.2 ± 28.8	56.3 ± 15.4

Table 4 shows the summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment B (TMC114 and ketoconazole) compared to treatment A (TMC114 alone).

Table 4: Summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment B (TMC114 and ketoconazole) compared to treatment A (TMC114 alone).

Parameter	n	Least square means		Least square means ratio, %	90% CI[1]	p-value		
		Treatment A (reference)	Treatment B (test)			Treatment	Period	Sequence
C_{tau}, ng/ml	6	87.95	199.1	226.3	88.8 - 577	0.1388	-	0.0347
C_{min}, ng/ml	6	60.90	170.1	279.3	158 - 493	0.0149	-	-
C_{max}, ng/ml	6	1497	2659	177.6	128 - 247	0.0172	-	-
$AUC_{(tau)}$, ng.h/ml	6	5465	13925	254.8	180 - 361	0.0029	-	-
		Median				p-value		
Parameter	n	Treatment A (reference)	Treatment B (test)	Treatment difference median	90% CI[1]	Treatment	Period	Sequence
t_{max}, h	6	2.5	3.0	0.00	(-1.00) - (2.00)	0.6374	0.3458	0.1213

Table 5 shows the summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment E (TMC114/RTV/Ketoconazole) compared to treatment C (TMC114/RTV).

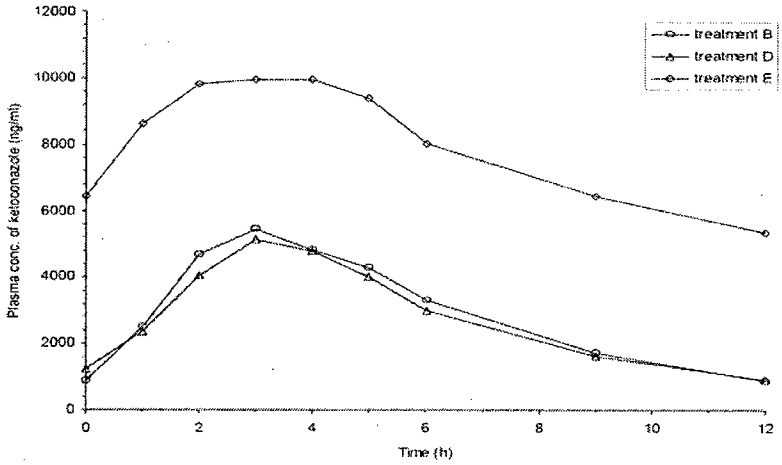
Table 5: Summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment E (TMC114/RTV/ketoconazole) compared to treatment C (TMC114/RTV).

Parameter	n	Least square means		Least square means ratio, %	90% CI[1]	p-value		
		Treatment C (reference)	Treatment E (test)			Treatment	Period	Sequence
C_{tau}, ng/ml	14	2385	4110	172.3	124 - 239	0.0112	-	-
C_{min}, ng/ml	14	1946	3362	172.8	139 - 214	0.0006	-	-
C_{max}, ng/ml	14	5000	6943	120.9	104 - 140	0.0408	-	-
$AUC_{(tau)}$, ng.h/ml	14	40251	57308	142.4	123 - 165	0.0010	-	-
		Median				p-value		
Parameter	n	Treatment C (reference)	Treatment E (test)	Treatment difference median	90% CI[1]	Treatment	Period	Sequence
t_{max}, h	14	2.5	3.0	-0.50	(-1.50) - (0.00)	0.1333	0.1455	0.4223

Ketoconazole

Fig 2 shows the mean plasma concentration-time curves of ketoconazole on day 7, after oral administration of 400 mg TMC114/200 mg ketoconazole b.i.d (treatment B), 200 mg ketoconazole b.i.d. (treatment D) and 400 mg TMC114/100 mg RTV/200 mg ketoconazole b.i.d. (treatment E).

Fig 2: Mean plasma concentration-time curves of ketoconazole on day 7, after oral administration of 400 mg TMC114/200 mg ketoconazole b.i.d (treatment B), 200 mg ketoconazole b.i.d. (treatment D) and 400 mg TMC114/100 mg RTV/200 mg ketoconazole b.i.d. (treatment E).



Visual inspection of the data reveals that at steady-state, maximum plasma concentrations were reached approximately 3h postdose. When ketoconazole was co-administered with TMC114 (Treatment B), the plasma concentration-time curve of ketoconazole was comparable to that of ketoconazole given alone.

Table 6 shows the pharmacokinetic parameters of ketoconazole on days 5-7.

Table 6: Pharmacokinetic results of ketoconazole on Days 5-7

Pharmacokinetics of ketoconazole (mean±SD t_{max} median (range))	Treatment B: ketoconazole 200 mg b.i.d. and TMC114 400 mg b.i.d.	Treatment D: ketoconazole 200 mg b.i.d	Treatment E: ketoconazole 200 mg b.i.d. and TMC114/RTV 400/100 mg b.i.d.
n	6	15	17
Day 5			
$C_{ss,\tau}$ ng/ml	834 ± 214	1190 ± 855	6368 ± 2328
Day 6			
$C_{ss,\tau}$ ng/ml	1054 ± 865	1249 ± 956	6734 ± 2540
Day 7			
$C_{ss,\tau}$ ng/ml	887 ± 774	1235 ± 1421	6451 ± 2146
C_{max} ng/ml	5458 ± 747	5311 ± 2018	10501 ± 2524
t_{max} h	3.0 (2.0 - 3.0)	3.0 (1.0 - 4.0)	3.0 (1.0 - 5.0)
$C_{min,ss}$ ng/ml	692 ± 565	851 ± 794	5354 ± 1627
$AUC_{0-\tau,ss}$ ng.h/ml	35292 ± 7209	33098 ± 16014	94343 ± 25129
$C_{ss,av}$ ng/ml	2941 ± 601	2758 ± 1335	7862 ± 2094
FL %	167 ± 44.0	174 ± 38.3	67.1 ± 13.6

Table 7 shows the summary of the statistical analysis of the pharmacokinetic parameters of ketoconazole of treatment E (TMC114/RTV/ketoconazole) compared to treatment D (ketoconazole).

Table 7: Summary of the statistical analysis of the pharmacokinetic parameters of Ketoconazole of treatment E (TMC114/RTV/ketoconazole) compared to treatment D (ketoconazole).

Parameter	n	Least square means		Least square means ratio, %	90% CI[1]	p-value		
		Treatment D (reference)	Treatment E (test)			Treatment	Period	Sequence
C_{ss}, ng/ml	15	615.0	5460	883.4	541 - 1442	< 0.0001	-	0.0941
C_{max}, ng/ml	15	472.6	4575	968.0	644 - 1455	< 0.0001	-	0.0577
C_{min}, ng/ml	15	4220	8884	210.5	181 - 244	< 0.0001	-	0.0033
AUC_{tau}, ng.h/ml	15	25418	79338	312.1	265 - 368	< 0.0001	-	0.0063
		Median				p-value		
Parameter	n	Treatment D (reference)	Treatment E (test)	Treatment difference median	90% CI[1]	Treatment	Period	Sequence
t_{max}, h	15	3.0	3.0	0.00	(-1.00) - (1.00)	0.9519	0.5068	0.9515

[1] 90% confidence intervals

-: excluded from final model

RTV

Fig 3 shows the mean plasma concentration-time curve of RTV on day 7, after oral administration of 400 mg TMC114/100 mg RTV b.i.d. (treatment C) and 400 mg TMC114/100 mg RTV/200 mg ketoconazole b.i.d. (treatment E).

Fig 3: Mean plasma concentration-time profiles of RTV on day 7, after oral administration of 400 mg TMC114/RTV b.i.d. (treatment C) and 400 mg TMC114/100 mg RTV/200 mg ketoconazole b.i.d. (treatment E).

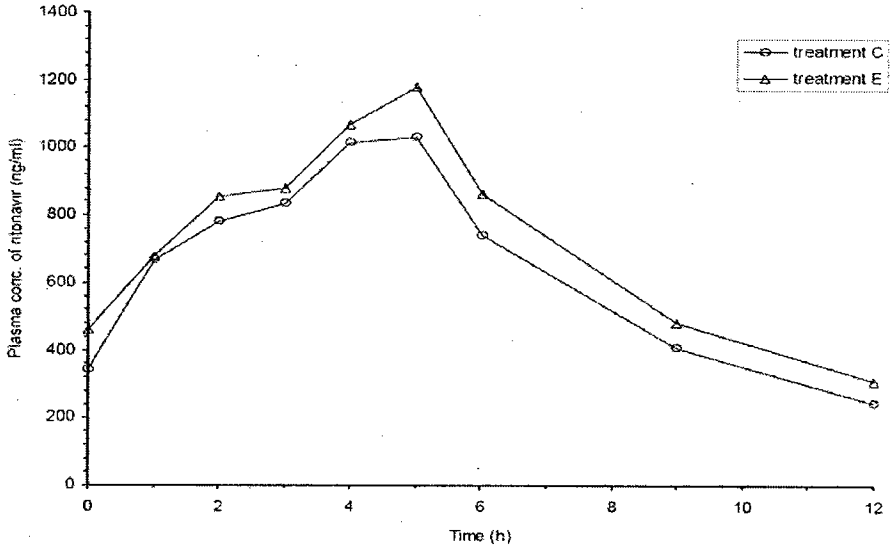


Table 8 shows the pharmacokinetic results of RTV on days 5-7.

Table 8: Pharmacokinetic results of RTV on Days 5-7

Pharmacokinetics of RTV (mean±SD, t_{max} median (range))	Treatment C: TMC114/RTV 400/100 mg b.i.d.	Treatment E: TMC114/RTV 400/100 mg b.i.d. and ketoconazole 200 mg b.i.d.
n	14	17
Day 5		
C_{tr}, ng/ml	284 ± 181	401 ± 180
Day 6		
C_{tr}, ng/ml	275 ± 182	461 ± 241
Day 7		
C_{tr}, ng/ml	342 ± 263	460 ± 296
C_{max}, ng/ml	1232 ± 750	1568 ± 553
t_{max}, h	4.0 (1.0 - 5.0)	4.0 (1.0 - 5.0)
C_{min}, ng/ml	215 ± 142	287 ± 129
AUC_{12h}, ng·h/ml	7556 ± 4721	8515 ± 3646
$C_{tr,av}$, ng/ml	630 ± 393	710 ± 304
FU, %	165 ± 29.4	155 ± 27.1

7. Safety Assessments

No deaths or SAEs were reported in this trial. Overall 22 of the 26 subjects enrolled in the trial reported at least 1 AE during the trial. Most of the AEs were considered possibly related to the medication (See details in Medical Officer's review).

8. Conclusion

- In the presence of ketoconazole, the C_{max} and AUC_{12h} values of TMC114 (when administered alone) were increased by approximately 78 % and 155 % respectively, based on ratios of the LS means.
- When ketoconazole was added to the treatment with TMC114/RTV, the exposure to TMC114 was significantly increased by 42 % compared to treatment with TMC114/RTV. Thus, it is possible to inhibit the metabolism of TMC114 more than the inhibition provided by 100 mg RTV.
- Compared to TMC114 alone, systemic exposure to TMC114 was almost three times higher in combination with ketoconazole, and approximately 6.5 times higher in combination with low dose ritonavir. This suggests that low-dose RTV co-administration with TMC114 results in a "better" boosting of TMC114 than with ketoconazole administration.
- The fraction of TMC114 not bound to protein was 3.6 % (range 2.9 %-4.5 %) when TMC114 was given alone and 8.1 % (range 3.3 %-13.3 %) when TMC114 was co-administered with RTV.
- Systemic exposure to RTV was comparable between both treatments (TMC114/RTV and TMC114/RTV/ketoconazole).

- When ketoconazole was co-administered with TMC114/RTV, the C_{max} and AUC_{12h} of ketoconazole were increased by approximately 111 % and 212 % respectively, based on the ratio of the LS means, as compared to ketoconazole administered alone.
- The exposure to ketoconazole, when combined with TMC114 alone, was comparable to that after treatment with ketoconazole alone thereby suggesting that the effect of TMC114/RTV on ketoconazole is due to RTV (inhibition of CYP3A).

Labeling Recommendation

Ketoconazole and itraconazole are potent inhibitors as well as substrates of CYP3A4. Concomitant systemic use of ketoconazole, itraconazole, and darunavir/ritonavir may increase plasma concentration of darunavir.

Plasma concentrations of ketoconazole or itraconazole may be increased in the presence of darunavir/ritonavir. When coadministration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg.

Co-administration of voriconazole with darunavir/ritonavir has not been studied. Administration of voriconazole with ritonavir (100 mg twice daily) decreased the AUC of voriconazole by an average of 39%. Voriconazole should not be administered to patients receiving darunavir/ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.

1. Title

The effect of TMC114 boosted with a low dose of ritonavir on the pharmacokinetics of atorvastatin in healthy volunteers **(TMC114-C133).**

2. Objectives

The objectives of this trial were to determine:

- The pharmacokinetic effect of repeated doses of TMC114, with co-administration of low-dose ritonavir (RTV), on the pharmacokinetics of repeated doses of atorvastatin.
- The pharmacokinetic effect of repeated doses of TMC114, with co-administration of low-dose ritonavir (RTV), on the pharmacokinetics of atorvastatin lactone and 2- and 4-hydroxy-atorvastatin, after repeated doses of atorvastatin.
- The effect of atorvastatin on the steady-state pharmacokinetics of TMC114, with-co-administration of low dose RTV, as compared to historical data.

3. Study Design

Phase I, open-label, one way cross-over trial to investigate the effect of TMC114, formulated as an oral solution, with co-administration of low-dose RTV, on the pharmacokinetics of atorvastatin, atorvastatin lactone, and 2- and 4-hydroxy-atorvastatin. Sixteen healthy volunteers were randomized to treatment sequence A-B or B-A as follows: Treatment A: 40 mg atorvastatin q.d. for 4 days, Treatment B: TMC114/RTV 300/100 mg b.i.d. for 9 days with 10 mg atorvastatin q.d. from days 4-7. A 6-day washout period separated the two treatments. Full pharmacokinetic profiles were determined on Day 4 of treatment A and on Day 7 of treatment B for atorvastatin, atorvastatin lactone, and 2- and 4-hydroxy-atorvastatin, and on day 7 of treatment B for TMC114 and RTV. TMC114/RTV and atorvastatin were taken with food (during meal or within 15 minutes of meal).

3.1 Discussion of Trial Design, Including Choice of Control Group.

- An open label, randomized, one-way cross-over trial design was used so that the pharmacokinetics of 40 mg atorvastatin could be compared with the pharmacokinetics of 10 mg atorvastatin during co-administration with TMC114/RTV.
- A one-way cross over design in which only the effect of TMC114/RTV on atorvastatin pharmacokinetics was investigated as it was expected that the impact of atorvastatin on TMC114 pharmacokinetics would be minimal and a significant drug interaction was not anticipated.
- In a study to investigate the effect of TMC114 (600/100 b.i.d.; formulated as a solution) on the PK of a single dose of pravastatin (TMC114-C120), the mean systemic exposure to pravastatin increased by 81 % compared to pravastatin alone (although this increase was not consistent among all subjects). Therefore, a lower dose of TMC114/RTV 300/100 mg b.i.d was chosen for this study.
- Atorvastatin is licensed at a dosing regimen of 10, 20, 40, and 80 mg q.d. The rationale for administering atorvastatin 10 mg q.d. was based on the results from a

Kaletra® and atorvastatin interaction trial where the C_{max} and AUC of atorvastatin were increased by 4.67-fold and 5.88-fold, respectively. A similar interaction was expected with TMC114/RTV because of the use of low dose RTV, and therefore, the dose of atorvastatin was decreased by 4-fold when co-administered with TMC114/RTV.

4. Drugs Used in the Trial

Table 1 shows the drugs used in the trial.

Table 1: Description of Drugs Used in the Trial

	TMC114	RTV	Atorvastatin (Lipitor®)
Dosage Form	Solution (TF019)	Capsule	Tablet
Strength	20 mg/mL	100 mg	10 mg
Batch Number	127645	130277	130326/130319 (Trt. A/Trt. B)
Expiry Date	Sep 9, 2003	Dec 1, 2003	August 31, 2004

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Plasma samples for treatment A and treatment B were collected as follows: for treatment A (session I for group 1 and session II for group 2), pre-dose samples were collected on days 2, 3, and 4. On day 4, in addition to pre-dose sample, plasma samples were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, and 72 hours. For treatment B (session II for group 1 and session I for group II), the samples were collected at pre-dose on day 3, 4, 5, 6, and 7. On day 7, in addition to pre-dose sample, plasma samples were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, and 72 hours.

The plasma concentrations of TMC114, RTV, atorvastatin, atorvastatin lactone, and 2- and 4-hydroxy atorvastatin were determined using validated liquid chromatography tandem mass spectrometry methods. The lower limit of quantification (in plasma) was 10 ng/mL for TMC114, 5 ng/mL for RTV, and 0.5 ng/mL atorvastatin and its metabolites.

Pharmacokinetic Assessments

Non-parametric analyses were performed using Winnonlin Professional ™ [redacted] using a [redacted]
Descriptive statistics were calculated for the serum concentratations of atorvastatin, atorvastatin lactone, 2-hydroxy-atorvastatin and TMC/RTV. Comparison of the pharmacokinetic parameters between treatment A and B were performed using linear mixed effect modeling with factors for subjects, treatment, sequence and period for treatment B (test). The least square (LS) mean and 90 % confidence interval (CI) of the

LSmean ratio of C_{max}, C_{min}, and AUC_{24h} of atorvastatin and atorvastatin lactone for treatment B were reported with treatment for atorvastatin administered alone (treatment A) as reference. The pharmacokinetic parameters for TMC114/RTV were compared with data obtained in trial TMC114-C124, in which healthy volunteers received TMC114/RTV 300/100 mg b.i.d. Formulation TF019 was used in both studies.

6. Results

6.1 Subject Disposition

16 subjects were randomized to sequence A-B (n = 8) and sequence B-A (n = 8). 8 subjects completed all assessments in sequence A-B whereas 7 subjects completed all assessments in sequence B-A (1 subject withdrew consent).

Table 2: Demographics in Study TMC 114-C133

Parameter	A-B N=8		B-A N=8		All subjects N=16	
Age (years), median (range)	23.0	(18-33)	31.0	(20-39)	27.0	(18-39)
Height (cm), median (range)	167.0	(157-183)	169.0	(159-184)	167.5	(157-184)
Weight (cm), median (range)	65.5	(57-82)	70.0	(53-87)	69.5	(53-87)
BMI (kg/m^2), median (range)	23.9	(20-27)	24.0	(21-28)	23.9	(20-28)
Male/female, n/n (%/%)	4/4	(50/50)	4/4	(50/50)	8/8	(50/50)

6.2 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time curve and trough values of TMC114.

Fig 1: Mean plasma concentration-time profiles and trough values of TMC114.

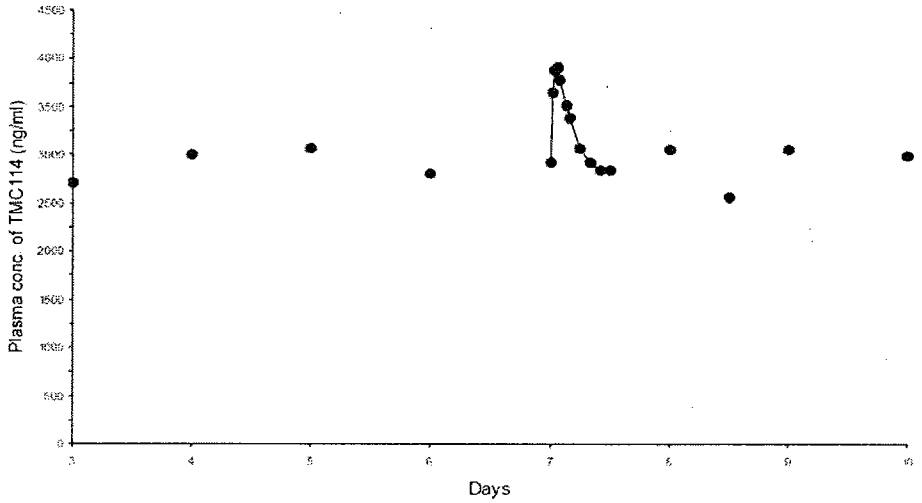


Table 3 shows the steady-state pharmacokinetic results of TMC114/RTV given alone (TMC114-C124) or given in combination with atorvastatin.

Table 3: Steady state pharmacokinetic results of TMC114 given alone (TMC114-C124) or given in combination with atorvastatin (treatment B).

Pharmacokinetics of TMC114 (mean±SD, t_{max}: median (range))	TMC114 + atorvastatin TMC114-C133	TMC114 alone TMC114-C124
n	15	12
t_{max}, h	1.5 (0.5 - 4.0)	0.5 (0.5 - 4.0)
C_{0h}, ng/ml (Day 7)	2930 ± 839	2262 ± 908
C_{min}, ng/ml	2569 ± 716	1845 ± 842
C_{max}, ng/ml	4121 ± 734	3971 ± 1385
AUC_{12h}, ng.h/ml	38385 ± 9235	29837 ± 10345
$C_{ss,av}$, ng/ml	3200 ± 770	2486 ± 862
FI, %	51.9 ± 25.5	90.6 ± 31.5

RTV

Fig 2 shows the mean plasma concentration-time curve and trough values of RTV

Fig 2: Mean plasma concentration-time profiles and trough values of RTV

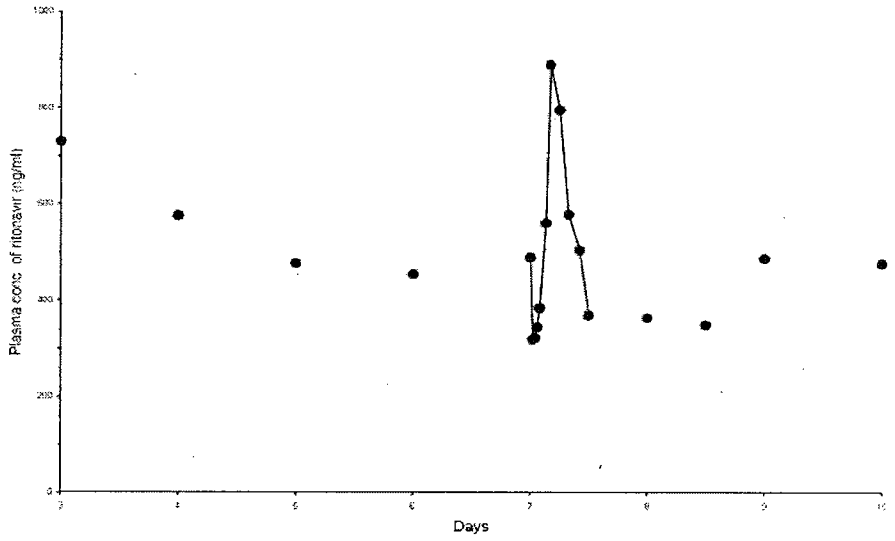


Table 4 shows the pharmacokinetic results of RTV given alone (TMC114-C124) or given in combination with atorvastatin (treatment B).

Table 4: Pharmacokinetic results of RTV given alone (TMC114-C124) or given in combination with atorvastatin (treatment B).

Pharmacokinetics of RTV (mean±SD, t_{max} median (range))	RTV + atorvastatin This study (C133)	RTV alone Reference study (C124)
N	15	12
t_{max}, h	6.0 (4.0 - 10.0)	4.0 (2.0 - 6.0)
C_{0h}, ng/ml	489 ± 158	340 ± 181
C_{min}, ng/ml	265 ± 69.9	174 ± 84.6
C_{max}, ng/ml	1049 ± 445	1030 ± 343
AUC_{12h}, ng.h/ml	6906 ± 2266	5811 ± 1960
$C_{ss, av}$, ng/ml	576 ± 189	484 ± 163
FI, %	132 ± 32.8	181 ± 42.2

Atorvastatin

Fig 3 shows the mean plasma concentration-time of atorvastatin.

Fig 3: Mean serum concentration-time curves of atorvastatin.

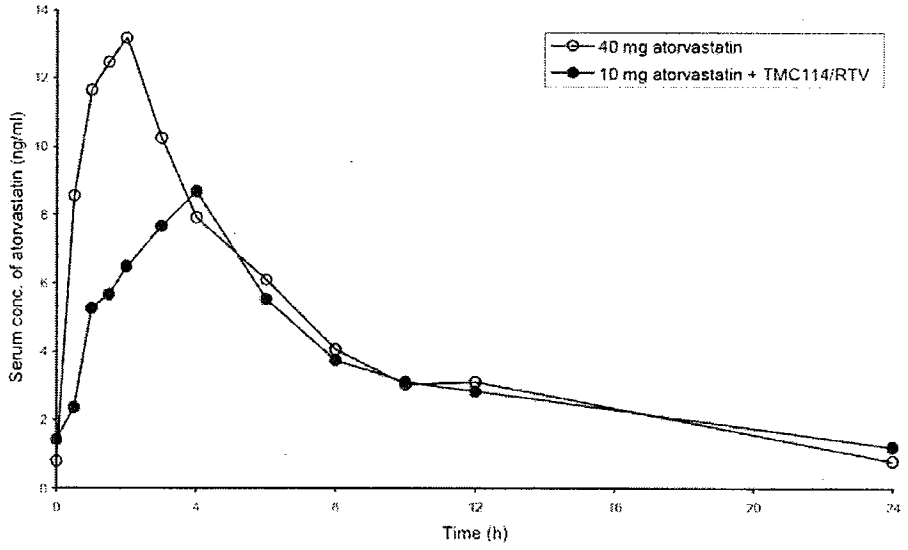


Table 5 shows the steady-state pharmacokinetic parameters of atorvastatin given alone at 40 mg q.d. and in combination with TMC/RTV given at 10 mg q.d.

Table 5: Steady-state pharmacokinetic results of atorvastatin given alone at 40 mg q.d. and in combination with TMC114/RTV given at 10 mg q.d.

Pharmacokinetics of atorvastatin (mean±SD, t_{max}: median (range))	40 mg atorvastatin alone	10 mg atorvastatin + TMC114/RTV
n	15	15
t_{max}, h	1.5 (0.5 - 3.0)	4.0 (1.0 - 6.0)
C_{0h}, ng/ml	0.795 ± 0.526	1.42 ± 0.562
C_{min}, ng/ml	0.668 ± 0.615	1.16 ± 0.441
C_{max}, ng/ml	17.4 ± 7.93	9.58 ± 4.96
AUC_{24h}, ng.h/ml	102 ± 43.1	84.4 ± 30.3
AUC_{last}, ng.h/ml	102 ± 52.0	93.9 ± 38.5
$t_{1/2term}$, h	6.98 ± 1.94	11.7 ± 5.83
$C_{ss,av}$, ng/ml	4.23 ± 1.80	3.52 ± 1.26
FI, %	418 ± 182	239 ± 78.3

Table 6 shows the statistical evaluation of the pharmacokinetics of atorvastatin between treatment A and treatment B.

Table 6: Statistical evaluation of the pharmacokinetics of atorvastatin.

Parameter	n	Least square means		Least square means ratio, %	90% CI [1]	p-value		
		Treatment A (reference)	Treatment B (test)			Treatment	Period	Sequence
C_{min}, ng/ml	15	0.5933	1.074	181.0	137 - 240	0.0023	-	-
C_{max}, ng/ml	15	15.62	8.817	56.46	47.5 - 67.2	0.0001	0.0469	-
AUC_{24h}, ng.h/ml	15	93.88	80.19	85.42	75.6 - 96.5	0.0387	-	-
Parameter	n	Median		Treatment difference median	90% CI [2]	p-value		
		Treatment A (reference)	Treatment B (test)			Treatment	Period	Sequence
t_{max}, h	15	1.5	4.0	-2.0	(-2.25) - (-1.5)	0.0011	0.1733	0.9530

[1] 90% confidence intervals (note that a significant change excludes 100%)
[2] 90% confidence intervals (note that a significant change excludes 0)
- : excluded from final model

When 10 mg atorvastatin was co-administered with TMC114/RTV, C_{min} was increased by 81 % compared to 40 mg atorvastatin given alone (based on the LS mean ratio) while C_{max} and AUC_{24h} values for atorvastatin were statistically significantly decreased by 44 % and 15 %, respectively.

Atorvastatin lactone

Table 7 shows the steady-state pharmacokinetic results of atorvastatin lactone after 40 mg q.d. atorvastatin given alone and after 10 mg q.d. atorvastatin given in combination with TMC114/RTV.

Table 7: Steady-state pharmacokinetic results of atorvastatin lactone after 40 mg q.d. atorvastatin given alone and after 10 mg q.d. atorvastatin given in combination with TMC114/RTV.

Pharmacokinetics of atorvastatin lactone (mean±SD, t_{max}: median (range))	40 mg atorvastatin alone	10 mg atorvastatin + TMC114/RTV
N	15	15
t_{max}, h	3.0 (1.5 - 4.0)	4.0 (3.0 - 6.0)
C_{0h}, ng/ml (Day 7)	0.524 ± 0.432	1.36 ± 0.675
C_{min}, ng/ml	NQ	1.10 ± 0.518
C_{max}, ng/ml	6.84 ± 3.74	5.61 ± 2.69
AUC_{24h}, ng.h/ml	63.1 ± 29.1	66.1 ± 25.2
AUC_{last}, ng.h/ml	61.3 ± 31.6	75.3 ± 36.8
$t_{1/2term}$, h	7.57 ± 2.60	12.9 ± 8.87
$C_{ss,av}$, ng/ml	2.63 ± 1.21	2.75 ± 1.05
FI, %	243 ± 59.7	168 ± 47.1

Table 8 shows the statistical evaluation of the pharmacokinetics of atorvastatin lactone.

Table 8: Statistical evaluation of the pharmacokinetics of atorvastatin lactone.

Parameter	n	Least square means		Least square means ratio, %	90% CI [1]	p-value		
		Treatment A (reference)	Treatment B (test)			Treatment	Period	Sequence
C_{min}, ng/ml	15	0.4804	0.9999	208.1	163 - 265	0.0001	-	-
C_{max}, ng/ml	15	6.058	5.176	85.43	76.1 - 95.9	0.0309	-	-
AUC_{24h}, ng.h/ml	15	57.42	61.42	107.0	96.3 - 119	0.2786	-	-
Parameter	n	Median		Treatment difference median	90% CI [2]	p-value		
		Treatment A (reference)	Treatment B (test)			Treatment	Period	Sequence
t_{max}, h	15	3.0	4.0	-1.5	(-2.0) - (-1.0)	0.0016	0.6715	0.5942

[1] 90% confidence intervals (note that a significant change excludes 100%)
[2] 90% confidence intervals (note that a significant change excludes 0)
-: excluded from final model

When 10 mg atorvastatin was co-administered with TMC114/RTV, mean C_{min} of atorvastatin lactone was increased by 108 % compared to 40 mg atorvastatin given alone while C_{max} of atorvastatin lactone was decreased by approximately 15 %. AUC_{24hr} was not statistically significantly different.

2-hydroxy-atorvastatin

Table 9 shows the steady-state pharmacokinetic results of 2-hydroxy-atorvastatin for treatment A.

Table 9: Steady-state pharmacokinetic results of 2-hydroxy-atorvastatin for treatment A.

Pharmacokinetics of 2-hydroxy-atorvastatin (mean±SD, t_{max}: median (range))	40 mg atorvastatin alone
N	15
t_{max}, h	3.0 (1.0 - 4.0)
C_{0h}, ng/ml (Day 7)	1.01 ± 0.442
C_{min}, ng/ml	0.790 ± 0.496
C_{max}, ng/ml	11.3 ± 4.71
AUC_{24h}, ng.h/ml	92.1 ± 27.6
AUC_{last}, ng.h/ml	93.8 ± 35.5
$t_{1/2term}$, h	7.07 ± 1.87
$C_{ss, av}$, ng/ml	3.84 ± 1.15
FI, %	274 ± 90.2

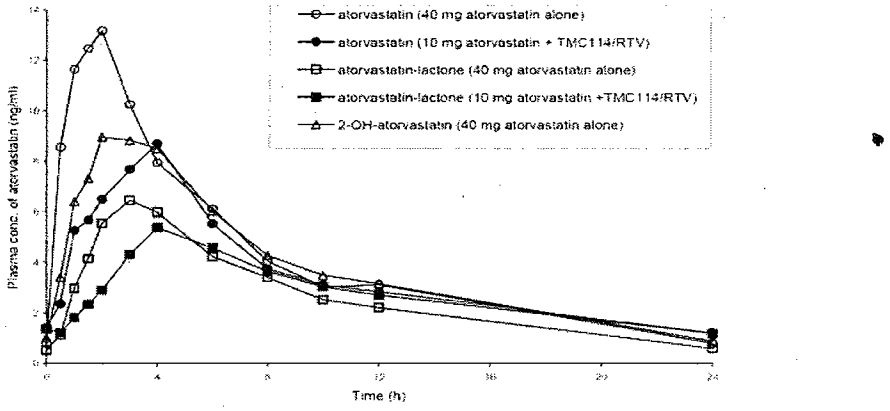
The pharmacokinetic parameters were not determined for treatment B because all serum concentrations of 2-hydroxy-atorvastatin were below the limit of quantification.

4-hydroxy-atorvastatin

The majority of concentrations for treatment A and all concentrations for treatment B were below the limit of quantification.

Fig 4 presents the mean serum concentration-time curves of atorvastatin and its metabolites.

Fig 4: Mean serum concentration-time curves for atorvastatin and its metabolites.



7. Safety Assessments

Overall, 10 subjects had treatment related adverse events. No adverse events were serious or led to discontinuation. G.I. disorders were more common with TMC114/RTV and nervous system disorders and psychiatric disorders were more common during TMC114/RTV/atorvastatin. The majority of adverse events were mild/grade 1. There

were no grade 3 or grade 4 adverse events and all events resolved before the end of treatment (See details in Medical Officer's review).

8. Conclusion

- The results of the study show that the combination of TMC114/RTV 300/100 mg b.i.d. and 10 mg atorvastatin q.d. provides a lower exposure to atorvastatin (decrease of 15 %) when combined with TMC114/RTV, as compared to 40 mg atorvastatin q.d. alone. After dose normalization, the atorvastatin exposure is 240 % higher when given with TMC114/RTV as compared to when given alone.
- The major metabolite detected following administration of 40 mg atorvastatin was 2-hydroxy-atorvastatin. However, following co-administration of 10 mg atorvastatin with TMC114/RTV, this metabolite could not be detected. The 4-hydroxy metabolite was detected in limited quantities following atorvastatin alone and could not be detected following combination therapy.

Labeling Recommendation

When atorvastatin and PREZISTA/rtv is co-administered, it is recommended to start with the lowest possible dose of atorvastatin with careful monitoring. A gradual dose increase of atorvastatin may be considered based on the clinical response.

1. Title

The pharmacokinetic interaction between boosted TMC114 and boosted saquinavir in healthy subjects **(TMC114-C138)**.

2. Objectives

The objectives of this trial were to determine:

- The effect of steady-state concentrations of saquinavir on the steady-state pharmacokinetics of TMC114, in combination with low dose ritonavir.
- The effect of steady-state concentrations of TMC114 on the steady-state pharmacokinetics of saquinavir, in combination with a low dose of ritonavir.

3. Study Design

Phase I, open-label, controlled, randomized, cross-over trial to investigate the pharmacokinetic interaction between TMC114, formulated as experimental tablet TF036 and saquinavir (formulated as hard gel capsule Invirase®), both in combination with a low dose of ritonavir. The study population consisted of 2 panels, with 16 healthy subjects each. The trial was divided into two sessions, separated by a wash-out period of at least 14 days. Panel 1 received 400/100 mg TMC114/RTV b.i.d. (treatment A) in one session and 400/1000/100 mg TMC114/SQV/RTV b.i.d. (treatment C) in the other session. Panel 2 received 1000/100 mg SQV/RTV b.i.d. (treatment B) in one session and 400/1000/100 mg TMC114/SQV/RTV b.i.d. (treatment C) in the other session. All the treatments were administered under fed conditions for 13 days b.i.d. with an additional single dose on Day 14. In every session, full pharmacokinetic profiles were determined for each compound on day 14 up to 12h after intake of study medication.

4. Drugs Used in the Trial

Table 1 shows the drugs used in the trial.

Table 1: Description of Drugs used in the Trial.

	TMC114	RTV	Saquinavir (Invirase®)
Dosage Form	Tablet (TF036)	Capsule	Capsule
Strength	400 mg	100 mg	200 mg

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

For session 1 and 2, plasma samples were collected within 2 hours of drug intake on day 1 and immediately before drug intake on days 4, 7, 10, 12, 13, and 14. In addition to pre-dose sample on day 14, additional blood samples were collected at 0, 1, 2, 3, 4, 5, 6, 9, and 12 hours after dosing.

The plasma concentrations of TMC114, RTV, and SQV were determined using a validated LC-MS/MS method. The lower limit of quantification (LLOQ) was 10 ng/mL for TMC114, 5 ng/mL for RTV, and 1.0 ng/mL for saquinavir.

Pharmacokinetic Assessments

Pharmacokinetic and statistical analysis were performed using Winnonlin Professional ™ [redacted] using a [redacted] Descriptive statistics were calculated for the plasma concentrations of TMC114, RTV, and SQV at each time point and of the derived pharmacokinetic parameters. Statistical analysis was performed comparing treatment C *vs* treatment A for TMC114, comparing treatment C (panel 1) vs treatment A and treatment C (panel 2) *vs* treatment B for RTV and comparing treatment C *vs* treatment B for SQV. The primary pharmacokinetic parameters were C_{min}, C_{max}, and AUC_{12h} on the logarithmic scale. Only paired observations for the compared treatments were included in the statistical analysis. The least square means of the primary parameters for each treatment group were estimated with a linear mixed effects model, controlling for period and randomization group as fixed effects and subject (nested in randomization group) as the random effect. If the p-values for the primary pharmacokinetic parameters between treatments were less than 0.05, a statistically significant drug interaction was noted.

6. Results

6.1 Subject Disposition

32 subjects were randomized to two different panels (1 and 2). Subjects in panel 1 received treatments A and C (n = 8 subjects per treatment) in a cross over fashion. Similarly, subjects in panel 2 received treatment B and C in a cross over fashion. In panel 1, 1 subject (randomized to sequence A-C) discontinued after session 1 and 1 subject (randomized to sequence C-A) discontinued after receiving both the treatments. In panel 2, 2 subjects (randomized to sequence C-B) discontinued after session 1. One subject each (randomized to sequence B-C) discontinued after receiving treatment B and receiving both the treatments respectively. Table 2 shows the demographics in the study.

Table 2: Demographics in Study TMC 114-C138

		Panel 1	Panel 2	All Panels
Age (years) median (range)		40.5 (24-53)	38.5 (20-53)	40.5 (20-53)
Height (cm) median (range)		179.0 (156-192)	174.0 (161-185)	177.0 (156-192)
Weight (kg) median (range)		78.5 (55-96)	71.5 (56-92)	73.0 (55-96)
BMI (kg m^{-2}) median (range)		24.8 (22-28)	22.1 (20-28)	23.4 (20-28)
Gender	Male N (%)	13 (81.3)	12 (75.0)	25 (78.1)
	Female N (%)	3 (18.8)	4 (25.0)	7 (21.9)

6.2 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time curve of TMC114 on day 14 after oral administration of TMC114/RTV 400/100 mg b.i.d. (treatment A) and TMC114/SQV/RTV 400/1000/100 mg b.i.d. (treatment C).

Fig 1: Mean plasma concentration-time profiles of TMC114 on day 14 after oral administration of TMC114/RTV 400/100 mg b.i.d. (treatment A) and TMC114/SQV/RTV 400/1000/100 mg b.i.d. (treatment C).

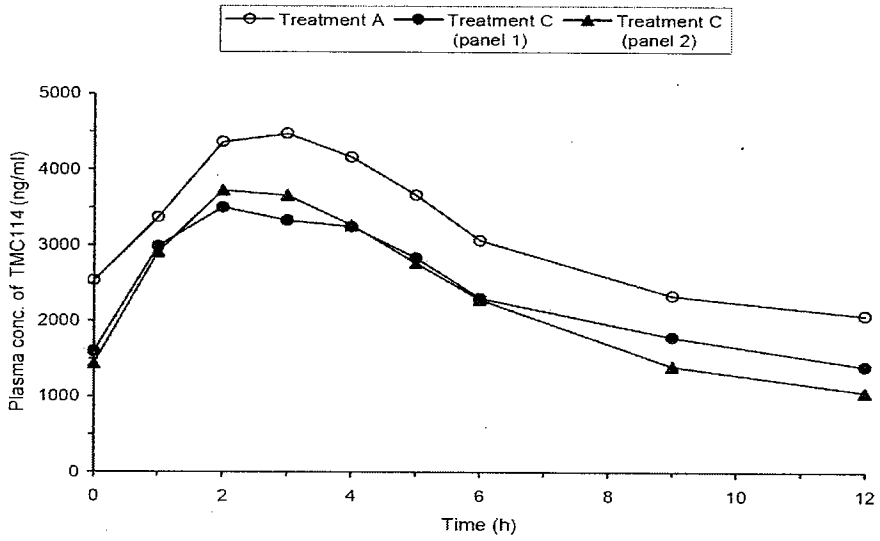


Table 3 shows the pharmacokinetic results of TMC114 for treatment A and treatment C.

Table 3: Steady-state pharmacokinetic results of TMC114 for treatment A and treatment C.

Pharmacokinetics of TMC114 (mean±SD, t_{max} median (range))	Treatment A, Panel 1: 400 mg TMC114/ 100 mg RTV b.i.d.	Treatment C, Panel 1: 400 mg TMC114/ 1000 mg SQV/ 100 mg RTV b.i.d.	Treatment C, Panel 2: 400 mg TMC114/ 1000 mg SQV/ 100 mg RTV b.i.d.
n	14	15	12
t_{max}, h	3.0 (1.0 - 5.0)	2.0 (1.0 - 9.0)	2.0 (1.0 - 3.0)
C_{max}, ng/ml	2011 ± 709	1220 ± 459	1042 ± 448
C_{max}, ng/ml	4855 ± 1353	4053 ± 924	4029 ± 1147
AUC_{12h}, ng.h/ml	37525 ± 10930	28753 ± 8898	27389 ± 9187
C_{tau}, ng/ml	3127 ± 911	2396 ± 741	2282 ± 766
Fl, %	92.5 ± 15.5	125 ± 29.8	138 ± 40.9
LSmean ratio (90% CI), %	-	**C vs A**	-
n	-	14	-
C_{max}	-	58.2 (46.8 - 72.3)*	-
C_{max}	-	83.1 (75.0 -92.1)*	-
AUC_{12h}	-	73.7 (63.3 - 85.8)*	-

* p-value < 0.05

Table 4 shows the statistical evaluation of the pharmacokinetics of TMC114 for treatment A and treatment C (panel 1).

