MODULE 2.7 CLINICAL SUMMARY

2.7.1 SUMMARY OF BIOPHARMACEUTIC STUDIES AND ASSOCIATED ANALYTICAL METHODS

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LIST OF ABBREVIATIONS

ART	antiretroviral therapy
ARV	antiretroviral
AUC_t	area under the plasma concentration-time curve to t hours post-dosing
AUC_{last}	area under the plasma concentration-time curve to last measurable or measured concentration
AUC_∞	area under the plasma concentration-time curve to infinity
BCS	Biopharmaceutics Classification System
b.i.d.	bis in die, twice daily
CI	confidence interval
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CV	coefficient of variation
ECD	electrochemical detection
f_2	similarity factor (dissolution)
FaSSIF	fasted-state simulated intestinal fluid
FeSSIF	fed-state simulated intestinal fluid
FI	fluctuation index
FL	fluorescence (detection)
GC	gas chromatography
HBr	hydrobromic acid
HCl	hydrochloric acid
HIV	human immunodeficiency virus
HPMC	hydroxypropylmethylcellulose or hypromellose
J&JPRD	Johnson & Johnson Pharmaceutical Research and Development
LC-MS/MS	liquid chromatography with tandem mass-spectrometry
LLOQ	lower limit of quantification
LPV	lopinavir
LS	least squares
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
PEG	polyethylene glycol
PVP	polyvinyl pyrolidone
RNA	ribonucleic acid
RTV	ritonavir
rtv	low-dose ritonavir, co-administered as a pharmacokinetic enhancer
SD	standard deviation
SGF_{sp}	simulated gastric fluid without pepsin
SLS	sodium lauryl sulfate
SQV	saquinavir
SUPAC	Scale-Up and Post Approval Changes
$t_{1/2,term}$	terminal elimination half-life
TBME	tertiary-butyl methyl ether
t_{max}	time to reach maximum plasma concentration
TMC	Tibotec Medicinal Compound

USA	United Sates of America
USP	United States Pharmacopeia
VitE-TPGS	d-alpha tocopheryl polyethylene glycol 1000 succinate

1 BACKGROUND AND OVERVIEW

1.1 OVERVIEW OF BIOPHARMACEUTIC TRIALS

Data from 20 clinical trials evaluating the bioavailability of oral capsule, tablet, granulate, and powder formulations of TMC125 are presented in this Summary of Biopharmaceutic Studies. Due to the low aqueous solubility and low permeability of TMC125 (which is therefore a Biopharmaceutics Classification System [BCS] Class IV drug[1]), 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 more than 25 formulation concepts.

TMC125 is a highly lipophilic compound and is almost insoluble in water. Because an acceptable intravenous formulation suitable for use in humans is not available, the absolute bioavailability of TMC125 after oral administration has not been investigated.

Early Phase I and Phase IIa clinical trials mainly used TMC125 formulated as a polyethylene glycol (PEG) 4000-based capsule (formulation 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 hydroxypropylmethylcellulose (hypromellose, HPMC) (formulation U*) or [redacted] (formulation V*), which had a lower bioavailability than formulation T*, and capsule formulation concepts containing TMC125 as a hydrobromic acid (HBr) salt (TMC125.HBr). Some of the HBr salt concepts had a relatively low bioavailability (TMC125.HBr as drug substance [formulation W*] or as a granulate [formulation X*]) compared to formulation T*, while others had a relatively high bioavailability (TMC125.HBr in HPMC [formulations Y*, E* and Z*] or [redacted] [formulation a*]). However, these formulation concepts of TMC125.HBr in HPMC 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 (formulation T*) was replaced by tablet formulations manufactured using granulo-layering technology (formulations S* and F*). These tablet formulations had a comparable bioavailability to that of the capsule formulation 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. For example, the dosing regimens of TMC125 tested in Phase IIb trials were 400, 800, and 1200 mg twice daily (b.i.d.), resulting in a daily intake of 4, 8, and 12 tablets, respectively.

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. Because TMC125 is a BCS Class IV drug, various approaches were taken to improve the aqueous solubility by physical modification of the drug, in particular by developing solid dispersion formulations with TMC125 in an amorphous form homogenously dispersed in a polymer matrix.

In a comparison of a capsule formulation of TMC125 in HPMC manufactured using bead-coating technology (formulation M*) and tablet formulations of TMC125 in HPMC manufactured using

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spray-drying technology (formulations J*and 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 (formulation 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 (formulation F*), and with different spray-dried formulations, showed that the use of HPMC as the polymer (formulations J* and K*) provided a higher bioavailability than the use of [redacted] (formulation 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] (formulations J*, O*, P*) and [redacted] (formulations K*, Q*) to [redacted] (formulation G*). The [redacted] ratio is used in formulation A*, which was selected for the registrational Phase III clinical trials and intended commercialization. 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 (formulations C*, B*, and F*), was confirmed for a number of formulations of differing compositions (Table 5) in healthy subjects (formulations J*, K*, O*, N*, Q*, G*, P*, I*, A*, H*) and in human immunodeficiency virus (HIV)-1 infected subjects (formulation A*).

The final formulation and manufacturing process were selected on the basis of trial TMC125-C170 (Section 2.1.3), in which healthy subjects receiving a single 400-mg dose of the spray-dried tablet formulation of TMC125 in HPMC (formulation 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 (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 (formulation 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 intended commercialization, resulting in a significant reduction in the pill burden and thereby potentially having a beneficial effect on patient adherence.

However, trial TMC125-C228 in HIV-1 infected subjects (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 less 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 the same 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* (see Section 3.2.1.2 for further details).

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* was confirmed in the

pharmacokinetic substudy of trial TMC125-C229 (Module 2.7.2/Section 2.6.2.5), as shown in Figure 31 for individual AUC_{12h} values, and a comparison between population pharmacokinetic estimates obtained after administration of TMC125 as formulations F* and A* in Phase IIb and III trials, respectively (Module 2.7.2/Section 3.6.1).

Having selected the spray-dried tablet formulation of TMC125 in HPMC (formulation A*) for use in planned clinical trials and for intended commercialization, further testing of tablet formulation A* was conducted to investigate the effects of changing the scale and site of manufacture (Section 1.3.2.4).

The effect of concomitant food intake on the bioavailability of TMC125 when administered as tablet formulation A* was investigated in 2 trials. In each trial the effect of concomitant food intake was evaluated by administering TMC125 10 minutes after a standardized breakfast, compared to administration either under fasted conditions (trial TMC125-C147) or before the standardized breakfast (trial TMC125-C116) (Section 3.3). In addition, trial TMC125-C147 investigated the effect of 4 different meal types. In 4 other trials, the effect of concomitant food intake on the bioavailability of TMC125 was investigated when administered as tablet formulations (formulations S* and F*) and capsule formulations (formulations T* and E*) that are no longer being developed.

A spray-dried 25-mg tablet formulation of TMC125 in HPMC that is compositionally proportional to the 100-mg tablet formulation A* (formulation b*) has been developed for pediatric use. Formulation b* is being investigated in ongoing trial TMC125-C126 (investigating the pharmacokinetics of TMC125 in HIV-1 infected children) and will be investigated in planned trial TMC125-C173 (investigating the relative oral bioavailability of formulation b* compared to formulation A* in healthy adults).

Healthy subjects were enrolled into most of the biopharmaceutic trials because conducting trials in HIV-1 infected subjects was generally not considered feasible or ethical due to the need for concomitant therapies and chronic therapy in HIV-1 infected subjects, and interruption of their usual antiretroviral (ARV) therapy would be undesirable. Furthermore, it is common practice to conduct certain types of biopharmaceutic trials, such as bioavailability and bioequivalence trials, in healthy subjects.

A tabular listing of the completed biopharmaceutic trials with TMC125 is presented by dosage form and formulation number in Table 1. A more detailed listing, including information on trial design, subjects evaluated, and dosing regimens, is provided in Appendix 2.7.1.2 and Module 2.7.1 Appendix: Summary of Completed Biopharmaceutical Studies and Module 2.7.2 Appendix: Summary of Completed Clinical Pharmacology Studies - Drug-Drug Interaction (for trial TMC125-C116). An overview of ongoing and planned biopharmaceutic trials with TMC125 is available in Module 2.7.3 Appendix: Tabular Overview of Ongoing and Planned Trials with TMC125.

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Table 1: Clinical Biopharmaceutic Trials by Dosage Form and Formulation Number

Clinical Trial (Location of Trial Report)	TMC125	
	Dosage Form	Formulation Number [e]
Relative Bioavailability Trials - Testing of Experimental Formulations		
TMC125-C115 (Module 5.3.1.2)	100 mg capsule (TMC125.HBr in HPMC)	formulation E*
	200 mg tablet (TMC125 in HPMC, granulo-layered)	formulation B*
	200 mg powder (TMC125 in HPMC)	formulation D*
	100 mg tablet (TMC125 in HPMC, granulo-layered)	formulation C*
TMC125-C142 (Module 5.3.1.2)	200 mg tablet (TMC125 in HPMC, granulo-layered)	formulation F*, Batch 1(L129)
	200 mg tablet (TMC125 in HPMC, granulo-layered)	formulation F*, Batch 2 (L130)
	200 mg tablet (TMC125 in HPMC, granulo-layered)	formulation B*
TMC125-C170 (Module 5.3.1.2)	200 mg tablet (TMC125 in HPMC, granulo-layered)	formulation F*
	133 mg tablet (TMC125 in HPMC, spray-dried)	formulation G*
	100 mg tablet (TMC125 in HPMC, spray-dried)	formulation A*
	133 mg tablet (TMC125 in HPMC, spray-dried)	formulation H*
	100 mg tablet (TMC125 in HPMC, spray-dried)	formulation I*
TMC125-C141 (Module 5.3.1.2)	200 mg tablet (TMC125 in HPMC, granulo-layered)	formulation F*
	100 mg tablet (TMC125 in HPMC, spray-dried)	formulation A*
TMC125-C228 (Module 5.3.1.2)	200 mg tablet (TMC125 in HPMC, granulo-layered)	formulation F*
	100 mg tablet (TMC125 in HPMC, spray-dried)	formulation A*
Relative Bioavailability Trials - Optimization of Selected Tablet Formulation		
TMC125-C150 (Module 5.3.1.2)	200 mg tablet (TMC125 in HPMC, granulo-layered)	formulation F*
	200 mg tablet (TMC125 in HPMC, spray-dried)	formulation J*
	133 mg tablet (TMC125 in HPMC, spray-dried)	formulation K*
	200 mg tablet (TMC125 in [redacted], spray-dried)	formulation L*
	200 mg capsule (TMC125 in HPMC, bead-coated)	formulation M*
TMC125-C155 (Module 5.3.1.2)	200 mg tablet (TMC125 in HPMC, granulo-layered)	formulation F*
	133 mg tablet (TMC125 in HPMC, granulo-layered)	formulation c*
	200 mg tablet (TMC125 in HPMC, spray-dried)	formulation O*
TMC125-C146 (Module 5.3.1.2)	200 mg tablet (TMC125 in HPMC, granulo-layered)	formulation F*
	200 mg tablet (TMC125 in HPMC; spray-dried)	formulation P*
	200 mg tablet (TMC125 in HPMC, spray-dried)	formulation Q*
	133 mg tablet (TMC125 in HPMC, spray-dried)	formulation G*
TMC125-C162 (Module 5.3.1.2)	100 mg tablet (TMC125 in HPMC, spray-dried)	formulation A*, Batch L051
	100 mg tablet (TMC125 in HPMC, spray-dried)	A*, BatchL054
	100 mg tablet (TMC125 in HPMC, spray-dried)	A*, BatchL055
	133 mg tablet (TMC125 in HPMC, spray-dried)	formulation K*
TMC125-C169 (Module 5.3.1.2)	100 mg tablet (TMC125 in HPMC, spray-dried) [a]	formulation A*, Batch L071
	100 mg tablet (TMC125 in HPMC, spray-dried) [b]	formulation A*, Batch L158
	100 mg tablet (TMC125 in HPMC, spray-dried) [c]	formulation A*, Batch L157
	100 mg tablet (TMC125 in HPMC, spray-dried) [d]	formulation A*, Batch L159

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Table 1: Clinical Biopharmaceutic Trials by Dosage Form and Formulation Number, Cont'd

Clinical Trial (Location of Trial Report)	TMC125	
	Dosage Form	Formulation Number [c]
TMC125-C172 (Module 5.3.1.2)	100 mg tablet (TMC125 in HPMC, spray-dried) 200 mg powder (TMC125 base in HPMC, spray-dried) 200 mg powder (TMC125 base in HPMC, spray-dried)	formulation A* formulation R* Batch L099 formulation R* Batch L098
Food Effect Trials		
TMC125-C147 (Module 5.3.1.1)	100 mg tablet (TMC125 in HPMC, spray-dried)	formulation A*
TMC125-C116 (Module 5.3.3.4)	100 mg tablet (TMC125 in HPMC, spray-dried)	formulation A*
TMC125-C133 (Module 5.3.1.1)	100 mg tablet (TMC125 in HPMC, granulo-layered)	formulation S*
TMC125-C137 (Module 5.3.1.1)	200 mg tablet (TMC125 in HPMC, granulo-layered)	formulation F*
TMC125-C103 (Module 5.3.1.1)	50 mg capsule (TMC125 in PEG 4000)	formulation T*
TMC125-C112 (Module 5.3.1.1)	100 mg capsule (TMC125.HBr in HPMC)	formulation E*
Relative Bioavailability Trials - Formulations Not Being Developed Further		
TMC125-C102 (Module 5.3.1.2)	50 mg capsule (TMC125 in PEG 4000) 100 mg capsule (TMC125 in HPMC) 40 mg capsule (TMC125 in [redacted])	formulation T* formulation U* formulation V*
TMC125-C114 (Module 5.3.1.2)	50 mg capsule (TMC125 in PEG 4000) 100 mg capsule (TMC125.HBr) 50 mg capsule (TMC125.HBr in HPMC) 50 mg capsule (TMC125.HBr in [redacted]) 100 mg tablet (TMC125.HBr as granulate)	formulation T* formulation W* formulation Y* formulation a* formulation X*
TMC125-C136 (Module 5.3.1.2)	400 mg powder (TMC125 in HPMC) 400 mg powder (TMC125 in HPMC)	formulation D*, Batch L126 formulation D*, Batch L124

[a] Manufactured (small-scale) by [redacted] with spray-dried TMC125 powder from [redacted] and HPMC from [redacted].
[b] Manufactured (full-scale) by [redacted] with spray-dried TMC125 powder from [redacted] and HPMC from [redacted]
[c] Manufactured (full-scale) by [redacted] with spray-dried TMC125 powder from [redacted] and HPMC from [redacted].
[d] Manufactured (full-scale) by [redacted] with spray-dried TMC125 powder from [redacted] and HPMC from [redacted].
[e] Batch numbers are provided only where relevant to the trial design.

The objective of this summary document is to provide an overall view of the clinical biopharmaceutic trials conducted as part of the clinical development program for TMC125. In addition, the results of the supportive in vitro dissolution trials with clinically relevant batches of TMC125 tablets (formulation A*) used in the biopharmaceutic trials are also summarized.

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A total of 527 subjects were treated with TMC125 in the 20 completed biopharmaceutic trials summarized in this document, as shown in Table 2.

Table 2: Numbers of Subjects Treated with TMC125 in Completed Biopharmaceutic Trials

Type of Trial	Number of Trials	Population	Number of Subjects
Relative bioavailability trials			
Testing of experimental formulations	3	Healthy subjects	87
Testing of experimental formulations	2	HIV-1 infected subjects	73
Optimization of selected tablet formulation	6	Healthy subjects	206
Formulations not being developed further	3	Healthy subjects	45
Food effect trials	6	Healthy subjects	116
Total	**20**		**527**

Source: Appendix 2.7.1.2

The numbers of subjects treated in the individual trials are available in Appendix 2.7.1.2.

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

1.2 OVERVIEW OF ANALYTICAL METHODS

1.2.1 Determination of TMC125 in Plasma

During the clinical development of TMC125, 5 bioanalytical assays for the determination of TMC125 in plasma were developed to support the TMC125 pharmacokinetic program. These assays were developed at different laboratories, but they were all based upon the same sample clean-up procedure, liquid-liquid extraction, and detection technique (liquid chromatography with tandem mass-spectrometry [LC-MS/MS]). The performance of these assays was characterized by means of a validation process, in line with internal procedures and bioanalytical guidelines.[1,3]

Validated LC-MS/MS methods were developed for the determination of TMC125 in human heparin plasma. Small changes were subsequently made to these methods during the development of TMC125, including improvements in the chromatographic conditions, implementation of a stable isotope-labeled internal standard, and a switch to other instrumentation. The validation data for all TMC125 bioanalytical methods are summarized in Table 3, and are described in detail in the individual method validation reports (refer to Module 5.3.1.4).

In-trial validation was conducted for the individual trials, and validation data are included in the respective clinical research reports. An overview of the analytical methods employed for each trial is provided in Appendix 2.7.1.1.

1.2.1.1 LC-MS/MS ASSAY FOR HUMAN HEPARIN PLASMA, DEVELOPED AT [redacted]

In the initial method ([redacted]1846, refer to Module 5.3.1.4/TMC125-[redacted]1846-AVR), an aliquot of heparin plasma sample (0.5 mL) was diluted with [redacted] solution and spiked with an internal standard (compound C*). The analytes were then extracted once using 4 mL [redacted] ether ([redacted]) under alkaline conditions, after addition of 25 µL of 25% [redacted] solution. After equilibration and centrifugation, the organic layer was isolated by decantation, after flash freezing the aqueous layer in a cryogenic bath at −40°C. The organic layer was evaporated to dryness under a gentle stream of heated nitrogen. The extract residue was reconstituted in injection solvent, vortexed and centrifuged, and an aliquot (10 µL) was injected for analysis. A mixture of 0.008 M [redacted] and acetonitrile (25/75, v/v), adjusted to pH [redacted], was used as the elution mixture.

After injection onto the LC-MS/MS system, isocratic chromatographic separation was achieved at [redacted]°C on a [redacted] µm [redacted] C18 [redacted] ([redacted] x [redacted] mm) column at a flow rate of [redacted] mL/min. An MS/MS system in the electrospray ionization, multiple-reaction monitoring mode was used for detection. Initially, the following transitions were monitored for TMC125 and the internal standard: *m/z* [redacted] to [redacted] and *m/z* [redacted] to [redacted] on an [redacted] instrument ([redacted]). The effective linear range of quantification was 2.00 to 5000 ng/mL.

In the next phase of the method validation (Method [redacted]3134), newer MS/MS instrumentation was implemented ([redacted] instrument, [redacted]) (refer to Module 5.3.1.4/TMC125-ABL3134-AVR). The injection volume was increased to 20 µL, the elution mixture was modified to a 30/70 (v/v) ratio, and the multiple-reaction monitoring transitions were adapted to *m/z* [redacted] to [redacted] and *m/z* [redacted] to [redacted] for TMC125 and the internal standard, respectively, improving the selectivity of the method.

Subsequently (Method [redacted]5151), more sensitive MS/MS instrumentation was used ([redacted] instrument, [redacted]) (refer to Module 5.3.1.4/TMC125-[redacted]5151-AVR). The plasma aliquot needed for analysis was reduced to 0.1 mL, the elution mixture was set to a 20/80 (v/v) ratio at pH [redacted], the flow was set at [redacted] mL/min, and the multiple-reaction monitoring transitions were adapted to *m/z* [redacted] to [redacted] and *m/z* [redacted] to [redacted] for TMC125 and the internal standard, respectively. In addition, the extract residues were reconstituted in 200 µL of injection solvent to comply with the more sensitive LC-MS/MS instrumentation used.

In the final stage of the assay development (Method [redacted]5258), a stable isotope-labeled internal standard ([redacted], compound E*) was included in the method (refer to Module 5.3.1.4/TMC125-[redacted]5258-AVR). The elution mixture was changed to [redacted] and acetonitrile in a 30/70 (v/v) ratio, and the multiple-reaction monitoring transitions were adapted to *m/z* [redacted] to [redacted] and *m/z* [redacted] to [redacted] for TMC125 and the internal standard, respectively. In addition, the extract residues were reconstituted in 400 µL of injection solvent to comply with the more sensitive LC-MS/MS instrumentation used, and the injection volume was set to 5 µL.

According to the respective method validation reports, the reported multiple-reaction monitoring settings were applied during validation. However, for each individual trial, small adaptations to the instrument settings were allowed in order to optimize the assay performance for the analysis of trial samples.

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1.2.1.2 LC-MS/MS ASSAY FOR HUMAN HEPARIN PLASMA, DEVELOPED AT [redacted])

In Method [redacted]-RD-643 ([redacted]-040563) (refer to Module 5.3.1.4/TMC125-[redacted]-RD-643), an aliquot of heparin plasma sample (0.3 mL) was diluted with water and spiked with the internal standard (compound D*). The analytes were then extracted once using 1 mL [redacted] under alkaline conditions, i.e., after addition of 50 µL 25% [redacted] solution. After equilibration and centrifugation, the organic layer was isolated by decantation, after flash freezing the aqueous layer in a cryogenic bath. The organic layer was evaporated to dryness under a gentle stream of heated nitrogen. The extract residue was reconstituted in 0.2 mL acetonitrile. 0.1 mL 0.1% [redacted] was added and, after vortex mixing and centrifugation, an aliquot (25 µL) was injected for analysis. A mixture of 0.1% (v/v) [redacted] and acetonitrile (20/80, v/v) was used as the elution mixture.

After injection onto the LC-MS/MS system, isocratic chromatographic separation was achieved at [redacted]°C on a [redacted] µm [redacted] RP 18 chromatographic column ([redacted] x [redacted] mm) at a flow rate of [redacted] mL/min. An MS/MS system in the electrospray ionization, multiple-reaction monitoring mode was used for detection. Initially, the following transitions were monitored for TMC125 and the internal standard: *m/z* [redacted] to [redacted] and *m/z* [redacted] to [redacted] on an [redacted] instrument ([redacted]). The effective linear range of quantification was 2.00 to 5000 ng/mL.

In a further stage of the method validation, a stable isotope-labeled internal standard ([redacted], compound E*) was included in the method, and at the same time a more recent MS/MS instrumentation was used ([redacted] instrument, [redacted]). The injection volume was decreased (5 µL), and the multiple-reaction monitoring transitions for the internal standard were logically adapted to *m/z* [redacted] to [redacted].

The reported multiple-reaction monitoring settings were target values. However, for each individual trial, small adaptations to the instrument settings were allowed in order to optimize the assay performance for the analysis of trial samples.

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Table 3: Bioanalytical Assay Validation Characteristics for Determination of TMC125 in Plasma

Report No. (Location)	Method (Internal Standard)	Range of Quantification (ng/mL)	Recovery (%)	Compliance with Pre-specified Criteria		Permitted Dilution Ratio and Concentration	Specificity (Interfering Peaks)
				Accuracy	Precision		
[redacted]1846 (Module 5.3.1.4/ TMC125-[redacted]1846-AVR)	LC-MS/MS (compound C*)	2.00 to 5000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]3134 (Module 5.3.1.4/ TMC125-[redacted]3134-AVR)	LC-MS/MS (compound C*)	2.00 to 5000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]5151 (Module 5.3.1.4/ TMC125-[redacted]5151-AVR)	LC-MS/MS (compound C*)	2.00 to 5000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]5258 (Module 5.3.1.4/ TMC125-[redacted]5258-AVR)	LC-MS/MS (compound E*)	2.00 to 5000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]-RD-643 ([redacted]-040563) (Module 5.3.1.4/TMC125-[redacted]-RD-643	LC-MS/MS (compound D*, compound E*)	2.00 to 5000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ND = not determined.

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1.2.2 Stability of TMC125 in Human Heparin Blood and Human Heparin Plasma

Data on the stability of TMC125 in human heparin blood and human heparin plasma were obtained in 3 bioanalytical method validation trials, the results of which are summarized in Module 5.3.1.4/TMC125-NC331. Stability of TMC125 under a specific storage condition was concluded if the TMC125 concentration after storage deviated by a maximum of ± 15% from the original concentrations or ± 20% from the nominal concentrations in reference samples.

The stability of TMC125 in human heparin blood was tested for 2 hours at 0°C and at ambient temperature. No apparent deviations from the original TMC125 concentrations were observed under both conditions. Therefore, it was concluded that TMC125 was stable in human heparin blood after storage for up to 2 hours at 0°C and for up to 2 hours at ambient temperature.

The stability of TMC125 in human heparin plasma was tested for processed samples at room temperature, after repeated freeze/thaw cycles, after short-term storage in a refrigerator and on the bench, and after long-term storage in a freezer (approximately −20°C). No apparent deviations from the original TMC125 concentrations were observed, and it was therefore concluded that TMC125 was stable in human heparin plasma under the following storage conditions:

- Processed sample stability for up to 24 hours under regular autosampler conditions, and for up to 119 hours at 10°C;
- Freeze/thaw stability for up to 3 freeze/thaw cycles;
- Short-term stability for up to 24 hours in a refrigerator and for up to 24 hours on the bench at room temperature;
- Long-term stability for at least 34 months in a freezer.

1.2.3 Determination of Co-Administered Drugs in Plasma

In-trial validation of the assays for co-administered drugs was conducted for the individual trials, and validation data are included in the respective clinical research reports. An overview of the analytical methods employed for each trial is provided in Appendix 2.7.1.1.

The method validation reports for the methods used for quantitative determination of co-administered drugs in the clinical trials are available in Module 5.3.1.4.

1.2.4 Determination of TMC125 in Urine

In trial TMC125-C101 (refer to Module 2.7.2/Section 2.3.1), urine concentrations of TMC125 were determined using an exploratory non-validated LC-MS/MS method (refer to Module 5.3.1.4/TMC125-[redacted]1847-AVR). The analytical range of this assay was 2.00 to 5000 ng/mL. In this trial, the urine samples from subjects treated with the highest dosing levels (single doses of up to 1200 mg TMC125, administered as formulation T*) were close to the lower limit of quantification (LLOQ). In view of this minimal urinary excretion of TMC125, the bioanalytical assay for determination of TMC125 in urine was not developed further.

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1.3 OVERVIEW OF THE FORMULATION DEVELOPMENT PROCESS

1.3.1 Capsule Formulation Concepts

[redacted]

1.3.2 Tablet Formulation Concepts

[redacted]

1.3.2.1 SELECTION OF THE FORMULATION CONCEPT

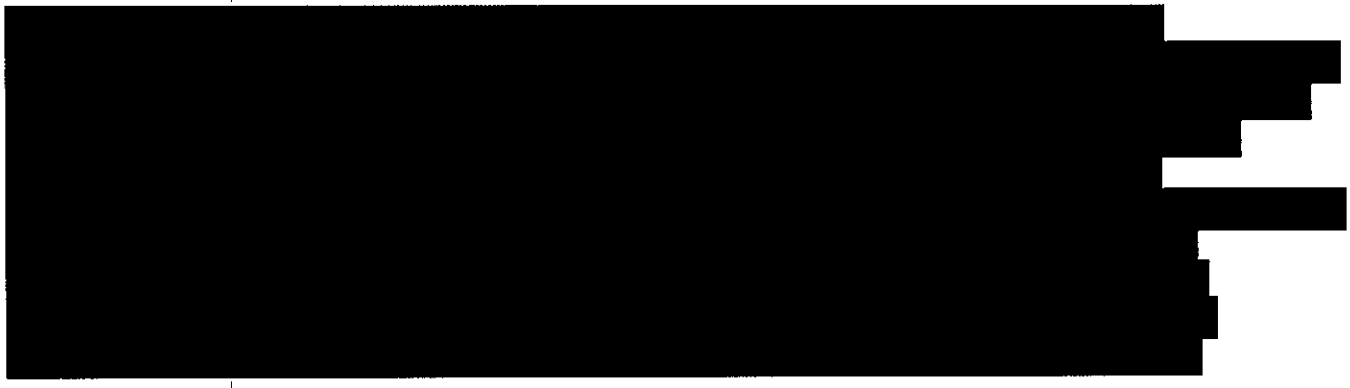
[redacted]

1.3.2.2 SELECTION OF THE COMPOSITION (TYPE OF POLYMER AND RATIO)

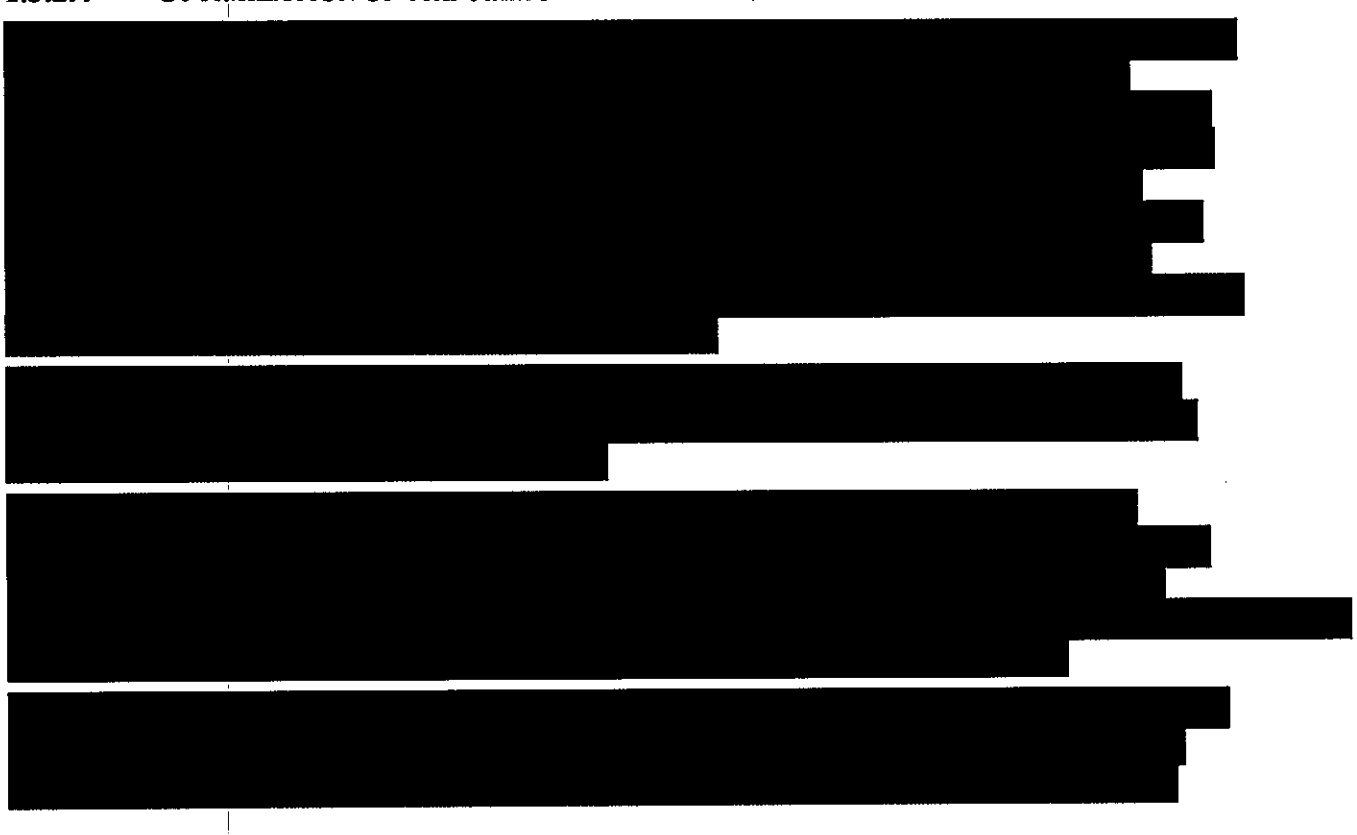
[redacted]

1.3.2.3 SELECTION OF THE MANUFACTURING TECHNOLOGY

[redacted]



1.3.2.4 Optimization of the Selected Tablet Formulation Concept



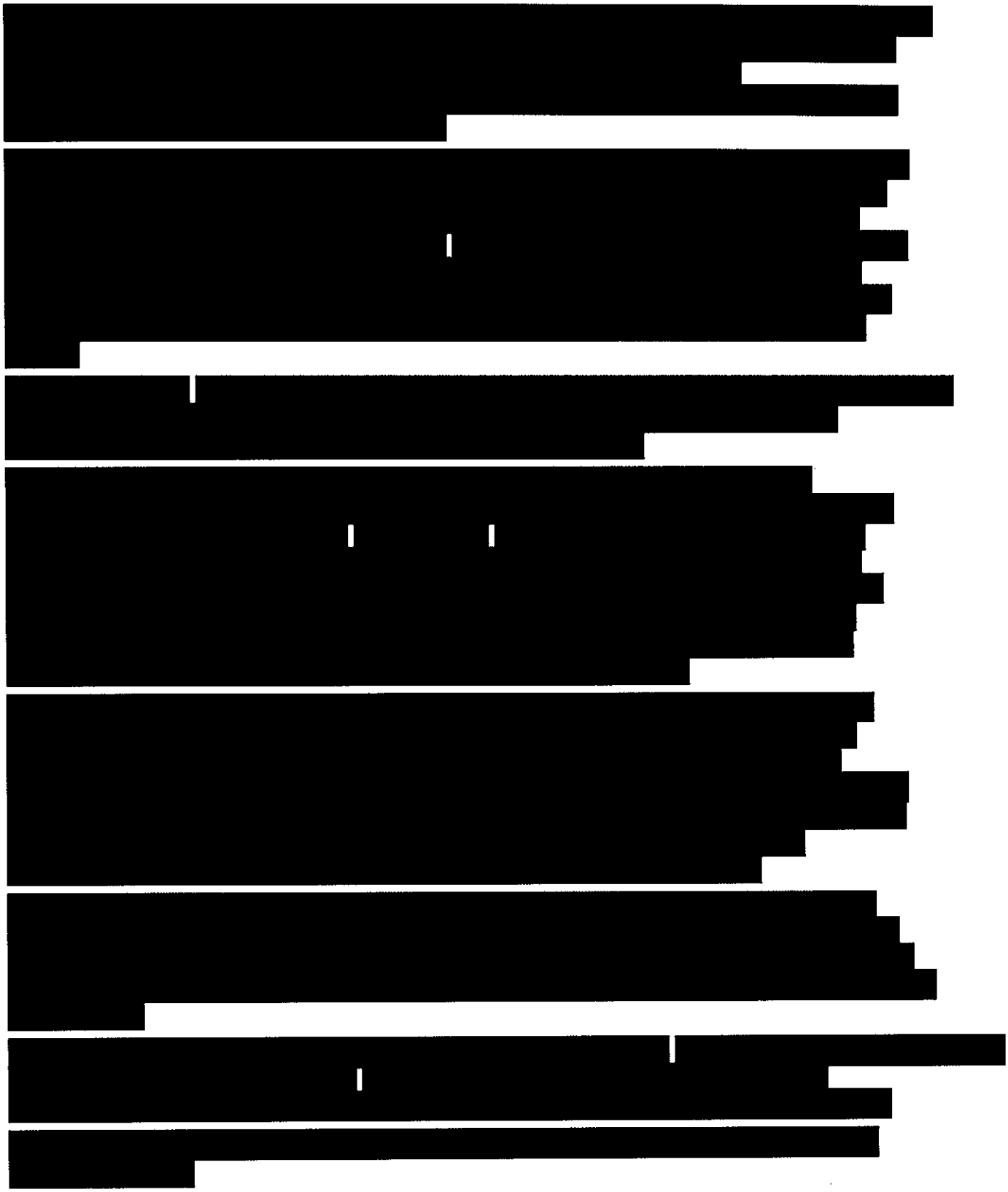


Table 4: Overview of TMC125 Oral Formulations Used in Completed and Ongoing Clinical Trials

Form #:* Formulation No. (Strength: TMC125 eq.)	Clinical Trial No.		
	• Pharmacokinetics in Healthy Subjects • Drug-Drug Interaction Pharmacokinetics • Food Effect	• Clinical Efficacy and Safety • Pharmacokinetics (Population and Full Profile) in HIV-1 Subjects	• Relative Bioavailability (Clinical Trials in Support of Formulation Development and Selection)
TMC125 in PEG 4000 (Capsule)			
Form T*(50 mg)	C101, C103, C104 [a], C105, C106, C109, C130 [b]	C207, C208	C102, C114
TMC125 in HPMC (Capsule)			
Form U* (100 mg)	-	-	C102
TMC125 in [redacted] (Capsule)			
Form V* (40 mg)	-	-	C102
TMC125.HBr (Capsule)			
Form W*(100 mg)	-	-	C114
TMC125.HBr in HPMC (Capsule)			
Form Y* (50 mg)	-	-	C114
Form E* (100 mg)	C112	-	C115
Form Z* (100 mg)	C128	-	-
TMC125.HBr in [redacted] (Capsule)			
Form a* (50 mg)	-	-	C114
TMC125.HBr as Granulate (Tablet)			
Form X* (100 mg)	-	-	C114
TMC125 in HPMC (Powder)			
Form D* (200 mg/g)	-	-	C115, C136
TMC125 in HPMC, Granulo-Layered (Tablet)			
Form C* (100 mg)	-	-	C115
Form S* (100 mg)	C133	C201	-
Form B* (200 mg)	-	-	C115, C142
Form F* (200 mg)	C111, C117, C122, C123, C137, C138, C139, C143, C145, C151, C153, C156, C157, C159, C161, C164, C165	C203, C209, C211 [c] (ongoing), C223, C227, C229 [c] (ongoing)	C141, C142, C146, C150, C155, C170, C228
Form N* (133 mg)	-	-	C155
TMC125 in HPMC, Spray-Dried (Tablet)			
Form J* (200 mg)	-	-	C150
Form K* (133 mg)	-	-	C150, C162
Form O* (200 mg)	-	-	C155
Form Q* (200 mg)	-	-	C146
Form G* (133 mg)	-	-	C146, C170
Form P* (200 mg)	-	-	C146
Form I* (100 mg)	-	-	C170

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Table 4: Overview of TMC125 Oral Formulations Used in Completed and Ongoing Clinical Trials, Cont'd

Form #:* Formulation No. (Strength: TMC125 eq.)	Clinical Trial No.		
	• Healthy Subject Pharmacokinetics • Drug-Drug Interaction Pharmacokinetics • Food Effect	• Clinical Efficacy and Safety • Population Pharmacokinetics • Patient Pharmacokinetics	• Relative Bioavailability (Clinical Trials in Support of Formulation Development and Selection)
FormA* (100 mg)	C116, C120, C125, C147, C158, C166, C168, C171, C174, C176, C177, C178	C206 (DUET-1, ongoing), C211 [c] (ongoing), C214 (ongoing), C216 (DUET-2, ongoing), C217 (ongoing), C229 [c] (ongoing)	C141, C162, C169, C170, C172, C228
Form H* (133 mg)	-	-	C170
TMC125 in HPMC, Spray-Dried (Powder)			
Form R* (200 mg/g)	-	-	C172
TMC125 in [redacted] Spray-Dried (Tablet)			
Form L*(200 mg)	-	-	C150
TMC125 in HPMC, Bead-Coated (Capsule)			
Form M* (200 mg)	-	-	C150

[a] Due to a problem with production of the drug product, the capsules used in this trial contained 43 mg instead of 50 mg TMC125.
[b] ^{14}C-labeled TMC125.
[c] Formulation F* was used initially, followed by a switch to formulation A*.

