MODULE 2.7 CLINICAL SUMMARY

2.7.2 SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

TABLE OF CONTENTS

＊：新薬承認情報提供時に置き換え

＊：新薬承認情報提供時に置き換え

＊：新薬承認情報提供時に置き換え

＊：新薬承認情報提供時に置き換え

＊：新薬承認情報提供時に置き換え

＊：新薬承認情報提供時に置き換え

＊：新薬承認情報提供時に置き換え

＊：新薬承認情報提供時に置き換え

＊：新薬承認情報提供時に置き換え

LIST OF IN-TEXT TABLES AND FIGURES

Tables

＊：新薬承認情報提供時に置き換え

＊：新薬承認情報提供時に置き換え

＊：新薬承認情報提供時に置き換え

＊：新薬承認情報提供時に置き換え

＊：新薬承認情報提供時に置き換え

＊：新薬承認情報提供時に置き換え

Figures

＊：新薬承認情報提供時に置き換え

＊：新薬承認情報提供時に置き換え

＊：新薬承認情報提供時に置き換え

＊：新薬承認情報提供時に置き換え

LIST OF ABBREVIATIONS

AAUCMB	averaged area under the curve minus Baseline
Ae	amount excreted
AIC	Akaike Information Criterion
ALAG1	absorption lag-time
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APV	amprenavir
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATP	adenosine triphosphate
ATV	atazanavir
AUC_{12h}, AUC_{24h}	area under the plasma concentration-time curve for the specified time period after dosing
AUC_{last}	area under the plasma concentration-time curve from time of intake until the last measurable or measured concentration
AUC_{∞}	area under the plasma concentration-time curve from time of intake until infinity
BCS	Biopharmaceutics Classification System
b.i.d.	twice daily
C_{0h}, C_{12h}	plasma concentrations at specified time after dosing
Caco-2	carcinoma-derived
CC50	50% cytotoxic concentration
CCI	concentration-controlled intervention
CD4	cluster of differentiation 4
CI	confidence interval
CL	clearance
CrCL	creatinine clearance
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration

$C_{ss,av}$	average steady-state plasma concentration (AUC/τ at steady-state)
CV	coefficient of variation
CYP	cytochrome P450
D1	duration of zero-order absorption
D_{urine}	urinary excretion
DAVG	time averaged difference
ddI	didanosine
DMSO	dimethyl sulfoxide
DRV	darunavir
DSMB	Data and Safety Monitoring Board
EC50	50% effective concentration in cell-based assays
ECG	electrocardiogram
EDDP	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene
EDTA	diaminoethanetetra-acetic acid
EFV	efavirenz
ENF	enfuvirtide
FC	fold change in EC50
FDA	Food and Drug Administration
FI	fluctuation index
fosAPV	fosamprenavir
FSH	follicle stimulating hormone
GAM	generalized additive models
GGT	gamma-glutamyltransferase
H2	histamine-2
HBr	hydrobromic acid
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HLM	human liver microsome
HMG CoA	3-hydroxy-3-methylglutaryl coenzyme A
HPLC	high-performance liquid chromatography

HPMC	hydroxypropylmethylcellulose (hypromellose)
IC_{50}	50% inhibitory concentration
IDV	indinavir
IQ	inhibitory quotient
ITT	intent-to-treat
Ka	absorption rate constant
K_i	inhibition constant
K_m	formation rate constant
$K_{m(,app)}$	(apparent) Michaelis-Menten constant
LC-MS/MS	liquid chromatography with tandem mass-spectrometry
LDL	low density lipoprotein
LH	luteinizing hormone
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LPV	lopinavir
LS	least squares
MAC	*Mycobacterium avium* complex
mRNA	messenger ribonucleic acid
MTCT	mother to child transmission
NADPH	nicotinamide adenine dinucleotide phosphate
NC = F	non-completer equals failure
NNRTI	non-nucleoside reverse transcriptase inhibitor
N(t)RTI	nucleoside/nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OATP	organic anion-transporting polypeptide
OC	oral contraceptive
OFV	objective function value
PBMC	peripheral blood mononuclear cells
PEG	polyethylene glycol
P-gp	P-glycoprotein
PI	protease inhibitor
POPIN	Pharmacologic Optimization of Protease Inhibitors and Non-nucleoside Reverse Transcriptase Inhibitors

PPT	plasma preparation tube
PSS	phenotypic sensitivity score
PT	prothrombin time
PTT	partial thromboplastin time
PVP	polyvinylpyrrolidone
q.d.	once daily
QTcF	QT interval corrected by Fridericia's formula
RAM	resistance-associated mutation
RNA	ribonucleic acid
RT-PCR	reverse transcriptase polymerase chain reaction
RTV	ritonavir
rtv	co-administered low-dose ritonavir
SD	standard deviation
SI	selectivity index
SQV	saquinavir
SSRI	selective serotonin re-uptake inhibitor
$t_{1/2, term}$	terminal half-life
TDF	tenofovir disoproxil fumarate
TDM	therapeutic drug monitoring
t.i.d.	three-times daily
TLOVR	time to loss of virologic response
t_{max}	time to reach the maximum plasma concentration
TMC125	etravirine
TPV	tipranavir
TSH	thyroid stimulating hormone
UDPGT	uridine disphosphate glucuronosyltransferase
V2	volume of distribution in the central compartment
VitE-TPGS	d-alpha-tocopheryl-polyethylene glycol-1000 succinate
V_{max}	maximum velocity

1 BACKGROUND AND OVERVIEW

TMC125 (etravirine), a substituted diarylpyrimidine derivative, is a non-nucleoside reverse transcriptase inhibitor (NNRTI) selected for its high potency against wildtype and NNRTI-resistant human immunodeficiency virus type 1 (HIV-1) found in treatment experienced HIV-1 infected subjects. TMC125 has a range of 50% effective concentration (EC50) values of 0.87 to 5.46 nM (0.38 to 2.38 ng/mL) against wildtype HIV-1 and a 50% in vitro cytotoxic concentration (CC50) value > 100 μM (refer to Module 2.7.2 Virology Summary/Section 3.1.4). With a selectivity index (SI) of > 62500, TMC125 is a potent and selective HIV-1 inhibitor. In the presence of 10% fetal calf serum, with or without 50% human serum, TMC125 showed a median EC50 ratio of 5.8 (refer to Module 2.7.2 Virology Summary/Section 3.1.8). The median protein binding-adjusted EC50 for MT cells infected with HIV-1/IIIB is thus 9.28 nM (4 ng/mL; median EC50 = 1.60 nM x 5.8; nM is converted to ng/mL by multiplying by 0.435).

Due to the low aqueous solubility and low permeability of TMC125, the development of an oral formulation concept for use in Phase III trials that had suitable characteristics in terms of an appropriate drug load, together with acceptable physical stability, dissolution, and bioavailability, was challenging and involved the clinical testing of 27 formulation concepts.

Early Phase I and IIa clinical trials investigating the pharmacokinetics of TMC125 mainly used TMC125 formulated as a polyethylene glycol (PEG) 4000-based capsule (Form T*). However, this capsule formulation had a relatively low drug load (50 mg), and therefore a high pill burden would have been necessary to achieve therapeutic concentrations. Alternative formulation concepts were subsequently investigated with the objective of increasing the bioavailability of TMC125, as described in Module 2.7.1. Among these concepts, improved bioavailability was noted when TMC125 was formulated as a hydrobromic acid salt (TMC125.HBr), particularly with hydroxypropylmethylcellulose (HPMC, hypromellose). The pharmacokinetics of TMC125.HBr in HPMC (Form Z*) were specifically investigated. However, the formulation concepts of TMC125.HBr in HPMC, including formulation Z* , were not developed further due to potential stability and/or manufacturing issues with formulations containing this HBr salt.

In later Phase I and II clinical trials, the capsule formulation of TMC125 in PEG 4000 (Form T*) was replaced by tablet formulations of TMC125 containing HPMC and manufactured using granulo-layering technology (mainly formulation F*). Formulation F* was used in most of the earlier drug-drug interaction trials. Subsequent development of TMC125 oral formulation concepts indicated that tablet formulations manufactured using spray-drying technology gave an improved (approximately 4-fold) bioavailability of TMC125 in healthy and HIV-1 infected subjects, and thus the spray-dried tablet formulation selected for further clinical development (formulation A*) was used in later Phase I trials (including drug-drug interaction trials) as well as in the registrational Phase III trials. Subjects participating in the Phase IIb clinical trials of TMC125 were switched from formulation F* to formulation A* in the open-label rollover trials (TMC125-C211 and TMC125-C229) when formulation A* became available.

The pharmacokinetics of TMC125 were assessed as either a primary or secondary objective of all Phase I, II, and III trials conducted to date. Healthy, non-HIV-1 infected adults were enrolled in all Phase I trials with the exception of 3 trials in which HIV-1 infected adults were enrolled (TMC125-C117, TMC125-C145 [summarized in the current document] and TMC125-C141 [summarized in Module 2.7.1]). HIV-1 infected adults were enrolled in all Phase II and III trials.

Pharmacokinetic/pharmacodynamic (antiviral as well as safety response) relationships were investigated in the 3 Phase II proof-of-principle trials as well as in 3 Phase IIb trials and in the 2 registrational Phase III trials.

Trials summarized in this document are listed in Table 1, together with dosage form and formulation number of TMC125 administered, and the dosage form of any co-administered drugs. Further information on these trials is provided in Appendix 2.7.2.5 and Module 2.7.2 Appendix: Summary of Completed Clinical Pharmacology Studies - Pharmacokinetics, Module 2.7.2 Appendix: Summary of Completed Clinical Pharmacology Studies - Drug-Drug Interaction, and Module 2.7.3 Appendix: Summary of Clinical Efficacy - Description of Completed Clinical Efficacy and Safety Studies.

Table 1: Clinical Pharmacology Trials Included in the Summary of Clinical Pharmacology Studies, by Dosage Form and Formulation Number

Clinical Trial (Location of Trial Report)	TMC125		Dosage Form of Co-Administered Drugs
	Dosage Form	Formulation Number	
Mass-Balance of TMC125 in Healthy Subjects			
TMC125-C130 (Module 5.3.3.1)	50 mg capsule (^{14}C-labelled TMC125 in PEG 4000)	TMC125/ KF4926 (based on Form T*)	NA
Single-Dose Pharmacokinetics of TMC125 in Healthy Subjects			
TMC125-C101 (Module 5.3.3.1)	50 mg capsule (TMC125 in PEG 4000)	Form T*	NA
Multiple-Dose Pharmacokinetics of TMC125 in Healthy Subjects			
TMC125-C104 (Module 5.3.3.1)	43 mg capsule (TMC125 in PEG 4000) [a]	Form T*	NA
TMC125-C128 (Module 5.3.3.1)	100 mg capsule (TMC125.HBr in HPMC)	Form Z*	NA
TMC125-C143 (Module 5.3.3.1)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	NA
TMC125-C153 (Module 5.3.3.1)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	NA
TMC125-C168 (Module 5.3.3.1)	100 mg tablet (TMC125 in HPMC, spray-dried)	Form A*	NA
Multiple-Dose Pharmacokinetics and Pharmacokinetic/Pharmacodynamic Relationships in HIV-1 Infected Subjects			
Phase IIa (Proof-of-Principle) Trials			
TMC125-C201 (Module 5.3.5.1)	100 mg tablet (TMC125 in HPMC, granulo-layered)	Form S*	NA
TMC125-C208 (Module 5.3.5.1)	50 mg capsule (TMC125 in PEG 4000)	Form T*	NA
TMC125-C207 (Module 5.3.5.2)	50 mg capsule (TMC125 in PEG 4000)	Form T*	NA
Phase IIb Trials			
TMC125-C203 (Module 5.3.5.1)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	NA
TMC125-C209 (Module 5.3.5.2)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	NA
TMC125-C223 (Module 5.3.5.1)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	NA

＊：新薬承認情報提供時に置き換え

Form :Formulation

Table 1: Clinical Pharmacology Trials Included in the Summary of Clinical Pharmacology Studies, by Dosage Form and Formulation Number (Cont'd)

Clinical Trial (Location of Trial Report)	TMC125		Dosage Form of Co-Administered Drugs
TMC125-C227 (Module 5.3.5.1)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	NA
TMC125-C229 (Module 5.3.5.2)	200 mg tablet (TMC125 in HPMC, granulo-layered) 100 mg tablet (TMC125 in HPMC, spray-dried)	Form F* Form A*	NA NA
Phase III Trials			
DUET-1 (TMC125-C206) (Module 5.3.5.1)	100 mg tablet (TMC125 in HPMC, spray-dried)	Form A*	NA
DUET-2 (TMC125-C216) (Module 5.3.5.1)	100 mg tablet (TMC125 in HPMC, spray-dried)	Form A*	NA
Effect of Intrinsic Factors			
TMC125-C125 (Module 5.3.3.3)	100 mg tablet (TMC125 in HPMC, spray-dried)	Form A*	NA
Effect of Extrinsic Factors: Concomitant Administration of TMC125 with Other Drugs			
Mechanistic Trials (Healthy Subjects)			
TMC125-C174 (Module 5.3.3.4)	100 mg tablet (TMC125 in HPMC, spray-dried)	Form A*	Midazolam (Dormicum®): 1 mL vial (5 mg/mL) Dextromethorphan (Hustenstiller-Ratiopharm®): 30 mg capsule Caffeine (Percoffedrinol® N): 50 mg tablet Omeprazole (Antra® MUPS): 40 mg tablet Warfarin (Coumadin®): 5 mg tablet Vitamin K1 (Konakion® MM): 10 mg vial
TMC125-C105 (Module 5.3.3.4)	50 mg capsule (TMC125 in PEG 4000)	Form T*	Ritonavir (Norvir®): 100 mg capsule
TMC125-C116 (Module 5.3.3.4)	100 mg tablet (TMC125 in HPMC, spray-dried)	Form A*	Ritonavir (Norvir®): 100 mg capsule
TMC125-C106 (Module 5.3.3.4)	50 mg capsule (TMC125 in PEG 4000)	Form T*	Saquinavir (Fortovase®): 200 mg capsule
TMC125-C109 (Module 5.3.3.4)	50 mg capsule (TMC125 in PEG 4000)	Form T*	Efavirenz (Sustiva®): 200 mg capsule Nevirapine (Viramune®): 200 mg tablet

＊：新薬承認情報提供時に置き換え

Table 1: Clinical Pharmacology Trials Included in the Summary of Clinical Pharmacology Studies, by Dosage Form and Formulation Number (Cont'd)

Clinical Trial (Location of Trial Report)	TMC125		Dosage Form of Co-Administered Drugs
Administration of TMC125 with Other Antiretrovirals (Healthy Subjects)			
TMC125-C157 (Module 5.3.3.4)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	Didanosine (Videx® ER): 400 mg enteric-coated capsule
TMC125-C138 (Module 5.3.3.4)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	Tenofovir Disoproxil Fumarate (Viread®): 300 mg tablet, equivalent to 136 mg tenofovir base
TMC125-C177 (Module 5.3.3.4)	100 mg tablet (TMC125 in HPMC, spray-dried)	Form A*	Tenofovir Disoproxil Fumarate (Viread®): 300 mg tablet, equivalent to 136 mg tenofovir base
TMC125-C151 (Module 5.3.3.4)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	Atazanavir (Reyataz®): 200 mg capsule Ritonavir (Norvir®): 100 mg capsule
TMC125-C139 (Module 5.3.3.4)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	Darunavir: 200 or 400 mg tablet Ritonavir (Norvir®): 100 mg capsule
TMC125-C176 (Module 5.3.3.4)	100 mg tablet (TMC125 in HPMC, spray-dried)	Form A*	Darunavir: 200 or 400 mg tablet Ritonavir (Norvir®): 100 mg capsule
TMC125-C111 (Module 5.3.3.4)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form B*	Indinavir (Crixivan®): 400 mg capsule
TMC125-C122 (Module 5.3.3.4)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	Lopinavir/ritonavir (Kaletra®): 133.3 mg lopinavir/ 33.3 mg ritonavir capsule
TMC125-C123 (Module 5.3.3.4)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	Saquinavir (Fortovase®): 200 mg capsule Ritonavir (Norvir®): 100 mg capsule
TMC125-C161 (Module 5.3.3.4)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	Tipranavir: 250 mg capsule Ritonavir (Norvir®): 100 mg capsule
TMC125-C179 (Module 5.4)	100 mg tablet (TMC125 in HPMC, spray-dried)	Form A*	Raltegravir: 400 mg tablet
Administration of TMC125 with Other Antiretrovirals (HIV-1 Infected Subjects)			
TMC125-C117 (Module 5.3.3.4)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	Fosamprenavir: Subject's individual ARV regimen Ritonavir: Subject's individual ARV regimen
TMC125-C145 (Module 5.3.3.2)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	Lopinavir / saquinavir / ritonavir: Subject's individual ARV regimen

＊：新薬承認情報提供時に置き換え

Table 1: Clinical Pharmacology Trials Included in the Summary of Clinical Pharmacology Studies, by Dosage Form and Formulation Number (Cont'd)

Clinical Trial (Location of Trial Report)	TMC125		Dosage Form of Co-Administered Drugs
Administration of TMC125 with Drugs other than Antiretrovirals (Healthy Subjects)			
TMC125-C164 (Module 5.3.3.4)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	Atorvastatin (Lipitor®): 10 mg tablet
TMC125-C166 (Module 5.3.3.4)	100 mg tablet (TMC125 in HPMC, spray-dried)	Form A*	Ethinylestradiol / norethindrone (Ortho-Novum 1/35®): 0.035 mg ethinylestradiol / 1 mg norethindrone tablet
TMC125-C156 (Module 5.3.3.4)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	Rifabutin (Mycobutin®): 150 mg capsule
TMC125-C159 (Module 5.3.3.4)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	Sildenafil (Viagra®): 50 mg tablet
TMC125-C171 (Module 5.3.3.4)	100 mg tablet (TMC125 in HPMC, spray-dried)	Form A*	Clarithromycin (Zeclar®): 500 mg tablet
TMC125-C165 (Module 5.3.3.4)	200 mg tablet (TMC125 in HPMC, granulo-layered)	Form F*	Paroxetine (Deroxat®): 20 mg tablet
TMC125-C120 (Module 5.3.3.4)	100 mg tablet (TMC125 in HPMC, spray-dried)	Form A*	Omeprazole (Losec MUPS 40®): 40 mg tablet Ranitidine (Zantac®): 150 mg tablet
TMC125-C158 (Module 5.3.3.4)	100 mg tablet (TMC125 in HPMC, spray-dried)	Form A*	Methadone (Symoron®): 5 mg tablet (Days -14 to 15)
Effect of TMC125 on ECG (Healthy Subjects)			
TMC125-C178 (Module 5.3.4.1)	100 mg tablet (TMC125 in HPMC, spray-dried)	Form A*	NA

NA = Not applicable.
[a] The capsules used in this trial contained 43 mg instead of 50 mg TMC125.

In addition to these trials, pharmacokinetic data are available from an investigator-initiated, open-label trial of TMC125 (tablet formulation A*) co-administered with darunavir (DRV) co-administered with low-dose ritonavir (rtv), 2 or more nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs), and optional enfuvirtide (ENF) in multi-experienced HIV-1 infected subjects with limited therapeutic options (see Section 2.6.4).

Ongoing and planned Phase I trials with TMC125 are summarized in Table 2.

＊：新薬承認情報提供時に置き換え

Table 2: Ongoing and Planned Phase I Trials with TMC125

Trial Number	Interacting Drug or Special Population	Status [a]
TMC125-C126	HIV-1 infected children	Ongoing
TMC125-C181	Maraviroc with and without co-administration of DRV/rtv	Ongoing
TMC125-C173	Bioavailability Form A* VS. Form b* or Form A* dispersed in water	Planned
TMC125-C180	Digoxin	Planned
TMC125-C182	LPV/rtv (Kaletra Meltrex®)	Planned
TMC125-C184	Elvitegravir/rtv	Planned

These trials are not part of the current submission.
[a] Status as of 12 January 2007.
Source: Module 2.7.3 Appendix: Tabular Overview of Ongoing and Planned Trials with TMC125

The objective of this Summary of Clinical Pharmacology Studies is to provide an overview of the clinical pharmacology trials (mostly in healthy subjects) as well as the pharmacokinetic and pharmacodynamic components of Phase II and Phase III trials (in HIV-1 infected subjects) conducted as part of the clinical development program for TMC125. In addition, nonclinical trials, generally conducted using human biomaterials, that assist in the interpretation of the pharmacokinetic data are also summarized.

Data from 45 Phase I, II, and III trials, in which 2821 healthy or HIV-1 infected subjects were treated with trial medication, are summarized in this document (see Section 2), as shown in Table 3.

Table 3: Numbers of Subjects in Phase I, II, and III Trials Included in the Summary of Clinical Pharmacology Studies

Type of Trial	Number of Trials	Population	Number of Subjects
Phase I, single-dose	1	Healthy subjects	27
Phase I, mass-balance	1	Healthy subjects	6
Phase I, multiple-dose	5	Healthy subjects	155
Phase I, effect of hepatic impairment	1	Healthy subjects	32
Phase I, drug-drug interaction	24	Healthy subjects	504
Phase I, drug-drug interaction	2	HIV-1 infected subjects	23
Phase I, effect on ECG	1	Healthy subjects	41
Phase IIa	3	HIV-1 infected subjects	60
Phase IIb	4	HIV-1 infected subjects	562
Phase IIb rollover	1	HIV-1 infected subjects	208
Phase III	2	HIV-1 infected subjects	1203
Total	**45**		**2821**

Source: Appendix 2.7.2.5

Numbers of subjects treated in individual trials are available in Appendix 2.7.2.5.

Most single- and multiple-dose pharmacokinetic trials and drug-drug interaction trials were conducted with TMC125 administered as formulation T* , F* , and later A* . A direct comparison of the bioavailability for TMC125 formulation T* with either the F* or A* formulation is not available. Trial TMC125-C228 in HIV-1 infected subjects indicated that the exposure to TMC125 at a dose of 200 mg twice daily (b.i.d.) with the spray-dried tablet

＊：新薬承認情報提供時に置き換え

formulation A* achieved a comparable exposure, with lower variability, to that achieved with TMC125 at a dose of 800 mg b.i.d. with formulation F* (refer to Module 2.7.1/Section 2.1.5).

The comparability between the range of exposures to TMC125 observed with the 200 mg b.i.d. dose of formulation A* and the 800 mg b.i.d. dose of formulation F* was confirmed in the pharmacokinetic substudy of trial TMC125-C229 in HIV-1 infected subjects (see Section 2.6.2.5.2).

The metabolic profile and routes of excretion of TMC125, administered as a ^{14}C-labeled 800 mg dose of TMC125 with formulation T* (TMC125 in PEG 4000), were investigated in one Phase I mass-balance trial (TMC125-C130, see Section 2.2.1).

In 3 Phase IIa proof-of-principle trials in HIV-1 infected subjects (TMC125-C201 and TMC125-C207 in antiretroviral (ARV)-naïve, HIV-1 infected subjects, and TMC125-C208 in HIV-1 infected subjects with phenotypically confirmed NNRTI resistance), TMC125 was administered as 100 mg b.i.d. (Form S*), 400 mg b.i.d. (Form S*) or 900 mg b.i.d. (Form T*) for 7 to 8 days.

In 2 Phase IIb dose-finding, efficacy and safety trials in ARV-experienced HIV-1 infected subjects (TMC125-C203 and TMC125-C223), TMC125 was administered as formulation F* at doses of 400, 800, and 1200 mg b.i.d. In 2 further Phase IIb efficacy and safety trials in ARV-experienced HIV-1 infected subjects (TMC125-C209 and TMC125-C227), TMC125 was administered as formulation F* 800 mg b.i.d. Subjects participating in the Phase IIb clinical trials were allowed to switch from tablet formulation F* to tablet formulation A* in an open-label rollover trial (TMC125-C211 or TMC125-C229). Trial TMC125-C211 is not discussed further in this summary document because the pharmacokinetics of TMC125 were not evaluated.

In 2 ongoing registrational Phase III efficacy and safety trials in ARV-experienced HIV-1 infected subjects (TMC125-C206 and TMC125-C216, hereafter referred to as DUET-1 and DUET-2, respectively), TMC125 is administered as formulation A* at a dose of 200 mg b.i.d.

Potential drug-drug interactions were investigated in 26 Phase I trials in which capsule and tablet formulations of TMC125 were used. The majority of trials were conducted with TMC125 administered either as 800 mg b.i.d. of formulation F* or as 200 mg b.i.d. of formulation A* .

The potential effect of mild or moderate hepatic impairment on the pharmacokinetics of TMC125 was investigated in a trial conducted with TMC125 tablet formulation A* at a dose of 200 mg b.i.d. in non-HIV-1 infected subjects with mild or moderate hepatic impairment (TMC125-C125).

An active- (moxifloxacin) and placebo-controlled thorough QT/QTc trial has been performed to investigate the potential effect of TMC125 on electrocardiogram (ECG) parameters in healthy subjects (TMC125-C178).

A total of 10 human biomaterial trials (one trial on protein binding, 8 trials on in vitro metabolism and potential for interactions, and one trial on in vitro transport characteristics) provided further supporting information on the clinical pharmacology of TMC125.

＊：新薬承認情報提供時に置き換え

The following sections give an overview of the information presented in this summary document. References to drug exposure refer to area under the plasma concentration-time curve (AUC) unless stated otherwise.

1.1 BIOANALYTICAL METHODS

The bioanalytical methods used for the determination of TMC125 during the clinical development program for TMC125 are described in Module 2.7.1/Section 1.2. An overview of the validated analytical methods for all analytes in the individual clinical trials is available in Module 2.7.1/Appendix 2.7.1.1.

1.2 ABSORPTION

1.2.1 In Vitro Absorption

Human colon carcinoma-derived (Caco-2) cells were used as an in vitro model to investigate the bi-directional transepithelial transport characteristics of ^{14}C-TMC125 (trial TMC125-NC183, see Section 2.1.3.1). Transepithelial permeation rates of TMC125 indicated low to intermediate permeability. TMC125 permeation across Caco-2 monolayers was polarized at the early time points (15 min) with a preference for the secretory transport direction over the absorptive transport, which appeared to be related to an initial delay in absorptive transport. However, transport polarity disappeared at later time points, indicating that P-glycoprotein (P-gp) (or another transport mechanism) does not play a role in TMC125 transepithelial permeation. Overall, TMC125 permeation is thought to occur predominantly via a passive transcellular diffusion mechanism. Furthermore, bi-directional transport experiments with the P-gp substrate ^{3}H-paclitaxel demonstrated that TMC125 has P-gp inhibitory properties, with an apparent 50% inhibitory concentration (IC50) value of 24.2 μM (10500 ng/mL).

1.2.2 Clinical Trials

The absolute bioavailability of TMC125 could not be investigated due to the inability to produce an acceptable intravenous formulation of TMC125.

In clinical trials, the oral absorption of TMC125 has been investigated in terms of the impact of concomitant food intake on the bioavailability of TMC125. The mean exposure (AUC from time of intake until the last measurable or measured concentration [AUC_{last}]) to TMC125, when administered as a single 100-mg dose of tablet formulation A* under fasted conditions, was 51% lower than when administered after a standardized breakfast (trial TMC125-C147, refer to Module 2.7.1/Section 2.3.1). In the same trial, the differences in exposure to TMC125 when taken after a high-fat breakfast, a standardized breakfast, or a snack (croissant) were not clinically relevant. Administration of TMC125 after an enhanced-fiber breakfast resulted in a 38% decrease in mean maximum plasma concentration (C_{max}) and a 25% decrease in mean AUC_{last}, compared to administration after the standardized breakfast.

In an investigation of the effect of the timing of the meal relative to administration of a single 200-mg dose of tablet formulation A* , the mean exposure to TMC125 was 17% lower when administered before starting a standardized breakfast, as compared to administration after a standardized breakfast (trial TMC125-C116, refer to Module 2.7.1/Section 2.3.2). Thus the

＊：新薬承認情報提供時に置き換え

greatest absorption of TMC125 was achieved when TMC125 was administered following a meal. Further details are available in Section 3.9.2.

The effect of co-administering TMC125 with drugs that alter intra-gastric pH (ranitidine or omeprazole) was explored in trial TMC125-C120 (see Section 2.8.3.7). There was no relevant effect of ranitidine on the exposure to TMC125 (formulation A*), indicating that the absorption of TMC125 is not sensitive to changes in intra-gastric pH. Co-administration with omeprazole resulted in a 1.4-fold increase in TMC125 exposure. The mechanism of this interaction is more likely due to the inhibition of cytochrome P450 (CYP) 2C19-mediated metabolism by omeprazole rather than a change in intra-gastric pH because an increase of similar magnitude was also observed with clarithromycin, a drug known to inhibit CYP3A but not known to alter intra-gastric pH (Section 2.8.3.5). The increase in TMC125 exposure is not clinically relevant given the lack of a relationship between TMC125 exposure and safety (see Section 3.11.3.7).

1.3 DISTRIBUTION

The in vitro plasma protein binding of TMC125, determined by equilibrium dialysis, is approximately 99% (trial TMC125-NC143, see Section 2.1.1.1). TMC125 is extensively bound to human albumin (87.9% to 99.7% at concentrations of 0.1 to 6.0 g/100 mL) and α1-acid glycoprotein (69.2% to 99.0% at concentrations of 0.02 to 0.20 g/100 mL). At TMC125 concentrations of 100 and 1000 ng/mL, the blood to plasma concentration ratio in man was approximately 0.7, and the fraction of TMC125 distributed to the plasma water compartment was 0.0008, the fraction distributed to plasma proteins was 0.77, and the fraction distributed to blood cells was 0.23.

The apparent volume of distribution for the central compartment (V2) when TMC125 was modeled with a sequential zero- and first-order absorption and 2-compartment disposition model was 422 L (Module 3.5.3.5/TMC125-C929/Section 5.3).

The distribution of TMC125 into compartments other than plasma (e.g., cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

1.4 METABOLISM AND EXCRETION

1.4.1 In Vitro Metabolism and Interaction Potential

The in vitro metabolism of TMC125 was studied in human hepatocytes and liver subcellular fractions (trial TMC125-NC142, see Section 2.1.2.1). Only limited metabolism was observed in human hepatocytes, with a mean of 95.4% of the added TMC125 being recovered unchanged in the hepatocyte suspensions and 46.4% being recovered unchanged in primary cell cultures. In the liver subcellular fractions, 86.6% of the added TMC125 was recovered unchanged in the microsomes and 87.1% was recovered unchanged in microsomes.

The major in vitro metabolic pathway of TMC125 is methylhydroxylation of the dimethylbenzonitrile moiety to form monohydroxylated (Metabolite 12) or dihydroxylated (Metabolite 8) TMC125. Hydroxylation at a site on the dimethylbenzonitrile moiety apart from the methyl groups (Metabolite 13) occurs to a minor extent. Glucuronide conjugates of these metabolites are also formed. Overall TMC125 metabolism is mainly catalyzed by CYP3A and

CYP2C isoforms. Taking into account the relative abundance of the different CYP isoforms, the CYP3A enzymes play the major role in the biotransformation of TMC125 in vitro.

1.4.2 Clinical Trials

A mass-balance trial (TMC125-C130, see Section 2.2.1) showed that most of the administered ^{14}C-TMC125-related radioactivity in a single 800-mg dose of the capsule formulation T* (TMC125 in PEG 4000) was excreted in feces. At 168 hours after dosing, a mean of 93.7% of the administered radioactivity was recovered in feces, and a mean of 1.2% of the administered radioactivity was recovered in urine. Unchanged TMC125 accounted for the majority of the radioactivity in the feces (81.2% to 86.4% of the administered dose). No unchanged TMC125 was detected in the urine.

Metabolite profiling and identification using samples obtained in trial TMC125-C130 indicated that the most important Phase 1 metabolic pathway of TMC125 in humans was hydroxylation of the methyl carbons of the dimethylbenzonitrile moiety (trial TMC125-NC205, see Section 2.1.2.3). Both the mono- and di-methyl hydroxylated metabolites (Metabolite 12 and Metabolite 8, respectively) and their glucuronides (Metabolite 6 and Metabolite 1) were formed. Overall, methyl hydroxylation accounted for 3.8% to 9.5% of the TMC125 dose. Aromatic hydroxylation at the dimethylbenzonitrile moiety (Metabolite 13) was only a minor metabolic pathway. In plasma, TMC125 represented the major fraction of the absorbed radioactivity at the 3 time points studied (2, 4, and 8 hours after TMC125 administration). Metabolite 1, Metabolite 8, and Metabolite 12 were detected in human plasma, of which Metabolite 8 was the most abundant, amounting for one-third to half of the TMC125 concentration.

The excretion of radioactivity in urine was low (a mean of 1.2% of the administered dose), indicating minimal renal metabolism and excretion of TMC125 and its metabolites; therefore, a specific trial to investigate TMC125 pharmacokinetics in subjects with renal impairment has not been conducted.

In trial TMC125-C174 (see Section 2.8.1.1), the drug-drug interaction potential of TMC125 administered as formulation A* (TMC125 in HPMC, spray-dried) was investigated using the Cooperstown 5+1 cocktail. TMC125 had no clinically relevant effect on the activity of CYP1A2 or 2D6. CYP3A4 activity was not changed by a single dose of TMC125, but was weakly induced by TMC125 at steady-state, with a 37% decrease in the parent to metabolite ratio of single-dose midazolam. CYP2C19 activity was inhibited by a single dose of TMC125, leading to a 1.3-fold increase in the parent to metabolite ratio; there was a higher degree of inhibition at steady-state concentrations of TMC125, with a 4.3-fold increase in the parent to metabolite ratio. Although TMC125 inhibits CYP2C9 in vitro (see Section 3.3.1.3), plasma concentrations of the probe drug for CYP2C9 in this trial (S-warfarin) did not change significantly. However, the 42% decrease in exposure to the metabolite of S-warfarin at steady-state indicated a weak inhibition of CYP2C9 by TMC125.

Overall, the in vivo results show that TMC125 is a substrate and weak inducer of CYP3A4 and a substrate and weak inhibitor of CYP2C9 and CYP2C19.

＊：新薬承認情報提供時に置き換え

1.5 PHARMACOKINETICS OF TMC125 AFTER SINGLE- AND MULTIPLE-DOSE ADMINISTRATION IN HEALTHY SUBJECTS

Data on the single- and multiple-dose pharmacokinetics of TMC125 in healthy subjects are available from trials conducted with various capsule and tablet formulations of TMC125. The most frequently used formulations were the 50-mg capsule formulation T* (TMC125 in PEG 4000) used in early Phase I trials (single dose), the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered) used in later Phase I and IIb trials, and the 100-mg tablet formulation A* (TMC125 in HPMC, spray-dried) used in more recent Phase I trials and in Phase III trials.

When administered as single doses of formulations T* (TMC125 in PEG 4000) and F* (TMC125 in HPMC, granulo-layered), the exposure to TMC125 increased dose proportionally at lower dose levels (Form T* : 50 to 600 mg; Form F* : 200 to 800 mg), and less than dose proportionally at higher dose levels (Form T* : 600 to 1200 mg; Form F* : 800 to 1600 mg). When administered as formulation Form A* (TMC125 in HPMC, spray-dried), the exposure to TMC125 increased dose proportionally across the 100 to 400 mg range of dose levels. The rate of TMC125 absorption was not influenced by the dose level or the formulation of TMC125 administered. The exposure to TMC125 was generally comparable across trials for a given dose level and formulation of TMC125 within the context of high pharmacokinetic variability.

When administered as formulation F* (TMC125 in HPMC, granulo-layered) for 8 days, the exposure to TMC125 increased dose proportionally when administered at doses of 200 to 800 mg b.i.d., but the increases in TMC125 exposure were less than dose proportional when administered once daily (q.d.) at doses of 400 to 1600 mg. When TMC125 was administered as formulation A* (TMC125 in HPMC, spray-dried) for 8 days, the increase in exposure to TMC125 was generally dose proportional between total daily doses of 200 and 400 mg, and the total exposure to TMC125 was similar irrespective of whether the total daily dose was administered in a once-daily or twice-daily regimen.

1.6 PHARMACOKINETICS OF TMC125 AFTER SINGLE- AND MULTIPLE-DOSE ADMINISTRATION IN HIV-1 INFECTED SUBJECTS

Data on the single- and multiple-dose pharmacokinetics of TMC125 in HIV-1 infected subjects are available from trials conducted with various tablet formulations of TMC125. These formulations included the 50-mg capsule formulation T* (TMC125 in PEG 4000) and the 100-mg tablet formulation S* (TMC125 in HPMC, granulo-layered) used in Phase IIa trials, the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered) used in Phase IIb trials, and the 100-mg tablet formulation A* (TMC125 in HPMC, spray-dried) used in Phase III trials.

When administered as the capsule formulation T* (TMC125 in PEG 4000) at a single dose of 900 mg, the exposure to TMC125 was comparable in ARV-naïve and ARV-experienced HIV-1 infected subjects. With the tablet formulation S* (TMC125 in HPMC, granulo-layered) in ARV-naïve HIV-1 infected subjects the exposure to TMC125 increased dose proportionally between the 100 and 400 mg dose levels.

＊：新薬承認情報提供時に置き換え

With the tablet formulation F* (also TMC125 in HPMC, granulo-layered) in ARV-experienced HIV-1 infected subjects the increase in exposure to TMC125 was either less than dose proportional or dose proportional between the 400 and 800 mg dose levels when given as a single dose. There was only a slight increase in the exposure to TMC125 with the administration of 2400 mg compared to the administration of 1600 mg, both at single doses. After multiple dosing of TMC125 given as formulation F* , TMC125 pharmacokinetics increased proportionally or more than proportionally between the 400 and 800 mg b.i.d. dose levels; the increase was less than proportional between the 800 and 1200 mg b.i.d. dose levels.

With the tablet formulation A* (TMC125 in HPMC, spray-dried), when given as a single dose, the increase in exposure to TMC125 was more than dose-proportional across the 100 to 300 mg dose level range. At steady-state, a more than dose proportional increase was observed between 100 and 200 mg b.i.d. The rate of TMC125 absorption was not influenced by the dose level or the formulation of TMC125 administered.

In general, the range of exposure to TMC125 when administered as tablet formulation F* at a dose of 800 mg b.i.d. was comparable to the range of exposure when TMC125 was administered as tablet formulation A* at a dose of 200 mg b.i.d.

1.7 COMPARISON OF EXPOSURE TO TMC125 BETWEEN HEALTHY SUBJECTS AND HIV-1 INFECTED SUBJECTS

Data enabling a comparison of the exposure to TMC125 between healthy subjects and HIV-1 infected subjects are available from across-trial comparisons. Irrespective of the formulation of TMC125 administered, the comparison of pharmacokinetic parameters between healthy subjects and HIV-1 infected subjects indicated that the exposure to TMC125 was generally lower in HIV-1 infected subjects, compared to healthy subjects, when the same formulation and the same dose was administered. The reason for this lower exposure in HIV-1 infected subjects has not been identified. Medication intakes following a meal were for the larger part witnessed and interacting concomitant medication was not allowed in the trials in ARV-naïve HIV-1 infected subjects.

1.8 POPULATION PHARMACOKINETIC ANALYSIS OF TMC125 IN HIV-1 INFECTED SUBJECTS

The estimated population pharmacokinetics of TMC125 exposure in HIV-1 infected subjects are available from 3 Phase IIb trials (TMC125-C203 [see Section 2.6.2.1], TMC125-C223 [see Section 2.6.2.3], and TMC125-C227 [see Section 2.6.2.4]), in which subjects were treated with tablet formulation F* (TMC125 in HPMC, granulo-layered) and 2 Phase III trials (DUET-1 [see Section 2.6.3.1] and DUET-2 [see Section 2.6.3.2]), in which subjects were treated with tablet formulation A* (TMC125 in HPMC, spray-dried). In general, the range of exposure to TMC125 when administered as tablet formulation F* at a dose of 800 mg b.i.d. was comparable to the range of exposure when TMC125 was administered as tablet formulation A* at a dose of 200 mg b.i.d.

Pharmacokinetic Variability of TMC125

The inter-subject variability of TMC125 exposure at steady-state when administered at a dose of 200 mg b.i.d. with formulation A* (expressed as %CV for AUC_{12h}) was relatively high, with

values of 80% in DUET-1 and 86% in DUET-2 based on population pharmacokinetics (Section 3.6.1.3). The variability was similar for formulation F* at a dose of 800 mg b.i.d. in Phase IIb trials, between 75% and 99% for the different doses in trial TMC125-C203 and between 81% and 89% for the different doses in trial TMC125-C223.

This variability was further confirmed in the population pharmacokinetic model of TMC125 used for the pooled DUET trials, with inter-subject variability for clearance being 60.4%. However, at the same time, the inter-occasion variability for this parameter was also high (40.1%), indicating that variability in the pharmacokinetics of TMC125 within a subject is almost as large as that between subjects.

1.9 EFFECT OF INTRINSIC FACTORS

In HIV-1 infected subjects, intrinsic factors that have been considered for their potential effect on the pharmacokinetics of TMC125 include sex, age, race, creatinine clearance, body weight, hepatitis B and/or C virus co-infection status (see Section 3.8.1). In the pooled analysis of DUET-1 and DUET-2, TMC125 clearance was not significantly associated with age; however, this observation is limited to the range of age observed in these trials. No consistent effect of sex on TMC125 pharmacokinetics was observed. Lower body weight and hepatitis B and/or C co-infection appeared to increase TMC125 exposure. The inter-subject variability in clearance was high (60.4%), as was the inter-occasion variability (40.1%).

A specific trial was conducted to investigate the effects of mild or moderate hepatic impairment on the pharmacokinetics of TMC125 administered as tablet formulation A* (TMC125 in HPMC, spray-dried) in non-HIV-1 infected subjects (trial TMC125-C125, see Section 2.7.1). No apparent effect on TMC125 pharmacokinetics was observed in subjects with mild or moderate hepatic impairment; the effect of severe hepatic impairment on the pharmacokinetics of TMC125 has not been evaluated.

In view of the negligible renal excretion of TMC125 (see Section 3.3.2), a trial to investigate the exposure to TMC125 in subjects with renal impairment has not been conducted.

1.10 EFFECT OF EXTRINSIC FACTORS

Extrinsic factors that have been considered for their potential effect on the pharmacokinetics of TMC125 include the impact of pharmaceutical formulation, concomitant food intake, and drug-drug interactions.

1.10.1 Impact of Pharmaceutical Formulation

Due to the low aqueous solubility and low permeability of TMC125, the development of an oral formulation concept for use in Phase III trials that had suitable characteristics in terms of an appropriate drug load, together with acceptable physical stability, dissolution, and bioavailability, was challenging and involved the testing of 27 formulation concepts. Overall, the type of oral formulation concept had a large effect on the pharmacokinetics of TMC125.

Early Phase I and IIa clinical trials mainly used TMC125 formulated as a PEG 4000-based capsule (From T*). However, this capsule formulation had a relatively low drug load (50 mg), and therefore a high pill burden would have been necessary to achieve therapeutic concentrations. Alternative formulation concepts were investigated with the objective of increasing the

bioavailability of TMC125, which would enable higher-strength formulation concepts. These concepts included TMC125 formulated as capsules containing TMC125 in HPMC (Form U*) or [redacted] (Form V*), which had a lower bioavailability than formulation Form T*, and capsule formulation concepts containing TMC125 as an HBr salt (TMC125.HBr). However, these formulation concepts were not developed further due to potential stability and/or manufacturing issues with formulations containing this HBr salt.

In later Phase I and II clinical trials, the 50-mg capsule formulation of TMC125 in PEG 4000 (Form T*) was replaced by tablet formulations manufactured using granulo-layering technology (Form S*, Form B*, and Form F*). These tablet formulations had a comparable bioavailability to that of the capsule formulation Form T*, but the drug load was higher (100 and 200 mg, respectively). Nevertheless a high dose (and high pill burden) still needed to be administered. The subsequent development of oral formulation concepts for TMC125 was therefore focused on increasing the bioavailability and/or increasing the drug load while maintaining a robust stability profile. In a comparison of a capsule formulation of TMC125 in HPMC manufactured using bead-coating technology (Form I*) and tablet formulations of TMC125 in HPMC manufactured using spray-drying technology (Form J*and From K*), the relative bioavailability of TMC125 was higher with the spray-dried tablets, and the bioavailability of TMC125 with the bead-coated tablets was even lower than with the earlier, granulo-layered tablet formulation of TMC125 in HPMC (Form F*). Hence spray-drying was selected as the manufacturing technology for the TMC125 solid dispersion. Relative bioavailability trials, generally involving comparisons with the earlier granulo-layered tablet formulation of TMC125 in HPMC (Form F*), and with different spray-dried formulations, showed that the use of HPMC as the polymer (formulations Form J*and Form K*) provided a higher bioavailability than the use of [redacted] (Form L*), and overall the solid dispersions of TMC125 showed improved physical stability, dissolution, and bioavailability when the TMC125 to polymer (HPMC) ratio evolved from [redacted] (Form J*, Fomr O* , Fomr P*) and [redacted] (Form K*, Fomr Q*) to [redacted] (Form G*). The [redacted] ratio is used in formulation A* , which was selected for the registrational Phase III clinical trials. A further increase in the relative proportion of the polymer was restricted by the inability to handle the solid dispersion product in the downstream processes.

The improved bioavailability of TMC125 when administered as a spray-dried tablet formulation using HPMC as the solubilizing polymer, compared to the earlier Phase II granulo-layered tablet formulations in HPMC (Form C*,Form B*, and Form F*), was confirmed for a number of formulations of differing compositions in healthy subjects (Form J*, Form K*,Form O*,Form N*,Form Q*, FormG*, Form P*,Form I*,Form A*, Form H*) and in HIV-1 infected subjects (Form A*).

The final formulation and manufacturing process were selected on the basis of trial TMC125-C170 (refer to Module 2.7.1/Section 2.1.3), in which healthy subjects receiving a single 400-mg dose of the spray-dried tablet formulation of TMC125 in HPMC (Form A*) had an approximately 8- to 9-fold higher mean exposure to TMC125 compared to the same dose of the Phase IIb granulo-layered tablet formulation F* .

Trial TMC125-C141 in HIV-1 infected subjects (refer to Module 2.7.1/Section 2.1.4) showed that the mean exposure to TMC125 after single-dose administration of 100 mg of the spray-dried tablet formulation A* corresponded to the mean exposure with 800 mg of the Phase IIb granulo-layered tablet formulation F* . The 100-mg spray-dried formulation (Form A*), with substantially improved bioavailability, was therefore chosen as the designated formulation and tablet strength for use in planned clinical trials, including registrational Phase III trials, and for

＊：新薬承認情報提供時に置き換え

intended commercialization. However, trial TMC125-C228 in HIV-1 infected subjects (refer to Module 2.7.1/Section 2.1.5) indicated that the exposure to TMC125 after multiple-dose administration of TMC125 at a dose of 100 mg b.i.d. with the spray-dried tablet formulation A* provided lower exposure than that achieved with multiple-dose administration of TMC125 at a dose of 800 mg b.i.d. with the Phase IIb granulo-layered tablet formulation F* . Subsequently in this trial, TMC125 at a dose of 200 mg b.i.d. with the spray-dried tablet formulation A* was shown to achieve comparable exposure, with lower variability, to that achieved with TMC125 at a dose of 800 mg b.i.d. with formulation F* .

The comparability between the range of exposure to TMC125 observed with the 200 mg b.i.d. dose of formulation A* and the 800 mg b.i.d. dose of formulation F* shown in trial TMC125-C228 was confirmed in the pharmacokinetic substudy of trial TMC125-C229 in HIV-1 infected subjects (in which the 800 mg b.i.d. dose with formulation F* was subsequently switched to the 200 mg b.i.d. dose with formulation A*) (see Section 3.5.2.5), and in a comparison of population pharmacokinetic estimates obtained after administration of TMC125 as formulations F* and A* in Phase IIb and III trials, respectively (see Section 3.6.1).

1.10.2 Impact of Concomitant Food Intake

The mean exposure (AUC_{last}) to TMC125, when administered as a single 100-mg dose of tablet formulation A* (TMC125 in HPMC, spray-dried) under fasted conditions, was 51% lower than when administered after a standardized breakfast (trial TMC125-C147, refer to Module 2.7.1/Section 2.3.1). In an investigation of the effect of the timing of the meal relative to administration of a single 200-mg dose of tablet formulation A* , the mean exposure to TMC125 was 17% lower when administered before a standardized breakfast, as compared to administration after a standardized breakfast (trial TMC125-C116, refer to Module 2.7.1/Section 2.3.2).

In trial TMC125-C147, TMC125 was also administered as formulation A* after one of 3 types of meals at breakfast, and the exposure to TMC125 was compared to the exposure obtained when TMC125 was administered after a standardized breakfast. The nutritional composition of the meals is summarized in Table 132. The differences in exposure to TMC125 when taken after a high-fat breakfast, a standardized breakfast, or a snack (croissant) were not clinically relevant. Administration of TMC125 after an enhanced-fiber breakfast resulted in a 38% decrease in mean maximum plasma concentration (C_{max}) and a 25% decrease in mean AUC_{last}, compared to administration after the standardized breakfast.

Based upon the food interaction data with formulation A* , it is recommended that TMC125 tablets be taken following a meal. In the Phase IIb trials and the registrational Phase III trials, the tablets were taken following a meal.

1.10.3 Drug-Drug Interactions

1.10.3.1 Human Biomaterial Trials and Potential Drug-Drug Interactions

In an in vitro trial, the interaction of TMC125 with human CYP enzymes was studied with probe substrates (trial TMC125-NC128, see Section 2.1.2.4). CYP2C9 was most potently inhibited (inhibition constant [K_i] value of 0.58 μM). The K_i values for CYP1A2, 2B6, 2C8, 2C19, 2D6, and 3A were at least 10-fold higher (7.0, 83, 20, 22, 15, and 6.7 μM, respectively), indicating a

lower affinity and potential to cause drug-drug interactions. Because of the low K_i value for CYP2C9, inhibition of this isoenzyme was considered to have a potential clinical relevance.

The potential of TMC125 to induce CYP isoenzymes was determined in primary hepatocyte cultures from cryopreserved human hepatocytes (trial TMC125-NC164, see Section 2.1.2.6). Treatment of the cells with different concentrations of TMC125 did not result in the induction of CYP1A2 messenger ribonucleic acid (mRNA) expression. However, treatment of the cells with TMC125 biphasically influenced the mRNA expression of CYP2B6, 2C-family, and 3A4. The potential of TMC125 to induce CYP isoenzyme activities was also determined in primary human hepatocyte cultures (trial TMC125-NC238, see Section 2.1.2.7). TMC125 was not an inducer of CYP1A2 or 2B6 in human hepatocytes. CYP2C19 activity of TMC125-treated hepatocytes was lower than the activity in dimethyl sulfoxide (DMSO) control cells. Treatment of the hepatocytes with TMC125 resulted in an increase in CYP3A4 activity, with maximal activity observed at 1.0 μM TMC125 (4.8- to 7.1-fold induction in comparison with DMSO treatment) and clearly lower induction (1.7- to 3.0-fold) at 25 μM TMC125.

In vitro, TMC125 is a P-gp inhibitor (trial TMC125-NC183, see Section 2.1.3.1), and thereby also has the potential to increase plasma concentrations of drugs that are transported by P-gp. However, because the apparent IC50 of TMC125 for P-gp inhibitory activity (24.2 μM [10500 ng/mL]) is considerably higher than the expected plasma concentrations of TMC125 when administered at the clinical dose of 200 mg b.i.d. as formulation A* , the P-gp inhibitory properties of TMC125 are anticipated to be weak when TMC125 is administered as recommended. A drug-drug interaction trial between TMC125 and the P-gp substrate digoxin (TMC125-C180) is planned (Table 2).

TMC125 is an inducer of CYP3A4 (trial TMC125-NC238, see Section 2.1.2.7) indicating a potential to decrease plasma concentrations of drugs that are primarily metabolized by CYP3A4, which could decrease or curtail their therapeutic effects.

TMC125 is a CYP2C9 and CYP2C19 inhibitor, indicating a potential to increase plasma concentrations of drugs that are primarily metabolized by CYP2C9 and/or CYP2C19, which could increase or prolong their therapeutic and adverse effects (see Section 3.9.3.1.1).

1.10.3.2 Clinical Drug-Drug Interaction Trials

Against the background of the in vitro findings and the theoretical considerations for potential drug-drug interactions, 26 clinical trials have been conducted to evaluate the effects of co administering TMC125 with various classes of drugs in vivo.

The first group of trials were 5 mechanistic trials, mostly with earlier TMC125 formulations, to characterize the in vivo interaction potential of TMC125. These trials included a cocktail probe trial, and trials in which TMC125 was co-administered with high-dose ritonavir (RTV) or rtv, unboosted saquinavir (SQV), and efavirenz (EFV), and nevirapine (NVP).

The second group of trials were 21 drug-drug interaction trials in which TMC125 was co-administered with drugs metabolized by, or potentially affecting, Phase I reactions and/or glucuronidation. The drugs chosen were either other ARVs or non-ARVs that are frequently taken by HIV-1 infected subjects. Among the second group of drug-drug interaction trials, 1 trial was conducted with formulation B* at a dose level of 1600 mg b.i.d., 13 trials were conducted with the Phase II formulation F* at a dose level of 800 mg b.i.d. (11 trials) or 1600 mg b.i.d. (2 trials), and 7 trials were conducted with the Phase III formulation A* at a

＊：新薬承認情報提供時に置き換え

dose level of 100 mg (single dose or b.i.d., 3 trials) and/or 200 mg b.i.d. (5 trials). Two specific drug-drug interaction trials that had been conducted with 800 mg TMC125 b.i.d. administered as the Phase II formulation F* were repeated with 200 mg TMC125 b.i.d. administered as the Phase III formulation A* to assess potential differences in the magnitude and direction of drug-drug interactions between formulations. The 2 ARVs chosen to be repeated were DRV co-administered with rtv (TMC125-C138 and TMC125-C176) and tenofovir disoproxil fumarate (TDF) (TMC125-C139 and TMC125-C177). Most importantly, the effect of TMC125 on DRV(/rtv) or TDF was similar irrespective of whether formulation F* or A* was used. The effects of the co-administered drugs on TMC125 were also similar, irrespective of the TMC125 formulation administered.

Drug-drug interaction trials between TMC125 and digoxin (TMC125-C180), LPV/rtv (Meltrex formulation, TMC125-C182), elvitegravir/rtv (TMC125-C184), and maraviroc with and without co-administration of DRV/rtv (TMC125-C181) are ongoing or planned (Table 2).

Interactions with Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

The 2-way drug-drug interaction between TMC125 and didanosine (ddI) or TDF was assessed in healthy subjects. No clinically relevant changes occurred in the pharmacokinetic parameters (minimum plasma concentration [C_{min}], C_{max}, AUC) for TMC125 or either co-administered drug. ddI and TDF can each be co-administered with TMC125 without dose adjustment for either drug. N[t]RTIs are primarily excreted renally and because TMC125 has minimal renal elimination (a mean of 1.2% based on radioactivity), no clinically relevant interaction is expected to occur with abacavir, emtricitabine, lamivudine, stavudine, zalcitabine, or zidovudine.

Interactions with Protease Inhibitors

The 2-way drug-drug interaction between TMC125 and atazanavir (ATV), ATV/rtv, DRV/rtv, indinavir (IDV), lopinavir (LPV)/rtv, SQV/rtv, or tipranavir (TPV)/rtv was assessed in healthy subjects. The one-way interaction to determine the effect of TMC125 on fosamprenavir (fosAPV)/rtv or SQV/LPV/rtv in HIV-1 infected subjects was also assessed. TMC125 should not be co-administered with unboosted protease inhibitors (PIs) or TPV/rtv. The dose of fosAPV(/rtv) may need to be reduced, and ATV/rtv, DRV/rtv, LPV/rtv, and SQV/rtv can be co-administered with TMC125 without dose adjustment for either drug. The interaction between TMC125 and nelfinavir has not been evaluated. Since nelfinavir is metabolized by CYP2C19 and TMC125 is an inhibitor of CYP2C19, an interaction between these 2 agents is anticipated.

Interactions with Other Non-Nucleoside Reverse Transcriptase Inhibitors

The one-way interaction to determine the effect of EFV or NVP on TMC125 was assessed in healthy subjects. Both EFV and NVP decrease the exposure to TMC125. The interaction between TMC125 and delavirdine has not been evaluated. It is not recommended to combine TMC125 with other NNRTIs.[29]

Interactions with Fusion Inhibitors

The interaction between TMC125 and ENF has not been evaluated in a formal Phase I drug-drug interaction trial. Since ENF is not metabolized by CYP and has little to no effect on CYP1A2, 2D6, 2E1, 2C19, 3A4, or N-acetyltransferase[64], no clinically relevant interaction is expected to occur.

＊：新薬承認情報提供時に置き換え

The effect of ENF on TMC125 pharmacokinetics was assessed prospectively in DUET-1 and DUET-2 using population pharmacokinetic estimates. There was no relevant difference in TMC125 exposure in subjects with or without concomitant use of ENF.

Interactions with Integrase Strand Transfer Inhibitors

The 2-way interaction between TMC125 and raltegravir was assessed in 19 healthy subjects. No clinically relevant changes occurred in the pharmacokinetic parameters (plasma concentration at 12 hours [C_{12h}], C_{max}, AUC) for either drug (see Section 2.8.2.13). Raltegravir can be co-administered with TMC125 without dose adjustment for either drug.

Interactions with Drugs other than Antiretrovirals

CYP3A Substrates

The effect of TMC125 200 mg (tablet formulation A* [TMC125 in HPMC, spray-dried]) on ethinylestradiol 0.035 mg and norethindrone 1 mg was studied in healthy women (trial TMC125-C166, see Section 2.8.3.2). TMC125 increased the mean exposure (AUC_{24h}) of ethinylestradiol 1.22-fold, with no change in the mean exposure to norethindrone. Plasma concentrations of progesterone, luteinizing hormone (LH), and follicle stimulating hormone (FSH) were unchanged during the co-administration, compared to administration of the oral contraceptive (OC) alone. Based on the results of this trial, no dose adjustments are necessary for TMC125 or estrogen- and/or progesterone-based contraceptives when co-administered, and co-administration with TMC125 is unlikely to decrease the effectiveness of estrogen- and/or progesterone-based contraceptives.

Rifabutin is a substrate and inducer of CYP3A. Co-administration of TMC125 800 mg b.i.d. (tablet formulation F* [TMC125 in HPMC, granulo-layered]) with rifabutin 300 mg q.d., both at steady-state, in healthy subjects decreased the mean exposure (AUC_{24h}) to rifabutin by 17% and the mean exposure (AUC_{12h}) to TMC125 by 37% (trial TMC125-C156, see Section 2.8.3.3). No dose adjustments are necessary for either drug when co-administered.

When atorvastatin 40 mg q.d. was co-administered with TMC125 800 mg b.i.d. (tablet formulation F* [TMC125 in HPMC, granulo-layered]), both at steady-state, in healthy subjects, the mean exposure (AUC_{24h}) to atorvastatin was reduced by 37%, compared to administration of atorvastatin alone (trial TMC125-C164, see Section 2.8.3.1). This decrease in atorvastatin exposure was likely due to CYP3A induction because the mean exposure to the active metabolite of atorvastatin, 2-hydroxy-atorvastatin, was increased 1.27-fold. When administration of TMC125 and atorvastatin is desired, no initial dose adjustment of either drug is required and the dose of atorvastatin may need to be tailored based on the clinical response.

CYP3A and 2C Substrates

When single-dose sildenafil 50 mg was co-administered with TMC125 800 mg b.i.d. (tablet formulation F* [TMC125 in HPMC, granulo-layered]) in healthy subjects, the mean exposure (AUC_{last}) to sildenafil and its metabolite *N*-desmethyl-sildenafil was decreased by 57% and 41%, respectively (trial TMC125-C159, see Section 2.8.3.4). Phosphodiesterase type 5 inhibitors (including sildenafil, vardenafil, and tadalafil) may be co-administered with TMC125, but a dose adjustment may be necessary to obtain a clinical effect.

＊：新薬承認情報提供時に置き換え

CYP3A and P-gp Substrates

Clarithromycin is a P-gp and CYP3A substrate. In healthy subjects, TMC125 200 mg b.i.d. (tablet formulation A* [TMC125 in HPMC, spray-dried]) decreased the mean exposure (AUC_{12h}) to clarithromycin (500 mg b.i.d.) by 39% and induced formation of the active metabolite 14-hydroxy-clarithromycin (trial TMC125-C171, see Section 2.8.3.5). 14-hydroxy-clarithromycin has reduced activity against MAC and therefore the overall activity against this pathogen may be altered. An alternative antibacterial (e.g., azithromycin) is recommended for treatment of MAC when TMC125 is administered. The effect of clarithromycin on TMC125 was a 1.4-fold increase in TMC125 exposure, which was likely a result of clarithromycin inhibiting CYP2C19. The increase in exposure is not considered clinically relevant given the lack of a relationship between TMC125 exposure and safety (see Section 3.11.3.7).

CYP2D6 Substrates

When the antidepressant paroxetine at a dose of 20 mg q.d. and TMC125 800 mg b.i.d. (tablet formulation F* [TMC125 in HPMC, granulo-layered]) were co-administered, the mean exposure to both drugs was not affected, compared to their administration alone (trial TMC125-C165, see Section 2.8.3.6). Drugs that are primarily metabolized by CYP2D6, such as paroxetine, may therefore be co-administered with TMC125 without dose adjustment.

Drugs That Alter Intragastric pH

In healthy subjects, the mean exposure (AUC_{last}) to TMC125 at a single-dose of 100 mg (tablet formulation A* [TMC125 in HPMC, spray-dried]) was not affected when co-administered with ranitidine 150 mg b.i.d. given for 8 days, compared to administration of TMC125 alone (trial TMC125.C120, see Section 2.8.3.7). In the same trial, omeprazole 40 mg q.d. given for 8 days resulted in a 1.41-fold increase in the mean exposure to single-dose TMC125 100 mg. This increase was likely the result of a metabolic interaction than reduced gastric acidity because no such effect was seen with ranitidine. No adverse effects or laboratory abnormalities have been associated with higher exposure to TMC125, therefore no dose adjustments are necessary when TMC125 is combined with ranitidine or omeprazole.

Other Frequently Co-Administered Drugs

Methadone is metabolized by several CYP isoenzymes to varying degrees, including CYP3A4, CYP2B6, CYP2C19, CYP2C8, and CYP2D6. The effect of TMC125 100 mg b.i.d. (tablet formulation A* [TMC125 in HPMC, spray-dried]) given for 14 days was assessed in healthy subjects currently receiving stable methadone treatment (trial TMC125-C158, see Section 2.8.3.8). The addition of TMC125 had no clinically relevant effect on plasma concentrations of the active R (-) or inactive S (+) isomers of methadone. Furthermore, no clinically relevant withdrawal symptoms were observed and no dose adjustments were required for methadone during the trial. The concomitant administration of TMC125 and methadone was generally safe and well tolerated. Based on these results, no a priori dose adjustments of either TMC125 or methadone are required when both drugs are co-administered.

＊：新薬承認情報提供時に置き換え

1.10.3.3 RATIONALE FOR EXTRAPOLATING INTERACTION DATA OBTAINED USING TMC125 TABLET FORMULATION F* TO THE SELECTED TMC125 TABLET FORMULATION A*

A total of 20 drug-drug interaction trials for TMC125 have been conducted with the Phase II formulation F* , at dose levels of 800 mg b.i.d. (11 trials) or 1600 mg b.i.d. (2 trials), and with the Phase III formulation A* at dose levels of 100 mg b.i.d. (3 trials) and/or 200 mg b.i.d. (5 trials) (Table 1 and Appendix 2.7.2.5). Two of the trials with formulation A* involved repetition of earlier trials (with DRV/rtv and TDF) that had used formulation F* . These 2 trials are particularly relevant because the concomitant use of DRV/rtv 600/100 mg b.i.d. and TDF 300 mg q.d. with TMC125 was allowed in the Phase III trials DUET-1 and DUET-2. In addition, potential interactions with these agents would theoretically occur through different mechanisms, thereby increasing the robustness of this analysis. The observed pharmacokinetic interaction between DRV/rtv 600/100 mg b.i.d. and TMC125 was similar when TMC125 was given as 800 mg b.i.d. using formulation F* (trial TMC125-C139, see Section 2.8.2.5) and as 100 mg b.i.d. using formulation A* (trial TMC125-C176, see Section 2.8.2.6). Similarly, the observed pharmacokinetic interaction between TDF 300 mg q.d. and TMC125 was similar when TMC125 was given as 800 mg b.i.d. using formulation F* (trial TMC125-C138, see Section 2.8.2.2) and as 200 mg b.i.d. using formulation A* (trial TMC125-C177, see Section 2.8.2.3).

Ongoing and planned drug-drug interaction trials (Table 2) are being (will be) conducted using the recommended clinical dosing regimen for TMC125 of 200 mg b.i.d. administered as formulation A* .

1.11 PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS

Pharmacokinetic/pharmacodynamic relationships were evaluated for the relationship between pharmacokinetic parameters and efficacy, between inhibitory quotient (IQ) and virologic response, and, in the Phase IIb and III trials, between pharmacokinetic and safety parameters.

For the pharmacokinetic/pharmacodynamic analysis of the pooled data from the Phase III trials (DUET-1 and DUET-2), the virologic response parameters < 50 and < 400 HIV-1 RNA copies/mL were analyzed using the time to loss of virologic response (TLOVR) algorithm[21] and change in viral load from baseline was analyzed using the non-completer equals failure (NC = F) algorithm. In addition, analyses of the changes in baseline $\log_{10}$ viral loads by quartiles based on pharmacokinetic values were conducted.

1.11.1 Relationships Between Pharmacokinetics and Efficacy

1.11.1.1 PHASE II TRIALS

In proof-of-principle trials in ARV-naïve and ARV-experienced HIV-1 infected subjects, TMC125 was administered either as the 100-mg tablet formulation S* (TMC125 in HPMC, granulo-layered) at a dose of 100 or 400 mg b.i.d. (trial TMC125-C201), or as the 50-mg capsule formulation T* (TMC125 in PEG 4000) at a dose of 900 mg b.i.d. (trials TMC125-C208 and TMC125-C207). No relationship was observed between the pharmacokinetics of TMC125 and virologic response in any of these trials (see Section 3.11.1).

＊：新薬承認情報提供時に置き換え

In the Phase IIb trials, TMC125 was administered as the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered) at doses of 400, 800, or 1200 mg b.i.d.

In HIV-1 infected, NRTI-, PI-, and NNRTI-experienced subjects (trial TMC125-C203), in which subjects were treated with TMC125 at doses of 400, 800, or 1200 mg b.i.d., there was a statistically significant relationship between the change in $\log_{10}$ viral load from Baseline at Week 24 and Week 48 vs. AUC_{12h} and C_{0h}, which was mainly driven by subjects with low exposure to TMC125. However, the Baseline $\log_{10}$ viral load, the use of a PI in the underlying antiretroviral therapy (ART), and region were generally stronger predictors of response than the pharmacokinetics of TMC125 (see Section 2.6.2.1.5).

In HIV-1 infected subjects resistant to currently available NNRTIs and with at least 3 primary PI mutations (trial TMC125-C223), in which subjects were treated with TMC125 at doses of 400 or 800 mg b.i.d., graphic analysis revealed no obvious relationship between the pharmacokinetics of TMC125 and the change in $\log_{10}$ viral load from Baseline at Week 48, or time averaged difference (DAVG) at Week 48 (see Section 2.6.2.3.5). However, in analysis of covariance (ANCOVA) models the pharmacokinetic parameters of TMC125 were statistically significantly associated with change in viral load from Baseline to Week 24 and 48, and the use of ENF was the covariate with the strongest relationship to efficacy in these models.

In PI-naïve HIV-1 infected subjects with documented genotypic evidence of NNRTI resistance from previous NNRTI use (trial TMC125-C227), in which subjects were treated with TMC125 at a dose of 800 mg b.i.d., the mean reduction from Baseline in $\log_{10}$ viral load during the pre therapy switch treatment phase appeared to be higher in the 2 AUC_{12h} quartiles with the highest TMC125 exposure (AUC_{12h} > 4521 to 6227 and AUC_{12h} > 6227 ng.h/mL) (see Section 2.6.2.4.5.1). However, an ANCOVA model showed no statistically significant relationship between AUC_{12h} and the change from Baseline in $\log_{10}$ viral load at Week 12. Subjects in the lowest quartile for IQ_{C0h} and $IQ_{Css,av}$ values showed a lesser response than subjects with higher IQ_{C0h} values and $IQ_{Css,av}$ (see Section 2.6.2.4.5.2).

1.11.1.2 Phase III Trials (Pooled Data from DUET-1 and DUET-2)

In DUET-1 and DUET-2, ARV-experienced HIV-1 infected subjects were treated with TMC125 tablet formulation A* (TMC125 in HPMC, spray-dried) at a dose of 200 mg b.i.d.

1.11.1.2.1 Relationships Between Pharmacokinetic Parameters and Efficacy Parameters

Two analyses were conducted, an analysis using generalized additive models (GAM) and an ANCOVA/logistic regression (see Section 3.11.3).

Using the GAM approach, the effect of TMC125 on $\log_{10}$ viral load was analyzed as a binary variable (success/failure) and the effects of TMC125 exposure and various prognostic factors on $\log_{10}$ viral load were evaluated (see Section 3.11.3.5). Cluster of differentiation 4 (CD4) cell counts were also analyzed using GAM but as a continuous variable incorporating the change from Baseline. The advantage of the GAM approach is that prognostic factor terms in the logistic regression model could be entered as either categorical, linear, or non-linear terms.

In the GAM analysis, exposure to TMC125 was not a prognostic factor for achieving viral load < 50 HIV-1 ribonucleic acid (RNA) copies/mL, the primary endpoint of the Week 24 analysis. However, exposure to TMC125 was a prognostic factor for viral load < 400 HIV-1 RNA copies/mL, but other factors such as DRV fold change in EC50 (FC), TMC125 FC, baseline CD4

cell count, and PSS were more important. None of the TMC125 parameters showed a relationship to change from baseline in CD4 cell counts.

