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APPLICATION NUMBER:

205123Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW - ADDENDUM Office of New Drug Quality Assessment			
Application No.:	NDA 205-123	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Dates:	3/28/2013; 6/26/13; 7/24/13; 9/25/13		
Division:	DAVP	**Team Leader:** Angelica Dorantes, Ph.D.	
Applicant:	Janssen	**Acting Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	TBD	**Date Assigned:**	4/4/2013
Generic Name:	Simeprevir	**Date of Review:**	9/26/2013
Indication:	Treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) with or without human immunodeficiency virus-1 (HIV-1) coinfection who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin.	**Type of Submission:** 505(b)(1) New Drug Application	
Formulation/strengths:	IR Capsule/ 150 mg		
Route of Administration:	Oral		

SYNOPSIS:

This document is an Addendum to the Original Biopharmaceutics review by Dr. Kareen Riviere dated August 27, 2013 in DARRTS. In the Original review it was reported that an approval recommendation could not be given for NDA 205123, because the submission of essential dissolution information needed for the final determination on the acceptability the dissolution acceptance criterion was pending. Dr. Riviere determined that the Applicant's proposed dissolution acceptance criterion of Q = (b) (4) at 30 minutes was not fully supported by the provided data and it was not acceptable.

In an Information Request (IR) letter sent to the Applicant on July 18, 2013, the ONDQA Biopharmaceutics Team recommended the implementation of a dissolution acceptance criterion of **Q = (b) (4) at 25 minutes,** based on the mean in-vitro dissolution profiles of the pivotal clinical and primary stability batches at release and 12 month stability.

In a submission dated September 25, 2013, the Applicant provided their response to the July 18th IR. After reviewing the information/data provided in the response, the Biopharmaceutics Team concurs with the Applicant that setting the sampling time point at 30 minutes instead of 25 minutes, will not allow the release of batches that differ on average by more than (b) (4) in the amount of drug delivered, and a difference of maximally (b) (4) in plasma concentrations is not expected to result in any clinical difference in the pharmacological action of the drug product, particularly given that Simeprevir takes about 6 hours to reach the maximum concentration (Cmax). Therefore, the Applicant's justification and proposed dissolution criterion are acceptable.

RECOMMENDATION:

Based on the evaluation of the provided additional information, Biopharmaceutics considers that the Applicant's justification for the proposed dissolution acceptance criterion is adequate and acceptable.

The following dissolution method and acceptance criterion are acceptable for batch release and stability testing:

- ***Dissolution Method:*** Apparatus II, 75 rpm agitation rate, 900 mL media volume, 37 °C, 50 mM phosphate buffer pH 6.8 with 1.0% Polysorbate 20.
- ***Acceptance Criterion:*** Q = (b) (4) at 30 minutes.

NDA 205-123 for Simeprevir 150 mg immediate release capsule is recommended for approval from a Biopharmaceutics standpoint.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Richard Lostritto

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/s/

KAREEN RIVIERE
09/26/2013

ANGELICA DORANTES
09/26/2013

CLINICAL PHARMACOLOGY REVIEW

NDA	205123
Submission Date	28 Mar 2013
Brand Name	To be determined
Generic Name	Simeprevir
Office of Clinical Pharmacology (OCP) Review Team	Leslie Chinn, Ph.D., Jiang Liu, Ph.D., Jeffrey Kraft, Ph.D., Yuzhuo Pan, Ph.D., Ping Zhao, Ph.D., Jeffry Florian, Ph.D., Michael Pacanowski, Pharm.D., M.P.H., Yoriko Harigaya, Ph.D., Yongheng Zhang, Ph.D., Islam Younis, Ph.D.
OCP Division	DCP4
OND Division	Division of Antiviral Products
Applicant	Janssen Research & Development, LLC
Formulation; Strength	IR capsules; 150 mg
Proposed Dosing Regimen	Simeprevir 150 mg administered once daily with food, in combination with peginterferon alfa and ribavirin for 12 weeks, followed by either 12 or 36 additional weeks of peginterferon alfa and ribavirin depending on on-treatment viral response and prior response status
Proposed Indication	Treatment of chronic hepatitis C genotype 1 infection in adult patients with compensated liver disease (including cirrhosis) who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin
Review Type	505(b)(1) New Drug Application, priority review

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TABLE OF DEFINITIONS

HCV	Hepatitis C virus
CHC	Chronic hepatitis C virus infection
PegIFN	Pegylated interferon
RBV	Ribavirin
PegIFN/RBV or **PR**	Pegylated interferon + ribavirin (previous standard-of-care)
RGT	Response-guided therapy: refers to treatment duration based on on-treatment response
SVR	Sustained virologic response: HCV RNA undetectable at end-of-treatment and <25 IU/mL detectable or undetectable at Week X
HCV RNA	Surrogate marker for virologic response
Detectable	Plasma HCV RNA >25 IU/mL
<25 IU/mL	Plasma HCV RNA is detectable but not quantifiable
Undetectable	Plasma HCV RNA is below the limit of detection
Prior non-responders	Patients who did not have durable SVR after prior PR treatment
Prior relapsers	HCV RNA was undetectable after PR treatment but detectable during follow-up
Prior partial responders	> 2 log reduction in HCV RNA at Week 12 but not undetectable by Week 24 of previous PR treatment
Prior null responders	< 2 log reduction in HCV RNA at Week 12 of previous PR treatment
Q80K	Mutation in the HCV genome

1. EXECUTIVE SUMMARY

Simeprevir (TMC435) is a novel inhibitor of hepatitis C virus (HCV) NS3/4A serine protease that prevents cleavage of HCV polyprotein, thereby obstructing viral replication. Two protease inhibitors are currently marketed (in combination with ribavirin and pegylated interferon alfa) for the treatment of chronic HCV genotype 1 infection: boceprevir (VICTRELIS®) and telaprevir (INCIVEK®). Both were approved in the US in May 2011.

In the current application, the **proposed indication** for simeprevir is the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with a peginterferon alfa and ribavirin (PegIFN/RBV), in adults with compensated liver disease (including cirrhosis) who are treatment-naïve or who have failed previous interferon therapy with or without ribavirin. The **proposed dose** of simeprevir is one 150 mg capsule taken once daily with food.

The safety and efficacy of simeprevir were established in two double-blind placebo-controlled Phase 3 studies in treatment-naïve HCV genotype 1 infected subjects (Trials C208 and C216) and one double-blind placebo-controlled Phase 3 study in treatment-experienced HCV genotype 1 infected subjects (Trial HPC3007). The Applicant submitted data characterizing the clinical pharmacology of simeprevir to support the proposed prescribing information, including 25 clinical pharmacology trials and 15 in vitro studies.

1.1. RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP) finds this application acceptable and recommends approval of simeprevir for the treatment of chronic HCV genotype 1 infection in adult patients with compensated liver disease who are treatment-naïve, pending agreement by the Applicant on the dosing recommendations described in Sections 2.3.2.4 and 2.3.2.6 (dose reduction to 100 mg QD in patients with East Asian ancestry or moderate hepatic impairment) and the labeling changes described in Section 3.0 of this review.

In addition, OCP recommends the approval of simeprevir for the treatment of chronic HCV genotype 1 infection in adult patients with compensated liver disease who have failed previous interferon therapy (including prior relapsers and prior partial and null responders) pending agreement by the Applicant to avoid use in patients with the HCV Q80K mutation at baseline from the intended treatment population, as described in Section 2.2.4.4 of this review.

1.2. POST-MARKETING COMMITMENTS OR REQUIREMENTS

The post-marketing commitments or requirements were under discussion at the time this review was completed. A potential PMC/PMR with relevance to this review includes (b) (4) patient populations with higher mean simeprevir exposures (i.e. patients of East Asian ancestry and patients with moderate hepatic impairment, see Section 1.1 above).

1.3. SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Dose Selection

The simeprevir dose and treatment duration were selected by the Applicant based on results from the Phase 2b dose-finding trials C205 (150 or 75 mg QD in treatment-naïve subjects) and C206 (150 or 100 mg QD in treatment-experienced subjects). The Applicant observed that in C205, sustained virologic response rates at post-treatment Week 24 (SVR24) trended higher following administration of simeprevir 150 mg compared to 75 mg in certain patient subgroups (e.g. subjects with HCV Q80K mutation present at baseline and subjects with more severe liver fibrosis and inflammation). The Applicant interpreted the results of C206 to suggest that SVR24 rates trended higher following administration of simeprevir 150 mg compared to 100 mg in the same patient subgroups (though limited in size) identified in C205. There were no meaningful differences in SVR rates with regard to treatment duration (12 or 24 weeks in C205 and 12, 24, or 48 weeks in C206). The Applicant therefore concluded that simeprevir 150 mg QD was the optimal dose and 12 weeks was the optimal duration.

In the Phase 3 trials, the Applicant also evaluated response-guided treatment criteria in which treatment-naïve patients or prior relapsers with HCV RNA <25 IU/mL at Week 4 and undetectable at Week 12 had a shortened PegIFN/RBV tail of 12 weeks; all other subjects (including prior nonresponders) received PegIFN/RBV for a total duration of 48 weeks.

Exposure-Response Relationship

Within the range of exposures observed in the Phase 3 trials, the relationship between efficacy (SVR12) and simeprevir exposures is flat. Individual simeprevir exposure (AUC_{24} and C_{trough}) was estimated from population PK analysis based on sparse sampling in the Phase 3 trials.

A positive relationship between simeprevir exposure and the incidence of adverse events (including rash, photosensitivity, anemia, dyspnea, increased bilirubin, and pruritus) was observed during the simeprevir treatment period.

Absorption, Distribution, Metabolism, and Excretion

Simeprevir is orally bioavailable. Results from the mass balance trial demonstrated that the majority of the simeprevir dose is absorbed, with only 31.0% of dose excreted as unchanged drug in the feces (Trial C103). Peak simeprevir plasma concentrations are reached approximately 6 h post-dose (t_{max}).

Simeprevir is highly protein-bound in plasma (>99.9%) at pharmacologically relevant concentrations, primarily by albumin. The blood:plasma ratio of simeprevir is approximately 0.66, indicating that simeprevir is largely contained in the plasma rather than the cellular components of the blood.

Following administration of a single dose of radiolabeled simeprevir 200 mg to six healthy volunteers, unchanged simeprevir was the primary substance in plasma (85% of circulating radioactivity 24 h postdose) and in the feces (31% of the dose). Only one metabolite, M21, was

identified in plasma (approximately 8% of simeprevir AUC) and, in combination with M22, was the major metabolite in feces (25.9% of dose, M21/M22 ratio of 60/40); several other metabolites were identified in feces, but on average, none composed more than 6% of the dose. M21 and M22 result from oxidation of simeprevir on the macrocyclic moiety, which, as evidenced by in vitro studies and drug-drug interaction trials, most likely occurs via CYP3A, with possible contributions from CYP2C8 and CYP2C19.

At 150 mg QD, simeprevir is a weak inhibitor of intestinal (but not hepatic) CYP3A. Simeprevir also inhibited P-gp, MRP2, BSEP, OATP1B1, and sodium taurocholate cotransporting polypeptide (NTCP) in vitro; results from drug-drug interaction trials with digoxin and rosuvastatin suggest that P-gp and OATP1B1, respectively, are also inhibited in vivo.

The primary route of simeprevir elimination is hepatobiliary excretion. Following administration of a single dose of ^{14}C-TMC435 200 mg, 91% of radioactivity was excreted in the feces (Trial C103). Urinary excretion was negligible (<0.05% of radioactivity).

Simeprevir exhibits nonlinear pharmacokinetics (Table 1). This phenomenon appears to be caused by saturation of hepatic uptake (via OATP1B1/3) and metabolism (via CYP3A4) of simeprevir at doses above 100 mg QD in healthy subjects and 75 mg QD in patients with HCV infection.

Table 1. Pharmacokinetic parameters following 28 days of administration of simeprevir with PegIFN/RBV to HCV genotype 1-infected treatment-naïve subjects (Trial C201)

	Mean (SD)		
	25 mg QD	**75 mg QD**	**200 mg QD**
n	9	9	10
t_{max}[a] (h)	5.92 (4.00-6.05)	6.00 (3.87-8.00)	6.00 (4.00-8.00)
C_0 (ng/mL)	95.8 (61.6)	633 (1128)	4818 (5071)
C_{max} (ng/mL)	329 (187)	1609 (1310)	10900 (6974)
AUC_{24} (ng.h/mL)	4527 (2806)	23610 (26780)	169400 (126500)
$t_{1/2,term}$[a] (h)	11.5 (2.4)	14.3 (8.2)	26.2 (18.5)

[a] Median (range)

Intrinsic Factors

Mean simeprevir AUC_{24} values were 2.4- and 5.2-fold higher in otherwise healthy subjects with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment. Taking into consideration 1) the magnitude of this increase, 2) the potential for an increase of greater magnitude in patients due to the pathological effects of HCV infection, 3) the nonlinear pharmacokinetics of simeprevir, and 4) the positive relationship between simeprevir exposures and adverse events including rash and photosensitivity, this Reviewer concludes that simeprevir should be administered at a reduced dose of 100 mg QD to patients with moderate hepatic impairment and should not be administered to patients with severe hepatic impairment.

Mean simeprevir AUC_{24} values were 1.6-fold higher in otherwise healthy subjects with severe renal impairment compared to matched healthy controls, indicating that no simeprevir dose adjustment is needed in HCV-infected patients with mild, moderate, or severe renal impairment. Simeprevir pharmacokinetics were not evaluated in subjects with end-stage renal disease; therefore, no dose recommendation can be made.

Mean simeprevir AUC_{24} values were 3.4-fold higher in Asian subjects in the Phase 3 trials (n=14) compared to the pooled Phase 3 population (C208, C216, HPC3007). Taking into consideration 1) the magnitude of this increase, 2) the potential for an increase of greater magnitude in patients with HCV infection, 3) the nonlinear pharmacokinetics of simeprevir, and 4) the positive relationship between simeprevir exposures and adverse events including rash and photosensitivity, this Reviewer concludes that simeprevir should be administered at a reduced dose of 100 mg QD to patients with East Asian ancestry.

Based on population PK analysis, body weight, age, sex, total bilirubin (TB) and liver disease status based on METAVIR score (MS) had statistically significant effects on some PK parameters. Simeprevir exposures tend to be higher for females versus males, elderly subjects, subjects with higher TB, and subjects with MS score 3 or 4 versus lower scores. However, given the impact of these covariates on simeprevir exposure compared to the uncharacterized between-subject variability, the clinical relevance of the identified factors on simeprevir exposure is limited.

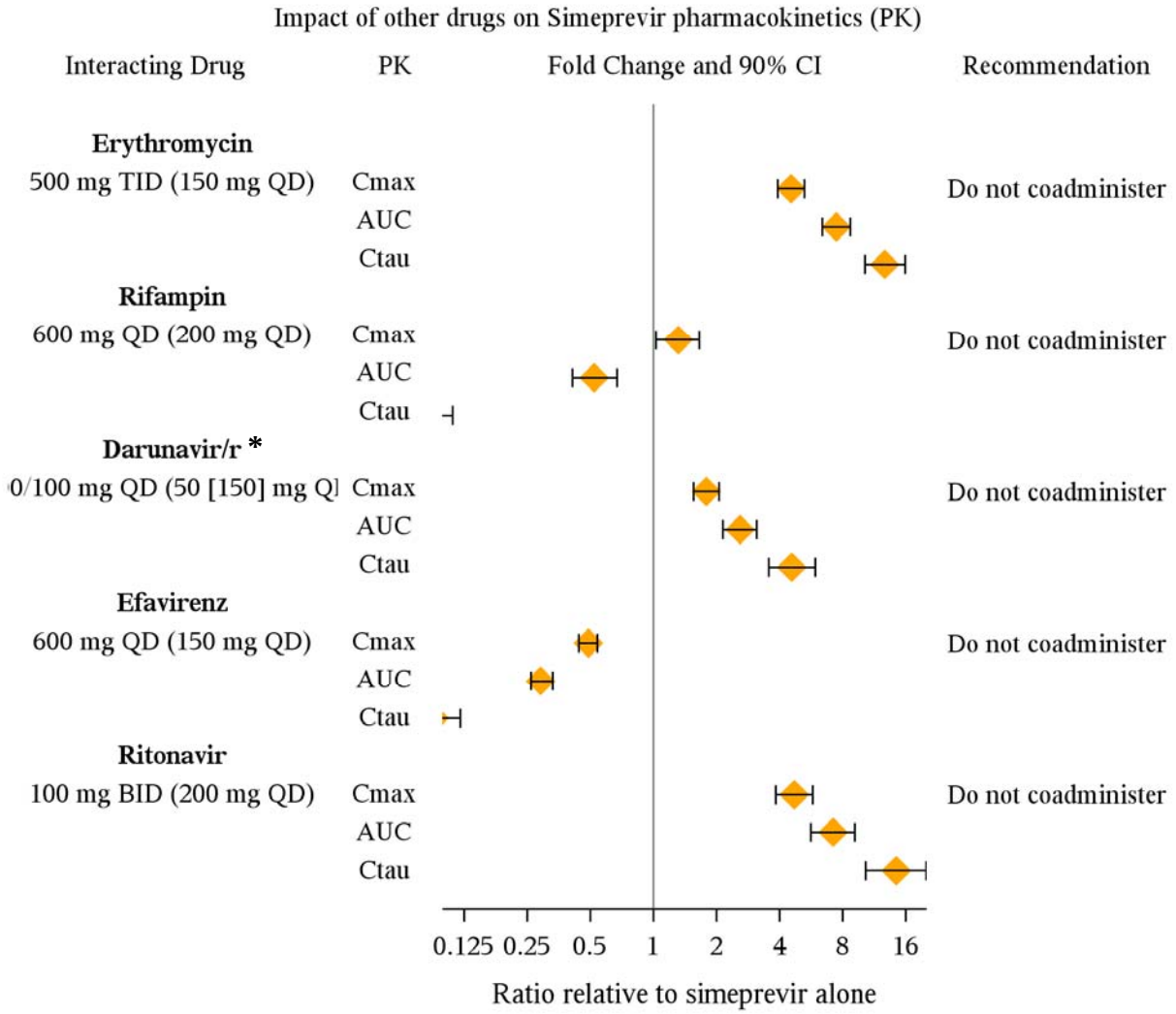
Extrinsic Factors

Based on in vivo drug-drug interaction trials with CYP probes, simeprevir is a mild inhibitor of intestinal CYP3A and a mild inhibitor of CYP1A2. In vitro studies suggest that simeprevir inhibits the uptake transporters OATP1B1 and NTCP and the efflux transporters P-gp, MRP2, and BSEP. The therapeutic effect and adverse event incidence rates of drugs which are substrates of these enzymes or transporters may be affected upon coadministration with simeprevir.

Simeprevir is a substrate of CYP3A and to a lesser extent CYP2C8 and CYP2C19. Simeprevir is also a substrate of P-gp, MRP2, BCRP, OATP1B1/3, and OATP2B1. Coadministered drugs that inhibit or induce these enzymes or transporters may affect simeprevir plasma concentrations and/or its efficacy or safety profile.

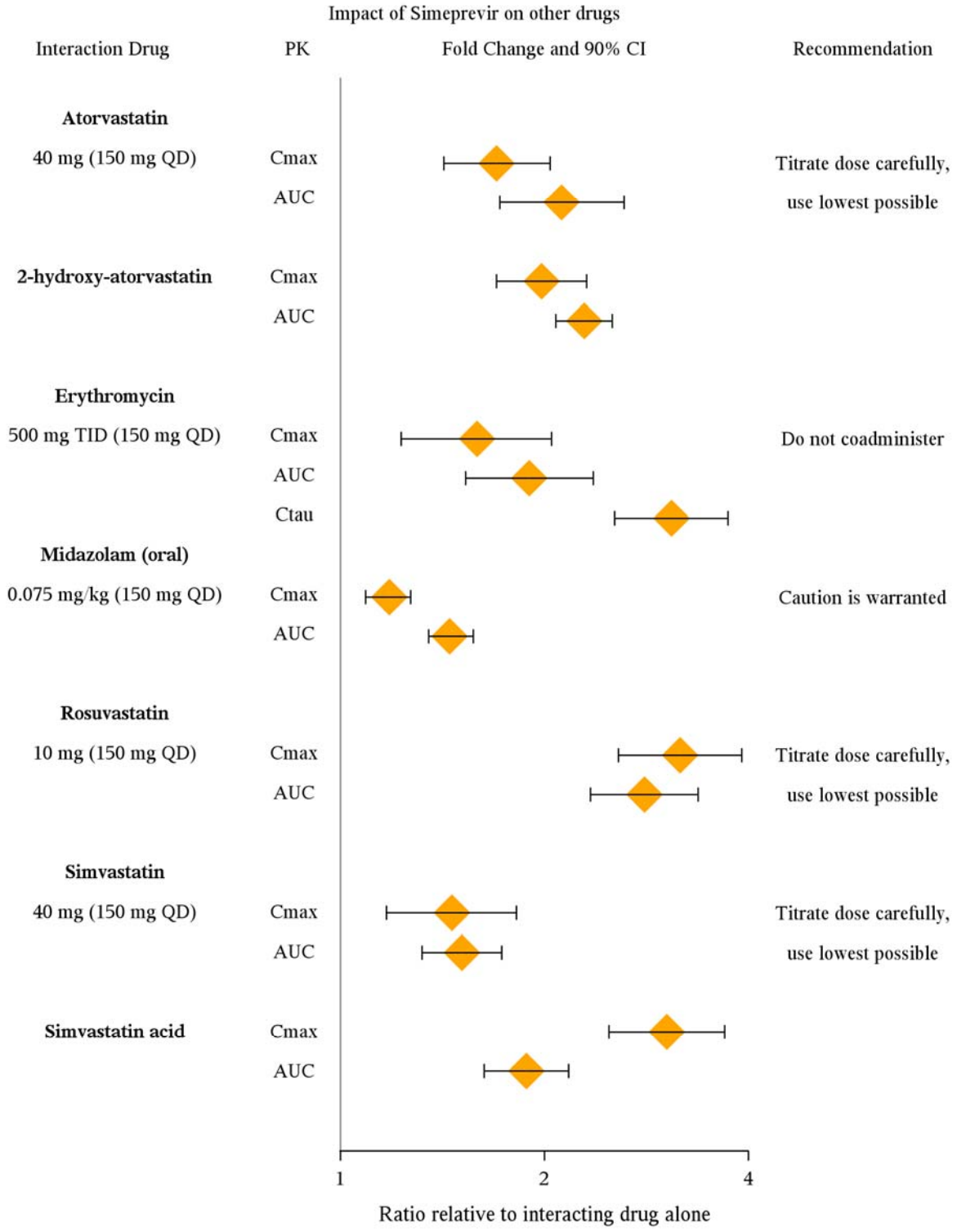
Figures 1 and 2 depict the effects of coadministered drugs on the pharmacokinetics of simeprevir and the effects of simeprevir on the pharmacokinetics of coadministered drugs, respectively, as well as the Applicant's proposed clinical recommendations regarding each pharmacokinetic interaction. Note that only clinically relevant drug-drug interactions are displayed. The magnitude of the increase in atorvastatin and rosuvastatin exposures was so large as to incur a recommendation from the Metabolic and Endocrine Clinical Pharmacology team that a maximum daily dose be instituted when coadministered with simeprevir (refer to Section 2.4.2.8 for details).

Figure 1. The impact of coadministered drugs on the pharmacokinetics of simeprevir and the Applicant's clinical recommendations regarding the drug combination



***** The simeprevir dose was prospectively lowered to 50 mg QD when coadministered with ritonavir-boosted darunavir; ratios are calculated with respect to simeprevir 150 mg QD.

Figure 2. The impact of simeprevir on the pharmacokinetics of coadministered drugs and the Applicant's clinical recommendations regarding the drug combination



Results from drug-drug interaction trials in which simeprevir was coadministered with a strong CYP3A inhibitor (i.e. ritonavir) were used by the Applicant to provide a general

recommendation against coadministration with strong CYP3A inhibitors. In addition, the Clinical Pharmacology review team recommends against coadministration with moderate CYP3A inhibitors based on the drug-drug interaction trial with erythromycin as well as PBPK simulations (please refer to the PBPK Memo for details).

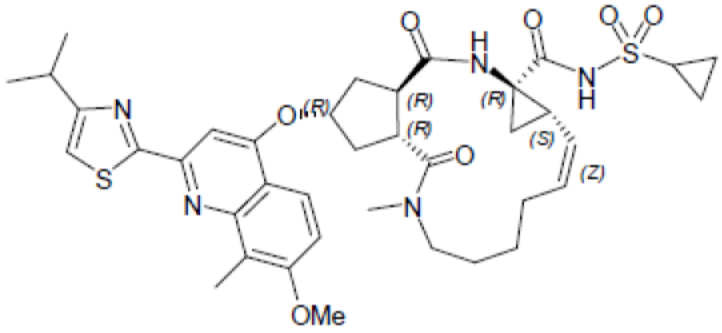
QUESTION-BASED REVIEW

2.1. GENERAL ATTRIBUTES OF THE DRUG

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

The molecular weight of simeprevir is 749.94 Da and the chemical structure is shown in Figure 3.

Figure 3. Chemical structure of simeprevir



Because simeprevir is practically insoluble in aqueous media, simeprevir [(b) (4)] sodium salt [(b) (4)] for oral administration via a [(b) (4)] process. [(b) (4)] Simeprevir immediate-release hard gelatin capsules (referred to as G028) contain 150 mg of simeprevir (154.6 mg of simeprevir salt) and are [(b) (4)] white in color with black "TMC435 150" print. The composition of simeprevir capsules is displayed in Table 2.

[(b) (4)]

(b) (4)

Table 2. Qualitative and quantitative composition of simeprevir 150 mg capsule (G028)

Component	Quality Reference[a]	Function	Quantity per Capsule (mg)
Simeprevir (b) (4)	Control of Critical Steps and Intermediates	Active	154.40
Sodium lauryl sulphate	Ph. Eur., NF	(b) (4)	
Magnesium stearate[b]	Ph. Eur., NF		
Colloidal anhydrous silica	Ph. Eur., NF		
Croscarmellose sodium	Ph. Eur., NF		
Lactose monohydrate	Ph. Eur., NF		
Nominal weight:			
Hard gelatin capsule (b) (4) white body/white cap with black "TMC435 150" print	Control of Excipients	Capsule	1 piece

[a] Where multiple compendia are listed, the compendium that is applied, is specific to the applicable region of the submission.

(b) (4)

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

Simeprevir is a novel inhibitor of the HCV NS3/4A protease that prevents proteolytic activity, thereby obstructing viral replication.

The indication proposed by the Applicant for simeprevir is for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin.

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

The proposed dosage is 150 mg once daily for 12 weeks in combination with peginterferon alfa and ribavirin per their respective prescribing information, followed by an additional 12 or 36

weeks of peginterferon and ribavirin depending on on-treatment response and prior response status. Simeprevir is to be administered orally with food.

2.2. GENERAL CLINICAL PHARMACOLOGY

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

The following primary efficacy parameters were used to support the proposed indication:

- SVRW72: sustained virologic response at Week 72 (HCV RNA undetectable at end of treatment [EOT] and Week 72)
- SVR24: sustained virologic response at Week 24 (HCV RNA undetectable at EOT and <25 IU/mL detectable or undetectable 24 weeks after EOT)
- SVR12: sustained virologic response at Week 12 (HCV RNA undetectable at EOT and <25 IU/mL detectable or undetectable 12 weeks after EOT)

The following studies are used to support the proposed dose and indication:

Phase 1 (26 studies):

- Biopharmaceutics – 3 studies
- Pharmacokinetics – 2 studies (including mass balance)
- Pharmacodynamics – 3 studies (including thorough QT)
- Specific populations – 4 studies (hepatic impairment, renal impairment, and Asian ancestry)
- Drug-drug interactions – 12 studies

Supportive (Phase 2b, two studies):

- C205 (n=309 treated with simeprevir) – This supportive study was a randomized, double-blind, placebo-controlled study evaluating simeprevir 75 and 150 mg QD in combination with PegIFN/RBV for 12 or 24 weeks in treatment-naïve HCV genotype 1 infected subjects. The primary endpoint was SVRW72. No clinically meaningful differences in SVR rates were observed between doses or treatment durations. A trend for higher SVR24 rates was observed with the 150 mg dose compared to the 75 mg dose in certain population subgroups (including subjects with genotype 1a infection with or without the HCV Q80K mutation present at baseline).

- C206 (n=396 treated with simeprevir) – This supportive study was a randomized, double-blind, placebo-controlled study evaluating simeprevir 100 and 150 mg QD in combination with PegIFN/RBV for 12, 24, or 48 weeks in treatment-experienced (prior relapsers and prior partial and nonresponders) HCV genotype 1 infected subjects. The primary endpoint was SVR24. A trend for higher SVR24 rates was observed with the 150 mg dose compared to the 100 mg dose across most subgroups (including subjects with genotype 1a infection and subjects with the HCV Q80K mutation present at baseline).

Pivotal (Phase 3, three studies):

- C208 and C216 – These pivotal studies were randomized, double-blind, placebo-controlled studies evaluating simeprevir 150 mg QD in combination with PegIFNα-2a/RBV (C208 and C216) or PegIFNα-2b/RBV (C216) for 12 weeks followed by an additional 12 or 36 weeks

of response-guided treatment with PegIFN/RBV in treatment-naïve subjects. The only difference between the study designs was the use of PegIFNα-2b at specific study sites in C216. The primary endpoint was SVR12 and the secondary endpoint was SVR24. The treatment outcomes are displayed in Table 3. Simeprevir in combination with PegIFN/RBV was superior in terms of SVR12 to PegIFN/RBV alone when SVR12 rates were compared. Note that the SVR rates differ between the two studies; the Applicant proposes that this is likely due to differences in baseline characteristics (e.g. IL28B genotype, race, baseline HCV RNA >800,000 IU/mL) between the two study populations. Treatment duration did not have a statistically significant effect.

Table 3. Treatment outcomes from Phase 3 studies in treatment-naïve subjects (Studies C208 and C216; ITT populations)

Study	Endpoint	Observed n/N (%)		Comparison vs. PBO	
		Placebo	Simeprevir	Difference in Proportions (95% CI)[b]	p-value[a]
C208	SVR12	65/130 (50.0)	210/264 (79.5)	29.3 (20.1, 38.6)	<0.001
	SVR24	18/30 (60.0)	205/247 (83.0)	18.1 (-0.4, 36.6)	0.025
C216	SVR12	67/134 (50.0)	209/257 (81.3)	32.2 (23.3, 41.2)	<0.001
	SVR24	28/61 (45.9)	206/253 (81.4)	33.2 (21.4, 45.0)	<0.001
Pooled (C208, C216)	SVR12	132/264 (50.0)	419/521 (80.4)	30.5 (24.1, 36.9)	<0.001
	SVR24	46/91 (50.5)	411/500 (82.2)	27.9 (17.3, 38.4)	<0.001

[a] Based on the Cochran-Mantel-Haenszel test controlling for stratification factors and type of PegIFN/RBV where necessary

[b] Difference in proportions (active-placebo) adjusted for stratification factors and type of PegIFN/RBV where necessary, with corresponding 95% CI based on the normal approximation

- HPC3007 – This ongoing pivotal study is a randomized, double-blind, placebo-controlled study evaluating simeprevir 150 mg QD in combination with PegIFNα-2a/RBV for 12 weeks followed by an additional 12 or 36 weeks of response-guided treatment with PegIFN/RBV in treatment-experienced (relapsed after prior PegIFN/RBV therapy) subjects. The primary endpoint was SVR12 and the secondary endpoint was SVR24. The treatment outcomes are displayed in Table 4. Simeprevir in combination with PegIFN/RBV was superior in terms of SVR12 to PegIFN/RBV alone when SVR12 rates are compared. Treatment duration did not have a statistically significant effect.

Table 4. Treatment outcomes from the Phase 3 study in treatment-experienced subjects (Study HPC3007; ITT populations)

Study	Endpoint	Treatment	Observed n/N (%)	Comparison vs. PBO Difference in Proportions (95% CI)[b]	p-value[a]
HPC3007	SVR12	placebo	49/133 (36.8)	43.0 (33.8, 52.3)	<0.001
		simeprevir	206/260 (79.2)		

	SVR24	placebo simeprevir	20/64 (31.3) 199/254 (78.3)	47.1 (34.8, 59.5)	<0.001

[a] Based on the Cochran-Mantel-Haenszel test controlling for stratification factors and type of PegIFN/RBV where necessary

[b] Difference in proportions (active-placebo) adjusted for stratification factors (HCV geno/subtype and IL28B genotype), with corresponding 95% CI based on the normal approximation

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

The primary efficacy endpoint was the proportion of subjects achieving SVR12 (aviremia 12 weeks after completion of antiviral therapy, see Section 2.1.1). SVR12 is a surrogate marker for long-term viral eradication (Pearlman and Traub Clin Infect Dis 52(7): 889-900, 2011).

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

Plasma concentrations of simeprevir were quantified in samples from all trials using validated LC-MS/MS analytical methods. Plasma concentrations of other coadministered drugs were quantified in one or more trials (depending on the trial objectives) using validated LC-MS/MS analytical methods.

2.2.4. Exposure-Response

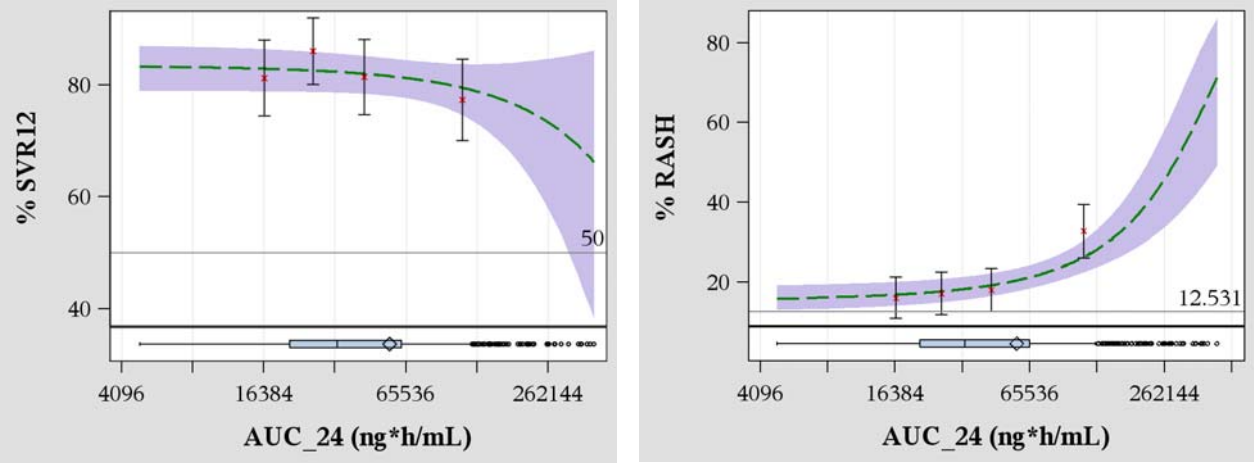
2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

No clear exposure-response relationships for efficacy [SVR (sustained viral response), RVR (rapid viral response), eRVR (extended rapid viral response), VBT (viral breakthrough), and relapse] were identified for simeprevir based on available data from two Phase 3 trials in treatment-naïve subjects (tmc435-tidp16-c208, N=264 and tmc435-tidp16-c216, N=257). In these trials, subjects were treated with simeprevir 150 mg q.d. for the first 12 weeks in combination with P/R for 24 weeks if HCV RNA was <25 IU/mL at week 4 or 48 weeks if HCV RNA was >25 IU/mL at week 4. SVR12 defined as undetectable HCV RNA at the end of treatment (EOT) visit and at 12 weeks after the planned EOT was the primary efficacy endpoint in the pivotal trials. As shown in Figure 4 (left), there was no clear relationship between simeprevir exposure and SVR12. Similarly, no clear exposure-response efficacy relationships were observed for prior relapsers at simeprevir 150 mg dose from the Phase 3 trial (HPC3007, N=260) and for overall treatment-experienced subjects at simeprevir 100 mg and 150 mg from the Phase 2 trial (tmc435-tidp16-c206, N=396).

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

Higher simeprevir exposure was significantly associated with an increased risk of rash, pruritus, anemia, photosensitivity and increased bilirubin. The exposure-safety analyses were conducted based on a pooled analysis of Phase 3 trials. Exposure-response adverse event relationships for any rash are shown in Figure 4 (right). Rash events occurred in 18% (35/194) of subjects in the 3rd quartile compared to 33% (63/193) of subjects in the 4th quartile. The rash event rate in all quartiles exceeded the event rate observed in the control arm (P/R: 12.5%). Similar relationships, as noted above, were observed for pruritus, anemia, photosensitivity, and increased bilirubin (not shown). Also, a significant exposure-response safety relationship was identified for simeprevir if the rash events were limited to grade 2 or higher (e.g., similar slope estimates for either any type or grade 2+ exposure-response rash relationships; please refer to the appended Pharmacometrics Review).

Figure 4. Simeprevir Exposure-Response for SVR (Left [a]) and Rash (Right [b])



[a] Univariate exposure-SVR relationship was plotted based on the pooled Phase 3 trials for treatment-naïve patients (Study c208 and c216). The predicted lower SVR rate at the high end of simeprevir exposure is likely due to the large uncertainty associated with the small number of subjects and the higher percentage of subjects with metavir score F3-F4 in the upper exposure quartile (METAVIR score was both a factor associated with increased simeprevir exposure and decreased likelihood of treatment response)..

[b] Univariate exposure-safety was plotted based on the pooled Phase 3 trials.

2.2.4.3 Does this drug prolong the QT or QTc interval?

Simeprevir does not prolong the QT interval. There was no significant relationship between QT interval and plasma simeprevir concentrations at a dose of 150 (therapeutic) or 350 (supratherapeutic) mg QD; Trial TMC435-TiDP16-C117). Moxifloxacin 400 mg was used to demonstrate assay sensitivity. The largest upper limit of the 90% CIs of the differences between simeprevir and placebo in QTcF change from baseline were 2.79 ms (150 mg, 3 h postdose) and 3.32 ms (350 mg, 1 h postdose); these fall below 10 ms, the threshold for regulatory concern per ICH E14 guidelines.

The supratherapeutic simeprevir dose of 350 mg QD resulted in a mean steady-state C_{max} of 16070 ng/mL, which is approximately 4-fold higher than the estimated mean steady-state C_{max} for the therapeutic dose of 150 mg QD in HCV-infected patients. These concentrations are

above those likely to be observed in a clinical setting (e.g. following a drug-drug interaction with allowed medications).

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

While some aspects of the dose and dosing regimen selected by the Applicant are acceptable, the Clinical Pharmacology review team disagrees with several issues as outlined below and summarized in Table 5.

Applicant's selection of dose and dosing regimen

The Applicant based selection of the dose and dosing regimen on results from Phase 2 trials. Simeprevir 25, 75, and 200 mg QD were evaluated with and without PegIFN/RBV in the Phase 2a trial C201. The antiviral activity of triple therapy (simeprevir plus PegIFN/RBV) was shown to be greater than that of simeprevir alone, in which administration of seven days of simeprevir 200 mg QD resulted in lower antiviral activity compared to seven days of triple therapy (0% vs. 11% with HCV RNA undetectable on Day 7; 11% vs. 33% with HCV RNA <25 IU/mL detectable or undetectable on Day 7). Based on these results, simeprevir was administered with PegIFN/RBV throughout clinical development. However, because elevations in plasma bilirubin levels were highest at the simeprevir 200 mg dose strength, this dose was not evaluated further.

In the Phase 2b studies C205 and C206, simeprevir doses of 75, 100, and 150 mg QD provided similar SVR rates when patients infected with the HCV Q80K mutation at baseline were excluded. Simeprevir 150 mg QD provided numerically greater efficacy (as measured by SVR rates) in certain subpopulations (e.g. harder-to-treat patients such as carriers of the HCV Q80K mutation) compared to 75 mg QD in treatment-naïve patients and 100 mg QD in treatment-experienced patients; therefore, simeprevir 150 mg QD was selected by the Applicant for further development.

The PK, efficacy, and safety of simeprevir 150 mg QD were assessed in the Phase 3 studies C208 and C216 (treatment-naïve patients) and HPC3007 (treatment-experienced patients). The 150 mg QD simeprevir (TMC435) dose in combination with PEG-IFN and RBV (PR) consistently demonstrated superior efficacy to the PR therapy in all of the Phase 3 clinical trials for treatment-naïve subjects and prior PR relapsers.

Clinical pharmacology evaluation of selected dose and dosing regimen

The simeprevir exposure-response relationships indicated that the exposure range observed with 150 mg once daily simeprevir offered a balance between efficacy and safety for the overall patient population evaluated (treatment-naïve and -experienced patients, including prior relapsers and prior partial and null responders). A lower simeprevir dose (e.g. 100 mg once daily) may provide similar efficacy for overall treatment-naïve subjects and prior PR relapsers compared to the 150 mg q.d. dosing regimen. This is based on the flat exposure-response relationship for efficacy and the results from the Phase 2 trials treatment-naïve and treatment-experienced trials (evaluated 75 mg q.d. and 100 mg q.d., respectively in addition to 150 mg q.d.). However, as the

safety events at the studied 150 mg QD dose were manageable and the simeprevir 100 mg QD was not evaluated in Phase 3 trials, the observation that simeprevir 100 mg QD may also be efficacious will be utilized to inform dose adjustments in special populations and not be recommended as a suitable dose for the overall population.

The Clinical Pharmacology review team has the following conclusions and recommendations regarding the Applicant's proposed dose and dosing regimen:

I. Simeprevir 150 mg q.d. is highly likely to be effective in overall prior P/R non-responders (including prior relapsers and prior partial and null responders). This conclusion is based on the clinical outcomes from the Phase 2 trial C206, the Japanese Phase 3 trials in treatment-experienced subjects, and the bridging analysis for the harder-to-treat treatment-naïve subpopulation from Phase 3 trials:

   a. In Study C206, simeprevir in combination with PR showed significantly higher SVR rates in the overall population of treatment-experienced subjects across all six simeprevir treatment groups compared to the placebo group. The SVR12 rate for subjects treated with simeprevir 150 mg for 12 weeks was 66.7%, which was significantly higher than the 22.7% rate in the PR treatment group. There were no substantial differences between response rates across different simeprevir treatment durations (C206 included simeprevir treatment durations of 12-, 24-, and 48-weeks) or different simeprevir doses (C206 included simeprevir doses of 100 and 150 mg once daily) among the treatment-experienced subpopulations. In addition, consistently higher SVR rates were shown in all simeprevir treatment groups for null responders (range from 38% to 59%), partial responders (52% to 86%), and relapsers (77% to 89%) when compared to placebo (19%, 9% and 37%, respectively). Based on the above results, statistical superiority for prior relapsers and partial responders (p-value < 0.0001) and a trend in the same direction for null responder (p-value = 0.11, likely due to the small sample size and the higher than anticipated response rate in null responders [19% - exceeds the response rate in prior partial responders]) were demonstrated when comparing simeprevir 12-wk/PR versus PR (see Statistics review).

   b. Results of Japanese Phase 3 trials, for which summary results but no datasets were submitted, also support the use of simeprevir in combination with PR in prior PR non-responders. The SVR response rates for the trials exceeds the historic 16% of SVR rate assumed for the P/R treatment:

      - SVR12 response rate was 53% (28/53) and 36% (19/53) for simeprevir 100 mg q.d. administered for 12 weeks and 24 weeks respectively in HPC3004
      - SVR12 response rate was 39% (10/26) for simeprevir 100 mg q.d. administered for 12 weeks in HPC3010

   c. Less likely to respond subjects, characterized as those subjects with specific baseline factors that are predictive of reduced response (e.g., with baseline non-CC IL28B genotype, higher baseline HCV RNA, and liver disease status METAVIR score F3-F4) in the treatment-naïve population could be considered as

putative PR-experienced subjects. The SVR12 rates in these subjects with multiple baseline factors associated with reduced likelihood of response was significantly higher with simeprevir 150 mg for 12 weeks compared to the response rates in similar subjects administered only PR.

II. Patients should be screened for the HCV Q80K mutation prior to treatment with simeprevir and PegIFN/RBV. Pretreatment screening would greatly simplify the treatment algorithm for patients and medical practitioners. Q80K is a common polymorphism in U.S. HCV 1a-infected subjects. Simeprevir has reduced activity against Q80K variants. Rather than screening out Q80K-infections, the sponsor proposed a treatment algorithm (b) (4)

(b) (4)

(b) (4) Considering the (b) (4) availability of alternative treatment options to simeprevir where Q80K is not an issue, prescreening Q80K prior to treatment with simeprevir/PR may offer a simpler and clinically more practical option which would permit:

a. Treatment-naïve and prior relapse patients receive a fixed 24-week course of PR in conjunction with 12 weeks of simeprevir.
b. Prior partial- and prior null-responders receive a fixed 48 week course of PR in conjunction with 12 weeks of simeprevir.
c. All patients treated with simeprevir/P/R with quantifiable (≥25 IU/mL) HCV RNA levels at Week 4 should stop treatment.

III. The simeprevir dose should be reduced in patients with East Asian ancestry and patients with moderate hepatic impairment. A positive relationship between simeprevir exposures and adverse events (including rash and photosensitivity) was observed in the Phase 3 trials, suggesting that patient subpopulations which are predisposed to higher simeprevir exposures (i.e. patients with East Asian ancestry, patients with moderate or severe hepatic dysfunction) compared to the Phase 3 patient population are likely to be at an increased

risk for adverse events. In the absence of an appropriate dose strength, no dose can be recommended for these patit subpopulations.

There are three patient subpopulations for which the Clinical Pharmacology review team is recommending doses or dosing algorithms that differ from the Applicant's proposed doses or dosing algorithms. These subpopulations, and the Clinical Pharmacology review team's recommendations, are listed in Table 5:

Table 5. Patient subpopulations with unresolved simeprevir dosing issues

	Patient subpopulation	Applicant's proposed dose or dosing algorithm	Review team's recommendation
1	Patients with HCV Q80K at baseline	Treatment algorithm (b) (4)	Avoid use (b) (4)
2	Patients with East Asian ancestry	150 mg QD	Decrease dose to 100 mg QD because of high exposures
3	Patients with moderate hepatic impairment	150 mg QD	Decrease dose to 100 mg QD because of high exposures

Please refer to the Pharmacometrics review and Sections 2.3.2.4 (Race) and 2.3.2.6 (Hepatic impairment) of this review for further discussion of issues 1 through 3, respectively.

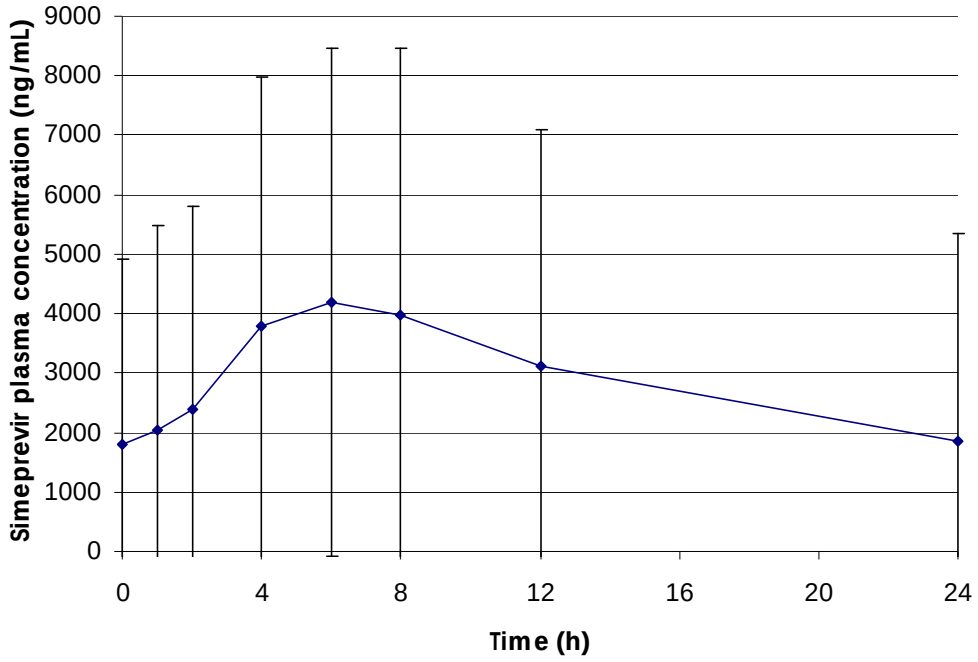
2.2.5. What are the PK characteristics of the drug and its major metabolite?

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

Simeprevir pharmacokinetics have been studied in healthy patients as single doses (50 to 600 mg) and multiple doses (100 to 400 mg QD and 200 mg BID). In patients, a single dose (200 mg) and multiple doses (25 to 200 mg QD) with or without PegIFN/RBV have been studied. The pharmacokinetics parameters of simeprevir differ between healthy volunteers and HCV-infected patients (see Section 2.2.5.2). The following discussion will focus on simeprevir pharmacokinetics in patients, as they are more relevant to the intended treatment population.

The mean simeprevir concentration-time profile following administration of simeprevir 150 mg QD with PegIFN/RBV to HCV-infected subjects from Trial C205 is shown in Figure 5.

Figure 5. Mean (±SD) plasma simeprevir concentration-time profile after administration of simeprevir 150 mg QD in combination with PegIFN/RBV in treatment-naïve HCV genotype 1-infected subjects (Trial C205)



The pharmacokinetic parameters of simeprevir 150 mg QD are listed in Table 6. (Note that an intensive pharmacokinetic evaluation was not performed in HCV-infected patients using the Phase 3 formulation; therefore, pharmacokinetic parameters from trials in which the Phase 2b formulation was administered, as well as population estimates of pharmacokinetic parameters for the Phase 3 trials, are displayed – the two formulations provide similar exposures [please refer to Section 2.5.2 for further discussion].) Simeprevir exposures increased more than dose-proportionally at doses above 75 mg QD in patients (an 8-fold increase in mean AUC_{24} over the dose range of 75 to 200 mg QD). Maximal plasma concentrations were reached approximately 4 to 6 hours postdose; the rate of absorption was not affected by dose. Steady-state conditions were reached by seven days of simeprevir administration. Based on single- and multiple-dose data on 200 mg QD in patients, the accumulation ratio for simeprevir AUC_{24} was 3.45 and the mean steady-state terminal half-life was 41.3 h.

Table 6. Summary of PK parameters after multiple-dose administration of simeprevir 150 mg QD in HCV-infected patients

Parameter	**Phase 2b formulation (F021) PK substudies** (mean ± SD)			**Phase 3 formulation (G007) Population estimates** (mean [%CV])		
	C205 (tx-naïve)	**C206** (tx-exp)	**C208** (tx-naïve)	**C216** (tx-naïve)	**HPC3007** (tx-exp)	**Pooled Phase 3**
N	23	26	259	255	259	773
t_{max} h	6.0 (2-12)	6.0 (4-8)	-	-	-	-
C_0 ng/mL	1796 ± 3116	1440 ± 1864	1825 (126)	1902 (146)	2081 (135)	1936 (136)

C_{min} ng/mL	1579 ± 3096	1345 ± 1795	-	-	-	-
C_{max} ng/mL	4394 ± 4430	3953 ± 2893	-	-	-	-
AUC_{24} ng·h/mL	70090 ± 93390	59810 ± 55650	54795 (102)	56611 (118)	60987 (111)	57469 (111)
$C_{ss,av}$ ng/mL	2919 ± 3892	2492 ± 2319	2283 (102)	2359 (118)	2541 (111)	2395 (111)

Metabolite M21 was identified in plasma in low abundance (up to 8% of unchanged drug). Following multiple dosing, no accumulation of M21 was observed. The pharmacokinetics of M21 were not routinely evaluated in clinical trials.

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

The pharmacokinetic parameters of single- and multiple-dose simeprevir 200 mg QD in patients and healthy volunteers are displayed in Table 7 (Trial C101). Simeprevir exposures are 2- to 3-fold higher in patients compared to healthy volunteers. This appears to be a function of the selected dose of 150 mg (at which CYP3A is saturated) as well as lower functional hepatic CYP3A content observed in patients with chronic HCV infection (Nakai et al. Drug Metab Dispos 2008; Ohnishi et al. J Clin Pharmacol 2005; Lin et al. Hepatogastroenterology 1998; Johnson et al. Clin Pharmacokinet 2010; Barreiro et al. Eur J Clin Pharmacol 2005), which results in slower simeprevir clearance in patients.

Table 7. Pharmacokinetics of simeprevir after administration of 200 mg QD in healthy volunteers and treatment-experienced subjects infected with HCV genotype 1

	Mean ± SD	
Parameter	TMC435 200 mg q.d. Healthy Subjects	TMC435 200 mg q.d. HCV-Infected Subjects
Day 1		
n	5	6
t_{max} [a], h	4.0 (3.0 - 6.0)	6.0 (4.0 - 8.0)
C_{max}, ng/mL	2304 ± 918	4067 ± 1479
AUC_{24h}, ng.h/mL	24630 ± 7331	56430 ± 22470
Day 5		
n	5	6
t_{max} [a], h	4.0 (3.9 - 8.0)	4.0 (4.0 - 8.0)
C_{0h}, ng/mL	1482 ± 791	6057 ± 4213
C_{min}, ng/mL	1445 ± 767	5743 ± 4089
C_{max}, ng/mL	6172 ± 2859	11470 ± 5337
AUC_{24h}, ng.h/mL	79710 ± 37230	206000 ± 113600
	3324 ± 1554	8584 ± 4732
$t_{1/2,term}$, h	16.0 ± 5.1	41.3 ± 33.0
Accumulation ratio [b]	3.16 ± 1.01	3.45 ± 0.67

n = maximum number of subjects with data.
[a] Median (range).
[b] AUC_{24h} on Day 5/AUC_{24h} on Day 1.
Source: Mod5.3.3.1/C101-CSR/Sec4.2.8.2

2.2.5.3 What are the characteristics of drug absorption?

Simeprevir is orally bioavailable. Results from the mass balance trial demonstrated that the majority of the simeprevir dose is absorbed, with only 31.0% of dose excreted as unchanged drug in the feces (Trial C103). Peak simeprevir plasma concentrations are reached approximately 6 h post-dose (t_{max}).

Absorption of simeprevir is greater when administered with food (mean AUC_{last} increased by 66-70% when administered in the fed state compared to fasted). Please see Section 2.4.3 of this review for information regarding the effect of food administration on simeprevir exposures.

Based on in vitro studies in Caco-2 cells, simeprevir is a low permeability compound, with an apparent permeability of 0.8×10^{-6} cm/s at a concentration of 20 uM (Study NC113).

Simeprevir demonstrated a B:A/A:B ratio of 3.2, with transport polarity inhibited by 95.5% upon addition of verapamil, indicating that it is a P-gp substrate. However, gut P-gp appears to play a minimal role in simeprevir 150 mg absorption as evidenced by the limited effect of cyclosporine 100 mg on simeprevir pharmacokinetics (16% and 19% increases in C_{max} and AUC_{last}, respectively; Trial C120).

2.2.5.4 What are the characteristics of drug distribution?

Simeprevir is >99.9% bound to plasma proteins, primarily human serum albunin (≥99.8%), over a simeprevir concentration range of 0.05 to 2.5 ug/mL (Studies NC202 and NC111). The blood:plasma ratio ranged from 61 to 69% over the timecourse evaluated, indicating that simeprevir predominantly distributed to plasma relative to the cellular components of blood.

Population PK analyses generated an estimated apparent volume of distribution of 38.4 L in the central compartment (V_c/F) and 250 L in the peripheral compartment (V_p/F).

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

The mass balance trial (Trial C103) demonstrated that the majority of the [^{14}C]-simeprevir dose was recovered in the feces (mean 91.2%), suggesting that the primary route of simeprevir elimination is hepatobiliary. A negligible fraction of the radioactive dose was recovered in the urine (0.039%). The radioactivity in feces consisted mainly of simeprevir (mean 31.0% of the radioactive dose) and oxidation products (M21+M22: mean 25.9% of the radioactive dose).

2.2.5.6 What are the characteristics of drug metabolism?

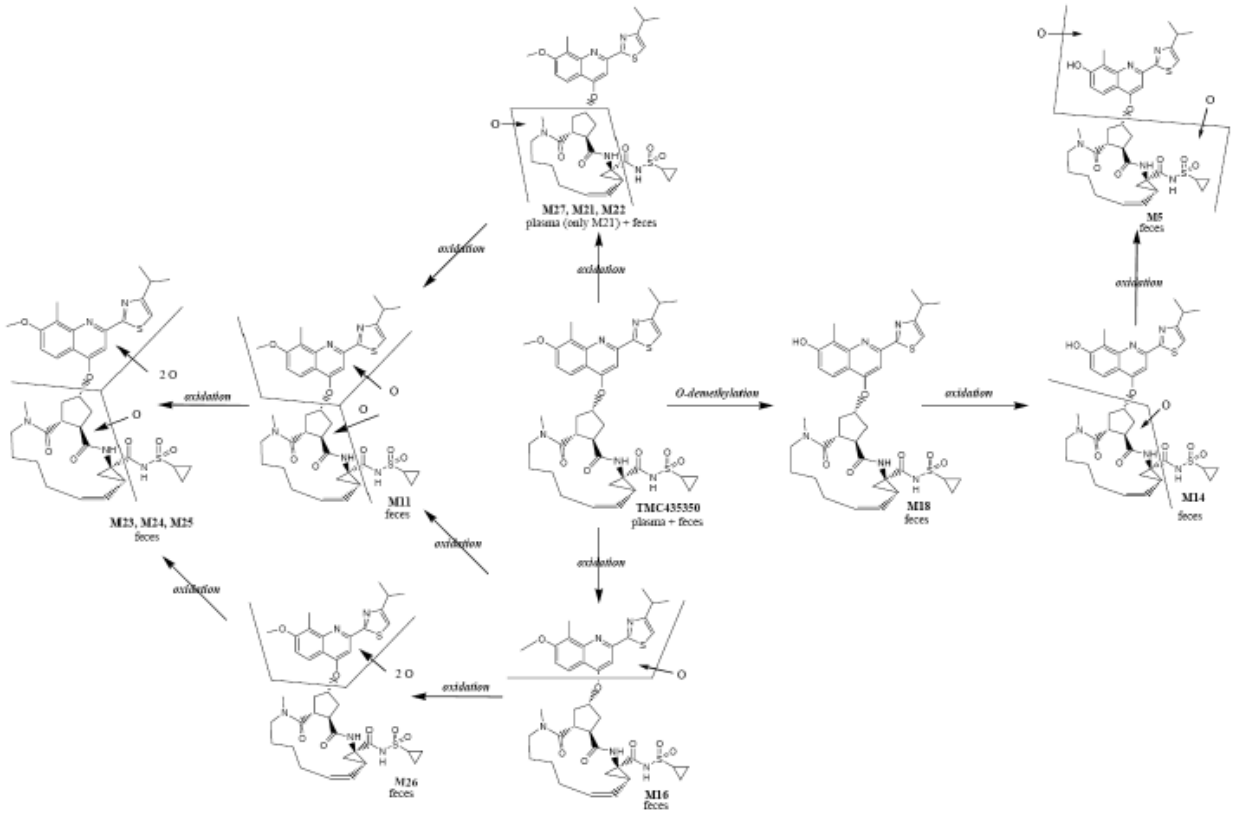
The biotransformation of simeprevir primarily occurs via CYP3A4-mediated oxidation (Figure 6), although in vitro studies suggested the potential for involvement by CYP2C8 and CYP2C19.

The primary route of metabolism is supported by the significant increase in simeprevir exposures in the presence of the potent CYP3A inhibitor ritonavir.

Only one metabolite was detected in plasma: M21 (GS-9202), which results from oxidation of simeprevir at the macrocyclic moiety. Plasma exposures of M21 were approximately 8% of plasma simeprevir exposures, making it a minor metabolite (ICH M3); therefore, M21 was not assessed in plasma samples from clinical trials.

Data from the mass balance trial indicated that the predominant circulating species in plasma is simeprevir (approximately 91% of radioactivity). Unchanged drug and the oxidative metabolites M21 and M22 were the primary species in the feces.

Figure 6. Proposed biotransformation pathway of simeprevir in humans



2.2.5.7 What are the characteristics of drug excretion?

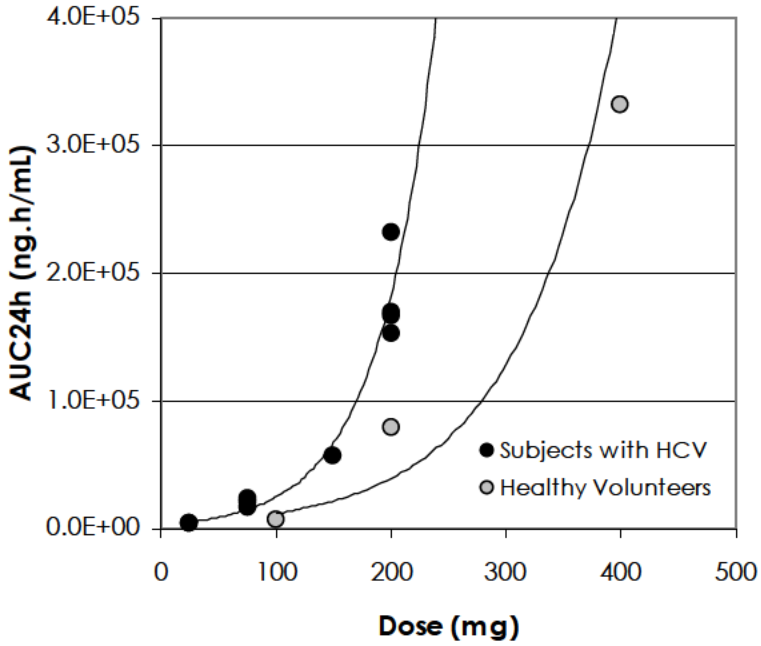
Please refer to Section 2.2.5.5 of this review.

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

Simeprevir exposures increased more than dose-proportionally in healthy volunteers and HCV-infected subjects at doses greater than 100 mg and 75 mg QD, respectively (Figure 7).

Simeprevir AUC_{24} increased by 53-fold over the dose range of 50 to 600 mg in healthy volunteers and 37-fold over the dose range of 25 to 200 mg in patients with HCV (Trials C101 and C201, respectively). Physiologically-based pharmacokinetic (PBPK) modeling indicates that this phenomenon is likely driven by the dose-dependent saturation of gut and liver CYP3A metabolism as well as the time-dependent saturation hepatic OATP1B1/3 uptake, both of which appear to occur after multiple-dose administration of simeprevir 150 mg QD (please refer to the PBPK Memo appended to this review for further details).

Figure 7. Nonlinearity of simeprevir pharmacokinetics



2.2.5.9 How do the PK parameters change with time following multiple dosing?

Please refer to Section 2.2.5.1 of this review.

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

The intersubject variability of simeprevir PK parameters after administration of simeprevir 150 mg was generally high in both healthy and HCV-infected subjects. In healthy subjects, following administration of multiple doses of simeprevir 150 mg, the coefficient of variation (%CV) values were 73%, 140%, and 87% for simeprevir C_{max}, C_{tau}, and AUC_{24} (pooled analysis of C112, C113, C114, C115, C117, C123, C125, C126, and HPC1005). The degree of interindividual variability was similar in patients with HCV infection: population PK analysis generated %CV values of 136% and 111% for simeprevir C_{tau} and AUC_{tau}, respectively (pooled individual estimates from C208, C216, and HPC3007).

The high degree of intersubject variability is likely a result of nonlinear simeprevir pharmacokinetics at the dose of 150 mg QD. Interindividual differences in the amount and functionality of OATP1B1/3 and CYP3A (i.e. the degree to which OATP1B1/3 and CYP3A are saturated for each individual) are reflected in the high degree of variability in exposures. Substantial intersubject variability was also reflected in PBPK simulations.

The Applicant submitted genetic data for several ADME related genes in an attempt to evaluate the role that genetic variation in these ADME genes might play in the large intersubject variability observed for simperevir PK parameters. Complete exon sequence data was submitted for the following 10 ADME related genes: CYP3A4, CYP3A5, CYP2C19, SLCO1B1, SLCO1B3, SLCO2B1, SLC10A1, ABCB1, ABCC2, & ABCG2. The Applicant's analysis showed no differences in the pattern of variation between subjects in the lowest quartile of simeprevir exposure (AUC) and subjects in the highest quartile of simeprevir exposure (AUC).

Additional analysis conducted by the Genomics and Targeted Therapy reviewer attempted to classify genetic variation as likely to be deleterious to protein function by using the in-silico prediction tool SIFT. The results of this analysis showed that the presence of deleterious variants was not associated with AUC (Low vs. High) across all genes, within a gene, or for individual variants (please refer to the Genomics and Targeted Therapy Memo in this review for further details). Based on the data provided from the sponsor, it does not appear that genetic variation within the coding regions of these genes is associated with the large PK variability of simeprevir. This is expected for CYP genes given that simeprevir undergoes limited metabolism.

Given that only the subjects in the highest and lowest quartiles of exposure were selected and that only a select few candidate genes were screened, it is difficult to exclude that genetic variations might be associated with the observed variations in simeprevir exposure. It is possible that pharmacogenetic analyses on the entire cohort (i.e., all available pharmacokinetic data) using a high-throughput ADME genotyping platform could be used to further account for the inter-individual variability.

There were insufficient data to evaluate the intrasubject variability of simeprevir PK parameters.

2.3. INTRINSIC FACTORS

2.3.1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response, and what is the impact of any differences in exposure on pharmacodynamics? What dosage regimen adjustments are recommended for each of these subgroups, if any?

Significant increases in simeprevir plasma concentrations were observed in patients with moderate or severe hepatic dysfunction (mean AUC_{24} approximately 2.4- and 5.2-fold higher, respectively, than the pooled Phase 3 population) or patients with East Asian ancestry (mean AUC_{24} approximately 3.4-fold higher than the pooled Phase 3 population. The increased exposures are likely a consequence of smaller liver size and lower amount of functional CYP3A in these subpopulations compared to the pooled Phase 3 population. These subpopulations are discussed in detail in Sections 2.3.2.4 (Race) and 2.3.2.6 (Hepatic impairment) of this review.

For a discussion about the utility of PBPK modeling and simulations to predict the PK of simeprevir in these subpopulations, please refer to the PBPK Memo appended to this review.

The Applicant does not propose simeprevir dose adjustments for any patient subpopulation. However, based on the exposure-response relationship for safety, this Reviewer recommends a dose reduction to simeprevir 100 mg QD for patients with moderate hepatic impairment and patients with East Asian ancestry. Note that the Applicant states that no dose recommendation can be made for patients with severe hepatic impairment; this Reviewer agrees but would prefer to include a specific recommendation against simeprevir administration to patients with severe hepatic impairment in the prescribing information.

From the population PK analysis, body weight, age, sex, total bilirubin (TB) and liver disease status based on METAVIR score (MS) had statistically significant effects on some PK parameters. Simeprevir exposures tend to be higher for females versus males, elderly subjects, subjects with higher TB, and subjects with MS score 3 or 4 versus lower scores. However, given the impact of these covariates on simeprevir exposure compared to the uncharacterized between-subject variability, the clinical relevance of the identified factors on simeprevir exposure is limited. No simeprevir dose adjustments are recommended based on any of these identified covariates.

Factors associated with efficacy based on the Pharmacometric reviewer's multivariate analysis included HCV genotype subtype (1a versus 1b), baseline HCV RNA value (higher baseline HCV RNA associated with decreased probability of response), liver disease status based on METAVIR score (MS), and baseline Q80K polymorphism. However, the exposure-response analyses did not detect any clinical meaningful effect of those factors on the exposure-efficacy relationship.

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

2.3.2.1 Elderly

The pivotal Phase 3 trials (total N=773 treated with simeprevir) included 21 subjects above 65 years of age. Although the size of the subpopulation of patients over 65 is small, mean AUC_{24} and C_{trough} values appeared to be similar to the rest of the Phase 3 population (Table 8). Population PK analysis indicated the variability in exposures introduced by age (in combination with other significant covariates) was less than the level of random variability in simeprevir exposures. No simeprevir dose adjustments are recommended in patients above the age of 65.

Table 8. Population pharmacokinetic estimates of mean (%CV) simeprevir exposures by age following administration of simeprevir 150 mg QD in HCV-infected subjects (C208, C216, HPC3007)

Age	AUC_{24} (ng·h/mL) mean (%CV)	C_0 (ng/mL) mean (%CV)
≤65 years of age (n=752)	57456 (111)	1857 (138)
>65 years of age (n=21)	57904 (92)	2132 (99)
Pooled population	57469 (111)	1936 (136)

2.3.2.2 Pediatrics

The pharmacokinetics of simeprevir have not been evaluated in healthy or HCV-infected subjects under the age of 18 years old.

The Applicant is seeking a waiver in children younger than 3 years of age and a deferral in children (b) (4) to less than 18 years of age until a simeprevir-containing interferon-free regimen is developed.

2.3.2.3 Gender

The pivotal Phase 3 trials (total N=773 treated with simeprevir) included 311 female subjects and 462 male subjects. Simeprevir exposures tended to be higher in female subjects compared to males (Table 9). Population PK analysis indicated that the variability in exposures introduced by sex (in combination with other significant covariates) was less than the level of random variability in simeprevir exposures. No simeprevir dose adjustments are recommended for female patients.

Table 9. Population pharmacokinetic estimates of mean (%CV) simeprevir exposures by sex following administration of simeprevir 150 mg QD in HCV-infected subjects (C208, C216, HPC3007)

Sex	AUC_{24} (ng·h/mL) mean (%CV)	C_0 (ng/mL) mean (%CV)
Female (n=311)	69706 (106)	2285 (126)
Male (n=462)	49231 (110)	1522 (145)

2.3.2.4 Race

Multiple doses of simeprevir 100 mg QD in small numbers of healthy Japanese (US) and Chinese (Hong Kong) subjects resulted in mean AUC_{24} values that were 2.3- and 1.9-fold higher (C109 and HPC1004), respectively, compared to healthy Caucasian subjects (C101). Collectively, these data suggest that saturation of the clearance pathway (i.e. CYP3A metabolism and OATP1B1/3 hepatic uptake) occurs at lower doses in people of East Asian ancestry (≤100 mg QD) compared to people of Caucasian ancestry (>100 mg QD but ≤200 mg QD), likely because of the smaller liver volume and lower CYP3A abundance in Asians relative to Caucasians (Nakai et al. Drug Metab Dispos 2008).

Similar exposure differences were observed in HCV-infected patients of Japanese descent compared to those of Caucasian descent. Mean simeprevir AUC_{24} values were 14% lower in subjects of Japanese ancestry receiving simeprevir 100 mg QD compared to Caucasian subjects receiving simeprevir 150 mg QD (Table 10).

Table 10. Simeprevir pharmacokinetic parameters after multiple dose administration of simeprevir in HCV genotype 1 infected subjects of Caucasian and Japanese descent (C205, C206, C215 [Japan])

	Mean ± SD					
	50 mg q.d.	75 mg q.d.	100 mg q.d.		150 mg q.d.	
Parameter	Japanese C215	Caucasian C205	Japanese C215	Caucasian C206	Caucasian C205	Caucasian C206
n	14	21	12	33	23	26
t_{max} [a], h	5.97 (3.95 - 8.00)	6.0 (2.0 - 8.0)	6.00 (4.00 - 12.00)	6.0 (4.0 - 12.0)	6.0 (2.0 - 12.0)	6.0 (4.0 - 8.0)
C_{0h}, ng/mL	192 ± 134	213 ± 177	1732 ± 2669	1103 ± 1488	1796 ± 3116	1440 ± 1864
C_{max}, ng/mL	1011 ± 725	1035 ± 522	4072 ± 3446	2626 ± 2192	4394 ± 4430	3953 ± 2893
AUC_{24h}, ng.h/mL	11182 ± 7763	13200 ± 6772	60197 ± 65364	39720 ± 41790	70090 ± 93390	59810 ± 55650

n = maximum number of subjects with data.
[a] Median (range).

The majority of patients enrolled in Phase 3 trials (total N=773 treated with simeprevir) were white (91.9%), with 6.1% of subjects who were black and 1.8% who were of East Asian ancestry. Substantially higher exposures were observed in Asian patients compared to non-Asian patients (mean and median AUC_{24} values were 3.6- and 6.3-fold higher, respectively, in Asian patients compared to Caucasian patients; Table 11). The magnitude of the increase in simeprevir exposures appears to be higher in Asian patients compared to healthy Asian subjects, likely because chronic HCV infection is associated with decreases in liver volume and functional hepatic CYP3A content.

Table 11. Population pharmacokinetic estimates of simeprevir exposures by race following administration of simeprevir 150 mg QD in HCV-infected subjects (C208, C216, HPC3007)

Sex	**AUC_{24} (ng·h/mL)** mean (%CV)	**AUC_{24} (ng·h/mL)** median (range)	**C_0 (ng/mL)** mean (%CV)
White (n=703)	55619 (109)	33296 (4868-449185)	1829 (137)
Black (n=47)	47986 (83)	32896 (14172-168130)	1628 (107)
Asian (n=14)	196750 (61)	209070 (22334-408855)	7176 (80)
Non-Asian (n=757)	54988 (106)	33300 (4868-449200)	1806 (135)

The Applicant states that no dose adjustment is necessary based on race because "there were no relevant differences among race categories for AEs in general, events of clinical interest, and events of special interest" in the pooled safety analysis for the Phase 3 studies but that "the number of Asian subjects in both treatment groups… was too small to draw meaningful conclusions." This Reviewer is in agreement that the number of Asian subjects in the Phase 3 studies was too small to derive conclusions regarding safety in this subpopulation. However, the

following points must be considered when evaluating the Applicant's proposed dose of simeprevir 150 mg QD in Asian patients in the current NDA:

1. Taking into account the high degree of intersubject variability, the safety profile of expected exposures in the Asian subpopulation following administration of simeprevir 150 mg QD has not been well-characterized in the Phase 3 trials;
2. Pharmacometric analyses have established a positive relationship between simeprevir exposures and adverse events, including rash and photosensitivity;
3. In addition, no safety data for simeprevir 150 mg QD are available from development programs in East Asian countries because the Applicant has selected a dose of simeprevir 100 mg QD for clinical development in these countries due to the exposure differences observed in the Phase 1 trial C109 (conducted in the US) and the efficacy data from the Phase 2b trial C215 (conducted in Japan);
4. Based on the flat exposure-response relationship for efficacy, no additional therapeutic benefit is gained from higher exposures.