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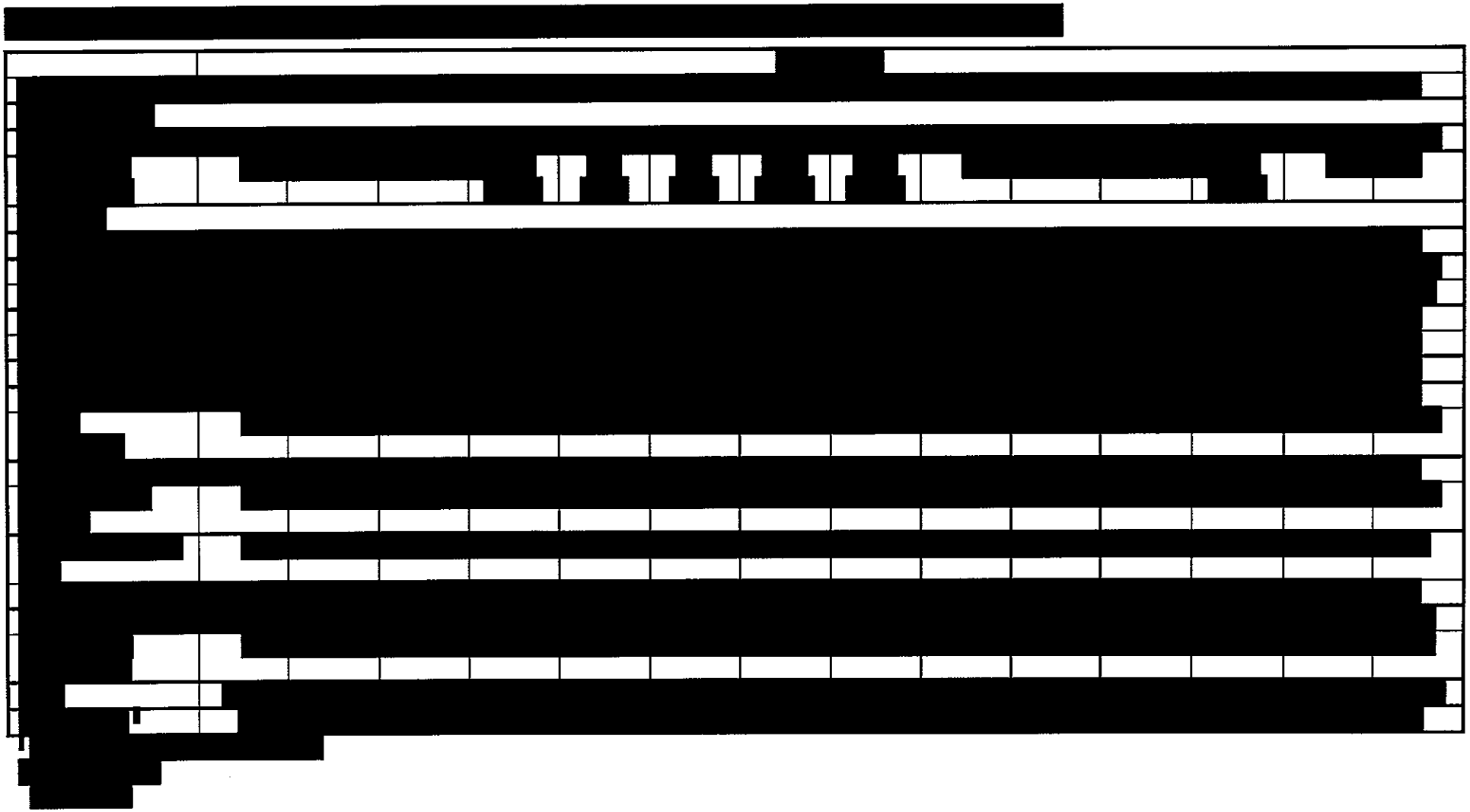


1.4 IN VITRO AND IN VIVO DOSAGE FORM PERFORMANCE

1.4.1 In Vitro Dissolution Data

1.4.1.1 OVERVIEW

[redacted]

1.4.1.2 DISSOLUTION EVALUATION METHOD AND SPECIFICATION FOR TMC125 TABLETS

1.4.1.2.1 Bio-relevant Dissolution Method

[redacted]

[redacted]

1.4.1.2.2 Quality Control Dissolution Method

[redacted]

[redacted]

[redacted]

[redacted]

1.4.1.2.3 Discriminative Power of the Quality Control Dissolution Method

[redacted]

[redacted]

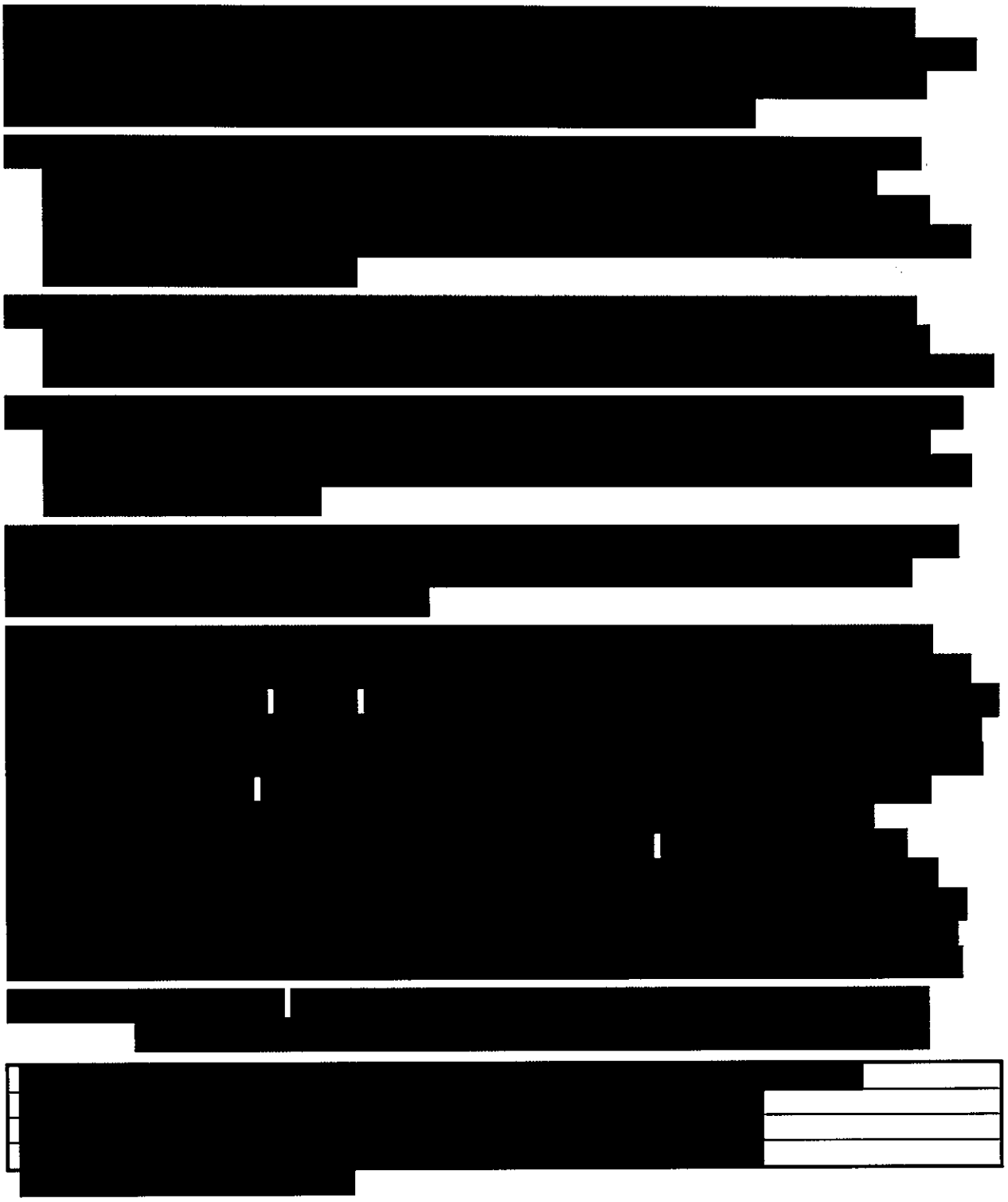
[redacted]

[redacted]

[redacted]

1.4.1.3 Dissolution Profiles of TMC125 Tablet Formulation A* - Effect of Manufacturing Site and Scale-Up

[redacted]



1.4.2 Clinical Biopharmaceutic Trials

1.4.2.1 Relative Bioavailability of Different Oral Formulation Types

Relative bioavailability trials were conducted to compare the systemic exposure of TMC125 after the administration of different oral formulation concepts used during the clinical development of TMC125. These trials included investigations with different experimental formulation concepts developed in the search for an oral dosage form with an acceptable bioavailability and/or drug load, and investigations conducted in the course of optimizing the selected tablet formulation concept to be used for further clinical development of TMC125 (TMC125 in HPMC, spray-dried). Unless mentioned otherwise, the trial medication was administered following a meal, and exposure (as a measure of bioavailability) refers to the mean AUC.

1.4.2.1.1 Testing of Experimental Formulations

Healthy Subjects

For later Phase I and II clinical trials, the capsule formulation of TMC125 in PEG 4000 (formulation T*) used in earlier trials (Section 3.2.3) was replaced by 100- and 200-mg tablet formulations of TMC125 in HPMC manufactured using granulo-layering technology (formulations S*, B*, and F*). Formulation T* and the granulo-layered tablets were not directly compared in clinical trials.

Because of the relatively high dose and pill burden that needed to be administered with the granulo-layered tablets, further formulation development focused on increasing the bioavailability and/or increasing the drug load while maintaining a robust stability profile (Section 1.3).

The bioavailabilities of 3 test formulations of TMC125 in HPMC (2 tablet formulations [formulations B* and C*] and a powder formulation [formulation D*]) were approximately 30% to 50% lower than the bioavailability of a capsule formulation of TMC125.HBr in HPMC (formulation E*) (trial TMC125-C115, Section 2.1.1). Although the capsule formulation of TMC125.HBr in HPMC (formulation E*) had

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the highest relative bioavailability, this formulation concept was not developed further due to potential stability and manufacturing issues with formulations containing the HBr salt.

The superiority of the spray-drying technique over granulo-layering was confirmed by trial TMC125-C155 (Section 2.2.2), in which the bioavailability of TMC125 administered as tablet formulation O* (TMC125 in HPMC, spray-dried) and tablet formulation N* (TMC125 in HPMC, granulo-layered) was compared. Compared to the test formulation F*, the mean exposure was 1.96-fold higher with formulation N* and 3.66-fold higher with formulation O*.

The bioavailability of 4 test spray-dry formulations (formulations G*, A*, H* and I*), which all had a TMC125 to HPMC ratio of [redacted] but varied in terms of the excipient composition, tablet compression, and the presence or absence of a [redacted] was 4.92- (formulation I*) to 9.37- (formulation A*) fold higher than for the reference tablet formulation F* (TMC125 in HPMC, granulo-layered), and the largest inter-subject variability occurred with formulation F* (trial TMC125-C170, Section 2.1.3).

Based on the results of these trials, formulation A*, which had the highest bioavailability of the spray-dried tablet formulations tested, was selected for use in planned clinical trials, including the registrational Phase III trials (TMC125-C206 [DUET-1] and TMC125-C216 [DUET-2]).

HIV-1 Infected Subjects

A comparison of data from earlier trials in which TMC125 was administered as formulations T* and F* indicated that HIV-1 infected subjects tended to have lower exposures to TMC125 than healthy subjects (refer to Module 2.7.2/Section 3.7). Therefore, the applicability of the increase in bioavailability of formulation A*, compared to formulation F*, demonstrated in healthy subjects in trial TMC125-C170 (Section 2.1.3) was investigated in the relevant target population of HIV-1 infected subjects.

In trial TMC125-C141 (Section 2.1.4), the mean exposure to TMC125 after single-dose administration of 100 mg TMC125 as formulation A* was comparable to the exposure (AUC_{last}) obtained with 800 mg TMC125 as formulation F*. For 200 mg TMC125 as formulation A* the ratio was 1.11, compared to 1600 mg TMC125 as formulation F*. For 300 mg TMC125 as formulation A* the ratio was 2.13, 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*, with the increase in exposure with 2400 mg TMC125 as formulation F* being less than dose proportional.

Because the results of trial TMC125-C141 indicated that administration of a single 800 mg dose of TMC125 with formulation F* (the selected dose based on 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 (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.

In contrast to trial TMC125-C141, the mean exposure (AUC_{12h}) to TMC125 in trial TMC125-C228 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 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*, 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. It was of note, though, that the mean exposure (AUC_{12h}) to TMC125 on Day 8 after administration of 800 mg b.i.d. as formulation F* in trial TMC125-C228 (2607 ng.h/mL) was lower than seen for the same dose in the Phase IIb trials TMC125-C203/TMC125-C209 (3589 ng.h/mL, Module 2.7.2/Section 2.6.2.2) and TMC125-C223 (9189 ng.h/mL, Module 2.7.2/Section 2.6.2.3) in HIV-1 infected subjects after 4 weeks of dosing.

Thus, TMC125 administered as formulation A* 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. The pharmacokinetic parameters showed considerable inter-individual variability for all treatments, but less variability with formulation A* than with formulation F*. An exploratory analysis to investigate whether this increase in exposure was homogenous across individual subjects 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 18). 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-individual variability with the 200 mg b.i.d. dose of formulation A*.

Overall, the results of trial TMC125-C228 showed that a 200-mg b.i.d. dose of TMC125 with formulation A* provides an exposure to TMC125 that is comparable to that provided by an 800-mg dose of TMC125 with formulation F*, with the latter dose previously having demonstrated substantial and sustained efficacy in the Phase IIb dose-escalating trial TMC125-C203 (Module 2.7.2/Section 2.6.2.1) and the dose-finding trial TMC125-C223 (Module 2.7.2/Section 2.6.2.3).

On this basis, a TMC125 dosing regimen of 200 mg b.i.d. with formulation A* was selected for use in all ongoing and planned clinical trials as this was expected to provide an exposure to TMC125 that was comparable to that provided by the 800 mg b.i.d. dosing regimen with formulation F*.

The comparability between the range of exposure to TMC125 in HIV-1 infected subjects observed with the 200 mg b.i.d. dose of formulation A* and the 800 mg b.i.d. dose of formulation F* was further supported by a pharmacokinetic substudy of trial TMC125-C229 (Module 2.7.2/Section 2.6.2.5), as shown in Figure 31 for individual AUC_{12h} values, and a comparison between population pharmacokinetic estimates obtained after administration of TMC125 as formulations F* and A* in Phase IIb and III trials, respectively (Module 2.7.2/Section 3.6.1).

1.4.2.1.2 Optimization of Selected Tablet Formulation

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[redacted]

1.4.2.2 CONCOMITANT FOOD INTAKE

The effect of concomitant food intake on the bioavailability of TMC125 when administered as tablet formulation A* (the spray-dried tablet formulation of TMC125 in HPMC selected for use in the registrational Phase III trials) was investigated in 2 trials. In each trial (TMC125-C147 and TMC125-C116) the effect of concomitant food intake was evaluated by administering TMC125 10 minutes after a standardized breakfast, consisting of 4 slices of bread, 2 slices of ham or cheese, butter, jelly and 2 cups of coffee or tea with milk and/or sugar, if desired, compared to administration either under fasted conditions (trial TMC125-C147) or before the standardized breakfast (trial TMC125-C116). In addition, trial TMC125-C147 investigated the effect of 4 different types of meals (see below) on the bioavailability of TMC125.

The mean exposure (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, 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, 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 mean exposure (AUC_{last}) to TMC125 was comparable when administered after a standardized breakfast and a high-fat breakfast. When administered after a snack (croissant with coffee or tea), the mean AUC_{last} for TMC125 was 20% lower than when administered after a standardized breakfast, but the mean maximum plasma concentration (C_{max}) was unaffected. Overall, the differences in exposure to TMC125 when taken with a high-fat breakfast, a standardized breakfast, or a snack were not considered to be clinically relevant. In contrast, administration of TMC125 after an enhanced-fiber breakfast (16.4 g fiber, compared to 8.1 g fiber in the standardized breakfast) resulted in 38% decrease in mean C_{max} and a 25% decrease in mean AUC_{last}, compared to administration after the standardized breakfast.

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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.

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2 SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

The relative bioavailability trials presented in this Summary of Biopharmaceutic Studies are organized into 4 groups.

The first group of trials (summarized in Section 2.1) involved testing of various experimental formulations of TMC125 in the search for an oral formulation concept with a higher oral bioavailability and/or drug load than the PEG 4000-based capsule (formulation T*) used in early Phase I and Phase IIa clinical trials. Based upon the results of these trials, a spray-dried tablet formulation concept was selected for further development.

The second group of trials (summarized in Section 2.2) involved testing of various experimental formulations of TMC125 during the process of optimizing the spray-dried tablet formulation concept selected for further development.

The third group of trials (summarized in Section 2.3) investigated the effect of administering various formulations of TMC125 under fed and fasted conditions.

A fourth group of trials (summarized in Appendix 2.7.1.3) involved testing of early oral formulation concepts that were not developed further. As these formulation concepts contributed no relevant pharmacokinetic data in the light of the spray-dried tablet formulation concept being selected for further development, these results are discussed only briefly in Section 3.2.3.

2.1 RELATIVE BIOAVAILABILITY TRIALS - TESTING OF EXPERIMENTAL FORMULATIONS

2.1.1 Trial TMC125-C115: Relative Bioavailability of TMC125 Given as Tablet Formulations B* or C* (TMC125 in HPMC, Granulo-Layered), or as Powder Formulation D* (TMC125 in HPMC), Compared to Reference Capsule Formulation E* (TMC125.HBr in HPMC), in Healthy Subjects

2.1.1.1 TRIAL DESIGN

This was an open-label, randomized, controlled, parallel-group, 2-period crossover trial to investigate the relative bioavailability of 3 experimental formulations of TMC125 in HPMC (2 tablet formulations differing in strength, and a powder formulation) compared to a capsule formulation of TMC125.HBr in HPMC. The trial population consisted of 24 healthy subjects. Each subject received a single, oral, 400-mg base-equivalent dose of TMC125 on 2 occasions. In each of 2 sessions, 12 of the 24 subjects received the reference formulation (Treatment A) and 3 groups of 4 subjects received the different test formulations (Treatments B, C, or D), as follows:

- Treatment A (reference): 4 capsules (formulation E*), each containing 100 mg base-equivalent of TMC125.HBr in HPMC;
- Treatment B (test): 2 tablets (formulation B*), each containing 200 mg TMC125 base in HPMC, granulo-layered;
- Treatment C (test): 2 g powder for suspension (formulation D*), each gram containing 200 mg TMC125 base in HPMC;

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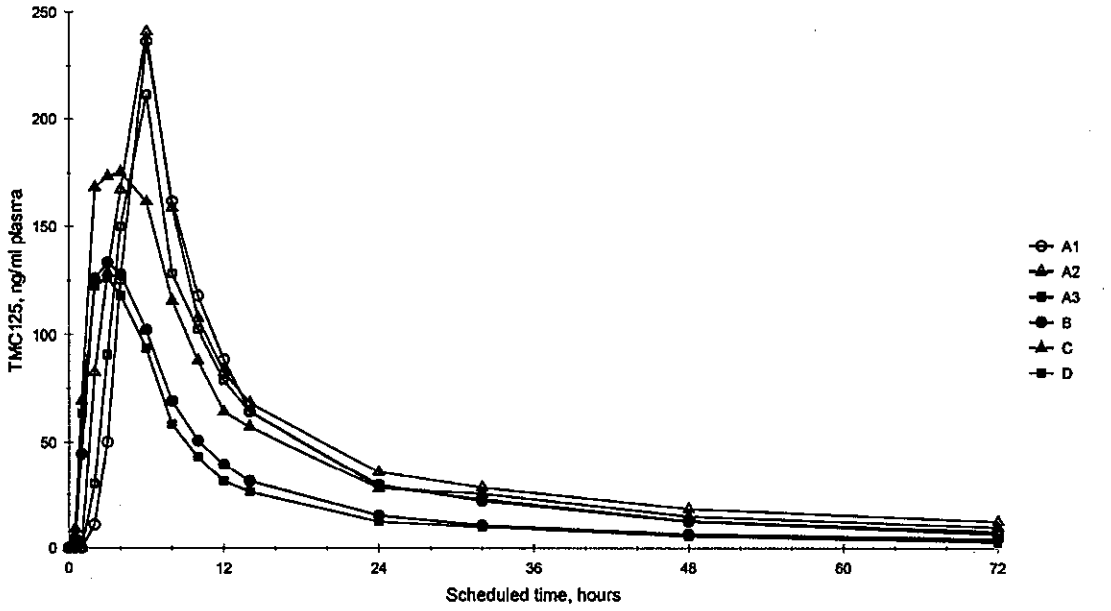
- Treatment D (test): 4 tablets (formulation C*), each containing 100 mg TMC125 base in HPMC, granulo-layered.

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

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.1.2/TMC125-C115).

2.1.1.2 PHARMACOKINETICS OF TMC125

For all formulations, 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 10). However, the mean maximum plasma concentrations were lower with all 3 test formulations than with the reference formulation.



Treatment A1: Reference Treatment A (formulation E*) for Treatment B (formulation B*).
Treatment A2: Reference Treatment A (formulation E*) for Treatment C (formulation D*).
Treatment A3: Reference Treatment A (formulation E*) for Treatment D (formulation C*).
N = 8 for all treatments.
Source: Module 5.3.1.2/TMC125-C115/Section 6.1/Supporting Data Display 10

Figure 10: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of Three Test Formulations of TMC125 in HPMC (formulations B*, D*, or C*) and a Reference Formulation of TMC125.HBr in HPMC (formulation E*) at a Single Dose of 400 mg (Trial TMC125-C115)

The median time to reach the maximum plasma concentration (t_{max}) values for the TMC125 test formulations (Treatments B, C, and D) were shorter, ranging from 3 to 4 hours, than the median value for the TMC125.HBr reference formulation (6 hours, Treatment A) (Table 7). Mean C_{max} and AUC values for the test formulations were approximately 30% to 50% lower than the corresponding values for the reference formulation. The inter-individual variability within each of the test formulations was comparable to the variability within the reference formulation

(Module 5.3.1.2/TMC125-C115/Section 4.2.5). There were no relevant differences between the mean elimination half-lives of the test and reference formulations.

Table 7: Pharmacokinetics of TMC125 after Administration of Three Test Formulations of TMC125 in HPMC (formulations B*, D*, or C*) and a Reference Formulation of TMC125.HBr in HPMC (formulation E*) at a Single Dose of 400 mg (Trial TMC125-C115)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment A: TMC125 400 mg (formulation E*) (Reference)	Treatments B, C, and D: TMC125 400 mg (formulations B*,D*, or C*) (Test)		
Treatment A (formulation E*) vs. Treatment B (formulation B*)				
N	8	8		
t_{max}, h	6.0 (4.0 - 10.0)	3.5 (2.0 - 6.0)	-	-
C_{max}, ng/mL	245.5 ± 121.5	143.5 ± 62.61	0.59	0.45 - 0.77
AUC_{last}, ng.h/mL	2667 ± 1250	1630 ± 622.8	0.62	0.50 - 0.79
AUC_{∞} [b], ng.h/mL	2889 ± 1377	1828 ± 704.3	0.65	0.50 - 0.85
$t_{1/2,term}$ [b], h	21.87 ± 3.665	27.79 ± 9.674	-	-
Treatment A (formulation E*) vs. Treatment C (formulation D*)				
N	8	8		
t_{max}, h	6.0 (4.0 - 6.0)	4.0 (2.0 - 6.0)	-	-
C_{max} (ng/mL)	277.8 ± 181.6	199.5 ± 173.5	0.61	0.41 - 0.92
AUC_{last} (ng.h/mL)	3200 ± 2569	2803 ± 3201	0.71	0.49 - 1.03
AUC_{∞} [b] (ng.h/mL)	3942 ± 3896	3326 ± 4248	0.70	0.49 - 1.01
$t_{1/2,term}$ [b], h	28.39 ± 10.83	23.51 ± 8.389	-	-
Treatment A (formulation E*) vs. Treatment D (formulation C*)				
N	8	8		
t_{max}, h	6.0 (3.0 - 6.0)	3.0 (2.0 - 6.0)	-	-
C_{max} (ng/mL)	242.2 ± 138.0	150.1 ± 123.0	0.53	0.24 - 1.16
AUC_{last} (ng.h/mL)	2619 ± 1619	1444 ± 1018	0.51	0.24 - 1.10
AUC_{∞} [b] (ng.h/mL)	2934 ± 1896	1745 ± 1080	0.52	0.20 - 1.31
$t_{1/2,term}$ [b], h	24.15 ± 4.032	23.11 ± 5.020	-	-

N = maximum number of subjects with data.
[a] Ratio based on geometric means.
[b] Accurate determination not possible in all subjects.
Source: Module 5.3.1.2/TMC125-C115/Section 4.2.5 and Section 4.2.6

2.1.1.3 CONCLUSIONS

The 3 test formulations of TMC125 in HPMC (formulations B*, D*, and C*) differed from the reference formulation of TMC125.HBr in HPMC (formulation E*) in the rate and extent of TMC125 absorption. The mean exposures (AUC_{last}) to TMC125 with the test formulations were approximately 30% to 50% lower than the mean exposure with the reference formulation. Although the capsule formulation of TMC125.HBr in HPMC (formulation E*) had the highest bioavailability, this formulation concept was not developed further due to potential stability and manufacturing issues with formulations containing the HBr salt. The tablet formulation B* was tested further.

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2.1.2 Trial TMC125-C142: Relative Bioavailability of TMC125 Given as Two Batches of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) and as Tablet Formulation B* (TMC125 in HPMC, Granulo-Layered) in Healthy Subjects

2.1.2.1 Trial Design

This was an open-label, randomized, 3-period crossover trial to investigate the relative bioavailability of two 200-mg tablet formulations of TMC125 (formulation F*, Batches 1 and 2, and formulation B*) (all TMC125 in HPMC, granulo-layered). The 2 batches of formulation F* were produced in different manufacturing runs. Formulation F* is an optimized formulation of formulation B*, with both formulations containing formulation D* as the intermediate powder. The total weight of formulation B* is 1400 mg while that of formulation F* is only 1300 mg.

The trial population consisted of 18 healthy subjects. Each subject received a single, oral, 400-mg dose of TMC125 on 3 occasions. In each of 3 sessions, subjects received Treatment A, B, or C, as follows:

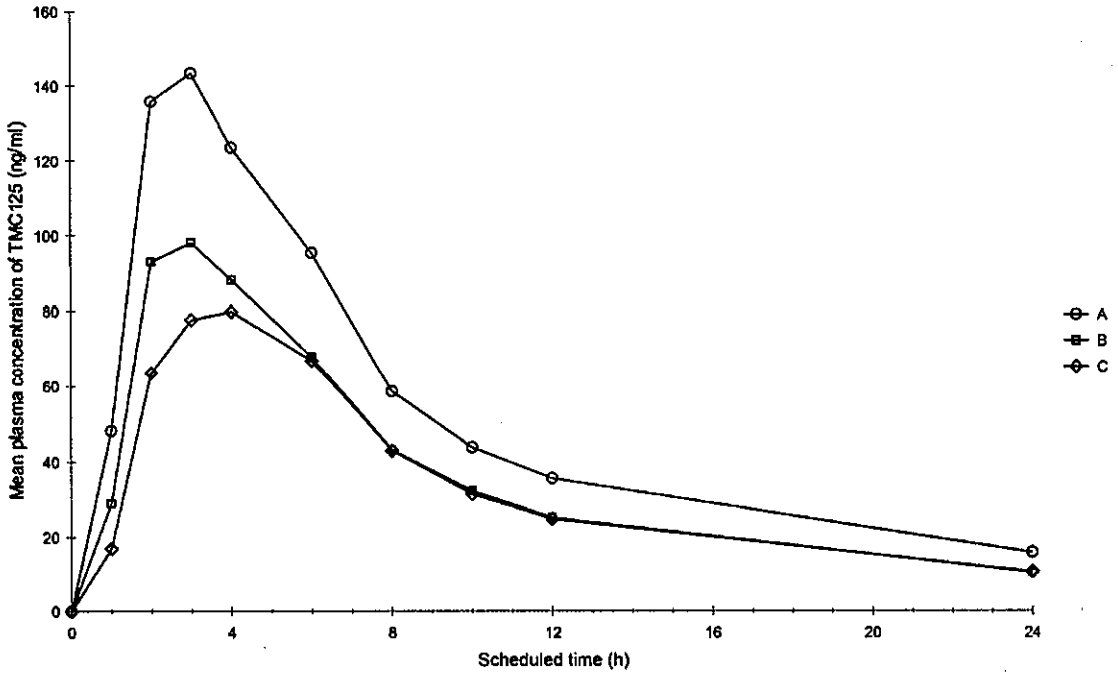
- Treatment A: 2 tablets (formulation F* , Batch 1 [L129]), each containing 200 mg TMC125 base in HPMC, granulo-layered;
- Treatment B: 2 tablets (formulation F*, Batch 2 [L130]), each containing 200 mg TMC125 base in HPMC, granulo-layered;
- Treatment C: 2 tablets (formulation B*), each containing 200 mg TMC125 base in HPMC, granulo-layered.

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

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.1.2/TMC125-C142).

2.1.2.2 Pharmacokinetics of TMC125

The mean plasma-concentration profiles showed a rapid absorption with both formulations, followed by 2 distinct distribution/elimination phases (Figure 11).



Treatment A: formulation F* Batch 1 (N = 17).
Treatment B: formulation F* Batch 2 (N = 17).
Treatment C: formulation B* (N = 17).
Source: Module 5.3.1.2/TMC125-C142/Section 4.2.4

Figure 11: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of Tablet Formulations F* (Batches 1 and 2; TMC125, Granulo-Layered) and B* (TMC125 in HPMC, Granulo-Layered) at a Single Dose of 400 mg (Trial TMC125-C142)

Comparing the 2 different batches of formulation F*, approximately 20% lower mean C_{max} and AUC values were observed for Batch 2 compared to Batch 1 (Table 8). The 90% confidence intervals (CIs) of the LS means ratios were outside the range of 80% to 125%.

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Table 8: Pharmacokinetics of TMC125 after Administration of Two Different Batches of Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at a Single Dose of 400 mg (Trial TMC125-C142)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment A: TMC125 400 mg formulation F* Batch 1 (Reference)	Treatment B: TMC125 400 mg formulation F* Batch 2 (Test)		
N	17	17		
t_{max}, h	2.0 (1.0 - 6.0)	3.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	160 ± 121	113 ± 65.3	0.82	0.66 - 1.02
AUC_{last}, ng.h/mL	1703 ± 1433	1155 ± 814	0.81	0.68 - 0.95
AUC_{∞}, ng.h/mL	2001 ± 1893	1321 ± 979	0.81	0.69 - 0.95
$t_{1/2,term}$, h	27.5 ± 10.3	26.8 ± 8.40	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.1.2/TMC125-C142/Section 4.2.5 and Section 4.2.6

The mean C_{max} and AUC_{last} of TMC125 with formulation B* were 33% and 28% lower, respectively, compared to formulation F* Batch 1, and 21% and 15% lower, respectively, compared to formulation F*Batch 2 (Table 9). The 90% CIs of the LS means ratios were outside the range of 80% to 125% for AUC and C_{max}.

Individual C_{max} values for TMC125 were achieved between 1 and 6 hours after dosing. The fastest absorption was seen with formulation F* Batch 1 and the slowest with formulation B*. The mean terminal elimination half-lives for TMC125 were longer with the formulations F*(approximately 27 hours) than with formulation B* (22.5 hours).

Table 9: Pharmacokinetics of TMC125 after Administration of Tablet Formulations F* (Batches 1 and 2; TMC125, Granulo-Layered) and B* (TMC125 in HPMC, Granulo-Layered) at a Single Dose of 400 mg (Trial TMC125- C142)

Parameter	Mean ± SD; t_{max}: Median (Range) Treatment A or B: TMC125 400 mg formulation F* Batch 1 or Batch 2 (Reference)	Mean ± SD; t_{max}: Median (Range) Treatment C: TMC125 400 mg formulation B* (Test)	Ratio [a] (Test:Reference)	90% CI
Treatment A (formulation F* Batch 1) vs. Treatment C (formulation B*)				
N	17	17		
t_{max}, h	2.0 (1.0 - 6.0)	4.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	160 ± 121	93.6 ± 64.5	0.67	0.49 - 0.92
AUC_{last}, ng.h/mL	1703 ± 1433	1049 ± 923	0.72	0.54 - 0.96
AUC_{∞} [b], ng.h/mL	2001 ± 1893	1236 ± 1181	0.74	0.56 - 0.97
$t_{1/2,term}$ [b], h	27.5 ± 10.3	22.5 ± 10.0	-	-
Treatment B (formulation F* Batch 2) vs. Treatment C (formulation B*)				
N	17	17		
t_{max}, h	3.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	113 ± 65.3	93.6 ± 64.5	0.79	0.59 - 1.06
AUC_{last}, ng.h/mL	1155 ± 814	1049 ± 923	0.85	0.65 - 1.12
AUC_{∞} [b], ng.h/mL	1321 ± 979	1236 ± 1181	0.86	0.67 - 1.11
$t_{1/2,term}$ [b], h	26.8 ± 8.40	22.5 ± 10.0	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
[b] Accurate determination not possible in all subjects.
Source: Module 5.3.1.2/TMC125-C142/Section 4.2.5 and Section 4.2.6

2.1.2.3 CONCLUSIONS

The mean exposure (AUC_{last}) to TMC125 was 19% lower with formulation F* Batch 2, compared to formulation F* Batch 1. The mean exposure (AUC_{last}) with formulation B* was 28% and 15% lower than the exposure with formulation F* Batch 1 and Batch 2, respectively.