Using the other approach, a conventional logistic regression model was fitted to the data with the factors ENF use, trial (DUET-1 vs. DUET-2), baseline viral load, and AUC_{12h}. In this model, the AUC_{12h} was a significant predictor of response; baseline viral load and ENF use were also significant (see Section 3.11.3.1).

The change in log_{10} viral load for the placebo group at Week 24 was -1.7 log_{10} HIV-1 RNA copies/mL. In subjects with the lowest exposure quartile ($AUC_{12h} \leq 3091$ ng.h/mL, n = 134), the overall mean response was -2.3 log_{10} HIV-1 RNA copies/mL (see Section 3.11.3.2). Thus, TMC125 provided an additional clinically relevant decline of at least 0.6 log_{10} HIV-1 RNA copies/mL irrespective of the TMC125 exposure achieved. Of note, some subjects in the lower exposure quartile had lower adherence rates, thus adherence is a potential confounding factor in this analysis.

1.11.2 Relationships Between Pharmacokinetics and Safety

In the Phase IIb trials, no relevant associations were found between the pharmacokinetics of TMC125 and adverse events or laboratory safety parameters of interest (see Section 3.11.2).

Similarly, no apparent relationships were seen in the 2 Phase III trials DUET-1 and DUET-2 (3.11.3.7).

1.12 EFFECT OF TMC125 ON ECG IN HEALTHY SUBJECTS

One active- (moxifloxacin) and placebo-controlled Phase I trial (TMC125-C178, see Section 2.9.1) was conducted in healthy subjects to evaluate the effect of TMC125 at doses of 200 mg b.i.d. and 400 mg q.d. (tablet formulation A* (TMC125 in HPMC, spray-dried) on ECG parameters. At these clinically relevant doses, TMC125 did not prolong the QT interval and there was no indication for any correlation between plasma concentrations of TMC125 and the corresponding QT value.

1.13 RATIONALE FOR TMC125 DOSE SELECTION IN HIV-1 INFECTED SUBJECTS

The dose selection for the registrational Phase III efficacy and safety trials with TMC125 in HIV-1 infected subjects (DUET-1 and DUET-2) was based on the antiviral activity (change in log_{10} plasma viral load from Baseline at Week 24), safety (incidence and severity of adverse events and laboratory parameters), pharmacokinetics, and pharmacokinetic/pharmacodynamic assessments that were obtained from the primary analysis of the Phase IIb dose-escalating trial TMC125-C203 (see Section 2.6.2.1) and the Phase IIb dose-finding trial TMC125-C223 (see Section 2.6.2.3), both conducted in HIV-1 infected subjects with previous NNRTI experience and/or resistance. These earlier trials were conducted using TMC125 administered as tablet formulation F* (TMC125 in HPMC, granulo-layered), and therefore a second stage of the dose selection process was to investigate the correspondence of TMC125 dosing between formulation F* and the final, selected formulation A* (TMC125 in HPMC, spray-dried) to be used in the Phase III efficacy and safety trials and intended for commercialization.

＊：新薬承認情報提供時に置き換え

1.13.1 Rationale for Dose Selection Based Upon Phase IIb Trials Conducted with Formulation F*

The dose selected from the TMC125 Phase IIb program for trials with TMC125 in HIV-1 infected subjects was based on the antiviral activity (change in $\log_{10}$ plasma viral load from Baseline at Weeks 12 and 24), safety (incidence and severity of adverse events and laboratory parameters), pharmacokinetics, and on pharmacokinetic/pharmacodynamic assessments that were obtained from the primary analysis (Week 24 data) of the dose-escalating trial TMC125-C203 and an interim analysis (Week 12 data) of the dose-finding trial TMC125-C223.

The baseline characteristics of the population in trial TMC125-C203 showed that this trial included a population that, although advanced in years of HIV-1 infection and treatment, still had treatment options in terms of sensitivity to available ARVs. In Stage 1 of this trial, there was no difference in the mean change in $\log_{10}$ viral load from Baseline between the 3 treatment groups (placebo, and TMC125 400 and 800 mg b.i.d.) at Week 24 imputed. However, in the subgroup of subjects with more than 2 primary PI mutations and in the subgroup of subjects with no sensitive PIs in the underlying ART, an added benefit of TMC125 800 mg b.i.d. was observed compared to both TMC125 400 mg b.i.d. and placebo at Week 24 imputed (see Section 3.13.1.1.1). In Stage 2, both the 800 and 1200 mg b.i.d. groups demonstrated an added benefit of TMC125 in antiviral activity compared to the placebo group. TMC125 was generally safe and well tolerated in this trial (see Section 3.13.1.1.2).

The pharmacokinetic parameters of TMC125 in trial TMC125-C203 showed significant inter-subject variability (see Section 3.13.1.1.3). Exposure was generally higher with increasing doses of TMC125. However, in the overall analysis AUC_{12h} and C_{0h} increased less than dose proportionally between 800 and 1200 mg b.i.d. Overall, a statistically significant difference in TMC125 exposure was observed for the 400 and 800 mg b.i.d. groups. No statistically significant difference in exposure was observed for the 800 and 1200 mg b.i.d. dose groups overall. In addition, no statistically significant difference in exposure was observed for the 800 and 1200 mg b.i.d. groups in Stage 2. A trend towards lower exposures of TMC125 was observed in subjects using TFD and/or a PI in the underlying ART though this difference did not reach statistical significance. TMC125 AUC_{12h} and C_{0h} were significantly related with the decrease in $\log_{10}$ viral load at Week 24 in Stage 2, but the magnitude of this effect was small. No apparent relationship was observed between the pharmacokinetics of TMC125 and safety parameters.

The baseline characteristics of the population included in the interim analysis of trial TMC125-C223 as well as the number of sensitive drugs available and used in the treatment regimen showed that this trial included a population with advanced HIV-1 infection and with limited or no treatment options. The efficacy results of the interim analysis showed that both doses of TMC125 (400 and 800 mg b.i.d.) had antiviral benefit compared to the control group (see Section 3.13.1.2.1). At Week 12 imputed, the mean change in $\log_{10}$ viral load was -1.27, -1.36, and -0.34 copies/mL for the 400 and 800 mg b.i.d. groups and control, respectively. If only 1 sensitive ARV was used in the underlying therapy, then an added benefit of TMC125 800 mg b.i.d. compared to TMC125 400 mg b.i.d. was observed; favoring the 800 mg b.i.d. dose in this population. If more than 2 sensitive ARVs were used in the underlying therapy, indicating that the underlying therapy was more potent, then the added benefit of both TMC125 dose groups was observed compared to placebo without dose differentiation between TMC125 400 and

800 mg b.i.d. groups. TMC125 was generally safe and well tolerated in this trial (see Section 3.13.1.2.2).

A large inter-subject variability of both pharmacokinetic parameters was observed in the interim analysis of trial TMC125-C223 (see Section 3.13.1.2.3). The estimated pharmacokinetic parameters for TMC125 were dose proportional between the doses of 400 and 800 mg b.i.d. The exposure to TMC125 was lower in subjects with a PI in the ART than in subjects without a PI in the ART, and no trends could be identified for differences in the pharmacokinetics in males vs. females or on the basis of race.

Based on the accumulated data at the time, 800 mg b.i.d. (formulation F*) was the recommended dose selected from the Phase IIb trials. Subsequently, data from the final analysis of trial TMC125-C203 (Week 48 data) and data from the primary analysis (Week 24 data) of the dose-finding trial TMC125-C223, performed when all subjects had been treated for 24 weeks or discontinued earlier and from the final analysis at 48 weeks (when all subjects had been treated for 48 weeks or discontinued earlier) confirmed the dose selection of 800 mg b.i.d. (formulation F*).

1.13.2 Selection of Appropriate Dose with Formulation A*

Although tablet formulation F* (TMC125 in HPMC, granulo-layered) gave an improved bioavailability of TMC125 compared to many of the earlier formulation concepts tested, further testing of alternative formulation concepts continued while this formulation was being used in Phase II clinical trials, with the objective of obtaining a formulation with an increased bioavailability and/or drug load while maintaining a robust stability profile (refer to Module 2.7.1/Section 1.3). The result of this further testing was that tablet formulation A* (TMC125 in HPMC, spray-dried), which had a notably enhanced bioavailability compared to formulation F* , was selected for use in the Phase III trials.

A comparison of data from earlier trials in which TMC125 was administered as formulations T* and F* indicated that HIV-1 infected subjects have lower exposure levels of TMC125 than healthy subjects (see Section 3.7). Therefore, the applicability of the increase in relative oral bioavailability of formulation A* vs. formulation F* demonstrated in healthy subjects in trial TMC125-C170 (refer to Module 2.7.1/Section 2.1.3) was also investigated in the relevant target population of HIV-1 infected subjects.

In trial TMC125-C141 conducted in HIV-1 infected subjects (refer to Module 2.7.1/Section 2.1.4), the mean AUC_{last} and C_{max} of TMC125 after single-dose administration of 100 mg TMC125 as formulation A* were both 1.03-fold higher than the values obtained with 800 mg TMC125 as formulation F* . For 200 mg TMC125 as formulation A* the ratios were 1.11 and 1.27, respectively, compared to 1600 mg TMC125 as formulation F* . For 300 mg TMC125 as formulation A* these ratios were 2.13 and 2.27, respectively, compared to 2400 mg TMC125 as formulation F* . The increase in ratios for the higher doses of TMC125 was likely caused by the differences in dose proportionality between formulations A* and F* .

Because the results of trial TMC125-C141 indicated that administration of a single 800 mg dose of TMC125 with formulation F* (the dose selected on the basis of Phase IIb trials) and administration of a single 100 mg dose of TMC125 with formulation A* resulted in comparable exposures of TMC125 in HIV-1 infected subjects, trial TMC125-C228 (refer to

Module 2.7.1/Section 2.1.5) was conducted to investigate the comparability of TMC125 exposure with these 2 treatments when administered as multiple doses in HIV-1 infected subjects. The mean exposure to TMC125 after administration of 100 mg b.i.d. as formulation A* was lower than the exposure after administration of 800 mg b.i.d. as formulation F* , on Day 1 and on Day 8. The least squares (LS) means ratio of formulation A* to formulation F* for AUC_{12h} was 0.72 on Day 1 and 0.54 on Day 8. The mean exposure to TMC125 following administration of 200 mg b.i.d. as formulation A* was higher than the exposure with 800 mg b.i.d. as formulation F* , again on Day 1 and on Day 8. The LS means ratio of formulation A* to formulation F* for AUC_{12h} was 1.91 on Day 1 and 1.67 on Day 8.

Thus TMC125 administered as formulation A* in trial TMC125-C228 showed a more than dose-proportional increase in pharmacokinetic parameters with increasing dose (100 to 200 mg b.i.d.), which was more pronounced after multiple-dose administration than after single-dose administration.

An exploratory analysis indicated that the 200 mg b.i.d. dose of formulation A* did not appear to increase the absolute exposures for those subjects who achieved higher exposures with the 800 mg b.i.d. dose of formulation F* (Figure 60). In contrast, for subjects with lower exposures with the 800 mg b.i.d. dose of formulation F* , treatment with 200 mg b.i.d. of formulation A* substantially increased the absolute exposures. Thus, there was lower inter-subject variability with the 200 mg b.i.d. dose of formulation A* . Overall, because of the high inter-subject variability, the range of exposure to TMC125 with the 200 mg b.i.d. dose of formulation A* was comparable to the range of exposure with the 800 mg b.i.d. dose of formulation F* , with the latter dose previously having been shown to be efficacious in the Phase IIb dose-escalating trial TMC125-C203 and the dose-finding trial TMC125-C223 (see Section 1.13.1)

On this basis, a TMC125 dosage of 200 mg b.i.d. with formulation A* was selected for use in the registrational Phase III efficacy and safety trials (DUET-1 and DUET-2) and in future clinical trials because this dosage was expected to provide an exposure to TMC125 that was comparable to that provided by the 800 mg b.i.d. dosage with formulation F* .

Retrospective support for this dose selection was provided by the observation that the exposure (AUC_{12h}) to TMC125 was comparable when TMC125 was administered as formulation A* at a dose of 200 mg b.i.d. in the Phase III trials (DUET-1 and DUET-2) and as formulation F* at a dose of 800 mg b.i.d. in Phase IIb trials TMC125-C203, TMC125-C223, and TMC125-C227 (Figure 61).

Further confirmation was provided by a pharmacokinetic substudy of trial TMC125-C229 (see Section 2.6.2.5), in which HIV-1 infected subjects being treated with TMC125 tablet formulation F* at a dose of 800 mg b.i.d. were switched to treatment with TMC125 tablet formulation A* at a dose of 200 mg b.i.d. The range of exposures was comparable between both formulations, as shown in Figure 24 for individual AUC_{12h} values.

1.14 THERAPEUTIC DRUG MONITORING

Although HIV inhibitory concentrations can be identified for ARV drugs, there are persistent issues surrounding the use of drug blood concentrations to guide treatment. In general, the higher the exposure (e.g., C_{0h} or AUC), the better the inhibition of HIV. However, precise therapeutic concentration ranges have not been identified for any ARV drug. More importantly, drug

＊：新薬承認情報提供時に置き換え

concentrations alone are not the ultimate determinant of treatment outcome; other important factors include adherence, resistance profile, other sensitive drugs in the regimen, tolerability, safety, and treatment history.

Treatment with TMC125 and an underlying ART resulted in significantly greater response compared to the underlying ART alone. In the 2 Phase III trials (DUET-1 and DUET-2), a GAM incorporating TMC125 exposure amongst other prognostic factors demonstrated that exposure to TMC125 was not a prognostic factor for achieving viral load < 50 HIV-1 RNA copies/mL, the primary endpoint, in the pooled DUET-1 and DUET-2 trials. Baseline CD4 cell count, PSS, adherence, DRV FC, TMC125 FC, Baseline HIV-1 RNA, and use of ENF were significantly associated with efficacy.

ANCOVA revealed a difference of 0.5 $\log_{10}$ HIV-1 RNA copies/mL for the change from Baseline in $\log_{10}$ viral load at Week 24 between subjects with the lowest exposure quartile compared to those with the highest exposure quartile, suggesting a possible relationship between the pharmacokinetics of TMC125 and efficacy. However, the overall mean response in the lowest quartile was still greater than that of placebo. Of note, some subjects in the lower exposure quartile had lower adherence rates, thus adherence is a confounding factor in this analysis. Although a difference of 0.5 $\log_{10}$ HIV-1 RNA copies/mL is considered clinically relevant, achieving higher exposures of TMC125 may be challenging for several reasons.

First, an increase in dose requires an increase in the number of pills taken. A meta-analysis consisting of 53 trials, 90 independent treatment groups, and 14264 subjects, demonstrated that pill count was significantly associated with the proportion of subjects achieving plasma < 50 HIV-1 RNA copies/mL at Week 48 in univariate analysis. This observation was no longer significant in multivariate analysis when factors such as baseline HIV-1 RNA and CD4 cell count were taken into account.[5] These observations suggest an incremental increase in dose may result in reduced adherence, with a subsequent decrease in response rates.

Second, "white coat compliance" limits the reliability of TDM for assessing long-term drug exposure. Subjects are more likely to be adherent in the days just prior to a clinic visit.

Third, the average inter-occasion variability of TMC125 exposure from population pharmacokinetic analyses was 40.1%. This high intra-subject variability limits the utility of plasma concentration measurements for deciding dose adjustments.[41]

Therefore, the use of TDM for efficacy is not considered relevant for TMC125.

TDM is often used to monitor toxicity associated with elevated drug concentrations, e.g., gentamycin. For TMC125, there have been no exposure-related safety findings to date (see Section 3.11.3.7). Therefore, the use of TDM for monitoring safety is not considered relevant for TMC125.

Taken together, the lack of a clear relationship between TMC125 pharmacokinetics and efficacy or safety, together with the high inter-occasion variability in TMC125 pharmacokinetics and the evidence from prospective clinical trials that TDM is not beneficial in HIV disease, provide arguments that monitoring viral load, resistance to TMC125, and adherence together with optimizing the background regimen are more relevant to TMC125 and treatment of HIV disease in general than TDM.

2 SUMMARY OF RESULTS OF INDIVIDUAL TRIALS

2.1 HUMAN BIOMATERIAL TRIALS

An overview of the nonclinical, human biomaterial trials that provide supporting information on the clinical pharmacology of TMC125 is shown in Table 4.

Table 4: Overview of Human Biomaterial Trials

Nonclinical Trial	Objective	Human Biomaterial	TMC125 Concentration [a]	Location of Trial Report
TMC125-NC143	Protein binding	Plasma	10, 100, 1000, 5000 ng/mL (0.02, 0.23, 2.3, 11.5 µM)	Module 4.2.2.3 TMC125-NC143
TMC125-NC142	Metabolism of ^{14}C-TMC125	Hepatocytes, liver subcellular fractions	2175 ng/mL (5 µM)	Module 4.2.2.4 TMC125-NC142
TMC125-NC210	Kinetics of TMC125 metabolism	Liver microsomes	218, 435, 1305, 2175, 4350, 8700, 13050, 21750 ng/mL (0.5, 1, 3, 5, 10, 20, 30, 50 µM)	Module 4.2.2.4 TMC125-NC210
TMC125-NC205	In vivo metabolism of ^{14}C-TMC125	Urine, feces, plasma	Single oral dose of 800 mg ^{14}C-TMC125 (PEG 4000 formulation)	Module 4.2.2.4 TMC125-NC205
TMC125-NC128	Inhibition of human cytochrome P450 enzymes by TMC125	CYP probe substrates, selective towards human CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A	500, 1000, 5000, 21750 ng/mL (1.15, 2.3, 11.5, 50 µM)	Module 4.2.2.4 TMC125-NC128
TMC125-NC360	Inhibition of CYP2C8 mediated paclitaxel 6-α-hydroxylase activity by TMC125	Pooled liver microsomes	44, 174, 653, 2610, 10875, 43500, 108750 ng/mL (0.1, 0.4, 1.5, 6, 25, 100, 250 µM)	Module 4.2.2.4 TMC125-NC360
TMC125-NC164	Potential of TMC125 to induce CYP mRNA	Hepatocytes	435, 2175, 4350, 10875 ng/mL (1, 5, 10, 25 µM)	Module 4.2.2.4 TMC125-NC164
TMC125-NC238	Potential of TMC125 to induce CYP enzyme activities	Hepatocytes	435, 10875 ng/mL (1, 25 µM)	Module 4.2.2.4 TMC125-NC238
TMC125-NC118	Interaction of 13 anti-HIV compounds with the CYP-mediated metabolism of TMC125	Pooled liver microsomes	870, 2175, 4350, 8700, 13050, 17400, 21750 ng/mL (2, 5, 10, 20, 30, 40, 50 µM)	Module 4.2.2.6 TMC125-NC118

Table 4: Overview of Human Biomaterial Trials (Cont'd)

Nonclinical Trial	Objective	Human Biomaterial	TMC125 Concentration a	Location of Trial Report
TMC125-NC183	Transport characteristics and P-gp inhibition	Colon carcinoma-derived (Caco-2) cells	1305, 4350, 13050, 43500, 130500 ng/mL (3, 10, 30, 100, 300 µM)	Module 4.2.2.2 TMC125-NC183

[a] Concentrations have been calculated from concentrations quoted in the trial report assuming 1 ng/mL = 0.002 µM (2.297 mM) and 1 µM = 435 ng/mL. The molecular weight of TMC125 is 435.28.

2.1.1 Protein Binding

2.1.1.1 Trial TMC125-NC143: Plasma Protein Binding and Blood Distribution of TMC125 in Man

The plasma protein binding of TMC125 was studied at 5 different concentrations ranging from 10 to 5,000 ng/mL by equilibrium dialysis of plasma samples from healthy male adult subjects after fortification with ^{3}H-labelled TMC125. The distribution of TMC125 to various compartments of blood and the binding of TMC125 to purified human serum albumin and α1-acid glycoprotein were also investigated.

The human plasma protein binding of TMC125 was 99.9%, irrespective of the TMC125 concentration. TMC125 was extensively bound to human albumin (87.9% to 99.7% at concentrations of 0.1 to 6.0 g/dL) and α1-acid glycoprotein (69.2% to 99.0% at concentrations of 0.02 to 0.20 g/dL). At TMC125 concentrations of 100 and 1,000 ng/mL, the blood to plasma concentration ratio in man was approximately 0.7, the fraction of TMC125 distributed to the plasma water compartment was 0.0008, the fraction distributed to plasma proteins was 0.77, and the fraction distributed to blood cells was 0.23.

Further details on the results of this trial are available in Module 4.2.2.3/TMC125-NC143.

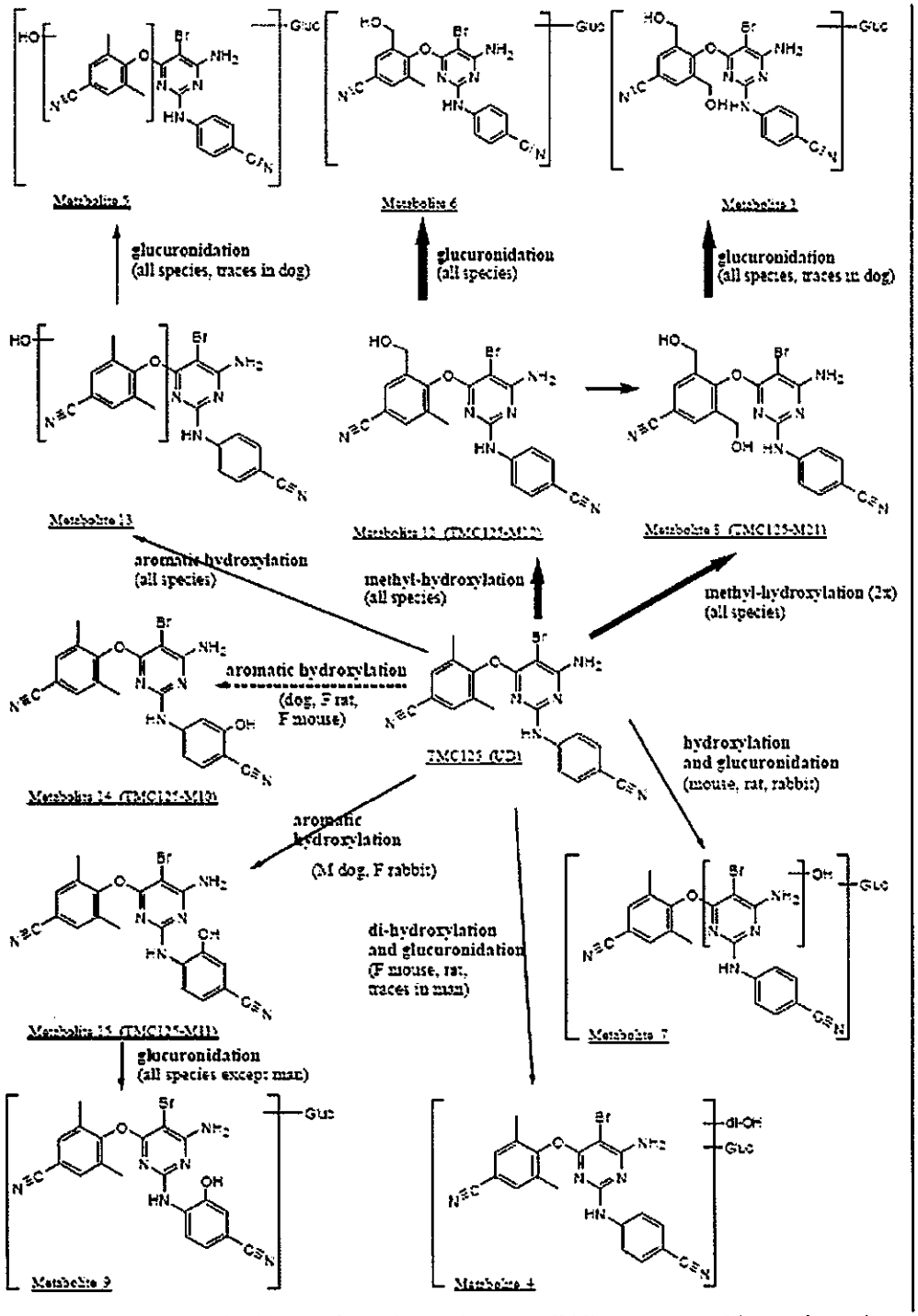
2.1.2 In Vitro Metabolism and Potential for Interactions

2.1.2.1 Trial TMC125-NC142: In-Vitro Metabolism of ^{14}C-TMC125 in Human Hepatocytes and Liver Subcellular Fractions

The in vitro metabolism of ^{14}C-TMC125 was studied in human and animal hepatocytes (suspensions and primary cultures) and liver subcellular fractions (microsomes and 12,000 x g supernatant fractions). TMC125 (5 µM, 2.18 ng/mL) was incubated in these matrices at 37°C for various time periods, and incubates were analyzed by radio-high-performance liquid chromatography (HPLC). Co-chromatography, enzyme hydrolysis, and liquid chromatography with tandem mass-spectrometry (LC-MS/MS) techniques were used for the identification of metabolites.

Only limited metabolism was observed in human hepatocytes, with a mean of 95.4% of the added TMC125 being recovered unchanged in the hepatocyte suspensions and 46.4% being recovered unchanged in primary cell cultures. In the liver subcellular fractions, 86.6% of the added TMC125 was recovered unchanged in the 12,000 x g supernatant and 87.1% was recovered unchanged in microsomes.

The major in vitro metabolic pathway of TMC125 was methylhydroxylation at one of the methyl groups of the dimethylbenzonitrile moiety in combination with glucuronide conjugation. Hydroxylation at both methyl groups of the dimethylbenzonitrile moiety of TMC125 also occurred, and a glucuronide conjugate of the latter dihydroxylated metabolite was relatively important. Hydroxylation at a site on the dimethylbenzonitrile moiety (apart from the methyl groups) occurred to a minor extent, and minor levels of a glucuronide conjugate of this hydroxylated metabolite were detected. A minor Phase 2 metabolite was identified as a glucuronide of di-hydroxylated TMC125. All TMC125 metabolites that were identified in human test systems in this trial were also found in at least one preclinical species, as summarized in Figure 1.



Bold lines represent major biotransformation pathways, solid lines represent biotransformation pathways of intermediate importance, and dotted lines represent biotransformation pathways of minor importance.
Source: Module 4.2.2.4/TMC125-NC142/Figure 6-9

Figure 1: In Vitro Biotransformation Pathways for TMC125 in Mice, Rats, Dogs, Rabbits, and Humans (Trial TMC125-NC142)

Further details on the results of this trial are available in Module 4.2.2.4/TMC125-NC142.

2.1.2.2 TRIAL TMC125-NC210: IN VITRO KINETICS OF TMC125 METABOLISM IN HUMAN LIVER MICROSOMES, AND IDENTIFICATION OF MICROSOMAL CYTOCHROME P450 ISOENZYMES MEDIATING TMC125 METABOLISM (REACTION PHENOTYPING)

The in vitro metabolism of ^{14}C-TMC125 was studied in human liver microsomes (HLMs) in the presence of a nicotinamide adenine dinucleotide phosphate (NADPH) generating system. Two metabolites were formed, resulting from mono-hydroxylation at one of the methyl groups of the dimethylbenzonitrile moiety (Metabolite 12), and from aromatic hydroxylation at the dimethylbenzonitrile moiety (Metabolite 13). After establishing appropriate incubation conditions (protein concentration of 0.25 mg/mL, incubation time of 15 minutes) for a pooled batch of HLMs, incubations were conducted at varying TMC125 concentrations (0.5 to 50 µM [218 to 21750 ng/mL]). Apparent Michaelis-Menten constant ($K_{m,app}$) and maximum velocity (V_{max}) values for the TMC125 overall metabolism in HLMs were 12.4 µM (5394 ng/mL) and 361 pmol.min/mg (157 pg.min/mg), respectively.

CYP reaction phenotyping of TMC125 metabolism was performed by different approaches (effect of CYP diagnostic inhibitors on TMC125 metabolism, metabolism in expressed CYP systems, *E. coli* systems and recombinant human microsomes [Supersomes®], correlation analysis of metabolism rate in a panel of 10 batches of characterized HLMs, and effect of CYP inhibitory antibodies on TMC125 metabolism). TMC125 overall metabolism and formation of its metabolites in HLMs was markedly inhibited by CYP3A diagnostic inhibitors ketoconazole, troleandomycin, clarithromycin, and RTV. The results with expressed CYP isoforms in *E. coli* systems and recombinant human microsomes indicated that CYP3A isoenzymes are involved in the formation of Metabolite 12 and Metabolite 13. In addition, the incubations with expression systems revealed that CYP2C isoforms show catalytic activity towards TMC125 metabolism, although some contradiction was found regarding CYP2C19 involvement between both CYP expressed systems. In the correlation experiments with different batches of characterized HLMs, metabolism of TMC125 correlated well with CYP3A isoform specific activities, in particular Metabolite 13 formation.

In conclusion, the different phenotyping approaches revealed that overall TMC125 metabolism, as well as formation of its Metabolite 12 and Metabolite 13, was mainly catalyzed by CYP3A enzymes. CYP3A4 and 3A5 proved to be involved, as well as the fetal isoform CYP3A7. Involvement of CYP2C isoforms in TMC125 metabolism was also demonstrated, although the different approaches did not always give consistent results with respect to formation of the individual metabolites. Taking into account the relative abundance of the different CYP isoforms, the CYP3A enzymes play the major role in the biotransformation of TMC125 in vitro.

Further details on the results of this trial are available in Module 4.2.2.4/TMC125-NC210.

2.1.2.3 TRIAL TMC125-NC205: MASS BALANCE OF UNCHANGED TMC125 AND ITS METABOLITES IN HUMAN URINE, FECES, AND PLASMA

The in vivo metabolism of ^{14}C-TMC125 was studied in feces, urine, and plasma collected from healthy male subjects after a single oral dose of 800 mg ^{14}C-TMC125 (PEG-4000 formulation) in trial TMC125-C130 (see Section 2.2.1). Feces extracts, pooled and concentrated urine of individual subjects, and pooled plasma samples were analyzed by radio-HPLC. Co-

chromatography of authentic substances, enzyme hydrolysis, and LC-MS/MS techniques were used for the identification of metabolites.

By far the major part of orally administered TMC125 was excreted unchanged in the feces (81.2% to 86.4 % of the dose). The most important Phase 1 metabolic pathway of TMC125 in humans was hydroxylation of the methyl carbons of the dimethylbenzonitrile moiety. Both the mono- and di-methyl hydroxylated metabolites (Metabolite 12 and Metabolite 8, respectively) and their glucuronides (Metabolite 6 and Metabolite 1) were formed. Overall, methyl hydroxylation accounted for 3.8% to 9.5% of the TMC125 dose administered. Aromatic hydroxylation at the dimethylbenzonitrile moiety (Metabolite 13) was only a minor metabolic pathway. In plasma, TMC125 represented the major fraction of the absorbed radioactivity at the 3 time points studied (2, 4, and 8 hours after TMC125 administration). Metabolite 1, Metabolite 8, and Metabolite 12 were detected in plasma, of which Metabolite 8 accounted for one-third to half of the TMC125 concentration.

Further details on the results of this trial are available in Module 4.2.2.4/TMC125-NC205.

2.1.2.4 TRIAL TMC125-NC128: IN VITRO INHIBITION OF HUMAN CYTOCHROME P450 ENZYMES BY TMC125

Incubations were performed with CYP probe substrates, selective towards human CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A, in the absence and presence of TMC125. In preliminary experiments the extent of inhibition was estimated with TMC125 concentrations of 1.15, 2.3, 11.5 and 50 µM (500, 1000, 5000, 21750 ng/mL). If inhibition was found, one concentration of TMC125 was selected for each enzyme to establish the K_i values. For this purpose, incubations were performed with 7 concentrations of the various CYP probe substrates in the absence and presence of TMC125. The goodness-of-fit criterion was used to assess whether the inhibition was competitive or non-competitive. If this assessment was inconclusive, the type of inhibition was investigated further using a Hanes-Woolf plot.

In the preliminary experiments, a concentration-dependent inhibition was observed for CYP1A2, 2B6, 2C9, 2C19, 2D6, and 3A activities. CYP2A6 was only slightly inhibited at the highest TMC125 concentration, while no inhibition of CYP2E1 could be detected. As less than 20% inhibition was found for CYP2A6 at the highest TMC125 concentration, inhibition of CYP2A6 activity was not investigated further.

In the final experiments, CYP2C9 was most potently inhibited by TMC125 (Table 5). The K_i values for the other CYP isoenzymes were at least 10-fold higher than for CYP2C9, indicating a lower affinity. As the K_i value for the inhibition of CYP2C9 was relatively low (< 1 µM [< 435 ng/mL]), the inhibition of this isoenzyme was considered to have a potential clinical relevance.

Table 5: Inhibition of Cytochrome P450 Isoenzymes by TMC125 (Trial TMC125-NC128)

Cytochrome P450 Isoenzyme	Selected TMC125 Concentration		Type of Inhibition	Mean ± SD Inhibition Constant K_i	
	(μM)	(ng/mL)		(μM)	(ng/mL)
CYP1A2	11.5	5000	Competitive	7.0 ± 1.1	3045 ± 479
CYP2B6	50	21750	Non-competitive	83 ± 13	36105 ± 5655
CYP2C9	1.15	500	Competitive	0.58 ± 0.09	252 ± 39
CYP2C19	11.5	5000	Non-competitive	22 ± 4	9570 ± 1740
CYP2D6	50	21750	Competitive	15 ± 1	6525 ± 435
CYP3A	11.5	5000	Competitive	6.7 ± 1.1	2915 ± 479

Source: Module 4.2.2.4/TMC125-NC128/Section 4 (Table 9)

Further details on the results of this trial are available in Module 4.2.2.4/TMC125-NC128.

2.1.2.5 Trial TMC125-NC360: In Vitro Inhibition of CYP2C8-mediated Paclitaxel 6-Alpha-Hydroxylase Activity by TMC125

The inhibition of CYP2C8-mediated paclitaxel 6-α-hydroxylation by TMC125 was investigated in a pooled batch of HLMs. The potential for inhibition of CYP2C8 by TMC125 was determined at different concentrations of paclitaxel (5 to 80 μM) and different concentrations of TMC125 (0.1 to 250 μM [44 to 108750 ng/mL]). In addition, inhibition experiments were performed with the CYP2C8 selective inhibitor montelukast in order to assess the response of the paclitaxel 6-α-hydroxylation assay.

The substrate saturation of the paclitaxel 6-α-hydroxylation rate fitted accurately to a rectangular hyperbola, indicating simple Michaelis-Menten kinetics. The $K_{m,app}$ and V_{max} for paclitaxel 6-α-hydroxylation was 25.5 ± 1.1 μM and 0.683 ± 0.013 μmol/min/mg, respectively. The formation of 6-α-hydroxypaclitaxel was inhibited by TMC125 in a concentration-dependent way. Analysis of the inhibition data with different inhibition models was performed to evaluate the type of inhibition. The corrected Akaike Information Criterion (AIC_c) was lowest for the noncompetitive model, indicating that the curve-fitting was better for the noncompetitive inhibition model than for the other types (competitive, uncompetitive, mixed) of inhibition. The apparent K_i for the inhibition of the CYP2C8 mediated paclitaxel 6-α-hydroxylation by TMC125, calculated from the noncompetitive inhibition model, was 19.6 ± 2.0 μM. The CYP2C8 selective inhibitor montelukast proved to be strongly inhibitory in the paclitaxel 6-α-hydroxylation assay, with an IC50 value of 0.68 ± 0.14 μM.

Further details on the results of this trial are available in Module 4.2.2.4/TMC125-NC360.

2.1.2.6 Trial TMC125-NC164: In Vitro Potential of TMC125 to Induce CYP mRNA in Cryopreserved Human Hepatocytes

The potential of TMC125 to induce CYP isoenzymes was determined in primary hepatocyte cultures established on collagen-coated 24-well plates from cryopreserved human hepatocytes that retained acceptable attachment characteristics. The hepatocytes were treated for 2 consecutive days either with vehicle, with various concentrations of TMC125, or with positive control compounds omeprazole, rifampin, phenobarbital, or EFV. Induction of CYP isoenzymes was assessed at the end of the 48 hour treatment period by measurement of the mRNA expression with TaqMan® quantitative reverse transcriptase polymerase chain reaction (RT-

PCR). In addition, possible cytotoxicity due to treatment of the cells was determined by measuring intracellular adenosine triphosphate (ATP) content. Treatment of the hepatocytes with increasing concentrations of TMC125 resulted in a decrease in mean intracellular ATP concentrations, resulting in an approximately 50% decrease at 10 and 25 μM (4350 and 10875 ng/mL) TMC125. In addition, incubation of the cells with 50 μM rifampin or 5 μM EFV also resulted in an approximately 20% decrease in the mean intracellular ATP content, as compared to the control cells.

Cells from the different donors responded well to treatment with positive control compounds. Treatment of the cells with different concentrations of TMC125 did not result in the induction of CYP1A2 mRNA expression. However, treatment of the cells with TMC125 biphasically influenced the mRNA expression of CYP2B6, CYP2C-family, and CYP3A4. At 5 μM (2175 ng/mL) TMC125, the maximal mean induction was 11.5-fold for CYP2B6 mRNA, 7.1-fold for CYP2C8 mRNA, 3.2-fold for CYP2C9 mRNA, 2.8-fold for CYP2C18 mRNA, 4.1-fold for CYP2C19 mRNA, and 6.6-fold for CYP3A4 mRNA. The rank order of induction potential of TMC125 in vitro and the positive controls for these CYPs was TMC125 > rifampin > EFV ≅ phenobarbital.

Further details on the results of this trial are available in Module 4.2.2.4/TMC125-NC164.

2.1.2.7 Trial TMC125-NC238: In Vitro Potential of TMC125 to Induce Cytochrome P450 Isoenzyme Activities in Human Hepatocytes

The potential of TMC125 to induce CYP isoenzyme activities was determined in primary human hepatocyte cultures established on collagen-coated 6-well plates from cryopreserved human hepatocytes that retained acceptable attachment characteristics. After establishing hepatocyte cultures, cells were treated for 3 consecutive days either with the vehicle DMSO, with various concentrations of TMC125 (1.0 and 25 μM, 435 and 10875 ng/mL), or with prototypical CYP inducers, i.e., omeprazole for CYP1A2 (25 μM) and rifampin for CYP2B6, 2C19, and 3A4 (50 μM). Induction of CYP activities (CYP1A2, 2B6, 2C19, and 3A4) was assessed at the end of a 72-hour treatment period, using corresponding probe substrates (7-ethoxyresorufin for CYP1A2, S-mephenytoin for CYP2B6 and CYP2C19, and testosterone for CYP3A4). Spectrofluorimetry and LC-MS/MS assays were used to measure the products (resorufin, *N*-desmethylmephenytoin, 4-hydroxymephenytoin, and 6β-hydroxytestosterone) of the probe substrates to determine the CYP activity of the hepatocytes. Cytotoxicity of TMC125 was evaluated in a previous trial (TMC125-NC164, see Section 2.1.2.6) using the same batches of human hepatocytes, and was therefore not evaluated in the current trial. According to the earlier trial, the TMC125 concentrations used in the current trial were not cytotoxic.

All batches responded well to the treatment with the prototypical inducers and the assays were able to detect CYP induction. CYP1A2 and 2B6 activities of TMC125-treated cells were comparable to those of vehicle (DMSO) control cells, indicating that TMC125 was not an inducer of CYP1A2 or 2B6 in human hepatocytes. CYP2C19 activity of TMC125-treated hepatocytes was lower than the activity in DMSO control cells. These results concurred with the finding that TMC125 is not able to induce CYP1A2 mRNA, but did not concur with the observed inducing effect of TMC125 on CYP2B6 and 2C19 mRNA (trial TMC125-NC164, see Section 2.1.2.6). Treatment of the cells with TMC125 resulted in an increase in CYP3A4 activity, with maximal activity observed at 1.0 μM TMC125 (4.8- to 7.1-fold induction

compared to DMSO treatment) and clearly lower induction (1.7- to 3.0-fold) at 25 μM (10875 ng/mL) TMC125.

Incubations of hepatocytes with ^{14}C-TMC125 revealed that the compound is highly bound to the cells. Upon treatment of hepatocytes with rifampin and subsequent incubation with TMC125, CYP2C19 and 3A4 activities were markedly lower than those of cells treated only with rifampin. These findings, together with the observation of TMC125-hepatocyte association, suggest that induction of CYP2C19 and 3A4 activities is likely masked due to residual TMC125 in the hepatocytes. Overall, the results show that TMC125 has no inducing effect on CYP1A2 or 2B6 activities in human hepatocytes, but the compound appears to be an inducer of CYP3A4. The in vitro enzyme activity data suggest an unlikely potential for CYP2C19 induction.

Further details on the results of this trial are available in Module 4.2.2.4/TMC125-NC238.

2.1.2.8 Trial TMC125-NC118: In Vitro Interaction of 13 anti-HIV Compounds with Cytochrome P450-Mediated Metabolism of TMC125 in Human Liver Microsomes

The interaction of 13 ARV compounds with the CYP-mediated metabolism of TMC125 was investigated by incubating pooled HLMs and TMC125 in the absence (controls) and presence of each ARV, and determining the K_i values of the ARV compounds towards the metabolism of TMC125.

TMC125 metabolism was determined by measuring decreases in the parent compound by LC-MS analysis. The K_m and V_{max} values for the CYP-mediated metabolism of TMC125 were 34 μM (14790 ng/mL) and 532 pmol.min/mg (231 pg.min/mg) microsomal protein, respectively.

RTV, IDV, SQV, nelfinavir, amprenavir (APV), delavirdine, EFV, and abacavir were inhibitors of TMC125 metabolism under the conditions used. K_i values for these compounds were 0.2 to 0.3 μM for RTV, 1.4 to 3.1 μM for IDV, 6.4 to 11 μM for SQV, 2.7 to 6.0 for nelfinavir, 1.4 to 2.8 for APV, 1.5 to 3.2 μM for delavirdine, 21 to 40 μM for EFV, and 64 to 121 μM for abacavir. The type of inhibition could not be determined.

At concentrations equal to the average plasma concentrations in vivo, it was predicted that the CYP-mediated metabolism of TMC125 would be only slightly inhibited (< 26%) by SQV, EFV, and abacavir, 48% to 72% inhibited by IDV, nelfinavir, and APV, and almost completely inhibited by RTV and delavirdine. At concentrations higher than the average plasma concentrations, the extent of inhibition would be higher.

If it is assumed that RTV, IDV, SQV, nelfinavir, APV, delavirdine, EFV, and abacavir are CYP substrates, that these compounds are competitive inhibitors of TMC125 metabolism and vice versa, that the K_m value for TMC125 metabolism is also the K_i value, and that the K_i values obtained are equal to the K_m values for the CYP-mediated metabolism of these compounds, then it can be predicted that TMC125 would not inhibit the CYP metabolism of these compounds at clinically relevant plasma concentrations in vivo.

Further details on the results of this trial are available in Module 4.2.2.6/TMC125-NC118.

2.1.3 In Vitro Transport Characteristics

2.1.3.1 Trial TMC125-NC183: In Vitro Transport Characteristics of TMC125 and the Potential for Inhibition of P-Glycoprotein Activity by TMC125

Human colon carcinoma-derived (Caco-2) cells were used to investigate the bi-directional transepithelial transport characteristics of ^{14}C-TMC125. In addition, possible inhibition of human P-gp activity by TMC125 was also studied.

Comparison of the transepithelial permeation rates of TMC125 with those obtained for the reference compounds alniditan, levocabastine, and theophylline indicated that TMC125 can be classified as a compound with low to intermediate permeability. Transepithelial transport rates of TMC125 across Caco-2 monolayers were unaffected by initial TMC125 concentrations between 3 and 100 µM (1305 and 43 500 ng/mL), whereas an apparent decrease in permeability at 300 µM (130 500 ng/mL) was attributable to gradual precipitation of TMC125 in the donor compartments. TMC125 permeation across Caco-2 monolayers was polarized at the early time points (15 minutes) with a preference for the secretory transport direction over the absorptive transport, which appeared to be related to an initial delay in absorptive transport. However, transport polarity disappeared at later time points and co-incubation with verapamil did not change initial or steady-state permeation rates of TMC125. These results indicate that P-gp (or another transport mechanism) does not play a role in TMC125 transepithelial permeation. Hence, overall, TMC125 permeation is thought to occur predominantly via a passive transcellular diffusion mechanism. Further, bi-directional transport experiments with the P-gp substrate ^{3}H-paclitaxel demonstrated that TMC125 has P-gp inhibitory properties, with an apparent IC50 value of 24.2 µM (10 500 ng/mL).

It is concluded that TMC125 will most likely exhibit sufficient membrane permeability to obtain adequate intestinal absorption, provided solubility and dissolution rate are not limiting. Inhibition of transepithelial permeation of P-gp substrates by TMC125 cannot be excluded, but for most drugs a possible effect is unlikely to be clinically relevant at the intestinal absorption level.

Further details on the results of this trial are available in Module 4.2.2.2/TMC125-NC183.

2.2 MASS-BALANCE OF TMC125 IN HEALTHY SUBJECTS

2.2.1 Trial TMC125-C130: Single-Dose, Mass-Balance Trial with ^{14}C-TMC125 Administered as Capsule Formulation T* (TMC125 in PEG 4000) in Healthy Subjects

2.2.1.1 Trial Design

This was an open-label, single-dose, mass-balance trial in 6 healthy male subjects. ^{14}C-labelled TMC125 was administered at a dose of 800 mg using 50-mg capsules based on formulation T* (TMC125 in PEG 4000) within 10 minutes after completion of a standardized breakfast.

Plasma, urine, and feces samples were collected for up to at least 168 hours after dosing. Unchanged TMC125 was determined in plasma, urine and feces. Metabolic profiles were determined in selected plasma, urine and feces samples, and the structures of major metabolites were characterized whenever possible. The total radioactivity was determined in blood, plasma, urine and feces, and the mass-balance was calculated.

＊：新薬承認情報提供時に置き換え

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.1/TMC125-C130).

2.2.1.2 PHARMACOKINETICS OF TMC125 AND TOTAL ^{14}C-RADIOACTIVITY

Radioactivity in plasma, representing plasma concentrations of total ^{14}C-radioactivity, TMC125, and metabolites, was only quantifiable at a limited number of time points. For time points at which the total ^{14}C radioactivity and the TMC125 concentration in plasma were both quantifiable, the TMC125 concentration was approximately half of the corresponding total ^{14}C-radioactivity (Table 6). The other half of the radioactivity can be attributed to metabolites of TMC125. The median time to reach the maximum plasma concentration (t_{max}) was identical for total ^{14}C-radioactivity and the TMC125 concentration.

Table 6: Pharmacokinetics of TMC125 and Total ^{14}C-Radioactivity in Plasma after Single-Dose Administration of 800 mg ^{14}C-Labelled TMC125 in Healthy Subjects (Trial TMC125-C130)

Parameter	Mean ± SD; t_{max}: Median (Range)	
	TMC125 800 mg	Total ^{14}C-Radioactivity
N	6	6
t_{max}, h	3.5 (2.0 - 10.0)	3.5 (2.0 - 10.0)
C_{max}, ng/mL	164 ± 50.3	319 ± 88.2
AUC_{last}, ng.h/mL	2350 ± 935	NA
AUC_{∞}, ng.h/mL	2515 ± 1001	NA
$t_{1/2,term}$, h	41.1 ± 19.6	NA

N = maximum number of subjects with data; NA = not assessable.
Source: Module 5.3.3.1/TMC125-C130/Section 4.2.5

2.2.1.3 BLOOD CONCENTRATION-TIME PROFILES OF TOTAL ^{14}C-RADIOACTIVITY

The whole blood concentrations of total ^{14}C-radioactivity were below the lower limit of quantification (LLOQ) of [redacted] ng.eq./mL at each time point for each subject (Module 5.3.3.1/TMC125-C130/Section 4.2.8). Therefore, no blood to plasma ratio could be calculated.

2.2.1.4 MASS-BALANCE OF TMC125, AND METABOLITE PROFILING AND IDENTIFICATION

At 168 hours after administration of the single oral dose of TMC125, a mean of 94.9% of the dose was recovered, based upon radioactivity (Module 5.3.3.1/TMC125-C130/Section 4.2.9.1). By far the major part of the radioactivity was recovered in feces (93.7%). The mean recovery of radioactivity in urine was 1.2% of the administered dose. Most of the radioactivity was excreted in the first 24 and 48 hours in urine and feces samples, respectively.

Unchanged TMC125 accounted for the majority of the radioactivity in feces (81.2% to 86.4% of the administered dose) (Module 5.3.3.1/TMC125-C130/Section 4.2.9.2). No unchanged TMC125 was detected in urine.

Details of the metabolic profiles in urine, feces, and plasma are available in Section 2.1.2.3.

2.2.1.5 CONCLUSIONS

Most of the radioactivity derived from the administered ^{14}C-TMC125 was recovered in feces (93.7%). The mean recovery of the radioactivity in urine was 1.2% of the administered dose.

Unchanged TMC125 accounted for the majority of the radioactivity in the feces (81.2% to 86.4% of the administered dose). No unchanged TMC125 was detected in the urine.

2.3 SINGLE-DOSE PHARMACOKINETICS OF TMC125 IN HEALTHY SUBJECTS

A single-dose escalation trial (TMC125-C101) was conducted in healthy subjects with the 50-mg PEG 4000-based oral capsule (Form T*) that was used in the early Phase I and Phase IIa trials (summarized in Section 2.3.1).

Single-dose pharmacokinetic data for the 200-mg oral tablet formulation manufactured using granulo-layering technology (Form F*) that was used in the later Phase I and IIb trials were obtained on Day 1 in the context of the multiple-dose ranging trials TMC125-C143, in which TMC125 was administered at doses of 200, 400, and 800 mg b.i.d. (summarized in Section 2.5.3), and TMC125-C153, in which TMC125 was administered at doses of 400, 800, and 1600 mg q.d. (summarized in Section 2.5.4).

Single-dose pharmacokinetic data for the 100-mg oral tablet formulation manufactured using spray-drying technology (Form A*) that was used in recent Phase I trials and in the Phase III trials, and is intended for commercialization, was obtained in trial TMC125-C170, in which TMC125 was administered at a single dose of 400 mg (summarized in Module 2.7.1/Section 2.1.3), and on Day 1 in the context of the multiple-dose trial TMC125-C168, in which the administration of TMC125 at doses of 100 mg b.i.d. and 200 mg q.d. was compared (see Section 2.5.5).

2.3.1 Trial TMC125-C101: Single-Dose Escalation of TMC125 Administered as Capsule Formulation T* (TMC125 in PEG 4000) in Healthy Subjects

2.3.1.1 TRIAL DESIGN

This was a double-blind, randomized, placebo-controlled Phase I trial in healthy subjects to investigate the pharmacokinetics of escalating single oral doses of TMC125 administered as the 50-mg capsule formulation T* (TMC125 in PEG 4000). The subjects were treated in 2 alternating panels of 9 subjects each with consecutively escalating single doses of TMC125 (or placebo) in 3 sessions as follows:

- Panel A: 50, 200, and 600 mg;
- Panel B: 100, 400, and 900 mg.

In case the maximum tolerated dose was not reached, an additional cohort of 9 subjects (Panel C) was planned to receive 1200, 1500, and 1800 mg of TMC125 (or placebo). However, due to insufficient drug substance, subjects in Panel C only received the 1200 mg dose.

For each session in each panel, 6 subjects received TMC125 and 3 subjects received placebo, with placebo being given to different subjects in each session. The washout period between treatments was at least 14 days.

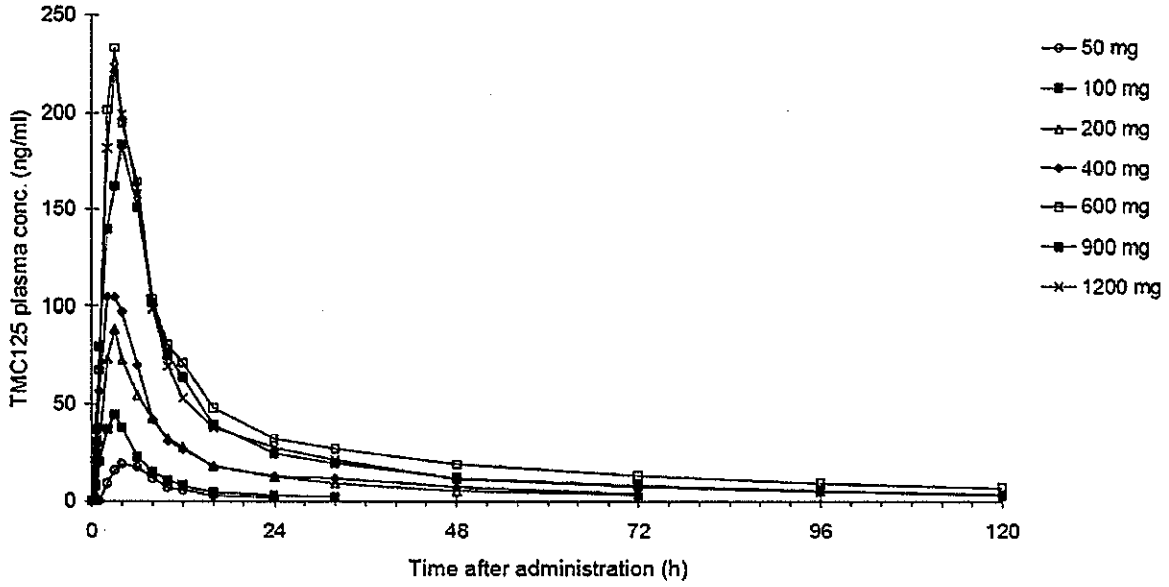
TMC125 was taken under fed conditions after completion of a standardized breakfast.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.1/TMC125-C101).

＊：新薬承認情報提供時に置き換え

2.3.1.2 PHARMACOKINETICS OF TMC125

For all doses, the plasma concentration-time profiles were characterized by a steep absorption phase, fast decay of the curve in the distribution phase, and a long elimination phase (Figure 2).



N = 6 in each treatment group.
Source: Module 5.3.3.1/TMC125-C101/Section 8.A/Display 6

Figure 2: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of Capsule Formulation T* (TMC125 in PEG 4000) at Single Doses of 50 to 1200 mg in Healthy Subjects (Trial TMC125-C101)

After administration of single oral doses of 50 to 1200 mg, the rate of absorption was not influenced by the dose level; the median t_{max} was 3 to 4 hours, and individual values ranged from 1 to 6 hours (Table 7). TMC125 single dose pharmacokinetics showed a moderate to high variability; coefficients of variation (CVs) for the different dose levels ranged from 28% to 68% for C_{max} and from 33% to 97% for AUC_{last} (Module 5.3.3.1/TMC125-C101/Section 4.C.5). The terminal elimination half-life could not be assessed at the 50 and 100 mg dose levels. At the higher dose levels, the mean terminal elimination half-life ranged from approximately 30 to 40 hours, with no clear dose relationship.

＊：新薬承認情報提供時に置き換え

Table 7: Pharmacokinetics of TMC125 after Administration of Capsule Formulation T* (TMC125 in PEG 4000) at Single Doses of 50 to 1200 mg in Healthy Subjects (Trial TMC125-C101)

Parameter	Mean ± SD; t_{max}: Median (Range)			
	50 mg	100 mg	200 mg	400 mg
N	6	6	6	6
t_{max}, h	4 (3 - 6)	3 (2 - 4)	3 (2 - 6)	3 (1 - 4)
C_{max}, ng/mL	19.9 ± 12.1	49.7 ± 16.1	97.9 ± 66.4	121 ± 40.8
$AUC_{0\text{-}24h}$, ng.h/mL	161 ± 124	308 ± 113	789 ± 606	931 ± 241
AUC_{last}, ng.h/mL	180 ± 156	323 ± 118	1180 ± 1130	1360 ± 461
$t_{1/2,term}$	NA	NA	41.1	30.2 ± 11.6
	600 mg	900 mg	1200 mg	
N	6	6	6	
t_{max}, h	3 (2 - 4)	4 (1 - 6)	3 (2 - 6)	
C_{max}, ng/mL	247 ± 154	202 ± 107	265 ± 74.3	
$AUC_{0\text{-}24h}$, ng.h/mL	2100 ± 1770	1830 ± 1030	1910 ± 535	
AUC_{last}, ng.h/mL	3520 ± 3410	2730 ± 1590	2820 ± 923	
$t_{1/2,term}$	33.6 ± 13.8	35.2	29.2 ± 11.8	

N = maximum number of subjects with data; NA = not assessable.
Source: Module 5.3.3.1/TMC125-C101/Section 4.C.5

To evaluate the dose-proportionality of AUC_{last} and C_{max} after single dose oral administration, pharmacokinetic parameters were dose-normalized to a dose of 200 mg (Table 8). At some dose levels, high individual values were observed. To account for the high inter-subject variability, median dose-normalized pharmacokinetic parameters were therefore considered. The pharmacokinetic behavior of TMC125 appeared to be dose-proportional over the dose range of 50 to 600 mg. Thereafter, an increase in pharmacokinetic exposure was observed, but this increase was less than dose-proportional for both C_{max} and AUC_{last}.

Table 8: Pharmacokinetics of TMC125 after Administration of Capsule Formulation T* (TMC125 in PEG 4000) at Single Doses of 50 to 1200 mg in Healthy Subjects, Dose-Normalized to a Dose of 200 mg (Trial TMC125-C101)

Parameter	Median			
	50 mg	100 mg	200 mg	400 mg
N	6	6	6	6
C_{max}, ng/mL	70.2	89.8	77.3	53.5
AUC_{last}, ng.h/mL	609	634	892	638
	600 mg	900 mg	1200 mg	
N	6	6	6	
C_{max}, ng/mL	65.5	40.9	48.7	
AUC_{last}, ng.h/mL	688	550	490	

N = maximum number of subjects with data.
Source: Module 5.3.3.1/TMC125-C101/Section 4.C.5

2.3.1.3 URINARY EXCRETION

At the highest dose levels, unchanged TMC125 could be detected in urine samples collected up to 8 hours after dosing in only 3 subjects. The concentrations determined were all close to the LLOQ ([redacted] ng/mL). All other concentrations in urine samples collected from 0 to 8 hours after dosing were below the LLOQ. Urine samples collected 8 hours after dosing were therefore

＊：新薬承認情報提供時に置き換え

analyzed only for the 1200 mg dose level, but concentrations of unchanged TMC125 in these samples were also below the LLOQ.

2.3.1.4 CONCLUSIONS

The pharmacokinetics of TMC125 administered as single doses of 50 to 600 mg of the 50-mg capsule formulation T* (TMC125 in PEG 4000) under fed conditions were dose-proportional. After single doses of 900 and 1200 mg, the pharmacokinetics of TMC125 were less than dose-proportional.

2.4 SINGLE-DOSE PHARMACOKINETICS OF TMC125 IN SUBJECTS WITH HIV-1 INFECTED SUBJECTS

Single-dose pharmacokinetic data on TMC125 administered as tablet formulation A* (TMC125 in HPMC, spray-dried) in HIV-1 infected subjects were obtained in the single-dose pharmacokinetic trial TMC124-C141, which is summarized in Module 2.7.1/Section 2.1.4.

Further single-dose pharmacokinetic data in HIV-1 infected subjects are also available from Day 1 of multiple-dose trials using tablet formulation A* , as well as capsule formulation T* (TMC125 in PEG 4000), tablet formulation S* (TMC125 in HPMC), and tablet formulation F* (TMC125 in HPMC, granulo-layered). These data are summarized in Appendix 2.7.2.3, and are discussed in Section 3.5.1.

2.5 MULTIPLE-DOSE PHARMACOKINETICS OF TMC125 IN HEALTHY SUBJECTS

2.5.1 Trial TMC125-C104: Multiple-Dose Comparison of TMC125 Administered Once or Twice Daily as Capsule Formulation T* (TMC125 in PEG 4000) in Healthy Subjects

2.5.1.1 TRIAL DESIGN

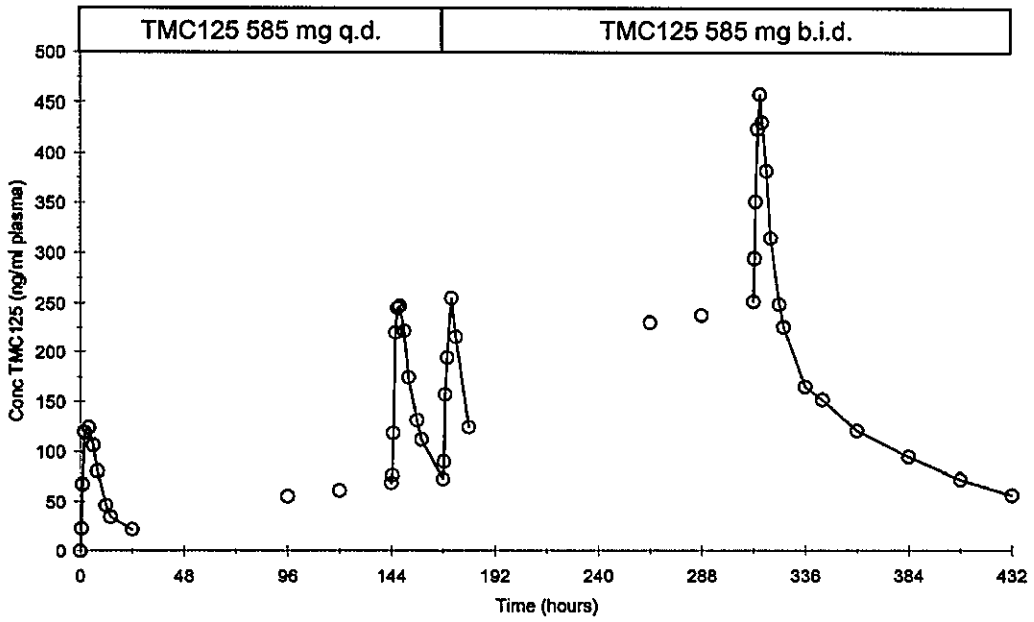
This was a double-blind, randomized, placebo-controlled, multiple-dose trial in healthy subjects to investigate the pharmacokinetics of TMC125 after once-daily dosing for 7 days followed by twice-daily dosing for 7 days. TMC125 was administered as the capsule formulation T* (45 mg TMC125 in PEG 4000) at a dose of 585 mg. A total of 12 subjects were randomized to receive TMC125 or placebo in a ratio of 2:1.

TMC125 was taken under fed conditions, within 10 minutes after completion of a standardized breakfast on pharmacokinetic sampling days.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.1/TMC125-C104).

2.5.1.2 PHARMACOKINETICS OF TMC125

The mean plasma-concentration profiles showed a rapid absorption of TMC125 after single and multiple dosing (Figure 3).



Source: Module 5.3.3.1/TMC125-C104/Section 8.A/Display 7

Figure 3: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of Capsule Formulation T* (TMC125 in PEG 4000) with Once-Daily Dosing of 585 mg TMC125 for 7 Days Followed by Twice-Daily Dosing of 585 mg TMC125 for 7 Days in Healthy Subjects (Trial TMC125-C104)

During once-daily dosing, the mean C_{max} increased from 140 ng/mL on Day 1 to 259 ng/mL on Day 7 (Table 9). The mean C_{0h} increased from 22 ng/mL on Day 2 (refer to Module 5.3.3.1/TMC125-C104/Section 8.A/Display 8) to 69 ng/mL on Day 7. The data indicated that steady-state was reached by Day 7 using once-daily dosing because plasma concentrations of TMC125 measured after dosing on Day 7 and after the morning dose on Day 8 were superimposable.

During twice-daily dosing, the mean C_{max} increased to 470 ng/mL and C_{0h} increased to 252 ng/mL. With the twice-daily dosing regimen, steady-state also appeared to be reached within 7 days.

The mean systemic exposure per dosing interval was 1403 ng.h/mL (AUC_{24h}) on Day 1, 3376 ng.h/mL (AUC_{24h}) at steady-state on Day 7, and 4212 ng.h/mL (AUC_{12h}) at steady-state on Day 14 after twice-daily dosing. The fluctuation index (FI) decreased from 139% to 64% after switching from once- to twice-daily dosing. The approximated mean elimination half-life (on Day 14) was 58 hours.

＊：新薬承認情報提供時に置き換え

Table 9: Pharmacokinetics of TMC125 after Administration of Capsule Formulation T* (TMC125 in PEG 4000) with Once-Daily Dosing of 585 mg TMC125 for 7 Days Followed by Twice-Daily Dosing of 585 mg TMC125 for 7 Days in Healthy Subjects (Trial TMC125-C104)

Parameter	Mean ± SD; t_{max}: Median (Range)		
	Day 1: TMC125 585 mg q.d.	Day 7: TMC125 585 mg q.d.	Day 14: TMC125 585 mg b.i.d.
N	8	8	7
t_{max}, h	4.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	3.0 (2.0 - 6.0)
C_{0h}, ng/mL	NA	69 ± 39	252 ± 104
C_{max}, ng/mL	140 ± 75	259 ± 104	470 ± 186
$C_{ss,av}$, ng/mL	NA	141 ± 65	351 ± 144
AUC_{12h}, ng.h/mL	1039 ± 572	NA	4212 ± 1732
AUC_{24h}, ng.h/mL	1403 ± 776	3376 ± 1564	NA
FI, %	NA	139 ± 26	64 ± 19
$t_{1/2,term}$[a], h	NA	NA	57.75 ± 23.00

N = maximum number of subjects with data; NA = not applicable.
[a] Accurate determination not possible in all subjects.
Source: Module 5.3.3.1/TMC125-C104/Section 4.C.5

2.5.1.3 CONCLUSIONS

After twice-daily dosing of TMC125 with capsule formulation T* (TMC125 in PEG 4000) at a dose of 585 mg, the trough concentration of TMC125 was 3.65-fold higher than the trough concentration after once-daily dosing of 585 mg.

2.5.2 Trial TMC125-C128: Multiple-Dose Escalation of TMC125 Administered as Capsule Formulation Z* (TMC125.HBr in HPMC) in Healthy Subjects

2.5.2.1 TRIAL DESIGN

This was a double-blind, randomized, placebo-controlled, multiple-dose trial in 4 panels of 12 healthy subjects each to investigate the pharmacokinetics of TMC125 after twice-daily dosing with the 100-mg (TMC125 base-equivalents) capsule formulation Z* (TMC125.HBr in HPMC). A total of 4 different dosing regimens were studied sequentially, each in a new panel of 12 subjects (9 treated with TMC125 and 3 with placebo). The following doses (as TMC125 base-equivalents) were administered in the 4 panels:

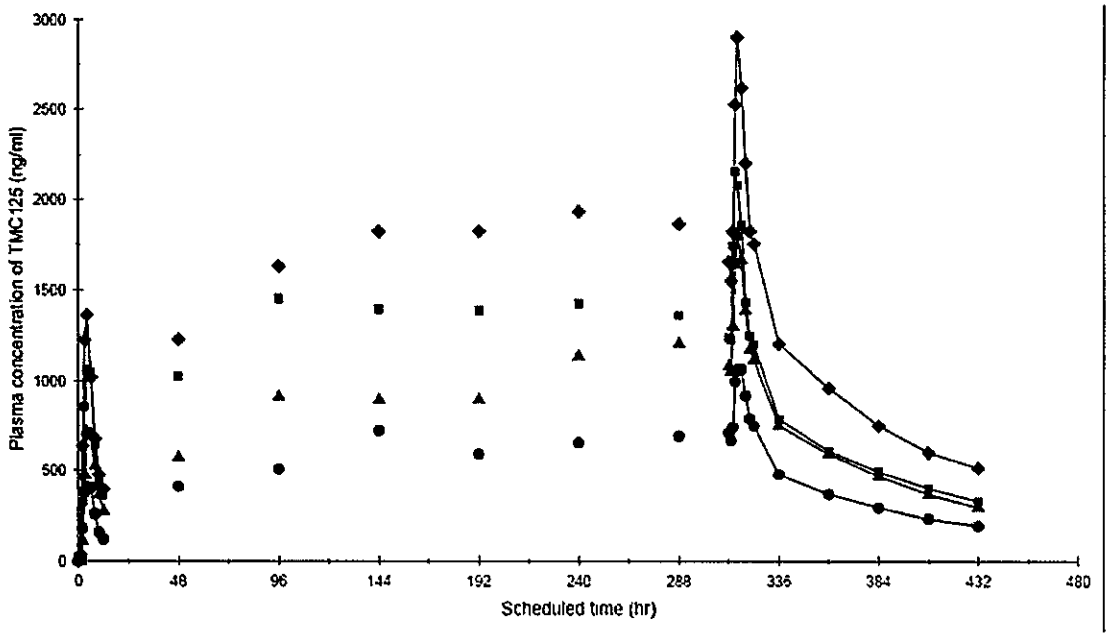
- Panel A: 600 mg b.i.d. for 13 days and an additional single dose on Day 14;
- Panel B: 800 mg b.i.d. for 13 days and an additional single dose on Day 14;
- Panel C: 400 mg b.i.d. for 13 days and an additional single dose on Day 14;
- Panel D: 200 mg b.i.d. for 13 days and an additional single dose on Day 14.

TMC125 was taken under fed conditions, within 10 minutes after completion of a standardized breakfast on pharmacokinetic sampling days.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.1/TMC125-C128).

2.5.2.2 PHARMACOKINETICS OF TMC125

The mean plasma-concentration time profiles showed that TMC125 was rapidly absorbed on Days 1 and 14 at all dose levels (Figure 4).



● 200 mg, ▲ 400 mg, ■ 600 mg, ◆ 800 mg base-equivalent TMC125.HBr. [

N = 9 in each treatment group.

