

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202022Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

ADDENDUM to ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	202-022/N-000
Submission Date:	03/14/11, 03/17/11, and 03/25/11
Brand Name:	To be determined
Generic Name:	Rilpivirine HCl
Formulation:	Oral immediate release (IR) tablets
Strength:	Only one strength 25 mg
Sponsor:	Tibotec
Type of submission:	Amendments
Reviewer:	Tien-Mien Chen, Ph.D.

The original NDA for rilpivirine IR 25 mg tablet that was submitted on 07/23/10 has been reviewed by the Biopharmaceutics team on 03/02/11. From the Biopharmaceutics perspective, the sponsor's proposed dissolution method is acceptable, but the proposed dissolution specification needs to be revised. This addendum is to address:

1. The Agency's conclusion on the dissolution specifications for rilpivirine IR 25 mg tablets.

The sponsor proposed $Q = (b) (4)$ at 45 min, but the Agency recommended a revision to $Q = (b) (4)$ at 45 min due to a mean of $(b) (4)$ of rilpivirine dissolved at 45 min. On 03/14/11, a teleconference was held between the sponsor and the Agency. The sponsor submitted the 24-month stability data for discussions (Appendix 1). Per request by the Agency in the teleconference, the sponsor further submitted on 03/17/11 for review the stability (dissolution) data of the clinical biobatch No. 8BL2H at initial manufacturing (April, 08; $t=0$) and at 18 months and 33 months under both 25°C/60% RH and 30°C/75% RH conditions. (Appendix 2)

The Agency concluded that

- The clinically tested batch (No. 8BL2H) that started at $(b) (4)$ at 45 min in dissolution at the time of initial manufacturing ($t=0$) still maintained $(b) (4)$ dissolved under 25°C/60% RH, and $(b) (4)$ under 30°C/75% RH conditions after 33 months.
- One of the three stability batches (No. 8JL3S) that started with low dissolution ($(b) (4)$ at 45 min) at the time of initial manufacturing ($t=0$) still maintained $(b) (4)$ dissolved under 25°C/60% RH, and $(b) (4)$ under 30°C/75% RH conditions after 24 months.

Based on the above findings, and the need to maintain similar exposure levels as was tested clinically, a dissolution specification of $Q = (b) (4)$ at 45 minutes is still recommended, as indicated earlier in our May 20, 2010, comments to IND 67,699, and March 11, 2011, Information Request letter to NDA 202-022. An advice letter was sent to the sponsor on 03/18/11.

The Agency recommended the following revisions.

- Change dissolution specification as follows:
From $Q = (b) (4)$ at 45 minutes to $Q = (b) (4)$ at 45 minutes
- Update section 3.2.P.5.1 to reflect this change in the dissolution specification.

Please see Appendices 1 and 2, and also the Agency's advice letter sent to the sponsor on 03/18/11 for details.

2. The comparative dissolution data submitted show that debossing does not affect the release characteristics of rilpivirine IR tablets.
3. The sponsor submitted the updated Section 3.2.P.5.1 for the dissolution specifications in the 03/25/11 Amendment (Appendix 3) which is acceptable. Please see Appendix 3 and the 03/25/11 Amendment for details.

Tien-Mien Chen, Ph.D.
Reviewer
ONDQA Biopharmaceutics

03/28/11
Date

Patrick Marroum, Ph.D.
ONDQA Biopharmaceutics

03/28/11
Date

CC: NDA
Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

**NDA 202-022/N-000 for TMC278 (Rilpivirine)
IR Tablet, 25 mg**

Appendix 1

**Stability/Dissolution Data Submitted on
03/14/11**

March 14, 2011

FDA Meeting on Rilpivirine Hydrochloride (TMC278) Drug Product

NDA 202022

March 14, 2011

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**NDA 202-022/N-000 for TMC278 (Rilpivirine)
IR Tablet, 25 mg**

Appendix 2

**Information on the Stability/Dissolution of the
Clinical Biobatch No. 8BL2H Submitted on
03/17/11**

03/17/11 Submission of the Additional Dissolution Data for Clinical Biobatch
Follow-up of teleconference dd 14 March 2011 with FDA – related to NDA202,022

Please find herewith the data as agreed to be provided during our teleconference of March 14, 2011.

From the clinical randomization system used for the pivotal Phase 3 studies, it is derived that primary clinical batch 8BL2H was last dispensed to patients (as a monthly supply) on December 2009. As this batch was manufactured in February 2008, this means that tablets of 21 months old have been supplied to patients.

Please find below in [Table 1](#), [Table 2](#), [Table 3](#), [Table 4](#) and [Table 5](#) the dissolution data of clinical batch 8BL2H tested with the current proposed dissolution method, at initial time point, 18 months time point (storage conditions 25°C/60%RH and 30°C/75%RH), and 33 months time point (storage conditions 25°C/60%RH and 30°C/75%RH). The applicant is providing all the dissolution data that were generated during development for this specific batch with the proposed dissolution method. Clinical batch 8BL2H was manufactured by the same manufacturing process, at the same scale and at the same manufacturing site (b) (4) as for all three primary stability batches.

[Figure 1](#) and [Figure 2](#) represent % dissolved at 45 min of batch 8BL2H in comparison with primary stability batches 8JL3H, 8JL3K and 8JL3S as a function of storage time, at storage conditions 25°C/60%RH and 30°C/75%RH respectively.

Table 1: Individual dissolution data of clinical batch 8BL2H at the initial time point for the 25°C/60%RH storage condition.

Batch: TMC278 25mg tablets Batch No: 8BL2H- Initial (April 2008)

(b) (4)

Table 2: Individual dissolution data of clinical batch 8BL2H after 18 months of storage 25°C/60%RH.

Batch: TMC278 25mg tablets Batch No: 8BL2H - 18 months (25°C/60%RH)

(b) (4)



Table 3: Individual dissolution data of clinical batch 8BL2H after 33 months of storage 25°C/60%RH.

Batch: TMC278 25mg tablets Batch No: 8BL2H - 33 months (25°C/60%) RH

(b) (4)



Table 4: Individual dissolution data of clinical batch 8BL2H after 18 months of storage 30°C/75%RH.

Batch: TMC278 25mg tablets Batch No: 8BL2H - 18 months (30°C/75%) RH

(b) (4)

Table 5: Individual dissolution data of clinical batch 8BL2H after 33 months of storage 30°C/75%RH.

Batch: TMC278 25mg tablets Batch No: 8BL2H - 33 months (30°C/75%) RH

(b) (4)

Figure 1: % Dissolved at 45 min of batch 8BL2H and of Primary Stability Batches 8JL3H, 8JL3K and 8JL3S for storage at 25°C/60%RH as a function of storage time,

(b) (4)



Figure 2: % Dissolved at 45 min of batch 8BL2H and of Primary Stability Batches 8JL3H, 8JL3K and 8JL3S for storage at 30°C/75%RH as a function of storage time,

(b) (4)



Compared with the primary stability batches, primary clinical batch 8BL2H shows a similar stability behavior, with a decline of (b) (4) after 18 and 33 months of storage at 25°C/60%RH and (b) (4) after 33 months of storage at 30°C/75%RH. The yearly rate of decline is similar if not slightly faster than that of the primary stability batches. These data confirm that the modest decline in dissolution during storage is an inherent characteristic of the product visualized by a discriminative dissolution method and that it is appropriate to take this consistent effect into account when setting the product specifications. Batches that have an initial dissolution value similar to that of the slowest primary stability batch are expected to approximate or even fail to meet an end of shelf-life specification of $Q = (b) (4)$ at 45 minutes after 36 months of storage. Also

(b) (4)

(b) (4) To ensure batch to batch consistency and to account for the decline of dissolution during storage it is also justified that a specification of $Q = (b) (4)$ at 45 minutes has to be met at the time of release of the product. Such an assurance could be provided either by the implementation of an in-house limit for dissolution testing at release or by agreeing to a dissolution limit of $Q = (b) (4)$ at 45 minutes specifically for release of the product similar to what the agency agreed for other products.

**NDA 202-022/N-000 for TMC278 (Rilpivirine)
IR Tablet, 25 mg**

Appendix 3

**Updated CMC Section of M3.2.P.5.1
Specifications Submitted on 03/25/11**

Response to FDA Communication of 23 March 2011 regarding TMC278 NDA 202,022

Background

This response includes feedback (including an updated section 3.2.P.5.1) to the information requests of March 18, 2011 and March 23, 2011.

Additionally, this response includes an updated section 2.3.P.8 and 3.2.P.8.1, related to the information request dated March 11, 2011. (b) (4)

(b) (4)

1. FDA QUESTION #1:

The proposed inclusion of microbiological purity testing into the marketed stability protocol (Section 3.2.P.8.2) for commitment batches and annual monitoring already appropriately captures the reduced testing justified by the microbiological purity assessment and the data provided. Specifications listed in Section 3.2.P.5.1 should be tested for every batch upon release and should not include reduced frequency testing plans.

Please keep microbiological purity testing in Section 3.2.P.5.1, only if it will be tested on every batch upon release. Otherwise, update NDA Section 3.2.P.5.1 accordingly.

Response:

Since microbiological purity testing will be performed as part of the marketed stability protocol (Section 3.2.P.8.2) for commitment batches and annual monitoring, and as it is not the intent to test microbiological purity for all batches at release, the microbiological purity test is removed from Section 3.2.P.5.1. An updated Section 3.2.P.5.1 is provided.

2. FDA QUESTION #2:

In addition, please update the drug product dissolution specification, as communicated on March 18, 2011.

Response:

An updated Section 3.2.P.5.1 is provided, with a dissolution specification of “Q is (b) (4) at 45 minutes”.

Updated Section M3.2.P.5.1

Rilpivirine Hydrochloride Film-Coated Tablet 25-mg

3.2.P.5.1 Specification(s)

Parameters	Regulatory Acceptance Criteria	Test Methods
Appearance		
GFI-314585-CA-026	White to off-white, round, biconvex tablets with debossing “TMC” on one side and “25” on the other side	Visual examination
Identification ^a		
IR	Complies to reference standard spectrum	AD-TM-R314585-TAB-FTIR-01
Assay	(b) (4) of label claim	AD-TM-R314585-TAB-HPLC-04
Chromatographic Purity		
Any Unspecified Degradation Product	Not more than (b) (4)	AD-TM-R314585-TAB-HPLC-04
Total Degradation Products	Not more than (b) (4)	AD-TM-R314585-TAB-HPLC-04
Uniformity of Dosage Units ^a	Conforms to USP <905> Uniformity of dosage units – content uniformity	AD-TM-R314585-TAB-HPLC-05
Dissolution	Q is (b) (4) at 45 minutes	AD-TM-R314585-TAB-DISS-04

^a This test is conducted for initial release only.

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/s/

TIEN MIEN CHEN
03/28/2011

PATRICK J MARROUM
03/28/2011

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 202-022	Submission Date: July 23, 2010
Brand Name	To be determined
Generic Name	Rilpivirine
Reviewers	Stanley Au, Pharm.D., BCPS Ruben Ayala, Pharm.D.
Pharmacometrics Reviewer	Jeff Florian, Ph.D.
Pharmacometrics Team Leader	Pravin Jadhav, Ph.D.
Clinical Pharmacology Team Leader	Sarah Robertson, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products (DAVP)
Applicant	Tibotec, Inc.
Formulation; strength(s) to-be-marketed	Rilpivirine oral tablets, 25 mg
Proposed Indication	Treatment of HIV-1 infection in treatment naïve adults in combination with other antiretroviral medications
Review Type	505 (b)(1) New Drug Application, standard review

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1 Executive Summary

Rilpivirine (also known as TMC278) is a non nucleoside reverse transcriptase inhibitor (NNRTI). The other NNRTIs that are currently approved for the treatment of HIV-1 infection are delavirdine, efavirenz, nevirapine and etravirine. The proposed indication is the treatment of HIV-1 infection in treatment naive patients in combination with other antiretroviral medications. The proposed dosage regimen is 25 mg once daily administered orally with a meal.

Based on the potential for QT prolongation at rilpivirine 75 mg/day and 300 mg/day, rilpivirine 25 mg once daily, which demonstrated favorable efficacy and safety results in the Phase 2b trial, was evaluated in the Phase 3 trials instead of rilpivirine 75 mg once daily as originally proposed. Two Phase 3 trials (TMC278-C209 and TMC-C215) were conducted to provide the necessary efficacy and supportive safety information in support of the New Drug Application (NDA). The primary endpoint for both trials was to establish the noninferiority of rilpivirine to efavirenz, with both NNRTIs administered in combination with nucleoside or nucleotide reverse transcriptase inhibitors, after 48 weeks of treatment as measured through the proportion of HIV-1 infected subjects that achieved a HIV-1 RNA viral load < 50 copies/mL. Both trials evaluated a rilpivirine dosage regimen of 25 mg once daily administered with a meal.

The clinical pharmacology studies or trials that were submitted in support of the NDA included eight in vitro studies, three trials to evaluate the effect of rilpivirine on the QT interval (thorough QT trials), one food effect trial, one hepatic impairment trial evaluating mild and moderate hepatic impairment, one mass balance trial, and 16 drug-drug interaction trials in healthy subjects. The majority of the drug-drug interaction trials and the food effect trial were conducted at 150 mg once daily and 75 mg once daily, respectively, and extrapolation of the results to 25 mg once daily dosing was required. In addition, a rilpivirine population pharmacokinetic model was developed using pharmacokinetic data from the Phase 3 trials and from one of the thorough QT trials (C152).

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the information in this NDA and the information provided supports the approval of the application. However, an issue was identified during the review in evaluating the impact of baseline viral load on virologic failure in the Phase 3 trials. To address this issue, the proposed rilpivirine label states that more HIV-1 infected subjects with baseline HIV-1 viral load >100,000 copies/mL experienced virologic failure compared to HIV-1 infected subjects with baseline HIV-1 viral load <100,000 copies/mL. The proposed label also states that a higher overall rate of treatment resistance and cross resistance to NNRTIs was observed for rilpivirine compared to efavirenz.

1.2 Postmarketing Commitments or Requirements

The Clinical Pharmacology review team proposes to conduct a trial evaluating the

inhibitory effects of rilpivirine on digoxin, a P-gp substrate as a postmarketing requirement. As discussed in section 1.3.2, the rilpivirine review team determined that a postmarketing commitment or postmarketing requirement to further evaluate rilpivirine's renal safety was not necessary.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

1.3.1 Exposure-response (efficacy) analysis

A detailed discussion of the rilpivirine exposure-response analysis for efficacy in treatment naïve HIV-1 infected subjects is provided in the Pharmacometrics review (section 4). The analysis was based on a dataset consisting of 645 subjects enrolled in the two Phase 3 trials. Subjects with < 90% self reported adherence were removed from the analysis. The exclusion of subjects with less than a 90% self reported compliance rate did not substantially alter the exposure-response relationship for rilpivirine compared to the initial analysis that included subjects with < 90% self reported adherence. Based on the analysis, an exposure-response relationship for rilpivirine with a dosage regimen of 25 mg once daily was observed for the predicted $AUC_{(0-\tau)}$ and C_{0h} population PK parameters. When the inhibitory quotient (IQ) was incorporated into the analysis, a more consistent exposure response trend was observed. In general, a lower virologic response (the percentage of subjects achieving HIV-1 RNA viral load <50 copies/mL) was observed in subjects with lower rilpivirine exposure.

The exposure-response relationship for HIV-1 infected subjects with baseline HIV-1 viral load <100,000 copies/mL compared to HIV-1 infected subjects with baseline HIV-1 viral load $\geq 100,000$ copies/mL was also evaluated. Subjects with baseline viral load $\geq 100,000$ copies/mL were less likely to achieve virologic response with a dosage regimen of rilpivirine 25 mg once daily compared to subjects with baseline viral load < 100,000 copies/mL.

1.3.2 Exposure-safety analyses

The exposure-safety analyses evaluated whether there was a potential relationship between predicted rilpivirine $AUC_{(0-\tau)}$ or trough (C_{0h}) and all adverse events in selected system organ classes (psychiatric, skin, hepatobiliary). In addition, specific adverse events that could be interpreted as “dizziness” were also evaluated. Exposure-safety analyses were also conducted for changes in bilirubin and changes in renal function. An exposure-safety analysis to evaluate whether there are any potential C_{max} related adverse events was not conducted because of the uncertainty in the C_{max} predictions generated through the rilpivirine population PK model. For all analyses, no relationship was observed between predicted $AUC_{(0-\tau)}$ or C_{0h} and the adverse event of interest.

An evaluation of the changes in renal function was conducted subsequent to the observation that there was a trend of increasing serum creatinine over time with rilpivirine versus the efavirenz arm. A renal consult from the Division of Cardiovascular and Renal Products concluded that while inhibition of tubular secretion by rilpivirine is a

plausible explanation, the possibility that rilpivirine may adversely affect renal function can not be excluded. Follow up analyses were conducted by the Pharmacometrics reviewer evaluating the creatinine clearance data from the Phase 3 trials. In subjects with decreased renal function, smaller changes in creatinine clearance were observed. Based on this information, the rilpivirine review team determined that a postmarketing commitment or postmarketing requirement to further evaluate rilpivirine's renal safety was not necessary.

An analysis of the impact of rilpivirine exposure on the QT interval indicates that rilpivirine 25 mg once daily does not affect the QT interval. The exposure-response analysis demonstrated a significant linear relationship between rilpivirine concentration and the baseline-and placebo-adjusted change in QTcF ($\Delta\Delta\text{QTcF}$). The predicted $\Delta\Delta\text{QTcF}$ at the 25 mg/day, 75 mg/day and 300 mg/day rilpivirine C_{max} concentration was 4 ms (90% CI: 2-6), 9 ms (90% CI: 7-11) and 23 ms (90% CI: 18-27), respectively. An analysis was also conducted to analyze a potential worst case scenario evaluating two factors: a) the highest increase in rilpivirine exposure from the drug-drug interaction trials, and b) the highest increase in rilpivirine exposure from the hepatic impairment trial. Based on these criteria, the change in rilpivirine exposure in mild hepatic impairment subjects receiving darunavir/ritonavir in combination with rilpivirine was evaluated. It was concluded based on the results of these analyses that it is not necessary to include additional precautionary statements in the proposed rilpivirine prescribing information (label) beyond the current statement that caution should be used when rilpivirine is administered with medications that have an established Torsades de Pontes risk.

1.3.3 Pharmacokinetics

Information on the pharmacokinetics of rilpivirine in healthy subjects is displayed in Table 1. The results of the population PK analysis for the Phase 3 trials are displayed in section 2.

Table 1-Rilpivirine pharmacokinetic parameters in healthy subjects with multiple dosing of rilpivirine dosage regimens ranging from 25 mg once daily to 150 mg once daily from the TMC278-C103 trial

Parameter	Mean \pm SD; t_{max} : Median (Range)			
	TMC278 25 mg q.d.	TMC278 50 mg q.d.	TMC278 100 mg q.d.	TMC278 150 mg q.d.
Day 1				
N	12	12	12	12
t_{max} , h	4.0 (2.0 - 6.0)	4.0 (3.0 - 4.0)	4.0 (2.0 - 6.7)	4.0 (3.0 - 6.0)
C_{max} , ng/mL	90.08 \pm 44.28	138.2 \pm 63.10	397.6 \pm 147.3	523.8 \pm 136.9
$\text{AUC}_{0-24\text{h}}$, ng.h/mL	1072 \pm 585.6	1551 \pm 596.0	4464 \pm 1520	5608 \pm 1902
Day 14				
N	12	12	11	11
t_{max} , h	4.0 (2.0 - 4.0)	4.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	4.0 (3.0 - 6.0)
$C_{0\text{h}}$, ng/mL	89.85 \pm 38.07	157.9 \pm 52.23	347.8 \pm 148.7	504.9 \pm 174.6
C_{min} , ng/mL	66.85 \pm 29.53	115.7 \pm 49.30	249.5 \pm 90.51	362.0 \pm 130.9
C_{max} , ng/mL	203.8 \pm 75.81	298.6 \pm 98.05	685.5 \pm 202.4	1019 \pm 222.0
$C_{\text{ss,av}}$, ng/mL	107.8 \pm 36.20	172.5 \pm 51.48	386.6 \pm 118.6	565.9 \pm 133.1
$\text{AUC}_{0-24\text{h}}$, ng.h/mL	2589 \pm 868.8	4139 \pm 1236	9278 \pm 2846	13581 \pm 3195
$t_{1/2, \text{term}}$, h	50.92 \pm 19.56	48.75 \pm 16.34	46.07 \pm 15.44	44.83 \pm 12.31
FI, %	128.5 \pm 41.71	107.8 \pm 45.20	113.7 \pm 35.59	121.7 \pm 46.55
Accum. ratio	3.020 \pm 1.966	2.880 \pm 0.7982	2.071 \pm 0.7491	2.503 \pm 0.7211

$C_{\text{ss,av}}$ = average steady-state plasma concentration (area under the plasma concentration-time curve/dosing interval at steady state); FI = fluctuation index; N = maximum number of subjects with data.