2.1.3 Trial TMC125-C170: Relative Bioavailability of TMC125 Given as Tablet Formulations G*, A*, H*, and I* (TMC125 in HPMC, Spray-Dried), Compared to Reference Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered), in Healthy Subjects

2.1.3.1 TRIAL DESIGN

This was an open-label, randomized, 2-period crossover trial to investigate the relative bioavailability of 4 tablet formulations of TMC125 in HPMC manufactured using spray-drying technology (formulation G*, A*, H*, and I*) compared to a tablet formulation of TMC125 in HPMC manufactured using granulo-layering technology (formulation F*). Formulations G*, A*, H*, and I* all had a TMC125 to HPMC ratio of [redacted], but varied in terms of the excipient composition and the presence or absence of a [redacted] (Table 5).

The trial population consisted of 45 healthy subjects. Each subject received a single, oral, 400-mg dose of TMC125 on 2 occasions. In each of 2 sessions, the 4 groups of subjects received

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either the reference formulation (Treatment A) or one of the 4 different test formulations (Treatments B, C, D, or E), as follows:

- Treatment A (reference): 2 tablets (formulation F*), each containing 200 mg TMC125 in HPMC, granulo-layered;
- Treatment B (test): 3 tablets (formulation G*), each containing 133 mg TMC125 in HPMC, spray-drie (TMC125 to HPMC ratio of [redacted]);
- Treatment C (test): 4 tablets (formulation A*), each containing 100 mg TMC125 in HPMC, spray-drie (TMC125 to HPMC ratio of [redacted]);
- Treatment D (test): 3 tablets (formulation H*), each containing 133 mg TMC125 in HPMC, spray-drie (TMC125 to HPMC ratio of [redacted]);
- Treatment E (test): 4 tablets (formulation I*), each containing 100 mg TMC125 in HPMC, spray-dried (TMC125 to HPMC ratio of [redacted]).

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

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.1.2/TMC125-C170).

2.1.3.2 PHARMACOKINETICS OF TMC125

The mean plasma concentration-time profiles of all 4 test spray-dried tablet formulations (Treatments B, C, D, and E) were higher than the profile of the reference granulo-layered tablet formulation (Treatment A) (Figure 12).

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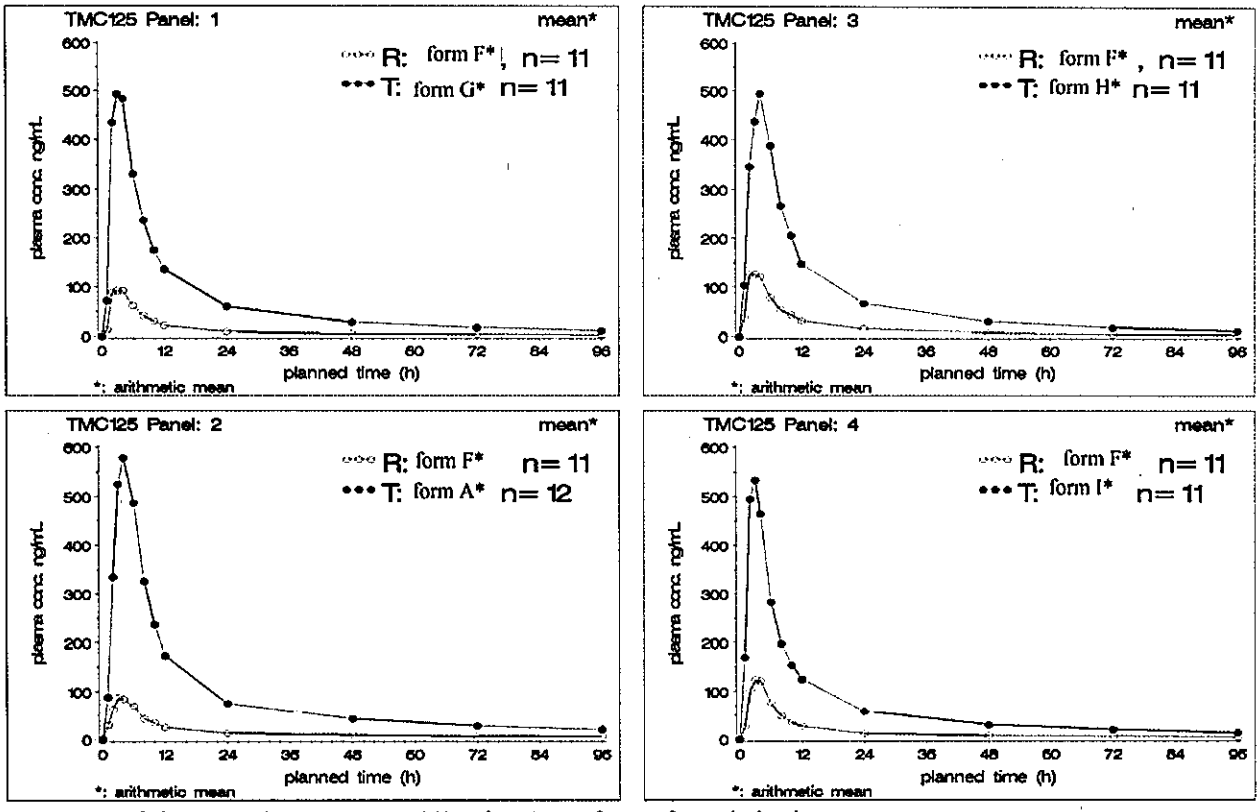

Source: Module 5.3.1.2/TMC125-C170/Section 4.2.4 form : formulation*

Figure 12: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of Four Test Spray-Dried Tablet Formulations of TMC125 in HPMC (formulation G*, A*, H*, and I*) and a Reference Granulo-Layered Tablet Formulation of TMC125 in HPMC (formulation F*) at a Single Dose of 400 mg (Trial TMC125-C170)

The mean C_{max} and AUC values for all 4 test formulations (Treatments B, C, D, and E) were considerably higher than the corresponding values for the reference formulation (Treatment A) (Table 10). The AUC_{last} values for test formulations G*, A*, H*, and I* were 6.78-, 9.37-, 6.96-, and 4.92-fold higher than for the reference formulation (formulation F*). The median t_{max} and mean elimination half-life values were comparable between the test and reference formulations.

Although not directly compared, [redacted] the tablets appeared to reduce the bioavailability of TMC125 relative to [redacted] tablets. The mean AUC_{last} values with the [redacted] tablet formulations G* and I* were 6.78- and 4.92-fold higher, respectively, than with formulation F*, whereas the mean AUC_{last} values for [redacted] tablet formulations A* and H* were 9.37- and 6.96-fold higher, respectively, than with formulation F* (Table 10).

C_{max} and AUC parameters showed considerable inter-individual variability in all treatment groups. In general, relatively large coefficients of variation (CVs) were observed for the reference (granulo-layered) tablet formulation, compared to the test (spray-dried) tablet formulations. The CV for AUC_{last} in the 4 panels for the reference formulation ranged from 55% to 92%, compared to 31% to 55% for the test formulations (Module 5.3.1.2/TMC125-C170/Section 6/Supporting Data Display 9).

Table 10: Pharmacokinetics of TMC125 after Administration of Four Test Spray-Dried Tablet Formulations of TMC125 (formulation G*, A*, H*, and I*) and a Reference Granulo-Layered Tablet Formulation of TMC125 in HPMC (formulation F*) at a Single Dose of 400 mg (Trial TMC125-C170)

Parameter	Mean ± SD; t_{max}: Median (Range) Treatment A: TMC125 400 mg (formulation F*) (Reference)	Mean ± SD; t_{max}: Median (Range) Treatments B, C, D, or E: TMC125 400 mg (formulation G*, A*, H*, I*) (Test)	Ratio [a] (Test:Reference)	90% CI
Treatment A (formulation F*) vs. Treatment B (formulation G*)				
N	11	11		
t_{max}, h	3.0 (2.0 - 4.0)	3.0 (2.0 - 4.0)	-	-
C_{max}, ng/mL	103 ± 49	530 ± 254	5.39	3.76 - 7.72
AUC_{last}, ng.h/mL	1080 ± 598	6535 ± 3283	6.78	4.79 - 9.59
AUC_{∞}, ng.h/mL	1198 ± 659	7132 ± 3967	6.52	4.71 - 9.03
$t_{1/2,term}$, h	25.3 ± 12.9	29.6 ± 8.3	-	-
Treatment A (formulation F*) vs. Treatment C (formulation A*)				
N	11	12		
t_{max}, h	4.0 (2.0 - 8.0)	4.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	100 ± 77	638 ± 213	8.47	5.33 - 13.48
AUC_{last}, ng.h/mL	1270 ± 1056	8482 ± 2823	9.37	6.03 - 14.55
AUC_{∞}, ng.h/mL	1540 ± 1346	9936 ± 4531	8.93	5.79 - 13.76
$t_{1/2,term}$, h	31.2 ± 22.8	39.3 ± 16.9	-	-
Treatment A (formulation F*) vs. Treatment D (formulation H*)				
N	11	11		
t_{max}, h	3.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	146 ± 108	512 ± 140	4.75	3.17 - 7.14
AUC_{last}, ng.h/mL	1506 ± 1380	6953 ± 2184	6.96	4.40 - 11.01
AUC_{∞}, ng.h/mL	1606 ± 1427	7571 ± 2676	6.69	4.38 - 10.22
$t_{1/2,term}$, h	19.5 ± 8.1	29.8 ± 10.7	-	-
Treatment A (formulation F*) vs. Treatment E (formulation I*)				
N	11	11		
t_{max}, h	3.0 (2.0 - 4.0)	2.0 (2.0 - 4.0)	-	-
C_{max}, ng/mL	135 ± 60	560 ± 213	4.18	3.28 - 5.34
AUC_{last}, ng.h/mL	1388 ± 830	6458 ± 3536	4.92	3.71 - 6.53
AUC_{∞}, ng.h/mL	1549 ± 950	7177 ± 4321	4.80	3.64 - 6.33
$t_{1/2,term}$, h	27.9 ± 15.1	32.5 ± 8.9	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.1.2/TMC125-C170/Section 4.2.5 and Section 4.2.6

An exploratory post-hoc analysis of the individual data showed that subjects with relatively low concentrations of TMC125 after administration of reference formulation F* had relatively high values for the test to reference ratio of AUC_{last} (Figure 13). Thus, in a given individual, the plasma concentrations of TMC125 were generally higher with the test formulation if the plasma concentrations obtained with the reference formulation F* were low.

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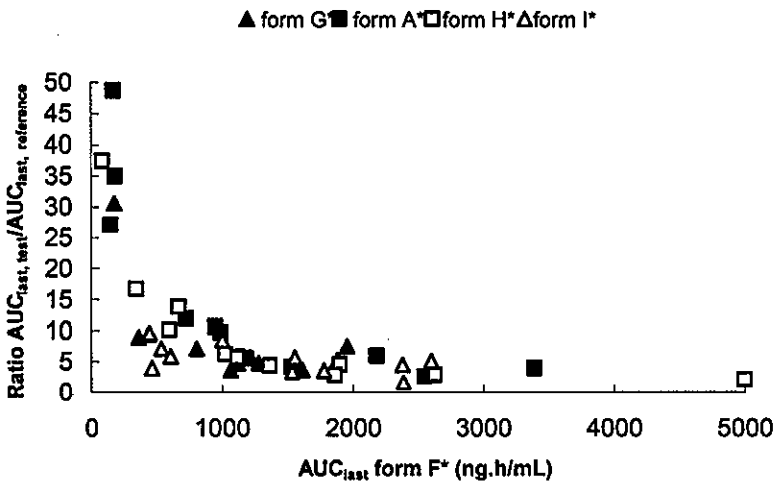

form: formulation *

Source: Module 5.3.1.2/TMC125-C170/Section 4.2.5

Figure 13: Individual Test to Reference Ratios of AUC_{last} for TMC125 after Administration of Four Test Spray-Dried Tablet Formulations of TMC125 (formulation G*, A*, H*, and I*) and a Reference Granulo-Layered Tablet Formulation of TMC125 in HPMC (formulation F*) at a Single Dose of 400 mg, as a Function of AUC_{last} for TMC125 When Administered as Reference Formulation F* (Trial TMC125-C170)

2.1.3.3 CONCLUSIONS

The 4 test tablet formulations of TMC125 manufactured by spray-drying technology (formulation G*, A*, H*, and I*) had a significantly higher bioavailability relative to the reference granulo-layered tablet formulation of TMC125 in HPMC (formulation F*). The AUC_{last} values for formulations G*, A*, H*, and I* were 6.78-, 9.37-, 6.96-, and 4.92-fold higher, respectively, than for the reference formulation (formulation F*). The [redacted] applied and the process used with tablet formulations G* and I* therefore decreased the bioavailability of TMC125. The bioavailability of TMC125 was highest with formulation A*, and this formulation was therefore chosen for further use in clinical trials with healthy and HIV-1 infected subjects.

2.1.4 Trial TMC125-C141: Relative Bioavailability of TMC125 Given as Single Doses of Tablet Formulation A* (TMC125 in HPMC, Spray-Dried), Compared to Reference Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered), in HIV-1 Infected Subjects

2.1.4.1 TRIAL DESIGN

This was an add-on, randomized, open-label, parallel-group, 2-period crossover trial in HIV-1 infected subjects to investigate the relative bioavailability of 3 single-dose levels of a tablet formulation of TMC125 in HPMC manufactured using spray-drying technology (formulation A*), compared to a single-dose of the 200 mg tablet formulation of TMC125 in HPMC manufactured using granulo-layering technology (formulation F*). The trial population consisted of 36 subjects (3 groups of 12 subjects each). Eligible subjects had non-nucleoside reverse transcriptase

inhibitor (NNRTI) experience for at least 3 months, an HIV-1 plasma viral load below 50 HIV-1 ribonucleic acid (RNA) copies/mL, and an ARV regimen that included lopinavir with low-dose ritonavir (LPV/rtv) or saquinavir with low-dose ritonavir (SQV/rtv) plus a minimum of one nucleoside reverse transcriptase inhibitor (NRTI) with or without enfuvirtide. In each of 2 sessions, subjects were treated in a randomized order in 3 parallel panels as follows:

- Panel 1: single dose of 100 mg TMC125 as formulation A* (test) or a single dose of 800 mg TMC125 as formulation F* (reference);
- Panel 2: single dose of 200 mg TMC125 as formulation A* (test) or a single dose of 1600 mg TMC125 as formulation F* (reference);
- Panel 3: single dose of 300 mg TMC125 as formulation A* (test) or a single dose of 2400 mg TMC125 as formulation F* (reference).

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

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.1.2/TMC125-C141).

2.1.4.2 PHARMACOKINETICS OF TMC125

The mean plasma concentration-time profiles in Panels 1 (100 mg TMC125 as formulation A* vs. 800 mg TMC125 as formulation F*) and 2 (200 mg TMC125 as formulation A* vs. 1600 mg TMC125 as formulation F*) were comparable between the test formulation and the reference formulation. For Panel 3 (300 mg TMC125 as formulation A* vs. 2400 mg TMC125 as formulation F*) the plasma concentrations of TMC125 were higher after administration of the test formulation A* compared to the reference formulation F* (Figure 14).

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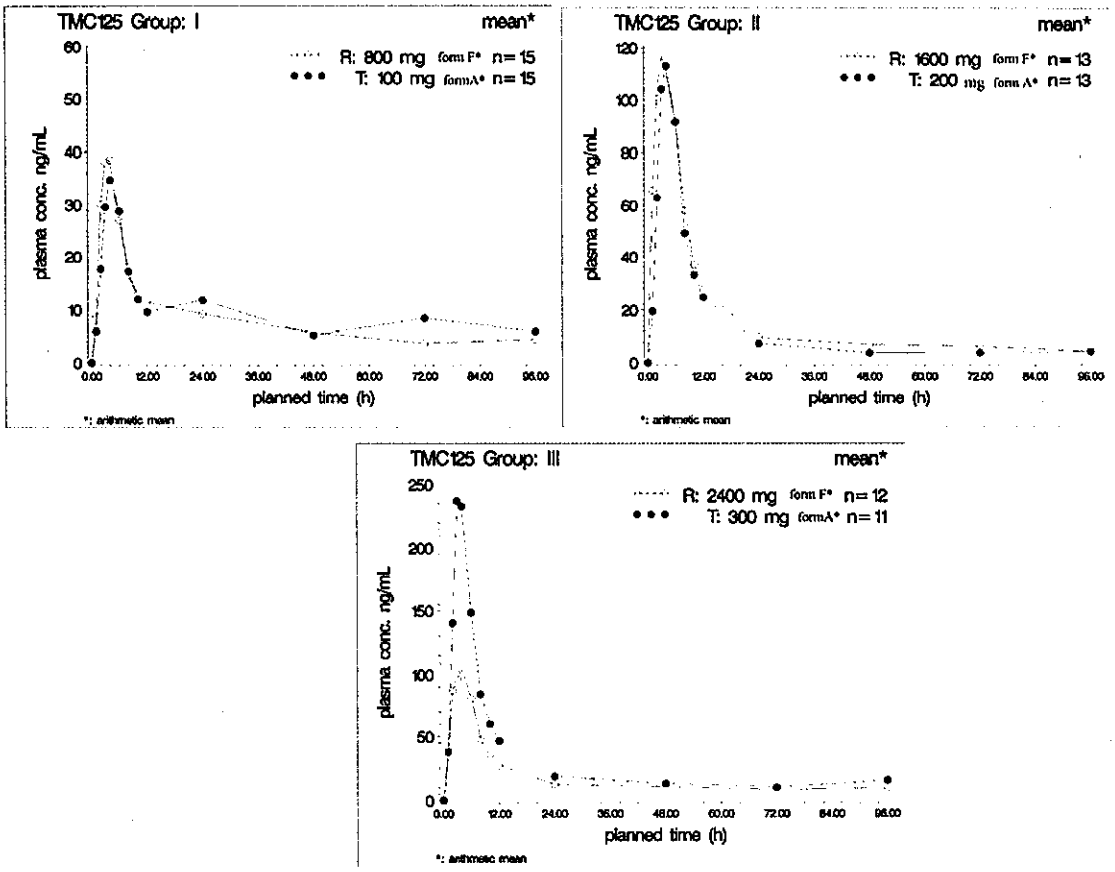

Source: Module 5.3.1.2/TMC125-C141/Section 4.2.4 form :formulation *

Figure 14: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of a Test Spray-Dried Tablet Formulation of TMC125 in HPMC (formulation A*) at Single Doses of 100, 200, and 300 mg and Administration of a Reference Granulo-Layered Tablet Formulation of TMC125 in HPMC (formulation F*) at Single Doses of 800, 1600, and 2400 mg (Trial TMC125-C141)

In Panels 1 and 2, the mean C_{max} and AUC parameters were comparable for the test and reference formulations, whereas in Panel 3, these parameters were 2.27- and 2.13-fold higher, respectively, for the test formulation A* compared to the reference formulation F* (Table 11). The C_{max} and AUC parameters showed considerable inter-individual variability for all treatments (Module 5.3.1.2/TMC125-C141/Section 4.2.5). The mean elimination half-life of TMC125 was generally shorter than in other trials, and increased with the dose. The relatively short elimination half-life and the substantial inter-individual variability were mainly caused by the generally low exposure to TMC125 in this trial and the fact that many plasma concentrations were below the LLOQ (< 2 ng/mL).

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Table 11: Pharmacokinetics of TMC125 after Administration of a Test Spray-Dried Tablet Formulation of TMC125 in HPMC (formulation A*) at Single Doses of 100, 200, and 300 mg and Administration of a Reference Granulo-Layered Tablet Formulation of TMC125 in HPMC (formulation F*) at Single Doses of 800, 1600, and 2400 mg (Trial TMC125-C141)

Parameter	Mean ± SD; t_{max}: Median (Range) TMC125 800, 1600, or 2400 mg (formulation F*) (Reference)	TMC125 100, 200 , or 300 mg (formulation A*) (Test)	Ratio [a] (Test:Reference)	90% CI
Panel 1: 800 mg TMC125 (formulation F*) vs. 100 mg TMC125 (formulation A*)				
N	15	15		
t_{max}, h	3.00 (2.00 - 6.00)	4.00 (2.00 - 12.00)	-	-
C_{max}, ng/mL	44.7 ± 48.5	37.6 ± 33.9	1.03	0.78 - 1.37
AUC_{last}, ng.h/mL	392 ± 508	360 ± 562	1.03	0.75 - 1.42
AUC_{∞}, ng.h/mL	470 ± 565	425 ± 641	0.93	0.71 - 1.21
$t_{1/2,term}$, h	9.94 ± 10.28	7.89 ± 8.50	-	-
Panel 2: 1600 mg TMC125 (formulation F*) vs. 200 mg TMC125 (formulation A*)				
N	12	13		
t_{max}, h	5.00 (2.00 - 6.00)	4.00 (3.00 - 6.00)	-	-
C_{max}, ng/mL	132.4 ± 207.2	131.4 ± 125.4	1.27	0.99 - 1.62
AUC_{last}, ng.h/mL	1285 ± 1887	1059 ± 906	1.11	0.84 - 1.46
AUC_{∞}, ng.h/mL	1358 ± 1982	1131 ± 955	1.11	0.85 - 1.45
$t_{1/2,term}$, h	13.55 ± 9.32	15.83 ± 8.86	-	-
Panel 3: 2400 mg TMC125 (formulation F*) vs. 300 mg TMC125 (formulation A*)				
N	12	11		
t_{max}, h	4.00 (2.00 - 6.00)	3.00 (3.00 - 12.00)	-	-
C_{max}, ng/mL	114.8 ± 81.6	257.7 ± 170.8	2.27	1.74 - 2.95
AUC_{last}, ng.h/mL	1348 ± 1349	2434 ± 2221	2.13	1.56 - 2.91
AUC_{∞}, ng.h/mL	1579 ± 1725	2831 ± 3090	2.03	1.49 - 2.76
$t_{1/2,term}$, h	20.58 ± 16.69	21.55 ± 17.31	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.1.2/TMC125-C141/Section 4.2.5 and Section 4.2.6

The test formulation A* showed a more than dose-proportional increase in pharmacokinetic parameters with increasing doses of TMC125. The increase in exposure to TMC125 after administration of the reference formulation F* was also more than dose-proportional between Panels 1 and 2 (800 and 1600 mg). There was almost no further increase in the exposure to TMC125 in Panel 3 after the administration of 2400 mg TMC125 as formulation F*, compared to Panel 2 (1600 mg TMC125 as formulation F*) (Table 11 and Figure 15).

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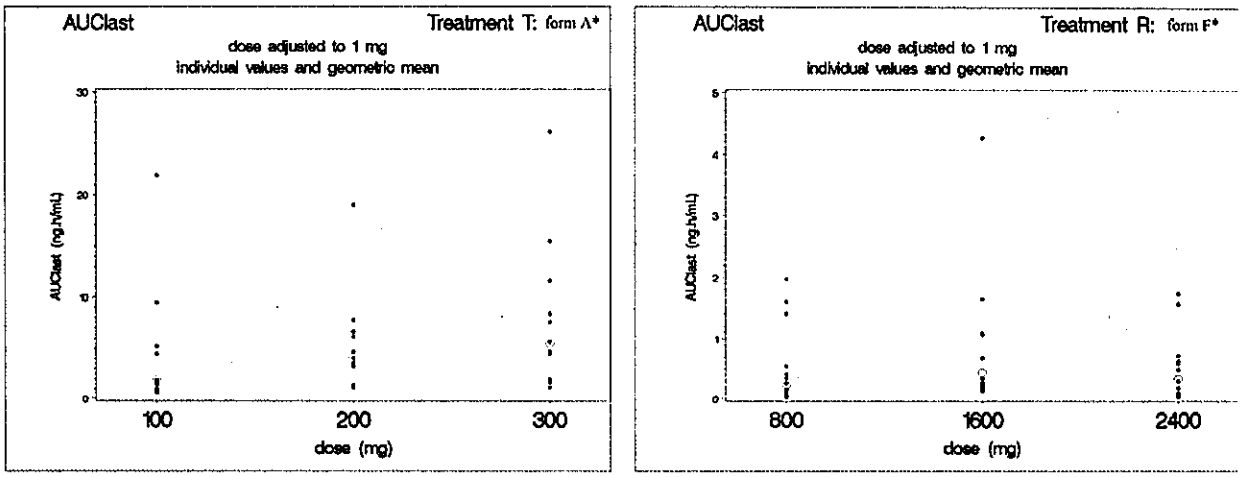

Open circles indicate geometric mean values.

Source: Module 5.3.1.2/TMC125-C141/Section 4.2.5 form: formulation *

Figure 15: Individual and Geometric Mean AUC_{last} Values for TMC125 after Administration of a Test Spray-Dried Tablet Formulation of TMC125 in HPMC (formulation A*) at Single Doses of 100, 200, and 300 mg and Administration of a Reference Granulo-Layered Tablet Formulation of TMC125 in HPMC (formulation F*) at Single Doses of 800, 1600, and 2400 mg (Trial TMC125-C141)

An exploratory post-hoc analysis of the individual data showed a trend towards subjects with relatively low concentrations of TMC125 after administration of the reference formulation F* at the 800 mg dose level having relatively high values for the test to reference ratio of AUC_{last} (Figure 16). Thus, in a given individual at this dose level, the plasma concentrations of TMC125 were relatively higher with the test formulation if the plasma concentrations obtained with the reference formulation F* were low. This trend was less obvious or absent for the higher dose levels of TMC125.

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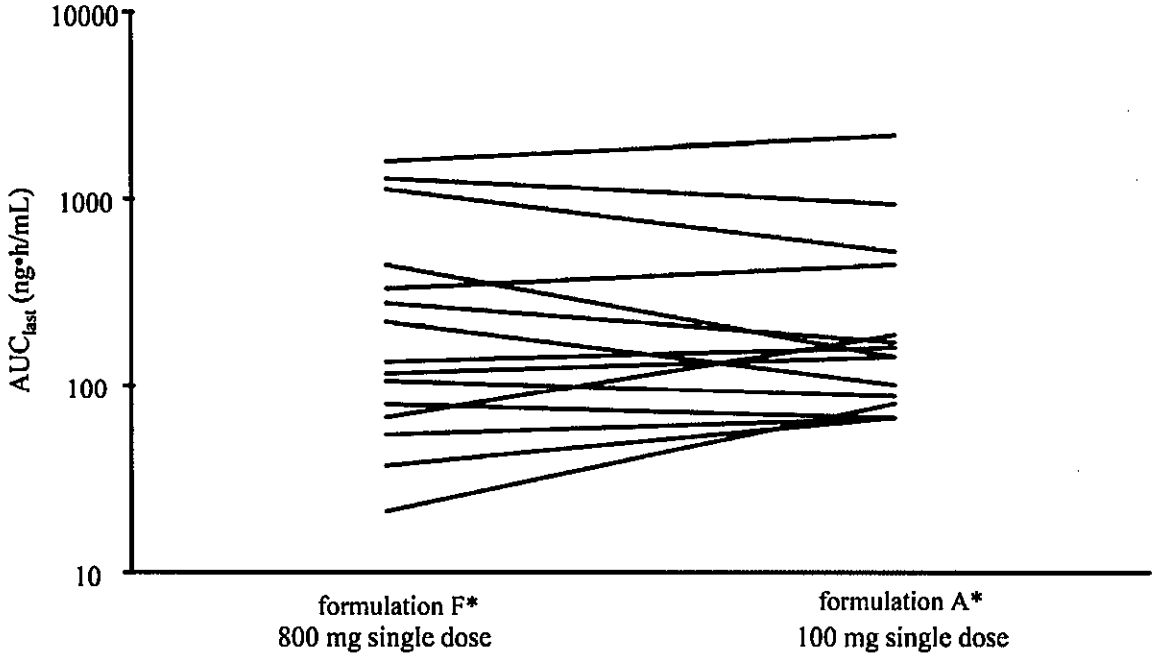

Source: Replotted from data available in Module 5.3.1.2/TMC125-C141/Supporting Data Display 9

Figure 16: Relationships Between Individual AUC_{last} Values of Single-Dose 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 (Trial TMC125-C141)

2.1.4.3 CONCLUSIONS

In HIV-1 infected subjects, the mean C_{max} and AUC_{last} of TMC125 after single-dose administration with food of 100 mg TMC125 as formulation A* were comparable to the values obtained with 800 mg TMC125 of the reference formulation F*. For 200 mg TMC125 administered as formulation A* the ratios were 1.27 and 1.11, respectively, compared to 1600 mg TMC125 administered as formulation F*. For 300 mg TMC125 administered as formulation A* the ratios were 2.27 and 2.13, respectively, compared to 2400 mg TMC125 administered as formulation F*. The increase in ratios for higher doses of TMC125 was likely caused by the differences in dose proportionality between formulations A* and F*.

2.1.5 Trial TMC125-C228: Relative Bioavailability of TMC125 Given as Multiple Doses of Tablet Formulation A* (TMC125 in HPMC, Spray-Dried), Compared to Reference Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered), in HIV-1 Infected Subjects

2.1.5.1 TRIAL DESIGN

This was an add-on, randomized, open-label, 2-period crossover trial in HIV-1 infected subjects to investigate the relative bioavailability of TMC125 after multiple dosing with the test tablet formulation A* (TMC125 in HPMC, spray-dried) compared to the reference tablet formulation F* (TMC125 in HPMC, granulo-layered). The trial population was originally planned to consist of 32 NNRTI-experienced subjects with a confirmed plasma viral load of < 50 HIV-1

RNA copies/mL, a current ARV regimen that included LPV/rtv, SQV/rtv, or SQV/LPV/rtv, and at least one NRTI with or without enfuvirtide. Subjects continued to take their current ARV regimen throughout the trial without interruption.

In each of the 2 originally planned sessions, subjects received either 100 mg TMC125 b.i.d. as formulation A* or 800 mg TMC125 b.i.d. as formulation F*, in each case for 7 days (Days 1 to 7) with an additional morning intake on Day 8. The 2 sessions were separated by a washout period of at least 14 days. The trial medication was taken under fed conditions, within 10 minutes after completion of a standardized breakfast.

Based on an evaluation of the preliminary pharmacokinetic data from Sessions 1 and 2, the original protocol was amended to implement an optional additional Session 3 in which subjects from the first 2 sessions received 200 mg TMC125 b.i.d. as formulation A* for 7 days (Days 1 to 7), with an additional morning intake on Day 8. Of the 33 subjects initially enrolled in the trial, 27 opted to participate in Session 3.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.1.2/TMC125-C228).

2.1.5.2 PHARMACOKINETICS OF TMC125

On Days 1 and 8, the mean plasma concentrations of TMC125 were lower after administration of the 100 mg dose of formulation A*, and higher after administration of the 200 mg dose of formulation A*, compared to the 800 mg dose of reference formulation F* (Figure 17). Due to accumulation, the predose concentrations of TMC125 increased up to Day 8 (Module 5.3.1.2/TMC125-C228/Section 4.2.4).

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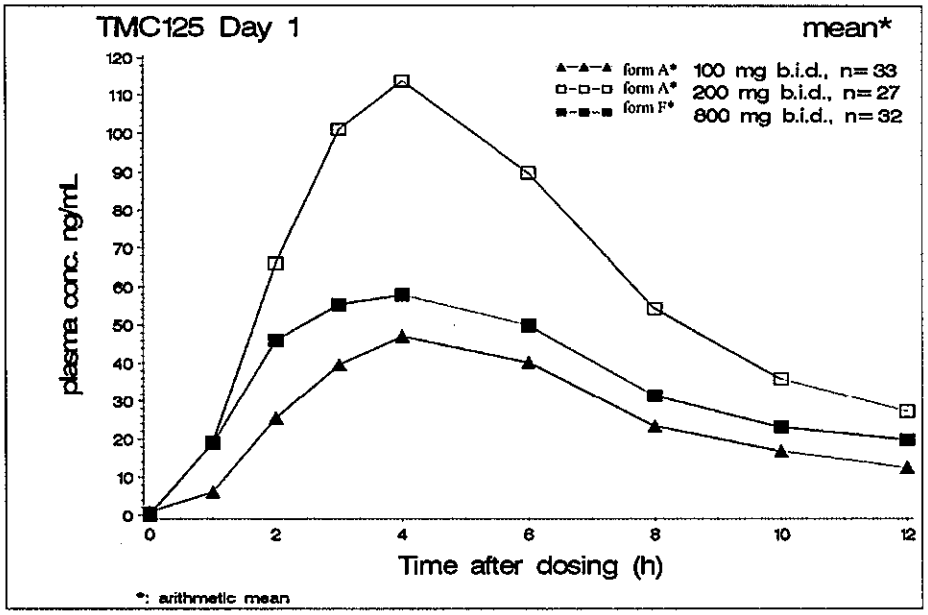

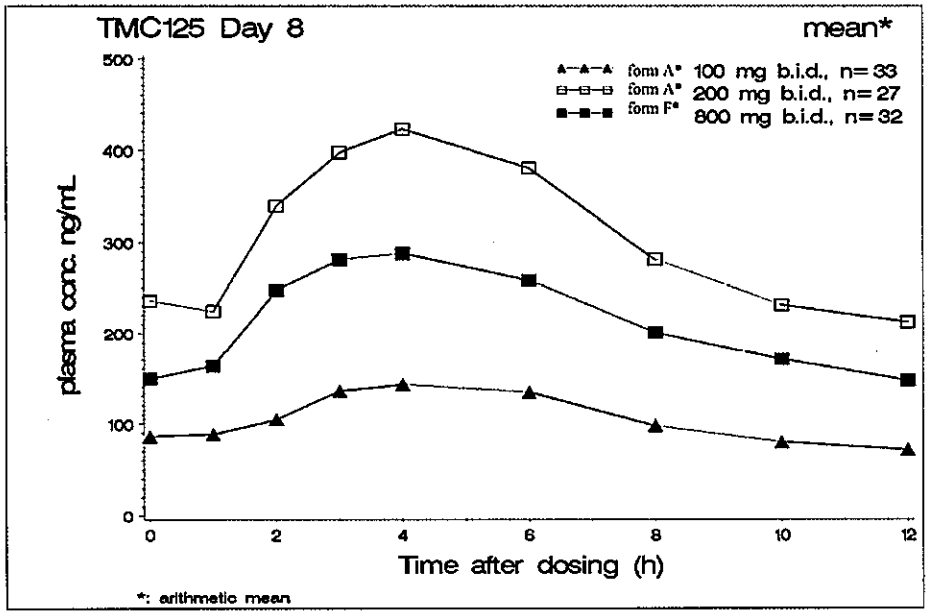

Source: Module 5.3.1.2/TMC125-C228/Section 4.2.4 form: formulation *

Figure 17: Plasma Concentration-Time Profiles of TMC125 on Days 1 and 8 after Administration of Test Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) at Doses of 100 and 200 mg b.i.d. and Reference Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at a Dose of 800 mg b.i.d. (TMC125-C228)

The exposure to TMC125 (in terms of concentration and AUC pharmacokinetic parameters) after single-dose (Day 1, Table 12) and multiple-dose (Day 8, Table 13) administration was lower with the 100 mg b.i.d. dose of formulation A*, and higher with the 200 mg b.i.d. dose of formulation A*, compared to the 800 mg b.i.d. dose of formulation F*. The C_{max} and AUC parameters showed considerable inter-individual variability for all treatments, but less variability with formulation A* than with formulation F*.

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The test formulation A* showed a trend towards a more than dose-proportional increase in pharmacokinetic parameters with increasing dose, which was more pronounced after multiple-dose administration than after single-dose administration.

The median t_{max} was 4 hours with all treatments. The fluctuation index (FI) was highest for the 100 mg b.i.d. dose of formulation A*, and comparable for the 200 mg b.i.d. dose of formulation A* and the 800 mg b.i.d. dose of formulation F*.