Table 4: Statistical evaluation of the pharmacokinetics of TMC114 for treatment A and treatment C (panel 1).

TMC114		Least square means		Least square means ratio, %	90% CI [1]	p-value		
Parameter	n	Treatment A (reference)	Treatment C (test)			Treatment	Period	Sequence
C_{min}, ng/ml	14	1888	1098	58.18	46.8 – 72.3	0.0007	-	-
C_{max}, ng/ml	14	4665	3876	83.08	75.0 – 92.1	0.0069	-	-
AUC_{12h}, ng.h/ml	14	35960	26506	73.71	63.3 – 85.8	0.0036	-	-
		Median				p-value		
Parameter	n	Treatment A (reference)	Treatment C (test)	Treatment difference median	90% CI [1]	Treatment	Period	Sequence
t_{max}, h	14	3.0	2.0	0.00	(-1.00) – (0.50)	0.8430	0.4677	0.6973

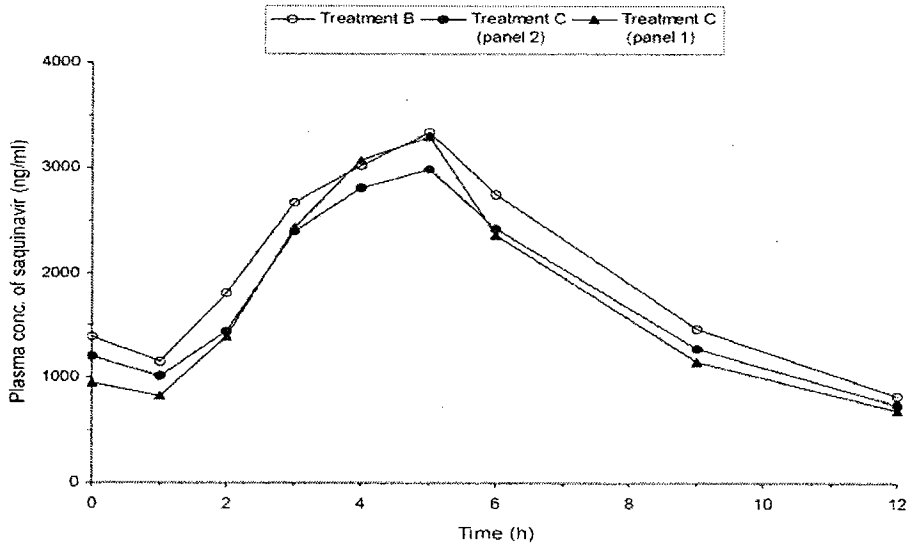
[1] 90% confidence intervals
- excluded from final model

Based on the estimated least square means ratios, C_{min}, C_{max}, and AUC_{12h} values of TMC114 were statistically significantly decreased by 42 %, 17 %, and 26 %, respectively, when SQV 1000 mg b.i.d. was added to TMC114/RTV 400/100 mg b.i.d.

SQV

Fig 2 shows the mean plasma concentration-time curve of SQV on day 14 after oral administration of SQV/RTV 1000/100 mg b.i.d. (treatment B) and TMC114/SQV/RTV 400/1000/100 mg b.i.d. (treatment C).

Fig 2: Mean plasma concentration-time profiles of SQV on day 14 after oral administration of SQV/RTV 1000/100 mg b.i.d. (treatment B) and TMC114/SQV/RTV 400/1000/100 mg b.i.d. (treatment C).



Visual inspection of the mean plasma concentration-time profiles revealed that plasma concentrations of SQV were slightly lower when SQV/RTV was combined with TMC114. However, the shape of the concentration-time curve was not affected. Furthermore, there was no difference between the two groups of subjects receiving treatment C.

Table 5 shows the pharmacokinetic results of saquinavir for treatment B and treatment C.

Table 5: Pharmacokinetic results of saquinavir for treatment B and treatment C.

Pharmacokinetics of saquinavir (mean±SD, t_{max}, median (range))	**Treatment B, Panel 2: 1000 mg SQV/ 100 mg RTV b.i.d.**	**Treatment C, Panel 2: 400 mg TMC114/ 1000 mg SQV/ 100 mg RTV b.i.d.**	**Treatment C, Panel 1: 400 mg TMC114/ 1000 mg SQV/ 100 mg RTV b.i.d.**
n	14	12	15
t_{max}, h	5.0 (3.0 - 5.0)	5.0 (3.0 - 6.0)	5.0 (3.0 - 5.0)
C_{min}, ng/ml	765 ± 1024	597 ± 504	658 ± 513
C_{max}, ng/ml	3612 ± 2833	3192 ± 1937	3451 ± 1734
AUC_{12h}, ng.h/ml	23833 ± 21355	21043 ± 13260	20698 ± 12032
C_{12h}, ng/ml	1986 ± 1780	1754 ± 1105	1725 ± 1003
FL %	161 ± 38.7	166 ± 53.2	175 ± 30.9
LSmean ratio (90% CI), %	-	**C vs B**	-
n	-	12	-
C_{min}	-	82.0 (51.8 - 130)	-
C_{max}	-	94.0 (78.0 - 113)	-
AUC_{12h}	-	94.0 (75.5 - 117)	-

Table 6 shows the statistical evaluation of the pharmacokinetics of SQV for treatment B and treatment C (panel 2).

Table 6: Statistical evaluation of the pharmacokinetics of SQV for treatment B and treatment C (panel 2).

SQV Parameter	n	Least square means: Treatment B (reference)	Least square means: Treatment C (test)	Least square means ratio, %	90% CI[1]	p-value: Treatment	Period	Sequence
C_{min}, ng/ml	12	453.6	372.1	82.03	51.8 - 130	0.4561	-	-
C_{max}, ng/ml	12	2735	2571	94.01	78.0 - 113	0.5637	-	-
AUC_{12h}, ng.h/ml	12	17020	15995	93.98	75.5 - 117	0.6200	-	-
Parameter	**n**	**Median: Treatment B (reference)**	**Median: Treatment C (test)**	**Treatment difference median**	**90% CI[1]**	**p-value: Treatment**	**Period**	**Sequence**
t_{max}, h	12	5.0	5.0	0.00	(-0.50 - 0.50)	0.5889	0.7879	0.2161

[1] 90% confidence intervals
- excluded from final model

Based on the estimated least square mean ratios, C_{min}, C_{max}, AUC_{12h} and tmax values of SQV were not statistically significantly affected when TMC114 400 mg b.i.d. was added to SQV/RTV 1000/100 mg b.i.d.

RTV

Fig 3 shows the mean plasma concentration-time curve of RTV on day 14 after oral administration of TMC114/RTV 400/100 mg b.i.d. (treatment A), SQV/RTV 1000/100 mg b.i.d. (treatment B) and TMC114/SQV/RTV 400/1000/100 b.i.d. (treatment C).

Fig 3: Mean plasma concentration-time profiles of RTV on day 14 after oral administration of TMC114/RTV 400/100 mg b.i.d. (treatment A), SQV/RTV 1000/100 mg b.i.d. (treatment B) and TMC114/SQV/RTV 400/1000/100 mg b.i.d. (treatment C).

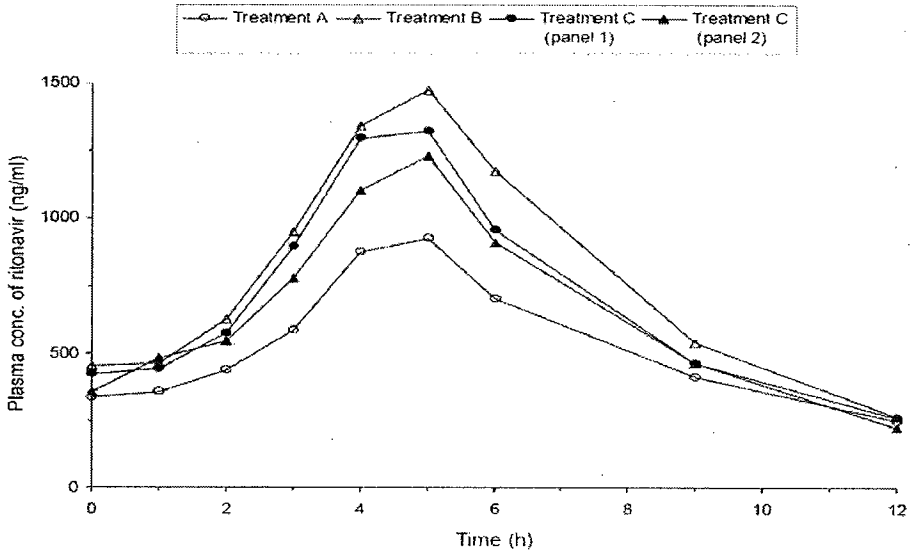


Table 7 shows the pharmacokinetic results of RTV for treatment A, treatment B, and treatment C.

Table 7: Pharmacokinetic results of RTV for treatment A, treatment B, and treatment C.

Pharmacokinetics of RTV (mean±SD $t_{1/2}$: median (range))	Treatment A, Panel 1: 400 mg TMC114/ 100 mg RTV b.i.d.	Treatment B, Panel 2: 1000 mg SQV/ 100 mg RTV b.i.d.	Treatment C, Panel 1: 400 mg TMC114/ 1000 mg SQV/ 100 mg RTV b.i.d.	Treatment C, Panel 2: 400 mg TMC114/ 1000 mg SQV/ 100 mg RTV b.i.d.
n	14	14	15	12
t_{max}, h	5.0 (4.0 - 5.0)	5.0 (1.0 - 6.0)	4.0 (0.0 - 5.0)	5.0 (1.0 - 6.0)
C_{max}, ng/ml	221 ± 87.9	248 ± 220	228 ± 120	186 ± 140
C_{max2}, ng/ml	1009 ± 468	1048 ± 746	1539 ± 660	1311 ± 554
AUC_{12h}, ng.h/ml	6362 ± 3147	9463 ± 5206	8432 ± 3959	7866 ± 3086
$C_{0,ss}$, ng/ml	530 ± 262	789 ± 434	703 ± 330	655 ± 257
FI, %	149 ± 38.3	179 ± 40.9	193 ± 34.0	172 ± 37.5
LSmean ratio (90% CI), %	-	-	C vs A	C vs B
n	-	-	14	12
C_{max}	-	-	105 (90.1 - 123)	58.9 (50.5 - 114)
C_{max2}	-	-	160 (143 - 179)*	78.5 (35.5 - 111)
AUC_{12h}	-	-	134 (118 - 153)*	81.2 (61.0 - 108)

* p-value < 0.05

Table 8 shows the statistical evaluation of the pharmacokinetics of RTV for treatment A and treatment C (panel 1).

Table 8: Statistical evaluation of the pharmacokinetics of RTV for treatment A and treatment C (panel 1).

RTV		Least square means		Least square means ratio %	90% CI[1]	p-value		
Parameter	n	Treatment A (reference)	Treatment C (test)			Treatment	Period	Sequence
C_{min}, ng/ml	14	199.0	209.4	105.2	98.1 - 123	0.5730	-	-
C_{max}, ng/ml	14	913.5	1463	160.2	143 - 179	0.0001	0.0230	-
AUC_{12h}, ng·h/ml	14	5766	7738	134.2	118 - 153	0.0015	-	-
		Median				p-value		
Parameter	n	Treatment A (reference)	Treatment C (test)	Treatment difference median	90% CI[1]	Treatment	Period	Sequence
t_{max}, h	14	5.0	4.5	0.50	(0.00 - 0.50)	0.0298	0.7624	0.4924

[1] 90% confidence intervals
- excluded from final model

Table 9 shows the statistical evaluation of the pharmacokinetics of RTV for treatment B and treatment C (panel 2).

Table 9: Statistical evaluation of the pharmacokinetics of RTV for treatment B and treatment C (panel 2).

RTV		Least square means		Least square means ratio %	90% CI[1]	p-value		
Parameter	n	Treatment B (reference)	Treatment C (test)			Treatment	Period	Sequence
C_{min}, ng/ml	12	201.7	118.8	58.89	30.5 - 114	0.1760	-	-
C_{max}, ng/ml	12	1467	1152	78.41	58.5 - 111	0.2365	-	-
AUC_{12h}, ng·h/ml	12	8613	6997	81.23	61.0 - 108	0.2183	-	-
		Median				p-value		
Parameter	n	Treatment B (reference)	Treatment C (test)	Treatment difference median	90% CI[1]	Treatment	Period	Sequence
t_{max}, h	12	5.0	5.0	0.00	(-1.00 - 1.50)	0.9347	0.8700	0.9353

[1] 90% confidence intervals
- excluded from final model

When TMC114 400 mg b.i.d. was added to SQV/RTV 1000/100 mg b.i.d, the C_{min}, C_{max}, and AUC_{12h} of RTV were decreased. However, these decreases did not reach statistical significance.

7. Safety Assessments

Fourteen subjects in panel 1 and all subjects in panel 2 reported at least one adverse event during the trial. No grade 4 abnormalities were reported in the trial. 4 subjects in panel 1 developed a treatment-emergent grade 3 elevation in cholesterol (3 during treatment with TMC/RTV and 2 during treatment with TMC114/RTV/SQV). For panel 2, a treatment-emergent grade 3 elevation was noted for cholesterol (1 subject during treatment with SQV/RTV), plasma prothrombin time (2 subjects during treatment with SQV/RTV) and total bilirubin (1 subject during treatment with TMC114/SQV/RTV). Six subjects in

panel 1 and 4 subjects in panel 2 developed laboratory abnormalities (See details in Medical Officer's review).

8. Conclusion

- The results of the demonstrate that C_{min}, C_{max}, and AUC_{12h} of TMC114 were statistically significantly decreased by 42 %, 17 %, and 26 % respectively, when SQV 1000 mg b.i.d. was added to TMC114/RTV 400/100 mg b.i.d.
- The addition of TMC114 400 mg b.i.d. to SQV/RTV 1000/100 mg b.i.d. did not lead to statistically significant changes in SQV pharmacokinetics.

Labeling Recommendation

Due to a decrease in the exposure (AUC) of darunavir by 26%, appropriate doses of the combination have not been established. Hence, it is not recommended to coadminister saquinavir and PREZISTA, with or without low-dose ritonavir.

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio- 1

1. Title

The pharmacokinetic interaction between TMC114 and indinavir, both co-administered with a low dose of ritonavir, in healthy subjects **(TMC114-C141).**

2. Objectives

The objectives of this trial were:

- To determine the effect of steady-state concentrations of TMC114 on the steady state concentrations of indinavir, both in combination with a low dose of RTV.
- To determine the effect of steady-state concentrations of indinavir on TMC114, both in combination with a low dose of RTV.
- To determine the short term safety and tolerability of co-administration of TMC114, low-dose RTV, and clarithromycin.

3. Study Design

Phase I, open label, randomized, 3-way crossover trial in healthy subjects to investigate the pharmacokinetic interaction between repeated dosing of indinavir (IDV) and TMC114, both in combination with a low dose (100 mg) of RTV, at steady-state. The study population consisted of 18 healthy subjects. Each subject received treatment A, B, and C in three sessions.

Treatment A: 400 mg TMC114/100 mg RTV b.i.d. was administered for 6 days, with an additional morning dose on day 7.

Treatment B: Indinavir 800 mg/RTV 100 mg b.i.d. was administered for 6 days, with an additional morning dose on day 7.

Treatment C: TMC114/IDV/RTV 400/800/100 mg b.i.d. was administered for 6 days, with an additional morning dose on day 7.

All the treatments were administered under fed conditions. Subsequent sessions were separated by a washout period of 7 days. In every session, full pharmacokinetic profiles were determined for each compound for one dosing interval after the morning dose on day 7.

4. Drugs Used in the Trial

Table 1 shows the drugs used in the trial.

Table 1: Description of Drugs Used in the Trial

	TMC114	RTV	IDV
Dosage Form	Tablet [redacted]	Capsule	Capsule
Strength	400 mg	100 mg	400 mg
Batch Number	PD1098	-	-
Expiry Date	October 2005	-	-

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

For session 1, 2, and 3, blood samples (5 mL) were collected (immediately before drug intake) on day 1, 5, and 6. On day 7, in addition to the pre-dose sample, blood samples were collected at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, and 12 hrs after dosing. The plasma concentrations of TMC114, RTV, and IDV were determined using validated LC-MS/MS methods. The lower limit of quantification was 10, 5, and 2 ng/mL for TMC114, RTV, and IDV respectively.

Pharmacokinetic Assessments

Winnonlin Professional™ ([redacted] was used for all pharmacokinetic assessments. Descriptive statistics were calculated for the plasma concentrations of TMC114, RTV, and IDV at each time point and for the derived pharmacokinetic parameters. The statistical analyses were performed comparing treatment C (test) versus treatment A (reference) for TMC114 and RTV and comparing treatment C (test) versus treatment B (reference) for IDV and RTV.

6. Results

6.1 Subject Disposition

18 subjects were randomized, however, 1 subject was excluded (the subject did not meet the inclusion/exclusion criteria) before any trial medication was administered. Therefore, in session 1, 17 subjects were randomized to the following six treatment sequences: ABC (3 subjects), CAB (2 subjects), BCA (3 subjects), ACB (3 subjects), CBA (3 subjects), and BAC (3 subjects). In going from session 1 to session 2, one subject discontinued from each of the following sequences ABC, CAB, BCA, and CBA. Similarly two subjects discontinued from the following sessions: ACB and BAC. There were no discontinuations between session 2 and session 3. Table 2 shows the demographics.

Table 2: Demographics in Study TMC114-C141

Parameter	Treatment ABC N = 3	Treatment CAB N = 2	Treatment BCA N = 3	Treatment ACB N = 3	Treatment CBA N = 3	Treatment BAC N = 3	All subjects N = 17
Age, years	25.0	27.5	24.0	20.0	26.0	28.0	25.0
Median (range)	(22-39)	(21-34)	(23-27)	(19-23)	(23-29)	(25-42)	(19-42)
Height, cm	155.0	171.0	170.0	156.0	160.0	155.0	160.0
Median (range)	(152-175)	(168-174)	(159-174)	(153-175)	(155-166)	(153-184)	(152-184)
Weight, kg	65.0	83.5	65.0	64.0	59.0	63.0	65.0
Median (range)	(46-77)	(78-89)	(49-89)	(55-70)	(49-68)	(62-73)	(46-89)
BMI, kg/m²	25.1	28.5	22.5	22.9	24.6	25.8	24.7
Median (range)	(20-28)	(28-29)	(19-29)	(23-27)	(19-25)	(22-27)	(19-29)
Gender, n (%)							
Male	0	1 (50)	1 (33)	1 (33)	0	1 (33)	4 (24)
Female	3 (100)	1 (50)	2 (67)	2 (67)	3 (100)	2 (67)	13 (76)
Ethnic Origin, n (%)							
Black	0	0	0	0	1 (33)	0	1 (6)
Caucasian/White	1 (33)	1 (50)	1 (33)	1 (33)	0	1 (33)	5 (29)
Hispanic	2 (67)	0	2 (67)	2 (67)	2 (67)	2 (67)	10 (59)
Other	0	1 (50)	0	0	0	0	1 (6)

n: number of subjects with data.

6.2 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time curve of TMC114 on day 7 after oral administration of 400/100 mg TMC114/RTV b.i.d. (treatment A) and 400/800/100 mg TMC114/IDV/RTV b.i.d. (treatment C).

Fig 1: Mean plasma concentration-time curve of TMC114 on day 7 after oral administration of 400/100 mg TMC114/RTV b.i.d. (treatment A) and 400/800/100 mg TMC114/IDV/RTV b.i.d. (treatment C).

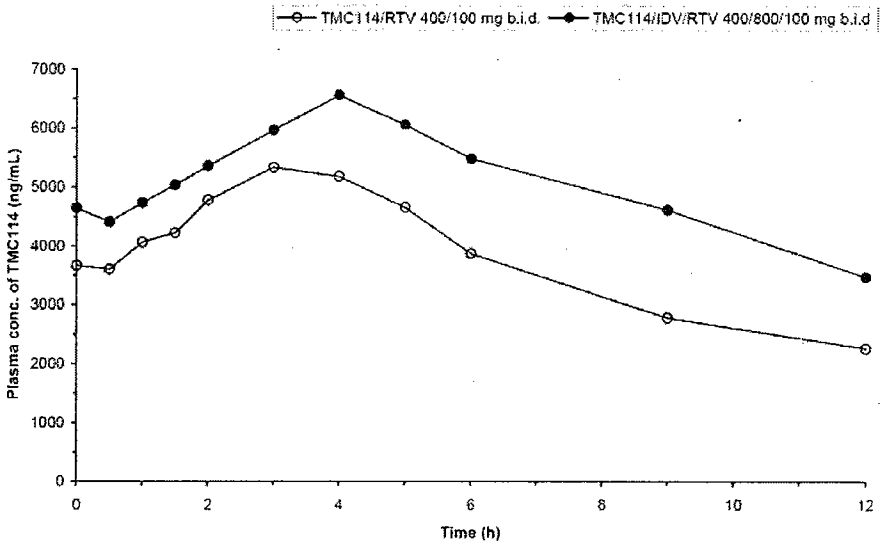


Table 3 shows the pharmacokinetic results of TMC114 after oral administration of TMC114/RTV alone (treatment A) and in the presence of IDV (treatment C).

Table 3: Pharmacokinetic results of TMC114 after oral administration of TMC114/RTV alone (treatment A) and in the presence of IDV (treatment C)

Pharmacokinetics of TMC114 (mean±SD, t_{max} median (range))	Treatment A: TMC114/RTV 400/100 mg b.i.d.	Treatment C: TMC114/IDV/RTV 400/800/100 mg b.i.d.
n	12[a]	11[b]
Day 1		
C_{0h}, ng/mL	0	0
Day 5		
C_{0h}, ng/mL	3474 ± 1240	4651 ± 2103
Day 6		
C_{0h}, ng/mL	3458 ± 1035	4607 ± 1890
Day 7		
C_{0h}, ng/mL	3666 ± 1168	4658 ± 2259
C_{min}, ng/mL	2160 ± 835.1	3331 ± 1554
C_{max}, ng/mL	5768 ± 1374	6831 ± 1999
t_{max}, h	3.0 (2.0 - 5.0)	4.0 (0.0 - 6.0)
AUC_{12h}, ng.h/mL	45698 ± 13727	60831 ± 22060
$C_{ss,av}$, ng/mL	3808 ± 1144	5069 ± 1838
FI, %	99.75 ± 29.36	76.52 ± 29.11

0 = NQ (< 10.0 ng/mL)
[a] n=11 for C_{0h} (Day 7) and n=10 for C_{min}, C_{max}, t_{max}, AUC_{12h}, $C_{ss,av}$ and FI
[b] n=10 for C_{0h} (Day 7), C_{min}, C_{max}, t_{max}, AUC_{12h}, $C_{ss,av}$ and FI

The plasma concentration of TMC114 in predose samples (C_{0h}) of day 1 in both treatments were below the LLOQ, indicating that a washout period of 7 days between consecutive treatments was sufficient.

Table 4 shows the summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment C (TMC114/IDV/RTV) compared to treatment A (TMC114/RTV).

Table 4: Statistical analysis of the pharmacokinetic parameters of TMC114 of treatment C (TMC114/IDV/RTV) compared to treatment A (TMC114/RTV).

Parameter	n	Least square means		Least square means ratio, %	90% CI [a]	p-value		
		Treatment A (reference)	Treatment C (test)			Treatment	Period	Sequence
C_{0h}, ng/mL	9	3493	3824	109.5	88.4 - 135	0.4529	-	-
C_{min}, ng/mL	9	1892	2721	143.8	113 - 182	0.0214	-	-
C_{max}, ng/mL	9	5642	6282	111.4	98.2 - 126	0.1493	-	-
AUC_{12h}, ng.h/mL	9	45901	57031	124.2	109 - 142	0.0159	-	0.0721
Parameter	n	Median		Treatment difference median	90% CI [a]	p-value		
		Treatment A (reference)	Treatment C (test)			Treatment	Period	Sequence
t_{max}, h	9	3.0	4.0	-0.75	(-1.50) - (0.00)	0.0808	0.3428	0.7710

[a] 90% confidence intervals
- excluded from final model

IDV

Fig 2 shows the mean plasma concentration time curves of IDV on day 7 after oral administration of 800/100 mg IDV/RTV b.i.d. (treatment B) and 400/800/100 mg TMC114/IDV/RTV b.i.d. (treatment C).

Fig 2: Mean plasma concentration time curves of IDV on day 7 after oral administration of 800/100 mg IDV/RTV b.i.d. (treatment B) and 400/800/100 mg TMC114/IDV/RTV b.i.d. (treatment C).

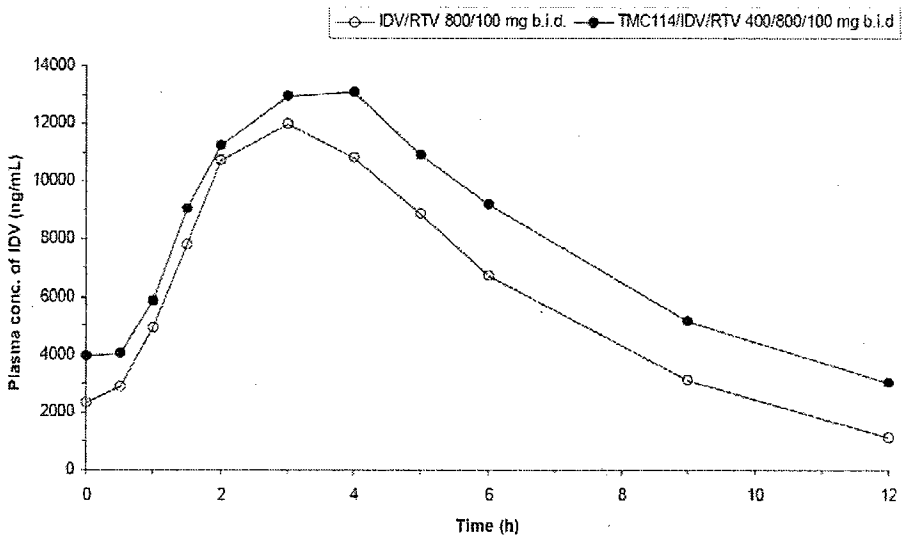


Table 5 shows the pharmacokinetic results of IDV after oral administration of IDV/RTV alone (treatment B) and in the presence of TMC114 (treatment C).

Table 5: Pharmacokinetic results of IDV after oral administration of IDV/RTV alone (treatment B) and in the presence of TMC114 (treatment C).

Pharmacokinetics of indinavir (mean±SD, t_{max} median (range))	Treat B: IDV/RTV 800/100 mg b.i.d.	Treat C: TMC114/IDV/RTV 400/800/100 mg b.i.d.
n	12[a]	11[b]
Day 1		
C_{tau}, ng/mL	0	0
Day 5		
C_{tau}, ng/mL	2970 ± 1173	4722 ± 2687
Day 6		
C_{tau}, ng/mL	3203 ± 1791	4627 ± 2705
Day 7		
C_{tau}, ng/mL	2305 ± 1175	3950 ± 1976
C_{min}, ng/mL	1134 ± 589.2	2750 ± 1257
C_{max}, ng/mL	12687 ± 1980	14100 ± 2688
t_{max}, h	3.0 (2.0 - 5.0)	3.0 (2.0 - 5.0)
AUC_{12h}, ng.h/mL	73058 ± 15896	94550 ± 23129
$C_{t,av}$, ng/mL	6088 ± 1325	7879 ± 1927
FL, %	193.4 ± 28.32	148.1 ± 23.09

0 = NQ (< 20.0 ng/mL)
[a] n=10 for C_{tau} (Day 7) and n=9 for C_{min}, C_{max}, t_{max}, AUC_{12h}, $C_{t,av}$ and FI (Day 7)
[b] n=10 for all parameters of Day 7

The plasma concentrations of IDV in predose samples of day 1 of both treatments were below LLOQ, indicating that a washout period of 7 days between consecutive treatments was sufficient.

Table 6 shows the summary of the statistical analysis of the pharmacokinetic parameters of IDV of treatment C (TMC114/IDV/RTV) compared to treatment B (IDV/RTV)

Table 6: Summary of the statistical analysis of the pharmacokinetic parameters of IDV of treatment C (TMC114/IDV/RTV) compared to treatment B (IDV/RTV)

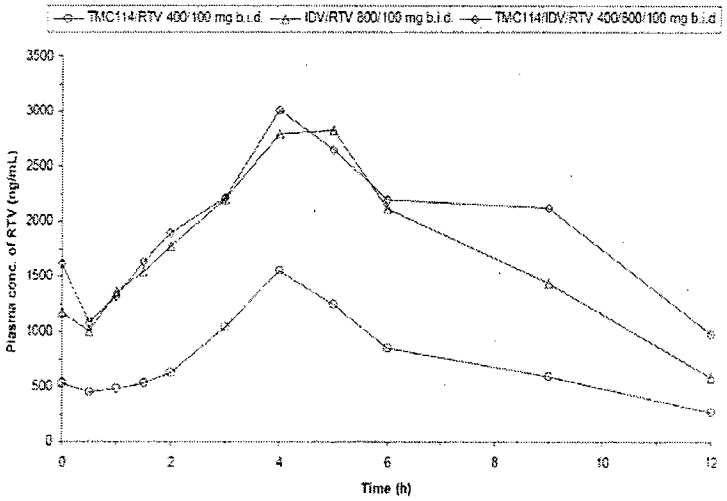
Parameter	n	Least square means		Least square means ratio, %	90% CI [a]	p-value		
		Treatment B (reference)	Treatment C (test)			Treatment	Period	Sequence
$C_{ss,max}$, ng/mL	9	2106	3261	154.8	112 - 215	0.0381	-	-
C_{min}, ng/mL	9	1027	2310	224.8	163 - 310	0.0016	-	-
C_{max}, ng/mL	9	12539	13525	107.8	95.0 - 122	0.3012	-	-
AUC_{12h}, ng·h/mL	9	71679	88028	122.8	106 - 142	0.0288	-	-
Parameter	n	Median		Treatment difference median	90% CI [a]	p-value		
		Treatment B (reference)	Treatment C (test)			Treatment	Period	Sequence
t_{max}, h	9	3.0	3.0	-0.50	(-1.50) - (0.50)	0.3105	1.000	1.000

[a] 90% confidence interval.
- : excluded from final model

RTV

Fig 3 shows the mean plasma concentration time curves of ritonavir on day 7 after oral administration of 400/100 mg TMC114/RTV b.i.d. (treatment A), 800/100 mg IDV/RTV b.i.d. (treatment B) and 400/800/100 mg TMC114/IDV/RTV b.i.d. (treatment C).

Fig 3: Mean plasma concentration time curves of ritonavir on day 7 after oral administration of 400/100 mg TMC114/RTV b.i.d. (treatment A), 800/100 mg IDV/RTV b.i.d. (treatment B) and 400/800/100 mg TMC114/IDV/RTV b.i.d. (treatment C).



Visual inspection of the mean plasma concentration-time curves reveals that at steady-state, co-administration of TMC114/RTV and IDV (treatment C) resulted in higher concentrations of RTV than after administration of TMC114/RTV alone (treatment A). Administration of IDV/RTV alone (treatment B) or in the presence of TMC114 (treatment C) resulted in comparable plasma concentration-time profiles of RTV.

Table 7 shows the pharmacokinetic results of RTV after oral administration of TMC114/RTV alone (treatment A), IDV/RTV alone (treatment B) and co-administration of TMC114, IDV, and RTV (treatment C).

Table 7: Pharmacokinetic results of RTV after oral administration of TMC114/RTV alone (treatment A), IDV/RTV alone (treatment B) and co-administration of TMC114, IDV, and RTV (treatment C).

Pharmacokinetics of ritonavir (mean±SD, t_{max} median (range))	Treatment A: TMC114/RTV 400/100 mg b.i.d.	Treatment B: IDV/RTV 800/100 mg b.i.d.	Treatment C: TMC114/IDV/RTV 400/800/100 mg b.i.d.
n	12[a]	12[b]	11[c]
Day 1			
C_{0h}, ng/mL	0	0	0
Day 5			
C_{0h}, ng/mL	459.7 ± 263.2	1383 ± 518.0	1789 ± 1174
Day 6			
C_{0h}, ng/ml	526.8 ± 203.3	1337 ± 430.9	1740 ± 1244
Day 7			
C_{0h}, ng/mL	525.6 ± 254.7	1177 ± 446.3	1613 ± 1280
C_{min}, ng/mL	279.5 ± 100.7	580.8 ± 194.6	801.2 ± 339.9
C_{max}, ng/mL	1696 ± 725.0	3127 ± 814.1	3516 ± 1247
t_{max}, h	4.0 (0.0 - 5.0)	4.0 (1.5 - 5.0)	4.0 (0.0 - 9.0)
AUC_{12h}, ng/h/mL	9167 ± 3219	20212 ± 5190	23937 ± 6314
$C_{ss,av}$, ng/mL	763.9 ± 268.2	1684 ± 432.5	1995 ± 526.2
F1, %	181.9 ± 39.84	146.0 ± 23.23	135.0 ± 39.13

0 = NQ (< 5.00 ng/mL)
[a] n=11 for C_{0h} and C_{min} (Day 7) and n=10 for C_{max}, t_{max}, AUC_{12h}, $C_{ss,av}$ and F1 (Day 7)
[b] n=10 for C_{0h}, C_{min} and t_{max} (Day 7) and n=9 for C_{max}, AUC_{12h}, $C_{ss,av}$ and F1 (Day 7)
[c] n=10 for all parameters of Day 7

When IDV and RTV were co-administered (treatment B), estimates of mean C_{0h}, C_{min}, C_{max}, and AUC_{24h} values for ritonavir at steady-state showed a comparable systemic exposure to RTV between treatment with IDV/RTV alone and in the presence of TMC114.

Table 8 shows the summary of the statistical analysis of the pharmacokinetic parameters of RTV of treatment C (TMC114/IDV/RTV) compared to treatment A (TMC114/RTV).

Table 8: Summary of the statistical analysis of the pharmacokinetic parameters of RTV of treatment C (TMC114/IDV/RTV) compared to treatment A (TMC114/RTV).

Parameter	n	Least square means: Treatment A (reference)	Least square means: Treatment C (test)	Least square means ratio, %	90% CI [a]	p-value: Treatment	p-value: Period	p-value: Sequence
C_{12h}, ng/mL	9	468.5	1137	242.8	174 - 338	0.0011	-	0.0291
C_{max}, ng/mL	9	243.3	687.7	282.6	230 - 348	<0.0001	-	-
C_{min}, ng/mL	9	1532	3178	207.5	152 - 283	0.0024	-	-
AUC_{12h}, ng.h/mL	9	8295	22030	265.6	215 - 328	<0.0001	-	-
Parameter	n	Median: Treatment A (reference)	Median: Treatment C (test)	Treatment difference median	90% CI [a]	p-value: Treatment	p-value: Period	p-value: Sequence
t_{max}, h	9	4.0	4.0	-1.00	(-3.00) - (1.00)	1.000	1.000	0.7972

[a] 90% confidence intervals.
- : excluded from final model

Table 9 shows the summary of the statistical analysis of the pharmacokinetic parameters of RTV of treatment C (TMC114/IDV/RTV) compared to treatment B (IDV/RTV).

Table 9: Summary of the statistical analysis of the pharmacokinetic parameters of RTV of treatment C (TMC114/IDV/RTV) compared to treatment B (IDV/RTV).

Parameter	n	Least square means: Treatment B (reference)	Least square means: Treatment C (test)	Least square means ratio, %	90% CI [a]	p-value: Treatment	p-value: Period	p-value: Sequence
C_{12h}, ng/mL	9	1070	1145	107.0	77.4 - 148	0.7069	-	0.0163
C_{max}, ng/mL	9	565.4	700.3	123.8	92.2 - 166	0.2147	-	0.0736
C_{min}, ng/mL	9	2929	3178	108.5	85.8 - 137	0.5364	-	-
AUC_{12h}, ng.h/mL	9	19606	22030	112.4	93.1 - 136	0.2818	-	-
Parameter	n	Median: Treatment B (reference)	Median: Treatment C (test)	Treatment difference median	90% CI [a]	p-value: Treatment	p-value: Period	p-value: Sequence
t_{max}, h	9	4.0	4.0	0.00	(-2.50) - (1.00)	0.7998	0.7062	0.2168

[a] 90% confidence intervals.
- : excluded from final model

7. Safety Assessments

All 17 subjects reported an adverse event at some time during the study. Eight of the 12 subjects (67 %) developed at least one AE during TMC114/RTV treatment, compared to 12/12 (100 %) and 11/11 (100 %) during IDV/RTV and TMC114/IDV/RTV treatment, respectively. The most commonly reported AEs were skin and subcutaneous disorders, nervous system disorders, and GI events. No deaths or SAEs were reported in the trial. (See details in Medical Officer's review).

8. Conclusion

- The results of this study showed that the AUC_{12h} and C_{min} of TMC114 were increased by 24 % and 44 % respectively, when co-administered with IDV, however, this difference was not considered clinically relevant.

- The AUC_{12h}, C_{0h}, and C_{min} of IDV were increased by 23 %, 55 %, and 125 % respectively, after co-administration with IDV. The change is clinically relevant because the 800/100 mg bid regimen provides higher exposure than the approved 800q8hr regimen.
- All three treatments resulted in relatively high discontinuation rates due to maculopapular rash (2-3 subjects, 17-25 %).

Labeling Recommendation

The reference regimen for indinavir used in this study was indinavir/ritonavir 800/100 mg b.i.d., which is an unapproved regimen. Therefore, the labeling recommendation is," The appropriate dose of indinavir in combination with PREZISTA/rtv has not been established".

1. Title

The pharmacokinetic interaction between clarithromycin and TMC114, co-administered with a low dose of ritonavir, in healthy subjects **(TMC114-C142).**

2. Objectives

The objectives of this trial were to determine:

- The effect of steady-state concentrations of TMC114, in combination with a low dose ritonavir, on the steady-state pharmacokinetics of clarithromycin and 14-hydroxy-clarithromycin.
- The effect of steady-state concentrations of clarithromycin on the steady-state pharmacokinetics of TMC114, in combination with a low dose of RTV.

3. Study Design

Phase I, open label, randomized, 3-way crossover trial in healthy subjects to investigate the pharmacokinetic interaction between repeated dosing of clarithromycin and TMC114, in combination with a low dose (100 mg) of ritonavir, all at steady state. The trial population consisted of 18 healthy subjects. Each subject received treatment A, B, and C in three sessions.

Treatment A: 400 mg TMC114/100 mg RTV b.i.d. administered for 6 days, with an additional morning dose on day 7.

Treatment B: 500 mg clarithromycin b.i.d. was administered for 6 days, with an additional morning dose on day 7.

Treatment C: 500 mg clarithromycin b.i.d. and TMC/RTV 400/100 mg b.i.d. was administered for 6 days, with an additional morning dose on day 7 of all the drugs and an evening dose of TMC114/RTV only on Day 7.

All the treatments were administered under fed conditions. Subsequent sessions were separated by a washout period of 7 days. Full pharmacokinetic profiles were determined after the morning dose on day 7 for treatment A and C for TMC114/RTV and on day 7 of treatment B and C for clarithromycin and 14-hydroxy-clarithromycin.

4. Drugs Used in the Trial

Table 1 shows the drugs used in the trial.

Table 1: Description of Drugs Used in the Trial

	TMC114	RTV	Clarithromycin
Dosage Form	Tablet (F001)	Capsule	Tablet
Strength	400 mg	100 mg	500 mg
Batch Number	PD1098	-	-
Expiry Date	April 21, 2005	-	-

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

For treatment A, B, and C, blood samples were collected on day 1 of each session within 2 hours pre-dose. On days 5 and 6, blood samples were collected in each session immediately before drug intake. On day 7, blood samples were collected immediately before drug intake and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, and 12 hours post dose. On day 8, samples were collected for treatment B and C only (for treatment C, only clarithromycin and 14-hydroxy-clarithromycin were measured).

The plasma concentrations of TMC114, RTV, clarithromycin, and 14-hydroxy-clarithromycin were determined by validated LC-MS/MS methods. The lower limit of quantification was 10 ng/mL for TMC114, 5 ng/mL for RTV, and 50 ng/mL for clarithromycin and 14-hydroxy-clarithromycin.

Pharmacokinetic Assessments

Pharmacokinetic and statistical analysis was performed using [redacted]®. The standard pharmacokinetic parameters were computed for TMC114, RTV, CLAR and 14-hydroxy-CLAR on Day 7.

6. Results

6.1 Subject Disposition

26 subjects were screened and 18 subjects were randomized (3 subjects per sequence) to one of the following six treatment sequences: ABC, BCA, CAB, CBA, BAC, and ACB. One subject in sequence ACB withdrew consent. One subject in treatment sequence CBA did not take part in session 2, however, this deviation was approved by the sponsor. Therefore, 16 subjects completed all the study assessments and 1 subject complete assessments during session 1 and session 3.

Table 2 shows the demographics of the study.