For the Phase 3 or to-be-marketed tablets, the rilpivirine exposure at 25 mg once daily in HIV-1 infected subjects was lower (the maximum difference in rilpivirine exposure was 50%) compared to healthy subjects. The differences in exposure are not clinically significant and the conclusions based on the results of trials conducted in healthy subjects can be applied to HIV-1 infected subjects.

1.3.4 **Absorption**

The absolute bioavailability of rilpivirine was not determined because of the lack of an available intravenous formulation. Rilpivirine is poorly soluble in aqueous media.

The absorption of rilpivirine is pH-dependent. Medications that alter gastric pH, such as H₂ antagonists (e.g. famotidine) and proton pump inhibitors (PPIs) [e.g. omeprazole] were demonstrated in the human drug-drug interaction trials to decrease rilpivirine exposure when coadministered or combined with rilpivirine.

Based on the in vitro information, rilpivirine is not significantly transported by P-gp under steady state conditions. The efflux ratios did not exceed 2 under steady state conditions.

Rilpivirine exposure is increased in the presence of food. The food effect trial was conducted with a single 75 mg dose of rilpivirine, however rilpivirine exposure is dose proportional from 25 mg to 150 mg, and the results are expected to be applicable to 25 mg once daily dosing. The 75 mg tablets that were administered in the food effect trial are proportional in terms of the active and inactive ingredients to the 25 mg tablets that were administered in the Phase 3 trials. The mean rilpivirine C_{max} and AUC_(0-∞) values were decreased by 46% and 41%, respectively, under fasted conditions in comparison to rilpivirine administered with a standard meal. The differences in rilpivirine exposure when comparing high fat meals to standard meals are not clinically significant. The proposed rilpivirine label recommends administration of rilpivirine with meals. This recommendation is acceptable.

1.3.5 **Distribution**

The protein binding of rilpivirine is >99% in human and animal species and is concentration independent. A greater percentage of rilpivirine is bound to albumin compared to α1-acid glycoprotein. The apparent volume of distribution from the central compartment that was derived from the population PK analysis was approximately 152 liters.

1.3.6 **Metabolism**

A significant portion of a rilpivirine dose is metabolized. In plasma, unchanged rilpivirine accounted for the majority of the total radioactivity. Based on the results of the mass balance trial, in the feces, the mean percentage of unchanged rilpivirine was 25.5% of the dose and in the urine unchanged rilpivirine was present in trace amounts. The major metabolic reaction for rilpivirine is oxidation to form metabolite 42. The in

vitro study results indicate that CYP 3A is the primary cytochrome P450 enzyme system responsible for rilpivirine's metabolism with CYP 2C19 also potentially contributing to rilpivirine's metabolism.

1.3.7 Excretion

After 336 hours, an average of $91 \pm 5\%$ of a single 150 mg rilpivirine (^{14}C labeled and unlabeled) dose was recovered based on total radioactivity. On average, based on total radioactivity, in the feces, $85 \pm 4\%$ was recovered after 336 hours, and in the urine, $6 \pm 2\%$ was recovered after 168 hours.

1.3.8 Intrinsic factors

A hepatic impairment trial was conducted evaluating mild and moderate hepatic impairment. The effect of severe hepatic impairment on rilpivirine exposure has not been evaluated. With multiple dosing, the greatest magnitude of change for C_{\max} and $\text{AUC}_{(0-24\text{h})}$ in comparison to healthy control subjects occurred with mild hepatic impairment subjects and was higher by 27%, and 47%, respectively. For subjects with mild or moderate hepatic impairment, no dosage adjustment is necessary.

Covariates were also evaluated as part of the population pharmacokinetic analysis. Body weight, race, gender, coinfection with Hepatitis B or Hepatitis C, or age (range: 18-75 years old) did not influence rilpivirine exposure. It should be noted that for age, definitive conclusions could not be made regarding the influence of age for subjects greater than 65 years old because there were only three subjects older than 65 years old.

A renal impairment trial was not conducted as part of the NDA submission. The Clinical Pharmacology and Pharmacometrics reviewers analyzed the potential impact of renal impairment based on the information from the rilpivirine population PK analysis. There were minimal differences in rilpivirine exposure when comparing HIV-1 infected subjects with mild renal impairment to HIV-1 infected subjects with normal renal function. No definitive conclusions could be made regarding the impact of moderate renal impairment because of the small number of available subjects (seven in total). There were no subjects with severe renal impairment that were included as part of the population PK analysis.

1.3.9 Extrinsic factors

Results from the in vitro studies and clinical trials

Rilpivirine is primarily CYP 3A metabolized. In addition, based on the results of the in vitro studies, the applicant conducted human drug-drug interaction trials to further evaluate the potential for rilpivirine to induce or inhibit CYP 2C19 or CYP 3A or to inhibit CYP 2E1. Therefore, the majority of the human drug-drug interaction trials that were conducted evaluated the following: a) the effects of CYP 3A inhibitors or CYP 3A inducers on rilpivirine exposure, b) the effect of rilpivirine CYP 3A or CYP 2C19 inhibition or induction on medications coadministered or combined with rilpivirine, or c) rilpivirine CYP 2E1 inhibition effects.

The recommendations in Section 7 of the proposed label for managing clinically relevant drug-drug interactions are displayed in section 2 (see 2.4.2.8). The proposed medications that are contraindicated with rilpivirine are potential CYP 3A inducers of rilpivirine metabolism (anticonvulsants, antimycobacterials [rifampin, rifabutin or rifapentine], dexamethasone, St. John's wort), and proton pump inhibitors (e.g. omeprazole) than can alter gastric pH and decrease rilpivirine exposure. The rationale for contraindicating use of these medications with rilpivirine is the potential for decreased rilpivirine exposure that could result in the development of resistance to rilpivirine or cross resistance to other NNRTIs. The proposed label also states that other NNRTIs that are in the same antiretroviral therapeutic class should not be coadministered with rilpivirine. As a precaution because of potential rilpivirine CYP 3A induction effects, increased monitoring is recommended with antifungals in the azole class and with methadone. Alternative antibacterial medications other than use of macrolides are also recommended because of potential inhibition of rilpivirine CYP 3A metabolism. For medications that than can alter gastric pH and decrease rilpivirine exposure (H_2 receptor antagonists and antacids) or for didanosine that must be administered on an empty stomach (the didanosine pediatric powder for oral solution also contains antacids), instructions for spacing out administration of these medications from rilpivirine were also specified.

For all other medications that were evaluated, there are no specific dose adjustments recommended for either rilpivirine or medications coadministered or combined with rilpivirine for any of the drug-drug interactions listed in section 7 of the proposed label.

Based on the in vitro results with a 25 mg once daily dosage regimen, rilpivirine may act as a P-gp inhibitor based on the IC_{50} value for P-gp inhibition of $9.2 \mu M$. The calculated $[I]_1/IC_{50}$ value of 0.0005 was less than < 0.1 but the $[I]_2/IC_{50}$ value of 27 was greater than the threshold of 10. The $[I]_2/IC_{50}$ value represents the potential rilpivirine P-gp inhibitory effects in the gastrointestinal tract.

Physiologically-based pharmacokinetic modeling (PBPK) and simulation

A potential safety issue that was identified with rilpivirine 25 mg once daily dosing is potentially greater ketoconazole CYP 3A inhibitory effects than was observed with 150 mg once daily dosing. This issue was further evaluated because of the potential for QT prolongation with rilpivirine exposures at 75 mg once daily dosing and higher. Physiologically-based pharmacokinetic modeling (PBPK) and simulation was used to predict the effects of ketoconazole on rilpivirine exposure.

The results of the simulations indicate that no dose adjustment is necessary for rilpivirine with 25 mg once daily dosing when combined with a strong CYP 3A inhibitor such as ketoconazole. Under the worst case scenario that was simulated of CYP 3A inhibition using 200 mg twice daily of ketoconazole, the increases in rilpivirine C_{max} and $AUC_{(0-24h)}$ are similar to the increase in rilpivirine exposure that was observed in the rilpivirine-darunavir/ritonavir drug-drug interaction trial. In general, the results of the drug-drug interaction trials that were conducted at rilpivirine 75 mg once daily or 150 mg once daily are expected to be applicable to a rilpivirine dosage regimen of 25 mg once daily.

2 Question based review (QBR)

2.1 General Attributes of the Drug

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

Rilpivirine (also known as TMC278) is a non nucleoside reverse transcriptase inhibitor (NNRTI). For the salt form, rilpivirine's chemical name is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2 pyrimidinyl]amino]benzonitrile monohydrochloride. The molecular formula for the salt form is $C_{22}H_{18}N_6 \cdot HCl$ and the molecular weight is 402.88 (366.42 + 36.46). Table 1 lists the active and inactive ingredients for the proposed to-be-marketed 25 mg rilpivirine tablets.

Table 1-Active and inactive ingredients for the proposed to-be-marketed 25 mg rilpivirine tablets

Component	Quality Standard ^a	Function	Amount	
			(mg/tablet)	(% w/w)
(b) (4)				(b) (4)
Povidone (K30)	USP/Ph.Eur.			
Polysorbate 20	USP/Ph.Eur.			
(b) (4)	NF/Ph.Eur.			
TMC278	CS	Active	27.50 ^c	25.00
Lactose Monohydrate	NF/Ph.Eur.			(b) (4)
Croscarmellose Sodium	NF/Ph.Eur.			
(b) (4)				
Silicified Microcrystalline Cellulose	NF			
Croscarmellose Sodium	NF/Ph.Eur.			
Magnesium Stearate	NF/Ph.Eur.			
(b) (4)	-			
	CS			
	USP/Ph.Eur.			
Total Tablet Weight:	NA			

^a Where multiple compendia are listed, the compendium that is applied is specific to the applicable region of the submission. (b) (4)

^c Quantity of TMC278 equivalent to the labeled amount TMC278 free base. (b) (4)

CS = Company Standard
NA = Not Applicable

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

Rilpivirine's mechanism of action is through non-competitive inhibition of HIV-1 reverse transcriptase (RT). The proposed indication is the treatment of HIV-1 infection in treatment naive patients in combination with other antiretroviral medications.

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

The proposed dosage regimen is 25 mg once daily administered orally with a meal.

2.2 General Clinical Pharmacology

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

Two Phase 3 trials (TMC278-C209 and TMC-C215) were conducted to provide the necessary efficacy information and supportive safety information in support of the New Drug Application (NDA). Both trials evaluated a rilpivirine dosage regimen of 25 mg once daily administered with a meal. In the TMC278-C209 trial, all subjects receiving either rilpivirine 25 mg once daily or efavirenz 600 mg once daily also received a background regimen of tenofovir and emtricitabine. In TMC278-C215 trial, all subjects receiving either rilpivirine 25 mg once daily or efavirenz 600 mg once daily also received two investigator selected nucleoside/nucleotide reverse transcriptase inhibitors: a) abacavir (ABC)/lamivudine (3TC), b) zidovudine (AZT)/3TC, or c) or tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC).

The primary endpoint for both trials was to establish the noninferiority of rilpivirine 25 mg once daily to efavirenz 600 mg once daily after 48 weeks of treatment as measured through the proportion of HIV-1 infected subjects that achieve a HIV-1 RNA viral load < 50 copies/mL. Information regarding the results of the Phase 3 trials is provided in the rilpivirine clinical review and the exposure response analysis is discussed in 2.2.4.1.

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 endpoint was plasma HIV-1 RNA viral load < 50 copies/mL. The HIV-1 viral load has been demonstrated to be a valid surrogate to establish the efficacy of antiretroviral medications for the treatment of HIV-1 infection.

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?

The relevant analytes were measured in plasma using validated LC/MS/MS or LC/UV analytical methods. The analytes that were measured were rilpivirine and medications that were administered in combination with rilpivirine in the drug-drug interaction trials.

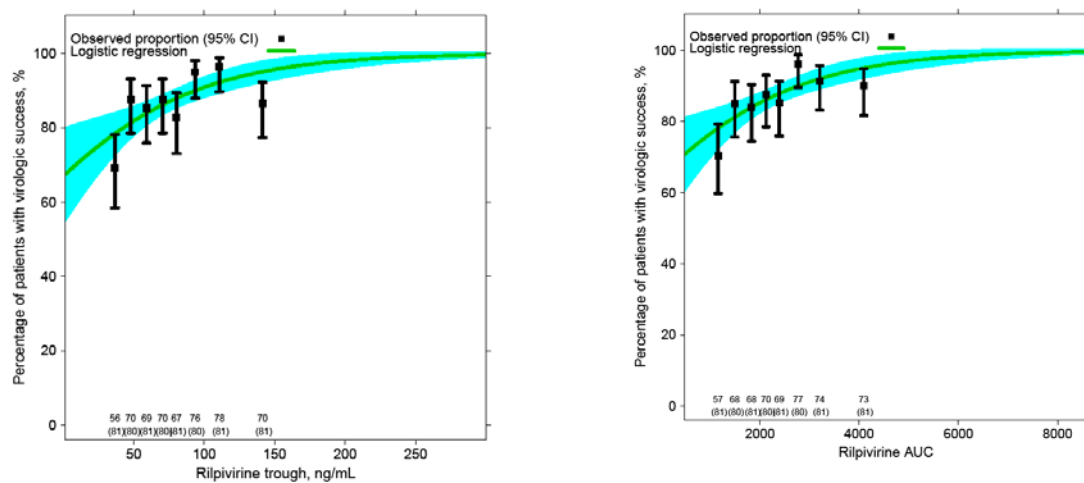
2.2.4 Exposure-response

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

An exposure response relationship for rilpivirine with a dosage regimen of 25 mg once

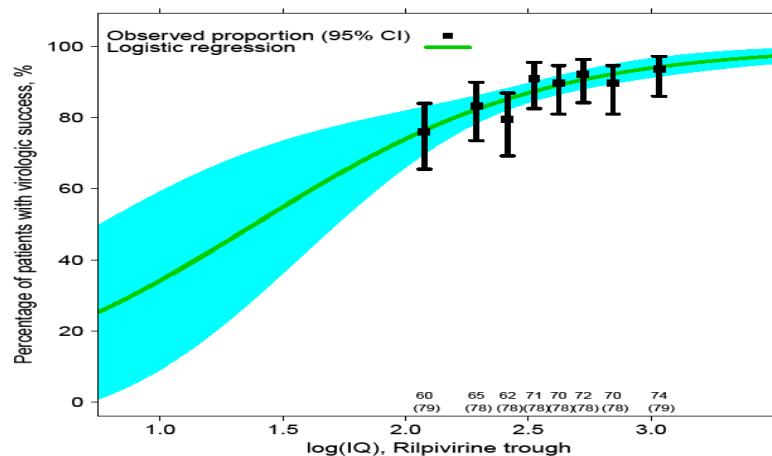
daily was observed (Figure 1 and Figure 2). The dataset consisted of 645 subjects enrolled in the two Phase 3 trials and excluded subjects with < 90% self reported adherence were removed from the analysis. The exclusion of subjects with less than a 90% self reported compliance rate did not substantially alter the exposure response relationship for rilpivirine compared to the initial analysis that included subjects with < 90% self reported adherence. When subject specific viral phenotypic IC_{50} were incorporated into the analysis, a more consistent exposure response trend was observed. In general, a lower virologic response (the percentage of subjects achieving HIV-1 RNA viral load <50 copies/mL) was observed in subjects with lower rilpivirine exposure.

Figure 1-Comparison of the percentage of treatment naïve subjects achieving HIV-1 RNA viral load <50 copies/mL versus rilpivirine C_{0h} or $AUC_{(0-\tau)}$ from the TMC278-C209 and TMC278-C215 trials



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Figure 2-Comparison of the percentage of treatment naïve subjects achieving HIV-1 RNA viral load <50 copies/mL versus rilpivirine log IQ from the TMC278-C209 and TMC278-C215 trials



The population pharmacokinetic (PK) analysis was generated using a model that incorporated pharmacokinetic data from the Phase 3 trials and from one of the thorough QT trials (C152). A detailed discussion of the population pharmacokinetic analysis is provided in the Pharmacometrics review (see section 4.2). Table 2 below displays the applicant's predicted $AUC_{(0-\tau)}$ and C_{0h} population PK parameters that were calculated by combining all the individual predicted $AUC_{(0-\tau)}$ and trough (C_{0h}) concentrations from 679 subjects for rilpivirine 25 mg once daily that was available up to Week 48 for subjects enrolled in the two Phase 3 trials. The apparent clearance (Cl/F) and the apparent volume of distribution (Vd/F) from the central compartment that was derived from the population PK analysis were approximately 11.8 liters/hour and 152 liters, respectively.

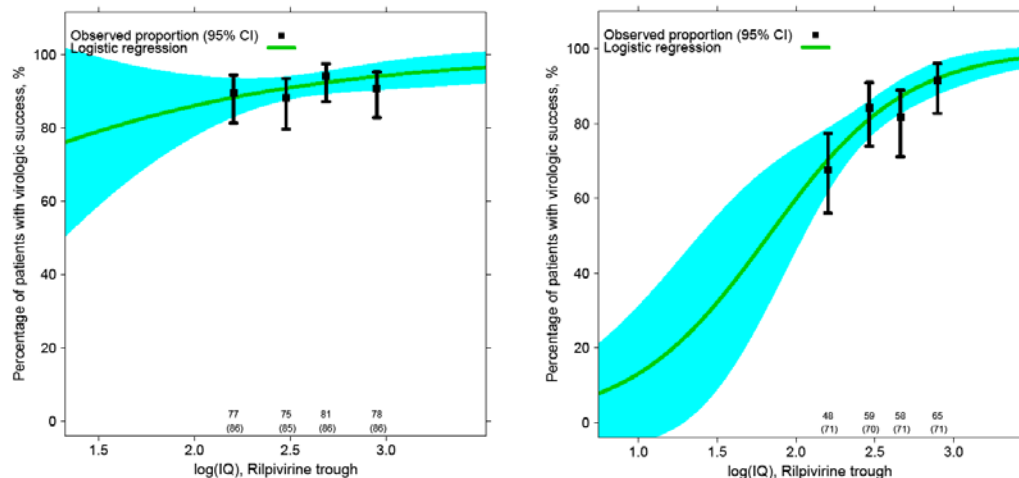
Table 2-Predicted rilpivirine population pharmacokinetic parameters (based on pharmacokinetic data through Week 48 from the TMC278-C209 and TMC278-C215 trials)

Parameter	Rilpivirine 25 mg once daily N = 679
AUC_{24h} (ng•h/mL)	
Mean \pm Standard Deviation	2397 \pm 1032
Median (Range)	2204 (482 - 8601)
C_{0h} (ng/mL)	
Mean \pm Standard Deviation	80 \pm 37
Median (Range)	74 (1 - 300)

Using data from the two Phase 3 trials (TMC278-C209 and TMC-C215 trials), the analysis of rilpivirine's exposure response relationship in treatment naïve subjects involved comparing virologic response at Week 48 (the percentage of subjects achieving HIV-1 RNA viral load <50 copies/mL) and either rilpivirine predicted trough (C_{0h}) concentrations or predicted $AUC_{(0-\tau)}$ values or the inhibitory quotient (IQ). The IQ is defined as the ratio of drug exposure (C_{0h}) to a HIV-1 infected subject's specific viral phenotypic IC_{50} (a measurement of the ability of rilpivirine to inhibit HIV-1 virus). C_{max} was not evaluated because of the uncertainty in the C_{max} predictions generated through the rilpivirine population PK model (shrinkage to the population value of C_{max} was observed).