For both comparisons of formulation A* vs. F*, the 90% CIs of the LS means ratios were outside the 80% to 125% range. After multiple dosing on Day 8, the LS means ratios for AUC_{12h}, C_{max}, and minimum plasma concentration (C_{min}) were each 1.67 for the comparison of the 200 mg b.i.d. dose of formulation A* compared to the 800 mg b.i.d. dose of formulation F*.

Table 12: Single-Dose (Day 1) Pharmacokinetics of TMC125 after Administration of Test Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) at Doses of 100 and 200 mg and Reference Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at a Dose of 800 mg (TMC125-C228)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	TMC125 800 mg (formulation F*) (Reference)	TMC125 100 or 200 mg (formulation A*) (Test)		
800 mg TMC125 (formulation F*) vs. 100 mg TMC125 (formulation A*)				
N	32	33		
t_{max}, h	4.00 (2.00 - 8.00)	4.00 (2.00 - 6.00)	-	-
C_{max}, ng/mL	70.6 ± 72.7	54.9 ± 54.0	0.81	0.65 - 1.00
AUC_{12h}, ng.h/mL	434 ± 437	312 ± 331	0.72	0.59 - 0.88
800 mg TMC125 (formulation F*) vs. 200 mg TMC125 (formulation A*)				
N	32	27		
t_{max}, h	4.00 (2.00 - 8.00)	4.00 (3.00 - 8.00)	-	-
C_{max}, ng/mL	70.6 ± 72.7	125.9 ± 109.6	1.97	1.59 - 2.45
AUC_{12h}, ng.h/mL	434 ± 437	745 ± 660	1.91	1.54 - 2.36

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.1.2/TMC125-C228/Section 4.2.5 and Section 4.2.6

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Table 13: Multiple-Dose (Day 8) Pharmacokinetics of TMC125 after Administration of Test Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) at Doses of 100 and 200 mg b.i.d. and Reference Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at a Dose of 800 mg b.i.d. (TMC125-C228)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	TMC125 800 mg (formulation F*) (Reference)	TMC125 100 or 200 mg (formulation A*) (Test)		
800 mg TMC125 (formulation F*) vs. 100 mg TMC125 (formulation A*)				
N	32	33		
t_{max}, h	4.00 (0.00 - 6.00)	4.00 (0.00 - 6.00)	-	-
C_{0h}, ng/mL	148.8 ± 119.3	86.3 ± 84.5	-	-
C_{min}, ng/mL	125.8 ± 116.4	59.9 ± 63.8	0.47	0.38 - .059
C_{max}, ng/mL	318.8 ± 245.8	170.9 ± 99.9	0.61	0.50 - 0.75
AUC_{12h}, ng.h/mL	2607 ± 2135	1284 ± 958	0.54	0.44 - 0.65
800 mg TMC125 (formulation F*) vs. 200 mg TMC125 (formulation A*)				
N	32	27		
t_{max}, h	4.00 (0.00 - 6.00)	4.00 (2.00 - 8.00)	-	-
C_{0h}, ng/mL	148.8 ± 119.3	235.9 ± 163.1	-	-
C_{min}, ng/mL	125.8 ± 116.4	184.7 ± 128.1	1.67	1.37 - 2.04
C_{max}, ng/mL	318.8 ± 245.8	451.3 ± 232.3	1.67	1.37 - 2.04
AUC_{12h}, ng.h/mL	2607 ± 2135	3713 ± 2069	1.67	1.38 - 2.02

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.1.2/TMC125-C228/Section 4.2.5 and Section 4.2.6

Given the observed inter-individual variability with the formulation F* and the non-proportional increase in exposures between the 100 and 200 mg b.i.d. doses of formulation A*, an exploratory post-hoc analysis was performed to investigate whether this increase was homogenous across individual subjects. For each individual, relationships between the individual steady-state AUC_{12h} (Day 8) values of TMC125 administered at a dose of 800 mg b.i.d. as formulation F* and at a dose of 200 mg b.i.d. as formulation A* were portrayed graphically (Figure 18). This 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*. 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 a lower inter-individual variability with the 200 mg b.i.d. dose of formulation A*.

Overall, on account of the high inter-individual variability with formulation F*, 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* that had been selected from the Phase IIb trials TMC125-C203 and TMC125-C223 (refer to Module 2.7.2/Section 3.13).

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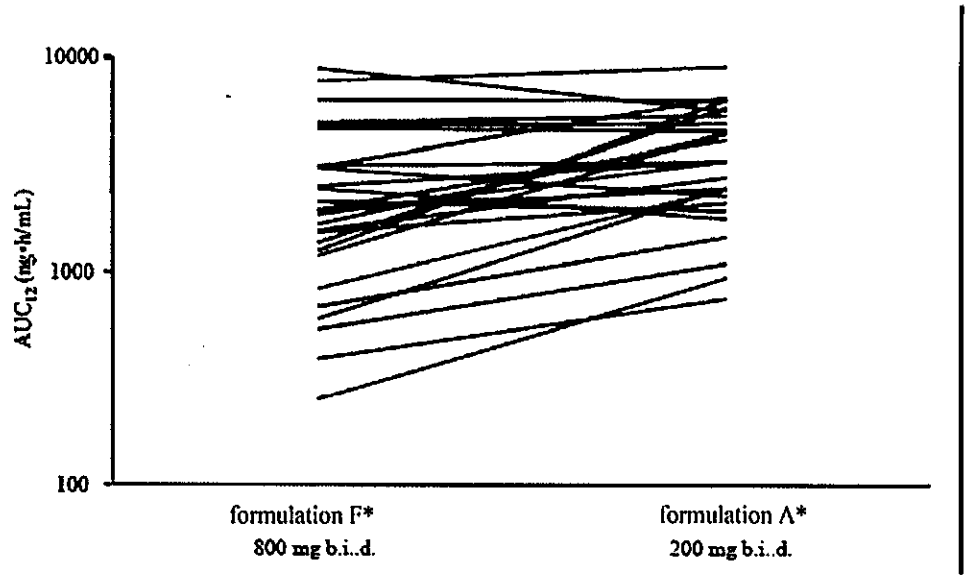


Source: Module 5.3.1.2/TMC125-C228/Section 4.2.6

Figure 18: Relationships 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 (Trial TMC125-C228)

2.1.5.3 CONCLUSIONS

Although the 90% CIs of the LS means ratios were outside the 80% to 125% range for the comparisons of the 100 and 200 mg b.i.d. doses of test formulation A* vs. the 800 mg b.i.d. dose of reference formulation F*, the range of exposure to TMC125 was comparable between treatment with the 200 mg b.i.d. dose of test formulation A* and the 800 mg b.i.d. dose of reference formulation F* after multiple dosing in HIV-1 infected subjects. Based upon these results, the 200 mg b.i.d. dose of TMC125 administered with formulation A* was selected for further clinical development, including use in the registrational Phase III trials (TMC125-C206 [DUET-1] and TMC125-C216 [DUET-2], refer to Module 2.7.2/Section 2.6.3).

2.2 RELATIVE BIOAVAILABILITY TRIALS - OPTIMIZATION OF SELECTED TABLET FORMULATION

2.2.1 Trial TMC125-C150: Relative Bioavailability of TMC125 Given as Test Tablet Formulations J* or K* (Both TMC125 in HPMC, Spray-Dried), or L* (TMC125 in [redacted], Spray-Dried), or as Test Capsule Formulation M* (TMC125 in HPMC, Bead-Coated), Compared to Reference Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered), in Healthy Subjects (Effect of Manufacturing Technology, Type of Solubilizing Polymer, and TMC125 to Polymer Ratio)

2.2.1.1 TRIAL DESIGN

This was an open-label, randomized, parallel-group, crossover trial to investigate the relative bioavailability of 3 [redacted] tablet formulations of TMC125 in HPMC or [redacted], manufactured using spray-drying technology (formulations J*, K*, and L*), and a capsule formulation of TMC125 in HPMC, manufactured using bead-coating technology (formulation M*), compared to a reference tablet formulation of TMC125 in HPMC, manufactured using granulo-layering technology (formulation F*). The different formulation concepts of TMC125 investigated in this trial varied in the manufacturing technology used, and in the type of solubilizing polymer and the TMC125 to polymer ratio used.

The trial population consisted of 4 parallel panels of 12 healthy subjects each. Each subject received a single, oral, 400-mg dose of TMC125 on 2 occasions. In each of 2 sessions, the 4 groups of subjects received either the reference formulation (Treatment A) or one of the 4 different test formulations (Treatments B, C, D, or E). The treatment groups were:

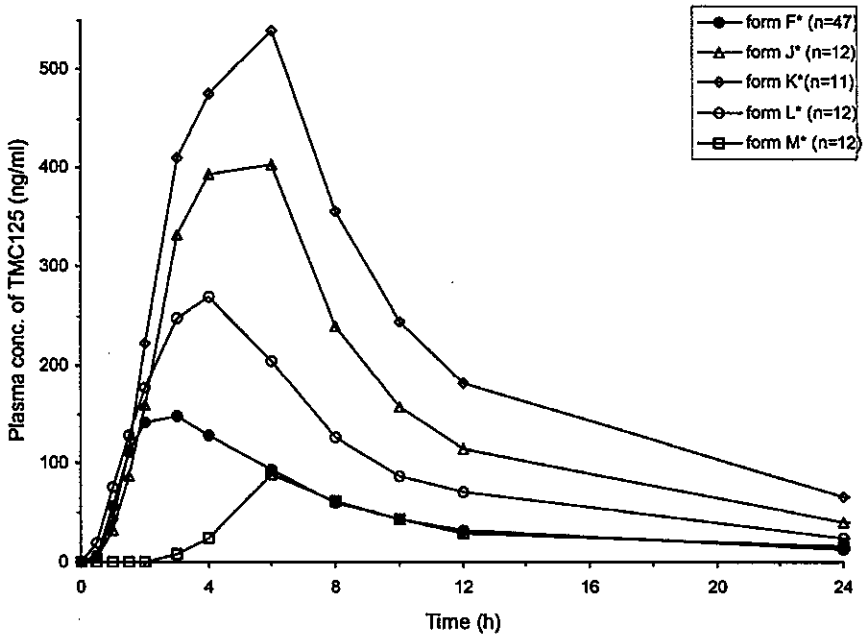
- Treatment A (reference): 2 tablets (formulation F*), each containing 200 mg TMC125 in HPMC, granulo-layered;
- Treatment B (test): 2 tablets (formulation J*), each containing 200 mg TMC125 in HPMC, spray-dried (TMC125 to HPMC ratio of [redacted]);
- Treatment C (test): 3 tablets (formulation K*), each containing 133 mg TMC125 in HPMC, spray-dried (TMC125 to HPMC ratio of [redacted]);
- Treatment D (test): 2 tablets (formulation L*), each containing 200 mg TMC125 in copolyvidone, spray-dried (TMC125 to [redacted] ratio of [redacted]);
- Treatment E (test): 2 capsules (formulation M*), each containing 200 mg TMC125 in HPMC, bead-coated (TMC125 to HPMC ratio of [redacted]).

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

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.1.2/TMC125-C150).

2.2.1.2 PHARMACOKINETICS OF TMC125

The mean plasma concentration-time profiles showed that TMC125 was rapidly absorbed when administered as the reference formulation F* and as test formulations J*, K*, and L*, with an initially fast distribution and/or elimination phase followed by a slower elimination phase (Figure 19). The mean plasma concentration-time profiles of the test tablet formulations J*, K*, and L* lay above the profile of the reference tablet formulation F*. In contrast, the mean plasma concentration-time profile for the test capsule formulation M* revealed a lag-time followed by a slower absorption rate than with the tablet formulations.



form: formulation *
Source: Module 5.3.1.2/TMC125-C150/Section 4.2.4

Figure 19: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of Three Test Spray-Dried Tablet Formulations of TMC125 (formulations J*, K*, and L*) and a Test Bead-Coated Capsule Formulation of TMC125 (formulation M*), Compared to a Reference Tablet Formulation of TMC125 in HPMC (formulation F*) at a Single Dose of 400 mg (Trial TMC125-C150)

The median t_{max} was shortest for the reference tablet formulation F* (3 hours), ranged from 4 to 5 hours for the test tablet formulations J*, K* and L*, and was longest for the test capsule formulation M* (6 hours) (Table 14).

The rate and extent of exposure (C_{max} and AUC_{last}) to TMC125 were highest with formulation K*, followe by formulations J*, L*, F*, and M*, respectively. Based on the LS means ratios, the mean C_{max} was 1.86- to 5.82-fold higher, and AUC_{last} 2.23- to 6.24-fold higher, with test formulations J*, K*, and L* than with the reference formulation F*. In contrast, the mean exposure to TMC125 with test formulation M* was lower than with the reference formulation F* with approximately 25% lower mean C_{max} and AUC_{last} values, compared to formulation F*.

In terms of the CV, the inter-individual variability was lowest for formujlation K*, and ranged from 35% tc 86% for C_{max} and from 48% to 99% for AUC_{last} across treatments (Module 5.3.1.2/TMC125-C150/Section 4.2.5).

Table 14: Pharmacokinetics of TMC125 after Administration of Three Test Spray-Dried Tablet Formulations of TMC125 (formulations J*, K*, and L*) and a Test Bead-Coated Capsule Formulation of TMC125 (formulation M*), Compared to a Reference Tablet Formulation of TMC125 in HPMC (formulation F*) at a Single Dose of 400 mg (Trial TMC125-C150)

Parameter	Mean ± SD; t_{max}: Median (Range) Treatment A: TMC125 400 mg (formulation F*) (Reference)	Treatment B, C, D, or E: TMC125 400 mg (formulations J*, K*, L*, M*) (Test)	Ratio [a] (Test:Reference)	90% CI
Treatment A (formulation F*) vs. Treatment B (formulation J*)				
N	47	12		
t_{max}, h	3.0 (1.5 - 6.0)	5.0 (3.0 - 6.0)	-	-
C_{max}, ng/mL	168 ± 145	450 ± 278	2.45	1.82 - 3.31
AUC_{last}, ng.h/mL	1665 ± 1468	5344 ± 3443	3.05	2.44 - 3.80
AUC_{∞} [b], ng.h/mL	1975 ± 1774	6089 ± 3967	-	-
$t_{1/2,term}$ [b], h	42.2 ± 37.3	39.8 ± 12.9	-	-
Treatment A (formulation F*) vs. Treatment C (formulation K*)				
N	47	11		
t_{max}, h	3.0 (1.5 - 6.0)	4.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	168 ± 145	654 ± 228	5.82	4.09 - 8.28
AUC_{last}, ng.h/mL	1665 ± 1468	7675 ± 3677	6.24	4.45 - 8.75
AUC_{∞} [b], ng.h/mL	1975 ± 1774	8741 ± 4424	-	-
$t_{1/2,term}$ [b], h	42.2 ± 37.3	40.0 ± 9.48	-	-
Treatment A (formulation F*) vs. Treatment D (formulation L*)				
N	47	12		
t_{max}, h	3.0 (1.5 - 6.0)	4.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	168 ±145	288 ± 171	1.86	1.27 - 2.72
AUC_{last}, ng.h/mL	1665 ±1468	3103 ± 2137	2.23	1.48 - 3.37
AUC_{∞} [b], ng.h/mL	1975 ±1774	3372 ± 2249	-	-
$t_{1/2,term}$ [b], h	42.2 ±37.3	33.9 ± 14.9	-	-
Treatment A (formulation F*) vs. Treatment E (formulation M*)				
N	47	12		
t_{max}, h	3.0 (1.5 - 6.0)	6.0 (4.0 - 8.0)	-	-
C_{max}, ng/mL	168 ± 145	90.1 ± 65.4	0.76	0.46 - 1.23
AUC_{last}, ng.h/mL	1665 ± 1468	1297 ± 1289	0.74	0.41 - 1.35
AUC_{∞} [b], ng.h/mL	1975 ± 1774	2427 ± 3847	-	-
$t_{1/2,term}$ [b], h	42.2 ± 37.3	57.2 ± 74.2	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
[b] Accurate determination not possible in all subjects.
Source: Module 5.3.1.2/TMC125-C150/Section 4.2.5 and Section 4.2.6

2.2.1.3 CONCLUSIONS

The spray-drying technology used for the manufacture of tablet formulations of TMC125 in HPMC or [redacted] (formulations J*, K*, and L*) led to considerable increases in the exposure to TMC125, compared to the reference tablet formulation of TMC125 in HPMC manufactured

using granulo-layering technology (formulation F*). In contrast, the bead-coating technology used for the manufacture of capsule formulation M* resulted in a decrease in exposure to TMC125, compared to tablet formulation F*. Among the spray-dried tablet formulations, the exposure to TMC125 was higher when HPMC was used as the polymer (formulations J* and K*) than when [redacted] was used as the polymer (formulation L*). With these [redacted], spray-dried tablet formulations of TMC125 in HPMC, the mean exposure to TMC125 was higher with a TMC125 to HPMC ratio of [redacted] (formulation K*) than with a ratio of [redacted] (formulation J*).

2.2.2 Trial TMC125-C155: Relative Bioavailability of TMC125 Given as Tablet Formulations N* (TMC125 in HPMC, Granulo-Layered) or O* (TMC125 in HPMC, Spray-Dried), Compared to Reference Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered), in Healthy Subjects (Effect of Manufacturing Technology)

2.2.2.1 Trial Design

This was an open-label, randomized, 3-period crossover trial to investigate the relative bioavailability of 2 test ([redacted]) tablet formulations of TMC125 (formulation N* [manufactured using granulo-layering technology] and formulation O* [manufactured using spray-drying technology]), compared to a reference tablet formulation of TMC125 in HPMC, manufactured using granulo-layering technology (formulation F*).

The trial population consisted of 34 healthy subjects. Each subject received a single, oral, 400-mg dose of TMC125 on 3 occasions. In each of 3 sessions, the subjects received either the reference formulation (Treatment A) or one of the 2 test formulations (Treatments B or C). The treatment groups were:

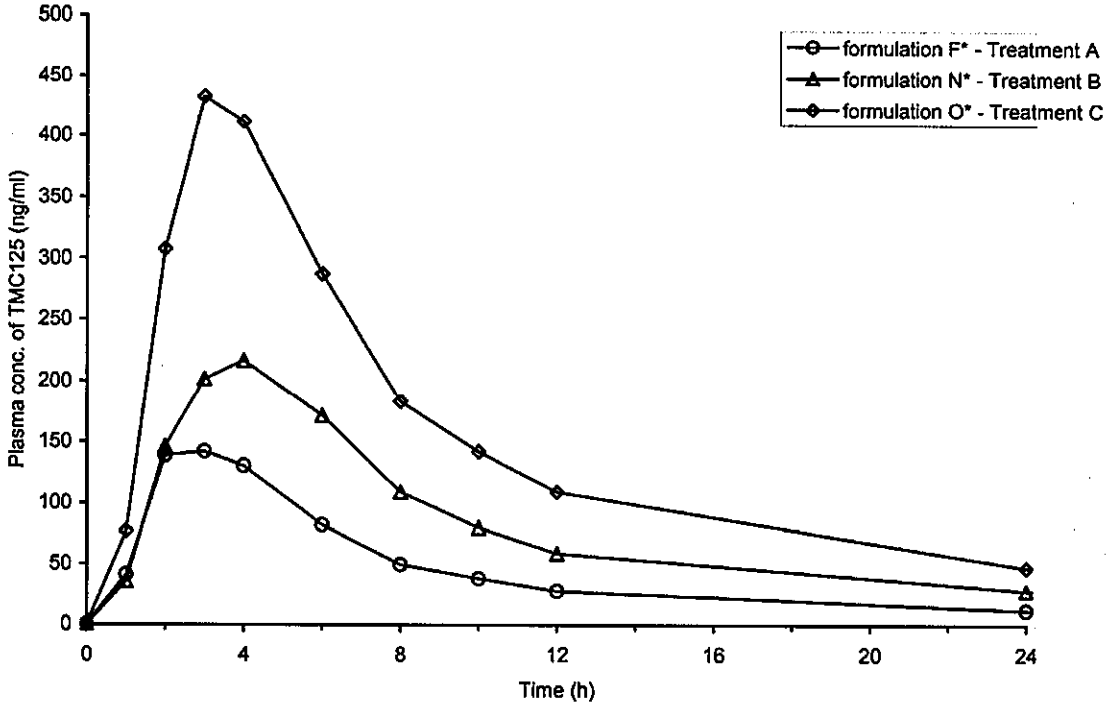
- Treatment A (reference): 2 tablets (formulation F*), each containing 200 mg TMC125 in HPMC, granulo-layered (TMC125 to HPMC ratio of [redacted]);
- Treatment B (test): 3 tablets (formulation N*), each containing 133 mg TMC125 in HPMC, granulo-layered (TMC125 to HPMC ratio of [redacted]);
- Treatment C (test): 2 tablets (formulation O*), each containing 200 mg TMC125 in HPMC, spray-drie (TMC125 to HPMC ratio of [redacted]).

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

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.1.2/TMC125-C155).

2.2.2.2 Pharmacokinetics of TMC125

With all 3 tablet formulations, TMC125 was rapidly absorbed, with generally no delay in absorption and an initially fast distribution/elimination phase followed by a slower elimination phase (Figure 20). The mean plasma concentrations attained with formulation O* were the highest, followed by those attained with formulation N*, while the mean plasma concentrations attained with formulation F* were the lowest.



N = 30 for Treatments A and C, and N = 31 for Treatment B.
Source: Module 5.3.1.2/TMC125-C155/Section 4.2.4

Figure 20: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of Two Test Formulations of TMC125 (formulation N* [TMC125 in HPMC, Granulo-Layered] and formulation O* [TMC125 in HPMC, Spray-Dried]) Compared to Reference Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at a Single Dose of 400 mg (Trial TMC125-C155)

The median t_{max} was 3 hours with formulations F* and O* and 4 hours with formulation N* (Table 15). The rate and extent of exposure (C_{max} and AUC_{last}) was highest with formulation O*, followed by formulation N*, and lowest with formulation F*. In terms of the CV, the inter-individual variability across treatments ranged from 43% to 59% for C_{max} and 57% to 88% for AUC_{last} (Module 5.3.1.2/TMC125-C155/Section 4.2.5).

The test formulations N* and O* resulted in increased exposures to TMC125, compared to the reference formulation F*. The mean C_{max} and AUC_{last} were 1.54- and 1.96-fold higher, respectively, with formulation N*, and 3.17- and 3.66-fold higher, respectively, with formulation O*. The 90% CIs of the LS means ratios of C_{max} and AUC_{last} for both comparisons were outside the 80% to 125% range.

Table 15: Pharmacokinetics of TMC125 after Administration of Two Test Formulations of TMC125 (formulation N* [TMC125 in HPMC, Granulo-Layered] and formulation O [TMC125 in HPMC, Spray-Dried]) Compared to Reference Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at a Single Dose of 400 mg (Trial TMC125-C155)

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

N = maximum number of subjects with data.
[a] Ratio based on LS means.
[b] Accurate determination not possible in all subjects.
Source: Module 5.3.1.2/TMC125-C155/Section 4.2.5 and Section 4.2.6

2.2.2.3 CONCLUSIONS

The spray-drying technology used for the manufacture of tablet formulation O* (TMC125 in HPMC, spray-dried) resulted in a substantially higher exposure to TMC125 than with the granulo-layering technology used for the manufacture of tablet formulation N* (TMC125 in HPMC, granulo-layered). Both of these formulations achieved higher exposures to TMC125 than the reference tablet formulation of TMC125 in HPMC manufactured using granulo-layering technology (formulation F*).

2.2.3 Trial TMC125-C146: Relative Bioavailability of TMC125 Given as Tablet Formulations P*, Q*, and G* (All TMC125 in HPMC, Spray-Dried), Compared to Reference Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered), in Healthy Subjects (Effect of TMC125 to Polymer Ratio)

2.2.3.1 TRIAL DESIGN

This was an open-label, randomized, parallel-group, 2-period crossover trial to investigate the relative bioavailability of 3 different [redacted] tablet formulations of TMC125 (formulations P*, Q* and G*, all manufactured by spray-drying technology but with different ratios of HPMC as

solubilizing polymer) compared to a reference tablet formulation of TMC125 in HPMC, manufactured using granulo-layering technology (formulation F*).

The trial population consisted of 36 healthy subjects in 3 parallel panels; in each panel, 12 subjects each received a single dose of 400 mg TMC125 on 2 occasions. In each of 2 sessions, the 3 groups of subjects received either the reference formulation (Treatment A) or one of the 3 different test formulations (Treatments B, C, or D). The treatment groups were:

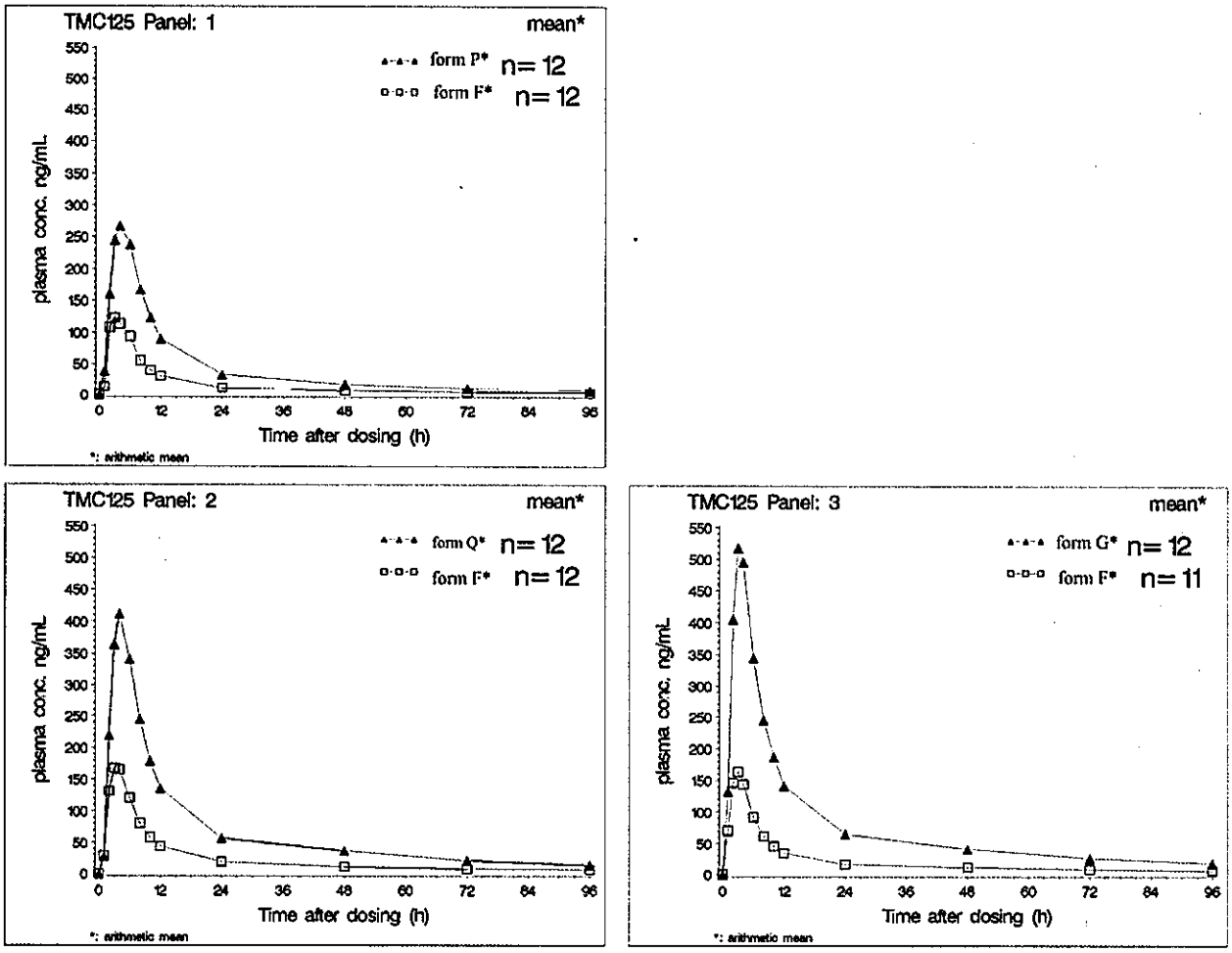
- Treatment A (reference): 2 tablets (formulation F*), each containing 200 mg TMC125 in HPMC, granulo-layered;
- Treatment B (test): 2 tablets (formulation P*), each containing 200 mg TMC125 in HPMC, spray-dried (TMC125 to HPMC ratio of [redacted]);
- Treatment C (test): 2 tablets (formulation Q*), each containing 200 mg TMC125 in HPMC, spray-dried (TMC125 to HPMC ratio of [redacted]);
- Treatment D (test): 3 tablets (formulation G*), each containing 133 mg TMC125 in HPMC, spray-dried (TMC125 to HPMC ratio of [redacted]).

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

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.1.2/TMC125-C146).

2.2.3.2 PHARMACOKINETICS OF TMC125

The mean plasma concentration-time profiles of the test tablet formulations P*, Q*, and G* were higher than the profile of the reference tablet formulation F* (Figure 21).



Source: Module 5.3.1.2/TMC125-C146/Section 4.2.4

Figure 21: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of Three Test Tablet Formulations of TMC125 (formulations P*, Q*, and G* [All TMC125 in HPMC, Spray-Dried]) Compared to Reference Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at a Single Dose of 400 mg (Trial TMC125-C146)

The mean exposure to TMC125 (C_{max} and AUC) was considerably higher for all 3 test formulations (formulations P*, Q*, and G*) than for the reference formulation F*, with the mean increases in exposure ranging from 2.29- to 3.77-fold for C_{max} and from 2.68- to 4.38-fold for AUC_{last} (Table 16). The increases in exposure were highest for formulation G* (TMC125 to HPMC ratio of [redacted]), and comparable for formulations Q* (TMC125 to HPMC ratio of [redacted]) and P* (TMC125 to HPMC ratio of [redacted]). The C_{max} and AUC parameters showed considerable inter-individual variability for all treatments (Module 5.3.1.2/TMC125-C146/Section 4.2.5). The mean elimination half-life of TMC125 was similar with all treatments, in the range of approximately 30 to 40 hours.

Although the pairwise comparisons to formulation F* indicated that the relative bioavailability of TMC125 with formulation Q* (TMC125 to HPMC ratio of [redacted]) was lower than with formulation P* (TMC125 to HPMC ratio of [redacted]), the absolute values for C_{max} and AUC indicate that the exposure to TMC125 was higher with formulation Q* than with

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formulation P*. The reason for the apparently lower exposure to TMC125 with formulation Q* when the data for formulations Q* and P* were analyzed by comparison to formulation F* lay with the fact that the exposure to TMC125 in the reference (formulation F*) group for formulation P* was lower than in the reference group for formulation Q* (and formulation G*), hence increasing the ratio for the comparison between formulations F* and P*. Thus, on the basis of the absolute exposure data, the results of this trial showed that the bioavailability of TMC125 increased when the TMC125 to HPMC ratio evolved from [redacted] and [redacted] to [redacted]

Table 16: Pharmacokinetics of TMC125 after Administration of Three Test Tablet Formulations of TMC125 (formulations P*, Q*, and G* [All TMC125 in HPMC, Spray-Dried]) Compared to Reference Tablet Formulation F* (TMC125 in HPMC, Granulo-Layered) at a Single Dose of 400 mg (Trial TMC125-C146)

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

N = maximum number of subjects with data.
[a] Ratio based on LS means.
[b] Accurate determination not possible in all subjects.
Source: Module 5.3.1.2/TMC125-C146/Section 4.2.5 and Section 4.2.6

2.2.3.3 CONCLUSIONS

The spray-drying technology used for the manufacture of tablet formulations of TMC125 in HPMC (formulations P*, Q*, and G*) led to considerable increases in the exposure to TMC125, compared to the reference tablet formulation of TMC125 in HPMC manufactured using granulo-layering technology (formulation F*). With these [redacted], spray-dried tablet formulations, the mean

exposure to TMC125 was higher with a TMC125 to HPMC ratio of [redacted] (formulation G*) than with a ratio of [redacted] (formulation Q*) or [redacted] (formulation P*).

2.2.4 Trial TMC125-C162: Relative Bioavailability of TMC125 Given as Tablet Formulations A* (Batches L054 and L055) or K* (Batch L039) (All TMC125 in HPMC, Spray-Dried), Compared to Reference Tablet Formulation A* (Batch L051) (TMC125 in HPMC, Spray-Dried), in Healthy Subjects (Effect of Manufacturing Scale and Long-Term Tablet Storage)

2.2.4.1 Trial Design

This was an open-label, randomized, 4-period crossover trial to investigate the relative bioavailability of TMC125 administered as 3 different batches of ([redacted]) tablet formulation A* (TMC125 in HPMC, spray-dried) manufactured on different scales, and as [redacted] tablet formulation K*, Batch L039 (TMC125 in HPMC, spray-dried). Formulation K*, Batch L039 , had previously been used in trial TMC125-C150 (Section 2.2.1 and Appendix 2.7.1.2), and tablets left over from this earlier trial were used in the current trial to investigate the effect of long-term storage (approximately 2 years at room temperature) on the bioavailability of the spray-dried tablet formulation of TMC125.

The trial population consisted of 16 healthy subjects. Each subject received a single 400 mg dose of TMC125 on 4 occasions. In each of 4 sessions, each subject received either the reference formulation (Treatment A) or one of the 3 different test formulations (Treatments B, C, or D). The treatment groups were:

- Treatment A (reference): 4 tablets (formulation A*, Batch L051), each containing 100 mg TMC125 in HPMC, spray-dried (small-scale manufacture);
- Treatment B (test): 4 tablets (formulation A*, Batch L055), each containing 100 mg TMC125 in HPMC, spray-dried (large-scale manufacture);
- Treatment C (test): 4 tablets (formulation A*, Batch L055), each containing 100 mg TMC125 in HPMC, spray-dried (large-scale manufacture);
- Treatment D (test): 3 tablets (formulation K*, Batch L039 , stored for approximately 2 years under uncontrolled conditions in a climate zone II country), each containing 133 mg TMC125 in HPMC, spray-dried.

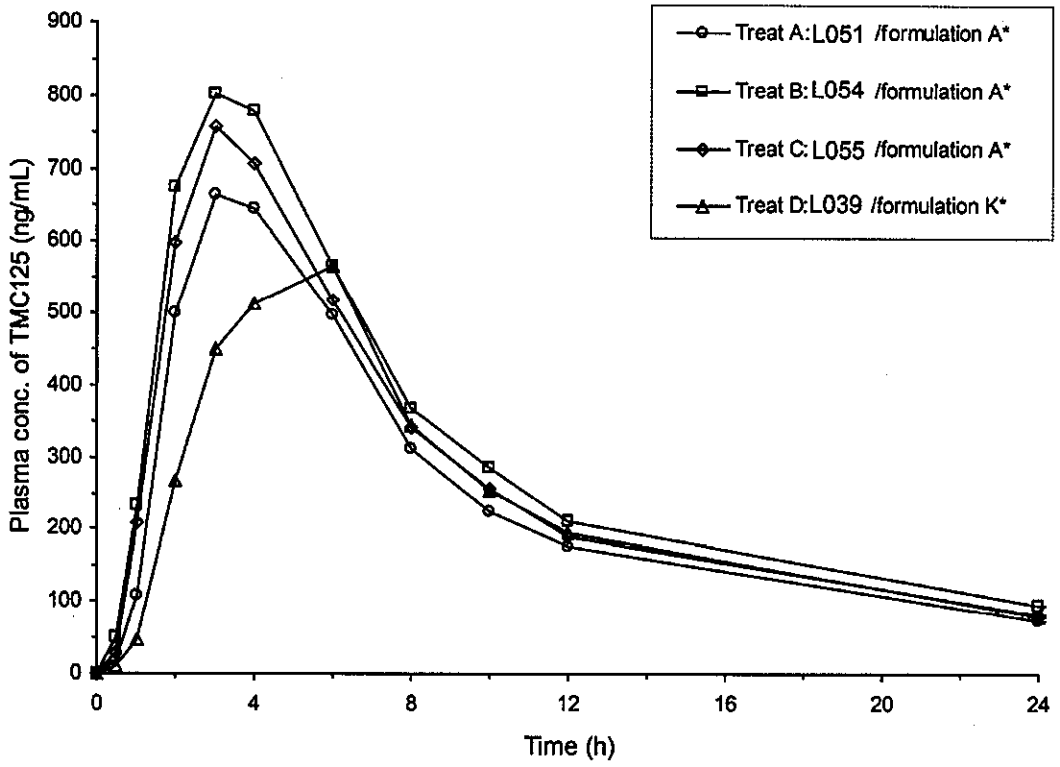
All treatments were taken under fed conditions within 10 minutes after completion of a standardized breakfast. The washout period between treatments was at least 14 days.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.1.2/TMC125-C162).