Based on the above reasons, this Reviewer recommends a dose reduction to simeprevir 100 mg QD for patients with East Asian ancestry.

2.3.2.5 Renal impairment

Simeprevir pharmacokinetics were evaluated in subjects with severe renal impairment (eGFR <30 mL/min) not on dialysis and matched healthy controls with normal renal function (eGFR ≥80 mL/min) following multiple-dose administration of simeprevir 150 mg QD (Trial C216). Steady-state simeprevir plasma concentrations were slightly higher in subjects with severe renal impairment (mean AUC_{24} was 1.6-fold higher in subjects with severe renal impairment compared to matched controls; Table 12). In addition, severe renal impairment was found to have no effect on simeprevir protein binding (% free fraction was around 0.01 in control subjects and in subjects with severe renal impairment).

Table 12. Pharmacokinetics of simeprevir in subjects with severe renal impairment compared to healthy matched subjects after multiple-dose administration of simeprevir 150 mg QD

Parameter	Mean ± SD: Subjects With Normal Renal Function TMC435 150 mg q.d. (Reference)	Mean ± SD: Subjects With Severe Renal Impairment TMC435 150 mg q.d. (Test)	Ratio [a] (Test:Reference)	90% CI
n	8	8		
t_{max} [b], h	6.0 (4.0 - 9.0)	6.0 (4.0 - 9.0)	-	-
C_{0h}, ng/mL	1112 ± 1480	2220 ± 2696	-	-
C_{min}, ng/mL	961 ± 1191	1707 ± 1741	1.71	0.65 - 4.50
C_{max}, ng/mL	3378 ± 2636	4671 ± 3823	1.34	0.66 - 2.72
AUC_{24h}, ng.h/mL	44380 ± 39920	76690 ± 71740	1.62	0.73 - 3.59
$C_{ss,av}$, ng/mL	1849 ± 1663	3195 ± 2989	-	-
$t_{1/2,term}$, h	16.7 ± 10.2	24.0 ± 18.8	-	-

n = maximum number of subjects with data.
[a] Ratio based on LS means.
[b] Median (range).

There was one treatment-emergent serious adverse event of grade 3 rhabdomyolysis (which started one day after the last dose of simeprevir) in a subject with severe renal impairment. The Day 7 simeprevir AUC_{24} and C_{max} values for this subject were near the mean values for the renal impairment group (refer to C126 review for details), indicating that high simeprevir plasma concentrations were not associated with this SAE.

Based on the relatively slight increase in simeprevir exposures (1.6-fold increase in mean AUC_{24}) observed in subjects with severe renal impairment as well as the simeprevir exposure-response relationship for safety, the effect of renal impairment on simeprevir exposure is not considered to be clinically relevant and no simeprevir dose adjustment is recommended in patients with mild, moderate, or severe renal impairment.

2.3.2.6 Hepatic impairment

Please refer to Section 2.3.1 of this review for a brief discussion regarding the influence of METAVIR score (a measure of liver fibrosis) on simeprevir pharmacokinetics.

Simeprevir pharmacokinetics were evaluated in subjects with moderate hepatic impairment (Child-Pugh B) and matched healthy controls as well as subjects with severe hepatic impairment (Child-Pugh C) who did not have matched healthy controls following multiple-dose administration of simeprevir 150 mg QD (C113). Steady-state simeprevir plasma concentrations were higher in subjects with hepatic impairment (mean AUC_{24} values were 2.4- and 5.2-fold higher in subjects with moderate and severe hepatic impairment, respectively, compared to healthy controls; Table 13).

Table 13. Pharmacokinetics of simeprevir in subjects with moderate and severe hepatic impairment compared to healthy subjects after multiple-dose administration of simeprevir 150 mg QD

	Mean ± SD			
Parameter	Subjects With Normal Hepatic Function TMC435 150 mg q.d. (Reference)	Subjects With Moderate or Severe Hepatic Impairment TMC435 150 mg q.d. (Test)	Ratio [a] (Test:Reference)	90% CI
Subjects With Moderate Hepatic Impairment vs. Subjects With Normal Hepatic Function				
n	8	8		
t_{max} [b], h	6.0 (4.0 - 9.0)	6.0 (6.0 - 9.0)	-	-
C_{0h}, ng/mL	455 ± 337	1637 ± 1191	-	-
C_{min}, ng/mL	378 ± 266	1517 ± 1092	-	-
C_{max}, ng/mL	2096 ± 959	3780 ± 1980	1.71	1.02 - 2.88
AUC_{24h}, ng.h/mL	23740 ± 10920	65140 ± 38130	2.44	1.36 - 4.38
$C_{ss,av}$, ng/mL	989 ± 455	2714 ± 1589	-	-
Subjects With Severe Hepatic Impairment vs. Subjects With Normal Hepatic Function				
n	8	8		
t_{max} [b], h	6.0 (4.0 - 9.0)	6.0 (3.0 - 12.0)	-	-
C_{0h}, ng/mL	455 ± 337	5568 ± 3519	-	-
C_{min}, ng/mL	378 ± 266	4414 ± 2923	-	-
C_{max}, ng/mL	2096 ± 959	7184 ± 4272	3.13	1.87 - 5.26
AUC_{24h}, ng.h/mL	23740 ± 10920	138000 ± 89890	5.22	3.10 - 8.79
$C_{ss,av}$, ng/mL	989 ± 455	5751 ± 3745	-	-

n = maximum number of subjects with data.
[a] Ratio based on LS means.
[b] Median (range).

In the proposed labeling, the Applicant states that no dose recommendation can be given for patients with severe hepatic impairment and that no dose adjustment is necessary in patients with (b) (4) hepatic impairment as "no clear relationship between exposure to simeprevir and adverse effects has been observed in clinical studies with [simeprevir]." The Applicant also notes that the "safety and efficacy of [simeprevir] have not been studied in HCV-infected patients with moderate or severe hepatic impairment," which may allude to the potential for hepatic (exclusive of Child-Pugh B or C designation) or extrahepatic manifestations of chronic HCV infection to affect simeprevir pharmacokinetics.

The following points must be considered when evaluating the Applicant's proposed dose of simeprevir 150 mg QD in patients with moderate hepatic impairment in the current NDA:

1. The magnitude of the increase in simeprevir exposures may be higher than that observed in C113, as trial subjects were not infected with HCV. The detrimental effects (in terms of simeprevir clearance) of chronic HCV infection in combination with hepatic impairment on liver volume and functional hepatic CYP3A content may contribute to an increase in plasma concentrations that is larger than that observed in uninfected subjects in C113;
2. Pharmacometric analyses have established a positive relationship between simeprevir exposures and adverse events, including rash and photosensitivity;
3. Taking into account the high degree of intersubject variability, the safety profile of expected exposures in patients with moderate hepatic impairment following administration of simeprevir 150 mg QD has not been well-characterized in the Phase 3 trials;

4. Based on the exposure-response relationship for efficacy, no additional therapeutic benefit is gained from higher exposures.

Based on the above reasons, this Reviewer recommends a dose reduction to simeprevir 100 mg QD for patients with moderate hepatic impairment. This Reviewer is in agreement that no simeprevir dose recommendation can be given for patients for severe hepatic impairment, but would propose the inclusion of a strongly-worded recommendation against administration of simeprevir to this subpopulation in the prescribing information.

It should be noted that the majority of patients enrolled in Phase 3 trials were classified as Child-Pugh A (C208: 81%, C216: 82%, HPC3007: 85%) while only 0.03% of the Phase 3 population was classified as Child-Pugh B and none as Child-Pugh C; thus, the safety and efficacy of simeprevir have been established in patients with mild hepatic impairment but not in patients with moderate or severe hepatic impairment.

2.3.2.7 What pregnancy and lactation use information is there in the application?

No information regarding the use of simeprevir in pregnant or lactating women was included in the application.

2.4. EXTRINSIC FACTORS

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

The effects of two extrinsic factors – the administration of simeprevir with food and the administration of simeprevir with other drugs – were evaluated by the Applicant. The first is discussed in Section 2.5.3 and the second is discussed in Section 2.4.2 of this review.

2.4.2. Drug-drug interactions

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

Yes, simeprevir is a substrate for CYP3A4, CYP2C8, CYP2C19, P-gp, MRP2, PCRP, OATP1B1/3, and OATP2B1 in vitro. It is also a moderate inhibitor of CYP2A6, CYP2C8, CYP2D6 and a weak inhibitor of CYP2C19 and CYP3A in vitro, as well as an inhibitor of OATP1B1, NTCP, P-gp, MRP2, and BSEP in vitro.

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

Yes, simeprevir is a substrate of CYP enzymes. It is primarily metabolized by CYP3A4, although metabolism by CYP2C8 and CYP2C19 was also detected (Study NC116). The major Phase I metabolic pathway in humans is oxidation of unchanged drug and oxidized metabolites.

CYP3A4 is polymorphic, but metabolism is not substantially influenced by genetics.

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

In human liver microsomes, simeprevir was a moderate inhibitor of CYP2A6, CYP2C8, and CYP2D6 (IC_{50} values of 44.8, 36.8, and 32.2 ug/mL, respectively) and a weak inhibitor of CYP2C19 and CYP3A (IC_{50} values of 64.6 and 98.4 ug/mL, respectively; Study NC117). Simeprevir did not inhibit or weakly inhibited all other CYP isoforms evaluated (CYP1A, CYP2C9, CYP2E1) in the concentration range tested (0.225 to 225 ug/mL; Study NC117). For reference, based on Phase 2b data, the mean steady-state simeprevir C_{max} is predicted to be approximately 4.2 ug/mL following oral administration of simeprevir 150 mg QD.

Simeprevir did not induce CYP1A2 or CYP3A4 in primary cultures from cryopresernved human hepatocytes at concentrations of up to 7.5 ug/mL (NC121).

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

Simeprevir is a substrate of P-glycoprotein (P-gp). *In vitro* studies demonstrated transport across LLC-PK1 cells transfected with the MDR1 gene in a polarized manner (B:A/A:B ratio of 20.4 compared to 25.6 for digoxin; NC239).

Simeprevir inhibited P-gp-dependent transport of paclitaxel in Caco-2 cells with an IC_{50} value of 64.4 ug/mL (Study NC113).

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

Transport of simeprevir was demonstrated in directional flux assays with MRP2 and Bcrp1 (mouse BCRP) in transduced LLC-PK1 cells (NC239) and OATP1B1, OATP1B3, and OATP2B1 in transfected HEK cells (Study FK10099).

The inhibitory potential of simeprevir at concentrations of up to 18.8 ug/mL (25 uM) on OATP1B1 transport was evaluated in human hepatocytes (Study NC241). At a concentration of 2.3 ug/mL, simeprevir inhibited OATP1B1-mediated transport of 17βEG by approximately 58-59% (similar to the cyclosporin A positive control). In inside-out vesicles, simeprevir inhibited MRP2-mediated transport of 17βEG (IC_{50} values ranged from 4.8 to 14.3 ug/mL, NC242) and BSEP-mediated transport of taurocholate (IC_{50} value of 1.25 ug/mL). In human hepatocytes, simeprevir inhibited NTCP-mediated taurocholate uptake (IC_{50} of 2.6 ug/mL).

The clinically observed transient hyperbilirubinemia is thought to result from the inhibition of bilirubin uptake and efflux by OATP1B1 and MRP2, respectively, by simeprevir.

2.4.2.6 Does the label specify coadministration of another drug (e.g. combination therapy in oncology) and if so, has the interaction potential between these drugs been evaluated?

The label specifies that simeprevir should be coadministered PegIFN and RBV. The pharmacokinetics of simeprevir and ribavirin alone and in combination with each other and PegIFN were characterized in the Phase 2a trial C201.

Simeprevir pharmacokinetics were evaluated after seven days of simeprevir 200 mg QD alone compared to after 21 days of simeprevir 200 mg QD in combination with PegIFN/RBV. Simeprevir pharmacokinetic parameters were slightly higher after 21 days of triple therapy (increases in C_{max} and AUC_{24} of 32% and 23%, respectively), possibly because steady-state conditions were not yet reached after seven days of monotherapy.

Mean steady-state RBV plasma concentrations were similar across simeprevir dose groups and placebo, indicating that RBV pharmacokinetics were not substantially influenced by simeprevir. After administration of simeprevir 200 mg QD, RBV C_{max} and AUC_{10} were almost unchanged (least squares mean ratio of 101.5 and 100.5, respectively).

In the Phase 2b studies C205 and C206, PegIFN trough concentrations were comparable when coadministered with RBV and simeprevir or RBV alone.

2.4.2.7 What other comedications are likely to be administered to the target patient population?

Medications that are likely to be coadministered to patients with chronic HCV infection include other HCV direct-acting antiviral agents (DAAs), opiate substitution therapy (i.e. methadone and buprenorphine), antiretroviral medications for the treatment of HIV-1 infection, and antidepressants and mood-stabilizing medications. Female patients may also be receiving combined oral contraceptives for the prevention of pregnancy.

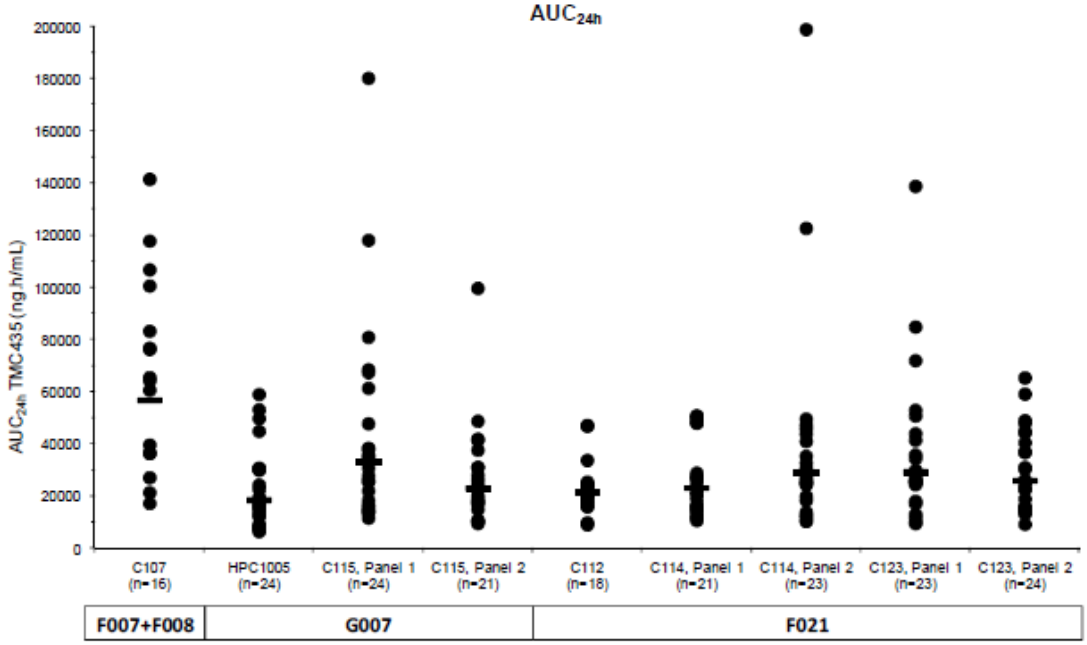
Note that in the ongoing Phase 3 trial in HCV/HIV-1 coinfected patients (C212), all HIV-1 protease inhibitors are disallowed because of anticipated or observed drug-drug interactions with simeprevir. Allowed medications for the treatment of HIV-1 include lamivudine, emtricitabine, tenofovir DF, abacavir, rilpivirine, enfuvirtide, raltegravir, and maraviroc.

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

Clinical recommendations regarding the administration of simeprevir and concomitant drugs are based on drug-drug interaction trials conducted as part of this NDA or suspected interactions based on mechanistic information.

Drug-drug interaction trials were conducted with four different simeprevir formulations: the Phase 2a capsule [F007 and F008], Phase 2b capsule [F021], Phase 3 capsule [G007], and G015 capsule, which should provide similar exposures to the Phase 3 capsule as it differs only in the [redacted] (b) (4) AUC_{24} values were similar between the Phase 2b and Phase 3 capsules but were slightly higher for the Phase 2a capsule; this is not expected to impact the clinical recommendations resulting from the relevant trials (Figure 8).

Figure 8. Cross-study summary of subject-level simeprevir AUC_{24} values and geometric means for formulations used in drug-drug interaction studies after administration of simeprevir 150 mg QD for at least seven days



● individual values — geometric mean.
F007 = 100-mg Phase IIa capsule; F008 = 25-mg Phase IIa capsule; F021 = 75-mg Phase IIb capsule; G007 = 150-mg Phase III capsule.

All drug-drug interaction trials were conducted in healthy subjects uninfected with HCV.

The pharmacokinetic results of drug-drug interaction trials submitted with this Application, as well as clinical recommendations regarding dosing of simeprevir and concomitant drugs, are listed in Tables 14 and 15.

Table 14. Tabulated summary of the results of drug-drug interaction trials conducted to determine the effect of coadministered drugs on simeprevir PK (actionable clinical recommendations are indicated in bold font)

Drug	Study	N	TMC Form.	Relevant treatments; Dosage regimens; Duration of treatment	Mean Ratio (90% CI) of TMC4354 With/Without Coadministered Drug			Clinical recommendation (bold) or Reviewer comment
					C_{max}	AUC	C_{min}	
BMS-790052	HPC1005	24	G007	• BMS 60 mg QD (7 days) • TMC 150 mg QD (7 days)	1.39 (1.27, 1.52)	1.44 (1.32, 1.56)	1.49 (1.33, 1.67)	BMS is an HCV NS5a inhibitor in development
GS-5885 (ledipasvir)	GS-US-256-0129	28	G007	• GS-5885 30 mg QD (10 days) • TMC 150 mg QD (10 days)	2.61 (2.34, 2.86)	2.69 (2.44, 2.96)		GS-5885 is an HCV NS5a inhibitor in development
Ritonavir	C104	12	F007	• RTV 100 mg BID (15 days) • TMC 200 mg (single dose)	1.60 (1.08, 1.56)	1.83 (1.64, 2.05)		**Do not coadminister** due to increased TMC

				• RTV 100 mg BID (15 days) • TMC 200 mg QD (7 days)	4.70 (3.84, 5.76)	7.18 (5.63, 9.15)	14.35 (10.29, 20.01)	
Darunavir/r	C115	25	G007	• DRV/r 800/100 QD (7 days) • **TMC 50 mg QD** with DRV/r (7 days) • TMC 150 mg QD alone (7 days)	1.79 (1.55, 2.06)	2.59 (2.15, 3.11)	4.58 (3.54, 5.92)	**Do not coadminister** due to increased TMC concentrations via CYP3A inhibition
Rilpivirine	C114	21	F021	• RPV 25 mg QD (11 days) • TMC 150 mg QD (11 days)	1.10 (0.97, 1.26)	1.06 (0.94, 1.19)	0.96 (0.83, 1.11)	
Tenofovir DF	C114	24	F021	• TDF 300 mg QD (7 days) • TMC 150 mg QD (7 days)	0.85 (0.73, 0.99)	0.86 (0.76, 0.98)	0.93 (0.78, 1.11)	
Efavirenz	C123	23	F021	• EFV 600 mg QD (14 days) • TMC 150 mg QD (14 days)	0.49 (0.44, 0.54)	0.29 (0.26, 0.33)	0.09 (0.08, 0.12)	**Do not coadminister** due to decreased TMC concentrations via CYP3A induction
Raltegravir	C123	24	F021	• RAL 400 mg BID (7 days) • TMC 150 mg QD (7 days)	0.93 (0.85, 1.02)	0.89 (0.81, 0.98)	0.86 (0.75, 0.98)	
Erythromycin	C115	24	G007	• Erythromycin 500 mg TID (7 days) • TMC 150 mg QD (7 days)	4.53 (3.91, 5.25)	7.47 (6.41, 8.70)	12.74 (10.19, 15.93)	**Do not coadminister** due to increased TMC and erythromycin concentrations due to CYP3A and P-gp inhibition
Rifampin	C105	18	F007	• Rifampin 600 mg QD (7 days) • TMC 200 mg QD (7 days)	1.31 (1.03, 1.66)	0.52 (0.41, 0.67)	0.08 (0.06, 0.11)	**Do not coadminister** due to decreased TMC concentrations via CYP3A induction
Escitalopram	C112	18	F021	• Escitalopram 10 mg QD (7 days) • TMC 150 mg QD (7 days)	0.80 (0.71, 0.89)	0.75 (0.68, 0.83)	0.68 (0.59, 0.79)	TMC concentrations decreased slightly; based on exposure-response, efficacy is not expected to be affected

* The simeprevir dose was prospectively lowered to 50 mg QD when coadministered with ritonavir-boosted darunavir; ratios are calculated with respect to simeprevir 150 mg QD.

Table 15. Tabulated summary of the results of drug-drug interaction trials conducted to determine the effect of simeprevir on the PK of coadministered drugs (actionable clinical recommendations are indicated in bold font)

Drug	**Study**	**N**	**TMC Form**	**Relevant treatments; Dosage regimens; Duration of treatment**	**Mean Ratio (90% CI) of Coadministered Drug With/Without TMC435**			**Clinical recommendation (bold) or Reviewer comment**
					C_{max}	**AUC**	**C_{min}**	
BMS-790052	HPC1005	24	G007	• BMS 60 mg QD (7 days) • TMC 150 mg QD (7 days)	1.50 (1.39, 1.62)	1.96 (1.84, 2.10)	2.68 (2.42, 2.98)	BMS is an HCV NS5a inhibitor in development
GS-5885 (ledipasvir)	GS-US-256-0129	28	G007	• GS-5885 30 mg QD (10 days) • TMC 150 mg QD (10 days)	1.81 (1.69, 2.94)	1.92 (1.77, 2.07)		GS-5885 is an HCV NS5a inhibitor in development

GS-7977* (sofosbuvir)	HPC2002	22	G015 or G019	• GS-7977 400 mg QD (12 or 24 weeks) • TMC 150 mg QD (12 or 24 weeks)	1.91 (1.26, 2.90)	3.16 (2.25, 4.44)		GS-7977 is an HCV NS5b inhibitor in development
GS-331007					0.69 (0.52, 0.93)	1.09 (0.87, 1.37)		
Ritonavir	C104	12	F007	• RTV 100 mg BID (7 days) • TMC 50 mg QD (7 days)	1.23 (1.14, 1.32)	1.32 (1.25, 1.40)	1.44 (1.03, 1.61)	**Do not coadminister** due to increased TMC concentrations via CYP3A inhibition
Darunavir/r	C115	25	G007	• DRV/r 800/100 QD (7 days) • TMC 50 mg QD with DRV/r (7 days) • TMC 150 mg QD alone (7 days)	1.04 (0.99, 1.10)	1.18 (1.11, 1.25)	1.31 (1.13, 1.52)	**Do not coadminister** due to increased TMC concentrations via CYP3A inhibition
Rilpivirine	C114	21	F021	• RPV 25 mg QD (11 days) • TMC 150 mg QD (11 days)	1.04 (0.95, 1.13)	1.12 (1.05, 1.19)	1.25 (1.16, 1.35)	
Tenofovir DF	C114	24	F021	• TDF 300 mg QD (7 days) • TMC 150 mg QD (7 days)	1.19 (1.10, 1.30)	1.18 (1.13, 1.24)	1.24 (1.15, 1.33)	
Efavirenz	C123	23		• EFV 600 mg QD (14 days) • TMC 150 mg QD (14 days)	0.97 (0.89, 1.06)	0.90 (0.85, 0.95)	0.87 (0.81, 0.93)	**Do not coadminister** due to decreased TMC concentrations via CYP3A induction
Raltegravir	C123	24	F021	• RAL 400 mg BID (7 days) • TMC 150 mg QD (7 days)	1.03 (0.78, 1.36)	1.08 (0.85, 1.38)	1.14 (0.97, 1.36)	
Erythromycin	C115	24	G007	• Erythromycin 500 mg TID (7 days) • TMC 150 mg QD (7 days)	1.59 (1.23, 2.05)	1.90 (1.53, 2.36)	3.08 (2.54, 3.73)	**Do not coadminister** due to increased TMC and erythromycin concentrations due to CYP3A and P-gp inhibition
Rifampin	C105	18	F007	• Rifampin 600 mg QD (7 days) • TMC 200 mg QD (7 days)	0.92 (0.80, 1.07)	1.00 (0.93, 1.08)		**Do not coadminister** due to decreased TMC concentrations via CYP3A induction
25-Desacetyl-rifampin					1.08 (0.98, 1.19)	1.24 (1.13, 1.36)		
Escitalopram	C112	17	F021	• Escitalopram 10 mg QD (7 days) • TMC 150 mg QD (7 days)	1.03 (0.99, 1.07)	1.00 (0.97, 1.03)	1.00 (0.95, 1.05)	
Midazolam (oral)	C107	16	F007	• MDZ 0.075 mg/kg oral • TMC 150 mg QD (10 days)	1.31 (1.19, 1.45)	1.45 (1.35, 1.57)		**Caution is warranted** due to narrow therapeutic index; MDZ concentrations increased following oral dose but not IV, suggesting TMC inhibition of gut but not hepatic CYP3A
Midazolam (iv)				• MDZ 0.025 mg/kg IV • TMC 150 mg QD (11 days)	0.78 (0.52, 1.17)	1.10 (0.95, 1.26)		

S-Warfarin	C107	16	F007	• Warfarin 10 mg • TMC 150 mg QD (11 days)	1.00 (0.94, 1.06)	1.04 (1.00, 1.07)		**Monitor INR** due to narrow therapeutic index; typical monitoring is acceptable
Caffeine	C107	16	F007	• Caffeine 150 mg • TMC 150 mg QD (11 days)	1.12 (1.06, 1.19)	1.26 (1.21, 1.32)		
Omeprazole	C107	16	F007	• Omeprazole 40 mg • TMC 150 mg QD (11 days)	1.14 (0.93, 1.39)	1.21 (1.00, 1.46)		
Dextromethor-phan	C107	16	F007	• Dextromethorphan 30 mg • TMC 150 mg QD (11 days)	1.21 (0.93, 1.57)	1.08 (0.87, 1.35)		
Dextrorphan					1.03 (0.93, 1.15)	1.09 (1.03, 1.15)		
Erythromycin	C115	24	G007	• Erythromycin 500 mg TID (7 days) • TMC 150 mg QD (7 days)	1.59 (1.23, 2.05)	1.90 (1.53, 2.36)	3.08 (2.54, 3.73)	**Do not coadminister** due to increased TMC and erythromycin concentrations due to CYP3A and P-gp inhibition
Ethinyl-estradiol	C124	18	G015	• EE 35 ug QD (21 days) • TMC 150 mg QD (10 days)	1.18 (1.09, 1.27)	1.12 (1.05, 1.20)	1.00 (0.89, 1.13)	
Norethindrone				• Norethindrone 1 mg QD (21 days) • TMC 150 mg QD (10 days)	1.06 (0.99, 1.14)	1.15 (1.08, 1.22)	1.24 (1.13, 1.35)	
Atorvastatin	HPC1006	18	G019	• Atorvastatin 40 mg • TMC 150 mg QD (10 days)	1.70 (1.42, 2.04)	2.12 (1.72, 2.62)		**Titrate dose carefully and use lowest necessary dose while monitoring for safety**; increased atorvastatin concentrations are due to TMC inhibition of OATP1B1 and/or CYP3A, **use the lowest effect dose of atorvastatin, do not exceed a daily dose of 40 mg**
Orthohydroxy-lated atorvastatin					1.98 (1.70, 2.31)	2.29 (2.08, 2.52)		
Simvastatin	HPC1006	18	G019	• Simvastatin 40 mg • TMC 150 mg QD (10 days)	1.46 (1.17, 1.82)	1.51 (1.32, 1.73)		**Titrate dose carefully and use lowest necessary dose while monitoring for safety**; increased simvastatin concentrations are due to TMC inhibition of OATP1B1 and/or CYP3A
Simvastatin acid					3.03 (2.49, 3.69)	1.88 (1.63, 2.17)		
Escitalopram	C112	17	F021	• Escitalopram 10 mg QD (7 days) • TMC 150 mg QD (7 days)	1.03 (0.99, 1.07)	1.00 (0.97, 1.03)	1.00 (0.95, 1.05)	

Tacrolimus	C120	14	G015	• Tacrolimus 2 mg • TMC 150 mg (7 days)	0.76 (0.65, 0.90)	0.83 (0.59, 1.16)		**Monitor blood concentrations** due to narrow therapeutic index; typical monitoring is acceptable
Cyclosporine	C120	14	G015	• Cyclosporine 100 mg • TMC 150 mg (7 days)	1.16 (1.07, 1.26)	1.19 (1.13, 1.26)		**Monitor blood concentrations** due to narrow therapeutic index; typical monitoring is acceptable
R(-) Methadone	C110	12	F021	• Methadone 30 to 150 mg QD stable maintenance therapy • TMC 150 mg QD (7 days)	1.03 (0.97, 1.09)	0.99 (0.91, 1.09)	1.02 (0.93, 1.12)	
S(+) Methadone					1.09 (1.02, 1.16)	1.03 (0.91, 1.16)	1.02 (0.89, 1.17)	
Digoxin	C108	16	G007	• Digoxin 0.25 mg • TMC 150 mg QD (7 days)	1.31 (1.14, 1.51)	1.39 (1.16, 1.67)		**Monitor blood concentrations and titrate dose to effect** due to narrow therapeutic index; increased digoxin concentrations are due to TMC inhibition of P-gp
Rosuvastatin	C108	16	G007	• Rosuvastatin 10 mg • TMC 150 mg (7 days)	3.17 (2.57, 3.91)	2.81 (2.34, 3.37)		**Titrate dose carefully and use lowest necessary dose while monitoring for safety**; increased atorvastatin concentrations are due to TMC inhibition of OATP1B1, **rosuvastatin dose should be limited to 10 mg once daily**

*This study is ongoing; validity of data were not evaluated for this review. Comparisons were made to historical data.

Simeprevir as a victim of drug-drug interactions

The Applicant recommends against coadministration with strong CYP3A inducers. This recommendation is appropriate based on the results of drug-drug interaction trial with rifampin (Trial C105) in which coadministration of simeprevir with this strong CYP3A inducer decreased simeprevir trough concentrations by >90%, resulting in several individual trough concentrations falling below the simeprevir EC_{90} (19 nM, 14.25 ng/mL). The occurrence of such exposure decreases in patients may increase the risk of development of viral resistance and/or decreased efficacy in patients.

In addition to strong inducers, the Clinical Pharmacology review team recommends against coadministration with moderate CYP3A inducers. This recommendation is based on the results

of a drug-drug interaction trial with the moderate CYP3A inducer efavirenz (Trial C123), which decreased simeprevir trough concentrations to a similar extent as rifampin (decreases of >90%, with several individual trough concentrations below the simeprevir EC_{90}).

The Applicant recommends against coadministration with strong CYP3A inhibitors. This recommendation is appropriate based on the results of a drug-drug interaction trial with the potent CYP3A inhibitor ritonavir (Trial C104) in which simeprevir exposures increased substantially (mean AUC_{24} increased 7.2-fold) following multiple dosing.

The Clinical Pharmacology review team also recommends against coadministration with moderate CYP3A inhibitors. This recommendation is based on the results of a drug-drug interaction trial with the moderate CYP3A inhibitor erythromycin (Trial C115), which increased simeprevir exposures to a similar extent as ritonavir (mean AUC_{24} increased 7.5-fold). Based on PBPK simulations, this phenomenon may be caused by the exacerbation of the effect of moderate CYP3A inhibitors due to the simultaneous saturation of the hepatic uptake transporter OATP1B1/3 (please refer to the PBPK Memo appended to this review for details).

For a discussion about the use of PBPK modeling to predict drug-drug interactions in which simeprevir is a victim, please refer to the PBPK Memo appended to this review.

Simeprevir as a perpetrator of drug-drug interactions

Actionable dosing recommendations for the coadministered drug include monitoring blood concentrations (tacrolimus, cyclosporine, digoxin) or markers of therapeutic effect (warfarin) for drugs with narrow therapeutic indices. These recommendations represent routine monitoring for these drugs and are appropriate as exposures of these drugs are not influenced by simeprevir to a clinically significant degree.

The Applicant also recommends dose titration and use of the lowest possible dose for inhibitors of HMG Co-A reductase (i.e. the statins, including atorvastatin, simvastatin, and rosuvastatin). In consultation with the Metabolic/Endocrine clinical pharmacology team, the clinical recommendations regarding the HMG Co-A reductase inhibitors atorvastatin and rosuvastatin should be revised as follows:

- Concomitant use of TRADENAME with atorvastatin resulted in increased plasma concentrations of atorvastatin due to inhibition of OATP1B1 and/or CYP3A. Use the lowest effective dose of atorvastatin, but do not exceed a daily dose of 40 mg when coadministered with TRADENAME.

- Concomitant use of TRADENAME with rosuvastatin resulted in increased plasma concentrations of rosuvastatin due to inhibition of OATP1B1. Initiate rosuvastatin therapy with 5 mg once daily. The rosuvastatin dose should not exceed 10 mg daily.

In addition, the clinical recommendations regarding pitavastatin, pravastatin, and lovastatin should be removed from the prescribing information, as the magnitude of the increase in statin exposures is unknown; therefore, no dosing recommendation can be made.

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

There are no known pharmacodynamic drug-drug interactions for simeprevir.

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

There are no unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding.

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

Please refer to Section 2.2.4.4 for discussion of unresolved issues related to dose, dosing regimens, and treatment populations.

2.5. General Biopharmaceutics

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

Simeprevir appears to be a low permeability, low solubility drug, which may classify it as a BCS Class 4 drug. Please refer to the ONDQA review for further details.

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

Trial HPC1002 compared the relative bioavailability of the Phase 3 (G007) and to-be-marketed (G019) formulations of simeprevir; as such, this trial was considered to be a pivotal relative BA trial. Although this trial was characterized as a "bridging trial" during formulation development, the Applicant did not consider it to be pivotal based on the differences between the two formulations (b) (4) and did not adhere to the regulatory guidelines that are applicable to pivotal BA/BE trials. Subsequently, the Office of Scientific Investigations (OSI) review team observed the absence of retention samples at the trial site, rendering the results of the trial unverifiable. Additional assessments were performed by the CMC review team and it was determined that there were sufficient data on the two formulations to deem an in vivo bioequivalence trial unnecessary (please refer to the Biopharmaceutics Review for details).

Although it did not constitute a pivotal BA/BE trial, the Applicant evaluated the relative bioavailability of G007 (the Phase 3 capsule), and F021 (the Phase 2b capsule) in trial C119. The latter formulation was used in a number of clinical trials, including the thorough QT evaluation and several drug-drug interaction trials. Single doses of each simeprevir formulation were administered under fed conditions (high-fat meal) separated by a washout period of at least

seven days. The Phase 2b formulation provided comparable simeprevir exposures to the Phase 3 formulation, with least square mean ratios close to 90% and 90% confidence intervals between 80 and 125% (Table 16).

Table 16. Pharmacokinetics of TMC435 after administration of a single oral dose of the Phase 2b or Phase 3 formulations under fed conditions

Parameter	LS means[a]		LS means ratio	90% CI[c]	p-value	
	Phase IIb capsule (F021) (reference)	Capsule with (b) (4) G005 and (b) (4) (G007) (test)			Period	Sequence
C_{max}, ng/mL	1479	1323	0.89	0.82 - 0.97	0.6668	0.1399
AUC_{last}, ng.h/mL	19130	17810	0.93	0.86 - 1.01	0.8840	0.1222
AUC_{∞}, ng.h/mL	19250	18000	0.93	0.86 - 1.01	0.8915	0.1145

[a] n = 23 for reference and n = 24 for test
[b] n = 23 for reference and test
[c] 90% CIs
* Statistically significant difference

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

During the review process, the CMC and Biopharmaceutics review teams determined that there were sufficient data on the Phase 3 (G007) and to-be-marketed (G019) formulations to deem an in vivo BE trial unnecessary (please refer to the Biopharmaceutics review for details).

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

The effect of food on the bioavailability of the Phase 3 formulation was assessed in C116. Administration of the Phase 3 capsule G007 under fed conditions resulted increased simeprevir exposures (mean AUC_{last} values increased 1.70- and 1.66-fold following a standard and high-fat breakfast, respectively). The Applicant recommends that simeprevir be administered with food. This recommendation is appropriate.

Note that in the Phase 3 trials, simeprevir was administered without regard to food intake. However, simeprevir was coadministered with ribavirin, which, per prescribing information, is to be taken with food. Therefore, it is likely that the majority of simeprevir doses were administered in the fed state; in fact, after completion of the trials, 82.2% of subjects reported taking simeprevir with food "always" or "most of the time" (62.4 and 19.9% of subjects, respectively). In addition, population PK analyses did not identify self-reported food intake as a covariate that significantly impacted simeprevir exposure (mean and median AUC_{24} values with food "always" or "most of the time": 54500 and 33670 ng·h/mL, respectively [range: 4868-449200 ng·h/mL]; mean and median AUC_{24} values with food "sometimes", "never", or not available: 71240 and 33270 ng·h/mL, respectively [range: 8883-408900 ng·h/mL]).

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

A fed BA/BE study was performed (see Section 2.4.2) because there is a substantial food effect on simeprevir exposure and because the label will instruct patients to take simeprevir with food.

2.6. ANALYTICAL

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

The active moiety was identified and measured in the plasma using validated LC-MS/MS assays.

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

No metabolites were analyzed because none represented >10% of total drug-related material.

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

The total concentration of simeprevir was measured, as was appropriate. Simeprevir is almost entirely bound to plasma proteins (>99.9%, refer to Section 2.2.5.4).

2.6.4. What bioanalytical methods are used to assess concentrations?

Please refer to the individual trial reviews for details on specific bioanalytical methods. Overall, the bioanalytical methods used to assess concentrations were acceptable.

3. LABELING RECOMMENDATIONS

The following section describes labeling recommendations made by the Clinical Pharmacology review team based on our interpretation of the review issues at the time this review was filed. Internal labeling discussions are ongoing and negotiations with the Applicant are in progress; therefore, some recommendations (e.g. with regard to patients with the Q80K mutation) are not discussed in this section.

Major changes to the sections of the prescribing information that are relevant to clinical pharmacology are highlighted in blue.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------DRUG INTERACTIONS----------

Co-administration of TRADENAME with drugs that are moderate or strong inducers or inhibitors of CYP3A may significantly affect the plasma concentrations of simeprevir. The potential for drug-drug interactions must be considered prior to and during treatment. (5.6, 7, 12.3)

2.4 Hepatic Impairment

No dose recommendation can be given for patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) [*see Pharmacokinetics (12.3)*]. Safety and efficacy of TRADENAME have not been studied in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh Class B or C).

2.5 Race

Patients of East Asian ancestry exhibit higher simeprevir exposures [*see Pharmacokinetics (12.3)*]. (b) (4) there are insufficient safety data to recommend an appropriate dose for patients with East Asian ancestry.

5.4 Drug Interactions

Co-administration of TRADENAME with substances that are moderate or strong inducers or inhibitors of cytochrome P450 3A (CYP3A) is not recommended as this may lead to significantly lower or higher exposure of simeprevir, respectively [*see Drug Interactions (7)*, and *Pharmacokinetics (12.3)*].

7.1 Potential for TRADENAME to Affect Other Drugs

Simeprevir does not induce CYP1A2 or CYP3A4 *in vitro*. Simeprevir is not a clinically relevant inhibitor of cathepsin A enzyme activity.

Simeprevir mildly inhibits CYP1A2 activity and intestinal CYP3A4 activity but does not affect hepatic CYP3A4 activity. Co-administration of TRADENAME with drugs that are primarily metabolized by CYP3A4 may result in increased plasma concentrations of such drugs (see Table 4). Simeprevir does not affect CYP2C9, CYP2C19 or CYP2D6 *in vivo*.

Simeprevir inhibits OATP1B1/3 and P-glycoprotein (P-gp) transporters. Co-administration of TRADENAME with drugs that are substrates for OATP1B1/3 and P-gp transport may result in increased plasma concentrations of such drugs (see Table 4).

7.2 Potential for Other Drugs to Affect TRADENAME

The primary enzyme involved in the biotransformation of simeprevir is CYP3A [*See Clinical Pharmacology (12.3)*]. Clinically relevant effects of other drugs on simeprevir pharmacokinetics via CYP3A may occur. Co-administration of TRADENAME with moderate or strong inhibitors of CYP3A may significantly increase the plasma exposure of simeprevir. Co-administration with moderate or strong inducers of CYP3A may significantly reduce the plasma exposure of simeprevir and lead to loss of efficacy (see Table 4). Therefore, co-administration of TRADENAME with substances that are moderate or strong inducers or inhibitors of CYP3A is not recommended [*see Warnings and Precautions (5.6)*].

7.3 Established and Other Potentially Significant Drug Interactions

Table 4 shows the established and other potentially significant drug interactions based on which alterations in dose or regimen of TRADENAME and/or co-administered drug may be recommended. Drugs that are not recommended for co-administration with TRADENAME are also included in Table 4.

Table 4: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction [*See Pharmacokinetics (12.3)* (Tables 5 and 6) for Magnitude of Interaction.]

Concomitant Drug Class: Drug Name	Effect on Concentration of Simeprevir or Concomitant Drug	Clinical Comment
Antiarrhythmics		
Digoxin*	↑ digoxin	Concomitant use of TRADENAME with digoxin resulted in increased concentrations of digoxin due to inhibition of P-gp by simeprevir. (b) (4) (b) (4) Routine therapeutic drug monitoring of digoxin concentrations is acceptable.
Amiodarone Disopyramide Flecainide (b) (4) Mexiletine Propafenone Quinidine	↑ antiarrhythmics	Concomitant use of TRADENAME with these antiarrhythmics may result in mild increases in concentrations of these antiarrhythmics due to intestinal CYP3A4 inhibition by simeprevir. Caution is warranted and therapeutic drug monitoring for these antiarrhythmics, if available, is recommended when co-administered with TRADENAME.
Anticoagulants		
Warfarin*	↔ warfarin	No dose adjustment is required when TRADENAME is co-administered with warfarin (b) (4) (b) (4) Routine monitoring of the international normalised ratio (INR) is acceptable.
Anticonvulsants		
Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	↓ simeprevir	Concomitant use of TRADENAME with carbamazepine, oxcarbazepine, phenobarbital or phenytoin may result in significantly decreased plasma concentrations of simeprevir due to strong CYP3A induction by these anticonvulsants. This may result in loss of therapeutic effect of TRADENAME. It is not recommended to co-administer TRADENAME with these anticonvulsants.
Anti-infectives		
Antibiotics: Erythromycin*	↑ simeprevir ↑ erythromycin	Concomitant use of TRADENAME with erythromycin resulted in significantly increased plasma concentrations of both erythromycin and simeprevir due to inhibition of CYP3A and P-gp by both erythromycin and simeprevir. It is not recommended to co-administer TRADENAME with erythromycin.
Antibiotics: Clarithromycin Telithromycin	↑ simeprevir	Concomitant use of TRADENAME with clarithromycin or telithromycin may result in increased plasma concentrations of simeprevir due to CYP3A inhibition by these antibiotics. It is not recommended to co-administer TRADENAME with clarithromycin or telithromycin.

Antifungals (oral administration): Itraconazole Ketoconazole Posaconazole	↑ simeprevir	Concomitant use of TRADENAME with systemic itraconazole, ketoconazole or posaconazole may result in significantly increased plasma concentrations of simeprevir due to strong CYP3A inhibition by these antifungals. It is not recommended to co-administer TRADENAME with systemic itraconazole, ketoconazole or posaconazole.
Antifungals (oral administration): Voriconazole	↑ simeprevir	Concomitant use of TRADENAME with voriconazole may result in increased plasma concentrations of simeprevir due to mild to moderate CYP3A inhibition by voriconazole. It is not recommended to co-administer TRADENAME with voriconazole.
Antimycobacterials: Rifampin*† Rifabutin Rifapentine	↓ simeprevir ↔ rifampin, rifabutin, rifapentine	Concomitant use of TRADENAME with rifampin, rifabutin or rifapentine may result in significantly decreased plasma concentrations of simeprevir due to CYP3A4 induction by these antimycobacterials. This may result in loss of therapeutic effect of TRADENAME. It is not recommended to co-administer TRADENAME with rifampin, rifabutin or rifapentine.
Calcium Channel Blockers		
Amlodipine (b) (4) Diltiazem Felodipine Nicardipine Nifedipine Nisoldipine Verapamil	↑ calcium channel blockers	Concomitant use of TRADENAME with calcium channel blockers may result in increased plasma concentrations of calcium channel blockers due to intestinal CYP3A4 and/or P-gp inhibition by simeprevir. Caution is warranted and clinical monitoring of patients is recommended when TRADENAME is co-administered with calcium channel blockers.
Corticosteroids		
Systemic Dexamethasone	↓ simeprevir	Concomitant use of TRADENAME with systemic dexamethasone may result in decreased plasma concentrations of simeprevir due to moderate induction of CYP3A4 by dexamethasone. This may result in loss of therapeutic effect of TRADENAME. It is not recommended to co-administer TRADENAME with systemic dexamethasone.
Gastrointestinal Products		
Propulsive: Cisapride	↑ cisapride	Cisapride has the potential to cause cardiac arrhythmias. Concomitant use of TRADENAME with cisapride may result in increased plasma concentrations of cisapride due to intestinal CYP3A4 inhibition by simeprevir. It is not recommended to co-administer TRADENAME with cisapride.
Herbal Products		
Milk thistle (*Silybum marianum*)	↑ simeprevir	Concomitant use of TRADENAME with milk thistle may result in increased plasma concentrations of simeprevir due to CYP3A inhibition by milk thistle. It is not recommended to co-administer TRADENAME with milk thistle.
St John's wort (*Hypericum perforatum*)	↓ simeprevir	Concomitant use of TRADENAME with products containing St John's wort may result in significantly decreased plasma concentrations of simeprevir due to CYP3A induction by St John's wort. This may result in loss of therapeutic effect of TRADENAME. It is not recommended to co-administer TRADENAME with products containing St John's wort.
HIV Products		

(b) (4)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs): Efavirenz*	↓ simeprevir ↔ efavirenz	Concomitant use of TRADENAME with efavirenz resulted in significantly decreased plasma concentrations of simeprevir due to CYP3A induction by efavirenz. This may result in loss of therapeutic effect of TRADENAME. It is not recommended to co-administer TRADENAME with efavirenz.
Other NNRTIs (Delavirdine, Etravirine, Nevirapine)	↑ or ↓ simeprevir	Concomitant use of TRADENAME with delavirdine, etravirine or nevirapine may result in altered plasma concentrations of simeprevir due to CYP3A inhibition (delavirdine) or induction (etravirine and nevirapine) by these drugs. It is not recommended to co-administer TRADENAME with delavirdine, etravirine or nevirapine.
Protease Inhibitors (PIs): Darunavir/ritonavir*‡	↑ simeprevir ↑ darunavir	Concomitant use of TRADENAME with darunavir/ritonavir resulted in increased plasma concentrations of simeprevir due to CYP3A inhibition by darunavir/ritonavir. It is not recommended to co-administer darunavir/ritonavir and TRADENAME.
Protease Inhibitors (PIs): Ritonavir*	↑ simeprevir	Concomitant use of TRADENAME with ritonavir resulted in significantly increased plasma concentrations of simeprevir due to strong CYP3A inhibition by ritonavir. It is not recommended to co-administer TRADENAME with ritonavir.
Other ritonavir-boosted or unboosted HIV PIs, e.g., Atazanavir, (Fos)amprenavir, Lopinavir, Indinavir, Nelfinavir, Saquinavir, Tipranavir	↑ or ↓ simeprevir	Concomitant use of TRADENAME with ritonavir-boosted or unboosted HIV PIs may result in altered plasma concentrations of simeprevir due to CYP3A inhibition or induction by these HIV PIs. It is not recommended to co-administer TRADENAME with any HIV PI, with or without ritonavir.
HMG CO-A Reductase Inhibitors		
Rosuvastatin*, (b) (4)	↑ rosuvastatin	Concomitant use of TRADENAME with rosuvastatin resulted in increased plasma concentrations of rosuvastatin due to inhibition of OATP1B1 by simeprevir. Initiate rosuvastatin therapy with 5 mg once daily. The rosuvastatin dose should not exceed 10 mg daily when co-administered with TRADENAME.
Atorvastatin* (b) (4) (b) (4)	↑ atorvastatin	Concomitant use of TRADENAME with atorvastatin resulted in increased plasma concentrations of atorvastatin, lovastatin or simvastatin due to inhibition of OATP1B1 and/or CYP3A4 by simeprevir. Use the lowest necessary dose of atorvastatin, but do not exceed a daily dose of 40 mg when co-administering with TRADENAME.
Simvastatin*	↑ simvastatin	Concomitant use of TRADENAME with simvastatin resulted in increased plasma concentrations of simvastatin due to inhibition of OATP1B1 and/or CYP3A4 by simeprevir. Titrate the simvastatin dose carefully and use the lowest necessary dose while monitoring for safety when co-administered with TRADENAME.
Immunosuppressants		

Cyclosporine*	↑ cyclosporine	No dose adjustment is required when TRADENAME is co-administered with cyclosporine. (b) (4) –Routine monitoring of blood concentrations of cyclosporine is acceptable.
Tacrolimus*	↓ tacrolimus	No dose adjustment is required when TRADENAME is co-administered with tacrolimus. (b) (4) –Routine monitoring of blood concentrations of tacrolimus is acceptable.
Sirolimus	↑ or ↓ sirolimus	Concomitant use of TRADENAME and sirolimus may result in mild increased or decreased plasma concentrations of sirolimus. (b) (4) Routine monitoring of blood concentrations of sirolimus is acceptable.
Phosphodiesterase Type 5 (PDE-5) Inhibitors		
Sildenafil Tadalafil Vardenafil	↑ PDE-5 inhibitors	Concomitant use of TRADENAME with PDE-5 inhibitors may result in mild increases in concentrations of PDE-5 inhibitors due to intestinal CYP3A4 inhibition by simeprevir. No dose adjustment is required when TRADENAME is co-administered with doses of sildenafil, vardenafil, or tadalafil indicated for the treatment of erectile dysfunction. Dose adjustment of the PDE-5 inhibitor may be required when TRADENAME is co-administered with sildenafil or tadalafil administered chronically at doses used for the treatment of pulmonary arterial hypertension. Consider starting with the lowest dose of the PDE-5 inhibitor and increase as needed, with clinical monitoring as appropriate.
Sedatives/Anxiolytics		
Midazolam* (oral administration)	↑ midazolam	Concomitant use of TRADENAME with orally administered midazolam resulted in increased plasma concentrations of midazolam due to mild inhibition of intestinal CYP3A4 by simeprevir. Caution is warranted when this drug with narrow therapeutic index is co-administered with TRADENAME via the oral route.
Triazolam (oral administration)	↑ triazolam	Concomitant use of TRADENAME with orally administered triazolam may result in mild increases in concentrations of triazolam due to intestinal CYP3A4 inhibition by simeprevir. Caution is warranted when this drug with narrow therapeutic index is co-administered with TRADENAME via the oral route.

The direction of the arrow (↑ = increase, ↓ = decrease, ↔ = no change) indicates the direction of the change in PK.

* These interactions have been studied in healthy adults with the recommended dose of 150 mg simeprevir once daily unless otherwise noted [*see Clinical Pharmacology (12.3)*, Tables 5 and 6].

† This interaction study was performed with a dose higher than the recommended dose for TRADENAME assessing the maximal effect on the co-administered drug. The dosing recommendation is applicable to the recommended dose of TRADENAME 150 mg once daily.

‡ The dose of TRADENAME in this interaction study was 50 mg when co-administered in combination with darunavir/ritonavir, compared to 150 mg in the TRADENAME alone treatment group.

8.6 Race

Patients of East Asian ancestry exhibit higher simeprevir exposures [*see Pharmacokinetics (12.3)*]. (b) (4) there are insufficient safety data to recommend an appropriate dose for patients with East Asian ancestry.

8.8 Hepatic Impairment

No dose adjustment of TRADENAME is required in patients with mild (b) (4) hepatic impairment (Child-Pugh Class A (b) (4)); no dose recommendation can be given for patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) [*see Pharmacokinetics (12.3)*]. The safety and efficacy of TRADENAME have not been studied in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh Class B or C).

(b) (4)

12.3 Pharmacokinetics

Distribution

Simeprevir is extensively bound to plasma proteins (> 99.9%), primarily to albumin and, to a lesser extent, alfa 1-acid glycoprotein. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment.

In animals, simeprevir is extensively distributed to gut and liver (liver:blood ratio of 29:1 in rat) tissues. *In vitro* data and physiologically-based PK modeling and simulations indicate that hepatic uptake in humans is modulated by OATP1B1/3.

(b) (4) ***Populations***

Hepatic Impairment

Simeprevir is primarily metabolized by the liver. Compared to healthy subjects with normal hepatic function, the mean steady-state AUC of simeprevir was 2.4-fold higher in subjects with moderate hepatic impairment (Child-Pugh Class B) and 5.2-fold higher in subjects with severe hepatic impairment (Child-Pugh Class C). No dose recommendation can be given for patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). No dose adjustment of TRADENAME is necessary in patients with mild (b) (4) hepatic impairment. The safety and efficacy of TRADENAME have not been studied in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) (b) (4)

Based on a population pharmacokinetic analysis of HCV-infected patients treated with TRADENAME, liver fibrosis stage did not have a clinically relevant effect on the pharmacokinetics of simeprevir.

Refer to the respective prescribing information for peginterferon alfa and ribavirin regarding use in patients with hepatic impairment.

Race

(b) (4)

Based on results from studies in (b) (4) subjects and HCV-infected patients, simeprevir exposures are higher in Asians compared to Caucasians. In the Phase 3 studies, the mean simeprevir plasma exposure in Asian patients was 3.4-fold higher than in the pooled Phase 3

population. There are insufficient safety data to recommend an appropriate dose for patients with East Asian ancestry.

Drug Interactions

[*See also Warnings and Precautions (5.6)*, and *Drug Interactions (7).*]

In vitro studies indicated that simeprevir is a substrate and mild inhibitor of CYP3A and a substrate and inhibitor of P-gp and OATP1B1. Simeprevir does not affect CYP2C9, CYP2C19 or CYP2D6 *in vivo*. Simeprevir does not induce CYP1A2 or CYP3A4 *in vitro*. *In vivo*, simeprevir mildly inhibits the CYP1A2 activity and intestinal CYP3A4 activity, while it does not affect hepatic CYP3A4 activity.

Simeprevir is transported into the liver by OATP1B1 where it undergoes metabolism by CYP3A. Based on results from *in vivo* studies, co-administration of TRADENAME with moderate or strong inhibitors of CYP3A may significantly increase the plasma exposure of simeprevir and co-administration with moderate or strong inducers of CYP3A may significantly reduce the plasma exposure of simeprevir, which may lead to loss of efficacy.

APPEARS THIS WAY ON ORIGINAL

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	NDA 205123
Submission Number (Date)	28 March 2013
Drug Name	Simeprevir (TMC435)
Proposed Indication	In combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C in adult patients
Clinical Division	DAVP
Primary CP Reviewer	Leslie Chinn, Ph.D.
Primary PM Reviewer	Jiang Liu, Ph.D.
Secondary CP Reviewer	Islam Younis, Ph.D.
Secondary PM Reviewer	Jeffry Florian, Ph.D.
Sponsor	Janssen

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

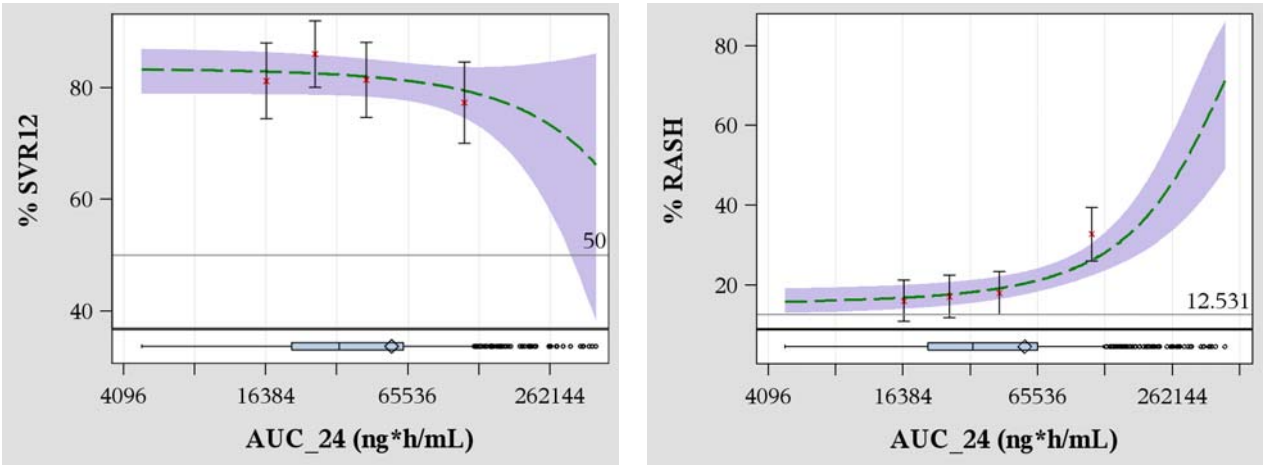
1.1.1 Does simeprevir exposure-response for efficacy and safety support 150 mg once daily dose in the general population?

Yes. The 150 mg once daily simeprevir (TMC435) dose in combination with PEG-IFN and RBV (PR) was consistently superior to the PR therapy in all of the Phase 3 clinical trials for treatment-naïve subjects (Trial C208 and C216) and prior PR relapsers (HPC3007). The exposure-response relationships indicated that the exposure range observed with the 150 mg once daily simeprevir offered a balance between efficacy (Figure 1, left) and safety (Figure 1, right). A lower simeprevir dose (e.g. 100 mg once daily) may provide similar efficacy for overall treatment-naïve subjects and prior PR relapsers compared to the 150 mg q.d. dosing regimen. This is based on the exposure-response relationship for efficacy from the Phase 3 trials and the results from the Phase 2 trials (evaluated 75 mg q.d. and 150 mg q.d. for treatment-naïve patients (Trial C205) and 100 mg q.d. and 150 mg q.d. for treatment-experienced patients (Trial C206) respectively, exposure-response analyses not shown). However, as the safety events at the studied 150 mg QD dose were manageable and the simeprevir 100 mg QD was not evaluated in Phase 3 trials, the observation that simeprevir 100 mg QD may also be efficacious will be utilized to inform dose adjustments in special populations and not be recommended as a suitable dose for the overall population.

Exposure-Response Efficacy: No clear simeprevir exposure-response relationships for efficacy [SVR (sustained viral response), RVR (rapid viral response), eRVR (extended rapid viral response), VBT (viral breakthrough), and relapse] were identified in either treatment-naïve or treatment-experienced populations at the 150 mg dose. As shown in Figure 1 (left), there was no clear relationship between simeprevir exposure and SVR12 based on available data from two Phase 3 trials in treatment-naïve subjects (tmc435-tidp16-c208 and tmc435-tidp16-c216). SVR12 defined as undetectable HCV RNA at the end of treatment (EOT) visit and at 12 weeks after the planned EOT was the primary efficacy endpoint in the pivotal trials. Similar exposure-response efficacy relationships were observed in prior relapsers from HPC3007 and treatment-experienced subjects from C206 (analyses not shown).

Exposure-Response Safety: Higher simeprevir exposure was significantly associated with an increased risk of rash, pruritus, anemia, photosensitivity and increased bilirubin based on all three Phase 3 trials. As shown in Figure 1 (right), events of any type of rash occurred in 18% (35/194) of subjects in the 3rd quartile compared to 33% (63/193) of subjects in the 4th quartile. Likewise, a significant exposure-response safety relationship was identified for simeprevir if the rash events were limited to grade 2 or higher (e.g., similar slope estimates for either any type or grade 2+ exposure-response rash relationships).

Figure 1. Simeprevir Exposure-Response for SVR (Left [a]) and Rash (Right [b])



[a] Univariate exposure-SVR relationship was plotted based on the pooled Phase 3 trials for treatment-naïve patients (Study c208 and c216). The predicted lower SVR rate at the high end of simeprevir exposure is likely due to the large uncertainty associated with the small number of subjects and the higher percentage of subjects with metavir score F3-F4 in the upper exposure quartile (metavir score was both a factor associated with increased simeprevir exposure and decreased likelihood of treatment response).

[b] Univariate exposure-response safety relationship was plotted based on the pooled Phase 3 trials versus incidence of any type of rash..

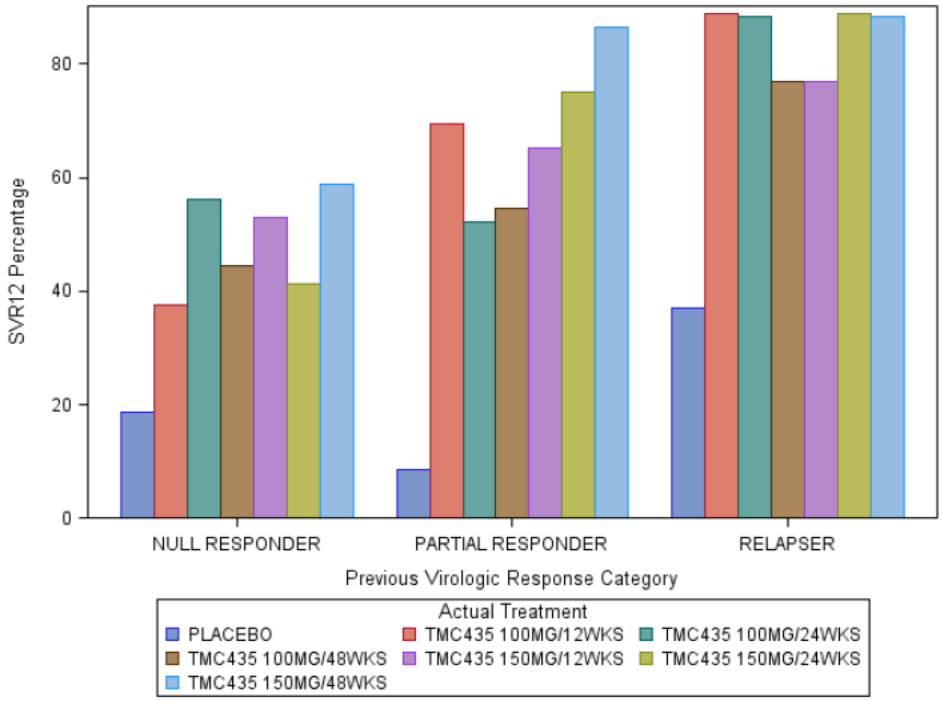
1.1.2 Are there sufficient evidence of simeprevir effectiveness in prior P/R non-responders to receive 12 weeks of triple therapy and an additional 36 weeks of P/R?

Yes. The reviewer identified the following three sources to support simeprevir effectiveness in prior P/R non-responders: i) the Phase 2 trial C206; ii) the Japanese Phase 3 trials in treatment-experienced subjects; and iii) a bridging analysis based on simeprevir response rates in a subset of treatment-naïve patients with baseline predictive factors for poor virological response. These sources of evidence are discussed in more detail below.

- In Study C206, simeprevir in combination with PR (S/PR) showed significantly higher SVR rates in the overall population of treatment-experienced subjects across all six simeprevir treatment groups compared to the placebo/PR (P/PR) group. The SVR12 rate for subjects treated with simeprevir 150 mg for 12 weeks was 66.7%, which was significantly higher than the 22.7% rate in the PR treatment group. There were no substantial differences between response rates across different simeprevir treatment durations (C206 included simeprevir treatment durations of 12-, 24-, and 48-weeks) or different simeprevir doses (C206 included simeprevir doses of 100 and 150 mg once daily) among the treatment-experienced subpopulations. In addition, consistently higher SVR rates were shown in all simeprevir treatment groups for null responders (range from 38% to 59%), partial responders (52% to 86%), and relapsers (77% to 89%) when compared to placebo (19%, 9% and 37%, respectively) (Figure 2). Based on the above results, statistical superiority for prior relapsers and partial responders (p-value < 0.0001) and a trend in the same direction for null responder (p-value = 0.11, likely due to the small sample size and the higher than anticipated response rate in null responders [19% - exceeds the response rate in prior partial responders) were demonstrated when comparing simeprevir 12-wk/PR versus PR (see statistic review).
- Results of Japanese Phase 3 trials, for which summary results but no datasets were submitted, also support the use of simeprevir in combination with PR in prior PR non-responders. The SVR response rates for the trials exceeds the historic 16% of SVR rate assumed for the P/R treatment:
  - SVR12 response rate was 53% (28/53) and 36% (19/53) for simeprevir 100 mg q.d. administered for 12 weeks and 24 weeks respectively in HPC3004
  - SVR12 response rate was 39% (10/26) for simeprevir 100 mg q.d. administered for 12 weeks in HPC3010
- Less likely to response subjects, characterized as subjects with the following baseline factors that are predictive of reduced response (e.g., with baseline non-CC IL28B genotype, higher baseline HCV RNA, and liver disease status metavir score F3-F4) in the treatment-naïve population could be considered as putative PR-experienced subjects. The SVR12 rates in these subjects with multiple baseline factors associated with reduced likelihood of response was significantly

higher with simeprevir 150 mg for 12 weeks compared to the response rates in similar subjects administered only PR (Table 4).

Figure 2. Comparison of SVR Rates from C206 for Different Treatments in Subjects Who Failed Prior IFN-Based Therapy (by Prior Response Status to PR)



1.1.3 Should simeprevir be given to patients with a baseline Q80K polymorphism?

While there is a subset of treatment-naïve subjects with baseline Q80K polymorphism who may respond to simeprevir treatment, a simpler and clinically more practical algorithm may be obtained if subjects with baseline Q80K polymorphism are screened prior to initiation of treatment. In addition, results from C206 suggest that treatment-experienced subjects with Q80K polymorphism may need screened prior to initiation of treatment as a majority of such subjects would meet the currently proposed week 4 futility rule.

Q80K is a common polypmorphism in U.S. HCV 1a-infected subjects. Simeprevir has reduced activity against Q80K variants (for additional details see the Virology review). Rather than screening out Q80K-infections, the sponsor proposed an on-treatment algorithm (b) (4)

(b) (4)

[redacted]

(b) (4) Considering the (b) (4) availability of alternative treatment options to simeprevir where Q80K is not an issue, prescreening Q80K prior to treatment with simeprevir/PR may offer a simpler and clinically more practical algorithm which would permit:

1) Treatment-naïve and prior relapse patients receive a fixed 24-week course of PR in conjunction with 12 weeks of simeprevir.
2) Prior partial- and prior null-responders receive a fixed 48 week course of PR in conjunction with 12 weeks of simeprevir.
3) All patients treated with simeprevir/P/R with quantifiable (≥25 IU/mL) HCV RNA levels at Week 4 should stop treatment.

1.2 Recommendations

- Based on the outcome from the pivotal trials and the exposure-response relationships for efficacy and safety, the 150 mg q.d. simeprevir dose is recommended for approval.
- Available data from the sponsor's Phase 2 treatment-experienced study supported by data from the sponsor's Japanese trials and a bridging analysis with the treatment-naïve population, provides adequate evidence that simeprevir is effective in prior overall P/R non-responders.
- Compared to the on-treatment proposed by the sponsor, prescreening Q80K prior to treatment with simeprevir/PR may offer a simpler and clinically more practical algorithm which would permit:
  1) Treatment-naïve and prior relapse patients receive a fixed 24-week course of PR in conjunction with 12 weeks of simeprevir.
  2) Prior partial- and prior null-responders receive a fixed 48 week course of PR in conjunction with 12 weeks of simeprevir.
  3) All patients treated with simeprevir/PR with quantifiable (≥25 IU/mL) HCV RNA levels at Week 4 should stop treatment.

2 PERTINENT REGULATORY BACKGROUND

This is the original submission (NDA 205123) that the sponsor is seeking approval of simeprevir (TMC435) in combination with peginterferon alfa (PEG-IFN, P) and ribavirin (RBV, R), for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment naïve or who have been previously treated.

Simeprevir is the third HCV NS3/4A protease inhibitors, a class of direct-acting antiviral agents.. In 2011, the FDA approved boceprevir and telaprevir (two other HCV NS3/4A protease inhibitors) in combination with P/R for the treatment of genotype 1 chronic hepatitis C in adult patients.

In subjects with genotype 1 CHC, simeprevir 150 mg once daily for 12 weeks, in combination with P/Rfor 24 or 48 weeks, resulted in significantly higher SVR rates than the treatment of 48 weeks of Peg-IFN/RBV alone. The primary efficacy and safety data in support of simeprevir comes from three Phase 3 and two Phase 2b placebo-controlled studies:

– Treatment-naïve population

- Two Phase 3 studies (C208, N=264 and C216, N=257)
- One Phase 2b study (C205, N=309)

– Prior treatment-failure population

- One Phase 3 study in subjects who relapsed after prior IFN-based therapy (HPC3007, N= 260)
- One Phase 2b study , including prior null responders, partial responders, and relapsers (C206: N=396)

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Explore the exposure-response relationship for efficacy parameters

3.1.1 Exposure-response analyses in Phase 2b dose-finding studies

In treatment-naïve subjects (Study C205): There was a trend for decreases in HCV RNA with increasing simeprevir exposure (AUC_{24h}) following 7 days of therapy at simeprevir doses of 75 or 150 mg q.d., particularly in subjects with a baseline Q80K polymorphism. There was no clear relationship between simeprevir pharmacokinetics and actual HCV RNA levels or change in HCV RNA from baseline at Weeks 12 and 24, and SVR. The viral kinetic model of study C205 showed an increase in inhibition of virion production with increasing AUC_{24h} only in subjects with baseline Q80K treated with 75 mg q.d. simeprevir. No relationship was expected for subjects without the Q80K baseline polymorphism, irrespective of the dose, or in subjects with the Q80K polymorphism who were treated with 150 mg q.d. simeprevir.

In treatment-experienced subjects (Study C206): There was a trend toward a shorter time to undetectable HCV RNA in subjects with higher exposure of simeprevir in the more difficult to treat partial and null responders at simeprevir doses of 100 or 150 mg q.d. No consistent relationship was observed between simeprevir exposure and SVR. As a 150 mg q.d. simeprevir dose was carried forward for treatment-naïve subjects, a similar dose was also selected for further study in the treatment-experienced population.

3.1.2 Exposure-response analyses in Phase 3 studies

In general, there were no consistent relationships between simeprevir exposure and virologic response parameters. The effects of baseline characteristics (e.g., age, BMI, body weight, baseline HCV RNA, Sex, Metavir score, race, HCV genotype, baseline presence of Q80K, IL28B genotype, and baseline interferon-inducible protein-10 (IP-10)) and early response parameters (e.g., RVR, ERVR, meeting RGT, and on-treatment HCV RNA < 25 IU/mL at Week4) on SVR were also explored using univariate and multivariate GAM analysis and recursive partitioning analysis. Early on-treatment responses had a dominant effect on predicting SVR. Baseline factors such as age, IL28B, baseline IP-10, HCV genotype 1 subtype, baseline Q80K, baseline HCV RNA value, and metavir score also seemed to be associated with probability of SVR response.

3.2 Explore the exposure-response relationship for safety parameters

The relationship between simeprevir exposure (AUC_{24h} quartiles) and selected safety parameters was explored. Higher incidences of rash (any type), pruritus, anemia, and increased bilirubin with increasing simeprevir exposure were observed (Table 2).

Table 2. Number (%) of Subjects with Selected Events During the TMC435/PBO+PR Phase by Simeprevir AUC_{24h} Quartiles

	≤ Q1 (Q1 = 21238.0)	> Q1 - ≤ Median (Median = 33618.0)	> Median - ≤ Q3 (Q3 = 65484.0)	> Q3
Analysis Set: ITT	194	193	193	193
Events of special interest				
Increased Bilirubin	14 (7.2%)	16 (8.3%)	7 (3.6%)	25 (13.0%)
Events of clinical interest				
Rash(Any Type)	32 (16.5%)	39 (20.2%)	39 (20.2%)	69 (35.8%)
Pruritus	28 (14.4%)	40 (20.7%)	41 (21.2%)	59 (30.6%)
Photosensitivity conditions	4 (2.1%)	7 (3.6%)	4 (2.1%)	11 (5.7%)
Neutropenia	36 (18.6%)	31 (16.1%)	29 (15.0%)	33 (17.1%)
Anemia	19 (9.8%)	28 (14.5%)	20 (10.4%)	37 (19.2%)
Additional events				
Dyspnoea (grouped)[a]	19 (9.8%)	25 (13.0%)	19 (9.8%)	28 (14.5%)
Constipation	5 (2.6%)	1 (0.5%)	7 (3.6%)	7 (3.6%)

For a list PTs included in the grouped term dyspnea, see Section 1.6.5.
Subjects are counted only once for any given event, regardless of the number of occurring PTs.
AEs are coded using MedDRA version 15.0

Source: the sponsor's clinical safety summary, summary-clin-safety-hepatitis-c.pdf, Table 55 on page 118.