Subjects with baseline viral load $\geq 100,000$ copies/mL were less likely to achieve virologic response with a rilpivirine dosage regimen of 25 mg once daily compared to subjects with baseline viral load < 100,000 copies/mL (Figure 3). For these two groups of HIV-1 infected subjects, Table 2 compares the percentage of treatment naïve subjects achieving HIV-1 RNA viral load <50 copies/mL stratified by quartiles. Please see the response for 2.2.4.4 for information regarding the proposed labeling recommendation to address this issue. In addition, the analysis evaluating the impact of baseline viral load on virologic failure is discussed in the Pharmacometrics review.

Figure 3-Comparison of the percentage of treatment naïve subjects achieving HIV-1 RNA viral load <50 copies/mL versus log IQ for subjects with baseline viral load < 100,000 copies/mL (left) and baseline viral load ≥ 100,000 copies/mL (right) from the TMC278-C209 and TMC278-C215 trials



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Table 3-Comparison of the percentage of treatment naïve subjects achieving HIV-1 RNA viral load <50 copies/mL stratified by quartiles for subjects with baseline viral load < 100,000 copies/mL (left) and baseline viral load ≥ 100,000 copies/mL (right) from the TMC278-C209 and TMC278-C215 trials (excluding subjects with less than a 90% self reported compliance rate)

Baseline viral load <100,000 copies/mL				Baseline viral load ≥100,000 copies/mL			
	n	Median C _{0h}	% subjects with virologic success		n	Median C _{0h}	% subjects with virologic success
Q1	89	43	87	Q1	73	42	68
Q2	88	69	91	Q2	72	62	81
Q3	88	90	92	Q3	73	83	86
Q4	89	123	94	Q4	73	116	88

Additional information regarding the rilpivirine exposure-response analysis is located in the Pharmacometrics review (section 4).

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

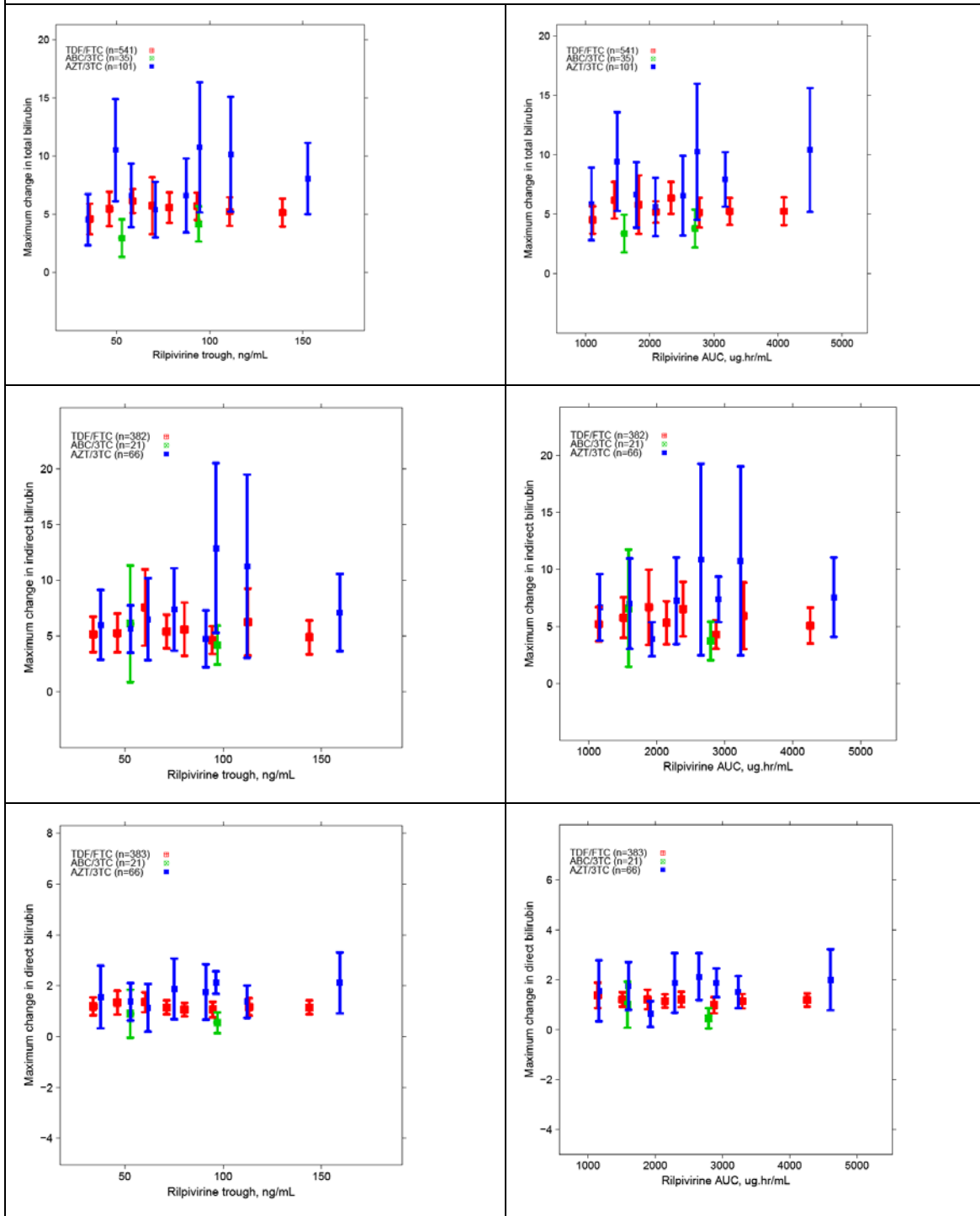
For all analyses, no relationship was observed between the predicted AUC_(0-τ) or trough (C_{0h}) and the adverse event of interest. The exposure-safety analyses evaluated whether

there was a potential relationship between the predicted rilpivirine $AUC_{(0-\tau)}$ or C_{0h} and all adverse events in selected system organ classes (psychiatric, skin, hepatobiliary). In addition, specific adverse events that could be interpreted as “dizziness” were also evaluated.

An exposure-safety analysis to evaluate whether there are any potential C_{max} related adverse events was not conducted because of the uncertainty in the C_{max} predictions generated through the rilpivirine population PK model.

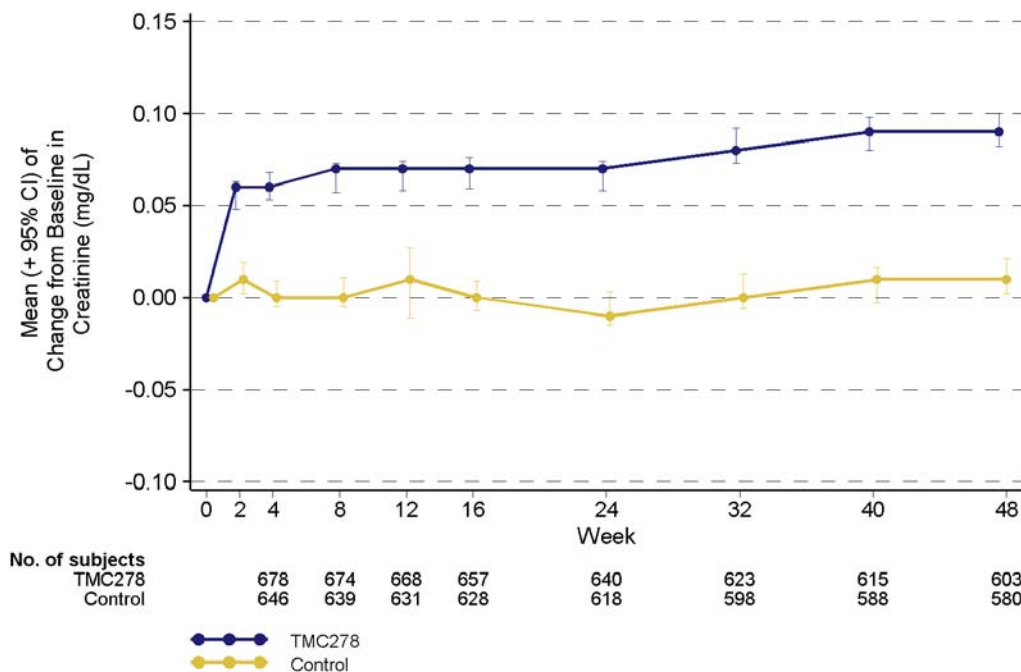
Exposure safety analyses were also conducted for changes in bilirubin and changes in renal function. There was no relationship observed between direct, indirect and total bilirubin and rilpivirine predicted $AUC_{(0-\tau)}$ or trough (C_{0h}) when sorted by the background antiretroviral regimen, as illustrated in Figure 4. An evaluation of the changes in bilirubin was conducted subsequent to the observation that in the C209 and C215 trials that there was more grade 1 through grade 3 hyperbilirubinemia events that were attributed to indirect bilirubin for the rilpivirine arm compared to the efavirenz arm.

Figure 4-Comparison of maximum changes in total (top), indirect (middle), and direct (bottom) bilirubin versus rilpivirine exposure: trough [C_{0h}] concentrations [left]; and $AUC_{(0-\tau)}$ [right]) sorted according to the background antiretroviral regimen.



An evaluation of the changes in renal function was conducted subsequent to the observation that there was a trend of increasing serum creatinine over time with rilpivirine versus the efavirenz arm as illustrated in Figure 5.

Figure 5-Mean change in creatinine over time (pooled analysis of the TMC278-C209 and TMC278-C215 trials)



In the TMC278-C215 trial, cystatin C was also measured because unlike creatinine, cystatin C is filtered but does not undergo renal tubular secretion. The applicant's interpretation of the analysis of the changes in cystatin C over time is that the changes in creatinine observed with rilpivirine administration may be due to an alternative mechanism (e.g. inhibition of tubular secretion).

A renal consult from the Division of Cardiovascular and Renal Products concluded that while inhibition of tubular secretion by rilpivirine is a plausible explanation, the possibility that rilpivirine may adversely affect renal function can not be excluded. Follow up analyses were conducted evaluating the creatinine clearance data from the Phase 3 trials. The percentage of subjects with two or more creatinine clearance calculations that indicated a change in renal function category (normal to mild renal impairment or mild to moderate renal impairment) was calculated. There were more subjects that transitioned from normal to mild renal impairment than from mild to moderate renal impairment. Additionally, the highest mean maximum change in creatinine clearance was observed in subjects with normal renal function and the lowest mean maximum change in creatinine clearance was observed in subjects with moderate renal impairment. Based on this information, the rilpivirine review team determined that a postmarketing commitment or postmarketing requirement to further evaluate rilpivirine's renal safety was not necessary. The Pharmacometrics and Clinical reviews provide further information regarding the renal safety analysis.

An exposure safety analysis evaluated the maximum change in eGFR that was calculated for creatinine and cystatin C and sorted by the background antiretroviral regimen. There were no clinically significant differences observed between the maximum change in eGFR for either creatinine or cystatin C and predicted rilpivirine AUC_(0-τ) or trough (C_{0h}) when sorted by the background antiretroviral regimen (Figure 6 and Figure 7).

Figure 6-Maximum change in eGFR based on serum creatinine versus rilpivirine exposure: trough [C_{0h}] concentrations [left]; and AUC_(0-τ) [right]) sorted according to the background antiretroviral regimen

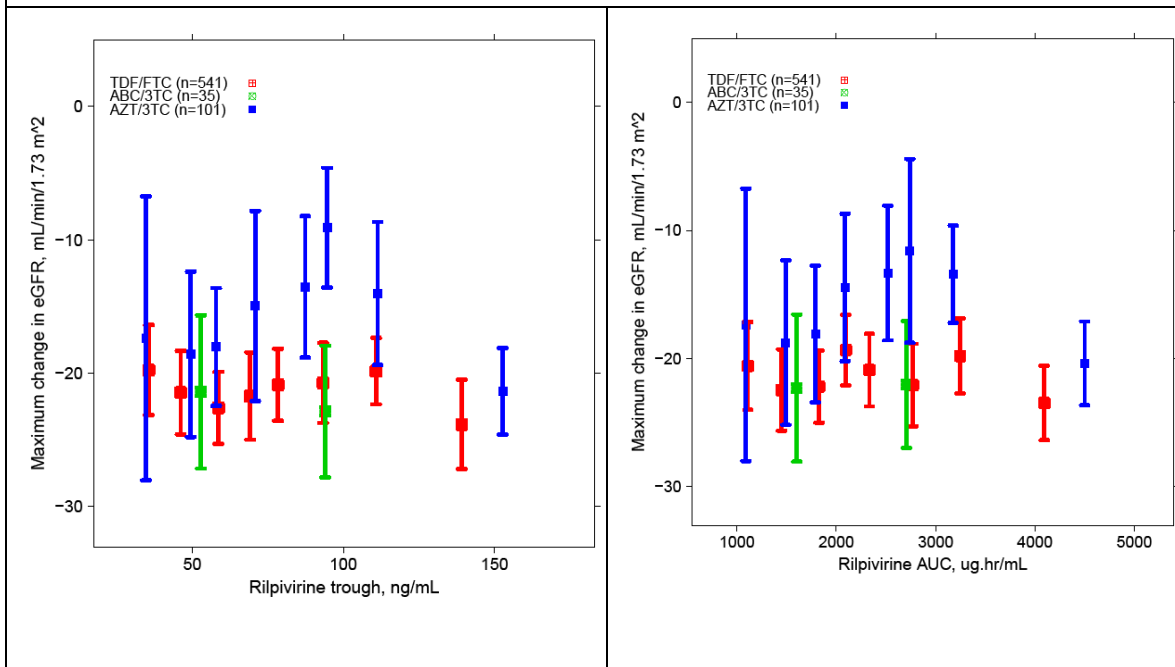
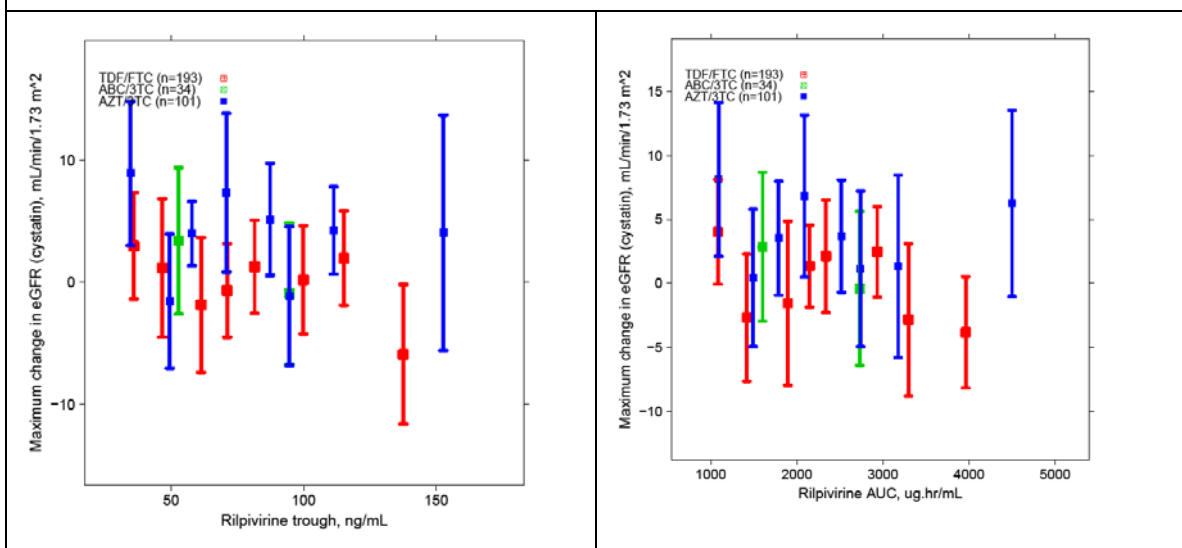


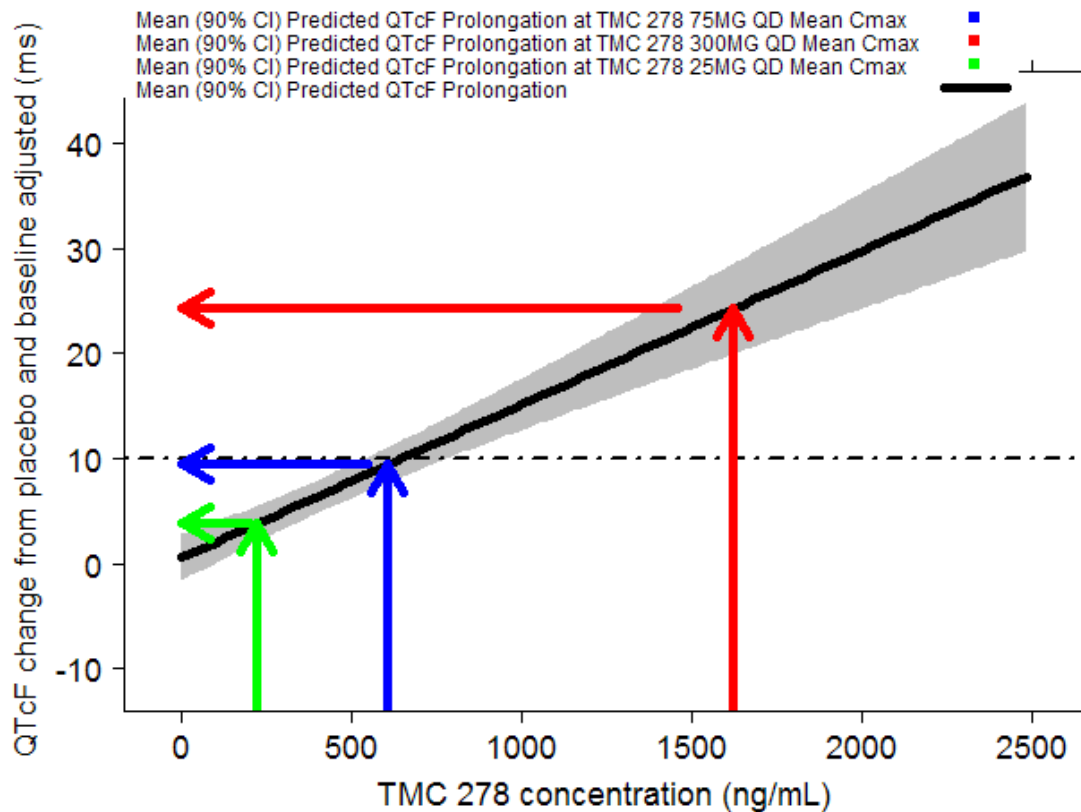
Figure 7-Maximum change in eGFR based on cystatin C versus rilpivirine exposure: trough [C_{0h}] concentrations [left]; and $AUC_{(0-\tau)}$ [right]) sorted according to the background antiretroviral regimen



2.2.4.3 Does this drug prolong the QT or QTc interval?

Based on the results of the analyses, it was determined that is not necessary to include additional precautionary statements in the proposed rilpivirine prescribing information (label) beyond the current statement that caution should be used when rilpivirine is administered with medications that have an established Torsades de Pontes risk. The exposure-response analysis demonstrated a significant linear relationship between rilpivirine concentration and the baseline-and placebo-adjusted change in QTcF ($\Delta\Delta\text{QTcF}$). The predicted $\Delta\Delta\text{QTcF}$ at the 25mg/day, 75 mg/day and 300 mg/day rilpivirine C_{max} concentration was 4 ms (90% CI: 2-6), 9 ms (90% CI: 7-11) and 23 ms (90% CI: 18-27), respectively. The supratherapeutic rilpivirine doses of 75 mg and 300 mg produced geometric mean C_{max} values of 605 ng/mL and 1620 ng/mL, respectively, that were 2.8 and 7.4 times higher than the geometric mean C_{max} of 220 ng/mL for 25 mg once daily based on data from TMC278- C131 and TMC278-C151 trials. These concentrations are above those for the predicted worst case scenario of patients with hepatic impairment on concomitant medication that is a CYP3A inhibitor (e.g. darunavir/ritonavir). At the exposure achieved with rilpivirine 25 mg once daily, there is no discernable effect on the QT interval based on data from TMC278-C151.