2.2.4.2 Pharmacokinetics of TMC125

With all treatments, TMC125 was rapidly absorbed without a notable lag-time (Figure 22). After the absorption phase, an initially fast distribution/elimination phase was followed by a slower elimination phase with all treatments. The 3 batches of formulation A* (Treatments A, B, and

C) yielded similar plasma concentrations of TMC125, whereas the plasma concentrations of TMC125 were lower with formulation K*, Batch L039 .



N = 16 for all treatments.
Source: Module 5.3.1.2/TMC125-C162/Section 4.2.4

Figure 22: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of Test Spray-Dried Tablet Formulations A* (Batches L054 and L055) and K* (Batch L039) (All TMC125 in HPMC, Spray-Dried) and Reference Spray-Dried Tablet Formulation A* (Batch L051) (TMC125 in HPMC, Spray-Dried) at a Single Dose of 400 mg (Trial TMC125-C162)

The median t_{max} of TMC125 in plasma was 3 hours with all 3 batches of formulation A*, and 6 hours with formulation K* (Table 17). The mean C_{max} and AUC_{last} of TMC125 were 1.26- and 1.28-fold higher, respectively, with formulation A*, Batch L054 , (Treatment B) compared to formulation A*, Batch L051 , (Treatment A). The exposure to TMC125 was comparable when TMC125 was administered as formulations A*, Batch L055 , (Treatment C) and A*, Batch L051 , (Treatment A).

Comparable exposures were also observed with formulations K*, Batch L039 (Treatment D) and A*, Batch L051 , (Treatment A). The 90% CI of the LS means ratio of C_{max} for Treatment C vs. A were just outside the 80% to 125% range, while the 90% CIs of AUC_{last} for Treatment C vs. A and Treatment D vs. A were within the 80% to 125% range.

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

The inter-individual variability of pharmacokinetic parameters was comparable between the different formulations (Module 5.3.1.2/TMC125-C162/Section 4.2.5).

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Table 17: Pharmacokinetics of TMC125 after Administration of Test Spray-Dried Tablet Formulations A* (Batches L054 and L055) and K* (Batch L039) (All TMC125 in HPMC, Spray-Dried) and Reference Spray-Dried Tablet Formulation A* (Batch L051) (TMC125 in HPMC, Spray-Dried) at a Single Dose of 400 mg (Trial TMC125-C162)

Parameter	Mean ± SD; t_{max}: Median (Range) Treatment A: TMC125 400 mg (formulation A* [L051]) (Reference)	Treatment B, C, or D: TMC125 400 mg (formulation A* [L054], formulation A* [L055], or formulation K* [L039]) (Test)	Ratio [a] (Test:Reference)	90% CI
Treatment A (formulation A* [L051]) vs. Treatment B (formulation A* [L054])				
N	16	15		
t_{max}, h	3.0 (2.0 - 6.0)	3.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	720.2 ± 275.3	885.7 ± 294.0	1.26	1.11 - 1.42
AUC_{last}, ng.h/mL	8742 ± 3714	10890 ± 4309	1.28	1.15 - 1.43
AUC_{∞} [b], ng.h/mL	10400 ± 5148	13020 ± 6056	-	-
$t_{1/2,term}$ [b], h	46.77 ± 17.79	48.96 ± 15.66	-	-
Treatment A (formulation A* [L051]) vs. Treatment C (formulation A* [L055])				
N	16	15		
t_{max}, h	3.0 (2.0 - 6.0)	3.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	720.2 ± 275.3	804.0 ± 280.8	1.11	0.96 - 1.28
AUC_{last}, ng.h/mL	8742 ± 3714	9670 ± 4013	1.10	0.97 - 1.24
AUC_{∞} [b], ng.h/mL	10400 ± 5148	11450 ± 5787	-	-
$t_{1/2,term}$ [b], h	46.77 ± 17.79	45.68 ± 12.38	-	-
Treatment A (formulation A* [L051]) vs. Treatment D (formulation K* [L039])				
N	16	16		
t_{max}, h	3.0 (2.0 - 6.0)	6.0 (3.0 - 6.0)	-	-
C_{max}, ng/mL	720.2 ± 275.3	647.8 ± 260.0	0.88	0.75 - 1.03
AUC_{last}, ng.h/mL	8742 ± 3714	8726 ± 3697	0.98	0.85 - 1.12
AUC_{∞} [b], ng.h/mL	10400 ± 5148	10390 ± 5272	-	-
$t_{1/2,term}$ [b], h	46.77 ± 17.79	43.75 ± 16.63	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
[b] Accurate determination not possible in all subjects.
Source: Module 5.3.1.2/TMC125-C162/Section 4.2.5 and Section 4.2.6

The comparison of the pharmacokinetics of TMC125 administered as formulation K*, Batch L039 , between the current trial and the earlier trial TMC125-C150 showed that the mean (inter-subject) C_{max} and AUC_{last} of TMC125 were comparable in the 2 trials (Table 18). There was no relevant treatment effect for C_{max} or AUC_{last}, suggesting that long-term storage did not affect the bioavailability of TMC125. However, the 90% CIs of the LS means ratios of these 2 parameters were outside the predefined 80% to 125% range.

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Table 18: Comparison of Pharmacokinetics of TMC125 after Administration of Tablet Formulation K* (Batch L039) at a Single Dose of 400 mg in Earlier Trial TMC125-C150 and in Trial TMC125-C162 after Long-Term Storage at Room Temperature (Trial TMC125-C162)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	TMC125-C150 Treatment C: TMC125 400 mg (formulation K* | L039 |) (Reference)	TMC125-C162 Treatment D: TMC125 400 mg (formulation K* [L039]) (Test)		
N	11	16		
t_{max}, h	4.0 (2.0 - 6.0)	6.0 (3.0 - 6.0)	-	-
C_{max}, ng/mL	654.5 ± 228.0	647.8 ± 260.0	0.97	0.71 - 1.33
AUC_{last}, ng.h/mL	7675 ± 3677	8726 ± 3697	1.16	0.80 - 1.67
AUC_{∞} [b], ng.h/mL	8741 ± 4424	10390 ± 5272	-	-
$t_{1/2,term}$ [b], h	40.02 ± 9.48	43.75 ± 16.63	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
[b] Accurate determination not possible in all subjects.
Source: Module 5.3.1.2/TMC125-C162/Section 4.2.7.2 and Section 4.2.7.3

2.2.4.3 CONCLUSIONS

The relative bioavailability (AUC_{last}) of a single dose of 400 mg TMC125 administered as formulation A* was comparable between Batches L055 (large-scale) and L051 (small-scale) but was 1.28-fold higher for Batch L054 (large-scale), compared to Batch L051 (small-scale). Long-term storage of formulation K*, Batch L039 , had no relevant effect on the bioavailability of TMC125.

2.2.5 Trial TMC125-C169: Relative Bioavailability of TMC125 Given as Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) Manufactured at Different Sites and with Different Sources of HPMC, in Healthy Subjects (Effect of Manufacturing Scale and Sources of TMC125 Powder and HPMC)

2.2.5.1 TRIAL DESIGN

This was an open-label, randomized, 4-period crossover trial to evaluate the oral bioavailability of a single 200-mg dose of TMC125 administered as 4 different batches of tablet formulation A* (TMC125 in HPMC, spray-dried) produced at different manufacturing scales and with spray-dried TMC125 powder from different manufacturing sites, and with different sources of HPMC, as follows:

- Reference Treatment: 2 tablets of TMC125 100 mg from a batch representative of the tablets used in the Phase III clinical trials. The tablets were manufactured on a small-scale by [redacted] in [redacted] with spray-dried TMC125 powder from [redacted] and HPMC from [redacted] in [redacted].

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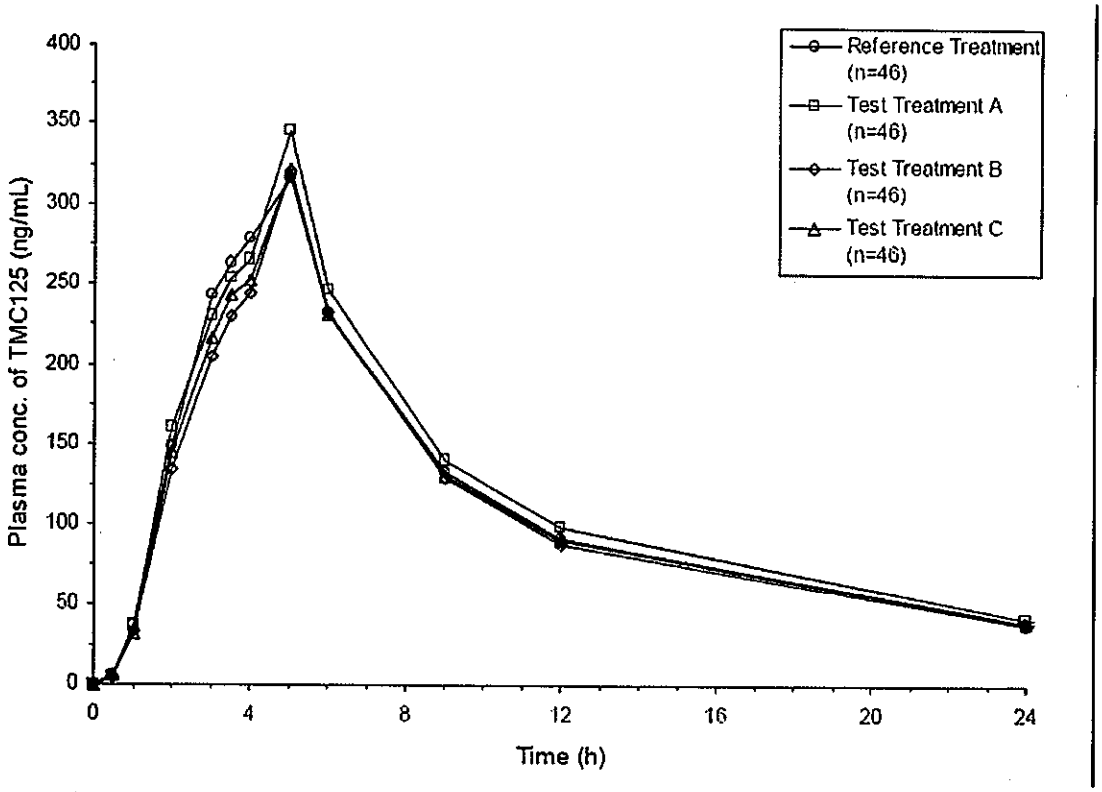
- Test Treatment A: 2 tablets of TMC125 100 mg, manufactured at full-scale by [redacted] in [redacted] with spray-dried TMC125 powder from [redacted] in [redacted] and HPMC from [redacted] in [redacted]
- Test Treatment B: 2 tablets of TMC125 100 mg, manufactured at full-scale by [redacted] in [redacted]
- Test Treatment C: 2 tablets of TMC125 100 mg, manufactured at full-scale by [redacted] in [redacted] with spray-dried TMC125 powder from [redacted] in [redacted] and HPMC from [redacted] in [redacted]

The trial population consisted of 48 healthy subjects. All treatments were taken under fed conditions within 10 minutes after completion of a standardized breakfast. The washout period between treatments was at least 14 days.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.1.2/TMC125-C169).

2.2.5.2 PHARMACOKINETICS OF TMC125

The mean plasma concentration-time profiles overlapped for all 4 treatments. The mean curves and all of the individual curves had a separate absorption phase and a biphasic distribution/elimination phase (Figure 23).



Source: Module 5.3.1.2/TMC125-C169/4.2.4

Figure 23: Plasma Concentration-Time Profiles for TMC125 After Administration of a Single Oral Dose of 200 mg TMC125 with 4 Different Batches of Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) (Trial TMC125-C169)

The median t_{max} was 5 hours for all 4 treatments, and the mean values for C_{max}, AUC_{last}, and AUC to infinity (AUC_{∞}) were comparable between all treatments (Table 19).

Table 19: Pharmacokinetics of TMC125 After Administration of a Single Oral Dose of 200 mg TMC125 with 4 Different Batches of Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) (Trial TMC125-C169)

Parameter	Reference Treatment TMC125 200 mg	Test Treatment A TMC125 200 mg	Test Treatment B TMC125 200 mg	Test Treatment C TMC125 200 mg
N	46	46	46	46
t_{max}, h	5.0 (2.0 - 6.0)	5.0 (2.0 - 5.0)	5.0 (3.0 - 6.0)	5.0 (2.0 - 6.0)
C_{max}, ng/mL	352.5 ± 104.8	372.2 ± 90.43	334.7 ± 96.73	341.5 ± 91.69
AUC_{last}, ng.h/mL	4129 ± 1463	4305 ± 1595	3916 ± 1614	4011 ± 1507
AUC_{∞}, ng.h/mL	4528 ± 1699	4746 ± 1855	4279 ± 1848	4459 ± 1843
$t_{1/2,term}$, h	32.25 ± 7.202	33.68 ± 10.27	31.71 ± 6.906	33.65 ± 9.336

N = maximum number of subjects with data.

Source: Module 5.3.1.2/TMC125-C169/Section 4.2.5

For all treatment comparisons, the 90% CIs of the LS means ratios were within the 80% to 125% range (Table 20).

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Table 20: Statistical Analysis of the Pharmacokinetic Parameters of TMC125 After Administration of a Single Oral Dose of 200 mg TMC125 with 4 Different Batches of Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) (Trial TMC125-C169)

Parameter	Ratio [a] (Test:Reference)	90% CI
Test Treatment A (Spray-Dried Powder from [redacted] with HPMC from [redacted]) vs. Reference Treatment		
N	46	46
C_{max}, ng/mL	1.07	1.01 - 1.14
AUC_{last}, ng.h/mL	1.04	0.99 - 1.09
AUC_{∞}, ng.h/mL	1.04	0.99 - 1.09
Test Treatment B (Spray-Dried Powder from [redacted] with HPMC from [redacted]) vs. Reference Treatment		
N	46	46
C_{max}, ng/mL	0.95	0.88 - 1.02
AUC_{last}, ng.h/mL	0.93	0.88 - 0.99
AUC_{∞}, ng.h/mL	0.93	0.87 - 0.99
Test Treatment C (Spray-Dried Powder from [redacted] with HPMC from [redacted]) vs. Reference Treatment		
N	46	46
C_{max}, ng/mL	0.98	0.92 - 1.04
AUC_{last}, ng.h/mL	0.97	0.92 - 1.03
AUC_{∞}, ng.h/mL	0.98	0.92 - 1.04

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.1.2/TMC125-C169/Section 4.2.6

2.2.5.3 CONCLUSIONS

The manufacturing site of the spray-dried powder and the scale of tablet manufacture, as well as the source of HPMC, had no effect on the bioavailability of TMC125 administered as tablet formulation A*, compared to the bioavailability of TMC125 administered as tablet formulation A* from a batch representative of the tablets used in the Phase III clinical trials.

2.2.6 Trial TMC125-C172: Relative Bioavailability of TMC125 Given as Powder Formulation R* (TMC125 in HPMC, Spray-Dried) Manufactured at Different Sites, Compared to Reference Tablet Formulation A* (TMC125 in HPMC, Spray-Dried), in Healthy Subjects (Effect of Powder Manufacturing Site)

2.2.6.1 TRIAL DESIGN

This was an open-label, randomized, 3-period crossover trial to evaluate the relative bioavailability of the TMC125 spray-dried drug product formulated as 2 batches of powder formulation R* (TMC125 in HPMC, spray-dried, termed "Powder 1" and "Powder 2") compared to tablet formulation A* (TMC125 in HPMC, spray-dried). The trial population consisted of 24 healthy subjects. Each subject received a single, oral, 200 mg dose of TMC125 on 3 occasions. In each of 3 sessions, each subject received either the reference formulation (Treatment A) or one of the 2 different test formulations (Treatments B or C). The treatment groups were:

- Treatment A (reference): 2 tablets (formulation A*), each containing 100 mg TMC125 in HPMC, spray-dried. The tablet was made with TMC125 base that was spray-dried by [redacted]. The powder used for manufacturing the tablets was the same powder formulation as used in Treatment C (formulation R*, "Powder 2");
- Treatment B (test): Powder (taken in water) (formulation R*, Batch L099 "Powder 1"), containing 200 mg TMC125 in HPMC, spray-dried. Powder 1 was manufactured by [redacted];
- Treatment C (test): Powder (taken in water) (formulation R*, Batch L098 , "Powder 2"), containing 200 mg TMC125 in HPMC, spray-dried. Powder 2 was manufactured by [redacted]

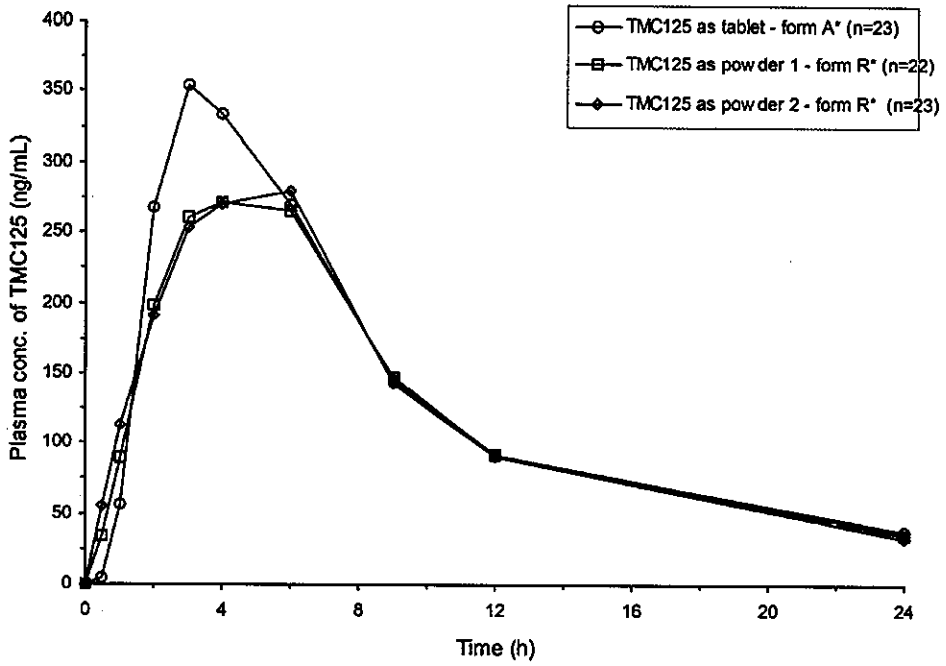
The reason for testing the 2 different batches of powder formulation R* was the plan to move the manufacture of TMC125 spray-dried powder from [redacted] to [redacted] in [redacted]. The powder formulation also served as a further potential oral formulation concept.

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

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.1.2/TMC125-C172).

2.2.6.2 PHARMACOKINETICS OF TMC125

The mean plasma concentration-time profiles of the 2 types of powder formulation R* were highly comparable, whereas a higher mean maximum concentration was attained with the tablet formulation A* (Figure 24).



Source: Module 5.3.1.2/TMC125-C172/Section 4.2.4 form :formulation *

Figure 24: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of Two Test Batches of Powder Formulation R* (TMC125 in HPMC, Spray-Dried) and Reference Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) at a Single Dose of 200 mg (Trial TMC125-C172)

The mean exposure to TMC125 was lower when administered as the Powder 1 or Powder 2 formulation R*, compared to administration of the tablet formulation A*. The mean C_{max} and AUC_{last} of TMC125 were 25% and 10% lower, respectively, with Powder 1, and 23% and 11% lower, respectively, with Powder 2 (Table 21).

Inter-individual variability (CV) in C_{max} and AUC_{last} values of TMC125 was 39% and 61% when TMC125 was administered as tablet formulation A*, 43% and 63% when administered as Powder 1, and 42% and 59% when administered as Powder 2 (Module 5.3.1.2/TMC125-C172/Section 4.2.5).

The median t_{max} with tablet formulation A* (3.0 hours) was slightly shorter than with formulation R* Powder 1 or Powder 2 (4.0 and 5.0 hours, respectively). The mean terminal elimination half-life of TMC125 was comparable after administration of formulation A* (58 hours) and formulation R* Powder 1 or Powder 2 (54 hours).

There was no difference in the mean exposure (C_{max} and AUC_{last}) to TMC125 when administered as formulation R* Powder 1 or Powder 2.

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Table 21: Pharmacokinetics of TMC125 after Administration of Two Test Batches of Powder Formulation R* (TMC125 in HPMC, Spray-Dried) and Reference Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) at a Single Dose of 200 mg (Trial TMC125-C172)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment A or B: TMC125 200 mg Tablet or Powder 1 (formulations A*or R*) (Reference)	Treatment B or C: TMC125 200 mg Powder 1 or Powder 2 (formulation R*) (Test)		
Treatment A (formulation A*, Tablet) vs. Treatment B (formulation R*, Powder 1)				
N	23	22		
t_{max}, h	3.0 (2.0 - 6.0)	5.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	422.2 ± 166.3	312.5 ± 134.3	0.75	0.68 - 0.82
AUC_{last}, ng.h/mL	4766 ± 2916	4361 ± 2768	0.90	0.85 - 0.95
AUC_{∞} [b], ng.h/mL	6105 ± 4646	5528 ± 4470	-	-
$t_{1/2,term}$ [b], h	58.35 ± 21.44	53.92 ± 20.25	-	-
Treatment A (formulation A*, Tablet) vs. Treatment C (formulation R*, Powder 2)				
N	23	23		
t_{max}, h	3.0 (2.0 - 6.0)	4.0 (1.0 - 6.0)	-	-
C_{max}, ng/mL	422.2 ± 166.3	328.3 ± 138.8	0.77	0.68 - 0.87
AUC_{last}, ng.h/mL	4766 ± 2916	4254 ± 2509	0.89	0.84 - 0.95
AUC_{∞} [b], ng.h/mL	6105 ± 4646	5223 ± 3561	-	-
$t_{1/2,term}$ [b], h	58.35 ± 21.44	54.42 ± 23.56	-	-
Treatment B (formulation R*, Powder 1) vs. Treatment C (formulation R*, Powder 2)				
N	22	23		
t_{max}, h	5.0 (2.0 - 6.0)	4.0 (1.0 - 6.0)	-	-
C_{max}, ng/mL	312.5 ± 134.3	328.3 ± 138.8	1.04	0.93 - 1.16
AUC_{last}, ng.h/mL	4361 ± 2768	4254 ± 2509	1.00	0.94 - 1.06
AUC_{∞} [b], ng.h/mL	5528 ± 4470	5223 ± 3561	-	-
$t_{1/2,term}$ [b], h	53.92 ± 20.25	54.42 ± 23.56	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
[b] Accurate determination not possible in all subjects.
Source: Module 5.3.1.2/TMC125-C172/Section 4.2.5 and Section 4.2.6

2.2.6.3 CONCLUSIONS

The mean exposure (AUC_{last}) to TMC125 after administration of a single dose of 200 mg TMC125 as formulation R* Powder 1 or Powder 2 was approximately 10% lower than after administration of TMC125 as the 100 mg tablet. The exposure to TMC125 was comparable when TMC125 was administered as formulation R* Powder 1 or Powder 2, indicating that the manufacturing site had no effect on the bioavailability of TMC125 formulation R*.

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2.3 FOOD EFFECT TRIALS

2.3.1 Trial TMC125-C147: Effect of Food on Bioavailability of TMC125 Given as Tablet Formulation A* in Healthy Subjects (TMC125 in HPMC, Spray-Dried)

2.3.1.1 TRIAL DESIGN

This was an open-label, randomized, 3-period crossover trial to investigate the effect of various types of meals on the relative bioavailability of TMC125 given as tablet formulation A* (TMC125 in HPMC, spray-dried). In all treatments, a single dose of 100 mg TMC125 was taken within 10 minutes after completion of one of the following 4 types of breakfast, or under fasted conditions, as follows:

- Standardized breakfast (Treatment A): 4 slices of bread, 2 slices of ham or cheese, butter, jelly, and 2 cups of decaffeinated coffee or tea with milk and/or sugar, if desired (486 g, 561 kcal; 15.33 g fat; 21.89 g proteins; 83.86 g carbohydrates; 8.08 g fiber);
- Fasted conditions (Treatment B): Fasted for at least 10 hours before administration of trial medication. Water intake was allowed up until 2 hours before administration of trial medication;
- Snack (Treatment C): Butter croissant with 1 teaspoon of unsalted butter and 1 teaspoon of jam, 1 cup of decaffeinated coffee or tea with milk and/or sugar as desired (213 g; 345 kcal; 17.44 g fat; 5.16 g proteins; 41.43 g carbohydrates; 1.25 g fiber);
- Enhanced-fiber breakfast* (Treatment D): 80 g grapes with skin, 80 g raw pineapple, 80 g raw pears, 80 g raw strawberries, 1 glass of orange juice (225 g), 1 raw banana (200 g), 2 slices of mixed grain bread, 2 tablespoons (40 g) of jam (855 g; 685 kcal; 3.12 g fat; 13.37 g proteins; 151.24 g carbohydrates; 16.4 g fiber);
- High-fat breakfast (Treatment E): 2 large fried eggs, 2 slices of fried bacon, 1 butter croissant, 2 slices of white bread, 1 teaspoon of unsalted butter, 1 bar of semisweet chocolate (30 g), 1 cup of decaffeinated coffee/tea with milk and/or sugar as desired (468 g; 1160 kcal; 70.26 g fat; 40.36 g proteins; 91.26 g carbohydrates; 2.21 g fiber).

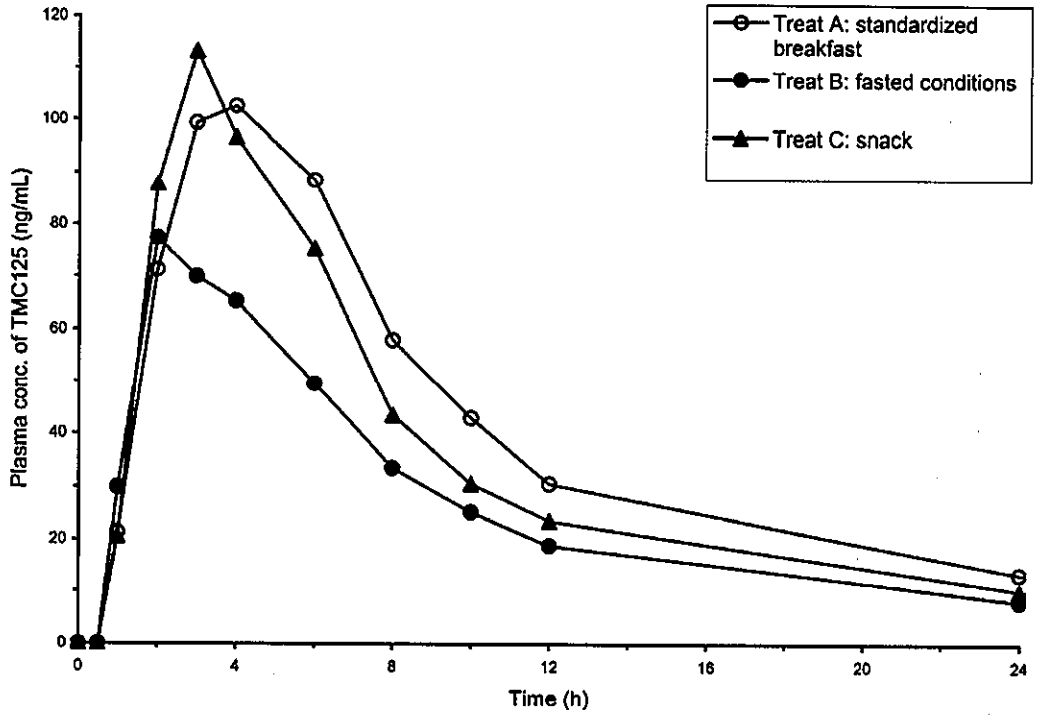
The trial population consisted of 2 parallel panels of 12 healthy subjects each. In 3 sessions, subjects in Panel 1 received Treatments A, B, and C, and subjects in Panel 2 received Treatments A, D, and E. The washout period between treatments was at least 14 days.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.1.1/TMC125-C147).

* Termed a "high-fiber breakfast" in the trial report.

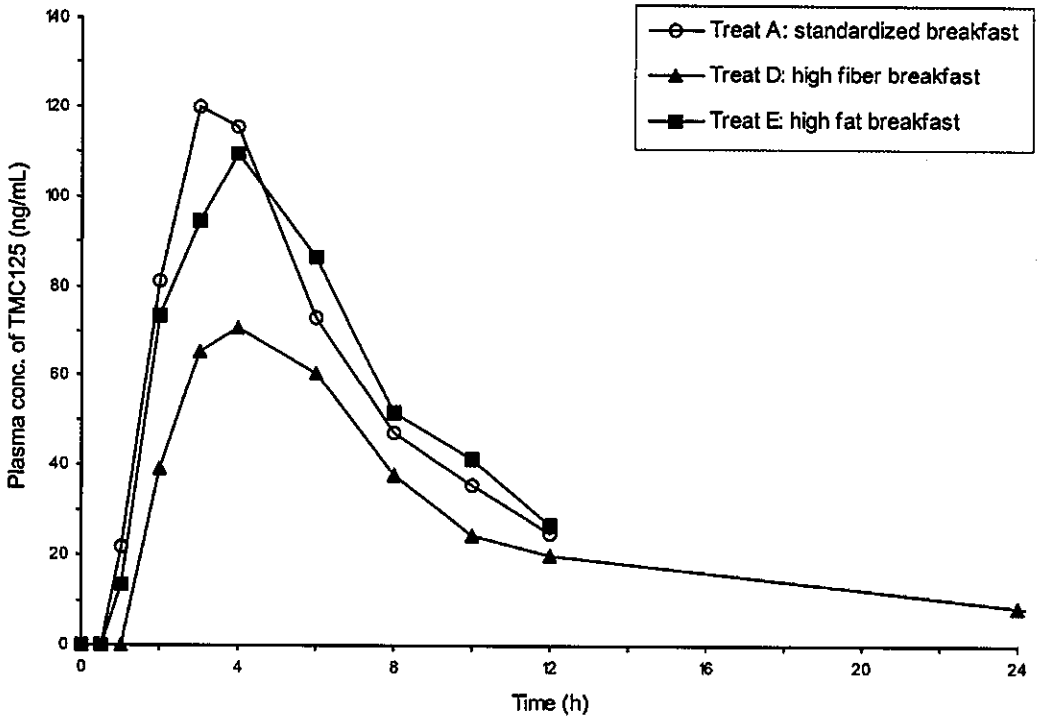
2.3.1.2 PHARMACOKINETICS OF TMC125

With all treatments, the mean plasma concentration-time profiles of TMC125 were characterized by a steep absorption phase after an initial lag time of approximately 0.5 hours, followed by an initially fast distribution/elimination phase and a slower terminal elimination phase (Figure 25 [Panel 1], Figure 26 [Panel 2]).



N = 12 in each treatment group.
Snack = croissant with coffee or tea.
Source: Module 5.3.1.1/TMC125-C147/Section 4.2.4

Figure 25: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of a Single Dose of 100 mg TMC125 (formulation A* [TMC125 in HPMC, Spray-Dried]) Given Either after a Standardized Breakfast or after a Snack, or Under Fasted Conditions (Panel 1) (Trial TMC125-C147)



N = 11 (Treatments A and D) or 12 (Treatment E).
Source: Module 5.3.1.1/TMC125-C147/Section 4.2.4

Figure 26: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of a Single Dose of 100 mg TMC125 (formulation A* [TMC125 in HPMC, Spray-Dried]) Given after a Standardized Breakfast, after a High-Fat Breakfast, or after an Enhanced ("High")-Fiber Breakfast (Panel 2) (Trial TMC125-C147)

The mean exposure to TMC125 (in terms of C_{max} and AUC_{last}) was comparable when administered after a standardized breakfast (Treatment A) and after a high-fat breakfast (Treatment E), although the 90% CIs of the LS means ratios were outside the 80% to 125% range (Table 22). Administration of TMC125 after a snack (Treatment C) had no effect on the mean C_{max} of TMC125, compared to administration after a standardized breakfast (Treatment A), but the mean AUC_{last} was 20% lower. Overall, the differences in exposure to TMC125 when administered with a high-fat breakfast, a standardized breakfast, or a snack were not considered to be clinically relevant.

In contrast, administration of TMC125 under fasted conditions (Treatment B) and after an enhanced-fiber breakfast (Treatment D) resulted in substantially lower exposure to TMC125, compared to intake after a standardized breakfast, with the effect being larger under fasted conditions than after an enhanced-fiber breakfast. In terms of C_{max} and AUC_{last}, the mean exposure was 44% and 51% lower, respectively, under fasted conditions, and 38% and 25% lower after administration with an enhanced-fiber breakfast.

The mean terminal elimination half-life of TMC125 was in the range of 20 to 26 hours, irrespective of the treatment administered.

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Table 22: Pharmacokinetics of TMC125 after Administration of a Single Dose of 100 mg TMC125 (formulation A* [TMC125 in HPMC, Spray-Dried]) Given Under Fasted Conditions or after a Standardized Breakfast or Other Meal Types (Trial TMC125-C147)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment A: TMC125 100 mg Standard Breakfast (Reference)	Treatment B, C, D, or E: TMC125 100 mg Fasted or Other Meal Types (Test)		
Panel 1: Treatment A (Standard Breakfast) vs. Treatment B (Fasted Conditions)				
N	12	12		
t_{max}, h	4.0 (2.0 - 6.0)	2.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	128.6 ± 63.73	88.83 ± 67.97	0.56	0.41 - 0.77
AUC_{last}, ng.h/mL	1417 ± 1140	920.5 ± 1024	0.49	0.39 - 0.61
AUC_{∞} [b], ng.h/mL	1641 ± 1437	1089 ± 1314	-	-
$t_{1/2,term}$ [b], h	24.14 ± 12.93	19.91 ± 15.43	-	-
Panel 1: Treatment A (Standard Breakfast) vs. Treatment C (Snack)				
N	12	12		
t_{max}, h	4.0 (2.0 - 6.0)	3.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	128.6 ± 63.73	127.5 ± 73.06	0.97	0.75 - 1.25
AUC_{last}, ng.h/mL	1417 ± 1140	1189 ± 1106	0.80	0.69 - 0.94
AUC_{∞} [b], ng.h/mL	1641 ± 1437	1462 ± 1691	-	-
$t_{1/2,term}$ [b], h	24.14 ± 12.93	25.02 ± 20.88	-	-
Panel 2: Treatment A (Standard Breakfast) vs. Treatment D (Enhanced-Fiber Breakfast)				
N	11	11		
t_{max}, h	3.0 (2.0 - 6.0)	3.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	138.4 ± 61.33	85.05 ± 40.31	0.62	0.47 - 0.83
AUC_{last}, ng.h/mL	1191 ± 699.6	863.6 ± 407.2	0.75	0.63 - 0.90
AUC_{∞} [b], ng.h/mL	1330 ± 762.6	960.3 ± 479.7	-	-
$t_{1/2,term}$ [b], h	24.67 ± 15.23	22.39 ± 18.89	-	-
Panel 2: Treatment A (Standard Breakfast) vs. Treatment E (High-Fat Breakfast)				
N	11	12		
t_{max}, h	3.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	138.4 ± 61.33	129.9 ± 64.12	0.95	0.70 - 1.29
AUC_{last}, ng.h/mL	1191 ± 699.6	1202 ± 585.7	1.09	0.84 - 1.41
AUC_{∞} [b], ng.h/mL	1330 ± 762.6	1342 ± 642.4	-	-
$t_{1/2,term}$ [b], h	24.67 ± 15.23	25.81 ± 12.91	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
[b] Accurate determination not possible in all subjects.
Source: Module 5.3.1.1/TMC125-C147/Section 4.2.5 and Section 4.2.6

2.3.1.3 CONCLUSIONS

Administration of a single dose of TMC125 (formulation A*) under fasted conditions or after an enhanced-fiber breakfast substantially decreased the exposure of TMC125, compared to administration after a standardized breakfast. The differences in exposure when TMC125 was taken with a high-fat breakfast, a standardized breakfast, or a snack were not clinically relevant. Based on the results of this trial, it is recommended to take TMC125 (formulation A*) following a meal.