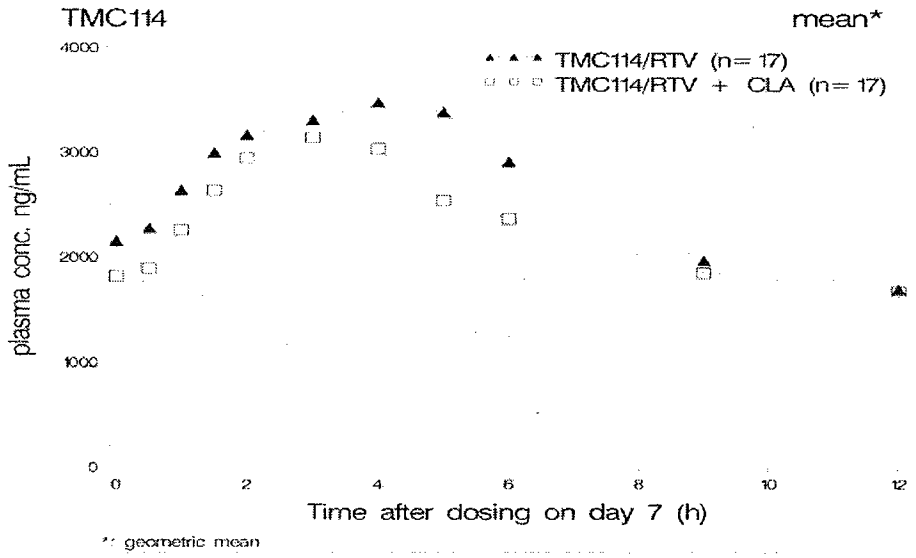
Table 2: Demographics in Study TMC114 C142

Parameter	Treatment A B C N = 3	Treatment B C A N = 3	Treatment C A B N = 3	Treatment C B A N = 3	Treatment B A C N = 3	Treatment A C B N = 3	All Subjects N = 18
Age, years	22.0	21.0	19.0	20.0	25.0	26.0	20.5
Median (range)	(20-30)	(20-30)	(19-19)	(19-46)	(18-28)	(18-44)	(18-46)
Height, cm	176.0	188.0	177.0	175.0	187.0	179.0	181.0
Median (range)	(171-182)	(186-189)	(176-185)	(174-187)	(180-188)	(172-184)	(171-189)
Weight, kg	67.0	79.0	66.0	70.0	83.0	74.0	75.0
Median (range)	(65-79)	(79-100)	(57-92)	(68-76)	(68-84)	(58-81)	(57-100)
BMI, kg/m²	22.9	22.8	21.3	22.2	23.5	23.1	22.9
Median (range)	(21-24)	(22-28)	(18-27)	(20-25)	(21-24)	(20-24)	(18-28)
Sex, n (%)							
Male	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)	18 (100)
Ethnic Origin, n (%)							
Caucasian white	3 (100)	2 (67)	3 (100)	3 (100)	3 (100)	3 (100)	17 (94)
Hispanic	0	1 (33)	0	0	0	0	1 (6)
Type of Smoker, n (%)							
Light	2 (67)	1 (33)	1 (33)	0	1 (33)	1 (33)	6 (33)
Nonsmoker	1 (33)	2 (67)	2 (67)	3 (100)	2 (67)	2 (67)	12 (67)

6.2 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time curve of TMC114 when administered alone or co-administered with clarithromycin.

Fig 1: Mean plasma concentration-time curves of TMC114 when administered alone or co-administered with clarithromycin.



Visual inspection of the plots indicates that the plasma concentration-time curves of TMC114 following the test treatment (TMC114/RTV + CLAR) are lower than or similar to those following the reference treatment. Table 3 shows the pharmacokinetic parameters of TMC114 when administered alone or when co-administered with clarithromycin.

Table 3: Pharmacokinetic parameters of TMC114, when administered alone or when co-administered with Clarithromycin.

Pharmacokinetics of TMC114 (mean ± SD, t_{max}: median [range])	Test TMC114/RTV + CLAR	Reference TMC114/RTV
n	17	17
C_{0h} (ng/mL)	2010 ± 832	2249 ± 654
C_{max} (ng/mL)	3506 ± 1015	4108 ± 874
C_{min} (ng/mL)	1612 ± 564	1613 ± 566
AUC_{12h} (ng.h/mL)	29154 ± 8471	32734 ± 7915
t_{max} (h)	3.0 [1.5-5.0]	3.0 [1.5-5.0]

Table 4 shows the results of the statistical comparison of the pharmacokinetic parameters of TMC114 between the combined treatment (test) and TMC114/RTV alone (reference).

Table 4: Statistical Evaluation of TMC114 Pharmacokinetics.

TMC114		Least squares means				p-value		
Parameter	n	Test TMC114/RTV + CLA	Reference TMC114/RTV	Ratio test/ref (%)	90% CI[a] (%)	Treatment	Period	Sequence
C_{min} (ng/mL)	17	1523	1509	101	81 – 126	0.9401	0.6220	0.4427
C_{max} (ng/mL)	17	3302	3982	83	72 – 96	0.0423	0.6136	0.3877
AUC_{12h} (ng.h/mL)	17	27287	31385	87	75 – 101	0.1166	0.6796	0.5308

ref: reference
[a] 90% confidence interval of ratio

RTV

Fig 2 shows the mean plasma concentration-time profiles of RTV, administered as 400/100 TMC114/RTV b.i.d. in the absence or presence of clarithromycin 500 mg bid.

Fig 2: Mean plasma concentration-time profiles of RTV, administered as 400/100 TMC114/100 mg RTV b.i.d. in the absence or presence of clarithromycin 500 mg bid.

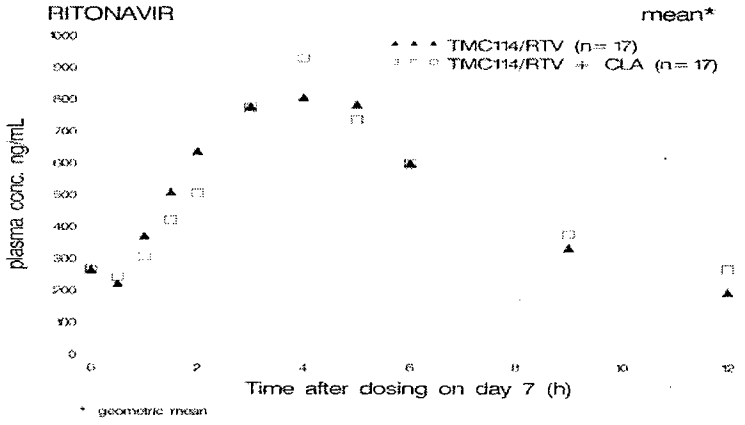


Table 5 shows the pharmacokinetic parameters of RTV, administered as 400/100 TMC114/100 mg RTV b.i.d., in the absence or presence of clarithromycin 500 mg bid.

Table 5: Pharmacokinetic parameters of RTV, administered as 400/100 TMC114/100 mg RTV b.i.d., in the absence or presence of clarithromycin 500 mg bid.

Pharmacokinetics of RTV (mean ± SD, t_{max}: median [range])	Test TMC114/RTV + CLAR	Reference TMC114/RTV
n	17	17
C_{0h} (ng/mL)	340 ± 243	325 ± 198
C_{max} (ng/mL)	1153 ± 585	1096 ± 393
C_{min} (ng/mL)	235 ± 182	197 ± 121
AUC_{12h} (ng.h/mL)	7139 ± 3699	6838 ± 2849
t_{max} (h)	4.0 [1.5-5.0]	3.0 [1.0-5.0]

Table 6 shows the statistical evaluation of the pharmacokinetics of RTV.

Table 6: Statistical evaluation of the pharmacokinetics of RTV.

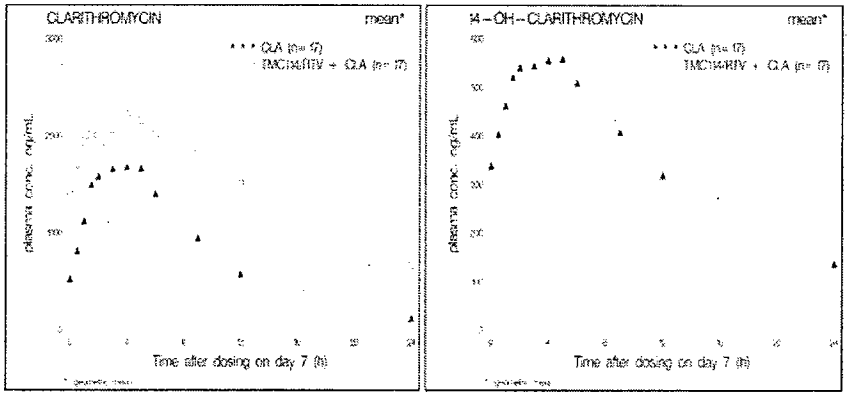
RTV		Least squares means				p-value		
Parameter	n	Test TMC114/RTV + CLA	Reference TMC114/RTV	Ratio test/ref (%)	90% CI* (%)	Treatment	Period	Sequence
C_{0h} (ng/mL)	17	197	158	124	94 - 164	0.1884	0.8264	0.0331
C_{max} (ng/mL)	17	1015	1032	98	84 - 115	0.8881	0.7032	0.2311
AUC_{12h} (ng.h/mL)	17	6227	6222	100	86 - 117	0.9931	0.8970	0.0710

*90% confidence interval of ratio
Ref: reference

Clarithromycin and 14-hydroxy Clarithromycin

Fig 3 shows the mean plasma concentration-time profiles of clarithromycin and 14-hydroxy clarithromycin alone, and in the presence of TMC114/RTV 400/100 mg.

Fig 3: Mean plasma concentration-time profiles of clarithromycin and 14-hydroxy clarithromycin alone, and in the presence of TMC114/RTV 400/100 mg.



Visual inspection of the plots suggests that clarithromycin plasma concentrations for the test (combined) treatment were higher than those following the reference treatment. 14-hydroxy-clarithromycin plasma concentration-time curves for the test treatment were all below the limit of quantification.

Table 7 and 8 show the summary of pharmacokinetic parameters of clarithromycin and 14-hydroxy clarithromycin respectively.

Table 7: Pharmacokinetic parameters of Clarithromycin when administered alone and in the presence of TMC114/RTV 400/100 mg BID.

Pharmacokinetics of CLAR (mean ± SD, t_{max}: median [range])	Test TMC114/RTV + CLAR	Reference CLAR
n	17	16
C_{0h} (ng/mL)	1514 ± 657	582 ± 267
C_{max} (ng/mL)	2711 ± 887	2261 ± 826
C_{min} (ng/mL)	1298 ± 466	501 ± 196
AUC_{12h} (ng.h/mL)	23867 ± 6169	15619 ± 4395
t_{max} (h)	2.0 [1.0-5.0]	3.0 [1.0-6.0]

Table 8: Pharmacokinetic parameters of 14-hydroxy Clarithromycin (after administration of clarithromycin) when administered alone and in the presence of TMC114/RTV 400/100 mg BID.

Pharmacokinetics of 14-hydroxy-CLAR (mean ± SD, t_{max}: median [range])	Test TMC114/RTV + CLA	Reference CLA
n	17	16
C_{0h} (ng/mL)	-*	355 ± 119
C_{max} (ng/mL)	-*	666 ± 269
C_{min} (ng/mL)	-*	319 ± 122
AUC_{12h} (ng.h/mL)	-*	5981 ± 2255
t_{max} (h)	-*	3.0 [1.5-6.0]

*: after combined treatment are concentration values were below LLOQ (50 ng/mL)

Table 9 shows the statistical evaluation of the pharmacokinetic parameters of clarithromycin.

Table 9: Statistical evaluation of the pharmacokinetics of clarithromycin.

Clarithromycin		Least squares means				p-value		
Parameter	n	Test TMC114/RTV + CLA	Reference CLA	Ratio test/ref (%)	90% CI[a] (%)	Treatment	Period	Sequence
C_{min} (ng/mL)	17	1348	492	274%	230–326%	<.0001	0.0857	0.7115
C_{max} (ng/mL)	17	2580	2051	126%	103–154%	0.0653	0.9343	0.0027
AUC_{12h} (ng.h/mL)	17	23271	14780	157%	135–184%	0.0002	0.3270	0.1769

[a] 90% confidence interval of ratio

7. Safety Assessments

- Sixteen (89%) subjects reported at least one AE during this trial, of which 4 (22%) reported at least one AE during treatment with TMC114/RTV, 7 (44%) during treatment with CLAR and 14 (82%) during treatment with TMC114/RTV/CLAR.
- The most commonly reported AEs were nervous system disorders (12/18, 67%) and GI disorders (9/18, 50%). In general, nervous system disorders occurred more frequently during treatments including CLAR, whereas the incidence of GI disorders was comparable between all treatments. Dysgeusia was the most commonly reported nervous system related AE in the trial and was reported in 10/17 (59 %) and 2/16 (13 %) subjects during treatment with TMC114/RTV/CLAR and CLAR, respectively. Dysgeusia was not reported during treatment with TMC114/RTV.

Note: For details, please refer to the Medical Officer's review.

8. Conclusion

- The results of this trial showed that the exposure to TMC114 (expressed as AUC_{12h}) decreased by 13 % when combined with CLAR. Similarly, the C_{max} of TMC114 is decreased by 17 % if combined with CLAR. The C_{min} of TMC114 was not significantly affected by concomitant administration of CLAR.
- The exposure to CLAR (expressed as AUC_{12h}) is increased by 57% when combined with TMC114/RTV. The C_{max} and C_{min} of CLAR were increased by 26% and 174%, respectively, when combined with TMC114/RTV.
- Plasma concentrations of 14-hydroxy-CLAR were reduced to below the limits of detection when combined with TMC/RTV. This is probably explained by the inhibition of CYP3A4 by TMC114/RTV.

Labeling Recommendation (based on similar drug interaction results as with other ritonavir boosted PIs)

No dose adjustment of darunavir or clarithromycin is required for patients with normal renal function. For patients with renal impairment, the following dose adjustments should be considered:

- *For subjects with CLcr of 30-60 mL/min, the dose of clarithromycin should be reduced by 50 %.*
- *For subjects with CLcr of <30 mL/min, the dose of clarithromycin should be reduced by 75 %.*

1. Title

The pharmacokinetic interaction between TMC114 and atazanavir, both in the presence of low dose of ritonavir, in healthy subjects **(TMC114-C149).**

2. Objectives

The objectives of this trial were:

- To investigate the effect of steady-state concentrations of atazanavir (ATV) on the steady state pharmacokinetics of TMC114, in combination with a low dose of ritonavir.
- To investigate the effect of steady-state concentrations of TMC114 on the steady-state pharmacokinetics of ATV, in combination with a low dose of RTV.

3. Study Design

Phase I, open label, randomized, 3-way crossover trial in healthy subjects to investigate the pharmacokinetic interaction between repeated dosing of TMC114 and atazanavir, both in combination with a low dose of RTV. The study population was to consist of 18 healthy subjects. Each subject received treatment A, B, and C in three sessions.

Treatment A: 400 mg TMC114/100 mg RTV b.i.d. was administered for 6 days, with an additional morning dose on day 7.

Treatment B: 300 mg ATV/100 mg RTV q.d. was administered for 7 days.

Treatment C: 300 mg ATV q.d. and 400 mg TMC114/100 mg b.i.d. RTV were administered for 7 days.

All the treatments were administered under fed conditions. Subsequent sessions were separated by a washout period of 7 days. In every session, full pharmacokinetic profiles were determined for each compound for one dosing interval after the morning dose on day 7.

4. Drugs Used in the Trial

Table 1 shows the drugs used in the trial.

Table 1: Description of Drugs Used in the Trial.

	TMC114	RTV	ATV (Reyataz™)
Dosage Form	Tablet (F001)	Capsule	Capsule
Strength	400 mg	100 mg	150 mg
Batch Number	343206	-	-
Expiry Date	April 2005	-	-

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

For treatment A, plasma samples (5 mL) were collected (immediately before drug intake) on day 1 (within 2 hours before drug intake), immediately before drug intake on days 5, 6, and 7, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12 hours after dosing on Day 7. The sample collection times of treatment B were identical to treatment A except that two additional samples (16 hours on day 7 and 24 hours on day 8) were also collected. Similarly, the sample collection times for treatment C were identical to treatment A except that two additional samples for determination of ATV (16 hours on day 7 and 24 hours on day 8) were also collected.

The plasma concentrations of TMC114, ATV, and RTV were determined by validated LC-MS/MS methods. The lower limit of quantification was 10 ng/mL for TMC114, 5 ng/mL for RTV, and 250 ng/mL for ATV.

Pharmacokinetic Assessments

Pharmacokinetic and statistical analysis was done using WinNonlin Professional™. [redacted] and Microsoft Excel® (version 2000; Microsoft, [redacted] was used for the pharmacokinetic analysis.

Statistical analyses were performed using Treatment C as test and Treatment A as reference for TMC114 and using Treatment C as test and Treatment B as reference for ATV. The primary pharmacokinetic parameters were C_{0h}, C_{min}, C_{max} and AUC_{12h} (for TMC114) or AUC_{24h} (for ATV) on the logarithmic scale. Only paired observations for test and reference were included in a statistical analysis. The least square (LS) means of the primary parameters for each treatment group were estimated with a linear mixed effects model, controlling for treatment, sequence and period as fixed effects and subject as a random effect.

6. Results

6.1 Subject Disposition

23 subjects were randomized to the following six treatment sequences: ABC (4 subjects), BCA (4 subjects), CAB (3 subjects), CBA (4 subjects), BAC (4 subjects), and ACB (4 subjects). 11 subjects prematurely discontinued treatment. Nine subjects discontinued during Session 1 (1 subject after Treatment A, 4 subjects during Treatment B and 3 subjects during Treatment C and 1 subject after Treatment C). Two subjects discontinued treatment in Session 2 (1 after Treatment B and 1 after Treatment C). Therefore, the number of subjects who completed all three sessions in a given sequence is as follows: ABC (4 subjects), BCA (2 subjects), CAB (1 subject), CBA (1 subject), BAC (2 subjects), and ACB (2 subjects).

Table 2 shows the demographics of the study.

Table 2: Demographics of Study TMC114-C149

Demographic parameter	Treatment A-B-C N=4	Treatment B-C-A N=4	Treatment C-A-B N=3	Treatment C-B-A N=4	Treatment B-A-C N=4	Treatment A-C-B N=4	All subjects N=23
Age (years) median (range)	27.0 (23-51)	25.5 (23-36)	29.0 (23-32)	36.0 (24-48)	27.5 (20-46)	25.0 (18-35)	26.0 (18-51)
Height (cm) median (range)	165.0 (154-168)	169.0 (163-176)	171.0 (160-186)	178.5 (150-191)	171.0 (166-180)	170.0 (160-183)	169.0 (150-191)
Weight (kg) median (range)	60.0 (53-73)	71.5 (66-81)	66.0 (58-84)	71.0 (48-104)	73.0 (64-82)	67.5 (65-86)	68.0 (48-104)
BMI (kg/m²) median (range)	22.7 (21-26)	25.5 (24-27)	24.3 (20-26)	23.7 (18-29)	24.6 (23-26)	24.5 (23-26)	24.3 (18-29)
Sex n (%)							
Male	2 (50)	1 (25)	2 (67)	2 (50)	4 (100)	2 (50)	13 (57)
Female	2 (50)	3 (75)	1 (33)	2 (50)	0	2 (50)	10 (43)
Ethnic origin n (%)							
Black	0	1 (25)	0	1 (25)	0	1 (25)	3 (13)
Caucasian	2 (50)	2 (50)	1 (33)	2 (50)	3 (75)	3 (75)	13 (57)
Hispanic	2 (50)	1 (25)	2 (67)	1 (25)	1 (25)	0	7 (30)

Note: The demographics is based on the number of subjects randomized to each treatment group and not the number of subjects who completed all three treatments of a given treatment sequence.

6.2 Pharmacokinetic Analysis

Due to discontinuations during the study, full pharmacokinetic profiles were available for 14 subjects for treatment A, 13 subjects for treatment B, and 15 subjects for treatment C. Since only paired observations were included in the statistical analysis, results of 13 subjects were used for comparing Treatment C versus Treatment A for TMC114 and results of 13 subjects were used for comparing Treatment C versus Treatment B for ATV.

Fig 1 shows the mean plasma concentration-time curve of TMC114 on Day 7, after oral administration of TMC114/RTV 400/100 mg BID (treatment A) and after oral administration of ATV 300 mg q.d. and TMC114/RTV 400/100 mg BID (treatment C).

Fig 1: Mean plasma concentration-time curve of TMC114 on Day 7, after oral administration of TMC114/RTV 400/100 mg BID (treatment A) and after oral administration of ATV 300 mg q.d. and TMC114/RTV 400/100 mg BID (treatment C).

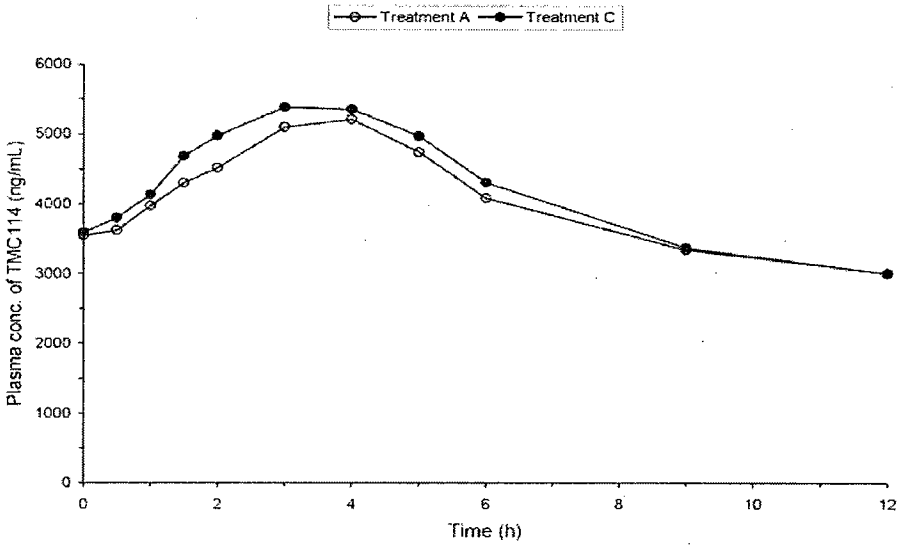


Table 3 shows the pharmacokinetic results of TMC114, after oral administration of TMC114/RTV (treatment A) and TMC114/RTV + ATV (treatment C).

Table 3: Pharmacokinetic results of TMC114, after oral administration of TMC114/RTV (treatment A) and TMC114/RTV + ATV (treatment C)

Pharmacokinetics of TMC114 (mean±SD, t_{max} median (range))	Treatment A: TMC114/RTV 400/100 mg b.i.d.	Treatment C: ATV 300 mg q.d. and TMC114/RTV 400/100 mg b.i.d.
n	14	15[a]
Day 1		
C_{0h}, ng/mL	0	0
Day 5		
C_{0h}, ng/mL	3738 ± 1411	3843 ± 1516
Day 6		
C_{0h}, ng/mL	3502 ± 1460	3544 ± 1415
Day 7		
C_{0h}, ng/mL	3545 ± 1359	3587 ± 1320
C_{min}, ng/mL	2871 ± 1145	2941 ± 1081
C_{max}, ng/mL	5592 ± 1404	5679 ± 1536
t_{max}, h	4.0 (1.5 - 5.0)	3.0 (2.0 - 5.0)
AUC_{12h}, ng.h/mL	47953 ± 15449	49866 ± 15363
$C_{av,12h}$, ng/mL	3996 ± 1287	4155 ± 1280
FI, %	72.5 ± 20.8	69.4 ± 18.3

0 = NQ = Not Quantifiable (< 10.0 ng/mL)
[a] for the parameter C_{0h} of Day 1: n = 20 and for C_{0h} of Day 5: n=17

Individual C/A treatment ratios ranged from 57 % to 147 % for C_{0h}, from 62 % to 162 % for C_{min}, from 89 % to 136 % for C_{max} and from 79 % to 148 % for AUC_{12h}, with geometric mean ratios of 97 %, 101 %, 102 % and 103 %, respectively. Interindividual

variability on C_{0h}, C_{min}, C_{max} and AUC_{12h} values of TMC114 was 38 % and 37 %, 40 % and 37 %, 25 % and 27 %, and 32 % and 31 %, respectively, for Treatments A and C.

Table 4 shows the summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment C (TMC114/RTV and ATV) compared to treatment A (TMC114/RTV).

Table 4: Summary of the statistical analysis of the pharmacokinetic parameters of TMC114 of treatment C (TMC114/RTV and ATV) compared to treatment A (TMC114/RTV)

		Least square means		Least square means ratio, %	90% CI [a]	p-value		
Parameter	n	Treatment A (reference)	Treatment C (test)			Treatment	Period	Sequence
C_{0h}, ng/mL	13	3393	3297	97.17	84.1 - 112	0.7285	-	-
C_{min}, ng/mL	13	2729	2761	101.2	88.0 - 116	0.8841	-	-
C_{max}, ng/mL	13	5471	5592	102.2	95.5 - 109	0.5746	-	-
AUC_{12h}, ng.h/mL	13	46957	48215	102.7	94.0 - 112	0.6021	-	-
		Median				p-value		
Parameter	n	Treatment A (reference)	Treatment C (test)	Treatment difference median	90% CI [a]	Treatment	Period	Sequence
T_{max}, h	13	4.0	3.0	0.0	(-0.5) - (0.75)	0.9362	0.4712	0.2386

[a] 90% confidence intervals.
- : excluded from final model

No statistically significant treatment effects on C_{0h}, C_{min}, C_{max} and AUC_{12h} of TMC114 were observed when comparing values between Treatment A (TMC114/RTV) and Treatment C (TMC114/RTV+ATV). The ratios of the LSmeans were close to 100% for these parameters. The time to reach maximum plasma concentrations (t_{max}) of TMC114 was not statistically significantly affected by the addition of ATV to treatment with TMC114/RTV.

ATV

Fig 2 shows the mean plasma concentration time curves of ATV on day 7, after oral administration of ATV/RTV 300/100 mg q.d. (treatment B), and after oral administration of ATV 300 mg q.d. and TMC114/RTV 400/100 mg b.i.d. (treatment C).

Fig 2: Mean plasma concentration time curves of ATV on day 7, after oral administration of ATV/RTV 300 mg q.d. (treatment B), and after oral administration of ATV 300 mg q.d. and TMC114/RTV 400/100 mg b.i.d. (treatment C).

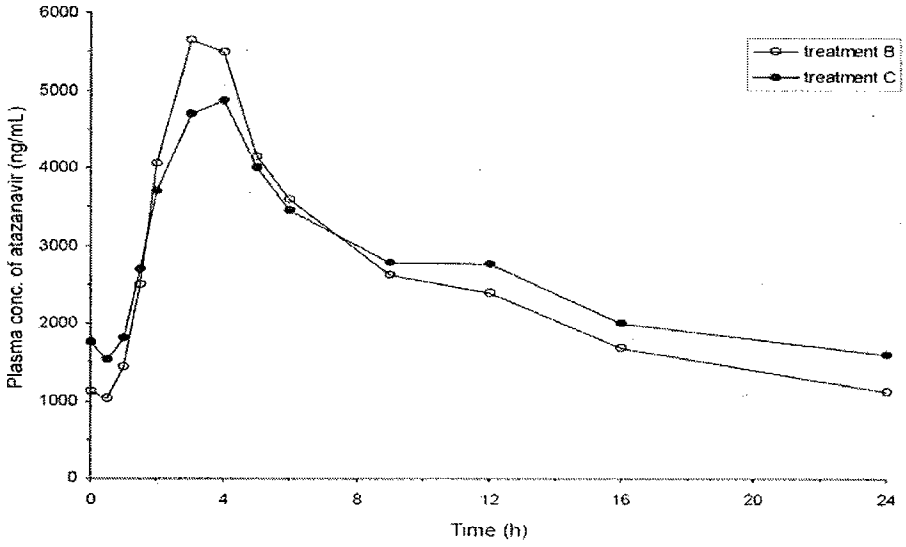


Table 5 shows the pharmacokinetic results of ATV, after oral administration of ATV/RTV (treatment B) and TMC114/RTV +ATV (treatment C).

Table 5: Pharmacokinetic results of ATV, after oral administration of ATV/RTV (treatment B) and TMC114/RTV +ATV (treatment C).

Pharmacokinetics of ATV (mean±SD. t_{max}: median (range))	**Treatment B: ATV/RTV 300/100 mg q.d.**	**Treatment C: ATV 300 mg q.d. and TMC114/RTV 400/100 mg b.i.d.**
n	13[a]	15[b]
Day 1		
C_{0h}, ng/mL	0	0
Day 5		
C_{0h}, ng/mL	1251 ± 486	1823 ± 515
Day 6		
C_{0h}, ng/mL	1061 ± 514	1723 ± 557
Day 7		
C_{0h}, ng/mL	1103 ± 629	1749 ± 575
C_{min}, ng/mL	921 ± 498	1383 ± 632
C_{max}, ng/mL	5827 ± 1837	5175 ± 1274
t_{max}, h	3.0 (2.0 -4.0)	4.0 (2.0 -5.0)
AUC_{24h}, ng.h/mL	59044 ± 20363	62557 ± 17450
$C_{ss,av}$, ng/mL	2460 ± 848	2627 ± 702
FI, %	206 ± 38.1	149 ± 30.6

[a] n=17 on day 1and n=16 on day 5
[b] n=20 on day 1 and n=17 on day 5

In the presence of TMC114 and RTV, systemic exposure to ATV was comparable to that of treatment with ATV/RTV alone, while the C_{0h} and C_{min} values of ATV were increased for all but one subject after the addition of TMC114.

Table 6 shows the summary of the statistical analysis of the pharmacokinetic parameters of ATV of treatment C (TMC114/RTV + ATV) compared to treatment B (ATV/RTV).

Table 6: Summary of the statistical analysis of the pharmacokinetic parameters of ATV of treatment C (TMC114/RTV + ATV) compared to treatment B (ATV/RTV)

		Least square means		Least square means ratio, %	90% CI [a]	p-value		
Parameter	n	Treatment B (reference)	Treatment C (test)			Treatment	Period	Sequence
C_{0h}, ng/mL	13	914.7	1713	187.3	141 - 248	0.0019	-	-
C_{min}, ng/mL	13	744.3	1132	152.1	99.0 - 234	0.1076	-	0.0369
C_{max}, ng/mL	13	5560	4941	88.87	77.9 - 101	0.1349	-	-
AUC_{24h}, ng.h/mL	13	55669	60147	108.0	93.9 - 124	0.3439	-	-
		Median				p-value		
Parameter	n	Treatment B (reference)	Treatment C (test)	Treatment difference median	90% CI [a]	Treatment	Period	Sequence
T_{max}, h	13	3.0	4.0	-0.5	(-1.0)-(0.015)	0.3110	0.6883	0.3656

[a] 90% confidence intervals.
- : excluded from final model

No statistically significant treatment effects on C_{min}, C_{max} and AUC_{24h} of ATV were observed when comparing values between Treatment B (ATV/RTV) and Treatment C (TMC114/RTV+ATV). The ratios of the LSmeans for C_{max} and AUC_{24h} were close to 100 % (89 % and 108 %, respectively). The ratio for the LSmean for C_{min} was higher than 100 %, with a large 90 % CI.

However, in the presence of TMC114/RTV (Treatment C), C_{0h} values of ATV were higher compared to ATV/RTV given alone (Treatment B). Based on the ratio of the LS_{means}, C_{0h} increased by 87 % when ATV/RTV was co-administered with TMC114. The time to reach maximum plasma concentrations (t_{max}) of ATV was not statistically significantly affected by the addition of TMC114 to treatment with ATV/RTV.

RTV

Fig 3 shows the mean plasma concentration-time curves of RTV on day 7, after oral administration of TMC114/RTV 400/100 mg b.i.d. (treatment A), ATV/RTV 300/100 mg q.d. (treatment B), and ATV 300 mg q.d. and TMC114/RTV 400/100 mg b.i.d. (treatment C).

Fig 3: Mean plasma concentration-time curves of RTV on day 7, after oral administration of TMC114/RTV 400/100 mg b.i.d. (treatment A), ATV/RTV 300/100 mg q.d. (treatment B), and ATV 300 mg q.d. and TMC114/RTV 400/100 mg b.i.d. (treatment C)

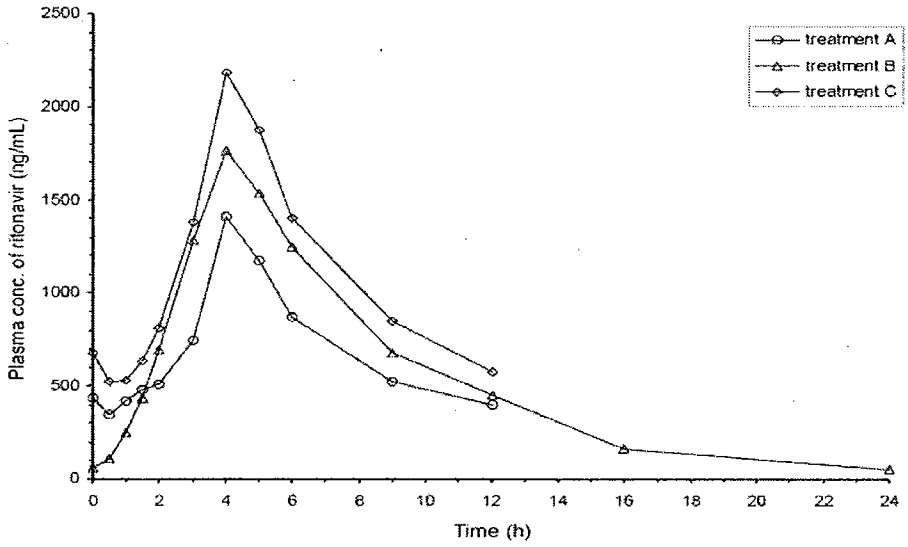


Table 7 shows the pharmacokinetic results of RTV, after oral administration of TMC114/RTV (treatment A), ATV/RTV (treatment B), and TMC114/RTV + ATV (treatment C).

Table 7: Pharmacokinetic results of RTV, after oral administration of TMC114/RTV (treatment A), ATV/RTV (treatment B), and TMC114/RTV + ATV (treatment C).

Pharmacokinetics of RTV (mean±SD. t_{max} median (range))	Treatment A: TMC114/RTV 400/100 mg b.i.d.	Treatment B: ATV/RTV 300/100 mg q.d.	Treatment C: ATV 300 mg q.d. and TMC114/RTV 400/100 mg b.i.d.
n	14	13[b]	15[c]
Day 1			
C_{0h}, ng/mL	0	0	0
Day 5			
C_{0h}, ng/mL	400 ± 211	68.4 ± 47.1	635 ± 248
Day 6			
C_{0h}, ng/mL	344 ± 115	51.9 ± 29.6	550 ± 291
Day 7			
C_{0h}, ng/mL	436 ± 173	59.9 ± 35.5	682 ± 222
C_{min}, ng/mL	309 ± 111	45.8 ± 26.0	471 ± 151
C_{max}, ng/mL	1496 ± 884	1902 ± 657	2263 ± 783
t_{max}, h	4.0 (1.5 -5.0)	4.0 (1.5 -5.0)	4.0 (4.0 -5.0)
AUC_{12h}, ng.h/mL[a]	8353 ± 2876	12864 ± 4399	13263 ± 3119
$C_{ss,av}$, ng/mL	696 ± 240	536 ± 183	1105 ± 260
FI, %	161 ± 64.4	348 ± 52.5	160 ± 37.7

[a] AUC_{24h} reported for Treatment B
[b] n=17 on day 1 and n=16 on Day 5
[c] n=20 on day 1 and n=17 on Day 5

7. Safety Assessments

21 subjects reported at least 1 AE in the trial. The most commonly reported AEs during treatment phases were GI disorders (loose stools, nausea) and nervous system disorders (dizziness and headache). No deaths were reported in this trial. One subject reported 2 SAEs, i.e., maculopapular rash in the washout period after TMC114/RTV administration and aseptic meningitis during follow-up. (See details in Medical Officer's review).

8. Conclusion

- The results of this study demonstrate that systemic exposure to TMC114 was not affected when 300 mg ATV q.d. was added to a b.i.d. treatment with 400/100 TMC114/RTV.
- For ATV, only C_{0h} was statistically significantly increased by approximately 87 %, while C_{max} and AUC_{24h} were not statistically significantly affected in the presence of TMC114/RTV.

Labeling Recommendation

PREZISTA/rtv and atazanavir (300 mg q.d.) can be co-administered.

MASS BALANCE AND QT STUDIES

1. Title

An open label, single dose, mass-balance study with ^{14}C labeled TMC114 with and without a low dose of ritonavir **(TMC114-C109).**

2. Objectives

The objectives of this trial were to characterize excretion and overall metabolic profile of TMC114 in humans, with and without co-administration of low-dose RTV.

3. Study Design

Phase 1, open label, single-dose, mass-balance study in 8 healthy male subjects. One group of 4 subjects received ^{14}C TMC114 alone at a dose level of 400 mg under fasted conditions. The other group of 4 subjects received a single dose of 400 mg ^{14}C TMC114 under fasted conditions, while from 2 days before until 6 days after ^{14}C TMC114, 100 mg RTV b.i.d was administered. On days when only ritonavir was administered, it was administered under fed conditions. Plasma, urine, and faeces samples were collected up to at least 168 hours after TMC114 administration, and thereafter in 24 hour intervals if less than 7 stools were delivered or if the radioactivity in one of the latest 2 urine collections accounted for 2 % or more of the dose in 24 hours. The concentrations of unchanged TMC114 and RTV were determined in plasma. The total radioactivity was determined in whole blood, plasma, urine, and faeces. The metabolic profiles were determined in selected plasma, urine, and faeces samples, and the structure of major metabolites were characterized, whenever possible.

4. Drugs Used in the Trial

Table 1 shows the drugs used in the trial.

Table 1: Drugs Used in the Trial

	TMC114	RTV
Dosage Form	Oral Solution (TMC114 eq. 20 mg/mL)	Capsule
Strength	20 mg/mL	100 mg
Batch Number	1805	95118VA

TMC114 was formulated as [redacted] oral solution, containing both ^{14}C-labeled and unlabeled TMC114 eq. 20 mg/mL and containing [redacted] and PEG400 as main solubilizing agents in the formulation. The solution was filled into an amber-colored flask. Each subject received 400 mg TMC114. The radioactivity amount per subject was 1.5 MBq (or 40.5µCi). All subjects received the same TMC114 dose: 400 mg TMC114 administered as 20.0 mL of an oral solution containing ^{14}C-labeled TMC114 and unlabelled TMC114 at a total TMC114 concentration of 20 mg/mL.

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Plasma

For treatment A and B, blood samples were collected on day 1 at predose (within 1 hour before drug intake), 0.5, 1, 1.5, 2, 3, 4, 6, 9, and 12 hours on day 1. Additional plasma samples were collected on day 2 (24 hr and 36 hr), day 3 (48 hrs), day 4 (72 hr), day 5 (96 hr), day 6 (120 hr), day 7 (144 hr) and day 8 (168 hr). In addition to the regular blood sample, additional 20 mL sample for the determination of radioactivity in whole blood, as well as for structural characterization of the metabolite profile was collected at 1, 2, 4, 9, 12, 24 and 48 hr after drug administration.

Urine Collection

On day 1, urine was collected in 3 intervals: 0-4, 4-9, and 9-24 hours. All other days, urine was collected in 24 hour intervals.

Fecal Collection

The complete fecal output was collected per stool on all study days.

Pharmacokinetic Assessments

Pharmacokinetic and statistical analysis was done using WinNonlin Professional. [redacted] and Microsoft Excel® (version 2000; Microsoft, [redacted] was used for the pharmacokinetic analysis.

6. Results

6.1 Subject Disposition

8 subjects were equally randomized to two treatment groups: treatment A (400 mg TMC114 q.d. on day 1) and treatment B (400 mg TMC114 q.d. on day 1 +100 mg RTV b.i.d. on day -2 to 7). All subjects completed all assessments.

Table 2 shows the demographics of the study.

Table 2: Demographics of Study TMC 114-C109

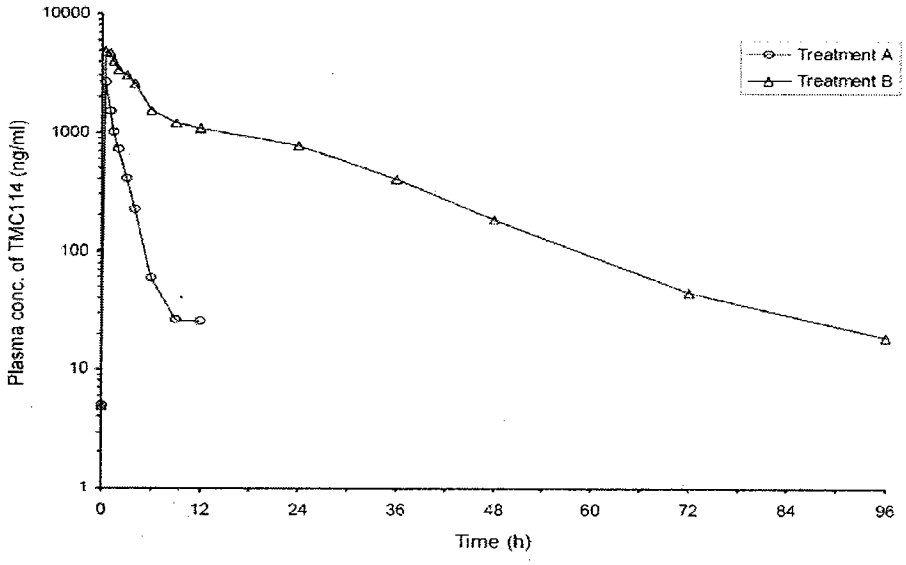
	Age (yrs), median (range)	Weight, (kg) median (range)	Height (cm), median (range)
Treatment A	49.5 (40-55)	84.5 (69-90)	183 (171-185)
Treatment B	51 (44-52)	78 (76-80)	174 (168-182)

6.2 Pharmacokinetic Analysis

PLASMA DISPOSITION OF UNCHANGED TMC114

Fig 1 shows the mean plasma concentration-time profiles of unchanged TMC114 after a single dose of 400 mg 14C-114 alone (treatment A) or in the presence of 100 mg 100 mg RTV b.i.d. (treatment B).

Fig 1: Mean plasma concentration-time profiles of unchanged TMC114 after a single dose of 400 mg ^{14}C-114 alone (treatment A) or in the presence of 100 mg 100 mg RTV b.i.d. (treatment B).



When TMC114 was given alone (Treatment A), plasma concentrations of unchanged TMC114 could be determined up to 24 hours post-dosing in 3 subjects and up to 12 hours post-dosing in one subject. When TMC114 was administered in the presence of RTV (Treatment B), plasma concentrations of unchanged TMC114 could be determined up to 96 hours post-dosing in every subject.

Table 3 shows the pharmacokinetic results of unchanged TMC114 after a single oral dose of 400 mg ^{14}C-TMC114 alone (treatment A) or in the presence of 100 mg RTV b.i.d. (treatment B).