Figure 8-Combined analysis of the mean and 90% confidence intervals for predicted $\Delta\Delta\text{QTcF}$ using geometric mean C_{max} for rilpivirine 25 mg, 75 mg, and 300 mg once daily



Additional information regarding the ability of rilpivirine to prolong the QT interval is available in the Pharmacometrics review (see section 4) and the consult from the Interdisciplinary Review Team for QT trials.

2.2.4.4 Is 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?

The dose and dosing regimen selected by the applicant is consistent with the known dose-concentration-response relationship. In HIV-1 infected subjects receiving rilpivirine 25 mg once daily, a exposure-response relationship approaching a plateau was identified for treatment naïve subjects with baseline HIV-1 viral load <100,000 copies/mL, and no additional efficacy benefit would be expected by increasing the rilpivirine dose while the higher rilpivirine exposure would potentially result in QT prolongation. In contrast, a steeper exposure-response relationship was identified for treatment naïve subjects with baseline viral load $\geq 100,000$ copies/mL. The higher rilpivirine exposure achieved with increasing the rilpivirine dose in these patients is expected to result in greater virologic response while also potentially increasing the risk of QT prolongation in a dose-

proportional manner. Because the potential benefit of increased efficacy is not outweighed by the risk of QT prolongation and other potential adverse events, the proposed rilpivirine dosage regimen of 25 mg once daily is appropriate for patients with baseline HIV-1 viral load $\geq 100,000$ or $< 100,000$ copies/mL. To address this issue, the proposed rilpivirine label states that more HIV-1 infected subjects with baseline HIV-1 viral load $> 100,000$ copies/mL experienced virologic failure compared to HIV-1 infected subjects with baseline HIV-1 viral load $< 100,000$ copies/mL. The proposed label also states that a higher overall rate of treatment resistance and cross resistance to NNRTIs was observed for rilpivirine compared to efavirenz.

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

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

In healthy subjects, dose proportionality was observed for rilpivirine C_{max} and $AUC_{(0-\tau)}$ for Day 1 and Day 14 with multiple dosing of rilpivirine dosage regimens ranging from 25 mg once daily to 150 mg once daily in the TMC278-C103 trial using tablets developed for use in the Phase 2b trial (Table 4). The rilpivirine pharmacokinetic parameters for Day 1 when the first dose is administered and on Day 14 with multiple dosing are displayed in Table 5. Using an elimination half life of 50.92 hours that was calculated for rilpivirine 25 mg once daily, steady state is anticipated to be achieved in approximately 15 days (seven half lives).

Table 4-Treatments administered in the TMC278-C103 trial

Panel	Treatment	Number of Subjects	Days	Dose	Volume
1	A	12	Days 1-14	25 mg q.d.	1 tablet containing 25 mg of TMC278
2	B	12	Days 1-14	50 mg q.d.	2 tablets each containing 25 mg of TMC278
3	C	12	Days 1-14	100 mg q.d.	1 tablet containing 100 mg of TMC278
4	D	12	Days 1-14	150 mg q.d.	1 tablet containing 100 mg of TMC278 and 2 tablets each containing 25 mg of TMC278

Table 5-Rilpivirine pharmacokinetic parameters in healthy subjects with multiple dosing of rilpivirine dosage regimens ranging from 25 mg once daily to 150 mg once daily from the TMC278-C103 trial

Parameter	Mean \pm SD; t_{max} : Median (Range)			
	TMC278 25 mg q.d.	TMC278 50 mg q.d.	TMC278 100 mg q.d.	TMC278 150 mg q.d.
Day 1				
N	12	12	12	12
t_{max} , h	4.0 (2.0 - 6.0)	4.0 (3.0 - 4.0)	4.0 (2.0 - 6.7)	4.0 (3.0 - 6.0)
C_{max} , ng/mL	90.08 \pm 44.28	138.2 \pm 63.10	397.6 \pm 147.3	523.8 \pm 136.9
AUC_{24h} , ng.h/mL	1072 \pm 585.6	1551 \pm 596.0	4464 \pm 1520	5608 \pm 1902
Day 14				
N	12	12	11	11
t_{max} , h	4.0 (2.0 - 4.0)	4.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	4.0 (3.0 - 6.0)
C_{0h} , ng/mL	89.85 \pm 38.07	157.9 \pm 52.23	347.8 \pm 148.7	504.9 \pm 174.6
C_{min} , ng/mL	66.85 \pm 29.53	115.7 \pm 49.30	249.5 \pm 90.51	362.0 \pm 130.9
C_{max} , ng/mL	203.8 \pm 75.81	298.6 \pm 98.05	685.5 \pm 202.4	1019 \pm 222.0
$C_{ss,av}$, ng/mL	107.8 \pm 36.20	172.5 \pm 51.48	386.6 \pm 118.6	565.9 \pm 133.1
AUC_{24h} , ng.h/mL	2589 \pm 868.8	4139 \pm 1236	9278 \pm 2846	13581 \pm 3195
$t_{1/2, term}$, h	50.92 \pm 19.56	48.75 \pm 16.34	46.07 \pm 15.44	44.83 \pm 12.31
FI, %	128.5 \pm 41.71	107.8 \pm 45.20	113.7 \pm 35.59	121.7 \pm 46.55
Accum. ratio	3.020 \pm 1.966	2.880 \pm 0.7982	2.071 \pm 0.7491	2.503 \pm 0.7211

$C_{ss,av}$ = average steady-state plasma concentration (area under the plasma concentration-time curve/dosing interval at steady state); FI = fluctuation index; N = maximum number of subjects with data.

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

The differences in exposure between HIV-1 infected subjects and healthy subjects are not clinically significant irrespective of the administered rilpivirine formulation and the conclusions based on the results of trials conducted in healthy subjects can be applied to HIV-1 infected subjects (Table 6 and Table 7). The rilpivirine exposure at 25 mg once daily for the Phase 3 tablets or 150 mg once daily in HIV-1 infected subjects for the Phase 2b tablets was lower (the maximum difference was 50% when comparing C_{max} , $AUC_{(0-\tau)}$, or C_{min}) in comparison to healthy subjects. For the rilpivirine exposure at 25 mg once daily for the Phase 2b tablets, C_{max} and C_{min} were lower and higher, respectively, in HIV-1 infected subjects compared to healthy subjects and no consistent trend was observed for $AUC_{(0-\tau)}$. The potential differences are not explained by sample processing of the plasma samples because there was no heat inactivation of samples from HIV-1 infected subjects. There were no metabolites that were analyzed in both healthy subjects and HIV-1 infected subjects.

Table 6-Comparison of pharmacokinetic parameters for healthy subjects versus HIV-1 infected subjects administered the Phase 2b tablets

Parameter	Mean \pm SD; t_{max} : Median (Range)				
	TMC278 25 mg q.d.			TMC278 150 mg q.d.	
	Healthy		HIV-1 Infected	Healthy	HIV-1 Infected
	Trial C103	Trial C151	Trial C204	Trial C103	Trial C204
Day 14 (Healthy) or Week 4 (HIV-1 Infected)					
N	12	24	19	11	21
t_{max} , h	4.0 (2.0 - 4.0)	4.5 (2.0 - 6.0)	4.0 (0 - 6.0)	4.0 (3.0 - 6.0)	4.0 (0 - 6.0)
C_{min} , ng/mL	66.85 \pm 29.53	87.56 \pm 27.49	90.85 \pm 44.61	362.0 \pm 130.9	307.9 \pm 122.3
C_{max} , ng/mL	203.8 \pm 75.81	229.4 \pm 65.73	171.8 \pm 69.22	1019 \pm 222.0	701.3 \pm 352.6
AUC_{24h} , ng.h/mL	2589 \pm 868.8	3146 \pm 758.4	2808 \pm 1281	13581 \pm 3195	9925 \pm 3502

N = maximum number of subjects with data.

Table 7-Comparison of pharmacokinetic parameters for healthy subjects versus HIV-1 infected subjects administered the 25 mg Phase 3 tablets

Parameter	Mean \pm SD; t _{max} : Median (Range)			
	Healthy		HIV-1 Infected	
	C130	C152	C209	C215
Day 11 (Healthy) or Week 4, 8, or Any Time in Between (HIV-1 Infected)				
N	16	57	12	32
t _{max} , h	5.0 (5.0 - 12.0)	5.0 (4.0 - 24.0)	4.01 (2.00 - 12.00)	4.00 (1.00 - 12.00)
C _{min} , ng/mL	66.48 \pm 16.29	95.23 \pm 29.07	61.79 \pm 28.69	50.58 \pm 27.94
C _{max} , ng/mL	145.5 \pm 31.97	246.8 \pm 74.36	138.6 \pm 66.73	132.5 \pm 74.79
AUC _{24h} , ng.h/mL	2235 \pm 460.4	3324 \pm 884.0	2133 \pm 1016	1958 \pm 964.5

N = maximum number of subjects with data.

2.2.5.3 What are the characteristics of drug absorption?

The absorption of rilpivirine is pH-dependent. Medications that alter gastric pH, such as H₂ antagonists (e.g. famotidine) and proton pump inhibitors (PPIs) [e.g. omeprazole] were demonstrated in the human drug-drug interaction trials to decrease rilpivirine exposure with coadministration of both medications.

Rilpivirine is not significantly transported by P-gp under steady state conditions based on the results of the in vitro study (TMC278-NC104) evaluating the potential for P-gp to transport rilpivirine. The efflux ratios did not exceed 2 under steady state conditions.

Rilpivirine exposure is increased in the presence of food. In the Phase 3 trials, rilpivirine was administered with meals. The food effect trial was conducted with a single 75 mg dose of rilpivirine but because rilpivirine exposure is dose proportional from 25 mg to 150 mg with the first dose and with multiple dosing, the results are expected to be applicable to 25 once daily dosing. The 75 mg tablets that were administered in the food effect trial are proportional in terms of the active and inactive ingredients to the 25 mg tablets that were administered in the Phase 3 trials. The mean rilpivirine C_{max}, AUC_(0-last), and AUC_(0-∞) values were decreased by 46%, 43%, and 41%, respectively, under fasted conditions in comparison to rilpivirine administered with a standard meal. The differences in rilpivirine exposure when comparing high fat meals to standard meals are not clinically significant.

2.2.5.4 What are the characteristics of drug distribution?

Based on the in vitro study results, the plasma protein binding of rilpivirine is >99% in humans and in animal species (mice, rats, dogs, and rabbits) and is concentration independent. A greater percentage of rilpivirine is bound to albumin compared to α 1-acid glycoprotein. The apparent volume of distribution from the central compartment that was derived from the population PK analysis was approximately 152 liters, indicating that rilpivirine is also found in sites outside of plasma.

unlabeled) dose was recovered based on radioactivity. In the feces, a mean total of 85±4% was recovered after 336 hours, and in the urine, a mean total of 6±2% was recovered after 168 hours.

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

In healthy subjects, dose proportionality was observed for rilpivirine C_{\max} and $AUC_{(0-\tau)}$ for Day 1 and Day 14 with multiple dosing of rilpivirine dosage regimens ranging from 25 mg once daily to 150 mg once daily in the TMC278-C103 trial using tablets developed for use in the Phase 2b trial. The TMC278-C103 pharmacokinetic data is displayed in Table 5 (see 2.2.5.1).

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

Based on the Day 11 pharmacokinetic data from the TMC278-C103 trial, for 25 mg once daily dosing, the rilpivirine half life is approximately 50 hours with an accumulation ratio of approximately 3. Therefore, it is anticipated that steady state will be achieved in approximately ten days (five half lives) or approximately 15 days (seven half lives). It was observed in the drug-drug interaction trials that in some subjects that a 14 day washout was not sufficient to completely wash out rilpivirine.

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?

Overall, in both healthy and HIV-1 infected subjects, low to moderate inter-individual and intra-individual variability was observed.

Based on the population PK analysis, the inter-individual variability for apparent oral clearance (CL/F) and apparent volume of distribution (V/F) was 40% and 49%, respectively, and the intra-individual variability for apparent oral clearance (CL/F) and apparent volume of distribution (V/F) was 23% and 64%, respectively. The inter-individual variability for the population PK $AUC_{(0-\tau)}$ or trough (C_{0h}) values was approximately 40% for both parameters.

In healthy subjects, based on pharmacokinetic data from TMC278-C103 trial for 25 mg, the mean inter-individual variability values (% coefficient of variation) for C_{\max} and $AUC_{(0-24h)}$ on Day 1 were 49% and 55%, respectively, and for Day 14, the mean inter-individual variability for trough (C_{0h}) and minimum plasma concentrations (C_{\min}) were 42%, and 44%, respectively, and the C_{\max} and $AUC_{(0-24h)}$ mean inter-individual variability were 37% and 34%, respectively. Similarly, the inter-individual variability for C_{0h} and C_{\min} were 49% and 43%, respectively, and the C_{\max} and $AUC_{(0-24h)}$ inter-individual variability were 43% and 39%, respectively, in HIV-1 infected subjects from the TMC278-C204 trial.

Intra-individual variability data with steady state dosing was not obtained in healthy subjects. Intra subject variability data with steady state dosing was obtained in HIV-1

infected subjects from the TMC278-C204 trial. The intra-individual variability for C_{0h} and C_{min} , were 33% and 29%, respectively, and the C_{max} and $AUC_{(0-24h)}$ intra-individual variability were 30% and 25%, respectively, and overall, was less than the associated inter-individual variability for each of the corresponding PK parameters.

There were no major causes of variability that were identified. The population pharmacokinetic analysis that was conducted using data from HIV-1 infected subjects enrolled on the Phase 3 trials determined that covariates including body weight, race, age less than 65 years old, sex, and hepatitis B/C co-infection only demonstrated a minimal or no influence on rilpivirine exposure.

2.3 Intrinsic Factors

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

The covariates that were evaluated had a minimal or no influence on rilpivirine exposure and dosage adjustments are not necessary. A population PK analysis was conducted to investigate the potential effects of selected covariates, including body weight, race, age, creatinine clearance (measured using the Cockcroft-Gault (C-G) equation), sex, and hepatitis B/C co-infection.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (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.

Based on the results from the population PK analysis that was conducted using data from HIV-1 infected subjects enrolled in the two Phase 3 trials or from the hepatic impairment trial, no dosage adjustment are necessary for the covariates discussed below (for the specific groups where data is available).

2.3.2.1 Elderly

Age appeared to have no effect on rilpivirine pharmacokinetics. However, only three subjects >65 years were included as part of the data analysis for the Phase 3 trials, and no definitive conclusions could be made regarding whether rilpivirine pharmacokinetics are different between elderly and younger patients. Section 8 of the proposed rilpivirine label has been modified to include a statement that rilpivirine should be used with caution in the elderly.

2.3.2.2 Pediatrics

The safety and effectiveness of rilpivirine in HIV-1 pediatric subjects has not been established, however, the applicant intends to conduct pediatric trials from birth to 18 years old.

2.3.2.3 Gender

Please see the response for 2.3.1.

2.3.2.4 Race

The population PK analysis indicated that there was no clinically significant effect of race (whites, blacks and Asians) on rilpivirine exposure.

2.3.2.5 Renal impairment

The potential changes in rilpivirine exposure with renal impairment were evaluated based on the population PK analysis. For subjects with mild renal impairment, no dosage adjustment is necessary. No definitive conclusions could be made regarding the impact of moderate renal impairment because of the small number of available subjects (seven in total). For subjects with severe renal impairment or end stage renal disease, caution and monitoring for adverse effects is recommended. Sections 8 and 12 of the proposed rilpivirine label have been modified to include these recommendations.

A renal impairment trial was not conducted as part of the NDA submission. The Clinical Pharmacology and Pharmacometrics reviewers analyzed the potential impact of renal impairment based on the information from the rilpivirine population PK analysis. There were minimal differences in rilpivirine exposure when comparing HIV-1 infected subjects with mild renal impairment to HIV-1 infected subjects with normal renal function. No definitive conclusions could be made regarding the impact of moderate renal impairment because of the small number of available subjects (seven in total). Further information is available in the Pharmacometrics review. There were no subjects with severe renal impairment that were included as part of the population PK analysis.

A trial evaluating the effect of renal impairment on rilpivirine using a reduced pharmacokinetic trial design is not necessary based on the available information. There is minimal elimination of rilpivirine in the urine (a mean total of $6 \pm 2\%$ was recovered after 168 hours with unchanged rilpivirine was present in trace amounts) and a 130% increase in rilpivirine $AUC_{(0-24h)}$ that was observed in the rilpivirine-darunavir/ritonavir drug-drug interaction trial does not require a dosage adjustment for rilpivirine.

2.3.2.6 Hepatic impairment

For subjects with mild or moderate hepatic impairment, no dosage adjustment is necessary. Eight healthy control subjects were matched to eight mild hepatic impairment subjects and eight healthy control subjects were matched to eight moderate hepatic

impairment subjects. The effect of severe hepatic impairment on rilpivirine exposure has not been evaluated. With multiple dosing, the greatest magnitude of change for $AUC_{(0-24h)}$ and C_{max} in comparison to healthy control subjects occurred with mild hepatic impairment subjects. On Day 11, in comparison to healthy control subjects, in mild hepatic impairment subjects, C_{24h} and $AUC_{(0-24h)}$ were higher by 76% and 47%, respectively, and C_{min} and C_{max} were higher by 31% and 27%, respectively. In moderate hepatic impairment subjects, on Day 11, in comparison to healthy control subjects, C_{min} , C_{24h} , and $AUC_{(0-24h)}$ were higher by 11%, 28%, and 5%, respectively, and C_{max} was lower by 5%. Rilpivirine plasma protein binding was not evaluated in the trial.

There were no factors identified that explained the fact that the greatest magnitude of difference when compared to the healthy control subjects occurred in mild hepatic impairment subjects. There were no specific subjects identified that could result in anomalous results and the lack of protein binding data precluded an analysis from being conducted on potential changes in the rilpivirine volume of distribution for mild and moderate hepatic impairment subjects.

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

There were no trials evaluating the use of rilpivirine in pregnant or lactating women that were included in the NDA submission.

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?

In the current NDA submission, two extrinsic factors were evaluated: the effect of food on rilpivirine exposure and drug-drug interactions. Both factors influence can potentially alter rilpivirine exposure. The effect of food is discussed in 2.2.5.3 and 2.5.3.

The drug-drug interaction trials are discussed in 2.4.2.8, including information regarding recommendations for managing clinically relevant drug-drug interactions. Sixteen drug-drug interaction trials in healthy subjects were submitted in the current NDA submission. A trial in HIV-1 infected subjects receiving an antiretroviral regimen containing either nevirapine or efavirenz that evaluated the pharmacokinetics of rilpivirine with the subsequent addition of a single dose of rilpivirine was not reviewed.

2.4.2 Drug-drug interactions

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

Cytochrome P450 enzymes

The information from the in vitro studies provides supportive evidence of potential in vivo drug-drug interactions.