2.3.2 Trial TMC125-C116: Pharmacokinetic Interaction Between Ritonavir and TMC125 Given as Tablet Formulation A* (TMC125 in HPMC, Spray-Dried) Under Various Dosing Regimens, Including Investigation of the Effect of the Timing of Food Administration on Bioavailability of TMC125, in Healthy Subjects

2.3.2.1 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 ritonavir (RTV) and a single dose of TMC125 given as 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 (Panel 2). The trial population consisted of 40 healthy subjects, equally divided between the 2 panels. In Panel 2, data from the following 2 treatment groups enabled the effect of the timing of food administration on the pharmacokinetics of TMC125 to be assessed:

- Treatment F: single dose of 200 mg TMC125 10 minutes after completion of a standardized breakfast;
- Treatment G: single dose of 200 mg TMC125 2 minutes before starting a 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).[2] There was a washout period of at least 14 days between subsequent TMC125 intakes.

The results obtained from the remaining treatment groups (Treatments A to D in Panel 1, and Treatments E and H in Panel 2), in which the interaction between TMC125 and co-administered RTV was investigated, are summarized in Module 2.7.2/Section 2.8.1.3. 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).

2.3.2.2 Pharmacokinetics of TMC125

The mean C_{max} and AUC_{last} of TMC125 were 23% and 17% lower when taken before breakfast (Treatment G), compared to when taken after breakfast (Treatment F) (Table 23). The 90% CIs of the LS means were outside the 80% to 125% range. There were no relevant differences in the median t_{max} or mean terminal elimination half-life.

Table 23: Pharmacokinetics of TMC125 after Administration of a Single Dose of 200 mg TMC125 (Formulation A* [TMC125 in HPMC, Spray-Dried]) before and after Breakfast (Panel 2) (Trial TMC125-C116)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment F: TMC125 200 mg after Breakfast (Reference)	Treatment G: TMC125 200 mg before Breakfast (Test)		
N	17	19		
t_{max}, h	4.0 (2.0 - 6.0)	3.0 (1.0 - 6.0)	-	-
C_{max}, ng/mL	419.1 ± 138.6	346.6 ± 211.1	0.77	0.67 - 0.87
AUC_{last}, ng.h/mL	6184 ± 4305	5409 ± 4713	0.83	0.76 - 0.90
AUC_{∞} [b], ng.h/mL	7632 ± 6708	6868 ± 8297	-	-
$t_{1/2,term}$ [b], h	42.43 ± 14.88	42.16 ± 15.85	-	-

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

2.3.2.3 CONCLUSIONS

The mean exposure (AUC_{last}) to TMC125 (formulation A*) was 17% lower when administered before a standardized breakfast, as compared to administration after a standardized breakfast. It is therefore recommended that TMC125 (formulation A*) be taken following a meal.

2.3.3 Trial TMC125-C133: Effect of Food on Bioavailability of TMC125 Given as Tablet Formulation S* in Healthy Subjects (TMC125 in HPMC, Granulo-Layered)

2.3.3.1 TRIAL DESIGN

This was an open-label, 2-period crossover trial to investigate the effect of a standardized breakfast, compared to fasted conditions, on the relative bioavailability of TMC125 given as tablet formulation S* (TMC125 in HPMC, granulo-layered). A single dose of 400 mg TMC125 was taken after completion of a standardized breakfast or under fasted conditions, as follows:

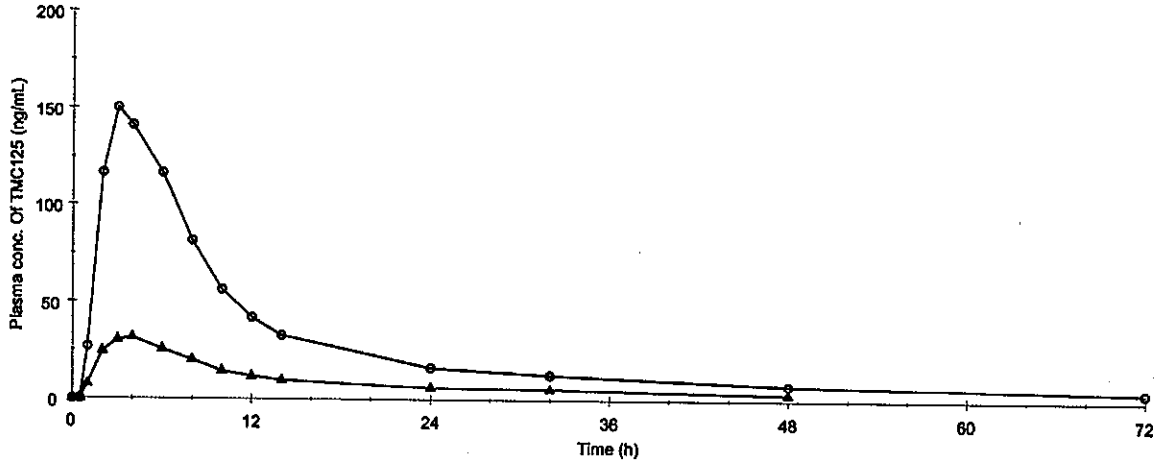
- Standardized breakfast (Treatment A): 4 slices of bread, 1 slice of ham, 1 slice of cheese, butter, jelly, and 2 cups of coffee or tea with, if desired, milk and/or sugar. The trial medication was given within 10 minutes after completion of the breakfast;
- Fasted conditions (Treatment B): Fasted for at least 10 hours before administration of trial medication. Water intake was allowed up until 2 hours before administration of trial medication.

The trial population consisted of 12 healthy subjects. In each of 2 sessions, subjects received either Treatment A or Treatment B. The washout period between treatments was at least 10 days.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.1.1/TMC125-C133).

2.3.3.2 PHARMACOKINETICS OF TMC125

TMC125 was rapidly absorbed when administered after a standardized breakfast (Figure 27). When administered under fasted conditions, TMC125 plasma concentrations were considerably lower.



o = Treatment A: Fed conditions (N = 12).
Δ = Treatment B: Fasted conditions (N = 12).
Source: Module 5.3.1.1/TMC125-C133/Section 8.A (Display 5)

Figure 27: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of a Single Dose of 400 mg TMC125 (formulation S* [TMC125 in HPMC, Granulo-Layered]) Given after a Standardized Breakfast or Under Fasted Conditions (Trial TMC125-C133)

The median t_{max} of TMC125 was 3 hours under the fed and fasted conditions (Table 24). The mean C_{max} and AUC_{last} of TMC125 were 4.78- and 3.18-fold higher, respectively, when TMC125 was administered after the standardized breakfast, compared to administration under fasted conditions.

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Table 24: Pharmacokinetics of TMC125 after Administration of a Single Dose of 400 mg TMC125 (formulation S* [TMC125 in HPMC, Granulo-Layered]) Given after a Standardized Breakfast or Under Fasted Conditions (Trial TMC125-C133)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment B: TMC125 400 mg Fasted (Reference)	Treatment A: TMC125 400 mg Fed (Test)		
N	12	12		
t_{max}, h	3 (2 - 6)	3 (2 - 6)	-	-
C_{max}, ng/mL	34 ± 19.0	174 ± 94.1	4.78	3.51 - 6.49
AUC_{last}, ng.h/mL	507 ± 279	1809 ± 961	3.18	2.19 - 4.61
AUC_{∞} [b], ng.h/mL	687 ± 311	2157 ± 959	2.80	1.97 - 3.98
$t_{1/2,term}$ [b], h	39.5 ± 22.24	24.7 ± 5.40	-	-

N = maximum number of subjects with data.
[a] Ratio based on geometric means.
[b] Accurate determination not possible in all subjects.
Source: Module 5.3.1.1/TMC125-C133/Section 4.C.5

2.3.3.3 CONCLUSIONS

The mean exposure (AUC_{last}) to TMC125 (formulation S*) was increased 3.18-fold when taken following a meal.

2.3.4 Trial TMC125-C137: Effect of Food and Different Types of Meals on Bioavailability of TMC125 Given as Tablet Formulation F* in Healthy Subjects (TMC125 in HPMC, Granulo-Layered)

2.3.4.1 TRIAL DESIGN

This was an open-label, randomized, 4-period crossover trial to investigate the effect of various types of meals on the relative bioavailability of TMC125 given as the 200-mg tablet formulation F* (TMC125 in HPMC, granulo-layered). In all treatments, a single dose of 1600 mg TMC125 was taken within 10 minutes after completion of the following 3 types of breakfast, or under fasted conditions, as follows:

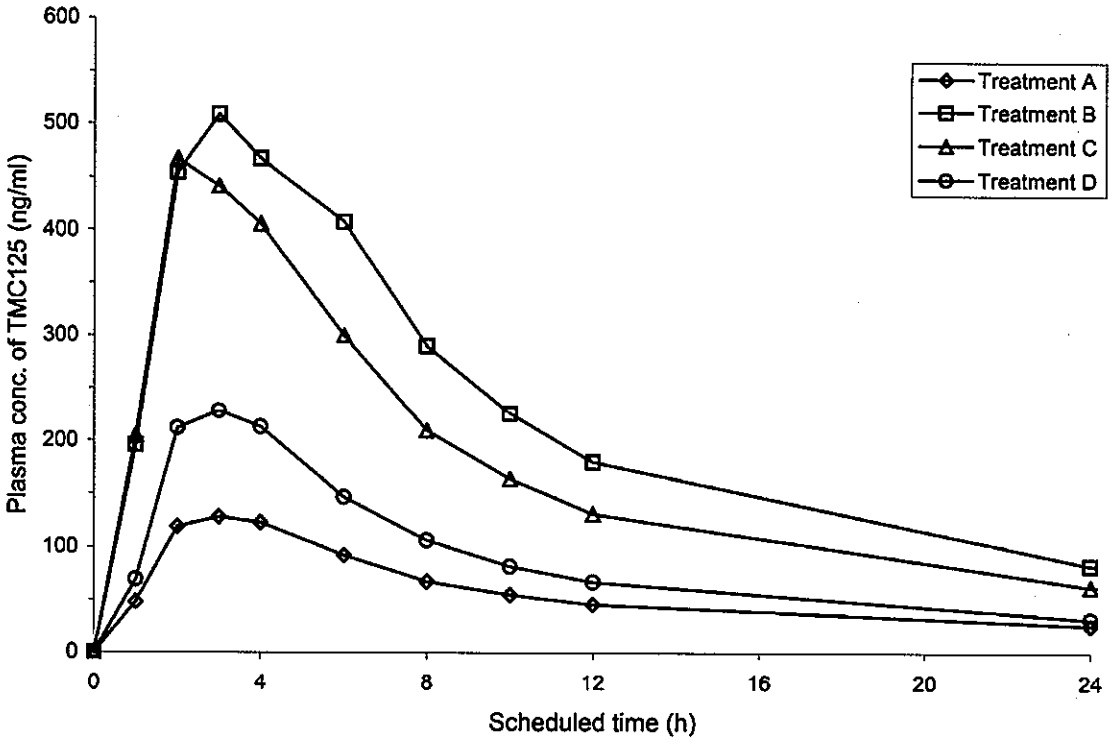
- Fasted treatment (Treatment A): Fasted for at least 10 hours before administration of trial medication. Water intake was allowed up until 2 hours before administration of trial medication;
- Standardized breakfast (Treatment B): 4 slices of bread, 2 slices of ham or cheese, butter, jelly and 2 cups of decaffeinated coffee or tea with milk and/or sugar, if desired;
- High-fat breakfast (Treatment C): 2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, a croissant with a slice of cheese, and 240 mL of whole milk;
- Snack (Treatment D): 2 slices of white bread, one teaspoonful low-fat margarine, one tablespoon jelly, 150 mL orange juice, and 150 mL skimmed milk.

The trial population consisted of 16 healthy subjects. In 4 sessions, subjects received Treatments A, B, C, and D. The washout period between treatments was at least 10 days.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.1.1/TMC125-C137).

2.3.4.2 PHARMACOKINETICS OF TMC125

The mean plasma concentration-time profiles of TMC125 when administered after a snack and under fasted conditions lay below the profiles when administered after a standard breakfast and after a high-fat breakfast (Figure 28). For all treatments, no lag time in absorption was observed.



Treatment A: Fasted conditions (N = 15).
Treatment B: Standard breakfast (N = 13).
Treatment C: High-fat breakfast (N = 15).
Treatment D: Snack (N = 15).
Source: Module 5.3.1.1/TMC125-C137/Section 4.2.4

Figure 28: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of a Single Dose of 1600 mg TMC125 (formulation F* [TMC125 in HPMC, Granulo-Layered]) Given under Fed Conditions with Different Types of Meals or under Fasted Conditions (Trial TMC125-C137)

The median t_{max} for TMC125 was 3 hours when administered under fasted conditions, after a standardized breakfast (Treatment B), and after a snack (Treatment D), whereas the median t_{max} after a high-fat breakfast (Treatment C) was achieved earlier (2 hours) (Table 25).

The highest exposure to TMC125 was observed when administered after a standardized breakfast (Treatment B), and the lowest exposure was observed under fasted conditions (Treatment A). Compared to administration after fasted conditions, the mean C_{max} and AUC_{last} of TMC125 were 4.53- and 3.72-fold higher, respectively, after a standardized breakfast, 4.09- and 3.04-fold higher after a high-fat breakfast, and 1.91- and 1.60-fold higher after a snack.

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For all treatments, the mean terminal elimination half-life was in the range of approximately 25 to 30 hours.

Table 25: Pharmacokinetics of TMC125 after Administration of a Single Dose of 1600 mg TMC125 (formulation F* [TMC125 in HPMC, Granulo-Layered]) Given Under Fed Conditions with Different Types of Meals or Under Fasted Conditions (Trial TMC125-C137)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment A: TMC125 1600 mg Fasted (Reference)	Treatment B, C, or D: TMC125 1600 mg Fed (Test)		
Treatment A (Fasted Conditions) vs. Treatment B (Standardized Breakfast)				
N	15	13		
t_{max}, h	3.0 (2.0 - 6.0)	3.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	141 ± 110	582 ± 257	4.53	3.24 - 6.33
AUC_{last}, ng.h/mL	2179 ± 1810	7871 ± 4435	3.72	2.82 - 4.92
AUC_{∞} [b], ng.h/mL	2819 ± 2300	9100 ± 5624	-	-
$t_{1/2,term}$ [b], h	29.4 ± 9.49	27.6 ± 7.12	-	-
Treatment A (Fasted Conditions) vs. Treatment C (High-Fat Breakfast)				
N	15	15		
t_{max}, h	3.0 (2.0 - 6.0)	2.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	141 ± 110	511 ± 274	4.09	3.21 - 5.22
AUC_{last}, ng.h/mL	2179 ± 1810	6135 ± 4313	3.04	2.43 - 3.80
AUC_{∞} [b], ng.h/mL	2819 ± 2300	7371 ± 5731	-	-
$t_{1/2,term}$ [b], h	29.4 ± 9.49	28.7 ± 7.25	-	-
Treatment A (Fasted Conditions) vs. Treatment D (Snack)				
N	15	15		
t_{max}, h	3.0 (2.0 - 6.0)	3.0 (2.0 - 4.0)	-	-
C_{max}, ng/mL	141 + 110	247 + 183	1.91	1.51 - 2.40
AUC_{last}, ng.h/mL	2179 ± 1810	3107 ± 2291	1.60	1.27 - 2.01
AUC_{∞} [b], ng.h/mL	2819 ± 2300	3644 ± 2938	-	-
$t_{1/2,term}$ [b], h	29.4 ± 9.49	25.7 ± 9.39	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
[b] Accurate determination not possible in all subjects.
Source: Module 5.3.1.1/TMC125-C137/Section 4.2.5 and Section 4.2.6

When comparing the treatments taken after different types of meals with each other, the mean exposures to TMC125 (in terms of C_{max} and AUC_{last}) when administered after a standardized breakfast and after a high-fat breakfast were comparable (Table 26). The mean exposure to TMC125 when administered after a snack was 59% lower than when administered after a standardized breakfast.

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Table 26: Pharmacokinetics of TMC125 after Administration of a Single Dose of 1600 mg TMC125 (formulation F* [TMC125 in HPMC, Granulo-Layered]) Given after a Standardized Breakfast, Compared to Administration after a High-Fat Breakfast or after a Snack (Trial TMC125-C137)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment B: TMC125 1600 mg Standardized Breakfast (Reference)	Treatment C or D: TMC125 1600 mg Other Meals (Test)		
Treatment B (Standardized Breakfast) vs. Treatment C (High-Fat Breakfast)				
N	13	15		
t_{max}, h	3.0 (2.0 - 6.0)	2.0 (2.0 - 6.0)	-	-
C_{max}, ng/mL	582 ± 257	511 ± 274	0.89	0.79 - 1.02
AUC_{last}, ng.h/mL	7871 ± 4435	6135 ± 4313	0.82	0.69 - 0.96
AUC_{∞} [b], ng.h/mL	9100 ± 5624	7371 ± 5731	-	-
$t_{1/2,term}$ [b], h	27.6 ± 7.12	28.7 ± 7.25	-	-
Treatment B (Standardized Breakfast) vs. Treatment D (Snack)				
N	13	15		
t_{max}, h	3.0 (2.0 - 6.0)	3.0 (2.0 - 4.0)	-	-
C_{max}, ng/mL	582 ± 257	247 ± 183	0.41	0.35 - 0.49
AUC_{last}, ng.h/mL	7871 ± 4435	3107 ± 2291	0.41	0.36 - 0.46
AUC_{∞} [b], ng.h/mL	9100 ± 5624	3644 ± 2938	-	-
$t_{1/2,term}$ [b], h	27.6 ± 7.12	25.7 ± 9.39	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means.
[b] Accurate determination not possible in all subjects.
Source: Module 5.3.1.1/TMC125-C137/Section 4.2.5 and Section 4.2.6

2.3.4.3 CONCLUSIONS

The highest exposure to TMC125 (administered as formulation F*) was observed when administered after a standardized breakfast, and the lowest exposure was observed under fasted conditions. Compared to administration after fasted conditions, the mean exposure to TMC125 (AUC_{last}) was 3.72-fold higher after a standardized breakfast, 3.04-fold higher after a high-fat breakfast, and 1.60-fold higher after a snack. The difference in mean exposure to TMC125 when administered after a standardized breakfast and after a high-fat breakfast was not relevant, but the mean exposure to TMC125 when administered after a snack was 59% lower than when administered after a standardized breakfast. Based on the results of this trial, it was recommended in Phase IIb trials that TMC125 (formulation F*) be taken following a substantial meal.

2.3.5 Trial TMC125-C103: Effect of Food on Bioavailability of TMC125 Given as Capsule Formulation T* in Healthy Subjects (TMC125 in PEG 4000)

2.3.5.1 TRIAL DESIGN

This was an open-label, randomized, 2-period crossover trial to investigate the effect of a standardized breakfast, compared to fasted conditions, on the relative bioavailability of TMC125 given as the 50-mg capsule formulation T* (TMC125 in PEG 4000). A single dose of

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200 mg TMC125 was taken after completion of a standardized breakfast or under fasted conditions, as follows:

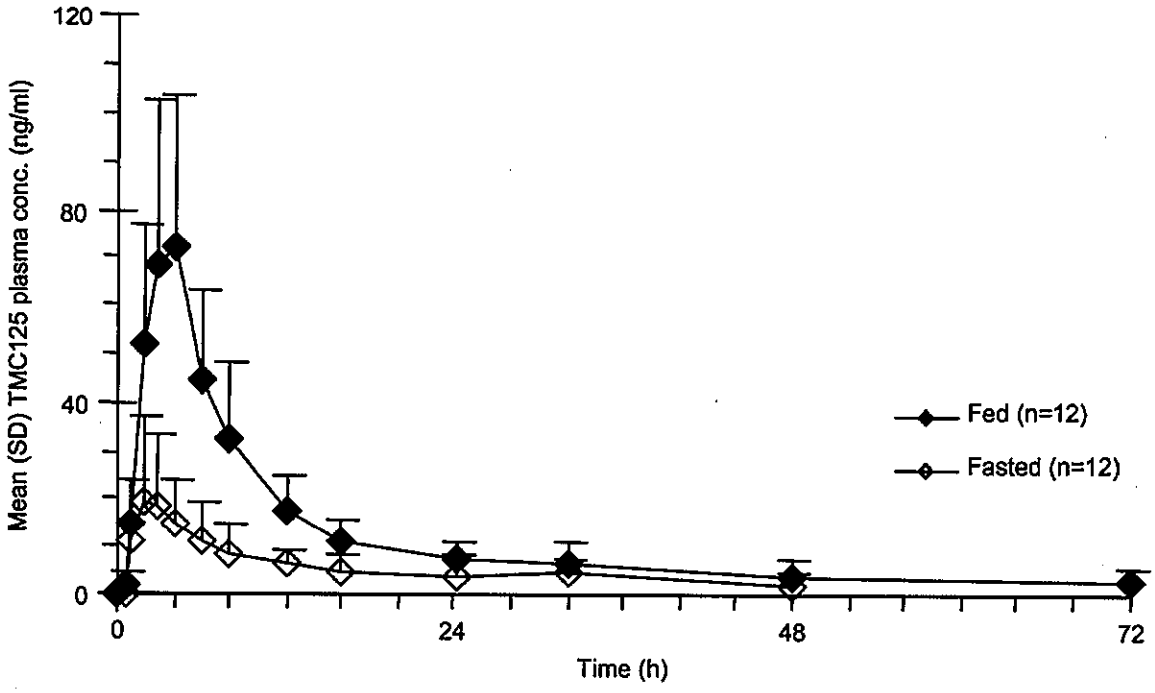
- Standardized breakfast (Treatment A): 4 slices of bread, 1 slice of ham, 1 slice of cheese, butter, jelly, and 2 cups of coffee or tea with, if desired, milk and/or sugar. The trial medication was given within 10 minutes after completion of the breakfast;
- Fasted conditions (Treatment B): Fasted for at least 10 hours before administration of trial medication. Water intake was allowed up until 2 hours before administration of trial medication.

The trial population consisted of 12 healthy subjects. In each of 2 sessions, subjects received either Treatment A or Treatment B. The washout period between treatments was 11 days.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.1.1/TMC125-C103).

2.3.5.2 PHARMACOKINETICS OF TMC125

The mean plasma concentration-time profile of TMC125 when given under fasted conditions was consistently lower than when given under fed conditions (Figure 29).



Source: Module 5.3.1.1/TMC125-C103/Display 5

Figure 29: Mean Plasma Concentration-Time Profiles of TMC125 after Administration of a Single Dose of 200 mg TMC125 (formulation T* [TMC125 in PEG 4000]) Given after a Standardized Breakfast or under Fasted Conditions (Trial TMC125-C103)

The median t_{max} was later (4 hours) after administration of TMC125 under fed conditions, compared to administration after fasted conditions (2 hours) (Table 27). The mean C_{max} and AUC_{last} of TMC125 when administered under fasted conditions were 77% and 69% lower, respectively, than when administered under fed conditions.

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Table 27: Pharmacokinetics of TMC125 after Administration of a Single Dose of 200 mg TMC125 (formulation T* [TMC125 in PEG 4000]) Given after a Standardized Breakfast or under Fasted Conditions (Trial TMC125-C103)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment A: TMC125 200 mg Fed (Reference)	Treatment B: TMC125 200 mg Fasted (Test)		
N	12	12		
t_{max}, h	4 (2 - 4)	2 (1 - 4)	-	-
C_{max}, ng/mL	77.4 ± 31.3	22.1 ± 16.1	0.23	0.15 - 0.35
AUC_{last}, ng.h/mL	834 ± 420	310 ± 274	0.31	0.22 - 0.43

N = maximum number of subjects with data.
[a] Ratio based on geometric means.
Source: Module 5.3.1.1/TMC125-C103/Section 4.C.5 and Section 4.C.6

2.3.5.3 CONCLUSIONS

The mean exposure (AUC_{last}) to TMC125 when administered as formulation T* under fasted conditions was 69% lower than when administered under fed conditions.

2.3.6 Trial TMC125-C112: Effect of Food on Bioavailability of TMC125 Given as Capsule Formulation E* in Healthy Subjects (TMC125.HBr in HPMC)

2.3.6.1 TRIAL DESIGN

This was an open-label, randomized, 2-period crossover trial to investigate the effect of a standardized breakfast, as compared to fasted conditions, on the relative bioavailability of TMC125 given as the 100-mg capsule formulation E* (TMC125.HBr salt in HPMC). A single dose of 600 mg TMC125 was taken under fasted conditions or after completion of a standardized breakfast, as follows:

- Fasted conditions (Treatment A): Fasted for at least 10 hours before administration of trial medication;
- Standardized breakfast (Treatment B): 4 slices of bread, 1 slice of ham, 1 slice of cheese, butter, jelly, and 2 cups of coffee or tea with, if desired, milk and/or sugar. The trial medication was given within 10 minutes after completion of the breakfast.

The trial population consisted of 12 healthy subjects. In each of 2 sessions, subjects received either Treatment A or Treatment B. The washout period between treatments was at least 14 days.

Further details on the design and results of this trial are available in the trial report (refer to Module 5.3.1.1/TMC125-C112).

2.3.6.2 PHARMACOKINETICS OF TMC125

The mean plasma concentration-time profile of TMC125 when given under fasted conditions was consistently lower than when given under fed conditions (Figure 30).

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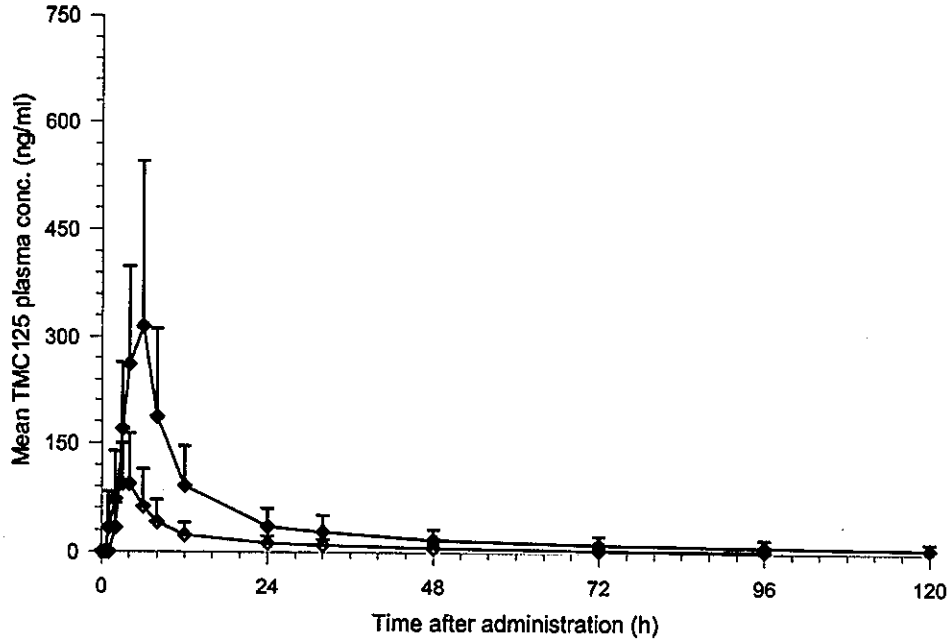

♦ = Fed; ◊ = Fasted
N = 12 in each treatment group. Mean and SD data are shown.
Source: Module 5.3.1.1/TMC125-C112/8.A (Display 4)

Figure 30: Plasma Concentration-Time Profiles of TMC125 after Administration of a Single Dose of 600 mg TMC125 (formulation E* [TMC125.HBr in HPMC]) Given after a Standardized Breakfast or under Fasted Conditions (Trial TMC125-C112)

The median t_{max} was later (4 hours) after administration of TMC125 under fed conditions, compared to administration after fasted conditions (3 hours) (Table 28).

The mean C_{max} and AUC_{last} of TMC125 when administered under fed conditions were 3.26- and 3.50-fold higher, respectively, than when administered under fasted conditions.

Table 28: Pharmacokinetics of TMC125 after Administration of a Single Dose of 600 mg TMC125 (formulation E* [TMC125.HBr in HPMC]) Given after a Standardized Breakfast or under Fasted Conditions (Trial TMC125-C112)

Parameter	Mean ± SD; t_{max}: Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Treatment A: TMC125 600 mg Fasted Conditions (Reference)	Treatment B: TMC125 600 mg Fed Conditions (Test)		
N	12	12		
t_{max}, h	3 (2 - 4)	4 (4 - 6)	-	-
C_{max}, ng/mL	113 ± 79	347 ± 220	3.26	2.23 - 4.76
AUC_{last}, ng.h/mL	1308 ± 1021	4111 ± 2880	3.50	2.51 - 4.89

N = maximum number of subjects with data.
[a] Ratio based on geometric means.
Source: Module 5.3.1.1/TMC125-C112/Section 4.C.5

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2.3.6.3 CONCLUSIONS

The mean exposure (AUC_{last}) to TMC125 when administered as formulation E* under fed conditions was 3.50-fold higher than when administered under fasted conditions.

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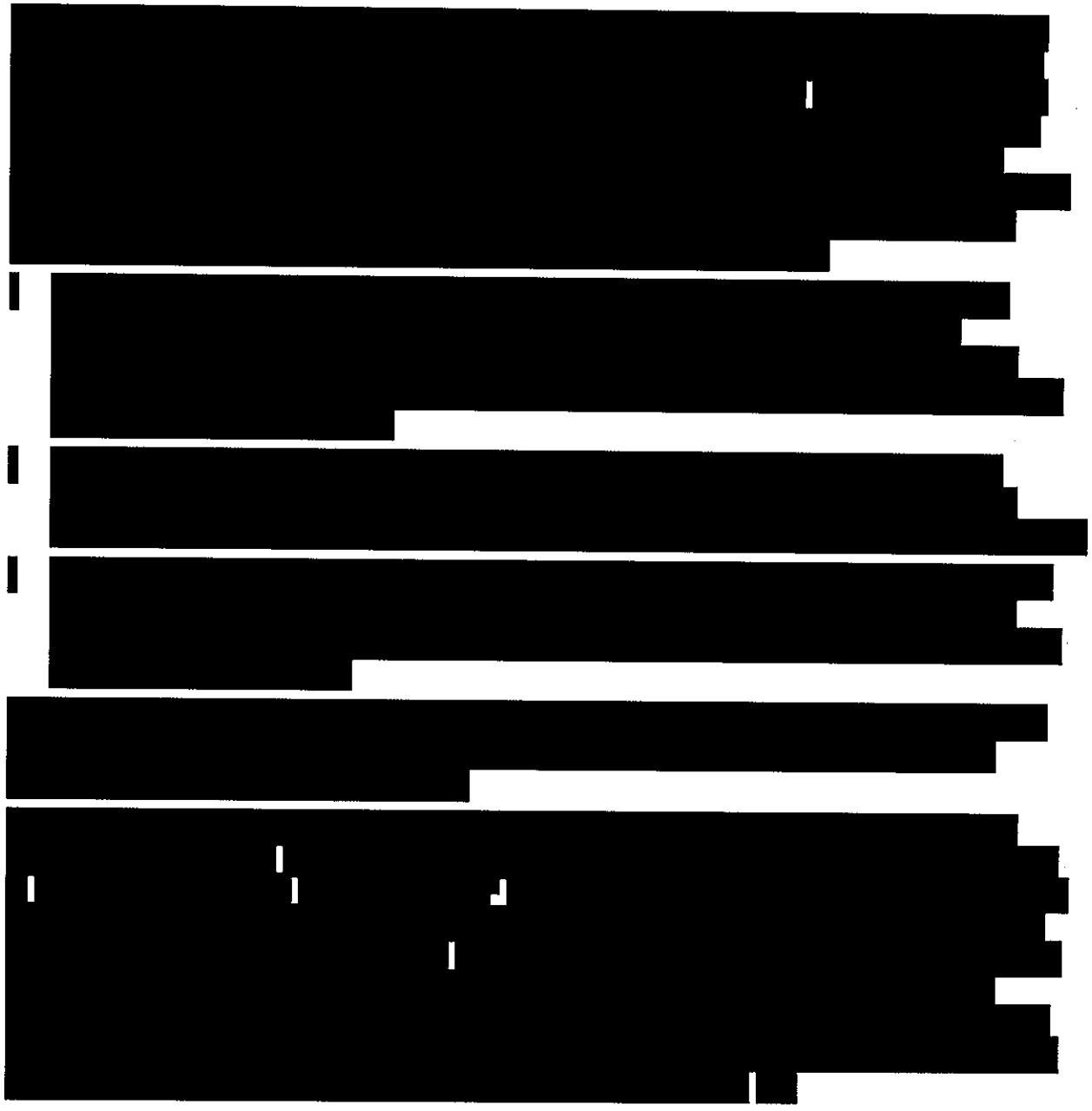
3 COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1 IN VITRO DISSOLUTION TRIALS



3.2 RELATIVE BIOAVAILABILITY OF DIFFERENT ORAL FORMULATION TYPES

Relative bioavailability trials were conducted to compare the systemic exposure of TMC125 after the administration of different oral formulation concepts used during the clinical development of TMC125. These trials included investigations with different experimental

formulation concepts developed in the search for an oral dosing form with an acceptable bioavailability and/or drug load, and investigations conducted in the course of optimizing the selected tablet formulation concept to be used for further clinical development of TMC125 (TMC125 in HPMC, spray-dried). Unless mentioned otherwise, the trial medication was administered following a meal, and exposure (as a measure of bioavailability) refers to the mean AUC.

3.2.1 Testing of Experimental Formulations

3.2.1.1 HEALTHY SUBJECTS

For later Phase I and Phase II clinical trials, the capsule formulation of TMC125 in PEG 4000 (formulation T*) used in earlier trials (Section 3.2.3) were replaced by 100- and 200-mg tablet formulations of TMC125 in HPMC manufactured using granulo-layering technology (formulations S*, B*, and F*). Formulation T* and the granulo-layered tablets were not directly compared in clinical trials.

A disadvantage of the granulo-layered tablets, though, remained the relatively high dose and pill burden that needed to be administered. The dosing regimens of TMC125 tested in Phase IIb trials were 400 mg b.i.d, 800 mg b.i.d. and 1200 mg b.i.d., resulting in a daily intake of 4, 8 and 12 tablets of formulation F*, respectively.

Further formulation development was therefore mainly focused on increasing the bioavailability and/or increasing the drug load while maintaining a robust stability profile (Section 1.3). During the ensuing development of an appropriate tablet formulation, the in vivo bioavailability of various experimental formulation concepts was investigated in healthy subjects.

In trial TMC125-C115 (Section 2.1.1), the relative bioavailability of 3 test formulations of TMC125 in HPMC (2 tablet formulations [formulations B* and C*] and a powder formulation [formulation D*]) was compared to that of a capsule formulation of TMC125.HBr in HPMC (formulation E In terms of the rate and extent of TMC125 absorption, the 3 test formulations of TMC125 in HPMC each had a lower bioavailability than the reference formulation of TMC125.HBr in HPMC. Mean C_{max} values of the test formulations were approximately 40% to 50% lower, and AUC values were approximately 30% to 50% lower, than the corresponding values for the reference formulation. Although the capsule formulation of TMC125.HBr in HPMC (formulation E*) had the highest relative bioavailability, this formulation concept was not developed further due to potential stability and manufacturing issues with formulations containing the HBr salt.

In the further development of tablet concepts of TMC125 in HPMC, the bioavailability of 2 different batches (Batches 1 [L129] and 2 [L130], produced in different manufacturing runs) of tablet formulation F* (200 mg) was investigated together with the relative bioavailability of tablet formulation B* (also 200 mg) (trial TMC125-C142, Section 2.1.2). Formulation F* was an optimized version of formulation B*, and both of these formulations were manufactured from the same powder formulation of TMC125 in HPMC (formulation D*). The mean exposure to TMC125 (measured as AUC_{last}) was approximately 20% lower with formulation F* Batch 2, as compared to formulation F* Batch 1. The exposure to TMC125 with formulation B* was 28% and 15% lower than the exposure with formulation F* Batch 1 and Batch 2, respectively.

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The superiority of the spray-drying technique over granulo-layering was confirmed by trial TMC125-C155 (Section 2.2.2), in which the bioavailability of TMC125 administered as tablet formulation O* (TMC125 in HPMC, spray-dried) and tablet formulation N* (TMC125 in HPMC, granulo-layered) was compared. Compared to the test formulation F* used in this trial, the mean C_{max} and AUC_{last} were 1.54- and 1.96-fold higher, respectively, with formulation N*, and 3.17- and 3.66-fold higher, respectively, with formulation O*(Table 15).