Source: Module 5.3.3.1/TMC125-C128/Section 8.A/Display 6

Figure 4: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of Capsule Formulation Z* (TMC125.HBr in HPMC) at Doses of 200 to 800 mg b.i.d. in Healthy Subjects (Trial TMC125-C128)

On Day 1, the median t_{max} was 4 hours for all 4 dose levels (Table 10). The increases in mean C_{max} and AUC_{12h} were less than dose proportional across the dose range of 200 to 800 mg. The inter-subject variability (CV) increased as the TMC125 dose increased, ranging from 26% to 44% (Module 5.3.3.1/TMC125-C128/Section 4.C.5).

After multiple dosing, pre-dose concentrations of TMC125 reached steady-state after 3 to 5 days of treatment at all doses levels. On Day 14, the CV of the pre-dose concentrations ranged from 25% to 35%. The accumulation index (mean $AUC_{12h,Day14}$ / mean $AUC_{12h,Day1}$) was approximately 3 for all 4 dose levels. The CV for AUC_{12h} was approximately 20% to 30%.

From Day 5 to Day 14, there was no time-dependency in the trough concentrations of TMC125 at any dose level. The morning and evening pre-dose concentrations on Day 14 were comparable, and in most subjects the TMC125 concentrations at 1 hour after dosing on Day 14 were lower than the pre-dose concentration on Day 14, indicating a lag time in absorption. The mean FI on Day 14 ranged between 50% and 70% across dose levels. Steady-state concentrations of TMC125 were reached within 3 to 5 days.

After multiple dosing, steady-state concentrations increased in a less than dose-proportional fashion. Mean dose-normalized AUC_{12h} values on Day 14 were 53.5 ng.h/mL/mg (200 mg group), 42.1 ng.h/mL/mg (400 mg group), 32.0 ng.h/mL/mg (600 mg group), and

＊：新薬承認情報提供時に置き換え

32.8 ng.h/mL/mg (800 mg group). This apparent dose disproportionality was observed for C_{max}, C_{0h} and AUC_{12h}, while the median t_{max} and the elimination phase appeared to be independent of the dose.

Table 10: Pharmacokinetics of TMC125 after Administration of Capsule Formulation Z* (TMC125.HBr in HPMC) at Doses of 200 to 800 mg b.i.d. in Healthy Subjects (Trial TMC125-C128)

Parameter	Mean ± SD; t_{max}: Median (Range)			
	200 mg b.i.d.	400 mg b.i.d.	600 mg b.i.d.	800 mg b.i.d.
Day 1				
N	9	9	9	9
t_{max}, h	4 (3 - 6)	4 (4 - 8)	4 (3 - 6)	4 (3 - 6)
C_{max}, ng/mL	504 ± 136	846 ± 226	1240 ± 627	1433 ± 721
AUC_{12h}, ng.h/mL	2922 ± 763	5112 ± 1541	7385 ± 3216	8695 ± 3884
Day 14				
N	9	7	8	7
t_{max}, h	6 (3 - 6)	4 (3 - 6)	3 (2 - 6)	4 (3 - 6)
C_{0h}, ng/mL	713 ± 182	1085 ± 393	1242 ± 422	1660 ± 578
C_{max}, ng/mL	1167 ± 267	1887 ± 554	2310 ± 866	3019 ± 1058
$C_{ss,av}$, ng/mL	891 ± 187	1404 ± 430	1601 ± 502	2185 ± 678
AUC_{12h}, ng.h/mL	10690 ± 2242	16851 ± 5156	19213 ± 6016	26216 ± 8127
FI, %	51.0 ± 27.3	57.5 ± 18.1	66.6 ± 16.1	62.1 ± 16.7

N = maximum number of subjects with data.
Source: Module 5.3.3.1/TMC125-C128/Section 4.C.5

2.5.2.3 CONCLUSIONS

TMC125 was rapidly absorbed after single-dose (Day 1) and multiple-dose (Day 14) administration of capsule formulation Z* (TMC125.HBr in HPMC) at dose levels of 200, 400, 600, and 800 mg b.i.d. After multiple dosing, pre-dose concentrations of TMC125 reached steady-state after 3 to 5 days of treatment at all doses levels. The mean steady-state exposure to TMC125 (C_{max}, C_{min}, and AUC_{12h}) increased in a less than dose proportional fashion, whereas the median t_{max} and the elimination phase appeared to be independent of the dose.

2.5.3 Trial TMC125-C143: Multiple-Dose Ranging Trial of TMC125 Administered Twice Daily as Tablet Formulation F* (TMC125 in HPMC) in Healthy Subjects

2.5.3.1 TRIAL DESIGN

This was a multicenter, open label, multiple-dose, dose-ranging trial to evaluate single-dose and steady-state (after twice-daily dosing) pharmacokinetics of TMC125 with the 200-mg tablet formulation F* (TMC125 in HPMC). A total of 36 healthy subjects were randomized to 3 parallel groups of 12 subjects each. The following doses of TMC125 were administered in the 3 groups:

- Treatment A: 200 mg as a single morning dose on Day 1, b.i.d. on Days 2 to 7, and as a single morning dose on Day 8;

＊：新薬承認情報提供時に置き換え

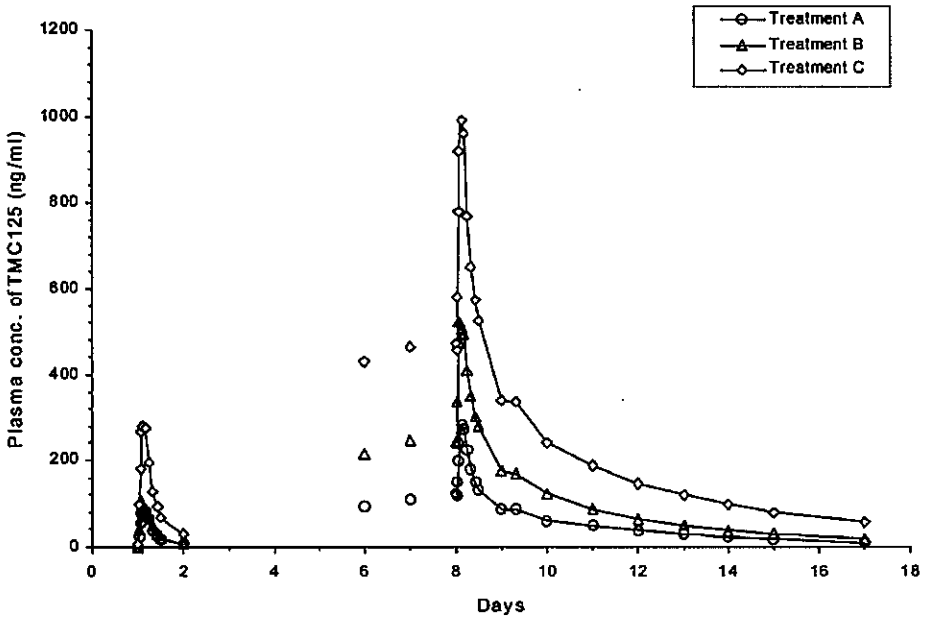
- Treatment B: 400 mg as a single morning dose on Day 1, b.i.d. on Days 2 to 7, and as a single morning dose on Day 8;
- Treatment C: 800 mg as a single morning dose on Day 1, b.i.d. on Days 2 to 7, and as a single morning dose on Day 8.

TMC125 was taken under fed conditions within 10 minutes after completion of a normal or heavy meal, defined as a meal with an energetic value higher than 500 kcal, or within 10 minutes after completion of a standardized breakfast on pharmacokinetic sampling days.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.1/TMC125-C143).

2.5.3.2 PHARMACOKINETICS OF TMC125

The mean plasma concentration-time profiles showed that TMC125 was rapidly absorbed followed by an initially fast distribution/elimination phase and a slower terminal elimination phase (Figure 5).



Treatment A = 200 mg b.i.d. (N = 12)
Treatment B = 400 mg b.i.d. (N = 11)
Treatment C = 800 mg b.i.d. (N = 12)
Source: Module 5.3.3.1/TMC125-C143/Section 4.2.4/Figure 2

Figure 5: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of Tablet Formulation F* (TMC125 in HPMC) at Doses of 200 to 800 mg b.i.d. in Healthy Subjects (Trial TMC125-C143)

On Day 1, the median t_{max} was between 2.0 and 3.0 hours for all 3 dose levels, and comparable median t_{max} values were also seen on Day 8 (Table 11).

Steady-state concentrations of TMC125 were reached prior to Day 8 for all dose levels. On Day 8, mean C_{max} values were 3- to 4-fold higher than the mean values on Day 1 for each dose

＊：新薬承認情報提供時に置き換え

level. Compared to Day 1, AUC_{12h} values were almost 6-fold higher on Day 8 in the 200 mg b.i.d. group, approximately 8-fold higher in the 400 mg b.i.d. group, and almost 5-fold higher in the 800 mg b.i.d. group.

Individual C_{0h}, C_{min}, C_{max}, and AUC values overlapped considerably between the different dose regimens. The CV on Day 8 ranged from 40.4% to 45.0% for C_{0h}, from 40.4% to 47.9% for C_{min}, from 40.7% to 61.2% for C_{max}, and from 36.3% to 51.4% for AUC_{12h}. However, dose-normalized pharmacokinetic parameter plots indicated that the systemic exposure to TMC125 (AUC_{12h}) increased dose-proportionally across the 200 to 800 mg b.i.d. dose levels (Module 5.3.3.1/TMC125-C143/Section 4.2.5/Figure 3). The mean FI was consistent at all 3 dose levels, ranging between 80.5% and 82.2% (Table 11). After dosing on Day 8, the mean terminal elimination half-lives of TMC125 increased from 62.3 to 72.8 hours across the 200 to 800 mg b.i.d. dose levels.

Table 11: Pharmacokinetics of TMC125 after Administration of Tablet Formulation F* (TMC125 in HPMC) at Doses of 200 to 800 mg b.i.d. in Healthy Subjects (Trial TMC125-C143)

	Mean ± SD; t_{max}: Median (Range)		
Parameter	**Treatment A 200 mg b.i.d.**	**Treatment B 400 mg b.i.d.**	**Treatment C 800 mg b.i.d.**
Day 1			
N	12	11	12
t_{max}, h	3.0 (2.0 - 6.0)	2.0 (1.5 - 6.0)	3.0 (1.5 - 4.0)
C_{max}, ng/mL	95.1 ± 66.2	142 ± 129	319 ± 165
AUC_{12h}, ng.h/mL	581 ± 407	684 ± 459	1940 ± 1048
AUC_{24h}, ng.h/mL	731 ± 513	871 ± 579	2533 ± 1411
Day 8			
N	12	11	12
t_{max}, h	3.5 (2.0 - 6.0)	3.0 (1.5 - 4.0)	3.0 (2.0 - 6.0)
C_{0h}, ng/mL	126 ± 56.2	247 ± 111	472 ± 191
C_{min}, ng/mL	115 ± 55.3	237 ± 112	446 ±180
C_{max}, ng/mL	294 ± 180	546 ± 269	1042 ± 423
$C_{ss,av}$, ng/mL	199 ± 102	386 ± 184	723 ± 263
AUC_{12h}, ng.h/mL	2389 ± 1228	4628 ± 2205	8674 ± 3152
$t_{1/2,term}$, h	62.3 ± 20.3	58.4 ± 23.2	72.8 ± 18.1
FI, %	82.0 ± 24.5	80.5 ± 19.6	82.2 ± 30.0
Ratio AUC_{12h} (Day 8/Day 1), %	570 ± 498	862 ± 371	490 ± 116

N = maximum number of subjects with data.
Source: Module 5.3.3.1/TMC125-C143/Section 4.2.5

2.5.3.3 CONCLUSIONS

The mean exposure to TMC125 (AUC_{12h}) when administered as tablet formulation F* (TMC125 in HPMC, granulo-layered) increased in a dose-proportional fashion across the 200 to 800 mg b.i.d. dose levels. The mean terminal elimination half-life ranged between 58 and 73 hours across the different dose levels.

＊：新薬承認情報提供時に置き換え

2.5.4 Trial TMC125-C153: Multiple-Dose Ranging Trial of TMC125 Administered Once Daily as Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) in Healthy Subjects

2.5.4.1 Trial Design

This was an open-label, multiple-dose-ranging trial to investigate the single-dose and steady-state pharmacokinetics of TMC125, administered as the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered), in once-daily dosing regimens. Subjects were randomized into 2 parallel panels (Treatments A and B) of 12 healthy subjects each. A sequential third panel (Treatment C) of 12 additional healthy subjects was treated after evaluation of the safety assessment of Panels 1 and 2. Subjects received the following doses of TMC125:

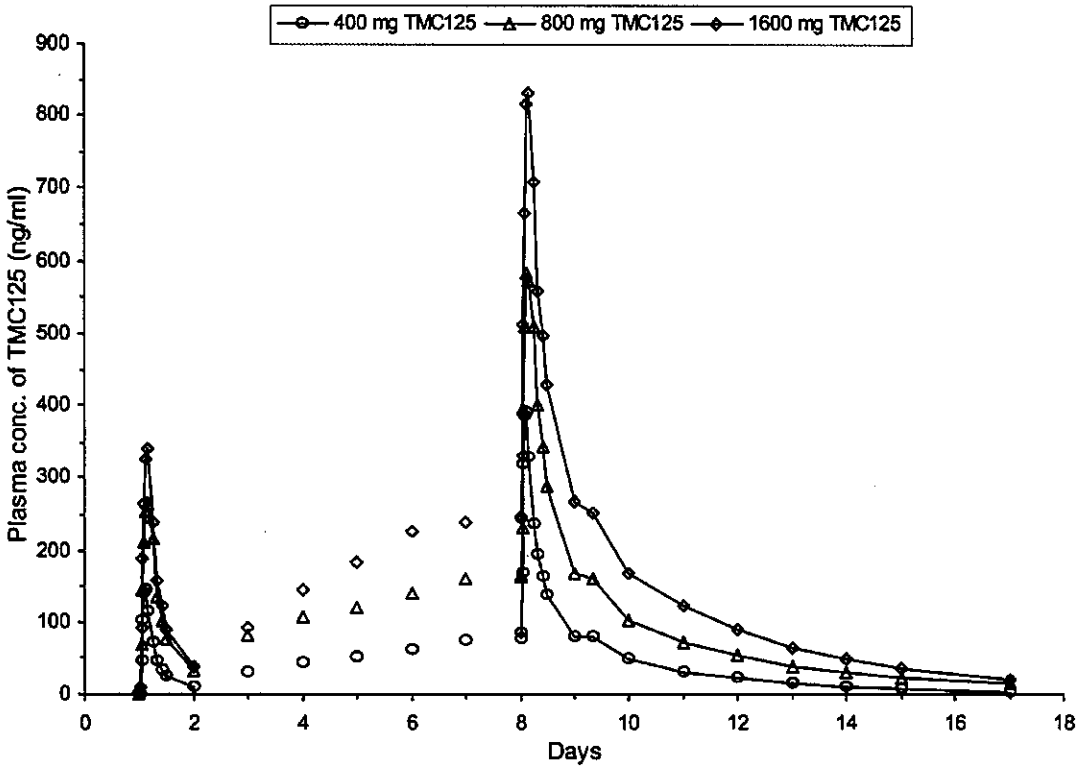
- Treatment A: TMC125 400 mg q.d. on Days 1 to 8;
- Treatment B: TMC125 800 mg q.d. on Days 1 to 8;
- Treatment C: TMC125 1600 mg q.d. on Days 1 to 8.

TMC125 was taken under fed conditions within 10 minutes after completion of a standardized breakfast.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.1/TMC125-C153).

2.5.4.2 Pharmacokinetics of TMC125

The mean plasma concentration-time profiles showed that TMC125 was rapidly absorbed, followed by an initially fast distribution/elimination phase and a slower terminal elimination phase (Figure 6).



400 mg q.d.: N = 12; 800 mg q.d.: N = 12; 1600 mg q.d.: N = 11
Source: Module 5.3.3.1/TMC125-C153/Section 4.2.4/Figure 2

Figure 6: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of Tablet Formulation F* (TMC125 in HPMC) at Doses of 400 to 1600 mg q.d. in Healthy Subjects (Trial TMC125-C153)

On Day 1, the median t_{max} of TMC125 was similar in all treatment groups (3.0 to 3.5 hours) (Table 12). Mean C_{max}, AUC_{12h}, and AUC_{24h} values increased dose proportionally between the 400 and 800 mg q.d. doses, but less than dose proportionally between the 800 and 1600 mg q.d. doses.

Steady-state concentrations of TMC125 were reached prior to Day 8 for all dose levels. On Day 8, the median t_{max} of TMC125 was slightly later with the 1600 mg q.d. dose (4.0 hours) than with the 400 and 800 mg q.d. doses (3.0 hours each). C_{max} increased less than dose proportionally across the range of dose levels, whereas AUC_{24h} increased dose proportionally between the 400 and 800 mg q.d. dose levels, but less than dose proportionally between the 800 and 1600 mg q.d. dose levels.For each dose level, mean C_{max} values on Day 8 were approximately 2-fold higher than the values on Day 1, and mean AUC_{24h} values on Day 8 were approximately 4-fold higher than the values on Day 1.

The mean FI ranged between 146% and 198% across treatment groups, and values for the individual pharmacokinetic values overlapped considerably between the different treatment groups. On Day 8, the CV ranged from 33.5% to 51.6% for C_{max} and from 30.4% to 52.3% for AUC_{24h} (Module 5.3.3.1/TMC125-C153/Section 4.2.5). After the last drug intake, the mean

terminal elimination half-life of TMC125 increased from 48.0 to 55.7 hours between the 400 and 1600 mg dose levels.

Table 12: Pharmacokinetics of TMC125 after Administration of Tablet Formulation F* (TMC125 in HPMC) at Doses of 400 to 1600 mg q.d. in Healthy Subjects (Trial TMC125-C153)

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

N = maximum number of subjects with data.
Source: Module 5.3.3.1/TMC125-C153/Section 4.2.5

2.5.4.3 Conclusions

After a single dose of TMC125 on Day 1, the mean C_{max}, AUC_{12h}, and AUC_{24h} values increased dose-proportionally between the 400 and 800 mg q.d. dose levels, but less than dose proportionally between the 800 and 1600 mg q.d. dose levels. After multiple-dose administration on Day 8, the mean C_{max} increased less than dose proportionally across all dose levels, whereas the mean AUC_{24h} increased dose proportionally between the 400 and 800 mg q.d. dose levels, but less than dose proportionally between the 800 and 1600 mg q.d. dose levels. The mean terminal elimination half-life of TMC125 increased from 48.0 to 55.7 hours between the 400 and 1600 mg dose levels.

2.5.5 Trial TMC125-C168: Multiple-Dose Comparison of TMC125 Administered Once or Twice Daily as Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) in Healthy Subjects

2.5.5.1 Trial Design

This was an open-label, randomized, multiple-dose, 2-period crossover trial in 24 healthy subjects to investigate the pharmacokinetics of TMC125, administered as the 100-mg tablet

formulation A* (TMC125 in HPMC, spray-dried) after once-daily and twice-daily dosing. The trial was divided into 2 sessions of 8 days each, with a washout period of at least 14 days between the 2 sessions. In each session, subjects received one of the following treatments:

- Treatment A: TMC125 100 mg b.i.d. on Days 1 to 7, with an additional morning dose of 100 mg on Day 8;
- Treatment B: TMC125 200 mg q.d. on Days 1 to 8.

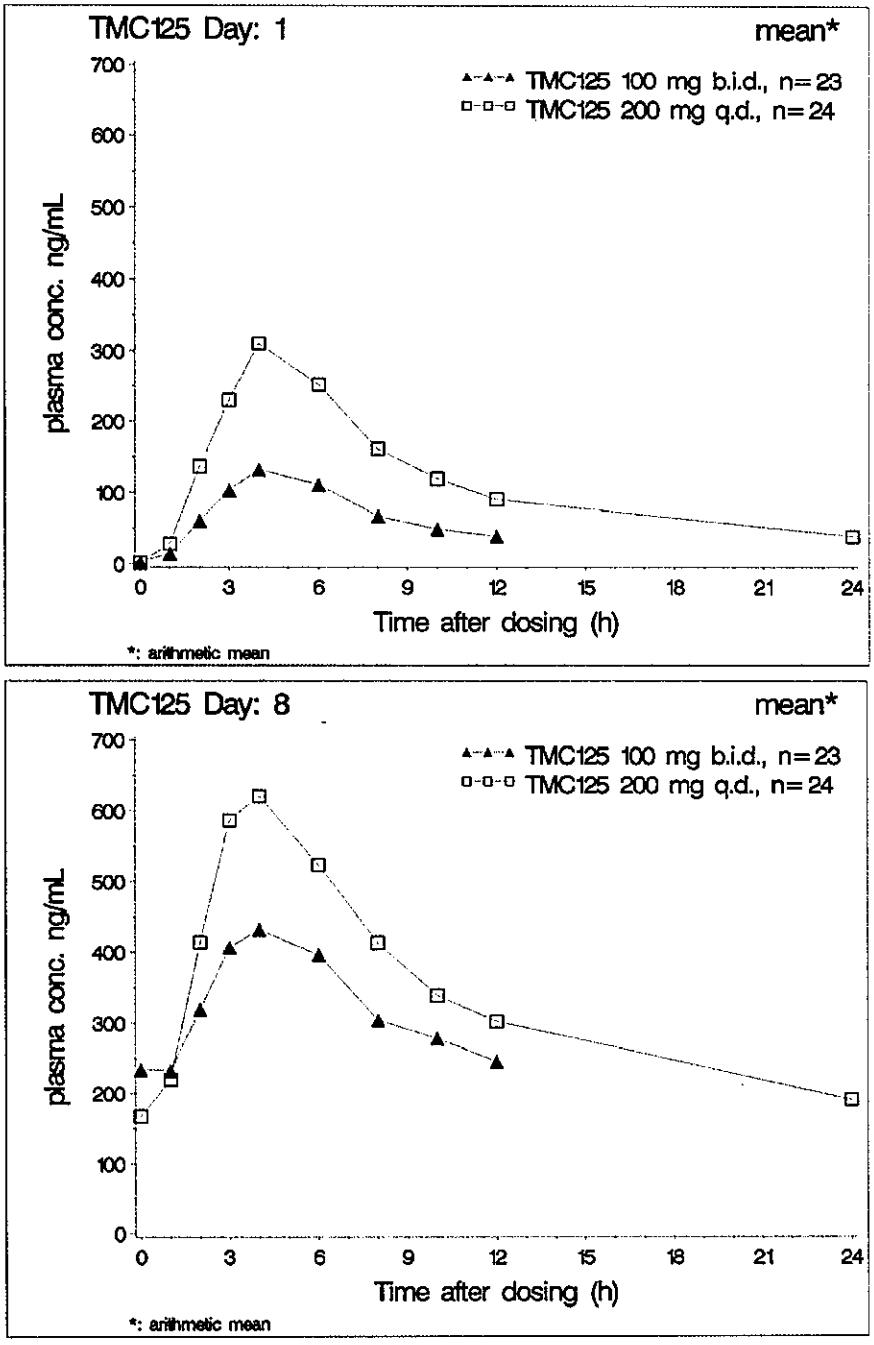
TMC125 was administered under fed conditions within 10 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.1/TMC125-C168).

2.5.5.2 PHARMACOKINETICS OF TMC125

The mean plasma concentration-time profiles of TMC125 on Days 1 and 8 are shown in Figure 7.

＊：新薬承認情報提供時に置き換え



Source: Module 5.3.3.1/TMC125-C168/Section 4.2.4/Figure 3

Figure 7: Mean Plasma Concentration-Time Profiles of TMC125 after Administration as Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) at Doses of 100 mg b.i.d. or 200 mg q.d. in Healthy Subjects (Trial TMC125-C168)

On Day 1, the mean C_{max} and AUC_{24h} of TMC125 were increased 2.31- and 1.66-fold, respectively, when TMC125 was administered as 200 mg q.d., compared to 100 mg b.i.d. (Table 13).

＊：新薬承認情報提供時に置き換え

Steady-state concentrations of TMC125 were reached after 7 to 8 days. On Day 8, the mean AUC_{24h} of TMC125 was similar between the 2 dosing regimens. However, the mean C_{max} of TMC125 was increased 1.42-fold, and mean C_{min} of TMC125 was decreased by 26%, when TMC125 was administered q.d. The 90% confidence intervals (CIs) of the LS means ratios for both comparisons were outside the 80% to 125% range. There was no difference between the 2 dosing regimens in the median t_{max} of TMC125. With both dosing regimens, the mean AUC values on Day 8 were approximately 3- to 4-fold higher than those on Day 1.

Table 13: Pharmacokinetics of TMC125 after Administration as Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) at Doses of 100 mg b.i.d. or 200 mg q.d. in Healthy Subjects (Trial TMC125-C168)

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

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.1/TMC125-C168/Section 4.2.5 and Section 4.2.6

2.5.5.3 CONCLUSIONS

The mean exposure to TMC125 (AUC_{24h}) at steady-state after administration as tablet formulation A* (TMC125 in HPMC, spray-dried) at a dose of 200 mg q.d. was comparable to the mean exposure after administration of 100 mg b.i.d. in healthy subjects. After multiple-dose administration, the mean C_{max} of TMC125 was 1.42-fold higher, and the mean C_{min} was 26% lower, with once-daily dosing compared to twice-daily dosing.

2.6 MULTIPLE-DOSE PHARMACOKINETICS AND PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS OF TMC125 IN HIV-1 INFECTED SUBJECTS

In addition to the Phase II and III trials summarized below, multiple-dose pharmacokinetic data in HIV-1 infected subjects are also available from trial TMC125-C228, in which TMC125 was administered as tablet formulation F* (TMC125 in HPMC, granulo-layered) at a dose of

800 mg b.i.d. for 8 days, and as tablet formulation A* (TMC125 in HPMC, spray-dried) at doses of 100 and 200 mg b.i.d. for 8 days (refer to Module 2.7.1, Section 2.1.5).

2.6.1 Phase IIa (Proof-of-Principle) Trials

2.6.1.1 TRIAL TMC125-C201: EFFICACY OF TMC125 MONOTHERAPY IN ANTIRETROVIRAL-NAÏVE, HIV-1 INFECTED SUBJECTS

2.6.1.1.1 Trial Design

This was a Phase IIa, randomized, double-blind, placebo-controlled, monotherapy, dose-ranging trial to assess efficacy, pharmacokinetics, and safety of TMC125 in HIV-1 infected subjects. Only male subjects who had never been treated with an ARV and who had a plasma viral load that ranged between 5000 and 150 000 HIV-1 RNA copies/mL were eligible for the trial. Subjects were required to stop taking specified disallowed medication 14 days prior to the first administration of trial medication.

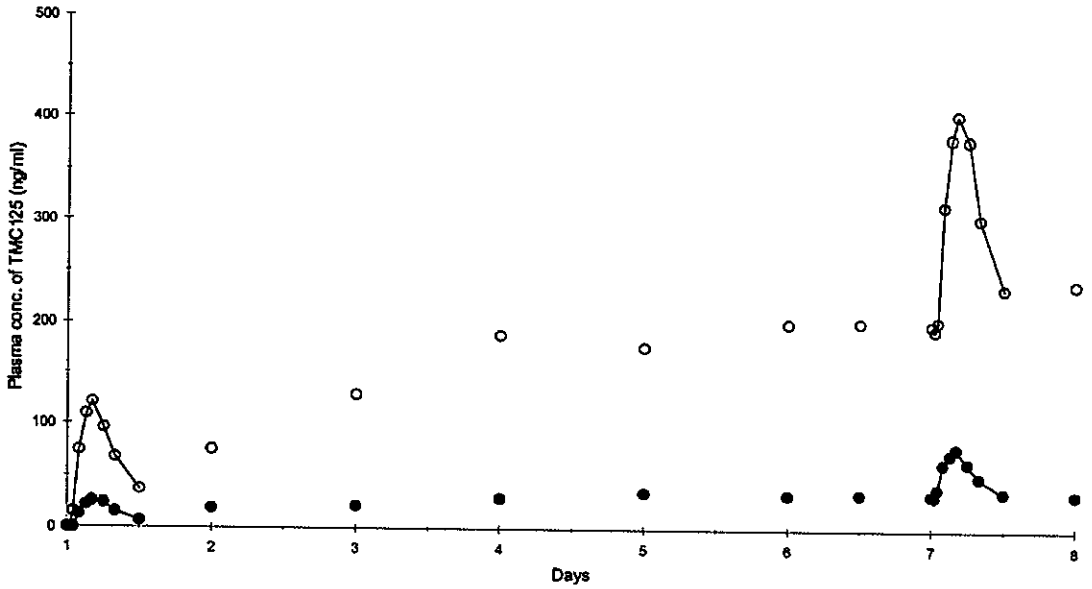
A total of 25 subjects were randomized to one of the 3 treatment groups: placebo, or TMC125 100 or 400 mg b.i.d. (ratio 1:2:2) for 7 days. TMC125 was administered as the 100-mg tablet formulation S* (TMC125 in HPMC, granulo-layered). The trial drug was administered every 12 hours, and within 15 minutes after completing breakfast and dinner.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.5.1/TMC125-C201).

2.6.1.1.2 Pharmacokinetics of TMC125

Mean plasma-concentration time profiles showed a rapid absorption of TMC125 on Days 1 and 7 (Figure 8).

＊：新薬承認情報提供時に置き換え



• = 100 mg TMC125 b.i.d. (N = 10); o = 400 mg TMC125 b.i.d. (N = 10)

Source: Module 5.3.5.1/TMC125-C201/Section 4.2.4

Figure 8: Mean Plasma Concentration-Time Profiles of TMC125 after Administration as Tablet Formulation S* (TMC125 in HPMC, Granulo-Layered) at Doses of 100 and 400 mg b.i.d. in HIV-1 Infected Subjects (Trial TMC125-C201)

After the first dose and after multiple-dose administration of TMC125 at doses of 100 and 400 mg, the median t_{max} of TMC125 was 4 hours (Table 14). On Day 1, a lag time in absorption of 1 to 2 hours was noted in the 100 mg b.i.d. group, and a lag time of 0.5 to 1 hours in the 400 mg b.i.d. group. The mean C_{max} and AUC_{12h} of TMC125 increased dose proportionally (approximately 4-fold) in the 400 mg b.i.d. group, compared to the 100 mg b.i.d. group.

The mean C_{min}, C_{max}, and AUC_{12h} values on Day 7 increased more than dose proportionally (approximately 5- to 6-fold) in the 400 mg b.i.d. group, compared to the 100 mg b.i.d. group.

Inter-subject variability in plasma concentrations decreased after multiple dosing at both dose levels. In the 100 mg b.i.d. group, the CVs for C_{max} and AUC_{12h} were 62% and 63%, respectively, on Day 1 and decreased to 43% and 42%, respectively, on Day 7. In the 400 mg b.i.d. group, the CVs for C_{max} and AUC_{12h} were 66% and 68%, respectively, on Day 1 and decreased to 31% and 33%, respectively, on Day 7 (refer to Module 5.3.5.1/TMC125-C201/Section 4.2.5).

When comparing mean values for AUC_{12h} on Days 1 and 7, the mean accumulation after multiple-dose administration was 3.7-fold for the 100 mg b.i.d. group and 4.4-fold for the 400 mg b.i.d. group. The difference between the mean C_{max} and C_{min} values during the dosing interval was small. Steady-state was reached within 4 to 5 days of TMC125 twice-daily dosing at both dose levels.

＊：新薬承認情報提供時に置き換え

Table 14: Pharmacokinetics of TMC125 after Administration as Tablet Formulation S* (TMC125 in HPMC, granulo-layered) at Doses of 100 and 400 mg b.i.d. in HIV-1 Infected Subjects (Trial TMC125-C201)

Parameter	Mean ± SD; t_{max}: Median (Range)	
	100 mg b.i.d.	400 mg b.i.d.
Day 1		
N	10	10
t_{max}, h	4.0 (3.0 - 6.0)	4.0 (3.0 - 6.0)
C_{max}, ng/mL	27.6 ± 17.1	127 ± 83.9
AUC_{12h}, ng.h/mL	182 ± 115	850 ± 578
Day 7		
N	10	10
t_{max}, h	4.0 (3.0 - 6.0)	4.0 (2.0 - 6.0)
C_{0h}, ng/mL	33.7 ± 13.5	201 ± 57.3
C_{min}, ng/mL	32.1 ± 14.4	190 ± 56.1
C_{max}, ng/mL	83.2 ± 35.5	426 ± 133
AUC_{12h}, ng.h/mL	676 ± 284	3760 ± 1238
$C_{ss,av}$, ng/mL	56.3 ± 23.7	313 ± 103
FI, %	91.9 ± 24.0	74.9 ± 13.6

N = maximum number of subjects with data.
Source: Module 5.3.5.1/TMC125-C201/Section 4.2.5

2.6.1.1.3 Pharmacodynamics

The primary efficacy endpoint was the viral load decrease (decay rate) during 7-day twice-daily treatment with TMC125 as monotherapy.

Secondary efficacy endpoints included:

- Plasma viral load nadir (i.e., the lowest value after Baseline);
- Change in plasma viral load as measured by averaging the area under the (viral load) curve minus Baseline (AAUCMB) (after calculating the AUC and dividing it by the individual total time, the Baseline value was subtracted to obtain the AAUCMB). AAUCMB is named DAVG in the analysis;
- Number of subjects with undetectable (< 50 HIV-1 RNA copies/mL) plasma viral load assessments;
- Number of subjects with plasma viral load assessments below 400 HIV-1 RNA copies/mL;
- Number of subjects with plasma viral load assessments with plasma viral load decrease of at least 1 log_{10} from Baseline;
- Change in CD4 cell count.

The 7-day treatment with TMC125 at doses of 100 and 400 mg b.i.d. had statistically significant ARV activity. The plasma viral load decrease rate estimates over 7 days were -0.14 and -0.19 log_{10} HIV-1 RNA copies/mL/day in the 100 and 400 mg b.i.d. groups, respectively (both $p<0.001$ vs. Baseline). No relevant change was observed in the placebo group (-0.03 log_{10} HIV-1 RNA copies/mL/day). A median decrease from Baseline in plasma viral load of -0.95 and -1.19 log_{10} HIV-1 RNA copies/mL was observed in the 100 and 400 mg b.i.d. groups, respectively (both $p = 0.002$). Small median decreases were observed in absolute and percentage CD4 cell counts in all treatment groups at the end of the treatment period.

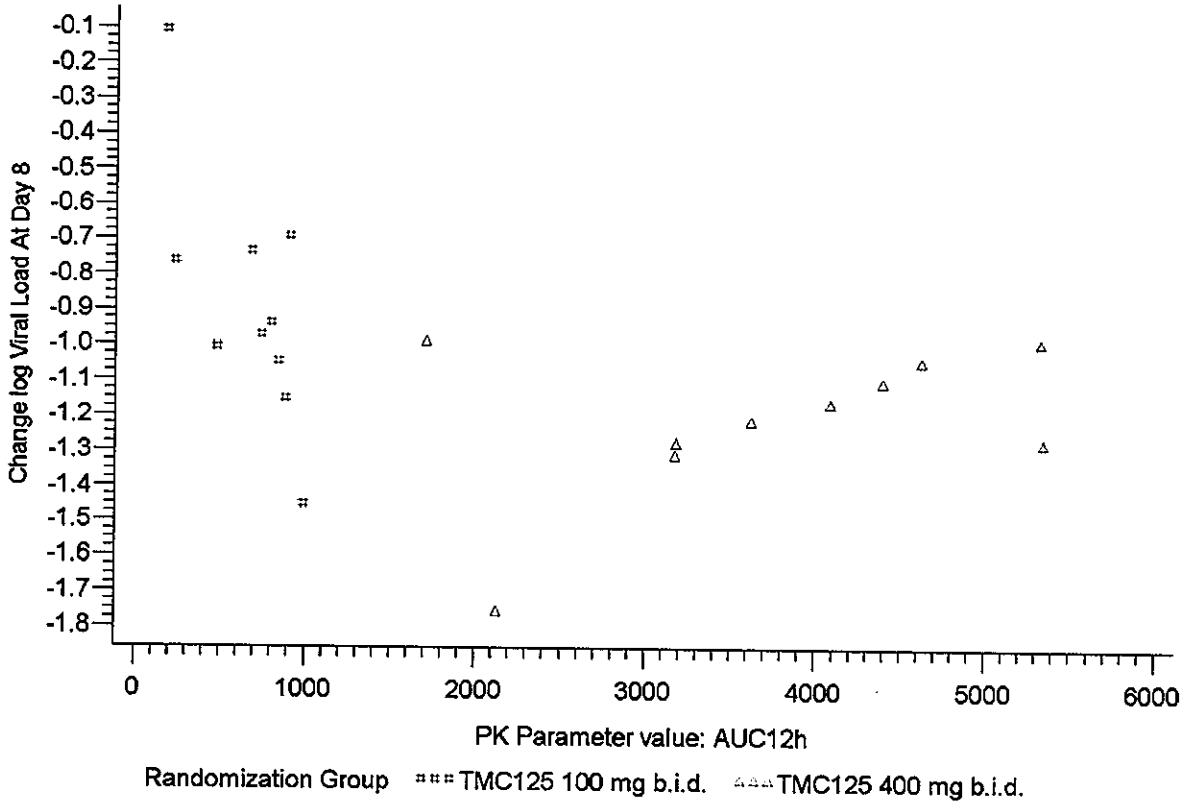
＊：新薬承認情報提供時に置き換え

Further details are available in Module 5.3.5.1/TMC125-C201.

2.6.1.1.4 Pharmacokinetic/Pharmacodynamic Relationships

Relationship Between Pharmacokinetics and Virologic Response

No relationship was observed between the pharmacokinetics of TMC125 (AUC_{12h} [Figure 9], C_{max}, C_{min}, average steady-state plasma concentration [$C_{ss,av}$]) (refer to Module 5.3.5.1/TMC125-C201/Section 6.1/Supporting Data Display 14) and the virologic response (change in log_{10} viral load from Baseline to Day 8). In addition, ANCOVA models showed no statistically significant relationship between the pharmacokinetics of TMC125 and the virologic response (refer to Module 5.3.5.1/TMC125-C201/Section 4.2.6).



Source: Module 5.3.5.1/TMC125-C201/Section 6.1/Supporting Data Display 14

Figure 9: Individual Changes in Log_{10} Viral Load from Baseline to Day 8 Versus TMC125 AUC_{12h} on Day 8 (Trial TMC125-C201)

Relationship Between Inhibitory Quotient and Virologic Response

No relationship was observed between the IQ values based upon TMC125 AUC_{12h}, C_{max}, C_{min}, or $C_{ss,av}$ and the virologic response (change in log_{10} viral load from Baseline to Day 8) (refer to Module 5.3.5.1/TMC125-C201/Section 6.1/Supporting Data Display 16). No statistically significant relationships were observed between the IQ values of TMC125 and the virologic response (refer to Module 5.3.5.1/TMC125-C201/Section 4.2.6).

2.6.1.1.5 Pharmacokinetic/Safety Relationships

Pharmacokinetic/safety relationships were not formally assessed. However, no obvious dose relationships were observed in the occurrence of adverse events (Module 5.3.5.1/TMC125-C201/Section 4.4.2.4). There were no consistent changes in biochemistry or hematology parameters.

2.6.1.1.6 Conclusions

- At doses of 100 and 400 mg b.i.d., steady-state was reached in 4 to 5 days. At both doses, the mean accumulation (AUC_{12h}) after multiple-dose administration for 7 days was approximately 4-fold.
- The mean exposure (AUC_{12h}) to TMC125 at steady-state increased more than dose proportionally between the 100 and 400 mg b.i.d. doses.
- The 7-day treatment with TMC125 at doses of 100 and 400 mg b.i.d. resulted in statistically significant ARV activity (-0.141 and -0.187 log_{10} HIV-1 RNA copies/mL/day, respectively).
- No apparent relationship was observed between the pharmacokinetics of TMC125 and the ARV activity of TMC125.
- No dose relationship was observed in the occurrence of adverse events, and there were no consistent changes in biochemistry or hematology parameters.

2.6.1.2 Trial TMC125-C208: Efficacy of TMC125 Monotherapy in Antiretroviral-Naïve, HIV-1 Infected Subjects

2.6.1.2.1 Trial Design

This was a Phase IIa, randomized, double-blind, placebo-controlled trial in ARV-naïve HIV-1 infected subjects to investigate the efficacy (antiviral activity), tolerability, safety, and pharmacokinetics of TCM125 after a 7-day period of drug monotherapy. Potential changes in the resistance profile of the virus during treatment were also assessed. Only male subjects who had never been treated with any ARV drug, and with a viral load of between 5000 and 125000 HIV-1 RNA copies/mL, were eligible for the trial. A total of 12 subjects received TMC125 900 mg b.i.d., administered as the 50-mg capsule formulation T* (TMC125 in PEG 4000), and 7 subjects received placebo, in all cases for 7 days.

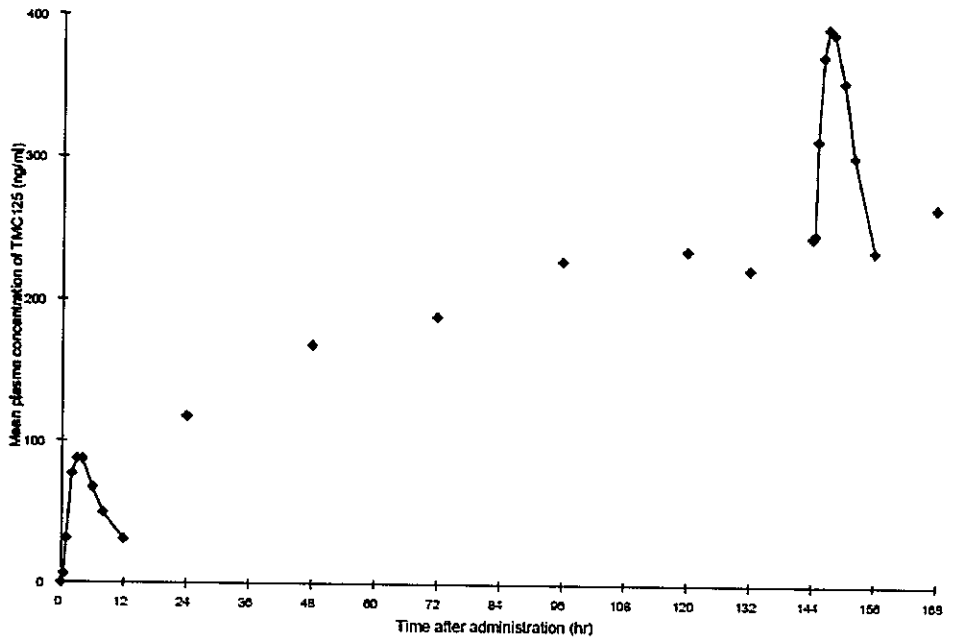
The trial medication was administered every 12 hours, within 15 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.5.1/TMC125-C208).

2.6.1.2.2 Pharmacokinetics of TMC125

The mean plasma concentration-time profile of TMC125 is shown in Figure 10.

＊：新薬承認情報提供時に置き換え



N = 12.
Source: Module 5.3.5.1/TMC125-C208/Supporting Data Display 23

Figure 10: Mean Plasma Concentration-Time Profile of TMC125 After Administration of TMC125 at a Dose of 900 mg b.i.d. (Trial TMC125-C208)

After the first dose and after multiple twice-daily dosing, the median t_{max} of TMC125 was 3 hours. Inter-subject variability in plasma concentrations decreased after multiple dosing; the CV for C_{max} and AUC_{12h} after the first intake were 53% and 56%, respectively, and decreased to approximately 30% for both parameters on Day 7 (refer to Module 5.3.5.1/TMC125-C208/Section 4.5.5). Comparing mean AUC_{12h} on Day 1 and Day 7, the accumulation was 5.8-fold. The fluctuation in plasma concentrations was small, with a mean C_{min} of 246 ng/mL on Day 7 and a mean C_{max} of 419 ng/mL. Based on the trough concentrations, steady-state was reached between 4 and 5 days of TMC125 b.i.d. dosing. No relevant difference was noted between morning and evening trough levels on Days 6 or 7.

Table 15: Pharmacokinetics of TMC125 on Days 1 and 7 After Administration of TMC125 at a Dose of 900 mg b.i.d. (Trial TMC125-C208)

Parameter	Mean ± SD; t_{max}: Median (Range)	
	Day 1	Day 7
N	12	12
t_{max}, h	3.0 (2.0 - 6.0)	3.0 (2.0 - 6.0)
C_{min}, ng/mL	-	246 ± 75.9
C_{max}, ng/mL	93.3 ± 49.7	419 ± 121
AUC_{12h}, ng.h/mL	662 ± 368	3862 ± 1152
$C_{ss,av}$, ng/mL	-	322 ± 96.0
FI, %	-	90.9 ± 14.1

N = maximum number of subjects with data.
Source: Module 5.3.5.1/TMC125-C208/Supporting Data Display 24

2.6.1.2.3 Pharmacodynamics

The primary efficacy parameter was the viral load decay rate during 7-day b.i.d. treatment with TMC125 as monotherapy.

Secondary efficacy endpoints included the following:

- Change in viral load as measured by AAUCMB;
- Nadir of viral load;
- Change in $\log_{10}$ viral load;
- Change in CD4 cell count.

For the primary efficacy parameter (viral load decay rate), there was a statistically significant difference between the TMC125 and placebo groups. The decay rate for the placebo group was -0.02 $\log_{10}$ HIV-1 RNA copies/mL/day, while the decay rate for the TMC125 group was -0.32 $\log_{10}$ HIV-1 RNA copies/mL/day. After 7 days of TMC125 treatment, an LS-mean estimate of a decrease of 2.04 $\log_{10}$ HIV-1 RNA copies/mL was achieved, comparing favorably with a decrease of only 0.11 $\log_{10}$ HIV-1 RNA copies/mL after 7 days of placebo intake. When comparing the changes in log viral load from Baseline, the difference between both groups became significant from Day 2, Hour 12 onwards.

All 12 subjects in the TMC125 group were responders (defined as viral load decreased by at least 1 $\log_{10}$) on Day 8. None of the subjects in the placebo group responded at any time throughout the trial. At the end of the trial (Day 8), the viral load had decreased below 400 HIV-1 RNA copies/mL in 8 subjects. Two subjects had viral loads of less than 50 HIV-1 RNA copies/mL. The CD4 cell count increased in the TMC125 group and decreased in the placebo group. The largest median increase in the TMC125 treatment group occurred on Day 4 (176 x 10^6 cells/L). On Day 8, a somewhat lesser increase in CD4 cell count (119 x 10^6 cells/L) was measured than on Day 4.

Further details are available in Module 5.3.5.1/TMC125-C208.

2.6.1.2.4 Pharmacokinetic/Pharmacodynamic Relationships

Graphic analysis revealed no obvious relationship between change from Baseline on Day 8 in $\log_{10}$ viral load (change $\log_{10}$ viral load, nadir, DAVG, and decrease in $\log_{10}$ viral load) and individual values for AUC_{12h}, C_{max}, C_{min}, and C_{ss} (refer to Module 5.3.5.1/TMC125-C208/Section 4.5.6). There was no statistically significant relationship between the pharmacokinetic parameters of TMC125 in plasma and the parameters of antiviral activity.

2.6.1.2.5 Pharmacokinetic/Safety Relationships

Pharmacokinetic/safety relationships were not assessed.

2.6.1.2.6 Conclusions

- At a dose of 900 mg b.i.d., steady-state was reached in 4 to 5 days. The mean accumulation (AUC_{12h}) after multiple-dose administration for 7 days was 5.8-fold.
- TMC125 administered as monotherapy at 900 mg b.i.d. for 7 days in ARV-naïve, HIV-1 infected subjects resulted in a significant reduction in viral load from Baseline (LS mean -2.04 $\log_{10}$ HIV-1 RNA copies/mL), and an increase in CD4 cell count.

- There was no obvious relationship between the pharmacokinetics of TMC125 and efficacy (change in viral load from Baseline at Day 8).

2.6.1.3 TRIAL TMC125-C207: EFFICACY OF TMC125 IN HIV-1 INFECTED SUBJECTS WITH PHENOTYPICALLY CONFIRMED NNRTI RESISTANCE

2.6.1.3.1 Trial Design

This was a Phase IIa, open-label trial to evaluate the antiviral activity of 8-day treatment with TMC125 at a dose of 900 mg b.i.d., administered as the 50-mg capsule formulation T* (TMC125 in PEG 4000). The trial involved a 7-day run-in period, an 8-day treatment period, and a 4-day follow-up period with an optional 1-month post-trial follow-up visit. TMC125 was administered b.i.d. on Days 1 to 7, followed by a single morning dose on Day 8, in all cases within 10 minutes after a meal.

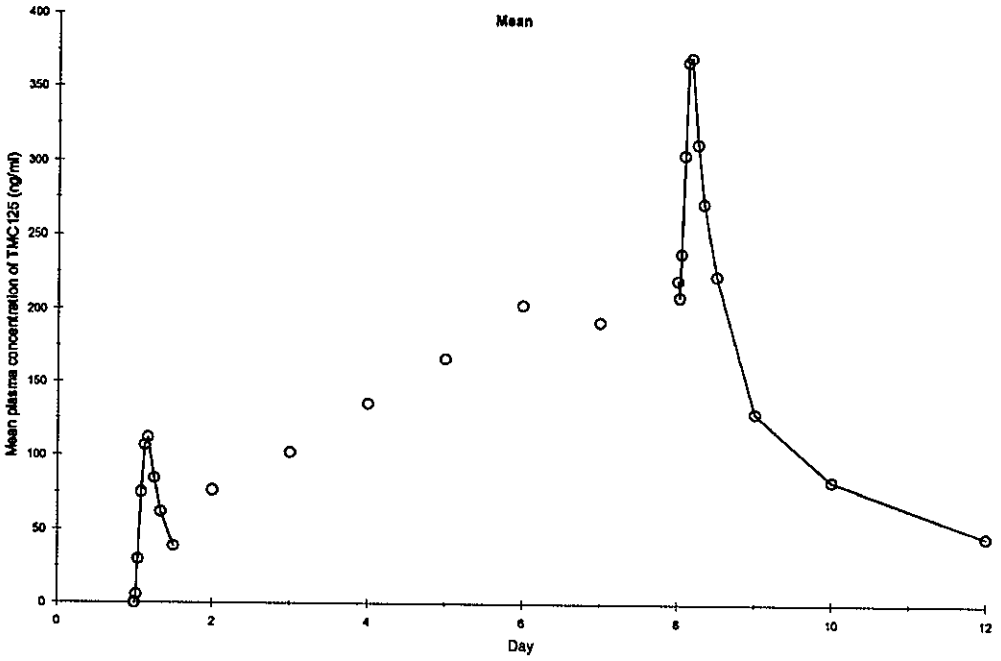
A total of 16 subjects who had been treated with an ARV regimen consisting of at least 2 NRTIs together with an NNRTI (EFV or NVP) for at least one month prior to enrollment, and who had failing NNRTI-containing therapy at screening, were eligible for the trial. Only subjects with a phenotypically confirmed viral resistance against EFV, and who had a viral load of > 2000 HIV-1 RNA copies/mL at screening, were to be enrolled. All subjects received TMC125 900 mg b.i.d. as a substitute for the NNRTI in their failing therapy, thus providing a treatment period of functional monotherapy. This substitution was performed on Day 1 of the treatment period. Subjects were not allowed to change the failing therapy until the end of the run-in period, or to change the NRTIs until the end of the treatment period. After completion of the 8-day treatment period, the investigator continued treating subjects according to the locally applicable standard of care.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.5.2/TMC125-C207).

2.6.1.3.2 Pharmacokinetics of TMC125

The mean plasma-concentration profiles showed a rapid absorption of TMC125 on Days 1 and 8 (Figure 11).

＊：新薬承認情報提供時に置き換え



N = 15.
Source: Module 5.3.5.2/TMC125-C207/Section 6.1/Supporting Data Display 15

Figure 11: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of Capsule Formulation T* (TMC125 in PEG 4000) at a Dose of 900 mg b.i.d. in HIV-1 Infected Subjects (Trial TMC125-C207)

After the first dose and after multiple-dose administration, the median t_{max} of TMC125 was 3 to 4 hours (Table 16). Based on pre-dose concentrations, steady-state was reached after 5 or 6 days of treatment. At steady-state, the exposure to TMC125 (AUC_{12h}) was approximately 4-fold higher than after the first dose.

Table 16: Pharmacokinetics of TMC125 after Administration of Capsule Formulation T* (TMC125 in PEG 4000) at a Dose of 900 mg b.i.d. in HIV-1 Infected Subjects (Trial TMC125-C207)

Parameter	Mean ± SD; t_{max}: Median (Range)	
	Day 1	Day 8
N	15	15
t_{max}, h	3.3 (1.0 - 6.1)	4.0 (1.0 - 6.0)
C_{0h}, ng/mL	-	224.4 ± 227.8
C_{min}, ng/mL	-	204.7 ± 209.9
C_{max}, ng/mL	117.0 ± 83.81	393.9 ± 321.5
$C_{ss,av}$, ng/mL	-	293.5 ± 258.1
AUC_{12h}, ng.h/mL	756.7 ± 622.5	3522 ± 3097
FI, %	-	76.43 ± 23.94
$t_{1/2,term}$ [a], h	-	35.64 ± 18.36

N = maximum number of subjects with data.
[a] Accurate determination not possible in all subjects.
Source: Module 5.3.5.2/TMC125-C207/Section 6.1/Supporting Data Display 16

2.6.1.3.3 Pharmacokinetics of TMC125 in Relation to Other Antiretrovirals

A graphic investigation of the influence of previously used ARV drugs (in the screening period) on the pharmacokinetics of TMC125 revealed no indications for a clinically relevant influence of prior NVP or EFV treatment on the pharmacokinetics of TMC125 (refer to Module 5.3.5.2/TMC125-C207/Section 4.2.5.3). However, this analysis was limited by the small sample size and the large variability in pharmacokinetic parameters. There was also no indication that any NRTI influenced the pharmacokinetics of TMC125.

2.6.1.3.4 Pharmacodynamics

The primary efficacy endpoint was the viral load decay rate for the 8-day treatment period.

Secondary efficacy endpoints included:

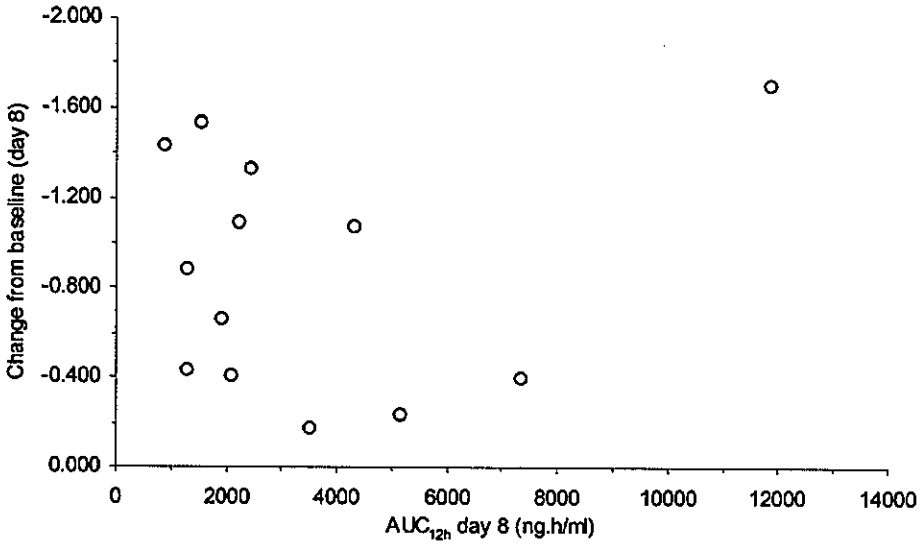
- Nadir (minimum value) of the viral load;
- Change from Baseline in $\log_{10}$ plasma viral load at all time points;
- Change from Baseline in CD4 cell counts.

The 8-day treatment with TMC125 900 mg b.i.d. resulted in a statistically significant decrease from Baseline in plasma viral load in HIV-1 infected subjects with phenotypically confirmed resistance to NNRTIs. The viral load decay rate was -0.12 $\log_{10}$ HIV-1 RNA copies/mL/day. The median change from Baseline after 8 days of treatment was -0.89 $\log_{10}$ HIV-1 RNA copies/mL (range -1.54 to -0.18). The median change from Baseline in CD4 cell count and % CD4 cell count on Day 8 was 2.0 and 0.0, respectively, and was not statistically significant.

Further details are available in Module 5.3.5.2/TMC125-C207.

2.6.1.3.5 Pharmacokinetic/Pharmacodynamic Relationships

No clear relationships were observed between the pharmacokinetics (C_{min}, C_{max}, and AUC_{12h}) of TMC125 and the change in viral load from Baseline on Day 8, as shown for AUC_{12h} in Figure 12 (refer also to Module 5.3.5.2/TMC125-C207/Section 6.1/Supporting Data Display 35).



Source: Module 5.3.5.2/TMC125-C207/Section 6.1/Supporting Data Display 35

Figure 12: Individual Changes in Log_{10} Viral Load from Baseline Versus TMC125 AUC_{12h} on Day 8 (Trial TMC125-C207)

ANCOVA models were used to test for any associations between the pharmacokinetics of TMC125 on Day 8 (AUC_{12h}, C_{max}, C_{min}, and $C_{ss,av}$) and virologic response, defined as change in log_{10} viral load from Baseline on Day 8, the DAVG, the nadir of the change in log_{10} viral load, a change of at least 0.5 or 1.0 log_{10} in viral load from Baseline on Day 8, and a plasma viral load < 400 HIV-1 RNA copies/mL on Day 8 (refer to Module 5.3.5.2/TMC125-C207/Section 6.1/Supporting Data Display 36). The Baseline viral load was included in these models as a covariate. These ANCOVA models revealed no statistically significant relationships between the pharmacokinetics of TMC125 and any of the response parameters.

2.6.1.3.6 Pharmacokinetic/Safety Relationships

Pharmacokinetic/safety relationships were not assessed.

2.6.1.3.7 Conclusions

- At a dose of 900 mg b.i.d., steady-state concentrations of TMC125 were reached in 5 to 6 days. The mean accumulation (AUC_{12h}) after multiple-dose administration for 8 days was approximately 4-fold.
- Treatment with TMC125 900 mg b.i.d. for 8 days resulted in a statistically significant decrease from Baseline in plasma viral load in HIV-1 infected subjects with phenotypically confirmed resistance to NNRTIs (viral load decay rate of -0.12 log_{10} HIV-1 RNA copies/mL/day). The median change from Baseline after 8 days of treatment was -0.89 log_{10} HIV-1 RNA copies/mL (range -1.54 to -0.18).
- There were no statistically significant relationships between the pharmacokinetics of TMC125 and measures of virologic response.

2.6.2 Phase IIb Trials

2.6.2.1 TRIAL TMC125-C203: SAFETY, TOLERABILITY, AND EFFICACY OF A COMBINATION OF AN INDIVIDUALLY OPTIMIZED ANTIRETROVIRAL THERAPY AND ESCALATING DOSES OF TMC125 IN HIV-1 INFECTED, NRTI-, PI-, AND NNRTI-EXPERIENCED SUBJECTS

2.6.2.1.1 Trial Design

This was a Phase IIb, randomized, placebo-controlled, dose-escalating trial conducted in 2 stages to evaluate safety, tolerability, and efficacy of a 48-week treatment with TMC125, administered as the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered), when added to an individually optimized underlying ART. Subjects had to be 3-class ARV experienced, i.e., having received at least 1 NRTI, 1 NNRTI, and 1 PI, each for a period of at least 3 months, in prior treatment regimens. The underlying ART was composed at the discretion of the investigator and consisted of a regimen of 3 or 4 licensed ARV drugs (not counting low-dose rtv). This regimen had to contain NRTIs alone or NRTIs in combination with 1 rtv-boosted PI (either SQV or LPV, dual PIs were not allowed), and/or the fusion inhibitor ENF. This individually optimized underlying ART had to contain at least 2 sensitive ARV drugs based on screening VirtualPhenotype™.

In Stage 1, 166 subjects were randomized in a 1:1:1 ratio to placebo b.i.d., TMC125 400 mg b.i.d., or 800 mg b.i.d. Four weeks after 120 subjects had started treatment in Stage 1, all available data (including efficacy and TMC125 plasma concentrations) were analyzed and reviewed by the Data and Safety Monitoring Board (DSMB) with special focus on all grade 3 and 4 adverse events and all serious adverse events. This was the time point the DSMB would make the decision to allow the opening of Stage 2 of the trial. In Stage 2, at least 74 subjects were randomized in a 1:2:4 ratio to placebo b.i.d., or TMC125 800 or 1200 mg b.i.d.

The primary analysis was performed once all subjects in the 2 stages had been treated for 24 weeks, or had discontinued.

Subjects continued up to 48 weeks of treatment. If they were deriving benefit from their ART (investigational medication inclusive), they were given the option to continue treatment with their blinded randomized dose of investigational medication, in addition to their ART, for an additional 48 weeks. Upon completion of 96 weeks of treatment, subjects had the option to prolong their treatment period for another additional 48 weeks. The sponsor provided open-label follow-up trials (TMC125-C229 [see Section 2.6.2.5] and TMC125-C211) for subjects who participated in this trial.

The final analysis was performed when all subjects had completed the trial, including the follow-up visits, or discontinued earlier.

A pharmacokinetic substudy was performed within the framework of this trial. Subjects enrolled in this substudy had full 12-hour pharmacokinetic profiles determined in addition to the assessments described in the main protocol to enable generation of a full pharmacokinetic profile of TMC125. The population pharmacokinetic model for TMC125 (formulation F*), developed using the full profiles obtained in the substudy as well as profiles obtained in selected Phase I trials, was the basis for the pharmacokinetic/pharmacodynamic analyses for the main trial.

＊：新薬承認情報提供時に置き換え

TMC125 was administered under fed conditions within 15 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.5.1/TMC125-C203).

2.6.2.1.2 Pharmacokinetics of TMC125

The single-dose and steady-state pharmacokinetics of TMC125 were characterized in a pharmacokinetic substudy. The pharmacokinetic profile in this subset of subjects was evaluated at Baseline (Day 1) and Week 4 after administration of different doses of TMC125 b.i.d. in addition to the individually optimized ART. One subject from trial TMC125-C209, who received TMC125 800 mg b.i.d. (also as tablet formulation F*) was included in the pharmacokinetic substudy analysis (see Section 2.6.2.2.1 for details).

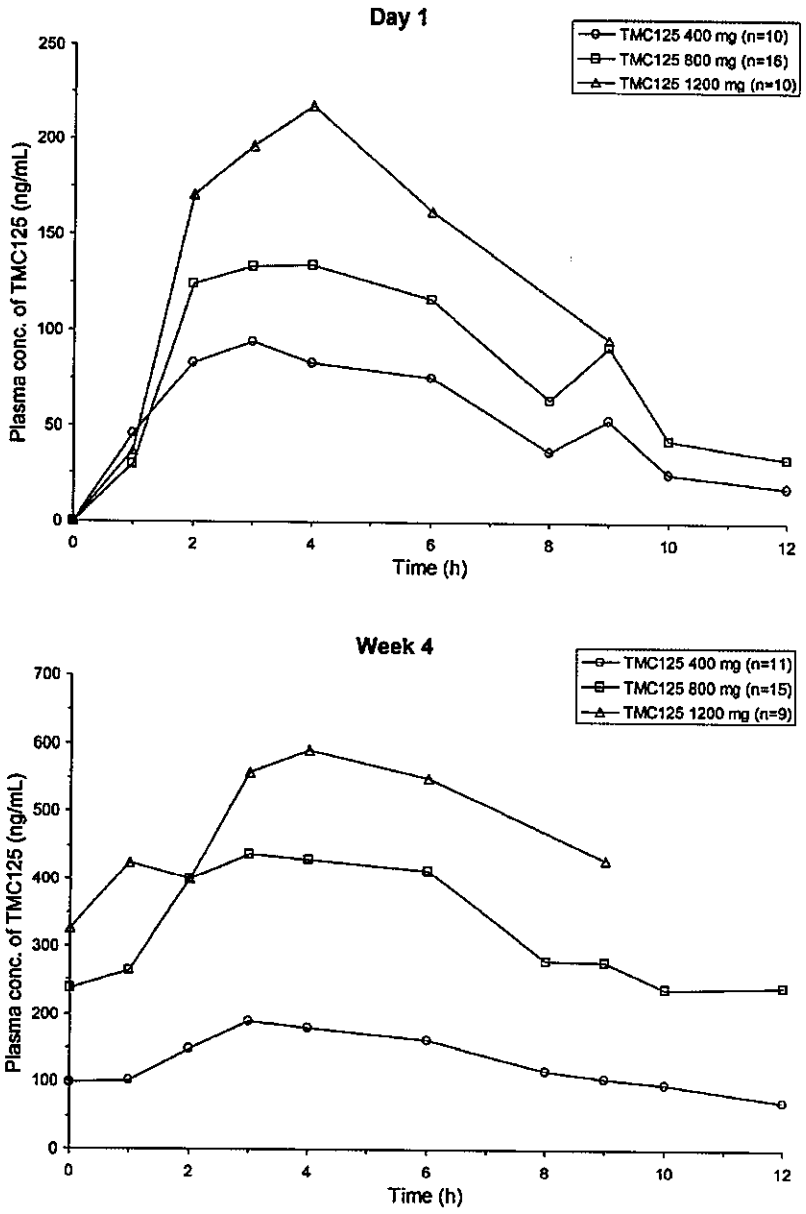
In addition to the pharmacokinetic substudy, and if applicable, predose and/or random plasma concentrations of TMC125 were determined at Baseline (Day 1) and at Weeks 2, 24, 48, 64, 80, 96, 112, 128, and 144. The AUC_{12h} and C_{0h} of TMC125 were then estimated in each subject using population pharmacokinetic techniques.

For the analysis of the pharmacokinetics of TMC125 administered at a dose of 800 mg b.i.d., the data from subjects treated with this dose of TMC125 in Stages 1 and 2 were combined.

Pharmacokinetics in the Substudy

The mean plasma concentration-time curves of TMC125 on Day 1 and at Week 4 are shown in Figure 13.

＊：新薬承認情報提供時に置き換え



The 800 mg b.i.d. group includes one subject from the pharmacokinetic substudy in trial TMC125-C209.
Source: Module 5.3.5.1/TMC125-C203/Section 4.6.1.4

Figure 13: Mean Plasma Concentration-Time Profiles of TMC125 at Baseline (Day 1) and Week 4 after Administration of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at Doses of 400, 800, and 1200 mg b.i.d. in HIV-1 Infected Subjects (Substudy of Trial TMC125-C203)

On Day 1, the median t_{max} was slightly later when TMC125 1200 mg b.i.d. was administered (4 hours), compared to the lower doses of TMC125 400 and 800 mg b.i.d. (3 hours) (Table 17). The TMC125 pharmacokinetic parameters increased less than proportionally between the doses of 400 and 800 mg b.i.d., but the increases were proportional between 800 and 1200 mg b.i.d.

＊：新薬承認情報提供時に置き換え

At Week 4, there were no dose-related differences in median t_{max} across the 3 dose levels. The TMC125 pharmacokinetic parameters increased proportionally between the doses of 400 and 800 mg b.i.d., but the increases were less than proportional between 800 and 1200 mg b.i.d.

The individual Week 4/Day 1 accumulation index for AUC_{12h} ranged from 0.8 to 13.3 for the 400 mg b.i.d. dose level, from 1.4 to 30.6 for the 800 mg b.i.d. dose level, and from 2.7 to 8.6 (but could only be calculated in 4 subjects) for the 1200 mg b.i.d. dose level, reflecting the high inter-subject variability in the accumulation index (Module 5.3.5.1/TMC125-C203/Section 4.6.1.5).

Table 17: Pharmacokinetics of TMC125 at Baseline (Day 1) and Week 4 after Administration of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at Doses of 400, 800, and 1200 mg b.i.d. in HIV-1 Infected Subjects (Substudy of Trial TMC125-C203)

Parameter	Mean ± SD; t_{max}: Median (Range)		
	400 mg b.i.d.	800 mg b.i.d. [a]	1200 mg b.i.d.
Day 1			
N	10	16	10
t_{max}, h	3.00 (2.00 - 6.00)	3.13 (1.75 - 8.00)	4.00 (2.00 - 6.00)
C_{max}, ng/mL	109.6 ± 96.17	160.2 ± 170.5	254.2 ± 176.3
AUC_{12h}, ng.h/mL	701.1 ± 613.3	778.2 ± 489.4	1679 ± 922.9
Week 4			
N	11	15	8
t_{max}, h	3.00 (1.00 - 6.00)	4.00 (1.00 - 6.00)	3.50 (2.00 - 6.00)
C_{0h}, ng/mL	98.73 ± 44.07	237.7 ± 200.2	323.8 ± 426.4
C_{min}, ng/mL	82.45 ± 38.14	216.3 ± 193.7	308.3 ± 393.7
C_{max}, ng/mL	208.6 ± 85.48	487.9 ± 358.4	632.8 ± 518.6
$C_{ss,av}$, ng/mL	144.0 ± 57.10	299.1 ± 258.2	336.5 ± 214.0
AUC_{12h}, ng.h/mL	1728 ± 685.0	3589 ± 3098	4038 ± 2568
FI, %	106.8 ± 37.31	90.24 ± 27.86	109.3 ± 55.75

N = maximum number of subjects with data.
[a] Includes one subject from the pharmacokinetic substudy in trial TMC125-C209.
Source: Module 5.3.5.1/TMC125-C203/Section 4.6.1.5

Population Pharmacokinetics

The AUC_{12h} and C_{0h} of TMC125 were estimated in each subject using population pharmacokinetic techniques. In general, the estimated pharmacokinetic parameters for TMC125 in the respective dose groups (Table 18) were slightly higher than, but in the same range as, the values observed in the pharmacokinetic substudy.