One in vitro study (FK4123) indicated that rilpivirine may potentially inhibit CYP 1A2, CYP 2C8/9/10, CYP 2C19, CYP 2D6, CYP 2E1, and CYP 3A4/5 based on the IC_{50} values. A second in vitro study (TMC278-NC283) evaluating the ability of rilpivirine to inhibit paclitaxel (CYP2C8-mediated) and S-warfarin (CYP2C9-mediated) metabolism indicated that for 25 mg once daily dosing of rilpivirine an interaction for CYP 2C8 substrates with rilpivirine is not likely or “remote” and the potential for a drug-drug interaction for CYP 2C9 substrates with rilpivirine is “possible”. A third nonclinical study (TMC278-NC194) indicated that rilpivirine may potentially inhibit CYP 3A, CYP 2C19, and CYP 2D6 based on the IC_{50} values.

The in vitro induction study indicated that rilpivirine may potentially induce CYP 2C19 and CYP 3A4 with lesser induction effects on CYP 1A2 and CYP 2B6. However, the in vitro CYP induction study did not evaluate rilpivirine concentrations below 2.5 μ M (for 25 mg once daily dosing, the C_{max} value is approximately 0.5 μ M).

P-gp inhibition

The in vitro study evaluating the P-gp inhibitory effects of rilpivirine (TMC278-NC104) indicated that rilpivirine has the potential to inhibit P-gp with an IC_{50} value for P-gp inhibition of 9.2 μ M. With a 25 mg once daily dosage regimen, rilpivirine may act as a P-gp inhibitor based on evaluating the $[I]_1/IC_{50}$ and $[I]_2/IC_{50}$ values. The $[I]_1$ value is the mean unbound steady C_{max} value for the highest proposed dosage regimen (the rilpivirine C_{max} value is approximately 0.5 μ M based on total concentrations and 0.005 μ M based on unbound concentrations assuming a free fraction of 1%). The $[I]_2$ value is defined as the dose of the potential inhibitor (in mole units) divided by 250 mL (if the IC_{50} is in molar units). The calculated $[I]_1/IC_{50}$ value of 0.0005 was less than < 0.1 but $[I]_2/IC_{50}$ value of 27 was greater than the threshold of 10. Therefore, the applicant will be requested to conduct a trial as a postmarketing commitment to evaluate the inhibitory effects of rilpivirine on digoxin, a P-gp substrate.

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

The in vitro study results indicate that CYP 3A is the primary cytochrome P450 enzyme system responsible for rilpivirine’s metabolism with CYP 2C19 also potentially contributing to rilpivirine’s metabolism.

The influence of genetics on rilpivirine metabolism was not evaluated as part of the NDA submission.

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

For rilpivirine 25 mg once daily, based on the simulations, a combination of potential rilpivirine 3A induction and CYP 3A inhibition effects are not expected to alter the exposure of CYP 3A substrates (please see 2.4.2.10 for further information regarding the rilpivirine physiologically-based pharmacokinetic modeling [PBPK] and simulations).

The inhibitory or induction effects of rilpivirine 150 mg once daily on CYP 2C19 were evaluated in the rilpivirine-omeprazole drug-drug interaction trial. Based on the results, the combination of rilpivirine and omeprazole does not result in clinically significant changes in omeprazole exposure (14% decrease in both C_{\max} and $AUC_{[0-24h]}$) and no dosage adjustment for omeprazole is necessary. It is expected that this conclusion would also be applicable to a rilpivirine dosage regimen of 25 mg once daily. With multiple dosing of rilpivirine and omeprazole, omeprazole C_{\max} and $AUC_{(0-24h)}$ were both decreased by 14% and the 90% confidence intervals were not within 80%-125%.

The potential inhibitory effects of rilpivirine on CYP 2E1 was evaluated in the rilpivirine-chlorzoxazone drug-drug interaction trial. Based on the results, the combination of rilpivirine and chlorzoxazone does not result in clinically significant changes in chlorzoxazone exposure and no dosage adjustment for chlorzoxazone is necessary. It is expected that this conclusion would also be applicable to a rilpivirine dosage regimen of 25 mg once daily. With multiple dosing of rilpivirine and single dosing of chlorzoxazone, the 90% confidence intervals for chlorzoxazone C_{\max} , $AUC_{(0-last)}$ and $AUC_{(0-\infty)}$ was within 80%-125%.

There were no human drug-drug interaction trials conducted to determine rilpivirine's inhibitory effects on CYP 1A2, CYP 2C8/9/10, or CYP 2D6 substrates. The C_{\max} with 25 mg once daily of rilpivirine is approximately 200 ng/mL or 0.5 μM and this value was used in calculating the CYP 1A2 and CYP 2D6 I/IC_{50} ratios. In the FK4123 study, the rilpivirine CYP 1A2 IC_{50} was 34 μM for phenacetin, and based on the I/IC_{50} ratio, the predicted potential of clinically relevant CYP 1A2 inhibition is "remote". In the same study, of the two CYP 2D6 substrates evaluated, the lowest rilpivirine CYP 2D6 IC_{50} was 3.88 μM for dextromethorphan and based on the I/IC_{50} ratio, the predicted potential of clinically relevant CYP 2D6 inhibition is "possible".

In the TMC278-NC283 study, the rilpivirine CYP 2C9 K_i was $1.70 \pm 0.301 \mu\text{M}$ for S-warfarin, and based on the I/K_i ratio for rilpivirine 25 mg once daily dosing, the predicted potential of clinically relevant CYP 2C9 inhibition is "possible". In the same study, the rilpivirine CYP 2C8 K_i was $10.0 \pm 3.22 \mu\text{M}$ for paclitaxel, and based on the I/K_i ratio for rilpivirine 25 mg once daily dosing, the predicted potential of clinically relevant CYP 2C8 inhibition is "remote".

Based on the in vitro study results, no in vivo drug-drug interaction trials are necessary for CYP 1A2 and CYP 2C8 substrates and human drug-drug interaction trials are recommended for CYP 2C9 and CYP 2D6 substrates. However, based on the similar or lower IC_{50} values for CYP 3A substrates from the FK4123 and TMC278-NC194 studies and the lack of clinically relevant rilpivirine CYP 3A inhibition in the human drug-drug interaction trials, additional rilpivirine drug-drug interaction trials with CYP 2C9 and CYP 2D6 substrates are not necessary.

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

Please see the response for 2.2.5.3 and 2.4.1.

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

In the current NDA submission, only CYP enzyme metabolism and P-gp transport were evaluated.

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

There are no specific antiretroviral medications in the proposed rilpivirine label that are to be coadministered with rilpivirine. The nucleoside or nucleotide reverse transcriptase inhibitors that were administered in combination with rilpivirine in the Phase 3 trials were zidovudine/lamivudine, abacavir/lamivudine and tenofovir/emtricitabine. The different antiretroviral background regimens coadministered with rilpivirine in the Phase 3 trials did not cause clinically significant changes in rilpivirine exposure.

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

Based on the potential for a drug-drug interaction with rilpivirine, the applicant has sufficiently evaluated the appropriate representative medications likely to be administered to HIV-1 infected patients. HIV-1 infected patients may receive a variety of concurrent medications for treatment or prevention of comorbidities. These include medications for treatment of tuberculosis, psychiatric disorders (e.g. depression), cardiovascular disorders (e.g. dyslipidemias) and substance abuse.

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

The recommendations in Section 7 of the proposed label for managing clinically relevant drug-drug interactions are displayed in section 2. The proposed medications that are contraindicated with rilpivirine are potential CYP 3A inducers of rilpivirine metabolism (anticonvulsants, antimycobacterials [rifampin, rifabutin or rifapentine], dexamethasone, St. John's wort), and proton pump inhibitors (e.g. omeprazole) than can alter gastric pH and decrease rilpivirine exposure. The rationale for contraindicating use of these medications with rilpivirine is the potential for decreased rilpivirine exposure that could result in the development of resistance to rilpivirine or cross resistance to other NNRTIs. The proposed label also states that other NNRTIs that are in the same antiretroviral therapeutic class should not be coadministered with rilpivirine. As a precaution because of potential rilpivirine induction effects, increased monitoring is recommended with antifungals in the azole class and with methadone. Alternative antibacterial medications other than use of macrolides are also recommended because of potential inhibition of rilpivirine CYP 3A metabolism. For medications that can alter gastric pH and decrease

rilpivirine exposure (H_2 receptor antagonists and antacids) or for didanosine that must be administered on an empty stomach (the didanosine pediatric powder for oral solution also contains antacids), instructions for spacing out administration of these medications from rilpivirine were also specified.

Most of the human drug-drug interaction trials were conducted to evaluate the potential bidirectional changes in rilpivirine exposure or the exposure of medications with one or more of the following characteristics: a) CYP 3A or 2E1 metabolized, or b) inhibitors or inducers of CYP 3A. In addition, a trial was conducted to evaluate the effect of omeprazole on the absorption of rilpivirine and to evaluate the potential CYP 2C19 inhibitory effects of omeprazole and the potential CYP 2C19 induction or inhibition effects of rilpivirine. The effect of famotidine on the absorption of rilpivirine was also evaluated. Drug-drug interaction trials were also conducted with rilpivirine administered in combination with didanosine, tenofovir, and acetaminophen.

Table 8 displays the recommendations in Section 7 of the proposed label for managing clinically relevant drug-drug interactions. Table 9 and Table 10 summarize the changes in the mean C_{max} , AUC, and C_{min} ratios for rilpivirine when coadministered or combined with another medication, and vice versa, respectively, from section 12.3 of the proposed rilpivirine label.

8 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

CI = Confidence Interval; N = number of subjects with data; N.A. = not available; ↑ = increase; ↓ = decrease; ↔ = no change; q.d. = once daily ; b.i.d. = twice daily
 † This interaction study has been performed with a dose higher than the recommended dose for TRADE NAME™ (25 mg once daily) assessing the maximal effect on the co-administered drug.

Two issues regarding the rilpivirine drug-drug interaction trials were reviewed.

The first issue evaluated whether the results of the drug-drug interaction trials using the Phase 2b formulation are applicable to the Phase 3 formulation. The majority of the drug-drug interaction trials were conducted with a rilpivirine dosage regimen of 150 mg once daily instead of the proposed dosage regimen of 25 mg once daily. Most of the drug-drug interaction trials used a combination of rilpivirine Phase 2b formulations (either the 25 mg or 50 mg tablets administered with 100 mg tablets) instead of the Phase 3/to-be-marketed formulation. The different strengths of the Phase 2b tablets were not designed to be proportional in terms of the active and inactive ingredients. There were no relevant relative bioavailability trials conducted that provide a direct comparison to determine whether the results of the drug-drug interaction trials using the Phase 2b formulations are applicable to 25 mg once daily dosing using the Phase 3 formulation. Of note, clinically significant differences in rilpivirine exposure for the Phase 2b and Phase 3 tablet formulations were not observed in a cross trial comparison of the multiple dosing C_{min} , C_{max} , and $AUC_{(0-24h)}$ data in Table 6 and Table 7 for 25 mg once daily dosing in healthy subjects.

The second issue that was reviewed evaluated whether the results of the drug-drug interaction trials that were conducted using rilpivirine dosage regimens of 75 mg once daily or 150 mg once daily are applicable to rilpivirine 25 mg once daily dosing using the Phase 3 formulation (assuming that the rilpivirine exposure is similar regardless of the formulation that is administered). Physiologically-based pharmacokinetic modeling (PBPK) and simulation was used to answer this question. In general, the results of the drug-drug interaction trials that were conducted at rilpivirine 75 mg once daily or 150 mg once daily are expected to be applicable to a rilpivirine dosage regimen of 25 mg once daily. The results are further discussed in 2.4.2.10.

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

There are no pharmacodynamic drug-drug interactions for rilpivirine.

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

To determine whether the results of the drug-drug interaction trials that were conducted using rilpivirine dosage regimens of 75 mg once daily and 150 mg once daily are applicable to rilpivirine 25 mg once daily dosing using the Phase 3 formulation,

physiologically-based pharmacokinetic modeling (PBPK) and simulation was used.

A potential safety issue that was identified with rilpivirine 25 mg once daily dosing is potentially increased ketoconazole exposure and greater ketoconazole CYP 3A inhibitory effects. Greater ketoconazole CYP 3A inhibitory effects can occur because of decreased rilpivirine CYP 3A induction effects that ultimately results in a potential increase in rilpivirine exposure higher than the increase observed with 150 mg once daily dosing. This issue was further evaluated because of the potential for QT prolongation with rilpivirine exposures at 75 mg once daily dosing and higher. Physiologically-based pharmacokinetic modeling (PBPK) and simulation was used to predict the effects of ketoconazole on rilpivirine exposure.

In the current NDA submission, a drug-drug interaction trial was conducted evaluating the potential interaction between rilpivirine 150 mg once daily and a representative strong CYP 3A inhibitor (e.g. ketoconazole). The results indicated that ketoconazole exposure is decreased (C_{max} , $AUC_{(0-24h)}$ and C_{min} values were decreased by 15%, 24%, and 66%) and rilpivirine exposure is increased (C_{max} , $AUC_{(0-24h)}$ and C_{min} values were increased by 30%, 49%, and 76%, respectively). The rilpivirine-ketoconazole drug-drug interaction trial was not repeated using the proposed rilpivirine dosage regimen of 25 mg once daily.

The physiologically-based pharmacokinetic modeling (PBPK) and simulations were conducted using SIMCYP software (Version 10.10, Simcyp Limited). One important limitation of the simulations evaluating rilpivirine CYP 3A drug-drug interactions at 25 mg once daily is the assumption that the rilpivirine exposure is similar regardless of the formulation that is administered. In support of this assumption, clinically significant differences in rilpivirine exposure for the Phase 2b and Phase 3 tablet formulations were not observed in a cross trial comparison of the multiple dosing C_{min} , C_{max} , and $AUC_{(0-24h)}$ data in Table 6 and Table 7 for 25 mg once daily dosing in healthy subjects.

A model could not be developed that included a time based interaction to predict the effects of rilpivirine on ketoconazole exposure. To determine the potential induction or inhibition effects of rilpivirine, the effects of rilpivirine 75 mg once daily and 25 mg once daily on a single dose of sildenafil 50 mg, a CYP 3A substrate, were simulated. Based on the results displayed in Table 11, a model that included both rilpivirine CYP 3A inhibition effects and rilpivirine CYP 3A induction effects was selected to predict the effects of ketoconazole on rilpivirine exposure. The basis for this decision was the inclusion of both rilpivirine CYP 3A induction and inhibition effects best matched the observed effects of rilpivirine on sildenafil from the drug-drug interaction trial. The potential combination of rilpivirine 3A induction and CYP 3A inhibition effects with rilpivirine 25 mg once daily dosing is not expected to alter the exposure of sildenafil, a CYP 3A substrate.

Table 11-Drug-drug interaction simulations for changes in sildenafil exposure when combined with rilpivirine

		Rilpivirine 75 mg once daily administered for 12 days	Rilpivirine 25 mg once daily administered for 12 days
Simulated ^a	Assuming no CYP3A induction by rilpivirine (CYP 3A inhibition effects only)	1.04	1.02
	Assuming CYP3A induction by rilpivirine (CYP 3A induction and inhibition effects)	0.93	0.98
Observed ^b		0.97	Not determined
^a Mean AUC Ratio using population representative			
^b Least square mean ratio (Trial C123)			

To simulate the effects of ketoconazole on rilpivirine 25 mg once daily exposure, ketoconazole dosage regimens of 300 mg once daily and 400 mg once daily were evaluated. The purpose of simulating a ketoconazole dosage regimen of 300 mg once daily was to evaluate the assumption that the same rilpivirine induction effects on ketoconazole exposure (a 24% decrease in AUC_[0-24h]) observed with 150 mg once daily of rilpivirine also occurs with 25 mg once daily dosing of rilpivirine. The purpose of simulating a ketoconazole dosage regimen of 400 mg once daily was to evaluate the assumption that there are no rilpivirine induction effects on ketoconazole exposure with 25 mg once daily dosing of rilpivirine. A worst case scenario evaluating sustained ketoconazole CYP 3A inhibition using 200 mg twice daily of ketoconazole was also simulated.

The results of the simulations indicate that no dose adjustment is necessary for rilpivirine with 25 mg once daily dosing when combined with a strong CYP 3A inhibitor such as ketoconazole. In general, the results of the drug-drug interaction trials are expected to be applicable to a rilpivirine dosage regimen of 25 mg once daily. The rilpivirine C_{max} and AUC_(0-24h) ratios were similar in scenarios A, B, and C in Table 12 below. Under the worst case scenario of CYP 3A inhibition using 200 mg twice daily of ketoconazole, the increases in rilpivirine C_{max} and AUC_(0-24h) are similar to the increase in rilpivirine exposure that was observed in the rilpivirine-darunavir/ritonavir drug-drug interaction trial.

Table 12-Drug-drug interaction simulations for changes in rilpivirine exposure when combined with ketoconazole

	Scenario	Purpose and assumptions	Rilpivirine Day 12-22	Ketoconazole Day 1-22	Rilpivirine C _{max} ratio	Rilpivirine AUC _(0-24h) ratio
Simulated	A	Match decreased ketoconazole exposure (~24%) by rilpivirine	150 mg once daily	300 mg once daily	1.53	1.64
	B	Match decreased ketoconazole exposure (~24%) by rilpivirine	25 mg once daily	300 mg once daily	1.52	1.63
	C	Assume minimal induction by rilpivirine	25 mg once daily	400 mg once daily	1.56	1.69
	D	Explore sustained inhibition	25 mg once daily	200 mg twice daily	1.91	2.17
Observed			150 mg once daily	400 mg once daily	1.30	1.49

Further information regarding the SIMCYP simulations is located in section 4 in the memorandum for physiologically-based pharmacokinetic modeling (PBPK) and simulation.

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

The applicant will be requested to conduct a trial as a postmarketing requirement to evaluate the inhibitory effects of rilpivirine on digoxin, a P-gp substrate. The rationale for requesting the trial is discussed in 2.2.5.3.

2.5 General Biopharmaceutics

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

A biopharmaceutics classification system (BCS) category was not provided for rilpivirine. Solubility information is provided in Table 13. Rilpivirine demonstrates low solubility in aqueous media.

Table 13-Rilpivirine solubility in aqueous media as a function of pH

Solvent	Solubility in g/100 mL solution	pH of solution	Solubility Description ^a
Water	0.001	2.2	Practically insoluble
0.1N HCl	<0.001	1.1	Practically insoluble
0.01N HCl	0.003	2.0	Practically insoluble
Citrate-HCl buffer pH 2	<0.001	2.0	Practically insoluble
Citrate-NaOH buffer pH 5	<0.001	5.0	Practically insoluble
Phosphate buffer pH 7	<0.001	6.9	Practically insoluble
Borate-KCl-NaOH buffer pH 9	<0.001	8.9	Practically insoluble
Phosphate-NaOH buffer pH 12	<0.001	11.9	Practically insoluble
0.1N NaOH	<0.001	12.9	Practically insoluble

^a based upon USP definitions

The results from the in vitro P-gp study indicate that rilpivirine demonstrates intermediate transepithelial permeability.

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

The to-be-marketed formulation is the same formulation that was administered in the two Phase 3 trials with the exception of debossing. The debossing issue will be evaluated by the Biopharmaceutics reviewer.

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

A biowaiver of in vivo BE data was not requested for this application. Currently, only a 25 mg tablet is being reviewed for marketing approval.

- 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?

Rilpivirine exposure is increased in the presence of food. In the Phase 3 trials, all subjects were administered rilpivirine 25 mg once daily with a meal. The food effect trial (TMC278-C137) was conducted with a single 75 mg dose of rilpivirine but because rilpivirine exposure is dose proportional from 25 mg to 150 mg with the first dose and with multiple dosing, the results are expected to be applicable to 25 once daily dosing.