Table 3: Pharmacokinetic results of unchanged TMC114 after a single oral dose of 400 mg ^{14}C-TMC114 alone (treatment A) or in the presence of 100 mg RTV b.i.d. (treatment B).

Pharmacokinetics of unchanged TMC114 (mean ± SD, t_{max}: median (range))	Treatment A: TMC114 alone	Treatment B: TMC114 + RTV
n	4	4
t_{max}, h	0.5 (0.5 - 1.0)	0.75 (0.5 - 1.5)
C_{max}, ng/mL	2730 ± 648	5125 ± 906
AUC_{last}, ng.h/mL	4291 ± 1956	50389 ± 15631
AUC_{∞}, ng.h/mL	4746[#] ± 1647	50760 ± 15600
$t_{1/2term}$, h	29.4[#] ± 45.3	13.5 ± 1.83

[#] Accurate determination not possible

Total Radioactivity in Plasma and Blood

Fig 2 shows the mean plasma concentration-time profiles of total radioactivity (TR) and unchanged drug (UR) after a single oral dose of 400 mg ^{14}C-TMC114 alone (in 4 non-boosted subjects), or after a single oral dose of 400 mg ^{14}C-TMC114 with co-administration of 100 mg ritonavir b.i.d.

Fig 2: Mean plasma concentration-time profiles of total radioactivity (TR) and unchanged drug (UD) after a single oral dose of 400 mg ^{14}C-TMC114 alone (in 4 non-boosted subjects), or after a single oral dose of 400 mg ^{14}C-TMC114 with co-administration of 100 mg ritonavir b.i.d.

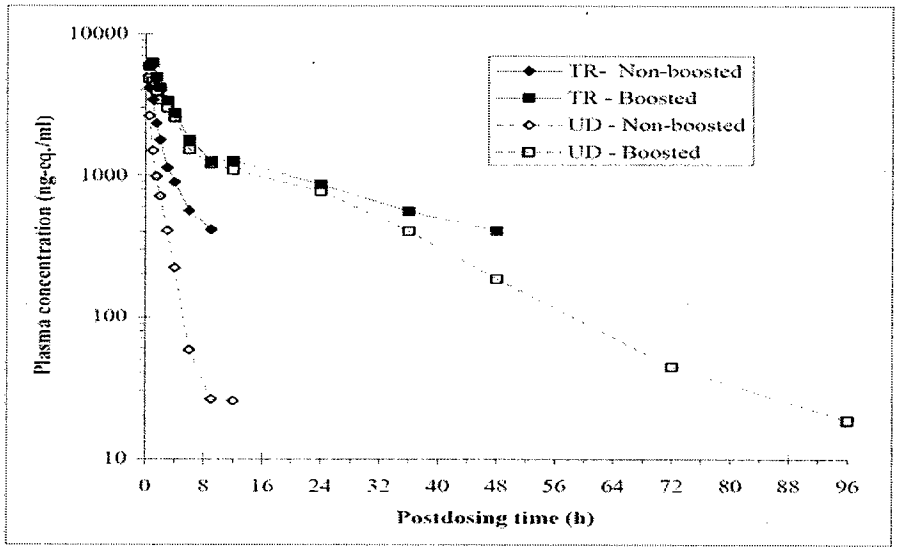


Table 4 shows the pharmacokinetic parameters of total radioactivity in plasma samples of healthy male adult subjects, collected after single oral administration of 400 mg ^{14}C-

TMC114 alone (non-boosted subjects), or in a combination with 100 mg ritonavir b.i.d. (boosted subjects).

Table 4: Pharmacokinetic parameters (mean ± sd) of total radioactivity in plasma samples of healthy male adult subjects, collected after single oral administration of 400 mg ^{14}C-MC114 alone (non-boosted subjects), or in a combination with 100 mg ritonavir b.i.d. (boosted subjects).

	C_{max}	T_{max}	AUC_{∞} (ng-eq*hr/mL)	AUC_{last} (ng-eq*hr/mL)
^{14}C-TMC114	4763 ± 1110	0.63 ± 0.25	12779 ± 5361	10349 ± 5011
^{14}C-TMC114 + 100 mg RTV b.i.d.	6812 ± 1585	0.75 ± 0.29	74966 ± 19090	53301 ± 21270

When TMC114 was administered alone, $AUC_{0-\infty}$ and AUC_{last} estimates of total radioactivity were on average 12779 ng-eq.h/ml and 10349 ng-eq.h/ml, respectively. Mean unchanged $AUC_{0-\infty}$ and AUC_{last} estimates of TMC114 were 4746 ng.h/ml and 4291 ng.h/ml, respectively. When coadministered with low-dose RTV, $AUC_{0-\infty}$ and AUC_{last} estimates of total radioactivity amounted on average to 74966 ng-eq.h/ml and 53301 ng-eq.h/ml, respectively, those of unchanged TMC114 amounted on average to 50760 ng.h/ml and 50389 ng.h/ml, respectively

Based on the ratio of $AUC_{0-\infty}$ values for unchanged drug and total radioactivity, unchanged TMC114 accounted for about 37 % and 68 % of the total radioactivity in plasma of un-boosted and boosted subjects, respectively indicating that the exposure to TMC114 and its metabolites was significantly higher in boosted than in non-boosted subjects. The results also showed that when TMC114 was coadministered with low-dose RTV, the mean C_{max} of unchanged TMC114 was increased by approximately 2-fold and the mean AUC values were increased by approximately 11-fold when compared to TMC114 alone.

Total Radioactivity in Urine and Faeces

Table 5 and 6 show the excretion of total radioactivity in urine and faeces of 4 healthy male adult subjects after single oral administration of 400 mg ^{14}C-TMC114 alone (non-boosted subjects), or in a combination with 100 mg ritonavir b.i.d. (boosted subjects) respetively.

Table 5: Excretion of total radioactivity in urine and faeces of 4 healthy male adult subjects after single oral administration of 400 mg ^{14}C-TMC114 alone (non-boosted subjects).

NON-BOOSTED		Subject 1090001	Subject 1090003	Subject 1090005	Subject 1090007	Mean ± SD
Urine	0-4 h					4.66 ± 1.39
	4-9 h					2.01 ± 0.57
	9-24 h					2.32 ± 0.29
	24-48 h					1.95 ± 0.44
	48-72 h					0.83 ± 0.17
	72-96 h					0.38 ± 0.11
	96-120 h					0.28
	120-144 h					
	144-168 h					
Sum	0-24 h	7.17	11.85	7.53	9.42	8.99 ± 2.15
Sum	0-48 h	8.91	14.14	8.96	11.76	10.94 ± 2.51
Sum	0-168 h	10.21	15.94	9.85	12.87	12.22 ± 2.82
Faeces	0-168 h	93.40[a)]	79.67[a)]	72.84[a)]	80.81[a)]	81.68[a)] ± 8.57[a)]
Total	0-168 h	103.61	95.61	82.69	93.68	93.90 ± 8.62

Table 6: Excretion of total radioactivity in urine and faeces of 4 healthy male adult subjects after single oral administration of 400 mg ^{14}C-TMC114 in combination with 100 mg ritonavir b.i.d. (boosted subjects).

BOOSTED		Subject 1090002	Subject 1090004	Subject 1090006	Subject 1090008	Mean ± SD
Urine	0-4 h					5.78 ± 0.93
	4-9 h					1.74 ± 0.73
	9-24 h					2.87 ± 0.58
	24-48 h					2.39 ± 0.43
	48-72 h					0.75 ± 0.20
	72-96 h					0.30 ± 0.06
	96-120 h					0.24
	120-144 h					
	144-168 h					
Sum	0-24 h	10.15	11.07	7.55	12.75	10.38 ± 2.17
Sum	0-48 h	12.26	13.98	9.52	15.33	12.77 ± 2.51
Sum	0-168 h	13.58	15.53	10.23	16.39	13.93 ± 2.73
Faeces	0-168 h	83.96[a)]	68.47[a)]	86.91[a)]	78.81[a)]	79.54[a)] ± 8.10[a)]
Total	0-168 h	97.54	84.00	97.14	95.20	93.47 ± 6.40

[a)]: Data relate to the sum of the radioactivity amounts in methanolic extracts and residues.

After a single oral dose of 400 mg ^{14}C-TMC114 in healthy male subjects, alone or in combination with the major part of the ^{14}C-TMC114 related radioactivity was excreted *via* the faeces. Up to 168 h after dose administration, on average, 81.7 % and 79.5 % of the administered radioactivity was excreted *via* the faeces in non-boosted and boosted subjects, respectively. The cumulative excretion of the radioactivity in faeces ranged from 72.8 to 93.4 % of the dose in non-boosted subjects, and from 68.5 to 86.9 % of the dose in boosted subjects. At 168 h after dose

administration, the percentages of administered radioactivity excreted in urine amounted on average to 12.2 % and 13.9 % in non-boosted and boosted subjects, respectively. The cumulative excretion of the radioactivity in urine ranged from 9.9 to 15.9 % of the dose in non-boosted subjects, and from 10.2 to 16.4 % of the dose in boosted subjects. The co-administration of ritonavir did not appear to have any substantial effect on the total excretion of the radioactivity in male subjects. Based on the analysis of the urinary excretion time profiles (from the 9-24 hour collection period on), the urinary excretion rate of radioactivity declined with an half-life of 20.2 ± 3.8 h and 17.5 ± 2.5 h in un-boosted and ritonavir boosted subjects.

Identification of Metabolites

Unchanged TMC114 and its major metabolites were identified by HPLC chromatography. Table 7 provides the description of the metabolites identified in the study.

Table 7: Description of Metabolites Identified in Study TMC114-C109

Metabolite Code	Identification method	Matrix in which identified	Identity
UD	LC-MS/MS Co-elution	Faeces, urine, plasma	Unchanged drug (R319064; TMC114)
6	LC-MS/MS NMR Co-elution	Faeces, urine, plasma	Carbamate hydrolysis and mono-hydroxylation at the isobutyl function towards a tertiary alcohol function (R426855)
11	LC-MS/MS	Urine	Glucuronide of metabolite 15
15	LC-MS/MS	Faeces, urine	Carbamate hydrolysis and mono-hydroxylation of the aniline moiety
17	LC-MS/MS	Urine	Mono-hydroxylation and glucuronidation at the [(4-amino-benzenesulfonyl)-isobutylamino]-1-benzyl-2-hydroxypropyl moiety
18	LC-MS/MS	Urine	*N*-glucuronidation of parent drug at the aniline moiety
19	LC-MS/MS Co-elution	Faeces, urine	Carbamate hydrolysis (R374699)
20	LC-MS/MS	Urine	Glucuronidation of parent drug at the [(4-amino-benzenesulfonyl)-isobutylamino]-1-benzyl-2-hydroxypropyl moiety
33	LC-MS/MS Co-elution	Faeces	Mono-hydroxylation at the benzylic function (R330689)
23	LC-MS/MS NMR Co-elution	Faeces, urine, plasma	Mono-hydroxylation at the isobutyl function towards a tertiary alcohol function (R426857)
29	LC-MS/MS NMR Co-elution	Faeces, urine, plasma	Mono-hydroxylation at the ortho position with respect to the amine function of the aniline moiety (R330326)

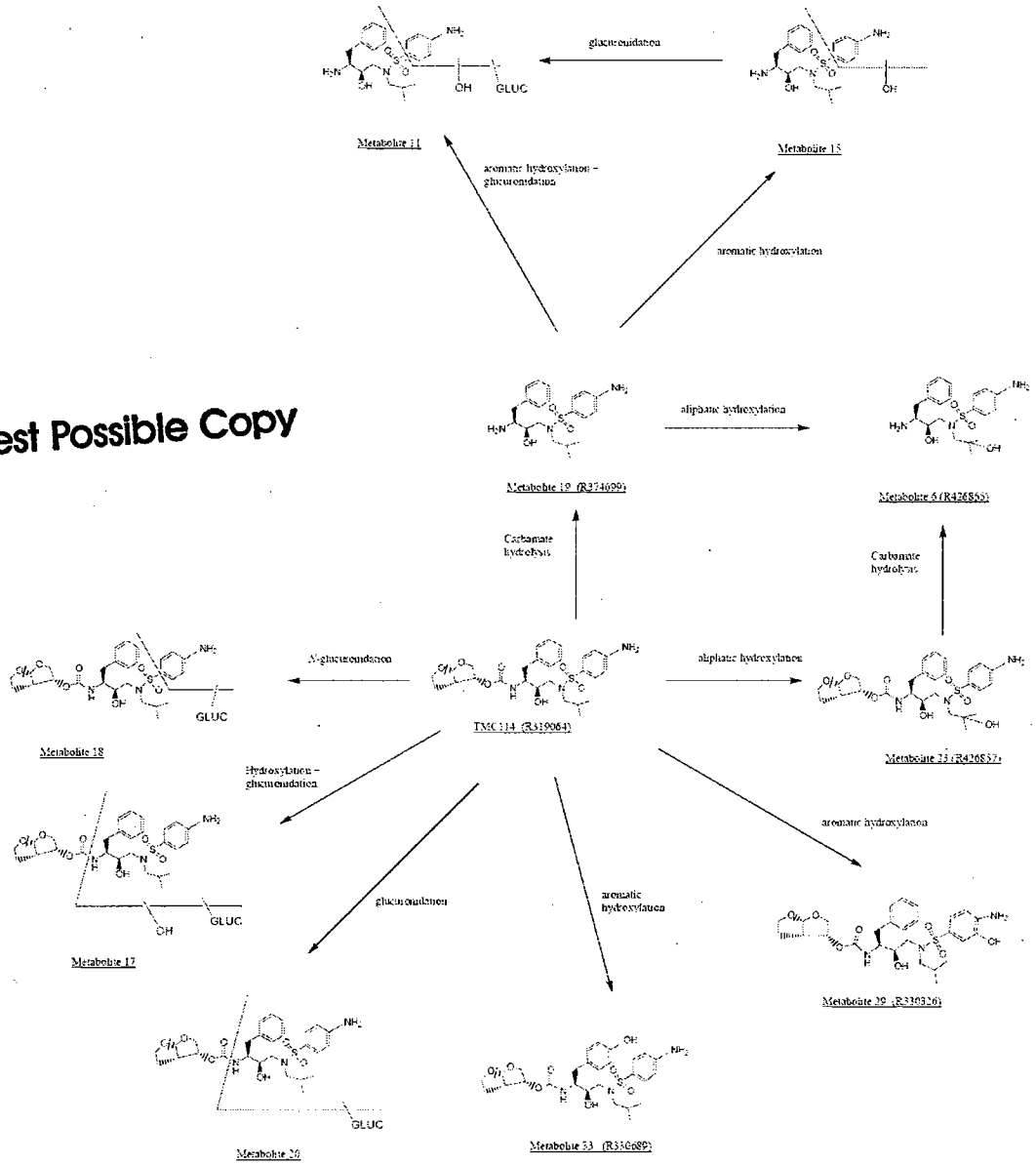
Table 8 provides the percentage of administered dose per major pathway in humans with or without ritonavir.

Table 8: Percentage of administered dose per major pathway in humans with or without ritonavir in urine and feces.

Pathway (metabolite #(s) from table 7)	^{14}C-TMC114	^{14}C-TMC114 + RTV
Aliphatic hydroxylation at the isobutyl moiety towards the tertiary alcohol function (# 6, 23)	9.8	2.3
Aromatic hydroxylation at the benzylic moiety (#33)	1.6	1.7
Aromatic hydroxylation at the aniline moiety (# 29)	4.5	1.4
Carbamate hydrolysis (# 6,11, 15 and 19)	13.2	0.67
Glucoronidation (# 11, 17, 18, and 20)	0.57	2.2

Fig 3 shows the metabolic pathways of 14C-TMC114 in human volunteers after oral administration.

Fig 3: Metabolic Pathways of ^{14}C-TMC114 in Human Volunteers after Oral Administration



Excretion of Metabolites in Urine and Faeces

Unchanged TMC114 represented only 0.64 – 1.60 % (1.15 % on average) of the dose in urine of the non-boosted subjects. When normalized to the percentage of the sum of unchanged drug and detected metabolites, unchanged drug accounted for 18.9 - 26.4 % (23.0 % on average) of the sample radioactivity in urine of non-boosted subjects. In urine of boosted subjects, unchanged drug represented 5.37 – 9.24 % (7.65 % on average) of

the dose in urine of boosted subjects, and accounted for 65.5 – 81.2 % (72.5 % on average) of the sample radioactivity when normalized to the percentage of the sum of unchanged drug and detected metabolites.

Fig 4 shows the excretion profile of TMC114 (unchanged drug) and identified metabolites in 0-48 h urine pools and in methanolic faeces extracts after a single oral dose of 400 mg ^{14}C-TMC114 alone (non-boosted subjects).

Fig 4: Excretion profile of TMC114 (unchanged drug) and identified metabolites in 0-48 h urine pools and in methanolic faeces extracts after a single oral dose of 400 mg ^{14}C-TMC114 alone.

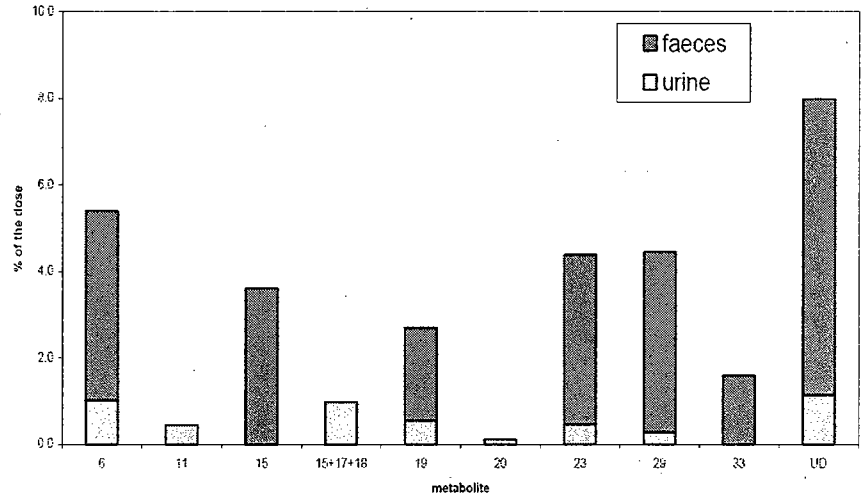
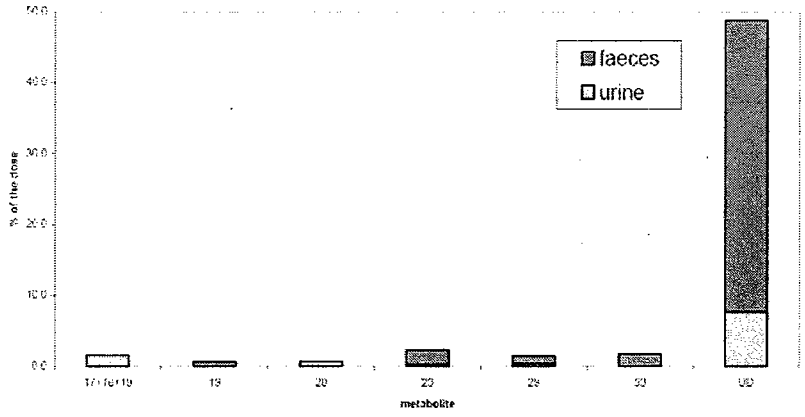


Fig 5 shows the excretion profile of TMC114 (unchanged drug) and identified metabolites in 0-48 h urine pools and in methanolic faeces extracts after a single oral dose of 400 mg ^{14}C-TMC114 with co-administration of 100 mg ritonavir b.i.d. (boosted subjects)

Fig 5: Excretion profile of TMC114 (unchanged drug) and identified metabolites in 0-48 h urine pools and in methanolic faeces extracts after a single oral dose of 400 mg ^{14}C-TMC114 co-administered with 100 mg ritonavir b.i.d.



Metabolites of TMC114 in Plasma

The sample radioactivity in the plasma pools of non-boosted and ritonavir boosted subjects was mainly accounted for by unchanged TMC114. In 1-h, 2-h and 4-h plasma pools of un-boosted subjects, unchanged TMC114 represented 48.5 %, 50.0 % and 25.9 % of injected sample radioactivity, respectively, and corresponding plasma concentrations of unchanged drug amounted to 1653 ng-eq./ml, 889 ng-eq./ml and 232 ng-eq./ml, respectively. In ritonavir boosted subjects, the percentage of radioactivity accounted for by the unchanged drug was 79.4 % (4960 ng-eq/mL), 79.7 % (ng-eq/mL), and 86.3 % (ng-eq/mL). Besides unchanged TMC114, metabolites 6, 23, and 29 (accounting for 4.8 %, 7.7 %, and 2.4 % of the injected sample radioactivity) were detected in 1-h plasma. Some metabolites, eluting between 53 and 56 min were present, in total accounting for 6.0 % of injected sample radioactivity in pooled 1-h plasma of non-boosted subjects. LC-MS data revealed that these metabolites were formed by carbamate hydrolysis, carbamate hydrolysis in combination with mono-hydroxylation, glucuronidation, and glucuronidation in combination with mono-hydroxylation of the parent drug. In plasma pools of boosted subjects, none of the metabolites detected in plasma of non-boosted subjects were present, except for some metabolites eluting between 53 and 56 min, which accounted in total for 7.9 % of injected sample radioactivity in pooled 1-h plasma of the boosted subjects. In 4-h plasma samples of both un-boosted and boosted subjects, only unchanged drug could be detected.

8. Conclusion

- After administration of a single oral dose of 400 mg ^{14}C-TMC114 to male subjects, TMC114 was extensively metabolized. The excretion of unchanged TMC114 (in urine and feces) amounted to 8.0 % of the dose in non-boosted subjects.
- After administration of a single oral dose of 400 mg ^{14}C-TMC114 in combination with 100 mg ritonavir b.i.d. to male subjects, TMC114 was considerably less metabolized than in non-boosted subjects. The excretion of unchanged TMC114 (in urine and feces) amounted to 48.8 % of the dose in boosted subjects.
- Based on the ratio of $AUC_{0-\infty}$ values for unchanged drug and total radioactivity, unchanged TMC114 accounted for about 37 % and 68 % of the total radioactivity in plasma of un-boosted and boosted subjects, respectively.
- In un-boosted subjects, TMC114 was metabolized mainly by carbamate hydrolysis, aliphatic hydroxylation at the isobutyl moiety, aromatic hydroxylation at the aniline moiety, to a lesser extent by aromatic hydroxylation at the benzylic moiety, and to a very minor extent by glucuronidation.
- In ritonavir boosted subjects, there was significant inhibition of carbamate hydrolysis, isobutyl aliphatic hydroxylation and aniline aromatic hydroxylation pathways. However, there was no effect on the aromatic hydroxylation at the benzylic moiety. The excretion of glucuronide metabolites was markedly increased but still represented as a minor pathway.

1. Title

Open label, randomized, placebo-controlled and active controlled, four-way crossover study evaluating ECG intervals in healthy adults receiving TMC114/RTV **(TMC114-C153)**.

2. Objectives

The primary objective of the present trial was to assess the cardiac safety of TMC114 in the presence of low-dose RTV in healthy adults, with respect to QT/QT_cF interval duration and the influence of TMC114/RTV on other ECG parameters, such as QRS and PR intervals.

3. Study Design

This was an open-label, randomized, 4-way crossover, placebo-controlled and active-controlled trial to evaluate the cardiac safety of TMC114 administered with low-dose RTV under steady-state conditions. Two dose regimens of TMC114 were tested, i.e., TMC114/RTV 1600/100 mg q.d. and TMC114/RTV 800/100 mg b.i.d. Moxifloxacin (400 mg, single oral dose for 7 days) was used as an active positive control for the evaluation of QT/QT_c. In the placebo arm, placebo TMC114 tablets were used for 7 days. The trial was designed to evaluate the initial treatment effect (Day 1) and the steady-state treatment effect (Day 7). All intakes of TMC114/RTV, moxifloxacin and placebo control were under fed conditions. There was a washout period of at least 7 days between consecutive treatments. Safety and tolerability evaluations were recorded continuously. 40 subjects were randomized to the following four treatments:

Treatment A: TMC114/RTV 1600/100 mg q.d. for 7 days.

Treatment B: TMC114/RTV 800/100 mg b.i.d. for 7 days.

Treatment C: 400 mg moxifloxacin q.d. for 7 days.

Treatment D: Placebo control (Placebo TMC114 tablets) q.d. for 7 days.

3.1 Discussion of Trial Design, Including Choice of Control Group.

- Dose regimens in the present trial were TMC114/RTV 1600/100 mg q.d. and 800/100 mg b.i.d. A total daily dose of 1600 mg TMC114 exceeds the highest dose being studied in clinical trials with the tablet formulation, while still being within the range covered by animal exposure. Further, the b.i.d. dose selected in this trial is 30 % higher than the clinically recommended dose (600 mg b.i.d.) in HIV-1 infected subjects.

- To demonstrate if a potential ECG effect was caused by AUC or C_{max}, two regimens of TMC114/RTV were used that provide a similar AUC, but a different C_{max}.
- The study design also allows evaluation of any impact of dosing of RTV as 100 mg q.d. or 100 mg b.i.d.

- The time points of the ECG assessments were selected in order to study potential ECG effects as a function of plasma drug concentrations, including C_{max}, in compliance with ICH E14 guidance.
- Pharmacokinetic samples were taken within 5 minutes after each ECG to permit an exploration of the relationship between TMC114, RTV, or moxifloxacin, and any resulting ECG changes.

4. Drugs Used in the Trial

Table 1 shows the drugs used in the trial.

Table 1: Drugs Used in the Trial

	TMC114	RTV	Moxifloxacin
Dosage Form	Tablet	Capsule	Tablet
Strength (mg)	400	100	400
Batch #	PD1098		
Expiry Date	April 2005		

The placebo control for TMC114 was formulated as a tablet (F004) containing the inactive ingredients [redacted] microcrystalline cellulose, [redacted]

5. Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Plasma

For treatment A and B, blood samples were collected (within 5 minutes after each ECG recording) on day 1 at pre-dose (immediately before drug intake) and at 0.5, 1, 2, 3, 4, 6, 9, and 12 hrs. Pre-dose samples were collected on day 2, 5, 6, 7, in addition to intensive sampling at 0.5, 1, 2, 3, 4, 6, 9, 12, 24 (day 8) hrs. For moxifloxacin intake (treatment C), identical sampling scheme was followed.

ECG Measurements

ECG measurements (triplicate 10-second recording collected at 60-second intervals) on day -1 and day 1, and day 7 at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hrs. Additional ECG assessments were conducted on day 2 and day 8 (24 hrs after drug intake on day 7).

The plasma concentrations of TMC114, RTV, and moxifloxacin were determined using validated LC-MS/MS methods. The lower limit of quantification (in plasma) was 10 ng/mL for TMC114, 5 ng/mL for RTV, and 25 ng/mL for moxifloxacin.

Pharmacokinetic Assessments

Pharmacokinetic and statistical analysis was done using WinNonlin Professional. [redacted] and Microsoft Excel® (version 2000; Microsoft, [redacted] was used for the pharmacokinetic analysis.

6. Results

6.1 Subject Disposition

40 subjects were equally randomized to the following four treatment sequences: BACD, CBDA, DCAB, and ADBC. 1 subject each in sequence BACD and CBDA discontinued due to adverse event and withdrawal of consent respectively. The discontinuations were after treatment B for sequence BACD and treatment A for sequence CBDA. 2 subjects discontinued in sequence DCAB (one subject discontinued after treatment C due to withdrawal of consent) and 1 subject discontinued after treatment A (due to adverse event). Table 2 shows the demographic data of subjects enrolled in the trial.

Table 2: Demographic Data of Subjects Enrolled in Study TMC114-C153

Parameter	Treatment B/A/C/D N = 10	Treatment C/B/D/A N = 10	Treatment D/C/A/B N = 10	Treatment A/D/B/C N = 10	All Subjects N = 40
Age, years	34.0	27.0	29.5	34.0	31.0
Median (range)	(21-52)	(19-37)	(21-43)	(20-43)	(19-52)
Height, cm	172.5	172.0	169.5	178.0	172
Median (range)	(160-183)	(164-176)	(150-186)	(165-198)	(150-198)
Weight, kg	74.5	70.5	65.5	74.0	72.5
Median (range)	(53-84)	(60-79)	(47-91)	(55-93)	(47-93)
BMI, kg m^{-2}	24.4	22.9	22.1	22.9	23.2
Median (range)	(18-30)	(21-29)	(20-26)	(20-29)	(18-30)
Sex, n (%)					
Male	7 (70)	7 (70)	5 (50)	7 (70)	26 (65)
Female	3 (30)	3 (30)	5 (50)	3 (30)	14 (35)
Ethnic Origin, n (%)					
Black	2 (20)	5 (50)	5 (50)	3 (30)	15 (38)
Caucasian-White	8 (80)	4 (40)	5 (50)	6 (60)	23 (58)
Oriental-Asian	0	1 (10)	0	0	1 (3)
Other	0	0	0	1 (10)	1 (3)

N = number of subjects per randomization group

6.2 Pharmacokinetic Analysis

Darunavir/rtv

Fig 1 shows the mean plasma concentration-time profiles of darunavir on days 1 and 7 after oral administration of darunavir/ritonavir 1600/100 mg q.d. (treatment A).

Fig 1: Mean plasma concentration-time profiles of darunavir on days 1 and 7 after oral administration of darunavir/ritonavir 1600/100 mg q.d. (treatment A).

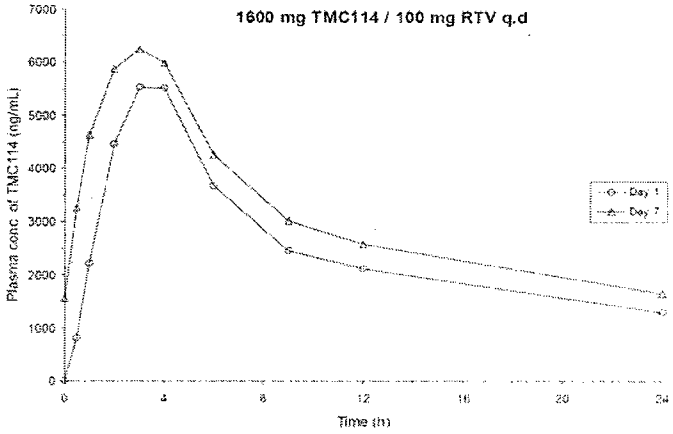


Fig 2 shows the mean plasma concentration-time profiles of darunavir on days 1 and 7 after oral administration of darunavir/ritonavir 800/100 mg b.i.d (treatment B).

Fig 2: Mean plasma concentration-time profiles of darunavir on days 1 and 7 after oral administration of darunavir/ritonavir 800/100 mg b.i.d (treatment B).

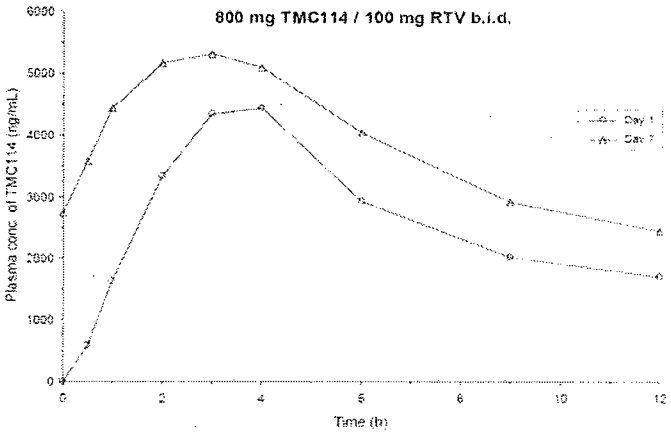


Table 3 shows the pharmacokinetics of darunavir on days 1 and 7 of treatment A and treatment B.

Table 3: Pharmacokinetics of darunavir on days 1 and 7

Parameter	Mean ± SD; t_{max}: Median (Range)	
	Treatment A: Darunavir/Ritonavir 1600/100 mg q.d.	Treatment B: Darunavir/Ritonavir 800/100 mg b.i.d.
N	37	37
Day 1		
t_{max}, h	3.08 (2.05 - 4.08)	3.08 (2.00 - 6.05)
C_{0h}, ng/mL	0	0
C_{max}, ng/mL	5914 ± 1758	4740 ± 1405
AUC_{12h}, ng.h/mL	-	31717 ± 11113
AUC_{24h}, ng.h/mL	60328 ± 21012	-
Day 7		
t_{max}, h	3.05 (1.05 - 6.05)	3.05 (1.05 - 6.05)
C_{0h}, ng/mL	1550 ± 879.3	2526 ± 1024
C_{max}, ng/mL	1428 ± 780.1	2282 ± 849.1
C_{min}, ng/mL	6599 ± 1754	5689 ± 1535
AUC_{12h}, ng.h/mL	-	46511 ± 13380
AUC_{24h}, ng.h/mL	75629 ± 25615	-

Table 4 shows the pharmacokinetics of ritonavir on days 1 and 7.

Table 4: Pharmacokinetics of ritonavir on days 1 and 7

Parameter	Mean ± SD; t_{max}: Median (Range)	
	Treatment A: Darunavir/Ritonavir 1600/100 mg q.d.	Treatment B: Darunavir/Ritonavir 800/100 mg b.i.d.
N	37	37
Day 1		
t_{max}, h	4.05 (1.05 - 6.07)	4.05 (1.07 - 9.00)
C_{0h}, ng/mL	0	0
C_{max}, ng/mL	516.2 ± 257.7	508.3 ± 302.5
AUC_{12h}, ng.h/mL	-	3119 ± 1475
AUC_{24h}, ng.h/mL	4471 ± 2618	-
Day 7		
t_{max}, h	4.05 (1.05 - 6.05)	4.05 (1.07 - 6.05)
C_{0h}, ng/mL	37.96 ± 18.80	302.9 ± 185.4
C_{max}, ng/mL	35.28 ± 18.19	212.9 ± 125.9
C_{min}, ng/mL	813.2 ± 400.3	1272 ± 538.0
AUC_{12h}, ng.h/mL	-	7649 ± 3051
AUC_{24h}, ng.h/mL	6186 ± 2581	-

Moxifloxacin

Fig 3 shows the mean plasma concentration-time curves of moxifloxacin on days 1 and 7, after oral administration of moxifloxacin 400 mg q.d. (treatment C).

Fig 3: Mean plasma concentration-time curves of moxifloxacin on days 1 and 7, after oral administration of moxifloxacin 400 mg q.d. (treatment C).

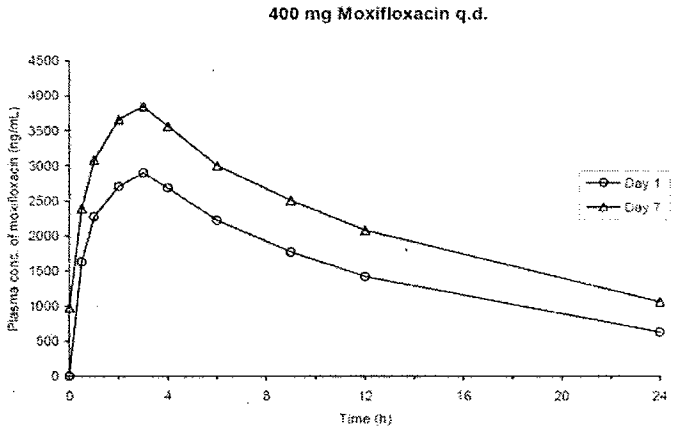


Table 5 shows the pharmacokinetics of moxifloxacin on days 1 and 7.

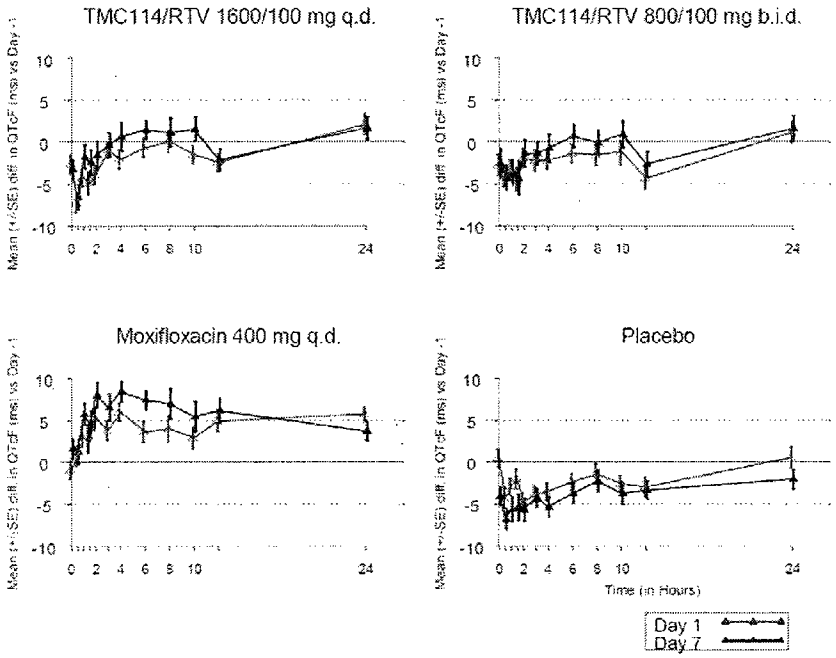
Table 5: Pharmacokinetics of moxifloxacin on days 1 and 7

Parameter	Mean ± SD; t_{max}: Median (Range) Treatment C: Moxifloxacin 400 mg q.d.
N	38
Day 1	
t_{max}, h	2.08 (0.57 - 6.05)
C_{24}, ng/mL	0
C_{max}, ng/mL	3453 ± 728.9
AUC_{24}, ng·h/mL	37345 ± 8145
Day 7	
t_{max}, h	2.05 (0.55 - 6.07)
C_{24}, ng/mL	974.7 ± 364.1
$C_{ss,av}$, ng/mL	979.0 ± 349.9
C_{max}, ng/mL	4295 ± 1075
AUC_{24}, ng·h/mL	53662 ± 15411

6.3 ECG Findings

Descriptive statistics were calculated per treatment and per time point for each ECG interval i.e., HR, PR, QRS, QT, and QT/QTc. The Fridericia QT correction was chosen as primary correction. Fig 4 shows the mean-time matched changes in QT_cF versus day-1 (predose) over time for the different treatment groups.

Fig 4: Mean differences in QT_cF versus day -1 (predose) over time.



In general, for TMC114 and placebo treatments, the values for the time matched decrease in QTcF were slightly higher on day 7 (i.e., decreases were smaller and increases were larger than on Day 1). In both treatment groups, the largest treatment mean increase versus predose was observed 24 hours after dosing on both days (range 1.2 to 2.1 ms). The observations made in the TMC114/RTV 800/100 mg b.i.d. group were similar to those in the TMC114/RTV 1600/100 mg q.d. group, although differences were generally smaller (i.e., decreases were larger and increases were smaller).

Table 6 shows the QT_c Fridericia values (ms) and mean time-matched changes from day -1.

Table 6: QT_c Fridericia values (ms) and mean time-matched changes from day -1.

Time point	Treatment A: TMC114/RTV 1600/100 mg q.d. (N = 38)[b]		Treatment B: TMC114/RTV 800/100 mg b.i.d. (N = 38)		Treatment C: Moxifloxacin 400 mg q.d. (N = 39)[c]		Treatment D: Placebo control (N = 39)	
	Mean value	Mean change (SD)	Mean value	Mean change (SD)	Mean value	Mean change (SD)	Mean value	Mean change (SD)
Day 1								
PD	392.2	-2.7 (6.73)	391.9	-2.8 (7.85)	393.4	-1.0 (6.54)	393.9	0.4 (6.71)
+0.5h	392.1	-7.3 (7.03)	393.1	-4.2 (7.61)	398.8	0.7 (7.52)	394.4	-4.3 (7.48)
+1h	391.8	-4.3 (6.89)	393.0	-3.5 (7.79)	399.6	3.0 (7.43)	395.9	-2.9 (6.26)
+1.5h	391.9	-4.9 (8.33)	392.3	-4.5 (8.21)	400.2	2.6 (9.19)	393.5	-2.0 (7.48)
+2h	392.9	-4.0 (6.79)	393.2	-2.0 (6.95)	401.6	5.2 (9.10)	392.1	-4.7 (6.63)
+3h	394.5	-1.9 (5.87)	393.1	-2.2 (7.65)	401.5	5.8 (7.13)	391.4	-3.8 (6.33)
+4h	395.2	-2.1 (6.81)	393.9	-2.2 (6.72)	403.3	6.0 (6.57)	393.6	-3.5 (6.36)
+6h	393.5	-0.7 (6.98)	391.9	-1.4 (6.58)	398.1	3.6 (7.47)	391.0	-2.4 (6.26)
+8h	392.4	0.0 (8.23)	390.8	-1.6 (7.81)	398.5	4.0 (9.73)	390.9	-1.4 (7.61)
+10h	392.2	-1.6 (6.60)	391.7	-1.3 (9.15)	398.5	2.9 (7.95)	392.0	-2.6 (6.01)
+12h	395.8	-2.5 (6.78)	391.8	-4.4 (7.56)	401.7	4.9 (7.85)	392.9	-3.0 (7.18)
+24h	394.3	2.1 (7.40)	393.1	1.2 (7.73)	399.1	5.7 (5.64)	394.5	0.6 (7.59)
Day 7								
PD	391.6	-3.3 (6.57)	392.1	-2.6 (10.20)	396.0	1.6 (7.20)	389.4	-4.1 (6.55)
+0.5h	392.8	-6.6 (8.82)	392.9	-4.3 (8.93)	399.3	1.2 (9.07)	391.9	-6.8 (7.54)
+1h	394.3	-1.8 (8.53)	392.7	-3.7 (9.19)	402.4	5.7 (8.11)	391.2	-5.6 (9.26)
+1.5h	394.5	-2.5 (9.20)	392.4	-4.4 (12.31)	402.1	4.5 (9.68)	390.1	-5.4 (9.59)
+2h	395.6	-1.6 (10.57)	393.8	-1.4 (9.88)	404.4	8.0 (9.37)	391.2	-5.7 (8.21)
+3h	395.2	-0.4 (8.79)	393.9	-1.4 (8.80)	404.3	6.6 (9.86)	391.0	-4.2 (6.72)
+4h	397.9	0.6 (10.26)	395.4	-0.8 (10.25)	405.5	8.4 (7.46)	391.8	-5.3 (7.42)
+6h	395.6	1.4 (6.64)	393.9	0.6 (8.36)	401.7	7.4 (7.03)	389.6	-3.3 (7.47)
+8h	393.2	1.1 (10.39)	392.3	-0.1 (8.89)	401.1	7.0 (11.16)	390.1	-2.3 (7.89)
+10h	394.8	1.5 (8.86)	393.9	0.9 (9.93)	400.9	5.4 (10.81)	390.9	-3.7 (8.24)
+12h	396.1	-2.2 (7.82)	393.5	-2.7 (9.39)	402.8	6.2 (8.76)	392.6	-3.3 (6.64)
+24h	393.4	1.6 (8.18)	395.5	1.6 (9.35)	397.9	3.7 (6.81)	391.9	-2.1 (7.45)

SD: standard deviation; N = total number of subjects per treatment; PD = pre dose
[b] time matched change versus the corresponding time points of Day -1; [c] N was 37 on Day 7 of TMC114/RTV 1600/100 mg q.d. treatment; [d] N was 38 from 4 h after Day 7 moxifloxacin treatment onwards

Table 7 shows the largest observed and estimated differences in time-matched QTcF changes (ms) between the active treatments and placebo control.