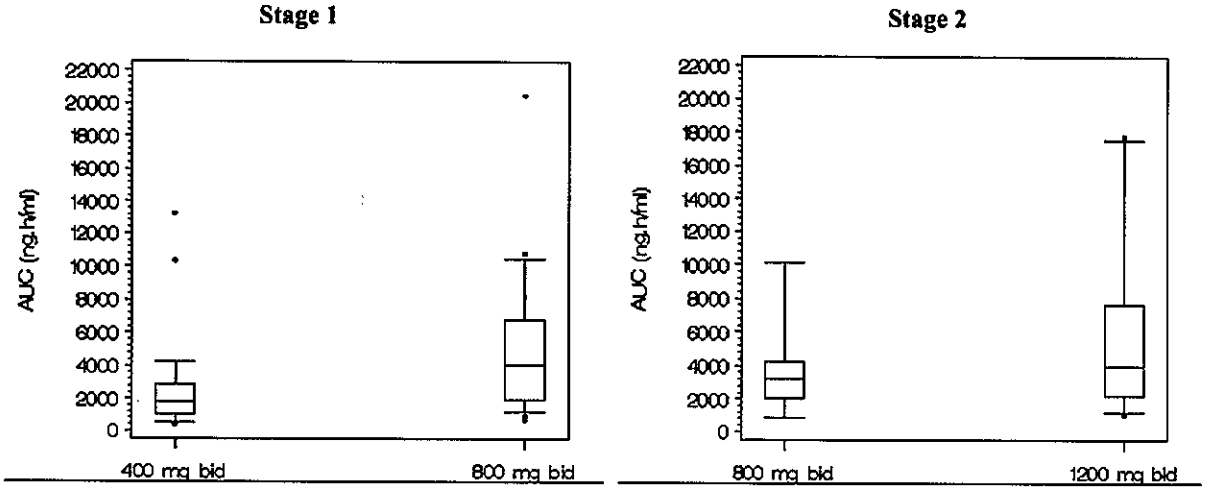
Table 18: Population Pharmacokinetic Estimates of TMC125 after Administration of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at Doses of 400, 800, and 1200 mg b.i.d. in HIV-1 Infected Subjects (Trial TMC125-C203)

Parameter	Mean ± SD		
	400 mg b.i.d.	800 mg b.i.d.	1200 mg b.i.d.
N	51	68	40
C_{0h}, ng/mL	131.3 ± 134.1	278.4 ± 263.2	342.6 ± 341.4
AUC_{12h}, ng.h/mL	2277.4 ± 2248.4	4450.4 ± 3353.1	5545.8 ± 4677.9

N = maximum number of subjects with data.
Source: Module 5.3.5.1/TMC125-C203/Section 4.6.2.4

＊：新薬承認情報提供時に置き換え

The estimated mean pharmacokinetic parameters for TMC125 appeared to increase dose proportionally between the 400 and 800 mg b.i.d. dose levels, but less than dose proportionally between the 800 and 1200 mg b.i.d. dose levels. The variability of the estimated pharmacokinetic parameters was substantial, as illustrated for AUC_{12h} in Figure 14.



Note: Horizontal line in box = median value; box = 25% and 75% percentiles; vertical lines = 5% and 95% percentiles; circles = outliers
Source: Module 5.3.5.1/TMC125-C203/Section 4.6.2.4

Figure 14: Median, 25% and 75% Percentiles, 5% and 95% Percentiles, and Outlier Values for AUC_{12h} of TMC125 in the Respective Dosing Regimens (Trial TMC125-C203)

Hepatitis B and/or C co-infection status, region, and body weight had no apparent effect on AUC_{12h} or C_{0h} values, but the number of subjects per subgroup was limited (Module 5.3.5.1/TMC125-C203/Section 4.6.2.4). Trends of lower AUC_{12h} and C_{0h} values were observed in women and Black subjects, but the low number of subjects per subgroup again prevented definite conclusions from being drawn.

Trends towards lower AUC_{12h} and C_{0h} values were also observed in subjects using TDF or a PI in their underlying ART, but these differences were not statistically significant.

A multivariate ANCOVA analysis with the covariates PI use in the underlying ART, race, sex, weight, age, phenotypic sensitivity score (PSS), treatment groups, hepatitis co-infection status, region of the site, and TDF use in the underlying ART, showed significantly lower values for TMC125 AUC_{12h} and C_{0h} for subjects randomized to TMC125 400 mg b.i.d. (Module 5.3.5.1/TMC125-C203/Supporting Data Display 126). All other factors did not achieve statistical significance.

2.6.2.1.3 Inhibitory Quotients of TMC125

The IQ for TMC125 was calculated on an individual basis using values for TMC125 plasma concentration (obtained via Bayesian feedback) and EC50 from the phenotypic assay at Baseline. Two IQ values were determined in each subject: IQ_{C0h} used the plasma trough concentration of TMC125 as the input for the plasma concentration factor, and $IQ_{Css,av}$ used the $C_{ss,av}$ as the input.

In general, a substantial variability in IQ values was observed within each dose group (Table 19), which was caused mainly by the large variability in the pharmacokinetics of TMC125. The mean values for $IQ_{Css,av}$ and for IQ_{C0h} increased between the 400 and 800 mg b.i.d. dose levels, but there was no clear difference between the mean values at the 800 and 1200 mg b.i.d. dose levels.

Table 19: Inhibitory Quotient of TMC125 after Administration of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at Doses of 400, 800, and 1200 mg b.i.d. in HIV-1 Infected Subjects (Trial TMC125-C203)

Parameter	Mean (Range)		
	400 mg b.i.d.	800 mg b.i.d.	1200 mg b.i.d.
N	45	67	40
IQ_{C0h}	222 (1 - 1267)	593 (2 - 6310)	569 (1 - 6310)
$IQ_{Css,av}$	326 (1 - 1829)	894 (3 - 7742)	822 (1 - 7742)

N = maximum number of subjects with data.
$IQ_{Css,av}$ = average total plasma concentration/EC50; IQ_{C0h} = plasma trough concentration/EC50.
Source: Module 5.3.5.1/TMC125-C203/Section 4.6.3

2.6.2.1.4 Pharmacodynamics

The primary efficacy endpoint was the change from Baseline in log_{10} plasma viral load at Week 24.

Secondary efficacy endpoints included the following:

- Change from Baseline in log_{10} viral load at all other time points;
- DAVG of log_{10} viral load over 24 and 48 weeks, and over the entire treatment period, defined as the AUC of the change in log_{10} plasma viral load from Baseline divided by the time elapsed;
- Proportion of subjects with at least a 0.5 and 1 log_{10} decrease in plasma viral load (compared to Baseline) at each time point and the time from Baseline to achieve this;
- Proportion of subjects with plasma viral load levels < 50 and < 400 HIV-1 RNA copies/mL at each time point and time from Baseline to achieve this;
- Time to loss of virologic response.

At the start of the trial, plasma preparation tubes (PPTs) were used to measure the viral load. As demonstrated also by other trials (Module 5.3.5.1/TMC125-C203/Section 3.1.3.1), the use of plasma preparation tubes confounds the viral load results at the lower end of the range (values < 1000 copies/mL), resulting in a lower number of values < 400 and < 50 HIV-1 RNA copies/mL. Later in the trial, diaminoethanetetra-acetic acid (EDTA) tubes were also used at specific time points. At corresponding time points, viral load values with EDTA tubes were substantially lower than values with PPT tubes.

The primary efficacy parameter was the (imputed) change in log_{10} plasma viral load from Baseline at Week 24. To adjust for the differences in potency in the underlying ART, an ANCOVA model was fitted with covariates including treatment, Baseline log_{10} viral load, region, treatment interruption at screening, presence of primary PI mutations, and use of ENF. In Stage 1, no difference was noted between the treatment groups, either in the PPT analysis or the EDTA analysis; the LS means estimates of the (imputed) change in log_{10} plasma viral load from Baseline at Week 24 were -1.00, -1.07 and -0.86 with PPT, and -1.65, -1.63 and -1.42 with

EDTA for the TMC125 400 mg b.i.d., 800 mg b.i.d. and placebo groups, respectively. In Stage 2, a trend was noted to show an additional benefit of the 2 TMC125 groups over placebo in the PPT analysis; the LS means estimates of the (imputed) change in $\log_{10}$ plasma viral load from Baseline at Week 24 were -1.37, -1.17 and -0.60 for the TMC125 800 mg b.i.d., 1200 mg b.i.d. and placebo groups, respectively. In the EDTA analysis, statistical superiority was noted for the TMC125 800 mg b.i.d. group; the LS means estimates for the (imputed) change in $\log_{10}$ plasma viral load from Baseline at Week 24 were -1.63, -1.28, and -0.53 for the TMC125 800 mg b.i.d., 1200 mg b.i.d., and placebo groups, respectively.

In subgroup analyses of Stage 1 where the potency of the PI component of the underlying ART was most compromised (e.g. subjects with more than 2 primary PI mutations or not using a sensitive PI in the underlying ART), an additional antiviral effect was noted for the TMC125 800 mg b.i.d. group.

Virologic response was defined as viral load < 400 HIV-1 RNA copies/mL, < 50 HIV-1 RNA copies/mL, and decrease in viral load from Baseline of > 1 $\log_{10}$. It should be noted that the response rates were substantially higher with the EDTA data as compared with the PPT data for all treatment groups. In Stage 1, no differences in virologic response (any definition) were noted between the treatment groups. In Stage 2, statistical superiority was noted for the TMC125 800 mg b.i.d. group over placebo for the virologic response (< 400 HIV-1 RNA copies/mL, and decrease of > 1 $\log_{10}$) at Week 24 in the EDTA analyses. At Week 48, an added benefit was still noted, although not statistically significant.

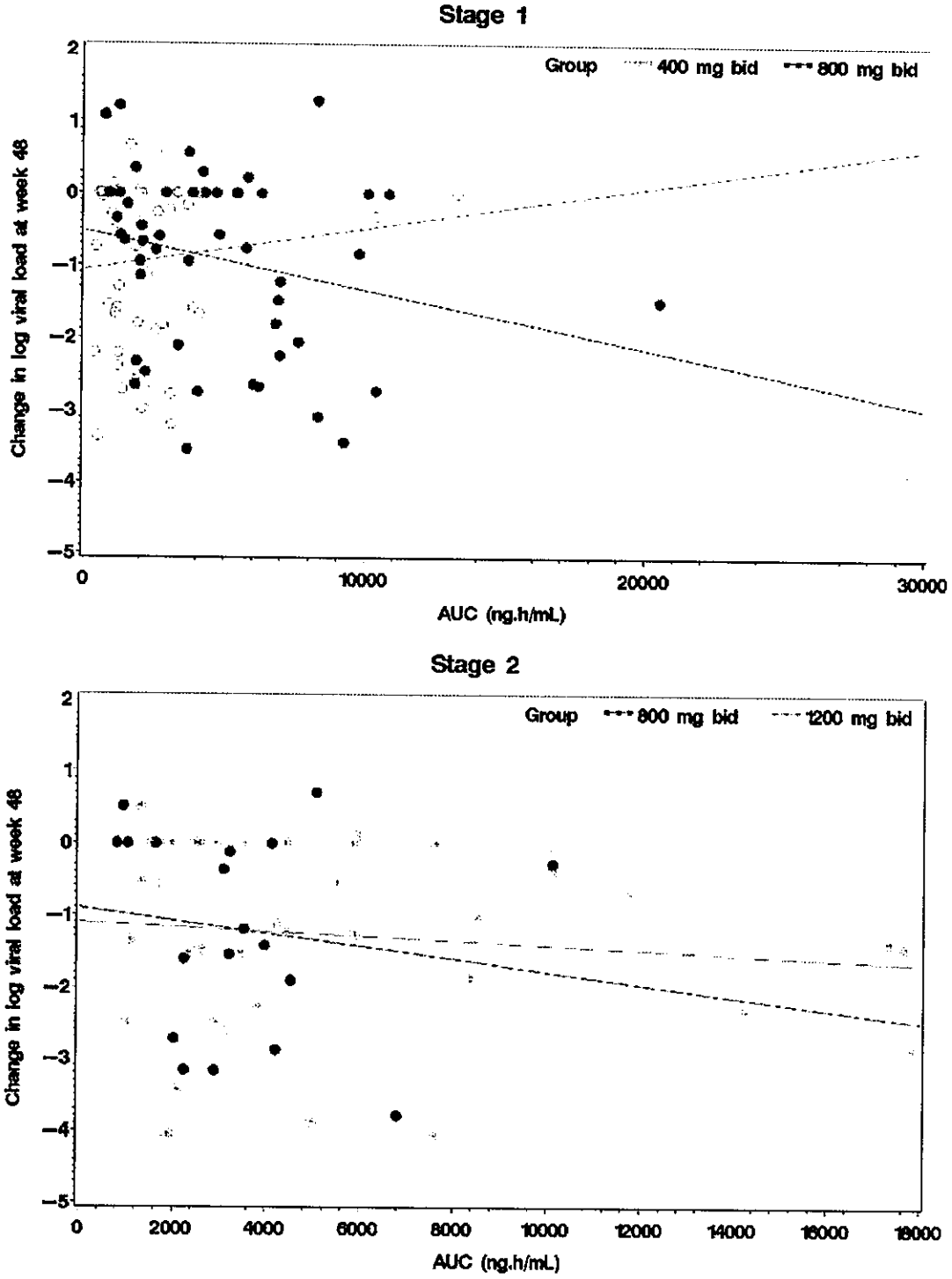
No relevant differences in absolute CD4 cell count were observed between any of the treatment groups in Stage 1, while in Stage 2, the mean (imputed) change from Baseline in CD4 cell count at Week 48 was +128.7, +122.2, and -24.8 x 10^6 cells/L in the TMC125 800 mg b.i.d., TMC125 1200 mg b.i.d., and placebo groups, respectively. Both TMC125 dose groups were also statistically superior over placebo in Stage 2 at Weeks 24 and 48.

Further details are available in Module 5.3.5.1/TMC125-C203.

2.6.2.1.5 Pharmacokinetic/Pharmacodynamic Relationships

Pharmacokinetic Parameters and Log_{10} Viral Load

Graphical analysis of the data suggested a relationship between the pharmacokinetics of TMC125 (AUC_{12h} or C_{0h}) and efficacy (observed or imputed change in viral load from Baseline at Week 48, or DAVG at Week 48) during Stage 1 (Module 5.3.5.1/TMC125-C203/Section 4.7.1), as illustrated by the change in $\log_{10}$ viral load vs. AUC_{12h} in Figure 15. A relationship between TMC125 pharmacokinetics and efficacy was not apparent during Stage 2 (Figure 15).



Source: Module 5.3.5.1/TMC125-C203/Section 4.7.1

Figure 15: Individual Changes in Log_{10} Viral Load from Baseline Versus TMC125 AUC_{12h} at Week 48, Imputed (Trial TMC125-C203)

ANCOVA and logistic regression analyses revealed a statistically significant relationship between the change in log_{10} viral load from Baseline at Week 24 and Week 48 vs. AUC_{12h} and C_{0h} (overall analysis) that was mainly driven by subjects with low exposure to TMC125. However, the Baseline log_{10} viral load, the use of a PI in the underlying ART, and region were generally stronger predictors of response than the pharmacokinetics of TMC125 (Module 5.3.5.1/TMC125-C203/Section 4.7.1).

Inhibitory Quotient and Log_{10} Viral Load

IQ_{C0h} was statistically significantly associated with DAVG and change in log_{10} viral load from Baseline at Week 48 but not at Week 24 (Module 5.3.5.1/TMC125-C203/Section 4.7.2). The $IQ_{Css,av}$ was significantly associated with DAVG but only showed marginal association with change in viral load from Baseline at Week 48; there was no significant association at Week 24. The Baseline log_{10} viral load, the use of a PI in the underlying ART, and region were generally stronger predictors of response than the $IQ_{Css,av}$ or IQ_{C0h} (overall analysis).

2.6.2.1.6 Pharmacokinetic/Safety Relationships

No apparent relationship was observed between TMC125 pharmacokinetics and rash, skin events of interest, nervous system, psychiatric, or gastrointestinal disorders, or the individual events of headache, dizziness, tachycardia, palpitations, or blurred vision (Module 5.3.5.1/TMC125-C203/Section 4.7.3.2). Graphically, no relationship was observed between TMC125 exposure and maximum change from Baseline in pancreatic amylase, lipase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), direct, indirect, and total bilirubin, cholesterol, high density lipoprotein (HDL), triglycerides, T_3, T_4, thyroid stimulating hormone (TSH), or partial thromboplastin time (PTT). There were no relationships between TMC125 exposure (AUC) and the maximum change from Baseline in QRS width or QTcF.

2.6.2.1.7 Conclusions

- In both the pharmacokinetic substudy and the population pharmacokinetic analysis, a dose proportional increase was observed at steady-state between the doses of 400 and 800 mg b.i.d., but a less than dose-proportional increase was observed between 800 and 1200 mg b.i.d.
- Trends of lower AUC_{12h} and C_{0h} values were observed in women, Black subjects, and subjects using TDF or PI, but the low number of subjects per subgroup prevented definite conclusions from being drawn.
- In Stage 1, no efficacy difference was noted between the treatment groups. In subgroups of Stage 1 where the potency of the underlying ART was most compromised, an additional antiviral benefit with TMC125 was demonstrated. In the subgroups of subjects with no sensitive PI in the underlying ART or with primary PI mutations > 2, a benefit of TMC125 800 mg b.i.d. was observed compared to TMC125 400 mg b.i.d. and placebo.
- In Stage 2, both TMC125 groups showed an added benefit in antiviral activity over the placebo group that was statistically significant only in the EDTA analyses, as well as a statistically significant benefit in CD4 cell response.
- Graphical analysis suggested a relationship between the pharmacokinetics of TMC125 and efficacy during Stage 1, but not during Stage 2.

- TMC125 AUC_{12h} and C_{0h} were significantly related to the decrease in viral log_{10} load, but Baseline viral load, use of PI, and region showed a stronger relationship to efficacy.
- No apparent relationship was observed between the pharmacokinetics of TMC125 and adverse events or changes in laboratory safety parameters.

2.6.2.2 TRIAL TMC125-C209: SAFETY, TOLERABILITY, AND EFFICACY OF A COMBINATION OF AN INDIVIDUALLY OPTIMIZED ANTIRETROVIRAL THERAPY AND TMC125 IN HIV-1 INFECTED, NRTI-, PI-, AND NNRTI-EXPERIENCED SUBJECTS

2.6.2.2.1 Trial Design

This was an open-label, single group Phase IIb trial conducted in 7 HIV-1 infected, 3-class (NNRTI, PI, and NRTI) ART-experienced subjects who had received at least 1 NRTI, 1 NNRTI and 1 PI each for at least 3 months prior to the treatment regimen. The primary objective was to evaluate the safety and tolerability of TMC125 800 mg b.i.d. when combined with an individually optimized ARV regimen for 48 weeks. Efficacy was assessed as a secondary objective. The trial was originally designed to investigate higher doses of TMC125 (1200 and 1600 mg b.i.d.) given as formulation F* (TMC125 in HPMC, granulo-layered). Shortly after the start of the trial, an unexpected cluster of atypical rashes occurred in a Phase I trial with TMC125 in healthy subjects. It was therefore decided that the evaluation of higher doses of TMC125 would be more appropriate in a dose escalation design and trial TMC125-C203 was redesigned to incorporate this approach (see Section 2.6.2.1). Enrolment into trial TMC125-C209 was stopped and the few subjects already included were given the option to continue with open-label TMC125 at a lower dose (800 mg b.i.d.).

The revised objective of trial TMC125-C209 was to evaluate the safety and tolerability of TMC125 800 mg b.i.d. (formulation F*). In addition, antiviral activity, immunologic changes, changes in viral genotype and drug susceptibility, and pharmacokinetics of TMC125 were determined. Eligible subjects received TMC125 800 mg b.i.d. combined with an individually optimized ART for at least the original 48 week treatment period. The individually optimized ART consisted of 3 or 4 approved ARVs, i.e., a combination of 1 rtv-boosted PI (either LPV or SQV) and at least 2 NRTIs, and had to contain at least 2 sensitive ARV drugs based on screening *Virtual*Phenotype™. Subjects deriving clinical benefit after 48 weeks, in the opinion of the investigator, were offered the option to extend treatment for 2 additional 48-week periods.

A population pharmacokinetic analysis was conducted using samples obtained in the main trial up to Week 144 (sparse sampling). The pharmacokinetics of TMC125 were also planned to be analyzed using samples obtained in a pharmacokinetic substudy (rich sampling). However, only one subject was enrolled in the substudy, so the pharmacokinetic data from this subject were combined with the data from subjects in the 800 mg b.i.d. group in the pharmacokinetic substudy of trial TMC125-C203 (using the same dose and formulation of TMC125). These combined results are summarized in Section 2.6.2.1.2.

TMC125 was administered under fed conditions within 15 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.5.2/TMC125-C209).

＊：新薬承認情報提供時に置き換え

2.6.2.2.2 Pharmacokinetics of TMC125 (Population Pharmacokinetics)

The population estimates for C_{0h} and AUC_{12h} were slightly higher than, but within the range of, estimates obtained in other Phase II trials using the same dose and formulation of TMC125 (trials TMC125-C203 [see Section 2.6.2.1.2] and TMC125-C223 [see Section 2.6.2.3.2]), which was likely due to the very small sample size and potentially also the presence of 2 outliers in this analysis (refer to Module 5.3.5.2/TMC125-C209/Section 4.6.2.4).

Table 20: Population Pharmacokinetic Estimates of TMC125 after Administration of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at a Dose of 800 mg b.i.d. in HIV-1 Infected Subjects (Trial TMC125-C209)

Parameter	Mean (SD), Range
N	7
C_{0h}, ng/mL	504.76 (725.64), 52.17 - 2037
AUC_{12h}, ng.h/mL	9125 (10467), 1214 - 25337

N = maximum number of subjects with data.
Source: Module 5.3.5.2/TMC125-C209/Section 4.6.2.4

2.6.2.2.3 Conclusions

The population pharmacokinetic estimates for TMC125 exposure in these 7 subjects were higher than, but within the range of, estimates obtained in other Phase II trials using the same dose and formulation of TMC125.

2.6.2.3 Trial TMC125-C223: Dose-Finding Trial Investigating the Efficacy of TMC125 in HIV-1 Infected Subjects Resistant to Currently Available NNRTIs and with at Least 3 Primary PI Mutations

2.6.2.3.1 Trial Design

This was a Phase IIb, randomized, controlled, partially blinded dose-finding trial in HIV-1 infected subjects to investigate the dose-response relationship of TMC125 antiviral activity at Week 24 as well as to evaluate the antiviral activity, safety, tolerability, immunological changes, changes in viral genotype and drug susceptibility, and pharmacokinetics of 2 doses of TMC125 administered for 48 weeks.

Eligible subjects had a plasma viral load of at least 1000 HIV-1 RNA copies/mL, demonstrated genotypic evidence of resistance to currently available NNRTIs, had at least 3 primary PI mutations at screening, and previous NRTI experience. A total of 199 subjects were randomized (1:2:2) to either a control group, or to TMC125 treatment at a dose of 400 or 800 mg b.i.d. TMC125 was administered as the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered). The control group was open-label, whereas the TMC125 groups were blinded.

The background therapy of the subjects randomized to the TMC125 groups consisted of an investigator-selected therapy of at least 2 approved ARV drugs (any combination of NRTI[s] and/or LPV/rtv and/or ENF). The ART of the subjects randomized to the control group consisted of an investigator-selected therapy (standard of care) consisting of at least 3 approved ARV drugs (any combination of NRTIs and/or PIs and/or ENF). Dose adjustments and within-class substitutions were allowed for tolerability reasons except for the PI class, which in the TMC125 group was to remain LPV/rtv.

The pharmacokinetics of TMC125, when administered in addition to an individually optimized ART, were analyzed using samples obtained in a pharmacokinetic substudy at Baseline (Day 1) and Week 4 (rich sampling), and a population pharmacokinetic analysis was conducted using samples obtained in the main trial up to Week 48 (sparse sampling).

TMC125 was administered under fed conditions within 15 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.5.1/TMC125-C223).

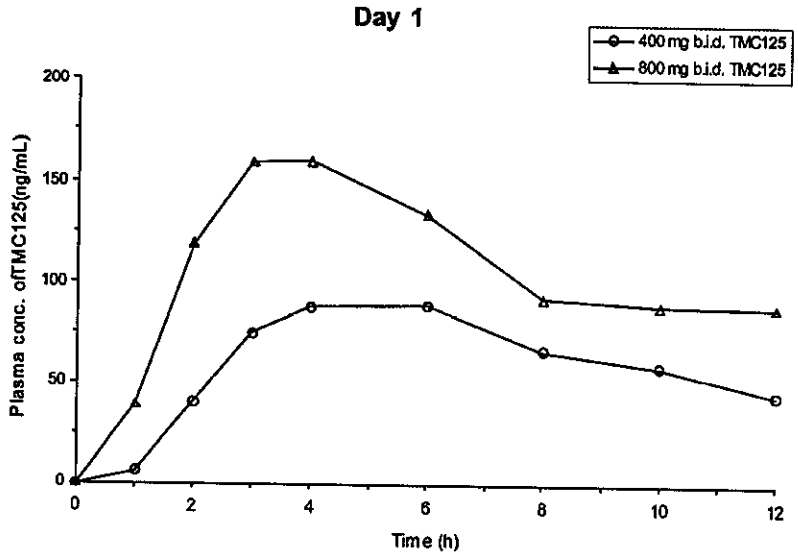
2.6.2.3.2 Pharmacokinetics of TMC125

The single-dose and steady-state pharmacokinetics of TMC125 were characterized in a pharmacokinetic substudy. The pharmacokinetic profile in this subset of subjects was evaluated at Baseline (Day 1) and Week 4 after administration of different doses of TMC125 b.i.d. in addition to the individually optimized ART. The model developed using the full profiles obtained in this substudy was the basis for the pharmacokinetic/pharmacodynamic analysis in the main trial.

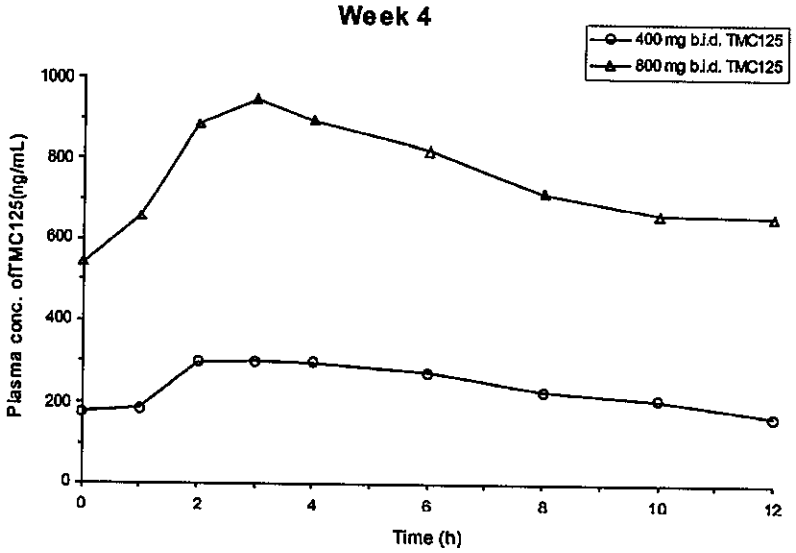
In addition to the pharmacokinetic substudy, predose and/or random plasma concentrations of TMC125 were determined in all subjects at Baseline (Day 1) and at Weeks 4, 8, 12, 24, and 48. The AUC_{12h} and C_{0h} of TMC125 were then estimated in each subject using population pharmacokinetic techniques.

Pharmacokinetics in the Substudy

The mean plasma concentration-time curves of TMC125 on Day 1 and at Week 4 are shown in Figure 16.



400 mg b.i.d.: N = 12; 800 mg b.i.d.: N = 17



400 mg b.i.d.: N = 10; 800 mg b.i.d.: N = 15
Source: Module 5.3.5.1/TMC125-C223/Section 4.6.1.4

Figure 16: Mean Plasma Concentration-Time Profiles of TMC125 at Baseline (Day 1) and Week 4 after Administration of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at Doses of 400 and 800 mg b.i.d. in HIV-1 Infected Subjects (Substudy of Trial TMC125-C223)

On Day 1, the median t_{max} was slightly later when TMC125 400 mg b.i.d. was administered (5 hours), compared to the higher dose of TMC125 800 mg b.i.d. (4 hours) (Table 21). The mean C_{max} and AUC_{12h} of TMC125 were increased 1.9- and 1.7-fold, respectively, for TMC125 800 mg b.i.d., compared to TMC125 400 mg b.i.d.

＊：新薬承認情報提供時に置き換え

At Week 4, the mean C_{max} and AUC_{12h} of TMC125 were increased 3.0- and 3.3-fold, respectively, for the TMC125 800 mg b.i.d. group, compared to the TMC125 400 mg b.i.d. group, indicating a more than dose proportional increase. The mean C_{0h}, C_{12h}, C_{min}, and $C_{ss,av}$ of TMC125 were also increased 3.1- to 3.9-fold. There was no difference in median t_{max} at the 2 dose levels.

The individual Week 4/Day 1 accumulation ratios for AUC_{12h} of TMC125 400 and 800 mg b.i.d. ranged from 223% to 865% and 328% to 2167%, respectively, with geometric means of 423% and 644% (Module 5.3.5.1/TMC125-C223/Section 4.6.1.5).

Table 21: Pharmacokinetics of TMC125 at Baseline (Day 1) and Week 4 after Administration of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at Doses of 400 and 800 mg b.i.d. in HIV-1 Infected Subjects (Substudy of Trial TMC125-C223)

Parameter	Mean ± SD; t_{max}: Median (Range)	
	400 mg b.i.d.	800 mg b.i.d.
Day 1		
N	12	17
t_{max}, h	4.99 (2.17 - 10.00)	4.00 (1.98 - 12.02)
C_{max}, ng/mL	106.7 ± 81.85	206.0 ± 133.6
AUC_{12h}, ng.h/mL	751.2 ± 544.9	1309 ± 939.1
Week 4		
N	10	15
t_{max}, h	3.00 (0.00 - 8.17)	3.00 (0.00 - 12.00)
C_{0h}, ng/mL	177.4 ± 116.1	543.2 ± 375.5
C_{12h}, ng/mL	167.4 ± 131.5	660.4 ± 605.3
C_{min}, ng/mL	154.9 ± 116.9	510.0 ± 386.8
C_{max}, ng/mL	339.5 ± 235.3	1013 ± 717.4
$C_{ss,av}$, ng/mL	231.3 ± 169.4	765.5 ± 562.8
AUC_{12h}, ng.h/mL	2775 ± 2033	9189 ± 6752
FI, %	83.56 ± 27.26	64.89 ± 26.97

N = maximum number of subjects with data.

Source: Module 5.3.5.1/TMC125-C223/Section 4.6.1.5

Population Pharmacokinetics

The AUC_{12h} and C_{0h} of TMC125 were estimated in each subject using population pharmacokinetic techniques. The estimated mean pharmacokinetic parameters for TMC125 in the respective dose regimens appeared to be dose proportional (Table 22). However, no formal statistical testing was performed.

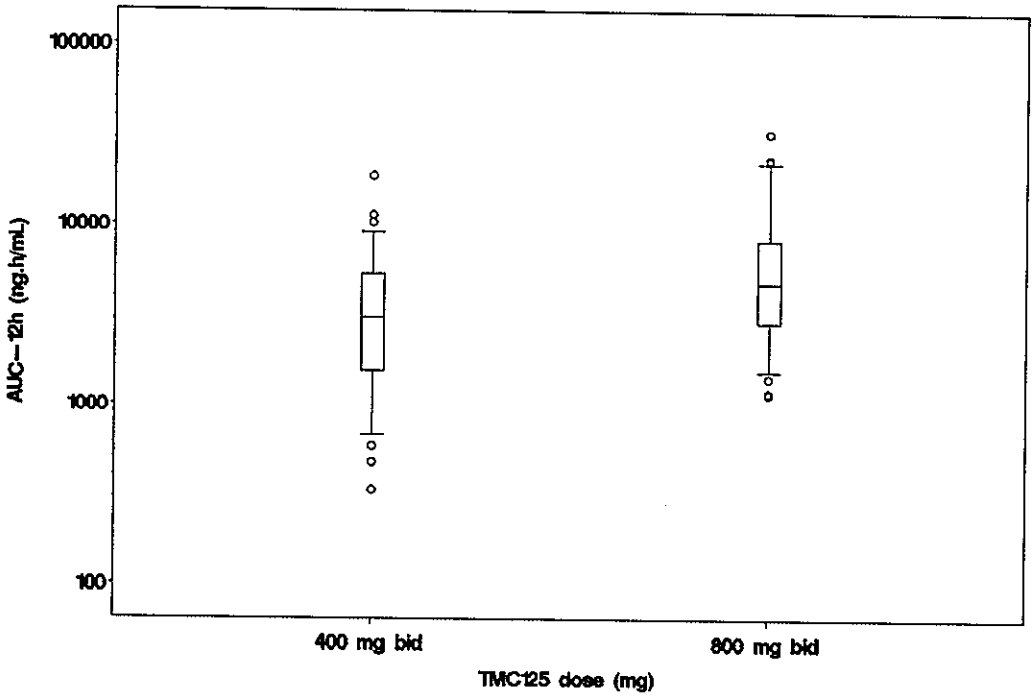
＊：新薬承認情報提供時に置き換え

Table 22: Population Pharmacokinetic Estimates of TMC125 after Administration of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at Doses of 400 and 800 mg b.i.d. in HIV-1 Infected Subjects (Trial TMC125-C223)

Parameter	Mean (SD), Range	
	400 mg b.i.d.	800 mg b.i.d.
N	75	75
C_{0h}, ng/mL	240.2 (204.38), 20 - 939	416.0 (370.48), 58 - 1682
AUC_{12h}, ng.h/mL	3952.3 (3193.87), 333 - 18666	6930.6 (6177.73), 1157 - 32673

N = maximum number of subjects with data.
Source: Module 5.3.5.1/TMC125-C223/Section 4.6.2.4

The variability of the estimated AUC_{12h} (Figure 17) and C_{0h} values was substantial.



400 mg b.i.d.: N = 75; 800 mg b.i.d.: N = 75
Note: Horizontal line in box = median value; box = 25% and 75% percentiles; vertical lines = 5% and 95% percentiles; circles = outliers
Source: Module 5.3.5.1/TMC125-C223/Section 4.6.2.4

Figure 17: Median, 25% and 75% Percentiles, 5% and 95% Percentiles, and Outlier Values for AUC_{12h} of TMC125 in the Respective Dosing Regimens (Trial TMC125-C223)

A multivariate analysis, including the covariates age and body weight and the factors sex, viral hepatitis co-infection status, use of a PI, race, randomization group and use of TDF, showed that randomization to TMC125 400 mg b.i.d., use of a PI (LPV/rtv), or use of TDF in the background regimen were all associated with a statistically significant lower exposure and trough concentration of TMC125 (Table 23 and Table 24). With a PI or use of TDF in the background regimen, there were reductions in TMC125 exposure, compared to the absence of a PI or no use

＊：新薬承認情報提供時に置き換え

of TDF in the background regimen (see Section 2.6.2.3.5). Further, it should be noted that most of the subjects with a PI in their ART were also using TDF.

Table 23: Population Pharmacokinetic Estimates of TMC125 after Administration of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at Doses of 400 and 800 mg b.i.d. in HIV-1 Infected Subjects, with or without a PI in the Underlying ART (Trial TMC125-C223)

Parameter	Mean (SD), Range	
	400 mg b.i.d.	800 mg b.i.d.
No PI in the ART		
N	28	34
C_{0h}, ng/mL	317.5 (200.89), 70 - 688	496.4 (374.46), 87 - 1682
AUC_{12h}, ng.h/mL	4905.9 (2656.14), 1222 - 10313	7963.9 (5850.43), 1564 - 23413
PI in the ART		
N	47	41
C_{0h}, ng/mL	194.2 (194.21), 20 - 939	349.3 (358.04), 58 - 1533
AUC_{12h}, ng.h/mL	3384.2 (3374.27), 333 - 18666	6073.7 (6380.15), 1157 - 32673

N = maximum number of subjects with data.
Source: Module 5.3.5.1/TMC125-C223/Section 4.6.2.4

Table 24: Population Pharmacokinetic Estimates of TMC125 after Administration of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at Doses of 400 and 800 mg b.i.d. in HIV-1 Infected Subjects, with or without TDF in the Underlying ART (Trial TMC125-C223)

Parameter	Mean (SD), Range	
	400 mg b.i.d.	800 mg b.i.d.
No TDF in the ART		
N	13	13
C_{0h}, ng/mL	250.5 (170.99), 91 - 584	720.6 (524.59), 128 - 1682
AUC_{12h}, ng.h/mL	4215.5 (2540.81), 1426 - 8890	10777.6 (7234.12), 2332 - 22902
TDF in the ART		
N	62	62
C_{0h}, ng/mL	238.1 (211.88), 20 - 939	352.1 (297.35), 58 - 1533
AUC_{12h}, ng.h/mL	3897.1 (3329.70), 333 - 18666	6123.9 (5673.40), 1157 - 32673

N = maximum number of subjects with data.
Source: Module 5.3.5.1/TMC125-C223/Section 4.6.2.4

2.6.2.3.3 Inhibitory Quotients of TMC125

IQ values of TMC125 were calculated on an individual basis. The IQ was calculated using the TMC125 plasma concentration (as obtained via Bayesian feedback) and the EC50 for TMC125 from the phenotypic assay at Baseline (or screening if the Baseline value was missing). For each subject, 2 IQ values were determined: IQ_{C0h} used the plasma trough concentration of TMC125 as the input for the plasma concentration factor, and $IQ_{Css,av}$ used $C_{ss,av}$ as the input.

＊：新薬承認情報提供時に置き換え

IQ values were above 1.0 for all subjects, and the IQ values were generally high (Table 25). The mean IQ values increased with the higher dose of TMC125.

Table 25: Inhibitory Quotient of TMC125 after Administration of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at Doses of 400 and 800 mg b.i.d. in HIV-1 Infected Subjects (Trial TMC125-C223)

Parameter	Geometric Mean (Range)	
	400 mg b.i.d.	800 mg b.i.d.
N	75	74
IQ_{C0h}	259 (2 - 11813)	333 (2 - 15411)
$IQ_{Css,av}$	367 (3 - 13115)	466 (2 – 31276)

N = maximum number of subjects with data.
$IQ_{Css,av}$ = average total plasma concentration/EC50; IQ_{C0h} = plasma trough concentration/EC50.
Source: Module 5.3.5.1/TMC125-C223/Section 4.6.3

2.6.2.3.4 Pharmacodynamics

The primary efficacy endpoint was the change from Baseline in log_{10} plasma viral load at Week 24.

Secondary efficacy endpoints included the following:

- DAVG of log_{10} viral load over 12, 24, and 48 weeks, which is defined as the AUC of the change in log_{10} plasma viral load from Baseline divided by the time elapsed;
- Change from Baseline in log_{10} viral load at all other time points;
- Proportion of subjects with 0.5 and 1 log_{10} decrease in plasma viral load (compared to Baseline) at each time point and the time from Baseline to achieve this;
- Proportion of subjects with plasma viral load levels < 50 and < 400 HIV-1 RNA copies/mL at each time point and time from Baseline to achieve this;
- Time to loss of virologic response over the 48-week treatment period.

Both TMC125 groups achieved a mean reduction (imputed data) of approximately 1.0 log_{10} HIV-1 RNA copies/mL in viral load relative to Baseline at Week 24, and this was well sustained to Week 48. In the primary analysis, an ANCOVA model including stratification factors of actual ENF use in the ART (which differed slightly from what was included by the investigator in the stratification for randomization) and actual treatment interruption at screening, and covariates of imputed Baseline CD4 cell count and imputed Baseline log_{10} viral load, no statistically significant difference was observed between the 2 TMC125 groups at Week 24 ($p = 0.337$) or Week 48 ($p = 0.376$), while both TMC125 groups were statistically superior to the control group at Week 24 (400 mg b.i.d.: $p = 0.003$; 800 mg b.i.d.: $p < 0.001$) and Week 48 (400 mg b.i.d.: $p = 0.018$; 800 mg b.i.d.: $p = 0.002$).

In contrast to treatment interruption at screening and Baseline viral load, the use of ENF at both time points as well as Baseline CD4 cell count at Week 24 were significant predictors of the change in log_{10} viral load in this model.

In the subgroup of subjects that used ENF de novo, the change in viral load from Baseline was more pronounced than in those subjects who re-used or did not use ENF. Furthermore, the number of sensitive drugs used in the underlying ART had an important impact on the antiviral efficacy. The change from Baseline in viral load was greater in all treatment groups, when more

＊：新薬承認情報提供時に置き換え

sensitive drugs were used in the underlying ART. When either one or no sensitive drug was used, there was a trend towards the TMC125 400 mg b.i.d. group having a lesser decrease in viral load from Baseline than in the TMC125 800 mg b.i.d. group.

Both TMC125 treatment groups were statistically superior compared to the control group for the virologic response parameters (viral load < 50 or < 400 HIV-1 RNA copies/mL, or a decrease from Baseline of at least 1.0 log_{10} in viral load) at Week 48, with no statistically significant difference between the 2 TMC125 groups.

A higher number of subjects in the control group (77.5%) than in the TMC125 groups (8.8%) discontinued due to virologic failure.

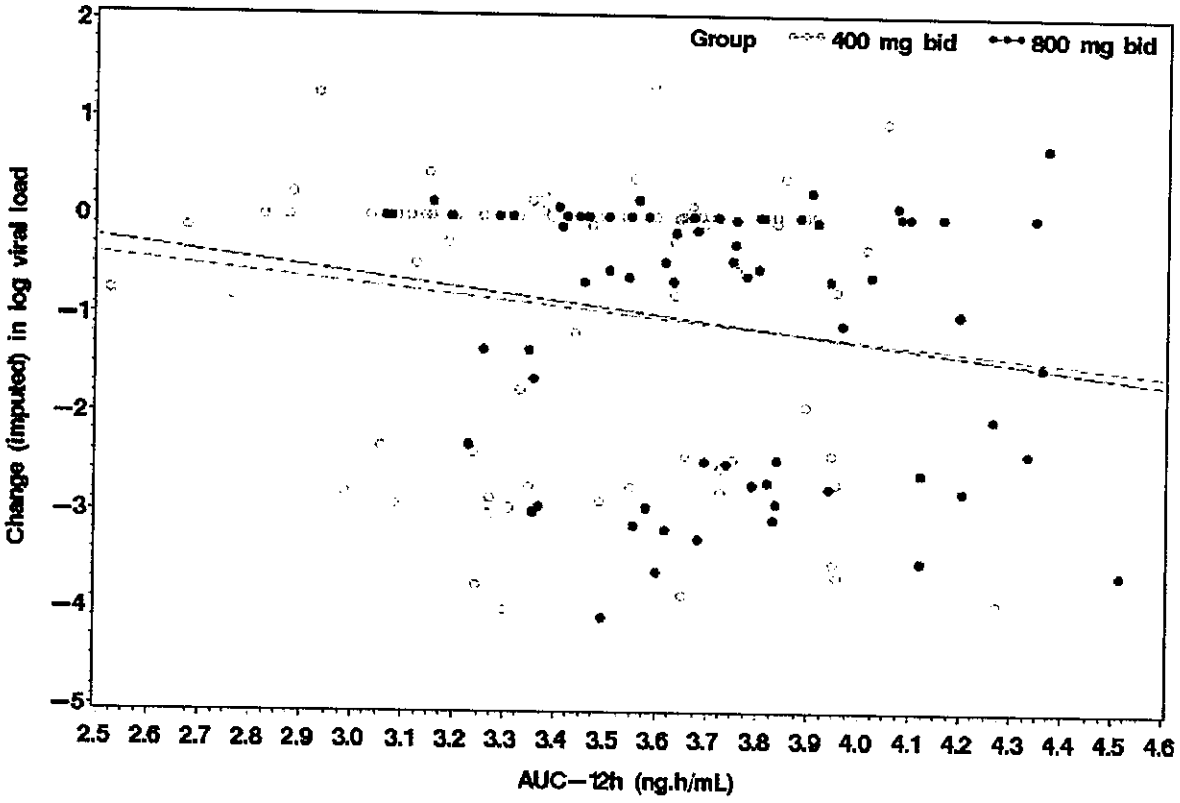
The ANCOVA model used to analyze the change in immunologic parameters at Weeks 24 and 48 showing no statistically significant difference between the 2 TMC125 groups. The numerically greater changes in CD4 cell count in the TMC125 groups were not statistically significantly different from the control group.

Further details are available in Module 5.3.5.1/TMC125-C223.

2.6.2.3.5 Pharmacokinetic/Pharmacodynamic Relationships

Pharmacokinetic Parameters and Log_{10} Viral Load

Graphic analysis of the data revealed no obvious relationship between the pharmacokinetics of TMC125 (AUC_{12h} or C_{0h}) and efficacy (observed or imputed change in log_{10} viral load from Baseline at Week 48, or DAVG at Week 48). The relationship for AUC_{12h} is shown in Figure 18, and further details are available in Module 5.3.5.1/TMC125-C223/Section 4.7.1.



Source: Module 5.3.5.1/TMC125-C223/Section 4.7.1

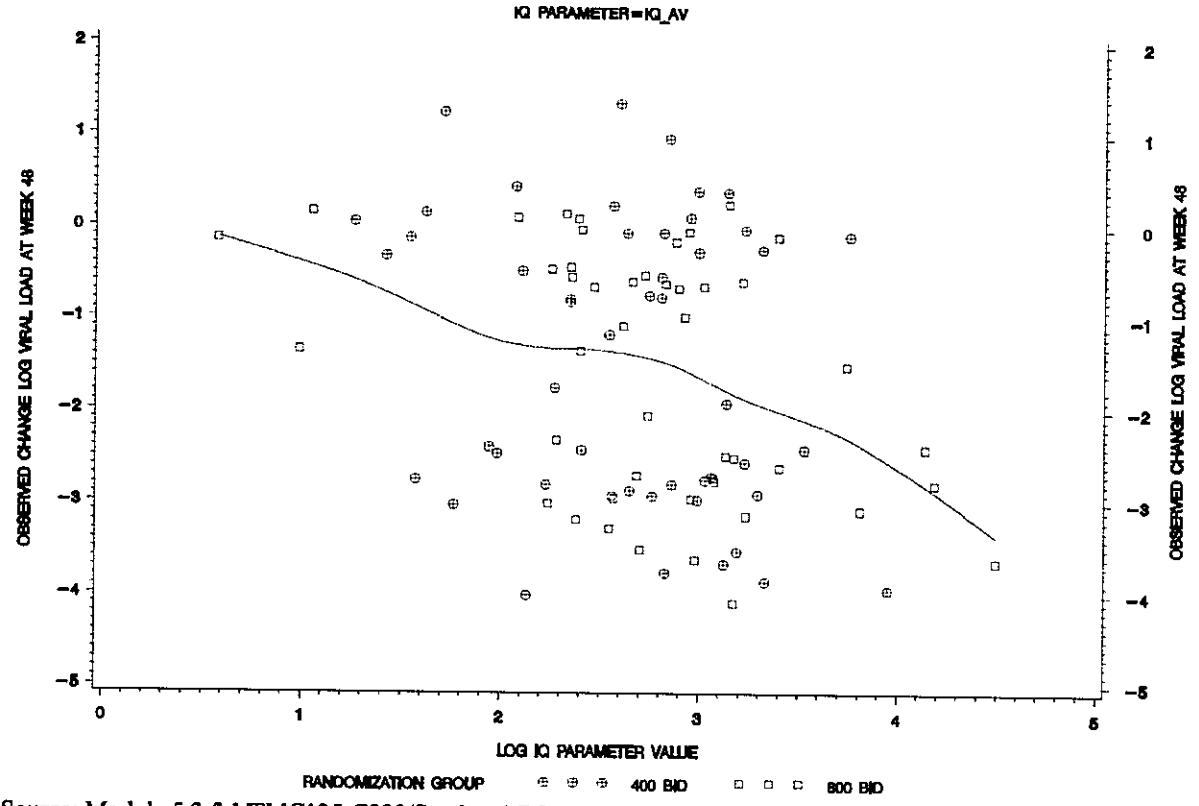
Figure 18: Individual Changes in Log_{10} Viral Load from Baseline Versus Log_{10} TMC125 AUC_{12h} at Week 48, Imputed (Trial TMC125-C223)

In ANCOVA models, with covariates of Baseline log_{10} viral load, Baseline CD4 cell count, treatment interruption at screening, PSS, use of ENF (categorized as de novo use, re-use, not used), TDF use (categorized as no, yes and sensitive, or yes and resistant) or PI use (categorized as no, yes and sensitive, or yes and resistant), the pharmacokinetic parameters of TMC125 (AUC, C_{0h}, and $C_{ss,av}$) were statistically significantly associated with change in viral load from Baseline to Week 24 and 48 (intent-to-treat [ITT] or last observation carried forward [LOCF]) with p-values in the range of 0.013 to 0.041. The use of ENF de novo was the covariate with the strongest relationship to efficacy in these models ($p < 0.001$).

TMC125 AUC was no longer statistically significantly associated with change in viral load from Baseline to Weeks 24 or 48 with multivariate analysis using only the 800 mg b.i.d. group with covariates of Baseline log_{10} viral load, Baseline CD4 cell count, treatment interruption at screening, FC, use of ENF, and use of TDF. The use of ENF de novo was the only covariate with a statistically significant relationship to efficacy in these models ($p \leq 0.01$).

Inhibitory Quotient and Log_{10} Viral Load

ANCOVA and logistic regression models with the covariates described above were run using $IQ_{Css,av}$ and IQ_{C0h}. In all models, the $IQ_{Css,av}$ and IQ_{C0h} were statistically significantly associated with efficacy (p-values were generally < 0.001) (Figure 19). In addition, the use of ENF de novo was statistically significantly associated with efficacy (p-values generally < 0.001).



Source: Module 5.3.5.1/TMC125-C223/Section 4.7.2

Figure 19: Individual Changes in Log_{10} Viral Load from Baseline Versus TMC125 $IQ_{Css,av}$ at Week 48 With Smoothed Spline (Trial TMC125-C223)

$IQ_{Css,av}$ was no longer statistically significantly associated with change in viral load from Baseline at Weeks 24 or 48 with multivariate analysis using only the 800 mg dose group with covariates of Baseline log_{10} viral load, Baseline CD4 cell count, treatment interruption at screening, FC, use of ENF, AUC, and $IQ_{Css,av}$. The use of ENF de novo was the only covariate with a statistically significant relationship to efficacy in these models ($p \leq 0.01$).

2.6.2.3.6 Pharmacokinetic/Safety Relationships

No apparent relationship was observed between TMC125 exposure and rash, skin events of interest, nervous system, psychiatric, or gastrointestinal disorders, or the individual events of headache, dizziness, tachycardia, palpitations, or blurred vision (see Module 5.3.5.1/TMC125-C223/Section 4.7.3).

Graphically, no relationship was observed between TMC125 exposure and maximum change from Baseline in pancreatic amylase, lipase, ALT, AST, ALP, direct, indirect, and total bilirubin, cholesterol, low density lipoprotein (LDL), HDL, triglycerides, PTT, or prothrombin time (PT).

2.6.2.3.7 Conclusions

- In a population pharmacokinetic analysis, TMC125 appeared to be dose proportional between the 400 and 800 mg b.i.d. groups.
- With a PI or use of TDF in the background regimen, TMC125 exposure was lower compared to the absence of a PI and no use of TDF in the background regimen.

- TMC125 showed significant and durable efficacy in an ARV-experienced and advanced population with confirmed NNRTI and PI resistance.
- The use of ENF de novo was the only covariate with a statistically significant relationship to efficacy in both the larger model and the subgroup analysis conducted with the 800 mg b.i.d. dose cohort.
- No apparent relationship was observed between TMC125 pharmacokinetics and adverse events or maximum change in laboratory parameters.
- Based on these results, and those of trial TMC125-C203, the 800-mg b.i.d. dose of TMC125 (formulation F*) was the dose selected from the Phase IIb program for further clinical development of TMC125.

2.6.2.4 TRIAL TMC125-C227: EFFICACY AND TOLERABILITY OF TMC125 IN PI-NAÏVE HIV-1 INFECTED SUBJECTS WITH DOCUMENTED GENOTYPIC EVIDENCE OF NNRTI RESISTANCE FROM PREVIOUS NNRTI USE

2.6.2.4.1 Trial Design

This was a randomized, active controlled, open-label, Phase IIb trial in HIV-1 infected subjects. The primary objective of the trial was to evaluate the antiviral activity of TMC125 800 mg b.i.d. at 24 weeks as part of an ART containing 2 NRTIs over 48 weeks of treatment. Eligible subjects had to be PI-naïve and to have documented genotypic evidence of resistance (either at screening or historically) to EFV, NVP and delavirdine after treatment with a first-line NNRTI regimen, or after treatment with an NNRTI, either alone or with other ARVs, for prevention of mother to child transmission (MTCT).

Initially, this was an exploratory trial with a planned sample size of 120 subjects (60 subjects per treatment group). However, following suggestions from regulatory agencies, the goals of the trial were modified to be powered to show non-inferiority of TMC125, and therefore the planned sample size was increased to 300 subjects (150 subjects per treatment arm). Subjects were randomized in a 1:1 ratio to receive TMC125 800 mg b.i.d. (formulation F*) or an active control. The TMC125 group received TMC125 800 mg b.i.d. in addition to 2 investigator-selected NRTIs. The control group received an investigator-selected PI in addition to 2 investigator-selected NRTIs. ENF was not allowed in either treatment group. For both groups, subjects had to be sensitive (by screening virco®TYPE HIV-1) to the 2 selected NRTIs used in the underlying ART. Antiviral efficacy was determined through plasma viral load levels and immunology and safety and tolerability were evaluated.

Due to the identification of a suboptimal virologic response in TMC125 treated subjects, an early, unplanned evaluation of the data in this trial was performed. Results showed that there was a difference in the proportion of subjects achieving or maintaining an undetectable viral load (< 50 HIV-1 RNA copies/mL) in favor of the control group who were receiving a PI-based therapy. Based on these data, Tibotec decided to prematurely discontinue treatment with TMC125 in the 59 subjects who had been randomized and treated with TMC125 (57 subjects were randomized to the control group), and to end enrolment of new subjects into the trial. This decision was endorsed by the independent DSMB for the trial. All subjects receiving TMC125 were recommended to be switched to an investigator-selected PI-containing ARV and followed for an additional 24 weeks after the treatment switch. Subjects in the control group who were

＊：新薬承認情報提供時に置き換え

still in the trial at the time recruitment was halted were followed for at least 24 weeks (with the same standard of care regimen) and then discontinued the trial. In the final analysis, the main focus of the efficacy analyses of the pre therapy switch treatment phase was the change from baseline in $\log_{10}$ viral load, which was investigated to identify possible reasons for the lower response in subjects who received TMC125.

A substudy to evaluate the pharmacokinetic profile of TMC125 at Baseline and at Week 4 (rich sampling) was conducted in a subset of subjects in the pre therapy switch treatment phase. In addition, blood samples were collected for a population pharmacokinetic analysis of all subjects randomized to TMC125 during the pre therapy switch treatment phase (sparse sampling).

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.5.1/TMC125-C227).

2.6.2.4.2 Pharmacokinetics of TMC125

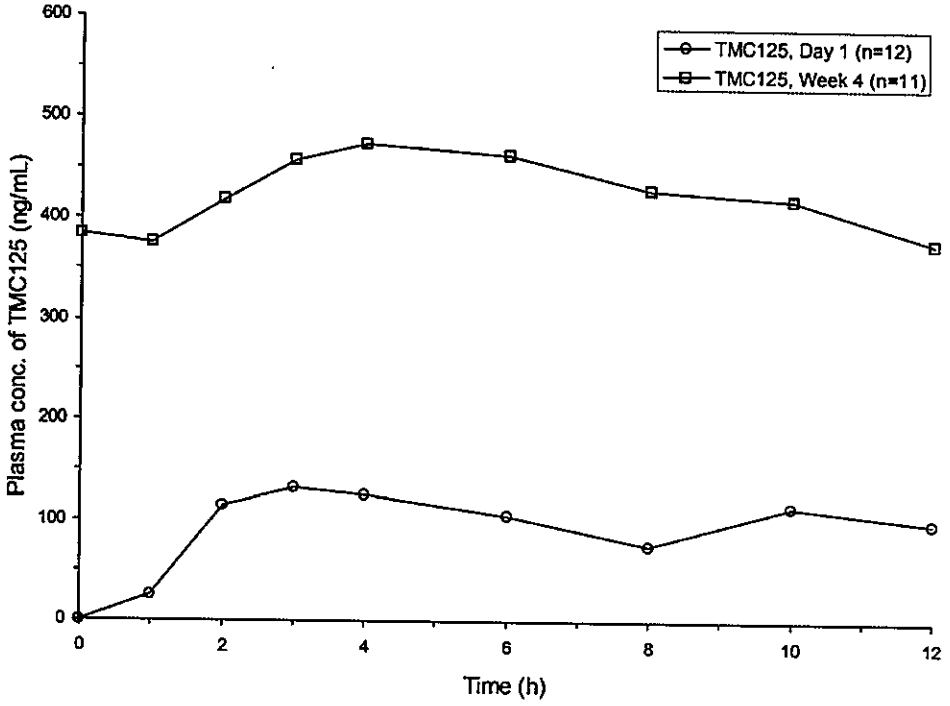
The absorption phase of TMC125 and steady-state pharmacokinetics were characterized in a pharmacokinetic substudy. The pharmacokinetic profile in this subset of subjects was evaluated at Baseline (Day 1) and Week 4 after administration of TMC125 at a dose of 800 mg b.i.d. in addition to the investigator-selected NRTIs.

In addition to the pharmacokinetic substudy, blood samples were collected for a population pharmacokinetic analysis of all subjects randomized to TMC125. A Bayesian feedback model previously developed for TMC125 formulation F* was used to determine the population pharmacokinetic parameters for the main trial. Predose and/or random plasma concentrations of TMC125 were determined in all subjects at Weeks 4, 12, 24, and 48. The AUC_{12h} and C_{0h} of TMC125 were then estimated in each subject using population pharmacokinetic techniques.

Pharmacokinetics in the Substudy

The mean plasma concentration-time curves of TMC125 on Day 1 and at Week 4 are shown in Figure 20.

＊：新薬承認情報提供時に置き換え



Source: Module 5.3.5.1/TMC125-C227/Section 4.6.1.4

Figure 20: Mean Plasma Concentration-Time Profiles of TMC125 at Baseline (Day 1) and Week 4 after Administration of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at a Dose of 800 mg b.i.d. in HIV-1 Infected Subjects (Substudy of Trial TMC125-C227)

The mean plasma concentrations of TMC125 were approximately 100 ng/mL on Day 1, and between 376 ng/mL and 475 ng/mL at Week 4.

The inter-subject variability (%CV) on Day 1 was 119% for C_{max} and 103% for AUC_{12h}, compared to 59% for C_{max} and 63% for AUC_{12h} at Week 4 (Module 5.3.5.1/TMC125-C227/Section 4.6.1.5). The mean accumulation index, comparing AUC_{12h} at Week 4 and on Day 1, was 8.4, but inter-subject variability was high, varying between 1.0 and 31.7, with a %CV of 106%. The geometric mean of the accumulation index was 5.7. The median t_{max} was 4.0 hours on Day 1 and at Week 4, with a wide range from 0 to 10 hours at both time points (Table 26).

＊：新薬承認情報提供時に置き換え

Table 26: Pharmacokinetics of TMC125 at Baseline (Day 1) and Week 4 after Administration of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at a Dose of 800 mg b.i.d. in HIV-1 Infected Subjects (Substudy of Trial TMC125-C227)

Parameter	Mean ± SD; t_{max}: Median (Range)
	800 mg b.i.d.
Day 1	
N	12
t_{max}, h	4.00 (2.00 - 10.00)
C_{max}, ng/mL	178.7 ± 213.3
AUC_{12h}, ng.h/mL	1148 ± 1186
Week 4	
N	11
t_{max}, h	4.00 (0.00 - 10.00)
C_{0h}, ng/mL	384.5 ± 242.6
C_{12h}, ng/mL	377.9 ± 284.3
C_{min}, ng/mL	317.8 ± 199.7
C_{max}, ng/mL	528.5 ± 314.2
$C_{ss,av}$, ng/mL	430.4 ± 269.9
AUC_{12h}, ng.h/mL	5165 ± 3238
FI, %	50.86 ± 19.12

N = maximum number of subjects with data.
Source: Module 5.3.5.1/TMC125-C227/Section 4.6.1.5

Population Pharmacokinetics

In general, the estimated pharmacokinetic parameters for TMC125 were slightly lower than, but in the same range as, those observed in the pharmacokinetic substudy (Table 27).

Table 27: Population Pharmacokinetic Estimates of TMC125 after Administration of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at a Dose of 800 mg b.i.d. in HIV-1 Infected Subjects (Trial TMC125-C227)

Parameter	Mean (SD), Range
	800 mg b.i.d.
N	51
C_{0h}, ng/mL	275.3 (158.10), 61 - 737
AUC_{12h}, ng.h/mL	4608.8 (2380.56), 1129 - 11068

N = maximum number of subjects with data.
Source: Module 5.3.5.1/TMC125-C227/Section 4.6.2.4

An ANCOVA model revealed no statistically significant association between TMC125 pharmacokinetic parameters and race, sex, weight, age, hepatitis co-infection status, or TDF use in the underlying ART (Module 5.3.5.1/TMC125-C227/Section 4.6.2.4).

2.6.2.4.3 Inhibitory Quotients of TMC125

IQ values of TMC125 were calculated on an individual basis. The IQ was calculated using the TMC125 plasma concentration (as obtained via Bayesian feedback) and the EC50 for TMC125 from the phenotypic assay at Baseline (or screening if the Baseline value was missing). For each subject, 2 IQ values were determined: IQ_{C0h} used the plasma trough concentration of TMC125 as the input for the plasma concentration factor, and $IQ_{Css,av}$ used $C_{ss,av}$ as the input.

＊：新薬承認情報提供時に置き換え

IQ values were above 1.0 for all subjects, and the IQ values were generally high, with a substantial inter-subject variability (Table 28).

Table 28: Inhibitory Quotient of TMC125 after Administration of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at a Dose of 800 mg b.i.d. in HIV-1 Infected Subjects (Trial TMC125-C227)

Parameter	Geometric Mean (Range)
	800 mg b.i.d.
N	45
IQ_{C0h}	291.5 (8 - 4326)
$IQ_{Css,av}$	420.5 (12 - 5370)

N = maximum number of subjects with data.
$IQ_{Css,av}$ = average total plasma concentration/EC50; IQ_{C0h} = plasma trough concentration/EC50.
Source: Module 5.3.5.1/TMC125-C227/Section 4.6.3

2.6.2.4.4 Pharmacodynamics

In the original protocol, the primary efficacy parameter was the proportion of subjects with undetectable plasma viral load values (i.e., < 50 HIV-1 RNA copies/mL) at Week 24. However, due to the premature discontinuation of TMC125 treatment, not all subjects in the TMC125 group had reached Week 24. Therefore, the main focus of the efficacy analyses of the pre therapy switch treatment phase was the change from Baseline in $\log_{10}$ viral load. The subjects in the control group had data up to at least 24 weeks.

The secondary antiviral efficacy variables were:

- Proportion of subjects with plasma viral load values below 5 HIV-1 RNA copies/mL;
- Proportion of subjects with 1 $\log_{10}$ decrease in plasma viral load (compared to Baseline) at each time point, and time from Baseline to achieve this;
- Proportion of subjects with plasma viral load levels < 50 and < 400 HIV-1 RNA copies/mL at each time point, and time from Baseline to achieve this;
- Time to loss of virologic response over the 48-week treatment period;
- Time to loss of virologic response over the whole treatment period for subjects participating in the optional extended treatment period.

As pharmacokinetic/pharmacodynamic relationships could be described only for the pre therapy switch treatment phase, only the efficacy results for this phase are summarized.

During the pre therapy switch treatment phase, all virologic response parameters indicated a lower response in the subjects treated with TMC125 compared to the control group.

In the TMC125 group, a mean decrease from Baseline in the $\log_{10}$ viral load was observed with -1.50 copies/mL at Week 4, which was maintained up to Week 12 (-1.39 copies/mL). After Week 12, a rebound was observed.

In the control group, the mean change from Baseline in $\log_{10}$ viral load was -1.66 copies/mL at Week 4, -2.16 copies/mL at Week 12, and remained the same up to Week 24 (-2.13 copies/mL).

At Week 12, the virologic response was lower in the TMC125 group compared to the control group (< 50 copies/mL: 25.0% versus 52.8%; < 400 copies/mL: 47.5% versus 84.9%; > 1 $\log_{10}$ decrease: 60.0% versus 88.7%).

Median Baseline CD4 cell counts were 180.0 x 10^6 cells/L in the TMC125 group and 245.0 x 10^6 cells/L in the control group. In both groups, CD4 cell counts increased over time. The mean increase in CD4 cell counts was greater in the control group (Week 12: +41.6 x 10^6 cells/L in the TMC125 group and +78.5 x 10^6 cells/L in the control group; Week 24: +111.8 x 10^6 cells/L in the TMC125 group [N=6]) and +123.5 x 10^6 cells/L for the control group [N=51]).

High levels of resistance to NRTIs and NNRTIs were the main drivers of virologic failure in the TMC125 group.

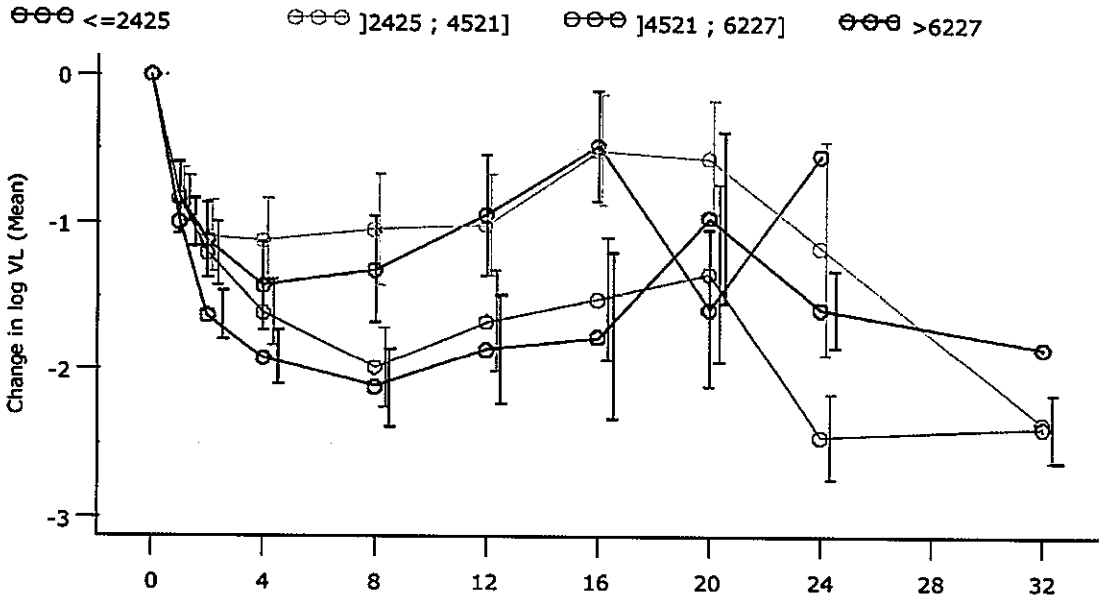
Further details are available in Module 5.3.5.1/TMC125-C227.

2.6.2.4.5 Pharmacokinetic/Pharmacodynamic Relationships

Pharmacokinetic/pharmacodynamic relationships are described only for the pre therapy switch treatment phase.

2.6.2.4.5.1 Pharmacokinetic Parameters and Log_{10} Viral Load

To explore the relationship between the AUC_{12h} and change from Baseline in log_{10} viral load, the mean change from Baseline in log_{10} viral load over time was grouped by quartiles for AUC_{12h}. The mean reduction from Baseline in log_{10} viral load appeared to be greater in subjects with TMC125 exposure above the median AUC_{12h} (> 4521 ng.h/mL) compared to those below the median (Figure 21). Viral rebound appeared to be less likely in those subjects with higher TMC125 exposure; however, the number of subjects in this analysis was small, particularly at later time points.