4 REVIEWER'S ANALYSIS

4.1 Introduction

This is the original submission of simeprevir (TMC435), the third drug of a class of direct-acting antiviral agents, the HCV NS3/4A protease inhibitors. The sponsor is seeking approval of simeprevir in combination with peginterferon alfa (PEG-IFN) and ribavirin (RBV), for the treatment of genotype 1 chronic hepatitis C. A thorough review of the dosing strategy and exposure-response relationships for efficacy and safety was performed and is detailed below. In addition, the reviewer evaluated the evidence supporting that simeprevir was effective in treatment-experience subjects, the sponsor's proposed on-treatment dosing algorithm, and the impact of Q80K baseline polymorphisms on treatment-response.

4.2 Objectives

Analysis objectives are:

1. to assess the 150 mg q.d. simeprevir dose based on the exposure-response relationship for efficacy and safety from the Phase 3 trials
2. to assess the evidence of simeprevir effectiveness in prior P/R non-responders

3. to assess treatment algorithms based on information obtained from the current submission regarding impact of Q80K polymorphism on simeprevir efficacy

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 3.

Table 3. Analysis Data Sets

Study Number	Name	Link to EDR
C206	adeffout.xpt	\\Cdsesub1\evsprod\NDA205123\0004\m5\datasets\tmc435-tidp16-c206\analysis\adam\datasets\adeffout.xpt
ise	adsl.xpt	\\Cdsesub1\evsprod\NDA205123\0000\m5\datasets\ise\analysis\adam\datasets\adsl.xpt
ise	adhcv.xpt	\\Cdsesub1\evsprod\NDA205123\0000\m5\datasets\ise\analysis\adam\datasets\adhcv.xpt
ise	adgt.xpt	\\Cdsesub1\evsprod\NDA205123\0000\m5\datasets\ise\analysis\adam\datasets\adgt.xpt
ise	adttgt.xpt	\\Cdsesub1\evsprod\NDA205123\0000\m5\datasets\ise\analysis\adam\datasets\adttgt.xpt
iss-phase-2and3	adae.xpt	\\Cdsesub1\evsprod\NDA205123\0000\m5\datasets\iss-phase23\analysis\adam\datasets\adae.xpt
iss-phase-2and3	adlb.xpt	\\Cdsesub1\evsprod\NDA205123\0000\m5\datasets\iss-phase23\analysis\adam\datasets\adlb.xpt
global-poppk	nm-pk-cov-global-v5-prn.xpt	\\Cdsesub1\evsprod\NDA205123\0000\m5\datasets\tmc435-global-poppk\analysis\legacy\datasets\nm-pk-cov-global-v5-prn.xpt

4.3.2 Software

SAS, R, and NONMEM were used for the reviewer's analyses.

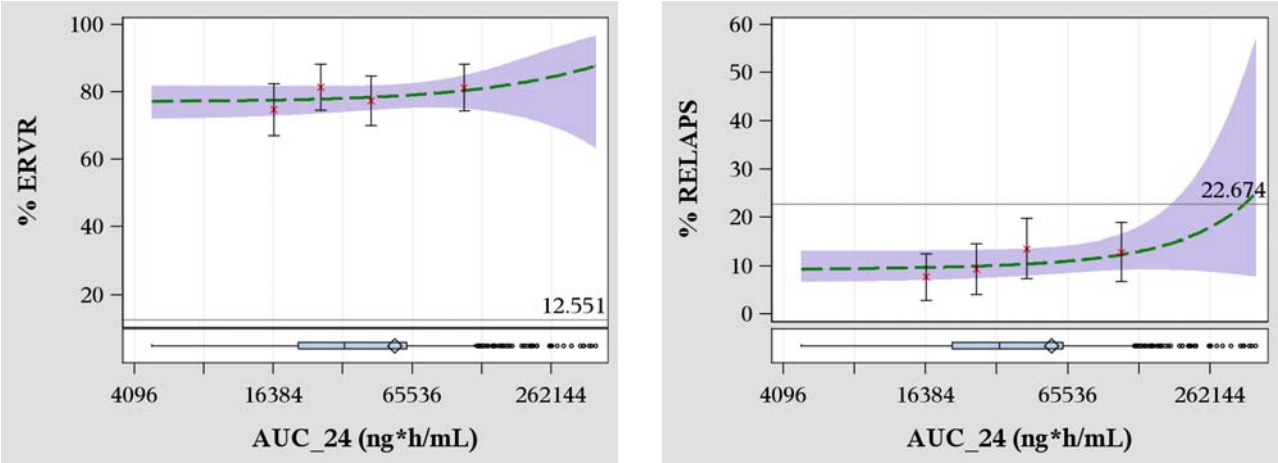
4.3.3 Models and Results

4.3.3.1 Exposure-response relationship for efficacy

Univariate and multivariate logistic regressions were performed to explore the simeprevir exposure-response (ER) relationships for efficacy [SVR, eRVR, VBT, and relapse]. Individual simeprevir exposure (AUC_{24} and C_{trough}) used for the ER analysis was estimated from the population PK analysis based on sparse sampling in the Phase 3 trials.

No clear exposure-response relationship was identified for any of the above efficacy variables based on the data from two Phase 3 trials in treatment-naïve subjects (C208, N=264 and C216, N=257) (Figure 1 (left) and Figure 3). In these trials, subjects were treated with simeprevir 150 mg q.d. for the first 12 weeks in combination with P/R for 24 weeks if HCV RNA was <25 IU/mL at week 4 or 48 weeks if HCV RNA was >25 IU/mL at week 4. Subgroup analyses in subjects with baseline Q80K also did not identify any clear exposure-response efficacy relationship. Similarly, no clear exposure-response efficacy relationships were observed for prior relapsers at simeprevir 150 mg dose from the Phase 3 trial (tmc435hpc3007, N=260) and for overall treatment-experienced subjects at simeprevir 100 mg and 150 mg from the Phase 2 trial (tmc435-tidp16-c206, N=396).

Figure 3. Simeprevir Exposure-Response for ERVR (Left) and Relapse (Right)

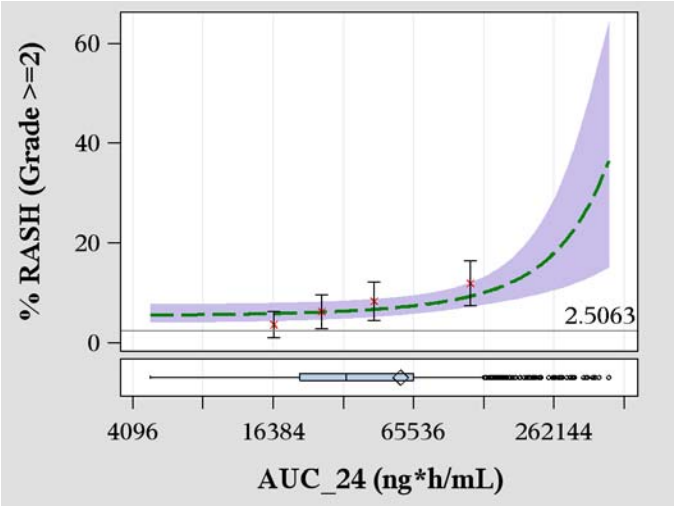


Univariate exposure-efficacy relationships were plotted based on the pooled Phase 3 trials for treatment-naïve patients (Study c208 and c216). The predicted higher relapse rate at the high end of simeprevir exposure is likely due to the large uncertainty associated with the small number of subjects and the higher percentage of subjects with metavir score F3-F4.

4.3.3.2 Exposure-response relationship for safety

Higher simeprevir exposure was significantly associated with an increased risk of rash, pruritus, anemia, photosensitivity and increased bilirubin. The exposure-safety analyses were conducted based on a pooled analysis of Phase 3 trials. Exposure-response adverse event relationships for any rash are shown in Figure 1 (right). Rash events occurred in 18% (35/194) of subjects in the 3rd quartile compared to 33% (63/193) of subjects in the 4th quartile. The rash event rate in all quartiles exceeded the event rate observed in the control arm (P/R: 12.5%). Likewise, a significant exposure-response safety relationship was identified for simeprevir if the rash events were limited to grade 2 or higher (Figure 4).

Figure 4. Simeprevir Exposure-Response for Grade 2 or Higher Rash



4.3.3.3 SVR rate in treatment-naïve subjects who had baseline harder-to-treat factors

Our previous experience of the treatment-naïve population and the treatment-experienced population (Florian J et al. *Hepatology 2012*, Liu J et al. *Clinical Infectious Diseases 2012*, and Liu J et al. *Hepatology 2012*) has indicated that the PR treatment-experienced subjects were putatively included in the treatment-naïve population. Population mapping based on baseline factors can be used to identify a subset of the treatment-naïve subjects in the Phase trials that matches the PR treatment-experienced population, i.e., the putative PR-experienced cohort embedded in the Phase 3 trials of treatment-naïve population. The subjects in the putative PR-experienced cohort are the harder-to-treat subjects with IL28B genotypes CT and TT, advanced liver fibrosis (e.g., metavir score F3-F4), and/or high baseline HCV RNA (e.g., baseline HCV RNA ≥ 800,000 IU/mL). Significant higher SVR rates with simeprevir/PR versus Placebo/PR in the harder-to-treat subpopulation should support effectiveness of simeprevir in the PR treatment-experienced population. As shown in Table 4, the SVR12 rates for the harder-to-treat subjects with simeprevir 150 mg for 12 weeks were significantly higher compared to those with the PR treatment.

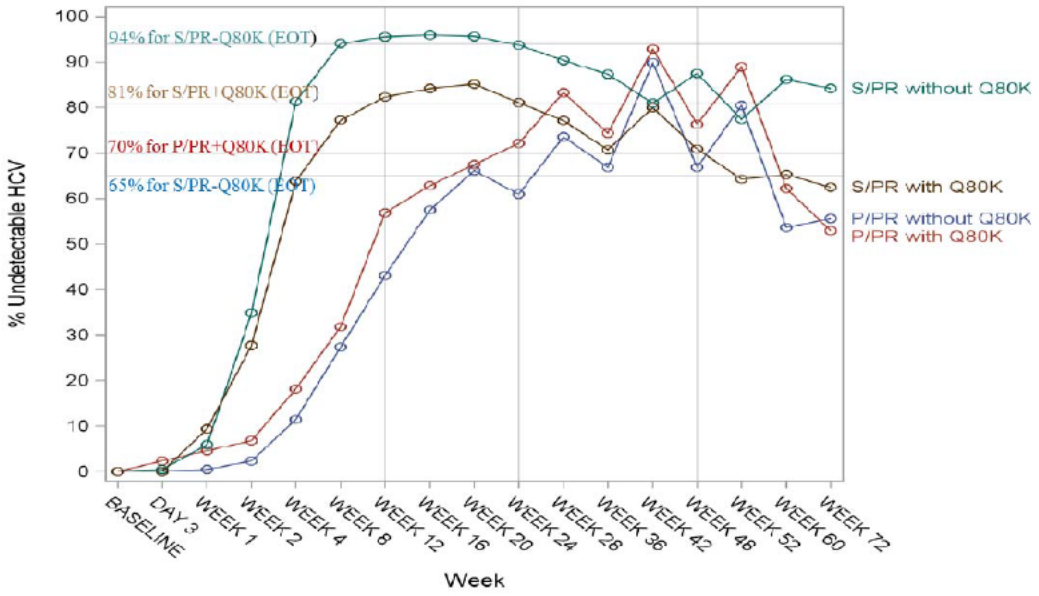
Table 4. Comparison of SVR Rate between Simeprevir/PR and PR Treatment in Treatment-Naïve Subjects Who Had Baseline Harder-to-Treat Factors

Baseline Factors		SVR12, n/N (%)	
		Placebo	Simeprevir
IL28B	CC	63/79 (80%)	144/152 (95%)
	CT	61/147 (42%)	228/292 (78%)
	TT	8/38 (21%)	47/77 (61%)
Liver disease status	F0-F2	106/192 (55%)	317/378 (84%)
	F3-F4	26/72 (36%)	89/130 (68%)
Baseline HCV RNA	< 800 KIU/mL	54/70 (77%)	96/104 (92%)
	≥ 800 KIU/mL	78/194 (40%)	323/417 (77%)
nonCC & F3-F4 & BL HCV ≥ 800 KIU/mL		3/38 (8%)	37/73 (51%)

4.3.3.4 Treatment algorithms based on information of Q80K on simeprevir efficacy

Q80K is a common polypmorphism in U.S. HCV 1a-infected subjects. Although simeprevir is less effective against Q80K variants, it does have activity against Q80K variants based on the on-treatment viral response in treatment-naïve population (Figure 5). Rather than screening out Q80K-infections, the sponsor proposed a treatment algorithm (b) (4)

Figure 5. Time Course of Proportion of Achieving Undetectable HCV RNA (by Treatment and Baseline Q80K Status)



S/PR − Q80k (N):	420	421	422	419	423	422	422	416	413	417	404	411	21	399	31	404	139	428 (EOT)
S/PR + Q80k (N):	83	83	85	83	83	79	79	76	74	79	70	75	10	72	14	72	32	86 (EOT)
P/PR + Q80K (N):	44	42	44	44	44	44	44	43	40	43	36	39	28	38	27	37	17	44 (EOT)
P/PR Q80K (N):	210	210	212	212	209	212	211	202	189	205	170	196	138	193	133	194	63	214 (EOT)

(b) (4)


(b) (4)


(b) (4)

(b) (4)

Considering the (b) (4) availability of alternative treatment options to simeprevir where Q80K is not an issue, screening every patients for Q80K prior to treatment with simeprevir/PR should be a simpler and clinical more practical algorithm which would permit:

1) Treatment-naïve and prior relapse patients receive a fixed 24-week course of PR in conjunction with 12 weeks of simeprevir.
2) Prior partial- and prior null-responders receive a fixed 48 week course of PR in conjunction with 12 weeks of simeprevir.
3) All patients treated with simeprevir/PR with quantifiable (≥25 IU/mL) HCV RNA levels at Week 4 should stop treatment. In Phase 3 trials, the virologic stopping criterion for discontinuation of treatment at Week 4 is HCV RNA > 1,000 IU/mL. Form Table 5 and Table 6, the contribution from patients treated with simeprevir/P/R with ≥25 IU/mL HCV RNA levels at Week 4 to the overall SVR rate of simeprevir/PR is very limited.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\
ER.sas	ER analysis	\Simeprevir_NDA205123_JL\ER Analyses\
quartilePlot_logistic_log.sas	ER plotting	\Simeprevir_NDA205123_JL\ER Analyses\
quartilePlot_linear.sas	ER plotting	\Simeprevir_NDA205123_JL\ER Analyses\
boxplotScatterOverlay r	Plotting simeprevir exposure in Asian subjects vs. that in the overall population	\Simeprevir_NDA205123_JL\ER Analyses\

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APPENDIX - POPULATION PK ANALYSES OF SIMEPREVIR

6 SUMMARY OF FINDINGS

The final population PK model for orally administered simeprevir was a two-compartment model with lagged first-order absorption, dose-dependent oral bioavailability, and saturable clearance, described using Michaelis-Menten kinetics and with intersubject variability on relative bioavailability and maximum elimination rate. Covariate analysis showed that body weight, age, sex, total bilirubin (TB) and liver disease status based on metavir score (MS) had statistically significant effects on some PK parameters. Simeprevir exposure tend to be higher for females versus males, elderly subjects, subjects with higher TB, and subjects with MS score 3 or 4 versus lower scores. However, given the impact of these covariates on simeprevir exposure compared to the uncharacterized between subject variability, the clinical relevance of the identified factors on simeprevir exposure is limited. No simeprevir dose adjustments are recommended based on any of these identified covariates.

7 RESULTS OF SPONSOR'S ANALYSIS

The sponsor conducted a population pharmacokinetic analysis to:

1. Characterize the pharmacokinetics of simeprevir in adults with genotype 1 hepatitis C virus infection
2. Evaluate the effects of covariates on simeprevir exposure
3. Obtain individual estimates of simeprevir exposure to be used in exposure-response analysis

The dataset consisted of plasma concentrations from two Phase 2 studies (C205 and C206) and three Phase 3 studies (C208, C216 and HPC3007). In all studies and all groups, two blood samples were obtained for simeprevir determination on visits for sparse sampling. The second blood sampling was conducted at a time point at least 2 hours after the first sampling time. For a selection of subjects in studies C205 and C206, an additional visit for intense sampling was also scheduled and 8 samples were taken at regular time intervals. A summary of the sampling design and simeprevir dosing information is shown in Table 7. Records for which concentrations were missing or below the limit of quantification (BLQ) were removed from the database. The raw dataset contained 1482 subjects. A total of 1477 subjects were included in the analysis.

Table 7. Summary of Data Included in the Population Pharmacokinetic Analysis

Item	Details				
Trial code	C205	C206	C208	C216	HPC3007
Duration of TMC435 treatment (weeks)	12 (*GRP*[a] *1,2*) 24 (*GRP 3,4*)	12 (*GRP 1,2*) 24 (*GRP 3,4*) 48 (*GRP 5,6*)	12	12	12
TMC435 dose QD (mg)	75 (*GRP 1, 3*) 150 (*GRP 2, 4*)	100 (*GRP 1, 3, 5*) 150 (*GRP 2, 4, 6*)	150	150	150
Sampling occasions (Week)	2, 4, 8, 12 (*GRP 1,2*) 2, 4, 8, 12, 16, 24 (*GRP 3,4*)	2, 4, 8, 12 (*GRP 1,2*) 2, 4, 8, 12, 16, 24 (*GRP 3,4*) 2, 4, 8, 12, 16, 24, 48 (*GRP 5,6*)	2, 4, 8, 12	2, 4, 8, 12	2, 4, 8, 12
Samples per subject per occasion	2[b]	2[c]	2	2	2
Samples per subject	8 (*GRP 1,2*) 12 (*GRP 3,4*)	8 (*GRP 1,2*) 12 (*GRP 3,4*) 14 (*GRP 5,6*)	8	8	8

[a]GRP: group
[b]For a selection of subjects in study C205 an additional visit with 8 samples was scheduled
[c]For a selection of subjects in study C206 an additional visit with 8 samples was scheduled

(Source: Sponsor's Population PK Report: Table 1)

7.1 Pharmacokinetics Structural Model

The selection of the structural model was informed by population pharmacokinetic analysis of earlier studies. As a first run, the existing model was fitted to the current data by fixing all the model parameters to the previously obtained parameter values. This model already described the exposure in the current population reasonably well, indicating that the exposure in Phase II and Phase III studies were comparable. The final model was a two-compartment model with first order absorption (with lag time), saturable clearance, described using Michaelis-Menten kinetics and a dose-dependent relative bioavailability (F1). Compared to the previous model, (1) a distinct value for the apparent volume of distribution for the peripheral compartment (Vp) was estimated instead of considering the central and peripheral compartments being characterized by the same volume, (2) the maximum elimination rate in the Michaelis-Menten equation was expressed in terms of amount over time instead of concentration over time and (3) the dose dependency of F1 was assessed by considering a dose-dependent categorical covariate instead of assuming a linear relationship between F1 and dose. IIV was identified on F1 and Vmax. Adding IIV on other PK parameters, ALAG, ka, Vc/F, Vp/F, Q and Km, improved the model fit significantly, as judged by the ΔMVOF, but caused high η-shrinkage and centering problems. Random effects at the individual level were included as exponential terms, reflecting log-normal distributions of the individual model parameters. An additive residual error model for the natural log-transformed data was assumed.

7.2 Pharmacokinetics Final Model with Covariates

The effects of covariates on simeprevir pharmacokinetics were evaluated using a forward inclusion and backward deletion approach combined with graphical analyses. The continuous covariates age, body weight (WT), creatinine clearance (CRCL), body surface area (BSA), body mass index (BMI), lean body mass (LBM) and total bilirubin (TB) and categorical covariates sex and metavir score (MS) were investigated. One category in Child-Pugh liver score (CPLS=1) exceeded 99% and one category (White, Not Hispanic or Latino) in race was predominantly present (85%). Food intake was not prespecified in the Phase 3 trials. Therefore the categorical covariates CPLS, race and food intake were not considered for the covariate analysis. Continuous covariates were modeled using a power function normalized by the median value of the covariate. Categorical covariates were incorporated using indicator variables.

Following the full covariate analysis, the covariate effects of WT, age, MS and SEX on F1 and WT and TB on Vmax were included in the final model. The final model described the PK in the global trials well, as observed by the goodness of fit plots (Figure 6) and the visual predictive check. F1 decreased with increasing WT and decreasing age, while Vmax decreased with increasing WT and increasing TB. Furthermore, a higher F1 was observed for females versus males and subjects with MS score 3 or 4 versus lower scores (Table 8). The potential clinical relevance of the identified covariates on simeprevir PK was evaluated by simulations using the extremes of the combinations of covariates leading to the highest and the lowest model parameter value. The influence of the identified covariates on simeprevir exposure is limited compared to the observed random variability in the patient population (Figure 7.).

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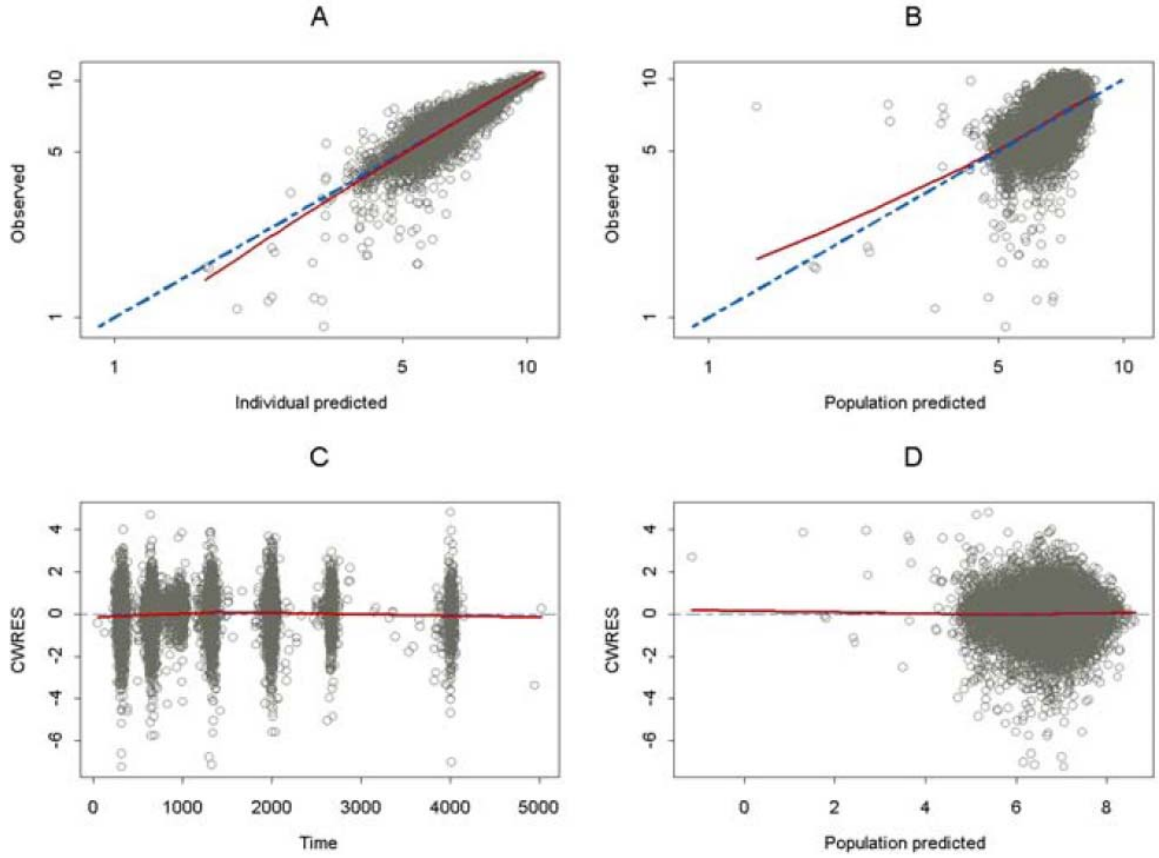
Table 8. Parameter Estimates of the Final Model

Parameter	Value[a]	SE[b]	CV (%)[c]	LLCI[d]	ULCI[e]
	Fixed effects				
$ALAG$ (h)	1.07	0.031	3	1.009	1.131
k_a (h^{-1})	0.165	0.02	12	0.126	0.204
$F_{1,150\ mg}$	1				
Relative change of $F_{1,100\ mg}$[f]	-0.142	0.04	-28	-0.221	-0.063
Relative change of $F_{1,75\ mg}$[g]	-0.203	0.048	-24	-0.297	-0.109
V_c/F (L)	38.4	4.1	11	30.4	46.4
V_p/F (L)	250	40	16	171	329
Q/F (L h^{-1})	5.89	0.87	15	4.18	7.6
V_{max}/F[h] ($\mu g\ h^{-1}$)	16000	1290	8	13472	18528
K_m (μg)	67100	9400	14	48676	85524
WT *vs* F_1[i]	-0.74	0.16	22	-1.05	-0.43
AGE *vs* F_1[j]	0.30	0.06	19	0.19	0.41
Relative change of $F_{1,female}$[k]	0.228	0.037	16	0.155	0.301
Relative change of $F_{1,MS=3}$[l]	0.129	0.038	30	0.054	0.204
Relative change of $F_{1,MS=4}$[m]	0.319	0.053	17	0.214	0.424
WT *vs* V_{max}/F[n]	-0.8	0.158	-20	-1.11	-0.49
TB *vs* V_{max}/F[o]	-0.127	0.028	-22	-0.182	-0.072
	Random effects: inter-individual variability (IIV)				
$\omega^2_{F_1}$	0.465	0.052	11	0.363	0.567
$\omega^2_{V_{max}/F}$	0.35	0.071	20	0.21	0.49
$\omega^2_{F_1} \times \omega^2_{V_{max}/F}$	0.296	0.058	20	0.182	0.41
	Random effects: residual error				
σ^2 (add[p])	0.315	0.01	3	0.295	0.335

[a] Reported by NONMEM
[b] Standard error of parameter estimate, reported by NONMEM
[c] Coefficient of variation, calculated as SE/Value*100%
[d] Lower limit of 95% confidence interval
[e] Upper limit of 95% confidence interval
[f] Fraction $F_{1,100\ mg}$ = $F_{1,150\ mg}$*(1 + Relative change of $F_{1,100\ mg}$)=0.858
[g] Fraction $F_{1,75\ mg}$ = $F_{1,150\ mg}$*(1 + Relative change of $F_{1,75\ mg}$)=0.797
[h] V_{max}/F is expressed as amount over time
[i] relationship between WT and F_1 is described using Equation 14
[j] relationship between AGE and V_c/F is described using Equation 14
[k] Fraction $F_{1,female}$ = $F_{1,male}$*(1 + Relative change of $F_{1,female}$)=1+0.228=1.228
[l] Fraction $F_{1,MS=3}$ = $F_{1,MS=1-2}$*(1 + Relative change of $F_{1,MS=3}$)=1+0.129=1.129
[m] Fraction $F_{1,MS=4}$ = $F_{1,MS=1-2}$*(1 + Relative change of $F_{1,MS=4}$)=1+0.319=1.319
[n] relationship between WT and V_{max}/F is described using Equation 15
[o] relationship between TB and V_{max}/F is described using Equation 15
[p] Additive error natural log (ln)-transformed data

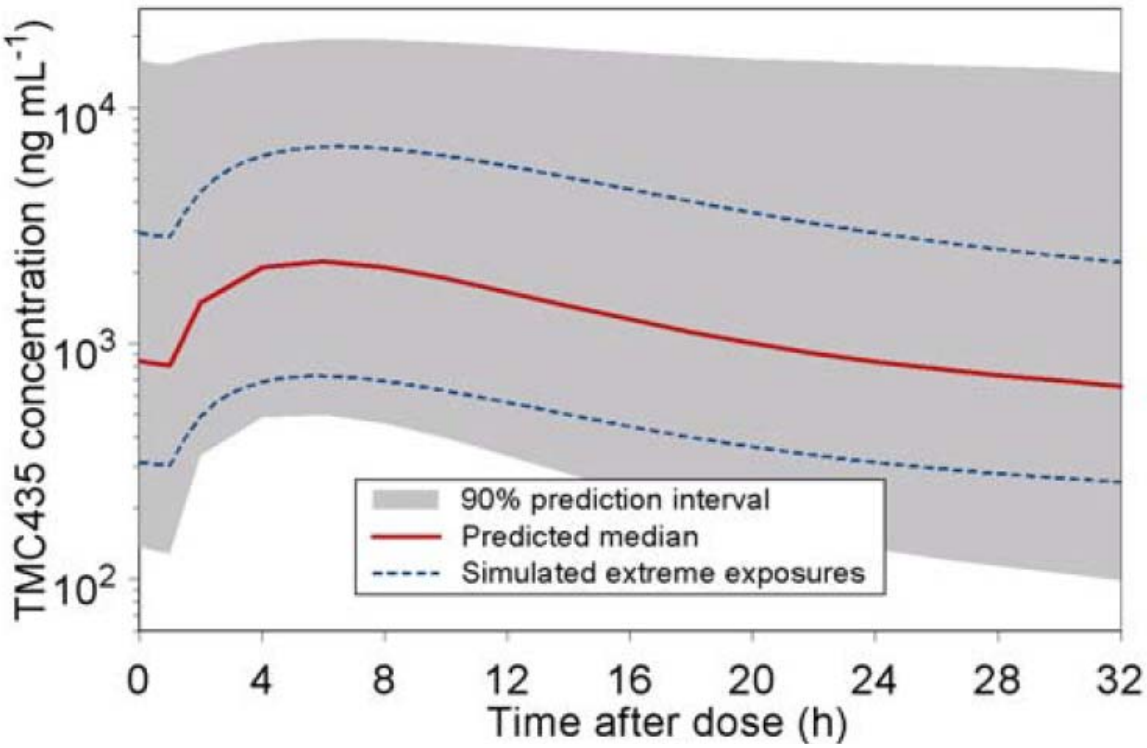
(Source: Sponsor's Population PK Report: Table 5)

Figure 6. Goodness-of-Fit Plots for the Final Model



(Source: Sponsor's Population PK Report: Figure 24)

Figure 7. Simulations to Assess the Potential Clinical Impact of the Covariates on Simeprevier Exposure

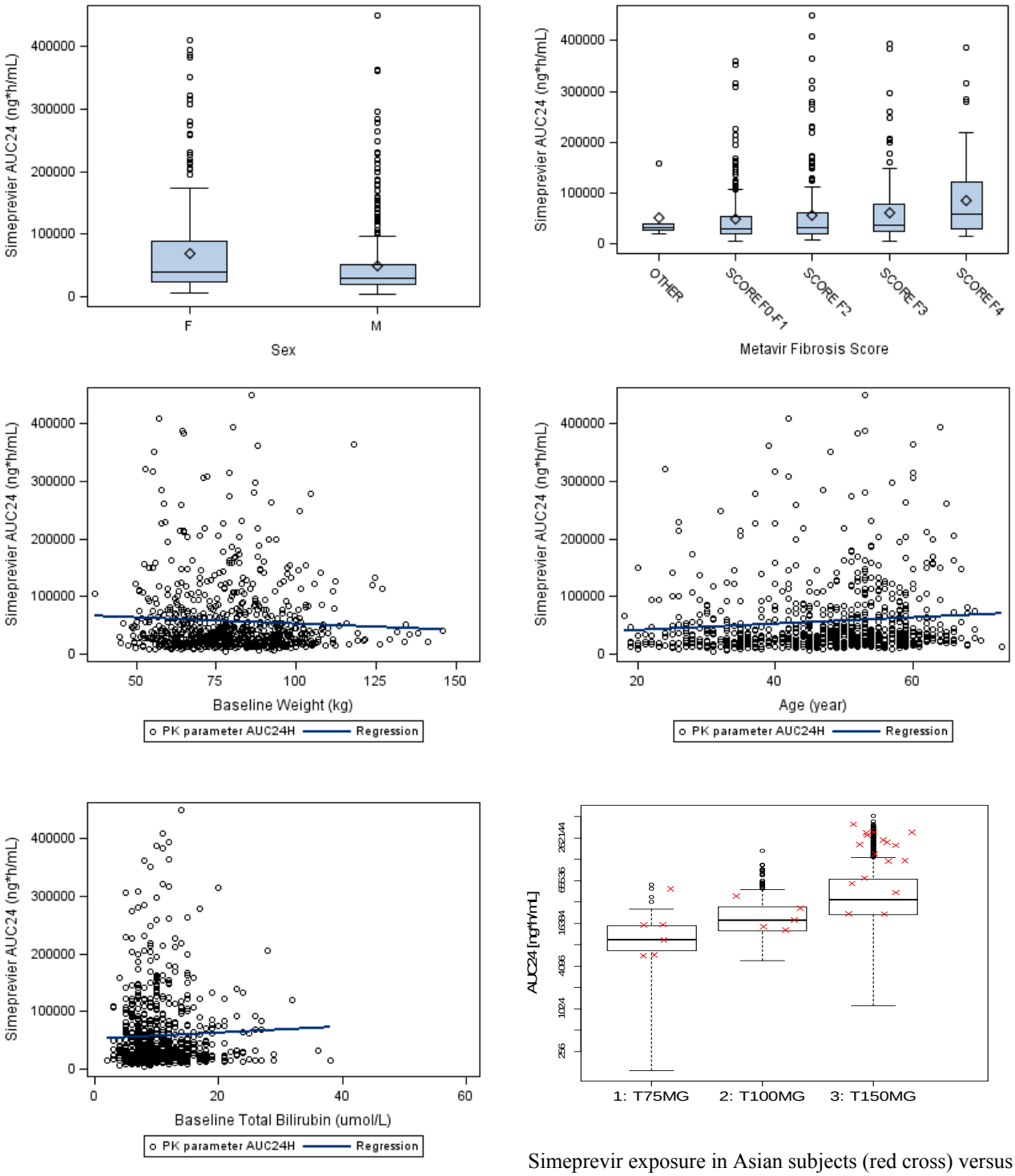


Grey area: 90% prediction interval of the simulated data using the final full covariate model (500 simulations after 12 weeks of 150 mg q.d. administration of simeprevier); red line: median of the simulated data using the final full covariate model; blue dotted line: Simulated PK profiles of the extreme covariate combinations (young heavy male (25 y and 107.5 kg) with MS score 1 and low TB (5 µmol/L) and older light female (63 y and 54.8 kg) with MS score 4 and high TB (21 µmol/ L)).

(Source: Sponsor's Population PK Report: Figure 7)

Reviewer's Comment: The population PK model provides a reasonable description of simeprevier exposure (Figure 6). Due to the sparse information, precisely characterizing the outcome from covariate effects should be interpreted only as the influence of covariates on the exposure of simeprevir and not on specific parameters. Simeprevir exposure tend to be higher for females versus males, elderly subjects, subjects with higher TB, and subjects with MS score 3 or 4 versus lower scores (Figure 8). However, given the impact of these covariates on simeprevir exposure compared to the uncharacterized between subject variability, the clinical relevance of the identified factors on simeprevir exposure is limited. MS score appears to affect both simeprevir exposure and virological response. Subjects with advanced liver fibrosis (e.g., MS score F3-F4) are less likely to achieve SVR. The percentage of subjects with MS score F3-F4 in the 4th exposure quartile is 36% which is higher compared to those in the lower quartiles (13%, 25%, and 27% in the 1st, 2nd, and 3rd quartiles respectively). Race effect on simeprevier exposure was not explored by the population PK modeling. There were only 14 Asian subjects in the pooled Phase 3 PK dataset, the median exposure of simeprevir in Asian subjects following administration of 150 mg q.d. simeprevir was 6.3-fold higher than other races(Figure 8).

Figure 8. Simeprevir Exposure Versus Baseline Covariates



Simeprevir exposure in Asian subjects (red cross) versus that in the overall population (box) by doses

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS AND TARGETED THERAPY GROUP REVIEW

NDA/BLA Number	205123
Submission Date	03/28/2013
Applicant Name	Janssen Research and Development
Generic Name	Simeprevir
Proposed Indication	Chronic HCV Infection
Primary Reviewer	Jeff Kraft, PhD
Secondary Reviewer	Mike Pacanowski, PharmD, MPH

1 Background

Simeprevir is an orally administered inhibitor of the HCV NS3/4A protease, which is essential for viral replication. The proposed indication for simeprevir in the current NDA is for the treatment of chronic HCV genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adults (b) (4) with compensated liver disease (including cirrhosis) who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin.

High inter-individual variability was observed for simeprevir pharmacokinetics in clinical trials (AUC CV% between 70%-140%). Additionally, Asian subjects (N=14) demonstrated a 3.4-fold higher AUC compared to the population mean. Given that several adverse events are associated with increased exposure (e.g. rash, photosensitivity), the sponsor included an analysis of exonic sequencing data in 10 candidate genes to investigate the effects of genetic variation on the PK of simeprevir. The purpose of this review is to evaluate the genotype information submitted by the sponsor regarding genotype effects on the disposition of simeprevir.

2 Submission Contents Related to Genomics

The sponsor submitted the following reports related to the pharmacogenetics (PGx) of simeprevir PK:

Table 1: Clinical Study Reports Related to PGx Analysis

Report ID	*Title*
2013026	Assessment of the potential influence on TMC435 plasma exposure of the genetic variation in 10 candidate genes encoding proteins with known or assumed involvement in the metabolism of TMC435.

The studies included in the PGx analysis are summarized below in Table 2. In all studies, subjects were treated with daily simeprevir doses of 75, 100, or 150 mg. DNA samples were collected from selected subjects who consented to optional participation in PGx research during each study. A total of 110 subjects were selected from Phase IIb clinical trials C205 (n=58) and C206 (n=52) for the current PGx analysis as follows: extreme high or extreme low simeprevir plasma concentrations (based on AUC) within each dose group, i.e. all subjects in upper 90th (n=30) and lower 10th (n=29) percentile of simeprevir plasma exposure complemented with subjects of the 75-90th (n=24) or 10-25th (n=24) percentile, respectively; non-Caucasian

subjects (n=11 Asian, n=6 Black or African-American); and subjects with elevated total bilirubin levels (Grade 3 or 4, n=11).

Table 2: Clinical Studies Utilized for PGx Analysis

Study	*Description*	*Total N Dosed*	*PGx N*
C205	A Phase IIb, randomized, double-blind, placebo-controlled trial to investigate the efficacy, tolerability, safety and pharmacokinetics of TMC435 as part of a treatment regimen including peginterferon alfa 2a and ribavirin in treatment-naïve genotype 1 hepatitis C infected subjects.	386	58
C206	A Phase IIb, randomized, double-blind, placebo-controlled trial to investigate the efficacy, tolerability, safety and pharmacokinetics ofTMC435 as part of a treatment regimen including PegIFNα-2a and ribavirin in HCV genotype 1 infected subjects who failed to respond or relapsed following at least 1 course of PegIFNα-2a/b and RBV therapy.	463	52
TOTAL		**849**	**110**

DNA samples were sequenced for genetic variants in the exonic regions of 10 candidate genes as follows: CYP3A4, CYP3A5, CYP2C19, SLCO1B1, SLCO2B1, SLCO1B3, SLC10A1, ABCG2, ABCB1, and ABCC2. The 156 exons comprising these genes were captured through a pooled PCR approach of 171 amplicons and sequenced using the Illumina HiSeq 2000. For CYP2C19 and SLCO1B1, subjects were classified using standard haplotype designations as listed in Table 3.

Table 3: Star Allele Annotation for CYP2C19 and SLCO1B1

Star Allele	dbSNP Identifier	Amino Acid Variation
CYP2C19*1A	n/a	None
CYP2C19*1B	n/a	Ile331Val
CYP2C19*2B	rs17878459	Glu92Asp; Ile331Val
CYP2C19*3A	rs4986893	Trp212Stp; Ile331Val
CYP2C19*8	rs41291556	Trp120Arg
CYP2C19*11	rs58973490	Arg150His; Ile331Val
SLCO1B1*1a	n/a	None
SLCO1B1*1b	rs2306283	Asn130Asp
SLCO1B1*5	rs4149056	Val174Ala
SLCO1B1*15	rs2306283, rs4149056	Asn130Asp; Val174Ala

Comment: The reviewer verified that the star allele annotation was correct based on literature and that subject status was correctly assigned, but did not replicate the sponsor's analyses.

3 Key Questions and Summary of Findings

3.1 Does genetic variation in one or more of the 10 examined candidate genes explain inter-individual variability in TMC435 exposure?

No. Analysis performed by the sponsor and repeated by the reviewer showed no significant association between any individual marker and extreme simeprevir exposures.

This PGx analysis focused on only a subset of subjects with either extreme high or low simeprevir exposures and focused on a predefined list of 10 candidate genes. Therefore, whether genetic variations account for any of the observed variations in simeprevir plasma exposure cannot be excluded.

3.1.1 Sponsor's Analysis

The primary aim of the sponsor's analysis was to compare the frequencies of any genetic variants in the extreme low and high plasma exposure subgroups. To this end, subjects falling within the "no extreme value" subgroup (i.e., those selected based on bilirubin or race; n=4) were excluded from the analysis and only 106 subjects were included in the analysis (high n=53 and low n=53).

Overall, the sponsor identified 234 unique single nucleotide polymorphisms (SNPs) in the coding regions of the 10 selected genes, 78 of which caused an amino acid change in the resulting protein (non-synonymous). The frequency of each variant was compared between the high and low exposure subjects. An overview of the identified coding (cSNPs) and non-synonymous SNPs (nsSNPs) per gene, together with the frequency of the 78 nsSNPs in the high and low simeprevir exposure subgroups, is presented in Table 4. Additionally, Figure 1 provides a graphical summary per candidate gene, which shows that genetic variations were distributed similarly among both extreme simeprevir plasma exposure subgroups.

Table 4: Frequency of Non-synonymous Genetic Variations in CYP, ABC, and SLC Gene Families Stratified per Subject Group (High versus Low Simeprevir Exposure)

Gene Symbol	# of Coding Variants (cSNPs)	# of Non-Synonymous Variants (nsSNPs)	Amino Acid Change	Frequency in High Exposure (n=53)	Frequency in Low Exposure (n=53)
CYP					
CYP2C19	17	9	Arg73Cys*	0.02	0
			Glu81Lys	0	0.02
			Glu92Asp	0.04	0.09
			Trp120Arg*	0.04	0.02
			Arg150His	0.02	0
			Trp212Stp*	0	0.02
			Asp262Asn	0	0.02
			Phe267Leu	0.02	0
			Ile331Val	0.98	1
CYP3A4	21	4	Thr11Ile*	0	0.02
			Asp174His*	0.02	0
			Leu292Pro	0.02	0
			Tyr398Cys*	0.02	0
CYP3A5	0	0	---	---	---
ABC					
ABCC2	46	20	Ser8Phe	0	0.02
			Phe39Tyr	0.02	0
			Ser281Asn	0.02	0.02
			Lys295fs	0	0.02
			Val417Ile	0.26	0.4
			Lys495Glu	0.02	0
			Phe548Leu	0.02	0

Gene Symbol	# of Coding Variants (cSNPs)	# of Non-Synonymous Variants (nsSNPs)	Amino Acid Change	Frequency in High Exposure (n=53)	Frequency in Low Exposure (n=53)
			Leu849Arg	0.04	0
			Ala898Val	0.02	0
			Arg905Ile	0	0.02
			Arg911Gln	0	0.02
			Gly921Ser	0	0.02
			Gln1019His	0.02	0
			Ile1036Thr	0	0.04
			Arg1181Leu*	0.02	0
			Val1188Glu	0.15	0.09
			Pro1291Leu*	0	0.02
			Ile1359Leu	0.02	0
			Cys1515Tyr	0.15	0.09
			Gln1523Pro	0	0.02
ABCB1	30	9	Phe17Leu	0	0.02
			Asn21Asp	0.11	0.21
			Asn183Ser	0.02	0
			Ile261Val	0.02	0
			Arg262Lys	0.02	0
			Ser400Asn	0.09	0.02
			Ser893Ala	0.77	0.83
			Ser893Thr	0.02	0.02
			Ser1141Thr	0.02	0
			Glu1144Lys	0.02	0
ABCG2	19	5	Val12Met	0.13	0.06
			Asp99His*	0	0.02
			Asp115Glu	0.02	0
			Gln141Lys	0.15	0.23
			Stp459Gln*	0.02	0
SLC					
SLC10A1	15	7	Arg21Cys*	0.02	0
			Val29Ile	0.02	0
			Gln68Glu*	0.02	0
			Phe234Leu	0	0.02
			Ser255Asn*	0.02	0
			Ser267Phe	0.02	0.02
			Gly332Arg	0.02	0
SLCO1B3	31	8	Thr30Ala*	0.02	0
			Cys45Gly*	0	0.02
			Val48Ile	0	0.02
			Ser65Ala	1	0.96
			Met116Ile	1	0.96
			Gly139Ala*	0.23	0.3
			Phe276fs*	0	0.02
			Glu566Lys*	0	0.02
SLCO2B1	20	7	Pro115Ser*	0.02	0
			Arg143Leu	0.02	0
			Val201Met	0.04	0.04
			Arg306His	0	0.02
			Arg312Gln	0.3	0.26
			Ser486Phe	0.09	0.08
			Val542Met*	0.02	0.06

Gene Symbol	# of Coding Variants (cSNPs)	# of Non-Synonymous Variants (nsSNPs)	Amino Acid Change	Frequency in High Exposure (n=53)	Frequency in Low Exposure (n=53)
SLCO1B1	35	7	Asn130Asp	0.75	0.66
			Pro155Thr	0.17	0.28
			Val174Ala*	0.38	0.34
			Val235Met	0.02	0
			Ile274Met*	0.02	0
			Leu643Phe	0.06	0.09
			Phe400Leu	0.02	0

* SNPs predicted to have a deleterious effect on protein function are denoted by an asterisk.

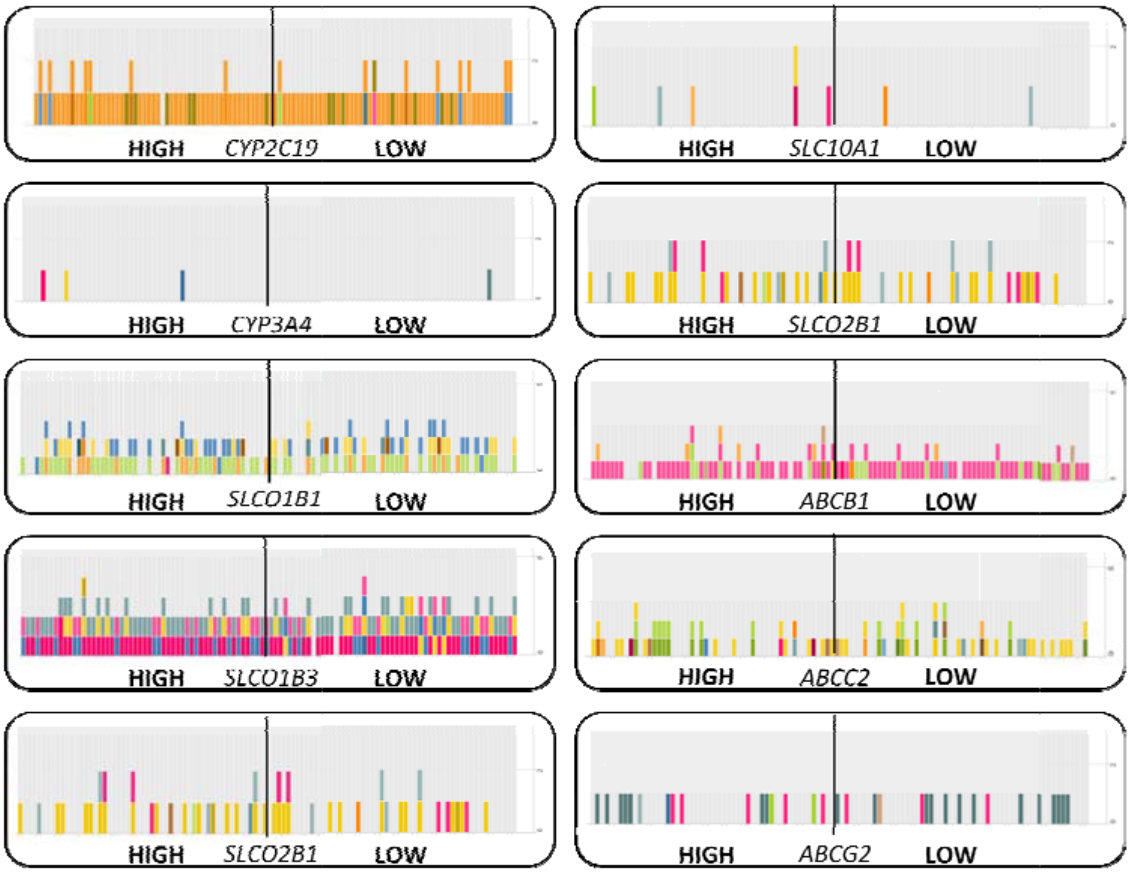


Figure 1: Graphical Representation of the Distribution of Amino Acid Variations of 10 Sequenced Genes in the Individual Subjects, Stratified by Patient Subgroups of High Versus Low Simeprevir Plasma Exposures.

In each of the graphs, each vertical bar represents one subject. Within a given gene, each amino acid changing alteration is shown as a different color. Multiple amino acid alterations in one individual are represented as stacked bars.

3.1.2 Reviewer's Analysis

Based on the raw data submitted to this application, 250 unique variants were discovered from the sequencing effort in the 10 candidate genes. This differs slightly from the sponsor's number

of 234 unique variants in that 16 of the 250 variants were outside of the actual exon but still captured by the sequencing primers. Reviewer's analysis confirmed that the frequencies of the identified variants were not significantly different between high and low simeprevir exposure groups.

The variants that resulted in amino acid changes in the protein were analyzed with the in-vitro prediction tool, SIFT, in order to ascertain the effects of the amino acid substitution on the resulting protein's function. Twenty-two of the variants were predicted by SIFT to have deleterious effects on the proteins, as denoted by the asterisk in Table 4. Analysis focusing on these variants also failed to show that deleterious variants in any gene segregated in subjects with high or low exposures (P=0.6926 Fischer's exact test) in individual dose groups or when all dose groups were combined (Table 5). Additionally, no single gene was significant when investigating the presence of a deleterious variant and its association with simeprevir exposure.

Table 5: Reviewer's Analysis of Predicted Deleterious Variants by Dose Group

	Presence of Deleterious Variant, n (%)			
Group	***All Dose Groups***	***75mg***	***100mg***	***150mg***
High	33 (52%)	4 (57%)	3 (37%)	26 (54%)
Low	30 (48%)	3 (43%)	5 (63%)	22 (46%)
	P = 0.69	*P = 1.0*	*P = 1.0*	*P = 0.49*

4 Summary and Conclusions

The sponsor submitted genetic sequencing data for several ADME related genes in an attempt to evaluate whether genetic factors contribute to the high intersubject variability observed for simeprevir pharmacokinetics in Phase 2 trial participants.

Complete exon sequence data was submitted for the following 10 ADME related genes: CYP3A4, CYP3A5, CYP2C19, SLCO1B1, SLCO1B3, SLCO2B1, SLC10A1, ABCB1, ABCC2, and ABCG2. The Applicant's analysis showed no differences in the pattern of variation between subjects in the lowest quartile of simeprevir exposure (AUC) and subjects in the highest quartile of simeprevir exposure (AUC) (i.e., genetic variants did not segregate in patients with high or low exposures).

Additional analysis conducted by the reviewer attempted to isolate the differences in only those genetic variations that were predicted in silico to have deleterious effects. The results of this analysis further supported that the presence of deleterious variants was not associated with high or low simeprevir AUC across all genes, within a gene, or for individual variants.

Based on the data provided from the sponsor, it does not appear that genetic variation within the coding regions of these genes is associated with the large PK variability of simeprevir. This is expected for CYP genes given that simeprevir undergoes limited metabolism.

Given that only the subjects in the highest and lowest quartiles of exposure were selected and

that only a select few candidate genes were screened, it is difficult to exclude that genetic variations might be associated with the observed variations in simeprevir exposure. It is possible that pharmacogenetic analyses on the entire cohort (i.e., all available pharmacokinetic data) using a high-throughput ADME genotyping platform could be used to further account for the inter-individual variability.

5 Recommendations

The pharmacogenetic analyses submitted by the applicant are acceptable from the perspective of the Genomics and Targeted Therapy Group. No additional action is required on the basis of these results. Alternative approaches (e.g., high-throughput genotyping to resolve PK differences in the entire cohort) could be pursued to identify other sources of variability not otherwise expected from in vitro studies.

5.1 Post-marketing studies

None.

5.2 Label Recommendations

None.

Physiological-based Pharmacokinetic Modeling Review Memo (Question based review)

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	NDA 205123
Drug Name	TMC435 (simeprevir)
Proposed Indication	Treatment of chronic hepatitis C, in combination with pegylated interferon (PegIFN) and ribavirin (RBV), in adults with compensated liver disease (including cirrhosis) with or without human immunodeficiency virus (HIV) co-infection.
Clinical Division	DAVP
PBPK Consult request	Leslie Chinn, Ph.D.
Primary PBPK Reviewer	Yuzhuo Pan, Ph.D.
Secondary PBPK Reviewer	Ping Zhao, Ph.D
Sponsor	JANSSEN RESEARCH AND DEVELOPMENT LLC

1. Objectives

To review Sponsor's physiologically-based pharmacokinetic (PBPK) report entitled "Simeprevir (NDA-205123) study report: Physiologically Based Pharmacokinetic Simulations for TMC435 in human subjects" [1] in NDA205123.

2. Background

2.1. Regulatory history on PBPK submission

Simeprevir (TMC435) is a NS3/4A proteinase inhibitor being developed for treatment of chronic hepatitis C virus infection. A PBPK model was developed by the sponsor as part of the NDA submission to "simulate drug-drug interaction with simeprevir as victim drug, and PK difference between healthy subjects and HCV infected patients, to understand the variability and ethnicity difference in PK of simeprevir, and the key drivers of non- linear pharmacokinetics (PK) in function of dose and time of simeprevir" [1]. After initial review of the report, an information request (IR) was sent to the sponsor on April 29, 2013 (See appendix 1.1 on IR). On May 9, 2013, sponsor submitted additional information according to the information request [2].]. On August 21, 2013, the review team sent the second IR to

the sponsor after reviewing their response to FDA's post mid-cycle comments (see appendix 1.2 on IR). On August 23, sponsor submitted additional information according to the second IR [3].

Highlight of drug absorption and disposition

Simeprevir demonstrated dose- and time-dependent nonlinear pharmacokinetics in humans. At lower doses, simeprevir has an absolute bioavailability (F_{abs}) of 46% in humans [4]. The rate of absorption does not seem to be influenced by the dose [5]. The mass-balance study results showed the majority of simeprevir was absorbed after oral administration (fa =0.9). TMC 435 is extensively bound to human plasma proteins (>99.9%), mainly to albumin. The blood to plasma ratio of simeprevir was time-independent, with a mean value of 0.7. In vitro, simeprevir is a substrate of the hepatic uptake transporters organic anion transporting polypeptide (OATP)1B1/3, and the process was saturable. This active uptake process is a major mechanism for the distribution of simeprevir into the liver, and likely contributes to the nonlinear pharmacokinetics (PK). In vitro and in vivo metabolism studies showed that simeprevir was subject primarily to oxidative metabolism. In vitro simeprevir metabolism was mainly catalyzed by CYP3A, which may also be saturable and contribute to the observed nonlinear PK [3]. Simeprevir is predominantly excreted in feces (91%). Renal excretion of simeprevir is negligible (≤0.2%).

Questions addressed by the submitted PBPK modeling report and additional information requested by OCP include:

1. What are the major mechanisms contributing to non- linear pharmacokinetics of simeprevir?
2. Can drug-drug interaction with simeprevir be predicted?

In addition, sponsor simulated PK of simeprevir in various specific populations and projected liver concentrations of simeprevir in Caucasian and Asian HCV subjects.

3. Methods

SimCYP® (V12, Sheffield, UK) [4-6] was used to construct and verify PBPK model. Final model parameters and their sources are summarized in Appendix Table 1. Key assumptions of sponsor's model are:

- Volume of distribution largely depends on the permeability limited liver distribution of simeprevir, and the active uptake via OATP1B1/3 transporters is saturable
- exclusive metabolism by CYP3A4, and the process is saturable

PBPK modeling of simeprevir followed three steps:

1. Model building: in vitro metabolism and uptake data, clinical PK data after single and multiple dose of simeprevir in healthy Caucasian subjects (clinical study simeprevir-C116) were used. Dose and time-dependent nonlinear PK data were used to refine simeprevir regarding saturation of OATP1B1/3 and CYP3A4
2. Model Verification: Clinical DDI data (coadministration with ritonavir, daurunavir/ritonavir, Efavirenz, Erythromycin, or Rifampin)
3. Model Prediction:
   After model verification, sponsor used the model to predict the effect of rifampin on simeprevir PK on the first day of co-administration of both drugs. Sponsor also conducted simulations to evaluate variability and ethnicity difference in PK of simeprevir in Caucasian, Japanese and Chinese Populations. In addition, FDA reviewers used

sponsor's models to predict the effect of other CYP3A inhibitors. Inhibitor model of ketoconazole in PBPK software's drug library was directly used. The model for a weak CYP3A4 inhibitor fluvoxamine was developed by the sponsor (b) (4)

4. Results (Question-based review)

4.1. What are the major mechanisms contributing to non- linear PK of semiprevir?

Using PBPK model incorporating a saturable distribution via hepatic uptake transporters OATP1B1/1B3 into the liver, and a saturable metabolism by CYP3A4, sponsor simulated simeprevir PK profiles that were comparable to the observed data after single and multiple doses of simeprevir (Figures 1A and 1B). These mechanisms of nonlinear PK are further confirmed during the model verification process using drug-drug interaction data (see 4.2 below).

4.2. Can drug-drug interaction with simeprevir as a victim drug be predicted?

Yes. As part of the PBPK model verification process, the following interactions were simulated and compared to clinical data from drug-drug interaction studies in healthy subjects (Table 2):

a. CYP3A4 interactions without impact on hepatic uptake

Ritonavir at 100 mg once daily or twice daily potently inhibits intestinal and hepatic CYP3A4, but does not inhibit hepatic OATPs. When single oral dose (200 mg) of simeprevir was given with ritonavir (100 mg twice daily for 3 days), simeprevir AUC increased by 1.8-fold. When simeprevir (200 mg once-daily) was coadministered with ritonavir (100 mg twice daily) for 7 days, simeprevir AUC on day 7 increased by 7.2 fold. This time-dependent phenomenon was largely captured by the PBPK simulations (2.1 and 10.0-fold for single dose and multiple doses of simeprevir, respectively). It appears that inhibition of hepatic CYP3A4 metabolism augments the saturation of hepatic uptake of simeprevir, resulting in greater drug accumulation in systemic circulation after multiple dosing of both drugs.

Similarly, erythromycin is a moderate inhibitor of CYP3A4, but it does not inhibit hepatic OATPs. When simeprevir (150 mg once-daily) was coadministered with erythromycin (at 500 mg three times a day) for 7 days, simeprevir AUC on day 7 increased by 7.5-fold, a magnitude much higher than that observed for single dose of simeprevir with a strong CYP3A4 inhibitor ritonavir (2.1 fold, see above). Simulation of the effect of erythromycin on single dose of simeprevir, a condition not tested clinically, showed a 41% increase in simeprevir AUC, a magnitude consistent with the effect of erythromycin as a moderate CYP3A inhibitor.

b. OATP interactions with minimal impact on metabolism

Cyclosporine at 100 mg is an inhibitor of hepatic OATPs. After multiple dosing of simeprevir (150 mg once daily) and a single dose of cyclosporine (100 mg on day 7), exposure change of simeprevir was measured by comparing trough concentrations (Cmin) on day 7 versus trough concentration on day 6. The model simulated and observed Cmin ratios were 1.3 and 1.2, respectively. Sponsor conducted a cross-study comparison of mean Cmax values observed in the absence and in the presence of cyclosporine [1]. The

observed and model simulated Cmax ratios were 1.5 and 1.4, respectively. It is likely that after multiple dosing of simeprevir, OATP saturation becomes dominant as compared to the effect by an OATP inhibitor.

c. Combined OATP and CYP3A4 interactions

Rifampicin is a potent inhibitor of hepatic OATPs and a potent inducer of liver and intestinal CYP3A4. The interplay between hepatic uptake and CYP3A4 metabolism constructed in simeprevir PBPK model was further verified by simulations of rifampicin-simeprevir interaction. After multiple dosing of simeprevir (200 mg for 7 days) and rifampicin (600 mg once daily for 7 days), a modest decrease in simeprevir AUC was observed (48% reduction). This magnitude is similar to the value observed using a moderate/weak CYP3A4 inducer efavirenz that does not affect OATP transporters (after 14 days once-daily dosing of 150 mg simeprevir and 600 mg efavirenz, the AUC of simeprevir decreased by 51%). The modest decrease of simeprevir exposure when the drug was coadminstered with rifampicin is likely due to the concurrent inhibition of hepatic uptake by rifampicin. Efavirenz not only decreased simeprevir AUC but also significantly decreased its Cmax (by 71%), whereas rifampicin increased simeprevir Cmax by about 30%. Therefore, inhibition of hepatic uptake of simeprevir by rifampicin appeared to have masked the impact of the potent CYP3A4 induction by rifampicin. These findings on both AUC ratios and Cmax ratios were generally captured by the PBPK simulations (Table 1).

d. Prediction of untested drug-drug interaction scenarios

Besides different dosing regimens of the above mentioned drug-drug interaction pairs (such as the effect of erythromycin and rifampicin on single dose simeprevir, Table 1), the reviewer also simulated the effect of strong reversible CYP3A inhibitor ketoconazole, a weak CYP3A4 inhibitor fluvoxamine, and a non-inhibitor raltegrevir on the exposure of simeprevir using sponsor's PBPK models. The results are shown in Table 1. The predicted effect on single and multiple dose simeprevir exposure by ketoconazole is similar to that of ritonavir. The predicted effect on simeprevir PK by fluvoxamine appears minimal. Raltegrevir is predicted to have no effect on simeprevir after multiple dosing of both drugs.

Taking questions 1 and 2 together, saturation of hepatic uptake (via OATP transporters) and metabolism (via CYP3A4) appears to be the plausible explanation of the observed nonlinear PK of simeprevir. The established PBPK model considering saturable hepatic uptake reasonably predicted drug-drug interaction potential by different CYP3A4 and/or OATP modulators.

4.3. Predicting simeprevir PK in specific populations

The observed AUC increase from healthy subjects to HCV infected subjects in clinical trials was approximately 2.5-fold. Sponsor's PBPK model used software's built-in mild hepatic impairment population ("Child-Pugh A") [9] to represent HCV population characteristics, where numbers of functional hepatocytes and expression of CYP enzymes are different from that of the healthy subjects. The predicted AUC increase from healthy subjects to HCV subjects was 2.8-fold [1].

The observed AUC increase from Caucasians to Asian populations was about 2-fold. This may be largely explained by the known demographic differences between the two populations recently described by Barter and colleagues [10], including a smaller liver volume and the slightly lower CYP3A4 abundance in Chinese population. Simulations in healthy Chinese

subjects showed a 2.2-fold higher steady state mean simeprevir exposure after 100 mg q.d. dosing versus healthy Caucasian subjects. In responding to FDA's Mid-Cycle comments on the use of lower doses (e.g., 100 mg q.d.) in Asian HCV patients, sponsor suggested that in Asian patients, a dose of 100 mg q.d. may significantly decrease liver concentrations compared to the 150 mg q.d. dose, thereby reducing efficacy. FDA sent second PBPK IR (08212013) and asked sponsor to simulate simeprevir liver concentrations in the HCV-infected Caucasian, Chinese and Japanese patients following administration of 100 mg q.d. and 150 mg q.d. for 3 weeks [3]. Simulation results showed that the geometric mean total liver AUC at steady state after 3 weeks of 100 mg simeprevir q.d. in Chinese and Japanese HCV subjects were 1,920 mg*h/mL and 1,460 mg*h/mL, respectively. These values are comparable to the simulated geometric mean total liver AUC at steady state after 3 weeks of 150 mg simeprevir q.d. in Caucasians (1,919 mg*h/mL).

The sponsor also simulated exposure increase in subjects with severe hepatic impairment. In clinical study, the exposure (AUC_{24h}) of simeprevir at doses of 150 mg q.d. was higher in subjects with moderate or severe hepatic impairment compared with healthy subjects with normal hepatic function (2.4- or 5.2-fold higher, respectively). Sponsor's simulation using software built-in virtual populations ("Child-Pugh C" [9]) predicted 17.5 fold increase in simeprevir exposure, compared to healthy subjects. The significant over-prediction of exposure in severe hepatic impairment patients is consistent with sponsor's in-house experiences with other investigational drugs [2].

5. Conclusion

Sponsor's PBPK modeling and simulation reasonably captured non-linear pharmacokinetics of simeprevir. Saturation of OATP transporter mediated drug distribution into the liver and saturation of CYP3A4 metabolism together appear to be the plausible mechanisms contributing to the nonlinear PK and differential effects of CYP3A4 and/or OATP modulators observed in the drug-drug interaction studies. The model can be used to predict other untested drug-interaction situations and to evaluate the effect of various intrinsic factors (e.g., ethnicity, liver disease) on simeprevir exposure.

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Table 1. PBPK model simulated and observed exposure changes of simeprevir by different enzyme and/or transporter inhibitors and inducers

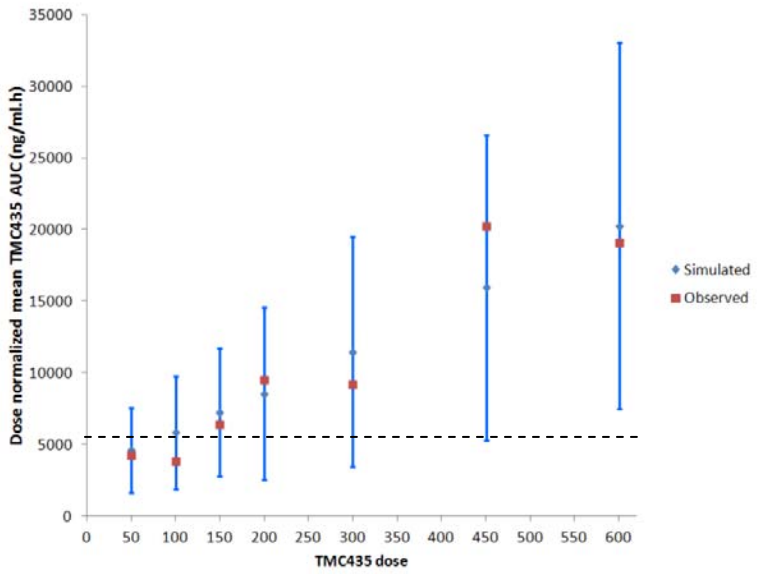
Inhibitor / inducer (mechanisms)	TMC435 dose	AUC (Cmax) ratio		Explanation of observed DDI findings
		Sim.	Obs.	
Ritonavir (Strong CYP3A inhibitor)	Single	**2.1 (1.3)**	**1.8 (1.3)**	CYP3A inhibition augmented OATP saturation over time
	Multiple	**10 (5.8)**	**7.2 (4.7)**	
Erythromycin (moderate CYP3A inhibitor)	Single	**1.4 (1.1)**	-	Time-dependent DDI potential similar to ritonavir: augmenting OATP saturation after multiple dosing
	Multiple	**6.2 (3.7)**	**7.5 (4.5)**	
Cyclosporine (OATP inhibitor)	Multiple	**1.3** (Cmin ratio)	**1.2** (Cmin ratio)	OATP saturation after multiple dosing diminished inhibitor effect
Rifampin (Strong CYP3A inducer, OATP inhibitor)	Single	**2.1 (1.8)**	-	OATP inhibition + CYP3A4 induction: ↑ Cmax and ↓AUC of simeprevir
	Multiple	**0.6 (1.1)**	**0.5 (1.3)**	
Efavirenz (Moderate CYP3A inducer)	Multiple	**0.3 (0.6)**	**0.5 (0.3)**	CYP3A induction only, no effect on OATP

Table 2. PBPK model predicted exposure changes of simeprevir by ketoconazole, fluvoxamine and raltegrevir (FDA analysis using sponsor's models. "Population Representative" was used for simulations)

Inhibitor / inducer (Mechanism)	TMC435 Dose	AUC(Cmax) ratio		Notes
		Sim.	Obs.	
Ketoconazole (Strong CYP3A inhibitor)	Single	2.3 (1.3)	-	Time-dependent DDI potential similar to ritonavir: augmenting OATP saturation after multiple dosing
	Multiple	8.5 (4.5)	-	
Fluvoxamine (weak CYP3A inhibitor)	Single	1.2 (1.1)	-	Minimal effect of simeprevir PK
	Multiple	1.3 (1.1)	-	
Raltegravir (does not inhibit CYP3A4 and OATP)	Single	1.0 (1.0)	0.9 (0.9)	No inhibition on CYP3A4 and OATP
	Multiple	1.0 (1.0)	-	

Figure 1. Observed and PBPK model simulated dose-normalized simeprevir (TMC-435) AUC in healthy volunteers. (A) AUC after single dose simeprevir (Figure 10 from sponsor's PBPK report). (B) AUC0-24 hr on the last day of once-daily doses of simeprevir for 5-7 days (Figure 17 from sponsor's PBPK report). Dotted lines represent dose normalized AUC expected from the lowest dose under linear PK assumption.

A



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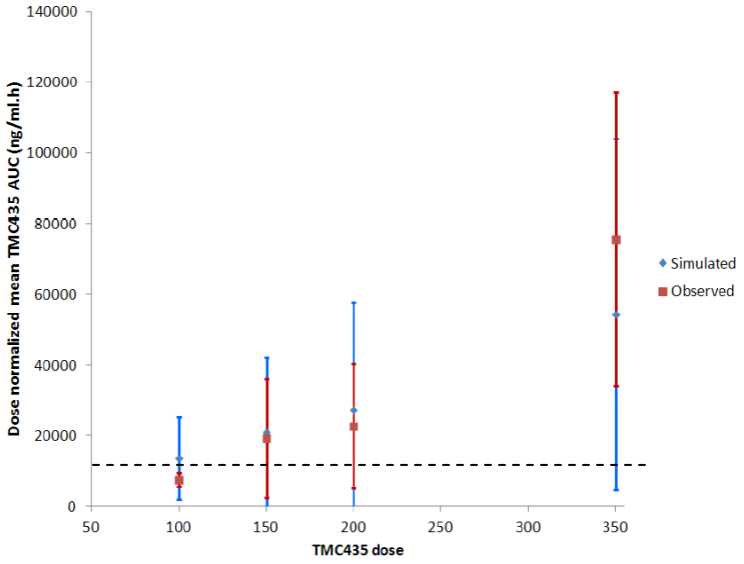

6. Appendices

Appendix 1. Information Request-Clinical Pharmacology

1.1 Information Request (04292013)

1. Please provide adequate justification for the exclusion of P-gp in the final PBPK model.

Such justification may include the results of simulations of drug-drug interactions (e.g. cyclosporine) that suggest similar simeprevir pharmacokinetics regardless of whether or not the PBPK model incorporated P-gp.

2. Please provide pharmacokinetic profiles of simeprevir in the following populations:

a. HCV-infected Asian patients;

b. HCV-infected Asian patients with severe hepatic impairment; and

c. HCV-infected Caucasian patients with severe hepatic impairment.

These profiles may be based on data from relevant clinical trials and/or predicted using PBPK modeling and simulation.

3. Please provide the files used to generate the final PBPK simulations (e.g. drug model files, population files, and workspace files). These files may be submitted via CD.

Please provide a response by COB, Monday, May 13, 2013.

1.2 Information Request (08202013)

You suggest that in Asian patients, a dose of 100 mg QD may significantly decrease liver concentrations compared to the 150 mg QD dose, thereby reducing efficacy. Please conduct deterministic simulations of simeprevir liver concentrations at steady state using your PBPK model in:

• HCV-infected Asian patients following administration of 100 mg QD and 150 mg QD.

• HCV-infected Caucasian patients following administration of 100 mg QD and 150mg QD

These simulations will support further review of simeprevir dose selection in Asian patients but may not be sufficient to fully alleviate the Division's concerns regarding the safety of the 150 mg dose in this population.

Please provide a response by COB, Friday, August 23, 2013.