Table 7: Largest observed and estimated differences in time-matched QTcF changes (ms) between the active treatments and placebo control.

Parameter	Treatment A: TMC114/RTV 1600/100 mg q.d.		Treatment B: TMC114/RTV 800/100 mg b.i.d.		Treatment C: moxifloxacin 400 mg q.d.	
	Time point	Mean (90% CI[a])	Time point	Mean (90% CI[a])	Time point	Mean (90% CI[a])
Day 1						
Observed mean	+ 3 h	3.0 (1.34; 4.62)	+ 2 h	2.9 (0.13; 5.61)	+ 2 h	10.0 (7.73; 12.19)
Est. LSmean	+ 3 h	3.5 (1.38; 5.65)	+ 3 h	2.0 (-0.16; 4.12)	+ 2 h	10.1 (8.00; 12.24)
Day 7						
Observed mean	+ 4 h	6.1 (2.61; 9.61)	+ 4 h	5.0 (1.27; 8.73)	+ 4 h	14.1 (11.32;16.82)
Est. LSmean	+ 4 h	6.6 (4.31; 8.96)	+ 6 h	4.1 (1.76; 6.39)	+ 4 h	14.5 (12.24;16.85)

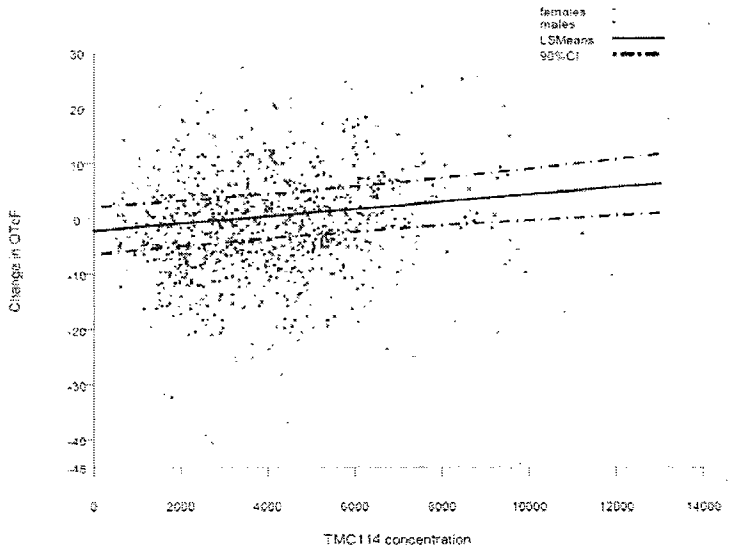
[a] Two-sided 90% CI; Est. LSmean= estimated least square mean

6.4 Pharmacokinetic/Pharmacodynamic Relationships

A linear mixed model was developed to estimate the relationship between QTcF and plasma TMC114 concentration. To account for study design aspects and for gender differences, a longitudinal model was applied including the following parameters: subject as a random effect, and treatment sequence, time-dependent baseline QT_cF, gender, time, treatment, and the interaction between time and treatment, and between gender and

treatment, and concentration as fixed effects. Fig 5 shows the observed and predicted time matched changes in QTcF versus concentration along with the 90 % two-sided CI.

Fig 5: Observed and predicted time matched changes in QT_cF versus concentration along with the 90 % two-sided CI.



The data showed that the variability in observed values for female subjects was greater than the male subjects. An additional analysis was performed to investigate the interaction between gender and concentration by adding this interaction term in the model. This resulted in a non-significant interaction between gender and concentration and therefore, the gender term was dropped from the final linear concentration-QT_cF model. The estimated slope of the QTcF versus plasma concentration was 0.000659 with a 90 % two-sided CI of 0.000184 to 0.001135. Although the CI excludes zero, for every 1000 ng/mL increase in darunavir concentrations, a small additional shift of 0.66 ms is predicted. At the mean maximum concentration of 6599 ng/mL observed in this study, the mean increase in QTcF is 2.2 ms with a 90 % CI of -2 to 6.3 ms.

8. Conclusion

- TMC114 treatments at the supratherapeutic doses evaluated in this study were associated with small prolongations in QT/QTc interval when compared to QT/QTc changes observed in the placebo control group.
- The upper bounds of the two-sided 90 % CIs on the time-matched mean changes versus placebo control of both TMC114/RTV groups never exceeded the 10 ms boundary on both Day 1 and Day 7.
- Based on the overall results, the results of this thorough QTc study can be interpreted as negative according to E14 ICH guidelines.

IN VITRO METABOLISM

TMC114-NC112

TITLE

Characterization of cytochrome P450 enzymes involved in the *in vitro* metabolism of TMC114, and metabolite profiling in rat, dog and human liver microsomes.

OBJECTIVES

To identify the cytochrome P450 enzymes involved in the in vitro metabolism of TMC114, and to compare the cytochrome P450 mediated metabolism in rat, dog and human liver microsomes

METHODS:

Incubations with TMC114 and rat, dog and human liver microsomes:

Incubations with TMC114 were performed for 15 minutes at 37°C in incubation mixtures containing 0.1 M potassium phosphate buffer pH 7.4 and 3 mM NADPH. The reactions were started by the addition of TMC114 to the incubation mixture as a solution in methanol (final concentration 2.5%, v/v). Controls were incubated in the absence of NADPH. The reactions were terminated by the addition of ice-cold acetonitrile. After centrifugation, the supernatant was analyzed by LC-MS/MS analysis.

TMC114 was incubated at 2, 5, 10, 20 and 50 μM for the estimation of Km and Vmax, and optimized microsomal protein concentrations of 0.2 mg/ml (human) or 0.5 mg/ml (rat, dog). Incubations were performed in duplicate.

Chemical inhibition experiments with rat, dog and human liver microsomes:

TMC114 was incubated with rat, dog and human liver microsomes using the incubation conditions described above and a TMC114 concentration around the Km value in the absence and presence of chemical inhibitors, which are selective towards human cytochrome P450 enzymes. Before starting the enzymatic reaction with TMC114, inhibitors were pre-incubated for 5 minutes at 37°C. Table 1 shows the various inihibitors and inhibitor concentrations used in the study.

Table 1: Inhibitors and inhibitor concentrations used

Inhibitor	Inhibition of human P450 enzyme	Inhibitor concentration
α-naphthoflavone	CYP1A	1 µM
Coumarin	CYP2A6	10 µM
Sulfaphenazole	CYP2C9	10 µM
Quinidine/Quinine[1]	CYP2D6	5 µM
Acetone	CYP2E1	2.5% v/v
Ketoconazole	CYP3A	1 µM

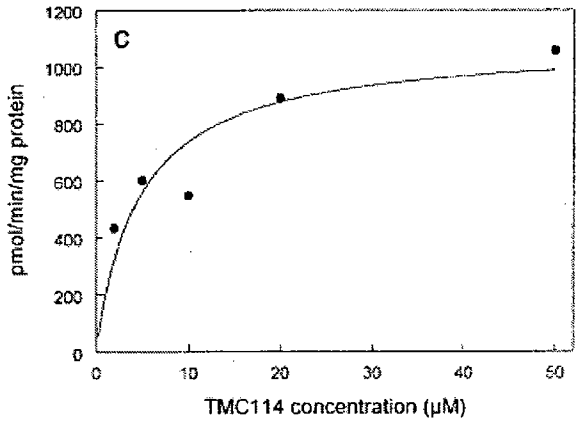
[1] quinidine was used for dog and human liver microsomes, quinine for rat liver microsomes.

Incubations with individual human cytochrome P450 enzymes:

Incubations with TMC114 and individual human cytochrome P450 enzymes were performed using the incubation conditions described above, a microsomal protein concentration of 1.0 mg/ml, and a TMC114 concentration around the Km value estimated for human liver microsomes.

RESULTS:

Figure 1: Fitted Michaelis-Menten curves of cytochrome P450 mediated metabolism of TMC114 by human liver microsomes.



The calculated K_m and V_{max} for human liver microsomes were 4.6 ± 2.3 µM and 1080 ± 155 pmol/min/ mg protein, respectively.

Table 2. Enzymatic activities and % inhibition of enzyme activities of incubations in the absence and presence of chemical inhibitors of cytochromes P450. Enzyme activities are expressed as pmol/min/mg protein.

Sample	RAT		DOG		HUMAN	
	activity	inhibition	activity	inhibition	activity	inhibition
No inhibitor[1]	629	-	303	-	370	-
α-naphthoflavone	217	66 %	298	2 %	398	-
Coumarin	270	57 %	245	19 %	392	-
Sulfaphenazole	603	4 %	209	31 %	334	10 %
Quinidine/Quinine[2]	403	36 %	320	-	410	-
Ketoconazole	275	56 %	93	69 %	167	55 %
No inhibitor[1]	755	-	314	-	462	-
Acetone	682	10 %	289	8 %	474	-

Table 3: Enzymatic activities of individual human cytochrome P450 enzymes towards TMC114

Enzymatic activity (pmol/min/mg protein)							
CYP1A2	CYP2A6	CYP2B6	CYP2C9	CYP2C19	CYP2D6	CYP2E1	CYP3A4
8	6	-	-	-	-	-	134

- = no detectable activity

CONCLUSIONS:

Incubations with individual human cytochrome P450 enzymes indicated that TMC114 was mainly metabolized by CYP3A4. Incubations in the absence and presence of chemical inhibitors demonstrated that only ketoconazole showed significant inhibition of TMC114 metabolism in human liver microsomes. These data suggest that CYP3A4 is responsible for the metabolism of TMC114 in humans.

TMC114-NC154

TITLE:

The *in vitro* metabolism of ^{14}C-TMC114 in hepatocytes and liver subcellular fractions of male and female Swiss albino mice, male and female black Agouti rasH2 microinjected mice, male and female rats, female rabbit, male dog and man.

OBJECTIVES:

To investigate the *in vitro* metabolism of TMC114 in hepatocytes (suspension and primary cell cultures) and liver subcellular fractions (microsomes and 12,000 x g supernatants) of male and female Swiss albino mice, male and female Sprague-Dawley rats, female rabbit, male dog and man.

METHODS:

The *in vitro* metabolism of ^{14}C-TMC114 was studied in hepatocytes (suspensions and primary cultures) and liver subcellular fractions (microsomes and 12,000 x g supernatant fractions) of male and female Swiss albino mice, male and female black agouti rasH2 microinjected mice, male and female Sprague-Dawley rats, female rabbit, male dog and man. TMC114 (5 μM, 2.74 μg/ml) was incubated in the above matrices at 37°C for various time periods, and incubates were analyzed by radio-HPLC. Co-chromatography, enzyme hydrolysis and LC-MS/MS techniques were used for the identification of metabolites.

Freshly prepared human hepatocytes were supplied by [redacted] Previously prepared and stored (-80 °C) batches of liver subcellular fractions (microsomes and 12,000 x g supernatants) from humans were also used in this study.

RESULTS:

Table1: Summary of the various metabolites with the metabolite identification code, the technique(s) used in the identification along with the metabolic route

Metabolite code	Identification method	Metabolic route
UD	LC-MS/MS Co-elution	Unchanged drug (R319064: TMC114)
1	LC-MS/MS Enzymatic hydrolysis	Glucuronide of metabolite 6
2	LC-MS/MS	Carbamate hydrolysis and mono-hydroxylation at the isobutyl function
3	LC-MS/MS	Glucuronidation and mono-hydroxylation of metabolite 19 (hydroxylation at the aniline moiety)
6	LC-MS/MS Co-elution	Carbamate hydrolysis and mono-hydroxylation of the benzene moiety (R330701)
8	LC-MS/MS	Acid formation (oxidation of metabolite 21)
10, 22	LC-MS/MS Enzymatic hydrolysis	Glucuronidation and mono-hydroxylation at the [(4-amino-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl moiety (For metabolite 10, hydroxylation at an aliphatic moiety)
11	LC-MS/MS Enzymatic hydrolysis	Glucuronide of metabolite 15
12, 27, 28	LC-MS/MS	Mono-hydroxylation at the hexahydro-furo-[2,3-b]furan moiety
14	LC-MS/MS Co-elution	Oxidative *N*-dealkylation (R330576)
15	LC-MS/MS	Carbamate hydrolysis and mono-hydroxylation of the aniline moiety

Table 2 Mass balance and metabolite profile of TMC114 in hepatocyte suspensions (SK, 120 min), primary cell culture (PCK, 24 h), microsomes (MICR, 120 min) and 12,000 x g supernatant fractions (120 min) of human. The figures represent the percentage of the injected sample radioactivity accounted for by UD and its metabolites

	Hepatocytes (Donor 1)		Hepatocytes (Donor 2)		Hepatocytes (Donor 3)		Hepatocytes (Donor 4)		Hepatocytes (Mean of Donors 1-4)		Liver subcellular fractions	
	SK	PCK	SK	PCK	SK	PCK	SK	PCK	SK	PCK	12,000 g	MICR
2	-	4.5	-	3.1	-	3.6	-	6.9	-	4.5	-	-
4	-	4.6	-	2.8	-	2.2	-	3.9	-	3.4	-	-
6	3.6	13.5	T	8.1	1.4	9.4	2.9	12.8	2.0	11.0	6.8	5.4
10	-	2.5	-	2.3	-	1.9	-	3.2	-	2.5	-	-
11	-	4.5	-	2.2	-	2.4	-	4.2	-	3.3	-	-
13	-	2.5	-	3.4	-	2.9	-	2.5	-	2.8	-	-
15	2.0	7.6	T	6.2	T	5.6	2.9	10.7	1.2	7.5	9.2	5.6
24	-	-	-	-	-	-	-	-	-	-	8.3	7.0
18(+17*)	7.1*	3.0*	5.2*	20.8*	2.4*	17.2*	3.7*	11.3*	4.6*	13.1*	-	-
19	11.2	4.5	3.7	9.8	3.8	10.2	7.4	11.5	6.5	9.0	18.8	16.7
21	2.4	4.0	1.0	5.1	-	3.1	-	2.2	0.9	3.6	4.0	2.8
23	8.7	-	2.7	9.9	3.8	9.0	6.8	4.6	5.5	5.9	10.9	13.9
24	1.4	-	-	3.6	-	1.7	-	7.0	0.4	3.1	-	-
25	-	-	-	-	-	-	-	-	-	-	4.1	3.3
27	-	-	-	-	-	-	-	-	-	-	9.0	8.0
28	-	-	-	-	-	-	-	-	-	-	2.7	4.3
29	5.5	-	2.3	T	-	T	4.2	T	3.0	T	7.6	7.8
UD	45.2	-	81.7	2.1	83.3	2.2	65.2	-	68.9	1.1	5.7	16.3
31	-	-	-	-	-	-	-	-	-	-	-	1.4
32	-	-	-	-	-	-	-	-	-	-	-	3.2
Sum	87.1	51.2	96.6	79.4	94.7	71.4	93.1	80.8	93.0	70.7	87.1	95.7

* The figures represent the sum of the percentages of metabolites 17 and 18.
T: ≤ 1%

CONCLUSIONS:

In human, TMC114 was metabolized *via* different metabolic pathways. The different hydroxylated metabolites of TMC114 were all detected in human and usually also in all animal species. Secondary metabolites, originating from further metabolism of the hydroxylated metabolites of TMC114, were observed in human and also in one or more of the animal species. Carbamate hydrolysis occurred in human and in all animal species. Subsequent biotransformation *via* hydroxylation and glucuronidation was also observed in human and in several of the animal species.

TMC114-NC202

TITLE:

An *in vitro* study to (a) determine the kinetics of TMC114 metabolism in human liver microsomes (HLM); (b) identify the microsomal cytochrome P-450 isoenzymes mediating TMC114 metabolism (reaction phenotyping) and (c) determine the inhibitory potency of atazanavir on the metabolism of TMC114.

METHODS:

Enzyme kinetics:

To determine kinetics (Km and Vmax) of TMC114 metabolism, varying concentrations of ^{14}C-TMC114 (1 µM, 3 µM, 5 µM, 10 µM, 30 µM, 50 µM and 100 µM) were incubated in HLM. A protein concentration (HLM) of 0.5 mg/ml with 20 min incubation time was adopted for all incubations in this experiment.

CYP P450 reaction phenotyping:

A preliminary experiment was carried out to determine the contribution of microsomal CYP P450 enzymes to the metabolism of TMC114 in HLMs. In this experiment, 1-aminobenzotriazole was used as a non-specific CYP P450 inhibitor. A pooled batch of HLMs was preincubated with 4-aminobenzotriazole (1000 µM) in the presence of a NADPH-regenerating system for 15 min and reactions were started by addition of 14C-TMC114. The experimental conditions, i.e., the final concentration of TMC114 (3 µM), microsomal protein concentration (0.5 mg/ml, pooled batch of HLMs, and time of incubation (20 min)), were adopted from the enzyme kinetics experiment.

Incubations of 14C-TMC114 in HLMs were carried out in triplicate in the presence of CYP isoform specific diagnostic chemical inhibitors. The extent of inhibition of TMC114 metabolism was determined following addition of 5-µl aliquots of the inhibitors formulated in methanol per ml of incubate. The inhibitors were added to the incubates prior to the addition of co-factor mixture and TMC114. The experimental conditions, i.e., the final concentration of TMC114 (3 µM), microsomal protein concentration (0.5 mg/ml, pooled batch of HLMs, and time of incubation (20 min)), were adopted from the enzyme kinetics experiment.

^{14}C-TMC114 incubations in the presence of heterologously expressed recombinant enzymes:

E.coli systems: CYP P450 isozymes involved in the metabolism of TMC114 was studied in various membrane preparations of E. coli expressing human reductase in combination with one of the following human CYP P450s: CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP2E1, CYP2C8 or CYP2B6. Vector controls (0.5 mg protein/ml) were run parallel to the test samples. The incubations were carried out at a CYP P450 concentration of 100 pmol/incubate in a total volume of 1.0 ml. The co-factor mixture in each incubate contained 0.5 mg of glucose-6-phosphate, 0.25 units of glucose-6-phosphate dehydrogenase, 0.125 mg of

NADP and 0.5 mg of MgCl2.6H2O in 0.5 ml of 0.5 M Na,K phosphate buffer pH 7.4. After a preincubation of 5 min, the reactions were started by addition of the ^{14}C-TMC114 (final concentration in incubation: 30 µM). The samples were incubated for 60 min. All incubations were performed in triplicate.

[redacted]): Incubations were also conducted in commercially available recombinant CYP P450 enzymes [redacted]) in the similar way (i.e., same test conditions, same test concentrations of drug and CYP isoforms) as that mentioned in *E. coli* systems. In addition to the above CYP isoforms, the extent of metabolism of ^{14}C-TMC114 was examined in CYP 3A7 [redacted] (100 pmol CYP P450/incubate).

Correlation analysis:

The metabolism of ^{14}C-TMC114 was studied in microsomal preparations of various human livers, which have previously been characterized for the major forms of human cytochrome P-450s. The experimental conditions were same as the enzyme kinetics experiment. The incubations were carried out in triplicate.

Effect of atazanavir on the metabolism of TMC114:

^{14}C TMC114 was incubated in HLM in the presence of various concentrations of atazanavir (0, 0.15, 0.30, 1.0, 2.0, 5.0, 10.0 and 30.0 µM). The final concentration of ^{14}C-TMC114 and the incubation conditions were same as that used in the experiment of effect of diagnostic inhibitors on the metabolism of TMC114.

RESULTS:

Enzyme kinetics of TMC114 metabolism

The kinetic parameters were calculated based on the rate of disappearance of TMC114. The kinetics of TMC114 metabolism was examined by Michaelis-Menten plots. As the variability was higher at 50 µM, a weighting factor (1/y2) was applied to the model while fitting the equation to the data. The kinetic data analyzed by Michaelis Menten plot reveals that the metabolism of TMC114 followed monophasic Michaelis Menten kinetics. In the concentration range tested, the mean apparent Km and Vmax values for the metabolism of TMC114 were 3.82 (Std. Error ± 0.70) µM and 328.0 (Std. Error ± 24.1) pmol/mg/min, respectively. The Km value obtained from this experiment was used in selecting the concentration in the subsequent reaction phenotyping experiments in the same pooled batch of HLMs.

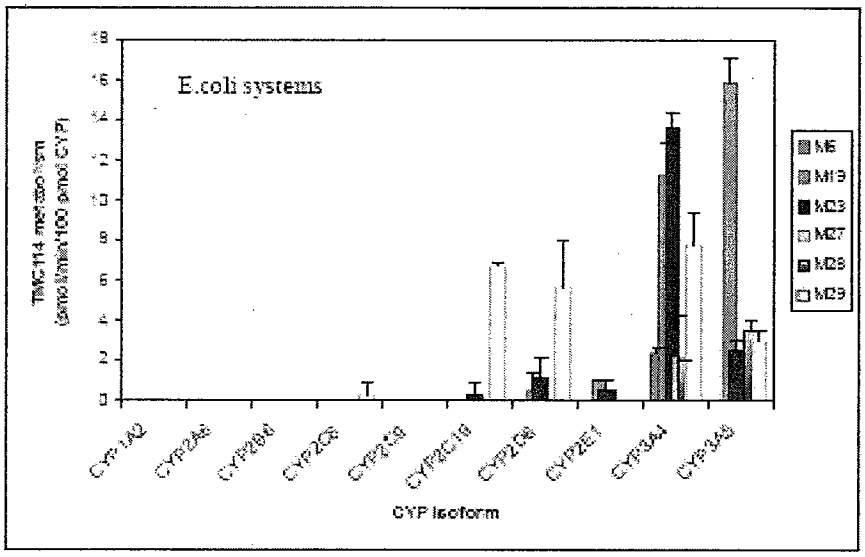
M27, M28 and M29) were formed *via* CYP P450 pathway from TMC114. Although complete inhibition of the metabolites was observed, there was an unusual peak observed in this sample. This was not observed any of the HLM samples.

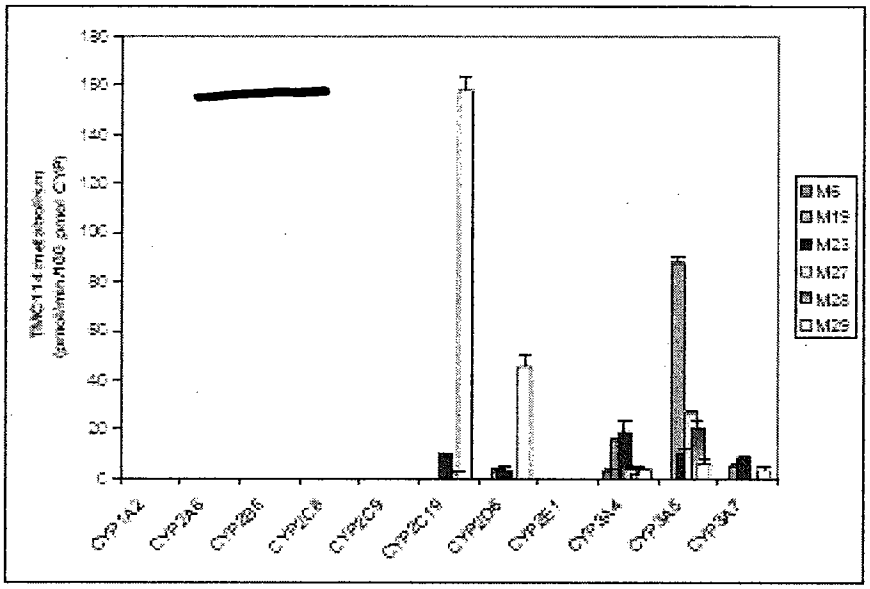
Among all diagnostic inhibitors, CYP3A inhibitors showed a marked effect on the overall metabolism of TMC114. The percent inhibition of the overall TMC114 metabolism by various CYP3A inhibitors was ritonavir (0.15 μM), ketoconazole (1.0 μM), clarithromycin (15.0 μM) and troleadomycin (200 μM) was 60 %, 47 %, 32% and 79 %, respectively. The other diagnostic CYP inhibitors [CYP1A2-furafylline (10 μM), CYP2A6-coumarin (100 μM), CYP2C8/9/10-sulphaphenazole (10 μM), CYP2D6-quinidine (10 μM), CYP2E1-4-methylpyrazole (20 μM), CYP2C19/2D6-ticlopidine (5 μM)] had a minor or no effect on the overall metabolism of TMC114.

With all metabolites (M6, M19, M23, M27, M28 and M29) CYP3A inhibitors showed much more extensive inhibition (up to 100 %) of metabolism compared to the other diagnostic CYP inhibitors studied. The other diagnostic inhibitors did inhibit the formation of metabolites M23, M27, M28 and M29 compared to the control. For metabolites M6 and M19, although maximum inhibition was observed with CYP3A inhibitors, all other diagnostic inhibitors also showed inhibition to an appreciable extent. These two metabolites require a metabolic step 'carbamate hydrolysis' and probably along with CYP3A other CYPs were also mediating this reaction to some extent.

^{14}C-TMC114 incubations in the presence of heterologously expressed recombinant enzymes

Figure 2. CYP reaction phenotyping- Metabolism of ^{14}C-TMC114 in heterologously expressed human CYP isoforms. M6, M19, M23, M27, M28 and M29 are the metabolites of TMC114 observed in these systems





Correlation analysis: Metabolism of TMC114 in 10 batches of HLMs

Table 2. CYP reaction phenotyping by correlation analysis - Spearman's rank order correlation analysis of ^{14}C-TMC114 metabolite(s) (M6, M19, M23, M27, M28 and M29) with various CYP isoform dependent enzyme activities in 10 individual batches of human liver microsomes

Enzyme activities (CYP isoform)	Overall TMC114 metabolism (R_r)	TMC114 Metabolite Correlation coefficient (R_r)					
		M6	M19[1]	M23[1]	M27	M28	M29[1]
7-ethoxyresorufine *O*-deethylase (1A2)	-0.176	-0.128	-0.285	0.032	-0.333	-0.285	-0.212
Phenacetin *O*-dethylase (1A2)	-0.273	-0.297	-0.321	-0.194	-0.430	-0.467	-0.248
Coumarin 7-hydroxylase (2A6)	0.033	0.200	0.000	0.251	-0.083	-0.050	0.067
Taxol 6-α-hydroxylase (2C8)	-0.236	-0.504	-0.151	-0.462	-0.224	-0.273	-0.273
Tolbutamide methyl hydroxylase (2C9,10)	-0.721	-0.717	-0.636	-0.515	-0.636	-0.684	0.300
S-mephenytoin 4-hydroxylase (2C19)	0.300	0.205	0.500	0.500	0.500	0.300	0.262
Dextromethorphan *O*-demethylase (2D6)	-0.260	-0.389	-0.164	-0.626	-0.078	-0.164	-0.297
Bufuralol hydroxylase (2D6)	-0.176	-0.292	-0.103	-0.468	-0.078	-0.164	-0.200
Chlorzoxazone 6-hydroxylase (2E1)	-0.018	-0.207	-0.067	-0.152	-0.200	-0.188	-0.054
Lauric acid ω-1 hydroxylase (2E1)	-0.273	-0.248	-0.164	-0.444	-0.333	-0.358	-0.285
Testosterone 6-β-hydroxylase (3A4)	0.697	0.699	0.661	0.605	0.636	0.515	0.660
Cyclosporine oxidase (3A)	0.794	0.736	0.794	0.723	0.733	0.697	0.770
Taxol 3'-hydroxylase (3A4)	0.673	0.790	0.612	0.603	0.561	0.454	0.668
Midazolam 4-hydroxylase (3A4/A5)	0.805	0.772	0.636	0.705	0.685	0.636	0.721
Midazolam 1'-hydroxylase (3A5/A4)	0.770	0.564	0.721	0.772	0.806	0.770	0.661
Lauric acid ω-hydroxylase (4A)	-0.188	0.006	-0.200	-0.213	-0.380	-0.370	-0.261

Additional Information
1. Major metabolites in human liver microsome.
Bolded numbers: Positive correlations equal or higher than 0.500

Significant correlation coefficients (Rr) > 0.500 (range: 0.515-0.806) were obtained for CYP3A enzyme activity and metabolite formation except for M28 formation rate versus taxol 3'-hydroxylase activities of HLMs, where the correlation coefficient (Rr) was 0.454. For M27 along with the CYP3A enzymes, CYP2C19 also gave a positive correlation coefficient higher than 0.500 (Rr = 0.561). Other CYP activities (CYP1A2, 2A6, 2C8, 2C9/10, 2D6, 2E1, 4A) showed either negative or poor positive correlations (r2 < 0.400), indicating that these enzymes have no or very limited role in the metabolism of TMC114.

Effect of atazanavir on the metabolism of TMC114

Table 3: Effect of atazanavir on the metabolism of ^{14}C-TMC114 in a pooled batch of human liver microsomes

Conc. atazanavir (μM)	% metabolized TMC114	% inhibition of TMC114 metabolism
0.00	48.43	0.00
0.15	47.27	2.41
0.30	49.80	-2.82
1.00	43.33	10.53
2.00	38.53	20.44
5.00	35.13	27.46
10.00	22.70	53.13
30.00	15.27	68.48
IC_{50}^{*} of atazanavir = 11 μM		

(*calculated from linear relationship of Conc. of atazanavir and % inhibition of metabolism of TMC114)

CONCLUSIONS:

CYP3A enzymes appeared to be the major enzymes that catalyze TMC114 oxidative metabolism *in vitro*. CYP3A inhibitors (troleandomycin, ritonavir, ketoconazole, clarithromycin) showed a significant inhibition of formation of all metabolites, M6, M19, M23, M27, M28 and M29 (up to 100 %) and the overall metabolism of TMC114 (up to 80 %). The observation was in good agreement with correlation analysis and incubation with heterologously expressed recombinant CYP3A enzymes.

For M6 and M19, there was also a moderate inhibition with other CYP inhibitors. This observation was not in line with the other methods. This was considered as an exception and probably resulted from some extent of cross-specificity of the chemical inhibitor.

CYP inhibitors (CYP1A2, 2A6, 2C8/9/10, 2D6, 2E1 and 2C19) have no impact on the overall inhibition of TMC114 metabolism

With E. coli CYP systems and [redacted]-CYP systems it appears that CYP2C19 and CYP2D6 have some role in the formation of M29. The relative activity of these enzymes with respect to the abundance in the human liver was not factored and the involvement of these enzymes in M29 formation cannot be ruled out.

Although not confirmed by methods using HLMs, based on expressed CYP systems M29 formation might also be catalyzed by CYP2C19 and CYP2D6 along with CYP3A enzymes.

The correlation analysis results clearly showed TMC114 metabolism as well as metabolite rates correlated well (positive correlation coefficients > 0.500 (range: 0.502 – 0.899) with the CYP activities of CYP3A enzymes.

In conclusion, overall TMC114 metabolism as well as formation of all metabolites (M6, M19, M23, M27, M28, M29), was mainly catalyzed by CYP3A enzymes.

TMC114-NC123

TITLE:

Inhibition of human cytochrome P450 enzymes by TMC114 *in vitro*.

METHODS:

Pooled human liver microsomes (mixed gender, n = 20, lot number 2.0) were purchased from [redacted]

The cytochrome P450 probe substrates (Table 1) were incubated at concentrations around the K_m values (Table 2) in the absence and presence of the following concentrations of TMC114: 0.5, 5, 50 and 100 µM. Concentrations higher than 100 µM could not be used due to the limited solubility of TMC114 in methanol.

Table 1. List of probe substrates for individual P-450 enzymes

Cytochrome P450 enzyme	Substrate	Metabolite
CYP1A2	7-ethoxyresorufin	resorufin
CYP2A6	coumarin	7-hydroxycoumarin
CYP2B6	7-ethoxy-4-trifluoro-methyl coumarin	7-hydroxy-4-trifluoro-methyl coumarin
CYP2C9	diclofenac	4'-hydroxydiclofenac
CYP2C19	S-mephenytoin	4'-hydroxy-mephenytoin
CYP2D6	bufuralol	1'-hydroxybufuralol
CYP2E1	chlorzoxazone	6-hydroxy-chlorzoxazone
CYP3A	testosterone	6ß-hydroxy-testosterone

Table 2. Concentrations of P450 probe substrates in the preliminary inhibition experiments

CYP1A2	CYP2A6	CYP2B6	CYP2C9	CYP2C19	CYP2D6	CYP2E1	CYP3A
0.5 µM	5 µM	5 µM	10 µM	20 µM	10 µM	100 µM	100 µM

In order to estimate the inhibition constants K_i of TMC114 towards the various cytochrome P450 enzymes, incubations were performed with seven concentrations of the various P450 probe substrates (Table 3) in the absence and presence of one concentration of TMC114 for each P450 enzyme. The latter concentrations were based on the results of the preliminary inhibition experiments. If these preliminary experiments showed less than 20% inhibition of a specific P450 activity at the highest TMC114 concentration, inhibition of that cytochrome P450 enzyme was not investigated any further.

Table 3. Concentrations of P450 probe substrates (pM) used in the K, experiments

CYP1A2	CYP2A6	CYP2B6	CYP2C9	CYP2C19	CYP2D6	CYP2E1	CYP3A
0.05	0.5	0.5	1	2	1	5	5
0.1	1	1	2	5	2	10	10
0.2	2	2	5	10	5	20	20
0.5	5	5	10	20	10	50	50
1	10	10	20	50	20	100	100
2	20	20	50	100	50	200	200
5	50	50	100	200	100	500	500

RESULTS:

In the preliminary experiments, a concentration-dependent inhibition was observed for CYP2C9, CYP2C19, CYP2D6 and CYP3A activities. CYP1A2 and CYP2B6 were only slightly inhibited at the highest TMC114 concentration, while no inhibition of CYP2A6 and CYP2E1 could be detected. Since for CYP1A2 less than 20% inhibition was found at the highest TMC114 concentration, inhibition of CYP1A2 activity was not further investigated.

Table 4. Inhibition of cytochrome P450 probe substrates by TMC114

Sample	CYP1A2	CYP2A6	CYP2B6	CYP2C9	CYP2C19	CYP2D6	CYP2E1	CYP3A
Enzyme activities (pmol/min/mg microsomal protein)								
Control	31.1	662	129	1178	1.85	31.9	721	3950
Enzyme activities relative to the controls (control = 100%)								
TMC114 0.5 uM	103	98	94	102	87	84	88	57
TMC114 5 uM	99	95	90	99	107	82	85	22
TMC114 50 uM	89	94	87	67	93	57	90	6
TMC114 100 uM	84	97	79	49	67	32	104	5

Appears This Way
On Original

Table 5. Inhibition constants Ki of TMC114 towards various cytochrome P450 enzymes

P450 enzyme	Selected TMC114 concentration (µM)	Type of inhibition	Inhibition constant K_i (µM)
CYP2B6	100	non-competitive	500 ± 91
CYP2C9	100	competitive	52 ± 4
CYP2C19	50	competitive	25 ± 3
CYP2D6	50	competitive	41 ± 4
CYP3A	0.5	competitive	0.40 ± 0.09

Table 6: Summary of Inhibition potential of Cytochrome P450 Probe Substrates by TMC114

P450 Enzyme	Darunavir Concentration (µM)	Type of Inhibition	Mean Inhibition Constant K_i (µM)	I/K_i		
				I=7.1 µM[a]	I=10.0 µM[b]	I=10.5 µM[c]
CYP2B6	100	Non-competitive	500	0.01	0.02	0.02
CYP2C9	100	Competitive	52	0.14	0.19	0.20
CYP2C19	50	Competitive	25	0.28	0.40	0.42
CYP2D6	50	Competitive	41	0.17	0.24	0.26
CYP3A	0.5	Competitive	0.40	17.8	25.0	26.3

I = C_{max} at the recommended dose in µM.
[a] I = 7.1 µM (3913 ng/mL) for darunavir/ritonavir 400/100 mg b.i.d. (Study TMC114-C137).
[b] I = 10.0 µM (5460 ng/mL) for darunavir/ritonavir 600/100 mg b.i.d. (Study TMC125-C139).
[c] I = 10.5 µM (5736 ng/mL) for darunavir/ritonavir 800/100 mg b.i.d. (Study TMC114-C137).

CONCLUSIONS:

Based on I/K_i values, the inhibitory potential of TMC114 on CYP3A4 enzyme is high. *The I/K_i values is greater than 0.1 for CYP2C9, CYP2C19, and CYP2D6, therefore, the induction/inhibitory potential of steady state TMC114/RTV (600/100 mg b.i.d.) on the metabolism of CYP450 probe substrates for CYP2C9, CYP2C19, and CYP2D6 will be evaluated as part of the phase 4 commitments.*

TMC114-NC134

TITLE:

Interaction of 6 anti-HIV compounds with the cytochrome P450-mediated metabolism of TMC114 in vitro

OBJECTIVES:

To investigate the interaction of six anti-HIV compounds, i.e. delavirdine, saquinavir, ritonavir, indinavir, nelfinavir and amprenavir, with TMC114 in pooled human liver microsomes

METHODS:

Incubations with liver microsomes and TMC114 were performed in the absence (controls) and presence of the anti-HIV compounds in order to establish the type of inhibition of TMC114 metabolism (competitive or non-competitive) and to determine the inhibition constants Ki. TMC114 metabolism was determined by measuring the decrease of the parent compound by LC-MS analysis. Pooled human liver microsomes (mixed gender, n = 20) were obtained from

Inhibition experiments (preliminary): TMC114 was incubated with pooled human liver microsomes in the absence and presence of four concentrations of the anti- HIV compounds (0.02, 0.2, 2 and 20 μM). Both the anti-HIV compounds and TMC114 were added to the incubation mixture as solutions in methanol (final concentration of methanol: 2.5%, v/v). Controls were incubated without NADPH and without inhibitor. Before starting the reaction with TMC114, the incubation mixtures were pre-incubated with the anti- HIV compounds for 5 minutes at 37°C. Incubations without inhibitors were pre-incubated with methanol only. The reactions were terminated by the addition of ice-cold acetonitrile. After centrifugation, the supernatant was analyzed by LC-MS. TMC114 concentration was 5 μM. Incubations in the presence of anti-HIV compounds were performed in duplicate. Controls and incubations without anti-HIV compounds were incubated in triplicate.

Inhibition experiments (final): TMC 114 (concentrations of 1, 2, 5, 10, 20, 30 and 50 μM) was incubated with pooled human liver microsomes in the absence and presence of the following concentrations of the anti-HIV compounds: Delavirdine 10 μM, Saquinavir 5 μM, Ritonavir 0.1 μM, Indinavir 0.2 μM, Nelfinavir 1 μM, and Amprenavir 2 μM. Both the anti-HIV compounds and TMC114 were added to the incubation mixture as solutions in methanol (final concentration of methanol: 2.5%, v/v). Controls were incubated without NADPH and without inhibitor. Before starting the enzymatic reactions with TMC114, the incubation mixtures were pre-incubated with the anti-HIV compounds for 5 minutes at 37°C. Incubations without inhibitors were pre-incubated with methanol only. The reactions were terminated by the addition of ice-cold acetonitrile. After centrifugation, the supernatant was analyzed by LC-MS. Incubations in the presence of anti-HIV compounds were performed in duplicate. Controls and incubations without anti-HIV compounds were incubated in triplicate.

RESULTS:

Table 1. Inhibition of cytochrome P450-mediated metabolism of TMC114 by delavirdine, saquinavir, ritonavir, indinavir, nelfinavir and amprenavir

Inhibitor	% inhibition of TMC114 metabolism			
	concentration of anti-HIV compounds			
	0.02 µM	0.2 µM	2 µM	20 µM
Delavirdine	-	5	16	78
Saquinavir	-	17	13	100
Ritonavir	22	71	98	97
Indinavir	25	46	100	100
Nelfinavir	1	18	58	100
Amprenavir	19	12	38	77

- = no inhibition of TMC114 metabolism

The calculated K_i values of delavirdine, saquinavir, ritonavir, indinavir, nelfinavir and amprenavir were 2.5, 1.6, 0.014, 0.28, 0.18 and 2.0, respectively.

Table 2. Average plasma concentrations of TMC114 and anti-HIV compounds

compound	average plasma concentration	molecular weight	average plasma concentration (µM)
TMC114	C_{min} = 250 ng/ml C_{max} = 6000 ng/ml	547.7	C_{min} = 0.46 µM C_{max} = 11.0 µM
Delavirdine	19 µM	456.6	19 µM
Saquinavir	906 ng/ml	670.9	1.35 µM
Ritonavir	7.5 µg/ml	721.0	10.4 µM
Indinavir	3.8 µM	613.8	3.8 µM
Nelfinavir	3.1 mg/l	567.7	5.46 µM
Amprenavir	1.54 µg/ml	505.6	3.05 µM

CONCLUSIONS:

Based on the K_i values and *in vivo* plasma concentrations of these anti-HIV drugs, delavirdine, ritonavir, indinavir and nelfinavir are likely to inhibit TMC114 metabolism *in vivo* while saquinavir and amprenavir are minor to moderate inhibitors of TMC114 metabolism.