The 75 mg tablets that were administered in the food effect trial are proportional in terms of the active and inactive ingredients to the 25 mg tablets that were administered in the Phase 3 trials. The mean rilpivirine C_{\max} , $AUC_{(0-\text{last})}$, and $AUC_{(0-\infty)}$ values were decreased by 46%, 43%, and 41%, respectively, under fasted conditions in comparison to rilpivirine administered with a standard meal. The differences in rilpivirine exposure when comparing high fat meals to standard meals are not clinically significant. The proposed rilpivirine label recommends administration of rilpivirine with food. This recommendation is acceptable.

The impact of a protein containing drink on the bioavailability of rilpivirine was also evaluated in the food effect trial. After a dose of rilpivirine 75 mg administered with a protein containing drink, the mean rilpivirine C_{\max} , $AUC_{(0-\text{last})}$, and $AUC_{(0-\infty)}$ values were decreased by 50%, 50%, and 49%, respectively, compared to rilpivirine administered with a standard meal.

In the food effect trial, one important deviation from the recommendations in the FDA guidance document for food effect trials was that rilpivirine was administered within 10 minutes after the meal was completed (this differs from the recommendation in the FDA guidance document for food effect trials which states that medication should be administered 30 minutes after initiation of the meal). The specific impact of this deviation is unknown.

All subjects were to fast overnight for a minimum of 10 hours before administration of rilpivirine with approximately 240 mL of water. Water was allowed up to two hours before and two hours after rilpivirine administration. All breakfast meals with Treatments A, C, and D (see Table 14) were to be consumed in 30 minutes or less. Information on the calorie content for the treatments administered in the food effect trial are displayed in Table 15.

Table 14-Treatments administered in the food effect (TMC278-C137) trial

	Treatment A	Treatment B	Treatment C	Treatment D
TMC278, 75 mg tablet (F008)	Day 1: 1 tablet orally in the morning after a standard breakfast	Day 1: 1 tablet orally in the morning under fasting conditions	Day 1: 1 tablet orally in the morning after a high-fat breakfast	Day 1: 1 tablet orally in the morning after a nutritional drink rich in proteins

Table 15-Calorie content for the treatments administered in the food effect (TMC278-C137) trial

Treatment	Fat (g)	Total Kcal	Kcal from fat	Kcal from carbohydrates	Kcal from proteins
A (standard breakfast)	21	533	189	268	76
B (fasted)	0	0	0	0	0
C (high-fat breakfast)	56	928	504	260	164
D (protein-rich drink)	7.9	300	72	153	75

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

This question is not applicable to the rilpivirine NDA submission.

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

Please refer to the rilpivirine biopharmaceutics review for information regarding dissolution conditions and specifications.

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

There are no in vivo BA and BE issues that need to be addressed for the rilpivirine NDA submission. Please refer to the rilpivirine biopharmaceutics review for information regarding the review of the in vitro dissolution data for rilpivirine.

2.6 Analytical section

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

Rilpivirine plasma samples were analyzed using a LC/MS/MS analytical method. For the rilpivirine LC/MS/MS analytical method, in plasma matrix, heparin was used as an anticoagulant. The Clinical Pharmacology reviewer examined the relevant rilpivirine method validation reports in addition to the bioanalytical reports for the clinical pharmacology trials that are summarized in section 4 and for the Phase 3 trials. There were no issues identified that would impact the reliability of the reported rilpivirine concentration plasma data. The submitted rilpivirine long term stability data of 1528 days at -20°C covered the duration of long term rilpivirine stability data necessary for the trials with rilpivirine samples analyzed that were submitted as part of the NDA.

For the drug-drug interaction trials that were reviewed, plasma samples for medications coadministered or combined with rilpivirine were analyzed using either a LC/MS/MS or LC/UV analytical method. The Clinical Pharmacology reviewer examined the relevant method validation reports for medications coadministered or combined with rilpivirine in addition to the bioanalytical reports for the drug-drug interaction trials. There were no issues identified that would impact the reliability of the reported concentration plasma data for medications coadministered or combined with rilpivirine with the exception of the rifabutin plasma concentration data. The applicant was not able to provide an explanation for the failure of the rifabutin and 25-O-desacetyl-rifabutin long term stability experiment and the Clinical Pharmacology reviewer initially recommended that the rifabutin pharmacokinetic data should be removed from section 12.3 of the proposed rilpivirine label. The applicant has proposed to submit new rifabutin long term stability data. The submitted long term stability data for medications coadministered or combined with rilpivirine covered the duration of long term stability data necessary for the drug-drug interaction trials that were submitted as part of the NDA where plasma samples for medications coadministered or combined with rilpivirine were analyzed. For didanosine, a long term stability experiment was not conducted, however the applicant used the duration of freezer storage of the QC samples used in the drug-drug interaction trial as a substitute-this approach was acceptable to the Clinical Pharmacology reviewer.

2.6.2 Which metabolites have been selected for analysis and why?

With the exception of the metabolites that were identified in the mass balance trial (TMC278-C119), there were no metabolites that were routinely analyzed to further characterize the exposure, exposure response, or exposure safety of rilpivirine.

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?

For rilpivirine, total plasma concentrations were determined. The plasma protein binding of rilpivirine is concentration independent. Analysis of free or pharmacologically active concentrations is not expected to provide additional information to further characterize the exposure, exposure-response, or exposure-safety of rilpivirine.

2.6.4 What bioanalytical methods are used to assess concentrations?

Please see the individual trial reviews in section 4 for information regarding the bioanalysis of rilpivirine plasma samples in the clinical trials. For the rilpivirine LC/MS/MS method validation, two separate bioanalytical laboratories analyzed rilpivirine samples: (b) (4) and Tibotec Pharmaceuticals Ltd.

For the rilpivirine bioanalytical method that was validated at Tibotec, three separate validations were conducted. After the initial method validation that included conducted rilpivirine stability experiments (BA28), the analytical method was further optimized (BA218). During the optimization process for BA218, the amount of plasma volume was decreased to 50 µL and a stable labeled internal standard was added (b) (4). In the third validation, an Ultra High Performance Liquid Chromatography (UPLC) LC/MS/MS

method was validated (BA1071). For the clinical trials that are reviewed in section 4 that had rilpivirine samples analyzed by Tibotec, it appears that either the BA218 or the BA1071 method was used to analyze rilpivirine plasma samples. Further information regarding the rilpivirine calibration curve range and the precision and accuracy of the QC samples for the three bioanalytical methods is displayed in Table 16.

Short term, freeze thaw and processed sample stability was demonstrated for the rilpivirine bioanalytical method validated in BA28. With the exception of processed sample stability, there were no additional stability experiments conducted for BA218 and BA1071. Processed samples stability was demonstrated for both BA218 and BA1071. Stock solution stability was also demonstrated with the exception of the experiment performed for 3 days at room temperature (not protected from light). Long term rilpivirine sample stability was demonstrated for 1528 days at -20°C.

A partial rilpivirine method validation was conducted by (b) (4) of the BA218 bioanalytical method. The only stability experiment that was conducted by (b) (4) as part of the partial method validation was a post preparative sample stability experiment. Processed samples stability was demonstrated for the (b) (4) partial method validation.

Table 16-Information regarding the rilpivirine bioanalytical methods validated at (b) (4) and Tibotec Pharmaceuticals Ltd.

Report No. (Location)	Method (Internal Standard)	Range of Quantification (ng/mL)	Recovery (%)	Compliance with Pre-specified Criteria		Permitted Dilution Ratio and Concentration	Specificity ^c (Interfering Peaks)
				Accuracy ^a	Precision ^b		
BA28 (Module 5.3.1.4/ TMC278-PRD BA28-AVR- Compl; -AVRA- 1; -AVRA-2)	LC-MS/MS (b) (4)	1.00 to 2000	5.00 ng/mL: 98.4 100 ng/mL: 94.8 2000 ng/mL: 94.2	1.00 ng/mL: ≤20% 2.50 ng/mL: ≤15% 62.6 ng/mL: ≤15% 1525 ng/mL: ≤15%	1.00 ng/mL: ≤20% 2.50 ng/mL: ≤15% 62.6 ng/mL: ≤15% 1525 ng/mL: ≤15%	Ratio: up to 1:100 Concentration: up to 200000 ng/mL	Interference ≤20%
BA218 (Module 5.3.1.4/ TMC278-BA218 -AVR-Compl [incl. -AVRA-1]; -AVRA-2; -AVRA-3)	LC-MS/MS (b) (4)	1.00 to 2000	5.00 ng/mL: 90.6 50.0 ng/mL: 89.6 2000 ng/mL: 88.8	1.00 ng/mL: ≤20% 2.50 ng/mL: ≤15% 50.1 ng/mL: ≤15% 1500 ng/mL: ≤15%	1.00 ng/mL: ≤20% 2.50 ng/mL: ≤15% 50.1 ng/mL: ≤15% 1500 ng/mL: ≤15%	Ratio up to 1:100 Concentration: up to 200000 ng/mL	Interference ≤20%
BA1071 (Module 5.3.1.4/ TMC278-PRD- BA1071-AVR)	UPLC- MS/MS (b) (4)	1.00 to 2000	ND	1.00 ng/mL: ≤20% 2.77 ng/mL: ≤15% 55.3 ng/mL: ≤15% 1570 ng/mL: ≤15%	1.00 ng/mL: ≤20% 2.77 ng/mL: ≤15% 55.3 ng/mL: ≤15% 1570 ng/mL: ≤15%	Ratio: up to 1:100 Concentration: up to 200000 ng/mL	Interference ≤20%
ABL6187 (Module 5.3.1.4/ TMC278- ABL6187-AVR)	LC-MS/MS (¹³ C-d ₄ - TMC278)	1.00 to 2000	5.00 ng/mL: 98.9 50.0 ng/mL: 94.7 500 ng/mL: 93.2	1.00 ng/mL: ≤20% 3.00 ng/mL: ≤15% 50.0 ng/mL: ≤15% 1600 ng/mL: ≤15% 16000 ng/mL: ≤15%	1.00 ng/mL: ≤20% 3.00 ng/mL: ≤15% 50.0 ng/mL: ≤15% 1600 ng/mL: ≤15% 16000 ng/mL: ≤15%	Ratio: up to 1:10 Concentration: up to 16000 ng/mL	No interfering peaks

ND = not determined; UPLC-MS/MS = ultra high-performance liquid chromatography with tandem mass-spectrometry.

^a % deviation from nominal concentration.

^b % variability of replicates.

^c Calculated as [(amount found – amount added) / amount added] × 100.

3 Labeling Recommendations

The labeling changes below as of March 2011 include both the proposed revisions recommended by the Clinical Pharmacology review team for relevant clinical pharmacology sections of the label and the applicant's revisions that have been accepted. Minor editorial changes are not displayed.

(b) (4)

20 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4 Appendices

4.1 Individual Trial Reviews

Trial Reviews	Page Numbers
Drug-drug interaction trials	72-251
Food effect trial	252-261
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Drug-drug interaction trials

Trial Number	Title	Page Number
TMC278-C104	A Phase I open-label trial to investigate the pharmacokinetic interaction between tenofovir (administered as tenofovir disoproxil fumarate) and TMC278 at steady-state in healthy subjects	75
TMC278-C105	A Phase I, open label, randomized, 2-way crossover trial in 16 healthy subjects to investigate the potential pharmacokinetic interaction between TMC278 and lopinavir/ritonavir at steady-state	84
TMC278-C106	A Phase I, open-label trial to investigate the pharmacokinetic interaction between didanosine (ddI) and TMC278 at steady-state in healthy individuals	95
R278474-C108	A Phase I, open-label, randomized, three-way crossover trial in 16 healthy subjects to establish the two-way pharmacokinetic interaction between rilpivirine and rifampin at steady-state	106
TMC278-C109	A Phase I, open-label, randomized, 2-way crossover trial in 16 healthy subjects to establish the 2-way pharmacokinetic interaction between steady-state TMC278 and paracetamol	113
TMC278-C112	A Phase I, open-label, randomized 2-way crossover trial in 16 healthy subjects to investigate the	125

	steady-state pharmacokinetic interaction between TMC278 and TMC114/ritonavir (rtv)	
TMC278-C114	A Phase I, open-label trial to investigate the two-way, pharmacokinetic drug-drug interaction between single-dose and steady-state TMC278 and steady-state omeprazole in healthy volunteers	137
TMC278-C116	A Phase I, open-label, randomized, two-way crossover trial in 16 healthy subjects to investigate the potential pharmacokinetic interaction between steady-state rilpivirine and steady-state atorvastatin	155
TMC278-C121	A Phase I, open-label, single-sequence drug-drug interaction trial in subjects on stable methadone maintenance therapy, to investigate the potential interaction between TMC278 25 mg q.d. and methadone, at steady-state	171
TMC278-C123	A Phase I, open-label, randomized, 2-way crossover trial in 16 healthy subjects to investigate the potential pharmacokinetic interaction between TMC278 and sildenafil	183
TMC278-C125	A Phase I, open label, randomized, three-way crossover trial in 18 healthy subjects to investigate the pharmacokinetic interaction between steady-state TMC278 and steady state rifabutin	194
TMC278-C127	A Phase I, open-label, randomized, two-way	206

	crossover trial in 16 healthy subjects to investigate the potential pharmacokinetic interaction between steady-state rilpivirine and steady-state ketoconazole	
TMC278-C136	A Phase I, open-label drug-drug interaction trial to investigate the effect of TMC278 25 mg q.d. on the steady-state pharmacokinetics of ethinylestradiol and norethindrone, in healthy women	213
TMC278-C139	A Phase I, open label trial in 16 healthy subjects to investigate the effect of single-dose and steady-state TMC278 on the pharmacokinetics of chlorzoxazone	226
TMC278-C140	A Phase I, open-label, randomized, 4-way, crossover trial in 24 healthy subjects to investigate the pharmacokinetic interaction between single doses of TMC278 and famotidine in 3 different dosing regimens	239

1. Title

A Phase I open-label trial to investigate the pharmacokinetic interaction between tenofovir (administered as tenofovir disoproxil fumarate) and TMC278 at steady-state in healthy subjects.

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at [REDACTED] (b) (4)
[REDACTED] from September 9, 2004 to December 7, 2004.

3. Objectives

The objectives of the trial were to evaluate the effect at steady state of tenofovir on rilpivirine pharmacokinetics and the effect of steady state rilpivirine on tenofovir pharmacokinetics and urinary excretion.

4. Trial Design

TMC278-C104 was a Phase I, open label, randomized, clinical trial that enrolled male and female subjects between 18 and 55 years old. A schematic of the trial design was not provided in the trial report. The trial was divided into two sessions. In the first session or treatment arm, subjects were administered 150 mg of rilpivirine from Day 1 to Day 8 followed by a 14 day washout period. In the second session or treatment arm, 300 mg of tenofovir was administered from Day 1 to Day 16 and 150 mg of rilpivirine was administered from Day 9 to Day 16 in 8 subjects (Group 1) and Day 1 to Day 8 in 8 subjects (Group 2).

5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Use of ibuprofen was permitted up to three days before administration of trial medication. Afterwards, ibuprofen use was permitted up to 400 mg/day until the end of each treatment arm. Any medications were to be discontinued a minimum of fourteen days before administration of trial medication (with the exception of ibuprofen). Use of herbal medicines or dietary supplements was not permitted from fourteen days before initiation of the trial and throughout the trial.

Use of liquids containing alcohol or quinine was not permitted from 24 hours before administration of trial medication until 96 hours after the last administration of trial medication in each session or treatment arm. Intake of grapefruit and grapefruit juice was not permitted from 7 days before administration of trial medication until 96 hours after the last administration of trial medication in each session or treatment arm.

In the event of an adverse event, the following medications were permitted:

- A) Rash or an allergic reaction: cetirizine, topical corticosteroids, or antipruritic agents (specific medications were not included in the trial report)
- B) Nausea: antiemetics (specific medications were not included in the trial report)
- C) Diarrhea: loperamide

6. Dosage and Administration

A standard meal was administered in the morning and medication (either rilpivirine or tenofovir administered by itself) was administered within 10 minutes after completion of the meal. When both medications were coadministered, rilpivirine was administered within 10 minutes of a standard meal and tenofovir was administered within 5 minutes after rilpivirine.

7. Rationale for Doses Used in the Trial

The rilpivirine dosage regimen that was administered to all subjects was 150 mg once daily. In contrast, the rilpivirine dosage regimen that was evaluated in the Phase 3 clinical trials and the recommended dosage regimen in the proposed prescribing information is 25 mg once daily with a meal. Across the dose range of 25 mg to 150 mg, increases in rilpivirine exposure were approximately dose proportional. However, tenofovir is not anticipated to cause clinically significant changes in rilpivirine exposure.

The tenofovir dosage regimen administered in the trial (300 mg once daily) is the recommended dosage regimen in the tenofovir (Viread) prescribing information (label) for the treatment of HIV-1 infection. Tenofovir can be administered with or without food.

8. Drugs Used in the Trial

Rilpivirine 25 mg tablets (formulation F001) and 100 mg tablets (formulation F002) were administered in the trial. Both of these tablets were Phase 2b formulations that were used in the Phase 1 or 2 trials.

Tenofovir (Viread[®]) 300 mg tablets were administered in the trial.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

For the first session (rilpivirine administered alone), blood samples for analysis of rilpivirine concentrations were obtained on Days 8 and 9 at predose and up to 24 hours postdose. Predose rilpivirine blood samples were also obtained on Days 1, 3, 5, and 7.

For the second session, in Group 1, blood samples for analysis of rilpivirine concentrations were obtained on Days 16 and 17 at predose and up to 24 hours postdose. On Days 9, 11, 13 and 15, a predose blood sample was drawn to determine rilpivirine

concentrations. In Group 2, blood samples for analysis of rilpivirine concentrations were obtained on Days 8 and 9 at predose and up to 24 hours postdose. Tenofovir concentrations were obtained at Day 8 and 9 at predose and up to 24 hours postdose and on Days 16 and 17 at predose and up to 24 hours postdose for both groups. For both groups, on Days 1, 3, 5 and 7 and on Days 11, 13 and 15, a predose blood sample was drawn to determine tenofovir predose concentrations. Urine for analysis of tenofovir was also collected on Days 8 and 16 up to 24 hours postdose.

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a validated LC/MS/MS method by Johnson and Johnson Pharmaceutical Research and Development. The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the TMC278-C104 trial, precision and accuracy were evaluated using the low (2.51 ng/mL), medium (50.1 ng/mL), and high (1550 ng/mL) QC samples. The corresponding rilpivirine inter-run accuracy values were 0.8% for the low QCs, -2% for the medium QCs, and -1.9% for the high QCs, and the rilpivirine inter-run precision values were 10.3% for the low QCs, 6.8% for the medium QCs, and 6.9% for the high QCs. The submitted rilpivirine long term stability data of 1528 days at -20°C covered the duration of long term rilpivirine stability data necessary for the TMC278-C104 trial.

The method and bioanalysis of tenofovir in plasma is acceptable. Plasma samples were analyzed for tenofovir concentrations using a validated LC/MS/MS method by (b) (4). The lower limit of quantification for tenofovir was 4 ng/mL and the upper limit of quantification was 500 ng/mL. There were no precision or accuracy issues identified for tenofovir in plasma based on the bioanalytical report. For the TMC278-C104 trial, precision and accuracy were evaluated using plasma QC samples at 12 (low QC), 75 (medium QC) and 400 ng/mL (high QC). The low QC sample that was analyzed in the TMC278-C104 trial was different from the concentration that was evaluated as part of the method validation (6 ng/mL). In addition, in three out of the six runs, one QC out of the six QCs that were evaluated failed to meet acceptance criteria and in a fourth run, two QCs (one QC at 12 ng/mL and the other QC at 75 ng/mL) out of the six QCs that were evaluated failed to meet acceptance criteria. However, in all four runs, the acceptance criterion of at least 67% of the QCs calculated to be within $\pm 15\%$ of the theoretical or nominal value was still achieved. The corresponding tenofovir inter-run accuracy values were 1.8% for the low QCs, -6.2% for the medium QCs, and -2.2% for the high QCs, and the rilpivirine inter-run precision values were 11.4% for the low QCs, 12.2% for the medium QCs, and 9.1% for the high QCs. The submitted tenofovir long term stability data in plasma matrix at -20°C indicated that tenofovir was stable for 60 days but not at 90 days. However, 60 days appears to cover the duration of tenofovir long term stability data in plasma matrix at -20°C necessary for the TMC278-C104 trial.