N(<=2425)=13	12	13	11	10	6	3	1	.
N(]2425 ; 4521])=13	13	13	12	11	8	7	3	1
N(]4521 ; 6227])=13	13	13	11	10	7	4	2	2
N(>6227)=12	12	12	10	8	6	3	2	1

Source: Module 5.3.5.1/TMC125-C227/Section 4.7.1

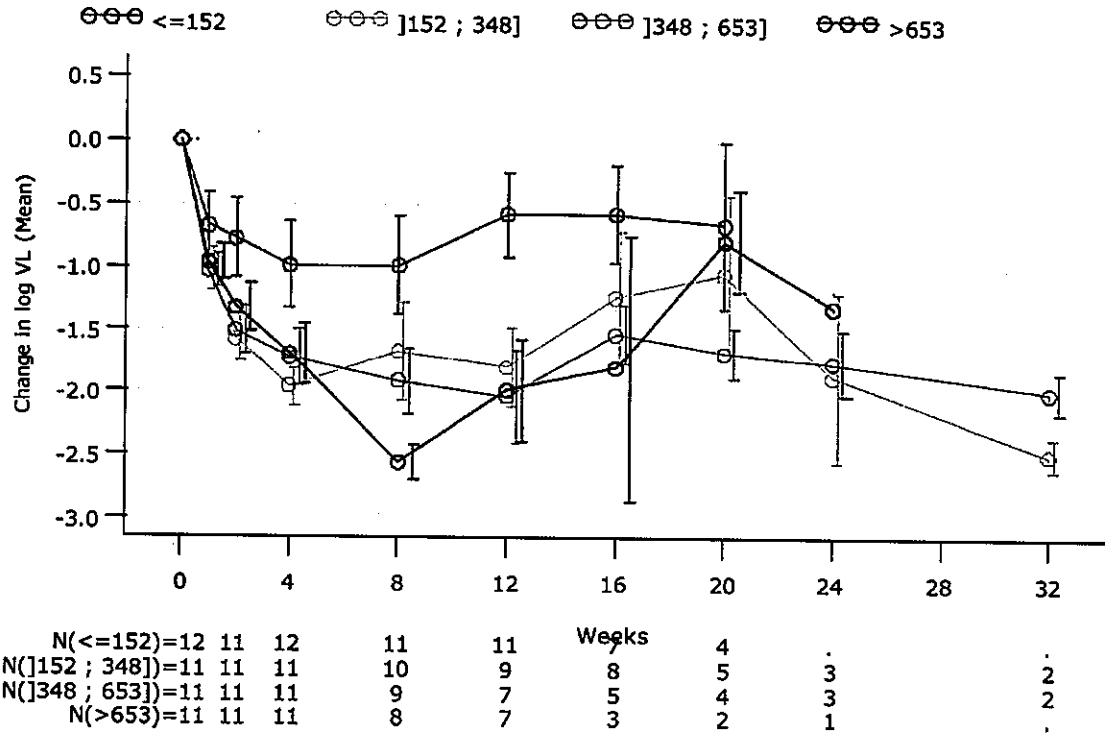
Figure 21: Mean Change From Baseline in Log_{10} Viral Load by AUC_{12h} Quartiles – Pre Therapy Switch Treatment Phase (Trial TMC125-C227)

An ANCOVA model (with factors including region, treatment status at screening, actual treatment interruption at screening, imputed Baseline log_{10} plasma viral load, Baseline CD4 cell count, use of TDF in the initial underlying therapy, the number of sensitive NRTIs in the underlying therapy) showed no statistically significant relationship between the AUC_{12h} versus the change from Baseline in log_{10} viral load at Week 12 (Module 5.3.5.1/TMC125-C227/Section 4.7.1).

2.6.2.4.5.2 Inhibitory Quotient and Log_{10} Viral Load

To explore the relationship between the IQ based on the C_{0h} (IQ_{C0h}) and changes from Baseline in log_{10} viral load, the mean change from Baseline in log_{10} viral load over time was plotted versus the IQ_{C0h} grouped by quartiles. Subjects in the lowest quartile for IQ_{C0h} values showed a lesser response than subjects with higher IQ_{C0h} values (Figure 22).

Similar results were obtained with analyses for IQ based on $C_{ss,av}$ ($IQ_{Css,av}$). Subjects with low $IQ_{Css,av}$ values had a lesser virologic response than subjects with higher $IQ_{Css,av}$ values (Module 5.3.5.1/TMC125-C227/Section 4.7.2).



Source: Module 5.3.5.1/TMC125-C227/Section 4.7.2

Figure 22: Mean Change From Baseline in Log_{10} Viral Load by IQ_{C0h} Quartiles - Pre Therapy Switch Treatment Phase (Trial TMC125-C227)

2.6.2.4.6 Pharmacokinetic/Safety Relationships

No apparent relationship was observed between TMC125 exposure and rash, skin events of interest, nervous system, psychiatric, or gastrointestinal disorders, or the individual events of headache, dizziness, tachycardia, palpitations, or blurred vision (see Module 5.3.5.1/TMC125-C227/Section 4.7.3).

Graphically, no relationship was observed between TMC125 exposure and maximum change from Baseline in ALT, AST, indirect bilirubin, direct bilirubin, alkaline phosphatase, pancreatic amylase, lipase, HDL cholesterol, LDL cholesterol, triglycerides, cholesterol, HDL/total cholesterol, PTT, or PT.

2.6.2.4.7 Conclusions

- In general, the estimated population pharmacokinetic parameters for TMC125 were slightly lower than, but in the same range as, those observed in the pharmacokinetic substudy.
- There was no statistically significant association between TMC125 pharmacokinetic parameters and race, sex, weight, age, hepatitis co-infection status, or TDF use in the underlying ART.
- Subjects treated with TMC125, while exhibiting a substantial initial decrease in viral load, had inferior responses compared to the control PI-treated subjects, which was primarily driven by levels of NRTI and NNRTI resistance.

- The mean reduction from Baseline in log_{10} viral load appeared to be higher in the 2 quartiles with the highest TMC125 exposure.
- Subjects in the lower quartiles for IQ_{C0h} and $IQ_{Css,av}$ values showed a lesser response than subjects with higher values.
- No apparent relationship was observed between TMC125 pharmacokinetics and adverse events or maximum change in laboratory parameters.

2.6.2.5 TRIAL TMC125-C229: ROLLOVER TRIAL TO ASSESS LONG-TERM SAFETY AND TOLERABILITY OF TMC125

2.6.2.5.1 Trial Design

This is an ongoing Phase IIb, open-label, rollover trial in HIV-1 infected subjects to evaluate the long-term efficacy, safety, and tolerability of TMC125 administered as part of an individually optimized ART. In addition, antiviral activity, immunologic response and changes in genotype and phenotype were to be evaluated. Eligible subjects were those randomized to a TMC125 treatment arm in a sponsor-selected Phase II TMC125 trial, who were treated for at least 48 weeks with TMC125, and who may derive continued benefit from TMC125 therapy, as judged by the investigator.

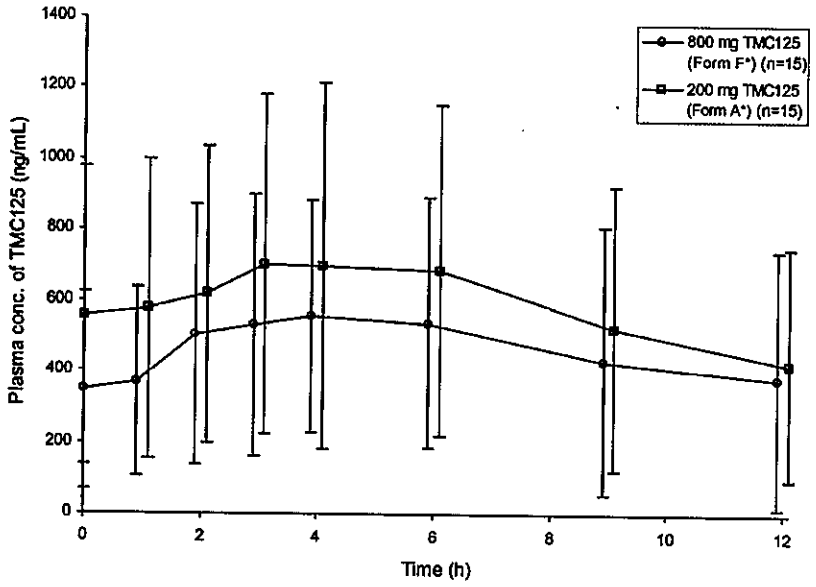
From the final visit of the sponsor-selected Phase II TMC125 trial onwards, all subjects were to receive TMC125 at a dose of 800 mg b.i.d. (formulation F* , TMC125 in HPMC, granulo-layered) until the new formulation A* was available, after which all subjects were switched to TMC125 at a dose of 200 mg b.i.d. (formulation A* , TMC125 in HPMC, spray-dried) and were to continue treatment until they no longer showed benefit from the TMC125 therapy or until the drug is commercially available.

A substudy to evaluate the pharmacokinetic profile of TMC125 (rich sampling) at Week 4 of treatment with each formulation was conducted in a subset of subjects, enabling an intra-subject comparison to be made of the pharmacokinetics of TMC125 after long-term administration with the earlier formulation F* and the new formulation A* . Only these pharmacokinetic data are presented here.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.5.2/TMC125-C229sub-CPK).

2.6.2.5.2 Pharmacokinetics in the Substudy

The mean plasma concentration-time curves of TMC125 at Week 4 for each tablet formulation of TMC are shown in Figure 23.



Source: Module 5.3.5.2/TMC125-C229sub-CPK/Section 2.3.1

Figure 23: Mean Plasma Concentration-Time Profiles of TMC125 at Week 4 after Administration of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at a Dose of 800 mg b.i.d. and Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) at a Dose of 200 mg b.i.d. in HIV-1 Infected Subjects (Substudy of Trial TMC125-C229)

The exposure to TMC125, as expressed by the ratios of the LS means on C_{min}, C_{max}, and AUC_{12h}, was increased 1.28- to 1.32-fold when TMC125 was given as formulation A* at a dose of 200 mg b.i.d., compared to formulation F* at a dose of 800 mg b.i.d. (Table 29). The range of exposures was comparable between both formulations. The 90% CIs of the LS means ratios were generally wide and above the upper limits of the 80% to 125% range.

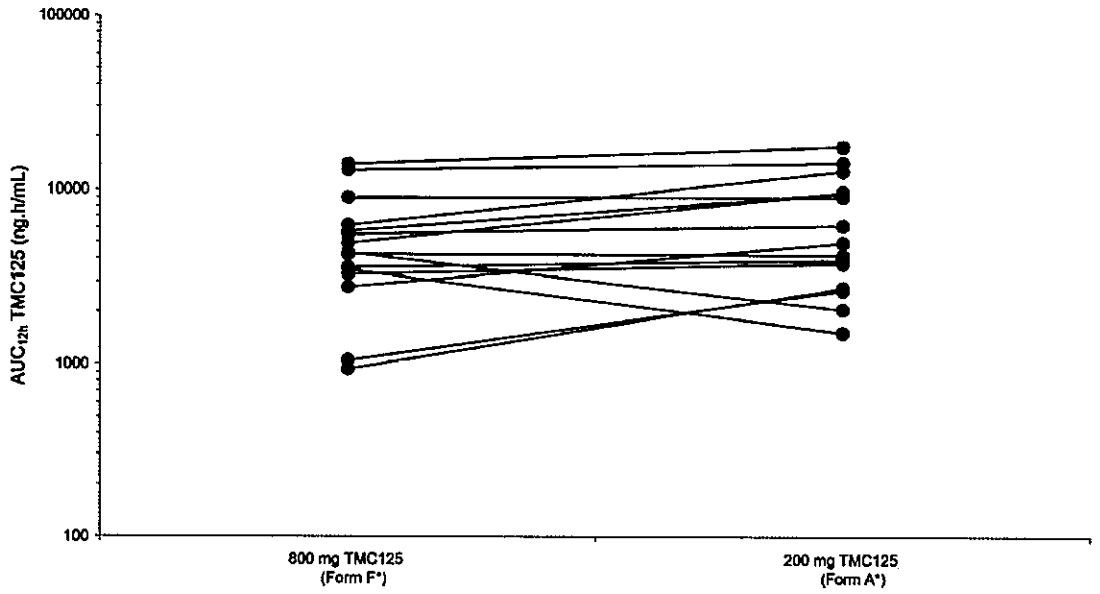
＊：新薬承認情報提供時に置き換え

Table 29: Pharmacokinetics of TMC125 at Week 4 after Administration of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at a Dose of 800 mg b.i.d. and Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) at a Dose of 200 mg b.i.d. in HIV-1 Infected Subjects (Substudy of Trial TMC125-C229)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	TMC125 800 mg b.i.d. Formulation F* (Reference)	TMC125 200 mg b.i.d. Formulation A* (Test)		
N	15	15		
t_{max}, h	4.00 (2.00 - 9.00)	3.00 (0.00 - 6.00)	-	-
C_{0h}, ng/mL	346.3 ± 278.5	557.0 ± 421.9	-	-
C_{min}, ng/mL	309.7 ± 256.8	418.2 ± 325.2	1.32	1.00 - 1.74
C_{max}, ng/mL	629.0 ± 426.4	805.6 ± 524.2	1.32	1.04 - 1.68
$C_{ss,av}$, ng/mL	469.3 ± 336.3	594.8 ± 418.5	-	-
AUC_{12h}, ng.h/mL	5513 ± 3844	7115 ± 5018	1.28	1.00 - 1.64
FI, %	78.59 ± 35.15	82.77 ± 45.70	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.5.2/TMC125-C229sub-CPK/Section 2.3.2

The comparability between the range of exposure to TMC125 observed with the 800 mg b.i.d. dose of formulation F* and the 200 mg b.i.d. dose of formulation A* is shown in Figure 24 for individual AUC_{12h} values. For 2 subjects with low exposure on formulation F* (AUC_{12h} < 3000 ng.h/mL), an improvement in bioavailability was observed when switched to formulation A* .



Source: Module 5.3.5.2/TMC125-C229sub-CPK/Section 2.3.2

Figure 24: Relationship Between Individual Steady-State AUC_{12h} (Day 8) Values of TMC125 Administered as Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) and as Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) in HIV-1 Infected Subjects (Substudy of Trial TMC125-C229)

2.6.2.5.3 Conclusions

The exposure (AUC_{12h}) to TMC125 was increased 1.28-fold when TMC125 was administered as formulation A* at a dose of 200 mg b.i.d., compared to formulation F* at a dose of 800 mg b.i.d., but the range of exposures was comparable between these 2 formulations. Subjects with low exposure on formulation F* had improved bioavailability when switched to formulation A* .

2.6.3 Phase III Trials

2.6.3.1 DUET-1: Efficacy, Tolerability, and Safety of TMC125 as Part of an Antiretroviral Therapy including Darunavir/rtv and an Investigator-Selected Optimized Background Regimen

2.6.3.1.1 Trial Design

This is an ongoing, randomized, double-blind, placebo-controlled, international Phase III trial conducted in the USA, France, Thailand, and Latin America. The trial was designed to evaluate the long-term efficacy, tolerability, and safety of TMC125 compared to placebo as part of an underlying ART, including DRV/rtv, in ARV-experienced HIV-1 infected subjects.

Subjects on a stable but virologically failing regimen with at least 1 documented NNRTI resistance-associated mutation (RAM) (either at screening or from historical genotypic reports), an HIV-1 plasma viral load of > 5000 HIV-1 RNA copies/mL at screening and 3 or more documented primary PI mutations at screening were eligible for the trial. A total of 612 subjects

were randomized in a double-blind manner to receive treatment with either TMC125 200 mg b.i.d. (administered as tablet formulationA* [TMC125 in HPMC, spray-dried]) or placebo for 48 weeks, both in combination with DRV/rtv (600/100 mg b.i.d.) and an underlying ART of at least 2 ARVs consisting of NRTIs with or without ENF.

Subjects who, in the opinion of the investigator, were deriving clinical benefit from their ART had the possibility to extend the treatment period for an additional 48-week period.

Randomization was stratified by the intended use of ENF in the underlying ART (not using ENF, using ENF de novo, or re-using ENF), previous use of DRV (yes/no) and screening plasma viral load (< or ≥ 30 000 HIV-1 RNA copies/mL).

The pharmacokinetics of TMC125, DRV, and rtv were assessed in a pharmacokinetic substudy conducted at selected sites, and population pharmacokinetic estimates of TMC125 and DRV exposure were obtained in the main trial. The population pharmacokinetic estimates of TMC125 were used for evaluating pharmacokinetic/pharmacodynamic relationships.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.5.1/TMC125-C206).

2.6.3.1.2 Pharmacokinetics

2.6.3.1.2.1 Pharmacokinetics in the Substudy

The objective of the pharmacokinetic substudy (rich sampling) was to obtain pharmacokinetic information for TMC125, DRV, and rtv after 4 and 24 weeks of treatment in HIV-1 infected subjects. At both time points, subjects participated in a 12-hour pharmacokinetic sampling period in addition to the assessments required for the main study. Full pharmacokinetic profiles of 9 and 10 subjects were available for TMC125 at Weeks 4 and 24, respectively.

The pharmacokinetics of TMC125, DRV, and rtv in the pharmacokinetic substudy are summarized in Module 5.3.5.1/TMC125-C206/Section 4.4.1.

There was no indication of a difference between Weeks 4 and 24 in the individual pharmacokinetic parameters of TMC125 (see also Appendix 2.7.2.4).

2.6.3.1.2.2 Population Pharmacokinetics in the Main Study

Pharmacokinetic parameters (AUC_{12h} and C_{0h}) for TMC125 in all subjects randomized to the TMC125 group were estimated by population pharmacokinetic modeling based on full pharmacokinetic profiles at Week 4 in a subset of subjects participating in the pharmacokinetic substudies of DUET-1 and DUET-2 (N = 25) and sparse sampling in all available subjects (N = 345) at the time of data transfer. The final model for TMC125 consisted of a 2-compartment disposition model with sequential zero- and first-order absorption with lag-time. A 2-compartment model with first-order absorption previously developed for DRV was used to estimate pharmacokinetic parameters (AUC_{12h} and C_{0h}) of DRV. The impact of the factors weight, age, sex, race, hepatitis B and/or C co-infection at screening, ENF or TDF used in initial underlying ART on the TMC125 and DRV pharmacokinetic parameters (log_{10} transformation) was determined adopting a univariate and multivariate approach.

Only the results for TMC125 are presented in this summary.

Further details are available in Module 5.3.5.1/TMC125-C206/Section 4.4.2.

＊：新薬承認情報提供時に置き換え

The population pharmacokinetic parameters for TMC125 estimated from sparse sampling in the main study were consistent with the values observed in the pharmacokinetic substudy, as summarized in Table 30.

Table 30: Population Pharmacokinetic Estimates of TMC125 after Administration of TMC125 Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) at a Dose of 200 mg b.i.d. with an Underlying ART in HIV-1 Infected Subjects (DUET-1)

Parameter	Mean (SD), Range TMC125 200 mg b.i.d. + Underlying ART
N	294
C_{0h}, ng/mL	393.1 (364.2), 34 - 4619
AUC_{12h}, ng.h/mL	5498 (4386), 815 - 56279

N = maximum number of subjects with data.
Source: Module 5.3.5.1/TMC125-C206/Section 4.4.2.1

Age, sex, race, and use of ENF in the underlying ART showed no apparent effect on the estimated pharmacokinetic parameters of TMC125 (Module 5.3.5.1/TMC125-C206/Section 4.4.2.1). A trend towards higher AUC_{12h} and C_{0h} was observed in subjects with lower weight.

Use of TDF in the underlying ART was significantly associated with lower AUC_{12h} and C_{0h}. The median AUC_{12h} in 233 subjects receiving TDF was 4331 ng.h/mL compared to 5781 ng.h/mL in 61 subjects not treated with TDF (a 25% decrease); for C_{0h} these values were 290.8 ng/mL and 407.7 ng/mL, respectively (a 29% decrease).

A positive relationship was also observed between hepatitis B and/or C co-infection and AUC_{12h} and C_{0h}. The median AUC_{12h} in 32 subjects with hepatitis B and/or C co-infection was 6321 ng.h/mL compared to 4342 ng.h/mL in 239 subjects without co-infection (a 44% increase); for C_{0h} these values were 449.3 ng/mL and 291.7 ng/mL, respectively (a 54% increase). Despite the difference in TMC125 exposure, the incidence and severity of adverse effects was similar in subjects with co-infection compared to those without (refer to Module 2.7.4/Section 7.1.3).

2.6.3.1.3 Inhibitory Quotients

Inhibitory quotients for TMC125 were calculated as follows: IQ_{C0h} was defined as C_{0h}/EC50 at Baseline x molecular weight, and $IQ_{Css,av}$ was defined as $C_{ss,av}$/EC50 at Baseline x molecular weight (Module 5.3.5.1/TMC125-C206/Section 4.4.2.3).

IQ values were above 1.0 for most subjects, and the IQ values were generally high (Table 31). There was a substantial inter-subject variability caused mainly by the variability in the pharmacokinetics of TMC125 but also by variability in the EC50 for TMC125.

＊：新薬承認情報提供時に置き換え

Table 31: Inhibitory Quotient of TMC125 after Administration of TMC125 Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) at a Dose of 200 mg b.i.d. with an Underlying ART in HIV-1 Infected Subjects (DUET-1)

Parameter	Mean (SD), Range TMC125 200 mg b.i.d. + Underlying ART
N	291
IQ_{C0h}	1023 (1409), 0 - 8319
$IQ_{Css,av}$	1203 (1546), 1 - 8728

N = maximum number of subjects with data.
$IQ_{Css,av}$ = average total plasma concentration/EC50; IQ_{C0h} = plasma trough concentration/EC50.
Source: Module 5.3.5.1/TMC125-C206/Section 4.4.2.3

2.6.3.1.4 Pharmacodynamics

The primary efficacy parameter was the proportion of subjects with undetectable plasma viral load values (< 50 HIV-1 RNA copies/mL) at Week 24. The Food and Drug Administration (FDA) TLOVR imputation algorithm was used in the calculation of this proportion.

The secondary efficacy parameters were:

- Virologic response (using the TLOVR algorithm), defined as:
  - % of subjects with plasma viral load < 50 and < 400 HIV-1 RNA copies/mL at all other time points in addition to the Week 24 time point,
  - % of subjects with at least 1 log_{10} decrease in plasma viral load compared to Baseline at all time points;
- Time to reach first virologic response, and TLOVR, for the definitions of plasma viral load < 50 and < 400 HIV-1 RNA copies/mL;
- Time to virologic failure for the definitions of plasma viral load < 50 and < 400 HIV-1 RNA copies/mL;
- Change in log_{10} plasma viral load from Baseline at all time points;
- Time-averaged difference (DAVG) over 24 weeks;
- Change in CD4 cell count (absolute and percentage);
- Clinical endpoint of any AIDS-defining illness and/or death.

At the Week 24 primary analysis, TMC125 demonstrated superior efficacy compared to placebo when added to an underlying ART including DRV/rtv; a significantly higher proportion of subjects in the TMC125 group (55.9%) compared to the placebo group (38.6%) achieved a confirmed virologic response defined by the most stringent criterion of < 50 HIV-1 RNA copies/mL (TLOVR definition). Similarly, the TMC125 group demonstrated superior efficacy when virologic response (TLOVR definition) was defined as < 400 HIV-1 RNA copies/mL (73.7% vs. 51.3% in the placebo group) or > 1.0 log_{10} decrease in plasma viral load from Baseline (79.9% vs. 57.8% in the placebo group).

The virologic response rate was influenced by ENF use in the underlying ART. In subjects not using ENF as a de novo ARV, the difference in virologic response (< 50 HIV-1 RNA copies/mL,

TLOVR) between the TMC125 and placebo groups at Week 24 was 22.0% as opposed to 3.8% when ENF was used as a de novo ARV, both in favor of the TMC125 group.

In the multivariate analysis, other significant predictors of response were baseline plasma viral load and the FC values for both DRV and TMC125.

Subgroup analyses indicated that the use of TMC125 resulted in additional virologic activity regardless of baseline plasma viral load, CD4 cell count, or activity of the underlying PI (DRV/rtv in this trial) as the proportion of subjects with virologic response (< 50 HIV-1 RNA copies/mL, TLOVR) at Week 24 in each of these subgroups was always higher in the TMC125 group. Importantly, TMC125 provided additional antiviral efficacy even in the presence of multiple NNRTI RAMs or when used in regimens with no other active agents. Although the virologic response rates increased in both treatment groups as more sensitive ARVs were used in the underlying ART, an added effect of TMC125 was always observed. In general and as expected, the magnitude of the difference between the TMC125 group and the placebo group was larger in subjects who used a lower number of active drugs in the background (including not using de novo ENF and/or when the activity of DRV was significantly reduced [FC > 40]).

Treatment with TMC125 was associated with a significantly greater mean change from Baseline (imputed) in $\log_{10}$ plasma viral load at Week 24 (-2.4 HIV-1 RNA copies/mL) when compared with placebo (-1.7 HIV-1 RNA copies/mL). In subjects not using de novo ENF in the underlying ART, the mean change from Baseline in $\log_{10}$ plasma viral load at Week 24 in the TMC125 group was significantly larger than in the placebo group (-2.3 vs. -1.4 HIV-1 RNA copies/mL), while the difference between TMC125 and placebo observed in subjects with de novo ENF in the underlying ART did not reach significance (-2.7 vs. -2.5 HIV-1 RNA copies/mL).

Reconstitution of absolute and % CD4 cell count was more pronounced in the TMC125 group than in the placebo group at all time points up to Week 24. The mean change from Baseline in absolute CD4 cell count at Week 24 was +89.0 and +64.4 x 10^6 cells/L in the TMC125 and placebo groups, respectively. The proportion of subjects with CD4 cell count in the highest risk category (< 50 x 10^6 cells/L) at Baseline decreased over time in both treatment groups but more so with TMC125. In subjects with a baseline CD4 cell count of < 50 x 10^6 cells/L at Baseline, 76.2% of TMC125-treated subjects, compared with 54.4% of placebo subjects, moved above this threshold at Week 24.

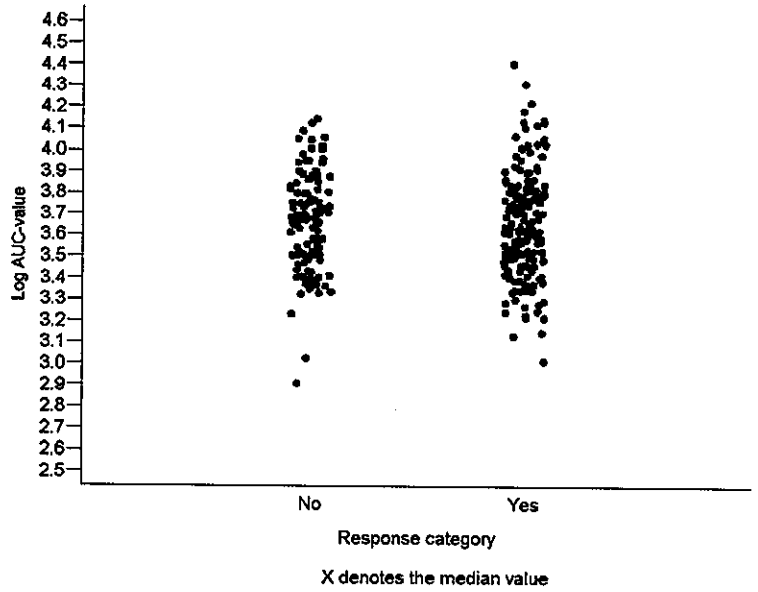
The incidence of the clinical endpoint (AIDS-defining illness and/or death) was significantly lower in the TMC125 group compared to the placebo group (2.6% vs. 6.8%).

Further details are available in Module 5.3.5.1/TMC125-C206/Section 4.2.

2.6.3.1.5 Pharmacokinetic/Pharmacodynamic Relationships

2.6.3.1.5.1 Pharmacokinetic Parameters and Virologic Response

The distribution of the TMC125 AUC_{12h} at Week 24 was generally comparable for the virologic responders and non-responders (viral load < 50 HIV-1 RNA copies/mL TLOVR) (Figure 25).



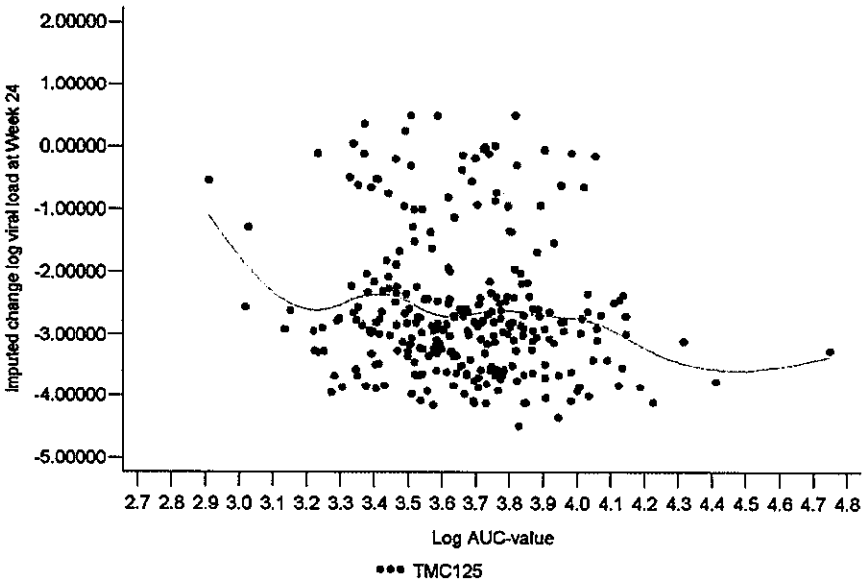
Source: Module 5.3.5.1/TMC125-C206/Section 4.5.1

Figure 25: Distribution of TMC125 AUC_{12h} According to Virologic Response (Viral Load < 50 HIV-1 RNA Copies/mL TLOVR) at Week 24 in HIV-1 Infected Subjects Treated with TMC125 200 mg b.i.d. and an Underlying ART (DUET-1)

For each of the response definitions, conventional univariate logistic regression modeling was performed at Week 24 with factors consisting of treatment group, log_{10} viral load at imputed Baseline, and each of the TMC125 pharmacokinetic parameters separately. For the conventional multivariate logistic regression model, the factor actual ENF use in the initial underlying ART was added. These models indicated that Baseline log_{10} viral load, but not TMC125 AUC_{12h} or ENF use, was a statistically significant predictor of response ($p < 0.0001$) (Module 5.3.5.1/TMC125-C206/Section 4.5.1). Similar results were obtained for C_{0h}.

2.6.3.1.5.2 Pharmacokinetic Parameters and Log_{10} Viral Load

The relationship between TMC125 AUC_{12h} and the change in log_{10} viral load from Baseline at Week 24 is shown in Figure 26.

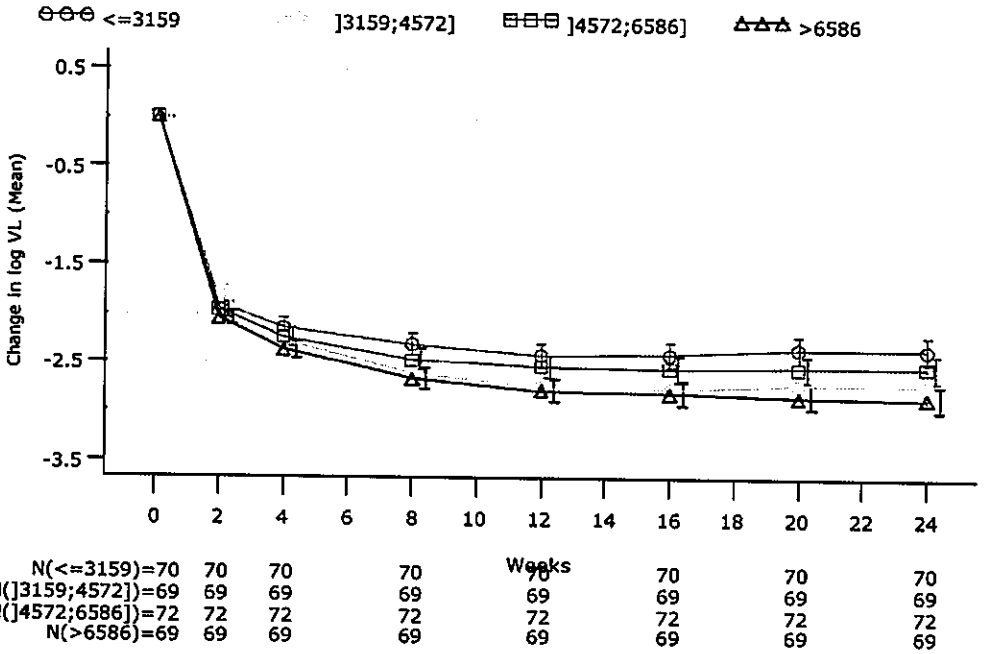


Note: Loess regression line is presented together with the actual data.
Source: Module 5.3.5.1/TMC125-C206/Section 4.5.2

Figure 26: Change in Log_{10} Viral Load From Baseline at Week 24 vs. TMC125 AUC_{12h} in HIV-1 Infected Subjects Treated with TMC125 200 mg b.i.d. and an Underlying ART (DUET-1)

To investigate the relationship between the change from imputed Baseline in log_{10} viral load at Week 24 and each of the TMC125 pharmacokinetic parameters (log_{10} transformed), ANCOVA models were applied with factors consisting of treatment group, actual ENF use in the initial underlying ART, and log_{10} viral load at imputed Baseline. In this model, both the AUC_{12h} and C_{0h} parameters were significantly associated with change in plasma viral load from Baseline ($p < 0.0001$). Use of ENF in the underlying ART was also a significant predictor ($p \leq 0.0117$) (Module 5.3.5.1/TMC125-C206/Section 4.5.2).

Grouping the AUC_{12h} values in quartiles indicated that for subjects within the lowest AUC quartile (TMC125 $AUC_{12h} \leq 3159$), the change in log_{10} viral load at Week 24 was -2.4 HIV-1 RNA copies/mL compared to -2.8 HIV-1 RNA copies/mL in subjects with the highest AUC quartile (post-hoc analysis) (Figure 27).

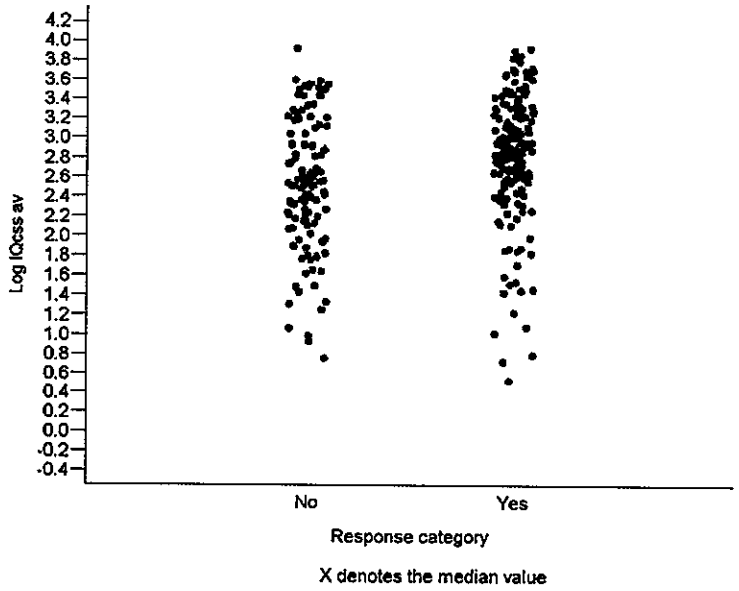


Source: Module 5.3.5.1/TMC125-C206/Section 4.5.2

Figure 27: Change in Log_{10} Viral Load From Baseline over Time by TMC125 AUC_{12h} Quartiles in HIV-1 Infected Subjects Treated with TMC125 200 mg b.i.d. and an Underlying ART (DUET-1)

2.6.3.1.5.3 Inhibitory Quotient and Virologic Response

The distribution of the TMC125 $IQ_{Css,av}$ values at Week 24 was generally comparable for the virologic responders and non-responders (viral load < 50 HIV-1 RNA copies/mL TLOVR), but the median value was higher for responders (Figure 28). Conventional logistic regression models with the covariates described in Section 2.6.3.1.5.1 were run using $IQ_{Css,av}$ and IQ_{C0h} (Module 5.3.5.1/TMC125-C206/Section 4.5.3). In this model, TMC125 $IQ_{Css,av}$ was a statistically significant predictor of response defined as viral load < 50 HIV-1 RNA copies/mL ($p = 0.0007$); Baseline log_{10} viral load was also statistically significant ($p < 0.0001$).



Source: Module 5.3.5.1/TMC125-C206/Section 4.5.3

Figure 28: Distribution of $IQ_{Css,av}$ Values According to Virologic Response (Viral Load < 50 HIV-1 RNA copies/mL TLOVR) at Week 24 in HIV-1 Infected Subjects Treated with TMC125 200 mg b.i.d. and an Underlying ART (DUET-1)

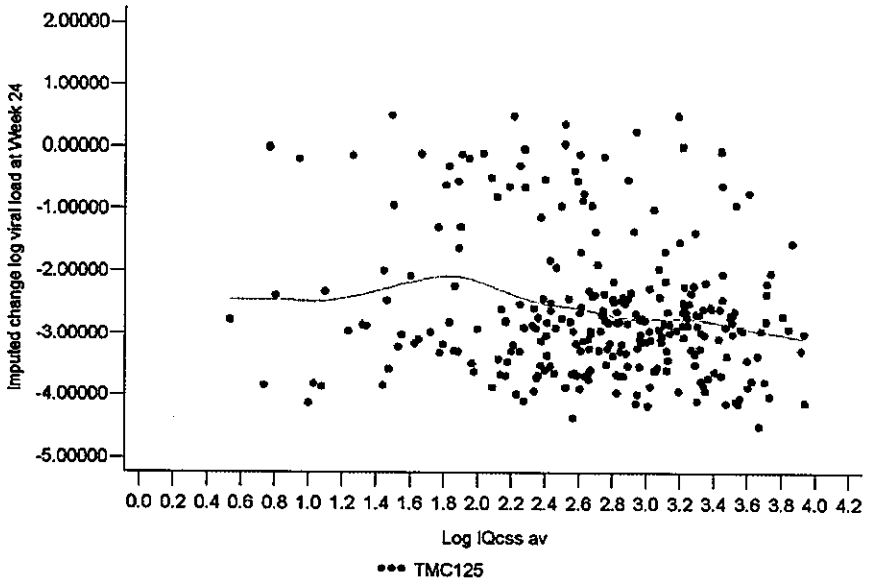
2.6.3.1.5.4 Inhibitory Quotient and Log_{10} Viral Load

The relationship between TMC125 $IQ_{css,av}$ and the change in log_{10} viral load from Baseline at Week 24 is shown in Figure 29.

ANCOVA models with the covariates described in Section 2.6.3.1.5.2 were run using $IQ_{Css,av}$ and IQ_{C0h} (Module 5.3.5.1/TMC125-C206/Section 4.5.4). The subjects in the TMC125 group were grouped according to the quartiles of the $IQ_{Css,av}$ values. The change in log_{10} plasma viral load over time by this grouping is presented in Figure 30.

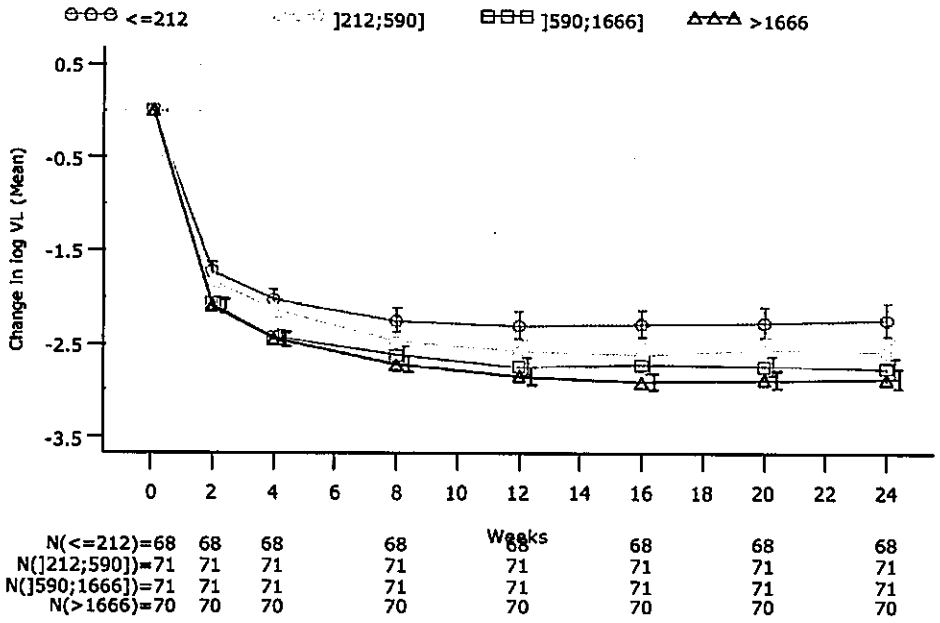
For subjects within the lowest $IQ_{Css,av}$ quartile (TMC125 IQ ≤ 212), the change in log_{10} viral load at Week 24 was -2.2 HIV-1 RNA copies/mL compared to -2.6 HIV-1 RNA copies/mL in subjects with the second lowest $IQ_{Css,av}$ quartile. For subjects with TMC125 $IQ_{Css,av}$ > 1666, the mean change in log_{10} viral load from Baseline was -2.9 HIV-1 RNA copies/mL at Week 24 (post-hoc analysis).

The clinical implications of these findings are unclear. IQ is the ratio of a pharmacokinetic parameter (AUC_{12h} or C_{0h}) to FC in resistance; thus a low IQ is either the result of low drug exposure, high FC in resistance, or a combination of both. These findings have been evaluated further in the context of a larger sample size in the pooled analysis of DUET-1 and DUET-2 using a GAM approach (see Section 3.11.3).



Note: Loess regression line is presented together with the actual data.
Source: Module 5.3.5.1/TMC125-C206/Section 4.5.4

Figure 29: Change in Log_{10} Viral Load From Baseline at Week 24 vs. TMC125 $IQ_{css,av}$ in HIV-1 Infected Subjects Treated with TMC125 200 mg b.i.d. and an Underlying ART (DUET-1)



Source: Module 5.3.5.1/TMC125-C206/Section 4.5.4

Figure 30: Change in Log_{10} Viral Load From Baseline over Time by TMC125 $IQ_{css,av}$ Quartiles in HIV-1 Infected Subjects Treated with TMC125 200 mg b.i.d. and an Underlying ART (DUET-1)

2.6.3.1.6 Pharmacokinetic/Safety Relationships

The relationships between pharmacokinetics (population estimates in the main study) and safety were explored using plots of TMC125 AUC vs. maximum changes in laboratory and ECG parameters tested, and by subgroup analyses of the pharmacokinetic parameters (AUC and C_{0h}) according to the presence or absence of adverse events of interest: rash (any type), skin events of interest, psychiatric disorders, nervous system disorders, gastro-intestinal disorders, dizziness, headache, blurred vision, tachycardia, or palpitations.

No associations were found between exposure to TMC125 and maximum change from Baseline in pancreatic amylase, lipase, PTT, PT, ALT, AST, ALP, direct, indirect, and total bilirubin, total cholesterol, HDL cholesterol, total cholesterol to HDL ratio, LDL cholesterol, triglycerides, heart rate, PR interval, QRS width, or QTcF. No apparent relationships were observed between the pharmacokinetics of TMC125 and the occurrence of adverse events of interest.

For further details, refer to Module 5.3.5.1/TMC125-C206/Section 4.5.6.

2.6.3.1.7 Conclusions

- Plasma concentrations of TMC125 were stable between Weeks 4 and 24.
- Use of TDF in the underlying ART was associated with lower exposures to TMC125. A positive relationship between hepatitis B and/or C co-infection and TMC125 AUC_{12h} or C_{0h} was also observed.
- TMC125 showed superior efficacy compared to placebo as part of an underlying ART in subjects with documented NNRTI RAMs.
- The efficacy of TMC125 was superior over placebo in subjects who did not use ENF as a de novo drug.
- Virologic response was generally greater in subjects with higher TMC125 exposure.
- No apparent relationship occurred between exposure to TMC125 and maximum changes in laboratory and ECG parameters. There were also no relationships between exposure to TMC125 and the occurrence of adverse events of interest.

2.6.3.2 DUET-2: Efficacy, Tolerability, and Safety of TMC125 as Part of an Antiretroviral Therapy including Darunavir/rtv and an Investigator-Selected Optimized Background Regimen

2.6.3.2.1 Trial Design

DUET-2, which was conducted in the USA, Canada, Europe, and Australia, had an identical design to that of DUET-1, which is described in Section 2.6.3.1.1. A total of 591 subjects were randomized in this trial.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.5.1/TMC125-C216).

2.6.3.2.2 Pharmacokinetics

2.6.3.2.2.1 Pharmacokinetics in the Substudy

The objective of the pharmacokinetic substudy (rich sampling) was to obtain pharmacokinetic information for TMC125, DRV, and rtv after 4 and 24 weeks of treatment in HIV-1 infected

subjects. At both time points, subjects participated in a 12-hour pharmacokinetic sampling period in addition to the assessments required for the main study. Full pharmacokinetic profiles of TMC125 were available for 16 and 12 subjects at Weeks 4 and 24, respectively.

The pharmacokinetics of TMC125, DRV, and rtv in the pharmacokinetic substudy are summarized in Module 5.3.5.1/TMC125-C216/Section 4.4.1.

There was no indication of a difference between Weeks 4 and 24 in the individual pharmacokinetic parameters of TMC125 (see also Appendix 2.7.2.4).

2.6.3.2.2.2 Population Pharmacokinetics in the Main Study

Pharmacokinetic parameters (AUC_{12h} and C_{0h}) for TMC125 in all subjects randomized to the TMC125 group were estimated by population pharmacokinetic modeling based on full pharmacokinetic profiles at Week 4 in a subset of subjects participating in the pharmacokinetic substudies of DUET-1 and DUET-2 (N = 25) and sparse sampling in all available subjects (N = 345) at the time of data transfer. The final model for TMC125 consisted of a 2-compartment disposition model with sequential zero- and first-order absorption with lag-time. A 2-compartment model with first-order absorption previously developed for DRV was used to estimate pharmacokinetic parameters (AUC_{12h} and C_{0h}) of DRV. The impact of the factors weight, age, sex, race, hepatitis B and/or C co-infection at screening, ENF or TDF used in initial underlying ART on the TMC125 and DRV pharmacokinetic parameters (log_{10} transformation) was determined adopting a univariate and multivariate approach.

Only the results for TMC125 are presented in this summary.

Further details are available in Module 5.3.5.1/TMC125-C216/Section 4.4.2.

The population pharmacokinetic parameters for TMC125 estimated from sparse sampling in the main study were consistent with the values observed in the pharmacokinetic substudy, as summarized in Table 32.

Table 32: Population Pharmacokinetic Estimates of TMC125 after Administration of TMC125 Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) at a Dose of 200 mg b.i.d. with an Underlying ART in HIV-1 Infected Subjects (DUET-2)

Parameter	Mean (SD), Range TMC125 200 mg b.i.d. + Underlying ART
N	280
C_{0h}, ng/mL	392.2 (391.7), 2 - 4070
AUC_{12h}, ng.h/mL	5504 (4712), 458 - 49711

N = maximum number of subjects with data.
Source: Module 5.3.5.1/TMC125-C216/Section 4.4.2.1

Weight, race, hepatitis B and/or C co-infection status, and use of ENF in the underlying ART did not show apparent differences in the estimated pharmacokinetic parameters of TMC125 (Module 5.3.5.1/TMC125-C216/Section 4.4.2.1). A trend towards higher AUC_{12h} and C_{0h} was observed in women (median 5406 ng.h/mL and 383 ng/mL, respectively) relative to men (median 4294 ng.h/mL and 289 ng/mL, respectively).

＊：新薬承認情報提供時に置き換え

Use of TDF in the underlying ART was significantly associated with lower AUC_{12h} or C_{0h}. The median AUC_{12h} in 201 subjects receiving TDF was 4137 ng.h/mL compared to 5149 ng.h/mL in 79 subjects not treated with TDF (a 20% decrease); for C_{0h} these values were 277 ng/mL and 366 ng/mL, respectively (a 24% decrease).

A positive relationship between age and AUC_{12h} or C_{0h} was also observed. This relationship was most apparent in the 3 lowest age quartiles where mean standard deviation (SD) AUC_{12h} for TMC125 was 4258 (2547), 5479 (3463), and 6768 (6945) ng.h/mL, respectively, for ages ≤ 41 (n = 74), 42 to 46 (n = 75), and 47 to 51 (n = 62) years, respectively. Among the eldest quartile (age > 51 years, n = 69), the mean (SD) AUC_{12h} for TMC125 was 5730 (4690) ng.h/mL.

2.6.3.2.3 Inhibitory Quotients

Inhibitory quotients for TMC125 were calculated as follows: IQ_{C0h} was defined as C_{0h}/EC50 at Baseline x molecular weight, and $IQ_{Css,av}$ was defined as $C_{ss,av}$/EC50 at Baseline x molecular weight (Module 5.3.5.1/TMC125-C216/Section 4.4.2.3).

IQ values were above 1 for most subjects, and the IQ values were generally high (Table 33). There was a substantial inter-subject variability caused mainly by the large variability in the pharmacokinetics of TMC125 but also by variability in the EC50 for TMC125.

Table 33: Inhibitory Quotient of TMC125 after Administration of TMC125 Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) at a Dose of 200 mg b.i.d. with an Underlying ART in HIV-1 Infected Subjects (DUET-2)

Parameter	Mean (SD), Range
	TMC125 200 mg b.i.d. + Underlying ART
N	279
IQ_{C0h}	1214 (1810), 0 - 11403
$IQ_{Css,av}$	1405 (1940), 0 - 11606

N = maximum number of subjects with data.
$IQ_{Css,av}$ = average total plasma concentration/EC50; IQ_{C0h} = plasma trough concentration/EC50.
Source: Module 5.3.5.1/TMC125-C216/Section 4.4.2.3

2.6.3.2.4 Pharmacodynamics

The primary efficacy parameter was the proportion of subjects with undetectable plasma viral load values (< 50 HIV-1 RNA copies/mL) at Week 24. The FDA TLOVR imputation algorithm was used in the calculation of this proportion.

The secondary efficacy parameters were:

- Virologic response (using the TLOVR algorithm), defined as:
  - % of subjects with plasma viral load < 50 and < 400 HIV-1 RNA copies/mL at all other time points in addition to the Week 24 time point,
  - % of subjects with at least 1 log_{10} decrease in plasma viral load compared to Baseline at all time points;
- Time to reach first virologic response, and TLOVR, for the definitions of plasma viral load < 50 and < 400 HIV-1 RNA copies/mL;

＊：新薬承認情報提供時に置き換え

- Time to virologic failure for the definitions of plasma viral load < 50 and < 400 HIV-1 RNA copies/mL;
- Change in $\log_{10}$ plasma viral load from Baseline at all time points;
- Time-averaged difference (DAVG) over 24 weeks;
- Change in CD4 cell count (absolute and percentage);
- Clinical endpoint of any AIDS-defining illness and/or death.

At the Week 24 primary analysis, TMC125 demonstrated superior efficacy compared to placebo when added to an underlying ART including DRV/rtv; a significantly higher proportion of subjects in the TMC125 group (62.0%) compared to the placebo group (43.6%) achieved a confirmed virologic response defined by the most stringent criterion of < 50 HIV-1 RNA copies/mL (TLOVR definition). Similarly, the TMC125 group demonstrated superior efficacy when virologic response (TLOVR definition) was defined as < 400 copies/mL (74.9% vs. 53.7% in the placebo group) or > 1.0 $\log_{10}$ decrease in plasma viral load from Baseline (79.7% vs. 59.1% in the placebo group).

The virologic response rate was influenced by ENF use in the underlying ART. In subjects not using ENF as a de novo ARV, the difference in virologic response (< 50 HIV-1 RNA copies/mL, TLOVR) between the TMC125 and placebo groups at Week 24 was 23.5% as opposed to 5.5% when ENF was used as a de novo ARV, both in favor of the TMC125 group.

In the multivariate analysis, other significant predictors of response were baseline plasma viral load and the FC values for both DRV and TMC125.

Subgroup analyses indicated that the use of TMC125 resulted in additional virologic activity regardless of baseline plasma viral load, CD4 cell count, or activity of the underlying PI (DRV/rtv in this trial) as the proportion of subjects with virologic response (< 50 HIV-1 RNA copies/mL, TLOVR) at Week 24 in each of these subgroups was always higher in the TMC125 group. Importantly, TMC125 provided additional antiviral efficacy even in the presence of multiple NNRTI RAMs or when used in regimens with no other active agents. Although the virologic response rates increased in both treatment groups as more sensitive ARVs were used in the underlying ART, an added effect of TMC125 was always observed. In general and as expected, the magnitude of the difference between the TMC125 group and the placebo group was larger in subjects who used a lower number of active drugs in the background (including not using de novo ENF and/or when the activity of DRV was significantly reduced [FC > 40]).

Treatment with TMC125 was associated with a significantly greater mean change from Baseline (imputed) in $\log_{10}$ plasma viral load at Week 24 (-2.3 HIV-1 RNA copies/mL) when compared with placebo (-1.7 HIV-1 RNA copies/mL). In subjects not using de novo ENF in the underlying ART, the mean change from Baseline in $\log_{10}$ plasma viral load at Week 24 in the TMC125 group was significantly larger than in the placebo group (-2.2 vs. -1.4 HIV-1 RNA copies/mL), while the difference between TMC125 and placebo observed in subjects with de novo ENF in the underlying ART did not reach significance (-2.7 vs. -2.5 HIV-1 RNA copies/mL).

Reconstitution of absolute and % CD4 cell count was more pronounced in the TMC125 group than in the placebo group at all time points up to Week 24. The mean change from Baseline in absolute CD4 cell count at Week 24 was +78.1 and +65.5 x 10^6 cells/L in the TMC125 and placebo groups, respectively. The proportion of subjects with CD4 cell count in the highest risk

category (< 50 x 10^6 cells/L) at Baseline decreased over time in both treatment groups but more so with TMC125. In subjects with a baseline CD4 cell count < 50 x 10^6 cells/L at Baseline, 72.2% of TMC125-treated subjects compared with 51.5% of placebo subjects moved above this threshold at Week 24.

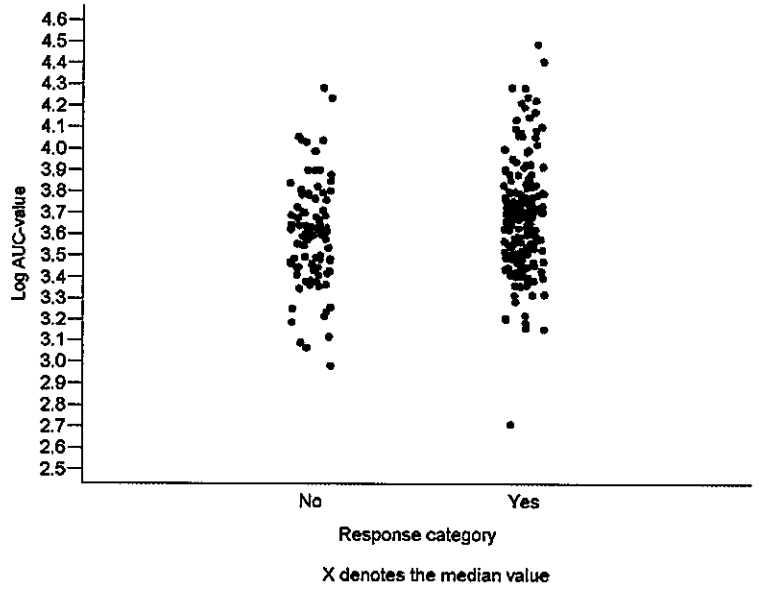
The incidence of the clinical endpoint (AIDS-defining illness and/or death) was lower in the TMC125 group compared to the placebo group (4.7% vs. 6.8%), with no statistically significant between-group difference.

Further details are available in Module 5.3.5.1/TMC125-C216/Section 4.2.

2.6.3.2.5 Pharmacokinetic/Pharmacodynamic Relationships

2.6.3.2.5.1 Pharmacokinetic Parameters and Virologic Response

The distribution of the TMC125 AUC_{12h} at Week 24 was generally comparable for the virologic responders and non-responders (viral load < 50 HIV-1 RNA copies/mL TLOVR), but the median AUC_{12h} was higher for the responders (Figure 31).



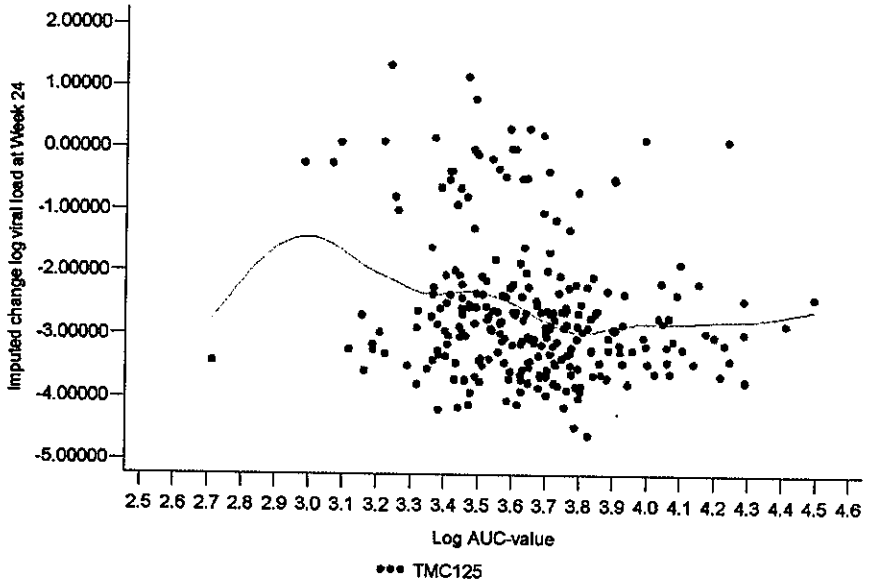
Source: Module 5.3.5.1/TMC125-C216/Section 4.5.1

Figure 31: Distribution of TMC125 AUC_{12h} According to Virologic Response (Viral Load < 50 HIV-1 RNA Copies/mL TLOVR) at Week 24 in HIV-1 Infected Subjects Treated with TMC125 200 mg b.i.d. and an Underlying ART (DUET-2)

For each of the response definitions, conventional univariate logistic regression modeling was performed at Week 24 with factors consisting of treatment group, log_{10} viral load at imputed Baseline, and each of the TMC125 pharmacokinetic parameters separately. For the conventional multivariate logistic regression model, the factor actual ENF use in the initial underlying ART was added. In the conventional logistic regression model for the proportion of subjects with viral load < 50 copies/mL at Week 24, TMC125 AUC_{12h} was a statistically significant predictor of response ($p = 0.0088$); ENF use was also statistically significant ($p = 0.0086$), as was baseline log_{10} viral load ($p < 0.0001$) (Module 5.3.5.1/TMC125-C216/Section 4.5.1). Similar results were observed with C_{0h}.

2.6.3.2.5.2 Pharmacokinetic Parameters and Log_{10} Viral Load

The relationship between TMC125 AUC_{12h} and the change in log_{10} viral load from Baseline at Week 24 is shown in Figure 32.

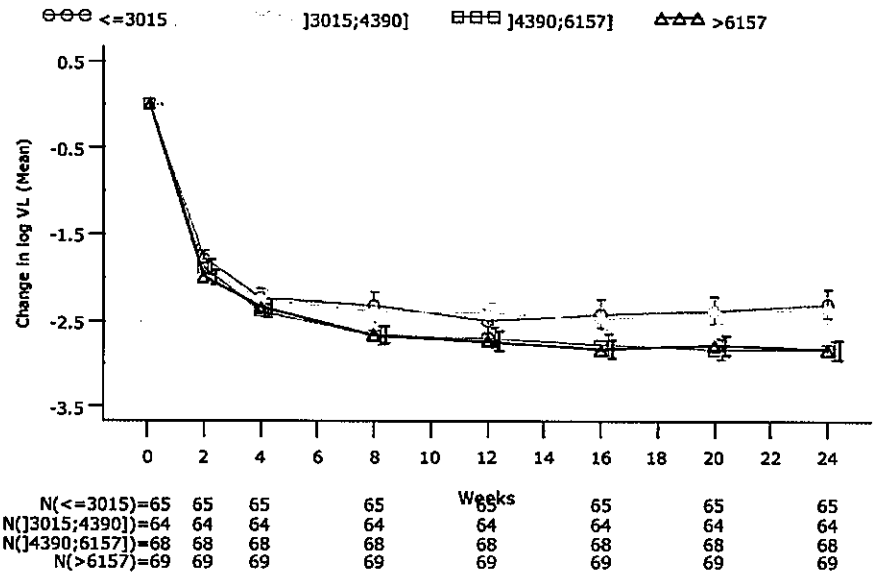


Note: Loess regression line is presented together with the actual data.
Source: Module 5.3.5.1/TMC125-C216/Section 4.5.2

Figure 32: Change in Log_{10} Viral Load From Baseline at Week 24 vs. TMC125 AUC_{12h} in HIV-1 Infected Subjects Treated with TMC125 200 mg b.i.d. and an Underlying ART (DUET-2)

To investigate the relationship between the change from imputed Baseline in log_{10} viral load at Week 24 and each of the TMC125 pharmacokinetic parameters (log_{10} transformed), ANCOVA models were applied with factors consisting of treatment group, actual ENF use in the initial underlying ART, and log_{10} viral load at imputed Baseline. This model indicated that AUC_{12h} and C_{0h} were significantly associated with change in viral load from Baseline ($p < 0.0001$) (Module 5.3.5.1/TMC125-C216/Section 4.5.2).

Grouping the AUC_{12h} values in quartiles indicated that for subjects with AUC_{12h} below 4390 ng.h/mL (median exposure), the change in log_{10} plasma viral load was approximately -2.4 HIV-1 RNA copies/mL from Baseline compared to -2.8 HIV-1 RNA copies/mL in subjects with an AUC_{12h} above 4390 ng.h/mL (post-hoc analysis) (Figure 33).

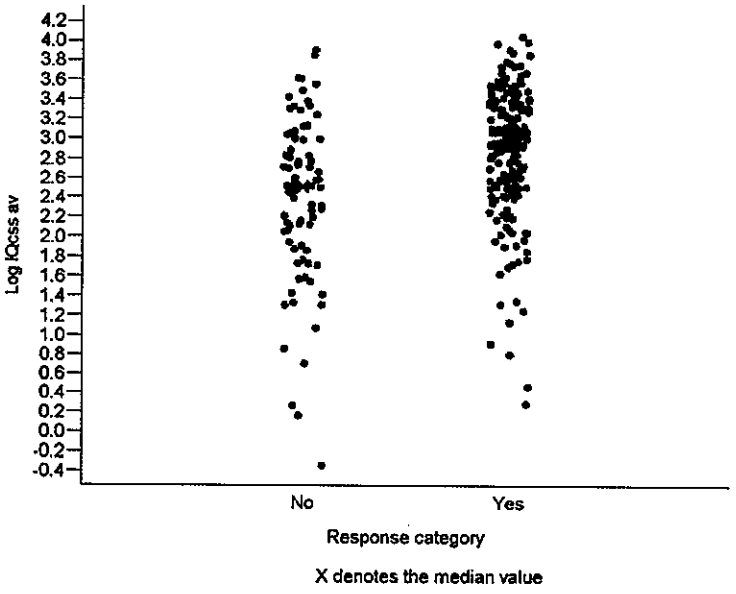


Source: Module 5.3.5.1/TMC125-C216/Section 4.5.2

Figure 33: Change in Log_{10} Viral Load From Baseline over Time by TMC125 AUC_{12h} Quartiles in HIV-1 Infected Subjects Treated with TMC125 200 mg b.i.d. and an Underlying ART (DUET-2)

2.6.3.2.5.3 Inhibitory Quotient and Virologic Response

The distribution of the TMC125 $IQ_{css,av}$ values at Week 24 was generally comparable for the virologic responders and non-responders (viral load < 50 HIV-1 RNA copies/mL TLOVR), but the median $IQ_{css,av}$ was higher for the responders (Figure 34). Conventional logistic regression models with the covariates described in Section 2.6.3.2.5.1 were run using $IQ_{Css,av}$ and IQ_{C0h} (Module 5.3.5.1/TMC125-C216/Section 4.5.3). In this model, TMC125 $IQ_{Css,av}$ was a statistically significant predictor of response defined as viral load < 50 HIV-1 RNA copies/mL ($p < 0.0001$); ENF use was also statistically significant ($p = 0.0105$).



Source: Module 5.3.5.1/TMC125-C216/Section 4.5.3

Figure 34: Distribution of $IQ_{css,av}$ Values According to Virologic Response (Viral Load < 50 HIV-1 RNA copies/mL TLOVR) at Week 24 in HIV-1 Infected Subjects Treated with TMC125 200 mg b.i.d. and an Underlying ART (DUET-2)

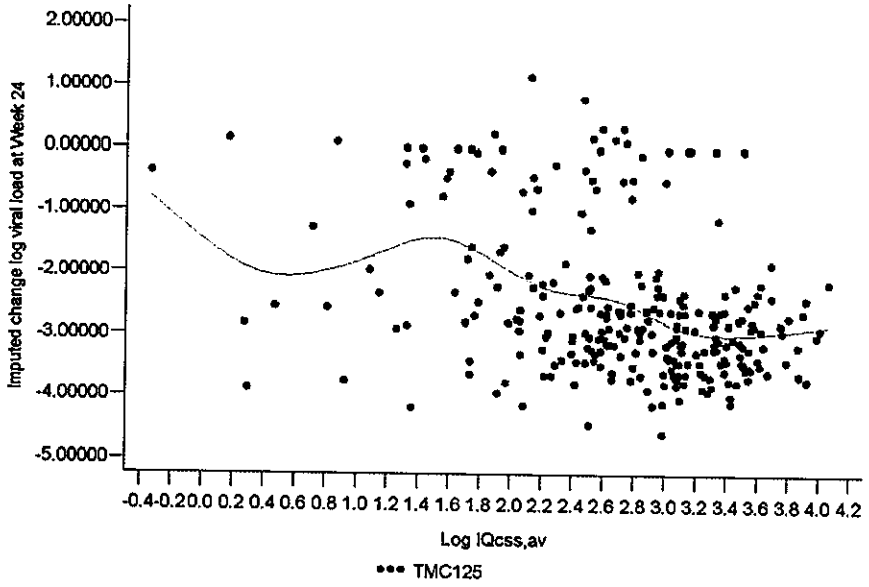
Conventional logistic regression models with the covariates described in Section 2.6.3.1.5.1 were run using $IQ_{Css,av}$ and IQ_{C0h}, which indicated that $IQ_{css,av}$ was a statistically significant predictor of response ($p < 0.001$); ENF use was also statistically significant ($p = 0.014$) (Module 5.3.5.1/TMC125-C216/Section 4.5.3).

2.6.3.2.5.4 Inhibitory Quotient and Log_{10} Viral Load

The relationship between TMC125 $IQ_{css,av}$ and the change in log_{10} viral load from Baseline at Week 24 is shown in Figure 35. ANCOVA models with the covariates described in Section 2.6.3.2.5.2 were run using $IQ_{Css,av}$ and IQ_{C0h} (Module 5.3.5.1/TMC125-C216/Section 4.5.4). The subjects in the TMC125 group were grouped according to the quartiles of the $IQ_{Css,av}$ values. The change in log_{10} plasma viral load over time by this grouping is presented in Figure 36.

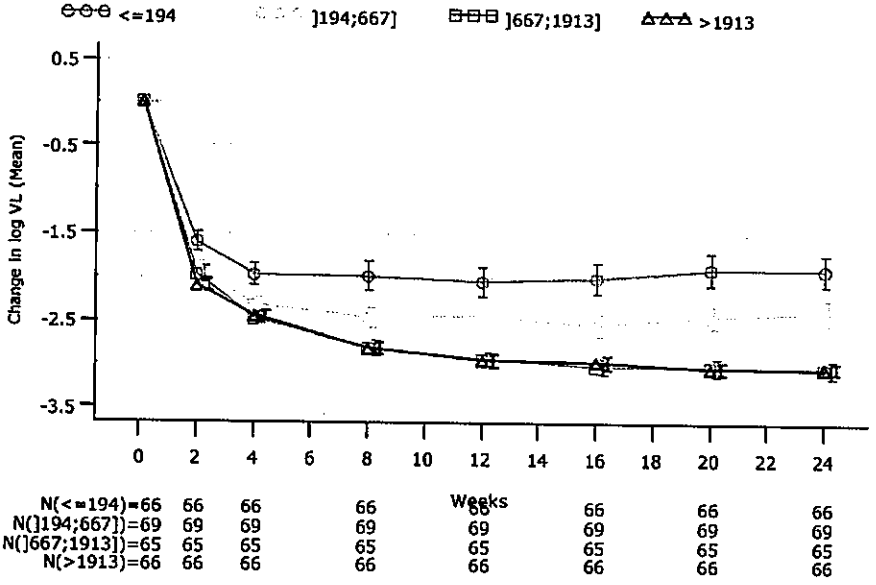
For subjects within the lowest $IQ_{Css,av}$ quartile (TMC125 IQ ≤ 194), the change in log_{10} viral load at Week 24 was -1.8 HIV-1 RNA copies/mL compared to -2.2 HIV-1 RNA copies/mL in subjects with the second lowest $IQ_{Css,av}$ quartile. For subjects with TMC125 $IQ_{Css,av} \geq 667$, the mean log_{10} viral load change from Baseline was -2.9 HIV-1 RNA copies/mL at Week 24 (post-hoc analysis).

The clinical implications of these findings are unclear. IQ is the ratio of a pharmacokinetic parameter (AUC_{12h} or C_{0h}) to FC in resistance; thus a low IQ is either the result of low drug exposure, high FC in resistance, or a combination of both. These findings have been evaluated further in the context of a larger sample size in the pooled analysis of DUET-1 and DUET-2 using a GAM approach (see Section 3.11.3).



Source: Module 5.3.5.1/TMC125-C216/Section 4.5.4

Figure 35: Change in Log_{10} Viral Load From Baseline at Week 24 vs. TMC125 $IQ_{css,av}$ in HIV-1 Infected Subjects Treated with TMC125 200 mg b.i.d. and an Underlying ART (DUET-2)



Source: Module 5.3.5.1/TMC125-C216/Section 4.5.4

Figure 36: Change in Log_{10} Viral Load From Baseline over Time by TMC125 $IQ_{css,av}$ Quartiles in HIV-1 Infected Subjects Treated with TMC125 200 mg b.i.d. and an Underlying ART (DUET-2)

2.6.3.2.6 Pharmacokinetic/Safety Relationships

The relationships between pharmacokinetics (population estimates in the main study) and safety were explored using plots of TMC125 AUC vs. maximum changes in laboratory and ECG

parameters tested, and by subgroup analyses of the pharmacokinetic parameters (AUC and C_{0h}) according to the presence or absence of adverse events of interest: rash (any type), skin events of interest, psychiatric disorders, nervous system disorders, gastro-intestinal disorders, dizziness, headache, blurred vision, tachycardia, or palpitations.

No associations were found between exposure to TMC125 and maximum change from Baseline in pancreatic amylase, lipase, PTT, PT, ALT, AST, ALP, direct, indirect, and total bilirubin, total cholesterol, HDL cholesterol, total cholesterol to HDL ratio, LDL cholesterol, triglycerides, heart rate, PR interval, QRS width, or QTcF. No apparent relationships were observed between the pharmacokinetics of TMC125 and the occurrence of adverse events of interest.