TMC114-NC171

TITLE:

In vitro study on the potential of TMC114 to induce CYP mRNA in cryopreserved human hepatocytes

OBJECTIVES:

To investigate the potential of TMC114 to induce liver cytochrome P450- (CYP) enzymes in humans

METHODS:

Briefly, the potential of TMC114 to induce cytochromes P450 (CYPs) was determined in primary hepatocyte cultures established on collagen-coated 24-well plates from cryopreserved human hepatocytes originating from 3 different donors that retained acceptable attachment characteristics. After the establishment of the hepatocyte cultures, human hepatocytes were treated for two consecutive days either with vehicle, with various concentrations of TMC114 (2.5 µM, 10 µM, 25 µM, or 50 µM), or with the positive control compounds, omeprazole (25 µM), rifampicin (25 µM), phenobarbital (100 µM), or ritonavir (10 µM). Induction of CYP enzymes was assessed at the end of the 48 h treatment period, by measurement of the mRNA expression with TaqMan quantitative RT-PCR.

RESULTS:

CYP mRNA expression in cryopreserved human hepatocytes:

Table 1. The mean fold induction of the different CYP-isoforms in cryopreserved human hepatocytes treated with 2.5, 10, 25, or 50 µM TMC114, 25 µM rifampicin (rif), 25 µM omeprazole (ome), 100 µM phenobarbital (phe), or 10 µM ritonavir (rit) as compared to the control cells. Bold numbers indicate statistically significant changes of the treated cells compared to the control cells as calculated with a Paired student's t test ($n = 3$, $p < 0.05$)

		Fold induction						
	Condition	CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C18	CYP2C19	CYP3A4
	con	1.0	1.0	1.0	1.0	1.0	1.0	1.0
TMC114	2.5	1.3	2.3	3.3	**2.0**	**1.7**	1.7	**3.4**
	10	1.3	3.1	5.0	2.7	**2.1**	2.3	**4.8**
	25	1.3	3.0	3.9	2.3	1.8	1.9	**4.2**
	50	2.2	**5.9**	**5.4**	**3.0**	**2.4**	2.6	**5.5**
	rif	0.5	**7.6**	6.0	2.9	2.2	3.5	**5.3**
	ome	22.0	**4.5**	2.3	**1.7**	1.5	1.8	**2.4**
	phe	1.3	5.6	4.7	2.1	**1.8**	1.9	3.3
	rit	0.9	3.7	3.1	**2.4**	**2.1**	2.3	**4.9**

Figure 1: CYP1A2 mRNA expression in control and treated cells, calculated as the mean ± SEM from the three different lots of cryopreserved human hepatocytes.

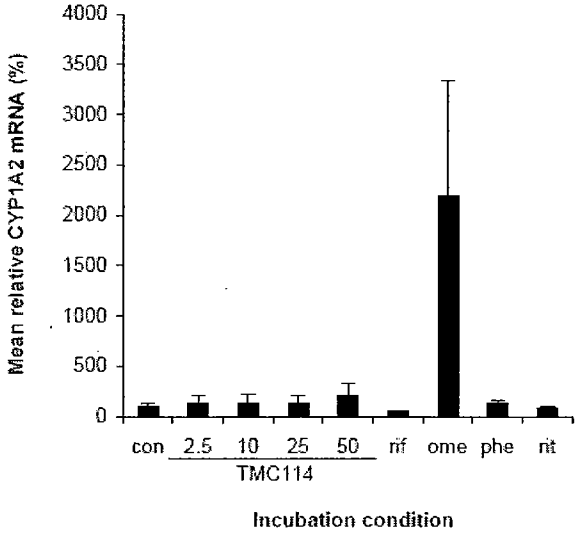


Figure 2: CYP2B6 mRNA expression in control and treated cells, calculated as the mean ± SEM from the three different lots of cryopreserved human hepatocytes. * p-value < 0.05, n = 3

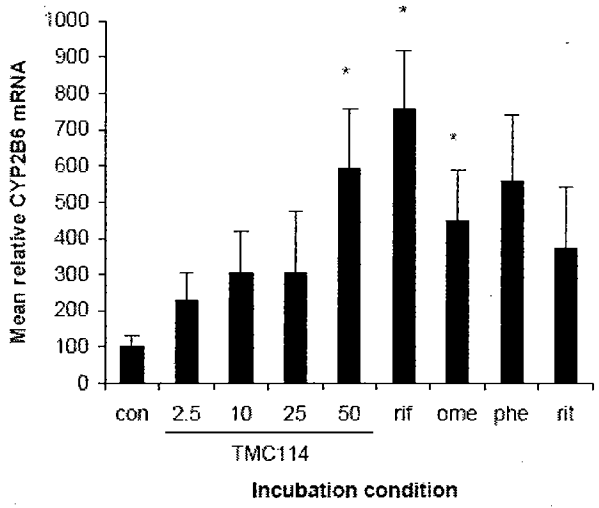
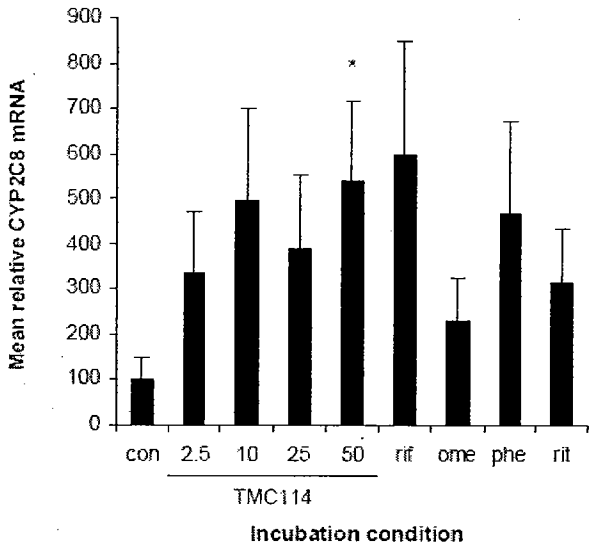


Figure 3: CYP2C8 mRNA expression in control and treated cells, calculated as the mean ± SEM from the three different lots of cryopreserved human hepatocytes. * p- value < 0.05, n = 3



Appears This Way
On Original

Figure 4: CYP2C9 mRNA expression in control and treated cells, calculated as the mean ± SEM from the three different lots of cryopreserved human hepatocytes. * p-value < 0.05, n = 3

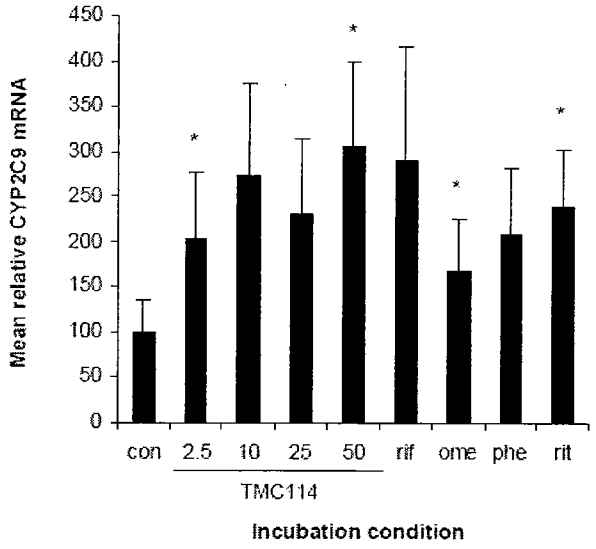


Figure 5: CYP2C18 mRNA expression in control and treated cells, calculated as the mean ± SEM from the three different lots of cryopreserved human hepatocytes. * p-value < 0.05, n = 3

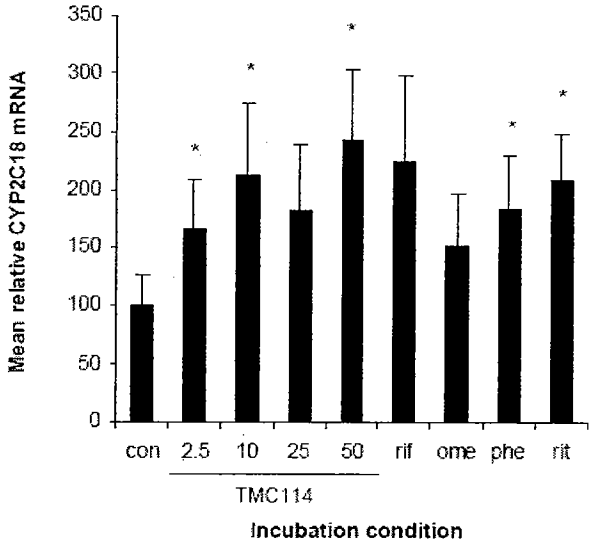


Figure 6: CYP2C19 mRNA expression in control and treated cells, calculated as the mean ± SEM from the three different lots of cryopreserved human hepatocytes. * p-value < 0.05, n = 3

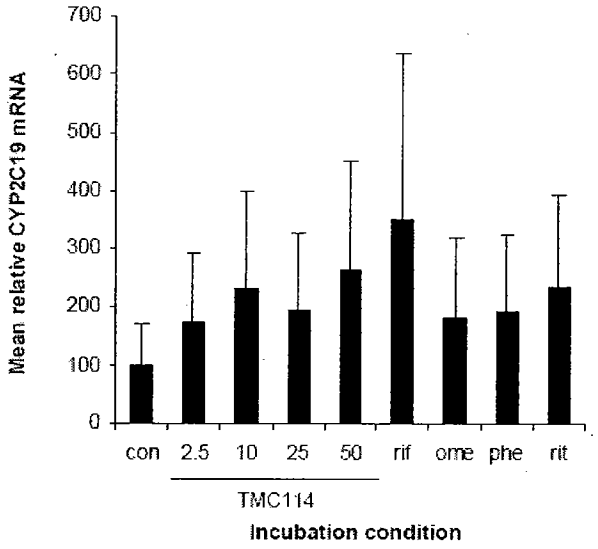
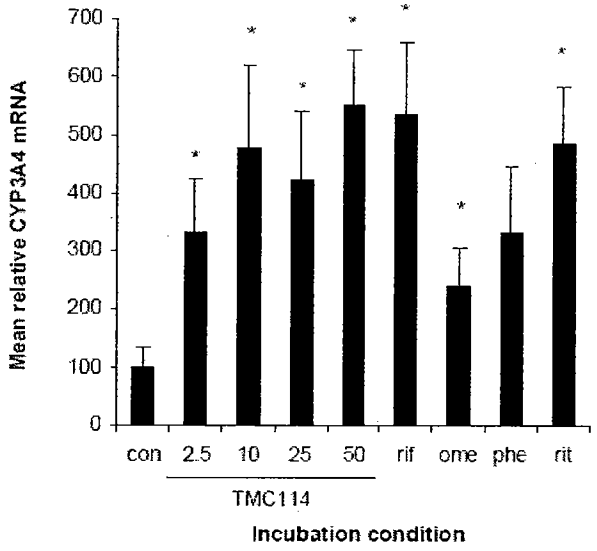


Figure 7: CYP3A4 mRNA expression in control and treated cells, calculated as the mean ± SEM from the three different lots of cryopreserved human hepatocytes. * p-value < 0.05, n = 3



CONCLUSIONS:

Treatment of the cells with different concentrations of TMC114 resulted in a minor, statistically non-significant mean 2.2-fold increase of CYP1A2 mRNA expression at the highest concentration (50 µM). In comparison, treatment of the cells with 25 µM omeprazole elicited an approximate 22.0-fold increase of CYP1A2 mRNA. However, treatment of the cells with 50 µM TMC114 resulted across the three batches of hepatocytes in a statistically significant mean 5.9-, 5.4-, 3.0-, 2.4-, 2.6-, and 5.5-fold increase of the CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, and CYP3A4 mRNA expression, respectively.

Further *in vitro* and *in vivo* studies may be needed to confirm the TMC114's CYP enzyme induction potentials. A CYP cocktail study will be conducted as part of Phase 4 commitment.

TMC114-NC137

TITLE:

Determination of the in vitro transport characteristics of TMC114, evaluation of the possible interaction of TMC114 as substrate and/or inhibitor with human P-glycoprotein, and assessment of the effect of the anti-HIV drug ritonavir on TMC114 transport: an in vitro study in Caco-2 monolayers

METHODS:

Transepithelial transport of TMC114 across cell monolayers:

Caco-2 cells (passage # 32) were seeded on 24-well cell culture inserts [redacted], at 63,000 cells/cm^2. Cell culture medium consisted of DMEM supplemented with 5% FCS, 1% NEAA, 1% L-glutamine and 100 U/ml Penicillin/streptomycin and was replaced the day after seeding and every other day thereafter. At the day of the transport experiments (21-22 days post seeding), the integrity of the cell monolayer in each insert was evaluated by measuring transepithelial electrical resistance (TEER) before the transport experiment and by determining the leakage of ^{14}C- or ^{3}H-mannitol during the transport experiment. The appropriate dosing solutions were applied either to the apical (AP; 0.4 ml; HBSS pH 6.5 + 10% FCS) or to the basolateral (BL; 0.6 ml; HBSS pH 7.4 + 10% FCS) side of the monolayers to initiate transport experiments in the absorptive (AP to BL) or the secretory (BL to AP) direction, respectively. Inserts were incubated at 37°C in a humidified incubator containing 5 % CO2. Cells were incubated for 120 min. Transport experiments were performed in quadruplicate. Final total (labelled + unlabelled) TMC114 concentrations were 3, 10, 30, 100 and 300 µM. At the time of administration of the dosing solution (0 min), dosing solutions were sampled in duplicate for determination of initial concentrations. Subsequently, during the transport experiments, samples (100 µl) were taken from the acceptor compartments at 15 min, 45 min, 90 min and 120 min. The volume taken from the acceptor compartment upon sampling was corrected by addition of 100 µl of the appropriate buffer solution (HBSS +10% FCS, at pH 7.4 or at pH 6.5 with 25 mM MES). At the end of the incubation (120 min), a sample was taken from the solution in the donor compartment.

Effect of TMC114 on bi-directional transport of the P-glycoprotein substrate taxol across Caco-2 monolayers:

The procedures were similar as described previously. TMC114 concentrations in dosing solutions were 0, 1, 3, 10, 30 and 100 µM. The dosing solutions were spiked with the ^{3}H-taxol stock solution to obtain a final taxol concentration of 75.8 nM.

RESULTS:

1. Bi-directional transport characteristics of TMC114 across Caco-2 monolayers:

Table 1: Transepithelial permeation of TMC114 across Caco-2 monolayers

Condition, Compound	P_{app} (10^{-6} cm/s) ± SD [n=]		Efflux Ratio (B to A/A to B)
	Apical to Basolateral	Basolateral to Apical	
3 µM TMC114	7.3 ± 0.5	70.7 ± 3.8	9.7
10 µM TMC114	5.6 ± 1.2	74.3 ± 3.8	13.4
30 µM TMC114	10.7 ± 1.5	57.1 ± 6.7	5.4
100 µM TMC114	12.1 ± 3.7	45.1 ± 1.7	3.7
300 µM TMC114	17.4 ± 4.6	34.9 ± 0.5	2.0
30 µM TMC114 + 100 µM verapamil	14.9 ± 1.7	45.9 ± 3.1	3.1
30 µM TMC114 + 100 nM ritonavir	13.0 ± 3.1	27.3 ± 3.4	2.1

2. Effect of TMC114 on bi-directional P-gp-mediated transport of taxol across Caco-2 monolayers:

Table 2: P-glycoprotein inhibitory effect of TMC114 in Caco-2 monolayers

Condition, Compound	Taxol P_{app} (10^{-6} cm/s) ± SD [n=]		Taxol Efflux Ratio (B to A/A to B)
	Apical to Basolateral	Basolateral to Apical	
Control (^{3}H-taxol only)	1.04 ± 0.10	19.8 ± 0.7	19
1 µM TMC114	0.96 ± 0.06	14.8 ± 0.7	15
3 µM TMC114	1.13 ± 0.03	17.0 ± 0.5	15
10 µM TMC114	1.28 ± 0.02	14.8 ± 1.9	12
30 µM TMC114	1.35 ± 0.04	10.6 ± 0.9	8
100 µM TMC114	1.55 ± 0.16	5.48 ± 0.7	4
100 µM verapamil	1.65 ± 0.07	7.43 ± 0.2	4

CONCLUSIONS:

Bi-directional transport experiments with the P-gp substrate taxol demonstrated that TMC114 has P-gp inhibitory potential. A clinical study is ongoing to investigate the interaction between digoxin (a P-gp substrate) and darunavir.

The *in vitro* data also indicate that darunavir appears to be a P-gp substrate, however, the clinical relevance of this *in vitro* finding at darunavir *in vivo* plasma concentrations of approximately 10µM is unclear.

TMC114-NC113

TITLE:

The *in vitro* binding of TMC114 to plasma proteins of rat, dog and human.

METHODS:

The plasma protein binding of TMC114 was assessed by equilibrium dialysis. Three concentrations of TMC114 (100, 1000, and 10000 ng/mL) were used in human plasma.

The equilibrium dialysis system was made from [redacted] based on the procedures described by Reinard and Jacobsen (1989). A dialysis membrane with a molecular weight cut-off of 12,000-14,000 [redacted] was used. The pH of plasma and phosphate-buffered saline was determined before the start of each experiment. If the pH was not within the range 7.35-7.40, 1 M phosphoric acid or 1 M sodium hydroxide was added to adjust the pH.

The time required to achieve dialysis equilibrium was assessed by subjecting a nominal concentration of 1000 ng/ml of TMC114 in human plasma to equilibrium dialysis for 1, 4, 8 and 24 hours. The data of this experiment were also used to examine the stability of TMC114 in human plasma during equilibrium dialysis. The observed dialysis equilibrium time was used to study the protein binding of TMC114. All equilibrium dialysis experiments were performed in duplicate. The recovery of TMC114 from the dialysis system was determined for each sample.

After equilibrium dialysis the concentration of TMC114 was determined in buffer and plasma compartments by LC-MS/MS analysis.

RESULTS:

Table 1: The mean fraction of TMC114 bound to proteins after 1, 4, 8 and 24-hour equilibrium dialysis of human plasma spiked at 905 ng/ml and the mean recovery from the dialysis system

Time (h)	Mean % bound	Mean recovery (%)
1	96.3	101
4	94.4	96.1
8	95.4	98.9
24	94.6	90.8

Table 2: The mean protein binding of TMC114 in plasma of human at three concentrations as determined by 8-hour equilibrium dialysis and the mean recovery from the dialysis system.

Species	Mean observed concentration of TMC114 in spiked plasma (ng/ml)	Mean % bound	Mean recovery (%)
Human	94.0	95.8	112
	800	96.1	127
	$76.2*10^2$	92.3	110

CONCLUSIONS:

TMC114 was found to be highly protein bound (>92%) in human plasma independent of the concentration tested.

TMC114-NC215

TITLE:

The plasma protein binding and blood distribution of TMC114 in animals and man.

METHODS:

The plasma protein binding of TMC114 was studied by equilibrium dialysis.

Binding of TMC114 to purified human plasma proteins: The binding of ^{14}C-TMC114 to purified human plasma proteins was studied. Human serum albumin [redacted] was dissolved in 0.067 M Sörensen phosphate buffer pH 7.40 at concentrations of 6.0, 4.3, 2.0, 1.0, 0.5, 0.25 and 0.1% (w/v). α1-acid glycoprotein [redacted] was dissolved in 0.067 M Sörensen phosphate buffer pH 7.40 at concentrations of 0.20, 0.15, 0.10, 0.05 and 0.02 % (w/v). The obtained plasma protein solutions were fortified with ^{14}C-TMC114 at 500 ng base-eq./ml (1.33 kBq/ml). Duplicate samples of the different fortified protein solutions were subjected to equilibrium dialysis against 0.067 M Sörensen phosphate buffer pH 7.40 for 4 h at 37 °C.

Blood distribution: Fresh whole blood samples were obtained from five healthy male adult subjects. Duplicate whole blood samples were fortified with ^{14}C-TMC114 at a concentration of 500 and 5000 ng base-eq./ml (1.33 kBq/ml). Haematocrit values were determined by centrifugation of haematocrit capillaries, containing an aliquot of the whole blood samples, in a [redacted] centrifuge. Duplicate fortified whole blood samples were incubated at 37 °C for 30 min in stoppered test tubes in a [redacted] incubation bath. The tubes were gently twisted around 3-5 times during the incubation period in order to prevent sedimentation of blood cells. At the end of the incubation, four 250-µl aliquots of the whole blood samples were taken for determination of the blood radioactivity levels. The remainder of the whole blood samples were centrifuged at approximately 1700 x g for approximately 10 min in a [redacted] centrifuge in order to obtain plasma samples. Plasma levels of total radioactivity were measured in duplicate 100-µl aliquots.

RESULTS:

Plasma protein binding of TMC114:

Table 1: Plasma protein binding at different concentrations of ^{14}C-TMC114 in plasma of healthy male subjects. Each value represents the mean of two determinations

Species and sex	Concentration (ng base-eq./ml)	Percentage bound (%)
Man (male)		
	52	93.86
	520	93.23
	1875	91.47
	4688	92.64
	18750	75.46

Table 2: Haematocrit, blood-to-plasma concentration ratio (Cb/C) of TMC114, and fractions of TMC114 distributed to plasma water [fub(1-H)], to plasma proteins [fpP(1-H)] and to blood cells [fBC.H] at 500 and 5000 ng base-eq./ml in blood from male human subjects. Each value represents the mean of two determinations

Species (sex)	H	C_b/C (at 500 [1] ng/ml)	$fu_b(1-H)$ (at 500 [1] ng/ml)	$f_{pP}(1-H)$ (at 500 [1] ng/ml)	$f_{BC}.H$ (at 500 [1] ng/ml)
Man (male)					
Subject 1	0.48	0.65	0.0434	0.7620	0.1947
Subject 2	0.48	0.60	0.0247 [2]	0.8444 [2]	0.1309 [2]
Subject 3	0.46	0.68	0.0370	0.7605	0.2027
Subject 4	0.49	0.66	0.0489	0.7236	0.2276
Subject 5	0.50	0.62	0.0354	0.7810	0.1837
Mean	0.48	0.64	0.0379	0.7743	0.1879
S.D.	0.01	0.03	0.0091	0.0444	0.0357

Table 3: Plasma protein binding of TMC114 at 500 ng baseeq./ml in solutions of human serum albumin or α1-acid glycoprotein at physiological concentrations. Each value represents the mean of two determinations.

Human serum albumin (g/100 ml)	Percentage bound (%)	Percentage unbound (%)
6.0	50.60	49.41
4.3	43.38	56.62
2.0	28.30	71.71
1.0	17.03	82.98
0.5	8.59	91.42
0.25	10.17	89.84
0.1	1.08	98.93

α_1-acid-glycoprotein (g/100 ml)	Percentage bound (%)	Percentage unbound (%)
0.20	97.06	2.95
0.15	94.59	5.42
0.10	93.44	6.56
0.05	83.63	16.37
0.02	41.01	59.00

CONCLUSIONS:

TMC114 was found to be highly protein bound (> 92%) in human plasma independent of the concentration up to 5000 ng/mL (the mean Cmax following 600/100 mg b.i.d. is approximately 6500 ng/mL). In human plasma, TMC114 was mostly bound to α1-acid glycoprotein and to a lesser extent to albumin.

Base on the haematocrit values, TMC114 appeared not to penetrate into red blood cells.

4.2 Consult Reviews (including pharmacometric reviews)

NDA:	21-976
Compound:	TMC-114
Submission Dates:	23 September 2005, 23 December 2005, 21 March 2006
Sponsor:	Tibotec
PM Reviewer:	Christine Garnett, PharmD
PM Team Leader and Secondary Reviewer	Joga Gobburu, PhD

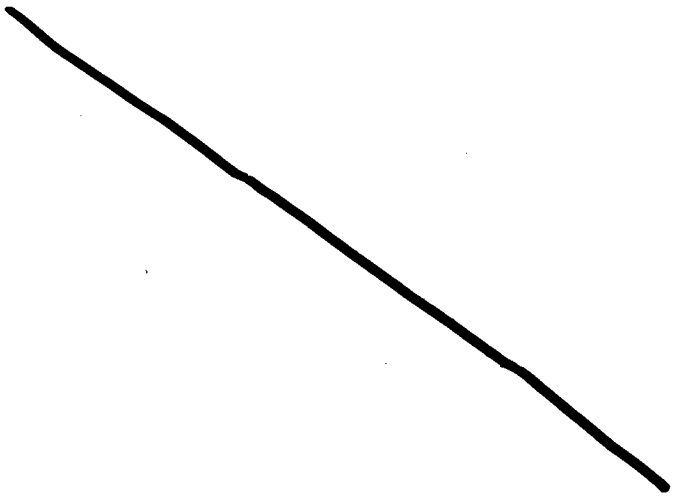
Executive Summary

Darunavir is an inhibitor of the HIV-1 protease and is being developed for the treatment of HIV infection in antiretroviral treatment-experienced adult patients. The recommended oral dose of darunavir is 600 mg (two 300 mg tablets) bid taken with ritonavir 100 mg bid and with food. Ritonavir is used as a pharmacokinetic enhancer of darunavir.

Recommendation

After reviewing the data presented in the PKPD analysis of the pooled phase 2b studies and the population PK analysis, the pharmacometrics reviewer finds the analysis and interpretation of the PKPD data by the sponsor to be acceptable. Individualized doses above 600/100 mg bid to compensate for an increased IC50 value is not expected to improve the response rate in antiretroviral experienced HIV-1 patients because of the less than proportional increase in plasma concentrations with increasing dose. The toxicity of darunavir above 1600 mg/day has not been evaluated.

Based on the population PK analysis, the following labeling changes are recommended:



Summary of Important Clinical Pharmacology Findings

Exposure-response analyses were conducted on pooled data from two dose-ranging controlled trials (studies C202 and C213) in antiretroviral treatment-experienced HIV-infected adult patients (total number of subjects, 637). In these studies, patients were randomized to a control group (investigator-selected PI regimen) or to 400/100 mg QD, 800/100 mg QD, 400/100 mg BID or 600/100 mg BID dosing regimens of darunavir/ritonavir in addition to an optimized background regimen. At 24 weeks, the virologic response rate was evaluated.

Exposure-response analyses consisted of graphical exploration of pharmacokinetic and pharmacodynamic data as well as logistic regression analysis of exposure (log10 C0h, log10 AUC24h) or IQ (log10 IQC0h, log10 IQCss,av) versus response rates (1 log10 reduction of viral load and < 50 copies/ml RNA) at week 24. The analysis showed that there was a strong relationship between inhibitory quotient (IQ) and virologic response. Higher response rates were observed for higher IQ values.

The IQ is the ratio between trough darunavir concentrations and IC50; therefore, additional analyses were conducted to determine which of these two components was primarily responsible for virologic response. Within each IQ quartile, the exposure to darunavir was comparable but the distribution of IC50 and fold-change values decreased with increasing IQ quartile. Therefore, the primary driver for response rate is the FC at baseline and response was less dependent on darunavir exposure. Increasing the dose over 600/100 mg bid is not expected to compensate for an increased IC50 because 1) the variability in IC50 values exceeds the variability in darunavir plasma concentrations and 2) plasma concentrations increase less than proportional with increasing doses.
Analysis of safety data from all four dosing regimens showed no apparent relationship between darunavir exposure (measured by AUC24h) and maximum change in cholesterol, lipids and LFT markers as well as in the incidence of adverse events.

A population analysis of pooled concentration-time data from five phase 1 and two phase 2 clinical trials showed that the data followed a two-compartment model with first order absorption. Oral clearance was modeled as a function of alpha-1 glycoprotein (AAG) concentrations and total daily dose of darunavir. For 1200 mg/day dose (corresponding to the 600/100 mg BID dosing regimen) mean population parameter parameters for CL/F at a normal AAG concentration of 90 mg/dL was 11.2 L/h (BSV, 26%). CL/F decreased with increasing AAG concentrations: estimates for CL/F were 5.9 L/h at AAG concentration of 200 mg/dL (maximum observed) and 18.9 L/h at 40 mg/dL (minimum observed). At the normal AAG concentration of 90 mg/dL, CL/F decreased to 7.3 L/h for a 400 mg/day dose. Volume of distribution (V/F) was 122 L (BSV, 88%).
Covariates assessed were age, body weight, creatinine clearance, sex, race, hepatitis B/C co-infection and HIV-1 infection. Statistically, there was a significant effect of body weight, creatinine clearance, sex, and hepatitis B/C co-infection on CL/F. These effects, however, had minimal effect on reducing the between-subject variability and the difference between the high-low values of covariates were less than 30%. Therefore, none of the covariates were retained in the model.

Based on the population pharmacokinetic analysis of darunavir, dose adjustments are not required for race, gender, moderate renal impairment, hepatitis B or C co-infection, and age greater than 65 years.

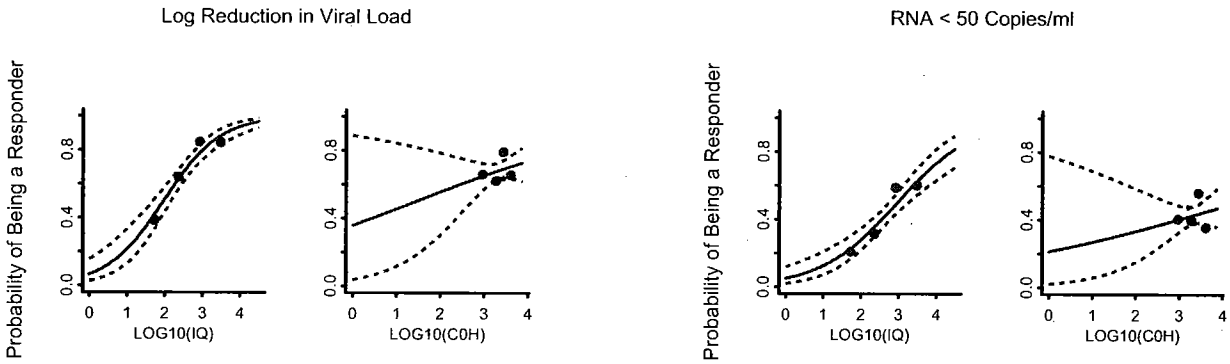
The population pharmacokinetic model was used to estimate the increase in exposure to darunavir with the commercial formulation. The relative bioavailability was estimated as 1.18 (BSV, 26%) in HIV-1 patients. There were 21 patients in the 600/100 mg BID dose group who had parameter estimates for both the clinical and commercial formulations. A two-way ANOVA showed that geometric mean AUCtau ratio for the commercial formulation relative to the clinical formulation was 1.09 (90% CI: 0.999, 1.18). Therefore, the increase in bioavailability of the commercial formulation has little impact on darunavir exposure in HIV-1 patients.

Christine Garnett, Pharm.D. _____
RD/FT Initialed by Joga Gobburu, Ph.D. _____
cc: NDA 21-976, HFD-, HFD-860 (Garnett, Reynolds, Arya, Gobburu), Central Documents Room (CDR-Biopharm)

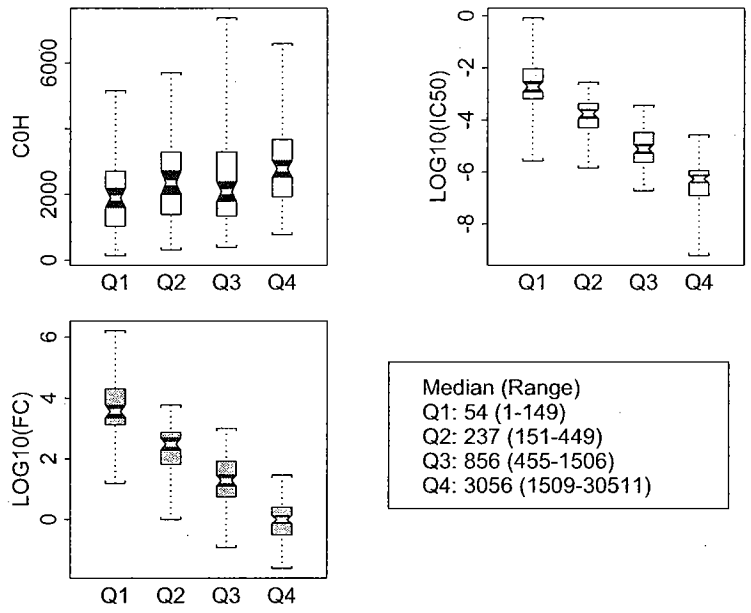
Question-Based Review

What are the characteristics of exposure-response relationships for efficacy?

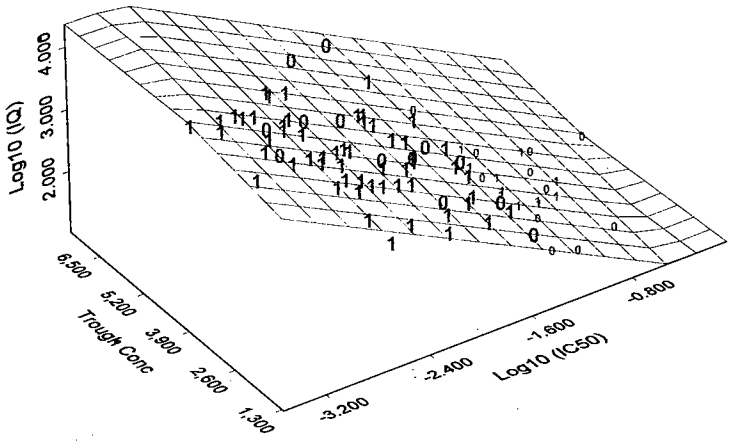
The exposure-response analysis of combined phase 2b trials (C202 and C213) demonstrated that the probability of having a response to darunavir treatment (measured either by 1 log reduction in viral load or HIV-1 RNA <50 copies/ml) by week 24 is related to the patient's darunavir inhibitory quotient. The inhibitory quotient (IQ) is the ratio between steady-state trough concentration and the baseline IC50 value. Larger IQ values are correlated with a higher response rates using logistic regression analysis.



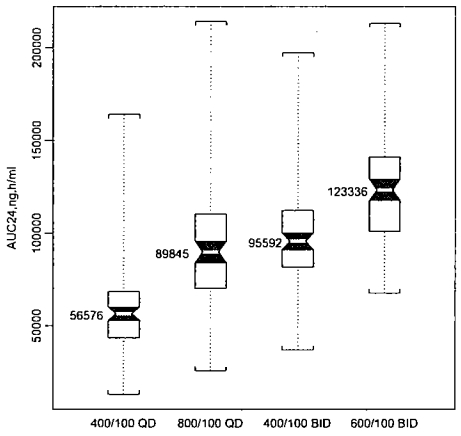
The figure below summarizes darunavir exposure, IC50, and fold-change values by darunavir IQ quartile. As illustrated, patients with the lowest IQ values in Q1 (and lowest response rate) have the highest IC50 values (increase in resistance). Fold-change (FC) is a measure of the fold-increase in the IC50 value relative to a standard IC50 value for a wild-type HIV-1 virus with no mutations. Patients with the lowest response rate have the highest darunavir FC at baseline.

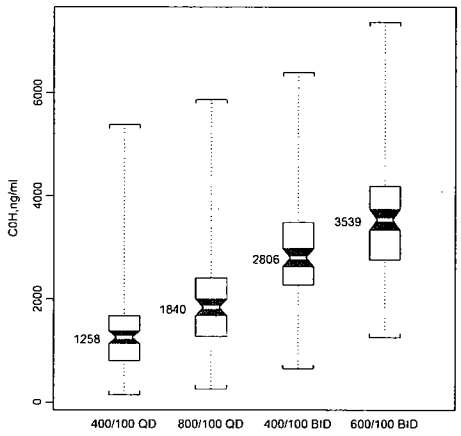


The relationship between trough concentrations, IC50, and IQ values is shown in following three-dimensional figure. Patients who were responders (defined as >1 Log reduction in viral load by 24 weeks) are indicated by "1" and nonresponders by "0." Patients with the highest IC50 values are highlighted using the smaller font size. Patients with the highest IC50 values (greater than the 75th percentile) have a clinical benefit from higher darunavir exposure; thereby supporting the 600/100 mg dose.



A key question is whether an individual patient's IQ can be increased by increasing trough concentrations of darunavir. Within the lowest quartile of IQ values (ranging from 1 to 149), median (95% CI) trough darunavir concentrations for the 600/100 mg BID dose group were lower than the range of values observed in larger IQ quartiles. Hypothetically doubling of the trough concentrations, would increase the IQ to a value that falls within second IQ quartile in 36% of the patients. However, due to the less than proportional increase in exposure to darunavir with increasing doses, doubling of the trough concentrations would require a greater than doubling of dose of darunavir. The toxicity of darunavir at doses above 1600 mg/day has not been evaluated.





What are the characteristics of exposure-response relationships (dose-response concentration-response) for safety?

The exposure-toxicity analysis of combined phase 2b trials demonstrated that there is no clear relationship between darunavir exposure (measured by AUC24h) and maximum change in cholesterol, lipids and LFT markers as well as in the incidence of adverse events.

Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The recommended oral dose of 600/100 mg BID is consistent with the known exposure-response and exposure-toxicity relationships. The highest IQ values were observed in the 600/100 mg dose group and there are no additional toxicities observed with higher exposure to darunavir.
The following table presents the number of subjects, response rate and median (range) of IQ values for subjects in the 600/100 dose group who had trough concentrations and IC50 values either lower or higher than the respective median values calculated from all subjects in the phase 2b studies. As shown, subjects with low IC50 values had the best response rates regardless if they had low or high trough concentrations. The response rates were lower for subjects with high IC50 values.

600/100 mg BID		Trough Concentrations Median: 2278 ng/mL	
		Low	High
IC50 Median: 7.8 nM	Low	N = 4 100 % 986 (420-1746)	N = 39 84% 3240 (842-23000)
	High	N = 5 40% 89 (10-405)	N = 48 65% 195 (10-1167)

Are there any proposed labeling changes?

Based on the population pharmacokinetic analysis of darunavir, there was a significant effect of body weight, creatinine clearance, sex, and hepatitis B/C co-infection on CL/F. These effects, however, had minimal effect on reducing the between-subject variability and the difference between the high-low values of covariates were less than 30%. Therefore, dose adjustments are not required for race, gender, moderate renal impairment, hepatitis B or C co-infection, and age greater than 65 years.

Run	Covariate tested	Implementation	DF	OBJ	Diff OBJ from reference	p	IIV	Difference High-Low	Keep covariate in model?
Reference Run: Run101BAAG8			---	75325	---	---	27	---	---
COV001AGE3	AGE	AGE/35**θ	1	75321	-3.655	0.0559	26	14.8%	no
COV002WT5	WT	(WT-75)*θ	1	75307	-18.186	<0.0001	26	29.4%	no
COV004CRCL5	CRCL	(CRCL-110)*θ	1	75312	-12.764	0.0004	26	26.2%	no
COV005SEX	SEX	θ**(SEX-1)	1	75302	-22.799	<0.0001	25	16.8%	no
COV006RACE	RACE	θ**RAC2*θ**RAC3*θ**RAC4	3	75321	-3.372	0.3377	26	7.0%	no
COV007HBC	HBC	θ**(HBC-1)	1	75320	-4.739	0.0295	26	11.7%	no
COV008HIV	HIV	θ**(HIV-1)	1	75323	-1.700	0.1923	26	4.1%	no

Based on the population PK analysis, the following labeling changes are recommended:

[redacted]

Reviewer's PKPD Graphical Analysis

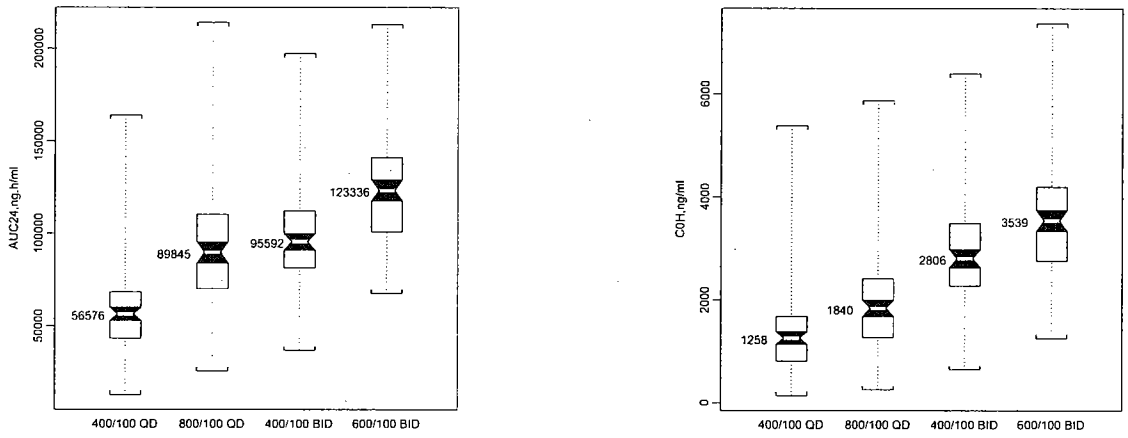
The reviewer conducted a graphical analysis of the PKPD data to independently assess the sponsor's conclusion that therapeutic drug monitoring is not warranted for darunavir because fold-change in IC50 is more predictive of virological response than darunavir exposure.

Data for this analysis came from the following sources:

1. \\Cdsesub1\evsprod\N021976\0006\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\tmc114-c926\datasets\analysis\xpk.xpt
2. \\Cdsesub1\evsprod\N021976\0006\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\tmc114-c926\datasets\analysis\xpk_ae.xpt
3. \\Cdsesub1\evsprod\N021976\0006\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\tmc114-c926\datasets\analysis\xpk_labo.xpt

As shown in Figure 1, exposure to darunavir increases less than proportional with increasing dose; median values of AUC24h and C0h increased by 60% and 50%, respectively, when the once daily dosing regimen increased from 400/100 mg to 800/100 mg QD and median values of the same parameters increased by 30% when the twice-daily regimens increased from 400/100 to 600/100 mg BID.

Figure 1. Darunavir exposure by dose group. The notch on box plot represents the median, the dark blue area represents the 95% confidence interval for the median, 50% of data lie within the box, and 100% of data lie within the whiskers.



There is a dose-dependant reduction in viral load. Figure 2 shows that the 600/100 mg BID dosing regimen reduces the viral load more than the other dosing regimens. Viral load reduction is maintained over 60 weeks (after this time all subjects were switched to the to-be-marketed formulation of 600/100 mg BID).

Figure 2. Viral load reduction by dose group. Points are observed values for individual subjects and the lines are the loess smooth within each dose group.