The method and bioanalysis of tenofovir in urine is acceptable. There were no stability experiments that were submitted as part of the method validation. Urine samples were

analyzed for tenofovir concentrations using a validated HPLC fluorescence detection method by (b) (4). The lower limit of quantification for tenofovir was 1 ng/mL and the upper limit of quantification was 20 ng/mL. There were no precision or accuracy issues identified for tenofovir in urine based on the bioanalytical report. For the TMC278-C104 trial, precision and accuracy were evaluated using plasma QC samples at 3 (low QC), 10 (medium QC) and 17.5 ng/mL (high QC). The corresponding tenofovir inter-run accuracy values were -8.4% for the low QCs, -5% for the medium QCs, and -3.6% for the high QCs, and the rilpivirine inter-run precision values were 0.9% for the low QCs, 0.9% for the medium QCs, and 3.1% for the high QCs. The long-term stability data for tenofovir in urine was not submitted. Therefore, the stability of the tenofovir urine samples from the day the first sample was collected to the day the last sample was analyzed is unknown and the reliability of the reported tenofovir pharmacokinetic data in urine can not be guaranteed.

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate plasma pharmacokinetic parameters, including C_{min} , C_{max} , and $AUC_{(0-\tau)}$. If a major difference (> 10.00% deviation from the scheduled time) was observed, the actual sampling time was used instead of the scheduled sampling time. In urine, the derived urine pharmacokinetic parameters for tenofovir included the total amount excreted in urine (Ae_{total} [mg]) and the total percentage of the dose excreted in urine ($D_{urine, total} [\%] = Ae_{total}/Dose$).

Statistical Analysis

Descriptive statistics were calculated for rilpivirine and tenofovir plasma concentrations and pharmacokinetic parameters and for tenofovir urine pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), geometric mean, median, and the minimum and maximum values.

Statistical analysis involved comparison of plasma rilpivirine log transformed pharmacokinetic parameters for rilpivirine when coadministered with tenofovir (test arm) compared to rilpivirine administration by itself (reference arm). In plasma, for tenofovir, statistical analysis involved comparison of tenofovir when coadministered with rilpivirine (test arm) compared to tenofovir administration by itself (reference arm). C_{0h} (the predose plasma concentrations), C_{min} (the minimum plasma concentrations between 0 hour and the dosing interval $[\tau]$), C_{max} , and $AUC_{(0-\tau)}$ were evaluated. In urine, for tenofovir, statistical analysis involved comparison of the total percentage of the tenofovir dose excreted in urine ($D_{urine, total} [\%]$) when coadministered with rilpivirine (test arm) compared to tenofovir administration by itself (reference arm). Using a linear mixed effects model, least squares means were calculated and 90% confidence intervals were derived based on the difference of the pharmacokinetic parameter's least squares means for the test and reference arms. The applicant did not specify predetermined "no effect boundaries" for the 90% confidence intervals.

An assessment was performed to determine if rilpivirine (both sessions) and tenofovir steady state concentrations were achieved, presumably by the eighth day of dosing.

10. Results

10.1 Subject Demographics and Disposition

Table 1-TMC278-C104 subject demographics

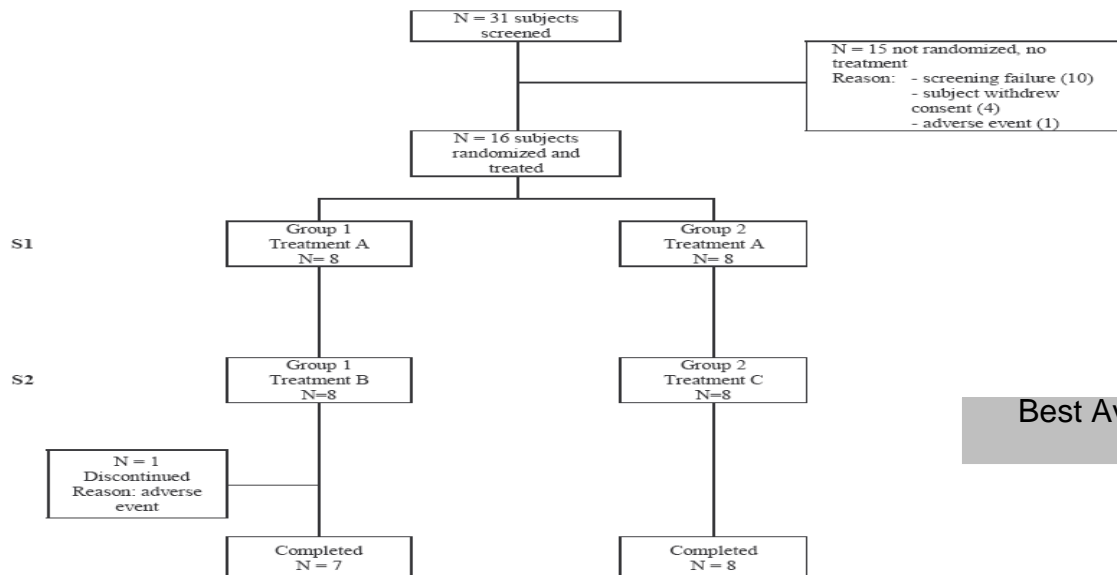
Parameter	Group 1 N =8	Group 2 N =8	All Subjects N =16
Age, years Median (range)	34.0 (21-47)	41.0 (20-51)	38.5 (20-51)
Height, cm Median (range)	178 (171-190)	176 (167-193)	177 (167-193)
Weight, kg Median (range)	74.0 (64-90)	79.0 (65-91)	76.5 (64-91)
BMI, kg/m ² Median (range)	24.1 (19-28)	24.1 (21-29)	24.1 (19-29)
Ethnic Origin, n (%)			
Caucasian/White	8 (100.0)	6 (75.0)	14 (87.5)
Black	0	1 (12.5)	1 (6.3)
Asian	0	1 (12.5)	1 (6.3)
Smoking Type			
Light	0	1 (12.5)	1 (6.3)

N = number of subjects per treatment group.

Group 1 received Treatment A during Session I and Treatment B during Session II.

Group 2 received Treatment A during Session I and Treatment C during Session II.

Figure 2-TMC278-C104 subject disposition



N: number of subjects; S: Session

Treatment A: 150 mg TMC278 q.d. from Day 1 to 8.

Treatment B: 300 mg tenofovir DF q.d. from Day 1 to 16, 150 mg TMC278 q.d. from Day 9 to 16.

Treatment C: 300 mg tenofovir DF q.d. from Day 1 to 16, 150 mg TMC278 q.d. from Day 1 to 8.

Treatment periods were separated by a washout period of at least 14 days.

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10.2 Prior and Concomitant Medications

One subject administered concurrent medications during the trial. The administered concurrent medication was acetaminophen. Acetaminophen would not be expected to alter CYP 3A metabolism.

10.3 Pharmacokinetic and Statistical Analysis

In the second session, there were five subjects with quantifiable rilpivirine concentrations either on Day 1 or on Day 9. However, these concentrations were 5% or less of the subject's C_{max} for the session and no adjustments were necessary for the pharmacokinetic analyses. All subjects had tenofovir concentrations that were less than the lower limit of quantification (LLOQ) on Day 1 in the second session.

Rilpivirine

Table 2-Pharmacokinetic parameters for rilpivirine 150 mg once daily and rilpivirine 150 mg once daily with tenofovir 300 mg once daily coadministration

Pharmacokinetics of TMC278 (mean \pm SD, t_{max} : median [range])	Test TMC278 + TDF	Reference TMC278
n	15	16
C_{0h} (ng/mL)	467 \pm 164	500 \pm 179
C_{max} (ng/mL)	921 \pm 230	1005 \pm 315
C_{min} (ng/mL)	391 \pm 139	409 \pm 141
AUC_{24h} (ng.h/mL)	14404 \pm 3925	14805 \pm 4609
t_{max} (h)	4.0 [3.0-24.0]	4.0 [2.0-6.0]

Table 3-Statistical analysis for rilpivirine 150 mg once daily and rilpivirine 150 mg once daily with tenofovir 300 mg once daily coadministration

TMC278	Least squares means				p-value		
Parameter	Test TMC278+ TDF	Reference TMC278	ratio	90% CI ^a	Treatment	Period	Group
n	15	16	-	-	-	-	-
C_{0h} (ng/mL)	447	462	0.97	0.84 - 1.12	0.6886	-	0.9362
C_{min} (ng/mL)	373	379	0.99	0.83 - 1.16	0.8756	-	0.6966
C_{max} (ng/mL)	902	940	0.96	0.81 - 1.13	0.6621	-	0.4250
AUC_{24h} (ng.h/mL)	14031	13832	1.01	0.87 - 1.18	0.8685	-	0.5482

^a 90% confidence interval of ratio

With tenofovir coadministration, minimal differences were observed in the mean rilpivirine C_{0h} , C_{min} , C_{max} , and $AUC_{(0-24h)}$ compared to rilpivirine when administered by itself. The 90% confidence interval for rilpivirine C_{0h} , C_{min} , C_{max} and $AUC_{(0-24h)}$ were within 80%-125%.

Based on evaluating the mean rilpivirine concentrations, steady state appears to have been achieved by Day 8 in either the first or second session (plots of the individual rilpivirine predose concentrations were not provided).

Tenofovir

Table 4-Tenofovir plasma and urine pharmacokinetic parameters (administered as tenofovir 300 mg once daily and tenofovir 300 mg once daily with rilpivirine 150 mg once daily coadministration)

Pharmacokinetics of Tenofovir (mean \pm SD, t_{max} : median [range])	Test TMC278 + TDF	Reference TDF
n	15	16
C_{0h} (ng/mL)	70 \pm 22	59 \pm 20
C_{max} (ng/mL)	353 \pm 64	305 \pm 80
C_{min} (ng/mL)	67 \pm 19	56 \pm 20
AUC_{24h} (ng.h/mL)	3593 \pm 800	2991 \pm 877
t_{max} (h)	2.5 [1.0-4.0]	2.0 [0.5-4.0]
$D_{urine, total}$ (%)	40.8 \pm 9.8	36.2 \pm 7.8

Table 5-Statistical analysis for tenofovir in plasma and urine (administered as tenofovir 300 mg once daily and tenofovir 300 mg once daily with rilpivirine 150 mg once daily coadministration)

TENOFOVIR	Least squares means				p-value		
Parameter	Test TMC278 + TDF	Reference TDF	ratio	90% CI ^a	Treatment	Period	Group
n	15	16	-	-	-	-	-
C_{0h} (ng/mL)	68	55	1.24	1.09 - 1.40	0.0090	0.0179	0.3818
C_{min} (ng/mL)	65	53	1.24	1.10 - 1.38	0.0054	0.0103	0.2858
C_{max} (ng/mL)	352	295	1.19	1.06 - 1.34	0.0167	0.2441	0.3388
AUC_{24h} (ng.h/mL)	3563	2885	1.23	1.16 - 1.31	<.0001	0.8778	0.2791
$D_{urine, total}$ (%)	40.4	36.2	1.12	1.00 - 1.24	0.1111	0.0953	0.5854

^a 90% confidence interval of ratio

With rilpivirine coadministration, in plasma, the mean tenofovir C_{0h} , C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were increased compared to tenofovir when administered by itself. The 90% confidence interval for tenofovir C_{0h} , C_{min} , C_{max} , and $AUC_{(0-24h)}$ were not within 80%-125%. In urine, with rilpivirine coadministration, the total percentage of the tenofovir dose excreted in urine ($D_{urine, total}$ [%]) was increased compared to tenofovir when administered by itself. The 90% confidence interval for tenofovir $D_{urine, total}$ was within 80%-125%.

Based on evaluating the mean tenofovir concentrations, steady state appears to have been achieved by Day 8 in the second session (plots of the individual tenofovir predose concentrations were not provided).

10.4 Safety Issues

No deaths or other serious adverse events were reported for the trial. One subject reported grade 3 adverse events of increased ALT and increased lipase during tenofovir and rilpivirine coadministration, as well as grade 3 increased AST and lipase and grade 4 increased ALT during follow up. The most common reported adverse events were headache, nausea and abdominal pain (see Table 6 for information regarding the number of subjects).

Table 6-Adverse event incidence categorized by system organ class and preferred term reported in more than one subject

<i>System Organ Class Preferred Term n (%)</i>	<i>Treatment Period N = 16</i>			<i>No-Treatment Period N = 16</i>		<i>Whole Trial N = 16</i>
	<i>TMC278</i>	<i>Tenofovir DF</i>	<i>TMC278/ tenofovir DF</i>	<i>Washout</i>	<i>Follow-up</i>	
<i>Any Adverse Event</i>	12 (75.0)	5 (31.3)	13 (81.3)	6 (37.5)	2 (12.5)	15 (93.8)
<i>Gastrointestinal Disorders</i>	7 (43.8)	2 (12.5)	4 (25.0)	1 (6.3)	1 (6.3)	10 (62.5)
Abdominal discomfort	0	1 (6.3)	0	0	1 (6.3)	2 (12.5)
Abdominal pain	2 (12.5)	1 (6.3)	1 (6.3)	0	1 (6.3)	4 (25.0)
Diarrhea	1 (6.3)	0	1 (6.3)	0	0	2 (12.5)
Loose stools	2 (12.5)	0	0	0	0	2 (12.5)
Nausea	3 (18.8)	2 (12.5)	3 (18.8)	0	0	5 (31.3)
<i>General disorders and administration site conditions</i>	0	1 (6.3)	2 (12.5)	1 (6.3)	0	4 (25.0)
Fatigue	0	1 (6.3)	1 (6.3)	0	0	2 (12.5)
Influenza like illness	0	0	1 (6.3)	1 (6.3)	0	2 (12.5)
<i>Injury, poisoning and procedural complications</i>	2 (12.5)	0	0	1 (6.3)	0	3 (18.8)
Cannula site reaction	1 (6.3)	0	0	1 (6.3)	0	2 (12.5)
<i>Nervous System Disorders</i>	10 (62.5)	4 (25.0)	8 (50.0)	0	0	13 (81.3)
Dizziness	1 (6.3)	0	2 (12.5)	0	0	2 (12.5)
Headache	9 (56.3)	4 (25.0)	6 (37.5)	0	0	12 (75.0)
<i>Respiratory, thoracic and mediastinal disorders</i>	0	0	2 (12.5)	2 (12.5)	0	3 (18.8)
Nasopharyngitis	0	0	0	2 (12.5)	0	2 (12.5)

n = number of subjects with 1 or more events; N = number of subjects per treatment group.

Table 7-Adverse event incidence at least possibly related to either rilpivirine or tenofovir categorized by system organ class and preferred term

System Organ Class Preferred Term n (%)	Treatment Period N = 16			Whole Trial N = 16
	TMC278	Tenofovir DF	TMC278/ Tenofovir DF	
<i>Any Adverse Event at Least Possibly Related^a</i>	2 (12.5)	0	1 (6.3)	3 (18.8)
<i>Gastrointestinal Disorders</i>	1 (6.3)	0	0	1 (6.3)
Abdominal pain	1 (6.3)	0	0	1 (6.3)
Frequent bowel movements	1 (6.3)	0	0	1 (6.3)
Nausea	1 (6.3)	0	0	1 (6.3)
<i>Nervous System Disorders</i>	2 (12.5)	0	1 (6.3)	3 (18.8)
Headache	2 (12.5)	0	1 (6.3)	3 (18.8)

^a Note that no AEs were probably or very likely related to the study medication.

n = number of subjects with 1 or more events; N = number of subjects per treatment group.

11. Discussion and Conclusions

Based on the results from the drug-drug interaction trial, the following conclusions can be made:

- With tenofovir coadministration, minimal differences were observed in the mean rilpivirine C_{0h} , C_{min} , C_{max} , and $AUC_{(0-24h)}$ compared to rilpivirine when administered by itself. Rilpivirine C_{0h} , C_{min} , and C_{max} were decreased by 3%, 1%, and 4%, respectively and rilpivirine $AUC_{(0-24h)}$ was increased by 1%. The 90% confidence interval for rilpivirine C_{0h} , C_{min} , C_{max} and $AUC_{(0-24h)}$ were within 80%-125%.
- With rilpivirine coadministration, in plasma, the mean tenofovir C_{0h} , C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were increased by 24%, 24%, 19% and 23%, respectively, compared to tenofovir when administered by itself. The 90% confidence interval for tenofovir C_{0h} , C_{min} , C_{max} , and $AUC_{(0-24h)}$ were not within 80%-125%. In urine, with rilpivirine coadministration, the total percentage of the tenofovir dose excreted in urine ($D_{urine, total}$ [%]) was increased by 12% compared to tenofovir when administered by itself. The 90% confidence interval for tenofovir $D_{urine, total}$ was within 80%-125%.

Tenofovir does not result in clinically relevant changes in the exposure of rilpivirine and a dose adjustment for rilpivirine is not necessary. Tenofovir is not a substrate of cytochrome P450 enzymes and is eliminated thorough glomerular filtration and active tubular secretion. The mechanism underlying the increase in tenofovir exposure is unclear. However, based on the results from this trial, a rilpivirine dosage regimen of 125 mg once daily does not result in clinically relevant changes in the exposure of tenofovir and a dose adjustment for tenofovir is not necessary. However, it is important to note that in the absence of identifying the mechanism behind the increase in tenofovir exposure, an extrapolation of the effects of rilpivirine 25 mg once daily on tenofovir 300 mg once daily can not be made.

TMC278-C105

1. Title

A Phase I, open label, randomized, 2-way crossover trial in 16 healthy subjects to investigate the potential pharmacokinetic interaction between TMC278 and lopinavir/ritonavir at steady-state

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at the [REDACTED] (b) (4) [REDACTED] from January 13, 2005 to May 4, 2005.

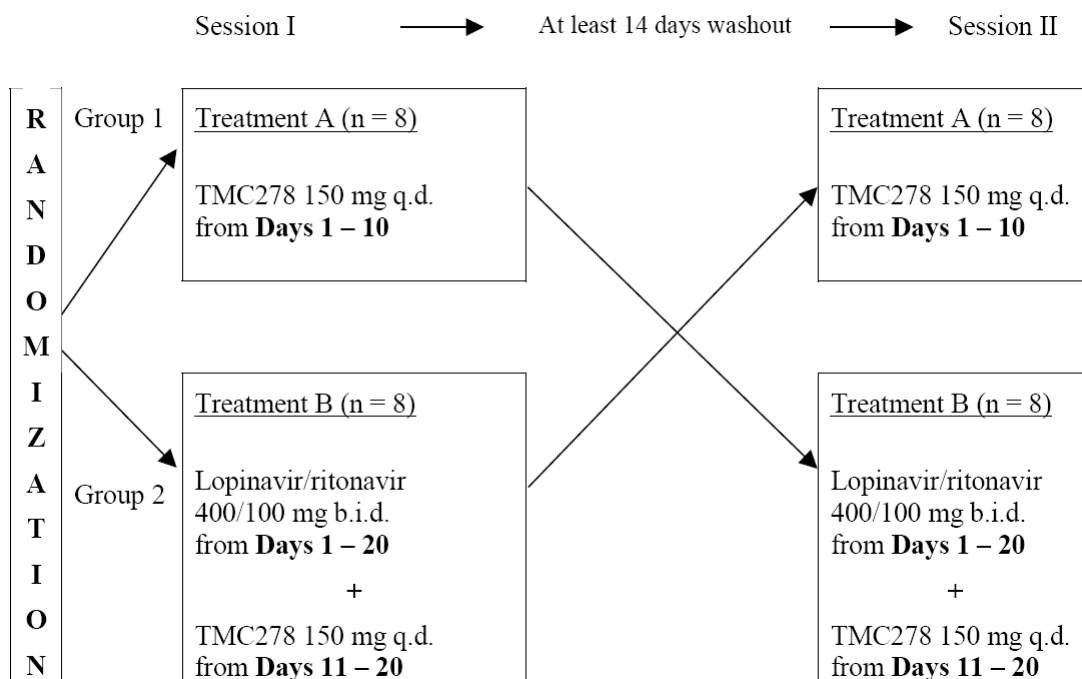
3. Objectives

The objectives of the trial were to evaluate the effect at steady state of lopinavir/ritonavir on rilpivirine pharmacokinetics and the effect of lopinavir and ritonavir on rilpivirine pharmacokinetics.