For further details, refer to Module 5.3.5.1/TMC125-C216/Section 4.5.6.

2.6.3.2.7 Conclusions

- Plasma concentrations of TMC125 were stable between Weeks 4 and 24.
- Use of TDF in the underlying ART was associated with lower exposures to TMC125. A positive relationship between age and TMC125 AUC_{12h} or C_{0h} was also observed.
- TMC125 showed superior efficacy compared to placebo as part of an underlying ART in subjects with documented NNRTI RAMs.
- The efficacy of TMC125 was superior over placebo in subjects who did not use ENF as a de novo drug.
- Virologic response was generally greater in subjects with higher TMC125 exposure.
- No apparent relationship occurred between exposure to TMC125 and maximum changes in laboratory and ECG parameters. There were also no relationships between exposure to TMC125 and the occurrence of adverse events of interest.

2.6.4 Investigator-Initiated Trial (SSAT-0012)

Trial SSAT-0012 was an investigator-initiated, open-label trial to evaluate the pharmacokinetics, efficacy, safety, and tolerability of TMC125 co-administered with DRV/rtv, 2 or more N(t)RTIs, and optional ENF in multi-experienced HIV-1 infected subjects with limited therapeutic options (refer to Module 5.4/SSAT-0012). All subjects were to receive TMC125 at a dose of 200 mg b.i.d. with tablet formulation A* (TMC125 in HPMC, spray-dried) and DRV/rtv at a dose of 600/100 mg b.i.d. On Days 7 and 28, serial blood samples for pharmacokinetics were collected.

The pharmacokinetic parameters for TMC125 on Days 7 and 28 are summarized in Table 34. Compared to the results from other trials in similar populations and with identical dosing regimens, the range of exposure to TMC125 observed in this investigator-initiated trial on Day 7 was comparable to the exposure in trial TMC125-C228 on Day 8, and the range of exposure on Day 28 was comparable to the exposure in the pooled Phase III trials DUET-1 and DUET-2 at Week 4 (see Section 3.5.2.4).

Table 34: Pharmacokinetics of TMC125 on Days 7 and 28 after Administration of Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) at a Dose of 200 mg b.i.d. in HIV-1 Infected Subjects (Trial SSAT-0012)

Parameter	Mean ± SD	
	Day 7	Day 28
N	10	10
C_{0h}, ng/mL	182 ± 72	340 ± 213
C_{min}, ng/mL	166 ± 66	291 ± 188
C_{max}, ng/mL	361 ± 125	569 ± 381
AUC_{12h}, ng.h/mL	3116 ± 1126	4921 ± 2982

N = maximum number of subjects with data.
Source: Module 5.4/SSAT-0012

2.7 EFFECT OF INTRINSIC FACTORS

2.7.1 Trial TMC125-C125: Effect of Hepatic Impairment - TMC125 Administered as Tablet Formulation A* (TMC125 in HPMC, Spray-Dried)

2.7.1.1 TRIAL DESIGN

This was a Phase I, open-label, controlled trial to investigate the steady-state pharmacokinetics, safety, and tolerability of TMC125 in subjects with mild or moderate hepatic impairment, each compared to matched subjects with normal hepatic function. The trial population consisted of a total of 32 subjects:

- Panel A consisted of 8 subjects with mild hepatic impairment (Child-Pugh score of 5 to 6) and 8 healthy matched controls;
- Panel B consisted of 8 subjects with moderate hepatic impairment (Child-Pugh score of 7 to 9) and 8 healthy matched controls.

Panels A and B were dosed sequentially, with all subjects in both panels receiving TMC125 200 mg b.i.d. as tablet formulation A* (TMC125 in HPMC, spray-dried) under fed conditions for 7 days, with an additional dose of 200 mg in the morning of Day 8. For both panels, full pharmacokinetic profiles of TMC125 were determined on Day 1 up to 12 hours after dosing, and on Day 8 up to 96 hours after dosing.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.3/TMC125-C125).

2.7.1.2 PHARMACOKINETICS OF TMC125

On Day 1, the mean C_{max} and AUC_{12h} of TMC125 were similar in subjects with mild hepatic impairment and matched healthy control subjects, but the 90% CIs of the LS means ratios for these comparisons were outside the 80% to 125% range (Table 35). On Day 8, the mean C_{max} and AUC_{12h} of TMC125 were decreased by 21% and 13%, respectively, in subjects with mild hepatic impairment, compared to the matched healthy control subjects. The mean C_{min} was decreased by 13%. The 90% CIs of the LS means ratios for these comparisons were also outside

the 80% to 125% range. There was no relevant change in the median t_{max} of TMC125 on Day 1 or 8.

Table 35: Pharmacokinetics of TMC125 after Administration of TMC125 at a Dose of 200 mg b.i.d. in Subjects with Mild Hepatic Impairment and Matched Healthy Control Subjects (Trial TMC125-C125)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Panel A: Healthy Control Subjects (Reference)	Panel A: Subjects with Mild Hepatic Impairment (Test)		
Day 1				
N	8	8		
t_{max}, h	4.0 (2.0 - 5.0)	4.5 (2.0 - 5.0)	-	-
C_{max}, ng/mL	498.8 ± 149.2	466.5 ± 157.8	0.92	0.69 - 1.21
AUC_{12h}, ng.h/mL	2972 ± 1105	2903 ± 816.1	0.99	0.75 - 1.29
Day 8				
N	8	8		
t_{max}, h	4.5 (3.0 - 5.0)	4.0 (3.0 - 6.0)	-	-
C_{0h}, ng/mL	618.6 ± 100.7	585.4 ± 186.4	-	-
C_{min}, ng/mL	593.8 ± 99.64	549.9 ± 192.1	0.87	0.65 - 1.17
C_{max}, ng/mL	1339 ± 356.9	1060 ± 267.8	0.79	0.63 - 1.00
AUC_{12h}, ng.h/mL	10650 ± 1688	9546 ± 2630	0.87	0.69 - 1.09

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.3/TMC125-C125/Section 4.2.4.2 and Section 4.2.4.3

On Day 1, the mean C_{max} and AUC_{12h} of TMC125 were decreased by 37% and 23%, respectively, in subjects with moderate hepatic impairment, compared to the matched healthy control subjects (Table 36). The 90% CIs of the LS means ratios for these comparisons were outside the 80% to 125% range. On Day 8, the mean C_{max} and AUC_{12h} of TMC125 were decreased by 28% and 18%, respectively, in subjects with moderate hepatic impairment, compared to the matched healthy control subjects. The mean C_{min} was not affected by moderate hepatic impairment. The 90% CIs of the LS means ratios for these comparisons were also outside the 80% to 125% range. There was no relevant change in the median t_{max} of TMC125 on Day 1 or 8.

Table 36: Pharmacokinetics of TMC125 after Administration of TMC125 at a Dose of 200 mg b.i.d. in Subjects with Moderate Hepatic Impairment and Matched Healthy Control Subjects (Trial TMC125-C125)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Panel B: Healthy Control Subjects (Reference)	Panel B: Subjects with Moderate Hepatic Impairment (Test)		
Day 1				
N	8	8		
t_{max}, h	5.0 (2.0 - 5.0)	5.0 (4.0 - 9.0)	-	-
C_{max}, ng/mL	413.9 ± 123.3	267.5 ± 100.6	0.63	0.47 - 0.85
AUC_{12h}, ng.h/mL	2293 ± 663.9	1846 ± 808.0	0.77	0.55 - 1.08
Day 8				
N	8	8		
t_{max}, h	4.0 (4.0 - 5.0)	5.0 (4.0 - 6.0)	-	-
C_{0h}, ng/mL	491.6 ± 127.5	568.5 ± 336.5	-	-
C_{min}, ng/mL	461.6 ± 128.4	499.0 ± 293.4	0.98	0.68 - 1.42
C_{max}, ng/mL	1054 ± 193.5	817.6 ± 393.7	0.72	0.54 - 0.96
AUC_{12h}, ng.h/mL	8584 ± 1560	7665 ± 4122	0.82	0.60 - 1.11

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.3/TMC125-C125/Section 4.2.4.2 and Section 4.2.4.3

2.7.1.3 CONCLUSIONS

The exposure to TMC125 in subjects with mild hepatic impairment and moderate hepatic impairment was comparable to healthy matched control subjects after the administration of TMC125 200 mg b.i.d. Based on the ratio of LS means, the C_{max} and AUC_{12h} values on Day 8 were 21% and 13% lower, respectively, for subjects with mild hepatic impairment, and 28% and 18% lower, respectively, for subjects with moderate hepatic impairment compared to healthy matched control subjects. TMC125 administered as 200 mg b.i.d. for 7 days with an additional morning dose on Day 8, was generally safe and well tolerated regardless of whether it was administered to healthy subjects or subjects with mild or moderate hepatic impairment. No dose adjustment of TMC125 is needed in subjects with mild or moderate hepatic impairment.

2.8 EFFECT OF EXTRINSIC FACTORS: CONCOMITANT ADMINISTRATION OF TMC125 WITH OTHER DRUGS

2.8.1 Mechanistic Trials

In the early development phase of TMC125, the capsule formulation T* (TMC125 in PEG 4000) was used in mechanistic interaction trials to characterize basic pharmacokinetic properties of TMC125. These trials were considered to be explorative. Further mechanistic information on the potential for drug-drug interactions was also obtained in more recent clinical trials involving co-administration of the tablet formulation A* (TMC125 in HPMC, spray-dried) with a drug cocktail of CYP substrates, and with rtv.

2.8.1.1 TRIAL TMC125-C174: CYP SUBSTRATES (DRUG COCKTAIL) - TMC125 ADMINISTERED AS TABLET FORMULATION A* (TMC125 IN HPMC, SPRAY-DRIED) IN HEALTHY SUBJECTS

2.8.1.1.1 Trial Design

This was an open-label, 2-period, crossover trial in 14 healthy subjects to assess the drug-drug interaction potential of TMC125, administered as the 100-mg tablet formulation A* (TMC125 in HPMC, spray-dried), with a drug cocktail of representative CYP probes. The drug cocktail consisted of:

- Caffeine 150 mg orally (CYP1A2);
- Warfarin 10 mg orally (CYP2C9) supplemented with vitamin K 10 mg orally (to counteract the effects of warfarin);
- Dextromethorphan 30 mg orally (CYP2D6);
- Midazolam 0.025 mg/kg intravenously (CYP3A4);
- Omeprazole 40 mg orally (CYP2C19).

The subjects were divided into 2 panels (7 subjects per panel). Panel 1 received Treatment A in Session I and Treatment B in Session II. Panel 2 received Treatment B in Session I and Treatment A in Session II, as follows:

- Treatment A: single dose of drug cocktail alone;
- Treatment B: TMC125 200 mg b.i.d. for 14 days, with a single dose of the drug cocktail on Days 1 and 14.

There was a washout period of at least 14 days between both treatments. TMC125 was given within 10 minutes after a meal and the drug cocktail was given within 5 minutes after TMC125 intake.

Plasma concentrations of TMC125 were determined on Days 1 and 14 of Treatment B. Plasma concentrations of midazolam and its metabolite 1-OH-midazolam, dextromethorphan and its metabolite dextrorphan, caffeine and its metabolite paraxanthine, omeprazole and its metabolite 5-OH-omeprazole, and S-warfarin and its metabolite 7-OH-warfarin were determined on Day 1 of Treatment A and on Days 1 and 14 of Treatment B.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C174).

2.8.1.1.2 Pharmacokinetics of Caffeine and Paraxanthine

The mean C_{max} and AUC_{12h} of caffeine and paraxanthine were decreased (caffeine: by 16% and 15%, respectively; paraxanthine: both parameters by 7%) when TMC125 was co-administered with the drug cocktail (Table 37). For caffeine the 90% CIs of the LS means ratios were outside the 80% to 125% range for the comparisons of both parameters, whereas for paraxanthine the 90% CIs of the LS means ratios were within the 80% to 125% range. Compared to treatment with drug cocktail alone, the parent to metabolite ratios of caffeine and paraxanthine decreased by approximately 10% after intake of the drug cocktail at steady-state concentrations of TMC125 (Day 14), but were similar after intake of the drug cocktail with a single dose of TMC125

＊：新薬承認情報提供時に置き換え

(Module 5.3.3.4/TMC125-C174/Section 4.2.5.3). There was no relevant change in the median t_{max} of caffeine or paraxanthine when the drug cocktail was administered with TMC125.

Table 37: Pharmacokinetics of Caffeine and Paraxanthine after Administration of Caffeine as Part of a Drug Cocktail in the Absence and Presence of TMC125 (Trial TMC125-C174)

Parameter	Mean ± SD; t_{max}: Median (Range) Treatment A: Drug Cocktail (Reference)	Treatment B, Day 14: Drug Cocktail + TMC125 200 mg b.i.d. (Test)	Ratio [a] (Test:Reference)	90% CI
Caffeine				
N	14	12		
t_{max}, h	1.50 (1.00 - 6.00)	2.21 (0.45 - 5.98)	-	-
C_{max}, ng/mL	2151 ± 562.1	1725 ± 480.5	0.84	0.75 - 0.94
AUC_{12h}, ng.h/mL	14640 ± 4676	12280 ± 3665	0.85	0.78 - 0.92
Paraxanthine				
N	14	12		
t_{max}, h	6.00 (2.98 - 12.02)	5.97 (5.95 - 11.88)	-	-
C_{max}, ng/mL	892.1 ± 129.8	827.3 ± 115.4	0.93	0.88 - 0.99
AUC_{12h}, ng.h/mL	7912 ± 1028	7329 ± 898.2	0.93	0.88 - 0.99

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C174/Section 4.2.5.2 and Section 4.2.5.3

2.8.1.1.3 Pharmacokinetics of S-Warfarin and 7-OH-Warfarin

There was no relevant change in the mean C_{max} and AUC_{24h} of S-warfarin when TMC125 was co-administered with the drug cocktail, but the mean C_{max} and AUC_{12h} of 7-OH-warfarin were decreased by 27% and 42%, respectively (Table 38). Compared to treatment with drug cocktail alone, the parent to metabolite ratios of S-warfarin and 7-OH-warfarin increased 1.38-fold for C_{max} and 1.82-fold for AUC_{24h} at steady-state concentrations of TMC125 (Day 14), but were similar after intake of the drug cocktail with a single dose of TMC125 (Module 5.3.3.4/TMC125-C174/Section 4.2.6.3). There was no relevant change in the median t_{max} of S-warfarin or 7-OH-warfarin when the drug cocktail was administered with TMC125.

Table 38: Pharmacokinetics of S-Warfarin and 7-OH-Warfarin after Administration of S-Warfarin as Part of a Drug Cocktail in the Absence and Presence of TMC125 (Trial TMC125-C174)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment A: Drug Cocktail (Reference)	Treatment B, Day 14: Drug Cocktail + TMC125 200 mg b.i.d. (Test)		
S-Warfarin				
N	14	12		
t_{max}, h	4.00 (1.00 - 8.00)	3.97 (0.97 - 7.98)	-	-
C_{max}, ng/mL	309.9 ± 50.86	307.8 ± 51.09	0.99	0.88 - 1.12
AUC_{24h}, ng.h/mL	5222 ± 593.4	5598 ± 1133	1.05	0.93 - 1.19
7-OH-Warfarin				
N	14	12		
t_{max}, h	24.02 (8.02 - 24.38)	23.95 (23.52 - 24.00)	-	-
C_{max}, ng/mL	21.42 ± 5.822	15.65 ± 3.451	0.73	0.60 - 0.88
AUC_{24h}, ng.h/mL	336.6 ± 101.2	197.9 ± 65.33	0.58	0.44 - 0.75

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C174/Section 4.2.6.2 and Section 4.2.6.3

2.8.1.1.4 Pharmacokinetics of Dextromethorphan and Dextrorphan

The mean C_{max} and AUC_{8h} of dextromethorphan and dextrorphan were decreased (dextromethorphan: by 15% and 6%, respectively; dextrorphan: by 19% and 15%, respectively) when TMC125 was co-administered with the drug cocktail (Table 39). For all comparisons, the 90% CIs of the LS means ratios were outside the 80% to 125% range. Compared to treatment with drug cocktail alone, the parent to metabolite ratios of dextromethorphan and dextrorphan increased approximately 1.1-fold after intake of the drug cocktail at steady-state concentrations of TMC125 (Day 14), and were increased approximately 1.3-fold after intake of the drug cocktail with a single dose of TMC125 (Module 5.3.3.4/TMC125-C174/Section 4.2.7.3). There was no relevant change in the median t_{max} of dextromethorphan or dextrorphan when the drug cocktail was administered with TMC125.

Table 39: Pharmacokinetics of Dextromethorphan and Dextrorphan after Administration of Dextromethorphan as Part of a Drug Cocktail in the Absence and Presence of TMC125 (Trial TMC125-C174)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment A: Drug Cocktail (Reference)	Treatment B, Day 14: Drug Cocktail + TMC125 200 mg b.i.d. (Test)		
Dextromethorphan				
N	14	12		
t_{max}, h	3.00 (1.00 - 5.00)	2.97 (1.95 - 7.98)	-	-
C_{max}, ng/mL	1.890 ± 1.620	1.292 ± 0.9701	0.85	0.59 - 1.23
AUC_{8h}, ng.h/mL	8.339 ± 7.648	5.865 ± 4.143	0.94	0.72 - 1.23
Dextrorphan				
N	14	12		
t_{max}, h	3.99 (2.00 - 5.00)	2.97 (1.97 - 7.98)	-	-
C_{max}, ng/mL	297.9 ± 84.15	236.1 ± 52.36	0.81	0.69 - 0.94
AUC_{8h}, ng.h/mL	1283 ± 235.2	1101 ± 239.7	0.85	0.76 - 0.94

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C174/Section 4.2.7.2 and Section 4.2.7.3

2.8.1.1.5 Pharmacokinetics of Midazolam and 1-OH-Midazolam

The mean C_{max} of midazolam remained unchanged when TMC125 was co-administered with the drug cocktail, whereas the mean AUC_{5h} was decreased by 31% (Table 40). The mean C_{max} of midazolam was increased 1.57-fold, whereas the mean C_{max} was increased only 1.09-fold, with 90% CIs of the LS means ratio within the 80% to 125% range. Compared to treatment with drug cocktail alone, the parent to metabolite ratios of midazolam and 1-OH-midazolam decreased by approximately 37% after intake of the drug cocktail at steady-state concentrations of TMC125 (Day 14), and were decreased by approximately 10% after intake of the drug cocktail with a single dose of TMC125 (Module 5.3.3.4/TMC125-C174/Section 4.2.8.3). There was no relevant change in the median t_{max} of midazolam or 1-OH-midazolam when the drug cocktail was administered with TMC125.

Table 40: Pharmacokinetics of Midazolam and 1-OH-Midazolam after Administration of Midazolam as Part of a Drug Cocktail in the Absence and Presence of TMC125 (Trial TMC125-C174)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment A: Drug Cocktail (Reference)	Treatment B, Day 14: Drug Cocktail + TMC125 200 mg b.i.d. (Test)		
Midazolam				
N	14	12		
t_{max}, h	0.08 (0.07 - 0.25)	0.07 (0.05 - 0.23)	-	-
C_{max}, ng/mL	35.95 ± 7.755	39.58 ± 14.43	1.00	0.78 - 1.27
AUC_{5h}, ng.h/mL	38.65 ± 6.626	27.48 ± 5.216	0.69	0.64 - 0.74
1-OH-Midazolam				
N	14	12		
t_{max}, h	0.25 (0.23 - 2.00)	0.23 (0.22 - 0.48)	-	-
C_{max}, ng/mL	2.582 ± 0.8024	4.310 ± 1.770	1.57	1.30 - 1.89
AUC_{5h}, ng.h/mL	5.852 ± 1.271	6.531 ± 1.633	1.09	1.00 - 1.18

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C174/Section 4.2.8.2 and Section 4.2.8.3

2.8.1.1.6 Pharmacokinetics of Omeprazole and 5-OH-Omeprazole

The mean C_{max} and AUC_{5h} of omeprazole were increased 1.80- and 1.83-fold, respectively, when TMC125 was co-administered with the drug cocktail, whereas the mean C_{max} and AUC_{5h} of 5-OH-omeprazole were decreased by 54% and 57%, respectively (Table 41). Compared to treatment with drug cocktail alone, the parent to metabolite ratios of omeprazole and 5-OH-omeprazole increased approximately 4.3-fold after intake of the drug cocktail at steady-state concentrations of TMC125 (Day 14), and were increased approximately 1.3-fold after intake of the drug cocktail with a single dose of TMC125 (Module 5.3.3.4/TMC125-C174/Section 4.2.9.3). There was no relevant change in the median t_{max} of omeprazole, but the median t_{max} of 5-OH-omeprazole increased by approximately 2 hours, when the drug cocktail was administered with TMC125.

Table 41: Pharmacokinetics of Omeprazole and 5-OH-Omeprazole after Administration of Omeprazole as Part of a Drug Cocktail in the Absence and Presence of TMC125 (Trial TMC125-C174)

Parameter	Mean ± SD; t_{max}: Median (Range)			
	Treatment A: Drug Cocktail (Reference)	Treatment B, Day 14: Drug Cocktail + TMC125 200 mg b.i.d. (Test)	Ratio [a] (Test:Reference)	90% CI
Omeprazole				
N	14	12		
t_{max}, h	2.99 (1.00 - 5.00)	2.98 (1.97 - 4.97)	-	-
C_{max}, ng/mL	364.8 ± 237.3	662.9 ± 356.7	1.80	0.92 - 3.50
AUC_{5h}, ng.h/mL	729.4 ± 527.1	1437 ± 945.0	1.83	0.78 - 4.29
5-OH-Omeprazole				
N	14	12		
t_{max}, h	2.99 (1.00 - 5.00)	4.95 (1.97 - 4.97)	-	-
C_{max}, ng/mL	244.2 ± 101.0	123.6 ± 66.10	0.46	0.26 - 0.81
AUC_{5h}, ng.h/mL	548.2 ± 285.6	279.7 ± 187.5	0.43	0.20 - 0.96

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C174/Section 4.2.9.2 and Section 4.2.9.3

2.8.1.1.7 Conclusions

TMC125 had no clinically relevant effect on the activity of CYP1A2 or 2D6. CYP3A4 activity was not changed by a single dose of TMC125, but was weakly induced by TMC125 at steady-state, with a 37% decrease in the parent to metabolite ratio. CYP2C19 activity was inhibited by a single dose of TMC125, leading to a 1.3-fold increase in the parent to metabolite ratio; there was a higher degree of inhibition at steady-state concentrations of TMC125, with a 4.3-fold increase in the parent to metabolite ratio. Although TMC125 inhibits CYP2C9 in vitro, plasma concentrations of the probe drug for CYP2C9 in this trial (S-warfarin) did not change significantly. However, the 42% decrease in exposure to the metabolite of S-warfarin at steady-state indicated a weak inhibition of CYP2C9 by TMC125.

2.8.1.2 TRIAL TMC125-C105: RITONAVIR (HIGH DOSE) - TMC125 ADMINISTERED AS CAPSULE FORMULATION T* (TMC125 IN PEG 4000) IN HEALTHY SUBJECTS

RTV is metabolized by CYP3A4 and is a potent CYP3A4 inhibitor, as well as an inducer of CYP2C, CYP1A2, and uridine disphosphate glucuronosyltransferase (UDPGT).[42] RTV is also a P-gp substrate and can acutely inhibit P-gp but induces P-gp after chronic use. In addition, the commercial preparation of RTV contains the surfactant polyoxyl 35 castor oil, which is a putative P-gp inhibitor. The potential for RTV to interact with TMC125 is therefore high and can involve one or more multiple pathways (i.e., CYP3A, 2C, or UDPGT).

2.8.1.2.1 Trial Design

This was an open-label, 2-period crossover trial to investigate the effect of multiple doses of (high-dose) RTV on the pharmacokinetics of a single dose of TMC125 given as the 50-mg capsule formulation T* (TMC125 in PEG 4000). The trial population consisted of 12 healthy male subjects. In Session 1, subjects received a single dose of TMC125 400 mg, followed by a washout period of at least 6 days. In Session 2, subjects were treated with RTV as follows:

＊：新薬承認情報提供時に置き換え

- Day 1: 300 mg b.i.d.;
- Day 2: 400 mg b.i.d.;
- Day 3: 500 mg b.i.d.;
- Days 4 to 7: 600 mg b.i.d.;
- Day 8: Single dose of 600 mg.

On Day 4 of this regimen, a single dose of TMC125 400 mg was co-administered.

TMC125 and (the morning dose of) RTV were taken under fed conditions within 10 minutes after completion of a standardized breakfast.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C105).

2.8.1.2.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{last} of TMC125 were decreased by 32% and 46%, respectively, when TMC125 was co-administered with RTV, compared to administration of TMC125 alone (Table 42). The 90% CIs of the LS means ratios for both comparisons were outside the 80% to 125% range. There was no change in the median t_{max} of TMC125.

Table 42: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Ritonavir (Trial TMC125-C105)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Day 1: TMC125 400 mg (Reference)	Day 4: TMC125 400 mg + RTV 600 mg b.i.d. (Test)		
N	11	11		
t_{max}, h	4.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	136 ± 123	105 ± 114	0.68	0.55 - 0.85
AUC_{last}, ng.h/mL	2193 ± 2506	1837 ± 3672	0.54	0.41 - 0.73

N = maximum number of subjects with data.
[a] Ratio based on LS means
Source: Module 5.3.3.4/TMC125-C105/Section 4.C.5

2.8.1.2.3 Conclusions

In healthy subjects, co-administration of RTV at a dose of 600 mg b.i.d. with a single dose of TMC125 400 mg resulted in a 46% decrease in the mean exposure (AUC_{last}) to TMC125.

2.8.1.3 TRIAL TMC125-C116: RITONAVIR (LOW DOSE) - TMC125 ADMINISTERED AS TABLET FORMULATION A* (TMC125 IN HPMC, SPRAY-DRIED) IN HEALTHY SUBJECTS

Like high-dose RTV (see Section 2.8.1.2), low-dose rtv also has the potential to impact the pharmacokinetics of TMC125. Single-dose rtv was investigated in this trial to isolate potential metabolic and P-gp inhibitory effects from induction effects.

2.8.1.3.1 Trial Design

This was an open-label, randomized, 2-panel, 4-period crossover trial in healthy subjects to investigate the pharmacokinetic interaction between a single dose of rtv and a single dose of TMC125 given as the 100-mg tablet formulation A* (TMC125 in HPMC, spray-dried) after simultaneous and staggered administration (Panel 1). The effect of rtv on the pharmacokinetics of TMC125 was also investigated, as well as the effect of the separation of the administration of rtv and TMC125 by a meal and the effect of timing of TMC125 administration with respect to food (Panel 2). The trial population consisted of 40 healthy subjects, equally divided into 2 panels.

In Panel 1, each subject was randomly assigned to a sequence consisting of the following 4 treatments administered in 4 sessions:

- Treatment A: single dose of 200 mg TMC125 and single dose of 100 mg rtv, both simultaneously after a standardized breakfast;
- Treatment B: single dose of 200 mg TMC125 and single dose of 400 mg RTV, both simultaneously after a standardized breakfast;
- Treatment C: single dose of 200 mg TMC125 after a standardized breakfast and single dose of 100 mg rtv 4 hours after TMC125 intake;
- Treatment D: single dose of 200 mg TMC125 after a standardized breakfast and single dose of 100 mg rtv 4 hours before TMC125 intake.

In Panel 2, each subject was randomly assigned to a sequence consisting of the following 4 treatments administered in 4 sessions:

- Treatment E: single dose of 200 mg TMC125 and single dose of 100 mg rtv, both simultaneously after a standardized breakfast;
- Treatment F: single dose of 200 mg TMC125 after a standardized breakfast;
- Treatment G: single dose of 200 mg TMC125 before a standardized breakfast;
- Treatment H: single dose of 200 mg TMC125 before a standardized breakfast and single dose of 100 mg rtv after the standardized breakfast.

The standardized breakfast consisted of 4 slices of bread, 2 slices of ham or cheese, butter, jelly, and 2 cups of decaffeinated coffee or tea with milk and/or sugar, if desired (nutritional value: 561 kcal; 15.33 g fat; 21.89 g proteins; 83.86 g carbohydrates; 8.08 g fiber).[6] There was a washout period of at least 14 days between subsequent intakes of TMC125.

The results of the investigation of the effect of timing of TMC125 administration with respect to food (Treatment F vs. G in Panel 2) are summarized in Module 2.7.1/Section 2.3.2. Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C116).

2.8.1.3.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{last} of TMC125 after a single dose of 200 mg TMC125 after breakfast (Treatment F) was not affected by the simultaneous administration of a single dose of 100 mg rtv (Treatment E) (Table 44).

＊：新薬承認情報提供時に置き換え

No changes in the pharmacokinetics of TMC125 were observed when the same dose of rtv was co-administered 4 hours after (Treatment A vs. Treatment C) or 4 hours before (Treatment A vs. Treatment D) intake of TMC125 (Table 43).

There was a trend towards a decrease in mean C_{max} and AUC_{last} of TMC125 when 400 mg RTV was co-administered with 200 mg TMC125 (Treatment B), compared to the simultaneous administration of 100 mg rtv (Treatment A) (LS means ratio of 0.91 and 0.92, respectively), although the 90% CIs remained within the 80% to 125% range (Table 43).

When TMC125 was given before breakfast and 100 mg rtv was given after breakfast (Treatment H), compared to the administration of TMC125 alone before breakfast (Treatment G), there was a small increase in the mean exposure to TMC125, with a 1.08-fold increase in mean C_{max} and a 1.17-fold increase in mean AUC_{last} (Table 44). The 90% CIs of the LS means ratios of both comparisons were outside the 80% to 125% range.

When TMC125 was given before breakfast and 100 mg rtv was given after breakfast (Treatment H), compared to the administration of TMC125 and 100 mg rtv after breakfast (Treatment E), the LS means ratios for C_{max} and AUC_{last} of TMC125 were 0.83 and 0.95, respectively, indicating a modest reduction in exposure to TMC125 when TMC125 was given before breakfast and rtv after breakfast, although the 90% CIs for the LS means ratios of this comparison were outside the 80% to 125% range only for C_{max} (Table 44).

Table 43: Pharmacokinetics of TMC125 after Administration of TMC125 Co-Administered with Ritonavir under Different Dosing Regimens (Panel 1) (Trial TMC125-C116)

Parameter	Mean ± SD; t_{max}: Median (Range) Treatment A: TMC125/rtv (Reference)	Treatment B, C, or D: TMC125/rtv (Test)	Ratio [a] (Test:Reference)	90% CI
Treatment A (TMC125/rtv 200/100 mg after Breakfast) vs. Treatment B (TMC125/rtv 200/400 mg after Breakfast)				
N	20	19		
t_{max}, h	4.0 (1.0 - 6.0)	4.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	365.4 ± 142.7	323.5 ± 104.8	0.91	0.82 - 1.02
AUC_{last}, ng.h/mL	4697 ± 1972	4369 ± 1518	0.92	0.84 - 1.01
AUC_{∞} [b], ng.h/mL	5637 ± 2932	5091 ± 2127	-	-
$t_{1/2,term}$ [b], h	44.69 ± 13.78	48.29 ± 17.89	-	-
Treatment A (TMC125/rtv 200/100 mg after Breakfast) vs. Treatment C (TMC125 200 mg after Breakfast + rtv 100 mg 4 h after TMC125 Intake)				
N	20	19		
t_{max}, h	4.0 (1.0 - 6.0)	4.0 (2.0 - 9.0)	-	-
C_{max}, ng/mL	365.4 ± 142.7	376.6 ± 191.9	1.00	0.89 - 1.13
AUC_{last}, ng.h/mL	4697 ± 1972	5222 ± 3063	1.03	0.94 - 1.13
AUC_{∞} [b], ng.h/mL	5637 ± 2932	6202 ± 4146	-	-
$t_{1/2,term}$ [b], h	44.69 ± 13.78	43.40 ± 10.38	-	-
Treatment A (TMC125/rtv 200/100 mg after Breakfast) vs. Treatment D (TMC125 200 mg after Breakfast + rtv 100 mg 4 h before TMC125 Intake)				
N	20	20		
t_{max}, h	4.0 (1.0 - 6.0)	4.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	365.4 ± 142.7	361.5 ± 150.9	0.99	0.88 - 1.11
AUC_{last}, ng.h/mL	4697 ± 1972	4787 ± 2217	1.00	0.94 - 1.07
AUC_{∞} [b], ng.h/mL	5637 ± 2932	5799 ± 3466	-	-
$t_{1/2,term}$ [b], h	44.69 ± 13.78	46.21 ± 18.12	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
[b] Accurate determination not possible in all subjects.
Source: Module 5.3.3.4/TMC125-C116/Section 4.2.4.2 and Section 4.2.4.3

Table 44: Pharmacokinetics of TMC125 after Administration of TMC125 before or after a Meal, in the Absence or Presence of Ritonavir (Panel 2) (Trial TMC125-C116)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment F, G, or E: TMC125/rtv (Reference)	Treatment E or H: TMC125/rtv (Test)		
Treatment F (TMC125 200 mg after Breakfast) vs. Treatment E (TMC125/rtv 200/100 mg after Breakfast)				
N	17	18		
t_{max}, h	4.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	419.1 ± 138.6	442.6 ± 186.9	1.00	0.89 - 1.12
AUC_{last}, ng.h/mL	6184 ± 4305	6795 ± 5044	1.03	0.91 - 1.17
AUC_{∞} [b], ng.h/mL	7632 ± 6708	8766 ± 8190	-	-
$t_{1/2,term}$ [b], h	42.43 ± 14.88	44.80 ± 16.71	-	-
Treatment G (TMC125 200 mg before Breakfast) vs. Treatment H (TMC125 200 mg before Breakfast + rtv 100 mg after Breakfast)				
N	19	18		
t_{max}, h	3.0 (1.0 - 6.0)	4.0 (1.0 - 6.0)	-	-
C_{max}, ng/mL	346.6 ± 211.1	359.3 ± 163.0	1.08	0.92 - 1.26
AUC_{last}, ng.h/mL	5409 ± 4713	6228 ± 4611	1.17	1.05 - 1.31
AUC_{∞} [b], ng.h/mL	6868 ± 8297	7600 ± 7027	-	-
$t_{1/2,term}$ [b], h	42.16 ± 15.85	38.87 ± 14.16	-	-
Treatment E (TMC125/rtv 200/100 mg after Breakfast) vs. Treatment H (TMC125 200 mg before Breakfast + rtv 100 mg after Breakfast)				
N	18	18		
t_{max}, h	4.0 (2.0 - 6.0)	4.0 (1.0 - 6.0)	-	-
C_{max}, ng/mL	442.6 ± 186.9	359.3 ± 163.0	0.83	0.72 - 0.96
AUC_{last}, ng.h/mL	6795 ± 5044	6228 ± 4611	0.95	0.84 - 1.08
AUC_{∞} [b], ng.h/mL	8766 ± 8190	7600 ± 7027	-	-
$t_{1/2,term}$ [b], h	44.80 ± 16.71	38.87 ± 14.16	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
[b] Accurate determination not possible in all subjects.
Source: Module 5.3.3.4/TMC125-C116/Section 4.2.4.2 and Section 4.2.4.3

2.8.1.3.3 Pharmacokinetics of Ritonavir

Delaying the administration of rtv to 4 hours after the administration of TMC125 after breakfast (Treatment C) resulted in a decrease in the mean C_{max} and AUC_{last} of rtv, compared to administration together with TMC125 after breakfast (Treatment A) (Table 45). The LS means ratios for rtv in this comparison were 0.84 and 0.82, respectively, and the 90% CIs were outside the 80% to 125% range.

When TMC125 was given after breakfast and 100 mg rtv was given 4 hours beforehand (Treatment D), compared to administration together with TMC125 after breakfast (Treatment A), the LS means ratios for C_{max} and AUC_{last} of RTV were 1.35 and 1.08, respectively, indicating a small increase in exposure to rtv when rtv was given before breakfast and TMC125 was given after breakfast, although the 90% CIs for the LS means ratios of this comparison were outside the 80% to 125% range only for C_{max}.

Table 45: Pharmacokinetics of Ritonavir after Administration of TMC125 Co-Administered with a Ritonavir under Different Dosing Regimens (Panel 1) (Trial TMC125-C116)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment A: TMC125/rtv (Reference)	Treatment B, C, or D: TMC125/rtv (Test)		
Treatment A (TMC125/rtv 200/100 mg after Breakfast) vs. Treatment B (TMC125/RTV 200/400 mg after Breakfast)				
N	20	19		
t_{max}, h	4.0 (1.0 - 12.0)	4.0 (2.0 - 9.0)	-	-
C_{max}, ng/mL	433.7 ± 170.7	8311 ± 2308	-	-
AUC_{last}, ng.h/mL	4291 ± 1693	76260 ± 25310	-	-
AUC_{∞}, ng.h/mL	4878 ± 2067	78670 ± 26600	-	-
$t_{1/2,term}$, h	6.676 ± 1.813	3.899 ± 1.091	-	-
Treatment A (TMC125/rtv 200/100 mg after Breakfast) vs. Treatment C (TMC125 200 mg after Breakfast + rtv 100 mg 4 h after TMC125 Intake)				
N	20	19		
t_{max}, h	4.0 (1.0 - 12.0)	3.0 (2.0 - 9.0)	-	-
C_{max}, ng/mL	433.7 ± 170.7	389.0 ± 192.5	0.84	0.68 - 1.04
AUC_{last}, ng.h/mL	4291 ± 1693	3543 ± 1356	0.82	0.72 - 0.93
AUC_{∞}, ng.h/mL	4878 ± 2067	3997 ± 1562	0.81	0.72 - 0.91
$t_{1/2,term}$, h	6.676 ± 1.813	6.619 ± 1.932	-	-
Treatment A (TMC125/rtv 200/100 mg after Breakfast) vs. Treatment D (TMC125 200 mg after Breakfast + rtv 100 mg 4 h before TMC125 Intake)				
N	20	20		
t_{max}, h	4.0 (1.0 - 12.0)	4.0 (2.0 - 4.0)	-	-
C_{max}, ng/mL	433.7 ± 170.7	589.4 ± 235.8	1.35	1.16 - 1.57
AUC_{last}, ng.h/mL	4291 ± 1693	4674 ± 1793	1.08	0.96 - 1.22
AUC_{∞}, ng.h/mL	4878 ± 2067	4975 ± 1947	1.01	0.90 - 1.14
$t_{1/2,term}$, h	6.676 ± 1.813	5.107 ± 1.212	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C116/Section 4.2.5.2 and Section 4.2.5.3

In Panel 2, when TMC125 was given before breakfast and rtv 100 mg was given after breakfast (Treatment H), compared to their administration together with TMC125 after breakfast (Treatment E), the exposure to rtv was unaffected (Table 46).

Table 46: Pharmacokinetics of Ritonavir after Administration of Ritonavir with TMC125 before or after a Meal (Panel 2) (Trial TMC125-C116)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment E: TMC125/rtv 200/100 mg after Breakfast (Reference)	Treatment H: TMC125 200 mg before Breakfast + rtv 100 mg after Breakfast (Test)		
N	17	18		
t_{max}, h	6.0 (1.0 - 6.0)	5.5 (3.5 - 5.5)	-	-
C_{max}, ng/mL	455.5 ± 166.0	450.6 ± 200.7	1.02	0.90 - 1.16
AUC_{last}, ng.h/mL	3979 ± 1421	3832 ± 1692	0.99	0.91 - 1.08
AUC_{∞}, ng.h/mL	4343 ± 1625	4186 ± 1915	0.99	0.91 - 1.07
$t_{1/2,term}$, h	5.971 ± 1.308	5.844 ± 1.049	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C116/Section 4.2.5.2 and Section 4.2.5.3

2.8.1.3.4 Conclusions

There was no clear evidence of a pharmacokinetic interaction between TMC125 and rtv in the absorption phase. Separation of the administration of TMC125 and rtv by time or by food intake is therefore not expected to have an effect on the interaction between TMC125 and rtv observed in multiple-dose trials.

2.8.1.4 Trial TMC125-C106: Saquinavir - TMC125 Administered as Capsule Formulation T* (TMC125 in PEG 4000) in Healthy Subjects

SQV is primarily metabolized by CYP3A4 and is a P-gp substrate.[22]

2.8.1.4.1 Trial Design

This was an open-label, 2-period crossover trial to investigate the effect of multiple 900 mg b.i.d. doses of TMC125 administered as the 50-mg capsule formulation T* (TMC125 in PEG 4000) on the pharmacokinetics of a single 1200 mg dose of SQV (200 mg soft-gel capsule). The trial population consisted of 12 healthy subjects. In Session 1, subjects received a single dose of 1200 mg SQV. After a washout period of at least 3 days, all subjects were treated in Session 2 as follows:

- TMC125 900 mg b.i.d. for 14 days;
- Concomitant single 1200 mg dose of SQV on Day 14.

The morning doses TMC125 and SQV were taken under fed conditions within 10 minutes after completion of a standardized breakfast. The evening doses of TMC125 were taken after dinner.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C106).

2.8.1.4.2 Pharmacokinetics of TMC125

The pharmacokinetics of TMC125 at steady-state were characterized by a median t_{max} of 4 hours and a small fluctuation between highest and lowest plasma concentrations (Table 47). Inter-subject variabilities in C_{max} and AUC_{12h} were modest, between 25% and 30%. Steady-state

pharmacokinetics of TMC125 were not altered to any relevant degree by concomitant intake of a single dose of SQV. Comparing the mean C_{max} and AUC_{12h} of TMC125 in both treatments, the 90% CIs were small and within the 80% to 125% range. Mean trough values of TMC125 varied between 357 and 392 ng/mL, and steady-state was reached within 5 days (Module 5.3.3.4/TMC125-C106/Display 4). No relevant difference was observed between morning pre-dose levels and evening pre-dose concentrations on Day 8 and on Day 14.

Table 47: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Saquinavir (Trial TMC125-C106)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Session 2, Day 8: TMC125 900 mg b.i.d. (Reference)	Session 2, Day 14: TMC125 900 mg b.i.d. + SQV 1200 mg (Test)		
N	12	12		
t_{max}, h	4.0 (3.0 - 6.0)	4.0 (3.0 - 6.0)	-	-
C_{0h}, ng/mL	388.3 ± 141.3	367.8 ± 120.6	-	-
C_{max}, ng/mL	613.8 ± 178.3	585.8 ± 149.0	0.96	0.88 - 1.04
AUC_{12h}, ng.h/mL	5701 ± 1808	5517 ± 1514	0.98	0.90 - 1.06

N = maximum number of subjects with data.
[a] Ratio based on geometric means.
Source: Module 5.3.3.4/TMC125-C106/Section 4.C.5

2.8.1.4.3 Pharmacokinetics of Saquinavir

Administration of SQV during multiple dosing with TMC125 resulted in decreased plasma concentrations of SQV (Table 48). The mean C_{max} and AUC_{last} of SQV were decreased by 46% and 52%, respectively. No relevant difference was observed in median t_{max} values for the 2 treatments. There was a large variability in SQV plasma concentrations during both treatments.

Table 48: Pharmacokinetics of Saquinavir after Administration of Saquinavir in the Absence and Presence of TMC125 (Trial TMC125-C106)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Session 1, Day 1: SQV 1200 mg (Reference)	Session 2, Day 14: TMC125 900 mg b.i.d. + SQV 1200 mg (Test)		
N	11	12		
t_{max}, h	1.0 (1.0 - 3.0)	2.0 (1.0 - 2.0)	-	-
C_{max}, ng/mL	212.4 ± 143.6	106.0 ± 52.96	0.54	0.34 - 0.86
AUC_{last}, ng.h/mL	627.5 ± 411.4	292.4 ± 175.8	0.48	0.29 - 0.80
AUC_{∞} [b], ng.h/mL	670.6 ± 435.7	347.1 ± 170.0	0.61	0.42 - 0.90
$t_{1/2,term}$ [b], h	9.8 ± 2.4	12.8 ± 7.7	-	-

N = maximum number of subjects with data.
[a] Ratio based on geometric means.
[b] Accurate determination not possible in all subjects.
Source: Module 5.3.3.4/TMC125-C106/Section 4.C.7

2.8.1.4.4 Conclusions

The mean exposure (AUC_{last}) to SQV was decreased by 52% when co-administered with TMC125. Steady-state pharmacokinetics of TMC125 were not affected by the co-administration

of a single dose of SQV. The interaction observed in this trial suggests an effect of TMC125 on SQV metabolism by induction of CYP3A4 activity.

2.8.1.5 TRIAL TMC125-C109: EFAVIRENZ AND NEVIRAPINE - TMC125 ADMINISTERED AS CAPSULE FORMULATION T* (TMC125 IN PEG 4000) IN HEALTHY SUBJECTS

EFV and NVP are potent CYP3A4 and 2B6 inducers[53,59] and can potentially decrease plasma concentrations of TMC125, which is a CYP3A4 substrate.

2.8.1.5.1 Trial Design

This was an open-label, 2-panel trial to investigate the effect of multiple doses of EFV or NVP on the pharmacokinetics of a single dose of TMC125 administered as the 50-mg capsule formulation T* (TMC125 in PEG 4000). Each panel of subjects was treated in 2 sessions. In the first session, all subjects received a single oral dose of 900 mg TMC125, which was followed by a washout period of 5 days. In the second session, the subjects were treated as follows:

- Panel 1: EFV 600 mg q.d. for 18 days. On Day 14, a single dose of 900 mg TMC125 was co-administered;
- Panel 2: NVP 200 mg q.d. for the first 7 days, followed by 200 mg b.i.d. for the next 11 days. On Day 14, a single dose of 900 mg TMC125 was co-administered.

Panel 1 included 15 healthy subjects, and Panel 2 included 7 healthy subjects.

TMC125 was taken under fed conditions within 10 minutes after completion of a standardized breakfast.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C109).

2.8.1.5.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{last} of TMC125 were decreased by 17% and 41%, respectively, when TMC125 was co-administered with EFV (Table 49). The 90% CIs of the LS means ratios were outside the 80% to 125% range for both comparisons. There were no relevant changes in the median t_{max} or the mean elimination half-life of TMC125.

＊：新薬承認情報提供時に置き換え

Table 49: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Efavirenz (Trial TMC125-C109)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Session 1, Day 1: TMC125 900 mg (Reference)	Session 2, Day 14: EFV 600 mg q.d. + TMC125 900 mg (Test)		
N	12	12		
t_{max}, h	3 (2 - 8)	2 (2 - 4)	-	-
C_{max}, ng/mL	246 ± 100	215 ± 117	0.83	0.73 - 0.93
AUC_{last}, ng.h/mL	3196 ± 1251	2064 ± 1373	0.59	0.52 - 0.68
AUC_{∞}, ng.h/mL	3473 ± 1506	2249 ± 1543	0.60	0.53 - 0.68
$t_{1/2,term}$, h	32.7 ± 9.7	28.8 ± 11.4	-	-

N = maximum number of subjects with data.
[a] Ratio based on geometric means.
Source: Module 5.3.3.4/TMC125-C109/Section 4.C.5

Due to the limited number of subjects who completed the trial, no formal statistical analysis was performed for the NVP panel. The limited data indicated decreased plasma concentrations of TMC125 when TMC125 was co-administered with NVP (Table 50).

Table 50: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Nevirapine (Trial TMC125-C109)

Parameter	Mean ± SD; t_{max}: Median (Range)	
	Session 1, Day 1: TMC125 900 mg Single Dose (Reference)	Session 2, Day 14: NVP 200 mg q.d. + TMC125 900 mg (Test)
N	5	5
t_{max}, h	3 (2 - 3)	3 (2 - 4)
C_{max}, ng/mL	309 ± 233	199 ± 107
AUC_{last}, ng.h/mL	4766 ± 3176	2335 ± 1299
AUC_{∞}, ng.h/mL	5475 ± 3898	2482 ± 1404
$t_{1/2,term}$, h	37.4 ± 13.6	26.6 ± 9.7

N = maximum number of subjects with data.
Source: Module 5.3.3.4/TMC125-C109/Section 4.C.5

2.8.1.5.3 Conclusions

In healthy subjects, the mean exposure (AUC_{last}) to TMC125 was decreased by 41% when TMC125 was co-administered with EFV. The limited data also indicated decreased plasma concentrations of TMC125 when TMC125 was co-administered with NVP. The observed decreases in plasma concentrations are consistent with the known metabolism-enzyme inducing potentials of NVP and EFV.

2.8.2 Administration of TMC125 with Other Antiretrovirals

2.8.2.1 TRIAL TMC125-C157: DIDANOSINE - TMC125 ADMINISTERED AS TABLET FORMULATION F* (TMC125 IN HPMC, GRANULO-LAYERED) IN HEALTHY SUBJECTS

ddI is primarily excreted by the kidney[58], and therefore no drug-drug interaction was anticipated when ddI was co-administered with TMC125.

2.8.2.1.1 Trial Design

This was an open-label, randomized, 2-period crossover trial to investigate the pharmacokinetic interaction between TMC125, administered as the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered), and ddI (enteric-coated capsule) at steady-state. The trial population consisted of 16 healthy subjects.

In Session 1, subjects in each of 2 groups received TMC125 800 mg b.i.d. from Day 1 to Day 7 and a single dose of TMC125 800 mg on Day 8, followed by a washout period of at least 2 weeks. In Session 2, subjects received the following treatments:

- Group 1: ddI 400 mg q.d. on Days 1 to 16, and TMC125 800 mg b.i.d. on Days 9 to 16;
- Group 2: ddI 400 mg q.d. on Days 1 to 16, and TMC125 800 mg b.i.d. on Days 1 to 8.

Co-administration of TMC125 and ddI in the morning was as follows: ddI was administered under fasted conditions; a standardized breakfast was taken 1.5 hours after ddI intake, and TMC125 was administered under fed conditions within 10 minutes after completion of the standardized breakfast. The evening dose of TMC125 was administered within 10 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C157).

2.8.2.1.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{12h} of TMC125 were slightly increased (1.16- and 1.11-fold, respectively) when TMC125 was co-administered with ddI (Table 51). The mean C_{min} and C_{0h} were also slightly increased (1.05- and 1.08-fold, respectively). However, for all comparisons, with the exception of C_{max}, the 90% CIs of the LS means ratios were within the 80% to 125% range. There was no relevant change in the median t_{max} of TMC125.

＊：新薬承認情報提供時に置き換え

Table 51: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Didanosine (Trial TMC125-C157)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	TMC125 800 mg b.i.d. (Reference)	TMC125 800 mg b.i.d. + ddI 400 mg q.d. (Test)		
N	15	14		
t_{max}, h	4.0 (2.0 - 6.0)	3.0 (1.5 - 6.0)	-	-
C_{0h}, ng/mL	489 ± 206	527 ± 206	1.08	0.99 - 1.18
C_{min}, ng/mL	450 ± 212	468 ± 196	1.05	0.93 - 1.18
C_{max}, ng/mL	759 ± 376	860 ± 371	1.16	1.02 - 1.32
AUC_{12h}, ng.h/mL	7262 ± 3371	8000 ± 3328	1.11	0.99 - 1.25

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C157/Section 4.2.4.2 and Section 4.2.4.3

2.8.2.1.3 Pharmacokinetics of Didanosine

Because the predose concentrations of ddI and the concentrations at 24 hours after dosing were below the LLOQ for all subjects, the C_{min} and C_{0h} of ddI were not quantifiable.

The mean C_{max} of ddI was slightly decreased (by 9%), and the mean AUC_{24h} of ddI was comparable, when ddI was co-administered with TMC125, compared to administration of ddI alone (Table 52). The 90% CIs of the LS means ratios for C_{max} were outside the 80% to 125% range. There was no change in the median t_{max} of ddI.

Table 52: Pharmacokinetics of Didanosine after Administration of Didanosine in the Absence and Presence of TMC125 (Trial TMC125-C157)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	ddI 400 mg q.d. (Reference)	ddI 400 mg q.d. + TMC125 800 mg b.i.d. (Test)		
N	14	14		
t_{max}, h	2.0 (1.0 - 3.0)	2.0 (1.0 - 9.0)	-	-
C_{max}, ng/mL	1323 ± 741	1210 ± 623	0.91	0.58 - 1.42
AUC_{24h}, ng.h/mL	2883 ± 941	2899 ± 877	0.99	0.79 - 1.25

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C157/Section 4.2.5.2 and Section 4.2.5.3

2.8.2.1.4 Conclusions

In healthy subjects, no relevant changes were observed in the steady-state pharmacokinetics of TMC125 or ddI during co-administration of these drugs, compared to their administration alone. Based on these results, TMC125 and ddI can be co-administered without dose adjustments but separated in time due to meal requirements (ddI is recommended for administration on an empty stomach and TMC125 following a meal).

2.8.2.2 TRIAL TMC125-C138: TENOFOVIR DISOPROXIL FUMARATE - TMC125 ADMINISTERED AS TABLET FORMULATION F* (TMC125 IN HPMC, GRANULO-LAYERED) IN HEALTHY SUBJECTS

TDF is primarily excreted by the kidney,[60] and is a multidrug resistance protein type 4 substrate.[51] No clinically relevant drug-drug interaction was anticipated when TDF was co-administered with TMC125.

2.8.2.2.1 Trial Design

This was an open-label, randomized, 2-period crossover trial to investigate the pharmacokinetic interaction between TMC125, administered as the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered), and TDF at steady state, and to investigate the effect of TMC125 on the urinary excretion of TDF. The trial population consisted of 16 healthy subjects.

In Session 1, subjects received TMC125 800 mg b.i.d. from Day 1 to Day 7 and an additional morning dose on Day 8, followed by a washout period of at least 14 days. In Session 2, subjects received the following treatments:

- Group 1: TDF 300 mg q.d. on Days 1 to 16, and TMC125 800 mg b.i.d. on Days 9 to 16;
- Group 2: TDF 300 mg q.d. on Days 1 to 16, and TMC125 800 mg b.i.d. on Days 1 to 8.

All treatments were taken under fed conditions within 10 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C138).

2.8.2.2.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{12h} of TMC125 were decreased by 30% and 31%, respectively, when TMC125 was co-administered with TDF, compared to administration of TMC125 alone (Table 53). The mean C_{min} and C_{0h} were also decreased by 28% and 24%, respectively. The 90% CIs of the LS means ratios for all these comparisons were outside the 80% to 125% range. There was no change in the median t_{max} of TMC125.

Table 53: Pharmacokinetics of TMC125 after administration of TMC125 in the Absence and Presence of Tenofovir Disoproxil Fumarate (Trial TMC125-C138)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	TMC125 800 mg b.i.d. (Reference)	TMC125 800 mg b.i.d. + TDF 300 mg q.d. (Test)		
N	15	13		
t_{max}, h	3.0 (2.0 - 6.0)	3.0 (1.5 - 6.0)	-	-
C_{0h}, ng/mL	439 ± 196	348 ± 104	0.76	0.68 - 0.86
C_{min}, ng/mL	428 ± 190	322 ± 97	0.72	0.65 - 0.81
C_{max}, ng/mL	953 ± 404	701 ± 299	0.70	0.60 - 0.82
AUC_{12h}, ng.h/mL	8556 ± 3533	6250 ± 2377	0.69	0.61 - 0.79

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C138/Section 4.2.5 and Section 4.2.6

＊：新薬承認情報提供時に置き換え

2.8.2.2.3 Pharmacokinetics of Tenofovir Disoproxil Fumarate

The mean C_{max} and AUC_{24h} of TDF were increased 1.15- and 1.16-fold, respectively, when TDF was co-administered with TMC125, compared to administration of TDF alone (Table 54). The mean C_{min} and C_{0h} were also increased 1.42- and 1.34-fold, respectively. The 90% CIs of the LS means ratios for all comparisons except AUC_{24h} were outside the 80% to 125% range. There was no relevant change in the median t_{max} of TDF.

Table 54: Pharmacokinetics of Tenofovir Disoproxil Fumarate after Administration of Tenofovir Disoproxil Fumarate in the Absence and Presence of TMC125 (Trial TMC125-C138)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	TDF 300 mg q.d. (Reference)	TDF 300 mg q.d. + TMC125 800 mg b.i.d. (Test)		
N	13	13		
t_{max}, h	2.5 (1.0 - 3.0)	2.0 (1.0 - 3.0)	-	-
C_{0h}, ng/mL	70.0 ±28.0	85.5 ± 23.1	1.34	1.11 - 1.61
C_{min}, ng/mL	62.4 ±29.2	78.2 ± 20.8	1.42	1.11 - 1.80
C_{max}, ng/mL	386 ±112	438 ± 101	1.15	1.04 - 1.29
AUC_{24h}, ng.h/mL	3421 ±947	3884 ± 816	1.16	1.09 - 1.23

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C138/Section 4.2.8 and Section 4.2.10

The total urinary excretion of TDF, as a percentage of the dose administered, was increased 1.07-fold when TDF was co-administered with TMC125, compared to administration of TDF alone (Table 55). The 90% CI of the LS means ratio was within the 80% to 125% range.

Table 55: Urinary Excretion of Tenofovir Disoproxil Fumarate after Administration of Tenofovir Disoproxil Fumarate in the Absence and Presence of TMC125 (Trial TMC125-C138)

Parameter	Mean ± SD		Ratio [a] (Test:Reference)	90% CI
	TDF 300 mg q.d. (Reference)	TDF 300 mg q.d. + TMC125 800 mg b.i.d. (Test)		
N	13	13		
Ae_{total}, mg	56.8 ± 10.8	60.5 ± 9.1	-	-
$D_{urine,total}$, %	23.2 ± 4.4	24.7 ± 3.7	1.07	1.00 - 1.14

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C138/Section 4.2.9 and Section 4.2.10

2.8.2.2.4 Conclusions

The mean exposure to TMC125 (AUC_{12h}) was decreased by 31% after co-administration of TDF, compared to administration of TMC125 alone. The exposure to TDF (AUC_{24h}) was increased 1.16-fold after co-administration with TMC125, compared to administration of TDF alone. No treatment effect was shown for the urinary excretion of TDF in the presence of TMC125.

Based upon these results, no dose recommendation was made because the trial was repeated (Trial TMC125-C177, see Section 2.8.2.3) using TMC125 tablet formulation A* (TMC125 in HPMC, spray-dried), which was selected for use in Phase III trials.

2.8.2.3 TRIAL TMC125-C177: TENOFOVIR DISOPROXIL FUMARATE - TMC125 ADMINISTERED AS TABLET FORMULATION A* (TMC125 IN HPMC, SPRAY-DRIED) IN HEALTHY SUBJECTS

Trial TMC125-C138 was repeated using TMC125 tablet formulation A* because this formulation is intended for commercial use and it was anticipated that TMC125 would be co-administered with TDF in the registrational Phase III trials.

2.8.2.3.1 Trial Design

This was an open-label, randomized, 2-period crossover trial to investigate the pharmacokinetic interaction between TMC125, administered as the 100-mg tablet formulation A* (TMC125 in HPMC, spray-dried), and TDF at steady-state, and to investigate the effect of TMC125 on the urinary excretion of TDF. The trial population consisted of 24 healthy subjects.

In Session 1, subjects received TMC125 200 mg b.i.d. from Day 1 to Day 7 and an additional single dose on Day 8, followed by a washout period of at least 14 days. In Session 2, subjects received the following treatments:

- Group 1: TDF 300 mg q.d. on Days 1 to 16, and
  TMC125 200 mg b.i.d. on Days 9 to 16;
- Group 2: TDF 300 mg q.d. on Days 1 to 16, and
  TMC125 200 mg b.i.d. on Days 1 to 8.

All treatments were taken under fed conditions within 10 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C177).

2.8.2.3.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{12h} of TMC125 were both decreased by 19% when TMC125 was co-administered with TDF, compared to administration of TMC125 alone (Table 56). The mean C_{min} and C_{0h} were also decreased by 18% and 12%, respectively. The 90% CIs of the LS means ratios for all comparisons were outside the 80% to 125% range. There was no change in the median t_{max} of TMC125.

＊：新薬承認情報提供時に置き換え

Table 56: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Tenofovir Disoproxil Fumarate (Trial TMC125-C177)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	TMC125 200 mg b.i.d. (Reference)	TMC125 200 mg b.i.d. + TDF 300 mg q.d. (Test)		
N	23	19		
t_{max}, h	4.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	-	-
C_{0h}, ng/mL	461.3 ± 170.5	388.8 ± 126.3	0.88	0.78 - 0.99
C_{min}, ng/mL	426.1 ± 154.6	338.4 ± 113.5	0.82	0.73 - 0.91
C_{max}, ng/mL	875.7 ± 232.8	695.2 ± 144.3	0.81	0.75 - 0.88
AUC_{12h}, ng.h/mL	7638 ± 2254	6040 ± 1557	0.81	0.75 - 0.88

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C177/Section 4.2.5 and Section 4.2.6

2.8.2.3.3 Pharmacokinetics of Tenofovir Disoproxil Fumarate

The mean C_{max} and AUC_{24h} of TDF were both increased 1.15-fold when TDF was co-administered with TMC125, compared to administration of TDF alone (Table 57). The mean C_{min} and C_{0h} of TDF were also increased 1.19- and 1.25-fold, respectively. With the exception of AUC_{24h}, the CIs of the LS means ratios for all comparisons were outside the 80% to 125% range. There was no relevant change in the median t_{max} of TDF.

Table 57: Pharmacokinetics of Tenofovir Disoproxil Fumarate after Administration of Tenofovir Disoproxil Fumarate in the Absence and Presence of TMC125 (Trial TMC125-C177)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	TDF 300 mg q.d. (Reference)	TDF 300 mg q.d. + TMC125 200 mg b.i.d. (Test)		
N	19	19		
t_{max}, h	2.0 (0.5 - 4.0)	1.5 (0.5 - 3.0)	-	-
C_{0h}, ng/mL	74.52 ± 19.38	92.69 ± 22.09	1.25	1.16 - 1.35
C_{min}, ng/mL	69.61 ± 16.37	82.15 ± 16.71	1.19	1.13 - 1.26
C_{max}, ng/mL	388.7 ± 97.28	443.1 ± 98.54	1.15	1.04 - 1.27
AUC_{24h}, ng.h/mL	3946 ± 778.2	4511 ± 827.6	1.15	1.09 - 1.21

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C177/Section 4.2.8 and Section 4.2.9

The urinary excretion of TDF during the 24 hours after administration, as a percentage of the dose administered, was increased 1.10-fold when TDF was co-administered with TMC125, compared to administration of TDF alone (Table 58). The 90% CI of the LS means ratio was within the 80% to 125% range.

Table 58: Urinary Excretion of Tenofovir Disoproxil Fumarate after Administration of Tenofovir Disoproxil Fumarate in the Absence and Presence of TMC125 (Trial TMC125-C177)

Parameter	Mean ± SD		Ratio [a] (Test:Reference)	90% CI
	TDF 300 mg q.d. (Reference)	TDF 300 mg q.d. + TMC125 200 mg b.i.d. (Test)		
N	19	19		
Ae_{24h}, mg	63.1 ± 8.3	73.3 ± 14.9	-	-
$D_{urine,24h}$, %	46.4 ± 6.1	53.9 ± 11.0	1.10	0.98 - 1.24

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C177/Section 4.2.8, Section 4.2.9, and Supporting Data Display 16

2.8.2.3.4 Conclusions

The mean exposure to TMC125 (AUC_{12h}) was decreased by 19% after co-administration of TDF, compared to administration of TMC125 alone, while the exposure to TDF (AUC_{24h}) was increased 1.15-fold after co-administration with TMC125, compared to administration of TDF alone. No treatment effect was shown for the urinary excretion of TDF in the presence of TMC125.

The changes in exposure to TMC125 and TDF after co-administration of both drugs were not clinically relevant. Thus, TDF can be co-administered with TMC125 without dose adjustments.

2.8.2.4 TRIAL TMC125-C151: ATAZANAVIR, WITH AND WITHOUT RITONAVIR - TMC125 ADMINISTERED AS TABLET FORMULATION F* (TMC125 IN HPMC, GRANULO-LAYERED) IN HEALTHY SUBJECTS

ATV is metabolized by CYP3A4; in vitro ATV inhibits CYP3A, 2C8, 2C19, and UDPGT1A1.[52,64]

2.8.2.4.1 Trial Design

This was an open-label, randomized, 2-period crossover, 2-parallel-group trial to investigate the pharmacokinetic interaction between TMC125 and ATV, administered with and without rtv, at steady state. TMC125 was administered as the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered). The trial population consisted of 32 healthy subjects (16 in each treatment group). The trial was divided into 2 sessions, separated by a washout period of at least 14 days, in which Treatments A and B were administered to Group 1 and Treatments C and D were administered to Group 2, as follows:

- Treatment A: ATV 400 mg q.d. on Days 1 to 7;
- Treatment B: TMC125 800 mg b.i.d. on Days 1 to 14, and ATV 400 mg q.d. on Days 8 to 14;
- Treatment C: ATV 300 mg q.d. on Days 1 to 7, and rtv 100 mg q.d. on Days 1 to 7;
- Treatment D: TMC125 800 mg b.i.d. on Days 1 to 14, and ATV 300 mg q.d. on Days 8 to 14, and rtv: 100 mg q.d. on Days 8 to 14.

＊：新薬承認情報提供時に置き換え

TMC125, ATV, and rtv were all taken under fed conditions within 10 minutes after a standardized meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C151).

2.8.2.4.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{12h} of TMC125 were increased 1.47- and 1.50-fold, respectively, when TMC125 was co-administered with ATV in the absence of rtv, and both parameters increased 1.30-fold when TMC125 was co-administered with ATV in the presence of rtv, in both cases compared to the administration of TMC125 alone (Table 59). In both treatment comparisons, the mean C_{min} of TMC125 was also increased, 1.58-fold with ATV in the absence of rtv and 1.26-fold with ATV in the presence of rtv. The 90% CIs of the LS means ratios for all comparisons were outside the 80% to 125% range. There was no change in the median t_{max} of TMC125 in either comparison.

Table 59: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Atazanavir (with and without Co-Administration of Low-Dose Ritonavir) (Trial TMC125-C151)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Group 1, Treatment B, Day 7: TMC125 800 mg b.i.d. (Reference)	Group 1, Treatment B, Day 14: TMC125 800 mg b.i.d. + ATV 400 mg q.d. (Test)		
N	14	14		
t_{max}, h	3.0 (2.0 - 4.0)	3.0 (3.0 - 4.1)	-	-
C_{0h}, ng/mL	331.3 ± 166.7	534.7 ± 297.0	-	-
C_{12h}, ng/mL	322.6 ± 162.3	515.1 ± 314.6	-	-
C_{min}, ng/mL	299.5 ± 158.0	492.9 ± 298.7	1.58	1.46 - 1.70
C_{max}, ng/mL	627.5 ± 301.0	926.9 ± 453.9	1.47	1.36 - 1.59
AUC_{12h}, ng.h/mL	5496 ± 2707	8341 ± 4353	1.50	1.41 - 1.59
	Mean ± SD; t_{max}: Median (Range)			
	Group 2, Treatment D, Day 7: TMC125 800 mg b.i.d. (Reference)	Group 2, Treatment D, Day 14: TMC125 800 mg b.i.d. +ATV/rtv 300/100 mg q.d. (Test)		
N	14	13		
t_{max}, h	3.0 (2.0 - 4.3)	3.0 (2.0 - 4.0)	-	-
C_{0h}, ng/mL	341.6 ± 164.1	422.8 ± 178.9	-	-
C_{12h}, ng/mL	313.1 ± 132.7	439.0 ± 202.3	-	-
C_{min}, ng/mL	307.9 ± 130.9	405.8 ± 181.4	1.26	1.12 - 1.42
C_{max}, ng/mL	643.3 ± 216.1	888.2 ± 366.8	1.30	1.17 - 1.44
AUC_{12h}, ng.h/mL	5457 ± 1999	7527 ± 3241	1.30	1.18 - 1.44

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C151/Section 4.2.5 and Section 4.2.6

2.8.2.4.3 Pharmacokinetics of Atazanavir

The mean C_{max} and AUC_{24h} of ATV were slightly decreased, by 3% and 17%, respectively, when ATV was co-administered with TMC125 in the absence of rtv, and by 3% and 14%, respectively, when ATV was co-administered with TMC125 in the presence of rtv (Table 60). With the exception of C_{max} with ATV in the presence of rtv, the CIs of the LS means ratios for all comparisons were outside the 80% to 125% range. The mean C_{min} of ATV was also decreased, by 47% in the absence of rtv and by 38% in the presence of rtv, and the 90% CIs of the LS means ratios for both comparisons were outside the 80% to 125% range. There was no relevant change in the median t_{max} of ATV in either comparison.

Table 60: Pharmacokinetics of Atazanavir after Administration of Atazanavir (with and without Co-Administration of Low-Dose Ritonavir) in the Absence and Presence of TMC125 (Trial TMC125-C151)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Reference	Test		
	Group 1, Treatment A, Day 7: ATV 400 mg q.d.	Group 1, Treatment B, Day 14: TMC125 800 mg b.i.d. + ATV 400 mg q.d.		
N	14	14		
t_{max}, h	2.5 (1.0 - 3.1)	2.0 (2.0 - 3.0)	-	-
C_{0h}, ng/mL	182.8 ± 118.2	99.8 ± 94.7	-	-
C_{min}, ng/mL	136.8 ± 103.7	78.7 ± 76.6	0.53	0.38 - 0.73
C_{max}, ng/mL	4188 ± 1709	3790 ± 1588	0.97	0.73 - 1.29
AUC_{24h}, ng.h/mL	22289 ± 9471	17350 ±7985	0.83	0.63 - 1.09
	Group 2, Treatment C, Day 7: ATV/rtv 300/100 mg q.d.	Group 2, Treatment D, Day 14: ATV/rtv 300/100 mg q.d. + TMC125 800 mg b.i.d.		
N	14	13		
t_{max}, h	2.0 (2.0 - 3.0)	2.0 (2.0 - 3.2)	-	-
C_{0h}, ng/mL	816.6 ± 299.2	533.5 ± 197.3	-	-
C_{min}, ng/mL	719.6 ± 295.6	455.3 ± 219.2	0.62	0.55 - 0.71
C_{max}, ng/mL	5230 ± 1102	5006 ± 785.7	0.97	0.89 - 1.05
AUC_{24h}, ng.h/mL	48528 ±10996	41246 ± 7044	0.86	0.79 - 0.93

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C151/Section 4.2.8 and Section 4.2.9

2.8.2.4.4 Pharmacokinetics of Ritonavir

The co-administration of TMC125 with ATV/rtv had no relevant effect on the mean C_{max} and AUC_{24h} of rtv, compared to administration of ATV/rtv alone (Table 61). However, the effect per individual was variable, e.g., the individual Day 14/Day 7 treatment ratios for AUC_{24h} ranged from 72.2% to 138.0% (Module 5.3.3.4/TMC125-C151/Section 4.2.11). The co-administration of TMC125 resulted in a 29% decrease in the mean C_{min} of rtv, and the 90% CI of the LS means ratio was outside the 80% to 125% range. There was no change in the median t_{max} of rtv.