In trial TMC125-C170 (Section 2.1.3), conducted in healthy subjects, the bioavailability of 4 test spray-dry formulations (formulations G*, A*, H* and I*) of TMC125 was compared to the reference formulation F*. Formulations G*, A*, H*, and I* all had a TMC125 to HPMC ratio of [redacted], but varied in terms of the excipient composition, tablet compression, and the presence or absence of a [redacted] (Table 5). The AUC_{last} values for formulations G*, A*, H*, and I* were 6.78-, 9.37-, 6.96-, and 4.92-fold higher, respectively, than for the reference formulation (formulation F*) (Table 10). For C_{max} a similar trend was seen, although the differences between the test and reference formulations were less pronounced. All the primary pharmacokinetic parameters showed a considerable variability between subjects, with the largest inter-subject variability occurring with the reference formulation F*. The [redacted] applied and the process used with tablet formulations G* and I* decreased the bioavailability of TMC125 (Section 3.2.2.3).

The results of trial TMC125-C170 demonstrated that single doses of tablet formulations manufactured by spray-drying technology all had a considerably higher bioavailability in healthy subjects than the reference formulation F*, manufactured using granulo-layering technology.

Further investigations into the oral bioavailability of tablet formulations manufactured by spray-drying technology that were tested during the optimization of the selected tablet formulation are summarized in Section 3.2.2.

Based on the results of these trials, formulation A*, which had the highest bioavailability of the spray-dried tablet formulations tested, was selected for use in planned clinical trials, including the registrational Phase III trials (TMC125-C206 [DUET-1] and TMC125-C216 [DUET-2]).

3.2.1.2 HIV-1 Infected Subjects

A comparison of data from earlier trials in which TMC125 was administered as formulations T* and F* indicated that HIV-1 infected subjects tended to have lower exposures to TMC125 than healthy subjects (refer to Module 2.7.2/Section 3.7). Therefore, the applicability of the increase in bioavailability of formulation A*, compared to formulation F*, demonstrated in healthy subjects in trial TMC125-C170 (Section 2.1.3) was investigated in the relevant target population of HIV-1 infected subjects.

In previous trials the same dose of the test and reference formulations was studied to investigate the bioavailability of the test formulations compared to the reference formulation. In contrast, based on the results of trial TMC125-C170 in healthy subjects, the objective of trial TMC125-C141 (Section 2.1.4) was to confirm comparable exposures between 3 clinically relevant dose levels of TMC125 administered as formulation A* and 3 corresponding doses of TMC125 administered as formulation F* in HIV-1 infected subjects (stable on an antiretroviral therapy (ART) with a plasma viral load < 50 HIV-1 RNA copies/mL), as follows:

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- Panel 1: 100 mg TMC125 (formulation A*) vs. 800 mg TMC125 (formulation F*);
- Panel 2: 200 mg TMC125 (formulation A*) vs. 1600 mg TMC125 (formulation F*);
- Panel 3: 300 mg TMC125 (formulation A*) vs. 2400 mg TMC125 (formulation F*).

In each case the trial medication was given as a single dose following a meal.

The mean AUC_{last} and C_{max} of TMC125 after administration of 100 mg TMC125 as formulation A* were both comparable to 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* the 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*, with the increase in AUC_{last} with 2400 mg TMC125 as formulation F* being less than dose proportional.

Because the results of trial TMC125-C141 indicated that administration of a single 800 mg dose of TMC125 with formulation F* (the selected dose based on 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 (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. As in trial TMC125-C141, the HIV-1 infected subjects were stable on an ART with a plasma viral load < 50 HIV-1 RNA copies/mL, and the trial medication was given following a meal.

In trial TMC125-C228, subjects received 100 mg TMC125 b.i.d. as formulation A* for 7 days with an additional morning intake on Day 8, or 800 mg TMC125 b.i.d. as formulation F* for 7 days with an additional morning intake on Day 8.

In contrast to trial TMC125-C141, the mean exposure to TMC125 in trial TMC125-C228 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 (Table 12) and on Day 8 (Table 13). 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. It was of note, though, that the mean exposure (AUC_{12h}) to TMC125 on Day 8 after administration of 800 mg b.i.d. as formulation F* in trial TMC125-C228 (2607 ng.h/mL, Table 13) was lower than seen for the same dose in the Phase IIb trials TMC125-C203/TMC125-C209 (3589 ng.h/mL, Module 2.7.2/Section 2.6.2.1) and TMC125-C223 (9189 ng.h/mL, Module 2.7.2/Section 2.6.2.3) in HIV-1 infected subjects after 4 weeks of dosing.

On the basis of the lower exposure with formulation A* after multiple dosing, the protocol for trial TMC125-C228 was amended to include an additional session in which 27 of the 33 subjects from the first 2 sessions received 200 mg TMC125 b.i.d. as formulation A* for 7 days with an additional morning intake on Day 8. The results showed that the exposure to TMC125 following administration of 200 mg b.i.d. as formulation A* in 27 patients was higher than the exposure with 800 mg b.i.d. as formulation F*, on Day 1 (Table 12) and on Day 8 (Table 13). 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* 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. The C_{max} and AUC parameters showed considerable inter-individual variability for all treatments, but less variability with formulation A* than with formulation F*.

Given the observed inter-individual variability with the formulation F* and the non-proportional increase in exposures between the 100 and 200 mg b.i.d. doses of formulation A*, an exploratory analysis was performed to investigate whether this increase was homogenous across individual subjects. For each individual, relationships between the individual steady-state AUC_{12h} (Day 8) values of TMC125 administered at a dose of 800 mg b.i.d. as formulation F* and at a dose of 200 mg b.i.d. as formulation A* were portrayed graphically (Figure 18). This 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*. 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-individual variability with the 200 mg b.i.d. dose of formulation A*.

Overall, the results of trial TMC125-C228 showed that a 200-mg b.i.d. dose of TMC125 with formulation A* provides an exposure to TMC125 that is comparable to that provided by an 800-mg dose of TMC125 with formulation F*, with the latter dose previously having demonstrated substantial and sustained efficacy in the Phase IIb dose-escalating trial TMC125-C203 (Module 2.7.2/Section 2.6.2.1) and the dose-finding trial TMC125-C223 (Module 2.7.2/Section 2.6.2.3).

On this basis, a TMC125 dosing regimen of 200 mg b.i.d. with formulation A* was selected for use in all ongoing and planned clinical trials as this was expected to provide an exposure to TMC125 that was comparable to that provided by the 800 mg b.i.d. dosing regimen 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* seen in trial TMC125-C228 was further supported by a pharmacokinetic substudy of trial TMC125-C229 in HIV-1 infected subjects (Module 2.7.2/Section 2.6.2.5), as shown in Figure 31 for individual AUC_{12h} values, and a comparison between population pharmacokinetic estimates obtained after administration of TMC125 as formulations F* and A* in Phase IIb and III trials, respectively (Module 2.7.2/Section 3.6.1).

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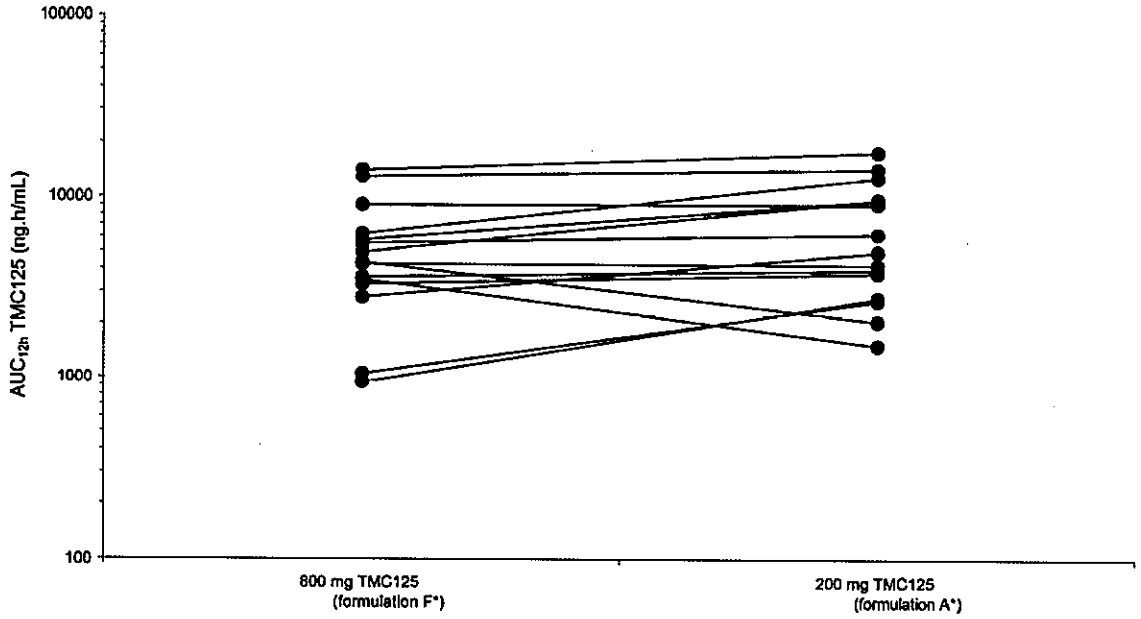

Source: Module 5.3.5.2/TMC125-C229sub-CPK/Section 2.3.2

Figure 31: Relationships 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 (Trial TMC125-C229)

3.2.2 Optimization of Selected Tablet Formulation

[redacted]

3.2.2.1 CHOICE OF SOLUBILIZING POLYMER

[redacted]

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[redacted]

3.2.2.2 CHOICE OF TMC125 TO SOLUBILIZING POLYMER RATIO

[redacted]

[redacted]

3.2.2.3 Effect of Tablet Film-Coating

[redacted]

3.2.2.4 Effect of Changes in Manufacturing Process

[redacted]

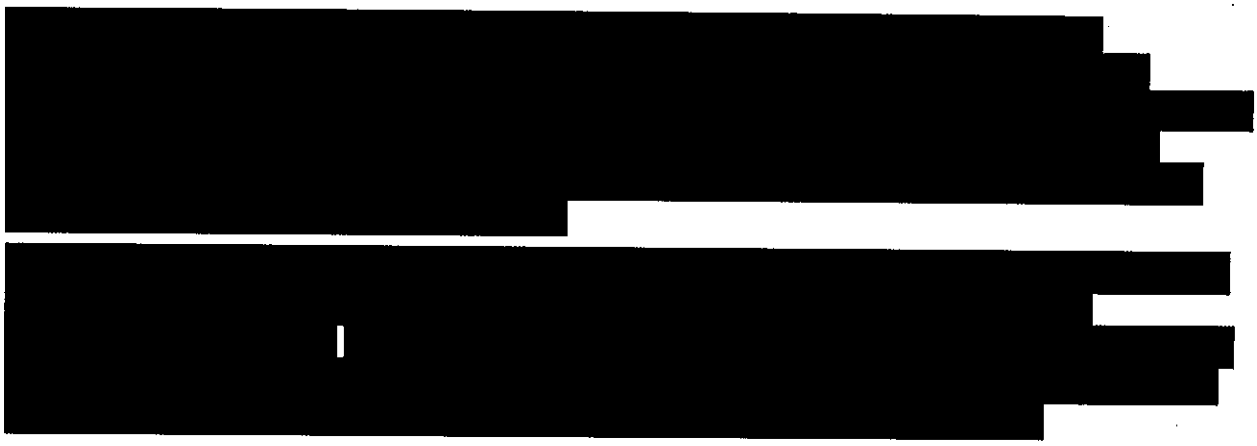
[redacted]

3.2.2.5 EFFECT OF LONG-TERM TABLET STORAGE

[redacted]

3.2.3 Early Formulation Concepts Not Developed Further

[redacted]



3.3 CONCOMITANT FOOD INTAKE

The effect of concomitant food intake on the bioavailability of TMC125 when administered as tablet formulation A* (the spray-dried tablet formulation of TMC125 in HPMC that was selected for use in the registrational Phase III trials) was investigated in 2 trials. In each trial (TMC125-C147 and TMC125-C116) the effect of concomitant food intake was evaluated by administering TMC125 10 minutes after a standardized breakfast, consisting of 4 slices of bread, 2 slices of ham or cheese, butter, jelly and 2 cups of coffee or tea with milk and/or sugar, if desired, compared to administration either under fasted conditions (trial TMC125-C147) or before the standardized breakfast (trial TMC125-C116). In addition, trial TMC125-C147 investigated the effect of 4 different types of meals (see below) on the bioavailability of TMC125.

In 4 other trials, the effect of concomitant food intake on the bioavailability of TMC125 was investigated when TMC125 was administered as tablet formulations (formulations S* [TMC125-C133] and F*[TMC125-C137]) and capsule formulations (formulations T* [TMC125-C103] and E* [TMC125-C112]) that are no longer being developed.

3.3.1 Tablet Formulation A* (TMC125 in HPMC, Spray-Dried)

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, Section 2.3.1 and Table 29). 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, Section 2.3.2 and Table 29).

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 mean exposure (AUC_{last}) to TMC125 was comparable when administered after a standardized breakfast and a high-fat breakfast (Table 29). When administered after a snack, the mean AUC_{last} for TMC125 was 20% lower than when administered after a standardized breakfast, but the mean C_{max} was unaffected. Overall, the differences in exposure to TMC125 when taken with a high-fat breakfast, a standardized breakfast, or a snack were not considered to be clinically relevant. In contrast,

administration of TMC125 after an enhanced-fiber breakfast (16.4 g fiber, compared to 8.1 g fiber in the standardized breakfast) resulted in 38% decrease in mean 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.

Table 29: Pharmacokinetics of TMC125 after Administration of a Single Dose of 100 or 200 mg TMC125 (formulation A* [TMC125 in HPMC, Spray-Dried]) Given under Fasted Conditions or before or after a Standardized Breakfast, or after Other Types of Meals (Trials TMC125-C116 and TMC125-C147)

Parameter	Mean ± SD: TMC125 100 or 200 mg Standardized Breakfast (Reference)	Mean ± SD: TMC125 100 or 200 mg (Test)	Ratio [a] (Test:Reference)	90% CI
TMC125-C116 (200 mg TMC125): after Standardized Breakfast vs. before Standardized Breakfast				
N	17	19		
C_{max}, ng/mL	419.1 ± 138.6	346.6 ± 211.1	0.77	0.67 - 0.87
AUC_{last}, ng.h/mL	6184 ± 4305	5409 ± 4713	0.83	0.76 - 0.90
TMC125-C147 (100 mg TMC125): after Standardized Breakfast vs. Fasted Conditions				
N	12	12		
C_{max}, ng/mL	128.6 ± 63.73	88.83 ± 67.97	0.56	0.41 - 0.77
AUC_{last}, ng.h/mL	1417 ± 1140	920.5 ± 1024	0.49	0.39 - 0.61
TMC125-C147 (100 mg TMC125) after Standardized Breakfast vs. Snack				
N	12	12		
C_{max}, ng/mL	128.6 ± 63.73	127.5 ± 73.06	0.97	0.75 - 1.25
AUC_{last}, ng.h/mL	1417 ± 1140	1189 ± 1106	0.80	0.69 - 0.94
TMC125-C147 (100 mg TMC125) after Standardized Breakfast vs. after Enhanced-Fiber Breakfast				
N	11	11		
C_{max}, ng/mL	138.4 ± 61.33	85.05 ± 40.31	0.62	0.47 - 0.83
AUC_{last}, ng.h/mL	1191 ± 699.6	863.6 ± 407.2	0.75	0.63 - 0.90
TMC125-C147 (100 mg TMC125) after Standardized Breakfast vs. after High-Fat Breakfast				
N	11	12		
C_{max}, ng/mL	138.4 ± 61.33	129.9 ± 64.12	0.95	0.70 - 1.29
AUC_{last}, ng.h/mL	1191 ± 699.6	1202 ± 585.7	1.09	0.84 - 1.41

N = maximum number of subjects with data.
[a] Ratio based on LS means.
Source: Module 5.3.3.4/TMC125-C116/Section 4.2.4.2 and Section 4.2.4.3;
Module 5.3.1.1/TMC125-C147/Section 4.2.5 and Section 4.2.6

3.3.2 Other Tablet and Capsule Formulations

In all 4 other trials in which the effect of concomitant food intake was investigated on the bioavailability of TMC125 when administered as other tablet and capsule formulations, the exposure to TMC125 was higher when taken after a standardized breakfast, compared to fasted conditions, irrespective of whether TMC125 was administered as a 400-mg single dose with tablet formulation S* (TMC125 in HPMC, granulo-layered) (trial TMC125-133, Section 2.3.3 and Table 24), as a 1600-mg single dose with tablet formulation F* (TMC125 in HPMC, granulo-layered) (trial TMC125-C137, Section 2.3.4 and Table 25), as a 200-mg single dose with capsule formulation T* (TMC125 in PEG 4000) (trial TMC125-103,

Section 2.3.5 and Table 27), or as a 600-mg single dose with capsule formulation E* (TMC125.HBr in HPMC) (trial TMC125-C112, Section 2.3.6 and Table 28),

Trial TMC125-C137 also investigated the effect of different types of meals on the bioavailability of TMC125 when administered as a 1600-mg single dose with tablet formulation F* (TMC125 in HPMC, granulo-layered). The mean exposure (AUC_{last}) to TMC125 was 3.04-fold higher when administered after a high-fat breakfast, and 1.60-fold higher when administered after a snack, compared to administration of TMC125 under fasted conditions (Table 25). When comparing the treatments with different types of meals with each other in this trial, the mean exposure to TMC125 was 18% lower when administered after the high-fat breakfast, and 59% lower when administered after the snack, compared to the exposure obtained when administered after the standardized breakfast (Table 26).

Based on the available data, TMC125 should be administered following a meal.

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4 REFERENCES

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5 APPENDICES

Appendix 2.7.1.1: Summary of Analytical Methods for Individual Trials

Trial No.	Matrix	Assay	Assay Validation Report	Analytical Method	Lower Limit of Quantification	Bioanalytical Report
TMC125-C101	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]1850
	Urine	TMC125	[redacted]1847	LC-MS/MS	2.00 ng/mL	[redacted]1851
TMC125-C102	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]1869
TMC125-C103	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]1856
TMC125-C104	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]1892
TMC125-C105	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]1899
	Plasma	Ritonavir	[redacted]99.804	LC-MS/MS	1.00 ng/mL	[redacted]1900
TMC125-C106	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]1907
	Plasma	Saquinavir	[redacted]99.806	LC-MS/MS	1.00 ng/mL	[redacted]1908
TMC125-C109	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]1909
	Plasma	Efavirenz	[redacted]271834	LC-MS/MS	100 ng/mL	[redacted]301253
	Plasma	Nevirapine	[redacted]271834	LC-MS/MS	100 ng/mL	[redacted]309331
TMC125-C111	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]1942
	Plasma	Indinavir	[redacted]1944	LC-MS/MS	20.0 ng/mL	[redacted]1943
TMC125-C112	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]2029
TMC125-C114	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]1941
TMC125-C115	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]2031
TMC125-C116	Plasma	TMC125	[redacted]-RD-643	LC-MS/MS	2.00 ng/mL	[redacted]-055633
	Plasma	Ritonavir	[redacted]-RD-642	LC-MS/MS	5.00 ng/mL	[redacted]-055643
TMC125-C117	Plasma	TMC125	[redacted]1846, [redacted]3134, 5151, [redacted]5258	LC-MS/MS	2.00 ng/mL	[redacted]5212
	Plasma	Amprenavir	[redacted]3070	LC-MS/MS	50.0 ng/mL	[redacted]5214
	Plasma	Ritonavir	[redacted]3021, [redacted]5150	LC-MS/MS	5.00 ng/mL	[redacted]5213
TMC125-C120	Plasma	TMC125	[redacted]-RD-643	LC-MS/MS	2.00 ng/mL	[redacted]-050203
TMC125-C122	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]2185
	Plasma	Lopinavir	[redacted]2184	LC-MS/MS	20.0 ng/mL	[redacted]2186
	Plasma	Ritonavir	[redacted]99.804	LC-MS/MS	10.0 ng/mL	[redacted]2187
TMC125-C123	Plasma	TMC125	[redacted]1846, [redacted]3134	LC-MS/MS	2.00 ng/mL	[redacted]3074
	Plasma	Ritonavir	[redacted]99.804, 3150	LC-MS/MS	10.0 ng/mL	[redacted]3116
	Plasma	Saquinavir	[redacted]99.806, 3151	LC-MS/MS	1.00 ng/mL	[redacted]3075
TMC125-C125	Plasma	TMC125	[redacted]-RD-643	LC-MS/MS	2.00 ng/mL	[redacted]-057723

Appendix 2.7.1.1: Summary of Analytical Methods for Individual Trials, Cont'd

Trial No.	Matrix	Assay	Assay Validation Report	Analytical Method	Lower Limit of Quantification	Bioanalytical Report
TMC125-C128	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]2030
TMC125-C130	Plasma	TMC125	[redacted]1846, [redacted]3134, [redacted]5151	LC-MS/MS	2.00 ng/mL	[redacted]4166
		Metabolites	not applicable			[redacted]4168
		Radioactivity	[redacted]-RD-559, [redacted]-RD-559-A1, [redacted]-RD-561, [redacted]-RD-562, [redacted]-RDL-562-A1, [redacted]-RDL-563			[redacted]-041113
TMC125-C133	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]2032
TMC125-C136	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]2230, [redacted]2230-A1 [redacted]3025
TMC125-C137	Plasma	TMC125	[redacted]1846, [redacted]3134	LC-MS/MS	2.00 ng/mL	[redacted]3069, [redacted]3069-A1
TMC125-C138	Plasma	TMC125	[redacted]1846, [redacted]3134, [redacted]5151	LC-MS/MS	2.00 ng/mL	[redacted]5111
	Plasma	Tenofovir	[redacted]3076	LC-FL	20.0 ng/mL	[redacted]5112
	Urine	Tenofovir	[redacted]3188	LC-FL	1000 ng/mL	[redacted]5129
TMC125-C139	Plasma	TMC125	[redacted]1846, [redacted]3134, [redacted]5151, [redacted]5258	LC-MS/MS	2.00 ng/mL	[redacted]5238
	Plasma	Darunavir	[redacted]3021, [redacted]5150	LC-MS/MS	10.0 ng/mL	[redacted]5239
	Plasma	Ritonavir	[redacted]3021, [redacted]5150	LC-MS/MS	5.00 ng/mL	[redacted]5239
TMC125-C141	Plasma	TMC125	[redacted]1846, [redacted]3134, [redacted]5151, [redacted]5258	LC-MS/MS	2.00 ng/mL	[redacted]5207
TMC125-C142	Plasma	TMC125	[redacted]1846, [redacted]3134	LC-MS/MS	2.00 ng/mL	[redacted]3066
TMC125-C143	Plasma	TMC125	[redacted]1846, [redacted]3134	LC-MS/MS	2.00 ng/mL	[redacted]3068, [redacted]3068-A1
TMC125-C145	Plasma	TMC125	[redacted]1846, [redacted]3134, [redacted]5151, [redacted]5258	LC-MS/MS	2.00 ng/mL	[redacted]4144
	Plasma	Lopinavir	[redacted]2184	LC-MS/MS	20.0 ng/mL	[redacted]4145
	Plasma	Ritonavir	[redacted]3021, [redacted]5150	LC-MS/MS	5.00 ng/mL	[redacted]4146
	Plasma	Saquinavir	[redacted]5200	LC-MS/MS	2.00 ng/mL	[redacted]4147

Appendix 2.7.1.1: Summary of Analytical Methods for Individual Trials, Cont'd

Trial No.	Matrix	Assay	Assay Validation Report	Analytical Method	Lower Limit of Quantification	Bioanalytical Report
TMC125-C146	Plasma	TMC125	[redacted]1846, [redacted]3134, 5151	LC-MS/MS	2.00 ng/mL	[redacted]5161
TMC125-C147	Plasma	TMC125	[redacted]-RD-643	LC-MS/MS	2.00 ng/mL	[redacted]-050233
TMC125-C150	Plasma	TMC125	[redacted]1846, [redacted]3134	LC-MS/MS	2.00 ng/mL	[redacted]4130
TMC125-C151	Plasma	TMC125	[redacted]1846, [redacted]3134, 5151, [redacted]5258	LC-MS/MS	2.00 ng/mL	[redacted]5137
	Plasma	Ritonavir	[redacted]3021, [redacted]5150	LC-MS/MS	5.00 ng/mL	[redacted]5138
	Plasma	Atazanavir	[redacted]5165, [redacted]5208	LC-MS/MS	1.00 ng/mL	[redacted]5139
TMC125-C153	Plasma	TMC125	[redacted]1846, [redacted]3134	LC-MS/MS	2.00 ng/mL	[redacted]4177
TMC125-C155	Plasma	TMC125	[redacted]1846, [redacted]3134	LC-MS/MS	2.00 ng/mL	[redacted]4200
TMC125-C156	Plasma	TMC125	[redacted]1846, [redacted]3134, 5151, [redacted]5258	LC-MS/MS	2.00 ng/mL	[redacted]5140
	Plasma	Rifabutin, 25-O-desacetylrifabutin	[redacted]2104	LC-MS/MS	2.00 ng/mL, 2.00 ng/mL	[redacted]5141
TMC125-C157	Plasma	TMC125	[redacted]1846, [redacted]3134, 5151	LC-MS/MS	2.00 ng/mL	[redacted]5108
	Plasma	Didanosine	[redacted]4267	LC-MS/MS	10.0 ng/mL	[redacted]5110
TMC125-C158	Plasma	TMC125	[redacted]1846, [redacted]1907, [redacted]3134, [redacted]4177, 5151, [redacted]5258	LC-MS/MS	2.00 ng/mL	[redacted]6124
	Plasma	R(-) and S(+) Methadone	[redacted]6078	LC-MS/MS	5.00 ng/mL, 5.00 ng/mL	[redacted]6125
TMC125-C159	Plasma	TMC125	[redacted]1846, [redacted]3134, 5151	LC-MS/MS	2.00 ng/mL	[redacted]5125
	Plasma	Sildenafil and N-desmethylsildenafil	[redacted]4247	LC-MS/MS	2.00 ng/mL, 2.00 ng/mL	[redacted]5126
TMC125-C161	Plasma	TMC125	[redacted]-RD-643	LC-MS/MS	2.00 ng/mL	[redacted]-045543
	Plasma	Tipranavir	[redacted]341382, 367155	LC-MS/MS	1000 ng/mL	[redacted]430987
	Plasma	Ritonavir	[redacted]341382, 367155	LC-MS/MS	25.0 ng/mL	[redacted]430987
TMC125-C162	Plasma	TMC125	[redacted]-RD-643	LC-MS/MS	2.00 ng/mL	[redacted]-051996

Appendix 2.7.1.1: Summary of Analytical Methods for Individual Trials, Cont'd

Trial No.	Matrix	Assay	Assay Validation Report	Analytical Method	Lower Limit of Quantification	Bioanalytical Report
TMC125-C164	Plasma	TMC125	[redacted]1846, [redacted]3134, [redacted]5151, [redacted]5258	LC-MS/MS	2.00 ng/mL	[redacted]5228
	Plasma	Atorvastatin, 2-hydroxy-atorvastatin, 4-hydroxy-atorvastatin, and atorvastatin lactone	[redacted]3161	LC-MS/MS	0.50 ng/mL, 0.50 ng/mL, 0.50 ng/mL, 0.50 ng/mL	[redacted]5229
TMC125-C165	Plasma	TMC125	[redacted]1846, [redacted]3134, [redacted]5151, [redacted]5258	LC-MS/MS	2.00 ng/mL	[redacted]5234
	Plasma	Paroxetine	[redacted]5242	LC-MS/MS	0.10 ng/mL	[redacted]5235
TMC125-C166	Plasma	TMC125	[redacted]1846, [redacted]1907, [redacted]3134, [redacted]4177, [redacted]5151, [redacted]5228, [redacted]5258	LC-MS/MS	2.00 ng/mL	[redacted]6097
	Plasma	Ethinylestradiol	[redacted]2083, [redacted]3200, [redacted]4125, [redacted]6094	LC-MS/MS	0.003 ng/mL	[redacted]6098
	Plasma	Norethindrone	[redacted]6095, [redacted]6212	GC-MS	0.050 ng/mL	[redacted]6099
	Serum	Human FSH	[redacted]2117	Immunoassay	1.00 IU/L	[redacted]6100
	Serum	Human LH	[redacted]2116	Immunoassay	0.62 IU/L	[redacted]6100
	Serum	Human progesterone	[redacted]2115	Immunoassay	0.31 ng/mL	[redacted]6100
TMC125-C168	Plasma	TMC125	[redacted]-RD-643	LC-MS/MS	2.00 ng/mL	[redacted]-047513
TMC125-C169	Plasma	TMC125	[redacted]-RD-643	LC-MS/MS	2.00 ng/mL	[redacted]-056743
TMC125-C170	Plasma	TMC125	[redacted]1846, [redacted]3134, [redacted]5151	LC-MS/MS	2.00 ng/mL	[redacted]5216
TMC125-C171	Plasma	TMC125	[redacted]-RD-643	LC-MS/MS	2.00 ng/mL	[redacted]-053743
	Plasma	Clarithromycin and 14-hydroxy-clarithromycin	[redacted]-RD-459, [redacted]-RD-459-A1, [redacted]-RD-459-A2, [redacted]-RD-459-A3	LC-ECD	50.0 ng/mL	[redacted]-053753
TMC125-C172	Plasma	TMC125	[redacted]-RD-643	LC-MS/MS	2.00 ng/mL	[redacted]-054213

Appendix 2.7.1.1: Summary of Analytical Methods for Individual Trials, Cont'd

Trial No.	Matrix	Assay	Assay Validation Report	Analytical Method	Lower Limit of Quantification	Bioanalytical Report
TMC125-C174	Plasma	TMC125	[redacted]-RD-643	LC-MS/MS	2.00 ng/mL	[redacted]-055933
	Plasma	Caffeine and paraxanthine	[redacted]-P734	LC-MS/MS	25.00 ng/mL, 25.00 ng/mL	[redacted]-ADWS
	Plasma	S-warfarin, and 7-OH-warfarin	[redacted]-P832	LC-MS/MS	5.00 ng/mL, 5.00 ng/mL	[redacted]-ADWT
	Plasma	Dextromethorphan and dextrorphan	[redacted]-P668	LC-MS/MS	0.05 ng/mL, 0.80 ng/mL	[redacted]-ADWU
	Plasma	Midazolam and 1-OH-midazolam	[redacted]-P594	LC-MS/MS	0.10 ng/mL, 0.10 ng/mL	[redacted]-ADWR
	Plasma	Omeprazole and 5-OH-omeprazole	[redacted]-P749	LC-MS/MS	1.00 ng/mL, 2.00 ng/mL	[redacted]-ADWQ
TMC125-C176	Plasma	TMC125	[redacted]-RD-643	LC-MS/MS	2.00 ng/mL	[redacted]-051586
	Plasma	Darunavir (TMC114)	[redacted]BA502	LC-MS/MS	5.00 ng/mL	[redacted]014
	Plasma	Ritonavir	[redacted]BA502	LC-MS/MS	5.00 ng/mL	[redacted]014
TMC125-C177	Plasma	TMC125	[redacted]1846, [redacted]1907, [redacted]3134, [redacted]4177, [redacted]5151, [redacted]5258	LC-MS/MS	2.00 ng/mL	[redacted]6153
	Plasma	Tenofovir	[redacted]3076, [redacted]5112, [redacted]6156	LC-FL	20.0 ng/mL	[redacted]6154
	Urine	Tenofovir	[redacted]3188, [redacted]6037	LC-FL	1000 ng/mL	[redacted]6155
TMC125-C178	Plasma	TMC125	[redacted]-RD-643	LC-MS/MS	2.00 ng/mL	[redacted]-057513
	Plasma	Moxifloxacin	[redacted]-RD-680			[redacted]-057523
TMC125-C201	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]2141
TMC125-C203	Plasma	TMC125 (main study)	[redacted]1846, [redacted]1907, [redacted]3134, [redacted]4177, [redacted]5151	LC-MS/MS	2.00 ng/mL	[redacted]2224
		TMC125 (substudy)	[redacted]1846, [redacted]1907, [redacted]3134, [redacted]4177	LC-MS/MS	2.00 ng/mL	[redacted]2225

Appendix 2.7.1.1: Summary of Analytical Methods for Individual Trials, Cont'd

TMC125-C206 (DUET-1)	Plasma	TMC125 (main study)	[redacted]RD-643	LC-MS/MS	2.00 ng/mL	[redacted]060173
	Plasma	Darunavir (main study)	[redacted]BA819	LC-MS/MS	5.00 ng/mL	[redacted]036
	Plasma	Ritonavir (main study)	[redacted]BA819	LC-MS/MS	5.00 ng/mL	[redacted]036
	Plasma	TMC125 (substudy)	[redacted]RD-643	LC-MS/MS	2.00 ng/mL	[redacted]060173
	Plasma	Darunavir (substudy)	[redacted]BA819	LC-MS/MS	5.00 ng/mL	[redacted]036
	Plasma	Ritonavir (substudy)	[redacted]BA819	LC-MS/MS	5.00 ng/mL	[redacted]036
TMC125-C207	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]1990
	Plasma	Nevirapine	[redacted]	LC-MS/MS	100.00 ng/mL	[redacted]3373321
		Amprenavir			25.00 ng/mL	
		Delavirdine			82.60 ng/mL	
		Indinavir			100.00 ng/mL	
		Efavirenz			100.00 ng/mL	
		Ritonavir			100.00 ng/mL	
		Saquinavir			43.70 ng/mL	
		Nelfinavir			50.00 ng/mL	
		Zalcitabine			0.60 ng/mL	
		Didanosine			25.00 ng/mL	
		Lamivudine			25.00 ng/mL	
		Stavudine			25.00 ng/mL	
		Zidovudine			25.00 ng/mL	
		Abacavir			50.00 ng/mL	
TMC125-C208	Plasma	TMC125	[redacted]1846	LC-MS/MS	2.00 ng/mL	[redacted]1945
TMC125-C209	Plasma	TMC125	[redacted]1846, [redacted]1907, [redacted]3134, [redacted]4177	LC-MS/MS	2.00 ng/mL	[redacted]2222
TMC125-C216 (DUET-2)	Plasma	TMC125 (main study)	[redacted]RD-643	LC-MS/MS	2.00 ng/mL	[redacted]060183
	Plasma	Darunavir (main study)	[redacted]BA819	LC-MS/MS	5.00 ng/mL	[redacted]-034
	Plasma	Ritonavir (main study)	[redacted]BA819	LC-MS/MS	5.00 ng/mL	[redacted]034
	Plasma	TMC125 (substudy)	[redacted]RD-643	LC-MS/MS	2.00 ng/mL	[redacted]060183
	Plasma	Darunavir (substudy)	[redacted]BA819	LC-MS/MS	5.00 ng/mL	[redacted]034
	Plasma	Ritonavir (substudy)	[redacted]BA819	LC-MS/MS	5.00 ng/mL	[redacted]034

Appendix 2.7.1.1: Summary of Analytical Methods for Individual Trials, Cont'd

TMC125-C223	Plasma	TMC125 (main study)	[redacted] 1846, [redacted] 1907, 3134, [redacted] 4177, 5151, [redacted] 5228, 5258	LC-MS/MS	2.00 ng/mL	[redacted] 5114
	Plasma	TMC125 (substudy)	1846, [redacted] 1907, 3134, [redacted] 4177, 5151, [redacted] 5228, 5258	LC-MS/MS	2.00 ng/mL	[redacted] 5259
TMC125-C227	Plasma	TMC125 (main study)	1846, [redacted] 3134, 5151, [redacted] 5258	LC-MS/MS	2.00 ng/mL	[redacted] 5223
	Plasma	TMC125 (substudy)	1846, [redacted] 3134, 5151, [redacted] 5258	LC-MS/MS	2.00 ng/mL	[redacted] 5224
TMC125-C228	Plasma	TMC125	1846, [redacted] 3134, 5151, [redacted] 5258	LC-MS/MS	2.00 ng/mL	[redacted] 5266
	Plasma	Tenofovir	3076, [redacted] 5112, 6156	LC-MS/MS	20.00 ng/mL	[redacted] 7194
	Plasma	Ritonavir	3021, [redacted] 5150, 5244, [redacted] 6044, 7024	LC-MS/MS	5.00 ng/mL	[redacted] 7195
	Plasma	Lopinavir	2184, [redacted] 7193	LC-MS/MS	20.00 ng/mL	[redacted] 7196
TMC125-C229	Plasma	TMC125	1846, [redacted] 1907, 3134, [redacted] 4177, 5151, [redacted] 5228, 5258	LC-MS/MS	2.00 ng/mL	[redacted] 6101