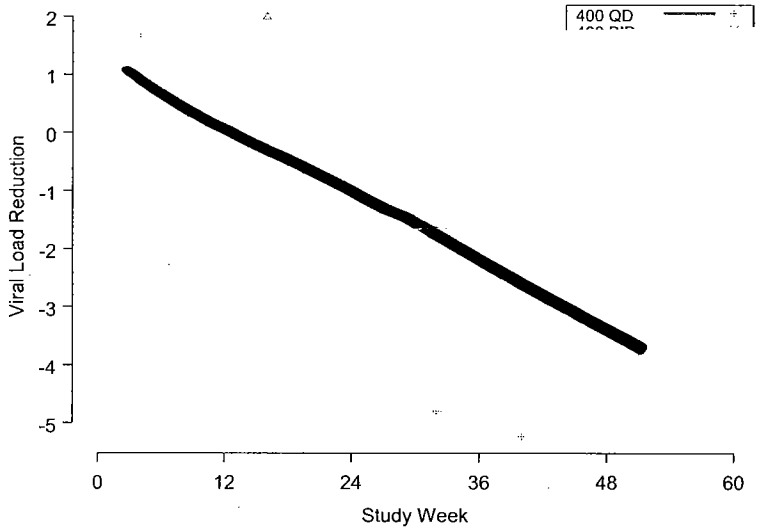


Figure 3 illustrates that the inhibitory quotient (IQ) was found to be a stronger predictor of virologic response at week 24 compared to trough darunavir concentrations. The probability of being a responder is increased with increasing IQ. The response rate is slightly higher in patients who receive enfuvirtide in addition to darunavir (Figure 4). For these analyses, IQ and trough darunavir concentrations values were log10-transformed to minimize the impact of extreme values (Figure 6).

Figure 3. Probability of patients achieving 1 log reduction in viral load or reduction of HIV-1 RNA to less than 50 copies/ml by inhibitory quotient (IQ) or trough concentration. The lines represent the mean and 95% confidence interval for the probability of response. The points on the lines represent the average response within each IQ or trough concentration quartile.

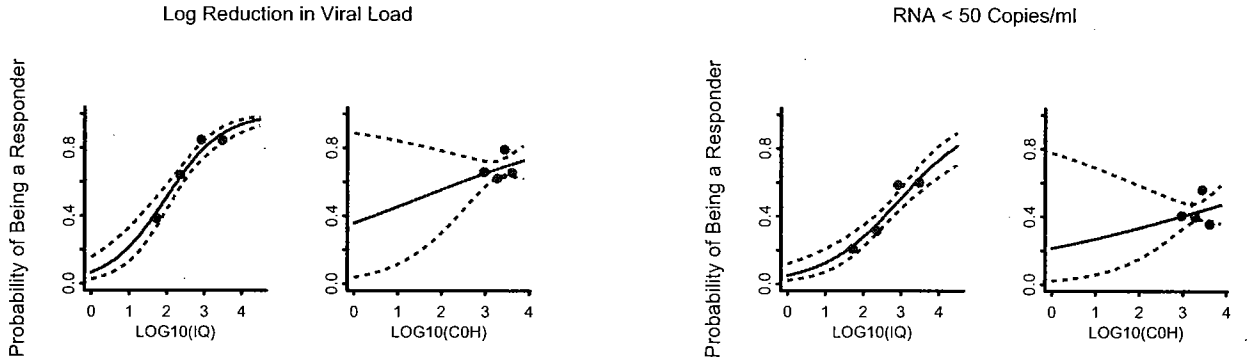


Figure 4. Viral response at Week 24 vs. IQ stratified by concomitant use of enfuvirtide (T20).

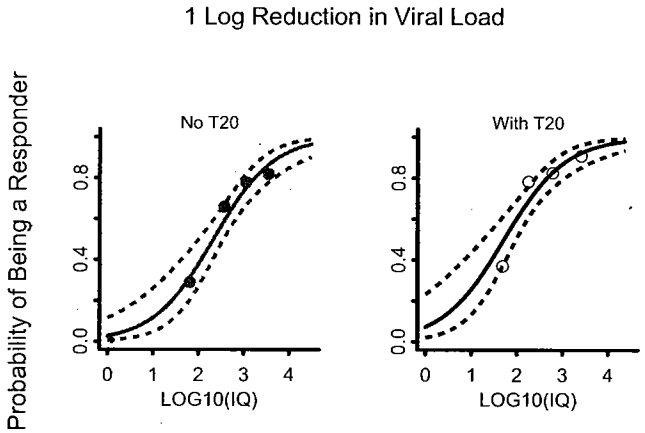


Figure 5 shows that subjects within each IQ quartile have comparable exposure to darunavir, and that the driving force for response is related to the baseline IC50 value. Patients with higher IC50 values have lower probability of response. This is directly related to the increase in PI mutations. Fold change (FC) measures the increase in IC50 relative to a standard wild type virus: the higher the FC the more mutations in the virus. For these plots, IC50 and fold change values were log10-transformed to minimize the influence of extreme values in the displays (Figure 6).

Figure 5. Boxplots of trough concentrations, IC50 values and fold change values by IQ quartile. The notch on box plot represents the median, the dark blue area represents the 95% confidence interval for the median, 50% of data lie within the box, and 100% of data lie within the whiskers.

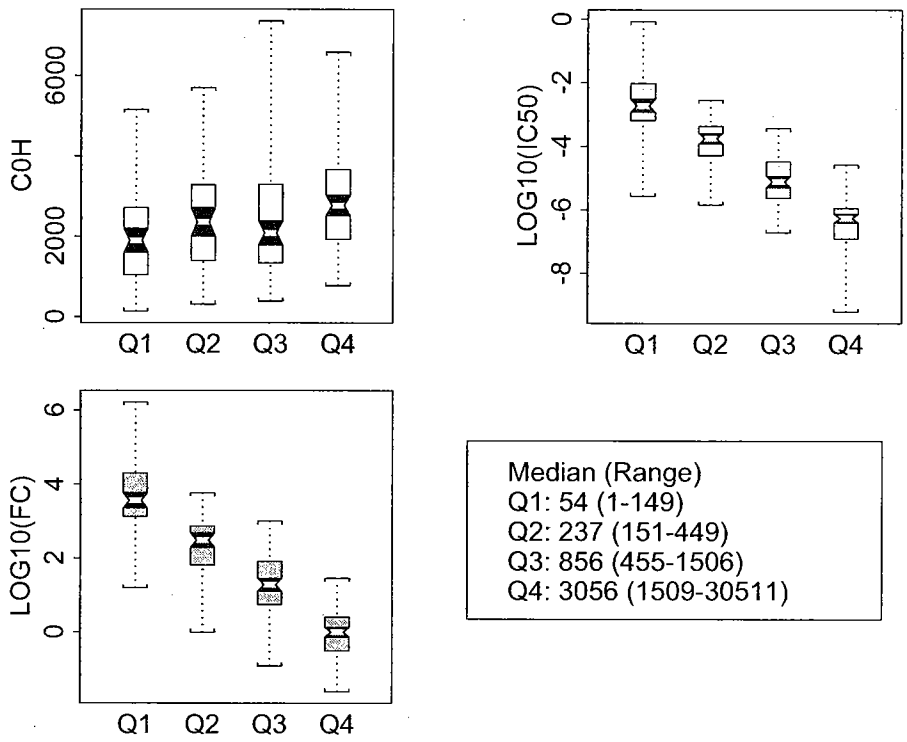
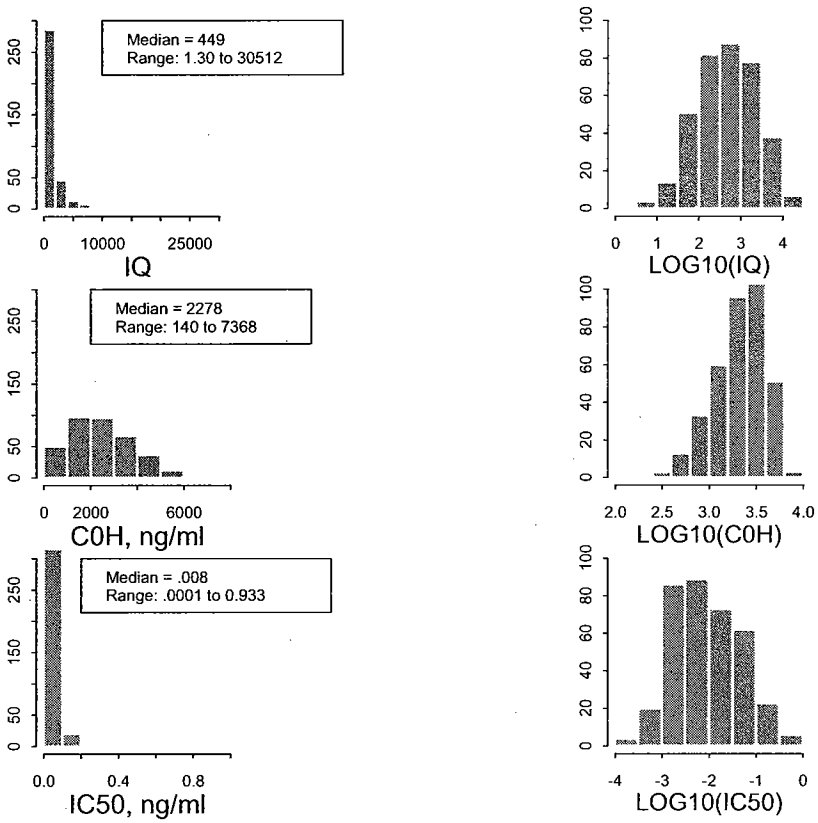


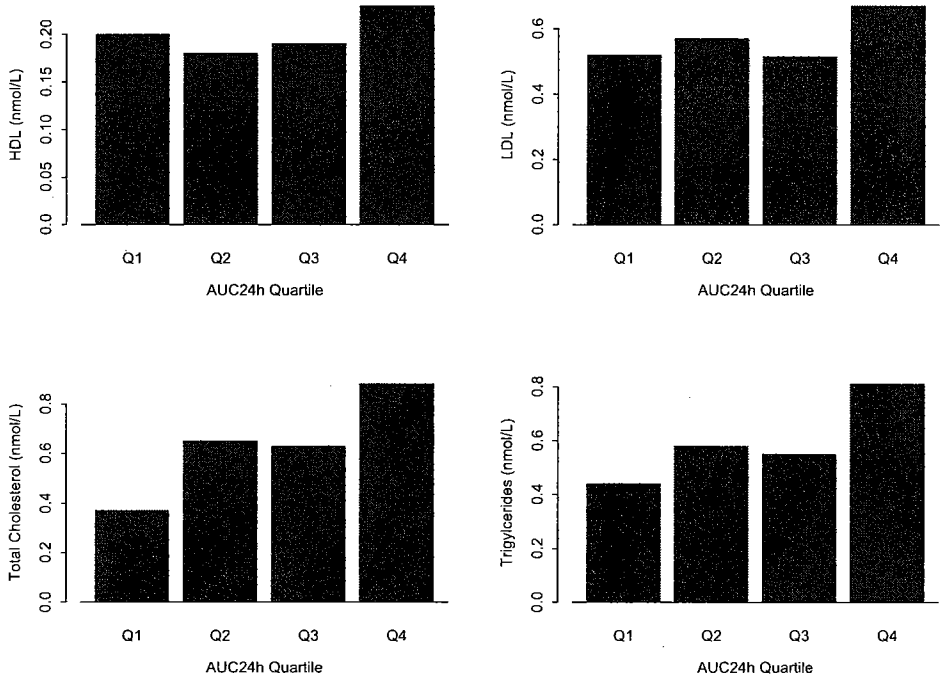
Figure 6. Log10-Transformed and untransformed distribution of IQ, C0H, and IC50 values.



Appears This Way
On Original

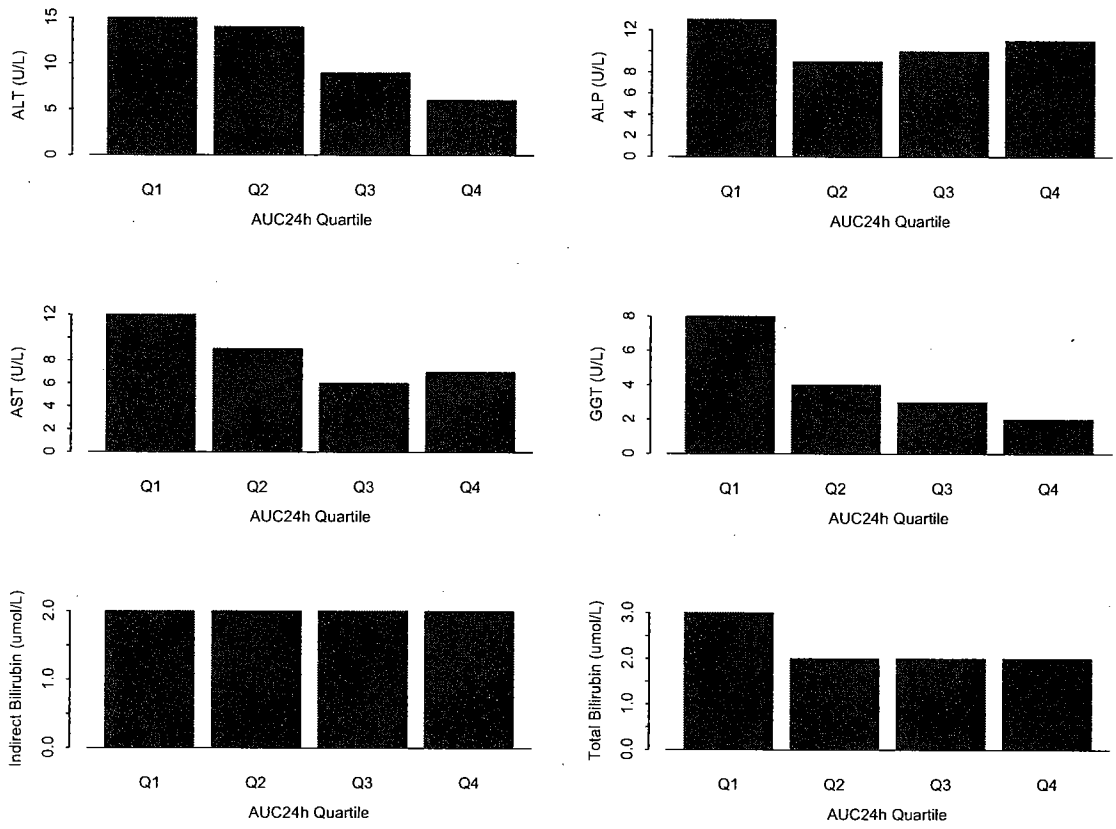
Evaluation of maximum change from baseline in laboratory values (LFTs, lipids, and cholesterol) and presence of AEs by body system (rash, psychiatric, nervous system, GI, cardiac, lipid, glucose, and liver) are shown in Figures 7, 8 and 9.

Figure 7. Maximum Change from Baseline in Lipids and Cholesterol Markers by AUC24h Quartile



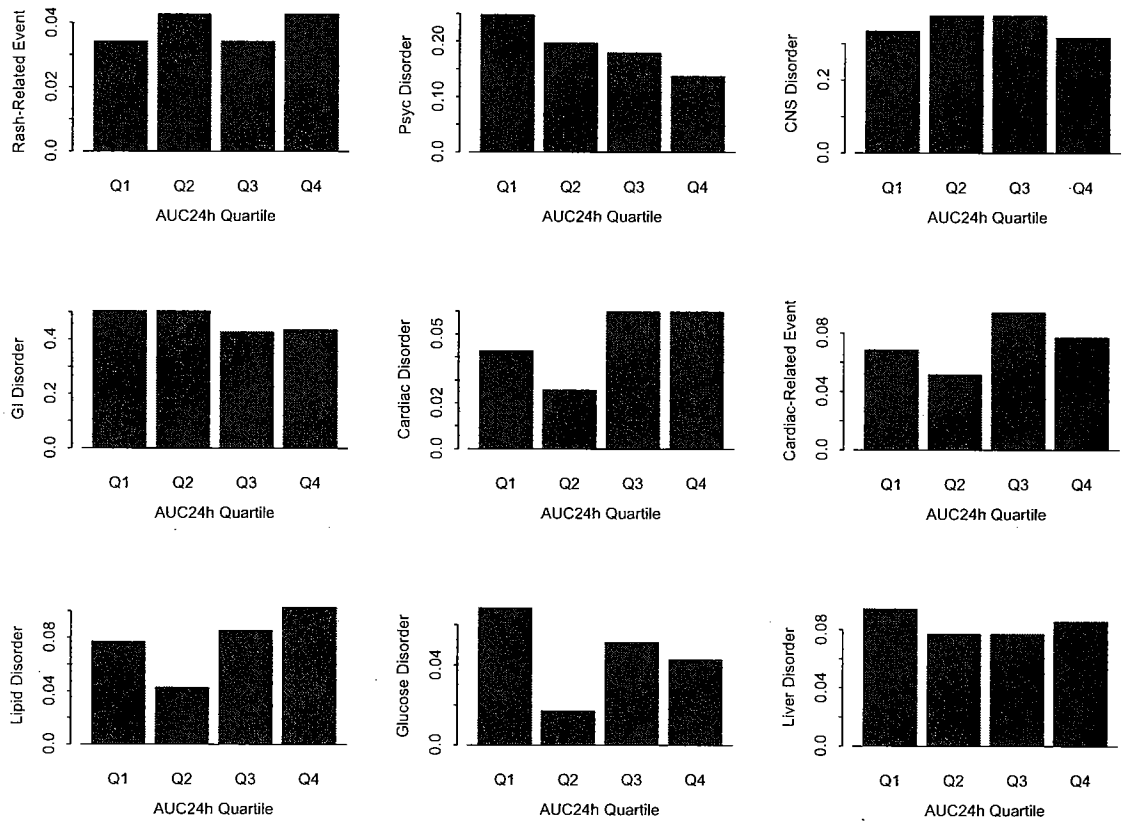
Appears This Way
On Original

Figure 8. Maximum Change from Baseline in Liver Functional Tests by AUC24h Quartile



Appears This Way
On Original

Figure 9. Proportion of Patients Experiencing AEs Stratified by AUC24h Quartile



Sponsor's PKPD Analysis (report tmc114-c926-cpkpd)

Clinical Trials

The data used for the PK-PD analysis were obtained from two ongoing Phase 2b clinical trials: TMC114-C202 and TMC114-C213 which are referred to as C202 and C213, respectively, in this review. The following table describes the study design of each study.

	C202	C213
Study Design	Randomized, controlled (standard of care), partially blinded, two-part hybrid dose-response trial. Included a 2-week functional monotherapy.	Randomized, controlled (standard of care), partially blinded, dose-response trial
Patients	HIV-1 infected subjects who are 3-class experienced and receiving PI for >8 wks prior to screening; have plasma HIV-1 RNA > 1000 copies/ml; and have at least 1 primary PI mutation. Excluded hepatitis co-infection.	HIV-1 infected subjects who are experienced to treatment; have plasma HIV-1 RNA > 1000 copies/ml; and have at least 1 primary PI mutation. Included hepatitis co-infection.
Number of Enrolled/Completed 24 weeks	278/201	318/301
Treatments (Total number subjects, M/F)	Control group (53, 47/6) 400/100 qd (57, 51/6) 800/100 qd (56, 50/6) 400/100 bid (55, 52/3) 600/100 bid (57, 53/4)	Control group (63, 55/8) 400/100 qd (64, 58/6) 800/100 qd (63, 55/8) 400/100 bid (63, 50/13) 600/100 bid (65, 55/10)
Endpoints	Change in viral load Decay rates of change in viral load Changes in CD4 and CD8 Proportion with 0.5 and 1.0 log10 drop in viral load Time to loss of virologic response	Change in viral load Changes in CD4 and CD8 Proportion with 0.5 and 1.0 log10 drop in viral load Time to loss of virologic response

The demographic characteristics were comparable between the treatment groups. The majority of subjects were male (88%) and Caucasian/White (72.6%). The median age was 43 y (range: 20 to 75 y) and median weight was 72.6 kg (range: 36 to 136 kg). Study C202 had had a higher median fold changes in EC50 values (FC) compared to study C213. The percentage of subjects with a FC ≤ 4 was 47% and 54% in studies C202 and C213, respectively.

PK/PD Analysis

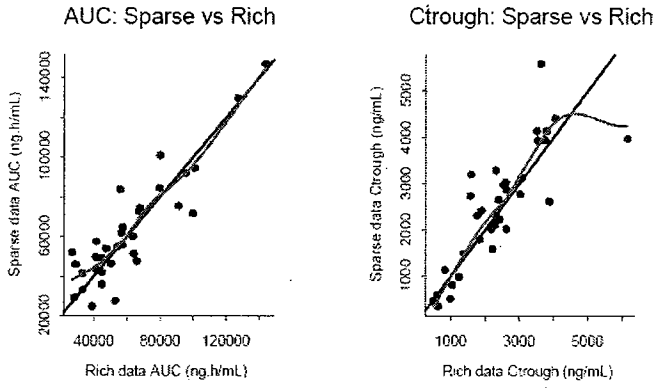
Pharmacokinetic Parameters

The pharmacokinetics of darunavir in C202 and C213 were derived via two methods: full pharmacokinetic profiles in a subset of patients, and sparse sampling for population pk analysis. Standard non-compartmental methods were used to calculate exposure parameters for subjects with full pharmacokinetic profiles.
The population PK model was a 2-compartment model with sequential zero- and first-order absorption. No covariates were included. Model parameters are shown in the table below. The performance of the model was evaluated using a posterior predictive check and comparing the empirical Bayesian parameter estimates between the rich and sparse data in HIV-1 infected subjects.

PopPK Model Parameters (Source: Table 4 TMC114-C925/Section3.4)

Parameter	Estimate (BSV)
CL/F, L/h	9.81 (35%)
Vc/F, L	82.3 (52%)
CL_{IC}/F, L/h	21.4 (54%)
Vp/F, L	85.7 (43%)
Ka, h-1	2.42 (159%)
K0, h	2.46 (not estimated)
F_{rel} (to Study 129)	0.794 to 1.42
Residual error, CV%	33%

Comparison Between Empirical Bayes' Estimates on the Basis of Sparse or Rich Data in the Same Subject (Source: Figure 2, TMC114-C925/Section 3.1)



Summary of Population PK Parameters Estimated from PopPK Model by Study and Dose Group (Source: Tables 12 and 16 TMC114-c926/Section 4.3.2)

	400/100 mg qd	800/100 mg qd	400/100 mg bid	600/100 mg bid
Values shown as Mean (CV%), Geometric Mean				
Study C202	N=56	N=56	N=52	N=55
AUC_{24}, ng.h/ml	61544 (39%), 57009	97405 (40%), 89779	96791 (29%), 93027	136393 (26%), 131635
C_{0h}, ng/ml	1361 (58%), 1147	1951 (57%), 1676	2786 (38%), 2596	3862 (33%), 3631
Study C213	N=62	N=62	N=61	N=64
AUC_{24}, ng.h/ml	55182 (38%), 54793	88394 (31%), 87973	102138 (26%), 100576	114646 (22%), 113314
C_{0h}, ng/ml	1324 (55%), 1269	1974 (45%), 1903	3197 (31%), 3073	3334 (29%), 3249
Combined Studies	N=118	N=118	N=113	N=119
AUC_{24}, ng.h/ml	58201 (39%), 5676	92670 (36%), 89845	99678 (27%), 95592	124697 (26%), 123336
C_{0h}, ng/ml	1342 (56%), 1258	1963 (51%), 1840	3008 (35%), 2806	3578 (32%), 3539

Comparison between PK parameters calculated by non-compartmental (Substudy) and population PK methods (Source: Tables 9 and 12 TMC114-c926/Section 4.3.2)

	Median											
	Darunavir/Ritonavir 400/100 mg q.d.			Darunavir/Ritonavir 800/100 mg q.d.			Darunavir/Ritonavir 400/100 mg b.i.d.			Darunavir/Ritonavir 600/100 mg b.i.d.		
	Substudy		Pop	Substudy		Pop	Substudy		Pop	Substudy		Pop
Parameter	W 4	W 24	PK	W 4	W 24	PK	W 4	W 24	PK	W 4	W 24	PK
N	10	11	118	9	13	118	15	13	113	8	9	119
AUC_{12h} (ng.h/mL)	-	-	-	-	-	-	50096	35690	47796	44986	51188	61668
AUC_{24h} (ng.h/mL)	67081	58022	56576	86440	74205	89845	-	-	95592	-	-	123336
C_{0h} (ng/ml)	1090	821	1258	2370	1900	1840	3590	2660	2806	3505	3760	3539

N = number of subjects with data.
Pop PK = population pharmacokinetics; W = week.
Source: Supporting Data Display 3, Supporting Data Display 7

Darunavir Inhitory Quotients

The IQ was expressed as the drug concentration divided by the HIV 50% inhibitory concentration (IC50) of the drug. The IQ was calculated by two methods: one based on trough concentrations (IQC0h) and the other based on the average steady-state concentration during dosing (IQCss,av).
IQ values increased with increasing doses in both studies. The large variability in IQ values is primarily due to the large variability in baseline IC50 values.

Summary of Uncorrected (for Protein Binding) Inhibitory Quotients by Study and Dose Group (Source: Table 88/TMC114-C202/Section 4.7.2.5, Table 85/TMC114-C213/Section 4.7.2.5)

	400/100 mg qd	800/100 mg qd	400/100 mg bid	600/100 mg bid
Values shown as Geometric Mean (range)				
Study C202	N=56	N=56	N=52	N=55
IQcss,av	396 (6-8890)	883 (2-19192)	765 (32-18182)	993 (17-29761)
IQC0h	196 (4-5702)	397 (1-7747)	512 (28-11287)	657 (11-23000)
Study C213	N=62	N=62	N=61	N=64
IQcss,av	477 (11-51159)	1040 (33-19305)	728 (12-11110)	1120 (13-19385)
IQC0h	256 (6-30512)	524 (18-9091)	538 (8-8113)	769 (10-13648)
Combined Studies	N=114	N=116	N=111	N=118
IQcss,av	436 (6-51159)	962 (2-19305)	745 (12-18182)	1059 (13-297610
IQC0h	225 (4-305120	460 (1-9091)	526 (8-11287)	715 (10-23000)

Pharmacodynamic Parameters

The efficacy markers used for analysis were virologic response at Week 24; proportion of subjects with at least 1.0 or 0.5 log10 decrease in plasma viral load; proportion of subjects with plasma HIV-1 RNA levels <50 or <400 copies/ml; time to virologic failure; change in log10 plasma viral load; and immunologic change determined by changes in CD4 cell counts.
Safety parameters investigated were maximum change from baseline in the following parameters: HDL, LDL, total cholesterol, trglycerides, ALT, AST, alkaline phosphatase, GGT, bilirubin, heart rate, PR interval, QRS width, and QTcF.

PK-PD Relationships

Relationships between AUC24 and Cmin and efficacy markers were determined using graphical and statistical methods. Statistical models included both ANCOVA and logistic regression models.

Efficacy Markers

Graphic displays as well as statistical analyses demonstrated that the IQ was the strongest predictor of efficacy and virologic response, with the relationship being primarily driven by the baseline FC and less by darunavir exposure.

2 Page(s) Withheld

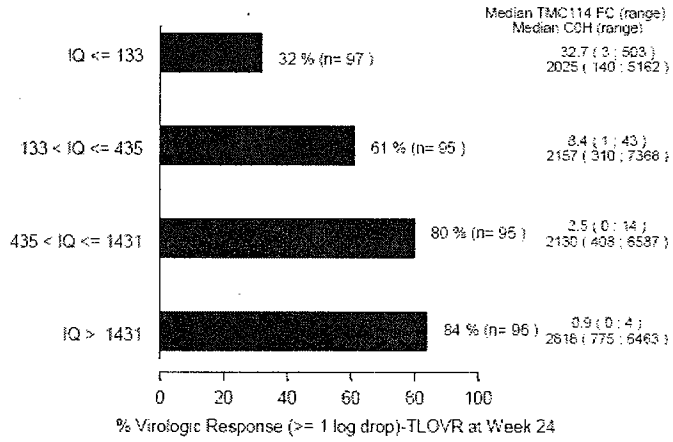
✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

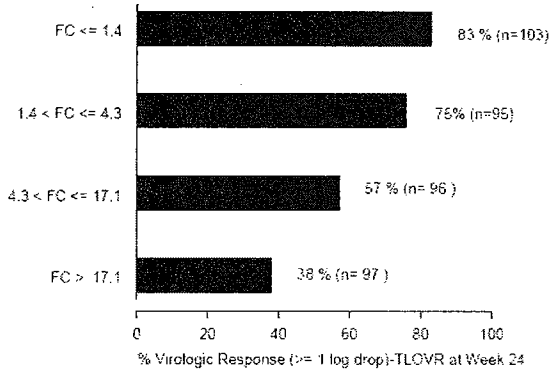
_____ § 552(b)(5) Draft Labeling

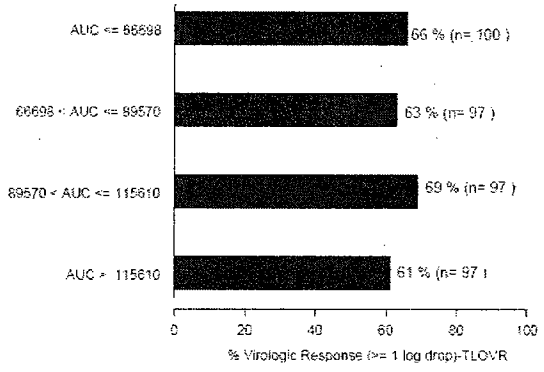
Withheld Track Number: Clin Pharm/Bio- 1

Percentage Virologic Response (≥ 1 log10 decrease) at Week 24 by Darunavir IQC0h Grouped in Quartiles



Left. Percentage Virologic Response (≥ 1 log10 decrease) at Week 24 by Darunavir Fold Change Grouped in Quartiles. Right. Percentage Virologic Response (≥ 1 log10 decrease) at Week 24 by Darunavir AUC24h Grouped in Quartiles





ANCOVA models were performed to investigate the relationship between the changes in log10 viral load and the pharmacokinetic parameters (log10 AUC24h and log10 C0h) including covariates of baseline log10 viral load, number of sensitive NRTIs, and darunavir log10 FC, and use of T20. The same analysis was conducted using log10 IQcss.ave and log10 IQC0h values.

Results of the ANCOVA model showed that antiviral activity is strongly correlated with the IQ of darunavir, with the relationship driven primarily by fold-change and less by exposure to darunavir.

ANCOVA Results for Reduction in Viral Load: Significance Values using Pharmacokinetic Parameters (top table) and IQ Values (bottom table) (Source: Table 21/TMC114-C926-cpkpd/Section 4.5.1.2 and Table 23/TMC114-C926-cpkpd/Section 4.5.2.2)

Response Parameter	AUC_{24h}	C_{0h}	Baseline Viral Load	Number of Sensitive NRTIs	Use of Enfuvirtide in OBR	Darunavir FC
Change in Viral Load Week 2	0.054	0.049	<0.001	<0.001	<0.001	<0.001
Change in Viral Load Week 24	0.036	0.015	<0.001	0.004	<0.001	<0.001
DAVG Week 24	0.046	0.020	<0.001	0.006	<0.001	<0.001

Note: p-values of covariates are from the models with AUC_{24h} as the pharmacokinetic parameter. For C_{0h} the p-values of the covariates are similar and in this table only the p-values associated with AUC_{24h} are mentioned.
Source: Supporting Data Display 11

Response Parameter	$IQ_{Css,av}$	IQ_{C0h}	Baseline Viral Load	Number of Sensitive NRTIs	Use of Enfuvirtide in OBR
Change in Viral Load Week 2	<0.001	<0.001	<0.001	<0.001	<0.001
Change in Viral Load Week 24	<0.001	<0.001	<0.001	0.004	<0.001
DAVG Week 24	<0.001	<0.001	<0.001	0.005	<0.001

Note: p-values of covariates are from the models with $IC_{Css,av}$ as the pharmacokinetic parameter. For IQ_{C0h} the p-values of the covariates are similar and in this table only the p-values associated with $IC_{Css,av}$ are mentioned.
Source: Supporting Data Display 23

A logistic regression model was also performed to investigate the relationship between response parameters and the pharmacokinetic parameters using the same covariates as in the ANCOVA model.
Results of the logistic model showed that virologic response at week 24 is strongly correlated with the IQ of darunavir, with the relationship driven primarily by fold-change and less by exposure to darunavir. Subjects taking T20 have increased virologic response.

Appears This Way On Original

Logistic Regression Results for PD Response: Significance Values for Pharmacokinetic Parameters (top table) and IQ values (bottom table) (Source: Table 22/TMC114-C926-cpkpd/Section 4.5.1.2 and Table 24/TMC114-C926-cpkpd/Section 4.5.2.2)

Response Parameter	AUC_{24h}	C_{0h}	Baseline Viral Load	Number of Sensitive NRTIs	Use of Enfuvirtide in OBR	Darunavir FC
<400 Week 2	0.564	0.489	<0.001	0.012	0.613	<0.001
<50 Week 2	0.049	0.044	<0.001	0.020	0.260	0.060
>1 log_{10} Week 2	0.690	0.508	0.001	0.194	0.018	<0.001
>0.5 log_{10}Week 2	0.006	0.004	0.980	0.006	.0.006	<0.001
<400 Week 24	0.020	0.005	<0.001	0.005	<0.001	<0.001
<50 Week 24	0.042	0.014	<0.001	0.078	<0.001	<0.001
>1 log_{10}Week 24	0.026	0.010	0.232	0.030	<0.001	<0.001
>0.5 log_{10}Week 24	0.006	0.005	0.630	0.003	<0.001	<0.001

Note: p-values of covariates are from the models with AUC_{24h} as the pharmacokinetic parameter. For C_{0h} the p-values of the covariates are similar and in this table only the p-values associated with AUC_{24h} are mentioned.

Source: Supporting Data Display 13

Response Parameter	$IQ_{Css,av}$	IQ_{C0h}	Baseline Viral Load	Number of Sensitive NRTIs	Use of Enfuvirtide in OBR
<400 Week 2	<0.001	<0.001	<0.001	0.012	0.684
<50 Week 2	0.056	0.040	<0.001	0.031	0.255
>1 log_{10} Week 2	<0.001	<0.001	0.003	0.134	0.022
>0.5 log_{10}Week 2	<0.001	<0.001	0.892	0.010	0.005
<400 Week 24	<0.001	<0.001	<0.001	0.006	<0.001
<50 Week 24	<0.001	<0.001	<0.001	0.092	<0.001
>1 log_{10}Week 24	<0.001	<0.001	0.206	0.038	<0.001
>0.5 log_{10}Week 24	<0.001	<0.001	0.696	0.005	<0.001

Note: p-values of covariates are from the models with $IQ_{Css,av}$ as the pharmacokinetic parameter. For IQ_{C0h} the p-values of the covariates are similar and in this table only the p-values associated with $IQ_{Css,av}$ are mentioned.

Source: Supporting Data Display 25

Exposure Toxicity Analysis

The sponsor concluded that there were no apparent relationships between the pharmacokinetics of darunavir and the maximum changes in laboratory and ECG parameters tested.

No associations were found between exposure to darunavir and changes in liver function test values or lipids. In the analysis by dose group, lipid-related events were more commonly reported with the darunavir/ritonavir b.i.d. regimens than with the q.d. regimens. Ritonavir concentrations were also higher with the b.i.d. regimens than with the q.d. regimens, therefore this relationship between dosing regimen and lipid related events may have been influenced by the increased ritonavir concentrations with the b.i.d. regimens.

Sponsor's Conclusions

Together with the efficacy and safety results of the clinical trials, this PKPD analysis provided additional evidence to support the 600/100 mg bid dosing regimen in treatment-experienced HIV-1 infected patients.

1. The pharmacokinetics of darunavir is not proportional between different dosing regimens. A 100% increase in dose between the 2 qd regimens resulted in ~ 60% increase in median AUC values, and a 50% increase in dose between the 2 bid regimens resulted in ~18% increase in median AUC.
2. A further increase in dose beyond 600/100 mg bid is not expected to provide clinically meaningful increase in virologic response. Results from ANCOVA analysis suggest that a 10-fold increase in dose is required for an additional 0.5log10 reduction in viral load.
3. The analysis showed a strong relationship between IQ values and antiviral activity and virologic response. The analysis also showed the stronger predictor of virologic response is the darunavir fold-change and not exposure to darunavir.
4. There was no relationship between darunavir exposure and maximum changes in laboratory parameters, vital signs, or ECG parameters.

Monitoring resistance to darunavir is a more relevant diagnostic tool to guide the use of darunavir than therapeutic drug monitoring.

1. The virologic response is mainly driven by the IQ, with this relationship being driven primarily by darunavir fold-change at baseline.
2. The variability in IQ values is caused by a large variability in IC50 values (~2500-fold difference between lowest and highest observed IC50) relative to exposure in AUC or C0h (~3.1-fold and 5.9-fold difference between lowest and highest observed values).
3. Given the less than proportional pharmacokinetics of darunavir, an increase in dose beyond 600/100 mg bid is not expected to provide clinically meaningful increase in virologic response.

Sponsor's Population PK Model (TMC114-c927a)

Population PK Dataset

The final analysis dataset consisted of 580 subjects, with 5082 records containing plasma TMC114 concentrations. Rich concentration-time profiles were available in 168 subjects (109 subjects from Phase I studies and 59 subjects from Phase II studies). Sparse data was available in 470 subjects (all from the Phase II studies) of whom also rich concentration-time profiles were obtained in 58 subjects. The TMC114 dose range was 400-800 mg bid and 400–1200 mg qd. The longest exposure in the dataset was 48 weeks.

Clinical Trials Included in Analysis

The data included in this analysis originated from five Phase I and two Phase IIb studies. A summary of each study is shown in tables below.

Table 1 Summary of Phase I data included in the analysis

Item	Study 001	Study 002	Study 003	Study 004	Study 005
Aim	Ketoconazole DDI	Repeated multiple dose escalation	Saquinavir DDI	Relative bioavailability for [redacted]	Relative bioavailability for different drug substance batches
Tibotec Code	TMC114-C129	TMC114-C137	TMC114-C138	TMC114-C154	TMC114-C156
No. and type of subjects	18 healthy subjects	40 healthy subjects	32 healthy subjects	24 healthy subjects	16 healthy subjects
Data used	TMC114/RTV	All	TMC114/RTV	Formulation F002 batch X	Formulation F002 batch X
No of available subjects for PK analysis	15	40	14	23	16
Dose	400 mg bid for 7 days	A: 400, 600, 1200 mg qd for 7 days B: 400, 800 mg bid for 7 days	400 mg bid for 14 days	400 mg	400 mg
Ritonavir dose	100 mg bid for 7 days	A: 100 mg qd for 7 days B: 100 mg bid for 7 days	100 mg bid for 14 days	100 mg bid from 2 days before to 2 days after TMC114 administration	100 mg bid from 2 days before to 2 days after TMC114 administration
Periods	1 (last dose on day 7)	2 (first and last dose on day 7)	1 (day 14)	1	1
Single/Multiple	Multiple	Multiple	Multiple	Single	Single
Formulation	Tablet F002	Tablet F001	Tablet F001	Tablet F002	Tablet F002
No samples/ Period	9 – plasma day 7 pre-dose day 1, 5, 6, 7	11 – plasma day 1 17 – plasma day 7 pre-dose day 1, 2, 4, 6, 7	9 – plasma day 14 pre-dose day 1, 4, 7, 10, 12, 13, 14	15 – plasma	14 – plasma
Assay (LLOQ)	LC-MS/MS (10 ng/ml)	LC-MS/MS (10 ng/ml)	LC-MS/MS (10 ng/ml)	LC-MS/MS (10 ng/ml)	LC-MS/MS (10 ng/ml)
Time range of PK profiles	0 – 12 h	0 – 24 h day 1 0 – 120 h day 7	0 – 12 h	0 – 72 h	0 - 72 h

Table 2 Summary of Phase II data included in the analysis

Item	Study 006	Study 007
Aim	Dose finding study in HIV-1 infected subjects	Dose finding study in HIV-1 infected subjects
Tibotec Code	TMC114-C202	TMC114-C213
No. and type of subjects	319 HIV+ subjects	318 HIV+ subjects
Data used	All	All
No of available subjects for PK analysis	219	249
Dose (number of subjects)	400 mg qd (56) 800 mg qd (56) 400 mg bid (52) 600 mg bid (55)	400 mg qd (62) 800 mg qd (62) 400 mg bid (61) 600 mg bid (64)
Ritonavir dose	100 mg qd or bid	100 mg qd or bid
Periods	6 (week 2, 4, 8, 12, 24 and 48)	5 (week 2, 4, 8, 12 and 24)
Single/Multiple	Multiple	Multiple
Formulation	Tablet F001 and F002	Tablet F001 and F002
Number of samples	main study: 1 - 7 over the 24-week time period sub study: 7 - 9 per sampling day	main study: 1 – 7 over the 24-week time period sub study: 6 - 9 per sampling day
Assay (LLOQ)	LC-MS/MS (10 ng/ml)	LC-MS/MS (10 ng/ml)
Time range of PK profiles	0 – 12 h (bid); 0 - 24 h (qd)	0 – 12 h (bid); 0 - 24 h (qd)

Table 4: Summary of continuous covariates for the subjects included in the analysis.

	statistic	400 mg bid	400 mg qd	800 mg qd	800 mg bid	1200 mg qd	600 mg bid	all subjects
Subjects	N	153	166	126	8	8	119	580
AGE	mean	43.9	42.4	43.1	40.9	41.1	43.5	43.2
(yrs)	median	43	43	42	44	44	43	43
	min	18	18	19	26	29	27	18
	max	75	75	65	46	51	71	75
WEIGHT	mean	73.4	74.9	74.7	75.3	79.4	73.6	74.3
(kg)	median	72.0	75.0	74.1	72.0	74.0	73.0	73.9
	min	35.5	47	43.2	50	71	48.5	35.5
	max	117.4	111.7	110	110	104	103.9	117.4
CRCL	mean	109	114	113	118	120	108	111
(mL/min)	median	107	115	113	116	108	106	111
	min	33.4	41.2	51.6	80.6	92.3	53.8	33.4
	max	195	231	208	164	200	198	231
AAG	mean	88.5	90.4	95.4	76.8	88.8	93.5	91.4
(mg/dL)	median	85.0	84.0	86.5	72.4	79.9	89.0	86.0
	min	40.0	43.0	39.0	56.0	65.2	52.0	39.0
	max	199	254	247	109	151	214	254

The AAG concentration is expressed as the median within a subject over the study period

Table 5: Summary of categorical covariates for the subjects included in the analysis.