Table 61: Pharmacokinetics of Ritonavir after Administration of Low-Dose Ritonavir (Co-Administered with Atazanavir) in the Absence and Presence of TMC125 (Trial TMC125-C151)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Group 2, Treatment C, Day 7: ATV/rtv 300/100 mg q.d. (Reference)	Group 2, Treatment D, Day 14: ATV/rtv 300/100 mg q.d. + TMC125 800 mg b.i.d. (Test)		
N	14	13		
t_{max}, h	4.0 (3.0 - 6.0)	4.0 (3.0 - 6.0)	-	-
C_{0h}, ng/mL	48.2 ± 34.6	34.4 ± 27.9	-	-
C_{min}, ng/mL	40.4 ± 29.3	29.6 ± 23.6	0.71	0.62 - 0.81
C_{max}, ng/mL	1949 ± 533	1952 ± 752	0.99	0.84 - 1.16
AUC_{24h}, ng.h/mL	11180 ± 2990	10415 ± 3317	0.92	0.83 - 1.01

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C151/Section 4.2.11 and Section 4.2.12

2.8.2.4.5 Conclusions

The mean exposure (AUC_{12h}) to TMC125 increased 1.50- and 1.30-fold when co-administered with ATV or ATV/rtv, respectively. When co-administered with TMC125, the mean exposure (AUC_{24h}) to ATV was decreased by 17% when administered without rtv. When administered with rtv and in the presence of TMC125, the mean exposure to ATV was decreased by 14%. In the presence of TMC125, the mean C_{min} of ATV was decreased by 47% without rtv, and by 38% with rtv.

TMC125 and ATV should not be co-administered in the absence of rtv due to the decrease in the C_{min} of ATV. If clinically indicated, the combination of TMC125 and ATV in the presence of rtv can be allowed.

2.8.2.5 TRIAL TMC125-C139: DARUNAVIR WITH RITONAVIR - TMC125 ADMINISTERED AS TABLET FORMULATION F* (TMC125 IN HPMC, GRANULO-LAYERED) IN HEALTHY SUBJECTS

DRV is a CYP3A4 substrate and inhibitor.[18]

2.8.2.5.1 Trial Design

This was an open-label, randomized, 2-period crossover trial to investigate the effect of steady-state concentrations of DRV, co-administered with rtv, on the steady-state pharmacokinetics of TMC125, administered as the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered), and vice versa. The trial population consisted of 24 healthy subjects. For all subjects, 2 treatment sessions were scheduled, separated by a washout period of at least 14 days: Session A and Session B1 for Panel 1, and Session A and Session B2 for Panel 2.

Subjects received the following treatments:

– Session A: TMC125 800 mg b.i.d. for 7 days, with an additional morning dose on Day 8;

- Session B1: DRV/rtv 600/100 mg b.i.d. on Days 1 to 15, with an additional morning dose on Day 16, and
  TMC125 800 mg b.i.d. on Days 9 to 15, with an additional morning dose on Day 16;
- Session B2: DRV/rtv 600/100 mg b.i.d. on Days 1 to 15, with an additional morning dose on Day 16, and
  TMC125 800 mg b.i.d. on Days 1 to 7, with an additional morning dose on Day 8.

The trial medication was taken within 15 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C139).

2.8.2.5.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{12h} of TMC125 were decreased by 34% and 33%, respectively, when TMC125 was co-administered with DRV/rtv, compared to administration of TMC125 alone (Table 62). The mean C_{min} of TMC125 was also decreased by 44%. The 90% CIs of the LS means ratios for all comparisons were outside the 80% to 125% range. The median t_{max} of TMC125 was slightly later in the presence of DRV/rtv.

Table 62: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Darunavir (Co-Administered with Low-Dose Ritonavir) (Trial TMC125-C139)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	TMC125 800 mg b.i.d. (Reference)	TMC125 800 mg b.i.d. + DRV/rtv 600/100 mg b.i.d. (Test)		
N	18	20		
t_{max}, h	3.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	-	-
C_{0h}, ng/mL	600 ± 213	399 ± 218	-	-
C_{min}, ng/mL	546 ± 191	386 ± 216	0.56	0.40 - 0.78
C_{max}, ng/mL	1118 ± 408	901 ± 421	0.66	0.52 - 0.84
AUC_{12h}, ng.h/mL	10030 ± 3557	7788 ± 3949	0.67	0.52 - 0.86

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C139/Section 6/Supporting Data Display 9 and Section 4.2.4.3

2.8.2.5.3 Pharmacokinetics of Darunavir

The mean C_{max} and AUC_{12h} of DRV were increased 1.26- and 1.23-fold, respectively, when DRV/rtv was co-administered with TMC125, compared to administration of DRV/rtv alone (Table 63). The mean C_{min} of DRV was also slightly increased (1.13-fold). With the exception of C_{min}, the 90% CIs of the LS means ratios for all comparisons were outside the 80% to 125% range. The median t_{max} was slightly later in the presence of TMC125.

Table 63: Pharmacokinetics of Darunavir after Administration of Darunavir (Co-Administered with Low-Dose Ritonavir) in the Absence and Presence of TMC125 (Trial TMC125-C139)

Parameter	Mean ± SD; t_{max}: Median (Range) DRV/rtv 600/100 mg b.i.d. (Reference)	DRV/rtv 600/100 mg b.i.d. + TMC125 800 mg b.i.d. (Test)	Ratio [a] (Test:Reference)	90% CI
N	17	20		
t_{max}, h	3.0 (1.5 - 4.0)	4.0 (2.0 - 6.0)	-	-
C_{0h}, ng/mL	3154 ± 945	3290 ± 887	-	-
C_{min}, ng/mL	2609 ± 654	3013 ± 777	1.13	1.05 - 1.23
C_{max}, ng/mL	5460 ± 1204	6854 ± 1355	1.26	1.17 - 1.35
AUC_{12h}, ng.h/mL	46250 ± 9451	56697 ± 10178	1.23	1.16 - 1.31
$t_{1/2,term}$, h	20.07 ± 10.94	10.33 ± 7.25	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C139/ Section 6/Supporting Data Display 14 and Section 4.2.5.3

2.8.2.5.4 Pharmacokinetics of Ritonavir

The mean C_{max} and AUC_{12h} of rtv were slightly decreased by 8% and 5%, respectively, when DRV/rtv was co-administered with TMC125, compared to administration of DRV/rtv alone (Table 64). The mean C_{min} of rtv was slightly decreased by 10%. The 90% CIs of the LS means ratios were outside the 80% to 125% range for C_{max} and C_{min}, but not for AUC_{12h}. There was no change in the median t_{max} of rtv, and no relevant change in the mean terminal elimination half-life.

Table 64: Pharmacokinetics of Low-Dose Ritonavir after Administration of Ritonavir (Co-Administered with Darunavir) in the Absence and Presence of TMC125 (Trial TMC125-C139)

Parameter	Mean ± SD; t_{max}: Median (Range) DRV/rtv 600/100 mg b.i.d. (Reference)	DRV/rtv 600/100 mg b.i.d. + TMC125 800 mg b.i.d. (Test)	Ratio [a] (Test:Reference)	90% CI
N	17	20		
t_{max}, h	4.0 (1.5 - 6.0)	4.0 (1.0 - 6.0)	-	-
C_{0h}, ng/mL	334 ± 148	271 ± 105	-	-
C_{min}, ng/mL	238 ± 84	203 ± 66	0.90	0.78 - 1.03
C_{max}, ng/mL	1166 ± 725	956 ± 417	0.92	0.79 - 1.07
AUC_{12h}, ng.h/mL	6969 ± 2701	6205 ± 1992	0.95	0.85 - 1.07
$t_{1/2,term}$, h	7.05 ± 6.59	5.14 ± 1.64	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C139/Section 6/Supporting Data Display 19 and Section 4.2.6.3

2.8.2.5.5 Conclusions

At steady-state, the mean exposure (AUC_{12h}) to TMC125 was decreased by 33% when co-administered with DRV/rtv. The mean exposure to DRV, given with rtv, was increased 1.23-fold when co-administered with TMC125. The mean exposure to rtv, given with DRV, was not

affected to any relevant degree by co-administration with TMC125. No dose recommendation was made on the basis of these results because the trial was repeated using TMC125 tablet formulation A* (TMC125 in HPMC, spray-dried), which was selected for use in Phase III trials (trial TMC125-C176, see Section 2.8.2.6).

2.8.2.6 TRIAL TMC125-C176: DARUNAVIR WITH RITONAVIR - TMC125 ADMINISTERED AS TABLET FORMULATION A* (TMC125 IN HPMC, SPRAY-DRIED) IN HEALTHY SUBJECTS

Trial TMC125-C139 was repeated using TMC125 tablet formulation A* because this formulation is intended for commercial use and TMC125 was to be co-administered with DRV/rtv in the registrational Phase III trials.

2.8.2.6.1 Trial Design

This was an open-label, randomized, 2-period crossover trial to investigate the effect of steady-state concentrations of DRV, co-administered with rtv, on the steady-state pharmacokinetics of TMC125, administered as the 100-mg tablet formulation A* (TMC125 in HPMC, spray-dried), and vice versa. The trial population consisted of 32 healthy subjects.

For all subjects, 2 treatment sessions were scheduled: Session A and Session B1 for Panel 1, and Session A and Session B2 for Panel 2. Each session was separated by a washout period of at least 14 days. Subjects received the following treatments:

- Session A: TMC125 100 mg b.i.d. for 7 days, with an additional morning dose on Day 8;
- Session B1: DRV/rtv 600/100 mg b.i.d. on Days 1 to 15, with an additional morning dose on Day 16, and
  TMC125 100 mg b.i.d. on Days 9 to 15, with an additional morning dose on Day 16;
- Session B2: DRV/rtv 600/100 mg b.i.d. on Days 1 to 15, with an additional morning dose on Day 16, and
  TMC125 200 mg b.i.d. on Days 9 to 15, with an additional morning dose on Day 16.

The trial medication (DRV/rtv and TMC125) was taken under fed conditions within 15 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C176).

2.8.2.6.2 Pharmacokinetics of TMC125

In Panel 1, the mean C_{max} and AUC_{12h} of TMC125 were decreased by 32% and 37%, respectively, when TMC125 (100 mg b.i.d.) was co-administered with DRV/rtv, compared to TMC125 (100 mg b.i.d.) administered alone (Table 65). The mean C_{min} of TMC125 was also decreased, by 49%. The 90% CIs of the LS means ratios for all comparisons were outside the 80% to 125% range. There was no change in the median t_{max} of TMC125.

In Panel 2, the mean C_{max} and AUC_{12h} of TMC125 were increased 1.81- and 1.80-fold when TMC125 (200 mg b.i.d.) was co-administered with DRV/rtv, compared to TMC125 (100 mg b.i.d.) administered alone (Table 65). (It should be noted that a dose-normalized comparison

would not be valid due to the possibility of a non-linear increase in TMC125 exposure between the 100 and 200 mg b.i.d. dose levels.) The mean C_{min} of TMC125 was also increased 1.67-fold. The 90% CIs of the LS means ratios for all comparisons were outside the 80% to 125% range. There was no change in the median t_{max} of TMC125.

Table 65: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Darunavir (Co-Administered with Low-Dose Ritonavir) (Trial TMC125-C176)

	Mean ± SD; t_{max}: Median (Range)			
Parameter	Panel 1, Session A: TMC125 100 mg b.i.d. (Reference)	Panel 1, Session B1: TMC125 100 mg b.i.d. + DRV/rtv 600/100 mg b.i.d. (Test)	Ratio [a] (Test:Reference)	90% CI
N	14	13		
t_{max}, h	3.0 (1.5 - 6.0)	3.0 (2.0 - 4.0)	-	-
C_{0h}, ng/mL	198 ± 101	112 ± 67	-	-
C_{12h}, ng/mL	204 ± 108	101 ± 55	-	-
C_{min}, ng/mL	189 ± 95	94 ± 49	0.51	0.44 - 0.61
C_{max}, ng/mL	452 ± 122	313 ± 118	0.68	0.57 - 0.82
AUC_{12h}, ng.h/mL	3592 ± 1388	2204 ± 952	0.63	0.54 - 0.73
FI, %	96.9 ± 32.7	125 ± 35.4	-	-
	Mean ± SD; t_{max}: Median (Range)			
Parameter	Panel 2, Session A: TMC125 100 mg b.i.d. (Reference)	Panel 2, Session B2: TMC125 200 mg b.i.d. + DRV/rtv 600/100 mg b.i.d. (Test)	Ratio [a] (Test:Reference)	90% CI
N	11	10		
t_{max}, h	3.0 (1.5 - 6.0)	3.0 (1.5 - 4.0)	-	-
C_{0h}, ng/mL	161 ± 48	289 ± 157	-	-
C_{12h}, ng/mL	166 ± 56	286 ± 164	-	-
C_{min}, ng/mL	156 ± 50	268 ± 151	1.67	1.38 - 2.03
C_{max}, ng/mL	405 ± 118	734 ± 305	1.81	1.56 - 2.11
AUC_{12h}, ng.h/mL	3062 ± 816	5519 ± 2452	1.80	1.56 - 2.08
FI, %	98.8 ± 24.7	107.3 ± 30.6	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C176/Section 4.2.4.2 and Section 4.2.4.3

2.8.2.6.3 Pharmacokinetics of Darunavir

In Panel 1, the mean C_{max} and AUC_{12h} of DRV were similar when DRV/rtv was co-administered with TMC125 (100 mg b.i.d.), compared to administration of DRV/rtv alone (Table 66). The mean C_{min} of DRV was also similar in both treatment periods. There was no relevant change in the median t_{max} of DRV.

In Panel 2, the mean C_{max} and AUC_{12h} of DRV were increased 1.11- and 1.15-fold, respectively, when DRV/rtv was co-administered with TMC125 (200 mg b.i.d.), compared to administration of DRV/rtv alone (Table 66). The mean C_{min} of DRV was similar in both treatments. With the exception of AUC_{12h}, the 90% CIs of the LS means ratios for all comparisons were within the 80% to 125% range. There was no change in the median t_{max} of DRV.

Table 66: Pharmacokinetics of Darunavir after Administration of Darunavir (Co-Administered with Low-Dose Ritonavir) in the Absence and Presence of TMC125 (Trial TMC125-C176)

Parameter	Mean ± SD; t_{max}: Median (Range) Panel 1, Session B1, Day 8: DRV/rtv 600/100 mg b.i.d. (Reference)	Mean ± SD; t_{max}: Median (Range) Panel 1, Session B1, Day 16: DRV/rtv 600/100 mg b.i.d. + TMC125 100 mg b.i.d (Test)	Ratio [a] (Test:Reference)	90% CI
N	14	13		
t_{max}, h	2.0 (1.5 - 4.0)	3.0 (1.0 - 4.0)	-	-
C_{0h}, ng/mL	2625 ± 934	2429 ± 631	-	-
C_{12h}, ng/mL	2586 ± 912	2425 ± 641	-	-
C_{min}, ng/mL	2254 ± 834	2217 ± 541	1.02	0.89 - 1.17
C_{max}, ng/mL	5599 ± 1104	5804 ± 1269	1.03	0.98 - 1.09
AUC_{12h}, ng.h/mL	42982 ± 12666	45199 ± 11583	1.06	1.00 - 1.13
FI, %	99.5 ± 31.5	96.5 ± 20.2	-	-
Parameter	**Mean ± SD; t_{max}: Median (Range) Panel 2, Session B2, Day 8: DRV/rtv 600/100 mg b.i.d. (Reference)**	**Mean ± SD; t_{max}: Median (Range) Panel 2, Session B2, Day 16: DRV/rtv 600/100 mg b.i.d. + TMC125 200 mg b.i.d. (Test)**	**Ratio [a] (Test:Reference)**	**90% CI**
N	15	10		
t_{max}, h	3.0 (1.0 - 4.0)	3.0 (1.0 - 3.0)	-	-
C_{0h}, ng/mL	2683 ± 820	2805 ± 758	-	-
C_{12h}, ng/mL	2497 ± 724	2529 ± 801	-	-
C_{min}, ng/mL	2337 ± 631	2301 ± 738	1.02	0.90 - 1.17
C_{max}, ng/mL	5234 ± 1060	5746 ± 1232	1.11	1.01 - 1.22
AUC_{12h}, ng.h/mL	41135 ± 9579	45449 ± 10864	1.15	1.05 - 1.26
FI, %	86.6 ± 16.1	93.0 ± 15.7	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C176/Section 4.2.5.2 and Section 4.2.5.3

2.8.2.6.4 Pharmacokinetics of Ritonavir

In Panel 1, the mean C_{max} and AUC_{12h} of rtv were decreased by 7% and 14%, respectively, when DRV/rtv was co-administered with TMC125 (100 mg b.i.d.), compared to administration of DRV/rtv alone (Table 67). The mean C_{min} of rtv was also slightly decreased (by 9%). With the exception of AUC_{12h}, the 90% CIs of the LS means ratios were within the 80% to 125% range. There was no change in the median t_{max} of rtv.

In Panel 2, exposure to rtv was generally higher than in Panel 1 for both treatment groups, probably due to inter-subject variability. The mean C_{max} and AUC_{12h} of rtv were decreased by 10% and 11%, respectively, when DRV/rtv was co-administered with TMC125 (200 mg b.i.d.), compared to administration of DRV/rtv alone (Table 67). The mean C_{min} of rtv was similar in both treatment periods. With the exception of C_{max}, the 90% CIs of the LS means ratios were within the 80% to 125% range. There was no change in the median t_{max} of rtv.

Table 67: Pharmacokinetics of Low-Dose Ritonavir after Administration of Ritonavir (Co-Administered with Darunavir) in the Absence and Presence of TMC125 (Trial TMC125-C176)

Parameter	Mean ± SD; t_{max}: Median (Range) Panel 1, Session B1, Day 8: DRV/rtv 600/100 mg b.i.d. (Reference)	Mean ± SD; t_{max}: Median (Range) Panel 1, Session B1, Day 16: DRV/rtv 600/100 mg b.i.d. + TMC125 100 mg b.i.d. (Test)	Ratio [a] (Test:Reference)	90% CI
N	14	13		
t_{max}, h	4.0 (1.5 - 6.0)	4.0 (1.0 - 6.0)	-	-
C_{0h}, ng/mL	226 ± 135	190 ± 70	-	-
C_{12h}, ng/mL	211 ± 95	161 ± 66	-	-
C_{min}, ng/mL	163 ± 86	142 ± 56	0.91	0.81 - 1.02
C_{max}, ng/mL	830 ± 239	766 ± 184	0.93	0.80 - 1.08
AUC_{12h}, ng.h/mL	5217 ± 1763	4396 ± 1087	0.86	0.76 - 0.97
FI, %	157.7 ± 31.5	172.4 ± 24.1	-	-
Parameter	**Mean ± SD; t_{max}: Median (Range) Panel 2, Session B2, Day 8: DRV/rtv 600/100 mg b.i.d. (Reference)**	**Mean ± SD; t_{max}: Median (Range) Panel 2, Session B2, Day 16: DRV/rtv 600/100 mg b.i.d. + TMC125 200 mg b.i.d. (Test)**	**Ratio [a] (Test:Reference)**	**90% CI**
N	15	10		
t_{max}, h	4.0 (3.0 - 6.0)	4.0 (3.0 - 4.0)	-	-
C_{0h}, ng/mL	269 ± 120	275 ± 130	-	-
C_{12h}, ng/mL	300 ± 126	238 ± 97	-	-
C_{min}, ng/mL	192 ± 85	206 ± 85	1.01	0.86 - 1.17
C_{max}, ng/mL	1061 ± 461	974 ± 351	0.90	0.74 - 1.08
AUC_{12h}, ng.h/mL	6129 ± 2218	5742 ± 1970	0.89	0.82 - 0.98
FI, %	169.2 ± 53.0	161.3 ± 20.2	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C176/Section 4.2.6.2 and Section 4.2.6.3

2.8.2.6.5 Conclusions

At steady-state, co-administration of DRV/rtv caused a 37% decrease and a 1.80-fold increase, respectively, in the mean exposure (AUC_{12h}) to TMC125 when TMC125 was administered at a dose of 100 mg b.i.d. and 200 mg b.i.d., respectively, in both cases compared to administration of TMC125 100 mg b.i.d. For DRV exposure, only the mean AUC_{12h} was increased 1.15-fold after co-administration of TMC125 200 mg b.i.d. The mean exposure to rtv was decreased by 14% and 11%, respectively, after co-administration of TMC125 100 mg and 200 mg b.i.d.

Based on the results of this trial, the dosing regimen of 200 mg b.i.d. TMC125 administered as formulation A* can be co-administered with DRV/rtv without any dose adjustments.

＊：新薬承認情報提供時に置き換え

2.8.2.7 TRIAL TMC125-C111: INDINAVIR - TMC125 ADMINISTERED AS TABLET FORMULATION F* (TMC125 IN HPMC, GRANULO-LAYERED) IN HEALTHY SUBJECTS

IDV is a CYP3A4 substrate and inhibitor as well as a UDPGT inhibitor.[16,64] As TMC125 is an inducer of CYP3A4, co-administration of IDV with TMC125 was expected to decrease the exposure to IDV.

2.8.2.7.1 Trial Design

This was an open-label, 2-period crossover trial to investigate the pharmacokinetic interaction between IDV and TMC125, administered as the 200-mg tablet formulation B* (TMC125 in HPMC, granulo-layered), at steady-state. The trial population consisted of 12 healthy subjects.

The subjects were treated in 2 sessions, separated by a washout period of one day, as follows:

- Session 1: IDV 800 mg three-times daily (t.i.d.) for 2 days, with an additional morning dose on Day 3;
- Session 2: TMC125 1600 mg b.i.d. on Days 1 to 13, with an additional morning dose on Day 14, and
  IDV 800 mg t.i.d. on Days 9 to 13, with an additional morning dose on Day 14.

The morning IDV dose was taken at least 1 hour before breakfast, the afternoon IDV dose at least 2 hours after lunch and at least 1 hour before dinner, and the evening IDV dose at least 2 hours after dinner. TMC125 was taken under fed conditions within 15 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C111).

2.8.2.7.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{12h} of TMC125 were both increased 1.51-fold when TMC125 was co-administered with IDV, compared to administration of TMC125 alone (Table 68). The mean C_{0h} was increased 1.52-fold. The 90% CIs of the geometric means ratios for these comparisons were outside the 80% to 125% range. There was no change in the median t_{max} of TMC125.

Table 68: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Indinavir (Trial TMC125-C111)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Session 2, Day 8: TMC125 1600 mg b.i.d. (Reference)	Session 2, Day 14: TMC125 1600 mg b.i.d. + IDV 800 mg t.i.d. (Test)		
N	10	10		
t_{max}, h	4.0 (2.0 - 8.0)	4.0 (4.0 - 6.0)	-	-
C_{0h}, ng/mL	406 ± 180	635 ± 363	1.52	1.20 - 1.91
C_{max}, ng/mL	662 ± 369	990 ± 517	1.51	1.16 - 1.97
AUC_{12h}, ng.h/mL	6182 ± 3269	9203 ± 4793	1.51	1.20 - 1.90

N = maximum number of subjects with data.
[a] Ratio based on geometric means.
Source: Module 5.3.3.4/TMC125-C111/Section 4.C.5

＊：新薬承認情報提供時に置き換え

2.8.2.7.3 Pharmacokinetics of Indinavir

The mean C_{max} and AUC_{8h} of IDV were decreased by 28% and 46%, respectively, when IDV was co-administered with TMC125, compared to administration of IDV alone (Table 69). The mean C_{0h} was also decreased, by 76%. The 90% CIs of the geometric means ratios for these comparisons were outside the 80% to 125% range. There was no change in the median t_{max} or mean terminal elimination half-life of IDV.

Table 69: Pharmacokinetics of Indinavir after Administration of Indinavir in the Absence and Presence of TMC125 (Trial TMC125-C111)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Session 1, Day 3: IDV 800 mg t.i.d. (Reference)	Session 2, Day 14: IDV 800 mg t.i.d. + TMC125 1600 mg b.i.d. (Test)		
N	10	10		
t_{max}, h	1.0 (0.5 - 2.0)	1.0 (0.5 - 2.0)	-	-
C_{0h}, ng/mL	561 ± 745	139 ± 189	0.24	0.17 - 0.34
C_{max}, ng/mL	10329 ± 1695	7679 ± 2264	0.72	0.58 - 0.89
AUC_{8h}, ng.h/mL	25032 ± 4974	13754 ± 4420	0.54	0.46 - 0.62
$t_{1/2,term}$, h	1.16 ± 0.124	1.27 ± 0.167	-	-

N = maximum number of subjects with data.
[a] Ratio based on geometric means
Source: Module 5.3.3.4/TMC125-C111/Section 4.C.7

2.8.2.7.4 Conclusions

Co-administration of IDV and TMC125 increased TMC125 steady-state exposure 1.51-fold, compared to administration of TMC125 alone. Co-administration of TMC125 and IDV decreased IDV steady-state exposure by 46%, compared to administration of IDV alone. Thus a mutual effect between TMC125 and IDV was observed. The increase in TMC125 plasma concentrations may be explained by decreased metabolism of TMC125 due to IDV inhibition of CYP3A4 and UDPGT. The lower plasma concentrations of IDV suggest an increased metabolism of IDV due to induction of CYP3A4 by TMC125. The co-administration of unboosted IDV with TMC125 is not recommended.

2.8.2.8 TRIAL TMC125-C122: LOPINAVIR WITH RITONAVIR - TMC125 ADMINISTERED AS TABLET FORMULATION F* (TMC125 IN HPMC, GRANULO-LAYERED) IN HEALTHY SUBJECTS

LPV/rtv is a CYP3A4 substrate and inhibitor, and CYP2C9 and 2C19 inducer.[28,62]

2.8.2.8.1 Trial Design

This was an open-label, parallel-group trial to investigate the pharmacokinetic interaction between TMC125, administered as the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered), and LPV, co-administered with rtv, at steady-state. The trial population consisted of 30 healthy subjects (15 subjects in each panel).

In Session 1, all subjects in both panels received a single dose of LPV/rtv 400/100 mg on Day 1, followed by a washout period of at least 3 days. In Session 2, subjects were treated in the 2 panels as follows:

- Panel 1: TMC125 1600 mg b.i.d. on Days 1 to 20, with an additional morning dose on Day 21, and
  LPV/rtv 400/100 mg b.i.d. on Days 8 to 20, with an additional morning dose on Day 21;
- Panel 2: LPV/rtv 400/100 mg b.i.d. on Days 1 to 13, with an additional morning dose on Day 14.

All trial medication was taken under fed conditions within 15 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C122).

2.8.2.8.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{12h} of TMC125 were increased 1.15- and 1.17-fold, respectively, when TMC125 was co-administered with LPV/rtv, compared to administration of TMC125 alone (Table 70). The mean C_{min} was increased 1.23-fold. The 90% CIs of the geometric means ratios for these comparisons were outside the 80% to 125% range. There was no relevant change in the median t_{max} of TMC125.

Table 70: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Lopinavir (Co-Administered with Low-Dose Ritonavir) (Trial TMC125-C122)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Panel 1, Day 7: TMC125 1600 mg b.i.d. (Reference)	Panel 1, Day 21: TMC125 1600 mg b.i.d. + LPV/rtv 400/100 mg b.i.d. (Test)		
N	13	13		
t_{max}, h	3.0 (2.0 - 4.0)	4.0 (2.0 - 6.0)	-	-
C_{0h}, ng/mL	776 ± 362	1104 ± 791	-	-
C_{min}, ng/mL	744 ± 335	1062 ± 751	1.23	0.98 - 1.53
C_{max}, ng/mL	1543 ± 608	1927 ± 1041	1.15	0.94 - 1.41
AUC_{12h}, ng.h/mL	13456 ± 5235	17744 ± 10697	1.17	0.96 - 1.43

N = maximum number of subjects with data.
[a] Ratio based on geometric means.
Source: Module 5.3.3.4/TMC125-C122/Section 4.2.5.1 and Section 4.2.6.1

2.8.2.8.3 Pharmacokinetics of Lopinavir

In Session 1, the mean exposure (AUC_{last}) to LPV was slightly higher (1.12-fold, 95% CI: 0.83 to 1.39) in Panel 1, compared to Panel 2 (Module 5.3.3.4/TMC125-C122/Section 4.2.6.2). There were no relevant differences in the mean C_{max} or median t_{max} of LPV between the 2 panels, indicating comparable LPV pharmacokinetics between the subjects in the 2 panels.

The mean C_{max} and AUC_{12h} of LPV in Session 2 were decreased by 15% and 20%, respectively, when LPV/rtv was co-administered with TMC125, compared to administration of LPV/rtv alone (Table 71). The mean C_{min} was only slightly decreased, by 8%. The 90% CIs of the geometric means ratios for these comparisons were outside the 80% to 125% range. There was no change in the median t_{max} of LPV.

Table 71: Pharmacokinetics of Lopinavir after Administration of Lopinavir (Co-Administered with Low-Dose Ritonavir) in the Absence and Presence of TMC125 (Trial TMC125-C122)

	Mean ± SD; t_{max}: Median (Range)			
	Panel 2, Day 14: LPV/rtv 400/100 mg b.i.d. (Reference)	Panel 1, Day 21: LPV/rtv 400/100 mg b.i.d. + TMC125 1600 mg b.i.d. (Test)	Ratio [a] (Test:Reference)	95% CI
N	14	13		
t_{max}, h	6.0 (2.0 - 6.0)	6.0 (2.0 - 8.0)	-	-
C_{0h}, ng/mL	4979 ± 3178	3525 ± 2097	-	-
C_{min}, ng/mL	3158 ± 2045	2656 ± 1620	0.92	0.15 - 1.68
C_{max}, ng/mL	8929 ± 2474	7539 ± 2193	0.85	0.62 - 1.05
AUC_{12h}, ng.h/mL	74858 ± 25776	60595 ± 22477	0.80	0.49 - 1.07

N = maximum number of subjects with data.
[a] Ratio based on geometric means.
Source: Module 5.3.3.4/TMC125-C122/Section 4.2.5.2 and Section 4.2.6.2

2.8.2.8.4 Pharmacokinetics of Ritonavir

In Session 1, the mean exposure to rtv (expressed as AUC_{last}) was slightly increased (1.15-fold, 95% CI: 0.68 to 1.60) in Panel 2, compared to Panel 1 (Module 5.3.3.4/TMC125-C122/Section 4.2.6.3). However, there were no differences in the mean C_{max} or median t_{max} of rtv between the 2 panels, indicating comparable rtv pharmacokinetics between the subjects in the 2 panels.

The mean C_{max} and AUC_{12h} of rtv were slightly decreased by 8% and 9%, respectively, when LPV/rtv was co-administered with TMC125, compared to administration of LPV/rtv alone (Table 72). The 90% CIs of the geometric means ratios for both comparisons were outside the 80% to 125% range. There were no relevant changes in the mean C_{min} or median t_{max} of rtv.

Table 72: Pharmacokinetics of Ritonavir (Co-Administered with Lopinavir) in the Absence or Presence of TMC125 (Trial TMC125-C122)

	Mean ± SD; t_{max}: Median (Range)			
	Panel 2, Day 14: LPV/rtv 400/100 mg b.i.d. (Reference)	Panel 1, Day 21: LPV/rtv 400/100 mg b.i.d. + TMC125 1600 mg b.i.d. (Test)	Ratio [a] (Test:Reference)	90% CI
N	14	13		
t_{max}, h	6.0 (2.0 - 8.0)	6.0 (4.0 - 8.0)	-	-
C_{0h}, ng/mL	148 ± 89.5	167 ± 124	-	-
C_{min}, ng/mL	99.7 ± 65.5	99.5 ± 65.0	1.01	0.39 - 1.62
C_{max}, ng/mL	512 ± 156	498 ±233	0.92	0.61 - 1.23
AUC_{12h}, ng.h/mL	3407 ± 1281	3228 ± 1494	0.91	0.58 - 1.24

N = maximum number of subjects with data.
[a] Ratio based on geometric means.
Source: Module 5.3.3.4/TMC125-C122/Section 4.2.5.3 and Section 4.2.6.3

2.8.2.8.5 Conclusions

In healthy subjects, co-administration of TMC125 and LPV/rtv had no relevant effect on the steady-state pharmacokinetics of TMC125, LPV, or rtv. The co-administration of these drugs is therefore permitted.

2.8.2.9 TRIAL TMC125-C123: SAQUINAVIR WITH RITONAVIR - TMC125 ADMINISTERED AS TABLET FORMULATION F* (TMC125 IN HPMC, GRANULO-LAYERED) IN HEALTHY SUBJECTS

2.8.2.9.1 Trial Design

This was an open-label, parallel-group trial to investigate the pharmacokinetic interaction between TMC125, administered as the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered), and SQV, co-administered with rtv, at steady-state. The trial population consisted of 30 healthy subjects (15 subjects in each panel).

In Session 1, all subjects in both panels received a single dose of SQV/rtv 1000/100 mg on Day 1, followed by a washout period of at least 3 days. In Session 2, subjects were treated in the 2 panels as follows:

- Panel 1: TMC125 1600 mg b.i.d. on Days 1 to 20, with an additional morning dose on Day 21, and
  SQV/rtv 1000/100 mg b.i.d. on Days 8 to 20, with an additional morning dose on Day 21;
- Panel 2: SQV/rtv 1000/100 mg b.i.d. on Days 1 to 13, with an additional morning dose on Day 14.

All trial medication was administered under fed conditions within 15 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C123).

2.8.2.9.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{12h} of TMC125 were decreased by 37% and 33%, respectively, when TMC125 was co-administered with SQV/rtv, compared to administration of TMC125 alone (Table 73). The mean C_{min} was also decreased by 29%. The 90% CIs of the LS means ratios for these comparisons were outside the 80% to 125% range. There was no relevant change in the median t_{max} of TMC125.

＊：新薬承認情報提供時に置き換え

Table 73: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Saquinavir (Co-administered with Low-Dose Ritonavir) (Trial TMC125-C123)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Session 2, Panel 1, Day 7: TMC125 1600 mg b.i.d. (Reference)	Session 2, Panel 1, Day 21: TMC125 1600 mg b.i.d. + SQV/rtv 1000/100 mg b.i.d. (Test)		
N	15	14		
t_{max}, h	3.0 (2.0 - 6.0)	3.5 (2.0 - 6.0)	-	-
C_{0h}, ng/mL	668 ± 293	496 ± 333	-	-
C_{min}, ng/mL	630 ± 271	469 ± 301	0.71	0.58 - 0.87
C_{max}, ng/mL	1291 ± 523	809 ± 392	0.63	0.53 - 0.75
AUC_{12h}, ng.h/mL	11199 ± 4637	7555 ± 4052	0.67	0.56 - 0.80

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C123/Section 4.2.5 and Section 4.2.6

2.8.2.9.3 Pharmacokinetics of Saquinavir

In Session 1, the pharmacokinetics of SQV were similar in both panels (Module 5.3.3.4/TMC125-C123/Section 4.2.14).

In Session 2, the mean C_{max} and AUC_{12h} of SQV were comparable when SQV/rtv was co-administered with TMC125, compared to administration of SQV/rtv alone (Table 74). The mean C_{min} and C_{0h} were decreased by 20% and 33%, respectively, after co-administration of TMC125. The 90% CIs of the LS means ratios for all these comparisons were outside the 80% to 125% range. There was no change in the median t_{max} of SQV.

Table 74: Pharmacokinetics of Saquinavir after Administration of Saquinavir (Co-administered with Low-Dose Ritonavir), in the Absence and Presence of TMC125 (Trial TMC125-C123)

	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Session 2, Panel 2, Day 14: SQV/rtv 1000/100 mg b.i.d. (Reference)	Session 2, Panel 1, Day 21: SQV/rtv 1000/100 mg b.i.d. + TMC125 1600 mg b.i.d. (Test)		
N	15	14		
t_{max}, h	3.0 (2.0 - 4.0)	3.0 (2.0 - 6.0)	-	-
C_{0h}, ng/mL	2106 ± 1596	1471 ± 1216	0.67	0.39 - 1.17
C_{min}, ng/mL	1282 ± 1137	963 ± 720	0.80	0.46 - 1.38
C_{max}, ng/mL	6503 ± 3936	6212 ± 3244	1.00	0.70 - 1.42
AUC_{12h}, ng.h/mL	41794 ± 27785	37536 ± 19103	0.95	0.64 - 1.42

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C123/Section 4.2.17 and Section 4.2.18

2.8.2.9.4 Pharmacokinetics of Ritonavir

In Session 1, the pharmacokinetics of rtv were similar in both panels (Module 5.3.3.4/TMC125-C123/Section 4.2.8).

In Session 2, the mean C_{max} and AUC_{12h} of rtv were decreased by 14% and 27%, respectively, when SQV/rtv was co-administered with TMC125, compared to administration of SQV/rtv alone (Table 75). The mean C_{min} and C_{0h} were also decreased, by 50% and 59%, respectively. The 90% CIs of the LS means ratios for all these comparisons were outside the 80% to 125% range. The median t_{max} for rtv was 2 hours earlier when SQV/rtv was co-administered with TMC125, compared to treatment without TMC125. However, for both treatments, the range for t_{max} was 2 to 6 hours.

Table 75: Pharmacokinetics of Ritonavir after Administration of Ritonavir, Co-Administered with Saquinavir, in the Absence and Presence of TMC125 (Trial TMC125-C123)

	Mean ± SD; t_{max}: Median (Range)			
	Session 2, Panel 2, Day 14: SQV/rtv 1000/100 mg b.i.d. (Reference)	Session 2, Panel 1, Day 21: SQV/rtv 1000/100 mg b.i.d. + TMC125 1600 mg b.i.d. (Test)	Ratio [a] (Test:Reference)	90% CI
N	15	14		
t_{max}, h	6.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	-	-
C_{0h}, ng/mL	639 ± 269	293 ± 162	0.41	0.26 - 0.63
C_{min}, ng/mL	333 ± 173	169 ± 81.9	0.50	0.34 - 0.73
C_{max}, ng/mL	1415 ± 691	1146 ± 341	0.86	0.66 - 1.12
AUC_{12h}, ng.h/mL	9766 ± 4442	6899 ± 2388	0.73	0.56 - 0.95

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C123/Section 4.2.11 and Section 4.2.12

2.8.2.9.5 Conclusions

The co-administration of TMC125 with SQV in the presence of rtv resulted in a 33% decrease in the mean exposure (AUC_{12h}) to TMC125 and a 27% decrease in the mean exposure to rtv. The exposure to SQV was not affected by co-administration of TMC125 in the presence of rtv. The decrease in TMC125 exposure is not clinically relevant, therefore the co-administration of TMC125 with SQV/rtv is permitted.

2.8.2.10 TRIAL TMC125-C161: TIPRANAVIR WITH RITONAVIR - TMC125 ADMINISTERED AS TABLET FORMULATION F* (TMC125 IN HPMC, GRANULO-LAYERED) IN HEALTHY SUBJECTS

In vitro, TPV/rtv inhibits CYP1A2, 2C9, 2C19, 2D6, and 3A4 in HLMs; and induces CYP3A activity in human hepatocytes when administered alone. TPV is a P-gp substrate, a weak P-gp inhibitor, and a potent P-gp inducer. The net effect of TPV when co-administered with rtv in vivo is CYP3A inhibition and P-gp induction. In addition, ritonavir has the ability to induce glucuronidation.[1,61]

＊：新薬承認情報提供時に置き換え

2.8.2.10.1 Trial Design

This was an open-label, randomized, 2-period crossover trial to investigate the effect of steady-state concentrations of TPV, co-administered with rtv, on the steady-state pharmacokinetics of TMC125, administered as the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered), and vice versa. The trial population consisted of 24 healthy subjects randomized to 2 panels in a 1:1 ratio (12 subjects in each panel).

For all subjects, 2 treatment sessions were scheduled: Session A and Session B1 for Panel 1, and Session A and Session B2 for Panel 2. Each session was separated by a washout period of at least 14 days. Subjects received the following treatments:

- Session A: TMC125 800 mg b.i.d. for 7 days, with an additional morning dose on Day 8;
- Session B1: TPV/rtv 500/200 mg b.i.d. on Days 1 to 15, with an additional morning dose on Day 16, and
  TMC125 800 mg b.i.d. on Days 9 to 15, with an additional morning dose on Day 16;
- Session B2: TPV/rtv 500/200 mg b.i.d. on Days 1 to 15, with an additional morning dose on Day 16, and
  TMC125 800 mg b.i.d. on Days 1 to 7, with an additional morning dose on Day 8.

The trial medication was taken under fed conditions within 15 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C161).

2.8.2.10.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{12h} of TMC125 were decreased by 71% and 76%, respectively, when TMC125 was co-administered with TPV/rtv (Table 76). The mean C_{min} and C_{0h} were also decreased, by 82% and 81%, respectively. The 90% CIs of the LS means ratios for all these comparisons were outside the 80% to 125% range. There was no relevant change in the median t_{max} of TMC125.

＊：新薬承認情報提供時に置き換え

Table 76: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Tipranavir (Co-Administered with Low-Dose Ritonavir) (Trial TMC125-C161)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	TMC125 800 mg b.i.d. (Reference)	TMC125 800 mg b.i.d. + TPV/rtv 500/200 mg b.i.d. (Test)		
N	19	19		
t_{max}, h	4.0 (2.0 - 8.0)	3.0 (2.0 - 5.0)	-	-
C_{0h}, ng/mL	676 ± 254	214 ± 259	0.19	0.13 - 0.27
C_{min}, ng/mL	625 ± 227	183 ± 234	0.18	0.13 - 0.25
C_{max}, ng/mL	1263 ± 345	456 ± 307	0.29	0.22 - 0.40
AUC_{12h}, ng.h/mL	11236 ± 3210	3697 ± 3336	0.24	0.18 - 0.33

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C161/Section 4.2.4.2 and Section 4.2.4.3

2.8.2.10.3 Pharmacokinetics of Tipranavir

The mean C_{max} and AUC_{12h} of TPV were increased 1.14- and 1.18-fold, respectively, when TPV/rtv was co-administered with TMC125 (Table 77). The mean C_{min} and C_{0h} were increased 1.24- and 1.27-fold, respectively. The 90% CIs of the LS means ratios for all these comparisons were outside the 80% to 125% range. There was no relevant change in the median t_{max} of TPV.

Table 77: Pharmacokinetics of Tipranavir, after Administration of Tipranavir, Co-Administered with Ritonavir, in the Absence and Presence of TMC125 (Trial TMC125-C161)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	TPV/rtv 500/200 mg b.i.d. (Reference)	TPV/rtv 500/200 mg b.i.d. + TMC125 800 mg b.i.d. (Test)		
N	17	19		
t_{max}, h	3.0 (1.5 - 5.0)	4.0 (2.0 - 5.0)	-	-
C_{0h}, ng/mL	22.5 ± 13.4	30.8 ± 26.4	1.27	1.01 - 1.61
C_{min}, ng/mL	18.6 ± 10.4	25.5 ± 24.3	1.24	0.96 - 1.59
C_{max}, ng/mL	68.5 ± 22.5	77.8 ± 30.5	1.14	1.02 - 1.27
AUC_{12h}, ng.h/mL	503.1 ± 188.3	607.4 ± 329.1	1.18	1.03 - 1.36

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C161/Section 4.2.5.2 and Section 4.2.5.3

2.8.2.10.4 Pharmacokinetics of Ritonavir

The mean C_{max} and AUC_{12h} of rtv were increased 1.19- and 1.23-fold, respectively, when TPV/rtv was co-administered with TMC125 (Table 78). The mean C_{min} and C_{0h} were increased 1.34- and 1.93-fold, respectively. The 90% CIs of the LS means ratios for all these comparisons were outside the 80% to 125% range. There was no relevant change in the median t_{max} of rtv.

Table 78:: Pharmacokinetics of Ritonavir, Co-Administered with Tipranavir, in the Absence and Presence of TMC125 (Trial TMC125-C161)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	TPV/rtv 500/200 mg b.i.d. (Reference)	TPV/rtv 500/200 mg b.i.d. + TMC125 800 mg b.i.d. (Test)		
N	17	19		
t_{max}, h	5.0 (1.0 - 5.0)	4.0 (2.0 - 5.0)	-	-
C_{0h}, ng/mL	178 ± 247	261 ± 202	1.93	1.03 - 3.62
C_{min}, ng/mL	84 ± 85	97 ±87	1.34	0.87 - 2.08
C_{max}, ng/mL	1874 ± 861	2237 ±1053	1.19	1.04 - 1.37
AUC_{12h}, ng.h/mL	8542 ± 3952	10561 ± 5076	1.23	1.05 - 1.45

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C161/Section 4.2.6.2 and Section 4.2.6.3

2.8.2.10.5 Conclusions

The mean TMC125 exposure (AUC_{12h}) was decreased by 76% when TMC125 was co-administered with TPV/rtv. The mean exposures to TPV and rtv were increased 1.18- and 1.23-fold, respectively, when co-administered with TMC125. The co-administration of TMC125 with TPV/rtv is not recommended.

2.8.2.11 TRIAL TMC125-C117: FOSAMPRENAVIR WITH RITONAVIR - TMC125 ADMINISTERED AS TABLET FORMULATION F* (TMC125 IN HPMC, GRANULO-LAYERED) IN HIV-1 INFECTED SUBJECTS

APV, administered as fosAPV, is a CYP3A4 substrate, inducer, and inhibitor, as well as a P-gp substrate.[33,48]

2.8.2.11.1 Trial Design

This was an open-label trial to investigate the effect of steady-state TMC125 on the pharmacokinetics of APV (given as fosAPV, co-administered with rtv) in HIV-1 infected subjects with documented NNRTI experience. The trial population consisted of HIV-1 infected subjects with an HIV-1 plasma viral load of < 50 HIV-1 RNA copies/mL and an ART that included fixed doses of fosAPV/rtv 700/100 mg b.i.d. plus a minimum of 2 NRTIs, with or without ENF.

The subjects received TMC125 800 mg b.i.d. as the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered) for 13 days with an additional morning dose of 800 mg on Day 14, in addition to their current ART. Trial medication was administered under fed conditions within 10 minutes after completion of a standardized breakfast.

The trial population was planned to consist of 16 subjects. However, the trial was terminated prematurely because of slow recruitment and difficulty in finding eligible subjects; 8 subjects were recruited over a total screening period of 5 months.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C117).

2.8.2.11.2 Pharmacokinetics of TMC125

Concentrations of TMC125 in trial TMC125-C117 (i.e., in the presence of fosAPV/rtv) were variable and only a low number of subjects was evaluated, as summarized in Table 79. The pharmacokinetic parameters for TMC125 were in the same range as observed in trial TMC125-C223 (in which HIV-1 infected subjects were treated with TMC125 formulation F* at a dose of 800 mg b.i.d., see Section 2.6.2.3.2), particularly compared to subjects with no PI in the underlying ART.

Table 79: Pharmacokinetics of TMC125 after Administration of TMC125 in the Presence of Fosamprenavir (Co-Administered with Low-Dose Ritonavir) (Trial TMC125-C117)

Parameter	Mean ± SD; t_{max}: Median (Range)
	TMC125 800 mg b.i.d. + fosAPV/rtv 700/100 mg b.i.d.
N	8
t_{max}, h	3.00 (3.00 - 6.00)
C_{0h}, ng/mL	495 ± 278
C_{min}, ng/mL	422 ± 227
C_{max}, ng/mL	1019 ± 723
$C_{ss,av}$, ng/mL	719 ± 451
AUC_{12h}, ng.h/mL	8633 ± 5408
$t_{1/2,term}$, h	8.64 ± 2.34

N = maximum number of subjects with data.
[a] Data at Week 24, estimated by population pharmacokinetic methods.
Source: Module 5.3.3.4/TMC125-C117/Section 4.2.4.2

2.8.2.11.3 Pharmacokinetics of Amprenavir

The mean C_{max} and AUC_{12h} of APV were increased 1.62- and 1.69-fold, respectively, when fosAPV/rtv was co-administered with TMC125 (Table 80). The mean C_{min} was increased 1.77-fold. The 90% CIs of the LS means ratios for all comparisons were outside the 80% to 125% range. The median t_{max} of APV decreased after co-administration with TMC125 (2 hours), compared to administration of fosAPV/rtv without TMC125 (3.5 hours), but there was no relevant difference in the mean terminal elimination half-life.

＊：新薬承認情報提供時に置き換え

Table 80: Pharmacokinetics of Amprenavir after Administration of Fosamprenavir (Co-Administered with Low-Dose Ritonavir) in the Absence and Presence of TMC125 (Trial TMC125-C117)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Day -1: fosAPV/rtv 700/100 mg b.i.d. (Reference)	Day 14: fosAPV/rtv 700/100 mg b.i.d. + TMC125 800 mg b.i.d. (Test)		
N	8	8		
t_{max}, h	3.50 (0.50 - 4.00)	2.00 (1.50 - 4.00)	-	-
C_{0h}, ng/mL	1956 ± 855	3196 ± 1242	1.73	1.37 - 2.18
C_{min}, ng/mL	1538 ± 700	2595 ± 1135	1.77	1.39 - 2.25
C_{max}, ng/mL	5505 ± 1152	8983 ± 2369	1.62	1.47 - 1.79
$C_{ss,av}$, ng/mL	2939 ± 926	4887 ± 1427	-	-
AUC_{12h}, ng.h/mL	35270 ± 11115	58645 ± 17120	1.69	1.53 - 1.86
$t_{1/2,term}$, h	6.03 ± 1.79	5.91 ± 1.60	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C117/ Section 4.2.5.2 and Section 4.2.5.3

2.8.2.11.4 Pharmacokinetics of Ritonavir

The mean C_{max} and AUC_{12h} of rtv were unchanged when fosAPV/rtv was co-administered with TMC125 (Table 81). The mean C_{min} was also almost unchanged. There was no change in the median t_{max} of rtv, and there was no relevant change in the terminal elimination half-life.

Table 81: Pharmacokinetics of Ritonavir after Administration of Ritonavir [Co-Administered with Fosamprenavir] in the Absence and Presence of TMC125 (Trial TMC125-C117)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Day -1: fosAPV/rtv 700/100 mg b.i.d. (Reference)	Day 14: fosAPV/rtv 700/100 mg b.i.d. + TMC125 800 mg b.i.d. (Test)		
N	8	8		
t_{max}, h	4.00 (3.00 - 4.00)	4.00 (2.00 - 6.00)	-	-
C_{0h}, ng/mL	248 ± 129	202 ± 116	0.81	0.66 - 1.01
C_{min}, ng/mL	140 ± 65	130 ± 60	0.93	0.70 - 1.24
C_{max}, ng/mL	1073 ± 422	1158 ± 664	1.02	0.79 - 1.31
$C_{ss,av}$, ng/mL	491 ± 179	506 ± 266	-	-
AUC_{12h}, ng.h/mL	5889 ± 2153	6077 ± 3189	1.00	0.81 - 1.23
$t_{1/2,term}$, h	3.16 ± 0.50	2.92 ± 0.46	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C117/Section 4.2.6.2 and Section 4.2.6.3

2.8.2.11.5 Conclusions

In HIV-1 infected subjects on a stable ART including fosAPV/rtv, the mean exposure to APV (in the presence of rtv) increased 1.69-fold (AUC_{12h}) when co-administered with TMC125. Thus, the dose of fosAPV might need to be reduced when co-administered with TMC125.

In the presence of fosAPV, TMC125 exposure was comparable to the exposure in the absence of fosAPV in a historic comparison.

The mean exposure to rtv (in the presence of fosAPV) remained unchanged when co-administered with TMC125.

2.8.2.12 TRIAL TMC125-C145: SAQUINAVIR, LOPINAVIR, AND RITONAVIR, TOGETHER WITH NRTIS (CURRENT ART) - TMC125 ADMINISTERED AS TABLET FORMULATION F* (TMC125 IN HPMC, GRANULO-LAYERED) IN HIV-1 INFECTED SUBJECTS

2.8.2.12.1 Trial Design

This was a multicenter, open-label trial to investigate the effect of co-administration of TMC125, administered as the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered), on the steady-state pharmacokinetics of SQV, LPV, and rtv in HIV-1 infected subjects with documented resistance to at least one of the currently available NNRTIs. The trial population consisted of 16 subjects with a plasma viral load of < 50 HIV-1 RNA copies/mL and an underlying ARV regimen that included SQV and LPV/rtv, and a minimum of 2 NRTIs. Use of ENF was optional.

All subjects received TMC125 800 mg b.i.d. for 14 days, while they continued to take their current regimen throughout the treatment period without interruption. The actual administered doses of SQV and LPV/rtv, and the number of subjects per dosage combination of these ARVs, were as follows:

- Combination 1: SQV/LPV/rtv 1000/400/100 mg b.i.d. (7 subjects, plus one discontinued subject before treatment with trial medication);
- Combination 2: SQV/LPV/rtv 800/400/100 mg b.i.d. (5 subjects);
- Combination 3: SQV/LPV/rtv 800/400/200 mg b.i.d. (1 subject);
- Combination 4: SQV/LPV/rtv 800/533/133 mg b.i.d. (3 subjects).

TMC125 (on Day 14), SQV, and LPV/rtv were administered under fed conditions, together with the subject's other ARVs, within 10 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.2/TMC125-C145).

2.8.2.12.2 Pharmacokinetics of TMC125

For each combination of TMC125 and underlying SQV and LPV/rtv therapy (except Combination 3 with only one subject, for which the mean pharmacokinetic parameters were not assessable), the median t_{max} of TMC125 on Day 14 was 3 to 4 hours (Table 82). The exposure to TMC125, in terms of C_{max} and AUC_{12h}, was highest in Combination 1 and lowest in Combination 4.

Inter-subject variability in pharmacokinetic parameters of TMC125 was substantial for each dosage combination. For C_{min}, C_{max}, and AUC_{12h}, inter-subject variability (CV) ranged from 98% to 135%, 69% to 98%, and 53% to 66% for Combinations 1, 2, and 4, respectively (Module 5.3.3.2/TMC125-C145/Section 4.2.4.2).

＊：新薬承認情報提供時に置き換え

An exploratory comparison of the pharmacokinetic parameters obtained in trials TMC125-C145 and TMC125-C203 (800 mg TMC125 b.i.d. [Form F*] and 400/100 mg LPV/rtv b.i.d. in HIV-1 infected subjects; historic data) indicated no relevant effect of SQV, in combination with LPV/rtv, on TMC125 exposure (Module 5.3.3.2/TMC125-C145/Section 4.2.4.3). However, large CIs for the LS means ratios were observed. It was concluded that the sample size was too small in comparison to the substantial inter-subject variability, resulting in insufficient power to draw relevant conclusions for this comparison.

Table 82: Pharmacokinetics of TMC125 after Administration of TMC125 for 14 Days as an Add-On Therapy to Existing ARV Regimens Including Saquinavir, Lopinavir, and Ritonavir (Trial TMC125-C145)

Parameter (Day 14)	Mean ± SD; t_{max}: Median (Range)		
	Combination 1: TMC125 800 mg b.i.d. + SQV/LPV/rtv 1000/400/100 mg b.i.d.	Combination 2: TMC125 800 mg b.i.d. + SQV/LPV/rtv 800/400/100 mg b.i.d.	Combination 4: TMC125 800 mg b.i.d.+ SQV/LPV/rtv 800/533/133 mg b.i.d.[a]
N	6	5	3
t_{max}, h	4.0 (1.5 - 6.0)	3.0 (1.5 - 4.0)	4.0 (1.6 - 6.0)
C_{min}, ng/mL	172.7 ± 233.1	134.3 ± 131.4	87.5 ± 46.4
C_{max}, ng/mL	379.9 ± 373.5	341.4 ± 236.0	293.7 ± 193.0
AUC_{12h}, ng.h/mL	3566 ± 4138	2754 ± 2109	2117 ± 1198
$t_{1/2\alpha}$[b], h	8.183 ± 7.854	8.731 ± 7.694	5.802 ± 0.2979
FI, %	97.5 ± 41.7	103.5 ± 47.2	114.1 ± 28.2

Note: Combination 3: 800/400/200 mg SQV/LPV/rtv b.i.d. (n = 1): mean parameters not assessable.
N = maximum number of subjects with data.
[a] Or 1000 mg SQV b.i.d. for 1 subject.
[b] Accurate determination not possible in all subjects.
Source: Module 5.3.3.2/TMC125-C145/Section 4.2.4.2

2.8.2.12.3 Pharmacokinetics of Lopinavir

For Combinations 1, 2, and 4, the median t_{max} of LPV was 4 hours after the LPV morning dose on Day –1 (ARV regimen alone) and 4 to 6 hours after the LPV morning dose on Day 14 (ARV regimen with TMC125) (Table 83). With all 3 ARV regimen combinations the exposure to LPV was decreased with co-administration of TMC125, and the 90% CIs of the LS means ratios were outside the 80% to 125% range.

Combinations 1 and 2 differed only in their dose of SQV (800 vs. 1000 mg b.i.d.). As this difference in dose was considered small compared to the underlying inter-subject variability, a statistical comparison based on the pooled results for these 2 ARV regimen combinations was also performed. Based upon this analysis, the mean C_{max} and AUC_{12h} values of LPV were decreased in the presence of TMC125 (Day 14) to a relevant degree, compared to ARV treatment with SQV/LPV/rtv without TMC125 (Day -1) (Module 5.3.3.2/TMC125-C145/Section 4.2.5.3). Based on the ratio of the LS means, the mean C_{max} and AUC_{12h} values were decreased by 16% and 18%, respectively.

＊：新薬承認情報提供時に置き換え

Table 83: Pharmacokinetics of Lopinavir after Administration of Existing ARV Regimens, Including Saquinavir, Lopinavir, and Ritonavir, without and with Co-Administration of TMC125 (Trial TMC125-C145)

Parameter	Mean ± SD; t_{max}: Median (Range) Day -1: ARV Alone (Reference)	Day 14: ARV + TMC125 800 mg b.i.d. (Test)	Ratio [a] (Test:Reference)	90% CI
Combination 1: SQV/LPV/rtv 1000/400/100 mg b.i.d.				
N	6	6		
t_{max}, h	4.0 (0.0 - 6.0)	6.0 (4.0 - 9.0)	-	-
C_{min}, ng/mL	5240 ± 3728	4262 ± 2802	0.75	0.38 - 1.51
C_{max}, ng/mL	11620 ± 4204	9750 ± 3281	0.83	0.68 - 1.02
AUC_{12h}, ng.h/mL	103600 ± 40780	87240 ± 33710	0.83	0.62 - 1.11
$t_{1/2\alpha}$ [b], h	7.360 ± 2.760	10.14 ± 9.353	-	-
Combination 2: SQV/LPV/rtv 800/400/100 mg b.i.d.				
N	5	5		
t_{max}, h	4.0 (1.1 - 6.0)	4.0 (4.0 - 6.0)		
C_{min}, ng/mL	6122 ± 2782	4786 ± 2323	0.77	0.54 - 1.09
C_{max}, ng/mL	12370 ± 3844	10500 ± 3622	0.84	0.69 - 1.04
AUC_{12h}, ng.h/mL	111500 ± 38290	90880 ± 32880	0.81	0.65 - 0.99
$t_{1/2\alpha}$ [b], h	9.460 ± 5.918	7.566 ± 4.498		
Combination 4: SQV/LPV/rtv 800/533/133 mg b.i.d.[c]				
N	3	3		
t_{max}, h	4.0 (2.0 - 6.0)	6.0 (4.1 - 12.0)		
C_{min}, ng/mL	5630 ± 1796	4750 ± 1722	0.83	0.53 - 1.29
C_{max}, ng/mL	11680 ± 2551	8973 ± 3546	0.73	0.50 - 1.08
AUC_{12h}, ng.h/mL	104000 ± 20130	79200 ± 34620	0.71	0.39 - 1.28
$t_{1/2\alpha}$ [b], h	10.16 ± 2.708	NA		

N = maximum number of subjects with data; NA = not assessable.
[a] Ratio based on LS means.
[b] Accurate determination not possible for all subjects.
[c] Or 1000 mg SQV b.i.d. for 1 subject.
Source: Module 5.3.3.2/TMC125-C145/Section 4.2.5.2 and Section 4.2.5.3

2.8.2.12.4 Pharmacokinetics of Ritonavir

For Combinations 1, 2, and 4, the median t_{max} of rtv was 3 to 4 hours after the morning dose of rtv on Day –1 (ARV regimen alone) and 4 to 6 hours after the morning dose of rtv on Day 14 (ARV regimen with TMC125) (Table 84).

There was a trend of decreased concentrations of rtv when the ARV regimen was combined with TMC125. The 90% CIs of the LS means ratios for all comparisons were outside the 80% to 125% range when the data were analyzed separately for each combination of rtv with LPV and SQV, and after a pooled analysis of the data from Combinations 1 and 2 (Module 5.3.3.2/TMC125-C145/Section 4.2.6.3). Administration of different dosage combinations of rtv, LPV, and SQV (Combinations 1 and 2) did not affect the mean C_{min}, C_{max}, or AUC_{12h} of rtv to any relevant degree.

Table 84: Pharmacokinetics of Ritonavir after Administration of Existing ARV Regimens, Including Saquinavir, Lopinavir, and Ritonavir, without and with Co-Administration of TMC125 (Trial TMC125-C145)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Day -1: ARV Alone (Reference)	Day 14: ARV + TMC125 800 mg b.i.d. (Test)		
Combination 1: SQV/LPV/rtv 1000/400/100 mg b.i.d.				
N	6	6		
t_{max}, h	4.0 (0.0 - 6.1)	5.2 (4.0 - 6.0)	-	-
C_{min}, ng/mL	223.5 ± 168.6	201.5 ± 138.1	0.89	0.37 - 2.15
C_{max}, ng/mL	929.5 ± 301.9	948.7 ± 509.3	0.93	0.59 - 1.47
AUC_{12h}, ng.h/mL	6463 ± 2662	6040 ± 2853	0.92	0.59 - 1.42
$t_{1/2\alpha}$ [b], h	3.304 ± 0.6553	3.900 ± 1.806	-	-
Combination 2: SQV/LPV/rtv 800/400/100 mg b.i.d.				
N	5	5		
t_{max}, h	4.0 (1.5 - 6.0)	6.0 (4.0 - 6.0)	-	-
C_{min}, ng/mL	237.0 ± 167.9	192.5 ± 93.72	0.87	0.59 - 1.28
C_{max}, ng/mL	1307 ± 406.7	1069 ± 244.9	0.84	0.57 - 1.22
AUC_{12h}, ng.h/mL	8384 ± 2478	6715 ± 1840	0.81	0.55 - 1.20
$t_{1/2\alpha}$ [b], h	4.129 ± 3.040	4.061 ± 3.030	-	-
Combination 4: SQV/LPV/rtv 800/533/133 mg b.i.d.[c]				
N	3	3		
t_{max}, h	3.3 (2.0 - 6.0)	4.1 (4.0 - 12.0)	-	-
C_{min}, ng/mL	171.0 ± 74.51	165.3 ± 51.19	0.99	0.54 - 1.81
C_{max}, ng/mL	1318 ± 715.2	941.0 ± 540.9	0.69	0.54 - 0.89
AUC_{12h}, ng.h/mL	7514 ± 2373	4984 ± 2301	0.63	0.43 - 0.91
$t_{1/2\alpha}$ [b], h	3.915[b] ± 0.9847	NA	-	-

N = maximum number of subjects with data; NA = not assessable.
[a] Ratio based on LS means.
[b] Accurate determination not possible for all subjects.
[c] Or 1000 mg SQV b.i.d. for 1 subject.
Source: Module 5.3.3.2/TMC125-C145/Section 4.2.6.2 and Section 4.2.6.3

2.8.2.12.5 Pharmacokinetics of Saquinavir

For Combinations 1, 2, and 4, the median t_{max} of SQV was approximately 3 to 4 hours after the SQV morning dose on Day –1 (ARV regimen alone) and 4 hours after the SQV morning dose on Day 14 (ARV regimen with TMC125) (Table 85).

There was a trend towards lower SQV concentrations, especially with Combination 4, when the ARV was combined with TMC125. The 90% CIs of the LS means ratios for all comparisons were outside the 80% to 125% range when the data were analyzed separately for each combination of SQV with LPV and rtv, or after a pooled analysis of the data from Combinations 1 and 2 (Module 5.3.3.2/TMC125-C145/Section 4.2.7.3).

Table 85: Pharmacokinetics of Saquinavir after Administration of Existing ARV Regimens, Including Saquinavir, Lopinavir, and Ritonavir, without and with Co-Administration of TMC125 (Trial TMC125-C145)

Parameter	Mean ± SD; t_{max}: Median (Range) Day -1: ARV Alone (Reference)	Day 14: ARV + TMC125 800 mg b.i.d. (Test)	Ratio [a] (Test:Reference)	90% CI
Combination 1: SQV/LPV/rtv 1000/400/100 mg b.i.d.				
N	6	6		
t_{max}, h	4.0 (0.0 - 4.1)	4.0 (4.0 - 6.0)	-	-
C_{min}, ng/mL	581.8 ± 473.9	497.8 ± 339.0	0.87	0.43- 1.78
C_{max}, ng/mL	3093 ± 1341	2648 ± 1858	0.78	0.47 - 1.30
AUC_{12h}, ng.h/mL	20400 ± 8328	18270 ± 13310	0.83	0.47 - 1.44
$t_{1/2\alpha}$ [b], h	3.641 ± 0.6802	4.371 ± 2.205	-	-
Combination 2: SQV/LPV/rtv 800/400/100 mg b.i.d.				
N	5	5		
t_{max}, h	3.1 (2.0 - 4.0)	4.0 (4.0 – 4.0)	-	-
C_{min}, ng/mL	1447 ± 803.2	1341 ± 797.0	0.87	0.53 - 1.42
C_{max}, ng/mL	7040 ± 3565	7094 ± 3947	0.95	0.51 - 1.76
AUC_{12h}, ng.h/mL	48490 ± 24160	48590 ± 29160	0.92	0.53 - 1.62
$t_{1/2\alpha}$ [b], h	3.827 ± 1.228	3.999 ± 0.9925	-	-
Combination 4: SQV/LPV/rtv 800/533/133 mg b.i.d.[c]				
N	3	3		
t_{max}, h	4.0 (3.3 – 6.0)	4.0 (2.1 - 6.0)	-	-
C_{min}, ng/mL	932.0 ± 495.6	689.3 ± 400.4	0.68	0.32 - 1.45
C_{max}, ng/mL	3407 ± 1574	3063 ± 2522	0.64	0.16 - 2.46
AUC_{12h}, ng.h/mL	26290 ± 12920	21670 ± 16650	0.64	0.20 - 2.06
$t_{1/2\alpha}$ [b], h	3.990 ± 0.4629	NA	-	-

N = maximum number of subjects with data; NA = not assessable.
[a] Ratio based on LS means.
[b] Accurate determination not possible for all subjects.
[c] Or 1000 mg SQV b.i.d. for 1 subject.
Source: Module 5.3.3.2/TMC125-C145/Section 4.2.7.2 and Section 4.2.7.3

2.8.2.12.6 Conclusions

In HIV-1 infected subjects using comparable boosted PI regimens, plasma concentrations of SQV, LPV, and rtv were slightly lower when co-administered with 800 mg TMC125 b.i.d. (formulation F*). The pooled pharmacokinetic data from subjects receiving SQV/LPV/rtv 800-1000/400/100 mg b.i.d. co-administered with 800 mg TMC125 b.i.d. showed a decrease in LPV exposure by 16% and 18%, respectively, for C_{max} and AUC_{12h}. For rtv and SQV, no relevant treatment effects on the pharmacokinetic parameters were observed after co-administration with 800 mg TMC125 b.i.d. The exposures to TMC125 observed in subjects using a dual boosted PI regimen in the current trial were in the range of those observed in subjects using a single boosted PI (historic control).

2.8.2.13 Trial TMC125-C179: Raltegravir - TMC125 Administered as Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) in Healthy Subjects

Raltegravir is an investigational integrase strand transfer inhibitor of HIV being developed by Merck & Co., Inc. It is metabolized principally by UDPGT, and there is potential for TMC125 to

affect the pharmacokinetics of raltegravir. In contrast, raltegravir does not appear to be an inducer or inhibitor of enzymes involved in drug metabolism, including those involved in TMC125 metabolism; thus, it is unlikely that raltegravir would influence the pharmacokinetics of TMC125.

2.8.2.13.1 Trial Design

This was an open-label, randomized, 3-period crossover trial to investigate the effect of steady-state concentrations of raltegravir on the steady-state pharmacokinetics of TMC125, administered as the 200-mg tablet formulation A* (TMC125 in HPMC, spray-dried), and vice versa. The trial population consisted of 20 healthy subjects.

For all subjects, 3 periods were scheduled as follows:

- Period 1: All subjects received raltegravir 400 mg b.i.d. for 4 days, with no evening dose on Day 4;
- Period 2: After a washout period of at least 4 days, all subjects received TMC125 200 mg b.i.d. for 8 days;
- Period 3: After no washout period, all subjects received TMC125 200 mg b.i.d. and raltegravir 400 mg b.i.d. for 4 days, with no evening dose on Day 4.