Appendix 2.7.1.2: Clinical Biopharmaceutic Trials

Trial No. Principle Investigator (Country) Start/End Dates	Trial Description/Design	Subjects Treated Sex (M/F) Age (yr): Median (Range) Race: W/B/O	Treatment Regimen/Duration Route of Administration Formulation (Batch No.)	Trial Status Type of Report Location of Trial Report
Relative Bioavailability Trials - Testing of Experimental Formulations				
TMC125-C115 [redacted] (Belgium) Start: [redacted] 20[redacted] End: [redacted] 20[redacted]	Open-label, randomized, controlled, 3-parallel group, 2-period crossover trial in healthy subjects to investigate the relative bioavailability of 3 experimental TMC125 formulations (2 tablet formulations and 1 powder formulation) compared to a TMC125.HBr capsule formulation in HPMC. TMC125 was administered under fed conditions after a standardized breakfast.	24 24M/0F 24.0 (18-48) 22/0/2	*Treatment A (reference)*: single dose of TMC125.HBr 400 mg base-equivalents (formulation E*), oral. *Treatment B (test)*: single dose of TMC125 base 400 mg (formulation B*), oral. *Treatment C (test)*: single dose of 2 g TMC125 powder for suspension (formulation D*), each gram containing 200 mg TMC125 base, oral. *Treatment D (test)*: single dose of TMC125 base 400 mg (formulation C*), oral. *TMC125 Formulations:* formulation E* (100 mg capsule, TMC125 HBr in HPMC; Batch No.L036). formulation B* (200 mg tablet, TMC125 in HPMC, granulo-layered; Batch No. L123). formulation D* (200 mg/g powder, TMC125 in HPMC; Batch No. L006). formulation C* (100 mg tablet, TMC125 in HPMC, granulo-layered; Batch No. L132).	Completed [redacted] 20[redacted] Full report Module 5.3.1.2/TMC125-C115

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Appendix 2.7.1.2: Clinical Biopharmaceutic Trials, Cont'd

Trial No. **Principle Investigator** **(Country)** **Start/End Dates**	**Trial Description/Design**	**Subjects Treated** **Sex (M/F)** **Age (yr): Median (Range)** **Race: W/B/O**	**Treatment Regimen/Duration** **Route of Administration** **Formulation (Batch No.)**	**Trial Status** **Type of Report** **Location of Trial Report**
TMC125-C142 [redacted] (Belgium) Start: [redacted] 20[redacted] End: [redacted] 20[redacted]	Open-label, randomized, 3-period crossover trial in healthy subjects to investigate the relative bioavailability of 2 different tablet formulations (and 2 batches of one formulation) of TMC125 in HPMC. TMC125 was administered under fed conditions after a standardized breakfast.	18 18M/0F 24.0 (20-37) 16/0/2	*Treatment A*: single dose of TMC125 400 mg (formulation F* Batch 1), oral. *Treatment B*: single dose of TMC125 400 mg (formulation F* Batch 2), oral. *Treatment C*: single dose of TMC125 400 mg (formulation B*), oral. *TMC125 Formulations*: formulation F*(200 mg tablet, TMC125 in HPMC, granulo-layered; Batch No. L129 [Batch 1] and L130 [Batch 2]) formulation B*(200 mg tablet, TMC125 in HPMC, granulo-layered; Batch No. L128).	Completed [redacted] 20[redacted] Full report Module 5.3.1.2/TMC125-C142

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Appendix 2.7.1.2: Clinical Biopharmaceutic Trials, Cont'd

Trial No. Principle Investigator (Country) Start/End Dates	Trial Description/Design	Subjects Treated Sex (M/F) Age (yr): Median (Range) Race: W/B/O	Treatment Regimen/Duration Route of Administration Formulation (Batch No.)	Trial Status Type of Report Location of Trial Report
TMC125-C170 [redacted] (The Netherlands) Start: [redacted] 20[redacted] End: [redacted] 20[redacted]	Open-label, randomized, 2-period crossover trial in 4 parallel panels of healthy subjects to investigate the relative bioavailability of 4 different spray-dried formulations of TMC125, compared to the reference formulation F*. TMC125 was administered under fed conditions after a standardized breakfast.	45 34M/11F 39.0 (18-55) 43/1/1	*Treatment A:* single dose of TMC125 400 mg (formulation F*), oral. *Treatment B:* single dose of TMC125 400 mg (formulation G*, spray-dry 1), oral. *Treatment C:* single dose of TMC125 400 mg (formulation A*, spray-dry 2), oral. *Treatment D:* single dose of TMC125 400 mg (formulation H*, spray-dry 3), oral. *Treatment E:* single dose of TMC125 400 mg (formulation I*, spray-dry 4), oral. *TMC125 Formulations*: formulation F* (200 mg tablet, TMC125 in HPMC, granulo-layered; Batch No. L133). formulation G*(133 mg tablet, TMC125 in HPMC, spray-dried; Batch No.L049). formulation A*(100 mg tablet, TMC125 in HPMC, spray-dried; Batch No. L051). formulation H*(133 mg tablet, TMC125 in HPMC, spray-dried; Batch No. L052). formulation I*(100 mg tablet, TMC125 in HPMC, spray-dried; Batch No.L053).	Completed [redacted] 20[redacted] Full report Module 5.3.1.2/TMC125-C170

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Appendix 2.7.1.2: Clinical Biopharmaceutic Trials, Cont'd

Trial No. Principle Investigator (Country) Start/End Dates	Trial Description/Design	Subjects Treated Sex (M/F) Age (yr): Median (Range) Race: W/B/O	Treatment Regimen/Duration Route of Administration Formulation (Batch No.)	Trial Status Type of Report Location of Trial Report
TMC125-C141 [redacted] (Australia) [redacted] (United Kingdom) [redacted] (Germany) Start: [redacted] 20[redacted] End: [redacted] 20[redacted]	Add-on, open-label, randomized, crossover trial in HIV-1 infected subjects to investigate the relative bioavailability of 3 dose levels of TMC125 tablet formulation A*, compared to the tablet formulation F*. TMC125 was administered under fed conditions after a standardized breakfast.	40 40M/0F 42.0 (30-62) 37/3/0	*Treatment A:* single dose of TMC125 100 mg (formulation A*) and single dose of TMC125 800 mg (formulation F*), oral. *Treatment B:* single dose of TMC125 200 mg (formulation A*) and single dose of TMC125 1600 mg (formulation F*), oral. *Treatment C:* single dose of TMC125 (formulation A*) 300 mg and single dose of TMC125 2400 mg (formulation F*), oral. *TMC125 Formulations*: formulation F*(200 mg [redacted], TMC125 in HPMC, granulo-layered; Batch No. L133). formulation A* (100 mg [redacted], TMC125 in HPMC, spray-dried; Batch No. L051).	Completed [redacted] 20[redacted] Full report Module 5.3.1.2/TMC125-C141
TMC125-C228 [redacted] (Australia) [redacted] (Germany) [redacted] (United Kingdom) Start: [redacted] 20[redacted] End: [redacted] 20[redacted]	Add-on, open-label, randomized, multiple-dose crossover trial in HIV-1 infected subjects to investigate the bioavailability of TMC125 tablet formulation A* as compared to the reference tablet formulation F*. TMC125 was administered under fed conditions after breakfast or dinner.	33 33M/0F 42.0 (30-55) 32/1/0	Subjects received the following medication in addition to their current ARV regimen: *Treatment A:* TMC125 100 mg b.i.d. for 7 days + single dose on Day 8 (formulation A*), oral. *Treatment B:* TMC125 800 mg b.i.d. for 7 days + single dose on Day 8 (formulation F*), oral. *Treatment C:* TMC125 200 mg b.i.d. for 7 days + single dose on Day 8 (formulation A*), oral. *TMC125 Formulations*: formulation A* (100 mg tablet, TMC125 in HPMC, spray-dried; Batch No. L055). formulation F* (200 mg tablet, TMC125 in HPMC, granulo-layered; Batch No. L133).	Completed [redacted] 20[redacted] Full report Module 5.3.1.2/TMC125-C228

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Appendix 2.7.1.2: Clinical Biopharmaceutic Trials, Cont'd

Trial No. Principle Investigator (Country) Start/End Dates	Trial Description/Design	Subjects Treated Sex (M/F) Age (yr): Median (Range) Race: W/B/O	Treatment Regimen/Duration Route of Administration Formulation (Batch No.)	Trial Status Type of Report Location of Trial Report
Relative Bioavailability Trials - Optimization of Selected Tablet Formulation				
TMC125-C150 [redacted] (Belgium) [redacted] (The Netherlands) Start: [redacted] 20[redacted] End: [redacted] 20[redacted]	Open-label, randomized, 2-period crossover trial in healthy subjects to investigate the bioavailability of 4 different TMC125 formulations (3 tablet formulations and 1 capsule formulation) as compared to the reference tablet formulation F* (effect of manufacturing technology, type of solubilizing polymer, and TMC125 to polymer ratio). TMC125 was administered under fed conditions after a standardized breakfast.	48 36M/12F 42.0 (22-55) 46/0/2	*Treatment A (reference):* single dose of TMC125 400 mg (formulation F*), oral. *Treatment B (test):* single dose of TMC125 400 mg (formulation J*), oral. *Treatment C (test):* single dose of TMC125 400 mg (formulation K*), oral. *Treatment D (test):* single dose of TMC125 400 mg (formulation L*), oral. *Treatment E (test):* single dose of TMC125 400 mg (formulation M*), oral. All subjects received the reference formulation (Treatment A) and 1 of the 4 test formulations (Treatment B, C, D or E). *TMC125 Formulations*: formulation F* (200 mg tablet, TMC125 in HPMC, granulo-layered; Batch No. L132). formulation J* (200 mg tablet, TMC125 in HPMC, spray-dried; Batch No. L040). formulation K*(133 mg tablet, TMC125 in HPMC, spray-dried; Batch No. L039). formulation L* (200 mg tablet, TMC125 in [redacted] spray-dried; Batch No. L038). formulation M* (200 mg capsule, TMC125 in HPMC, bead-coated; Batch No. L041).	Completed [redacted] 20[redacted] Full report Module 5.3.1.2/TMC125-C150

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Appendix 2.7.1.2: Clinical Biopharmaceutic Trials, Cont'd

Trial No. Principle Investigator (Country) Start/End Dates	Trial Description/Design	Subjects Treated Sex (M/F) Age (yr): Median (Range) Race: W/B/O	Treatment Regimen/Duration Route of Administration Formulation (Batch No.)	Trial Status Type of Report Location of Trial Report
TMC125-C155 [redacted] (The Netherlands) Start: [redacted] 20[redacted] End: [redacted] 20[redacted]	Open-label, randomized, 3-period crossover trial in healthy subjects to investigate the bioavailability of 2 different TMC125 tablet formulations as compared to the reference tablet formulation F* (effect of manufacturing technology). TMC125 was administered under fed conditions after a standardized breakfast.	34 28M/6F 35.0 (19-53) 29/4/1	*Treatment A*: single dose of TMC125 400 mg (formulation F*), oral. *Treatment B:* single dose of TMC125 400 mg (formulation N*), oral. *Treatment C:* single dose of TMC125 400 mg (formulation O*), oral. *TMC125 Formulations*: formulation F* (200 mg tablet, TMC125 in HPMC, granulo-layered; Batch No. L133). formulation N* (133 mg tablet, TMC125 in HPMC, granulo-layered; Batch No. L044). formulation O* (200 mg tablet, TMC125 in HPMC, spray-dried; Batch No. L046).	Completed [redacted] 20[redacted] Full report Module 5.3.1.2/TMC125-C155

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Appendix 2.7.1.2: Clinical Biopharmaceutic Trials, Cont'd

Trial No. Principle Investigator (Country) Start/End Dates	Trial Description/Design	Subjects Treated Sex (M/F) Age (yr): Median (Range) Race: W/B/O	Treatment Regimen/Duration Route of Administration Formulation (Batch No.)	Trial Status Type of Report Location of Trial Report
TMC125-C146 [redacted] (The Netherlands) Start: [redacted] 20[redacted] End: [redacted] 20[redacted]	Open-label, randomized, 2-period crossover trial in healthy subjects to investigate the relative bioavailability of 3 different spray-dried tablet formulations of TMC125 as compared to the granulo-layered tablet formulation F* (effect of TMC125 to polymer ratio). TMC125 was administered under fed conditions after a standardized breakfast.	36 33M/3F 34.5 (19-54) 32/2/2	*Treatment A (reference):* single dose of TMC125 400 mg (formulation F*), oral. *Treatment B (test):* single dose of TMC125 400 mg (formulation P*), oral. *Treatment C (test):* single dose of TMC125 400 mg (formulation Q*), oral. *Treatment D (test):* single dose of TMC125 400 mg (formulation G*), oral. All subjects received the reference formulation (Treatment A) and 1 of the 3 test formulations (Treatment B, C, or D). *TMC125 Formulations*: formulation F* (200 mg tablet, TMC125 in HPMC, granulo-layered; Batch No. L133). formulation P*(200 mg tablet, TMC125 in HPMC, spray-dried; Batch No. L048). formulation Q*(200 mg tablet, TMC125 in HPMC, spray-dried; Batch No. L050). formulation G*(133 mg tablet, TMC125 in HPMC, spray-dried; Batch No. L049).	Completed [redacted] 20[redacted] Full report Module 5.3.1.2/TMC125-C146

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Appendix 2.7.1.2: Clinical Biopharmaceutic Trials, Cont'd

Trial No. Principle Investigator (Country) Start/End Dates	Trial Description/Design	Subjects Treated Sex (M/F) Age (yr): Median (Range) Race: W/B/O	Treatment Regimen/Duration Route of Administration Formulation (Batch No.)	Trial Status Type of Report Location of Trial Report
TMC125-C162 [redacted] (The Netherlands) Start: [redacted] 20[redacted] End: [redacted] 20[redacted]	Open-label, randomized, 4-period crossover trial in healthy subjects to investigate the relative bioavailability of TMC125 administered as formulation K* and 3 different batches of formulation A*, to investigate the effect of scale increase of the spray-drying process and variation in the formulation A* manufacturing process on the relative bioavailability of TMC125, and to investigate the influence of storage on the relative bioavailability of a spray-dried TMC125 formulation after single dosing (effect of manufacturing scale and long-term tablet storage). TMC125 was administered under fed conditions after a standardized breakfast.	16 12M/4F 46.5 (19-55) 13/1/2	*Treatment A*: single dose of TMC125 400 mg (L051 /formulation A*), oral. *Treatment B*: single dose of TMC125 400 mg (L054 /formulation A*), oral. *Treatment C*: single dose of TMC125 400 mg (L055 /formulation A*), oral. *Treatment D*: single dose of TMC125 400 mg (formulation K*), oral. *TMC125 Formulations*: formulation A* (100 mg tablet, TMC125 in HPMC, spray-dried; Batch No. L051 , L054 ,and L055). formulation K*(133 mg tablet, TMC125 in HPMC, spray-dried; Batch No.L039).	Completed [redacted] 20[redacted] Full report Module 5.3.1.2/TMC125-C162

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Appendix 2.7.1.2: Clinical Biopharmaceutic Trials, Cont'd

Trial No. Principle Investigator (Country) Start/End Dates	Trial Description/Design	Subjects Treated Sex (M/F) Age (yr): Median (Range) Race: W/B/O	Treatment Regimen/Duration Route of Administration Formulation (Batch No.)	Trial Status Type of Report Location of Trial Report
TMC125-C169 [redacted] (France) Start: [redacted] 20[redacted] End: [redacted] 20[redacted]	Open-label, randomized, 4-period crossover trial in healthy subjects to evaluate the oral bioavailability of a single dose of TMC125 administered as 4 different batches of tablet formulation A* (TMC125 in HPMC, spray-dried) produced at different scales of manufacture and with spray-dried TMC125 powder from different manufacturing sites, and with different sources of HPMC (effect of manufacturing scale and sources of TMC125 powder and HPMC). TMC125 was administered under fed conditions after a standardized breakfast.	48 47/1 28.0 (19-53) 31/9/8	*Reference:* single dose of TMC125 200 mg (form A*): tablets manufactured (small-scale) by [redacted] with spray-dried TMC125 powder from [redacted] and HPMC from [redacted] oral. *Test A:* single dose of TMC125 200 mg (form A*): tablets manufactured (full-scale) by [redacted] with spray-dried TMC125 powder from [redacted] and HPMC from [redacted] *Test B:* single dose of TMC125 200 mg (form A*): tablets manufactured (full-scale) by [redacted] with spray-dried TMC125 powder from Niro (Denmark) and HPMC from [redacted] oral. *Test C:* single dose of TMC125 200 mg (form A*): tablets manufactured (full-scale) by [redacted] with spray-dried TMC125 powder from [redacted] and HPMC from [redacted] oral. *TMC125 Formulations*: Reference: form A* (100 mg tablet, TMC125 in HPMC, spray-dried; Batch No. L072). Test A: form A* (100 mg tablet, TMC125 in HPMC, spray-dried; Batch No. L158). Test B: form A* (100 mg tablet, TMC125 in HPMC, spray-dried; Batch No. L157). Test C: form A* (100 mg tablet, TMC125 in HPMC, spray-dried; Batch No. L159).	Completed [redacted] 20[redacted] Full report Module 5.3.1.2/TMC125-C169

form :formulation *

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Appendix 2.7.1.2: Clinical Biopharmaceutic Trials, Cont'd

Trial No. Principle Investigator (Country) Start/End Dates	Trial Description/Design	Subjects Treated Sex (M/F) Age (yr): Median (Range) Race: W/B/O	Treatment Regimen/Duration Route of Administration Formulation (Batch No.)	Trial Status Type of Report Location of Trial Report
TMC125-C172 [redacted] (Belgium) Start: [redacted] 20[redacted] End: [redacted] 20[redacted]	Open-label, randomized, 3-period crossover trial in healthy subjects to investigate the relative bioavailability of a single dose of spray-dried TMC125 formulated as powder (Powder 1 and Powder 2, manufactured at different sites; formulation R*) compared to a tablet formulation (formulation A*) (effect of powder manufacturing site). TMC125 was administered under fed conditions after a standardized breakfast.	24 17M/7F 42.5 (32-50) 24/0/0	*Treatment A:* single dose of TMC125 200 mg (formulation A*), oral. *Treatment B:* single dose of TMC125 200 mg (formulation R*, Powder 1), oral. *Treatment C:* single dose of TMC125 200 mg (formulation R*, Powder 2), oral. *TMC125 Formulations*: formulation A* (100 mg tablet, TMC125 in HPMC, spray-dried; Batch No. L158). formulationR* (200 mg powder, TMC125 in HPMC, spray-dried; Batch No. L099 [Powder 1] and L098 [Powder 2]).	Completed [redacted] 20[redacted] Full report Module 5.3.1.2/TMC125-C172
Food Effect Trials				
TMC125-C147 [redacted] (United Kingdom) Start: [redacted] 20[redacted] End: [redacted] 20[redacted]	Open-label, randomized 3-period crossover trial in healthy subjects to investigate the effect of different types of meals on the relative bioavailability of a single intake of TMC125 100 mg as tablet formulation A*. TMC125 was administered under fed conditions after different types of breakfast (Treatments A, C, D, and E) or under fasted conditions (Treatment B).	24 24M/0F 27.5 (20-51) 23/1/0	*Treatment A:* single dose of TMC125 100 mg after a standardized breakfast, oral. *Treatment B:* single dose of TMC125 100 mg under fasted conditions (at least 10 hours), oral. *Treatment C:* single dose of TMC125 100 mg after a snack (croissant with coffee or tea), oral. *Treatment D:* single dose of TMC125 100 mg after an enhanced-fiber breakfast, oral. *Treatment E:* single dose of TMC125 100 mg after a high fat breakfast, oral. *TMC125 Formulations*: formulation A* (100 mg tablet, TMC125 in HPMC, spray-dried; Batch No. L055).	Completed [redacted] 20[redacted] Full report Module 5.3.1.1/TMC125-C147

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Appendix 2.7.1.2: Clinical Biopharmaceutic Trials, Cont'd

Trial No. Principle Investigator (Country) Start/End Dates	Trial Description/Design	Subjects Treated Sex (M/F) Age (yr): Median (Range) Race: W/B/O	Treatment Regimen/Duration Route of Administration Formulation (Batch No.)	Trial Status Type of Report Location of Trial Report
TMC125-C116 [redacted] (France) Start: [redacted] 20[redacted] End: [redacted] 20[redacted]	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 administered as formulation A* after simultaneous and staggered administration. The trial also investigated the effect of RTV dose level on TMC125 pharmacokinetics, the effect of separation of the administration of RTV and TMC125 by a meal, and the effect of timing of food administration on the bioavailability of TMC125.	40 36M/4F 31.5 (19-55) 30/7/3	*Treatment A:* single dose of TMC125 200 mg + single dose of RTV100 mg, simultaneously after a standardized breakfast, oral. *Treatment B*: single dose of TMC125 200 mg + single dose of RTV400 mg, simultaneously after a standardized breakfast, oral. *Treatment C*: single dose of TMC125 200 mg, after a standardized breakfast + single dose of RTV 100 mg, 4 hours after TMC125 intake, oral. *Treatment D:* single dose of TMC125 200 mg, after a standardized breakfast + single dose of RTV 100 mg, 4 hours before TMC125 intake, oral. *Treatment E:* single dose of TMC125 200 mg + single dose of RTV 100 mg, simultaneously after a standardized breakfast, oral. *Treatment F:* single dose of TMC125 200 mg, after a standardized breakfast, oral. *Treatment G:* single dose of TMC125 200 mg, before a standardized breakfast, oral. *Treatment H:* single dose of TMC125 200 mg, before a standardized breakfast + single dose of RTV 100 mg, after the standardized breakfast, oral. *TMC125 Formulation*: formulation A* (100 mg tablet, TMC125 in HPMC, spray-dried; Batch No. L019).	Completed [redacted] 20[redacted] Full report Module 5.3.3.4/TMC125-C116

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Appendix 2.7.1.2: Clinical Biopharmaceutic Trials, Cont'd

Trial No. Principle Investigator (Country) Start/End Dates	Trial Description/Design	Subjects Treated Sex (M/F) Age (yr): Median (Range) Race: W/B/O	Treatment Regimen/Duration Route of Administration Formulation (Batch No.)	Trial Status Type of Report Location of Trial Report
TMC125-C133 [redacted] (Belgium) Start: [redacted]20[redacted] End: [redacted]20[redacted]	Open-label, 1-sequence, crossover trial in healthy subjects to investigate the bioavailability of a TMC125 HPMC tablet formulation (formulation S*) under fed and fasted conditions. TMC125 was administered after a standardized breakfast or after at least 10 hours of fasting.	12 12M/0F 39.5 (25-55) 12/0/0	*Treatment A:* single dose of TMC125 400 mg, taken after a standardized breakfast, oral. *Treatment B*: single dose of TMC125 400 mg, taken under fasted conditions, oral. *TMC125 Formulation*: formulation S* (100 mg tablet, TMC125 in HPMC, granulo-layered; Batch No. L037).	Completed [redacted]20[redacted] Full report Module 5.3.1.1/TMC125-C133
TMC125-C137 [redacted] (Belgium) Start: [redacted]20[redacted] End: [redacted]20[redacted]	Open-label, randomized, 4-period crossover trial in healthy subjects to investigate the relative bioavailability of TMC125 after different types of meals. TMC125 was administered after at least 10 hours of fasting (Treatment A) or after different types of breakfast (Treatments B, C, and D).	16 16M/0F 30.0 (19-49) 16/0/0	*Treatment A:* single dose of TMC125 1600 mg, fasted conditions, oral. *Treatment B:* single dose of TMC125 1600 mg, after standard breakfast, oral. *Treatment C:* single dose of TMC125 1600 mg, after high-fat breakfast, oral. *Treatment D:* single dose of TMC125 1600 mg, after a snack, oral. *TMC125 Formulation*: formulation F* (200 mg tablet, TMC125 in HPMC, granulo-layered; Batch No. L130).	Completed [redacted]20[redacted] Full report Module 5.3.1.1/TMC125-C137
TMC125-C103 [redacted] (Belgium) Start: [redacted]20[redacted] End: [redacted]20[redacted]	Open-label, randomized, 2-period crossover trial in healthy subjects to investigate the effect of food on the bioavailability of TMC125 when administered under fasted (at least 10 hours) and fed (after breakfast) conditions.	12 12M/0F 39.5 (23-54) 12/0/0	*Treatment A*: single dose of TMC125 200 mg, fed conditions, oral. *Treatment B*: single dose of TMC125 200 mg, fasted conditions, oral. *TMC125 Formulation*: formulation T* (50 mg capsule; TMC125 in [redacted] Batch No. L024).	Completed [redacted]20[redacted] Full report Module 5.3.1.1/TMC125-C103

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Appendix 2.7.1.2: Clinical Biopharmaceutic Trials, Cont'd

Trial No. **Principle Investigator** **(Country)** **Start/End Dates**	**Trial Description/Design**	**Subjects Treated** **Sex (M/F)** **Age (yr): Median (Range)** **Race: W/B/O**	**Treatment Regimen/Duration** **Route of Administration** **Formulation (Batch No.)**	**Trial Status** **Type of Report** **Location of Trial Report**
TMC125-C112 [redacted] (Belgium) Start: [redacted] 20[redacted] End: [redacted] 20[redacted]	Open-label, randomized, 2-period crossover trial to investigate the effect of food on the bioavailability of a capsule formulation of TMC125.HBr in HPMC (formulation E*). TMC125 was administered after at least 10 hours of fasting (Treatment A) or after breakfast (Treatment B).	12 10M/2F 33.5 (20-52) 12/0/0	*Treatment A:* single dose of TMC125 600 mg, fasted conditions, oral. *Treatment B:* single dose of TMC125 600 mg, fed conditions, oral. *TMC125 Formulation*: formulation E*(100 mg capsule, TMC125 .HBr in HPMC; Batch No. L035).	Completed [redacted] 20[redacted] Full report Module 5.3.1.1/TMC125-C112

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Appendix 2.7.1.3: Relative Bioavailability Trials - Early Formulation Concepts Not Developed Further

Trial No. Investigator Start/End Dates Trial Status Type of Report Location	Trial Description/Design	Treatment Regimen/Duration Route of Administration Formulation (Batch No.)	Subjects Treated Sex (M/F) Age (yr): Median (Range) Race: W/B/O	TMC125 Pharmacokinetic Results				Conclusions
					Mean ± SD; t_{max}: Median (Range)			
				Parameter	Treatment A (Reference)	Treatment B or C (Test)	Ratio [a] (90% CI)	
TMC125-C102 [redacted] (Belgium) Start: [redacted] 20[redacted] End: [redacted] 20[redacted] Completed [redacted] 20[redacted] Full report Module 5.3.1.2/TMC125-C102	Open-label, randomized, controlled, 3-period crossover trial in healthy subjects to investigate the relative bioavailability of a single dose of TMC125 200 mg administered as 3 different capsule formulations. TMC125 was administered under fed conditions after breakfast.	*Treatment A*: single dose of TMC125 200 mg (form T*), oral. *Treatment B*: single dose of TMC125 200 mg (form U*), oral. *Treatment C*: single dose of TMC125 200 mg (form V*), oral. *TMC125 Formulations*: form T*(50 mg capsule, TMC125 in PEG 4000, Batch No.L026). form U* (100 mg capsule, TMC125 in HPMC, Batch No. L005). form V* (40 mg capsule, TMC125 in [redacted], Batch No. L027).	9 9M/0F 35.0 (21-55) 9/0/0	**Treatment A (form T*) vs. Treatment B (form U*)**				The 2 test formulations (capsules containing TMC125 in HPMC [form U*] or [redacted] [form V*]) resulted in lower exposures to TMC125, compared to the reference capsule formulation of TMC125 in PEG 4000 (form T*).
				N	9	9		
				C_{max}, ng/mL	87.2 ± 26.3	34.4 ± 25.2	0.33 (0.22 - 0.48)	
				AUC_{last}, ng.h/mL	929 ± 492	337 ± 438	0.25 (0.17 - 0.37)	
				Treatment A (form T*) vs. Treatment C (form V*)				
				N	9	9		
				C_{max}, ng/mL	87.2 ± 26.3	20.2 ± 13.3	0.20 (0.14 - 0.28)	
				AUC_{last}, ng.h/mL	929 ± 492	262 ± 255	0.19 (0.12 - 0.31)	
				N = maximum number of subjects with data. [a] Ratio (test:reference) based on LS means.				

form :formulation *

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Appendix 2.7.1.3: Relative Bioavailability Trials - Early Formulation Concepts Not Developed Further, Cont'd

Trial No. Investigator Start/End Dates Trial Status Type of Report Location	Trial Description/Design	Treatment Regimen/Duration Route of Administration Formulation (Batch No.)	Subjects Treated Sex (M/F) Age (yr): Median (Range) Race: W/B/O	TMC125 Pharmacokinetic Results				Conclusions
TMC125-C114 [redacted] (Belgium) Start: [redacted] 20[redacted] End: [redacted] 20[redacted] Completed [redacted] 20[redacted] Full report Module 5.3.1.2/TMC125-C114	Open-label, 2-period crossover trial with 4 parallel groups of healthy subjects to investigate the relative bioavailability of 4 capsule formulations of TMC125 containing TMC125.HBr, compared to a reference capsule formulation containing TMC125-base in PEG 4000. TMC125 was administered under fed conditions after breakfast.	*Treatment A:* single dose of TMC125 400 mg (form T*), oral. *Treatment B:* single dose of TMC125 400 mg (form W*), oral. *Treatment C:* single dose of TMC125 400 mg (form Y*), oral. *Treatment D:* single dose of TMC125 400 mg (form a*), oral. *Treatment E:* single dose of TMC125 400 mg (form X*), oral. *TMC125 Formulations*: form T*(50 mg capsule, TMC125 in PEG 4000; Batch No. L029). form W* (100 mg capsule, TMC125.HBr as drug substance; Batch No. L031). form Y* (50 mg capsule, TMC125.HBr in HPMC; Batch No. L033). form a* (50 mg capsule, TMC125.HBr in [redacted]; Batch No. L032). form X*(100 mg tablet, TMC125.HBr as granulate; Batch No. L030).	24 24M/0F 38.5 (21-54) 24/0/0	Parameter	Mean ± SD; t_{max}: Median (Range) Treatment A (Reference)	Treatment B, C, D, or E (Test)	Ratio [a] (90% CI)	The mean exposure to TMC125 after administration of TMC125.HBr as drug substance (form W*) or as a granulate (form X*) was low, compared to the exposure with the reference formulation of TMC125 in PEG 4000 (form T*), while the mean exposure to TMC125 after administration of TMC125.HBr in HPMC (form Y*) or [redacted] (form a*) was much higher than with the reference formulation (form T*).
				Treatment A (form T*) vs. Treatment B (form W*)				
				N	6	6		
				C_{max}, ng/mL	107 ± 37	34 ± 12	0.32 (0.20 - 0.51)	
				AUC_{last}, ng.h/mL	1049 ± 390	250 ± 98	0.24 (0.13 - 0.43)	
				Treatment A (form T*) vs. Treatment C (form Y*)				
				N	6	6		
				C_{max}, ng/mL	156 ± 92	305 ± 235	1.77 (1.17 - 2.67)	
				AUC_{last}, ng.h/mL	2048 ± 1519	3235 ± 2378	1.50 (1.13 - 1.98)	
				Treatment A (form T*) vs. Treatment D (form a*)				
				N	6	6		
				C_{max}, ng/mL	142 ± 70	338 ± 161	2.37 (2.06 - 2.73)	
				AUC_{last}, ng.h/mL	2091 ± 1442	4673 ± 3196	2.24 (1.92 - 2.61)	
				Treatment A (form T*) vs. Treatment E (form X*)				
				N	6	6		
				C_{max}, ng/mL	145 ± 51	31 ± 12	0.22 (0.19 - 0.25)	
				AUC_{last}, ng.h/mL	1868 ± 948	382 ± 364	0.18 (0.14 - 0.23)	
				N = maximum number of subjects with data. [a] Ratio (test:reference) based on LS means.				

form :formulation *

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Appendix 2.7.1.3: Relative Bioavailability Trials - Early Formulation Concepts Not Developed Further, Cont'd

Trial No. Investigator Start/End Dates Trial Status Type of Report Location	Trial Description/Design	Treatment Regimen/Duration Route of Administration Formulation (Batch No.)	Subjects Treated Sex (M/F) Age (yr): Median (Range) Race: W/B/O	TMC125 Pharmacokinetic Results				Conclusions
				Parameter	Mean ± SD; t_{max}: Median (Range) Treatment A, B, or C (Reference)	Treatment B, C, or D (Test)	Ratio [a] (90% CI)	
TMC125-C136 [redacted] (Belgium) Start: [redacted] 20[redacted] End: [redacted] 20[redacted] Completed [redacted] 20[redacted] Full report Module 5.3.1.2/TMC125-C136	Open-label, randomized, 4-period crossover, single dose trial in healthy subjects to investigate the bioavailability of TMC125 intermediate powder, intended for oral suspension, with different particle size distribution and grinding frequencies. TMC125 was administered under fed conditions after breakfast.	*Treatment A:* single dose of TMC125 400 mg; particle size distribution: [redacted] to [redacted] µm, ground once, oral. *Treatment B:* single dose of TMC125 400 mg; particle size distribution: [redacted] to [redacted] µm, ground once, oral. *Treatment C:* single dose of TMC125 400 mg; particle size distribution: [redacted] to [redacted] µm, ground 3 times, oral. *Treatment D:* single dose of TMC125 400 mg; particle size distribution: [redacted] to [redacted] µm, ground 3 times, oral. *TMC125 Formulations*: form D* (200 mg powder, TMC125 in HPMC; Batch No. L126 [Treatments A and B] and L125 [Treatments C and D]).	12 10M/2F 43.5 (31-51) 12/0/0	**Treatment A ([redacted] to [redacted] µm, ground once) vs. Treatment B ([redacted] to [redacted] µm, ground once)**				There were no relevant differences in the bioavailability of TMC125 between the 4 different powder formulations of TMC125. A trend towards higher TMC125 bioavailability was observed with the smaller particle size distribution ([redacted] to [redacted] µm vs. [redacted] to [redacted] µm) and the higher grinding frequency (3 times vs. once).
				N	9	9		
				C_{max}, ng/mL	112.8 ± 111.1	73.99 ± 45.19	0.73 (0.51 - 1.04)	
				AUC_{last}, ng.h/mL	1442 ± 1884	921.4 ± 730.2	0.77 (0.51 - 1.16)	
				Treatment A ([redacted] to [redacted] µm, ground once) vs. Treatment C ([redacted] to [redacted] µm, ground 3 times)				
				N	9	9		
				C_{max}, ng/mL	112.8 ± 111.1	127.8 ± 81.89	1.02 (0.90 - 1.61)	
				AUC_{last}, ng.h/mL	1442 ± 1884	1605 ± 1153	1.37 (0.99 - 1.90)	
				Treatment B ([redacted] to [redacted] µm, ground once) vs. Treatment D ([redacted] to [redacted] µm, ground 3 times)				
				N	9	9		
				C_{max}, ng/mL	73.99 ± 45.19	101.0 ± 61.53	1.32 (1.01 - 1.71)	
				AUC_{last}, ng.h/mL	921.4 ± 730.2	1301 ± 1082	1.32 (0.93 - 1.86)	
				Treatment C ([redacted] to [redacted] µm, ground 3 times) vs. Treatment D ([redacted] to [redacted] µm, ground 3 times)				
				N	9	9		
				C_{max}, ng/mL	127.8 ± 81.89	101.0 ± 61.53	0.80 (0.57 - 1.12)	
				AUC_{last}, ng.h/mL	1605 ± 1153	1301 ± 1082	0.74 (0.52 - 1.05)	
				N = maximum number of subjects with data. [a] Ratio (test:reference) based on LS means.				

form D*:formulation D*

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