Appendix 2. PBPK model information

Appendix Table 1. Input parameters of simeprevir for PBPK model using SimCYP (V12)

Parameters (units)	*simeprevir*	*Source*
Physicochemical Properties		
Molecular weight (g/mol)	749.94	Investigator's Brochure
Log P	3.79	Log D ranged between 3.79 and 5.37 between pH 2 and pH7.
Compound type	Ampholyte	Investigator's Brochure
pKa1, pKa2	5.24, 2.85	Investigator's Brochure
Fraction unbound in plasma	0.001	Measured
Blood/plasma ratio		Limited distribution to blood assumed
Absorption (First-order kinetics)		
Fraction absorbed	0.9	Human mass balance study
ka (hr^{-1})	0.6	Compartmental modeling
$F_{u,Gut}$	1	Assumed
Lag time (hr)	1	PK study C105.
Distribution (full PBPK)		[12,13]
Liver Kp (tissue/plasma unbound concentration ratio)	dynamic	See permeability liver model below
Heart Kps	1	Animal study
Elimination		almost exclusively metabolized by CYP3A4.
CYP3A4 Vmax (pmol/min/pmol CYP)	0.046	hepatocyte data, further optimized according to nonlinear PK data [1]
CYP3A4 Km,unbound (μM)	0.010	hepatocyte data, further optimized according to nonlinear PK data [1]
Biliary intrinsic clearance (μL/min/million cells)	18	Retrograde calculation based on massbalance data [1]
CLr (L/h)	0	Human mass balance data
Transport in permeability-limited liver model		
Lpd: passive diffusion (mL/min/million cells)	2	Hepatocyte experiment, optimized using nonlinear PK data. Further discussion see [1]
Fuew – fraction unbound (extracellular water)	0.001	
Fuiw – fraction unbound (intracellular water)	0.0001	
OATP1B1 Km,unbound (μM)	0.003	Hepatic uptake experiments using
OATP1B3 Km,unbound (μM)	0.003	primary human hepatocytes, HEK293
OATP1B1 Jmax (pmol/min/million cells)	12.27	expressed cell systems, using positive
OATP1B3 Jmax (pmol/min/million cells)	17.73	control substrates. Further discussion see [1]

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CLINICAL PHARMACOLOGY *in-vitro* STUDY REVIEW				
Study #	TMC435350-TiDP16-NC111	**Report date**	09/20/2006	EDR Link
Title	The protein binding of TMC435350 in plasma from animals and man			

STUDY DESIGN	
Objectives	To obtain information on the protein binding of TMC435350 in plasma of man, monkeys, dogs, rabbits, rats and mice.
Methods	The protein binding of TMC435350 was determined by equilibrium dialysis. The blank plasma samples of the various species were fortified with TMC435350 at final concentrations of 50, 200, 500 or 2500 ng/ml (human) and 200 or 20000 ng/ml (animals). The fortified plasma samples were subjected to equilibrium dialysis against 0.067 M phosphate buffer, pH 7.17, at 37°C for 4h in a Dianorm system with identical macro-1 Teflon cells and Diachema 10.17 dialysis membranes (MW cut-off of 10 000). The dialysis was performed in duplicate in two individuals (monkeys, dogs, man) or in pools (rabbits, rat, mice). The protein binding of TMC435350 to purified human α1-acid glycoprotein and purified human serum albumin was determined by equilibrium dialysis. Purified human α1-acid glycoprotein was dissolved in 0.067 M phosphate buffer pH 7.4 at concentrations of 0.20, 0.15, 0.10, 0.05 and 0.02 % (w/v). Purified human serum albumin was dissolved in 0.067 M phosphate buffer pH 7.4 at concentrations of 0.10, 0.25, 0.50, 1.00, 2.00, 4.30 and 6.00 % (w/v). The obtained protein solutions were fortified with TMC435350 at 2000 ng/ml. The fraction of the unbound test compounds (fu) was calculated as the ratio of the unbound concentrations (Cu) in the buffer compartment to the total concentrations (CED) in the plasma compartment of the dialysis cells (Formula: fu = Cu/ CED). The bound fractions were calculated as fb = 1 - fu. The percentages of the free and bound test compounds were calculated as fu x 100, and fb x 100, respectively.

STUDY RESULTS

The plasma protein binding of TMC435350 was very high in all tested species.
At 200 ng/ml: >99.32% in male cynomolgus monkey, >98.76% in New Zealand White rabbit, >99.35% in male Beagle dog, >99.25% in male Sprague-Dawley rat, >99.26% in female Sprague-Dawley rat, >99.24% in male Swiss-CD1 mouse and in >99.40% in female Swiss-CD1 mouse.
At 20,000 ng/ml, 99.97% in male cynomolgus monkey, >99.99% in New Zealand White rabbit, >99.99 in male Beagle dog, >99.99% in male Sprague-Dawley rat, 99.99% in female Sprague-Dawley rat, >99.99% in male Swiss-CD1 mouse and in 99.99% in female Swiss-CD1 mouse.
The plasma protein binding of TMC435350 in healthy male subjects was >97.22%, >99.25%, >99.69% and >99.94 at 50, 200, 500 and 2500 ng/ml, respectively.

The protein binding of TMC435350 at 2000 ng/ml to human serum albumin at a physiological concentration amount to 99.93%. No conclusive results were obtained for binding to human α1-acid glycoprotein.

CONCLUSIONS

TMC435350 is highly plasma protein bound in all species tested.

CLINICAL PHARMACOLOGY *in-vitro* STUDY REVIEW				
Study #	TMC435350-TiDP16-NC202	**Report date**	04/08/2008	EDR Link
Title	The protein binding of ^{3}H-TMC435350 in plasma from animals and man			

STUDY DESIGN	
Objectives	To obtain information on the protein binding of TMC435350 in plasma of man, monkeys, dogs, rabbits, rats and mice.
Methods	The protein binding of ^{3}H-TMC435350 was determined by equilibrium dialysis.

STUDY RESULTS

Free fractions of TMC435350 after equilibrium dialysis ranged from 0.16% to 0.20% for mouse, rat and rabbit, between 0.08% and 0.10% for dog and monkey at 200 and 20000 ng/ml of TMC435350.

Free fractions of TMC435350 after equilibrium dialysis ranged from 0.07% to 0.09% for male human at 200, 2000 and 10000 ng/ml of TMC425350.

TMC435350 was preferentially bound to purified serum albumin.

CONCLUSIONS

TMC435350 is highly plasma protein bound in all species tested.

CLINICAL PHARMACOLOGY *IN VITRO* STUDY REVIEW				
Study #	NC116 (FK5911)	**Report date**	27 Oct 2006	EDR Link
Title	An in vitro study to determine the kinetics of TMC435 metabolism in human liver microsomes, and to identify the microsomal cytochrome P450 iso-enzymes mediating TMC435 metabolism (reaction phenotyping)			

STUDY DESIGN	
Objectives	To identify the CYP enzymes involved in Phase 1 metabolism of TMC435
Methods	The CYP metabolism of TMC435 was evaluated in 1) pooled human liver microsomes (TMC435 1-150 uM, 0.25 mg/mL protein, 15 min incubation) using CYP-specific inhibitors (15 uM TMC435, 0.25 mg/mL protein, 15 min incubation; Table 1); 2) heterologously expressed CYP systems (Supersomes®; 15 uM TMC435, 100 pmol/mL protein, 60 min incubation); 3) a panel of human liver microsomes in which the rate of metabolite formation was correlated with the CYP isoenzyme-specific activities of the microsomes (15 uM TMC435, 0.25 mg/mL protein, 15 min incubation).

Table 1. CYP-specific inhibitors used to evaluate isoenzyme-specific metabolism in HLMs

Diagnostic inhibitor	Batch/Ref No:	Formulat. conc. (mM)	Final conc. incubation (µM)	Main CYP inhibited
Furafylline* (R110937)	EXTE_0201_295_1	2	10	CYP1A2
Tranylcypromine (R003041)	EXTE_0001_962_1	1	5	CYP2A6
8-methoxypsoralen* (R102745)	EXTE_0001_548_1	1	5	CYP2A6
Triethylenethiophosphoramide* (ThioTEPA; R600147))	EXTE_0201_347_1	10	50	CYP2B6
Montelukast (R206728)	EXTE_0201_318_1	1	5	CYP2C8
Quercetin (R061040)	EXTE_0201_343_1	20	100	CYP2C8
Sulphaphenazole (R110938)	EXTE_001_797_4	2	10	CYP2C9
3-Benzyl-phenobarbital (R312426)	BJVE_0006_069_4	2	10	CYP2C19
Ticlopidine HCl (R046266)	EXTE_001_945_3	1	5	CYP2C19/D6
Quinidine sulphate (R013010)	EXTE_0001_582_1	2	10	CYP2D6
Diethyldithiocarbamate* (R108631)	EXTE_0001_765_1	20	100	CYP2E1
Ketoconazole (R041400)	ZR041400PUF551	0.2	1	CYP3A4
Troleandomycin* (R082013)	EXTE_0001_596_1	40	200	CYP3A4
Clarithromycin* (R101296)	EXTE_0101_474_4	3	15	CYP3A
1-aminobenzotriazole	Sigma: 063K3492	200	1000	CYP P450

* mechanism based inhibitors (were incubated for 15 min, prior to the addition of TMC435350 formulation).

STUDY RESULTS
In vitro, the major TMC435 metabolites were identified as 18, 23, and 25; formation of these metabolites was maximally inhibited by the CYP3A4 inhibitors ketoconazole and troleandomycin, and to a lesser extent by the CYP3A inhibitor clarithromycin. The CYP2C8 inhibitors montelukast and quercetin, the CYP2B6 inhibitor thioTEPA, and the CYP2E1 inhibitor diethyldithiocarbamate also provided modest inhibition of metabolite formation.
Table 2. Effect of CYP-specific inhibitors on metabolism of TMC435 to M18, M23, and M25 om J:<s

Diagnostic Inhibitor	CYP isoform	% Inhibition of Metabolism [1] M18	M23	M25
Furafyllin	CYP1A2	11	14	3
8-Methoxypsoralen	CYP2A6	39	44	36
Tranylcypromin	CYP2A6	-6 [2]	27	-3
ThioTEPA	CYP2B6	70	57	39
Ticlopidin	CYP2B6/2C19	15	10	14
Montelukast	CYP2C8	66	52	46
Quercetin	CYP2C8	100	25	41
Sulphaphenazole	CYP2C9	-1	8	6
3-benzylphenobarbital	CYP2C19	28	32	30
Quinidin	CYP2D6	16	23	17
Diethyldithiocarbamate	CYP2E1	66	57	49
Ketoconazole	CYP3A4	100	100	100
Troleandomycin	CYP3A4	100	100	100
Clarithromycin	CYP3A	100	89	75
1-Aminobenzotriazole	CYP450	100	100	100

Additional Information
1. Calculated from control incubation (without inhibitor).
2. Negative values indicates higher % product formation in test sample compared to the control. For all qualitative purposes, all negative values were considered as no inhibition.

In Supersomes®, overall metabolism of TMC435 was primarily catalyzed by CYP3A4, 3A5, and 3A7. Some metabolism was observed with CYP1A2, CYP2A6, and CYP2B6, and marginal metabolism was observed with CYP2C9, CYP2C19, CYP2D6, and CYP2E1.

Table 3. Formation rate of M18, M23, and M25 in Supersomes®

Cytochrome P-450 Form (100 pmol/ml)	Overall % Metabolism[1]	Product formation rate (% formed) M18	M23	M25
CYP1A2	1.12 ± 0.47	-[2]	-	-
CYP2A6	2.12 ± 1.59	-	-	-
CYP2B6	1.08 ± 0.44	-	-	-
CYP2C8	5.86 ± 2.95	-	-	-
CYP2C9	0.58 ± 0.71	-	-	-
CYP2C19	0.60 ± 0.11	-	-	
CYP2D6	0.71 ± 1.13	-	-	-
CYP2E1	0.70 ± 1.07	-	-	-
CYP3A4	33.67 ± 2.78	1.63 ± 0.06	4.33 ± 0.12	9.47 ± 0.06
CYP3A5	11.83 ± 3.74	-	3.40 ± 0.96	6.27 ± 2.05
CYP3A7	3.38 ± 1.47	-	1.47 ± 0.40	1.17 ± 0.32

Additional Information
1. Overall % metabolism of TMC435350 calculated from % drug remained in the sample at the end of the incubation
2. No measurable product observed in UV-HPLC profile.

In HLMs, overall metabolism of TMC was primarily correlated with CYP3A-catalyzed midazolam and cyclosporine metabolism (in particular metabolite 18), although there were also correlations with CYP4A-catalyzed lauric acid metabolism, CYP2E1-catalyzed chlorozoxazone metabolism, and CYP2C8-catalyzed taxol metabolism.

Table 4. Correlation analysis of TMC435 metabolite formation with CYP isoform activity

Enzyme activities (CYP isoform)	Overall TMC435350 metabolism Correlation (r^2)	TMC435350 Metabolites Correlation coefficient (r^2)		
		M18	M23	M25
7-ethoxyresorufine *O*-dethylase (**1A2**)	-0.086	-0.207	-0.092	-0.312
Phenacetin *O*-dethylase (**1A2**)	0.134	-0.223	-0.178	-0.274
Coumarin 7-hydroxylase (**2A6**)	-0.048	-0.555	-0.352	-0.049
Taxol 6-α-hydroxylase (**2C8**)	0.307	-0.060	-0.107	-0.278
Tolbutamide methyl hydroxylase (**2C9,10**)	0.057	-0.357	-0.412	-0.574
S-mephenytoin 4-hydroxylase (**2C19**)	-0.600	0.567	0.630	**0.743** [1]
Dextromethorphan *O*-demethylase (**2D6**)	0.131	0.196	0.047	-0.131
Bufuralol hydroxylase (**2D6**)	0.228	0.159	0.040	-0.121
Chlorozoxazone 6-hydroxylase (**2E1**)	0.560	0.181	0.010	0.208
Lauric acid (ω-1)-hydroxylase (**2E1**)	0.156	-0.123	-0.306	-0.412
Testosterone 6-β-hydroxylase (**3A4**)	0.250	**0.924**	**0.809**	**0.786**
Cyclosporine oxidase (**3A**)	0.407	**0.868**	**0.739**	**0.876**
Taxol 3'-hydroxylase (**3A4**)	0.011	**0.717**	0.651	**0.745**
Midazolam 4-hydroxylase (**3A4/A5**)	0.371	**0.909**	**0.865**	**0.826**
Midazolam 1'-hydroxylase (**3A5/A4**)	0.452	**0.855**	**0.774**	**0.803**
Lauric acid ω-hydroxylase (**4A**)	0.608	0.103	0.116	0.111

Additional Information

1. Bolded numbers: Positive correlations higher than 0.700

CONCLUSIONS

The CYP3A enzymes are the primary enzymes involved in TMC435 metabolism, with possible involvement of CYP2C8 and CYP2C19.

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY *in-vitro* STUDY REVIEW				
Study #	TMC435350- TiDP16-NC117 (FK5924)	**Report date**	10/13/2006	EDR Link
Title	An *in-vitro* study on the direct inhibition of the metabolism of cytochrome P-450 (CYP) probe substrates by TMC435350			

STUDY DESIGN

Objectives

To investigate the potential for inhibition of human CYP by TMC435350 by the determination of the IC_{50}-values in human liver microsomes and by comparison to positive control inhibitors.

Methods

The effect of TMC435350 on the diagnostic CYP probe substrates was studied in pooled batches of human liver microsomes in presence of different concentrations of TMC435350. The incubations were performed in triplicate in the following conditions.

Table 1: Incubation conditions for determination of the metabolism of specific CYP substrates in human liver microsomes.

CYP P-450 Substrate	Human CYP-form	Substrate concentration (µM)	Protein concentration (mg/ml)	Incubation time (min)	Incubation volume (ml)	Analytical method
Phenacetin	CYP1A2	100	0.5	15	1	LC-MSMS
Coumarin	CYP2A6	50	0.1	10	1	Fluorimetric
S-Mephenytoin	CYP2C19	100	0.5	30	0.5	LC-MSMS
Tolbutamide	CYP2C8,9,10	100	1.0	30	0.5	LC-MSMS
Dextromethorphan	CYP2D6	3	0.2	20	0.25	LC-MSMS
Chlorzoxazone	CYP2E1	50	0.5	20	1	LC-MSMS
Testosterone	CYP3A4	100	0.5	25	0.5	LC-MSMS
Paclitaxel	CYP2C8	25	0.5	20	1	LC-UV
Midazolam	CYP3A4/5	50	0.5	10	1	LC-MSMS
Midazolam	CYP3A4/5	2	0.5	10	1	LC-MSMS
Lauric acid	CYP2E1	100	1	10	1	Radio-HPLC

Final inhibitory concentrations of TMC435350 of 0, 0.3, 1, 3, 10, 30, 100, and 300 µM except for testosterone (0, 0.3, 1, 3, 10, 30 and 40 µM) and chlorzoxazone (0, 0.3, 1, 3, 10 and 20 µM) were tested. IC_{50}-values were determined from the linear part of a plot of the percentage of inhibition against the logarithm of the inhibitor concentration using linear regression analysis.

STUDY RESULTS

CYP IC_{50}-values of TMC435350 in human liver microsomes

Table 2: The interaction of TMC435350 with the metabolism of a number of specific CYP substrates investigated *in vitro* in pooled batches of human liver microsomes.

Substrate	I_{50}-values	
	µM (or % inhibition at highest concentration tested)	µg/ml (or % inhibition at highest concentration tested)
Phenacetin (CYP1A2) **phenacetin *O*-deethylation**	> 300 (28.0)	> 225 (28.0)
Coumarin (CYP2A6) **coumarin 7-hydroxylation**	59.7	44.8
Tolbutamide (CYP2C8/9/10) **tolbutamide 4-hydroxylation**	> 300 (46.5)	> 225 (46.5)
S-Mephenytoin (CYP2C19) **S-mephenytoin 4-hydroxylation (HH-DE-V)**	86.1	64.6
Dextromethorphan (CYP2D6) **dextrorphan**	42.9	32.2
Chlorzoxazone (CYP2E1) **chlorzoxazone 6-hydroxylation**	> 20 (0)	> 15.0 (0)
Paclitaxel (CYP2C8) **paclitaxel 6α-hydroxylation**	49.1	36.8
Testosterone (CYP3A4) **6β-hydroxy-testosterone formation**	> 40 (6.96)	> 30.0 (6.96)
Midazolam		
4-OH midazolam formation (CYP3A4/5) (2 µM)	152.8	114.6
1'-OH midazolam formation (CYP3A4/**5**) (2 µM)	84.5	63.4
4-OH midazolam formation (CYP3A4/5) (50µM)	154.6	116
1'-OH midazolam formation (CYP3A4/**5**) (50µM)	132.8	99.6
Lauric acid		
ω-hydroxylated acids (CYP4A)	> 300 (36.4)	> 225 (36.4)
(ω-1)-hydroxylated acids (CYP2E1)	> 300 (46.3)	> 225 (46.3)

CONCLUSIONS

In the human liver microsomes, inhibition of CYP2D6, CYP2C8 and CYP2A6 by TMC435350 was observed with IC_{50}-values ranging between 32.2 µg/ml and 44.8 µg/ml. Inhibition of CYP2C19 and CYP3A by TMC435350 was observed with IC_{50}-values of 64.6 µg/ml and 98.4 µg/ml, respectively. Given that the mean steady-state simeprevir (TMC435350) C_{max} is predicted to be approximately 4.2 µg/mL following oral administration of simeprevir 150 mg QD, TMC435350 is a moderate inhibitor of CYP2D6, CYP 2C8 and CYP2A6 and a weak inhibitor of CYP2C19 and 3A *in vitro*.

CLINICAL PHARMACOLOGY *in-vitro* STUDY REVIEW				
Study #	TMC435350-TiDP16-NC121 (FK6276)	**Report date**	27/06/2007	EDR Link
Title	An *in vitro* study to assess the potential of TMC435350 to induce CYP enzyme activities in cryopreserved human hepatocytes			

STUDY DESIGN

Objectives

To determine the potential of TMC435350 to induce CYP1A2 and CYP3A4 in cryopreserved human hepatocyte cultures, originating from 3 different donors.

Methods

Human hepatocytes were treated for 48 hours with either vehicle (0.5% DMSO), TMC435350 or with positive controls (Omeprazole or Rifampicin). The incubations were carried out for 1 hour at 37 ± 1 °C. Samples were analyzed using a spectrofluorimetry or LC-MS/MS method. The mean fold induction of the different CYP-isoforms in human hepatocytes treated with TMC435350 and positive controls was expressed against the vehicle control (=1.0).

Table 1: Incubation conditions for determination of the metabolism of CYP1A2 and CYP3A4 substrates in human hepatocytes.

INDUCTION			**ACTIVITY TESTING**			
Inducer	**Concentration (µM)**	**CYP**	**Substrate**	**Solvent**	**Reaction**	**Conc. (µM)**
Omeprazole	10, 25	**1A2**	7-Ethoxyresorufin	CH_3OH	O-deethylation	2
TMC435350	0, 2.5, 10, 25, 75					
Rifampicin	25, 50	**3A4**	Testosterone	ACN	6β-hydroxylation	125
TMC435350	0, 2.5, 10, 25, 75					

STUDY RESULTS

Induction of CYP1A2 and CYP3A4 activities in cryopreserved human hepatocyte cultures

Table 2: CYP activities in human hepatocytes treated for 48 hours with either TMC435350 or with positive controls (Omeprazole and Rifampicin).

	Fold induction		Activity (pmol/min·mg)	
	CYP1A2	CYP3A4	CYP1A2	CYP3A4
	avg ± sd	avg ± sd	avg ± sd	avg ± sd
TMC435350 (0 µM)	1.0 ± 0.1	1.0 ± 0.1	0.132 ± 0.019	155 ± 73.9
TMC435350 (2.5 µM)	1.0 ± 0.2	0.3 ± 0.2	0.138 ± 0.029	42.1 ± 14.3
TMC435350 (10 µM)	0.9 ± 0.1	0.2 ± 0.1	0.118 ± 0.003	20.5 ± 9.1
Omeprazole (10 µM)	5.0 ± 2.0	-	0.643 ± 0.213	-
Omeprazole (25 µM)	7.2 ± 2.1	-	0.927 ± 0.176	-
Rifampicin (25 µM)	-	6.6 ± 2.2	-	1073 ± 696
Rifampicin (50 µM)	-	6.1 ± 1.3	-	985 ± 553
Omeprazole (25 µM)+ TMC435350 (25 µM)	5.9 ± 1.1	- ±	0.765 ± 0.049	-
Rifampicin (25 µM)+ TMC435350 (25 µM)	-	4.8 ± 1.0	-	709 ± 307

TMC435350 did not induce CYP1A2-mediated metabolism of 7-ethoxyresorufin, as indicated by the calculated fold induction (1.0±0.2 at 2.5 µM and 0.9±0.1 fold induction at 10 µM TMC435350). TMC435350 did not induce CYP3A4-mediated metabolism of testosterone, as indicated by the calculated fold induction (0.3±0.2 at 2.5 µM and 0.2±0.1 fold induction at 10 µM TMC435350).

CONCLUSIONS
TMC435350 is not an inducer of CYP1A2 or CYP3A4 *in vitro*.

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CLINICAL PHARMACOLOGY *IN VITRO* STUDY REVIEW				
Study #	NC197 (FK6333)	**Report date**	4 Mar 2008	EDR Link
Title	An in vitro study on the inhibitory effect of TMC435 on the metabolism of potential comedication			

STUDY DESIGN	
Objectives	To evaluate the potential for drug interactions between TMC435 and budesonide, diazepam, digoxin, glybenclamide, metoprolol, paroxetine, and simvastatin in human liver microsomes
Methods	TMC435 (1-300 uM) and potential comedications were incubated with HLMs at 37˚C for between 5 and 60 minutes, depending on linearity of metabolism of each comedication. Due to its solubility profile, TMC435 300 uM was the highest evaluable concentration in vitro.

STUDY RESULTS

Based on C_{max}/I_{50} values less than 0.1, the potential for a drug interaction between TMC435 and digoxin, metoprolol, and simvastatin via hepatic metabolism is expected to be remote. Based on C_{max}/I_{50} values greater than 0.1 but less than 1, the potential for a drug interaction between TMC435 and budesonide, diazepam, glybenclamide, and paroxetine are possible but are expected to be mild.

Table 1. Potential for interaction between TMC435 and comedications based on C_{max}/I_{50} values

Substrate and/or metabolite(s)	I_{50}-values in µM (or % inhibition at highest concentration tested)	I_{50}-values in µg/ml (or % inhibition at highest concentration tested)	C_{max}/I_{50} ratio at a plasma concentration of 11.5 µg/ml[1] (about 400 µg/ml in liver)
budesonide	57.8	43.4	0.265 (*possible*)
MET (16α-OH-prednisolone)	129	96.7	0.119 (*possible*)
diazepam	(60.6)*	(45.5)*	(0.253)*
MET (RT29.1)	51.1	38.3	0.300 (*possible*)
digoxin	(< 1.00)*	(< 0.750)*	(> 15.3)*
MET1 (ketodigoxigenin)	> 300 (0.00)	> 225 (0.00)	< 0.051 (*remote*)
MET2 (3β-digoxigenin)	> 300 (32.6)	> 225 (32.6)	< 0.051 (*remote*)
glybenclamide	53.9	40.4	0.285 (*possible*)
metoprolol	288	216	0.053 (*remote*)
MET1(OH)	222	167	0.069 (*remote*)
MET2 (desmethyl)	233	175	0.066 (*remote*)
paroxetine (RT31.5)	(248)*	(186)*	(0.062)*
MET (RT25.5)	118	88.5	0.130 (*possible*)
MET (RT26.4)	72.1	96.1	0.120 (*possible*)
simvastatin	> 300 (2.02)	> 225 (2.02)	< 0.051 (*remote*)
MET (hydroxy-simvastatin)	> 300 (0.00)	> 225 (0.00)	< 0.051 (*remote*)
MET (hydroxy-simvastatin acid) (RT1.60)	21.3**	16.0**	0.719**

CONCLUSIONS

IC_{50} values between 21.3 and >300 uM indicate that TMC435 is a weak inhibitor of CYP metabolism. It should be noted that liver concentrations are expected to be 20- to 40-fold higher than plasma concentrations; therefore,

liver concentrations may exceed 300 uM (peak concentrations are expected to be approximately 400 ug/mL).

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CLINICAL PHARMACOLOGY *IN VITRO* STUDY REVIEW				
Study #	NC239 (FK6846)	**Report date**	17 Nov 2009	EDR Link
Title	Study on ABCB1, Abcg2, and ABCC2 mediated transport of TMC435 in LLCPK1 (ABCB1) and MDCKII (Abcg2, ABCC2) cell lines transduced with this transporter			

STUDY DESIGN

Objectives

To evaluate the potential of ABCB1, Abcg2, and ABCC2 to transport TMC435

Methods

TMC435 was incubated with ABCB1-LLCPK1, Abcg2-MDCKII, or ABCC2-MDCKII cells in the presence or absence of the transporter-specific inhibitors or stimulators GF120918 (ABCB1 inhibitor), KO143 (Abcg2 inhibitor), or probenecid (ABCC2 stimulator) for 120 minutes. Radioactivity was detected in medium at the end of the incubation period. Digoxin, topotecan, ,and paclitaxel were used as positive controls. Note that mouse Abcg2 was used in this study as it is 86% homologous to human ABCG2 and expression levels in the MDCKII cell line remain constant, whereas ABCG2 expression decreases over time.

Table 1. Test conditions used to study transport of TMC435

investigated transporter	cell line	Substrate (present apical or basolateral, from t = 0 min. on)			Inhibitor or stimulator * (present apical and basolateral from t = -2 h. on)		
		Compound	Conc. Final	Conc. Stock	Compound	Conc. Final	Conc. Stock
TRANSPORT							
ABCB1	LLC-PK1	^{14}C-TMC435	1 µM	0.4 mM	GF120918	0, 5 µM	0, 2 mM
		^{3}H-digoxin	30 nM	0.012 mM	GF120918	0, 5 µM	0, 2 mM
*Abcg2***	MDCKII	^{14}C-TMC435	1 µM	0.4 mM	KO143	0, 1 µM	0, 0.4 mM
		^{3}H-topotecan	1 µM	0.4 mM	KO143	0, 1 µM	0, 0.4 mM
*ABCC2***	MDCKII	^{14}C-TMC435	1 µM	0.4 mM	/	/	/
		^{3}H-paclitaxel	30 nM	0.012 mM	probenecid	0, 500 µM	0, 200 mM

STUDY RESULTS

TMC435 is a potent substrate of ABCB1, Abcg2, and ABCC2 in vitro. Directional transport was similar to the ABCB1 substrate digoxin (Table 2) and greater than the Abcg2 substrate topotecan (Table 3) and the ABCC2 substrate paclitaxel (Table 4).

Table 2. ABCB1-mediated transport of digoxin (positive control) and TMC435

		LLC-PK1-Parent		LLC-PK1-*ABCB1*	
Transported compound (Condition)	**Direction***	**P_{app}(10^{-6} cm/s)**	**Ratio BA/AB**	**P_{app}(10^{-6} cm/s)**	**Ratio BA/AB**
Digoxin (30 nM) (-)	AB	1.67 ± 0.03	3.09 ± 0.16	0.34 ± **	25.6 ± 2.48
	BA	5.15 ± 0.30		8.68 ± 0.84	
Digoxin (30 nM) (+ 5 µM GF120918)	AB	2.47 ± 0.14	1.00 ± 0.09	2.37 ± 0.05	0.98 ± 0.03
	BA	2.46 ± 0.21		2.32 ± 0.08	
TMC435 (1 µM) (-)	AB	0.73 ± 0.05	2.73 ± 0.25	0.33 ± 0.13	20.4 ± 7.12
	BA	1.99 ± 0.15		6.67 ± 0.11	
TMC435 (1 µM) (+ 5 µM GF120918)	AB	0.77 ± 0.06	1.44 ± 0.19	0.93 ±0.08	1.54 ± 0.17
	BA	1.11 ± 0.15		1.44 ± 0.13	

* AB = Apical to basolateral, BA= basolateral to apical
** n=1, due to high mannitol values and/or no sample result

Table 3. Abcg2-mediated transport of topotecan (positive control) and TMC435

Transported compound (Condition)	Direction*	MDCKII-Parent $P_{app}(10^{-6}$ cm/s)	MDCKII-Parent Ratio BA/AB	MDCKII -*Abcg2* $P_{app}(10^{-6}$ cm/s)	MDCKII -*Abcg2* Ratio BA/AB
Topotecan (1 µM) (-)	AB	1.88 ± 0.08	0.90 ± 0.06	1.05 ± 0.05	3.57 ± 0.20
	BA	1.69 ± 0.12		3.74 ± 0.15	
Topotecan (1 µM) (+ 1 µM Ko143)	AB	2.01 ± 0.10	0.93 ± 0.05	1.82 ± 0.08	0.65 ± 0.05
	BA	1.86 ± 0.09		1.19 ± 0.08	
TMC435 (1 µM) (-)	AB	0.58 ± 0.01	2.98 ± 0.08	0.09 ± 0.01	74.3 ± 11.6
	BA	1.74 ± 0.04		6.57 ± 0.83	
TMC435 (1 µM) (+ 1 µM Ko143)	AB	0.56 ± 0.03	3.30 ± 0.28	0.65 ±0.06	0.79 ± 0.14
	BA	1.86 ± 0.16		0.51 ± 0.09	

* AB = Apical to basolateral, BA= basolateral to apical

Table 4. ABCC2-mediated transport of paclitaxel (positive control) and TMC435

Transported compound (Condition)	Direction*	MDCKII –Parent $P_{app}(10^{-6}$ cm/s)	MDCKII –Parent Ratio BA/AB	MDCKII -*ABCC2* $P_{app}(10^{-6}$ cm/s)	MDCKII -*ABCC2* Ratio BA/AB
Paclitaxel (30 nM) (-)	AB	1.33 ± 0.06	1.50 ± 0.16	1.16 ± 0.22	3.87 ± 0.78
	BA	1.99 ± 0.23		4.49 ± 0.47	
Paclitaxel (30 nM) (+ 500 µM probenecid)	AB	1.10 ± 0.22	5.06 ± 1.01	0.78 ± 0.28	16.4 ± 6.44
	BA	5.55 ± 0.36		12.7 ± 0.10	
TMC435 (1 µM) (-)	AB	0.62 ± 0.00	1.88 ± 0.06	0.33 ± 0.06	12.1 ± 2.32
	BA	1.17 ± 0.05		4.04 ± 0.16	

* AB = Apical to basolateral, BA= basolateral to apical

CONCLUSIONS

TMC435 is a potent substrate for the ABCB1, Abcg1, and ABCC2 transporters.

CLINICAL PHARMACOLOGY *IN VITRO* STUDY REVIEW				
Study #	NC282 (FK7339)	**Report date**	16 Jun 2010	EDR Link
Title	In vitro study on the use of human sandwich-cultured hepatocytes for the assessment of the effect of TMC435 on the uptake and efflux of taurocholate and 17β-estradiol-D-glucuronide			

STUDY DESIGN	
Objectives	To evaluate the inhibitory effect of TMC435 on hepatic uptake and biliary efflux of taurocholate (NTCP uptake, BSEP canalicular efflux) and 17β-estradiol-D-glucuronide (OATP1B1 uptake, MRP2 canalicular efflux).
Methods	Inhibition by TMC435 (0.5, 2, and 5 uM; predicted unbound concentrations 0.2, 0.8, and 2 uM) of hepatobiliary transport of 1 uM taurocholate and 1 uM 17β-estradiol-D-glucuronide was tested in sandwich cultures prepared from human cryopreserved hepatocytes. Cultures were incubated for 10 min, then cells were lysed and radioactivity was quantified. Bosentan (NTCP inhibitor), R121919 (BSEP inhibitor), and atazanavir and rifampicin (OATP1B1 and MRP2 inhibitors) were used as positive controls.

STUDY RESULTS

TMC435 inhibited taurocholate uptake and biliary efflux, with inhibition of uptake being slightly more potent compared to efflux (TMC435 5 uM resulted in 47% and 31% inhibition, respectively; Table 1). TMC435 inhibited 17β-estradiol-D-glucuronide uptake and biliary efflux, with inhibition of uptake being substantially more potent compared to efflux (TMC435 5 uM resulted in 72% and 33% inhibition, respectively; Table 2). Lower concentrations of TMC435 did not influence uptake or efflux of taurocholate or 17β-estradiol-D-glucuronide.

Table 1. Effect of TMC435 on taurocholate uptake and biliary efflux

	Uptake		BEI	inhibition uptake	inhibition efflux
	+Ca/+Mg (pmol/mg)	-Ca/-Mg (pmol/mg)	(%)	(%)	(%)
TC 1 µM	100 ± 9.3	35.5 ± 5.2	64.5		
TC 1 µM + TMC435 0.5 µM	104 ± 7.7	40.9 ± 9.9	60.6	0	6.1
TC 1 µM + TMC435 5 µM	52.6 ± 5.6	29.1 ± 1.4	44.7	47.4	30.7
TC 1 µM + R121919 20 µM	93.3 ± 14	70.2 ± 10	24.8	6.6	61.6
TC 1 µM + Bosentan 35 µM	52.6 ± 4.9	22.9 ± 3.1	56.5	47.4	12.5

TC : taurocholate
BEI: Biliary excretion index
Uptake data are expressed as mean ± standard deviation (n ≥ 3)

Table 2. Effect of TMC435 on 17β-estradiol-D-glucuronide uptake and biliary efflux

	Uptake		BEI	inhibition uptake	inhibition efflux
	+Ca/+Mg (pmol/mg)	-Ca/-Mg (pmol/mg)	(%)	(%)	(%)
EG 1 µM	18.5 ± 1.7	12.4 ± 1.2	33.0		
EG 1 µM + TMC435 0.5 µM	16.3 ± 2.8	10.6 ± 2.3	35.0	12	0.0
EG 1 µM + TMC435 2 µM	16.0 ± 0.98	10.8 ± 0.68	32.5	14	1.4
EG 1 µM + TMC435 5 µM	5.22 ± 0.60	4.10 ± 0.60	21.6	72	33
EG 1 µM + Atazanavir 5 µM	6.7 ± 0.39	5.7 ± 1.2	14.9	64	55
EG 1 µM + Rifampicin 5 µM	7.1 ± 0.60	6.4 ± 0.22	9.86	62	70
EG 1 µM + Rifampicin 20 µM	3.3 ± 0.22	3.2 ± 0.42	3.03	82	91

EG: 17β-estradiol glucuronide
BEI: Biliary excretion index
Uptake data are expressed as mean ± standard deviation (n ≥ 3)

CONCLUSIONS

At unbound concentrations of approximately 2 uM, TMC435 inhibited the hepatic uptake transporters OATP1B1 and NTCP. TMC435 also inhibited the biliary efflux transporters MRP2 and BSEP.

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY *IN VITRO* STUDY REVIEW				
Study #	FK10099	**Report date**	10 Jul 2012	EDR Link
Title	The uptake of TMC435 in HEK293 cell lines overexpressing the transporters OATP1B1, OATP1B3, OATP2B1, or OATP1B1*15			

STUDY DESIGN	
Objectives	To test whether TMC435 is a substrate of the transporters OATP1B1, OATP1B3, OATP2B1, or OATP1B1*15
Methods	The potential for TMC435 transport by OATP1B1, OATP1B3, and OATP2B1 was evaluated in stably transfected HEK293 cell lines. Mock transfected HECK293 cells were used as controls. Experiments were performed in HBSS buffer with 25% human serum for incubation times of 1, 5, and 10 min. Tritiated 17β-estradiol glucuronide was used as a positive control for transport activity.

STUDY RESULTS

TMC435 is transported by OATP1B1, OATP1B3, and OATP2B1 (Table 1). TMC435 uptake was lower in the OATP1B1*15-transfected cells compared to the OATP1B1-transfected cells; however, the uptake was not normalized for OATPx expression so direct comparisons cannot be made. The addition of serum precluded estimation of K_m/V_{max} kinetics.

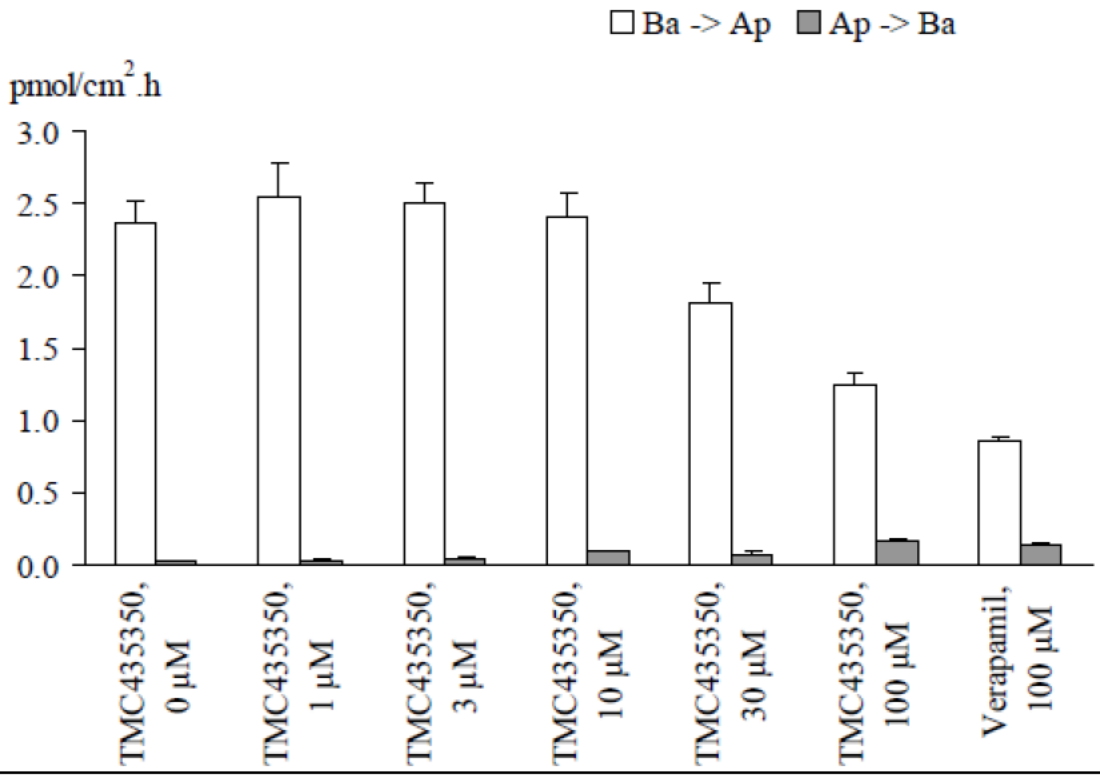
Table 1: Uptake of ^{14}C-TMC435 in mock- or OATP1Bx-transfected cells

	pmol ^{14}C-TMC435/mg total protein per well			
Incubation Time	1 min	5 min	10 min	1 min
Temp	37 °C	37 °C	37 °C	4 °C
	avg ± sd	avg ± sd	avg ± sd	avg ± sd
No cells	0.00 ± 0.00	0.25 ± 0.44	0.86 ± 1.5	0.00 ± 0.00
Mock	1.3 ± 0.06	4.4 ± 0.13	7.7 ± 0.38	0.00 ± 0.00
OATP1B1	4.4 ± 0.12	18 ± 0.12	33 ± 0.63	0.15 ± 0.13
OATP1B1*15	1.4 ± 0.08	6.0 ± 2.0	13 ± 0.15	0.04 ± 0.07
OATP1B3	10 ± 0.72	37 ± 0.61	50 ± 5.6	0.30 ± 0.07
OATP2B1	8.8 ± 0.80	37 ± 2.9	55 ± 1.4	0.16 ± 0.10

CONCLUSIONS

In stably-transfected HEK293 cells, TMC435 was transported by OATP1B1, OATP1B3, OATP2B1, and OATP1B1*15.

Figure 2: Inhibitory effects of TMC435 on P-gp transport of taxol



CONCLUSIONS
In Caco-2 cells, TMC435 was transported by P-gp (B:A/A:B ratio of 3.2). Transport was inhibited by verapamil. TMC435 inhibits P-gp transport of taxol (IC_{50} 85.9 uM).

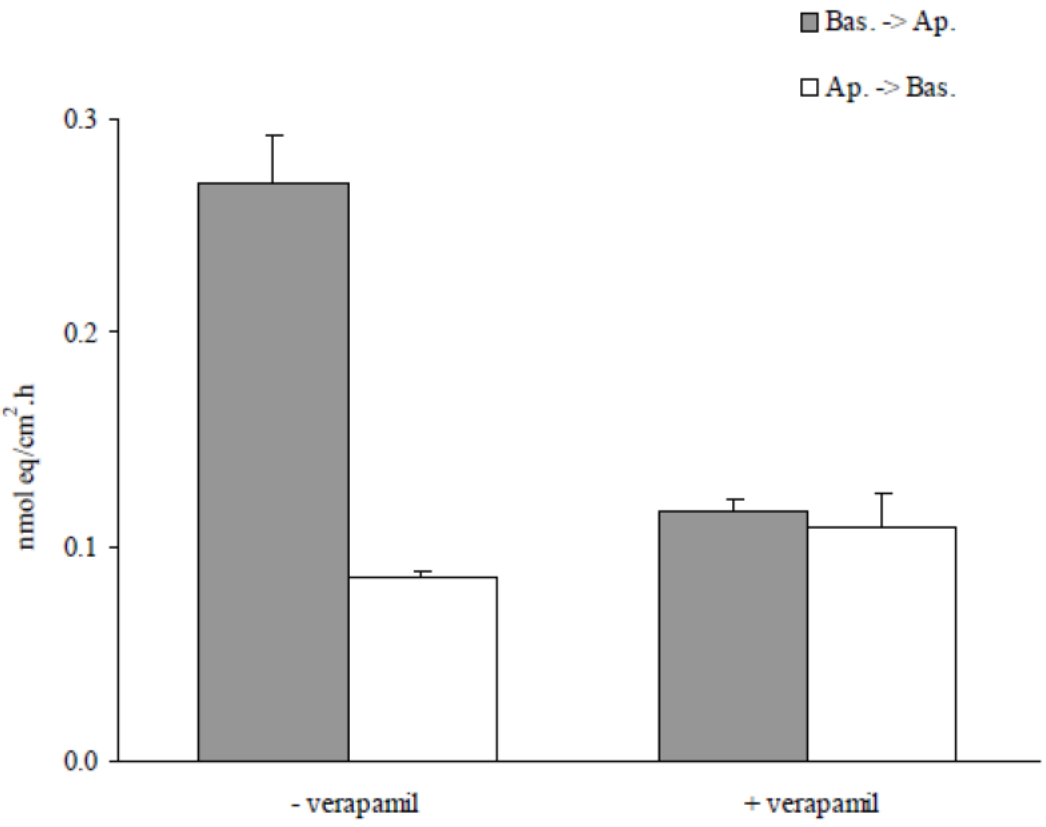
CLINICAL PHARMACOLOGY *IN VITRO* STUDY REVIEW				
Study #	NC113 (FK6019)	**Report date**	1 Jun 2012	EDR Link
Title	Study on the transepithelial transport of TMC435350, the role of P-glycoprotein (P-gp) in the transepithelial transport of TMC435350 across Caco-2 monolayers and on the possible inhibition of human intestinal P-gp by TMC435350			

STUDY DESIGN	
Objectives	To investigate the bidirectional transport of TMC435 across Caco-2 monolayers; to evaluate the role of P-gp in the intestinal absorption of TMC435; to evaluate the potential of TMC435 to inhibit P-gp
Methods	Bidirectional transport of 20 uM TMC435 was measured in Caco-2 cells. Mannitol was used as a negative control. The P-gp inhibitor verapamil (100 uM) was used to evaluate P-gp involvement in TMC435 transport. The P-gp probe substrate taxol (37.5 nM) was used to determine inhibitory effects of TMC435 (range: 1-100 uM). Incubation times were 15, 60, and 120 min; incubations were carried out in triplicate.

STUDY RESULTS

TMC435 is transported by P-gp, with a B:A/A:B ratio of 3.2. Permeability was similar to that of alniditan, a low-permeability compound. Transport was 95.5% inhibited in the presence of 100 uM verapamil (Figure 1). TMC435 inhibited taxol transport with an IC_{50} of 85.9 uM.

Figure 1. Bidirectional transport of TMC435 in the absence and presence of 100 uM verapamil



CLINICAL PHARMACOLOGY *in-vitro* STUDY REVIEW				
Study #	TMC435350-TiDP16-NC242	**Report date**	10/14/2009	EDR Link
Title	Assessing transport inhibition of TMC435 on ABCC2 (MRP2) and ABCB11 (BSEP) using inside-out vesicles			

STUDY DESIGN	
Objectives	To assess inhibition of ABCC2 (MRP2) and ABCB11 (BSEP) function by TMC435 or Ribavirin using inside-out vesicles (b) (4) 'overexpressing' these transporters
Methods	Inhibition of MRP2 and BSEP function by TMC435 was evaluated in inside-out vesicles stably expressing these transporters. ^{3}H-17βEG and CDCF (5/6-carboxy- 2',7'-dichlorofluorescein) were used as reference substrates for transport by MRP2, and ^{3}H-taurocholate was used as reference substrate for transport by BSEP. TMC435 concentrations tested were between 0.026 and 19.1 µM [0.02 and 14.3 µg/mL] in the presence and absence of 1% BSA. **Incubation procedure** (identical for all incubations): - 96 well plate on ice - 3.75 µL inhibitor/well added - 50 µL BSEP/MRP2 membrane suspension or parent membrane suspension added/well - The plate, ATP solution and Assay mix in an incubator for 10 min, 37 °C, 50 rpm - Reaction started by adding 25 µL ATP or assay mix - Incubation: 10 minutes (BSEP), 30 minutes (MRP2) - Reaction stopped by adding 200 µL ice cold washing mix **Filtration** - Samples transferred to a 96 well filterplate - Washed 5x with 200 µL ice cold washing mix/well using a vacuum-manifold system - The filter plate was dried using a flow of warm air. All radioactive samples were analysed with a liquid scintillation counter (Perkin Elmer) and/or the topcount reader (Perkin Elmer). All fluorescent samples were analysed with Tecan Safire (Ex: 485 nm, Em: 538 nm).

STUDY RESULTS

Transporter	Substrate	Inhibitor	IC50 (µM) -BSA	IC50 (µM) +BSA
BSEP	0.71 µM taurocholate	Cyclosporine A	1.54±0.39	1.60±0.37
BSEP	0.71 µM taurocholate	TMC435	1.67±0.38	1.77±0.29
BSEP	1.0 µM taurocholate	Ribavirin	Not performed	> 47.6
MRP2	5 µM CDCF	Benzbromarone	5.97±0.45	> 143
MRP2	5 µM CDCF	TMC435	6.4-19.1	6.4-19.1
MRP2	50 µM E17βG	TMC435	6.4-19.1	No inhib.

Note: IC50 values were calculated and compared with the data obtained with positive control inhibitors for MRP2 (benzbromarone) and BSEP (cyclosporine A) -mediated transport.

CONCLUSIONS

TMC435 was an inhibitor of BSEP- and MRP2-mediated transport in vitro. The in vivo implications are

unknown.

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY *in-vitro* STUDY REVIEW				
Study #	TMC435350-TiDP16-NC275	**Report date**	10/07/2009	EDR Link
Title	The effect of TMC435 on transport of 17β-estradiol-glucuronide and taurocholate mediated by OATP1B1 and NTCP in CHO cell lines overexpressing these transporters			

STUDY DESIGN	
Objectives	To test whether TMC435 or ribavirin can inhibit transport of prototypical substrates of OATP1B1 (17β-estradiol-glucuronide) or NTCP (taurocholate) using CHO-cells stably transfected with cDNA encoding for these transporters
Methods	**T=-18 hours** CHO-Parental, CHO-NTCP and CHO-OATP1B1 cells were seeded into 24w plates (1mL/well, 600,000 cells/well) medium containing 5 mM Na-butyrate. **Day of the experiment** All media added to the cells and plates were kept at 37 ºC. Before the (pre)incubation, the cells in each well were washed twice with 1.25mL HBSS+/+, 10mM HEPES, 1% BSA, pH 7.4, after which the (pre)incubation medium is added (500 µL/well). During the incubation period, the plates were placed in a humidified cell culturing incubator (37ºC, **0.0%** CO2). To stop the reaction, 1.5 mL ice-cold HBSS + 1% BSA was added to each well; the plate was placed on melting ice and the liquids were aspirated. Again, to each well 1.5 mL ice-cold HBSS +1% BSA was added and aspirated while keeping the plate angled. Following the aspiration of the last well, all the wells were aspirated again taking care of not touching the cells. 200 µL mPER lysis buffer was added to each well and the plates are shaken (120 rpm, 5-10min). 150 µL samples are taken for LSC, the plates were frozen and on a number of wells protein analysis was performed (25 µL samples). All samples containing radioactivity were counted by LSC and protein determination was performed using Thermo's BCA Protein Assay Kit

STUDY RESULTS

In preliminary experiments, it was observed that TMC435 adsorbs to CHO-cells, even in the presence of 1% BSA, masking potential transport. Steady-state is reached after 60 min. Consequently, direct transport of TMC435 mediated by these transporters could not be tested.

The IC50 value of TMC435 inhibiting the uptake of 1 µM ^{3}H-17β-estradiolglucuronide in *OATP1B1* transfected CHO cells (5 min and in presence of 1% BSA), following a 60 min pre-incubation of different concentrations of TMC435 is 0.06±0.004 µM. Without pre-incubation (=direct inhibition), this value is 0.26±0.02 µM. Ribavirin did not inhibit this transport, with or without pre-incubation, at a concentration of 300 µM.

The IC50 value of TMC435 inhibiting the uptake of 1 µM ^{3}H-taurocholate in *NTCP* transfected CHO cells (10 min and in presence of 1% BSA), following a 60 min pre-incubation of different concentrations of TMC435 is 0.44±0.03 µM. Without pre-incubation (=direct inhibition), this value is 2.16±0.52 µM. Ribavirin did not inhibit this transport, with or without preincubation, at a concentration of 300 µM.

Note: No positive control inhibitors were included in the study.

CONCLUSIONS
The data suggested that TMC435 was an inhibitor of OATP1B1- and NTCP-mediated transport in vitro. It should be noted that no positive control inhibitors were included in the study, therefore the validity of the results are questionable.

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY *IN VITRO* STUDY REVIEW				
Study #	1986 0049051 (FK10436)	**Report date**	18/02/2013	EDR Link
Title	*In vitro* study on the Inhibition of Cathespin A (Cat A) by TMC435			

STUDY DESIGN	
Objectives	To investigate the possible inhibition of Cat A activity by TMC435.
Methods	Cat A activity was evaluated by the procedure entails the activation of recombinant human Cat A by Cathepsin L (Cat L), followed by a fluorometric assessment of Cat A activity using a fluorogenic peptide substrate. Cleaving of the amide bond between the fluorescent group and the quencher group by Cat A causes an increase in fluorescence which can be used as a quantitative assessment of Cat A activity. Boceprevir and Telaprevir have been shown to result in a potent and dose dependent inhibition of Cat A activity *in vitro* and used as reference inhibitors in this study. Activated Cat A (2 ng/µL) was incubated at 37°C for up to 30 minutes in the presence of solvent controls or test compounds (0.05-50 µM). Cat A activity was expressed as the percentage activity compared to solvent controls in function of test compound concentration and corresponding IC_{50} values for each test compound were calculated.

Table 1: Test compound formulations

Substrate	Solvent	Fold-dilution	Final conc.	Sampling time at 37°C (min)
TMC435	DMSO	100x	0.05-50 µM	0.5-30 min
Boceprevir	DMSO	100x	0.05-50 µM	0.5-30 min
Telaprevir	DMSO	100x	0.05-50 µM	0.5-30 min

STUDY RESULTS

Inhibition of Cat A activity by TMC435 was markedly less potent compared with that of Boceprevir and Telaprevir. At the highest concentration tested (50 µM), Cat A activity was reduced by 43%, resulting in an IC_{50} value of TMC435 >50 µM. In the presence of 10 µM TMC435, Cat A activity was reduced by less than 12%.

Table 2: Inhibition of Cat A by TMC435 and known reference inhibitors

Compound Identification	Compound code	MW	IC_{50} (µM)
Test Compounds			
TMC435	JNJ-38733214-AAA	749.95	>50
Reference inhibitors			
Boceprevir	JNJ-39720564-AAA	519.69	0.34±0.038
Telaprevir (VX950)	JNJ-38940655-AAA	679.85	0.074±0.0073

CONCLUSIONS

TMC435 is not a clinically relevant inhibitor of Cat A activity *in vitro*.

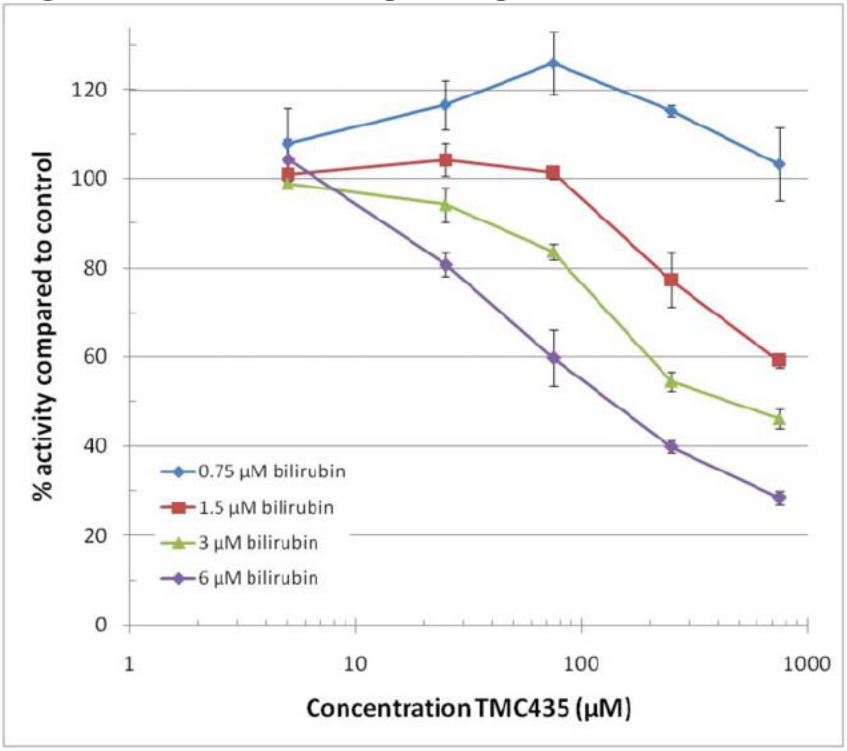
CLINICAL PHARMACOLOGY *in-vitro* STUDY REVIEW				
Study #	TMC435350- TiDP16-NC273 (FK7237)	**Report date**	27/11/2009	EDR Link
Title	An *in-vitro* study on the inhibition of UGT1A1 mediated bilirubin glucuronidation by TMC435 and Ribavirin in human liver microsomes			

STUDY DESIGN	
Objectives	To investigate potential inhibition of human UGT1A1 by TMC435, by determination of the IC_{50} and apparent inhibition constants K_i on the glucuronidation of bilirubin in pooled human liver microsomes.
Methods	The inhibitory effect of TMC435 on the UGT1A1-mediated bilirubin glucuronosyltransferase activity was investigated by incubating human liver microsomes at 37°C with different bilirubin concentrations (final concentrations of 0.75, 1.5, 3, 6 µM) in the presence of different TMC435 concentrations (final concentrations of 0, 5, 25, 75, 250, 750 µM). The formation of bilirubin mono- and diglucuronides was determined by LCUV method.

STUDY RESULTS

- The study results indicate that the inhibition of bilirubin glucuronidation was dependent on the concentration of TMC435.

Figure 1: Effect of TMC435 on the UGT1A1-mediated bilirubin glucuronosyltransferase activity in function of concentration in human liver microsomes.
The formation of both mono- and diglucuronides was taken into account for quantitation of total bilirubin glucuronidation. The data points represent the mean of three determinations.



CONCLUSIONS

In the human liver microsomes, the apparent inhibition constant K_i for the inhibition of the UGT1A1 mediated bilirubin glucuronidation by TMC435 was 119 ±14 µM (approximately 89 µg/mL). Given that the mean

steady-state simeprevir (TMC435) C_{max} is predicted to be approximately 4.2 µg/mL following oral administration of simeprevir 150 mg QD, it is most unlikely that TMC435 can give a relevant *in vivo* interaction on glucuronidation of bilirubin.

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY DRUG-DRUG INTERACTION STUDY REVIEW				
Study #	TMC435350-TiDP16-C105	**Study Period**	18-June-2008 to 01-December-2008	EDR Link
Title	Phase I, open-label, 3-way crossover trial in healthy subjects to determine the drug-drug interaction between TMC435350 and rifampin after multiple dosing			

STUDY DESIGN	
This was a Phase I, open-label, randomized, 3-way crossover trial planned to enroll 18 healthy subjects to investigate the potential drug-drug interaction between rifampin and TMC435350. During 3 sessions, subjects were to receive 3 treatments according to a 6-sequence, 3-period design.	
Population	☒ Healthy Volunteers ☐ Patients
Study Rationale	The study was conducted to assess the potential drug-drug interaction between rifampin (a CYP3A inducer) and TMC435350
Treatments	Treatment A: TMC435350 200 mg q.d. for 7 days. Treatment B: rifampin 600 mg q.d. for 7 days. Treatment C: TMC435350 200 mg q.d. + rifampin 600 mg q.d. for 7 days. There was a washout period of at least 10 days between subsequent sessions
Dose Selection Rationale	A 200 mg dose of TMC435350 q.d. was selected, based on PK and safety results from trial TMC435350-TiDP16-C1011. In this trial, the dose of 200 mg q.d. for 5 days was shown to be active and to induce a 3 up to 4 log decrease in plasma HCV viral load of genotype 1 infected patients. Rifampin was administered at 600 mg q.d., which is the recommended clinical dose
Administration	☒ Fasted ☐ Fed
Formulation	**Treatment** / TMC435350 / rifampin Dose Strength: 100 mg / 300 mg Dosage Form (F No.): capsule (F007) / capsule Usage: oral / oral Batch Number: 08D23/F007 / ML080104
Interfering Substances Excluded	None
Sampling Times	In Treatment A and C, blood samples for determination of TMC435350: - on Day 1 (within 2 h before drug intake) - on Days 2, 4, and 6 (immediately before drug intake) - on Day 7 (predose) and at 0.5, 1, 2, 3, 4, 6, 9, and 12 h postdose - on Days 8, 9 & 10 (i.e., 24 h, 48h, & 72 after last dosing) In Treatment B and C, blood samples for determination of rifampin and 25-desacetyl-rifampin were taken according to the same schedule.
PK Parameters	Cmax, Cmin, AUC24hr
PK Analysis	Non-compartmental analysis
Statistical Analysis	Intent-to-Treat analysis, descriptive statistics, frequency tabulations and linear mixed effects model for estimation of least square (LS) means were used.
Is the study design acceptable? ☒ Yes ☐ No	

STUDY CONDUCT				
Bioanalytical Method:				
	Method Name	Bioanalytical Study Summary TMC435350/023		
	Method Type	LC-MS/MS	Matrix	Plasma
	Analytes	TMC435350, rifampin, and 25-desacetyl-rifampin		

Range	2.00 -2000 ng/mL; 100 -10000 ng/mL; 25.0 -2500 ng/mL

Validation	▪ Method validated prior to use	☒ Yes ☐ No ☐ NA
	▪ Method validation acceptable	☒ Yes ☐ No ☐ NA
Study Samples Analysis	▪ Samples analyzed within the established stability period	☒ Yes ☐ No
	▪ Quality control samples range acceptable	☒ Yes ☐ No
	▪ Chromatograms provided	☒ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	▪ Incurred samples analysis is acceptable	☒ Yes ☐ No
	▪ Overall performance acceptable	☒ Yes ☐ No
Inspection	▪ Will the bioanalytical site be inspected	☐ Yes ☒ No

Protocol Deviations

- Are there any protocol deviations listed in the study report? ☒ Yes ☐ No
- Do any of the listed deviations affect the integrity of the study? ☐ Yes ☒ No ☐ NA

Notes: Six subjects (28.6%) were not fasting before obtaining dropout/follow-up samples. Although these deviations were labeled as major protocol violations, these were not considered to affect the results and the subjects were therefore included in the PK analysis.

STUDY RESULTS

Study Population

Randomized	21
Treated	21
Completed	16
Discontinued Due to AE	2
PK Population/Safety Population	18
Age [Median (range)]	39.0 (24-52)
Male/Female	20/1
Race (Caucasian/Black/Other)	10/10/1

Pharmacokinetics

- Effect of rifampin on TMC435350 PK

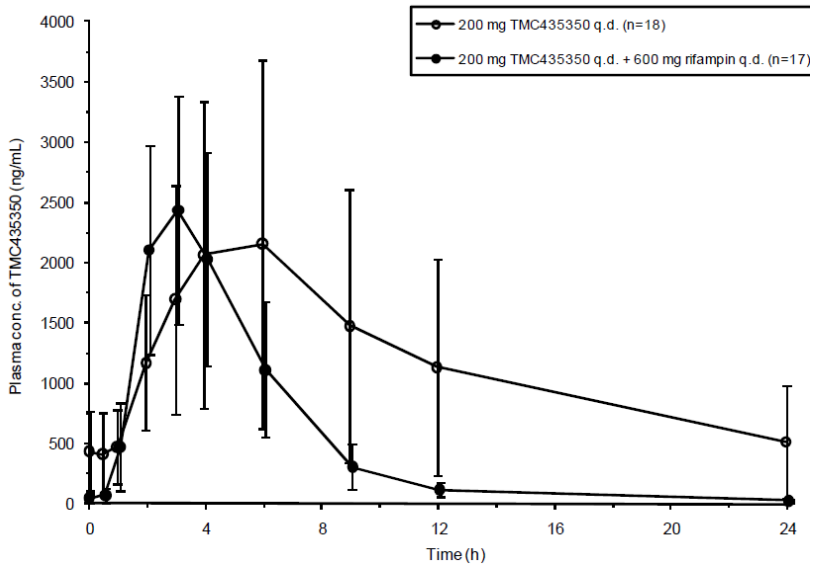


Figure 1: Mean Plasma Concentration-Time Curves of TMC435350 (with SD Bars) on Day 7 After Administration of TMC435350 Alone (Treatment A) and in Combination With Rifampin (Treatment C)

Table 1: Summary of the Statistical Analysis of the PK Parameters of TMC435350 After Administration of TMC435350 Alone (Treatment A) and in Combination With Rifampin (Treatment C)

Parameter	LSmeans[a]		LSmeans ratio, %	90% CI,% [b]	p-value	
	200 mg TMC435350 q.d. (reference)	200 mg TMC435350 q.d. + 600 mg rifampin q.d. (test)			Period	Sequence
C_{min}, ng/mL	255.5	20.79	8.137	6.076 - 10.90	0.0664	0.2126
C_{max}, ng/mL	1886	2469	130.9	103.0 - 166.3	0.5798	0.8280
AUC_{24h}, ng.h/mL	22460	11760	52.39	41.00 - 66.94	0.3528	0.7829

[a] n=18 for reference and n=17 for test
[b] 90% confidence intervals

Based on the ratios of the LSmeans, Cmin and AUC24h of TMC435350 decreased by 92% and 48%, respectively, when TMC435350 was administered in the presence of rifampin (Treatment C), compared to intake of TMC435350 alone (Treatment A). Cmax of TMC435350 increased by 31% after coadministration with rifampin compared to intake of TMC435350 alone.

- Effect of TMC435350 on rifampin PK

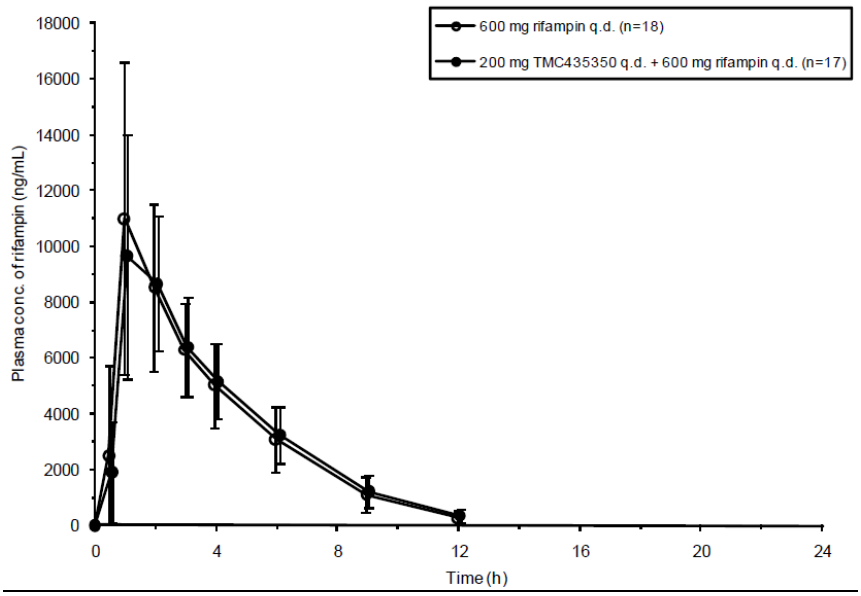


Figure 2: Mean Plasma Concentration-Time Curves of Rifampin (with SD Bars) on Day 7 After Administration of Rifampin Alone (Treatment B) and in Combination With TMC435350 (Treatment C)

Table 2: Summary of the Statistical Analysis of the PK Parameters of Rifampin After Administration of Rifampin Alone (Treatment B) and in Combination With TMC435350 (Treatment C)

Parameter	LSmeans[a]		LSmeans ratio, %	90% CI,% [b]	p-value	
	600 mg rifampin q.d. (reference)	200 mg TMC435350 q.d. + 600 mg rifampin q.d. (test)			Period	Sequence
C_{max}, ng/mL	10830	10010	92.46	80.26 - 106.5	0.0956	0.9263
AUC_{24h}, ng.h/mL	42900	42990	100.2	92.60 - 108.4	0.2883	0.6081

[a] n=18 for reference and n=17 for test
[b] 90% confidence intervals

Based on the ratios of the LSmeans, Cmax and AUC24h of rifampin were comparable when rifampin was administered alone (Treatment B) or in the presence of TMC435350 (Treatment C). For both parameters the 90% confidence intervals (CIs) of the LSmeans ratios fell within the 80% to 125% limits. There were no statistically significant period or sequence effects.

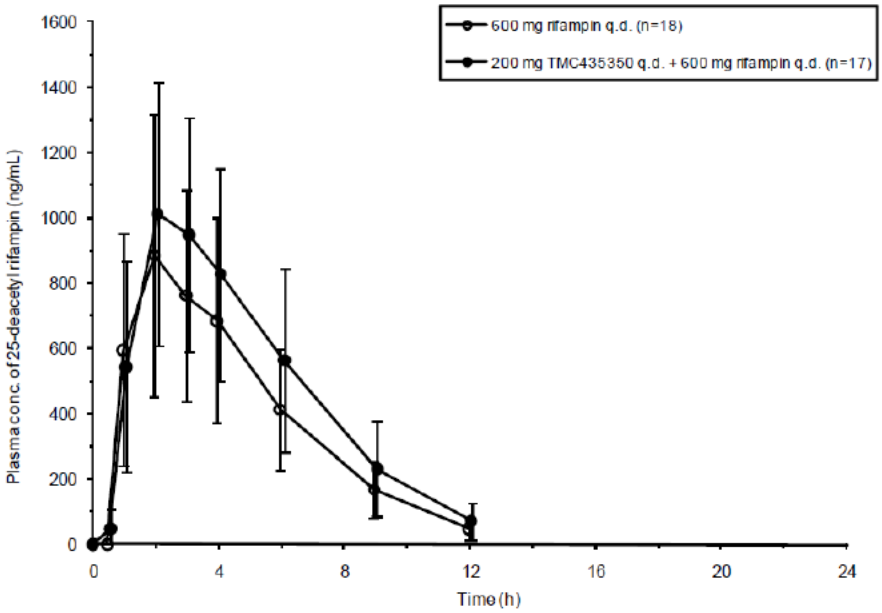


Figure 3: Mean Plasma Concentration-Time Curves of 25-Desacetyl-Rifampin (with SD Bars) on Day 7 After Administration of Rifampin Alone (Treatment B) and in Combination With TMC435350 (Treatment C)

Table 3: Summary of the Statistical Analysis of the PK Parameters of 25-Desacetyl-Rifampin After Administration of Rifampin Alone (Treatment B) and in Combination With TMC435350 (Treatment C)

Parameter	LSmeans[a]		LSmeans ratio, %	90% CI,% [b]	p-value	
	600 mg rifampin q.d. (reference)	200 mg TMC435350 q.d. + 600 mg rifampin q.d. (test)			Period	Sequence
C_{max}, ng/mL	873.2	943.4	108.0	98.49 - 118.5	0.0259*	0.3776
AUC_{24h}, ng.h/mL	4603	5695	123.7	112.9 - 135.6	0.0072*	0.6586

[a] n=18 for reference and n=17 for test
[b] 90% confidence intervals
* Statistically significant difference

Cmax of 25-deaceylrifampin was comparable when rifampin was administered alone (Treatment B) or in the presence of TMC435350 (Treatment C). AUC24h of 25-desacetylrifampin was increased by 24% after the combined intake of rifampin and TMC435350 compared to intake of rifampin alone, based on the ratio of the LSmeans.

- Were there any outliers or excluded data from analysis? ☐ Yes ☒ No ☐ NA, if yes explain
- Are the study results acceptable? ☒ Yes ☐ No, if no explain

Safety

Was there any death or serious adverse events? ☐ Yes ☒ No

CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS

CONCLUSIONS

The study showed that TMC435 PK was significantly affected by the coadministration of rifampin, but rifampin PK was little affected by the coadministration of TMC 535: TMC435 Cmin and AUC24h decreased by 92% and 48%, respectively, after coadministration compared to intake of TMC435 alone, while Cmax increased by 31%. Rifampin Cmax and AUC24h were comparable when rifampin was administered alone or in the presence

of TMC435. While 25-desacetyl-rifampin Cmax was comparable when rifampin was administered alone or in the presence of TMC435, 25-desacetyl-rifampin AUC24h increased by 24% after the combined intake of rifampin and TMC435.

The sponsor's conclusions appear valid.

COMMENTS

None

LABEL RECOMMENDATIONS

The label should state that coadministration of TMC435350 with strong CYP3A inducer such as rifampin is not recommended.

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY BIOAVAILABILITY STUDY REVIEW				
Study #	TMC435350-TiDP16-C106	**Study Period**	22/07/2008-14/01/2009	EDR Link
Title	Phase I, open-label, crossover trial in healthy subjects to compare the bioavailability of a single oral dose of TMC435350 formulated as 4 different solid formulations to that of a single oral dose of TMC435350 formulated as a (b) (4) capsule			

STUDY DESIGN	
Population	☑ Healthy Volunteers ☐ Patients
Study Rationale	The study was conducted to compare the oral bioavailability and plasma PK of TMC435350 for 4 different solid formulations to those of TMC435350 formulated as a (b) (4) Na-salt capsule (F007), after a single oral dose of 200 mg in healthy subjects.
Treatments	A: a single dose of 200 mg TMC435350 formulated as a (b) (4) Na-salt capsule (F007; reference) B: a single dose of 200 mg TMC435350 formulated as a Na-salt tablet (F019) C: a single dose of 200 mg TMC435350 formulated as a capsule (b) (4) in situ Na-salt (F018) D: a single dose of 200 mg TMC435350 formulated as a (b) (4) -salt tablet (F002) E: a single dose of 200 mg TMC435350 formulated as a (b) (4) Na-salt capsule (F020) *All medication intakes were oral and under fed conditions. *A washout period of at least 7 days between medication intakes. **Sequence** Part I: A-B-C/B-C-A/C-A-B/C-B-A/B-A-C/A-C-B Part II: A-D-E/D-E-A/E-A-D/E-D-A/D-A-E/A-E-D
Dose Selection Rationale	A 200-mg dose of TMC435350 had been selected based on PK and safety results from trial TMC435350-TiDP16-C101 in healthy adult subjects.
Administration	☐ Fasted ☑ Fed
Formulation and Batch No.	(b) (4) Na-salt capsule (F007): Batch #08D23/F007(Part I), #08G25/F007 (Part II) -Na-salt tablet (F019): Batch #08F04/F019 - (b) (4) in situ Na-salt (F018): Batch #08E19/F018 (b) (4) salt tablet (F002): Batch #08I04/F002 (b) (4) Na-salt capsule (F020): Batch #08J01/F020
Interfering Substances Excluded	None
Sampling Times	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 , 24, 36, 48 , and 72 hours post-dose in each group.
PK Parameters	C_{max}, t_{max}, AUC_{last}, AUC_{∞}, λ_z, $t_{1/2term}$, Ratio $C_{max,test/ref}$, Ratio $AUC_{last,test/ref}$ and Ratio $AUC_{\infty,test/ref}$
PK Analysis	Non-compartmental analysis
Statistical Analysis	The least square (LS) means of the primary parameters (i.e., C_{max}, AUC_{last} and AUC_{∞}, on the logarithmic scale) for each treatment group was estimated with a linear mixed effects model, controlling for treatment, sequence and period as fixed effects, and subject as a random effect. The LS mean ratio and its 90% confidence interval (CI) were calculated.
Is the study design acceptable? ☑ Yes ☐ No	

STUDY CONDUCT

Bioanalytical Method

Method Name	BA883		
Method Type	LC-MS/MS	Matrix	Plasma
Analytes	TMC435350		
Range	2-2000 ng/mL		

Validation	▪ Method validated prior to use	☑ Yes ☐ No ☐ NA
	▪ Method validation acceptable	☑ Yes ☐ No ☐ NA
Study Samples Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Incurred samples analysis is acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No
Inspection	▪ Will the bioanalytical site be inspected	☐ Yes ☑ No

Protocol Deviations

- Are there any protocol deviations listed in the study report? ☐ Yes ☑ No
- Do any of the listed deviations affect the integrity of the study? ☐ Yes ☐ No ☑ NA

STUDY RESULTS

Study Population

Part 1

Randomized	12
Treated	12
Completed	12
Discontinued Due to AE	0
PK Population/Safety Population	12
Age [Median (range)]	48.5 (20-52)
Male/Female	8/4
Race: Caucasian (%)	100

Part 2

Randomized	12
Treated	12
Completed	12
Discontinued Due to AE	0
PK Population/Safety Population	12
Age [Median (range)]	48.5 (21-52)
Male/Female	8/4
Race: Caucasian (%)	100

Note: Full PK profiles of TMC435350 were available for 12 subjects for Treatments A-I, A-II, B, C, D and E. However, for Treatment B, D and E, one subject in each of the treatments vomited within 12 hours and was therefore excluded from further PK analysis.