	400 mg bid	400 mg qd	800 mg qd	800 mg bid	1200 mg qd	600 mg bid	all subjects
Subjects N	153	166	126	8	8	119	580
SEX							
male	129	155	111	6	6	105	512
female	24	11	15	2	2	14	68
RACE							
Caucasian	119	128	87	8	8	97	447
Black	20	16	22	0	0	12	70
Hispanic	11	12	11	0	0	7	41
Other	3	10	6	0	0	3	22
HIV							
patients	115	119	118	0	0	119	109
healthy subjects	38	47	8	8	8	0	471
HBC							
Hep B/C co-infection	5	8	11	0	0	7	31
No Hep B/C co-infection	148	158	115	8	8	112	549

Handling of missing data

The following plasma TMC114 concentrations were excluded from the analysis:

- Samples for which no record of dosing on the same day or previous day was available.
- Samples that were reported to be taken more than 25 h after the last reported dose for bid dosing or more than 40 h after the last reported dose for qd dosing (applicable for data from the Phase II studies C202 and C213 only; exclusion of 14 data records).
- Pre-dose samples that were taken more than 1 hour prior to dosing (exclusion of 12 data records).
- Samples with a measurable TMC114 concentration at baseline (i.e. before the start of treatment). This was observed in subjects 202-9603 and 202-0419 (exclusion of 2 data records).
- Sparse samples for which the time of dose was either missing or recorded to have occurred at midnight (exclusion of 5 data records).

The excluded data were not considered for re-analysis using the final model.

Handling of outliers

Outliers, which are data points in the dataset that appear to be outside the norm for that dataset, were identified as such based on inspection of the output from initial satisfactory runs. The impact of the presence of these outliers on the model parameters was evaluated in the analysis.

Graphical Analyses of Data

Exploratory graphical analysis of the observed data for 168 subjects with full pharmacokinetic profiles was performed prior to modeling the data. This analysis showed the following:

1. A two-compartmental model is probably appropriate to describe the data.
2. Plotting the AUCtau and apparent total oral clearance values against the total daily dose, shows a consistent dose-dependent change in the pharmacokinetic parameters.
3. Individual AUC and apparent total oral clearance values are related to individual AAG concentrations.
4. Subjects with HIV-1 infection had higher AAG concentrations.

PopPK Model

NONMEM V level 1.1 [redacted] was used for the population pharmacokinetic analysis using Digital Visual Fortran version 6.6A. The computing environment was a Dell Precision 650 Workstation with dual Xeon Processors at 2.8 GHz, running Windows XP.

Structural and Random Variance Models

A two-compartment model with first-order absorption without a lag time was used to describe the darunavir concentration-time data. The sponsor evaluated more complex absorption models but not provide significant improvements to the model.
The model was parameterized with CL/F and V/F. CL/F was modeled as a function of AAG concentrations according to the following equation:

$$CL/Fi = CL_{INT}\left(\frac{1}{1+K_{AFF}*AAG}\right)\bullet e^{\eta_i}$$

Where CL_{INT} is the intrinsic clearance, K_{AFF} is the affinity constant of the TMC114-AGG complex and AAG is the AAG concentration in mg/dL. Implementation of this model allowed the clearance within an individual to vary during the course of treatment according to AAG concentrations.
CL/F was also modeled according to dose to account for the less than proportional increase in exposure with increasing doses of darunavir. The dose effect was applied as follows:

$$CL/Fi = CL_{INT}\left(\frac{1}{1+K_{AFF}*AAG}\right)\bullet\left(\frac{TDD}{1200}\right)^{\theta}\bullet e^{\eta_i}$$

Where TDD is the total daily dose. The cause for the increase in clearance with respect to dose is not known but the sponsor suggested that it may be due to a potential saturable binding of darunavir to AAG or induction of its own metabolism.

Model	Implementation of CL/F	OBJ
2-C, first order input, no lag, CCV model for residual error	CL/F*EXP(ETA_{CL})	76114.696
2-C, first order input, no lag, CCV model for residual error	CL_{INT}*(1/1+K_{AFF}*AAG)*EXP(ETA_{CL})	75462.309 (-652.387)
2-C, first order input, no lag, CCV model for residual error (run 019)	CL_{INT}*(1/1+K_{AFF}*AAG)*(TDD/1200)^2*EXP(ETA_{CL})	75324.833 (-789.863)

Base Model Parameter Estimates

Parameter	Estimate (BSV)
CL/F, L/h	41.4 (27%)
Vc/F, L	115 (65%)
CL_{IC}/F, L/h	15.4 (57%)
Vp/F, L	82.5 (65%)
Ka, h-1	0.404 (51%)
Influence of TDD	0.386
K_{AFF} of AAG, dL/mg	0.03
Residual error, CV%	34%

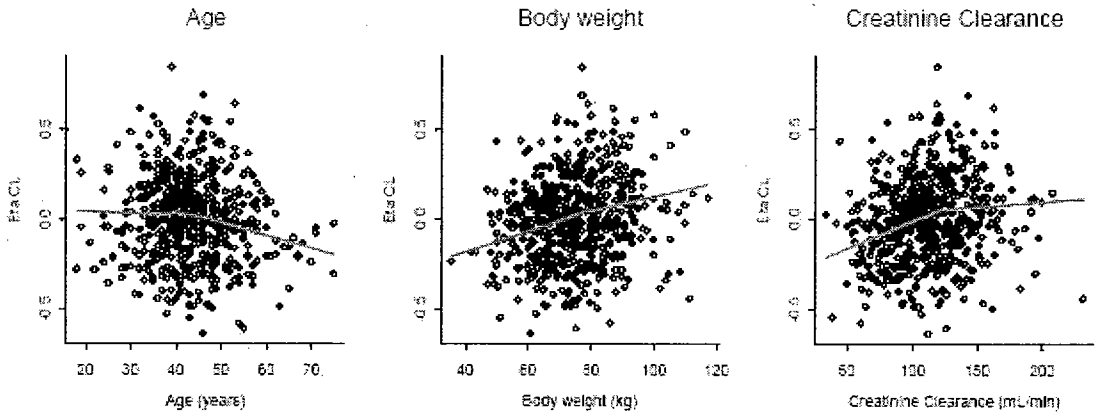
Covariate Models

There was a statistical effect of body weight, creatinine clearance, sex and hepatitis B/C co-infection on CL/F. However, these covariates had little impact on reducing the BSV for clearance and the sponsor did not retain any of them in the final model.

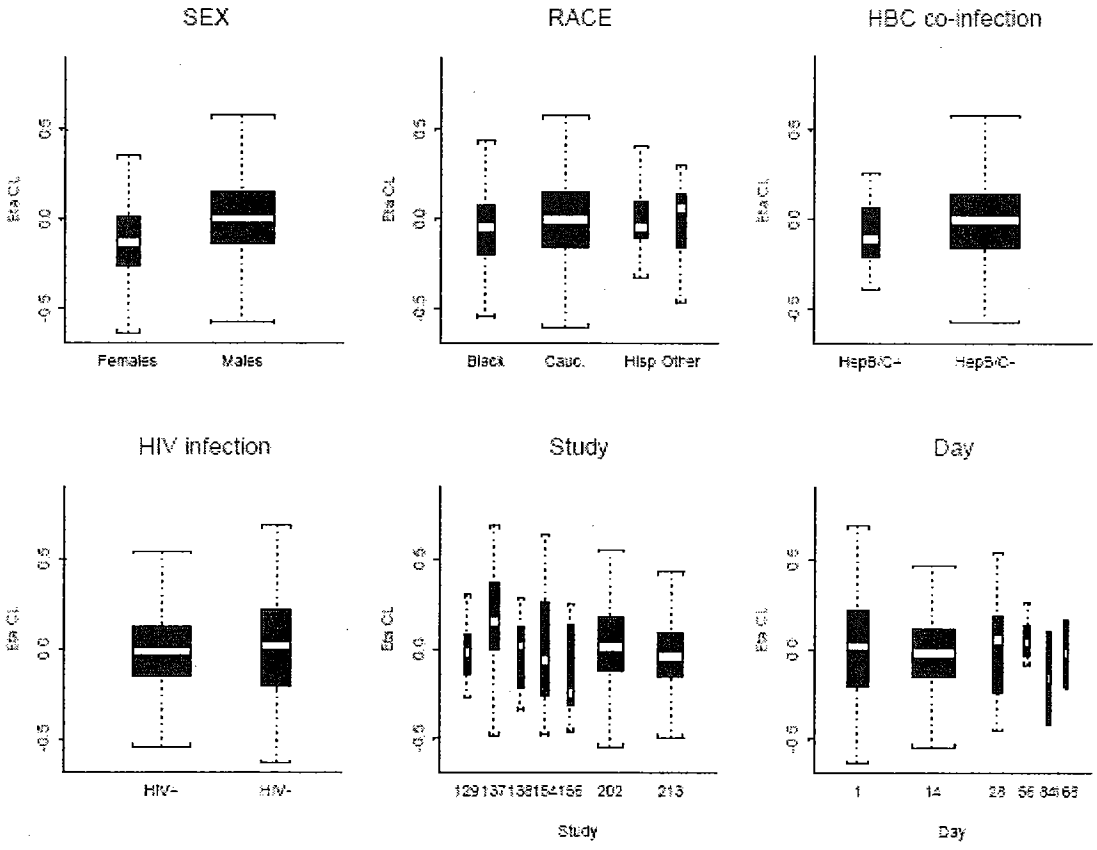
Univariate Covariate Model Results

Run	Covariate tested	Implementation	DF	OBJ	Diff OBJ from reference	p	IIV	Difference High-Low	Keep covariate in model?
Reference Run: Run101BAAG8			---	75325	---	---	27	---	---
COV001AGE3	AGE	AGE/35**θ	1	75321	-3.655	0.0559	26	14.8%	no
COV002WT5	WT	(WT-75)*θ	1	75307	-18.186	<0.0001	26	29.4%	no
COV004CRCL5	CRCL	(CRCL-110)*θ	1	75312	-12.764	0.0004	26	26.2%	no
COV005SEX	SEX	θ**(SEX-1)	1	75302	-22.799	<0.0001	26	16.8%	no
COV006RACE	RACE	θ**RAC2*θ**RAC3*θ**RAC4	3	75321	-3.372	0.3377	26	7.0%	no
COV007HBC	HBC	θ**(HBC-1)	1	75320	-4.739	0.0295	26	11.7%	no
COV008HIV	HIV	θ**(HIV-1)	1	75323	-1.700	0.1923	26	4.1%	no

Continuous covariate relationships for random effects on clearance. The line indicates the trend in the data



Categorical covariate relationships for random effects on clearance.



Final Model

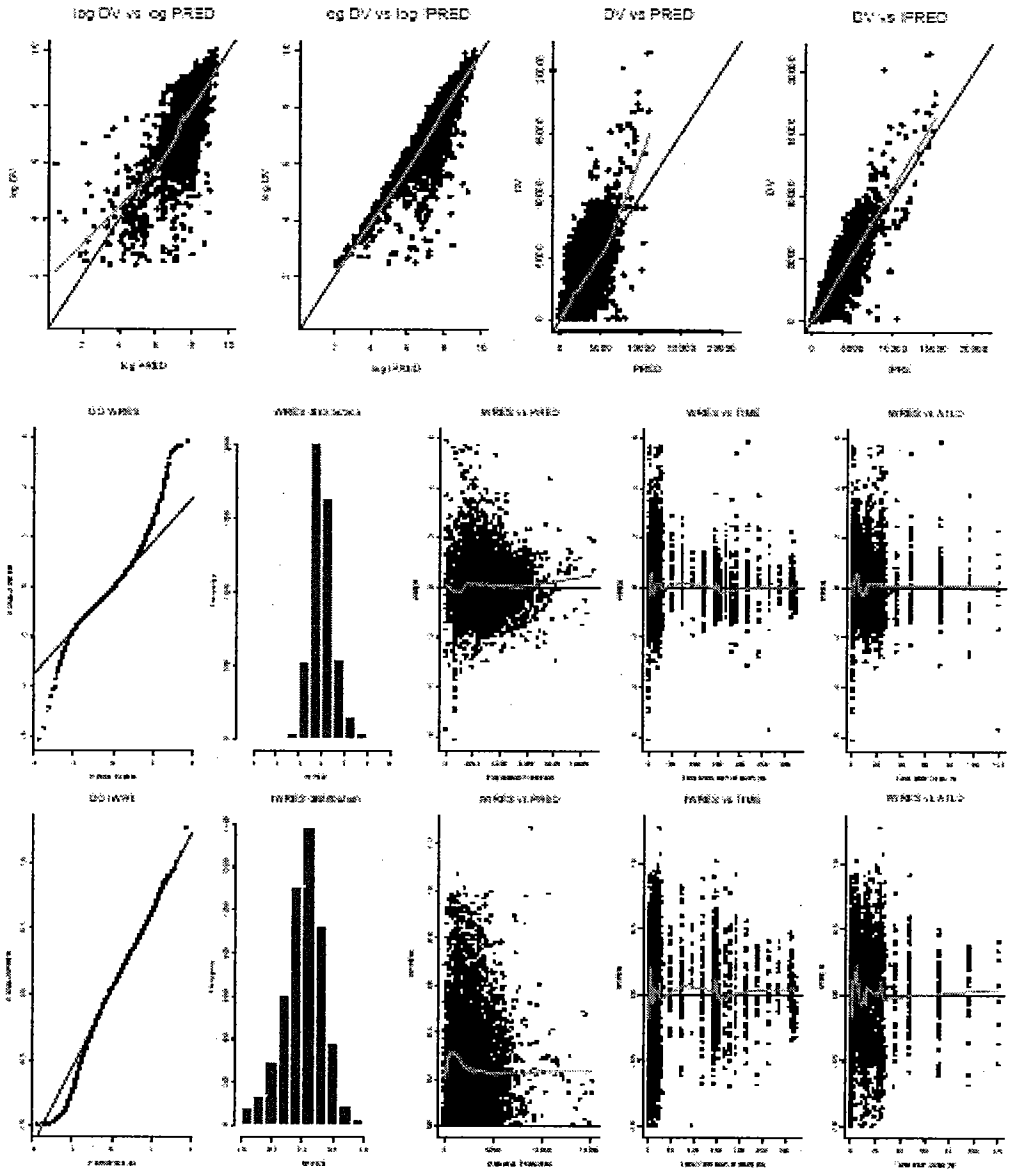
The final model was the same as the base model except the sponsor added a covariance between the variances of Vc/F and ka. Addition of this parameter decreased the objective function by 42.777. The correlation between Vc/F and ka was 0.61.

Final model parameters and goodness-of-fit plots are shown below. There were several concentrations with large weighted residuals (WRES>10). These outliers had little impact on estimation of model parameters and, consequently retained in the dataset.

Final Model Parameter Estimates

Parameter	Parameter Estimate	Parameter SEE	Parameter SEE CV (%)	IIV Estimate (CV %)	IIV SEE CV (%)
CL_{int}/F (L/h)	41.9	5.520	13	26	8
influence of TDD[1]	0.388	0.0343	8.8		
K_{aff} of AAG (dL/mg)	0.0304	0.00539	18		
V2/F (L)	122	10.0	8.2	88	23
Q/F (L/h)	15.0	1.62	11	65	30
V3/F (L)	84.3	8.94	11	56	36
KA (1/h)	0.455	0.0370	8.1	74	17
Residual Error	0.122	0.00508	4.2	35	

Goodness-of-Fit Plots for Final Model with High Residuals excluded.



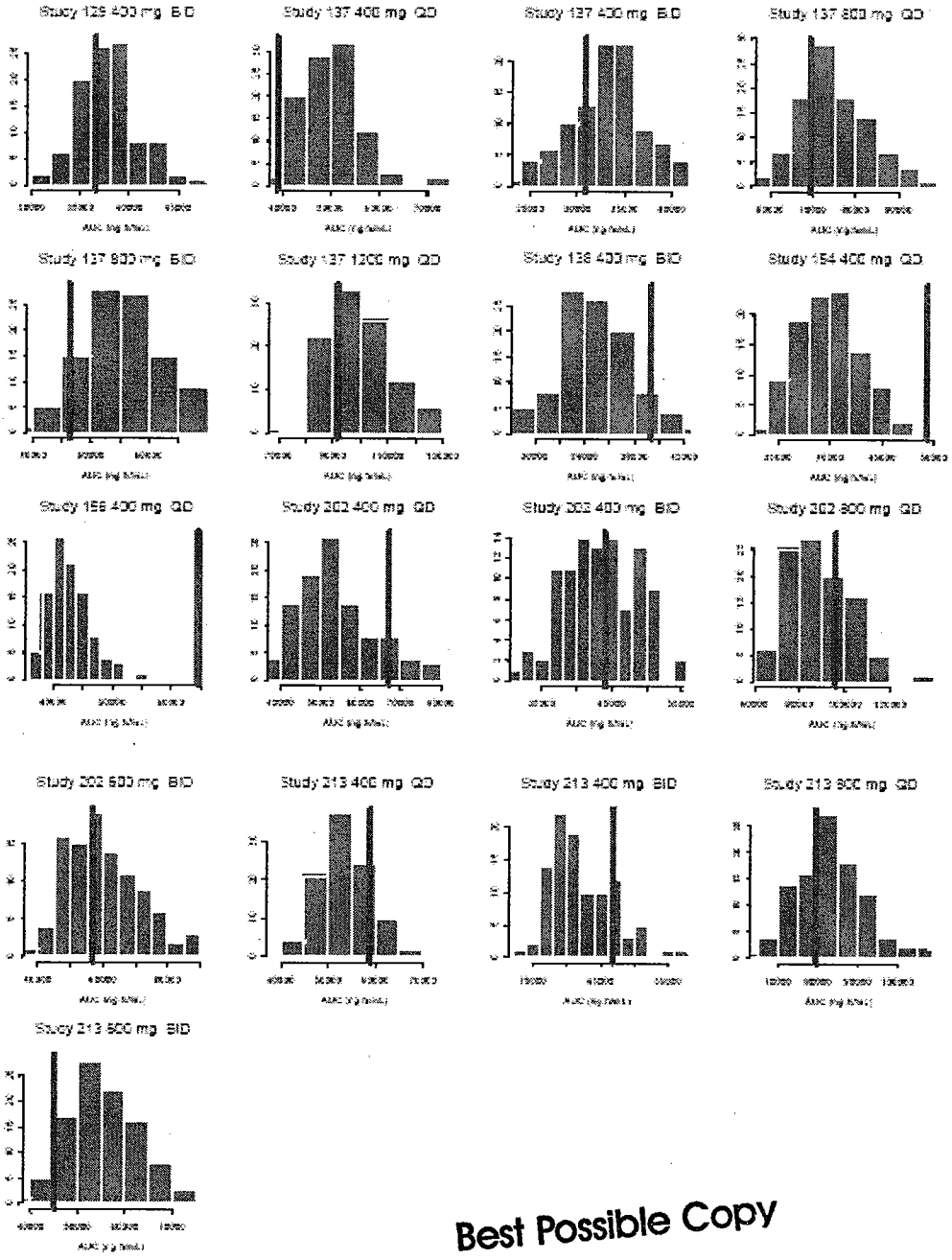
Best Possible Copy

Predictive Check of Final Model

The final model parameters were used to simulate 100 datasets. For each of the simulated datasets, C_{trough}, AUC and CL/F were calculated for each subject. The distribution of median values obtained from the 100 simulated datasets was compared to the same parameters calculated from the observed dataset.

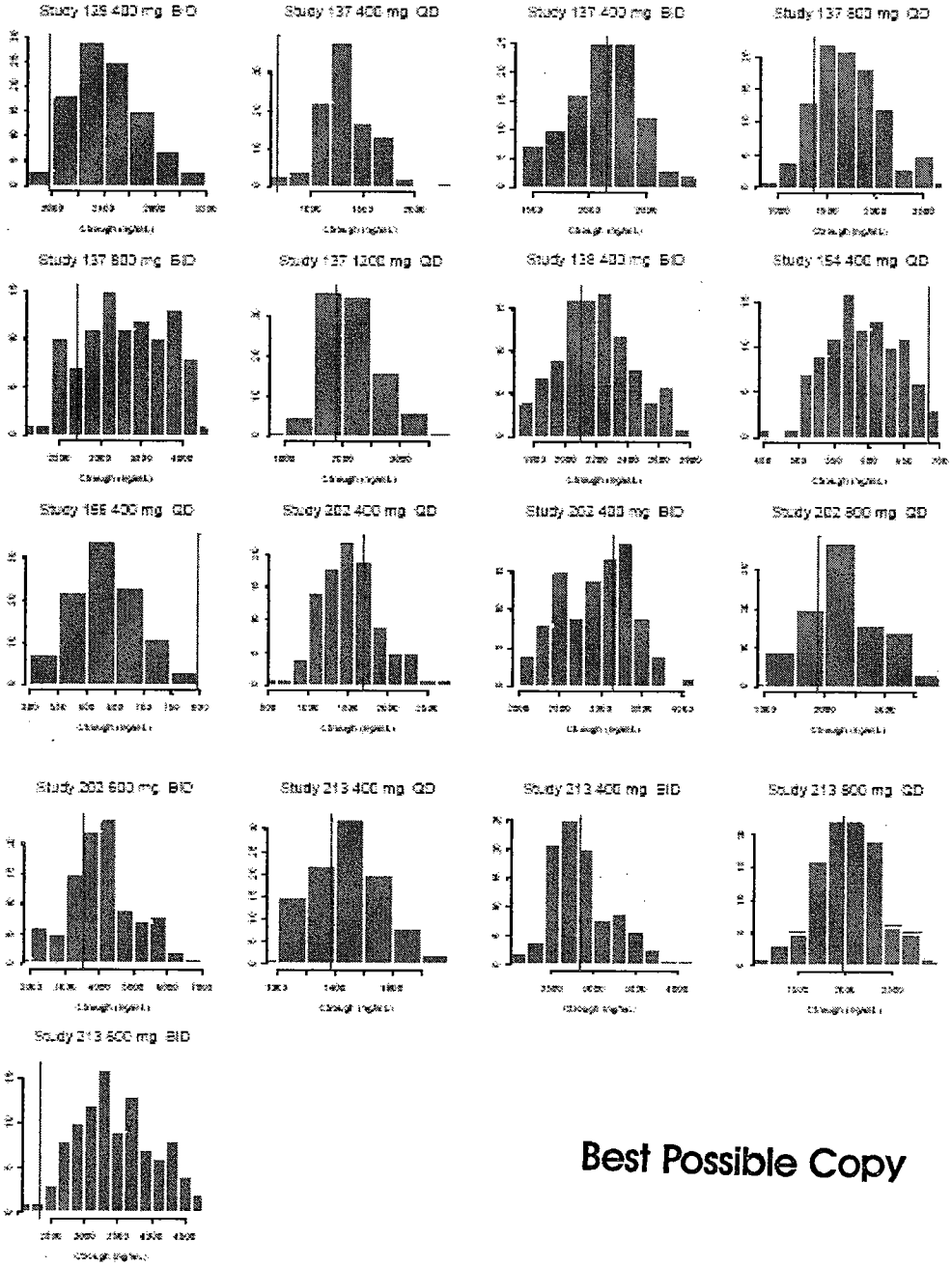
The sponsor concluded that the model is capable of simulating the concentrations that were used for model development.

Predictive Check: Comparison of the distribution of simulated AUC and observed values.



Best Possible Copy

Predictive Check: Comparison of the distribution of simulated C_{0h} and observed values.



Application of PopPK Model (TMC114-C927b)

The population PK model was used to provide empirical Bayesian feedback of exposure on sparse samples that were obtained from subjects that were switched from the clinical trial formulation to the commercial formulation.

Data

The data that were included in this analysis were from subjects in studies C202, C213, and TMC114-C215 that received darunavir as the new 300 mg commercial formulation. Study TMC114-C215 (referred to as C215) was an open-label, follow-up, safety and efficacy study in 460 HIV subjects. The following table summarizes the available data. Subjects who contributed data to the model development dataset retained their pharmacokinetic parameters, with the exception of CL/F which was allowed to vary according to AAG concentrations.

Clinical trial data

Item	Study 6	Study 7	Study 8
Aim	Dose finding study in patients	Dose finding study in patients	Open-label follow-up to evaluate safety and efficacy
Tibotec Code	TMC114-C202	TMC114-C213	TMC114-C215
No. of subjects	319 HIV+ subjects	318 HIV+ subjects	460 HIV+ subjects
Data used	Subjects receiving new formulation	Subjects receiving new formulation	327 'de novo' subjects
No of subjects for PK analysis	204 subjects	206 subjects	292 subjects
Dose	400 mg qd, 800 mg qd, 400 mg bid and 600 mg bid (Clinical Trial Formulations F001 and F002) 600 mg bid (commercial tablet formulation F016)	400 mg qd, 800 mg qd, 400 mg bid and 600 mg bid (Clinical Trial Formulations F001 and F002) 600 mg bid (commercial tablet formulation F016)	600 mg bid (commercial tablet formulation F016)
Ritonavir dose	100 mg qd or bid	100 mg qd or bid	100 mg bid
Periods	1 - 8 (week 2, 4, 8, 12, 24, 48, 72 and 96)	1 - 8 (week 2, 4, 8, 12, 24, 48, 72 and 96)	5 (week 2, 4, 8, 12 and 24)
Single/Multiple dose	Multiple	Multiple	Multiple
Formulation	Tablet	Tablet	Tablet
Number of samples	1 - 7 over a 96-week time period	1 - 7 over a 96-week time period	1 - 6 over the 24-week time period
Assay (LLOQ)	LC-MS/MS [redacted]	LC-MS/MS [redacted]	LC-MS/MS [redacted]

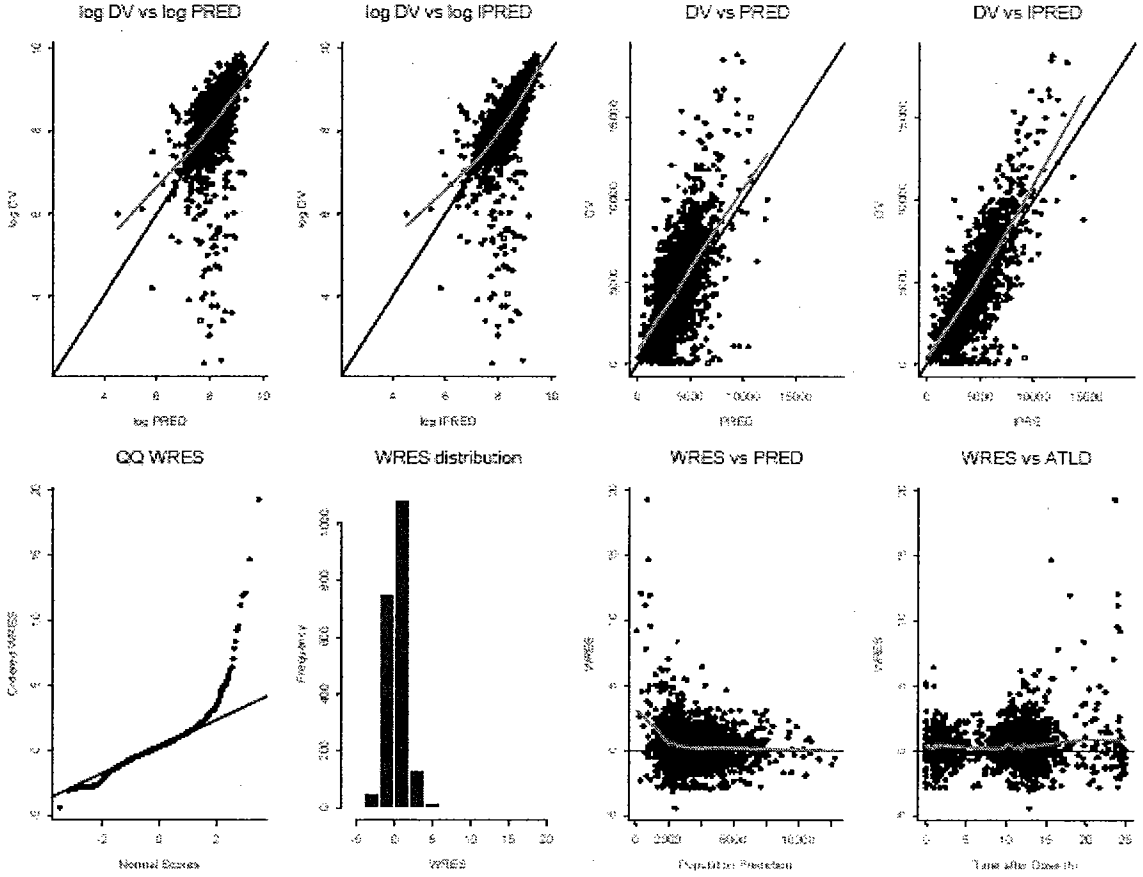
Methods

To estimate the relative bioavailability of the commercial formulation, the sponsor fixed all model parameter and only estimated the population estimate and between-subject variability for F. This updated model was then used to calculate model predicted estimates for AUC for the clinical and commercial formulations of darunavir. Two one-sided t-tests were performed to assess the impact of the higher bioavailability of the commercial formulation.

Results

Empirical Bayesian estimation was performed using NONMEM version V, using the MAXEVAL=0 option in the $ESTIMATION record. Goodness-of-fit plots for the feedback analysis are shown below. Bias is clearly evident in the plots and provides evidence of a change in bioavailability in the commercial formulation.

Goodness-of-fit Plots for Empirical Bayesian Estimation



The relative oral bioavailability of the commercial formulation was estimated to be 1.18 with a between-subject variability of 26%. When between-subject variability was excluded in the model, the population estimate was 1.37. This was a similar estimation of the relative bioavailability estimated using likelihood profiling of the formulation effect.

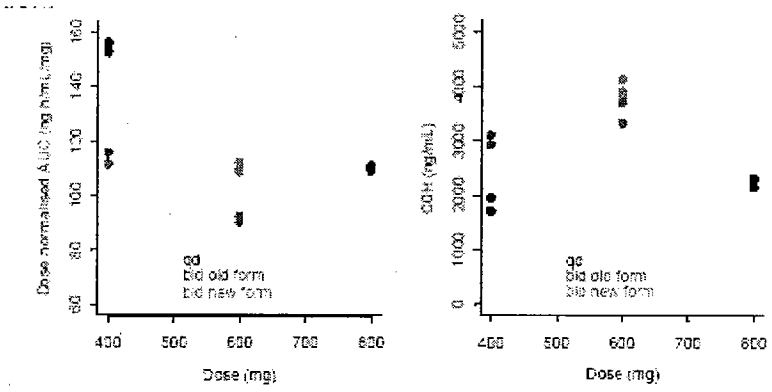
Comparison of the formulation effect for different estimation methods

Model	Bayes' estimation	Likelihood profiling of formulation effect	Estimation of the formulation effect, no IIV	Estimation of the formulation effect with IIV
Population effect	1 (Fixed)	1.37	1.37	1.18
CV (%)	---	1.31-1.44	4.3	1.6
5,50,95 percentiles				0.98-1.16-1.35
IIV (%)	---	---	---	26
Objective function	34190.903	33536.254	33536.228	33203.578

The sponsor performed simulations to obtain descriptive statistics for AUC_{tau} and C_{0h}. The following table shows a summary of the model-predicted estimates for each parameter for the clinical and commercial formulations.

Study	Treatment	N	C_{0h} (ng/mL) Mean	CV (%)	Median	Min	Max
202	400 mg qd	32	1701	55	1607		
	400 mg bid	41	2916	41	2614		
	600 mg bid	31	3701	47	3363		
	800 mg qd	30	2149	52	1970		
	600 mg bid NF	135	3812	44	3651		
213	400 mg qd	15	1945	40	1983		
	400 mg bid	17	3090	27	2815		
	600 mg bid	67	3316	35	3124		
	800 mg qd	15	2291	33	2137		
	600 mg bid NF	122	3897	39	3566		
215	600 mg bid NF	292	4119	40	3806		

Study	Treatment	N	AUC_{tau} (ng.h/mL) Mean	CV (%)	Median	Min	Max
202	400 mg qd	32	61015	35	58761		
	400 mg bid	41	44556	32	40698		
	600 mg bid	31	55301	32	53400		
	800 mg qd	30	87290	32	86023		
	600 mg bid NF*	135	67074	33	62968		
213	400 mg qd	15	62328	29	62689		
	400 mg bid	17	46193	19	44344		
	600 mg bid	67	54141	26	51982		
	800 mg qd	15	88609	20	85586		
	600 mg bid NF*	122	65791	36	61603		
215	600 mg bid NF*	292	65127	31	59929		



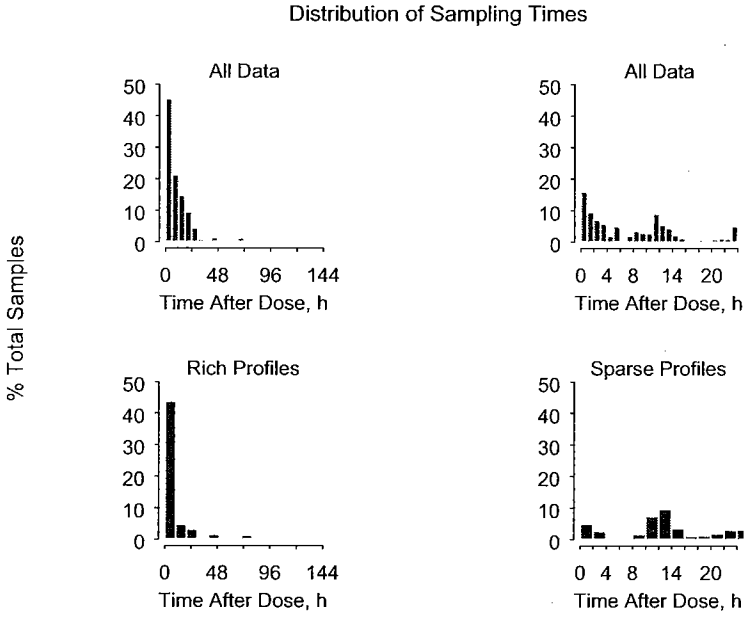
To estimate the impact of switching from the clinical to the commercial formulation, the sponsor performed a two one-sided test on dose-normalized, model predicted AUCtau values. According to the sponsor's analysis the increased bioavailability had little impact on the estimated exposure to darunavir when switching between formulations.

GRP	N	Ref GeoMean	Test GeoMean	Ratio	CI_90 Lower	CI_90 Upper	Prob<80	Prob>125
400 mg qd	11	146	122	83.51	76.2	91.6	0.209	0
800 mg qd	16	111	108	97.19	86.3	109	0.0058	0.001
400 mg bid	23	102	109	107.1	95.9	120	0.0001	0.0124
600 mg bid	21	94.6	103	108.6	99.9	118	0	0.0045

Ref GeoMean: Geometric mean of the exposure of the clinical trial formulation (ng/mL.h/mg)
Test GeoMean: Geometric mean of the exposure of the commercial formulation(ng/mL.h/mg)
CI_90 Lower: Lower limit of the 90% confidence interval for the ratio
CI_90 Upper: Upper limit of the 90% confidence interval for the ratio
Prob<80: Probability that the lower limit is less than 80% of the reference
Prob>125: Probability that the upper limit is greater than 125% of the reference

Reviewer's Comments

1. Sampling times for darunavir concentrations were adequate to characterize exposure (AUC, trough concentrations) in HIV-1 patients and healthy volunteers.



2. There is sufficient data (number of subjects and number of samples per subject) to assess covariate effects of age, creatinine clearance, sex, race, and Hepatitis B/C co-infection on darunavir exposure.

Covariate	Number of Subject	Rich or Sparse Profiles
Age: ≥ 65 y	12	3 (Rich), 9 (Sparse; 1-7 samples/subject)
Creatinine CL Moderate (30-60	20	1 (Rich), 19 (Sparse; 2-7

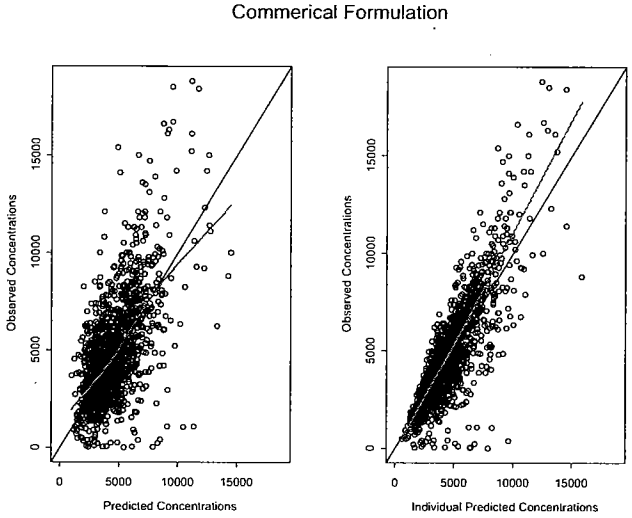
ml/min)		samples/subject)
Gender Female	68	13 (Rich), 55 (Sparse; 1-7 samples/subject)
Hepatitis B/C Co-infection	31	0 (Rich), 31 (Sparse; 2-7 samples/subject)
Race Black Hispanic	70 41	2 (Rich), 68 (Sparse; 1-7 samples/subject) 0 (Rich), 41 (Sparse; 1-7 samples/subject)

3. The model predicted estimates of exposure (AUC24) and trough concentrations (C0h) for the clinical formulation are comparable to the observed parameters calculated using non-compartmental methods of the full pharmacokinetic profiles obtained from a subset of subjects in C202 and C213. The table below shows that the 95% confidence intervals of both observed and simulated mean parameters are overlapping.

•	• Values shown as Number, Mean (CV%), [95% CI Mean]			
	• 400/100 qd	• 800/100 qd	• 400/100 bid	• 600/100 bid
• Observed AUC_{tau}	• N=11, 56894 (43%) [42436, 71352]	• N=13, 91485 (89%) [47224, 135746]	• N=13, 44042 (35%) [35662, 52422]	• N=8, 51951 (26%) [42591, 61311]
• C202, Simulated AUC_{tau}	• N=32, 61015 (35%) [53616, 68414]	• N=30, 87290 (32%) [77294, 97286]	• N=41, 44556 (32%) [40192, 48920]	• N=41, 55301 (32%) [49071, 61531]
• C213, Simulated AUC_{tau}	• N=15, 62328 (29%), [53181, 71475]	• N=15, 88609 (20%), [79641, 97577]	• N=17, 46193 (19%) [42021, 50365]	• N=67, 54141 (26%) [50770, 57512]
•	• 400/100 qd	• 800/100 qd	• 400/100 bid	• 600/100 bid
• Observed C_{0h}	• N=11, 1199 (74%) [675, 1723]	• N=13, 2667 (114%) [1014, 4320]	• N=13, 2567 (39%) [2023, 3111]	• N=8, 4086 (40%) [2953, 5219]
• C202, Simulated C_{0h}	• N=32, 1701 (55%) [1377, 2025]	• N=30, 2149 (52%) [1749, 2549]	• N=41, 2916 (41%) [2550, 3282]	• N=41, 3701 (47%) [3089, 4313]
• C213, Simulated C_{0h}	• N=15, 1945 (40%), [1551, 2339]	• N=15, 2291 (33%), [1908, 2674]	• N=17, 3090 (27%) [2693, 3487]	• N=67, 3316 (35%) [3038, 3594]

•

4. There is a high correlation between observed plasma concentrations and model-predicted concentrations for the commercial formulation. Individual predictions fall on the line of unity, except for high concentrations where the model over-predicts observed concentrations.



5. The 18% (CV% = 26) increase in exposure to darunavir is not expected to impose an increased safety risk. An exposure-safety assessment showed there was not a strong relationship between cholesterol, lipids, LFTs, and AEs and darunavir exposure.

5 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio- 1

4.3 DCP 4 Division Directors Concurrence on PMCs

From: Lazor, John A
Sent: Friday, June 16, 2006 10:36 AM
To: Arya, Vikram
Subject: RE: NDA 21-976 Prezista (Darunavir) Post Marketing Commitments
Sensitivity: Confidential

Concur. We should state which studies were proposed by the company and which ones we are asking for.

From: Arya, Vikram
Sent: Wednesday, June 14, 2006 4:33 PM
To: Lazor, John A
Cc: Reynolds, Kellie S; Arya, Vikram
Subject: NDA 21-976 Prezista (Darunavir) Post Marketing Commitments
Importance: High
Sensitivity: Confidential

John,
Your official concurrence is requested on the attached list of Post Marketing Commitments for Darunavir (NDA 21-976).

Thanks,

Vikram
<< File: Post Marketing Commitments for Darunavir.doc >>

4.4 OCPB Filing/Review Form

General Information About the Submission			
	Information		Information
NDA Number	**21-976**	**Brand Name**	**PREZISTA**
OCP Division	**DCP 4**	**Generic Name**	**Darunavir**
Medical Division	**DAVP**	**Drug Class**	**HIV Protease Inhibitor**
OCPB Reviewer	**Vikram Arya**	**Indication(s)**	**HIV-1 Infection**
OCPB Team Leader	**Kellie Reynolds**	**Dosage Form**	**Tablet**
		Dosing Regimen	**600 mg /100 mg ritonavir b.i.d.**
Date of Submission	**June 22, 2005**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review		**Sponsor**	**Tibotec Inc**
PDUFA Due Date	**June 23, 2006**	**Priority Classification**	**Priority Review**
Division Due Date			

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:	**X**	1		
Isozyme characterization:	**X**	4		
Blood/plasma ratio:	**X**	1		
Plasma protein binding:	**X**	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:	X	3		
Patients-				
single dose:				

multiple dose:	X	4		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	13		
In-vivo effects of primary drug:	X	15		
In-vitro:	X	1		
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	**X**	2		
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	3		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	**X**	1		
Relative bioavailability -				
solution as reference:	X	1		
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	**X**	1		
(IVIVC):				

Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		53		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Vikram Arya
6/23/2006 03:18:18 PM
BIOPHARMACEUTICS

Christine Garnett
6/23/2006 04:19:31 PM
PHARMACOLOGIST

Kellie Reynolds
6/23/2006 04:23:41 PM
BIOPHARMACEUTICS