The trial medication was taken under fed conditions within 15 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.4/TMC125-C179).

2.8.2.13.2 Pharmacokinetics of TMC125

The mean C_{max} of TMC125 was unaffected and the mean AUC_{12h} increased 1.10-fold when TMC125 was co-administered with raltegravir (Table 86). The mean C_{12h} of TMC125 increased 1.17-fold. Apart from C_{12h}, the 90% CIs of the LS means ratios for these comparisons were within the 80% to 125% range. There was no relevant change in the median t_{max} of TMC125.

Table 86: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Raltegravir (Trial TMC125-C179)

Parameter	Mean ± SD; t_{max}: Median		Ratio [a] (Test:Reference)	90% CI
	TMC125 200 mg b.i.d. (Reference)	TMC125 200 mg b.i.d. + Raltegravir 400 mg b.i.d. (Test)		
N	19	19		
t_{max}, h	4.4	3.9	-	-
C_{12h}, ng/mL	404 ± 162	478 ± 206	1.17	1.10 - 1.26
C_{max}, ng/mL	783 ± 279	829 ± 345	1.04	0.97 - 1.12
AUC_{12h}, ng.h/mL	6664 ± 2500	7336 ± 2937	1.10	1.03 - 1.16

N = maximum number of subjects with data.
[a] Ratio based on geometric means.
Source: Module 5.4/TMC125-C179/Section 11.2 and Table 11.2

2.8.2.13.3 Pharmacokinetics of Raltegravir

The mean C_{max} and AUC_{12h} of raltegravir were decreased by 11% and 10%, respectively, when raltegravir was co-administered with TMC125 (Table 87). The mean C_{12h} was decreased by

34%. The 90% CIs of the LS means ratios for all these comparisons were outside the 80% to 125% range. The median t_{max} of raltegravir increased in the presence of TMC125. Overall, the effect of TMC125 on raltegravir was not considered to be clinically relevant.

Table 87: Pharmacokinetics of Raltegravir after Administration of Raltegravir in the Absence and Presence of TMC125 (Trial TMC125-C179)

Parameter	Mean ± SD; t_{max}: Median		Ratio [a] (Test:Reference)	90% CI
	Raltegravir 400 mg b.i.d. (Reference)	Raltegravir 400 mg b.i.d. + TMC125 200 mg b.i.d. (Test)		
N	19	19		
t_{max}, h	2.0	3.2	-	-
C_{12h}, nM	547.5 ± 957.4	315.3 ± 554.0	0.66	0.34 - 1.26
C_{max}, µM	2.43 ± 2.26	1.92 ± 1.62	0.89	0.68 - 1.15
AUC_{12h}, µM.h	9.62 ± 8.04	7.46 ± 5.19	0.90	0.68 - 1.18

N = maximum number of subjects with data.
[a] Ratio based on geometric means.
Source: Module 5.4/TMC125-C179/Section 11.1 and Table 11.1

2.8.2.13.4 Conclusions

No clinically relevant changes occurred in the pharmacokinetic parameters (C_{12h}, C_{max}, AUC) for TMC125 or raltegravir. Raltegravir can therefore be co-administered with TMC125 without dose adjustment for either drug.

2.8.3 Administration of TMC125 with Drugs other than Antiretrovirals

2.8.3.1 Trial TMC125-C164: Atorvastatin - TMC125 Administered as Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) in Healthy Subjects

Atorvastatin is widely used in HIV-1 infected subjects to treat lipid disorders associated with the use of PIs. Atorvastatin is primarily metabolized by CYP3A4 to the active metabolites 2-hydroxy- and 4-hydroxy-atorvastatin, and the inactive metabolite atorvastatin lactone.[34] In vitro, atorvastatin acid is a substrate for UDPGT1A1 and 1A3, P-gp, organic anion-transporting polypeptide (OATP) C and H+-monocarboxylic acid co-transporter.[31] An interaction trial was therefore conducted to investigate the potential effect that TMC125 could have on atorvastatin exposure (including metabolites), and to provide dosing recommendations for the combination of TMC125 and atorvastatin in HIV-1 infected subjects.

2.8.3.1.1 Trial Design

This was an open-label, randomized, 2-period crossover trial to investigate the pharmacokinetic interaction between TMC125, administered as the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered), at steady-state and atorvastatin. Concentrations of the metabolites 2-hydroxy- and 4-hydroxy-atorvastatin, and atorvastatin lactone, were also assessed. The trial population consisted of 16 healthy subjects.

In 2 sessions, separated by a washout period of at least 14 days, subjects received the following treatments:

- Treatment A: atorvastatin 40 mg q.d. on Days 1 to 4;
- Treatment B: TMC125 800 mg b.i.d. on Days 1 to 13, and atorvastatin 40 mg q.d. on Days 8 to 11.

All trial medication was taken under fed conditions within 10 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.1.2/TMC125-C164).

2.8.3.1.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{12h} of TMC125 were similar when TMC125 was co-administered with atorvastatin, compared to administration of TMC125 alone (Table 88). The mean C_{min} of TMC125 increased 1.10-fold. The 90% CIs of the LS means ratios for all comparisons were within the 80% to 125% range. There was no change in the median t_{max} of TMC125.

Table 88: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Atorvastatin (Trial TMC125-C164)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	TMC125 800 mg b.i.d. (Reference)	TMC125 800 mg b.i.d. + Atorvastatin 40 mg q.d. (Test)		
N	16	16		
t_{max}, h	3.0 (1.5 - 6.0)	3.0 (2.0 - 6.0)	-	-
C_{0h}, ng/mL	840 ± 167	907 ± 240	-	-
C_{min}, ng/mL	760 ± 139	847 ± 207	1.10	1.02 - 1.19
C_{max}, ng/mL	1548 ± 339	1514 ±367	0.97	0.93 - 1.02
AUC_{12h}, ng.h/mL	13816 ± 3044	14098 ± 3290	1.02	0.97 - 1.07

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C164/ Section 4.2.4.2 and Section 4.2.4.3

2.8.3.1.3 Pharmacokinetics of Atorvastatin

The mean AUC_{24h} of atorvastatin was decreased by 37% when atorvastatin was co-administered with TMC125, compared to administration of atorvastatin alone, whereas the mean C_{max} was similar in both treatments (Table 89). The 90% CIs of the LS means ratios for both comparisons were outside the 80% to 125% range. More than half of the observations for C_{0h} and C_{min} were below the LLOQ (0.5 ng/mL) when atorvastatin was co-administered with TMC125. There was no relevant change in the median t_{max} of atorvastatin.

Table 89: Pharmacokinetics of Atorvastatin after Administration of Atorvastatin in the Absence and Presence of TMC125 (Trial TMC125-C164)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Atorvastatin 40 mg q.d. (Reference)	Atorvastatin 40 mg q.d. + TMC125 800 mg b.i.d. (Test)		
N	16	16		
t_{max}, h	2.0 (0.5 - 4.0)	1.5 (0.5 - 4.0)	-	-
C_{0h}, ng/mL	0.85 ± 0.60	NQ	-	-
C_{min}, ng/mL	0.82 ± 0.55	NQ	-	-
C_{max}, ng/mL	11.0 ± 5.86	11.5 ± 6.04	1.04	0.84 - 1.30
AUC_{24h}, ng.h/mL	82.7 ± 40.3	52.6 ± 29.4	0.63	0.58 - 0.68

N = maximum number of subjects with data; NQ = not quantifiable.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C164/ Section 4.2.5.2 and Section 4.2.5.3

2.8.3.1.4 Pharmacokinetics of 2-Hydroxy-Atorvastatin

The mean C_{max} and AUC_{24h} of the active metabolite 2-hydroxy-atorvastatin were increased 1.76- and 1.27-fold, respectively, when atorvastatin was co-administered with TMC125, compared to administration of atorvastatin alone (Table 90). The 90% CIs of the LS means ratios for both comparisons were outside the 80% to 125% range. There was no relevant change in the median t_{max} of 2-hydroxy-atorvastatin.

Table 90: Pharmacokinetics of 2-Hydroxy-Atorvastatin after Administration of Atorvastatin in the Absence and Presence of TMC125 (Trial TMC125-C164)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Atorvastatin 40 mg q.d. (Reference)	Atorvastatin 40 mg q.d. + TMC125 800 mg b.i.d. (Test)		
N	16	16		
t_{max}, h	3.0 (0.5 - 6.0)	4.0 (1.0 - 6.0)	-	-
C_{0h}, ng/mL	1.08 ± 0.41	0.96 ± 0.55	-	-
C_{min}, ng/mL	1.05 ± 0.41	0.79 ± 0.47	-	-
C_{max}, ng/mL	7.40 ± 2.25	13.66 ± 6.14	1.76	1.60 - 1.94
AUC_{24h}, ng.h/mL	82.9 ± 26.4	109.8 ± 46.8	1.27	1.19 - 1.36

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C164/Section 4.2.6.2 and Section 4.2.6.3

2.8.3.1.5 Pharmacokinetics of 4-Hydroxy-Atorvastatin

For both treatments, most of the plasma concentrations of the active metabolite 4-hydroxy-atorvastatin were below the LLOQ (0.50 ng/mL) (Module 5.3.3.4/TMC125-C164/Section 4.2.7). Therefore, the pharmacokinetics of 4-hydroxy-atorvastatin could not be calculated.

2.8.3.1.6 Pharmacokinetics of Atorvastatin Lactone

The mean C_{max} and AUC_{24h} of the inactive metabolite atorvastatin lactone were decreased by 38% and 62%, respectively, when atorvastatin was co-administered with TMC125, compared to administration of atorvastatin alone (Table 91). The 90% CIs of the LS means ratios for both comparisons were outside the 80% to 125% range. There was no relevant change in the median t_{max} of atorvastatin lactone.

Table 91: Pharmacokinetics of Atorvastatin Lactone after Administration of Atorvastatin in the Absence and Presence of TMC125 (Trial TMC125-C164)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Atorvastatin 40 mg q.d. (Reference)	Atorvastatin 40 mg q.d. + TMC125 800 mg b.i.d. (Test)		
N	16	16		
t_{max}, h	3.0 (1.0 - 9.0)	2.0 (1.0 - 4.0)	-	-
C_{0h}, ng/mL	0.95 ± 0.44	NQ	-	-
C_{min}, ng/mL	0.91 ± 0.42	NQ	-	-
C_{max}, ng/mL	6.04 ± 2.87	3.86 ±2.13	0.62	0.56 - 0.69
AUC_{24h}, ng.h/mL	70.9 ± 30.4	28.6 ± 17.2	0.38	0.34 - 0.42

N = maximum number of subjects with data; NQ = not quantifiable.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C164/Section 4.2.8.2 and Section 4.2.8.3

2.8.3.1.7 Conclusions

The pharmacokinetics of TMC125 were not affected by co-administration of atorvastatin. The mean exposure (AUC_{24h}) to atorvastatin and atorvastatin lactone (inactive metabolite) was decreased by 37% and 62%, respectively, whereas the exposure to 2-hydroxy-atorvastatin (active metabolite) increased 1.27-fold, when co-administered with TMC125. TMC125 and atorvastatin can be co-administered, but the dose of atorvastatin should be tailored to achieve the desired clinical response.

2.8.3.2 TRIAL TMC125-C166: ETHINYLESTRADIOL WITH NORETHINDRONE (ORAL CONTRACEPTIVE) - TMC125 ADMINISTERED AS TABLET FORMULATION A* (TMC125 IN HPMC, SPRAY-DRIED) IN HEALTHY SUBJECTS

OCs consist of an estrogen (e.g., 17α-ethinylestradiol) and/or a progesterone (e.g., norethindrone) component. 17α-ethinylestradiol is metabolized primarily by CYP3A4 (approximately 67%) and CYP2C9 (approximately 23%), and to a lesser extent by CYP2C8, 2C19, and 3A5. Conjugation via sulfotransferase 1E1 and UDPGT1A1 can also occur. 17α-ethinylestradiol is an inhibitor of CYP1A2, 3A4, 2B6 and 2C19 and may induce CYP2C9, 2D6 and UDPGT.[65] As OCs are often used by women of childbearing potential, a trial investigating the co-administration of TMC125 with an OC was considered necessary.

2.8.3.2.1 Trial Design

This was an open-label interaction trial to investigate the pharmacokinetic interaction between ethinylestradiol/norethindrone and TMC125, administered as the 100-mg tablet formulation A* (TMC125 in HPMC, spray-dried). The trial population consisted of 24 healthy women who were stable on OCs, specifically 35 µg ethinylestradiol and 1 mg norethindrone (the components of Ortho-Novum® 1/35) q.d. Subjects participated in the trial during 3 consecutive 28-day cycles, i.e., 3 full OC cycles. In each cycle, they received a daily dose of 35 µg ethinylestradiol and 1 mg norethindrone for 21 days. There was no OC treatment on Days 22 to 28 of each OC cycle. The trial consisted of 3 periods with the following treatments:

- Run-in period: ethinylestradiol 35 µg/norethindrone 1 mg q.d. for one OC cycle prior to the start of the treatment period;

＊：新薬承認情報提供時に置き換え

- First treatment period: ethinylestradiol 35 µg/norethindrone 1 mg q.d. on Days 1 to 21;
- Second treatment period: ethinylestradiol 35 µg/norethindrone 1 mg q.d. on Days 29 to 49, and
  TMC125 200 mg b.i.d. on Days 29 to 43.

TMC125 was administered under fed conditions within 10 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C166).

2.8.3.2.2 Pharmacokinetics of TMC125

The C_{max} and AUC_{12h} of TMC125 were higher when co-administered with ethinylestradiol and norethindrone, compared to historic comparisons of TMC125 administration alone in trials TMC125-C171 and TMC125-C177 in which the same tablet formulation and dosage of TMC125 were given (Table 92). Except for C_{max}, the corresponding 90% CIs of these parameters did not overlap with the 90% CIs of the historic data. Mean C_{min} and C_{0h} of TMC125 were also higher when combined with ethinylestradiol and norethindrone.

Of note, the historic data were derived from trials in which TMC125 alone was given to males for 1 week, in contrast to the current trial where TMC125 was co-administered with ethinylestradiol and norethindrone in females for 2 weeks. The observed difference in exposures could therefore have been a consequence of sex, interaction with ethinylestradiol, norethindrone or the combination thereof, accumulation due to the longer dosing period, and/or inter-subject variability, among other factors.

Table 92: Pharmacokinetics of TMC125 after Administration of TMC125 in the Presence (Trial TMC125-C166) and Absence (Trials TMC125-C171 and TMC125-C177, Historic Controls) of Ethinylestradiol and Norethindrone)

Parameter	TMC125-C166 TMC125 200 mg b.i.d. + Ethinylestradiol/ Norethindrone 0.035/1 mg q.d. Females	TMC125-C171 TMC125 200 mg b.i.d. Males	TMC125-C177 TMC125 200 mg b.i.d. Males
	Mean ± SD; t_{max}: Median (Range)		
N	16	15	23
t_{max}, h	4.0 (0.0 - 6.0)	4.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)
C_{0h}, ng/mL	886.5 ± 316.9	529.1 ± 162.1	461.3 ± 170.5
C_{min}, ng/mL	791.6 ± 186.7	498.1 ± 153.5	426.1 ± 154.6
C_{max}, ng/mL	1188 ± 292.8	1015 ± 243.8	875.7 ± 232.8
AUC_{12h}, ng.h/mL	11820 ± 2591	9008 ± 2392	7638 ± 2254
	90% CI		
C_{0h}, ng/mL	7.48 - 10.25	4.55 - 6.03	4.00 - 5.22
C_{min}, ng/mL	7.10 - 8.73	4.28 - 5.68	3.71 - 4.81
C_{max}, ng/mL	10.60 - 13.16	9.04 - 11.26	7.92 - 9.59
AUC_{12h}, ng.h/mL	106.84 - 129.56	79.20 - 100.96	68.31 - 84.44

N = maximum number of subjects with data.

Source: Module 5.3.3.4/TMC125-C166/Section 4.2.5; Module 5.3.3.4/TMC125-C171/ Section 4.2.4.2; Module 5.3.3.4/TMC125-C177/Section 4.2.5

2.8.3.2.3 Pharmacokinetics of Ethinylestradiol

The mean C_{max} and AUC_{24h} of ethinylestradiol were increased 1.33- and 1.22-fold, respectively, when ethinylestradiol/norethindrone was co-administered with TMC125, compared to administration of ethinylestradiol/norethindrone alone (Table 93). The 90% CIs of the LS means ratios were outside the 80% to 125% range for both parameters. The mean C_{min} was also slightly increased (1.09-fold), but the 90% CI of the LS means ratio was within the 80% to 125% range. There was no relevant change in the median t_{max} of ethinylestradiol.

Table 93: Pharmacokinetics of Ethinylestradiol after Administration of Ethinylestradiol and Norethindrone in the Absence and Presence of TMC125 (Trial TMC125-C166)

Parameter	Mean ± SD; t_{max}: Median (Range) Ethinylestradiol/ Norethindrone 0.035 /1 mg q.d. (Reference)	Ethinylestradiol/ Norethindrone 0.035 /1 mg q.d.+ TMC125 200 mg b.i.d. (Test)	Ratio [a] (Test:Reference)	90% CI
N	24	16		
t_{max}, h	3.0 (1.0 - 4.0)	2.0 (1.0 - 4.0)	-	-
C_{0h}, pg/mL	34.90 ± 10.80	37.89 ± 10.12	-	-
C_{min}, pg/mL	34.51 ± 10.29	37.66 ± 9.727	1.09	1.01 - 1.18
C_{max}, pg/mL	98.30 ± 25.83	134.1 ± 44.48	1.33	1.21 - 1.46
AUC_{24h}, pg.h/mL	1412 ± 356.9	1726 ± 382.3	1.22	1.13 - 1.31

N = maximum number of subjects with data.

[a] Ratio based on LS means.

Source: Module 5.3.3.4/TMC125-C166/Section 4.2.6.2 and Section 4.2.6.3

2.8.3.2.4 Pharmacokinetics of Norethindrone

The mean C_{max} and AUC_{24h} of norethindrone were similar when ethinylestradiol/norethindrone was co-administered with TMC125, compared to administration of ethinylestradiol/ norethindrone alone (Table 94). The mean C_{min} was decreased by 22% in the combined treatment, and the 90% CI of the LS means ratio was outside the 80% to 125% range. The median t_{max} of norethindrone was earlier in the presence of TMC125 (1.5 hours, compared to 3 hours in the absence of TMC125).

Table 94: Pharmacokinetics of Norethindrone after Administration of Ethinylestradiol and Norethindrone in the Absence and Presence of TMC125 (Trial TMC125-C166)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Ethinylestradiol/ Norethindrone 0.035 /1 mg q.d. (Reference)	Ethinylestradiol/ Norethindrone 0.035 /1 mg q.d.+ TMC125 200 mg b.i.d. (Test)		
N	24	16		
t_{max}, h	3.0 (1.0 - 6.0)	1.5 (1.0 - 4.0)	-	-
C_{0h}, ng/mL	3.597 ± 1.736	2.919 ± 1.422	-	-
C_{min}, ng/mL	3.511 ± 1.678	2.845 ± 1.490	0.78	0.68 - 0.90
C_{max}, ng/mL	16.73 ± 3.767	17.27 ± 4.127	1.05	0.98 - 1.12
C_{24h}, ng/mL	4.070 ± 1.943	3.621 ± 2.451	-	-
AUC_{24h}, ng.h/mL	203.3 ± 59.63	189.2 ± 53.92	0.95	0.90 - 0.99

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C166/Section 4.2.7.2 and Section 4.2.7.3

2.8.3.2.5 Pharmacodynamics of Ethinylestradiol and Norethindrone

No consistent, clinically relevant changes in luteinizing hormone, follicle stimulating hormone, or serum progesterone were observed when TMC125 was co-administered with ethinylestradiol and norethindrone (Module 5.3.3.4/TMC125-C166/Section 4.3).

2.8.3.2.6 Conclusions

The mean exposure to TMC125, when co-administered with ethinylestradiol and norethindrone in female subjects, was higher compared to historic control data for TMC125 administered alone in male subjects. When co-administered with TMC125, the mean exposure (AUC_{24h}) to ethinylestradiol was increased 1.22-fold, and the mean exposure to norethindrone was unaffected. In addition, no consistent, clinically relevant changes in luteinizing hormone, follicle stimulating hormone, or serum progesterone were observed when TMC125 was co-administered with ethinylestradiol and norethindrone. Thus, TMC125 can be co-administered with estrogen- and/or progesterone-based contraceptives without dose adjustments. Based on the results of this trial, co-administration with TMC125 is unlikely to decrease the effectiveness of estrogen- and/or progesterone-based contraceptives.

2.8.3.3 TRIAL TMC125-C156: RIFABUTIN - TMC125 ADMINISTERED AS TABLET FORMULATION F* (TMC125 IN HPMC, GRANULO-LAYERED) IN HEALTHY SUBJECTS

Rifabutin is an antimycobacterial agent that is a substrate for CYP3A4 and also a CYP3A4 inducer.[40] The metabolite 25-*O*-desacetylrifabutin is as active as the parent compound, but is normally present at 10-fold lower plasma concentrations compared to rifabutin. A pharmacokinetic drug-drug interaction can be expected when rifabutin and TMC125 are co-administered because both drugs are metabolized by CYP3A4. Rifabutin is an inducer of CYP3A4 and therefore may reduce plasma concentrations of CYP3A4 substrates.

2.8.3.3.1 Trial Design

This was an open-label, randomized, 2-period crossover trial to investigate the pharmacokinetic interaction between TMC125, administered as the 200-mg tablet formulation F* TMC125 in HPMC, granulo-layered), and rifabutin at steady-state. Concentrations of the metabolite 25-*O*-desacetylrifabutin were also assessed. The trial population consisted of 16 healthy subjects.

In 2 sessions, separated by a washout period of at least 14 days, subjects received the following treatments:

- Treatment A: rifabutin 300 mg q.d. on Days 1 to 14;
- Treatment B: TMC125 800 mg b.i.d. on Days 1 to 21, and rifabutin 300 mg q.d. on Days 8 to 21.

All doses of TMC125 and rifabutin were administered under fed conditions within 10 minutes after a normal or heavy meal, defined as a meal with an energetic value greater than 500 kcal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C156).

2.8.3.3.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{12h} of TMC125 were both decreased by 37% when TMC125 was co-administered with rifabutin, compared to administration of TMC125 alone (Table 95). The mean C_{min} was also decreased, by 35%. The 90% CIs of the LS means ratios for these comparisons were outside the 80% to 125% range. There was no change in the median t_{max} of TMC125.

＊：新薬承認情報提供時に置き換え

Table 95: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Rifabutin (Trial TMC125-C156)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment B, Day 7: TMC125 800 mg b.i.d. (Reference)	Treatment B, Day 21: TMC125 800 mg b.i.d. + Rifabutin 300 mg q.d. (Test)		
N	12	11		
t_{max}, h	4.0 (3.0 - 4.0)	4.0 (3.0 - 6.0)	-	-
C_{0h}, ng/mL	267.0 ± 118.9	192.4 ± 130.7	-	-
C_{min}, ng/mL	256.9 ± 117.9	178.3 ± 129.1	0.65	0.56 - 0.74
C_{max}, ng/mL	546.7 ± 234.2	371.4 ± 258.9	0.63	0.53 - 0.74
AUC_{12h}, ng.h/mL	4722 ± 1949	3220 ± 2196	0.63	0.54 - 0.74

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C156/Section 4.2.4.2 and Section 4.2.4.3

2.8.3.3.3 Pharmacokinetics of Rifabutin

The mean C_{max} and AUC_{24h} of rifabutin were decreased by 10% and 17%, respectively, when rifabutin was co-administered with TMC125, compared to administration of rifabutin alone (Table 96). The mean C_{min} was also decreased, by 24%. The 90% CIs of the LS means ratios for these comparisons were outside the 80% to 125% range. There was no relevant change in the median t_{max} of rifabutin.

Table 96: Pharmacokinetics of Rifabutin after Administration of Rifabutin in the Absence and Presence of TMC125 (Trial TMC125-C156)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment A, Day 14: Rifabutin 300 mg q.d. (Reference)	Treatment B, Day 21: Rifabutin 300 mg q.d. + TMC125 800 mg b.i.d. (Test)		
N	12	11		
t_{max}, h	3.0 (2.0 - 4.0)	4.0 (2.0 - 6.0)	-	-
C_{0h}, ng/mL	84.26 ± 28.36	62.94 ± 22.46	-	-
C_{min}, ng/mL	78.71 ± 27.45	58.80 ± 19.59	0.76	0.66 - 0.87
C_{max}, ng/mL	500.1 ± 148.3	447.9 ± 141.0	0.90	0.78 - 1.03
AUC_{24h}, ng.h/mL	4815 ± 1374	4012 ± 1123	0.83	0.75 - 0.94

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C156/ Section 4.2.5.2 and Section 4.2.5.3

2.8.3.3.4 Pharmacokinetics of 25-*O*-Desacetylrifabutin

The mean C_{max} and AUC_{24h} of the rifabutin metabolite 25-*O*-desacetylrifabutin were decreased by 15% and 17%, respectively, when rifabutin was co-administered with TMC125, compared to administration of rifabutin alone (Table 97). The mean C_{min} was also decreased, by 22%. The 90% CIs of the LS means ratios for these comparisons were outside the 80% to 125% range. There was no change in the median t_{max} of 25-*O*-desacetylrifabutin.

The mean AUC_{24h} ratio of metabolite 25-*O*-desacetylrifabutin to parent drug rifabutin was approximately 6% in the absence and presence of TMC125, indicating that co-administration of TMC125 had no effect on the metabolism of rifabutin.

Table 97: Pharmacokinetics of 25-*O*-Desacetylrifabutin after Administration of Rifabutin in the Absence and Presence of TMC125 (Trial TMC125-C156)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment A, Day 14: Rifabutin 300 mg q.d. (Reference)	Treatment B, Day 21: Rifabutin 300 mg q.d. + TMC125 800 mg b.i.d. (Test)		
N	12	11		
t_{max}, h	4.0 (3.0 - 4.0)	4.0 (3.0 - 6.0)	-	-
C_{0h}, ng/mL	4.363 ± 2.440	3.391 ± 1.888	-	-
C_{min}, ng/mL	4.072 ± 2.375	3.218 ± 1.881	0.78	0.70 - 0.87
C_{max}, ng/mL	28.67 ± 8.981	24.37 ± 7.553	0.85	0.72 - 1.00
AUC_{24h}, ng.h/mL	272.1 ± 102.7	229.8 ± 92.66	0.83	0.74 - 0.92
Ratio $AUC_{24h,\ desacetyl-RFB/RFB}$ (%)	5.741 ± 1.754	5.834 ± 1.840	-	-

N = number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C156/Section 4.2.6.2 and Section 4.2.6.3

2.8.3.3.5 Conclusions

In healthy subjects, steady-state plasma concentrations of TMC125, rifabutin and 25-*O*-desacetylrifabutin were decreased when TMC125 and rifabutin were co-administered. The 17% decrease in rifabutin and 25-*O*-desacetylrifabutin exposure were not considered to be clinically relevant. The 37% decrease in TMC125 exposure was comparable to the interaction with DRV/rtv in trial TMC125-C176 (see Section 2.8.2.6.2) and LPV/rtv in trial TMC125 C223 (see Section 2.6.2.3.2). The efficacy of TMC125 in the presence of LPV/rtv was demonstrated in Phase IIb trial TMC125-C223 (see Section 2.6.2.3.4) and for DRV/rtv in the 2 Phase III trials DUET-1 (see Section 2.6.3.1.4) and DUET-2 (see Section 2.6.3.2.4). Thus, rifabutin can be combined with TMC125 without dose adjustments.

2.8.3.4 TRIAL TMC125-C159: SILDENAFIL - TMC125 ADMINISTERED AS TABLET FORMULATION F* (TMC125 IN HPMC, GRANULO-LAYERED) IN HEALTHY SUBJECTS

Sildenafil is an oral therapy for erectile dysfunction. It is a CYP3A4 substrate and during hepatic elimination is converted to an active *N*-desmethyl metabolite with properties similar to the parent compound.[57] A pharmacokinetic drug-drug interaction is possible when sildenafil and TMC125 are co-administered because these drugs are both metabolized by CYP3A4.

2.8.3.4.1 Trial Design

This was an open-label, randomized, 2-period crossover trial to investigate the effect of TMC125, administered as the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered), at steady-state on the pharmacokinetics of a single dose of sildenafil. Concentrations of the metabolite *N*-desmethyl sildenafil were also assessed. The trial population consisted of 16 healthy male subjects.

＊：新薬承認情報提供時に置き換え

In 2 sessions, separated by a washout period of at least 14 days, 2 groups of subjects received the following treatments:

- Treatment A: sildenafil 50 mg single dose;
- Treatment B: TMC125 800 mg b.i.d. on Days 1 to 13, with an additional single dose on Day 14, and
  sildenafil 50 mg single dose on Day 14.

All treatments were given under fed conditions within 10 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C159).

2.8.3.4.2 Pharmacokinetics of TMC125

The pharmacokinetics of TMC125 when co-administered with sildenafil are summarized in (Table 98). A comparison with historic pharmacokinetic data from 6 other clinical trials suggested no effect of sildenafil on the pharmacokinetics of TMC125 (Module 5.3.3.4/TMC125-C159/Section 4.2.5).

Table 98: Pharmacokinetics of TMC125 after Administration of TMC125 in the Presence of Sildenafil (Trial TMC125-C159)

Parameter	Mean ± SD; t_{max}: Median (Range)
	TMC125 800 mg b.i.d. + Sildenafil 50 mg
N	14
t_{max}, h	3.5 (2.0 - 6.0)
C_{0h}, ng/mL	501 ± 195
C_{min}, ng/mL	464 ± 195
C_{max}, ng/mL	795 ± 266
AUC_{12h}, ng.h/mL	7538 ± 2663

N = maximum number of subjects with data.

Source: Module 5.3.3.4/TMC125-C159/Section 4.2.5

2.8.3.4.3 Pharmacokinetics of Sildenafil

The mean C_{max} and AUC_{last} of sildenafil were decreased by 45% and 57%, respectively, when sildenafil was co-administered with TMC125, compared to the administration of sildenafil alone (Table 99). The 90% CIs of the LS means ratios for both comparisons were outside the 80% to 125% range. There was no relevant change in the median t_{max} or the mean terminal elimination half-life of sildenafil.

Table 99: Pharmacokinetics of Sildenafil after Administration of Sildenafil in the Absence and Presence of TMC125 (Trial TMC125-C159)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Sildenafil 50 mg (Reference)	Sildenafil 50 mg + TMC125 800 mg b.i.d. (Test)		
N	15	14		
t_{max}, h	2.0 (0.5 - 3.0)	1.5 (0.5 - 4.0)	-	-
C_{max}, ng/mL	163.3 ± 47.7	110.6 ± 90.7	0.55	0.40 - 0.75
AUC_{last}, ng.h/mL	612 ± 236	264 ± 97	0.43	0.36 - 0.51
AUC_{∞}, ng.h/mL	640 ± 232	277 ± 99	0.43	0.37 - 0.51
$t_{1/2\ term}$, h	2.98 ± 0.69	2.61 ± 0.27	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C159/ Section 4.2.8 and Section 4.2.9

2.8.3.4.4 Pharmacokinetics of *N*-Desmethyl Sildenafil

The mean C_{max} and AUC_{last} of the active metabolite *N*-desmethyl sildenafil were decreased by 25% and 41%, respectively, when sildenafil was co-administered with TMC125, compared to the administration of sildenafil alone (Table 100). The 90% CIs of the LS means ratios for both comparisons were outside the 80% to 125% range. There was no relevant change in the median t_{max} of *N*-desmethyl sildenafil.

Table 100: Pharmacokinetics of *N*-Desmethyl Sildenafil after Administration of Sildenafil in the Absence and Presence of TMC125 (Trial TMC125-C159)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Sildenafil 50 mg (Reference)	Sildenafil 50 mg + TMC125 800 mg b.i.d. (Test)		
N	15	14		
t_{max}, h	2.0 (0.8 - 3.0)	1.8 (0.5 - 4.0)	-	
C_{max}, ng/mL	53.2 ± 19.8	43.3 ± 23.1	0.75	0.59 - 0.96
AUC_{last}, ng.h/mL	177 ± 80	110 ± 55	0.59	0.52 - 0.68
AUC_{∞}, ng.h/mL	194 ± 83	121 ± 59	0.60	0.52 - 0.69
$t_{1/2,term}$, h	3.50 ± 1.01	2.56 ± 0.97	-	

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C159/Section 4.2.11 and Section 4.2.12

2.8.3.4.5 Conclusions

In healthy subjects, the co-administration of TMC125 with sildenafil decreased the mean exposure (AUC_{last}) to sildenafil and the active metabolite *N*-desmethyl sildenafil by 57% and 41%, respectively. The combination of sildenafil and TMC125 is allowed, but dose adjustments may be necessary for sildenafil and other phosphodiesterase type 5 inhibitors to obtain a clinical effect.

2.8.3.5 TRIAL TMC125-C171: CLARITHROMYCIN - TMC125 ADMINISTERED AS TABLET FORMULATION A* (TMC125 IN HPMC, SPRAY-DRIED) IN HEALTHY SUBJECTS

Clarithromycin is a macrolide antibiotic with a broad in vitro antibacterial spectrum, and is indicated for the treatment and prevention of disseminated mycobacterial infections caused by *Mycobacterium avium* complex (MAC). Clarithromycin is a substrate and inhibitor for CYP3A and P-gp.[7,44] CYP3A4 is involved in the metabolism of TMC125 and is induced by TMC125 in vitro (see Section 3.3.1.3). Thus, there is a potential for interaction between these 2 agents when co-administered.

2.8.3.5.1 Trial Design

This was an open-label, randomized, 2-period crossover trial to investigate the pharmacokinetic interaction between TMC125, administered as the 100-mg tablet formulation A* (TMC125 in HPMC, spray-dried), at steady-state and clarithromycin at steady-state. Concentrations of the active metabolite 14-hydroxy-clarithromycin were also assessed. The trial population consisted of 16 healthy subjects. In 2 sessions, separated by a washout period of at least 14 days, subjects received the following treatments:

- Session A: TMC125 200 mg b.i.d. on Days 1 to 7, with an additional morning dose on Day 8;
- Session B: clarithromycin 500 mg b.i.d. on Days 1 to 12, with an additional morning dose on Day 13, and
  TMC125 200 mg b.i.d. on Days 6 to 12, with an additional morning dose on Day 13.

All trial medications was administered under fed conditions within 10 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C171).

2.8.3.5.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{12h} of TMC125 were increased 1.46- and 1.42-fold, respectively, when TMC125 was co-administered with clarithromycin, compared to administration of TMC125 alone (Table 101). The mean C_{min} and C_{0h} of TMC125 were increased 1.46- and 1.49-fold, respectively. The 90% CIs of the LS means ratios for all these comparisons were outside the 80% to 125% range. There was no relevant change in the median t_{max} of TMC125.

＊：新薬承認情報提供時に置き換え

Table 101: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Clarithromycin (Trial TMC125-C171)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	TMC125 200 mg b.i.d. (Reference)	TMC125 200 mg b.i.d.+ Clarithromycin 500 mg b.i.d. (Test)		
N	15	15		
t_{max}, h	4.0 (2.0 -6.0)	3.0 (2.0 - 4.0)	-	-
C_{0h}, ng/mL	529.1 ± 162.1	785.8 ± 253.5	1.49	1.37 - 1.61
C_{min}, ng/mL	498.1 ± 153.5	726.3 ± 233.0	1.46	1.36 - 1.58
C_{max}, ng/mL	1015 ± 243.8	1487 ± 389.7	1.46	1.38 - 1.56
AUC_{12h}, ng.h/mL	9008 ± 2392	12760 ± 3559	1.42	1.34 - 1.50

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C171/ Section 4.2.4.2 and Section 4.2.4.3

2.8.3.5.3 Pharmacokinetics of Clarithromycin

The mean C_{max} and AUC_{12h} of clarithromycin were decreased by 34% and 39%, respectively, when clarithromycin was co-administered with TMC125, compared to the administration of clarithromycin alone (Table 102). The mean C_{min} and C_{0h} of clarithromycin were also decreased, by 53% and 45%, respectively. The 90% CIs of the LS means ratios for all these comparisons were outside the 80% to 125% range. There was no change in the median t_{max} of clarithromycin.

Table 102: Pharmacokinetics of Clarithromycin after Administration of Clarithromycin in the Absence and Presence of TMC125 (Trial TMC125-C171)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Clarithromycin 500 mg b.i.d. (Reference)	Clarithromycin 500 mg b.i.d. + TMC125 200 mg (Test)		
N	15	15		
t_{max}, h	2.0 (0.5 - 8.0)	2.0 (1.0 - 4.0)	-	-
C_{0h}, ng/mL	823.6 ± 391.1	492.1 ± 374.2	0.55	0.45 - 0.67
C_{min}, ng/mL	734.8 ± 362.7	370.9 ± 288.4	0.47	0.38 - 0.57
C_{max}, ng/mL	3144 ± 917.1	2088 ± 571.6	0.66	0.57 - 0.77
AUC_{12h}, ng.h/mL	20240 ± 6208	12430 ± 4248	0.61	0.53 - 0.69

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C171/ Section 4.2.5.2 and Section 4.2.5.3

2.8.3.5.4 Pharmacokinetics of 14-Hydroxy-Clarithromycin

The mean C_{max} and AUC_{12h} of the active metabolite 14-hydroxy-clarithromycin were increased 1.33- and 1.21-fold, respectively, when clarithromycin was co-administered with TMC125, compared to administration of clarithromycin alone (Table 103). The mean C_{min} and C_{0h} of 14-hydroxy-clarithromycin were increased 1.05- and 1.16-fold, respectively. With the exception of C_{min}, the 90% CIs of the LS means ratios for these comparisons were outside the 80% to 125% range. There was no change in the median t_{max} of 14-hydroxy-clarithromycin.

The mean metabolite exposure (AUC_{12h}) ratio for 14-hydroxy-clarithromycin to clarithromycin increased from 0.36 to 0.73 upon co-administration of TMC125.

Table 103: Pharmacokinetics of 14-Hydroxy-Clarithromycin after Administration of Clarithromycin in the Absence and Presence of TMC125 (Trial TMC125-C171)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Clarithromycin 500 mg b.i.d. (Reference)	Clarithromycin 500 mg b.i.d. + TMC125 200 mg (Test)		
N	15	15		
t_{max}, h	2.0 (0.0 - 4.0)	2.0 (1.0 - 4.0)	-	-
C_{0h}, ng/mL	418.0 ± 165.8	488.0 ± 178.7	1.16	0.98 - 1.39
C_{min}, ng/mL	382.1 ± 134.3	393.8 ± 108.5	1.05	0.90 - 1.22
C_{max}, ng/mL	766.1 ± 205.3	1030 ± 317.9	1.33	1.13 - 1.56
AUC_{12h}, ng.h/mL	6761 ± 1893	8183 ± 2100	1.21	1.05 - 1.39
Ratio AUC_{12h} (%) [b]	35.92 ± 12.27	72.47 ± 28.68	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
[b] Ratio $AUC_{12h,14\text{-hydroxy-clarithromycin/clarithromycin}}$
Source: Module 5.3.3.4/TMC125-C171/Section 4.2.6.2 and Section 4.2.6.3

2.8.3.5.5 Conclusions

In healthy subjects, the mean exposure (AUC_{12h}) to TMC125 was increased 1.42-fold upon co-administration with clarithromycin. At the same time, the mean exposure to clarithromycin was decreased by 39% and the mean exposure to the active metabolite 14-hydroxy-clarithromycin was increased 1.21-fold. Thus, TMC125 and clarithromycin can be co-administered without dose adjustments. However, because 14-hydroxy-clarithromycin has reduced activity against MAC, the overall activity against this pathogen may be altered. For the treatment of MAC infections, alternatives to clarithromycin, such as azithromycin, should be considered.

2.8.3.6 TRIAL TMC125-C165: PAROXETINE - TMC125 ADMINISTERED AS TABLET FORMULATION F* (TMC125 IN HPMC, GRANULO-LAYERED) IN HEALTHY SUBJECTS

Paroxetine is a commonly used selective serotonin re-uptake inhibitor (SSRI) antidepressant agent that is metabolized mainly via CYP2D6.[45]

2.8.3.6.1 Trial Design

This was an open-label, randomized, 2-period crossover trial to investigate the pharmacokinetic interaction between paroxetine and TMC125, administered as the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered), at steady-state. The trial population consisted of 16 healthy subjects.

The trial consisted of 2 sessions, separated by a washout period of at least 14 days. Subjects were randomized to Panel 1 or 2 in a 1:1 ratio and received the following treatments:

- Treatment A: paroxetine 20 mg q.d. on Days 1 to7;
- Treatment B: TMC125 800 mg b.i.d. on Days 1 to 14, and paroxetine 20 mg q.d. on Days 8 to 14.

All trial medication was administered under fed conditions within 10 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C165).

2.8.3.6.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{12h} of TMC125 were each similar when TMC125 was co-administered with paroxetine, compared to administration of TMC125 alone (Table 104). The mean C_{min} and C_{0h} were slightly increased (1.07- and 1.08-fold, respectively). The 90% CIs of the LS means ratios for all these comparisons were within the 80% to 125% range. There was no relevant change in the median t_{max} of TMC125.

Table 104: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Paroxetine (Trial TMC125-C165)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	TMC125 800 mg b.i.d (Reference)	TMC125 800 mg b.i.d. + Paroxetine 20 mg q.d. (Test)		
N	16	15		
t_{max}, h	4.0 (2.0 - 6.0)	3.0 (1.5 - 4.0)	-	-
C_{0h}, ng/mL	665 ± 321	657 ± 248	1.08	0.98 - 1.19
C_{min}, ng/mL	637 ± 305	626 ± 241	1.07	0.98 - 1.17
C_{max}, ng/mL	1161 ± 449	1149 ± 377	1.05	0.96 - 1.15
AUC_{12h}, ng.h/mL	11099 ± 4524	10529 ± 3808	1.01	0.93 - 1.10

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C165/Section 4.2.4.2 and Section 4.2.4.3

2.8.3.6.3 Pharmacokinetics of Paroxetine

The mean C_{max} and AUC_{24h} of paroxetine were each similar when paroxetine was co-administered with TMC125, compared to administration of paroxetine alone (Table 105). The mean C_{min} and C_{0h} were decreased by 13% and 21%, respectively. For the latter comparisons, the 90% CIs of the LS means ratios were outside the 80% to 125% range. There was no change in the median t_{max} of paroxetine.

Table 105: Pharmacokinetics of Paroxetine after Administration of Paroxetine in the Absence and Presence of TMC125 (Trial TMC125-C165)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Paroxetine 20 mg q.d. (Reference)	Paroxetine 20 mg q.d. + TMC125 800 mg b.i.d. (Test)		
N	16	15		
t_{max}, h	5.0 (3.0 - 16.0)	5.0 (2.0 - 16.0)	-	-
C_{0h}, ng/mL	11.6 ± 10.8	9.3 ± 8.6	0.79	0.65 - 0.97
C_{min}, ng/mL	9.52 ± 8.47	8.63 ± 8.12	0.87	0.75 - 1.02
C_{max}, ng/mL	22.7 ± 16.3	22.8 ± 13.1	1.06	0.95 - 1.20
AUC_{24h}, ng.h/mL	375.6 ± 282.8	375.3 ± 252.1	1.03	0.90 - 1.18

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C165/Section 4.2.5.2; Module 5.3.3.4/TMC125-C159/Section 4.2.5.3

2.8.3.6.4 Conclusions

In healthy subjects, the systemic exposure to TMC125 and paroxetine was not affected when these drugs were co-administered. Thus, TMC125 can be combined with paroxetine without dose adjustments.

2.8.3.7 TRIAL TMC125-C120: RANITIDINE AND OMEPRAZOLE - TMC125 ADMINISTERED AS TABLET FORMULATION A* (TMC125 IN HPMC, SPRAY-DRIED) IN HEALTHY SUBJECTS

Ranitidine (a histamine-2 [H2] blocker) and omeprazole (a proton-pump inhibitor) are gastrointestinal agents that inhibit gastric acid secretion and thereby elevate intragastric pH.[63,50] The co-administration of ranitidine or omeprazole with TMC125 could alter the absorption, and hence the bioavailability, of TMC125 by decreasing the gastric acidity (or increasing pH).

2.8.3.7.1 Trial Design

This was an open label, randomized, 3-period crossover trial to investigate the effect of steady-state ranitidine and steady-state omeprazole on the pharmacokinetics of a single dose of TMC125, administered as the 100-mg tablet formulation A* (TMC125 in HPMC, spray-dried). The trial population consisted of 18 healthy subjects.

In 3 sessions, each subject received Treatment A, B, or C, as follows:

- Treatment A: TMC125 100 mg single dose;
- Treatment B: ranitidine 150 mg b.i.d. on Days 1 to 11, and TMC125 100 mg single dose on Day 8;
- Treatment C: omeprazole 40 mg q.d. on Days 1 to 11, and TMC125 100 mg single dose on Day 8.

Each session was separated by a washout period of at least 14 days.

Morning doses of ranitidine and omeprazole were administered under fasted conditions, 1 hour before breakfast. TMC125 was taken under fed conditions within 10 minutes after completion of breakfast. The evening intake of ranitidine took place 1 hour before dinner.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C120).

2.8.3.7.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{last} of TMC125 were decreased by 6% and 14%, respectively, when TMC125 was co-administered with ranitidine, compared to administration of TMC125 alone (Table 106). When co-administered with omeprazole, the mean C_{max} and AUC_{last} of TMC125 were increased 1.17- and 1.41-fold, respectively. With both combinations, the 90% CIs of the LS means ratios for both comparisons were outside the 80% to 125% range. There were no relevant changes in the median t_{max} of TMC125 with either combination.

＊：新薬承認情報提供時に置き換え

Table 106: Pharmacokinetics of TMC125 after Administration of TMC125 in the Absence and Presence of Ranitidine or Omeprazole (Trial TMC125-C120)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment A TMC125 100 mg (Reference)	Treatment B TMC125 100 mg + Ranitidine 150 mg b.i.d (Test)		
N	18	16		
t_{max}, h	3.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	146.2 ± 69.0	140.9 ± 77.7	0.94	0.75 - 1.17
AUC_{last}, ng.h/mL	1501 ± 685.6	1257 ± 653.2	0.86	0.76 - 0.97
AUC_{∞} [b], ng.h/mL	1768 ± 861.3	1422 ± 737.0	-	-
	Treatment A TMC125 100 mg (Reference)	Treatment C TMC125 100 mg + Omeprazole 40 mg q.d. (Test)		
N	18	17		
t_{max}, h	3.0 (2.0 - 6.0)	4.0 (3.0 - 6.0)	-	-
C_{max}, ng/mL	146.2 ± 69.0	165.0 ± 50.8	1.17	0.96 - 1.43
AUC_{last}, ng.h/mL	1501 ± 685.6	2113 ± 669.5	1.41	1.22 - 1.62
AUC_{∞} [b], ng.h/mL	1768 ± 861.3	2505 ± 845.5	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
[b] Accurate determination not possible in all subjects.
Source: Module 5.3.3.4/TMC125-C120/Section 4.2.5 and Section 4.2.6

2.8.3.7.3 Conclusions

The changes in the systemic exposure to TMC125 when co-administered with ranitidine or omeprazole at steady-state were not considered to be clinically relevant. Thus, TMC125 can be combined with ranitidine or omeprazole without dose adjustments.

2.8.3.8 TRIAL TMC125-C158: METHADONE - TMC125 ADMINISTERED AS TABLET FORMULATION A* (TMC125 IN HPMC, SPRAY-DRIED) IN HEALTHY SUBJECTS

Methadone is a synthetic narcotic analgesic that is widely used in HIV-infected subjects. It is administered as a combination of R(-) and S(+) isomers, with the R(-) isomer being biologically active.[27,20] Methadone is primarily metabolized by N-demethylation to an inactive metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP). Many methadone interactions are substantial and clinically relevant, such as the marked decrease in methadone concentrations that is seen with EFV.[14,12] Such interactions can induce withdrawal symptoms and warrant close monitoring. CYP enzymes, primarily CYP3A4 and to a lesser extent CYP2D6 and 2B6, are responsible for the conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in urine.[35] TMC125 is a CYP3A4 substrate and can also induce CYP3A4 (see Section 3.3.1.3). Thus, a decrease in plasma concentrations of methadone, accompanied by symptoms of methadone withdrawal, could be expected when TMC125 is co-administered.

2.8.3.8.1 Trial Design

This was an open-label, add-on trial to investigate the pharmacokinetic interaction between steady-state TMC125, administered as the 100-mg tablet formulation A* (TMC125 in HPMC, spray-dried), and methadone in subjects on stable methadone therapy. A total of 16 subjects

received TMC125 100 mg b.i.d. for 14 days added to their current, individualized methadone therapy (doses ranged from 60 to 130 mg/day, refer to Module 5.3.3.4/TMC125-C158/Section 4.1.5). TMC125 was administered under fed conditions within 10 minutes after a meal. Methadone was administered after TMC125 intake.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.3.4/TMC125-C158).

2.8.3.8.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{12h} of TMC125, when co-administered with methadone, was slightly increased on Day 14, compared to Day 7 (Table 107). There was no relevant difference in the median t_{max} of TMC125 between these 2 days.

In a historic comparison, the pharmacokinetic parameters of TMC125 on Day 14 of the current trial, in subjects on a stable, individualized methadone maintenance therapy, were comparable to the values observed previously after the administration of TMC125 100 mg b.i.d. alone, also given as the tablet formulation A* , in trial TMC125-C168 (refer to Module 5.3.3.1/TMC125-C168).

Table 107: Pharmacokinetics of TMC125 after Administration of TMC125 in the Presence (Trial TMC125-C158) and Absence (Trial TMC125-C168 as Historic Control) of Methadone

Parameter	Mean ± SD; t_{max}: Median (Range)		
	TMC125-C158		TMC125-C168
	Day 7: TMC125 100 mg b.i.d. + Methadone	Day 14: TMC125 100 mg b.i.d. + Methadone	Day 8: TMC125 100 mg b.i.d.
N	16	15	23
t_{max}, h	3.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)
C_{0h}, ng/mL	205 ± 95	242 ± 74	234 ± 92
C_{min}, ng/mL	188 ± 84	214 ± 61	215 ± 86
C_{max}, ng/mL	375 ± 120	401 ± 88	471 ± 141
AUC_{12h}, ng.h/mL	3282 ± 1200	3567 ± 858.5	3925 ± 1251

N = maximum number of subjects with data.

Source: Module 5.3.3.4/TMC125-C158/Section 4.2.4.2

2.8.3.8.3 Pharmacokinetics of R(-) Methadone

The mean C_{max} and AUC_{24h} of R(-) methadone were similar or only slightly increased (up to 1.08-fold), respectively, on Day 7 and Day 14 when methadone was co-administered with TMC125, compared to administration of methadone alone (Table 108). In both comparisons, the mean C_{min} and C_{0h} were increased approximately 1.1-fold. However, the 90% CIs of the LS means ratios were within the 80% to 125% range for all comparisons. There was no relevant change in the median t_{max} of R(-) methadone on either day.

＊：新薬承認情報提供時に置き換え

Table 108: Pharmacokinetics of R(-) Methadone in Subjects on a Stable Methadone Therapy in the Absence and Presence of TMC125 (Trial TMC125-C158)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [b] (Test:Reference)	90% CI
	Day -1 Methadone [a] (Reference)	Day 7 or Day 14 Methadone [a] + TMC125 100 mg b.i.d. (Test)		
Day 1 vs. Day 7				
N	16	16		
t_{max}, h	2.0 (1.5 - 4.0)	3.0 (1.5 - 6.0)	-	-
C_{0h}, ng/mL	125.4±39.26	137.2±47.32	1.08	1.01 - 1.16
C_{min}, ng/mL	120.4±38.73	135.3±44.65	1.12	1.05 - 1.19
C_{max}, ng/mL	222.0±73.55	225.8±68.87	1.03	0.97 - 1.09
AUC_{24h}, ng.h/mL	3807±1301	4070±1229	1.08	1.02 - 1.13
Day 1 vs. Day 14				
N	16	15		
t_{max}, h	2.0 (1.5 - 4.0)	3.0 (1.5 - 4.0)	-	-
C_{0h}, ng/mL	125.4±39.26	139.6±49.17	1.10	1.02 - 1.18
C_{min}, ng/mL	120.4±38.73	134.0±44.99	1.10	1.02 - 1.19
C_{max}, ng/mL	222.0±73.55	228.2±74.53	1.02	0.96 - 1.09
AUC_{24h}, ng.h/mL	3807±1301	4038±1309	1.06	0.99 - 1.13

N = maximum number of subjects with data.
[a] Subjects received individualized doses of methadone, ranging from 60 to 130 mg/day.
[b] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C158/ Section 4.2.6.2 and Section 4.2.6.3

2.8.3.8.4 Pharmacokinetics of S(+) Methadone

The mean C_{max} and AUC_{24h} of S(+) methadone were decreased by 9% and 7%, respectively, on Day 7 and decreased by 11% each on Day 14 when methadone was co-administered with TMC125, compared to administration of methadone alone (Table 109). In both comparisons, the mean C_{min} and C_{0h} were also decreased, by 6% and 10%, respectively, on Day 7 and by 11% and 13%, respectively, on Day 14. However, with the exception of C_{0h} on Day 14, the 90% CIs of the LS means ratios were within the 80% to 125% range for all comparisons. There was no relevant change in the median t_{max} of S(+) methadone on either day.

Table 109: Pharmacokinetics of S(+) Methadone in Subjects on a Stable Methadone Therapy in the Absence and Presence of TMC125 (Trial TMC125-C158)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [b] (Test:Reference)	90% CI
	Day -1: Methadone [a] (Reference)	Day 7 or Day 14: Methadone [a] + TMC125 100 mg b.i.d. (Test)		
Day 1 vs. Day 7				
N	16	16		
t_{max}, h	2.0 (1.0 - 3.0)	2.5 (1.5 - 4.05)	-	-
C_{0h}, ng/mL	133.6 ± 58.85	126.0 ± 64.51	0.90	0.81 - 1.01
C_{min}, ng/mL	125.6 ± 57.17	123.2 ± 62.18	0.94	0.86 - 1.04
C_{max}, ng/mL	284.6 ± 103.0	259.1 ± 92.97	0.91	0.85 - 0.98
AUC_{24h}, ng.h/mL	4378 ± 1809	4088 ± 1705	0.93	0.86 - 0.99
Day 1 vs. Day 14				
N	16	15		
t_{max}, h	2.0 (1.0 - 3.0)	2.0 (1.5 - 4.0)	-	-
C_{0h}, ng/mL	133.6 ± 58.85	122.2 ± 62.87	0.87	0.79 - 0.96
C_{min}, ng/mL	125.6 ± 57.17	117.7 ± 61.63	0.89	0.81 - 0.98
C_{max}, ng/mL	284.6 ± 103.0	263.5 ± 106.6	0.89	0.83 - 0.97
AUC_{24h}, ng.h/mL	4378 ± 1809	4029 ± 1834	0.89	0.82 - 0.96

N = maximum number of subjects with data.
[a] Subjects received individualized doses of methadone, ranging from 60 to 130 mg/day.
[b] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C158/ Section 4.2.5.2 and Section 4.2.5.3

2.8.3.8.5 Pharmacodynamic Assessment of Methadone Withdrawal

There were no increases in symptoms of opiate withdrawal during the trial, and no methadone dose adjustments needed during or shortly after the co-administration phase, substantiating the lack of any clinically relevant interaction when TMC125 is co-administered with methadone (Module 5.3.3.4/TMC125-C158/Section 4.3.7).

2.8.3.8.6 Conclusions

When added to the stable, individualized methadone maintenance therapy, TMC125 administered at a dose of 100 mg b.i.d. slightly increased plasma concentrations of the active R(-) methadone and slightly decreased plasma concentrations of the inactive S(+) methadone, but these changes were not clinically relevant. There were no increases in symptoms of opiate withdrawal during the trial, and no methadone dose adjustments needed during or shortly after the co-administration phase.

In the presence of methadone, TMC125 exposure was comparable to the exposure in the absence of methadone in a historic comparison.

Based on these results, no a priori dose adjustments of either methadone or TMC125 are required when these drugs are co-administered.

2.9 EFFECT OF TMC125 ON ECG IN HEALTHY SUBJECTS

2.9.1 Trial TMC125-C178: Thorough QT/QTc Trial on the Effect of TMC125 on ECG Intervals in Healthy Subjects - TMC125 Administered as Tablet Formulation A* (TMC125 in HPMC, Spray-Dried)

This was a double-blind, double-dummy, randomized, placebo- and active-controlled, 4-period crossover trial to evaluate the effect of TMC125, administered as the 100-mg tablet formulation A* (TMC125 in HPMC, spray-dried), on the QT/QTc interval in 41 healthy subjects (22 males and 19 females). Moxifloxacin was included as a positive control. Each subject received 4 different treatments in 4 sessions of 8 days each, with a washout period of at least 14 days between each session, as follows:

- Treatment A: TMC125 200 mg b.i.d.;
- Treatment B: TMC125 400 mg q.d.;
- Treatment C: Moxifloxacin 400 mg q.d.;
- Treatment D: Placebo.

On Days -1, 1 and 8 of each session, 12-lead, time-matched triplicate ECGs were recorded at 11 predefined time points covering the duration of exposure to the trial medication and accounting for diurnal variability. ECGs were also recorded on Days 2 to 7 (predose and at expected t_{max}), and on Day 15. Plasma samples for the determination of full 12-hour pharmacokinetic profiles of TMC125 or moxifloxacin were collected on Days 1 and 8, within 5 minutes after each ECG recording. Plasma samples were also collected on Day 2 (predose), Days 5 to 7 (predose), and Day 9 (24 h postdose).

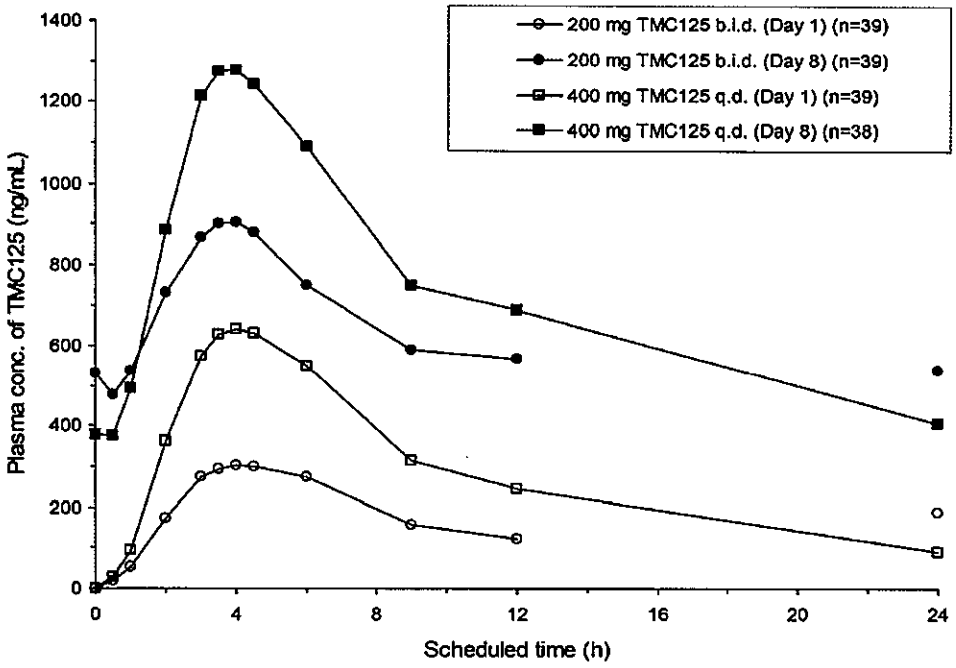
The trial medication was administered under fed conditions within 10 minutes after a meal.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.4.1/TMC125-C178).

2.9.1.1 PHARMACOKINETICS OF TMC125

The mean plasma concentration-time profiles of TMC125 on Days 1 and 8 are shown in Figure 37).

＊：新薬承認情報提供時に置き換え



Source: Module 5.3.4.1/TMC125-C178/Section 4.3.4.1/Figure 8

Figure 37: Mean Plasma Concentration-Time Profiles of TMC125 on Days 1 and 8 after Administration as Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) at Doses of 200 mg b.i.d. or 400 mg q.d. in Healthy Subjects (Trial TMC125-C178)

Steady-state concentrations of TMC125 were almost reached after 8 days (Module 5.3.4.1/TMC125-C178/Section 4.3.4.1). On Day 8, the mean AUC_{24h} of TMC125 was similar between the 2 dosing regimens (assuming AUC_{24h} for TMC125 200 mg b.i.d. was 2 x AUC_{12h}) (Table 110). However, the mean C_{max} of TMC125 was increased 1.44-fold, and mean C_{min} of TMC125 was decreased by 25%, when TMC125 was administered q.d. The 90% CIs of the LS means ratios for both comparisons were outside the 80% to 125% range. There was no difference between the 2 dosing regimens in the median t_{max} of TMC125. With both dosing regimens, the mean AUC values on Day 8 were approximately 3- to 4-fold higher than those on Day 1.

＊：新薬承認情報提供時に置き換え

Table 110: Pharmacokinetics of TMC125 on Days 1 and 8 after Administration as Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) at Doses of 200 mg b.i.d. or 400 mg q.d. in Healthy Subjects (Trial TMC125-C178)

Parameter	Mean ± SD; t_{max}: Median (Range) Treatment A: TMC125 200 mg b.i.d. (Reference)	Treatment B: TMC125 400 mg q.d. (Test)	Ratio [a] (Test:Reference)	90% CI
Day 1				
N	39	39		
t_{max}, h	4.08 (2.08 - 6.12)	4.08 (2.08 - 6.10)	-	-
C_{max}, ng/mL	370.1 ± 149.0	715.1 ± 263.8	-	-
AUC_{12h}, ng.h/mL	2281 ± 1005	-	-	-
AUC_{24h}, ng.h/mL	-	6688 ± 2749		
Day 8				
N	39	37		
t_{max}, h	4.08 (2.08 - 6.08)	4.08 (3.08 - 6.13)	-	-
C_{0h}, ng/mL	529.5 ± 172.5	382.1 ± 145.0	-	-
C_{min}, ng/mL	468.6 ± 149.0	364.2 ± 133.3	0.75	0.72 - 0.79
C_{max}, ng/mL	958.8 ± 278.1	1393 ± 385.9	1.44	1.37 - 1.50
$C_{ss,av}$, ng/mL	687.6 ± 203.8	719.9 ± 209.5	1.03	1.00 - 1.06
AUC_{12h}, ng.h/mL	8195 ± 2428	-	-	-
AUC_{24h}, ng.h/mL	-	17220 ± 5009	1.03 [b]	1.00 - 1.07
FI, %	72.06 ± 16.38	147.0 ± 32.60	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
For comparison, AUC_{24h} for TMC125 200 mg b.i.d. was calculated as 2 x AUC_{12h}.
Source: Module 5.3.4.1/TMC125-C178/Section 4.3.4.2 and Section 4.3.4.3

2.9.1.2 PHARMACOKINETICS OF MOXIFLOXACIN

The pharmacokinetics of moxifloxacin on Days 1 and 8 are summarized in Table 111.

Table 111: Pharmacokinetics of Moxifloxacin on Days 1 and 8 after Administration at a Dose of 400 mg q.d. in Healthy Subjects (Trial TMC125-C178)

Parameter	Mean ± SD; t_{max}: Median (Range) Treatment C: Moxifloxacin 400 mg q.d.
N	38
Day 1	
t_{max}, h	3.08 (0.58 - 6.08)
C_{max}, ng/mL	3241 ± 783.6
AUC_{24h}, ng.h/mL	34060 ± 7698
Day 7	
t_{max}, h	3.58 (0.58 - 6.08)
C_{0h}, ng/mL	895.3 ± 281.4
C_{min}, ng/mL	815.2 ± 258.9
C_{max}, ng/mL	3951 ± 771.9
AUC_{24h}, ng.h/mL	48320 ± 9947

N = number of subjects with data.
Source: Module 5.3.4.1/TMC125-C178/Section 4.3.5.2

The median t_{max} was 3.1 h on Day 1 and 3.6 h on Day 8, with similar ranges for both days.

＊：新薬承認情報提供時に置き換え

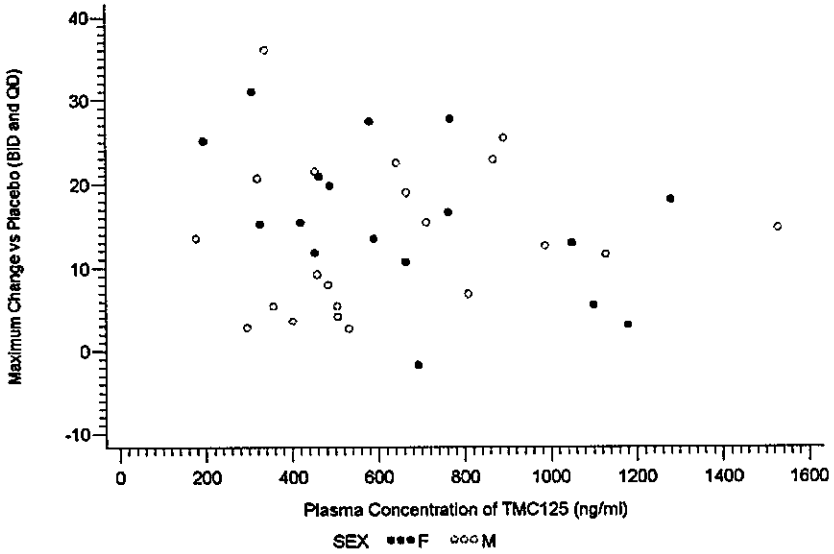
The mean C_{max} and AUC_{24h} values of moxifloxacin were 3241 and 3951 ng/mL, and 34060 and 48320 ng.h/mL, on Days 1 and 8, respectively, indicating accumulation of moxifloxacin. The mean accumulation ratio was 124.5% and 143.0% for C_{max} and AUC_{24h}, respectively.

These pharmacokinetic data were comparable to those reported in the United States Package Insert for Avelox® given at the same dose.[3]

2.9.1.3 PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP FOR TMC125

At clinically relevant doses, TMC125 did not prolong the QT interval (Module 5.3.4.1/TMC125-C178/Section 4.2).

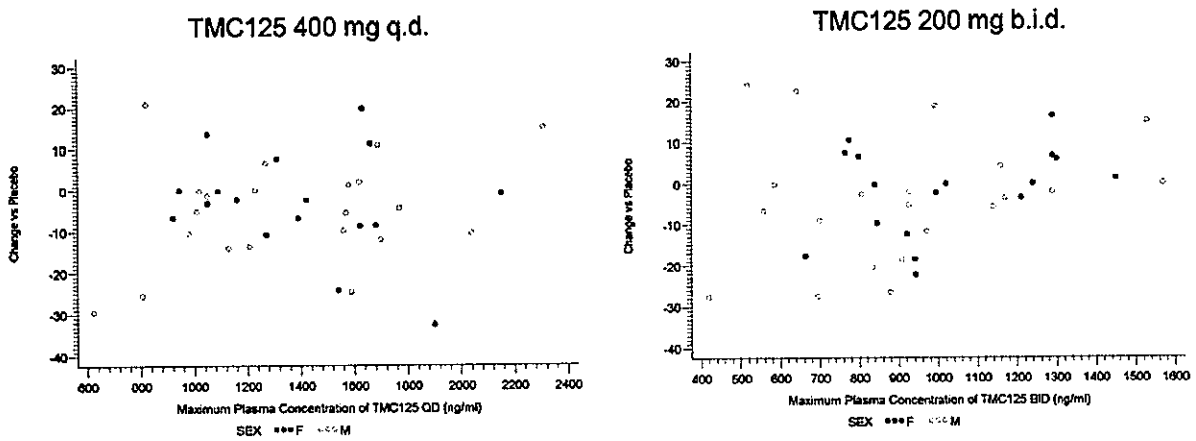
In a scatter plot of the time-matched plasma concentration on Day 8 vs. the maximum individual increase in QTcF for all subjects during TMC125 treatment, no correlation was apparent between the maximum QTcF increase and the corresponding TMC125 concentration in either males or females (Figure 38). The maximum QTcF increase was selected per subject from the QTcF data during both the b.i.d. and the q.d. TMC125 treatment phases.



Source: Module 5.3.4.1/TMC125-C178/Section 4.3.6/Figure 10

Figure 38: TMC125 Plasma Concentration vs. Time-Matched Maximum Increase in QTcF on Day 8 in Healthy Subjects (Trial TMC125-C178)

A scatter plot of C_{max} on Day 8 vs. the corresponding time-matched QTcF increase for all subjects at both TMC125 doses showed no apparent correlation between C_{max} and the corresponding QTcF change in males or females (Figure 39).



Source: Module 5.3.4.1/TMC125-C178/Section 4.3.6/Figure 11

Figure 39: TMC125 C_{max} vs. Time-Matched Increase in QTcF on Day 8 after Administration of TMC125 at a Dose of 400 mg q.d. or TMC125 200 mg b.i.d. in Healthy Subjects (Trial TMC125-C178)

2.9.1.3.1 Conclusions

The mean AUC_{24h} of TMC125 was similar for the TMC125 doses of 200 mg b.i.d. and 400 mg q.d. At the 400 mg q.d. dose, the mean C_{min} was 25% lower and the mean C_{max} was 44% higher than the respective values obtained at the 200 mg b.i.d. dose. The mean FI was about twice as high for TMC125 400 mg q.d. compared to 200 mg b.i.d.

At clinically relevant doses, TMC125 did not prolong the QT interval and there was no indication for any correlation between plasma concentrations of TMC125 and the corresponding QT value.