Pharmacokinetics

- PK Parameters and LS Mean Ratio & 90% CI

Panel 1

Pharmacokinetics of TMC435350 (Part I) (mean ± SD, t_{max}: median [range])	(b) (4) Na-salt capsule (F007) (reference)	Na-salt tablet (F019) (test 1)	Capsule (b) (4) (b) (4) in situ Na-salt (F018) (test 2)
n	12	11[a]	12
C_{max}, ng/mL	2743 ± 1047	1722 ± 1067	1044 ± 786.6
t_{max}, h	5.0 (4.0 - 8.0)	6.0 (6.0 - 6.0)	6.0 (4.0 - 8.0)
AUC_{last}, ng.h/mL	39640 ± 14990	24760 ± 11610	15430 ± 13840
AUC_{∞}, ng.h/mL	40180 ± 15290	23980 ± 11600	15610 ± 14080
$t_{1/2term}$, h	10.93 ± 1.803	10.63 ± 1.198	10.58 ± 1.275
LSmean ratio (90% CI), %			
	-	**test 1 vs reference**	**test 2 vs reference**
n	-	11[a] vs 12	12 vs 12
C_{max}	-	59.80 (44.07 - 81.16)	30.96 (20.91 - 45.84)
AUC_{last}	-	60.96 (48.41 - 76.78)	30.95 (21.80 - 43.95)
AUC_{∞}	-	59.00 (47.70 - 72.97)	30.94 (21.80 - 43.91)

[a]n= 10 for AUC_{last}

Panel 2

Pharmacokinetics of TMC435350 (Part II) (mean ± SD, t_{max}: median [range])	(b) (4) Na-salt capsule (F007) (reference)	(b) (4) salt tablet (F002) (test 3)	(b) (4) Na-salt capsule (F020) (test 4)
n	12	11	11[a]
C_{max}, ng/mL	2491 ± 1235	2485 ± 1487	2115 ± 1056
t_{max}, h	6.0 (3.0 - 6.0)	6.0 (4.0 - 8.0)	6.0 (4.0 - 8.0)
AUC_{last}, ng.h/mL	31480 ± 15850	30610 ± 13610	26680 ± 9991
AUC_{∞}, ng.h/mL	31710 ± 15990	30860 ± 13700	28970 ± 13500
$t_{1/2term}$, h	10.05 ± 0.9852	10.28 ± 1.367	10.47 ± 1.199
LSmean ratio (90% CI), %			
	-	**test 3 vs reference**	**test 4 vs reference**
n	-	11 vs 12	11[a] vs 12
C_{max}	-	102.7 (89.56 - 117.8)	87.37 (75.78 - 100.7)
AUC_{last}	-	105.1 (93.91 - 117.7)	95.74 (76.45 - 119.9)
AUC_{∞}	-	105.3 (94.18 - 117.8)	94.19 (79.49 - 111.6)

[a]n = 9 for AUC_{last}

Figure 1: Mean (±SD) Plasma Concentration-Time Curves of TMC435350 After Administration of a 200 mg Single Dose of TMC435350 Formulated as (b) (4) Na-Salt Capsule F007 (Treatment A-I), as Na-Salt Tablet F019 (Treatment B) and as Capsule (b) (4) in Situ Na-Salt F018 (Treatment C), all Under fed Conditions.

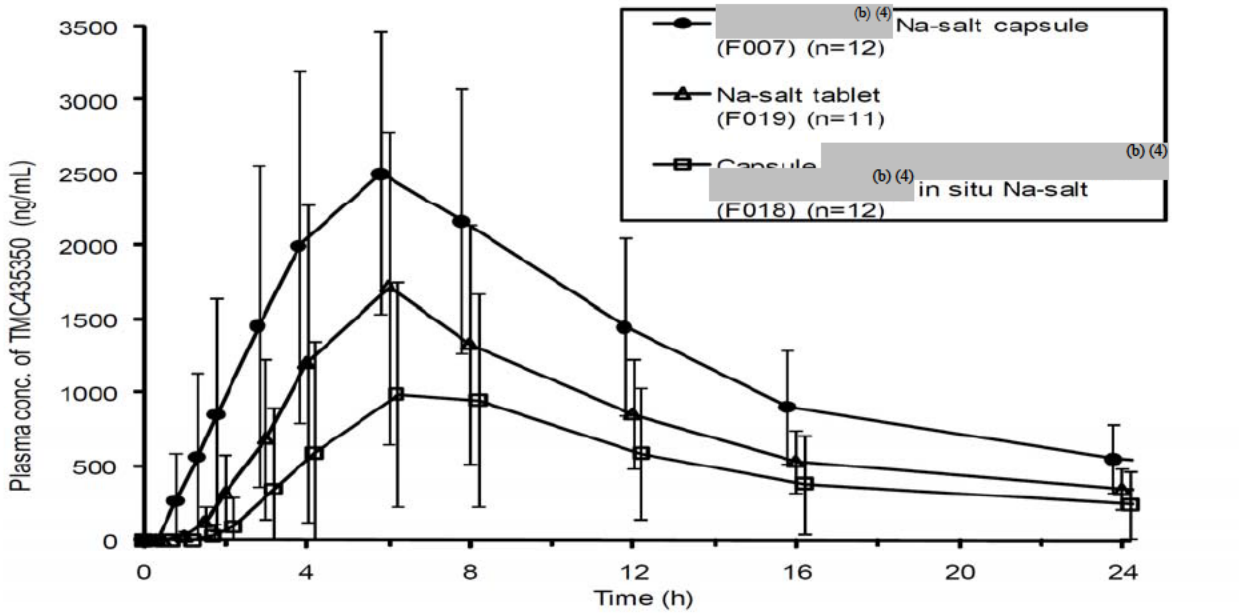
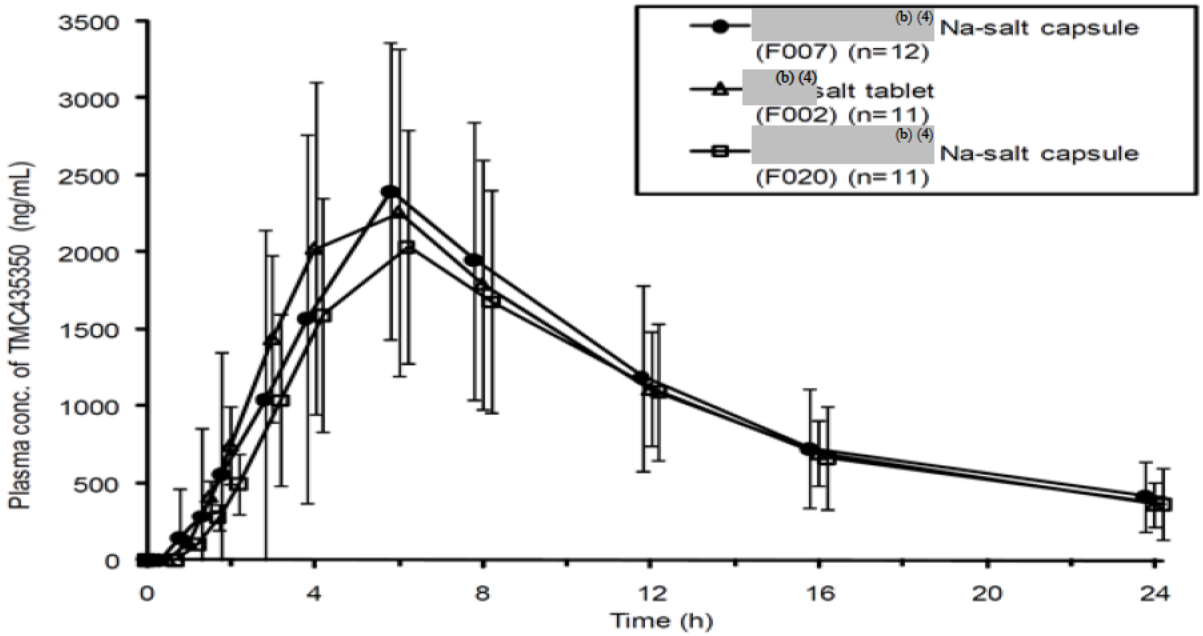


Figure 2: Mean (±SD) Plasma Concentration-Time Curves of TMC435350 After Administration of a 200 mg Single Dose of TMC435350 Formulated as (b) (4) Na-Salt Capsule F007 (Treatment A-II), as (b) (4)-Salt Tablet F002 (Treatment D) and as (b) (4) Na-Salt Capsule F020 (Treatment E), all Under fed Conditions.



- Were there any outliers or excluded data from analysis? ☐ Yes ☑ No ☐ NA
- Are the study results acceptable? ☑ Yes ☐ No

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No

CONCLUSIONS/COMMENTS

CONCLUSIONS

Does the study finding indicate the rate and extent of absorption of the tablet (F019), capsule (F018) or capsule (F020) is comparable to that of the capsule (F007)? ☐ Yes ☑ No

Does the study finding indicate the rate and extent of absorption of the tablet (F002) is comparable to that of the capsule (F007)? ☑ Yes ☐ No

The bioavailability of TMC435350 following oral administration of TMC435350 Na-salt tablet (F019) or as capsule [redacted] (F018) was lower compared to Na-salt capsule (F007). The bioavailability of TMC435350 was only slightly lower following administration of TMC435350 Na-salt capsule (F020) compared to Na-salt capsule (F007) and was comparable following administration of TMC435350 [redacted] salt tablet (F002) compared to Na-salt capsule (F007).

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY DRUG-DRUG INTERACTION STUDY REVIEW				
Study #	TMC435-TiDP16-C107	**Study Period**	27-March-2009 to 01-July-2009	EDR Link
Title	A Phase I, open label, 2-period, randomized, crossover trial in 16 healthy subjects to assess the drug interaction potential of TMC435 with oral midazolam and with a drug cocktail representative of CYP1A2, CYP2C9, CYP2D6, CYP3A4, and CYP2C19 substrates			

STUDY DESIGN

This was a Phase I, open-label, two-period, randomized, crossover trial in healthy adult subjects to assess the drug interaction potential of TMC435 with oral midazolam alone, as well as with a drug cocktail representative of CYP probes. The drug cocktail consisted of midazolam (given i.v), dextromethorphan, caffeine, omeprazole and warfarin (all given orally). These drugs are probes for CYP3A4, 2D6, 1A2, 2C19 and 2C9, respectively. Midazolam was given both orally and i.v. to enable differentiation between intestinal and hepatic CYP3A4 activity.

Population

☒ Healthy Volunteers ☐ Patients

Study Rationale

The study was conducted to assess the potential inhibitory and inducing effect of TMC435 on the single dose PK of oral midazolam and a cocktail of representative probes of common CYP enzymes.

Treatments

Treatment Sequence A/B (n = 8)

Phase	Screening	Treatment A		Washout	Treatment B		Follow-up
Duration	≤ 28 days	Day 1	Day 2	At least 14 days	11 days		30, 31 or 32 days
Treatment	None	Oral midazolam (0.075 mg/kg)	Drug cocktail[a]	None	TMC435 150 mg q.d. on Days 1-11		None
					Day 10	Day 11	
					Oral midazolam (0.075 mg/kg)	Drug cocktail[a]	

OR

Treatment Sequence B/A (n = 8)

Phase	Screening	Treatment B		Washout	Treatment A		Follow-up
Duration	≤ 28 days	11 days		At least 14 days	Day 1	Day 2	30, 31 or 32 days
Treatment	None	TMC435 150 mg q.d. on Days 1-11		None	Oral midazolam (0.075 mg/kg)	Drug cocktail[a]	None
		Day 10	Day 11				
		Oral midazolam (0.075 mg/kg)	Drug cocktail[a]				

[a] 0.025 mg/kg midazolam (i.v., given slowly over a 1-minute period via an i.v. cannula with the subject in a supine position), dextromethorphan (30 mg, orally), caffeine (150 mg, orally), omeprazole (40 mg, orally) and warfarin (10 mg, orally) supplemented with vitamin K (10 mg, orally).

Dose Selection Rationale

The dose (150 mg under fed condition) was used in Phase 2 and 3. The doses of the compounds in the drug cocktail was based on the validated doses reported in the literature

Administration

☐ Fasted ☒ Fed

Formulation

Treatment	Investigational Product		Midazolam	Drug Cocktail	
	TMC435	TMC435	Oral midazolam (Midazolam-ratiopharm®)	Midazolam (Dormicum®)	Caffeine (Percoffedrinol®)
Concentration Dosage Form (F No.) Usage	100 mg/capsule F007 oral	25 mg/capsule F008 oral	2 mg/mL liquid oral	5 mg/mL solution i.v.	50 mg/tablet tablet oral
Batch Number	08G25/F007	08G23/F008	147877	F102111	0701

Treatment	Drug Cocktail			
	Warfarin (Coumadin®)	Vitamin K (Konakion® MM)	Omeprazole (Antra® MUPS)	Dextromethorphan (Hustenstiller-ratiopharm®)
Concentration Dosage Form (F No.) Usage	5 mg/tablet tablet oral	10 mg/ampoule solution oral	20 mg/tablet tablet oral	30 mg/capsule capsule oral
Batch Number	9A39	F0155F71	KM8863A1	133193

Interfering Substances Excluded

None

Sampling Times

- Midazolam and 1-OH-midazolam

- at Day 1[a] and 10[b]: predose and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 5h, and 6h postdose;
- at Day 2[a] and 11[b]: predose, at 1 min (i.e., end of midazolam infusion), and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 5h, and 6h postdose.

- Omeprazole and 5-OH-omeprazole:

- at Day 2[a] and 11[b]: predose and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 5h, 6h, and 12h postdose.

- Dextromethorphan and dextrorphan:

- at Day 2[a] and 11[b]: predose and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 8h, and 12h postdose.

- Caffeine and paraxanthine:

- at Day 2[a] and 11[b]: predose and 1h, 2h, 3h, 4h, 5h, 6h, 8h, and 12h postdose.

- S-warfarin and 7-OH-S-warfarin:

- at Day 2[a] and 11[b]: predose and at 3h, 5h, 6h, and 12h postdose;
- at Day 3[a] and 12[b]: 24h and 36h postdose;
- at Day 4[a] and 13[b] (48h postdose), Day 5[a] and 14[b] (72h postdose), and Day 6[a] and 15[b] (96h postdose).

- TMC435 (only Treatment B):

- at Day 9 and Day 10: predose;
- at Day 11: predose and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 5h, 6h, 8h, and 12h postdose;
- at Day 12: at 24h and 36h after drug intake;
- at Day 13 (48h postdose), Day 14 (72h postdose), and Day 15 (96h postdose).

[a] Day of Treatment A
[b] Day of Treatment B

PK Parameters

Cmax; tmax; AUClast; Cl

PK Analysis

Non-compartmental analysis

Statistical Analysis

Intent-to-Treat analysis, descriptive statistics, linear mixed effects modeling

Is the study design acceptable? ☒ Yes ☐ No, if no please explain why

STUDY CONDUCT

Bioanalytical Method:

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	TMC435, midazolam, 1-OH-midazolam, S-warfarin, 7-OH-S-warfarin, caffeine, paraxanthine,		

	omeparzole, 5-OH-omeprazole, dextromethorphan, and dextrorphan
Range	2.00 – 8000 ng/mL for TMC435 ; LLOQ for midazolam, 1-OH-midazolam, S-warfarin, 7-OH-S-warfarin, caffeine, paraxanthine, omeparzole, 5-OH-omeprazole, dextromethorphan, and dextrorphan are 0.10, 0.10, 5.00, 5.00, 25.0, 25.0, 1.00, 1.00, 0.0500, and 0.800 ng/mL, respectively

Validation	▪ Method validated prior to use	☒ Yes ☐ No ☐ NA
	▪ Method validation acceptable	☒ Yes ☐ No ☐ NA
Study Samples Analysis	▪ Samples analyzed within the established stability period	☒ Yes ☐ No
	▪ Quality control samples range acceptable	☒ Yes ☐ No
	▪ Chromatograms provided	☒ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	▪ Incurred samples analysis is acceptable	☒ Yes ☐ No
	▪ Overall performance acceptable	☒ Yes ☐ No
Inspection	▪ Will the bioanalytical site be inspected	☐ Yes ☒ No

Notes:

Protocol Deviations

- Are there any protocol deviations listed in the study report? ☒ Yes ☐ No
- Do any of the listed deviations affect the integrity of the study? ☐ Yes ☒ No ☐ NA

STUDY RESULTS

Study Population

Randomized	16
Treated	16
Completed	16
Discontinued Due to AE	0
PK Population/Safety Population	16
Age [Median (range)]	47.0 (21-56)
Male/Female	5/11
Race (Caucasian)	16

Pharmacokinetics Results:

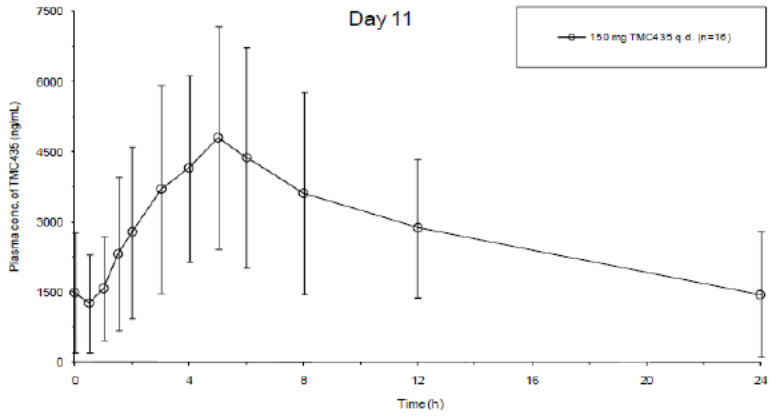


Figure 1: Mean Plasma Concentration-Time Curve of TMC435 on Day 11 of Treatment B

Effect on CYP3A4:

Pharmacokinetics of midazolam (mean ± SD, t_{max}: median [range])	**0.075 mg/kg midazolam oral or 0.025 mg/kg midazolam i.v. (reference)**	**150 mg TMC435 q.d. + 0.075 mg/kg midazolam oral or 0.025 mg/kg midazolam i.v. (test)**
Day 1/Day 10[a] (oral[c])		
n	16	16
C_{max}, ng/mL	13.99 ± 3.746	18.26 ± 4.175
t_{max}, h	1.3 (0.5-3.0)	1.8 (0.5-4.0)
AUC_{last}, ng.h/mL	47.03 ± 12.17	67.28 ± 13.80
Ratio $C_{max, P/M}$ (%)	287.0 ± 101.0	378.9 ± 112.8
Ratio $AUC_{last, P/M}$ (%)	307.3 ± 104.1	401.1 ± 120.5
Day 2/Day 11[b] (i.v.[d])		
n	16	16
C_{max}, ng/mL	154.4 ± 86.64	144.7 ± 132.0
t_{max}, h	0.02 (0.02-0.10)	0.02 (0.02-0.50)
AUC_{last}, ng.h/mL	79.45 ± 26.29	88.45 ± 38.95
CL, L/h	20.97 ± 8.014	18.35 ± 8.414
Ratio $C_{max, P/M}$ (%)	6257 ± 3921	6291 ± 5446
Ratio $AUC_{last, P/M}$ (%)	1132 ± 500.0	1184 ± 608.4
LSmean ratio (90% CI), %		
		Test vs reference
Day 1/Day 10[a] (oral[c])		
n	-	16 vs 16
C_{max}	-	131.3 (118.7-145.3)
AUC_{last}	-	145.3 (134.6-156.9)
Ratio $C_{max, P/M}$	-	133.1 (122.9-144.2)
Ratio $AUC_{last, P/M}$	-	130.7 (120.6-141.6)
Day 2/Day 11[b] (i.v.[d])		
n	-	16 vs 16
C_{max}	-	78.01 (52.14-116.7)
AUC_{last}	-	109.5 (95.41-125.6)
Ratio $C_{max, P/M}$	-	79.12 (53.11-117.9)
Ratio $AUC_{last, P/M}$	-	100.5 (85.78-117.8)

[a] Day 1: midazolam (oral) alone; Day 10: midazolam (oral) + TMC435
[b] Day 2: midazolam (i.v.) alone as part of the drug cocktail; Day 11: midazolam (i.v.) as part of the drug cocktail + TMC435
[c] Oral midazolam was administered to evaluate intestinal CYP3A4 activity.
[d] Intravenous midazolam was administered to evaluate hepatic CYP3A4 activity.

Pharmacokinetics of 1-OH-midazolam (mean ± SD, t_{max}: median [range])	0.075 mg/kg midazolam oral or 0.025 mg/kg midazolam i.v. (reference)	150 mg TMC435 q.d. + 0.075 mg/kg midazolam oral or 0.025 mg/kg midazolam i.v. (test)
Day 1/Day 10[a] (oral)		
n	16	16
C_{max}, ng/mL	5.456 ± 2.679	5.513 ± 3.252
t_{max}, h	1.3 (0.5-3.0)	1.8 (0.5-5.0)
AUC_{last}, ng.h/mL	16.39 ± 5.585	18.20 ± 6.528
Day 2/Day 11[b] (i.v.)		
n	16	16
C_{max}, ng/mL	2.765 ± 1.232	2.801 ± 1.456
t_{max}, h	0.5 (0.5-1.0)	0.5 (0.5-1.0)
AUC_{last}, ng.h/mL	7.738 ± 2.750	8.574 ± 3.525
LSmean ratio (90% CI), %		
		Test vs reference
Day 1/Day 10[a] (oral)		
n	-	16 vs 16
C_{max}	-	98.64 (88.63-109.8)
AUC_{last}	-	111.2 (105.7-117.0)
Day 2/Day 11[b] (i.v.)		
n	-	16 vs 16
C_{max}	-	98.60 (90.21-107.8)
AUC_{last}	-	108.9 (102.8-115.5)

Effect on CYP2C9:

Pharmacokinetics of S-warfarin (mean ± SD, t_{max}: median [range])	10 mg warfarin (reference)	150 mg TMC435 q.d. + 10 mg warfarin (test)
n	16	16
C_{max}, ng/mL	485.4 ± 71.19	485.9 ± 81.18
t_{max}, h	3.0 (3.0-5.0)	3.0 (3.0-5.0)
AUC_{last}, ng.h/mL	18510 ± 4356	19100 ± 4093
Ratio $C_{max, P/M}$ (%)	1494 ± 622.5	1508 ± 763.3
Ratio $AUC_{last, P/M}$ (%)	1303 ± 1258	1263 ± 1165
LSmean ratio (90% CI), %		
		Test vs reference
n	-	16 vs 16
C_{max}	-	99.83 (94.28-105.7)
AUC_{last}	-	103.7 (100.3-107.2)
Ratio $C_{max, P/M}$	-	98.45 (83.48-116.1)
Ratio $AUC_{last, P/M}$	-	98.19 (85.79-112.4)

Pharmacokinetics of 7-OH-S-warfarin (mean ± SD, t_{max}: median [range])	10 mg warfarin (reference)	150 mg TMC435 q.d. + 10 mg warfarin (test)
n	16	16
C_{max}, ng/mL	36.56 ± 11.92	38.24 ± 15.86
t_{max}, h	36.0 (12.0-36.0)	36.0 (12.0-36.0)
AUC_{last}, ng.h/mL	1911 ± 784.5	1993 ± 759.1
LSmean ratio (90% CI), %		
		Test vs reference
n	-	16 vs 16
C_{max}	-	101.4 (87.56-117.4)
AUC_{last}	-	105.6 (91.63-121.7)

Effect on CYP1A2:

Pharmacokinetics of caffeine (mean ± SD, t_{max}: median [range])	150 mg caffeine (reference)	150 mg TMC435 q.d. + 150 mg caffeine (test)
n	16	16
C_{max}, ng/mL	2996 ± 608.9	3357 ± 689.8
t_{max}, h	2.5 (1.0-3.0)	3.0 (1.0-5.0)
AUC_{last}, ng.h/mL	20430 ± 5784	25690 ± 6762
Ratio $C_{max, P/M}$ (%)	259.8 ± 53.12	321.6 ± 92.33
Ratio $AUC_{last, P/M}$ (%)	189.9 ± 52.60	263.4 ± 115.0
LSmean ratio (90% CI), %		
	-	**Test vs reference**
n	-	16 vs 16
C_{max}	-	112.2 (106.3-118.5)
AUC_{last}	-	126.4 (120.6-132.4)
Ratio $C_{max, P/M}$	-	121.7 (115.0-128.9)
Ratio $AUC_{last, P/M}$	-	134.1 (126.3-142.4)

Pharmacokinetics of paraxanthine (mean ± SD, t_{max}: median [range])	150 mg caffeine (reference)	150 mg TMC435 q.d. + 150 mg caffeine (test)
n	16	16
C_{max}, ng/mL	1165 ± 194.0	1077 ± 196.8
t_{max}, h	5.5 (3.0-12.0)	8.0 (4.0-12.0)
AUC_{last}, ng.h/mL	10850 ± 1768	10320 ± 2187
LSmean ratio (90% CI), %		
	-	**Test vs reference**
n	-	16 vs 16
C_{max}	-	92.16 (87.65-96.91)
AUC_{last}	-	94.24 (87.55-101.4)

Effect on CYP2C19:

Pharmacokinetics of omeprazole (mean ± SD, t_{max}: median [range])	40 mg omeprazole (reference)	150 mg TMC435 q.d. + 40 mg omeprazole (test)
n	16	16
C_{max}, ng/mL	422.2 ± 219.9	537.2 ± 458.7
t_{max}, h	4.0 (1.0-6.0)	3.5 (1.0-5.0)
AUC_{last}, ng.h/mL	1211 ± 1186	1602 ± 1992
Ratio $C_{max, P/M}$ (%)	149.1 ± 111.3	161.7 ± 158.6
Ratio $AUC_{last, P/M}$ (%)	118.0 ± 108.7	125.5 ± 145.8
LSmean ratio (90% CI), %		
	-	**Test vs reference**
n	-	16 vs 16
C_{max}	-	113.7 (92.78-139.3)
AUC_{last}	-	120.9 (100.4-145.7)
Ratio $C_{max, P/M}$	-	100.6 (90.16-112.3)
Ratio $AUC_{last, P/M}$	-	97.89 (85.34-112.3)

Pharmacokinetics of 5-OH-omeprazole (mean ± SD, t_{max}: median [range])	40 mg omeprazole (reference)	150 mg TMC435 q.d. + 40 mg omeprazole (test)
n	16	16
C_{max}, ng/mL	319.6 ± 104.9	357.5 ± 100.8
t_{max}, h	4.0 (1.0-6.0)	4.0 (1.0-6.0)
AUC_{last}, ng.h/mL	973.6 ± 221.6	1217 ± 333.7
LSmean ratio (90% CI), %		
	-	**Test vs reference**
n	-	16 vs 16
C_{max}	-	113.0 (98.90-129.1)
AUC_{last}	-	123.5 (113.3-134.7)

Effect on CYP2D6:

Pharmacokinetics of dextromethorphan (mean ± SD, t_{max}: median [range])	30 mg dextromethorphan (reference)	150 mg TMC435 q.d. + 30 mg dextromethorphan (test)
n	16	16
C_{max}, ng/mL	2.764 ± 4.419	2.854 ± 3.988
t_{max}, h	2.0 (1.5-8.0)	2.5 (1.0-8.0)
AUC_{last}, ng.h/mL	18.47 ± 34.93	18.10 ± 33.47
Ratio $C_{max, P/M}$ (%)	1.438 ± 3.815	1.248 ± 2.899
Ratio $AUC_{last, P/M}$ (%)	1.573 ± 4.112	1.256 ± 3.017
LSmean ratio (90% CI), %		
	-	**Test vs reference**
n	-	16 vs 16
C_{max}	-	120.6 (92.90-156.5)
AUC_{last}	-	108.1 (86.62-135.0)
Ratio $C_{max, P/M}$	-	116.9 (88.99-153.4)
Ratio $AUC_{last, P/M}$	-	99.18 (79.72-123.4)

Pharmacokinetics of dextrorphan (mean ± SD, t_{max}: median [range])	30 mg dextromethorphan (reference)	150 mg TMC435 q.d. + 30 mg dextromethorphan (test)
n	16	16
C_{max}, ng/mL	392.6 ± 109.6	409.2 ± 131.7
t_{max}, h	2.5 (1.5-4.0)	2.5 (1.5-8.0)
AUC_{last}, ng.h/mL	1890 ± 507.60	2051 ± 517.4
LSmean ratio (90% CI), %		
	-	**Test vs reference**
n	-	16 vs 16
C_{max}	-	103.2 (93.04-114.5)
AUC_{last}	-	109.0 (103.0-115.4)

- Were there any outliers or excluded data from analysis? ☐ Yes ☒ No ☐ NA
- Are the study results acceptable? ☒ Yes ☐ No

Safety

Was there any death or serious adverse events? ☐ Yes ☒ No

CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS

CONCLUSIONS

Coadministration of TMC435 150 mg q.d. and a drug cocktail, consisting of CYP enzyme probe drugs (for 3A4, 2C9, 1A2, 2C19, and 2D6), and oral midazolam suggests that TMC435 is a mild inhibitor of intestinal CYP3A4 activity, but does not affect hepatic CYP3A4 activity. The results also suggest that TMC435 is a mild inhibitor of CYP1A2, while CYP2C9, CYP2C19 and CYP2D6 enzyme activities are not significantly affected by TMC435. The sponsor's conclusions appear valid.

COMMENTS

None

LABEL RECOMMENDATIONS

None

CLINICAL PHARMACOLOGY DRUG-DRUG INTERACTION STUDY REVIEW				
Study #	TMC435-TiDP16-C110	**Study Period**	09/28/2009 - 01/06/2010	EDR Link
Title	A Phase I, open-label, single-sequence drug-drug interaction trial in subjects on stable methadone maintenance therapy, to investigate the potential pharmacokinetic interaction between TMC435 and methadone, at steady-state.			

STUDY DESIGN

A Phase I, open-label, single-sequence. The methadone therapy (dosage and formulation) was not to be changed from Day -14 until Day 8 inclusive, unless warranted for safety reasons. Subjects received simeprevir 150 mg q.d. for 7 days (Days 1 to 7), added to their methadone therapy.

30 days before screening	Screening	Run in (Day -14 to Day -1)	Day 1 to Day 7	Follow-up
Subject on stable methadone dosage for 30 days	≤ 21 days prior to Day-14	Supervised intake of individualized methadone Day -14 to Day -1	Simeprevir 150 mg QD	Continued intake of individualized methadone 30-32 days follow-up

Population	☐ Healthy Volunteers ☑ Patients: Subjects (HCV negative) on stable methadone maintenance therapy
Study Rationale	A drug-drug interaction between methadone and simeprevir cannot be excluded because simeprevir has been shown to be an inhibitor of CYP2D6 and CYP3A4/5. Recent in vivo findings do not support role of CYP3A4 in the metabolism of methadone. Prior to this study, methadone metabolism was believed to be mediated mainly by CYP3A4 and to a lesser extent by CYP2D6.
Treatments	Methadone: 30 to 150mg Simeprevir 150 mg QD
Dose Selection Rationale	Methadone dose was individualized for each subject and simeprevir is available in only one dose.
Administration	☐ Fasted ☑ Fed
Formulation	Simeprevir 75 mg capsules (F021), batch # 09C09/F021
Interfering Substances Excluded	Alcohol, grapefruit or grapefruit juice, apple juice, or orange juice, caffeinated beverages (e.g., coffee, tea, cola), drugs such as cocaine, amphetamines, benzodiazepines, barbiturates, or opiates (except for methadone)
Sampling Times	Days -4 to 7: Pre-dose Days -1 and 7: -2, -3, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 h post dose
PK Parameters	C_0, Cmin, tmax, Cmax, AUC_{0-24h}, $C_{ss,av}$, and FI
PK Analysis	Non-compartmental
Statistical Analysis	The least square (LS) means with 90% CI of the primary parameters for each treatment group (day) was estimated with a linear mixed effects model, controlling for treatment as a fixed effect, and subject as a random effect.
Is the study design acceptable? ☑ Yes ☐ No	

STUDY CONDUCT

Bioanalytical Method:

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	R-Methadone/S-Methadone		

Range	5-100 ng/mL

Validation	▪ Method validated prior to use	☑ Yes ☐ No ☐ NA
	▪ Method validation acceptable	☑ Yes ☐ No ☐ NA
Study Samples Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Incurred samples analysis is acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No
Inspection	▪ Will the bioanalytical site be inspected	☐ Yes ☑ No

Simeprevir bionalaysis was not reviewed because it is reviewed as part of other studies reviews.

Protocol Deviations

- Are there any protocol deviations listed in the study report? ☑ Yes ☐ No
- Do any of the listed deviations affect the integrity of the study? ☐ Yes ☑ No ☐ NA

If yes, explain why

Notes: One subject took forbidden medication (diovol) on day 4 within 4 hours of simeprevir intake.

STUDY RESULTS

Study Population

Screened	47
Treated	12
Completed	11
Discontinued Due to AE	1
PK Population/Safety Population	11/11
Age [Median (range)]	30.5(21-43)
Male/Female	10/2
Race (Caucasian/Black/Asian/Other)	11/0/0/0

Pharmacokinetics

Simeprevir steady state attainment was verified by comparing pre-dose plasma concentrations on days 4 to 7. R- and S-methadone plasma profiles were identical in the presence and absence of simeprevir.

1. **R-Methadone**

Parameter	LSmeans[a]		LSmeans ratio	90% CI[c]
	Individualized methadone therapy (reference)	Individualized methadone therapy + 150 mg TMC435 q.d. (test)		
C_{min}, ng/mL	143.6	146.6	1.021	0.9284 - 1.122
C_{max}, ng/mL	271.1	278.8	1.028	0.9669 - 1.094
AUC_{24h}, ng.h/mL[b]	4631	4607	0.9948	0.9108 - 1.086

[a] n=12 for reference and n=11 for test
[b] n=10 for test
[c] 90% confidence intervals

2. S-Methadone

Parameter	LSmeans[a]		LSmeans ratio	90% CI[c]
	Individualized methadone therapy (reference)	Individualized methadone therapy + 150 mg TMC435 q.d. (test)		
C_{min}, ng/mL	133.6	136.3	1.020	0.8921 - 1.166
C_{max}, ng/mL	325.7	354.0	1.087	1.017 - 1.162
AUC_{24h}, ng.h/mL[b]	4901	5029	1.026	0.9052 - 1.163

[a] n=12 for reference and n=11 for test
[b] n=10 for test
[c] 90% confidence intervals

- Were there any outliers or excluded data from analysis? ☐ Yes ☑ No ☐ NA, if yes explain
- Are the study results acceptable? ☑ Yes ☐ No, if no explain

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No

One subject prematurely discontinued study medication after 6 days of methadone + simeprevir intake due to grade 2 rash considered probably related to simeprevir and doubtfully related to methadone by the investigator

CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS

CONCLUSIONS

Does the study finding warrant dose adjustment upon the co-administration of the two drugs? ☐ Yes ☑ No

Is the interaction clinically significant? ☐ Yes ☐ No ☑ NA

COMMENTS

The reviewer could not locate the study samples bioanalytical run report.

LABEL RECOMMENDATIONS

The label should state that there is no need to adjust methadone dose upon the co-administration of simeprevir.

CLINICAL PHARMACOLOGY DRUG-DRUG INTERACTION STUDY REVIEW				
Study #	TMC435-TiDP16-C112	**Study Period**	27/05/2010-01/09/2010	EDR Link
Title	A Phase I, open-label, randomized, 3-way crossover trial in healthy subjects to investigate the pharmacokinetic interaction between TMC435 and escitalopram at steady-state			

STUDY DESIGN	
Population	☑ Healthy Volunteers ☐ Patients
Study Rationale	The study was conducted due to the likely co-administration of TMC435 and escitalopram in patients with chronic HCV infection as the treatment of HCV infection with PegIFNα plus RBV is associated with a high rate of depression. TMC435 is a substrate of CYP3A and to a lesser extent CYP2C8 and CYP2C19. TMC435 is also a substrate of P-gp, MRP2, BCRP, OATP1B1/3, and OATP2B1. TMC435 is a mild inhibitor of intestinal CYP3A and a mild inhibitor of CYP1A2. *In vitro*, TMC435 inhibits OATP1B1, sodium taurocholate cotransporting polypeptide (NTCP), P-gp, MRP2, and BSEP. Escitalopram is metabolized by CYP3A and CYP2C19 *in vitro*.
Treatments	A: TMC435 150 mg q.d. for 7 days. B: Escitalopram 10 mg q.d. for 7 days. C: A+B *The TMC435 and escitalopram terminal elimination half-lives are approximately 12 hours and 30 hours, respectively. **Sequence**: A-B-C/B-C-A/C-A-B/C-B-A/B-A-C/A-C-B *A washout period of at least 10 days between medication intakes.
Dose Selection Rationale	The TMC435 150 mg q.d. dose had been selected as this is the highest dose that is being studied in the Phase 2b and 3 trials. Escitalopram (Lexapro®) was administered at 10 mg q.d. as this is the recommended clinical dose regimen.
Administration	☐ Fasted ☑ Fed
Formulation	TMC435 capsule 75 mg (F021), Batch # 09C09/F021, Escitalopram (Lexapro®) tablet 10 mg, Batch# 2193182
Interfering Substances Excluded	None
Sampling Times	-0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16 and 24 hours post-dose on Day 7 in each group -Trough concentrations on Days 5 and 6 in each group
PK Parameters	C_{0h}, C_{min}, $C_{ss,av}$, C_{max}, fluctuation index, t_{max}, AUC_{24h}, Ratio $C_{min,test/ref}$, Ratio $C_{max,test/ref}$, and Ratio $AUC_{24h,test/ref}$
PK Analysis	Non-compartmental analysis
Statistical Analysis	The least square (LS) means of the primary parameters (i.e., C_{min}, C_{max}, and AUC_{24h} on the logarithmic scale) for each treatment group was estimated with a linear mixed effects model, controlling for treatment, sequence and period as fixed effects, and subject as a random effect. The LS mean ratio and its 90% confidence interval (CI) were calculated and retransformed to the original scale.
Is the study design acceptable? ☑ Yes ☐ No	

STUDY CONDUCT				
Bioanalytical Method				
	Method Name	TMC435 (SH-J01-R618/BA1238) Escitalopram (PBRL-RD-1123)		
	Method Type	LC-MS/MS	Matrix	Plasma

Analytes	TMC435, (S)-citalopram
Range	TMC435 (2-2000 ng/mL) (S)-citalopram (0.2-100 ng/mL)

Validation	▪ Method validated prior to use	☑ Yes ☐ No ☐ NA
	▪ Method validation acceptable	☑ Yes ☐ No ☐ NA
Study Samples Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Incurred samples analysis is acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No
Inspection	▪ Will the bioanalytical site be inspected	☐ Yes ☑ No

Protocol Deviations

- Are there any protocol deviations listed in the study report? ☐ Yes ☑ No
- Do any of the listed deviations affect the integrity of the study? ☐ Yes ☐ No ☑ NA

STUDY RESULTS

Study Population

Randomized	20
Treated	20
Completed	17
Discontinued Due to AE	1
PK Population/Safety Population	17
Age [Median (range)]	24 (19-52)
Male/Female	20/0
Race: Caucasian (%)	100

Note: One subject (112-0014) permanently discontinued study medication with last medication intake on Day 3 after co-administration of 150 mg q.d. TMC435 and 10 mg q.d. escitalopram due to grade 2 mydriasis and headache starting on Day 3 after co-administration of 150 mg q.d. TMC435 and 10 mg q.d. escitalopram (A-C-B). Mydriasis was considered not related to TMC435 and possibly related to escitalopram and headache was considered not related to TMC435 or escitalopram by the investigator.

Pharmacokinetics

- PK Parameters and LS Mean Ratio & 90% CI

Pharmacokinetics of TMC435 (mean ± SD)	150 mg q.d. TMC435 (reference)			150 mg q.d. TMC435 + 10 mg q.d. escitalopram (test)		
n	18			17		
C_{min}, ng/mL	340	±	197	240	±	176
C_{max}, ng/mL	2,147	±	847	1,778	±	831
t_{max}, h	5.28	±	1.23	4.98	±	1.12
AUC_{24}, ng.h/mL	23,283	±	10,350	17,820	±	9,545

Day 7

PK parameter	LSMean		Number of Subjects	Ratio test/reference	90% CI
	Reference (TMC435)	Test (TMC435 + escitalopram)			
C_{min}, ng/mL	288.30	195.72	17	0.679	0.59 - 0.79
C_{max}, ng/mL	2,009.32	1,600.33	17	0.797	0.74 - 0.89
AUC_{24}, ng.h/mL	21,358.88	15,953.21	17	0.747	0.68 - 0.83

Pharmacokinetics of escitalopram (mean ± SD)	10 mg q.d. escitalopram (reference)			150 mg q.d. TMC435 + 10 mg q.d. escitalopram (test)		
n	17			17		
C_{min}, ng/mL	11.40	±	5.42	11.50	±	5.17
C_{max}, ng/mL	21.00	±	6.46	21.40	±	5.94
t_{max}, h	3.09	±	1.43	2.88	±	1.39
AUC_{24}, ng.h/mL	377	±	145	377	±	136

Day 7

PK parameter	LSMean		Number of Subjects	Ratio test/reference	90% CI
	Reference (escitalopram)	Test (TMC435 + escitalopram)			
C_{min}, ng/mL	10.45	10.47	17	1.00	0.95 - 1.05
C_{max}, ng/mL	20.26	20.87	17	1.03	0.99 - 1.07
AUC_{24}, ng.h/mL	356.92	357.49	17	1.00	0.97 - 1.03

Figure 1: Mean (±SD) Plasma Time-Concentration Profiles of TMC435 (150 mg q.d.) Administered Alone and Co-administered With Escitalopram (10 mg q.d.)

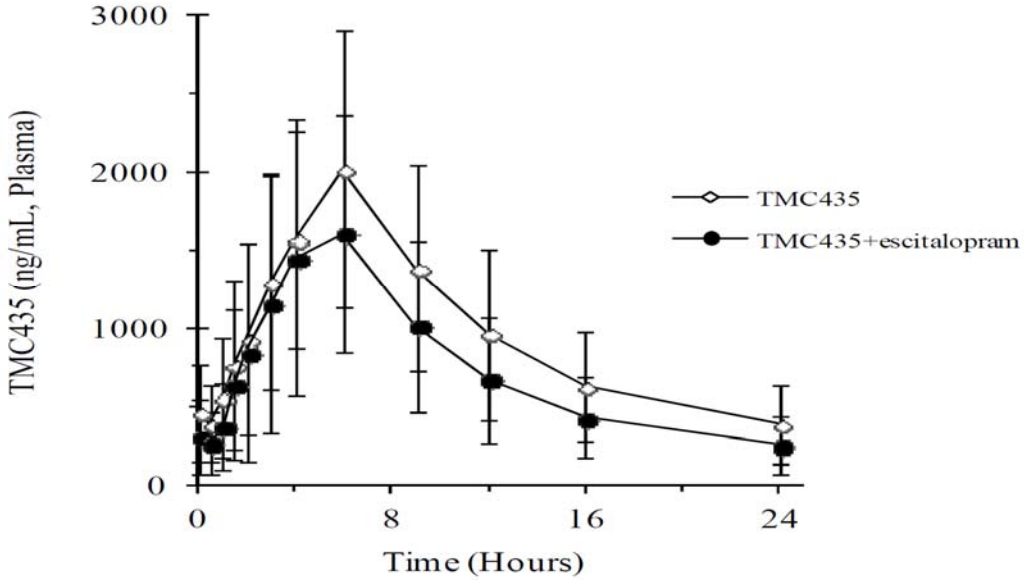
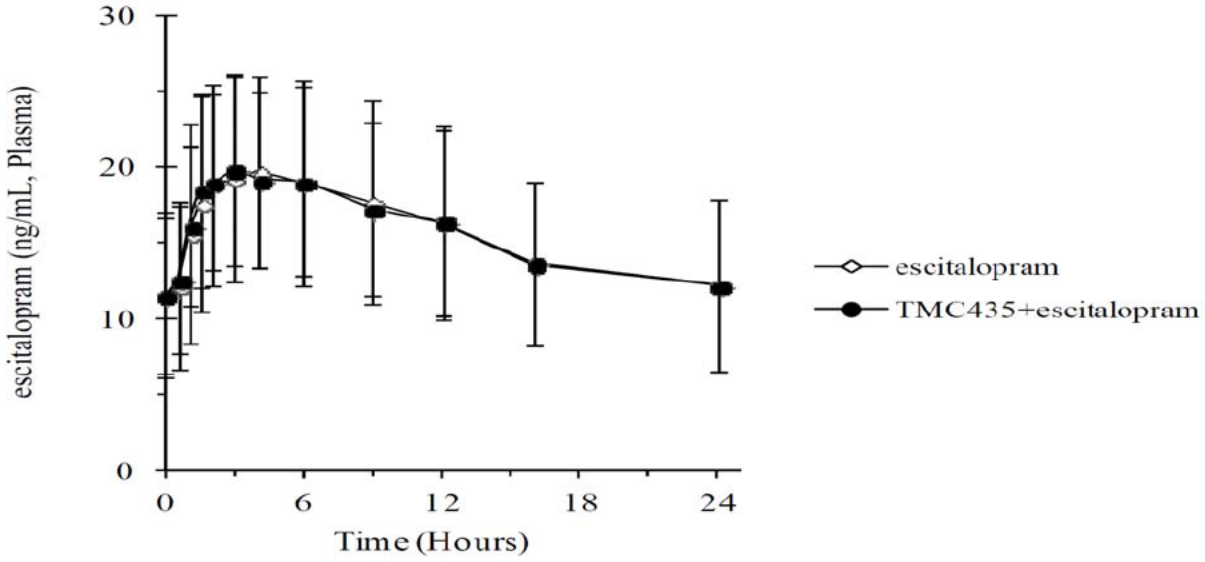


Figure 2: Mean (±SD) Plasma Time-Concentration Profiles of Escitalopram (10 mg q.d.) Administered Alone

and Co-administered With TMC435 (150 mg q.d.)



- Were there any outliers or excluded data from analysis? ☐ Yes ☑ No ☐ NA
- Are the study results acceptable? ☑ Yes ☐ No

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No

CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS

CONCLUSIONS

Does the study finding warrant avoiding or dose adjustment upon the co-administration of TMC435 with escitalopram? ☑ Yes ☐ No

Note: TMC435 AUC_{24h}, C_{min} and C_{max} were decreased by approximately 25%, 32% and 20% at steady-state, respectively, when co-administered with 10 mg of escitalopram.

Is the interaction clinically significant? ☑ Yes ☐ No ☐ NA

LABEL RECOMMENDATIONS

Co-administration of TMC435 and escitalopram decreases TMC435 concentrations, but efficacy is not expected to be affected. No dose adjustment of TMC435 is necessary when co-administered with escitalopram.

CLINICAL PHARMACOLOGY DRUG-DRUG INTERACTION STUDY REVIEW				
Study #	TMC435-TiDP16-C114	**Study Period**	15/11/2010-30/03/2011	EDR Link
Title	A Phase I, 2-panel, open-label, randomized, cross-over trial in healthy subjects to investigate the PK interaction between TMC435 and antiretroviral agents, TMC278 and tenofovir disoproxil fumarate (TDF), at steady-state			

STUDY DESIGN	
Population	☑ Healthy Volunteers ☐ Patients
Study Rationale	The study was conducted to provide the dosing recommendations for co-administration of TMC435 and these antiretroviral (i.e., TMC278 or TDF) in HIV and HCV co-infected patients. TMC435 is a substrate of CYP3A and to a lesser extent CYP2C8 and CYP2C19. TMC435 is also a substrate of P-gp, MRP2, BCRP, OATP1B1/3, and OATP2B1. TMC435 is a mild inhibitor of intestinal CYP3A and a mild inhibitor of CYP1A2. *In vitro*, TMC435 inhibits OATP1B1, sodium taurocholate cotransporting polypeptide (NTCP), P-gp, MRP2, and BSEP. TMC278 is a CYP3A4 substrate. TDF is not a substrate of CYP enzymes but a substrate of hOAT1, hOAT3, and MRP4.
Treatments	A: TMC435 150 mg q.d. for 11 days B: TMC278 25 mg q.d. for 11 days C: A+B D: TMC435 150 mg q.d. for 7 days E: TDF 300 mg q.d. for 7 days F: D+E *The TMC435, TMC278 and TDF terminal elimination half-lives are approximately 12 hours, 45 hours and 17 hours, respectively. **Sequence** Panel 1: A-B-C/B-C-A/C-A-B/C-B-A/B-A-C/A-C-B *A washout period of at least 14 days between medication intakes. Panel 2: D-E-F/E-F-D/F-D-E/D-F-E/F-E-D/E-D-F *A washout period of at least 7 days between medication intakes.
Dose Selection Rationale	The TMC435 150 mg q.d. dose had been selected as this is the highest dose that is being studied in the Phase 2b and 3 trials. The TMC278 25 mg q.d. dose had been selected as this is the selected dose for HIV-infected adult patients in the current clinical trials. The TDF 300 mg q.d dose had been selected as this is the recommended clinical dose regimen for HIV-1 infected patients.
Administration	☐ Fasted ☑ Fed
Formulation	TMC435 150 mg capsule (F021), Batch # 10A26/F021, TMC278 25 mg film-coated tablet (F006), Batch# 9CL1F, TDF 300 mg film-coated tablet, Batch# 10VR001D
Interfering Substances Excluded	None
Sampling Times	-0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16 and 24 hours post-dose on Day 11 in Panel 1 and on Day 7 in Panel 2. -Trough concentrations on Days 9 and 10 in Panel 1 and on Days 5 and 6 in Panel 2.
PK Parameters	C_{0h}, C_{min}, $C_{ss,av}$, C_{max}, fluctuation index, t_{max}, AUC_{24h}, Ratio $C_{min,test/ref}$, Ratio $C_{max,test/ref}$, and Ratio $AUC_{24h,test/ref}$
PK Analysis	Non-compartmental analysis
Statistical Analysis	The least square (LS) means of the primary parameters (i.e., C_{min}, C_{max}, and AUC_{24h} on the logarithmic scale) for each treatment group was estimated with a linear mixed

	effects model, controlling for treatment, sequence and period as fixed effects, and subject as a random effect. The LS mean ratio and its 90% confidence interval (CI) were calculated.
Is the study design acceptable? ☑ Yes ☐ No	

STUDY CONDUCT

Bioanalytical Method

Method Name	TMC435 (SH08-J01-R618/BA1238) TMC278 (SH08-J01-TR288) TDF (PBRL-RD-688 / PBR-044353 and PBRL-RD-688 / TIE555EL-085553-F and PBRL-RD-688 / PRALABIN-111003-A)		
Method Type	LC-MS/MS	Matrix	Plasma
Analytes	TMC435, TMC278, TDF		
Range	TMC435 (2-2000 ng/mL) TMC278 (1-2000 ng/mL) TDF (2-500 ng/mL)		

Validation	▪ Method validated prior to use	☑ Yes ☐ No ☐ NA
	▪ Method validation acceptable	☑ Yes ☐ No ☐ NA
Study Samples Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Incurred samples analysis is acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No
Inspection	▪ Will the bioanalytical site be inspected	☐ Yes ☑ No

Protocol Deviations

- Are there any protocol deviations listed in the study report? ☐ Yes ☑ No
- Do any of the listed deviations affect the integrity of the study? ☐ Yes ☐ No ☑ NA

STUDY RESULTS

Study Population

Panel 1: TMC435 150 mg q.d. for 11 days & TMC278 25 mg q.d. for 11 days

Randomized	24
Treated	21
Completed	21
Discontinued Due to AE	0
PK Population/Safety Population	21
Age [Median (range)]	42.5 (21-54)
Male/Female	12/12
Race: Black/White (%)	4.2/95.8

Panel 2: TMC435 150 mg q.d. for 7 days & TDF 300 mg q.d. for 7 days

Randomized	24
Treated	24
Completed	24
Discontinued Due to AE	0
PK Population/Safety Population	24
Age [Median (range)]	44.0 (27-55)
Male/Female	12/12
Race: Black/White (%)	0/100

Pharmacokinetics

- Pharmacokinetic Parameters and LS Mean Ratio & 90% CI

Panel 1

Pharmacokinetics of TMC435 (mean ± standard deviation [SD], t_{max}: median [range])	**Treatment A** 150 mg q.d. TMC435 for 11 days (reference)	**Treatment C** 150 mg q.d. TMC435 + 25 mg q.d. TMC278 for 11 days (test)
n	21	21[a]
Day 9		
C_{0h}, ng/mL	563.9 ± 472.3	674.8 ± 648.3
Day 10		
C_{0h}, ng/mL	551.0 ± 420.0	682.8 ± 617.2
Day 11		
C_{0h}, ng/mL	596.5 ± 455.6	653.5 ± 571.7
C_{min}, ng/mL	456.6 ± 305.6	483.6 ± 416.4
C_{max}, ng/mL	2297 ± 1092	2460 ± 1287
t_{max}, h	5.0 (5.0 - 6.0)	5.0 (5.0 - 6.0)
AUC_{24h}, ng.h/mL	26400 ± 14250	26840 ± 15250
$C_{ss,av}$, ng/mL	1100 ± 593.9	1118 ± 635.5
Fluctuation index, %	178.5 ± 55.63	191.8 ± 40.94
	LS mean ratio (90% CI)	
Day 11		**Test versus reference**
n		21[a] versus 21
C_{min}	-	0.96 (0.83 - 1.11)
C_{max}	-	1.10 (0.97 - 1.26)
AUC_{24h}	-	1.06 (0.94 - 1.19)

[a] n = 20 for Day 11 C_{max}, t_{max}, AUC_{24h}, $C_{ss,av}$ and fluctuation index (one subject for which the 6 h TMC435 pharmacokinetic sample was not available at Day 11); LS = least square; CI = confidence interval.

Pharmacokinetics of TMC278 (mean ± SD, t_{max}: median [range])	**Treatment B** 25 mg q.d. TMC278 for 11 days (reference)	**Treatment C** 150 mg q.d. TMC435 + 25 mg q.d. TMC278 for 11 days (test)
n	23	21
Day 9		
C_{0h}, ng/mL	87.28 ± 37.59	102.8 ± 47.13
Day 10		
C_{0h}, ng/mL	90.51 ± 28.90	102.8 ± 36.95
Day 11		
C_{0h}, ng/mL	95.07 ± 32.11	108.7 ± 34.43
C_{min}, ng/mL	71.60 ± 23.21	88.17 ± 27.12
C_{max}, ng/mL	190.7 ± 55.22	198.2 ± 59.15
t_{max}, h	5.0 (3.0 - 6.0)	4.0 (1.5 - 9.0)
AUC_{24h}, ng.h/mL	2716 ± 675.2	3012 ± 730.1
$C_{ss,\,av}$, ng/mL	113.2 ± 28.14	125.5 ± 30.42
Fluctuation index, %	106.3 ± 20.86	87.29 ± 24.61
	LS mean ratio (90% CI)	
Day 11		**Test versus reference**
n		21 versus 23
C_{min}	-	1.25 (1.16 - 1.35)
C_{max}	-	1.04 (0.95 - 1.13)
AUC_{24h}	-	1.12 (1.05 - 1.19)

Panel 2

Pharmacokinetics of TMC435 (mean ± SD, t_{max}: median [range])	**Treatment D** 150 mg q.d. TMC435 for 7 days	**Treatment F** 150 mg q.d. TMC435 + 300 mg q.d. TDF for 7 days
n	24[b]	24
Day 5		
C_{0h}, ng/mL	722.7 ± 1002	509.3 ± 336.3
Day 6		
C_{0h}, ng/mL	802.5 ± 1132	610.8 ± 491.9
Day 7		
C_{0h}, ng/mL	918.0 ± 1419	653.5 ± 591.4
C_{min}, ng/mL	742.3 ± 1170	521.9 ± 439.7
C_{max}, ng/mL	3119 ± 2412	2448 ± 1464
t_{max}, h	6.0 (5.0-12.0)	5.0 (3.0-12.0)
AUC_{24h}, ng.h/mL	39110 ± 41820	29830 ± 20280
$C_{ss,\,av}$, ng/mL	1630 ± 1742	1243 ± 845.2
Fluctuation index, %	174.4 ± 60.95	167.5 ± 53.22
	LS mean ratio (90% CI)[b]	
		Test versus reference
n		24 versus 24[a]
Day 7		
C_{min}	-	0.93 (0.78 - 1.11)
C_{max}	-	0.85 (0.73 - 0.99)
AUC_{24h}	-	0.86 (0.76 - 0.98)

[a] n = 23 for Day 7 C_{max}, t_{max}, AUC_{24h}, $C_{ss,av}$ and fluctuation index (one subject for which TMC435 pharmacokinetic sample was not available at Day 7).

[b] It must be noted that the high variation in TMC435 plasma concentrations in the reference treatment (TMC435 alone) was largely caused by the considerably higher plasma concentration values of Subjects 114-2048 and 114-2046. Therefore, an exploratory statistical analysis was performed in which these two subjects were excluded. In this analysis, the LSmeans ratios of C_{min}, C_{max}, and AUC_{24h} of TMC435 were, 1.01, 0.91, and 0.92, respectively. The 90% CIs of C_{min} and AUC_{24h} were within the [0.8-1.25] interval, while the lower limit of the CI of C_{max} was just below the 0.8 predetermined limit.

Pharmacokinetics of tenofovir (mean ± SD, t_{max}: median [range])	**Treatment E** 300 mg q.d. TDF for 7 days (reference)	**Treatment F** 150 mg q.d. TMC435 + 300 mg q.d. TDF for 7 days (test)
n	24	24
Day 5		
C_{0h}, ng/mL	76.89 ± 23.91	86.48 ± 31.01
Day 6		
C_{0h}, ng/mL	77.55 ± 21.78	93.03 ± 26.56
Day 7		
C_{0h}, ng/mL	74.75 ± 20.74	89.67 ± 23.77
C_{min}, ng/mL	66.25 ± 18.32	81.40 ± 20.07
C_{max}, ng/mL	350.8 ± 138.5	409.3 ± 117.9
t_{max}, h	2.0 (1.0-6.0)	3.0 (1.0-5.0)
AUC_{24h}, ng.h/mL	3602 ± 1052	4240 ± 1095
$C_{ss, av}$, ng/mL	150.1 ± 43.85	176.7 ± 45.62
Fluctuation index, %	186.3 ± 39.77	185.9 ± 37.07
	LS mean ratio (90% CI)	
		Test versus reference
n		24 versus 24
Day 7		
C_{min}	-	1.24 (1.15 - 1.33)
C_{max}	-	1.19 (1.10 - 1.30)
AUC_{24h}	-	1.18 (1.13 - 1.24)

Figure 1: Mean (±SD) Plasma Concentration-Time Curves of TMC435
During Administration of 150 mg q.d. TMC435 Alone (Treatment A, Day 11) and
During Coadministration of 150 mg q.d. TMC435 and 25 mg q.d. TMC278 (Treatment C, Day 11)

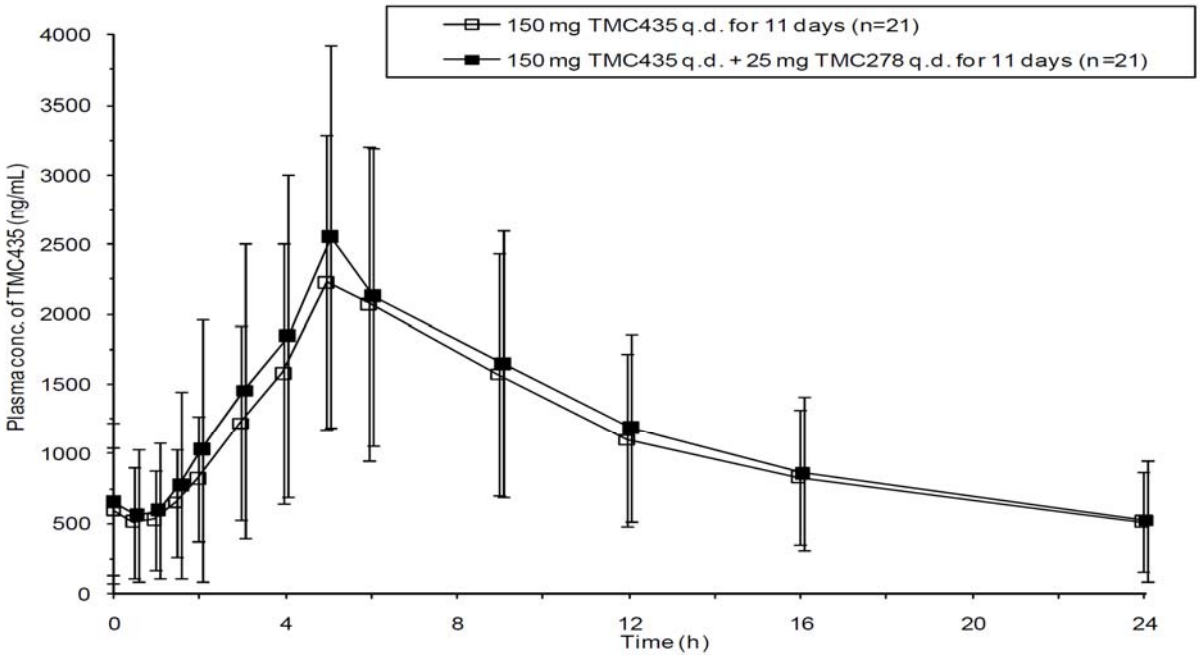


Figure 2: Mean (±SD) Plasma Concentration-Time Curves of TMC278
During Administration of 25 mg q.d. TMC278 Alone (Treatment B, Day 11) and
During Coadministration of 150 mg q.d. TMC435 and 25 mg q.d. TMC278 (Treatment C, Day 11)

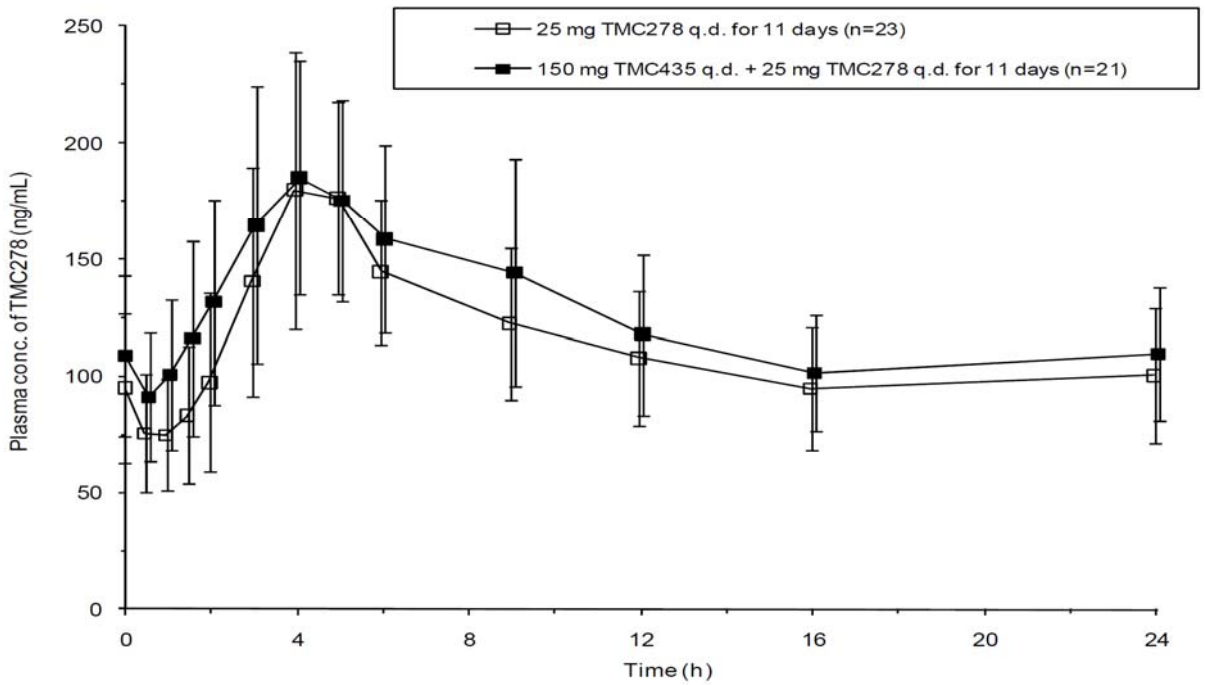


Figure 3: Mean (±SD) Plasma Concentration-Time Curves of TMC435
During Administration of 150 mg q.d. TMC435 Alone (Treatment D, Day 7) and
During Coadministration of 150 mg q.d. TMC435 and 300 mg q.d. TDF (Treatment F, Day 7)

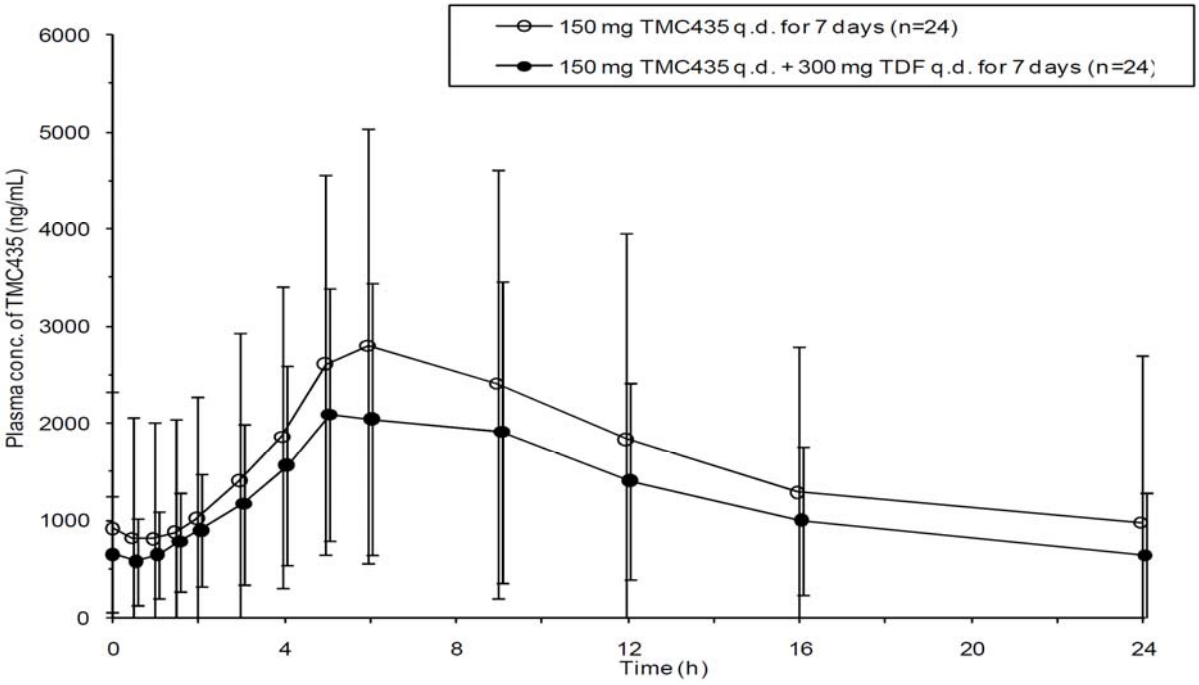
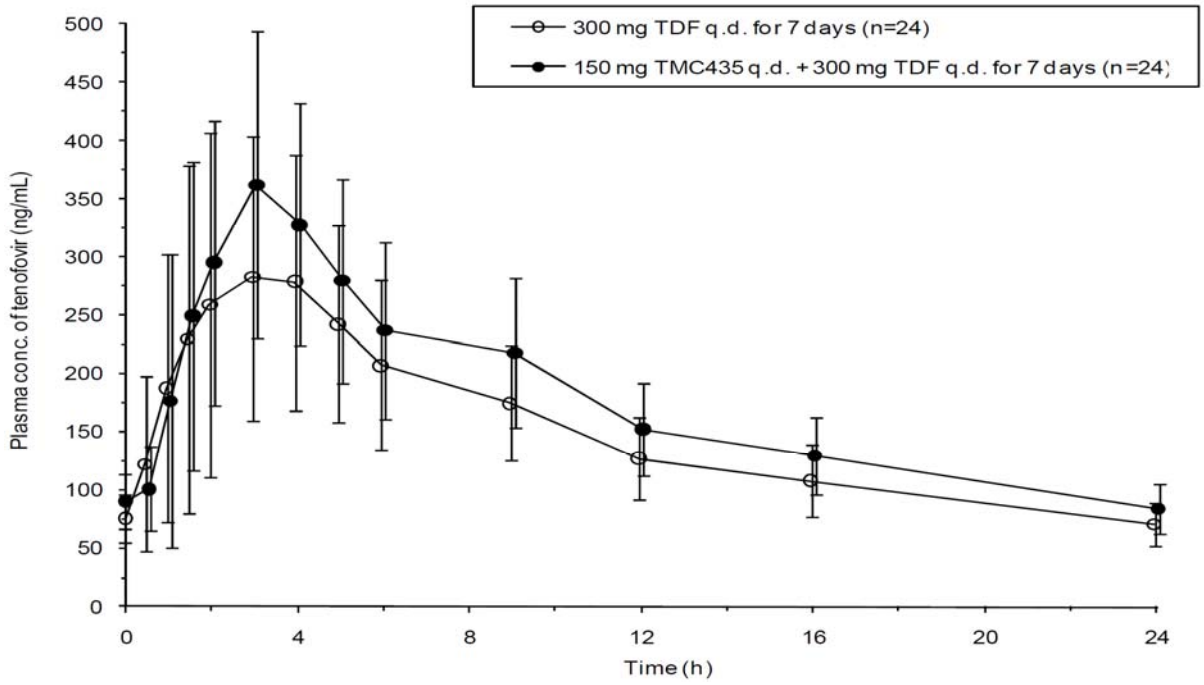


Figure 4: Mean (±SD) Plasma Concentration-Time Curves of TDF
During Administration of 300 mg q.d. TDF Alone (Treatment E, Day 7) and
During Coadministration of 150 mg q.d. TMC435 and 300 mg q.d. TDF (Treatment F, Day 7)



- Were there any outliers or excluded data from analysis? ☑ Yes ☐ No ☐ NA

Note: In Treatment D and F, there were two subjects (114-2048 and 114-2046) displayed considerably high TMC435 exposures especially when TMC435 was taken by itself. The reason for the higher exposures is not known. An exploratory statistical analysis was performed in which two subjects (114-2048 and 114-2046) were excluded. In this analysis, the LS means ratios of C_{min}, C_{max}, and AUC_{24h} of TMC435 were, 1.01, 0.91, and 0.92, respectively. The 90% CIs of C_{min} and AUC_{24h} were within the [0.8-1.25] interval, while the lower limit of the CI of C_{max} was just below the 0.8 predetermined limit.

Figure 5: AUC_{24h} of TMC435 in Treatment D (150 mg TMC435 q.d. for 7 days) and F (150 mg TMC435 q.d. + 300 mg TDF q.d. for 7 days).

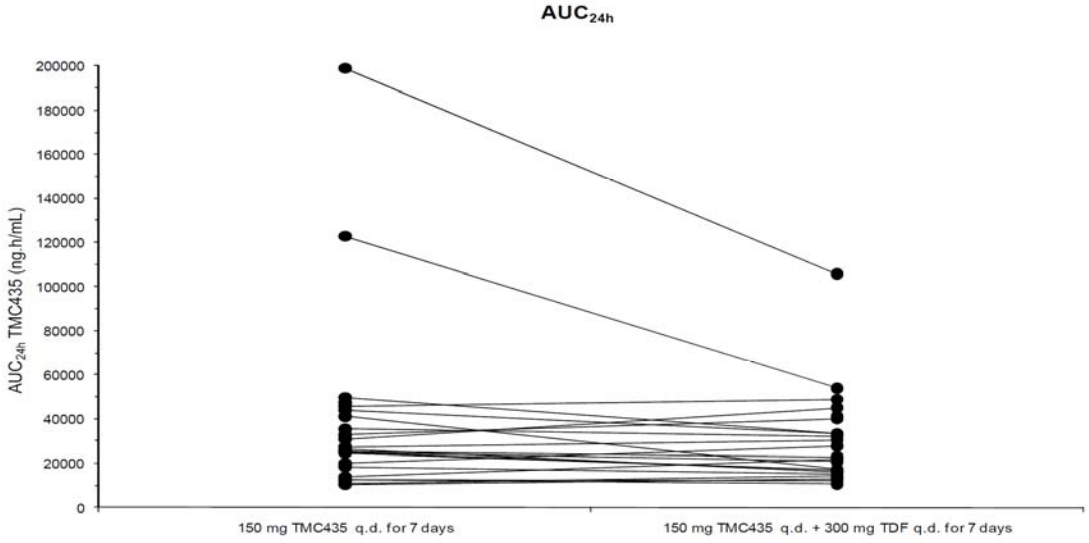
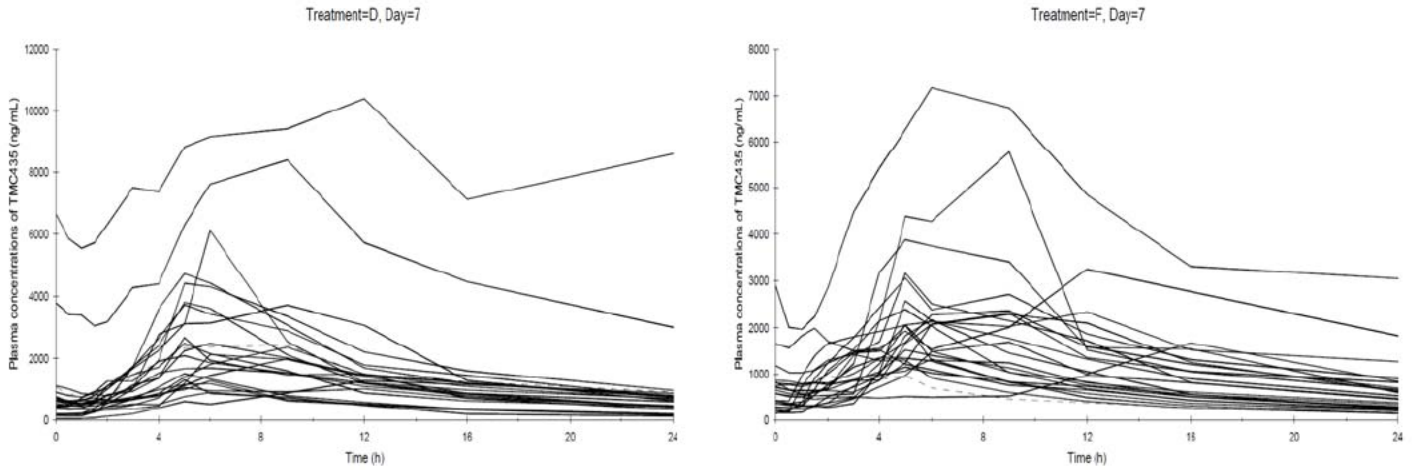


Figure 6: Combined plasma concentration-time curves of TMC435 in Treatment D (150 mg TMC435 q.d. for 7 days) and F (150 mg TMC435 q.d. + 300 mg TDF q.d. for 7 days).



- Are the study results acceptable? ☑ Yes ☐ No

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No

CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS

CONCLUSIONS

Does the study finding warrant dose adjustment upon the co-administration of TMC435 with TMC278? ☐ Yes ☑ No

Does the study finding warrant dose adjustment upon the co-administration of TMC435 with TDF? ☐ Yes ☑ No

Is the interaction clinically significant? ☐ Yes ☑ No ☐ NA

LABEL RECOMMENDATIONS

No dose adjustment of TMC435 is necessary when co-administered with TMC278 or TDF, and no dose adjustment of TMC278 or TDF is required when co-administered with TMC435.

CLINICAL PHARMACOLOGY DRUG-DRUG INTERACTION STUDY REVIEW				
Study #	TMC435-TiDP16-C115	**Study Period**	11 Mar to 5 Aug 2011	EDR Link
Title	A Phase I, open-label, randomized, crossover trial in healthy subjects to investigate the pharmacokinetic interaction between TMC435 and CYP3A inhibitors erythromycin and darunavir/ritonavir (DRV/r)			

STUDY DESIGN	
Population	☑ Healthy Volunteers ☐ Patients
Study Rationale	The study was conducted evaluate the effect of a moderate (erythromycin) or strong (DRV/r) CYP3A inhibitor on TMC435 pharmacokinetics.. TMC435 undergoes metabolism via CYP3A4.
Treatments	Panel 1 A: TMC435 150 mg QD for 7 days B: erythromycin 500 mg TID for 6 days (morning dose on Day 7) C: A+B for 7 days Panel 2 D: TMC435 150 mg QD for 7 days E: DRV/r 800/100 mg QD for 7 days F: D+E for 7 days **Sequence** Panel 1: A-B-C/A-C-B/B-A-C/B-C-A/C-A-B/C-B-A Panel 2: D-E-F/D-F-E/E-D-F/E-F-D/F-D-E/F-E-D A washout period of at least 10 days separated treatments
Dose Selection Rationale	The TMC435 150 mg QD dose was selected because it is the dose being used in Phase 3 studies. The TMC435 dose was prospectively reduced to 50 mg QD in combination with DRV/r based on anticipated exposure increases. The DRV/r 800/100 mg QD dose is used for the treatment of HIV infection. The erythromycin dose of 500 mg TID is the maximum dose recommended for the treatment of acute mild to moderate infections.
Administration	☐ Fasted ☑ Fed
Formulation	TMC435 150 mg capsule, Batch 11B02 (G012) or 11B03 (G007) Erythromycin 500 mg tablets, Batch BCZS032 Darunavir 400 mg tablets, Batch 0HG2350-X Ritonavir 100 mg tablets, Batch 86177eD
Interfering Substances Excluded	All concomitant medications (except acetaminophen, ibuprofen, and oral contraceptives) were prohibited beginning 14 days before study drug administration until study completion.
Sampling Times	Panels 1 and 2 Days 1, 5, 6: predose Day 7: 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours postdose Day 6: predose Day 7: 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours postdose
PK Parameters	C_{0h}, C_{min}, $C_{ss,av}$, C_{max}, fluctuation index, t_{max}, AUC_{24h}, Ratio $C_{min,test/ref}$, Ratio $C_{max,test/ref}$, and Ratio $AUC_{24h,test/ref}$
PK Analysis	Non-compartmental analysis
Statistical Analysis	The least square (LS) means of the primary parameters (i.e., C_{min}, C_{max}, and AUC_{24h}

	on the logarithmic scale) for each treatment group was estimated with a linear mixed effects model, controlling for treatment, sequence and period as fixed effects, and subject as a random effect. The LS mean ratio and its 90% confidence interval (CI) were calculated.

Is the study design acceptable? ☑ Yes ☐ No

STUDY CONDUCT

Bioanalytical Method

Method Name	TMC435 (PBRL-RD-1154 [BA1513]) DRV and RTV (PBRL-BV-1041 [BA1389, BA502]) Erythromycin (PBRL-RD-1308)		
Method Type	LC-MS/MS	Matrix	Plasma
Analytes	TMC435, DRV, RTV, erythromycin		
Range	TMC435 (2-2000 ng/mL) DRV (5-10000 ng/mL RTV (5-10000 ng/mL) Erythromycin (20-5000 ng/mL)		

Validation	▪ Method validated prior to use	☑ Yes ☐ No ☐ NA
	▪ Method validation acceptable	☑ Yes ☐ No ☐ NA
Study Samples Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Incurred samples analysis is acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No
Inspection	▪ Will the bioanalytical site be inspected	☐ Yes ☑ No

Protocol Deviations

- Are there any protocol deviations listed in the study report? ☐ Yes ☑ No
- Do any of the listed deviations affect the integrity of the study? ☐ Yes ☐ No ☑ NA

STUDY RESULTS

Study Population

Randomized	49
Treated	49
Completed	45
Discontinued Due to AE	3
PK Population/Safety Population	45/49
Age [Median (range)]	(19-55)
Male/Female	21/28
Race: Black/White (%)	48/1

TMC435 plasma concentrations were higher in the presence of the moderate CYP3A inhibitor erythromycin; the magnitude of exposure increases was comparable to that caused by the strong CYP3A inhibitor ritonavir (7.47- vs. 7.18-fold increases in AUC_{24}, respectively; Tables 1-2 and Trial C104). Erythromycin concentrations also increased in the presence of TMC435 (AUC_8 by approximately 90%, Table 3).

Table 1: Pharmacokinetics of TMC435350 after multiple dose administration of TMC435 150 mg QD alone and coadministered with erythromycin 500 mg TID

Pharmacokinetics of TMC435 (mean ± SD, t_{max}: median [range])	150 mg TMC435 q.d. (Reference)			150 mg TMC435 q.d. + 500 mg Erythromycin t.i.d. (Test)		
n	24[a]			24		
Day 5						
C_{0h}, ng/mL	888.5	±	919.2	6311	±	4657
Day 6						
C_{0h}, ng/mL	1068	±	1151	8034	±	5910
Day 7						
C_{0h}, ng/mL	1151	±	1392	9389	±	6574
C_{min}, ng/mL	817.2	±	968.3	8148	±	5525
C_{max}, ng/mL	3788	±	3011	15230	±	7133
t_{max}, h	5.5 (2.0 - 8.0)			5.5 (3.0 - 16.0)		
AUC_{24h}, ng.h/mL	43400	±	38850	283600	±	149400
λ_z, 1/h	0.06483	±	0.01157	0.04329	±	0.01855
$t_{1/2term}$, h	11.09	±	2.364	21.66	±	17.78
$C_{ss,av}$, ng/mL	1808	±	1619	11820	±	6227
FI, %	182.2	±	44.21	69.28	±	26.52

[a] n = 23 for Day 6, C_{0h}

Table 2: Statistical analysis of the PK parameters of TMC435350 after administration of multiple doses of TMC435 alone or with erythromycin

Parameter	LSmeans[a] 150 mg TMC435 q.d. (Reference)	LSmeans[a] 150 mg TMC435 q.d. + 500 mg Erythromycin t.i.d. (Test)	LSmeans Ratio	90% CI	p-value Period	p-value Sequence
C_{min}, ng/mL	507.6	6466	12.74	10.19 - 15.93	0.0090*	0.3853
C_{max}, ng/mL	3005	13610	4.53	3.91 - 5.25	0.2287	0.6929
AUC_{24h}, ng.h/mL	33000	246500	7.47	6.41 - 8.70	0.0292*	0.5791
Parameter	**Median[a] 150 mg TMC435 q.d. (Reference)**	**Median[a] 500 mg Erythromycin t.i.d. + 150 mg TMC435 q.d. (Test)**	**Treatment Difference Median**	**90% CI, h**	**p-value Period**	**p-value Sequence**
t_{max}, h	5.5	5.5	2.50	(-0.50) - (5.00)	0.9766	0.6419

[a] n = 24 for reference and for test
* Statistically significant difference

Table 3: Statistical analysis of the PK parameters of erythromycin after administration of multiple doses of erythromycin alone or with TMC435

Parameter	LSmeans[a] 500 mg Erythromycin t.i.d. (Reference)	LSmeans[a] 500 mg Erythromycin t.i.d. + 150 mg TMC435 q.d. (Test)	LSmeans Ratio	90% CI	p-value Period	p-value Sequence
C_{min}, ng/mL	90.16	277.5	3.08	2.54 - 3.73	0.0162*	0.4362
C_{max}, ng/mL	820.5	1304	1.59	1.23 - 2.05	0.0544	0.0713*
AUC_{8h}, ng.h/mL	2885	5485	1.90	1.53 - 2.36	0.0791	0.1925
Parameter	**Median[a] 500 mg Erythromycin t.i.d. (Reference)**	**Median[a] 500 mg Erythromycin t.i.d. + 150 mg TMC435 q.d. (Test)**	**Treatment Difference Median**	**90% CI, h**	**p-value Period**	**p-value Sequence**
t_{max}, h	1.75	1.0	-0.25	(-0.75) - (0.25)	0.8844	0.9535

[a] n = 24 for reference and for test
* Statistically significant difference

TMC435 plasma concentrations were higher in the presence of the strong CYP3A inhibitor ritonavir (DRV/r). The TMC435 dose was prospectively lowered to 50 mg QD, but coadministration with DRV/r resulted in TMC435 exposures that were still substantially higher compared to TMC435 150 mg QD alone (AUC_{24} was approximately 2.6-fold higher with DRV/r compared to TMC435 alone; Tables 4 and 5). Darunavir and ritonavir concentrations increased slightly in the presence of TMC435 (Tables 6 and 7).

Table 4: Pharmacokinetics of TMC435350 after multiple dose administration of TMC435 150 mg QD alone and TMC435 50 mg QD coadministered with DRV/r 800/100 mg QD

Pharmacokinetics of TMC435 (mean ± SD, t_{max}: median [range])	150 mg TMC435 q.d. (Reference)			50 mg TMC435 q.d. + 800/100 mg DRV/r q.d. (Test)		
n	21[a]			25[b]		
Day 5						
C_{0h}, ng/mL	478.4	±	420.8	1439	±	612.4
Day 6						
C_{0h}, ng/mL	546.2	±	489.2	1767	±	806.0
Day 7						
C_{0h}, ng/mL	661.2	±	777.9	2178	±	1089
C_{min}, ng/mL	505.0	±	586.8	1894	±	929.7
C_{max}, ng/mL	2381	±	1357	4256	±	1614
t_{max}, h	6.0 (4.0 - 8.0)			5.0 (2.0 - 6.0)		
AUC_{24h}, ng.h/mL	27650	±	20010	68630	±	27570
λ_z, 1/h	0.06824	±	0.01211	0.03390	±	0.009814
$t_{1/2term}$, h	10.48	±	1.949	22.39	±	7.637
$C_{ss,av}$, ng/mL	1152	±	833.6	2830	±	1149
FI, %	183.7	±	41.70	85.99	±	16.82

[a] n = 22 for Day 5, C_{0h} and Day 6, C_{0h}
[b] n = 24 for Day 7, AUC_{24h}, $C_{ss,av}$, and FI

Table 5: Statistical analysis of the PK parameters of TMC435350 after multiple dose administration of TMC435 150 mg QD alone and TMC435 50 mg QD coadministered with DRYV/r 800/100 mg QD

Parameter	LSmeans[a]		LSmeans Ratio	90% CI	p-value	
	150 mg TMC435 q.d. (Reference)	50 mg TMC435 q.d. + 800/100 mg DRV/r q.d. (Test)			Period	Sequence
C_{min}, ng/mL	364.4	1669	4.58	3.54 - 5.92	0.8346	0.2289
C_{max}, ng/mL	2206	3941	1.79	1.55 - 2.06	0.9385	0.3326
AUC_{24h}, ng.h/mL[b]	24080	62280	2.59	2.15 - 3.11	0.9055	0.2114
Parameter	Median[a]		Treatment Difference Median	90% CI, h	p-value	
	150 mg TMC435 q.d. (Reference)	50 mg TMC435 q.d. + 800/100 mg DRV/r q.d. (Test)			Period	Sequence
t_{max}, h	6.0	5.0	-1.00	(-1.50) - (-0.50)	0.3962	0.1004

[a] n = 21 for reference and n= 25 for test
[b] n = 24 for test

Table 6: Statistical analysis of the PK parameters of darunavir after administration of multiple doses of DRV/r alone or with TMC435 50 mg QD

Parameter	LSmeans[a]		LSmeans Ratio	90% CI	p-value	
	800/100 mg DRV/r q.d. (Reference)	800/100 mg DRV/r q.d. + 50 mg TMC435 q.d. (Test)			Period	Sequence
C_{min}, ng/mL	1172	1537	1.31	1.13 - 1.52	0.6101	0.7996
C_{max}, ng/mL	7061	7372	1.04	0.99 - 1.10	0.7151	0.7113
AUC_{24h}, ng.h/mL	71380	84010	1.18	1.11 - 1.25[c]	0.8204	0.8613
Parameter	Median[a]		Treatment Difference Median	90% CI, h	p-value	
	800/100 mg DRV/r q.d. (Reference)	800/100 mg DRV/r q.d. + 50 mg TMC435 q.d. (Test)			Period	Sequence
t_{max}, h	4.0	3.0	0.00	(-0.50) - (0.50)	0.6341	0.3951

[a] n = 23 for reference and n = 25 for test
[c] actual value is just above 1.25

Table 7: Statistical analysis of the PK parameters of ritonavir after administration of multiple doses of DRV/r alone or with TMC435 50 mg QD

Parameter	LSmeans[a]		LSmeans Ratio	90% CI	p-value	
	800/100 mg DRV/r q.d. (Reference)	800/100 mg DRV/r q.d. + 50 mg TMC435 q.d. (Test)			Period	Sequence
C_{min}, ng/mL	24.24	34.98	1.44	1.30 - 1.61	0.9587	0.8383
C_{max}, ng/mL	577.5	708.5	1.23	1.14 - 1.32	0.8070	0.5245
AUC_{24h}, ng.h/mL	4151	5484	1.32	1.25 - 1.40	0.8085	0.9120
Parameter	Median[a]		Treatment Difference Median	90% CI, h	p-value	
	800/100 mg DRV/r q.d. (Reference)	800/100 mg DRV/r q.d. + 50 mg TMC435 q.d. (Test)			Period	Sequence
t_{max}, h	4.0	4.0	0.00	(0.00) - (0.50)	0.7681	0.2331

[a] n = 23 for reference and n = 25 for test

- Were there any outliers or excluded data from analysis? ☐Yes ☑ No ☐ NA

- Are the study results acceptable? ☑ Yes ☐ No

Safety

Were there any deaths or serious adverse events? ☐ Yes ☑ No

CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS

CONCLUSIONS

Does the study finding warrant dose adjustment upon the co-administration of TMC435 with erythromycin? ☑ Yes ☐ No

TMC435 should not be coadministered with erythromycin because of the magnitude of TMC435 exposure increase observed.

Is the interaction clinically significant? ☑ Yes ☐No ☐ NA

Does the study finding warrant dose adjustment upon the co-administration of TMC435 with DRV/r? ☑ Yes ☐ No

TMC435 should not be coadministered with DRV/r because of the magnitude of TMC435 exposure increase observed upon coadministration with TMC435 50 mg QD. TMC435 exposures are expected to be significantly higher upon coadministration of DRV/r and TMC435 150 mg QD.

Is the interaction clinically significant? ☑ Yes ☐No ☐ NA

LABEL RECOMMENDATIONS

Do not coadminister TMC435 and erythromycin. TMC435 exposures increase approximately 7-fold due to CYP3A inhibition by erythromycin.

Do not coadminister TMC435 and DRV/r. TMC435 exposures increase approximately 2.6-fold due to CYP3A inhibition by ritonavir after prospective TMC435 dose reduction to 50 mg QD and are expected to be significantly higher at the proposed dose of 150 mg QD.

CLINICAL PHARMACOLOGY BIOAVAILABILITY & FOOD EFFECT STUDY REVIEW

Study #	TMC435-TiDP16-C116	**Study Period**	10/03/2011-07/06/2011	EDR Link
Title	A Phase I, open-label, randomized, single-dose, 2-panel, crossover trial in healthy subjects to assess the relative bioavailability of TMC435 following administration of the (b) (4) capsule formulation compared to the gelatin capsule formulation and to assess the effect of different meal types on the bioavailability of TMC435 following administration of the (b) (4) or gelatin TMC435 formulation			

STUDY DESIGN	
Population	☑ Healthy Volunteers ☐ Patients
Study Rationale	The study was conducted to compare the rate and extent of absorption of TMC435 following administration of the (b) (4) capsule (G011) to that following administration of the gelatin capsule (G007) formulation and compare the rate and extent of absorption of TMC435 following administration of G011 or G007 formulation in the fed (i.e., standard breakfast or high fat meal) and fasted state.
Treatments	A & C: Single oral dose of 150 mg TMC435 G007 (fasted) B: Single oral dose of 150 mg TMC435 G011 (fasted) D: Single oral dose of 150 mg TMC435 G007 (standard breakfast 533 kcal) E: Single oral dose of 150 mg TMC435 G007 (high fat meal 928 kcal) *A and C were references, and B, D and E were tests. **Sequence** Panel 1: A-B/B-A Panel 2: C-D-E/D-E-C/E-C-D/E-D-C/D-C-E/C-E-D *A washout period of minimally 7 days between successive sessions of drug intake.
Dose Selection Rationale	The TMC435 150 mg q.d. dose had been selected as this is the highest dose that is being studied in the Phase 2b and 3 trials.
Administration	☑ Fasted ☑ Fed
Formulation	(b) (4) capsule (G011) , Batch #11B04 and Gelatin capsule (G007), Batch#11B03
Interfering Substances Excluded	None
Sampling Times	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours post-dose in each group.
PK Parameters	C_{max}, t_{max}, AUC_{last}, AUC_{∞}, λ_z, $t_{1/2term}$, Ratio $C_{max,test/ref}$, Ratio $AUC_{last,test/ref}$ and Ratio $AUC_{\infty,test/ref}$
PK Analysis	Non-compartmental analysis
Statistical Analysis	The least square (LS) means of the primary parameters (i.e., C_{max}, AUC_{last} and AUC_{∞} on the logarithmic scale) for each treatment group were estimated with a linear mixed effects model, controlling for treatment, sequence and period as fixed effects, and subject as a random effect. The LS mean ratio and its 90% confidence interval (CI) were calculated.
Is the study design acceptable? ☑ Yes ☐ No	

STUDY CONDUCT			
Bioanalytical Method			
Method Name	PBRL-RD-1154/JJP135EL-091353-B/BA1513		
Method Type	LC-MS/MS	Matrix	Plasma
Analytes	TMC435		
Range	2-2000 ng/mL		

Validation	▪ Method validated prior to use	☑ Yes ☐ No ☐ NA
	▪ Method validation acceptable	☑ Yes ☐ No ☐ NA
Study Samples Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Incurred samples analysis is acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No
Inspection	▪ Will the bioanalytical site be inspected	☐ Yes ☑ No

Protocol Deviations

- Are there any protocol deviations listed in the study report? ☐ Yes ☑ No
- Do any of the listed deviations affect the integrity of the study? ☐ Yes ☐ No ☑ NA

STUDY RESULTS

Study Population

Panel 1: Bioavailability Study

Randomized	24
Treated	24
Completed	24
Discontinued Due to AE	0
PK Population/Safety Population	24
Age [Median (range)]	42.5 (19-54)
Male/Female	6/18
Race: Not Hispanic or Latino (%)	100

Panel 2: Food Effect Study

Randomized	24
Treated	24
Completed	24
Discontinued Due to AE	0
PK Population/Safety Population	24
Age [Median (range)]	45.0 (20-55)
Male/Female	15/9
Race: Not Hispanic or Latino (%)	100

Pharmacokinetics

- Pharmacokinetic Parameters and LS Mean Ratio & 90% CI

Panel 1: Bioavailability Study

Pharmacokinetics of TMC435 (mean ± SD, t_{max}: median [range])	a single oral dose of 150 mg TMC435 formulated as the Gelatin capsule (G007), fasted	a single oral dose of 150 mg TMC435 formulated as the (b) (4) capsule (G011), fasted
n	24	24
C_{max}, ng/mL	966.4 ± 525.3	998.5 ± 623.0
t_{max}, h	4.0 (2.0 - 8.0)	4.0 (2.0 - 6.0)
AUC_{last}, ng.h/mL	13500 ± 8315	12860 ± 8670
AUC_{∞}, ng.h/mL	13630 ± 8426	12980 ± 8760
λ_z, 1/h	0.07933 ± 0.01598	0.08088 ± 0.01610
$t_{1/2term}$, h	9.098 ± 1.923	8.909 ± 1.823
LSmean ratio (90% CI)		
	-	**Test vs reference**
n	-	24 vs 24
C_{max}	-	1.03 (0.91 - 1.16)
AUC_{last}	-	0.97 (0.85 - 1.09)
AUC_{∞}	-	0.97 (0.86 - 1.09)

Panel 2: Food Effect Study

Pharmaco-kinetics of TMC435	a single oral dose of 150 mg TMC435 formulated as the Gelatin capsule (G007), fasted (reference)	a single oral dose of 150 mg TMC435 formulated as the Gelatin capsule (G007), standard breakfast	a single oral dose of 150 mg TMC435 formulated as the Gelatin capsule (G007), high-fat breakfast
n	24	24[a]	24[a]
C_{max}, ng/mL	817.9 ± 423.5	1286 ± 593.7	1162 ± 456.7
t_{max}, h	4.0 (3.0 – 8.0)	6.0 (3.0 – 24.0)	6.0 (2.0 – 24.0)
AUC_{last}, ng.h/mL	11340 ± 5680	19280 ± 8840	18270 ± 7056
AUC_{∞}, ng.h/mL	11460 ± 5724	19450 ± 9311	17840 ± 6726
λ_z, 1/h	0.07099 ± 0.014022	0.069244 ± 0.010800	0.071877 ± 0.009444
$t_{1/2term}$, h	10.17 ± 2.245	10.25 ± 1.673	9.819 ± 1.433
LSmean ratio (90% CI)			
		Test vs reference	**Test vs reference**
N	-	24[a] vs 24	24[a] vs 24
C_{max}	-	1.60 (1.30 – 1.96)	1.49 (1.22 – 1.82)
AUC_{last}	-	1.70 (1.38 – 2.09)	1.66 (1.38 – 1.99)
AUC_{∞}	-	1.69 (1.36 – 2.08)	1.61 (1.33 – 1.93)

[a] n = 23 for AUC_{∞}, λ_z, $t_{1/2term}$

Figure 1: Mean (±SD) Plasma Concentration-Time Curves of TMC435 After Administration of a Single 150-mg Dose of G007 (A) and G011 (B), Both under Fasted Conditions in Healthy Subjects (Panel 1).

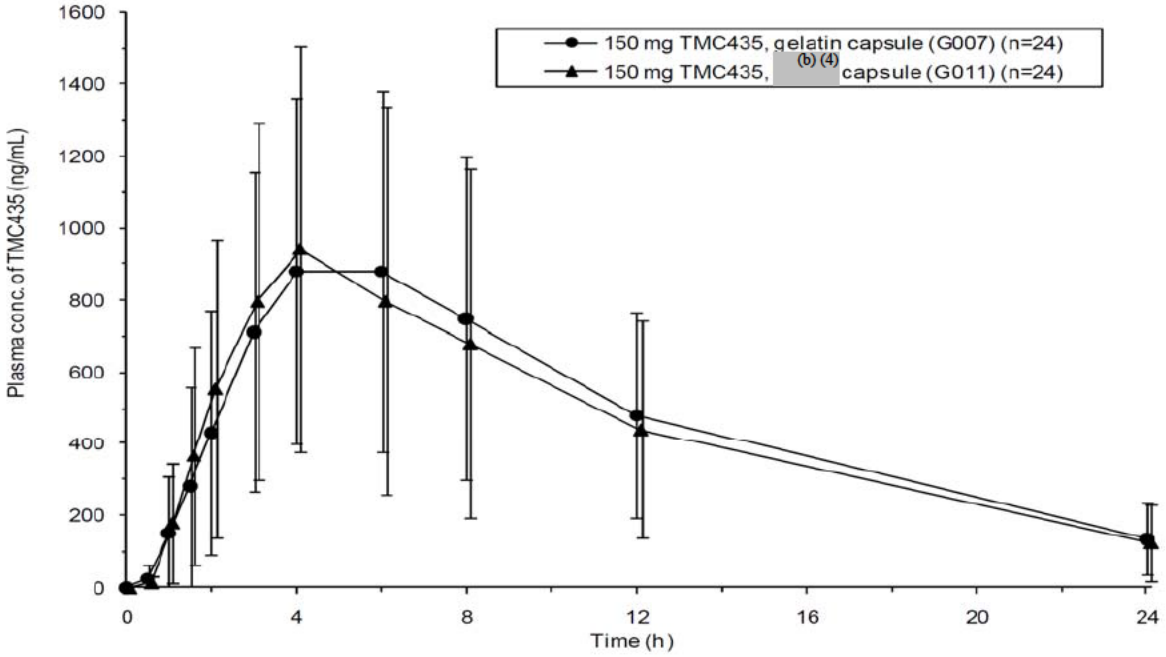
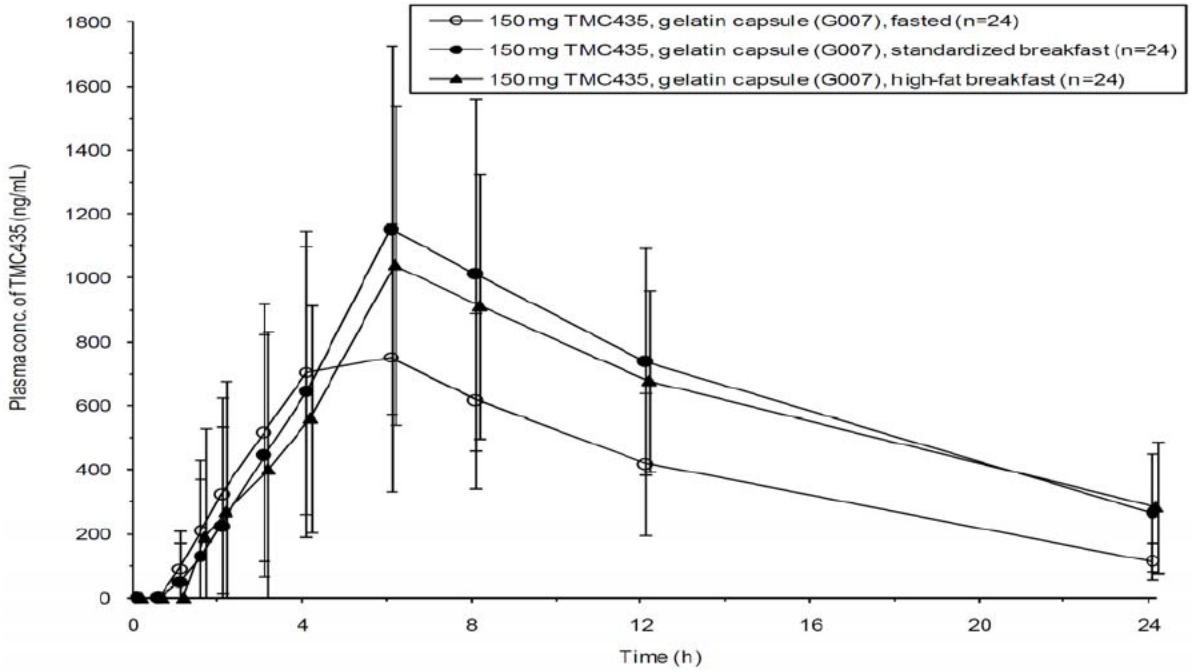


Figure 2: Mean (±SD) Plasma Concentration-Time Curves of TMC435 After Administration of a Single 150-mg Dose of G007 Under Fasted Conditions (C), Following a Standard Breakfast (D) and Following a High-Fat Breakfast (E), in Healthy Subjects (Panel 2).



- Were there any outliers or excluded data from analysis? ☐ Yes ☑ No ☐ NA
- Are the study results acceptable? ☑ Yes ☐ No

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No

CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS

CONCLUSIONS

Does the study finding indicate the rate and extent of absorption of (b) (4) capsule (G011) is comparable to that

of Gelatin capsule (G007)? ☑ Yes ☐ No
Does the study finding indicate that the effects of food (i.e., standard breakfast and high-fat breakfast) are clinically significant? ☑ Yes ☐ No

LABEL RECOMMENDATIONS

The increase in exposure to TMC435 under fed conditions appears to be clinically significant. Therefore, the (b) (4) capsule (G011) or gelatin capsule (G007) should be taken only on either an empty stomach or with meals to reduce variability in the drug efficacy and safety.

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY DRUG-DRUG INTERACTION STUDY REVIEW				
Study #	TMC435-TiDP16-C119	**Study Period**	16-June-2010 – 27-August-2010	EDR Link
Title	A Phase I, open-label, randomized, single dose, crossover study in healthy subjects to assess the relative bioavailability of TMC435 following administration of potential Phase III formulations compared to the Phase IIb capsule			

STUDY DESIGN	
This was an open-label, randomized, single-dose, 3-way crossover study. Each treatment is one day with at least 7 days washout between sessions.	
Population	☒ Healthy Volunteers ☐ Patients
Study Rationale	The relative bioavailability study was conducted to bridge the potential Phase 3 formulations given as 150 mg potential Phase III formulations (G006, G007) with the Phase IIb capsule (F021) in healthy subjects
Treatments	During 3 subsequent sessions, each subject received 3 treatments (Treatments A, B, and C):

Treatment	Number of Subjects	Dose Regimen	Volume
A	24	single dose TMC435 Phase IIb capsule (F021, fed)	2 oral capsules of 75 mg
B	24	single dose TMC435 capsule with G005 (b) (4) (G006, fed)	1 oral capsule of 150 mg
C	24	single dose TMC435 capsule with (b) (4) G005 (b) (4) and (b) (4) (G007, fed)	1 oral capsule of 150 mg

Dose Selection Rationale	The dose to be bridged is the Phase 3 dose, i.e., 150 mg under fed condition
Administration	☐ Fasted ☒ Fed
Formulation	Include dosage form and formulation #, lot # Treatment A: formulation F021, Batch # 10A26 Treatment B: formulation G006, Batch # 10F02 Treatment C: formulation G007, Batch # 10F01
Interfering Substances Excluded	None
Sampling Times	Predose, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hour post-dose
PK Parameters	Cmax, tmax, AUClast, AUC∞, T1/2
PK Analysis	Non-compartmental analysis
Statistical Analysis	Statistical analysis was performed comparing Treatments B and C (test) versus Treatment A (reference) for TMC435. The primary PK parameters were Cmax, AUClast, and AUC∞, on the logarithmic scale. All observations for test and reference, paired and unpaired, were included in the statistical analysis. The least square (LS) means of the primary parameters for each treatment phase were estimated with a linear mixed effects model, controlling for treatment, sequence, and period as fixed effects, and subject as a random effect. A 90% confidence interval (CI) was constructed around the difference between the LS means of test and reference. Period effects were considered significant at the 5% level and sequence effects were considered significant at the 10% level.
Is the study design acceptable? ☒ Yes ☐ No, if no please explain why	

STUDY CONDUCT

Bioanalytical Method:

Method Name	BA883		
Method Type	LC-MS/MS	Matrix	Human EDTA plasma
Analytes	TMC435		
Range	2-2000 ng/mL		

Validation	▪ Method validated prior to use	☒ Yes ☐ No ☐ NA
	▪ Method validation acceptable	☒ Yes ☐ No ☐ NA
Study Samples Analysis	▪ Samples analyzed within the established stability period	☒ Yes ☐ No
	▪ Quality control samples range acceptable	☒ Yes ☐ No
	▪ Chromatograms provided	☒ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	▪ Incurred samples analysis is acceptable	☒ Yes ☐ No
	▪ Overall performance acceptable	☒ Yes ☐ No
Inspection	▪ Will the bioanalytical site be inspected	☐ Yes ☒ No

Protocol Deviations

- Are there any protocol deviations listed in the study report? ☐ Yes ☒ No
- Do any of the listed deviations affect the integrity of the study? ☐ Yes ☐ No ☒ NA

STUDY RESULTS

Study Population

Randomized	24
Treated	24
Completed	24
Discontinued Due to AE	24
PK Population/Safety Population	24
Age [Median (range)]	48.0(21-55)
Male/Female	13/11
Race (Caucasian/Black/Asian)	21/1/2

Pharmacokinetics

- LS Mean Ratio & 90% CI

Table 1: Summary of the statistical analysis of the PK parameters

Pharmacokinetics of TMC435 (mean ± SD, t_{max}: median [range])	TMC435 150 mg		
	Phase IIb capsule (F021) (reference)	Capsule with G005 (b) (4) (G006) (test 1)	Capsule with (b) (4) G005 (b) (4) and (b) (4) (G007) (test 2)
n	23[a]	24[b]	24
C_{max}, ng/mL	1585 ± 627.7	1603 ± 714.8	1415 ± 556.9
t_{max}, h	5.0 (4.0 - 8.0)	5.0 (2.0 - 12.0)	5.0 (4.0 - 8.0)
AUC_{last}, ng.h/mL	20610 ± 8439	19980 ± 6638	19060 ± 7400
AUC_{∞}, ng.h/mL	20760 ± 8499	20870 ± 7524	19250 ± 7441
λ_z, 1/h	0.07577 ± 0.01574	0.07920 ± 0.01382	0.07705 ± 0.01717
$t_{1/2term}$, h	9.476 ± 1.703	9.019 ± 1.623	9.379 ± 1.864
LS mean ratio (90% CI)			
		Test 1 vs reference	**Test 2 vs reference**
n		24[b] vs 23	24 vs 23
C_{max}, ng/mL	-	1.00 (0.93 - 1.08)	0.89 (0.82 - 0.97)
AUC_{last}, ng.h/mL	-	1.01 (0.93 - 1.09)	0.93 (0.86 - 1.01)
AUC_{∞}, ng.h/mL	-	1.03 (0.95 - 1.11)	0.93 (0.86 - 1.01)

[a] n = 24 for λ_z and $t_{1/2term}$
[b] n = 23 for AUC_{last}

- Pharmacokinetic Profile

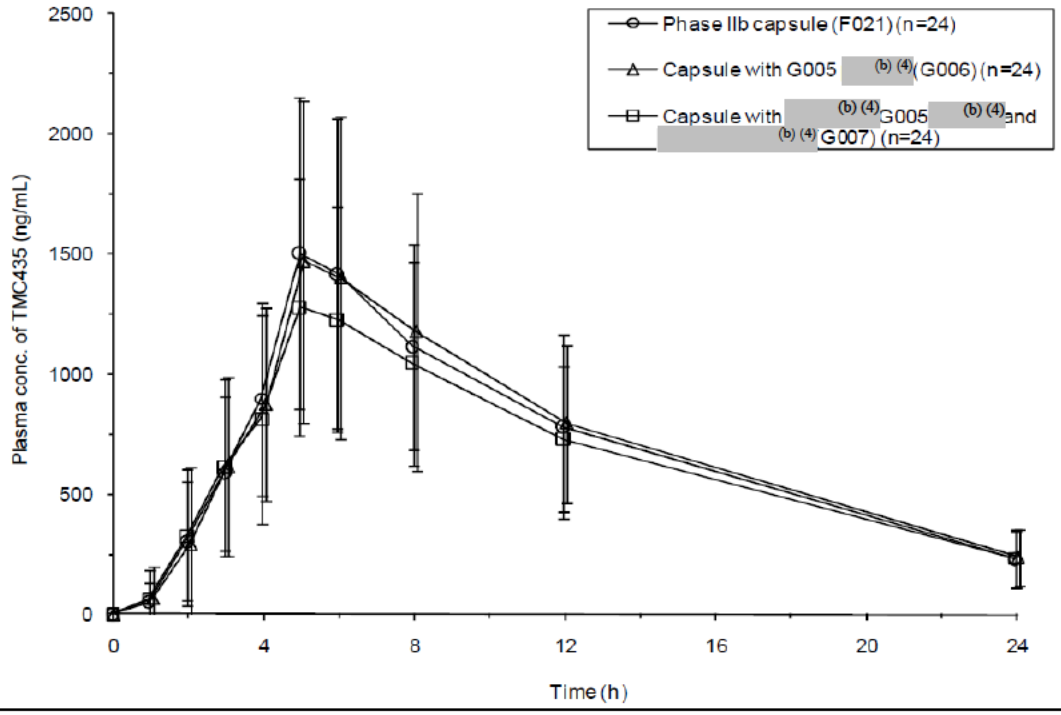


Figure 1: Linear Mean Plasma Concentration-Time Curves of TMC435 (Including SD Bars) After Administration of a Single 150 mg Dose of TMC435 in Treatment A, B, and C

- Were there any outliers or excluded data from analysis? ☒ Yes ☐ No ☐ NA, if yes explain"

Five samples in total with the actual sampling time unknown were excluded from data analysis. In addition, for Subject 119-0024 in Treatment A the actual sampling time of the 5 hours postdose sample was unknown. As this sample is around Cmax, all parameters were set to NA except t1/2term and λz. For Subject 119-0021 in Treatment B, the plasma concentration of the 72 hours postdose sample was considered unreliable (more than 3 times higher than plasma concentration in the 48 hours postdose sample). The plasma concentration was excluded from descriptive statistics and further PK analysis, and AUClast and Ratio AUClast were set to NA.

- Are the study results acceptable? ☒ Yes ☐ No, if no explain

Safety

Was there any death or serious adverse events? ☐ Yes ☒ No

CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS

CONCLUSIONS

The PK results from this study show that the rate and extent of absorption were similar following intake of TMC435 150 mg formulated as one of the potential Phase III formulations (G006 or G007) or formulated as the Phase IIb capsule (F021). The 90% CI for TMC435 Cmax, AUClast, and AUC∞ were within the limits of bioequivalence. No difference in tmax was observed between the Phase IIb capsule (F021) and the potential Phase III formulations (G006 or G007). The sponsor's conclusions appear valid.

COMMENTS

None

LABEL RECOMMENDATIONS

None

CLINICAL PHARMACOLOGY DRUG-DRUG INTERACTION STUDY REVIEW				
Study #	TMC435-TiDP16-C120	**Study Period**	02/11/2011-23/12/2011	EDR Link
Title	A Phase I, 2-panel, open-label, randomized, cross-over trial in healthy subjects to investigate the effect of TMC435 at steady-state on the PK of the immunosuppressants cyclosporine and tacrolimus			

STUDY DESIGN	
Population	☑ Healthy Volunteers ☐ Patients
Study Rationale	The study was conducted due to the likely co-administration of TMC435 and cyclosporine or tacrolimus in patients with HCV infection. TMC435 is a substrate of CYP3A and to a lesser extent CYP2C8 and CYP2C19. TMC435 is also a substrate of P-gp, MRP2, BCRP, OATP1B1/3, and OATP2B1. TMC435 is a mild inhibitor of intestinal CYP3A and a mild inhibitor of CYP1A2. *In vitro*, TMC435 inhibits OATP1B1, sodium taurocholate cotransporting polypeptide (NTCP), P-gp, MRP2, and BSEP. Cyclosporine is metabolized by CYP3A and is an inhibitor of CYP3A4. Cyclosporine is a substrate and inhibitor of P-gp. Tacrolimus is a substrate of CYP3A and an inhibitor of P-gp.
Treatments	A: A single oral dose of 100 mg cyclosporine B: TMC435 150 mg q.d. for 10 days + a single 100 mg oral dose of cyclosporine on Day 7 C: A single oral dose of 2 mg tacrolimus D: TMC435 150 mg q.d. for 12 days + a single 2 mg oral dose of tacrolimus on Day 7 *The TMC435, cyclosporine and tacrolimus terminal elimination half-lives are approximately 12 hours, 16-27 hours and 35 hours, respectively. **Sequence** Panel 1: A-B/B-A Panel 2: C-D/D-C *A washout period of at least 10 days between medication intakes in each group.
Dose Selection Rationale	The TMC435 150 mg q.d. dose had been selected as this is the highest dose that is being studied in the Phase 2b and 3 trials. Cyclosporine 100 mg and tacrolimus 2 mg had been selected as a single oral dose to minimize potential risk to the subjects.
Administration	☐ Fasted ☑ Fed
Formulation	TMC435 150 mg capsule (G015), Batch # 11G20/G015, Cyclosporine 100 mg capsule (Neoral®), Batch# BHZS00W, Tacrolimus 1 mg capsule (Prograf®), Batch# 1D4610B
Interfering Substances Excluded	None
Sampling Times	-0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72, 96, 120 and 144 hours post-dose on Day 1 in group A and C, on Day 7 in group B and D. -Trough concentrations on Days 5 and 6 in group B and D.
PK Parameters	C_{0h}, $C_{max, tmax}$, AUC_{last}, AUC_{∞}, λ_z, $t_{1/2,term}$, Ratio $C_{max,test/ref}$, Ratio $AUC_{last,test/ref}$, Ratio $AUC_{\infty,test/ref}$, fluctuation index
PK Analysis	Non-compartmental analysis
Statistical Analysis	The least square (LS) means of the primary parameters (i.e., C_{max}, and AUC_{last} on the logarithmic scale) for each treatment group was estimated with a linear mixed effects model, controlling for treatment, sequence and period as fixed effects, and subject as a random effect. The LS mean ratio and its 90% confidence interval (CI) were calculated.

Is the study design acceptable? ☑ Yes ☐ No

STUDY CONDUCT

Bioanalytical Method

Method Name	Cyclosporine (Method LCMSC 582 Version 1.00) Tacrolimus (Method LCMS 356 Version 2.02)		
Method Type	LC-MS/MS	Matrix	Whole blood
Analytes	Cyclosporine, Tacrolimus		
Range	Cyclosporine (5-5000 ng/mL) Tacrolimus (0.25-100 ng/mL)		

Validation	▪ Method validated prior to use	☑ Yes ☐ No ☐ NA
	▪ Method validation acceptable	☑ Yes ☐ No ☐ NA
Study Samples Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Incurred samples analysis is acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No

Protocol Deviations

- Are there any protocol deviations listed in the study report? ☐ Yes ☑ No
- Do any of the listed deviations affect the integrity of the study? ☐ Yes ☐ No ☑ NA

STUDY RESULTS

Study Population

Panel 1

Randomized	14
Treated	14
Completed	14
Discontinued Due to AE	0
PK Population/Safety Population	14
Age [Median (range)]	48.5 (35-53)
Male/Female	8/6
Race: Caucasian (%)	100

Panel 2

Randomized	14
Treated	14
Completed	14
Discontinued Due to AE	0
PK Population/Safety Population	14
Age [Median (range)]	44.0 (25-55)
Male/Female	7/7
Race: Caucasian (%)	100

APPEARS THIS WAY ON ORIGINAL

Pharmacokinetics

- PK Parameters and LS Mean Ratio & 90% CI

Pharmacokinetics of Cyclosporine (Panel 1) (mean ± SD, t_{max}: median [range])	A Single Dose of 100 mg Cyclosporine (Reference)	150 mg TMC435 q.d. + a Single Dose of 100 mg Cyclosporine (Test)
Subjects treated	*14*	*14*
Day 1/Day 7		
C_{max}, ng/mL	640.1 ± 166.9	738.1 ± 163.0
t_{max}, h	1.5 [1.0 - 2.0]	1.5 [1.0 - 2.0]
AUC_{last}, ng.h/mL	2076 ± 532.4	2497 ± 718.8
AUC_{∞}, ng.h/mL	2196* ± 558.1*	2635* ± 757.8*
λ_z, 1/h	0.07818* ± 0.01375*	0.06367* ± 0.02898*
$t_{1/2,term}$, h	9.189* ± 2.001*	13.86* ± 7.555*
LSmean Ratio (90% CI)		
		Test vs reference
n		14 vs 14
C_{max}	-	1.16 (1.07 - 1.26)
AUC_{last}	-	1.19 (1.13 - 1.26)

0 = NQ = Not Quantifiable (< 5.00 ng/mL)

Pharmacokinetics of Tacrolimus (Panel 2) (mean ± SD, t_{max}: median [range])	A Single Dose of 2 mg Tacrolimus (Reference)	150 mg TMC435 q.d. + a Single Dose of 2 mg Tacrolimus (Test)
Subjects treated	*14*	*14*
Day 1/Day 7		
C_{max}, ng/mL	16.09 ± 5.978	12.05 ± 3.232
t_{max}, h	1.5 [1.0 - 2.0]	1.5 [1.0 - 2.0]
AUC_{last}, ng.h/mL	140.7 ± 82.78	118.1 ± 57.27
AUC_{∞}, ng.h/mL	156.2 ± 83.19	136.0* ± 61.56*
λ_z, 1/h	0.02414 ± 0.004205	0.02308* ± 0.005686*
$t_{1/2,term}$, h	29.60 ± 5.598	32.42* ± 11.20*
LSmean Ratio (90% CI)		
		Test vs reference
n		14 vs 14
C_{max}	-	0.76 [0.65 - 0.90]
AUC_{last}	-	0.83 [0.59 - 1.16]

0 = NQ = Not Quantifiable (< 0.250 ng/mL)

Figure 1: Mean (±SD) Whole Blood Concentration-Time Curves of Cyclosporine After Administration of a Single Dose of 100 mg Cyclosporine Alone (Treatment A, Day 1) and in Combination With TMC435 at 150 mg q.d. (Treatment B, Day 7)

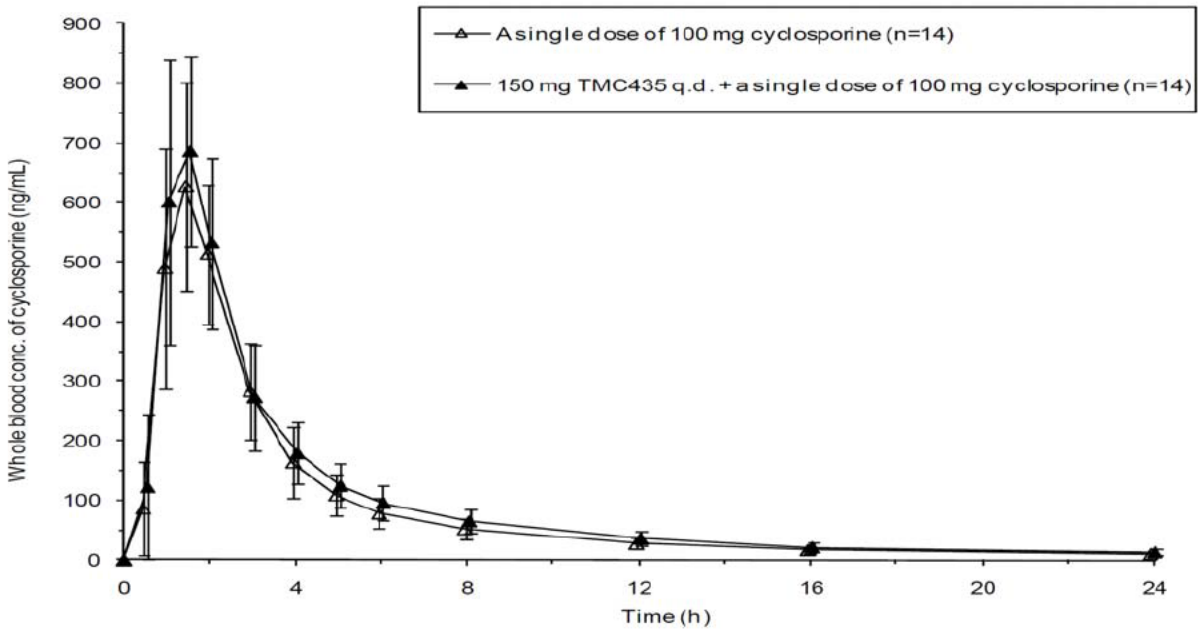
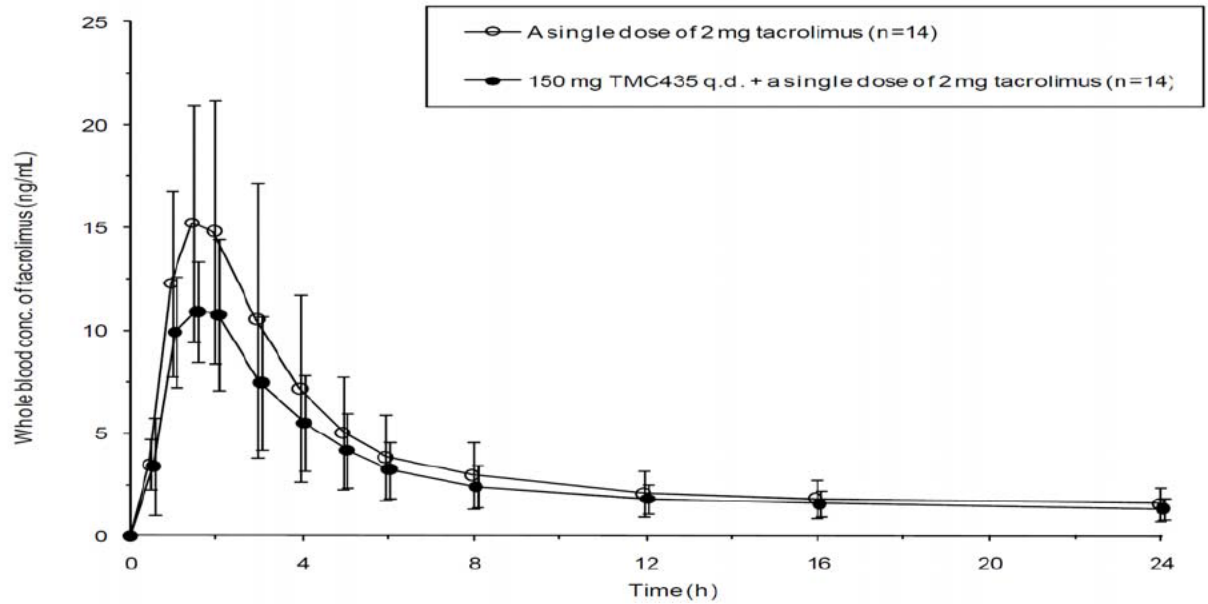


Figure 2: Mean (±SD) Whole Blood Concentration-Time Curves of Tacrolimus After Administration of a Single Dose of 2 mg Tacrolimus Alone (Treatment C, Day 1) and in Combination With TMC435 at 150 mg q.d. (Treatment D, Day 7)



- Were there any outliers or excluded data from analysis? ☐ Yes ☑ No ☐ NA
- Are the study results acceptable? ☑ Yes ☐ No

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No

CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS

CONCLUSIONS

Does the study finding warrant dose adjustment upon the co-administration of TMC435 with cyclosporine? ☑ Yes ☐ No

Does the study finding warrant dose adjustment upon the co-administration of TMC435 with tacrolimus? ☑ Yes ☐ No

Is the interaction clinically significant? ☑ Yes ☐ No ☐ NA

LABEL RECOMMENDATIONS

No dose adjustment of TMC435 is necessary when co-administered with cyclosporine or tacrolimus. Co-administration with TMC435 increases cyclosporine whole blood concentrations and decreases tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of cyclosporine or tacrolimsu are recommended when TMC435 and cyclosporine or tacrolimus are used concomitantly.

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY DRUG-DRUG INTERACTION STUDY REVIEW				
Study #	TMC435350-TiDP16-C123	**Study Period**	18-Nov-2010 to 29-April-2011	EDR Link
Title	A Phase 1, 2-panel, open-label, randomized, cross-over trial in healthy subjects to investigate the pharmacokinetic interaction between TMC435 and antiretroviral agents, efavirenz and raltegravir at steady-state			

STUDY DESIGN	
This was a Phase 1, 2-panel, open-label, randomized, 3-way crossover trial in healthy subjects to investigate the potential drug-drug interaction between TMC435 and efavirenz, and between TMC435 and raltegravir. The trial population consisted of 48 healthy subjects, evenly divided into 2 panels	
Population	☒ Healthy Volunteers ☐ Patients
Study Rationale	To investigate the PK interaction between TMC435 and antiretroviral agents, efavirenz (a CYP3A4/CYP2B6 substrate and an inducer of CYP3A4) and raltegravir (a UGT1A1 substrate) at steady-state
Treatments	Panel 1: Treatment A: TMC435 150 mg q.d.; Treatment B: efavirenz 600 mg q.d. . Treatment C: the combination of TMC435 150 mg q.d. + efavirenz 600 mg q.d. Each treatment lasted for 14 days; Panel 2: Treatment D: TMC435 150 mg q.d.; Treatment E: raltegravir 400 mg b.i.d.; Treatment F: the combination of TMC435 150 mg q.d. + raltegravir 400 mg b.i.d.; each treatment lasted for 7 days.
Dose Selection Rationale	TMC435 at 150 mg q.d. was the highest dose that was used in the Phase IIb studies C205 and C206 and was selected for Phase 3 clinical studies. Both the 600 mg q.d. dose of efavirenz (Sustiva®) and 400 mg b.i.d. dose of raltegravir (Isentress®) are the recommended adult doses. With q.d. dosing, steady-state plasma concentrations for efavirenz are achieved within approximately 6 to 10 days. With b.i.d dosing, the steady-state for raltegravir is achieved within 4 days.
Administration	☐ Fasted ☒ Fed (for TMC435 and raltegravir). Efavirenz intakes on an empty stomach, 2 hours after finishing a breakfast.
Formulation	**Treatment** / TMC435 / Efavirenz (Sustiva®) / Raltegravir (Isentress®) Strength: 75 mg / 600 mg / 400 mg Dosage Form (F No.): capsule (F021) / film-coated tablet / film-coated tablet Usage: oral / oral / oral Batch Number: 10A26 / 0G64124 / NM41490
Interfering Substances Excluded	None
Sampling Times	Panel 1: Day 14: predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9 ,10, 11, 12, 14, 16, 18, 24, 26, 48, 72, and 96 hr post dose; and one sample each on Days 1, 12, and 13 (for predose or trough) Panel 2: Day 7: predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9 ,11.5, 12, 14, 16, 24, 48, 72, and 96 hr post dose; and one sample each on Days 1, 5, and 6 (for predose or trough)
PK Parameters	Cmin, Cmax, AUC24h, Css
PK Analysis	Non-compartmental analysis
Statistical Analysis	Intent-to-treat analysis, descriptive statistics, frequency tabulations, linear mixed effects modeling, nonparametric test (Wilcoxon signed rank test) (for tmax)
Is the study design acceptable? ☒ Yes ☐ No, if no please explain why	

STUDY CONDUCT

Bioanalytical Method:

Method Type	LC-MS/MS	Matrix	EDTA Plasma
Analytes	TMC435, efavirenz, and raltegravir		
Range	2.00-2000 ng/mL; 0.100 - 10 µg/mL; 10.0-10,000 ng/mL		

Validation	▪ Method validated prior to use	☒ Yes ☐ No ☐ NA
	▪ Method validation acceptable	☒ Yes ☐ No ☐ NA
Study Samples Analysis	▪ Samples analyzed within the established stability period	☒ Yes ☐ No
	▪ Quality control samples range acceptable	☒ Yes ☐ No
	▪ Chromatograms provided	☒ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	▪ Incurred samples analysis is acceptable	☒ Yes ☐ No
	▪ Overall performance acceptable	☒ Yes ☐ No
Inspection	▪ Will the bioanalytical site be inspected	☐ Yes ☒ No

Protocol Deviations

- Are there any protocol deviations listed in the study report? ☒ Yes ☐ No
- Do any of the listed deviations affect the integrity of the study? ☐ Yes ☒ No ☐ NA

STUDY RESULTS

Study Population

	Panel 1	Panel 2
Randomized	24	24
Treated	24	24
Completed	23	23
Discontinued Due to AE	0	0
PK Population/Safety Population	23	23
Age [Median (range)]	42.5(22-54)	42.5(26-53)
Male/Female	13/11	17/7
Race (Caucasian/Asian/Native)	22/1/1	24/0/0

Pharmacokinetics

• Effect of Efavirenz on TMC435 PK:

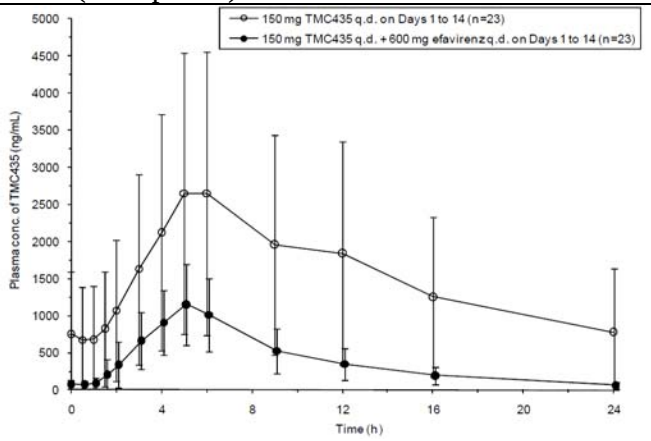


Figure 1: Mean Plasma Concentration-Time Curves of TMC435 (Including SD Bars) After Administration of TMC435 Alone (Treatment A, Day 14) and in Combination With Efavirenz (Treatment C, Day 14)

Table 1: Summary of the Statistical Analysis of the PK Parameters of TMC435 After Administration of TMC435 Alone (Treatment A, Reference) and in Combination With Efavirenz (Treatment C, Test)

	LSmeans[a]		LSmeans ratio	90% CI[b]	p-value	
Parameter	150 mg TMC435 q.d. on Days 1 to 14 (reference)	150 mg TMC435 q.d. + 600 mg efavirenz q.d. on Days 1 to 14 (test)			Period	Sequence
C_{min}, ng/mL	431.1	40.72	0.09	0.08 - 0.12	0.2537	0.1662
C_{max}, ng/mL	2321	1131	0.49	0.44 - 0.54	0.0417*	0.2789
AUC_{24h}, ng.h/mL	28960	8500	0.29	0.26 - 0.33	0.0635	0.2460
	Median[a]		Treatment difference median	90% CI, h[b]	p-value	
Parameter	150 mg TMC435 q.d. on Days 1 to 14 (reference)	150 mg TMC435 q.d. + 600 mg efavirenz q.d. on Days 1 to 14 (test)			Period	Sequence
t_{max}, h	5.0	5.0	-0.50	(-1.00) - 0.00	0.2326	0.1691

[a] n=23 for reference and test
[b] 90% confidence intervals
* Statistically significant difference

- Effect of TMC435 on Efavirenz PK:

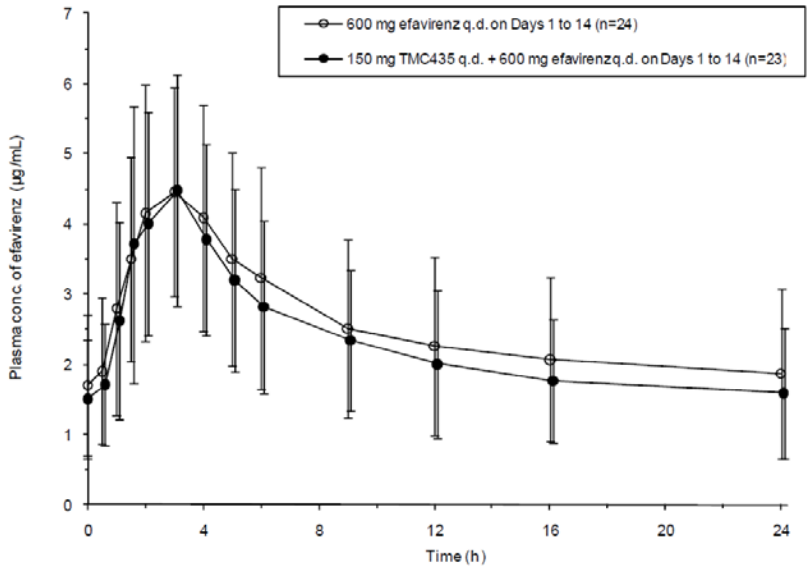


Figure 2: Mean Plasma Concentration-Time Curves of Efavirenz (Including SD Bars) After Administration of

Efavirenz Alone (Treatment B, Day 14) and in Combination With TMC435 (Treatment C, Day 14).

Table 2: Summary of the Statistical Analysis of the PK Parameters of Efavirenz After Administration of Efavirenz Alone (Treatment B, Reference) and in Combination With TMC435 (Treatment C, Test)

Parameter	LSmeans[a]		LSmeans ratio	90% CI[c]	p-value	
	600 mg efavirenz q.d. on Days 1 to 14 (reference)	150 mg TMC435 q.d. + 600 mg efavirenz q.d. on Days 1 to 14 (test)			Period	Sequence
C_{min}, µg/mL	1.449	1.263	0.87	0.81 - 0.93	0.6677	0.3052
C_{max}, µg/mL	4.867	4.726	0.97	0.89 - 1.06	0.7798	0.3126
AUC_{24h}, µg.h/mL	55.96	50.46	0.90	0.85 - 0.95	0.9317	0.1821
	Median[b]				p-value	
Parameter	600 mg efavirenz q.d. on Days 1 to 14 (reference)	150 mg TMC435 q.d. + 600 mg efavirenz q.d. on Days 1 to 14 (test)	Treatment difference median	90% CI, h[c]	Period	Sequence
t_{max}, h	2.04	2.46	0.00	(-0.49) - 0.50	0.7915	0.5517

[a] n=23 for reference and test

[b] n=22 for reference and test

[c] 90% confidence intervals

- Effect of Reltegravir on TMC435 PK

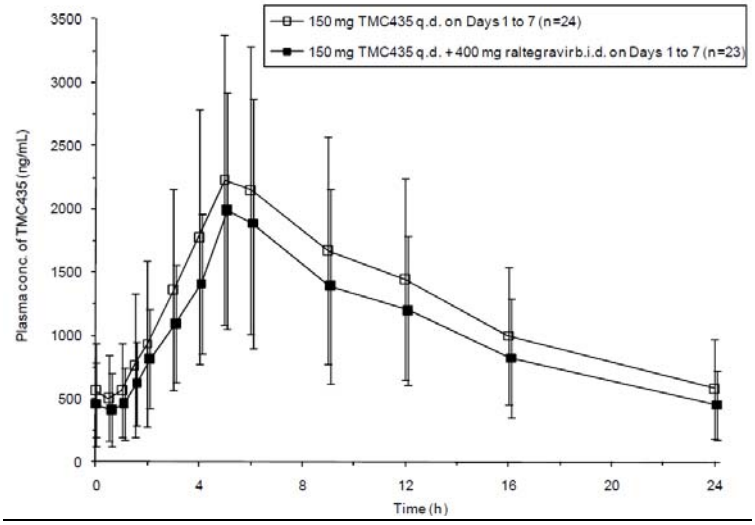


Figure 3: Mean Plasma Concentration-Time Curves of TMC435 (Including SD Bars) After Administration of TMC435 Alone (Treatment D, Day 7) and in Combination With Raltegravir (Treatment F, Day 7)

Table 3: Summary of the Statistical Analysis of the PK Parameters of TMC435 After Administration of TMC435 Alone (Treatment D, Reference) and in Combination With Raltegravir (Treatment F, Test)

Parameter	LSmeans[a]		LSmeans ratio	90% CI[c]	p-value	
	150 mg TMC435 q.d. on Days 1 to 7 (reference)	150 mg TMC435 q.d. + 400 mg raltegravir b.i.d. on Days 1 to 7 (test)			Period	Sequence
C_{min}, ng/mL	387.6	333.9	0.86	0.75 - 0.98	0.6545	0.7625
C_{max}, ng/mL	2082	1941	0.93	0.85 - 1.02	0.7180	0.7638
AUC_{24h}, ng.h/mL	25920	23100	0.89	0.81 - 0.98	0.8483	0.8164
	Median[b]		Treatment difference median	90% CI, h[c]	p-value	
Parameter	150 mg TMC435 q.d. on Days 1 to 7 (reference)	150 mg TMC435 q.d. + 400 mg raltegravir b.i.d. on Days 1 to 7 (test)			Period	Sequence
t_{max}, h	5.0	5.0	0.00	0.00 - 0.50	0.3928	0.6535

[a] n=24 for reference and n=23 for test

[b] n=23 for reference and test

[c] 90% confidence intervals

- Effect of TMC435 on Reltegravir PK

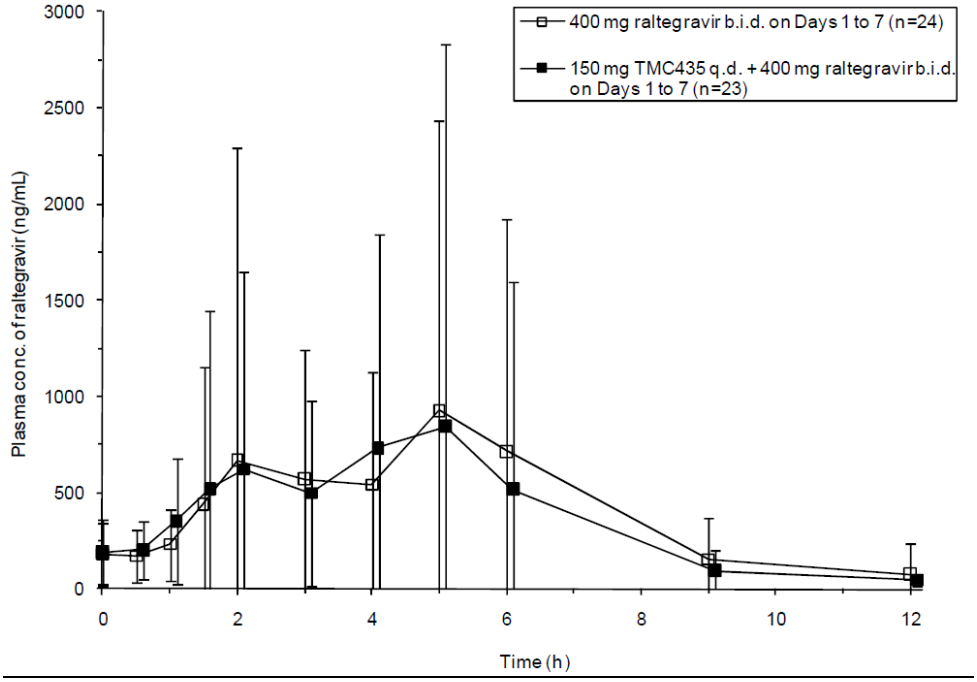


Figure 4: Mean Plasma Concentration-Time Curves of Raltegravir (Including SD Bars) After Administration of Raltegravir Alone (Treatment E, Day 7) and in Combination With TMC435 (Treatment F, Day 7)

Table 4: Summary of the Statistical Analysis of the PK Parameters of Raltegravir After Administration of Raltegravir Alone (Treatment E, Reference) and in Combination With TMC435 (Treatment F, Test)

Parameter	LSmeans[a]		LSmeans ratio	90% CI[c]	p-value	
	400 mg raltegravir b.i.d. on Days 1 to 7 (reference)	150 mg TMC435 q.d. + 400 mg raltegravir b.i.d. on Days 1 to 7 (test)			Period	Sequence
C_{min}, ng/mL	37.12	42.49	1.14	0.97 - 1.36	0.1385	0.2427
C_{max}, ng/mL	786.2	809.0	1.03	0.78 - 1.36	0.3804	0.6132
AUC_{12h}, ng.h/mL	3034	3283	1.08	0.85 - 1.38	0.1913	0.4201
	Median[b]		Treatment difference median	90% CI, h[c]	p-value	
Parameter	400 mg raltegravir b.i.d. on Days 1 to 7 (reference)	150 mg TMC435 q.d. + 400 mg raltegravir b.i.d. on Days 1 to 7 (test)			Period	Sequence
t_{max}, h	3.0	3.0	-0.25	(-1.00) - 0.50	0.0588	0.1732

[a] n=24 for reference and n=23 for test

[b] n=23 for reference and test

[c] 90% confidence intervals

- Were there any outliers or excluded data from analysis? ☒ Yes ☐ No ☐ NA, if yes explain

Subject 123-0052 (Treatment B) was suspected to be non-compliant because there was no quantifiable efavirenz in Day 12 predose sample. Therefore the concentrations of Treatment B were excluded from descriptive statistics and the calculation of the PK parameters.

- Are the study results acceptable? ☒ Yes ☐ No, if no explain

Safety

Was there any death or serious adverse events? ☐ Yes ☒ No

CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS

CONCLUSIONS

TMC435 PK was significantly affected by the coadministration of efavirenz: Cmin, Cmax and AUC24h of TMC435 were decreased by 91%, 51% and 71%, respectively, in the presence of efavirenz compared to administration of TMC435 alone. In the presence of efavirenz, there was a continuing decline in TMC435 C0h between days 12 to 14, indicating that steady-state induction of cytochromes P450 enzymes by efavirenz was not yet completely achieved by Day 14. Therefore, the magnitude of the drug-drug interaction as measured on Day 14 in this study is likely an underestimation of the drug-drug interaction at steady-state.

Efavirenz PK was little affected by the coadministration of TMC435: Cmin, Cmax and AUC24h of efavirenz were comparable for test and reference. The 90% CIs of the LS means ratios were all within the 0.8-1.25 interval. Based on 90% CI of the ratio of the LS means, Cmin of TMC435 was decreased by 14%, in the presence of raltegravir compared to after administration of TMC435 alone. Cmax and AUC24h were comparable.

Either TMC PK or raltegravir PK was little affected by coadministration of the two drugs: Based on 90% CI of the ratio of the LS means, Cmin of TMC435 was decreased by 14%, in the presence of raltegravir compared to after administration of TMC435 alone. Cmax and AUC24h were comparable. Cmin and AUC12h of raltegravir were increased by, respectively, 14% and 8% in the presence of TMC435 compared to administration of raltegravir alone. Cmax was unchanged, although the lower limit of the 90% CI of the LS mean ratio fell below 0.8 and the upper limit was above 1.25.

The coadministration of 150 mg q.d. TMC435 and 600 mg q.d. efavirenz or 400 mg b.i.d. raltegravir in healthy subjects was generally safe and well-tolerated.

The sponsor's conclusions appear valid.

COMMENTS

None

LABEL RECOMMENDATIONS

The DDI information should be adequately presented in the label.

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY DRUG-DRUG INTERACTION STUDY REVIEW				
Study #	TMC435-TiDP16-C124	**Study Period**	11/07/2011 – 02/09/2012	EDR Link
Title	A Phase I, open-label trial in healthy female subjects to investigate the effect of TMC435 at steady-state on the steady-state pharmacokinetics of ethinylestradiol and norethindrone.			

STUDY DESIGN

This was a phase I, open-label study.

Cycle I First OC Cycle				Cycle II Second OC Cycle			
Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4
Day 1-21			Day 22-28	Day 29-49			Day 50-56
Treatment: Ovysmen® q.d.			OC-free period	Treatment: Ovysmen® q.d.			OC-free period
						Day 40-49	
						Treatment: TMC435 150 mg q.d.	
Day 21: full pharmacokinetic profile of ethinylestradiol and norethindrone				**Day 49**: full pharmacokinetic profile of ethinylestradiol, norethindrone and TMC435			

Population	☑ Healthy Volunteers ☐ Patients
Study Rationale	Simeprevir is a weak inhibitor of CYP3A4, the enzyme that mediates the metabolism of ethinylestradiol and norethindrone.
Treatments	Simeprevir 150 mg. Ovysmen®, containing 35 µg of ethinylestradiol and 1 mg of norethindrone.
Dose Selection Rationale	Simeprevir is available in one dose (150 mg) and Ovysmen® is commercially available oral contraceptive.
Administration	☐ Fasted ☑ Fed
Formulation	Simeprevir 150 mg capsules (G015), batch # 11G20/G015 Ovysmen® tablets, batch # BCS2J00
Interfering Substances Excluded	Alcohol or quinine (e.g., tonic, bitter lemon, bitter alcoholic beverages containing quinine), grapefruit, Seville oranges, and juices from these, energy drinks, (Methyl)xanthines (e.g., coffee, tea, cola, chocolate) , and any food containing poppy seeds.
Sampling Times	• PK: Last day of treatment in each cycle at: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 hours post-dose. OC in both cycles and simeprevir in cycle II. • PD: Serum levels of progesterone, LH and FSH were done pre-dose on Day 1 and at 2 hours post-dose on Days 19, 20, and 21 (Cycle I), and pre-dose on Day 29 and at 2 hours post-dose on Days 47, 48, and 49 (Cycle II).
PK Parameters	C_0, Cmin, tmax, Cmax, AUC_{0-24h}, $C_{ss,av}$, and FI
PK Analysis	Non-compartmental
Statistical Analysis	The least square (LS) means with 90% CI of the primary parameters for each treatment group (day) was estimated with a linear mixed effects model, controlling for treatment as a fixed effect, and subject as a random effect.
Is the study design acceptable? ☑ Yes ☐ No	

STUDY CONDUCT

Bioanalytical Method:

Method Type	LC-MS/MS	Matrix	Plasma	
Analytes	Ethinylestradiol/Norethindrone			
Range	2-500 pg/mL/50-25000 pg/mL			
Validation	▪ Method validated prior to use			☑ Yes ☐ No ☐ NA
	▪ Method validation acceptable			☑ Yes ☐ No ☐ NA
Study Samples Analysis	▪ Samples analyzed within the established stability period			☑ Yes ☐ No
	▪ Quality control samples range acceptable			☑ Yes ☐ No
	▪ Chromatograms provided			☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable			☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable			☑ Yes ☐ No
	▪ Incurred samples analysis is acceptable			☑ Yes ☐ No
	▪ Overall performance acceptable			☑ Yes ☐ No
Inspection	▪ Will the bioanalytical site be inspected			☐ Yes ☑ No

Protocol Deviations

- Are there any protocol deviations listed in the study report? ☑ Yes ☐ No
- Do any of the listed deviations affect the integrity of the study? ☐ Yes ☑ No ☐ NA

One major aberration (> 10.00% deviation) from the scheduled time was identified for the actual sampling time of the 0.5 hour post-dose sample for TMC435 on Day 49 (Cycle II) of one subject. For this subject, pharmacokinetic parameters for TMC435 on Day 49 were calculated on actual sampling times.

STUDY RESULTS

Study Population

Screened	47
Treated	18
Completed	17
Discontinued Due to AE	1
PK Population/Safety Population	11/11
Age [Median (range)]	32.5 [154,177]
Male/Female	0/18
Race (Caucasian/Black/Asian/Other)	18/0/0/0

Pharmacokinetics

Simeprevir steady sates was attained prior to PK sampling in cycle II.

Ethinylestradiol

Parameter	LSmeans[a] 35 µg Ethinylestradiol and 1 mg Norethindrone q.d. (Reference)	LSmeans[a] 35 µg Ethinylestradiol and 1 mg Norethindrone q.d. + 150 mg TMC435 q.d. (Test)	LSmeans Ratio	90% CI
C_{min}, pg/mL	21.41	21.52	1.00	0.89 - 1.13
C_{max}, pg/mL	77.49	91.19	1.18	1.09 - 1.27
AUC_{24h}, pg.h/mL	984.7	1106	1.12	1.05 - 1.20
Parameter	**Median[a] 35 µg Ethinylestradiol and 1 mg Norethindrone q.d. (Reference)**	**Median[a] 35 µg Ethinylestradiol and 1 mg Norethindrone q.d. + 150 mg TMC435 q.d. (Test)**	**Treatment Difference Median**	**90% CI**
t_{max}, h	3.0	3.0	0.00	(0.0) – (0.5)

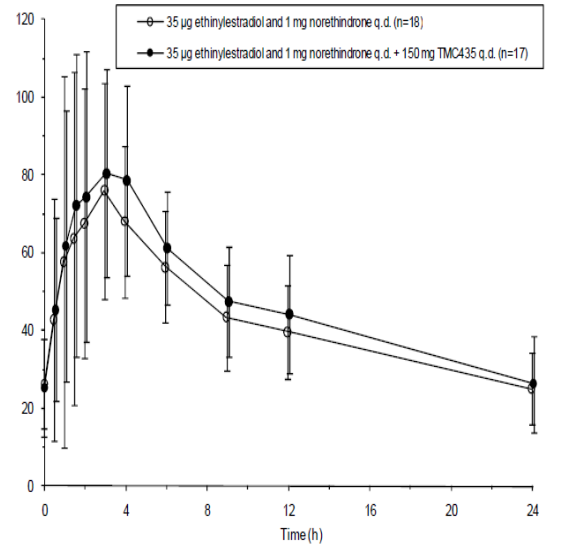
[a] n = 18 for reference and n = 17 for test

Norethindrone

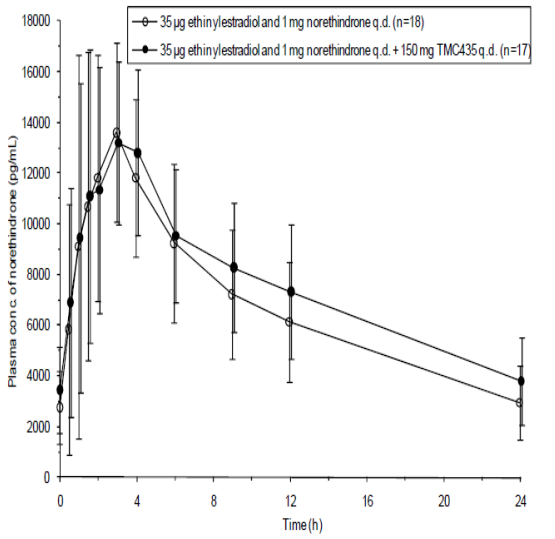
Parameter	LSmeans[a] 35 µg Ethinylestradiol and 1 mg Norethindrone q.d. (Reference)	LSmeans[a] 35 µg Ethinylestradiol and 1 mg Norethindrone q.d. + 150 mg TMC435 q.d. (Test)	LSmeans Ratio	90% CI
C_{min}, pg/mL	2298	2845	1.24	1.13 - 1.35
C_{max}, pg/mL	14390	15270	1.06	0.99 - 1.14
AUC_{24h}, pg.h/mL	152600	175200	1.15	1.08 - 1.22
Parameter	**Median[a] 35 µg Ethinylestradiol and 1 mg Norethindrone q.d. (Reference)**	**Median[a] 35 µg Ethinylestradiol and 1 mg Norethindrone q.d. + 150 mg TMC435 q.d. (Test)**	**Treatment Difference Median**	**90% CI**
t_{max}, h	2.5	3.0	0.00	(0.0) – (1.0)

[a] n = 18 for reference and n = 17 for test

Ethinylestradiol PK Profile



Norethindrone PK Profile



- Pharmacodynamic Results: PD results are not presented because of their minimal role in informing dosing recommendation especially in the absence of any significant PK interaction. In general change form baseline in PD markers was comparable in cycle I and II.
- Were there any outliers or excluded data from analysis? ☐ Yes ☑ No ☐ NA
- Are the study results acceptable? ☑ Yes ☐ No, if no explain

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No

One subject had grade 2 erythema (verbatim: solar erythema) and grade 1 edema (verbatim: face and hands edema) on Day 47. Study medication was permanently discontinued due to these AEs. The investigator considered both AEs as possibly related to simeprevir and not related to ethinylestradiol/norethindrone.

CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS

CONCLUSIONS

Does the study finding warrant dose adjustment upon the co-administration of the two drugs? ☐ Yes ☑ No

Is the interaction clinically significant? ☐ Yes ☐ No ☑ NA

COMMENTS: None

LABEL RECOMMENDATIONS

There is no need for dose adjustment of Ovysmen® upon the co-administration of simeprevir.

APPEARS THIS WAY ON ORIGINAL

Trial TMC435350-TiDP16-C126
A Phase I, open-label trial to investigate the effect of severe renal impairment on the pharmacokinetics and safety of TMC435

Trial Period
2 Aug 2011 to 9 Jan 2012
Final report date: 25 Jul 2012

Trial Site
PRA International, Prague, Czech Republic

Trial Rationale
Simeprevir (TMC435) is an inhibitor of the hepatitis C virus (HCV) NS3/4A protease, currently under development for the treatment, in combination with ribavirin and pegylated interferon alpha, of chronic HCV infection. Simeprevir inhibits viral replication with a protein binding-corrected 50% effective concentration (EC_{50}) of 12 nM in a cellular HCV genotype 1b replicon model. Simeprevir is primarily metabolized by CYP3A and undergoes minimal renal excretion. For these reasons, this study was designed as a reduced study conducted to evaluate the effect of severe renal impairment on the steady-state pharmacokinetics of simeprevir as well as the safety and tolerability of simeprevir in patients with severe renal impairment.

Trial Objectives
The primary objective of this trial was to:

- assess the steady-state pharmacokinetics of TMC435 in subjects with severe renal impairment

The secondary objective of this trial was to:

- assess the short-term safety and tolerability of TMC435 in subjects with severe renal impairment

Trial Design
This was an open-label trial that investigated the pharmacokinetics and safety of simeprevir in subjects with severe renal impairment.

The study population consisted of eight subjects with severe renal impairment (eGFR ≤29 mL/min/1.73 m^2) who were not on dialysis and eight matched controls with normal renal function (eGFR ≥80 mL/min/1.73 m^2). All subjects received simeprevir 150 mg QD for 7 days under fed conditions; simeprevir pharmacokinetics were evaluated over 72 h following the last dose.

Drug Administration

Study drug was taken once daily between 730a and 10a under supervised conditions. Capsules were to be swallowed whole with 240 mL of water, within 10 min of completion of a standardized breakfast. On the morning of intensive pharmacokinetic sampling (Day 7), a standardized breakfast was consumed within 30 min, followed by study drug administration within 10 min. Subjects could resume water and food intake two and four hours postdose, respectively.

Rationale for Dose Selection

The TMC435 dose of 150 mg QD was selected because it was the highest dose studied in the Phase 2b trials C205 and C206. TMC435 was administered for 7 days because steady-state conditions were reached in approximately 7 days.

Investigational Product

TMC435 was manufactured and provided by Tibotec Pharmaceuticals Ltd. TMC435 capsules contained 150 mg (formulation G007, Batch 11B03) of (b) (4) TMC435 sodium salt and excipients.

Key Inclusion and Exclusion Criteria

Subjects were nonsmoking (smoking no more than 10 cigarettes, 2 cigars, or 2 pipes per day) males and non-pregnant, non-breastfeeding females between the ages of 18 and 70 years, inclusive, with BMI between 18.0 and 35.0 kg/m^2, inclusive. Female subjects of childbearing potential had to use highly effective birth control methods (including at least one barrier method) during the trial and for at least 30 days after the treatment period. Subjects were excluded if they had HIV-1 or -2 or active hepatitis A, B, or C infection or if they had a positive urine drug test at screening.

Subjects with renal impairment had to have an eGFR ≤29 mL/min/1.73 m^2 (MDRD equation) with stable renal disease and on stable treatment (for at least 2 months) but in otherwise good health. Subjects were not to be on dialysis or expected to start dialysis in the next three months. Subjects with diabetes mellitus could be included as long as the disease was controlled (hemoglobin A1c <7%).

Subjects with normal renal function (eGFR ≥80 mL/min/1.73 m^2) were matched to those with severe renal impairment on the basis of sex, race, age, and BMI.

Concomitant Medications

Healthy subjects were not allowed to use any concomitant medication except for ibuprofen or paracetamol. Subjects with renal impairment could continue to use their regular medications to manage renal insufficiency or related conditions. In addition, for all subjects, the use of cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents for rash, antiemetics for nausea, or loperamide for diarrhea were permitted. Statin therapy was to be interrupted beginning 7 days prior to treatment until the last pharmacokinetic sample was obtained.

Sample Collection

Blood samples were collected for analysis of plasma simeprevir concentrations on Days 2, 5, and 6 immediately before study drug administration, and on Day 7 at the following sampling times: predose and 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, 48, and 72 h postdose.

Analytical Plan

Pharmacokinetic data

Pharmacokinetic and statistical analyses were performed (b) (4) using WinNonlin Professional™ (Pharsight Corporation, Mountain View, California, USA). Statistical demographic, safety, and tolerability analyses were performed (b) (4) using SAS (SAS Institute Inc., Cary, North Carolina, USA).

The primary pharmacokinetic parameters evaluated in this study were C_{max}, C_{min}, C_0, $C_{ss,av}$, T_{max}, AUC_{24}, λ_z, $t_{1/2,term}$, and $\%C_{unbound}$ for simeprevir; C_{max}, C_{min}, and AUC24h were the primary pharmacokinetic parameters. All pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods. Analyses were performed comparing subjects with severe renal impairment to those with normal renal function and included the 90% confidence intervals around the ratios of the geometric means of pharmacokinetic parameters. Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase (λ_z and $t_{1/2}$) were reported when there were at least three data points spanning at least twice the calculated $t_{1/2,term}$ with an r^2 of >0.9000.

Trial Results

Bioanalytical methods

Concentrations of TMC435 in plasma samples were determined using LC-MS/MS (SHAM-186-R0; LLOQ 2.00 ng/mL) by (b) (4). The first day of sample collection was 16 Aug 2011 and analysis was performed between 12 and 30 Jan 2012. The maximum storage sample time of 167 days was within the validated long-term frozen stability duration of 1184 days.

The TMC435 calibration standards ranged from 2-2000 ng/mL and the quality control (QC) concentrations were 5.59, 77.6, and 1550 ng/mL. The inter-assay accuracy estimates ranged from -1.3 to 2.0 % and the inter-assay precision estimates ranged from 2.3 to 5.4%. All of the estimates were within the acceptable criteria (≤20% deviation at the LLoQ concentration, and ≤15% deviation at all other concentrations).

Trial population

A total of 16 subjects (8 with severe renal impairment and 8 matched controls) were enrolled in the study; all were treated and completed the trial. The majority of subjects were male (87.5%). All were Caucasian and not of Hispanic descent. The median age was 56 years (range: 36 to 67 years).

Results of pharmacokinetic analyses

In this study, the steady-state pharmacokinetics under fed conditions of simeprevir 150 mg QD were evaluated in subjects with severe renal impairment and matched controls with normal renal function.

The mean simeprevir plasma concentration-time curves after 7 days of administration of 150 mg QD to subjects with normal renal function and severe renal impairment are shown in Figure 1. In most subjects (regardless of renal function), steady-state conditions were reached by Day 7. While the shapes of the concentration-time curves were similar, mean plasma concentrations were higher in subjects with renal impairment. Interindividual variability in plasma concentrations was high (75 to 206%) and similar in subjects with normal renal function and subjects with severe renal impairment.

A lag time in absorption was observed in all subject groups, indicating a delay in drug dissolution or release from the delivery system or drug migration to the absorbing surface. The lengths of the absorption phases were comparable across subject groups, but the terminal phases declined more slowly in subjects with hepatic impairment, particularly in those whose hepatic impairment was severe.

Figure 1: Mean plasma ± SD concentration-time curves of TMC435 after administration of 7 days of simeprevir 150 mg QD in subjects with normal renal function or severe renal impairment (linear scale; source: Study Report Figure 3)

The pharmacokinetic parameters of simeprevir in subjects with severe renal impairment and healthy matched controls are displayed in Table 1. Simeprevir exposures were higher in subjects with severe renal impairment compared to those with normal renal function. Terminal $t_{1/2}$ appeared to be slightly longer in subjects with renal impairment;

however, data from only four subjects contributed to this parameter. Note that simeprevir exposures are approximately 2-fold higher in subjects with HCV infection compared to subjects without HCV infection; therefore, exposures in HCV-infected subjects with renal impairment may be expected to be approximately 2-fold higher than those observed in the current trial.

Table 1: Pharmacokinetics of TMC435 after administration of simeprevir 150 mg QD administration in subjects with severe renal impairment and matched healthy controls (data presented as mean (SD) except for T_{max}, which is median (range); source: Study Report Table 4)

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The percentage of unbound TMC435 predose and 4 h postdose was very low in all subjects (approximately 0.0001%) and was comparable in subjects with normal renal function and severe renal impairment.

Statistical comparisons of simeprevir exposures between subjects with normal renal function and subjects with severe renal impairment are displayed in Table 2.

Table 2: Statistical analyses of TMC435 pharmacokinetics after simeprevir 150 mg QD administration in subjects with normal renal function or severe renal impairment (data presented as least squares mean ratio (90% CI); source: Study Report Table 5)

Parameter	LSmeans[a]		LSmeans Ratio	90% CI
	Matched Healthy Controls (Reference)	Renally Impaired Subjects (Test)		
C_{min}, ng/mL	577.5	985.5	1.71	0.65 - 4.50
C_{max}, ng/mL	2588	3459	1.34	0.66 - 2.72
AUC_{24h}, ng.h/mL	32010	51710	1.62	0.73 - 3.59
Parameter	Median[a]		Treatment Difference Median	90% CI
	Matched Healthy Controls (Reference)	Renally Impaired Subjects (Test)		
t_{max}, h	6.0	6.0	0.0	0.0 - 2.0

[a] N: 8 for reference and N: 8 for test

Results of safety analysis

During the treatment phase, four subjects with renal impairment reported one AE each (hyperbilirubinemia, blood alkaline phosphatase increased, myalgia, rhabdomyolysis, and hypertension); one subject with normal renal function reported an AE of hyperbilirubinemia. One subject (Subject 1260016) with severe renal impairment experienced a treatment-emergent SAE (rhabdomyolysis). The simeprevir exposures (AUC_{24} and C_{max}) observed in this subject were near the mean exposures for the renal impairment group (Figure 2).

Figure 2: TMC435 AUC_{24} after administration of 7 days of simeprevir 150 mg QD in subjects with severe renal impairment (source: Study C126 concentration data)

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There was one lab abnormality above grade 2 that was reported during the treatment phase (grade 4 increased AST in the subject who experienced rhabdomyolysis).

Trial Summary

This study was designed to evaluate the steady-state pharmacokinetics and safety of simeprevir 150 mg QD administration for 7 days in subjects with normal renal function and subjects with severe renal function. Compared to subjects with normal renal function, simeprevir exposures (AUC_{24}) increased by 1.62-fold in subjects with severe renal function, respectively. Visual evaluation of the simeprevir concentration-time curves suggests that the rate of simeprevir elimination was not substantially impacted by renal impairment. Likewise, simeprevir plasma protein binding was unaffected by renal impairment.

Simeprevir was relatively safe following administration for 7 days in subjects with renal impairment. One incident of rhabdomyolysis was reported in a subject with severe renal impairment; simeprevir exposures in this subject were near the mean for subjects with severe renal impairment.

Based on the magnitude of exposure increases in patients with renal impairment, no adjustment to the simeprevir dose is necessary in this patient population.

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Trial TMC435350-TiDP-C201
A blinded, randomized, placebo-controlled trial in genotype 1 hepatitis C-infected subjects to evaluate the efficacy, safety, tolerability, and pharmacokinetics of repeated doses of TMC435350, with or without peginterferon alpha-2a and ribavirin

Trial Period
18 Dec 2007 to 26 Apr 2010
Final report date: 24 Mar 2011

Trial Site
Academisch Medisch Centrum, Dept. of Hepatology, Amsterdam, The Netherlands (coordinating investigator); additional sites in Belgium, Germany, France, UK, and Poland

Trial Rationale
Simeprevir (TMC435) is an inhibitor of the hepatitis C virus (HCV) NS3/4A protease, currently under development for the treatment, in combination with ribavirin and pegylated interferon alpha, of chronic HCV infection. Simeprevir inhibits viral replication with a protein binding-corrected 50% effective concentration (EC_{50}) of 12 nM in a cellular HCV genotype 1b replicon model. Five days of TMC435 200 mg QD was safe and well-tolerated in healthy subjects and subjects with HCV infection in trial C101. The current study was conducted to investigate the antiviral activity of multiple doses of simeprevir ranging from 25 to 200 mg QD, with or without peginterferon alpha-2a and ribavirin, in treatment-naïve subjects with genotype 1 HCV infection.

Trial Objectives
The primary objectives of this trial were to:

- determine the dose dependency of the antiviral effect of TMC435 during 1 week of monotherapy in treatment-naïve genotype 1 HCV-infected subjects
- determine the dose dependency of the antiviral effect of TMC435 during triple therapy with peginterferon alpha-2a (PegIFNa-2a) and ribavirin (RBV) in treatment-naïve genotype 1 HCV-infected subjects

The secondary objectives of this trial were to:

- determine the safety, tolerability, and pharmacokinetic profile of TMC435 during 1 week of monotherapy, and during triple therapy with PegIFNa-2a and RBV in treatment-naïve genotype 1 HCV-infected subjects
- determine the 4-week efficacy and safety of three doses of TMC435 given in combination with PegIFNa-2a and RBV in treatment-experienced (prior non-responders/relapsers) genotype 1 HCV-infected subjects
- determine the frequency, kinetics, and genetics of viral breakthrough during monotherapy and combination therapy

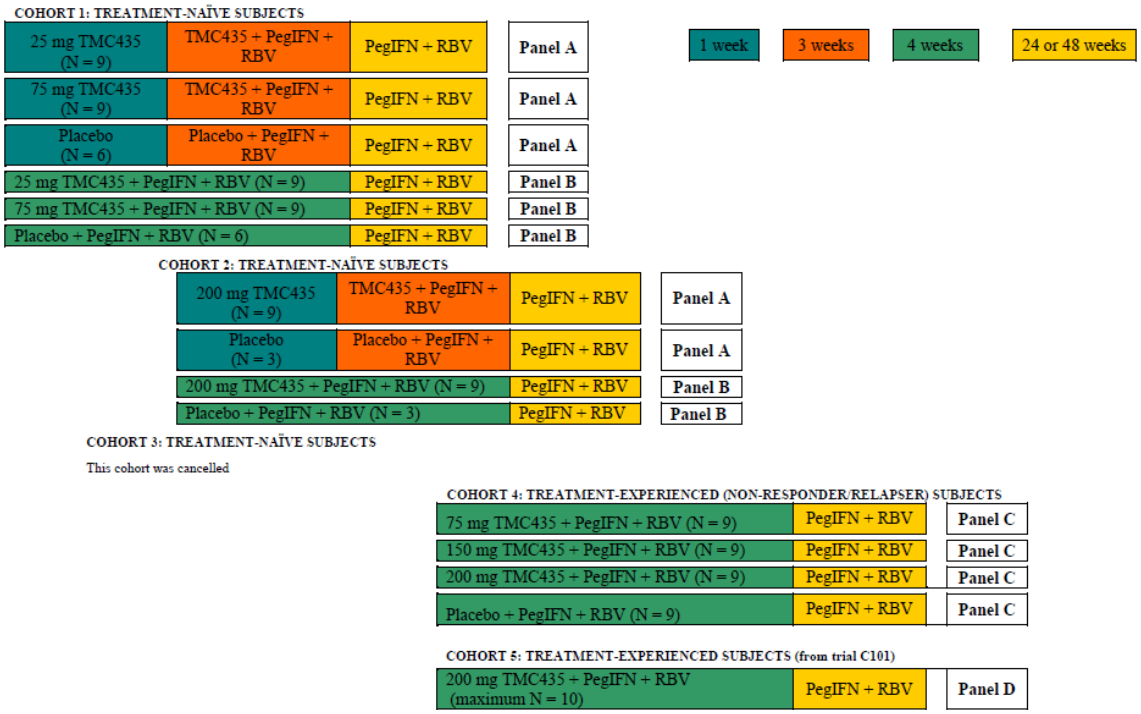
- follow RVR from Week 4 until Week 24 or 48 (after 20 or 44 weeks of PegIFNa-2a and RBV treatment); determine EOT response and the incidence of SVR24
- study the potential drug-drug interaction by TMC435 on RBV

Trial Design

This was a blinded, randomized, placebo-controlled trial. The efficacy, safety, tolerability, and pharmacokinetics of TMC435 (25, 75, 150, and 200 mg QD) with and without PegIFNa-2a and RBV were evaluated in this trial.

Treatment-naïve subjects were divided into two sequential cohorts (low and high doses) to ensure safety prior to dose escalation (note that Cohort 3 was intended to evaluate TMC435 400 mg QD, but was cancelled after antiviral activity was observed at lower doses). Cohorts were further divided into panels to test monotherapy versus triple therapy. A schematic of the trial design is shown in Figure 1.

Figure 1: Trial design



Drug Administration

Study drug was taken once daily at approximately the same time every morning under fed conditions. On mornings when pharmacokinetic sampling was to be performed (Days 1 and 28 for all panels and Day 7 for Panel A only), a standardized breakfast was consumed within 30 min, followed by study drug administration within 10 min. Capsules were to be swallowed whole with 240 mL of water. Subjects could resume water and food intake two and four hours postdose, respectively.

PegIFNa-2a was administered once weekly. Ribavirin was administered twice daily (the morning intake with study drug), with the doses separated by 12 h.

Rationale for Dose Selection

The initial TMC435 dose of 25 mg QD was selected because it was estimated to provide liver concentrations 64-fold higher than the protein binding-corrected mean EC_{50}. The high TMC435 dose of 400 mg QD (which was planned but was not administered) was generally safe and well-tolerated in healthy subjects.

Investigational Product

TMC435 and placebo formulations were manufactured and provided by Tibotec Pharmaceuticals Ltd. TMC435 capsules contained 100 (formulation F007, Batches 8GT0M, 07J15, and 08G25) or 25 (formulation F008, Batches 08GT0L, 07J16, and 08G23) mg of a (b) (4) TMC435 sodium salt and excipients; placebo capsules contained excipients only.

Commercially available syringes containing 180 ug PegIFNa-2a in 0.5 mL solution (Pegasys®) were manufactured by Genentech and provided by Tibotec Pharmaceuticals Ltd. Commercially available tablets containing 200 mg ribavirin (Copegus®) were manufactured by Genentech and provided by Tibotec Pharmaceuticals Ltd.

Key Inclusion and Exclusion Criteria

Subjects were nonsmoking males and females of non-childbearing potential between the ages of 18 and 70 years, inclusive, with normal weight (defined by BMI), normal ECG, and documented chronic genotype 1a or 1b HCV infection, including a viral load of at least 10,000 IU/mL. Male subjects with female partners of childbearing potential had to agree to use reliable birth control.

Potential subjects were excluded if they had Child Pugh B or C liver disease at Screening, received polymerase or protease inhibitors or PegIFNa-2a and RBV within 6 months prior to Screening, tested positive for HIV-1 or -2 or hepatitis A or B, or if they had any active disease of clinical significance.

Concomitant Medications

The following medications were not allowed during the TMC435 treatment period: any anti-HCV therapy except study drugs, all investigational drugs, and immunomodulators except Pegasys®. Erythropoiesis stimulating agents were not allowed from Screening onwards. The following medications were not allowed during the trial: CYP450 inducers (rifabutin, rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's Wort, systemic dexamethasone); CYP450 inhibitors (systemic ketoconazole and itraconazole, macrolide antibiotics); CYP3A4 and CYP2D6 substrates with small therapeutic indices; and any medications prohibited in the Pegasys® or Copegus® product information.

Sample Collection

Blood samples were collected for analysis of study drugs on Days 1, 2, 7, 8, 11, 14, 21, and 29 as described here.

TMC435 was quantified just before study drug administration and at the sampling times noted below:

Days 1 and 28 (all)	predose, 0.5, 1, 2, 4, 6, 8, 10 h postdose
Day 7 (Panel A only)	predose, 0.5, 1, 2, 4, 6, 8, 10 h postdose
Day 8 (Panel A only)	predose and 4 h postdose

Ribavirin was quantified just before study drug administration in the morning and at the sampling times noted below:

Day 1 (Panels B-D)	predose and 0.5, 1, 2, 4, 6, 8, and 10 h postdose
Day 28 (all)	predose and 0.5, 1, 2, 4, 6, 8, and 10 h postdose

Analytical Plan

Pharmacokinetic data

Pharmacokinetic and statistical analyses were performed (b) (4) using WinNonlin Professional™ (Pharsight Corporation, Mountain View, California, USA), Microsoft Excel® 2007 (Microsoft Corporation, Redmond, Washington, USA), and SAS (SAS Institute Inc., Cary, North Carolina, USA). Statistical demographic, safety, and tolerability analyses were performed (b) (4) (b) (4)

The primary pharmacokinetic parameters evaluated in this study were C_{max}, C_{min}, C_0, $C_{ss,av}$, T_{max}, λ_z, AUC_{24}, and $t_{1/2}$ for simeprevir and C_{max}, C_{min}, C_0, $C_{ss,av}$, T_{max}, and AUC_{24} for ribavirin. All pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods. Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase (λ_z, AUC_{inf}, and $t_{1/2}$) were reported when there were at least three data points (spanning at least twice the calculated $t_{1/2,term}$ with an r^2 of >0.9000.

Trial Results

Bioanalytical methods

Concentrations of TMC435 in plasma samples were determined using LC-MS/MS (Standard Analytical Method SAM JNJ-38733214/LCMS/005-d, 006-c, and 006-d; validated in Study BA883; LLOQ 2.00 ng/mL) by Janssen Research & Development (Beerse, Belgium). Frozen plasma samples were received between 19 Mar 2008 and 17 Sept 2009 and analysis was performed between 19 Mar 2008 and 20 Jan 2009. The maximum storage sample time of 307 days was within the validated long-term frozen stability duration of 1184 days.

The TMC435 calibration standards ranged from 2-2000 ng/mL and the quality control (QC) concentrations were 56.0, 76.0, and 1560 ng/mL. The inter-assay accuracy

estimates ranged from -8.1 to 4.9% and the inter-assay precision estimates ranged from 2.5 to 27.6%. Not all of the estimates were within the acceptable criteria (≤20% deviation at the LLoQ concentration, and ≤15% deviation at all other concentrations); however, as pharmacokinetic results from this study will not be included in the labeling, these deviations are acceptable.

Trial population

A total of 120 subjects were enrolled in the study; 116 (74 treatment-naïve and 42 treatment-experienced, 66.7% of whom were non-responders with the remainder relapsers, and 5 of whom were in Cohort 5 [i.e. previously treated in trial C101]) were treated and 73 subjects completed the study. Of the 43 subjects who discontinued, 25 did so because they reached a virologic endpoint, five were deemed ineligible to continue the trial, four experienced an adverse event, three were lost to follow-up, two withdrew consent, and four withdrew due to other reasons. The majority of subjects were male (73.3%) and Caucasian (96.6%), with 2.6% of African American and 1% of Arabian descent. The median age was 49 years (range: 19 to 70 years). Forty-four subjects (38.3%) had genotype 1a HCV infection, while 69 (60%) of patients had genotype 1b HCV infection.

Results of pharmacokinetic analyses

In this study, the steady-state pharmacokinetics under fed conditions of simeprevir 25 mg QD, 75 mg QD, and 200 mg QD with and without ribavirin and pegIFNa-2a were evaluated in treatment-naïve and -experienced subjects with genotype 1 HCV infection.

Pharmacokinetics of simeprevir in treatment-naïve subjects

Subjects in Panel A received simeprevir monotherapy for one week, followed by three weeks of combination therapy; subjects in Panel B received combination for four weeks. Intensive sampling was performed to assess simeprevir concentrations on Day 1 in Panels A and B and on Day 7 in Panel A only, as well as on Day 28 in Panels A and B (Figure 1). The mean simeprevir plasma concentration-time profiles were similar after monotherapy or combination therapy, indicating lack of a meaningful interaction between simeprevir and ribavirin (Table 1).

Figure 1: Mean plasma ± SD concentration-time curves of TMC435 after administration of one day (top plot) or one week of simeprevir monotherapy followed by three weeks of combination therapy (Panel A) or four weeks of combination therapy (Panel B) in treatment-naïve HCV-infected subjects (source: Study Report Figure 23)

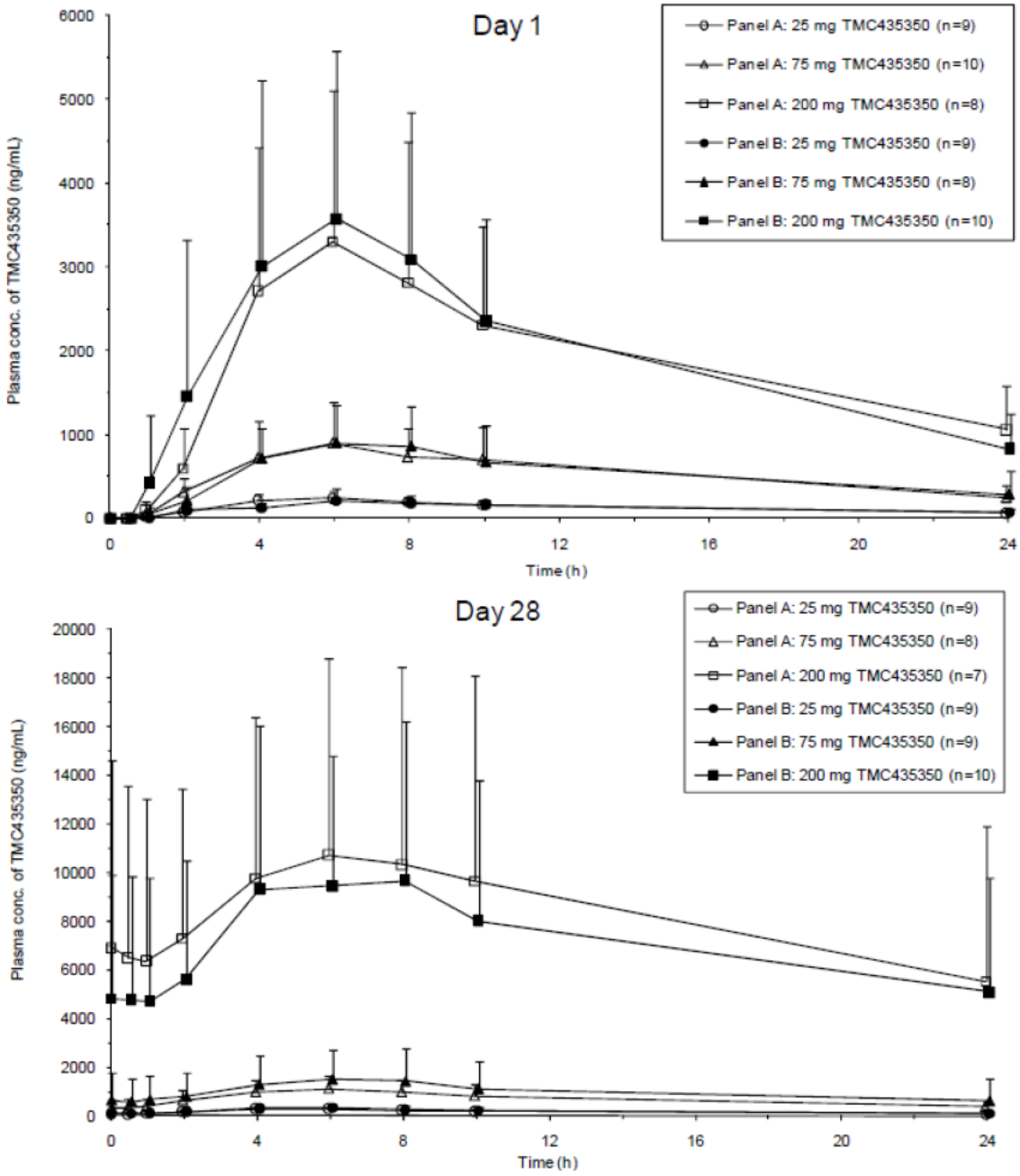


Table 1: Pharmacokinetics of TMC435 after administration of one week of simeprevir monotherapy followed by three weeks of combination therapy (Panel A) or four weeks of combination therapy (Panel B) in treatment-naïve HCV-infected subjects (data presented as mean (SD) except for T_{max}, which is median (range); source: Study Report Tables 59 and 60)

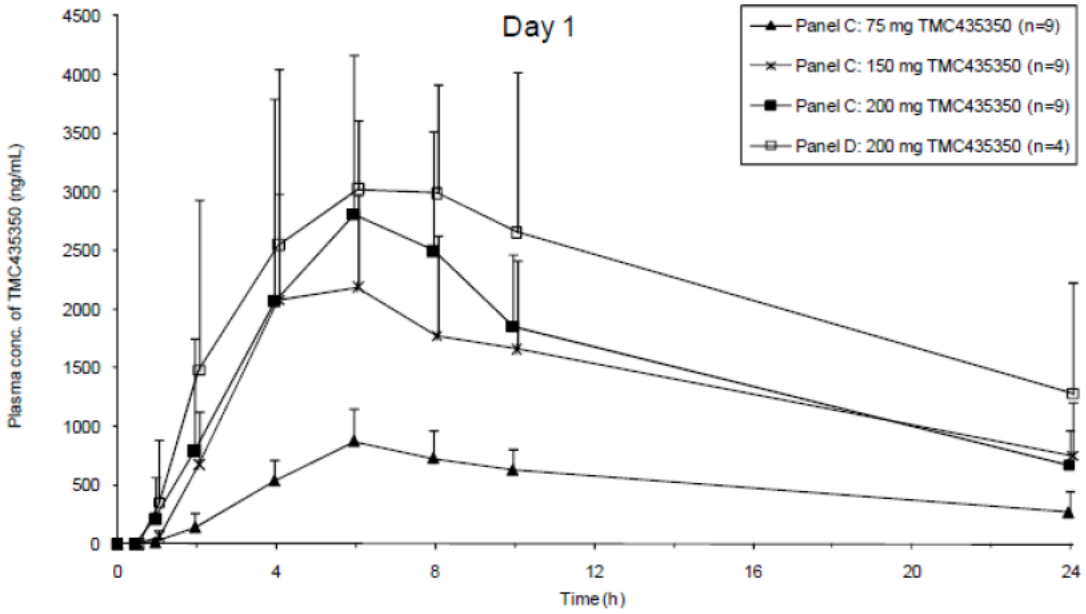
		Panel A			Panel B		
	TMC435 QD	**25 mg**	**75 mg**	**200 mg**	**25 mg**	**75 mg**	**200 mg**
Day 7	**N**	9	9	7	7	6	9
	C_0 ng/mL	72.97 (47.57)	459.4 (298.8)	4570 (4112)	96.89 (45.68)	767.2 (1102)	2837 (2883)

	C_{max}	299.2	1410	8450			
	ng/mL	(129.3)	(629.6)	(5157)			
	T_{max}	6.02	6.00	600			
	h	(2.1-8.0)	(4.0-6.0)	(4.0-6.0)			
	AUC_{24}	4393	20270	137500			
	ng.h/mL	(2394)	(10350)	(99150)			
Day 28	**N**	9	8	7	9	9	10
	C_0	64.78	331.6	6913	95.83	632.8	4818
	ng/mL	(35.15)	(326.6)	(7726)	(61.56)	(1128)	(5071)
	C_{max}	307.1	1058	11180	329.4	1609	10900
	ng/mL	(88.16)	(547.5)	(8522)	(186.9)	(1310)	(6974)
	T_{max}	4.07	6.00	6.04	5.92	6.00	6.00
	h	(4.0-10)	(4.0-6.0)	(4.0-10)	(4.0-6.1)	(3.9-8.0)	(4.0-8.0)
	AUC_{24}	3961	16600	167200	4527	23610	169400
	ng.h/mL	(1523)	(10680)	(154500)	(2806)	(26780)	(126500)
	$T_{1/2,term}$	10.84	11.05	16.49	11.48	14.29	26.15
	h	(2.08)	(3.12)	(6.38)	(2.45)	(8.24)	(18.5)

Simeprevir exposures increased in a dose-proportional manner between 25 and 75 mg and in a greater than dose-proportional manner between 75 and 200 mg. Accumulation was evident with multiple dosing. Steady-state was reached within approximately 7 days; addition of ribavirin and PegIFNa-2a did not substantially influence simeprevir exposures. Interindividual variability was high (range: 64 to 173%).

Pharmacokinetics of simeprevir in treatment-experienced subjects
Subjects in Panels C and D received four weeks of combination therapy followed by 24 or 48 weeks of PegIFNa-2a and ribavirin. Subjects in Panel D were previously enrolled in trial C101. Intensive sampling was performed to assess simeprevir concentrations on Days 1 and 28 in Panels C and D (Figure 2, Table 2).

Figure 2: Mean plasma ± SD concentration-time curves of TMC435 after administration of one day (top plot) or four weeks (bottom plot) of combination therapy (Panel A) or four weeks of combination therapy in treatment-experienced HCV-infected subjects (source: Study Report Figure 24)



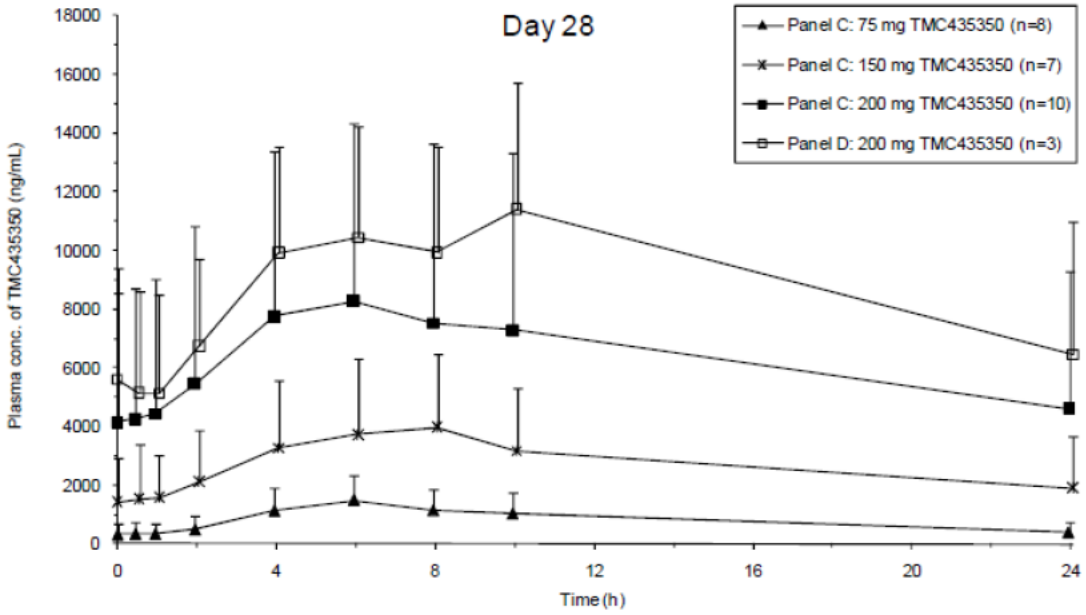


Table 2: Pharmacokinetics of TMC435 after administration of four weeks of combination therapy in treatment-experienced HCV-infected subjects (data presented as mean (SD) except for T_{max}, which is median (range); source: Study Report Table 61)

		Panel C			Panel D
TMC435 QD		**25 mg**	**75 mg**	**200 mg**	**200 mg**
Day 1	**N**	9	9	10	4
	C_0 ng/mL	489.9 (558.0)	2105 (2039)	2795 (1948)	6833 (6566)
Day 28	**N**	8	7	10	3

C_0 ng/mL	324.3 (351.9)	1431 (1501)	4145 (4425)	5593 (3817)
C_{max} ng/mL	1481 (879.6)	4383 (2374)	8452 (6112)	12220 (2917)
T_{max} h	6.00 (5.97-6.08)	6.02 (2.03-9.87)	6.00 (4.00-8.02)	6.00 (4.00-10.00)
AUC_{24} ng.h/mL	20150 (14720)	57440 (44730)	152600 (126600)	231300 (96890)
$T_{1/2,term}$ h	11.58 (3.29)	17.93 (8.02)	18.34 (10.83)	-

Similar to findings in treatment-naïve subjects, in Panels C and D, simeprevir exposures increased in a dose-proportional manner between 25 and 75 mg and in a greater than dose-proportional manner between 75 and 200 mg. Accumulation was evident with multiple dosing. Steady-state was reached within approximately 7 days. Interindividual variability was high (range: 24 to 113%).

Pharmacokinetics of ribavirin

The ribavirin concentration-time profiles in treatment-naïve and -experienced subjects were similar after administration of placebo or different doses of simeprevir (data not shown). Steady-state conditions were almost reached after four weeks of ribavirin administration. Interindividual variability in ribavirin exposures was moderate (range: 20-40%).

Results of efficacy analysis

The primary efficacy endpoint was the change from baseline in plasma HCV RNA levels at Week 4. Treatment-naïve subjects in Panel A received simeprevir monotherapy for one week followed by three weeks of combination therapy, while treatment-naïve subjects in Panel B and treatment-experienced subjects in Panels C and D received combination therapy for four weeks.

Following 7 days of monotherapy, subjects in Panel A experienced a dose-dependent reduction in plasma HCV RNA from baseline, while subjects receiving placebo experienced a smaller reduction in plasma HCV RNA (Figure 3, Table 3). When ribavirin and PegIFNa-2a were added to simeprevir or placebo, greater reductions in plasma HCV RNA were observed (Table 3). These reductions were also dependent on simeprevir dose.

Figure 3: Changes from Baseline in plasma HCV RNA (log_{10} IU/mL) up to Week 4 after administration of one week of TMC435 and three weeks of combination therapy (Panel A) or four weeks of combination therapy (Panel B) in treatment-naive HCV-infected subjects (source: Study Report Figure 5)

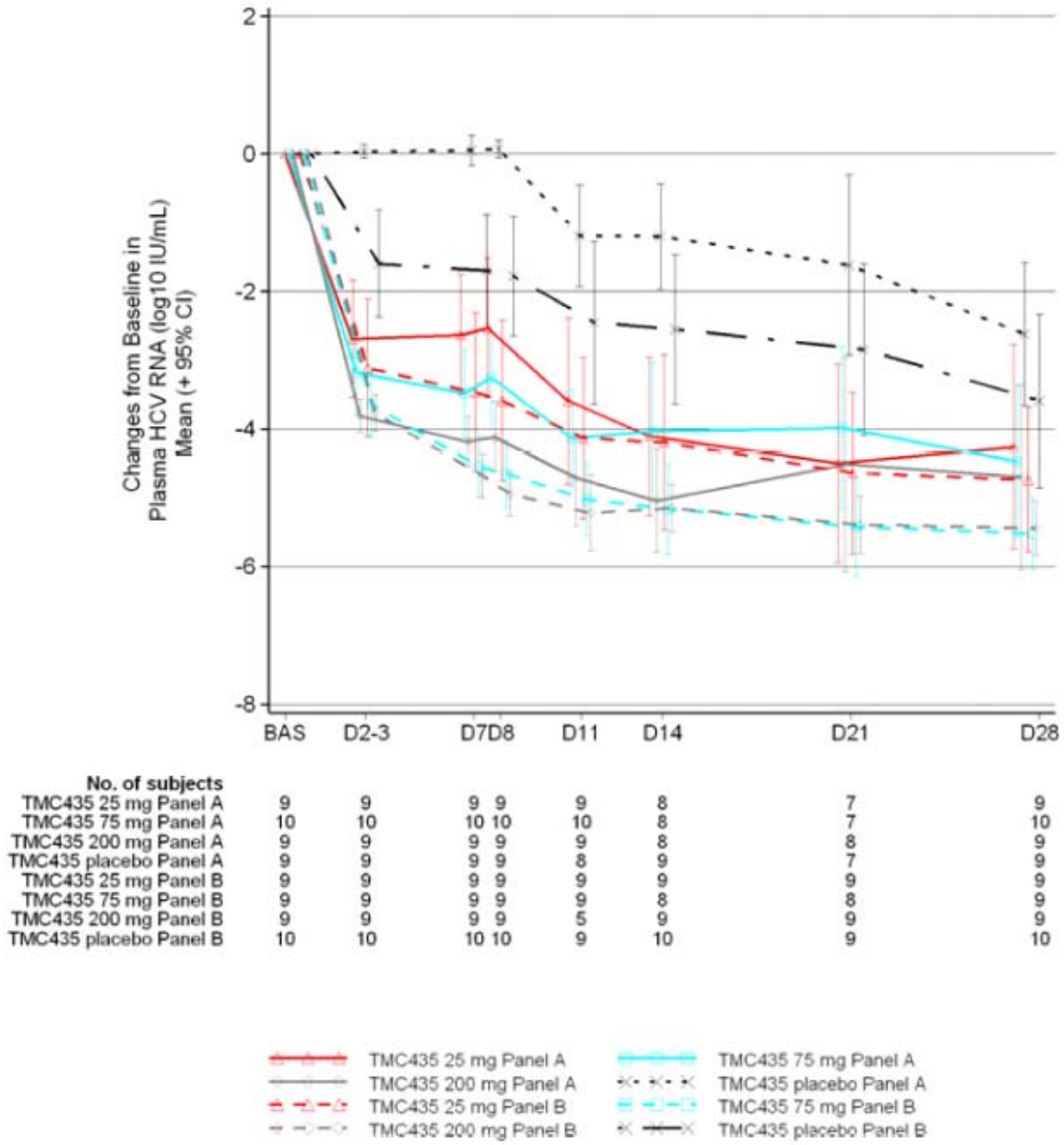


Table 3: Changes from Baseline in plasma HCV RNA (log_{10} IU/mL) on Day 28 after administration of one week of TMC435 and three weeks of combination therapy (Panel A) or four weeks of combination therapy (Panel B) in treatment-naive HCV-infected subjects (source: Study Report Tables 29 and 30)

		Cohort 1			Cohort 2	
		25 mg QD	**75 mg QD**	**Placebo**	**200 mg QD**	**Placebo**
Day 7	**Panel A**					
	Mean ± SE	-2.63±0.377	-3.48±0.285	-0.08±0.101	-4.18±0.158	0.30±0.080
	Median (Range)	-2.67 (-4.1, -0.6)	-3.78 (-4.7, -1.6)	0.01 (-1.5, 0.1)	-4.32 (-4.8, -3.5)	0.31 (0.2, 0.4)
	Panel B					

	Mean ± SE	-3.48±0.500	-4.55±0.192	-1.73±0.441	-4.68±0.135	-1.64±0.793
	Median (Range)	-3.88 (-5.6, -0.9)	-4.27 (-5.5, -3.9)	-1.52 (-3.7, -0.6)	-4.66 (-5.2, -3.9)	-1.85 (-2.9, -0.2)
Day 28	**Panel A**					
	Mean ± SE	-4.26±0.646	-4.47±0.489	-2.74±0.640	-4.70±0.584	-1.92 ±0.156
	Median (Range)	-4.85 (-6.5, -0.8)	-4.83 (-6.4, -1.0)	-2.94 (-5.6, -1.1)	-5.29 (-6.4, -0.7)	-1.94 (-2.2, -1.6)
	Panel B					
	Mean ± SE	-4.74±0.455	-5.52±0.228	-3.74±0.665	-5.44±0.169	-3.26±1.222
	Median (Range)	-5.31 (-6.0, -1.9)	-5.43 (-6.6, -4.5)	-3.21 (-6.0, -1.4)	-5.57 (-6.2, -4.5)	-3.72 (-5.1, -1.0)

Following 7 days of combination therapy, subjects Panels C and D experienced a reduction in plasma HCV RNA from baseline, with subjects receiving simeprevir 150 and 200 mg QD having greater reductions compared to those receiving simeprevir 75 mg QD, while subjects receiving placebo did not experience a reduction in plasma HCV RNA (Figure 4, Table 4).

Figure 4: Changes from Baseline in plasma HCV RNA (log_{10} IU/mL) up to Week 4 after administration of four weeks of combination therapy in treatment-experienced HCV-infected subjects (source: Study Report Figure 9)

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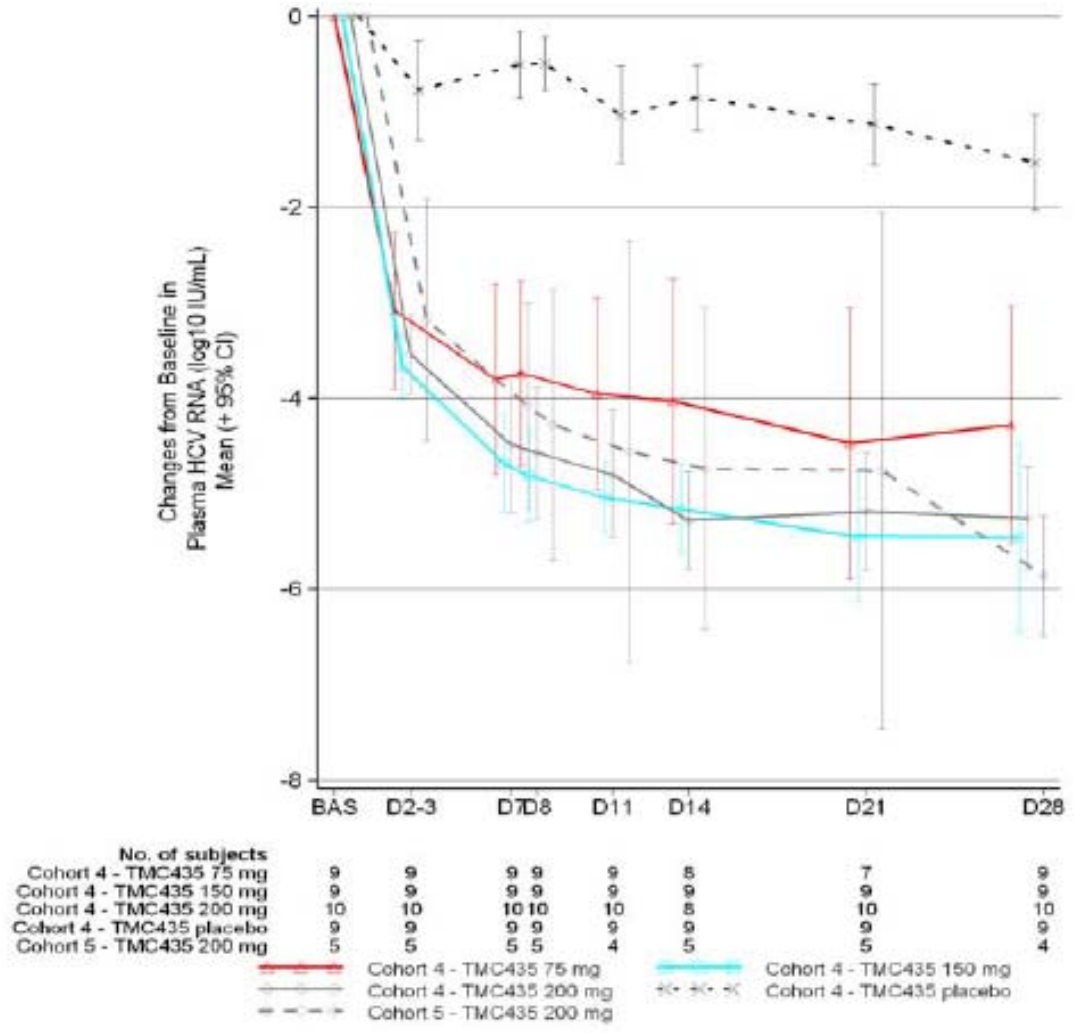


Table 4: Changes from Baseline in plasma HCV RNA (log_{10} IU/mL) on Day 28 after administration of four weeks of combination therapy in treatment-experienced HCV-infected subjects (source: Study Report Table 32)

	Panel C				Panel D
	75 mg QD	**150 mg QD**	**200 mg QD**	**Placebo**	**200 mg QD**
Cohort 4					
Mean ± SE	-4.28±0.539	-5.46±0.425	-5.26±0.238	-1.53±0.216	-5.86±0.198
Median (Range)	-5.18 (-5.7, -1.7)	-5.68 (-6.3, -0.4)	-5.40 (-6.2, 0.3)	-3.03 (-5.5, -0.3)	-5.80 (-6.4, -5.5)

While the changes from baseline in plasma HCV RNA increased with simeprevir dose, the proportion of subjects who experienced a rapid virologic response (RVR; plasma HCV RNA undetectable on Day 28) did not appear to have a strong dose-dependence (Table 5). The proportion of subjects with a sustained virologic response at Week 24 (SVR24) was also not dose-dependent.

Table 5: Percent of treatment-naïve (Panels A [one week monotherapy and three weeks combination therapy] and B [four weeks combination therapy]) or -experienced (Cohorts 4 and 5 [previous simeprevir exposure]) subjects with undetectable plasma HCV RNA on Day 28 (i.e. RVR)

		25 mg QD	75 mg QD	150 mg QD	200 mg QD	Placebo
Tx-naïve	**Panel A**	55.6	50.0	-	77.8	16.7
	Panel B	33.3	88.9		66.7	28.6
Tx-experienced	**Cohort 4**	-	22.2	55.6	30.0	0
	Cohort 5	-	-	-	75.0	-

Results of safety analysis

The most common treatment-emergent AEs during treatment with simeprevir (25% of subjects or greater) were headache, influenza-like illness, nausea, fatigue, asthenia, and neutropenia. The most common treatment-emergent laboratory abnormalities (grade 3 or 4) were increased neutrophils and hyperbilirubinemia.

Increases in mean bilirubin (direct and indirect) levels were seen in simeprevir treatment groups during the first two weeks of treatment (mostly with the 200 mg QD dose), were not associated with increases in other hepatic parameters, and returned to baseline after simeprevir treatment concluded. One subject in Cohort 5 discontinued due to increased blood bilirubin (grade 4); six subjects receiving PegIFNa-2a and RBV who had previously received simeprevir discontinued due to AEs. There were no deaths in the trial.

Trial Summary

This study was designed to evaluate the antiviral effect of four doses (25, 75, 150, and 200 mg QD) of one week of simeprevir administration, with or without PegIFNa-2a and ribavirin, followed by three weeks of simeprevir, PegIFNa-2a, and ribavirin combination therapy and 24 or 48 weeks of PegIFNa-2a and ribavirin administration, to treatment-naïve and -experienced subjects with HCV. Following 7 days of simeprevir monotherapy, treatment-naïve subjects experienced a simeprevir dose-dependent decrease from baseline in plasma HCV DNA; this dose-dependent relationship was maintained in the presence of PegIFNa-2a and RBV, with the simeprevir 150 and 200 mg QD doses providing greater antiviral activity compared to the 75 mg QD dose.

Simeprevir pharmacokinetics were evaluated in treatment-naïve and -experienced subjects with HCV infection. Steady-state conditions were reached after approximately 7 days of simeprevir administration. Simeprevir exposures were greater than dose-proportional at doses above 75 mg. Simeprevir plasma concentrations were similar in the presence and absence of ribavirin; plasma concentrations of both drugs were also similar in treatment-naïve and -experienced subjects.

Trial TMC435HPC1002
Phase I, open-label, randomized, 3-panel, 3-way crossover trial in healthy adult subjects to assess the relative bioavailability of TMC435 following administration of 2 liquid formulations or 2 different capsule concept formulations compared to the Phase III 150 mg capsule, and to assess the effect of food on the bioavailability of TMC435 following administration of the liquid formulations

Trial Period
3 Mar to 29 May 2012
Final report date: 19 Nov 2012

Trial Site
Parexel Early Phase Clinical Unit, Northwick Park Hospital, Middlesex, United Kingdom

Trial Rationale
Simeprevir (TMC435) is an inhibitor of the hepatitis C virus (HCV) NS3/4A protease, currently under development for the treatment, in combination with ribavirin and pegylated interferon alpha, of chronic HCV infection. Simeprevir inhibits viral replication with a 50% effective concentration (EC_{50}) of 8 nM in a cellular HCV genotype 1b replicon model. This study was conducted to evaluate the bioavailability of two different pediatric liquid formulations and two different capsule concept formulations relative to the Phase III capsule, all after administration of a single dose of TMC435 150 mg.

Trial Objectives
The primary objective of this trial was to:

- compare the rate and extent of absorption of a single 150 mg dose of 2 different liquid formulations of TMC435 to that of a single dose of the Phase III 150 mg capsule after a high-fat breakfast in healthy adult subjects
- compare the rate and extent of absorption of a single 150 mg dose of 2 different liquid formulations of TMC435 in the fed (high-fat) and fasted state in healthy adult subjects
- compare the rate and extent of absorption of a single 150 mg dose of 2 different capsule concept formulations of TMC435 to that of a single dose of the Phase III 150 mg capsule after a high-fat breakfast in healthy subjects

The secondary objective of this trial was to:

- evaluate the short-term safety and tolerability of TMC435 following administration of 3 single oral doses of 150 mg given as different formulations in healthy adult subjects
- assess the acceptability of the taste of both liquid formulations (oral solution and suspension)

Trial Design

This was a randomized, open-label, 3-way crossover trial in healthy adult subjects. Three formulations were evaluated: two potential pediatric formulations (G025, an oral solution; G026, an oral suspension); G007, the Phase 3 capsule; and G019, the to-be-marketed formulation, manufactured as concept capsules, which (b) (4) and are intended to represent manufacturing under worst-case process conditions.

Subjects were divided into three panels, each of which received three treatments:

Panel 1
Treatment A: G007 TMC435 150 mg Phase III capsule (high-fat breakfast)
Treatment B: G026 TMC435 150 mg oral suspension 20 mg/mL (fasted)
Treatment C: G026 TMC435 150 mg oral suspension 20 mg/mL (high-fat breakfast)

Panel 2
Treatment D: G007 TMC435 150 mg Phase III capsule (high-fat breakfast)
Treatment E: G025 TMC435 150 mg oral solution 10 mg/mL (fasted)
Treatment F: G025 TMC435 150 mg oral solution 10 mg/mL (high-fat breakfast)

Panel 3
Treatment G: G007 TMC435 150 mg Phase III capsule (high-fat breakfast)
Treatment H: G019 TMC435 150 mg concept capsule K (high-fat breakfast)
Treatment I: G019 TMC435 150 mg concept capsule L (high-fat breakfast)

Within each panel, subjects were randomized to one of six groups (i.e. one of six treatment sequences). For example, in Panel 1, Groups 1 through 6 received the following treatment sequences, respectively: ABC, BCA, CAB, CBA, BAC, and ACB.

Study drug was administered the morning of Day 1 of each treatment. Plasma samples were collected up to 72 h postdose to assess the pharmacokinetics of each profile. Treatment sessions were separated by a washout period of at least 7 days, which was equivalent to approximately 10.5 elimination half-lives ($t_{1/2}$ approximately 16 h).

Drug Administration

Administration of study drug was witnessed at the clinic. Capsules were to be swallowed whole with 240 mL of water. Administration of liquid formulations was followed by two 25 mL rinses of the dosing container and enough water to reach a total volume of 240 mL. The rinses and water had to be consumed within 5 min. Subjects were to have fasted overnight for at least 10 h before mornings on which a safety blood sample was collected. Subjects could resume water and food intake two and four hours postdose, respectively; the lunch was standardized on Day 1 of each treatment session.

The high-fat breakfast consisted of 56 g of fat and 928 kcal.

Rationale for Dose Selection
The TMC435 dose of 150 mg was selected as this was the dose used in Phase III subjects in HCV-infected subjects.

Investigational Product
All formulations were manufactured and provided by Tibotec Pharmaceuticals Ltd. The Phase III formulation (Batch 10K03/G007; Treatments A, D, and G) was an oral gelatin capsule containing 150 mg simeprevir in a (b) (4) TMC435 sodium salt and excipients. The oral suspension (Batch 12A26/G026; Treatments B and C) contained 20 mg/mL simeprevir. The oral solution (Batch 12A25/G025; Treatments E and F) contained 10 mg/mL simeprevir. The concept capsules (Treatments H and I) were oral gelatin capsules containing 150 mg simeprevir in a (b) (4) TMC435 sodium salt and excipients; formulation K (Batch 12C02/G019; Treatment H) had (b) (4) and formulation L (Batch 12C05/G019; Treatment I) had a (b) (4) ratio.

Key Inclusion and Exclusion Criteria
Subjects were healthy nonsmoking males and non-pregnant, non-breastfeeding females between the ages of 18 and 55 years, inclusive, with normal weight (defined by BMI) and normal ECG. Subjects agreed to follow adequate birth control methods from Screening until 1 month after study drug administration.

Potential subjects were excluded if they tested positive for HIV-1 or -2 or hepatitis A, B, or C, had active disease of clinical significance, or if they had taken any prescription or over-the-counter medication (including herbal products, and with the exception of acetaminophen and ibuprofen) within 14 days prior to study drug dosing.

Concomitant Medications
The following concomitant medications were allowed: hormone replacement therapy; hormonal contraceptives; cetirizine, levocetirizine, topical corticosteroids, antipruiritic agents in case of rash; antiemetics in case of nausea; loperamide in case of diarrhea. In addition, consumption of alcohol, quinine, caffeine, methylxanthines, and certain fruit juices was restricted.

Sample Collection
Blood was collected for the analysis of TMC435 at the times (in hours post-dose) listed below:

> -2:00 to 0:00 (predose), 0:30, 1:00, 1:30, 2:00, 3:00, 4:00, 6:00, 8:00, 12:00, 24:00, 48:00, and 72:00

Analytical Plan
Pharmacokinetic data

Pharmacokinetic and statistical analyses were performed [redacted] using WinNonlin Professional™ (Pharsight Corporation, Mountain View, California, USA), Microsoft Excel® 2007 (Microsoft Corporation, Redmond, Washington, USA), and SAS (SAS Institute Inc., Cary, North Carolina, USA). Statistical demographic, safety, and tolerability analyses were performed by [redacted]

The primary pharmacokinetic parameters evaluated in this study were C_{max}, T_{max}, λ_z, AUC_{last}, AUC_{inf}, and $t_{1/2}$ for simeprevir. A_e, CL_R, and D_{urine} (percent of dose excreted in the urine) were also evaluated; a similar analysis on fecal excretion was included. Total recovery was defined as D_{urine} (%) + D_{feces} (%) for each subject. All pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods. Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase (λ_z, AUC_{inf}, and $t_{1/2}$) were reported when there were at least three data points with an r^2 of >0.9000.

Trial Results

Bioanalytical methods

Concentrations of TMC435 in plasma samples were determined using LC-MS/MS (Analytical Method SHAM-186-R0; LLOQ 2.00 ng/mL) [redacted]. Frozen plasma samples were received between 15 May and 6 Jun 2012 and analysis was performed between 22 May and 8 Jun 2012. The maximum storage sample time of 71 days was within the validated long-term frozen stability duration of 1184 days.

The TMC435 calibration standards ranged from 2-2000 ng/mL and the quality control (QC) concentrations were 56.00, 100, and 1500 ng/mL. The inter-assay accuracy estimates ranged from 2.0 to 3.3% and the inter-assay precision estimates ranged from 5.3 to 5.7%. All estimates were within the acceptable criteria (≤20% deviation at the LLoQ concentration, and ≤15% deviation at all other concentrations).

Trial population

A total of 72 healthy adults were enrolled in the study (24 subjects per panel); all subjects completed the study. The majority of subjects were male (59.7%) and Caucasian (76.4%), with 18.1% African American, 4.2% Asian, and 1.4% of mixed ethnicity. The median age was 31 years (range: 19 to 53 years). All enrolled subjects were nonsmokers.

Results of pharmacokinetic analyses

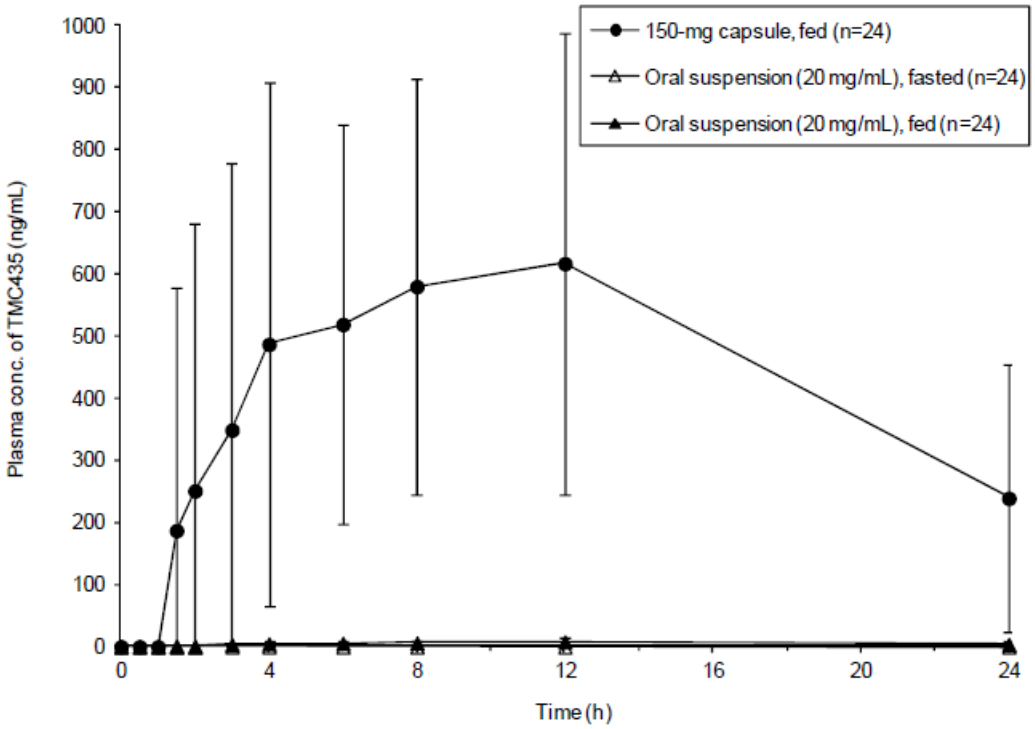
In this study, the pharmacokinetics of a single dose of simeprevir oral solution, oral suspension, and two different concept capsules (formulations K and L) were compared to the Phase 3 formulation in healthy subjects.

Pharmacokinetics of simeprevir oral suspension

Administration of the oral suspension resulted in very low plasma concentrations of simeprevir (Figure 1). Under fasted conditions, plasma concentrations remained BLQ at

all sampling time points in 13 of 24 subjects; most of the quantifiable concentrations were just above the LLOQ (2 ng/mL). Under fed conditions, all subjects had low but quantifiable simeprevir plasma levels at one or more sampling timepoints, although no subject had quantifiable simeprevir plasma concentrations by 72 h postdose.

Figure 1: Mean plasma ± SD concentration-time curves of TMC435 after administration of a single oral dose of the Phase 3 formulation (fed) or an oral suspension (fasted and fed) (source: Study Report Figure 3)



Due to the limited number of quantifiable plasma concentrations during the terminal phase, values for $t_{1/2,term}$, λ_z and AUC_{inf} were not calculated (Table 1) and no statistical analyses were performed to evaluate the effect of food on or the relative bioavailability of the simeprevir oral suspension.

Table 1: Pharmacokinetics of TMC435 after administration of a single oral dose of the Phase 3 formulation (fed) or oral suspension (fasted and fed) (source: Study Report Table 5)

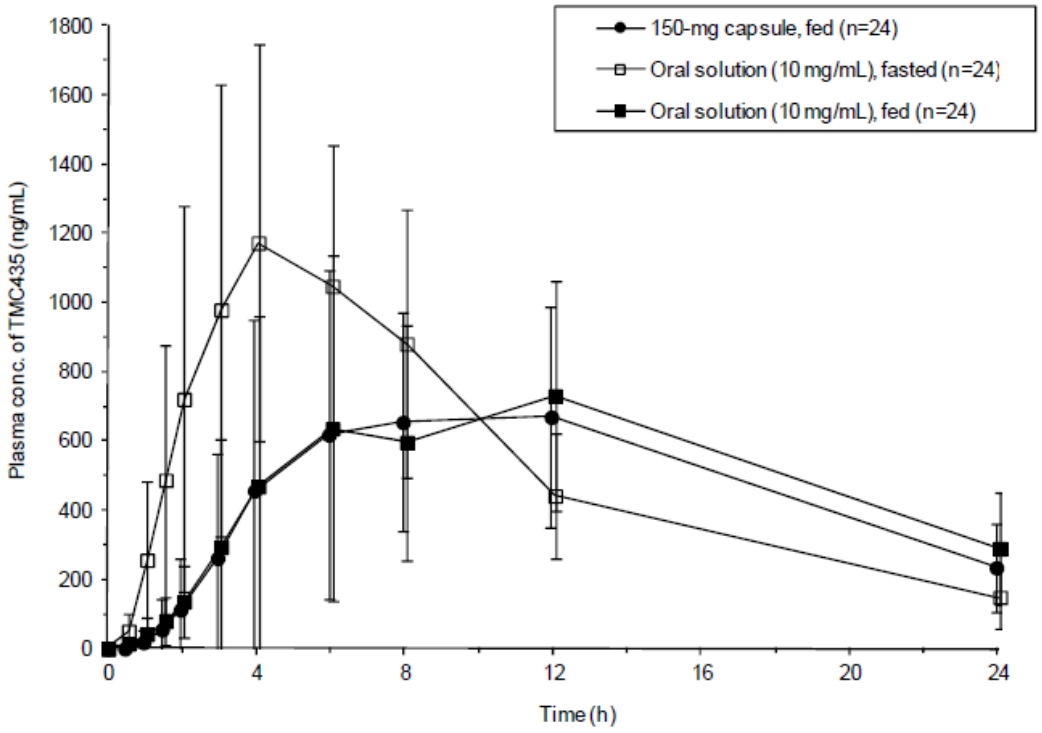
Pharmacokinetics of TMC435 (mean ± SD, t_{max}: median [range])	150 mg Capsule Fed (Reference)	Oral Suspension (20 mg/mL) Fasted (Test 1)	Oral Suspension (20 mg/mL) Fed (Test 2)
N	24[a]	24[b]	24
C_{max}, ng/mL	962 ± 331	BQL	9.30 ± 6.67
t_{max}, h	7.99 [1.98-24.05]	6.00 [3.00-8.02]	12.00 [3.98-24.02]
AUC_{last}, ng.h/mL	14503 ± 6308	NAs	129 ± 123
AUC_{∞}, ng.h/mL	13831 ± 5237	NAs	NAs
λ_z, 1/h	0.0793 ± 0.0118	NAs	NAs
$t_{1/2, term}$, h	8.9 ± 1.5	NAs	NAs

NAs: Not Assessable
[a] N = 23 for AUC_{∞}, λ_z and $t_{1/2, term}$
[b] N = 11 for t_{max} as only 11 subjects had a concentration above BQL

Pharmacokinetics of simeprevir oral solution

Following administration of the simeprevir oral solution under fed conditions, the concentration-time profile was similar to that of simeprevir Phase 3 formulation under fed conditions (Figure 2). When administered under fasted conditions, the oral solution resulted in a higher mean simeprevir C_{max} reached at an earlier median t_{max}, followed by a steeper distribution/elimination phase when compared to the Phase 3 formulation (Figure 2).

Figure 2: Mean plasma ± SD concentration-time curves of TMC435 after administration of a single oral dose of the Phase 3 formulation (fed) or an oral solution (fasted and fed) (source: Study Report Figure 4)



The pharmacokinetic parameters observed following a single dose of simeprevir Phase 3 formulation in the fed state or oral solution in the fasted and fed states are shown in Table 2. Similar to historical data, interindividual variability in simeprevir exposures is

moderate to high, especially in the fasted state. While simeprevir AUC values are similar across the three treatments, mean C_{max} is higher following administration of the oral solution in the fasted state, as is visible in Figure 2.

Table 2: Pharmacokinetics of TMC435 after administration of a single oral dose of the Phase 3 formulation (fed) or oral solution (fasted and fed) (source: Study Report Table 6)

Pharmacokinetics of TMC435 (mean ± SD, t_{max}: median [range])	150 mg Capsule Fed (Reference 1)	Oral Solution (10 mg/mL) Fasted (Reference 2)	Oral Solution (10 mg/mL) Fed (Test)
N	24[a]	24	24[a]
C_{max}, ng/mL	954 ± 375	1250 ± 537	1000 ± 440
t_{max}, h	8.01 [3.97-12.03]	4.00 [2.00-6.03]	11.97 [4.00-24.05]
AUC_{last}, ng.h/mL	14939 ± 5517	15223 ± 6971	16483 ± 5163
AUC_{∞}, ng.h/mL	15377 ± 5533	15321 ± 7027	16408 ± 5240
λ_z, 1/h	0.0760 ± 0.0134	0.0807 ± 0.0163	0.0806 ± 0.0118
$t_{1/2, term}$, h	9.4 ± 1.7	8.9 ± 1.6	8.8 ± 1.1

[a] N = 23 for AUC_{∞}, λ_z and $t_{1/2, term}$

Statistical comparisons demonstrate similar simeprevir bioavailability between the oral solution and Phase 3 formulation when each is administered in the fed state (Table 3). Comparisons of simeprevir oral solution administered in the fed and the fasted states suggest that food decreased mean C_{max} by 19% and increased median t_{max} and mean AUC_{inf} by 67% and 12%, respectively (analysis not shown).

Table 3: Statistical analysis of TMC435 after administration of a single oral dose of the Phase 3 formulation (fed) or oral solution, both in the fed state (source: Study Report Table 7)

Parameter	LSmeans[a] 150 mg Capsule Fed (Reference)	LSmeans[a] Oral Solution (10 mg/mL) Fed (Test)	LSmeans Ratio, %	90% CI, %	p-value Period	p-value Sequence
C_{max}, ng/mL	893	926	103.69	87.89 - 122.34	0.4959	0.2211
AUC_{last}, ng.h/mL	13989	15706	112.27	99.04 - 127.26	0.2921	0.1466
AUC_{∞}, ng.h/mL[b]	14190	15804	111.38	97.65 - 127.03	0.3537	0.1646
Parameter	**Median[a] 150 mg Capsule Fed (Reference)**	**Median[a] Oral Solution (10 mg/mL) Fed (Test)**	**Treatment Difference Median**	**90% CI, h**	**p-value Period**	**p-value Sequence**
t_{max}, h	8.01	11.97	1.04	0.01 - 2.13	0.4524	0.3259

[a] N = 24 for reference and test
[b] N = 23 for reference and test

Pharmacokinetics of simeprevir concept capsules

The simeprevir concentration-time profiles were similar after administration of the Phase 3 formulation and the two concept capsule formulations, all in the fed state (Figure 3). Both concept capsules K and L provided similar simeprevir exposures to the Phase 3 formulation, with least square mean ratios close to 100% and 90% confidence intervals within 80 and 125% (Table 4). Interindividual variability was slightly higher for concept

capsule L but remained within the range observed in clinical trials (approximately 40% compared to approximately 30% for concept capsule K and the Phase 3 formulation).

Figure 3: Mean plasma ± SD concentration-time curves of TMC435 after administration of a single oral dose of the Phase 3 formulation (fed) or concept capsule formulations K or L (fed) (source: Study Report Figure 5)

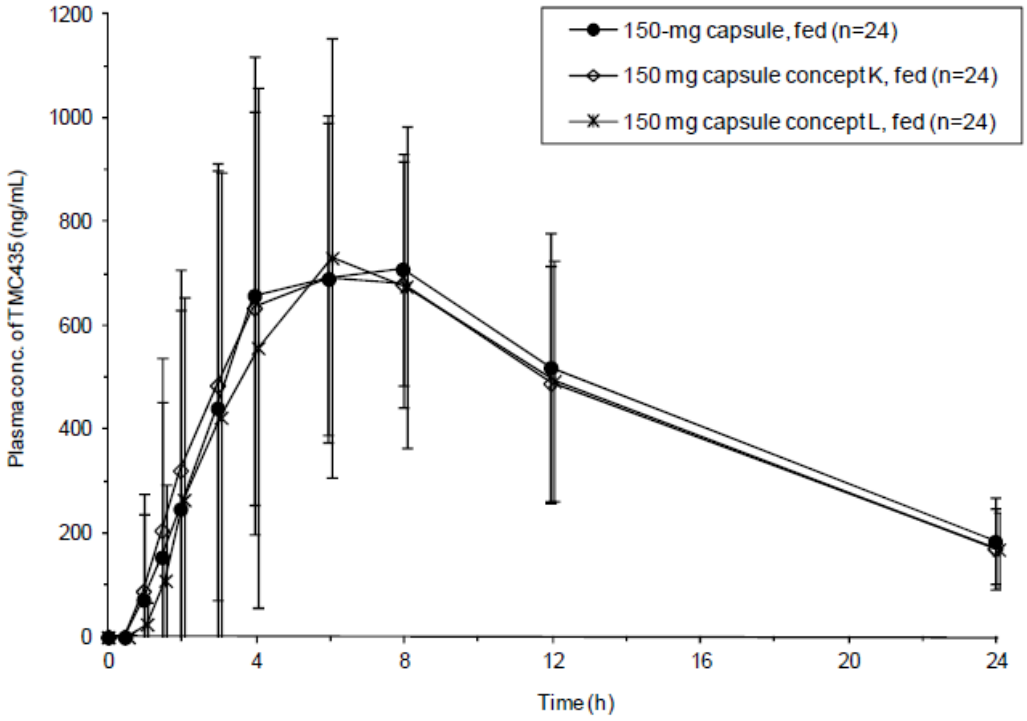


Table 4: Pharmacokinetics of TMC435 after administration of a single oral dose of the Phase 3 formulation (fed) or concept capsule formulations K or L (fed) (source: Module 2.7.1 Table 18)

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Parameter	Mean ± SD: Treatment G: TMC435 150 mg (Phase III Capsule) (Reference)	Mean ± SD: Treatment H or I: TMC435 150 mg (K or L Capsule) (Test)	Ratio [a] (Test:Reference)	90% CI
Treatment H (Capsule K, G019) vs. Treatment G (Phase III Capsule, G007)				
n	24	24		
t_{max} [b], h	6.00 (1.98 - 12.08)	6.02 (1.98 - 12.00)	0.03	−1.46 - 1.01
C_{max}, ng/mL	949 ± 330	910 ± 256	0.97	0.86 - 1.10
AUC_{last}, ng.h/mL	13477 ± 4332	12908 ± 3933	0.96	0.88 - 1.05
AUC_{∞}, ng.h/mL	13588 ± 4401	13007 ± 3991	0.96	0.88 - 1.05
$t_{1/2,term}$, h	8.8 ± 1.4	8.8 ± 1.4	-	-
Treatment I (Capsule L, G019) vs. Treatment G (Phase III Capsule, G007)				
n	24	24		
t_{max} [b], h	6.00 (1.98 - 12.08)	6.03 (1.98 - 12.02)	0.03	−0.05 - 1.03
C_{max}, ng/mL	949 ± 330	941 ± 379	0.98	0.86 - 1.10
AUC_{last}, ng.h/mL	13477 ± 4332	12750 ± 5069	0.94	0.86 - 1.02
AUC_{∞}, ng.h/mL	13588 ± 4401	12852 ± 5131	0.94	0.86 - 1.02
$t_{1/2,term}$, h	8.8 ± 1.4	8.9 ± 1.5	-	-

n = maximum number of subjects with data.
[a] Ratio based on LS means; t_{max}: median treatment difference in hours.
[b] Median (range).
Source: Mod5.3.1.2/HPC1002-CSR/Sec5.1.6.2

Results of safety analysis

A single oral dose of TMC435 was generally safe and well-tolerated, regardless of formulation. The most common treatment-emergent AEs were headache (n=10), nasopharyngitis (n=6), nausea (n=2), abdominal distention (n=2), diarrhea (n=2), and abnormal dreams (n=2); incidence rates did not differ substantially between treatments. The most common treatment-emergent lab abnormality was increased activated partial prothrombin time (n=25). There were no serious adverse events, discontinuations due to adverse events, or deaths during this trial.

Trial Summary

This study was designed to evaluate the bioavailability of simeprevir oral suspension (G026), oral solution (G025), and the to-be-marketed capsule (G019) formulations relative to the Phase 3 formulation (G007). In addition, the effect of food on the bioavailability of simeprevir oral suspension and oral solution were evaluated.

Administration of the oral suspension (G026) resulted in very low simeprevir exposures – especially in the fasted state – compared to administration of the Phase 3 formulation. In contrast, administration of the oral solution (G025) in the fed state provided similar exposures to administration of the Phase 3 formulation in the fed state, with a least square means ratio for AUC_{inf} of 111% and 90% confidence intervals of 98 to 127%.

The two concept capsules representing the to-be-marketed formulation (G019) provided simeprevir exposures that were comparable to those of the Phase 3 formulation (all administered under fed conditions), indicating that differences in manufacturing site and equipment, batch size, and formulation and process conditions do not substantially affect simeprevir bioavailability. Note that G019 is identical to the to-be-marketed formulation (G028) except for (b) (4) on the capsule. The results of the current trial

demonstrate that the bioavailability of simeprevir is similar following administration of the Phase 3 formulation and the to-be-marketed formulation.

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Trial TMC435350HPC1004
Phase I, open-label, randomized study to examine the pharmacokinetics, safety, and tolerability of different oral doses of TMC435 after single and repeated dosing in healthy Chinese subjects

Trial Period
1 Nov 2010 to 25 Jan 2011
Final report date: 18 Aug 2011

Trial Site
Prince of Wales Hospital, Hong Kong, China

Trial Rationale
Simeprevir (TMC435) is an inhibitor of the hepatitis C virus (HCV) NS3/4A protease, currently under development for the treatment, in combination with ribavirin and pegylated interferon alpha, of chronic HCV infection. Simeprevir inhibits viral replication with a 50% effective concentration (EC_{50}) of 8 nM in a cellular HCV genotype 1b replicon model. Results from trial C109 indicated that simeprevir exposures are approximately 2-fold higher in Japanese subjects compared to Caucasian subjects; lower exposures were also observed in a Phase 2 conducted in Japan (C215). This study was conducted to evaluate the pharmacokinetics, safety, and tolerability of single and multiple doses of simeprevir in healthy Chinese subjects and to determine whether or not exposures in Chinese are similar to Japanese subjects.

Trial Objectives
The objectives of this trial were to:

- determine the short-term safety and tolerability of TMC435350 after single oral doses of 100 mg and 200 mg in healthy Chinese subjects
- determine the plasma pharmacokinetics of TMC435350 after single oral doses of 100 mg and 200 mg in healthy Chinese subjects
- determine the short-term safety and tolerability of TMC435350 after multiple oral doses of 100 mg and 200 mg QD for 5 days in healthy Chinese subjects
- determine the plasma pharmacokinetics of TMC435350 after multiple oral doses of 100 mg and 200 mg QD for 5 days in healthy Chinese subjects

Trial Design
This was a randomized, double blind, placebo-controlled study evaluating single and multiple doses in healthy Chinese subjects. Subjects were randomized to either the 100 mg and 200 mg dose group (Panels 1 and 2, respectively); both panels were conducted in parallel. Subjects received a single dose of TMC435350 or placebo followed by a three-day washout period and five days of TMC435350 or placebo QD. Study drug was administered in the fed state.

Drug Administration

All study drugs were administered with 200 mL of water and within 10 minutes of completing a standardized breakfast. On days on which blood samples were collected, an overnight fast (at least 10 h) preceded the standardized breakfast. Water was allowed as desired except for 2 h before until 2 h after dosing. Subjects could resume their usual diet beginning 4 h after dosing.

Rationale for Dose Selection

Doses were selected to match trial C109, in which single and multiple doses of TMC435 were administered to healthy Japanese subjects.

Investigational Product

Hard gelatin capsules containing 100 mg TMC435 were manufactured by Tibotec Pharmaceuticals Ltd. (Batch 10A27/F020).

Key Inclusion and Exclusion Criteria

Subjects were healthy nonsmoking Chinese adults between the ages of 18 and 55 years, inclusive, with normal weight (defined by BMI) and normal ECG. Potential subjects were excluded if they tested positive for HIV-1 or -2 or hepatitis A, B, or C, had active disease of clinical significance, or if they had taken any prescription or over-the-counter medication (including herbal products, and with the exception of acetaminophen and ibuprofen) within 14 days prior to study drug dosing.

Concomitant Medications

The following concomitant medications were allowed: cetirizine, levocetirizine, topical corticosteroids, antipruiritic agents in case of rash; antiemetics in case of nausea; loperamide in case of diarrhea.

Sample Collection

Blood was collected for the analysis of TMC435350 at the times (in hours post-dose) listed below:

Single dose	0:00 (predose), 0:30, 1:00, 1:30, 2:00, 3:00, 4:00, 6:00, 8:00, 12:00, 16:00, 24:00, 36:00, 48:00, and 72:00
Multiple doses	
Days 1-4	0:00 (predose)
Day 5	0:00 (predose), 0:30, 1:00, 1:30, 2:00, 3:00, 4:00, 6:00, 8:00, 12:00, 16:00, 24:00, 36:00, 48:00, and 72:00

Analytical Plan

Pharmacokinetic data

Pharmacokinetic and statistical analyses were performed (b) (4) using WinNonlin Professional™ (Pharsight Corporation, Mountain View, California, USA), Microsoft Excel® 2007 (Microsoft Corporation, Redmond, Washington, USA), and SAS (SAS Institute Inc., Cary, North Carolina, USA).

The primary pharmacokinetic parameters evaluated in this study were C_{max}, T_{max}, C_{last}, T_{last}, C_0, λ_z, AUC_{last}, AUC_{tau}, and $t_{1/2}$ for simeprevir. All pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods. Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase (λ_z, AUC_{inf}, and $t_{1/2}$) were reported when there were at least three data points across a timespan of two half-lives or greater, with an r^2 of >0.9000.

Trial Results

Bioanalytical methods

Concentrations of TMC435 in plasma samples were determined using LC-MS/MS (Standard Analytical Method SHAM-186-R0) (b) (4) . Frozen plasma samples were received on 17 Dec 2010 and analysis was performed between 21 Dec 2010 and 5 Jan 2011. The maximum storage sample time was within the validated long-term frozen stability duration.

The TMC435 calibration standards ranged from 2-2000 ng/mL and the quality control (QC) concentrations were 5.80, 76.0, and 1560 ng/mL. The inter-assay accuracy estimates ranged from 4.2 to 8.6% and the inter-assay precision estimates ranged from -1.3 to 5.0%. All estimates met the acceptable criteria (≤20% deviation at the LLoQ concentration, and ≤15% deviation at all other concentrations).

Trial population

A total of 32 healthy Chinese subjects were enrolled in the study; all subjects completed the study. The majority of subjects were male (78.1%). Median age was 26 years (range: 18-49 years).

Results of pharmacokinetic analyses

In this study, the pharmacokinetics of single and multiple doses of simeprevir 100 and 200 mg were evaluated in healthy Chinese adult subjects.

Following single doses of 100 or 200 mg, the terminal phases declined in parallel (not shown). Peak simeprevir concentrations were reached approximately 6 hours post-dose, after which plasma concentrations decreased. Mean values of C_{max}, AUC_{last}, and AUC_{inf} increased with dose, but in a greater-than-dose proportional manner. Mean $t_{1/2}$ values were approximately 10 to 11 hours. The accumulation ratios (single dose:multiple dose) for 100 and 200 mg were 1.55 and 2.00 for AUC_{24}.

The pharmacokinetics of simeprevir 100 mg single dose and 100 mg QD multiple doses in healthy Chinese, Japanese (Trial C109), and Caucasian (Trial C101) subjects are displayed in Table 1; Table 2 lists the same parameters for the 200 mg dose level. Administration of the 100 mg dose (single or multiple doses) resulted in higher exposures in Chinese and Japanese subjects compared to Caucasian subjects (1.4- to 1.8-fold higher, respectively). However, administration of the 200 mg dose (single or multiple doses)

resulted in similar exposures (and overlapping ranges of exposures) in all three ethnic groups.

Table 1: Pharmacokinetics of TMC435350 after administration of a single dose or multiple daily doses of TMC435350 100 mg to healthy Chinese, Japanese, and Caucasian subjects (source: Study Report Table 5)

Pharmacokinetics of TMC435 (mean ± SD, t_{max}: median [range])	TMC435-C101 A single dose of 100 mg TMC435 (SAD) (Caucasian Subjects)	TMC435-C101 A single dose of 100 mg TMC435 (MAD) (Caucasian Subjects)	TMC435-C109 A single dose of 100 mg TMC435 (Japanese Subjects)	TMC435HPC1004 A single dose of 100 mg TMC435 (Chinese Subjects)
N	6	4	8	16
Single Dose				
t_{max}, h	5.0 (4.0 - 6.0)	5.0 (3.0 - 6.0)	6.0 (4.0-16.0)	6.0 (4.0-6.0)
C_{max}, ng/mL	582.0 ± 86.15	679.8 ± 174.3	926.9 ± 456.9	1037 ± 344.0
AUC_{24h}, ng.h/mL	-	6353 ± 1605	9653 ± 3831	9140 ± 3489
AUC_{last}, ng.h/mL	7550 ± 1630	-	12010 ± 4734	10880 ± 5169
AUC_{∞}, ng.h/mL	7621 ± 1630	-	12120 ± 4823	11020 ± 5231
$t_{1/2term}$, h	9.541 ± 1.261	-	9.659 ± 1.674	8.719 ± 2.094
N		4	7	16[a]
Multiple Dose				
t_{max}, h		4.0 (4.0 - 6.0)	6.0 (4.0-6.0)	6.0 (4.0 - 8.0)
C_{0h}, ng/mL		97.05 ± 38.93	307.6 ± 221.1	223.3 ± 195.1
C_{min}, ng/mL		88.33 ± 32.20	261.0 ± 194.9	193.6 ± 167.5
C_{max}, ng/mL		758.3 ± 208.2	1655 ± 652.6	1459 ± 750.2
AUC_{24h}, ng.h/mL		7620 ± 1912	17260 ± 8417	14750 ± 9477
$C_{ss,av}$, ng/mL		317.5 ± 79.68	719.3 ± 350.7	614.4 ± 394.9
Fluctuation index, %		213.2 ± 40.28	205.3 ± 39.19	224.7 ± 54.00
$t_{1/2term}$, h		7.708 ± 0.7297	9.980 ± 1.767	9.372 ± 2.036
Ratio $C_{max, md/sd}$, %		-	224.5 ± 120.6	145.6 ± 61.04
Ratio $AUC_{24h, md/sd}$, %		120.1 ± 5.272	193.9 ± 67.63	154.6 ± 53.84

[a] N = 15 for $t_{1/2term}$

Table 2: Pharmacokinetics of TMC435350 after administration of a single dose or multiple daily doses of TMC435350 200 mg to healthy Chinese, Japanese, and Caucasian subjects (source: Study Report Table 6)

Pharmacokinetics of TMC435 (mean ± SD, t_{max}: median [range])	TMC435-C101 A single dose of 200 mg TMC435 (Single ascending dose) (Caucasian Subjects)	TMC435-C101 A single dose of 200 mg TMC435 (Multiple ascending dose) (Caucasian Subjects)	TMC435-C109 A single dose of 200 mg TMC435 (Japanese Subjects)	TMC435HPC1004 A single dose of 200 mg TMC435 (Chinese Subjects)
N	6	5	8	16
Single Dose				
t_{max}, h	6.0 (4.0 - 6.0)	4.0 (3.0 - 6.0)	7.0 (4.0-8.0)	6.0 (4.0 - 8.0)
C_{max}, ng/mL	2957 ± 1022	2304 ± 917.8	3036 ± 942.1	4038 ± 1599
AUC_{24h}, ng.h/mL	-	24630 ± 7331	31480 ± 12980	31430 ± 12110
AUC_{last}, ng.h/mL	37550 ± 14820	-	39130 ± 17470	35790 ± 13910
AUC_{∞}, ng.h/mL	38150 ± 15500	-	39530 ± 17800	35920 ± 13980
$t_{1/2term}$, h	10.85 ± 2.824	-	10.78 ± 1.174	9.575 ± 1.518
N		5	8	16
Multiple Doses				
t_{max}, h		4.0 (3.93 - 8.0)	6.0 (4.0-8.0)	6.0 (4.0 - 8.0)
C_{0h}, ng/mL		1482 ± 791.3	2214 ± 1371	1070 ± 878.9
C_{min}, ng/mL		1445 ± 767.3	1984 ± 1224	901.9 ± 811.7
C_{max}, ng/mL		6172 ± 2859	6889 ± 3585	6139 ± 2631
AUC_{24h}, ng.h/mL		79710 ± 37230	89930 ± 45380	63580 ± 34630
$C_{ss,av}$, ng/mL		3324 ± 1554	3747 ± 1891	2649 ± 1443
Fluctuation index, %		144.7 ± 25.13	137.9 ± 35.61	215.8 ± 49.06
$t_{1/2term}$, h		16.04 ± 5.114	14.23 ± 3.817	10.55 ± 1.745
Ratio $C_{max, md/sd}$, %		-	220.7 ± 71.63	154.7 ± 50.05
Ratio $AUC_{24h, md/sd}$, %		316.0 ± 101.2	285.2 ± 106.9	199.5 ± 77.08

Results of safety analysis

Study drugs were generally safe and well-tolerated. Somnolence, rhinitis, and headache were the most frequently reported adverse events in the TMC435 arms. There were no serious adverse events, discontinuations due to adverse events, or deaths during this trial.

Trial Summary

This study was designed to evaluate the pharmacokinetics of single and multiple daily doses of TMC435350 100 and 200 mg following administration to healthy Chinese subjects.

Following single and multiple doses, exposures increased more than dose-proportionally. Mean AUC_{24} values were 1.9-fold higher and 21% lower in subjects enrolled in C101 (95% Caucasian, 5% Asian) relative to subjects enrolled in the current trial (100% Chinese) after administration of TMC435350 100 or 200 QD, respectively. The exposures observed after administration of 100 mg TMC435 are comparable to those observed in healthy Japanese subjects in C109. In general, administration of single and multiple doses of TMC435350 was safe and well-tolerated in healthy Chinese subjects.

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY DRUG-DRUG INTERACTION STUDY REVIEW				
Study #	TMC435HPC1005	**Study Period**	12-May-2011 to 13-July-2011	EDR Link
Title	A Phase 1, 2-panel, open-label, randomized, crossover trial in healthy subjects to investigate the pharmacokinetic interaction between TMC435 and the NS5A inhibitor BMS-790052 (Daclatasvir)			

STUDY DESIGN	
This was a Phase 1, 2-panel, open-label, randomized, 2-way crossover study in healthy subjects to investigate the potential drug-drug interaction between TMC435 and BMS-790052. A total of 42 healthy subjects were planned to be enrolled in this study. Subjects were to be divided over 2 panels (n=18 for Panel 1 and n=24 for Panel 2). The 2 panels were recruited in parallel. Subjects were randomized within a panel.	
Population	☒ Healthy Volunteers ☐ Patients
Study Rationale	TMC435 is in development for the treatment of chronic HCV infection in combination with Peg-IFN and RBV. BMS-790052 is an NS5A inhibitor also in development for the treatment of chronic HCV infection. Phase II studies in HCV subjects for each compound demonstrated a robust decline in HCV RNA when administered as monotherapy. Combinations of 2 or more direct-acting antiviral agents are expected to be part of future HCV therapy. Therefore, assessment of a potential DDI with these 2 compounds when given together is warranted prior to starting clinical studies with a longer duration with the combination in HCV-infected patients.
Treatments	Treatment A (Panel 1): BMS-790052 60 mg q.d. for 7 days. Treatment B (Panel 1): BMS-790052 60 mg q.d. and TMC435 150 mg q.d. for 7 days. Treatment C (Panel 2): TMC435 150 mg q.d. for 7 days. Treatment D (Panel 2): BMS-790052 60 mg q.d. and TMC435 150 mg q.d. for 7 days. Washout period: seven days between treatments
Dose Selection Rationale	The dose of TMC (150 mg qd) is the dose used in Phase 3. The dose of 60 mg q.d is the highest anticipated therapeutic dose and the highest dose tested in Phase 2 studies for daclatasvir
Administration	☐ Fasted ☒ Fed
Formulation	TMC435 administered as 1 capsule of 150 mg (G007; batch number: 11B03/G007); BMS-790052 administered as 2 tablets of 30 mg (batch number: 1B66991)
Interfering Substances Excluded	None
Sampling Times	Predose on Days 1, 5, and 6, and on Day 7 (predose, and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16, and 24 hours postdose
PK Parameters	Cmin, Cmax, and AUC24h
PK Analysis	Non-compartmental analysis
Statistical Analysis	Intent-to-treat analysis, descriptive statistics, frequency tabulations, linear mixed effects modeling
Is the study design acceptable? ☒Yes ☐ No, if no please explain why	

STUDY CONDUCT

Bioanalytical Method:

Method Type	LC-MS/MS	Matrix	EDTA plasma
Analytes	TMC435 and BMS-790052		
Range	2.00-2000 ng/mL; 2.00-2000 ng/mL		

Validation	▪ Method validated prior to use	☒ Yes ☐ No ☐ NA

	▪ Method validation acceptable	☒ Yes ☐ No ☐ NA
Study Samples Analysis	▪ Samples analyzed within the established stability period	☒ Yes ☐ No
	▪ Quality control samples range acceptable	☒ Yes ☐ No
	▪ Chromatograms provided	☒ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	▪ Incurred samples analysis is acceptable	☒ Yes ☐ No
	▪ Overall performance acceptable	☒ Yes ☐ No
Inspection	▪ Will the bioanalytical site be inspected	☐ Yes ☒ No

Notes:

Protocol Deviations

- Are there any protocol deviations listed in the study report? ☒ Yes ☐ No
- Do any of the listed deviations affect the integrity of the study? ☐ Yes ☒ No ☐ NA

Notes:
Subject 1005-0010 (A/B): the subject did not take study medication before and on an intensive PK sampling day (Day 5 to 7 of Treatment B);
Subject 1005-0001 (B/A): the subject did not take study medication 2 days before an intensive PK sampling day (Days 5 and 6 of Treatment A).

STUDY RESULTS

Study Population

	Panel 1	Panel 2
Randomized	19	25
Treated	19	25
Completed	18	25
Discontinued Due to AE	0	0
PK Population/Safety Population	18	24
Age [Median (range)]	28(19-47)	36(19-53)
Male/Female	18/1	20/5
Race (Caucasian/Black/Asian/Mixed)	4/15/0	10/12/2/1

Pharmacokinetics

- TMC435

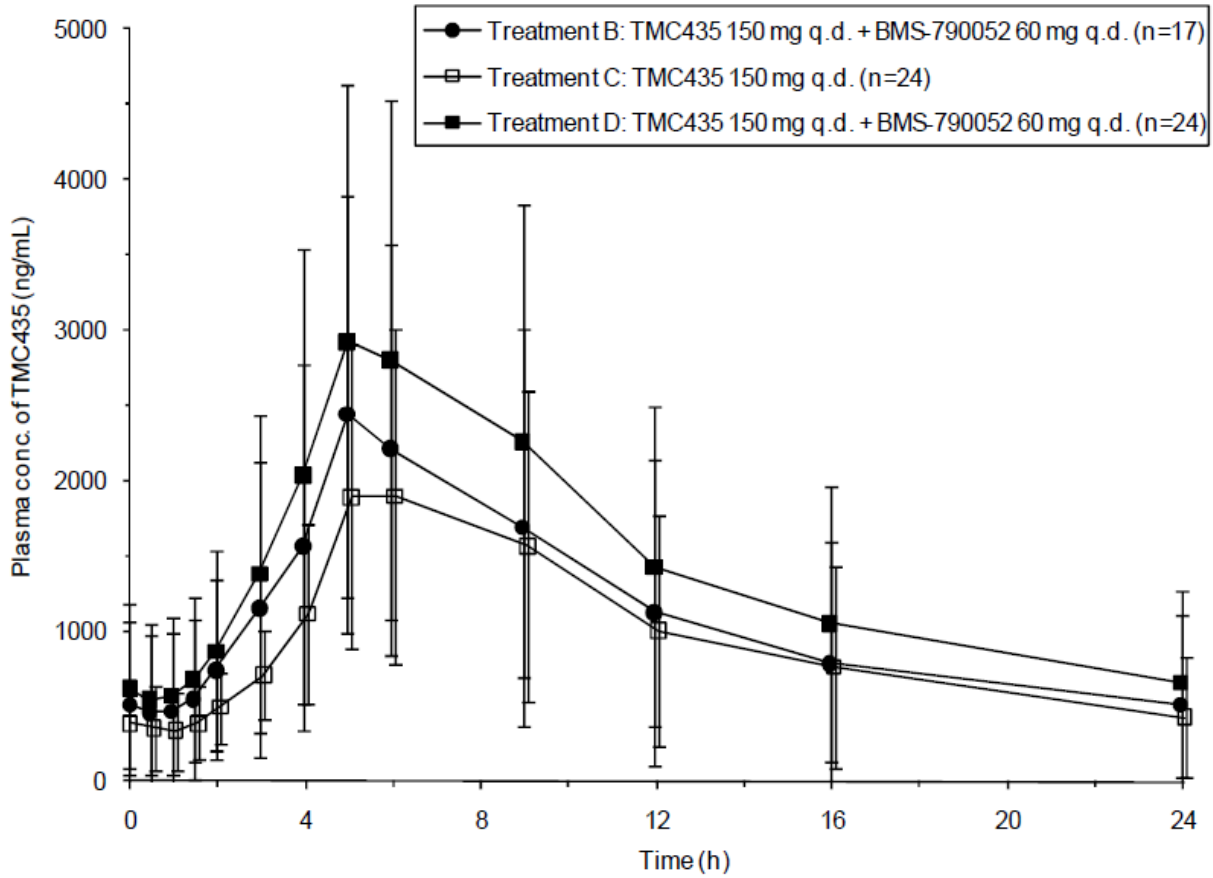

Figure 1: Mean Plasma Concentration-Time Curves of TMC435 (Including SD Bars) After Administration of TMC435 Alone (Treatment C, Day 7, Panel 2) and in Combination With BMS-790052 (Treatment B, Day 7, Panel 1 and Treatment D, Day 7, Panel 2)

Table 1: Summary of the Statistical Analysis of the PK Parameters of TMC435 After Administration of TMC435 Alone (Treatment C) and in Combination With BMS-790052 (Treatment D) in Panel 2

Parameter	LSmeans[a] TMC435 150 mg q.d. (reference)	LSmeans[a] TMC435 150 mg q.d. + BMS-790052 60 mg q.d. (test)	LSmeans ratio	90% CI[b]	p-value Period	p-value Sequence
C_{min}, ng/mL	224.6	334.2	1.49	1.33 - 1.67	0.3015	0.7744
C_{max}, ng/mL	1844	2565	1.39	1.27 - 1.52	0.6805	0.8165
AUC_{24h}, ng.h/mL	18530	26610	1.44	1.32 - 1.56	0.3835	0.8551
Parameter	Median[a] TMC435 150 mg q.d. (reference)	Median[a] TMC435 150 mg q.d. + BMS-790052 60 mg q.d. (test)	Treatment difference median	90% CI, h[b]	p-value Period	p-value Sequence
t_{max}, h	5.0	5.0	0.00	(-0.50) - (0.50)	0.1959	0.1930

[a] n = 24 for reference and test

[b] 90% confidence intervals

- BMS-790052

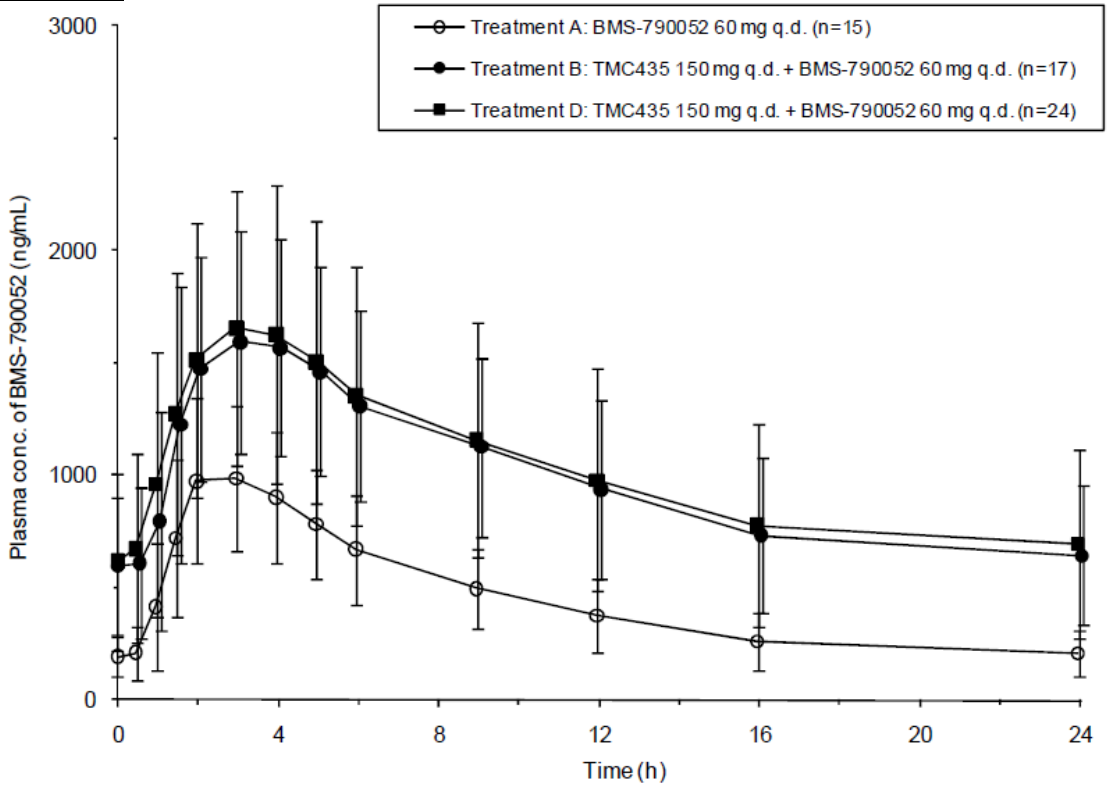

Figure 2: Mean Plasma Concentration-Time Curves of BMS-790052 (Including SD Bars) After Administration of BMS-790052 Alone (Treatment A, Day 7, Panel 1) and in Combination With TMC435 (Treatment B, Day 7, Panel 1 and Treatment D, Day 7, Panel 2)

Table 2: Summary of the Statistical Analysis of the PK Parameters of BMS 790052 After Administration of BMS-790052 Alone (Treatment A) and in Combination With TMC435 (Treatment B) in Panel 1

	LSmeans[a]				p-value	
Parameter	**BMS-790052 60 mg q.d. (reference)**	**BMS-790052 60 mg q.d. + TMC435 150 mg q.d. (test)**	LSmeans ratio	90% CI[c]	Period	Sequence
C_{min}, ng/mL	181.6	487.2	2.68	2.42 - 2.98	0.0347*	0.9003
C_{max}, ng/mL	1045	1568	1.50	1.39 - 1.62	0.6513	0.6479
AUC_{24h}, ng.h/mL	10770	21150	1.96	1.84 - 2.10	0.1145	0.6304
	Median[b]				p-value	
Parameter	**BMS-790052 60 mg q.d. (reference)**	**BMS-790052 60 mg q.d. + TMC435 150 mg q.d. (test)**	Treatment difference median	90% CI, h[c]	Period	Sequence
t_{max}, h	3.0	2.0	0.00	(0.00) - (0.75)	0.1751	0.9447

[a] n=17 for test and n=15 for reference

[b] n=14 for test and reference

[c] 90% confidence intervals

* Statistically significant difference

- Were there any outliers or excluded data from analysis? ☒ Yes ☐ No ☐ NA, if yes explain

Subject	Drug	Treatment	Sample	Issue	Corrective action
10050001	BMS-790052	A	Day 6 and Day 7 samples	Subject had no intake of BMS-790052 on Day 5 and Day 6	Day 6 and Day 7 samples excluded from descriptive statistics and PK analysis
10050010	TMC435, BMS-790052	B	Day 6 and Day 7 samples	Subject had no intake of TMC435 and BMS-790052 on Day 5, Day 6 and Day 7	Day 6 and Day 7 samples excluded from descriptive statistics and PK analysis
10050029	TMC435	D	16H	Sample excluded due to outlier rule	16H sample excluded from NCA
10050030	TMC435	C	16H	Sample excluded due to outlier rule	16H sample excluded from NCA

- Are the study results acceptable? ☒ Yes ☐ No, if no explain

Safety

Was there any death or serious adverse events? ☐ Yes ☒ No

CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS

CONCLUSIONS

Following the coadministration of TMC435 and BMS-790052, Cmin, Cmax, and AUC24h were 1.49, 1.39, and 1.44 fold higher, respectively, for TMC435, and 2.68, 1.50 and 1.96 fold higher, respectively, for BMS-790052, compared to that following the administration of each compound alone, based on the ratios of the LS means. For tmax of TMC435 and BMS-790052, no treatment difference was observed.

The combination of TMC435 150 mg q.d. and BMS-790052 60 mg q.d. was generally safe and well tolerated in

healthy subjects.
COMMENTS None
LABEL RECOMMENDATIONS None

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY DRUG-DRUG INTERACTION STUDY REVIEW				
Study #	TMC435HPC1006	**Study Period**	10 Jul to 28 Aug 2012	EDR Link
Title	A Phase I, 2-panel, open-label study in healthy subjects to investigate the pharmacokinetic interaction between TMC435 and the HMG-CoA reductase inhibitors atorvastatin and simvastatin			

STUDY DESIGN	
Population	☑ Healthy Volunteers ☐ Patients
Study Rationale	TMC435 is metabolized by CYP3A and inhibits P-gp and OATP1B1. The study was conducted evaluate the potential for an interaction between TMC435 and the CYP3A and OATP1B1 substrates atorvastatin and simvastatin.
Treatments	Panel 1 A: atorvastatin 40 mg single dose (Day 1), TMC435 150 mg QD (Days 4-15), atorvastatin 40 mg single dose (Day 13) Panel 2 B: simvastatin 40 mg single dose (Day 1), TMC435 150 mg QD (Days 4-15), simvastatin 40 mg single dose (Day 13) **Sequence** Panel 1: A Panel 2: B
Dose Selection Rationale	The TMC435 150 mg QD dose was selected because it is the dose being used in Phase 3 studies. The atorvastatin and simvastatin doses were selected because they fall into the range that is clinically recommended.
Administration	☐ Fasted ☑ Fed
Formulation	TMC435 150 mg capsule, Batch 12B14 (G019) Atorvastatin 40 mg tablet, Batch V120194 Simvastatin 40 mg tablet, Batch H005467
Interfering Substances Excluded	All concomitant medications (except acetaminophen, ibuprofen, and oral contraceptives) were prohibited beginning 14 days before study drug administration until study completion.
Sampling Times	Treatments A and B Days 1 and 13: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours postdose
PK Parameters	C_{0h}, C_{min}, $C_{ss,av}$, C_{max}, fluctuation index, t_{max}, AUC_{24h}, Ratio $C_{min,test/ref}$, Ratio $C_{max,test/ref}$, and Ratio $AUC_{24h,test/ref}$
PK Analysis	Non-compartmental analysis
Statistical Analysis	The least square (LS) means of the primary parameters (i.e., C_{min}, C_{max}, and AUC_{24h} on the logarithmic scale) for each treatment group was estimated with a linear mixed effects model, controlling for treatment, sequence and period as fixed effects, and subject as a random effect. The LS mean ratio and its 90% confidence interval (CI) were calculated.
Is the study design acceptable? ☑ Yes ☐ No	

STUDY CONDUCT		
Bioanalytical Method		
	Method Name	TMC435 (PBRL-RD-1154) Atorvastatin, 2- and 4-hydroxyatorvastatin (PBRL-RD-1392) Simvastatin, simvastatin acid (PBRL-RD-1391)

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	TMC435, DRV, RTV, erythromycin		
Range	TMC435 (2-2000 ng/mL) Atorvastatin, 2- and 4-hydroxyatorvastatin (0.25-250 ng/mL) Simvastatin, simvastatin acid (0.05-50 ng/mL)		

Validation	▪ Method validated prior to use	☑ Yes ☐ No ☐ NA
	▪ Method validation acceptable	☑ Yes ☐ No ☐ NA
Study Samples Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Incurred samples analysis is acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No
Inspection	▪ Will the bioanalytical site be inspected	☐ Yes ☑ No

Protocol Deviations

- Are there any protocol deviations listed in the study report? ☐ Yes ☑ No
- Do any of the listed deviations affect the integrity of the study? ☐ Yes ☐ No ☑ NA

STUDY RESULTS

Study Population

Randomized	36
Treated	36
Completed	36
Discontinued Due to AE	0
PK Population/Safety Population	36/36
Age [Median (range)]	29.5 (20-55)
Male/Female	26/10
Race: Native America/Asian/Black/Multiple/White	1/4/5/1/25

TMC435 plasma concentrations were quantified (Table 1) but were not evaluated for differences between TMC435 alone or with atorvastatin or simvastatin; however, TMC435 with atorvastatin and TMC435 with simvastatin yielded similar TMC435 pharmacokinetic profiles and parameters.

In the presence of TMC435, atorvastatin and orthohydroxylated atorvastatin concentrations increased by approximately 2-fold (Tables 2-4); concentrations of parahydroxylated atorvastatin also increased, but the magnitude of increase could not be determined due to undetectable concentrations in the atorvastatin alone treatments (data not shown). HMG-CoA reductase inhibitory activity increased approximately 2.6-fold upon coadministration of atorvastatin and TMC435 compared to administration of atorvastatin alone (Table 5).

In the presence of TMC435, simvastatin concentrations increased by approximately 1.5-fold (Tables 6-7) and

concentrations of simvastatin acid also increased by approximately 2.9-3.0-fold (Table 8). HMG-CoA reductase inhibitory activity increased approximately 1.8-fold upon coadministration of simvastatin and TMC435 compared to administration of atorvastatin alone (Table 9).

Table 1: Pharmacokinetics of TMC435350 after multiple dose administration of TMC435 150 mg QD with a single dose of atorvastatin 40 mg or simvastatin 40 mg

Pharmacokinetics of TMC435 mean ± SD, t_{max}: median [range]	Single Dose of 40 mg Atorvastatin + 150 mg TMC435 q.d.	Single Dose of 40 mg Simvastatin + 150 mg TMC435 q.d.
n	18	18
Day 11		
C_{0h}, ng/mL	628 ± 870	589 ± 479
Day 12		
C_{0h}, ng/mL	578 ± 890	572 ± 564
Day 13		
C_{0h}, ng/mL	573 ± 841	635 ± 652
C_{min}, ng/mL	532 ± 844	544 ± 551
C_{max}, ng/mL	3091 ± 2739	3219 ± 2302
t_{max}, h	6.00 [2.98-6.15]	6.00 [4.00-23.92]
AUC_{24h}, ng.h/mL	33115 ± 35275	38345 ± 35235
C_{avg}, ng/mL	1385 ± 1476	1603 ± 1473
Fluctuation index, %	208 ± 46.7	184 ± 44.3

Table 2: Pharmacokinetics of atorvastatin after single dose administration of atorvastatin 40 mg alone or after 10 days of administration of TMC435 150 mg QD

Pharmacokinetics of Atorvastatin mean ± SD, t_{max}: median [range]	Single dose of 40 mg Atorvastatin on Day 1 (Reference)	Single dose of 40 mg Atorvastatin + 150 mg TMC435 q.d. on Day 13 (Test)
n	18[a]	18[b]
C_{max}, ng/mL	12.8 ± 7.06	21.2 ± 10.5
t_{max}, h	1.00 [0.48-3.00]	1.00 [1.00-6.00]
AUC_{last}, ng.h/mL	62.5 ± 28.4	155 ± 87.9
AUC_{∞}, ng.h/mL	67.6 ± 27.5	148 ± 88.9
λ_z, 1/h	0.0894 ± 0.0310	0.134 ± 0.0563
$t_{1/2term}$, h	8.8 ± 3.4	6.3 ± 3.2

[a] n = 16 for AUC_{∞} and n = 17 for λ_z and $t_{1/2term}$
[b] n = 13 for AUC_{∞}, λ_z and $t_{1/2term}$

Table 3: Statistical analysis of the PK parameters of atorvastatin after administration of a single dose of atorvastatin alone or after multiple doses of TMC435

Parameter	LSmeans[a]		LSmeans Ratio	90% CI
	Single Dose of 40 mg Atorvastatin (Reference)	Single Dose of 40 mg Atorvastatin + 150 mg TMC435 q.d. (Test)		
C_{max}, ng/mL	11.1	18.8	1.70	1.42-2.04
AUC_{last}, ng.h/mL	56.3	131	2.33	1.99-2.73
AUC_{∞}, ng.h/mL[b]	61.2	130	2.12	1.72-2.62

[a] n = 18 for reference and n = 18 for test
[b] n = 16 for reference and n = 13 for test

Table 4: Statistical analysis of the PK parameters of orthohydroxylated atorvastatin after administration of a single dose of atorvastatin alone or after multiple doses of TMC435

Parameter	LSmeans[a]		LSmeans Ratio	90% CI
	Single Dose of 40 mg Atorvastatin (Reference)	Single Dose of 40 mg Atorvastatin + 150 mg TMC435 q.d. (Test)		
C_{max}, ng/mL	9.95	19.7	1.98	1.70-2.31
AUC_{last}, ng.h/mL	84.4	193	2.29	2.08-2.52

[a] n = 18 for reference and n=18 for test

Table 5: Statistical analysis of the PK parameters of HMG-CoA reductase inhibitor activity after single dose administration of atorvastatin 40 mg alone or after 10 days of administration of TMC435 150 mg QD

Parameter	LSmeans[a]		LSmeans Ratio	90% CI
	Single Dose of 40 mg Atorvastatin on Day 1 (Reference)	Single Dose of 40 mg Atorvastatin + 150 mg TMC435 q.d. on Day 13 (Test)		
C_{max}, ng eq./mL	43.0	95.7	2.23	1.91-2.59
AUC_{12h}, ng eq.h/mL	299	762	2.55	2.27-2.87

[a] n = 18 for reference and n = 18 for test

Table 6: Pharmacokinetics of simvastatin after single dose administration of simvastatin 40 mg alone or after 10 days of administration of TMC435 150 mg QD

Pharmacokinetics of Simvastatin mean ± SD, t_{max}: median [range]	Single Dose of 40 mg Simvastatin on Day 1 (Reference)	Single Dose of 40 mg Simvastatin + 150 mg TMC435 q.d. on Day 13 (Test)
n	18	18
C_{max}, ng/mL	10.6 ± 6.03	19.3 ± 17.6
t_{max}, h	1.48 [0.98-3.00]	1.00 [0.48-4.00]
AUC_{last}, ng.h/mL	28.3 ± 12.0	49.2 ± 37.0
AUC_{∞}, ng.h/mL	29.2 ± 12.1	49.9 ± 37.0
λ_z, 1/h	0.215 ± 0.0478	0.201 ± 0.0653
$t_{1/2term}$, h	3.4 ± 0.8	3.8 ± 1.1

Table 7: Statistical analysis of the PK parameters of simvastatin after administration of a single dose of simvastatin alone or after multiple doses of TMC435

Parameter	LSmeans[a]		LSmeans Ratio	90% CI
	Single Dose of 40 mg Simvastatin (Reference)	Single Dose of 40 mg Simvastatin + 150 mg TMC435 q.d. (Test)		
C_{max}, ng/mL	9.39	13.7	1.46	1.17-1.82
AUC_{last}, ng.h/mL	26.2	40.3	1.54	1.34-1.76
AUC_{∞}, ng.h/mL	27.2	41.1	1.51	1.32-1.73

[a] n = 18 for reference and n = 18 for test

Table 8: Statistical analysis of the PK parameters of simvastatin acid after administration of a single dose of simvastatin alone or after multiple doses of TMC435

Parameter	LSmeans[a]		LSmeans Ratio	90% CI
	Single Dose of 40 mg Simvastatin (Reference)	Single Dose of 40 mg Simvastatin + 150 mg TMC435 q.d. (Test)		
C_{max}, ng/mL	2.17	6.57	3.03	2.49-3.69
AUC_{last}, ng.h/mL	17.0	40.9	2.40	1.94-2.96
AUC_{∞}, ng.h/mL[b]	21.2	39.9	1.88	1.63-2.17

[a] n = 18 for reference and n = 18 for test
[b] n = 13 for reference and n = 15 for test

Table 9: Statistical analysis of the PK parameters of HMG-CoA reductase inhibitor activity after single dose administration of simvastatin 40 mg alone or after 10 days of administration of TMC435 150 mg QD

Parameter	LSmeans[a]		LSmeans Ratio	90% CI
	Single Dose of 40 mg Simvastatin on Day 1 (Reference)	Single Dose of 40 mg Simvastatin + 150 mg TMC435 q.d. on Day 13 (Test)		
C_{max}, ng eq./mL	35.1	54.0	1.54	1.19-1.98
AUC_{12h}, ng eq.h/mL	144	265	1.83	1.55-2.16

[a] n = 18 for reference and n = 18 for test

- Were there any outliers or excluded data from analysis? ☑ Yes ☐ No ☐ NA

Subject 108-0027 was excluded from analysis in Treatment A (digoxin alone) because a plasma concentration >5% of C_{max} was obtained predose.

- Are the study results acceptable? ☑ Yes ☐ No

Safety

Were there any deaths or serious adverse events? ☐ Yes ☑ No

CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS

CONCLUSIONS

Does the study finding warrant dose adjustment upon the co-administration of TMC435 with atorvastatin? ☑ Yes ☐ No

Due to the magnitude of atorvastatin exposure increases, the daily dose of atorvastatin should be limited to 40 mg when coadministered with TMC435 and the lowest possible atorvastatin dose should be used.

Is the interaction clinically significant? ☑ Yes ☐No ☐ NA

Does the study finding warrant dose adjustment upon the co-administration of TMC435 with simvastatin? ☐ Yes ☑ No

When coadministered with TMC435, the lowest necessary dose of simvastatin should be used; however, no dose reduction is required and no maximum dose is recommended.

Is the interaction clinically significant? ☐ Yes ☑ No ☐ NA

LABEL RECOMMENDATIONS

Concomitant use of TMC435 with atorvastatin resulted in increased atorvastatin plasma concentrations due to TMC435 inhibition of CYP3A and/or OATP1B1. Use the lowest necessary dose of atorvastatin but do not exceed a daily dose of 40 mg.

Concomitant use of TMC435 with simvastatin resulted in increased simvastatin plasma concentrations due to TMC435 inhibition of CYP3A and/or OATP1B1. Titrate carefully and use the lowest necessary dose of simvastatin.

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/s/

LESLIE W CHINN
08/28/2013

JIANG LIU
08/28/2013

JEFFREY B KRAFT
08/28/2013

YUZHUO PAN
08/28/2013

YORIKO HARIGAYA
08/28/2013

YONGHENG ZHANG
08/28/2013

PING ZHAO
08/28/2013

MICHAEL A PACANOWSKI
08/28/2013

JEFFRY FLORIAN
08/28/2013

SHIRLEY K SEO on behalf of ISLAM R YOUNIS
08/28/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205-123	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Dates:	3/28/2013; 6/26/13; 7/24/13		
Division:	DAVP	**Secondary Signature:** Angelica Dorantes, Ph.D.	
Applicant:	Janssen	**Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	TBD	**Date Assigned:**	4/4/2013
Generic Name:	Simeprevir	**Date of Review:**	8/27/2013
Indication:	Treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) with or without human immunodeficiency virus-1 (HIV-1) coinfection who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin.	**Type of Submission:** 505(b)(1) New Drug Application	
Formulation/strengths:	IR Capsule/ 150 mg		
Route of Administration:	Oral		

SUMMARY:

Submission: This submission is a 505(b)(1) New Drug Application for 150 mg simeprevir immediate release capsules. The proposed indication is for the treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) with or without human immunodeficiency virus-1 (HIV-1) coinfection who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin.

Review: The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of:
1) the proposed dissolution methodology,
2) the proposed acceptance criterion,
3) data supporting the manufacturing site for the commercial formulation, and
4) data supporting the bridging of the Phase 3 and to-be-marketed formulations.

A. Dissolution Method

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
II	75 rpm	900 mL	37°C	50 mM phosphate buffer pH 6.8 with 1.0% Polysorbate 20

The proposed dissolution method is deemed acceptable.

B. Dissolution Acceptance Criterion

Acceptance Criterion
Q = (b) (4) at 30 minutes

The proposed dissolution acceptance criterion is not supported by the data and is not acceptable. Therefore, in an IR letter to the Applicant dated July 18, 2013, the ONDQA Biopharmaceutics Team recommended a dissolution acceptance criterion of **Q =** (b) (4) **at 25 minutes** based on the mean in-vitro dissolution profiles of the pivotal clinical and primary stability batches at release and 12 month stability. In a submission dated July 24, the Applicant stated that they will submit additional data in September 2013 to address our request. Thus, at this time of the review process the approval of the final acceptance criterion for the dissolution test is pending.

C. Bridging of the Phase 3 and To-Be-Marketed Formulations

The Applicant provided comparative dissolution data with f2 testing using the proposed dissolution test conditions for a representative clinical phase 3 batch and a full scale stability batch produced at the Latina commercial facility in Italy. These data demonstrate that the Phase 3 batch and the commercial formulation have f2 similar dissolution profiles. Thus, these dissolution data adequately support the bridging of the Phase 3 and to-be marketed formulations.

D. Data to Support the Manufacturing Site for the Commercial Product

To support the approval of the manufacturing site for the commercial product, the Applicant provided comparative dissolution data with f2 testing using the proposed dissolution test conditions for a representative clinical phase 3 batch produced in Belgium and a batch produced at the Latina commercial facility in Italy. These data demonstrate that the drug products manufactured at Beerse (Belgium) and Latina (Italy) have similar dissolution profiles; therefore the proposed site for the manufacturing of the commercial product at Latina is acceptable.

RECOMMENDATION:

At this time of the review process, the submission of essential dissolution information needed for the final determination on the acceptability the dissolution acceptance criterion is pending. Therefore, from the Biopharmaceutics perspective, an approval recommendation cannot be given for NDA 205123. However, after the Applicant submits the dissolution data that are pending, Biopharmaceutics will revise the recommendation on the approvability of this NDA, as appropriate.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Richard Lostritto

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Table 4. Target Composition of the 150 mg Capsule

Component	Quality Reference[a]	Function	Quantity per Capsule (mg)
Simeprevir [redacted]	Control of Critical Steps and Intermediates	Active	154.60
Sodium lauryl sulphate	Ph. Eur., NF	[redacted]	
Magnesium stearate[b]	Ph. Eur., NF		
Colloidal anhydrous silica	Ph. Eur., NF		
Croscarmellose sodium	Ph. Eur., NF		
Lactose monohydrate	Ph. Eur., NF		
Nominal weight:			250.00
Hard gelatin capsule [redacted] white body/white cap with black "TMC435 150" print	Control of Excipients	Capsule	1 piece

2. Dissolution Method

The proposed dissolution method is shown below.

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
II	75 rpm	900 mL	37°C	50 mM phosphate buffer pH 6.8 with 1.0% Polysorbate 20

[redacted]

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Overall, the proposed dissolution method is discriminating; therefore, it is acceptable.

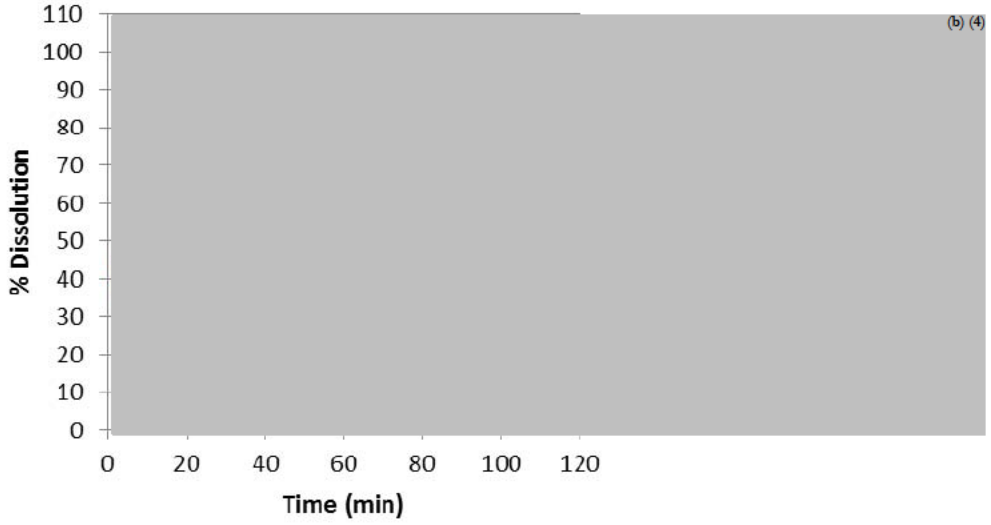
3. Dissolution Acceptance Criterion

The proposed dissolution acceptance criterion is shown below.

Acceptance Criterion
Q = (b) (4) at 30 minutes

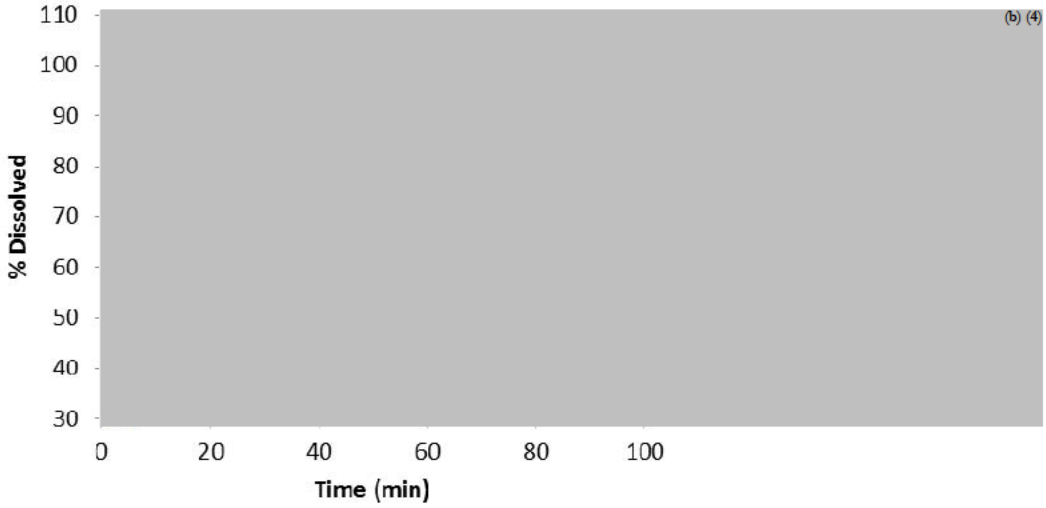
Reviewer's Figure 1 displays the dissolution data for the pivotal clinical batches of the proposed product.

Reviewer's Figure 1. Dissolution Profile Data for the Pivotal Clinical Batches



Reviewer's Figure 2 displays the dissolution data for a primary stability batch of the proposed product stored at 25°C / 60% RH. The same trend in the dissolution data can be seen in the stability data for Batch 12B14/G019 and Batch 12B21/G019 (refer to data in 3.2.P.8.3).

Reviewer's Figure 2. Dissolution Profile Data for Primary Stability Batch 12B07/G019 Stored at 25 °C / 60% RH for 12 months



Reviewer's Assessment:

Reviewer's Figure 1 demonstrates that (b) (4) of drug is released from the capsules by 20 minutes for all of the pivotal clinical batches. Therefore, a dissolution acceptance criterion of Q=(b) (4) at 20 minutes seems appropriate to ensure that future drug product batches have the same clinical performance as the pivotal clinical batches. However, Reviewer's Figure 2 shows that the dissolution rate slightly (b) (4) with stability and therefore a dissolution acceptance criterion of Q=(b) (4) at 25 minutes appears to be adequate because (b) (4) of drug is released from the capsules by 20 minutes for this batch measured after being stored for 3-12 months at 25 °C / 60% RH. The same trend in the dissolution data can be seen in the stability data for other batches (refer to data in 3.2.P.8.3).

Thus, the following comment was conveyed to the Applicant in an IR letter dated July 18, 2013.

FDA Comment
Based on the mean *in-vitro* dissolution profile data from the clinical and primary stability batches at release and under long term stability (12 months), the following dissolution acceptance criterion is recommended: Q = (b) (4) at 25 minutes. Revise the dissolution acceptance criterion accordingly and submit an updated table of specifications for the drug product.

Applicant Response (excerpt)
As agreed during the FDA/JRD mid cycle review meeting on 22 July 2013, response to this question will be submitted once additional data are available.

Considering the high risk of overall lot rejection of (b) (4) at 25 °C/60% RH based on a Q (b) (4) at 25 minutes acceptance criterion that was calculated using a Bayesian simulation and presented in 3.2.P.5.6 of the original dossier (and provided below for reviewer convenience), based on the currently available data the Applicant is not comfortable with narrowing the specification limits.

	Evaluation for Q = (b) (4) at 25 min specification		Evaluation for Q = (b) (4) at 30 min specification	
Condition	Stage 1 Failure Rate (%)	Overall Lot Rejection (%)	Stage 1 Failure Rate (%)	Overall Lot Rejection (%)
25 °C/60%RH	(b) (4)			
30 °C/75%RH				

Additional drug product stability data (18 months) will be available in September 2013, and the Applicant will at that time have sufficient data to adequately address the FDA request.

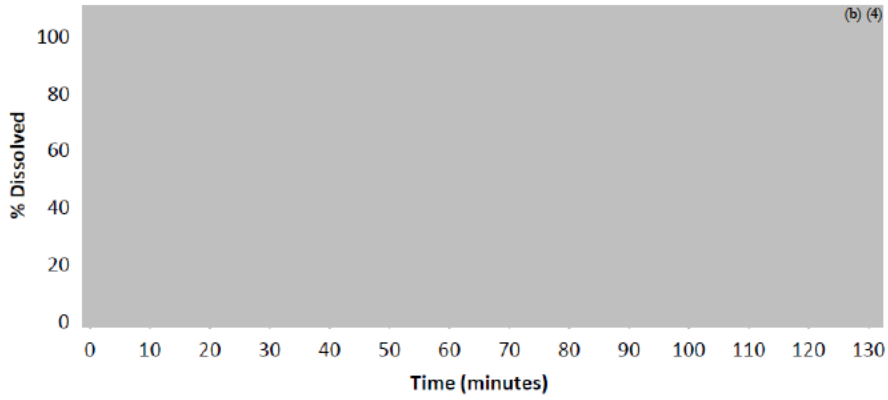
In a submission dated July 24, the Applicant stated that they will submit additional data in September 2013 to address our request. Thus, the final dissolution acceptance criterion will be set after these data are submitted and reviewed.

4. Data Supporting the Level 3 Manufacturing Site Change and Bridging the Phase 3 and To-be-Marketed Formulation

The Applicant made a Level 3 manufacturing site change from Beerse (Belgium) to Latina (Italy) to manufacture the commercial drug product. Additionally, the Applicant made some minor formulation and manufacturing process changes (b) (4) used to manufacture the Phase 3 and commercial drug product. Refer to Dr. Celia Cruz's CMC review for details on these changes.

Figure 13 below displays comparative dissolution data for the representative clinical phase 3 batch (10K03/G007), the 3 primary stability batches (12B07/G019, 12B14/G019, and 12B21/G019) produced in development site Beerse, and 1 full scale stability batch produced at the commercial facility in Latina (CJL67), generated with the proposed dissolution method.

Figure 13. Mean Dissolution Profiles (n=12) of the Phase 3 Clinical Batch and Registration Batches Produced at the Beerse site and the Full Scale Batch Produced at the Latina Site



The f2 similarity factor for each comparison is listed in Table 9 below.

Table 9. Similarity Factors f2

Batch	(b) (4)
10K03/G007	

Note: the 5 min time point was not taken into account as for some batches %RSD>20% for this time point.

Reviewer's Assessment:

The drug product manufactured at Beerse (i.e., the Phase 3 batch and the registration batches) and Latina (i.e., the commercial formulation) have f2 similar dissolution profiles; therefore, the proposed manufacturing site at Latina is deemed acceptable. Moreover, these dissolution data adequately bridge the Phase 3 and to-be marketed formulation.

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/s/

KAREEN RIVIERE
08/27/2013

ANGELICA DORANTES
08/27/2013

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General information about the submission	
NDA/BLA Number	205123 (0000/1)
OCP Division	DCP4
Medical Division	Division of Antiviral Products
OCP Reviewer	Leslie Chinn, Ph.D.
OCP Team Leader	Islam Younis, Ph.D.
Pharmacometrics Reviewer	Jiang Liu, Ph.D.
Pharmacometrics Secondary Reviewer	Jeffry Florian, Ph.D.
Pharmacogenomics Reviewer	Jeffrey Kraft, Ph.D.
Pharmacogenomics Secondary Reviewer	Michael Pacanowski, Pharm.D., MPH
Date of Submission	28 Mar 2013
OCP Review Estimated Due Date	28 Aug 2013
Medical Division Due Date	
PDUFA Due Date	27 Nov 2013
Relevant IND Number	75391

General information about the drug/biologic	
Brand Name	
Generic Name	Simeprevir
Drug Class	Hepatitis C virus (HCV) NS3/4A protease inhibitor
Indication(s)	Treatment of chronic hepatitis C genotype 1 infection
Dosage Form	150 mg simeprevir salt capsules
Dosing Regimen	Simeprevir 150 mg administered once daily with food, in combination with peginterferon alfa and ribavirin, for 12 weeks, followed by either 12 or 36 additional weeks of peginterferon alfa and ribavirin depending on on-treatment viral response and prior response status
Route of administration	Oral
Sponsor	Janssen Therapeutics, Johnson & Johnson
Priority Classification	Priority

Clinical pharmacology and biopharmaceutics information				
Study Type	**Incl. at Filing**	**No. of Studies Submitted**	**No. of Studies Reviewed**	**Critical Comments**

Table of Contents incl. reports, tables, data	☒			
Tabular Listing incl. all human studies	☒			
Human PK Summary	☒			
Labeling	☒			
Reference Bioanalytical and Analytical Methods	☒			
I. CLINICAL PHARMACOLOGY				
Mass Balance	☒	1		
Isoenzyme Characterization	☒	7		
Transporter Characterization	☒	7		
Blood/Plasma Ratio	☐			
Plasma Protein Binding	☒	2		
Pharmacokinetics (e.g. Phase 1)				
Healthy Volunteers				
Single Dose	☒	1		
Multiple Dose	☒			
Patients				
Single Dose	☐			
Multiple Dose	☐			
Dose Proportionality – Fasting/Non-Fasting				
Single Dose	☐			
Multiple Dose	☐			
Drug-Drug Interaction Studies				
In Vivo Effects on Primary Drug	☒	12		
In Vivo Effects of Primary Drug	☒			
In Vitro	☒	6		
Special Populations				
Ethnicity	☒	2		
Gender	☐			
Pediatrics	☐			
Geriatrics	☐			
Renal Impairment	☒	1		
Hepatic Impairment	☒	1		
Pharmacodynamics				
Phase 2	☒	2		

Phase 3	☐			
Pharmacokinetics/Pharmacodynamics				
Proof of Concept (Phase 1 or 2)	☒	3		
Clinical Trial (Phase 3)	☒	3		
Population Analyses				
Data-rich	☐			
Data-sparse	☒	1		
II. BIOPHARMACEUTICS				
Bioavailability				
Absolute Bioavailability	☒	1		ongoing
Relative Bioavailability (solution as reference)	☒	1		
Relative Bioavailability (alt. formulation as ref.)	☒	2		
Bioequivalence				
Traditional Design (single/multiple dose)	☐			
Replicate Design (single/multiple dose)	☐			
Food-Drug Interaction	☒	1		
Biowaiver Request (based on BCS class)	☐			
Dissolution (alcohol-induced dose-dumping)	☐			
III. OTHER CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS				
Genotype/Phenotype	☒			Dataset submitted
Chronopharmacokinetics	☐			
Pediatric Development Plan	☒	1		Waiver and deferral submitted
Literature References	☐			
TOTAL NUMBER OF STUDIES				

On **initial** review of the NDA/BLA application for filing:					
Content Parameter		**Yes**	**No**	**N/A**	**Comment**
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☒	☐	☐	

2	Has the applicant provided metabolism and drug-drug interaction information?	☒	☐	☐	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	☒	☐	☐	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	☒	☐	☐	
5	Has a rationale for dose selection been submitted?	☒	☐	☐	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	☒	☐	☐	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	☒	☐	☐	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	☒	☐	☐	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☒	☐	☐	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐	☐	☒	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	☒	☐	☐	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☒	☐	☐	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☒	☐	☐	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetics or pharmacodynamics?	☒	☐	☐	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐	☐	☒	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	☐	☐	☒	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of	☒	☐	☐	

	the label?				
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☒	☐	☐	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☒	☐	☐	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

☒ **Yes** ☐ **No**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Leslie Chinn, Ph.D. 29 April 2013

Reviewing Clinical Pharmacologist **Date**

Islam Younis, Ph.D. 29 April 2013

Team Leader/Supervisor **Date**

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/s/

LESLIE W CHINN
04/30/2013

ISLAM R YOUNIS
04/30/2013

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	205-123
Submission Date	3/28/2013
Product name, generic name of the active	Sovriad (simeprevir) Capsules
Dosage form and strength	IR Capsule/ 150 mg
Indication:	Treatment of chronic Hepatitis C infection
Applicant	Janssen Research & Development LLC
Clinical Division	DAVP
Type of Submission	505(b)(1) New Drug Application
Biopharmaceutics Reviewer	Kareen Riviere, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.
Acting Supervisor	Richard Lostritto, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING

	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		See the Initial Assessment section for the proposed dissolution method and acceptance criterion.
3.	Does the application contain the dissolution method development report?	x		
4.	Is there a validation package for the analytical method and dissolution methodology?	x		
5.	Does the application include a biowaiver request?		x	A biowaiver is not needed.
6.	Is there information provided to support the biowaiver request?		x	Not Applicable.
7.	Does the application include an IVIVC model?		x	Not Applicable.
8.	Is information such as BCS classification mentioned, and supportive data provided?	x		The Applicant reports that the drug substance is a BCS Class 4 compound.
9.	Is information on mixing the product with foods or liquids included?		x	Not Applicable.
10.	Is there any in *vivo* BA or BE information in the submission?	x		The Applicant conducted several relative BA studies during the formulation development process. These data will be reviewed by OCP.

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
11.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
12.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	-	-	
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		IR comments will be sent to the Applicant in the 74 day letter. The comments are outlined in the Initial Assessment.

{See appended electronic signature page}
Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

4/22/13
Date

{See appended electronic signature page}
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

4/22/13
Date

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

INITIAL ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

The Biopharmaceutics information in this submission includes a drug product development section with the proposed dissolution method and acceptance criterion, as well as data to support the manufacturing site for the commercial formulation.

The proposed dissolution method is:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
II	75 rpm	900 mL	37°C	50 mM phosphate buffer pH 6.8 with 1.0% Polysorbate 20

The proposed acceptance criterion is:

Acceptance Criterion
Q= (b) (4) at 30 min

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of 1) the proposed dissolution methodology, 2) the proposed acceptance criterion, and 3) data supporting the manufacturing site for the commercial formulation.

To aid the review of the Applicant's submission, the following comment should be conveyed to the Applicant:

1. Provide the complete dissolution profile data (raw data and mean values) from the pivotal clinical batches supporting your selection of the proposed dissolution acceptance criterion of Q = (b) (4) at 30 minutes for your proposed product.

RECOMMENDATION:

The ONDQA Biopharmaceutics team has reviewed NDA 205-123 for Sovriad (simeprevir) for filing purposes. We found this NDA **fileable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission.

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/s/

KAREEN RIVIERE
04/22/2013

ANGELICA DORANTES
04/22/2013