4. Trial Design

TMC278-C105 was a Phase I, open label, randomized, 2 way crossover clinical trial that enrolled male and female healthy subjects between 18 and 55 years old. The trial design is displayed in Figure 1.

Figure 1-TMC278-C105 trial design



5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Use of ibuprofen was permitted up to three days before first dosing. From three days before first dosing for a treatment arm until the end of the treatment arm, ibuprofen use was permitted up to 400 mg/day. Any medications besides ibuprofen were to be discontinued a minimum of fourteen days before first dosing and use of concurrent medications was not permitted up to seven days after the last administration of trial medication. Use of herbal medicines or dietary supplements was not permitted from fourteen days before first dosing up to 7 days after the last administration of trial medication.

Use of liquids containing alcohol or quinine was not permitted from 24 hours before administration of trial medication until the end of each treatment arm. Intake of grapefruit and grapefruit juice was not permitted from 7 days before administration of trial medication until the end of each treatment arm.

In the event of an adverse event, the following medications were permitted:

- A) Rash or an allergic reaction: cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents (specific medications were not included in the trial report)
- B) Nausea: antiemetics (specific medications were not included in the trial report)
- C) Diarrhea: loperamide

6. Dosage and Administration

On pharmacokinetic sampling days, subjects fasted overnight for a minimum of 10 hours. After a standard meal in the morning, rilpivirine was administered within 10 minutes after completion of the meal.

On pharmacokinetic sampling days, lopinavir/ritonavir was administered within 10 minutes after completion of the meal in the morning and in the evening within 10 minutes after completion of the meal and after the 12 hour pharmacokinetic sample. On days when both lopinavir/ritonavir and rilpivirine were administered, lopinavir/ritonavir was administered within 5 minutes after rilpivirine.

7. Rationale for Doses Used in the Trial

The rilpivirine dosage regimen that was administered to all subjects in Session 1 and Session 2 was 150 mg once daily. On Days 10 (Treatment A) and 20 (Treatment B), rilpivirine was administered with meals as recommended in the proposed prescribing information. In contrast, the rilpivirine dosage regimen that was evaluated in the Phase 3 clinical trials and the recommended dosage regimen in the proposed prescribing information is 25 mg once daily with a meal. Across the dose range of 25 mg to 150 mg, increases in rilpivirine exposure were approximately dose proportional. Therefore, the percentage change in rilpivirine exposure that is caused by the inhibitory effects of lopinavir/ritonavir should be similar with a rilpivirine dosage regimen of either 25 mg

once daily or 150 mg once daily in the absence of significant induction effects from either rilpivirine or ritonavir and if similar lopinavir/ritonavir inhibition effects occur with the two rilpivirine dosage regimens.

The lopinavir/ritonavir dosage regimen is the standard twice daily regimen that is used to treat HIV-1 infected patients. On Days 10 and 20 (Treatment B), lopinavir/ritonavir was administered with meals as recommended for the capsule formulation.

8. Drugs Used in the Trial

Rilpivirine 25 mg tablets (formulation F001) and 100 mg tablets (F002) were administered in the trial. Both of these tablets were Phase 2b formulations that were used in the Phase 1 or 2 trials.

Lopinavir/ritonavir soft gelatin capsules containing 133.3 mg of lopinavir and 33.3 mg of ritonavir were administered in the trial.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

For Treatment A, blood samples for analysis of rilpivirine concentrations were obtained on Days 10 and 11 at predose and up to 24 hours postdose. Predose rilpivirine blood samples were also obtained on Days 8 and 9. On Day 1, a predose sample was drawn to determine rilpivirine, lopinavir and ritonavir concentrations.

For Treatment B, plasma samples for analysis of lopinavir and ritonavir concentrations were obtained on Days 10 at predose and up to 12 hours postdose. Additionally, plasma samples for analysis of rilpivirine, lopinavir and ritonavir concentrations were obtained on Days 20 at predose and up to 12 hours postdose and a sample was drawn at Day 21 for analysis of rilpivirine concentrations only. Predose blood samples for analysis of lopinavir and ritonavir concentrations were also obtained on Days 8 and 9 and predose blood samples for analysis of rilpivirine, lopinavir and ritonavir concentrations were obtained on Days 18 and 19. On Day 1, a predose sample was drawn to determine rilpivirine concentrations.

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a validated LC/MS/MS method by Johnson and Johnson Pharmaceutical Research and Development. The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the TMC278-C105 trial, precision and accuracy were evaluated using the low (2.51 ng/mL), medium (50.2 ng/mL), and high (1560 ng/mL) QC samples. The corresponding rilpivirine inter-run accuracy values were 0% for the low QCs, -1.4% for

the medium QCs, and 0.6% for the high QCs, and the rilpivirine inter-run precision values were 10.4% for the low QCs, 6% for the medium QCs, and 5.7% for the high QCs. The submitted rilpivirine long term stability data of 1528 days covered the duration of long term rilpivirine stability data necessary for the TMC278-C105 trial.

The method and bioanalysis of lopinavir and ritonavir are acceptable. Plasma samples were analyzed for lopinavir and ritonavir concentrations using a validated LC/MS/MS method by (b) (4). The lower limit of quantification for lopinavir was 20 ng/mL and the upper limit of quantification was 20000 ng/mL. There were no precision or accuracy issues identified for lopinavir based on the bioanalytical report. For the TMC278-C105 trial, precision and accuracy were evaluated using the low (60 ng/mL), medium (500 ng/mL), and high (15000 ng/mL) QC samples. The corresponding lopinavir inter-run accuracy values were 2.5% for the low QCs, -0.3% for the medium QCs, and 4.3% for the high QCs, and the lopinavir inter-run precision values were 3.4% for the low QCs, 3.1% for the medium QCs, and 8.6% for the high QCs. The lower limit of quantification for ritonavir was 5 ng/mL and the upper limit of quantification was 5000 ng/mL. There were no precision or accuracy issues identified for ritonavir based on the bioanalytical report. For the TMC278-C105 trial, precision and accuracy were evaluated using the low (15 ng/mL), medium (200 ng/mL), and high (4000 ng/mL) QC samples. The corresponding ritonavir inter-run accuracy values were -0.8% for the low QCs, -1.6% for the medium QCs, and -1.5% for the high QCs, and the ritonavir inter-run precision values were 3.7% for the low QCs, 1.5% for the medium QCs, and 3.0% for the high QCs. There was no long term stability data that was generated by (b) (4). In response to a request for information, long term stability data for lopinavir or ritonavir was submitted that was generated by Tibotec not (b) (4). Long term stability for lopinavir or ritonavir was demonstrated based on the data generated by Tibotec. A definitive determination that lopinavir and ritonavir concentrations from the TMC278-C105 trial were stable for the required duration of long term rilpivirine stability data can not be made; however there is no specific requirement that long term stability data must be generated by the bioanalytical laboratory that analyzes the trial samples.

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate pharmacokinetic parameters, including C_{max} and $AUC_{(0-\tau)}$. If a major difference ($> 10.00\%$ deviation from the scheduled time) was observed, the actual sampling time was used instead of the scheduled sampling time.

Statistical Analysis

Descriptive statistics were calculated for rilpivirine, lopinavir and ritonavir plasma concentrations and pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), geometric mean, median, and the minimum and maximum values.

Statistical analysis involved comparison of rilpivirine log transformed pharmacokinetic parameters for Day 20, Treatment B (test arm) compared to Day 10, Treatment A

(reference arm). For lopinavir and ritonavir, statistical analysis involved comparison of lopinavir and ritonavir log transformed pharmacokinetic parameters for Day 20, Treatment B (test arm) compared to Day 10, Treatment B (reference arm). C_{min} , C_{max} , and $AUC_{(0-\tau)}$ were evaluated. Using a linear mixed effects model, least squares means were calculated and 90% confidence intervals were derived based on the difference of the pharmacokinetic parameter's least squares means for the test and reference arms. The applicant did not specify predetermined "no effect boundaries" for the 90% confidence intervals.

An assessment was performed to determine if rilpivirine steady state concentrations were achieved by Day 10 (Treatment A) based on predose concentrations from Days 8, 9 and 10 and Day 11 C_{24h} or by Day 20 (Treatment B) based on predose concentrations from Days 18, 19 and 20 and Day 21 C_{24h} . For lopinavir and ritonavir, an assessment was performed to determine if steady state concentrations were achieved by Day 10 (Treatment B) based on predose concentrations from Days 8, 9 and 10 and Day 10 C_{12h} or by Day 20 (Treatment B) based on predose concentrations from Days 18, 19 and 20 and Day 20 C_{12h} .

10. Results

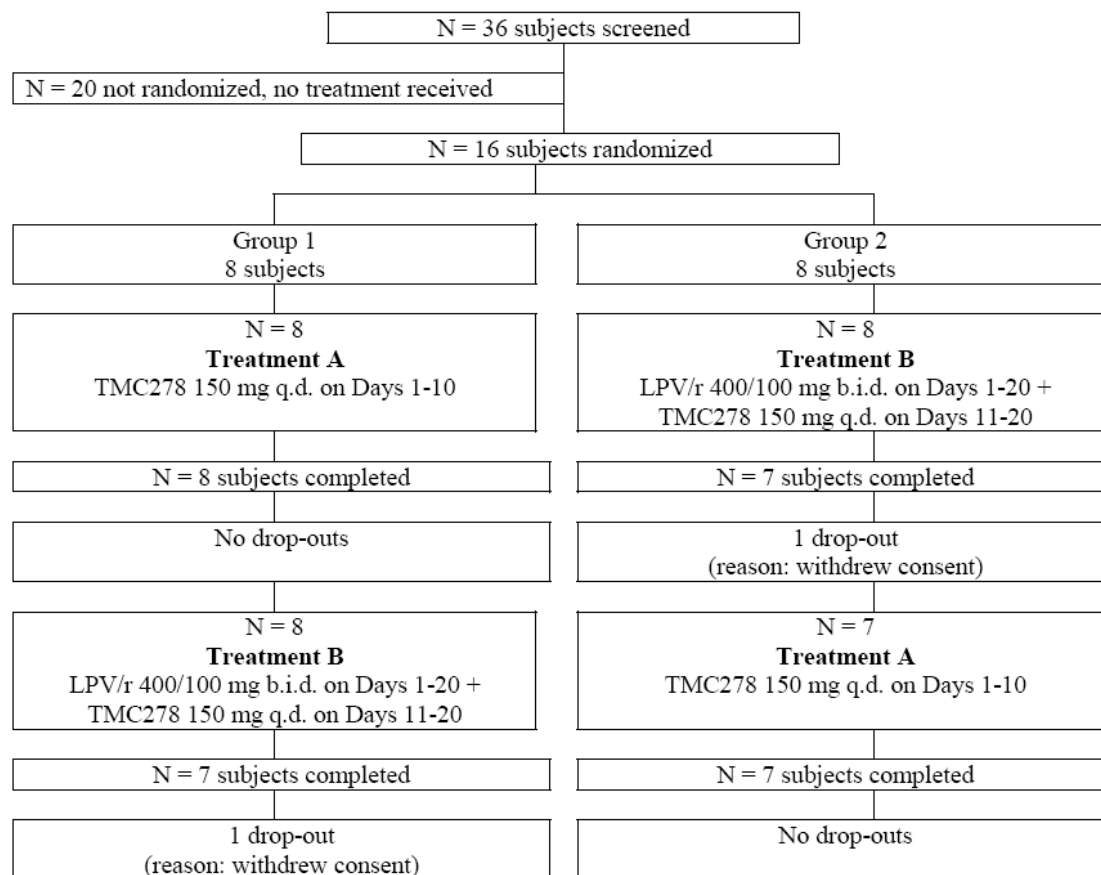
10.1 Subject Demographics and Disposition

Table 1-TMC278-C105 subject demographics

Parameter	Group 1 TMC278 → LPV/r/TMC278 N = 8	Group 2 LPV/r/TMC278 → TMC278 N = 8	Total N = 16
Age, years Median (range)	33.0 (21 – 47)	26.0 (19 – 48)	29.0 (19 – 48)
Height, cm Median (range)	177.0 (162 – 190)	175.0 (160 – 182)	175.0 (160 – 190)
Weight, kg Median (range)	69.5 (59 – 102)	77.5 (51 – 92)	73.5 (51 – 102)
BMI, kg/m ² Median (range)	24.25 (20.6 – 28.3)	24.95 (19.9 – 30.0)	24.55 (19.9 – 30.0)
Race, n (%)			
Caucasian/white	8 (100.0)	5 (62.5)	13 (81.3)
Black	0	2 (25.0)	2 (12.5)
Oriental/Asian	0	1 (12.5)	1 (6.3)
Sex, n (%)			
Male	8 (100.0)	8 (100.0)	16 (100.0)
Type of smoker, n (%)			
No	6 (75.0)	8 (100.0)	14 (87.5)
Yes (Light)	2 (25.0)	0	2 (12.5)

BMI: Body mass index, LPV/r: Lopinavir/ritonavir, N: Number of subjects per treatment group.

Figure 2-TMC278-C105 subject disposition



LPV/r: Lopinavir/ritonavir, N: Number of subjects per treatment group.

10.2 Prior and Concomitant Medications

The trial report states that there were no reports of concomitant medications administered to subjects in the trial.

10.3 Pharmacokinetic and Statistical Analysis

There were 4 subjects with a quantifiable rilpivirine drug concentration prior to starting Treatment A and 3 subjects with a quantifiable rilpivirine drug concentration prior to starting Treatment B. The applicant stated that the cause was rilpivirine administration in the previous session, despite a 14 day washout. However, these concentrations were 5% or less of the subject's C_{max} for the treatment arm and no adjustments were necessary for the pharmacokinetic analyses.

Rilpivirine

Table 2-Pharmacokinetic parameters for rilpivirine 150 mg once daily and rilpivirine 150 mg once daily with lopinavir and ritonavir coadministration (400 mg/100 mg twice daily) [%FI=100 x $([C_{\max}-C_{\min}]/C_{ss,av})$]

Pharmacokinetics of TMC278 (mean \pm SD, t_{\max} : median [range])	Treatment A (Day 10): TMC278 150 mg q.d.	Treatment B (Day 20): LPV/r 400/100 mg b.i.d. + TMC278 150 mg q.d.
n	15	15
C _{0h} , ng/mL	507.3 \pm 256.5	971.6 \pm 485.4
C _{24h} , ng/mL	649.3 \pm 337.4	1281 \pm 647.2
C _{min} , ng/mL	478.8 \pm 248.7	809.4 \pm 370.0
t_{\max} , h	5.0 (3.0 - 12.0)	4.0 (3.0 - 24.0)
C _{max} , ng/mL	1265 \pm 420.7	1619 \pm 603.0
AUC _{24h} , ng.h/mL	19770 \pm 8436	29990 \pm 12900
C _{ss,av} , ng/ml	823.9 \pm 351.5	1250 \pm 537.3
FI, %	104.5 \pm 37.94	68.02 \pm 20.75

Table 3-Statistical analysis for rilpivirine 150 mg once daily and rilpivirine 150 mg once daily with lopinavir and ritonavir coadministration (400 mg/100 mg twice daily)

Parameter	n		Least Square Means		Least Square Means Ratio, %	90% CI, % ^a	p-value		
	TMC278 Alone (Reference)	TMC278/LPV/r (Test)	TMC278 Alone (Reference)	TMC278/LPV/r (Test)			Treatment	Period	Sequence
C _{min} , ng/mL	15	15	422.1	735.4	174.2	146 - 208	0.0001	0.7813	0.8273
C _{max} , ng/mL	15	15	1172	1508	128.6	118 - 140	0.0002	0.7418	0.9942
AUC _{24h} , ng.h/mL	15	15	17934	27274	152.1	136 - 170	<0.0001	0.5595	0.9316

LPV/r = lopinavir/ritonavir.

^a 90% confidence intervals.

On Day 20 (Treatment B), with lopinavir/ritonavir coadministration, higher mean rilpivirine C_{min}, C_{max}, and AUC_(0-24h) values were observed in subjects compared to Day 10 (Treatment A), when rilpivirine was administered by itself. The 90% confidence interval for rilpivirine C_{min}, C_{max}, and AUC_(0-24h) were not within 80%-125%. Based on evaluating the individual rilpivirine predose or C_{24h} concentrations, steady state concentrations were achieved by Day 10 (Treatment A) and Day 20 (Treatment B) in most subjects.

Lopinavir/ritonavir

Table 4-Lopinavir pharmacokinetic parameters (administered as lopinavir/ritonavir 400 mg/100 mg twice daily and lopinavir/ritonavir 400 mg/100 mg twice daily with rilpivirine 150 mg once daily coadministration)

Pharmacokinetics of Lopinavir (mean \pm SD, t_{max} : median [range])	Treatment B (Day 10): LPV/r 400/100 mg b.i.d	Treatment B (Day 20): LPV/r 400/100 mg b.i.d + TMC278 150 mg q.d.
n	15	15
C_{0h} , ng/mL	7482 \pm 2386	7375 \pm 2868
C_{12h} , ng/mL	6285 \pm 2127	6297 \pm 2681
C_{min} , ng/mL	5982 \pm 1977	5555 \pm 2490
t_{max} , h	4.0 (3.0 - 5.0)	4.0 (1.0 - 5.0)
C_{max} , ng/mL	13850 \pm 2964	13300 \pm 3118
AUC_{12h} , ng.h/mL	112900 \pm 22170	113700 \pm 32450
$C_{ss,av}$, ng/mL	9411 \pm 1847	9479 \pm 2704
FI, %	85.00 \pm 22.47	86.00 \pm 26.89

Table 5-Statistical analysis for lopinavir (administered as lopinavir/ritonavir 400 mg/100 mg twice daily and lopinavir/ritonavir 400 mg/100 mg twice daily with rilpivirine 150 mg once daily coadministration)

Parameter	n		Least Square Means		Least Square Means Ratio, %	90% CI, % ^a	p-value
	LPV/r Alone (Reference)	LPV/r/ TMC278 (Test)	LPV/r Alone (Reference)	LPV/r/ TMC278 (Test)			Treatment
C_{min} , ng/mL	15	15	5643	5011	88.80	73.2 - 108	0.2972
C_{max} , ng/mL	15	15	13535	12994	96.01	87.5 - 105	0.4529
AUC_{12h} , ng.h/mL	15	15	110790	109806	99.11	89.1 - 110	0.8845

LPV/r = lopinavir/ritonavir.

^a 90% confidence intervals.

On Day 20 (Treatment B), with rilpivirine coadministration, a lower mean lopinavir C_{min} value was observed and minimal changes were observed with C_{max} and $AUC_{(0-12h)}$ in subjects compared to Day 10 (Treatment B), when lopinavir/ritonavir was administered by itself. The 90% confidence interval for lopinavir C_{max} and $AUC_{(0-12h)}$ were within 80%-125%. The 90% confidence interval for lopinavir C_{min} was not within 80%-125%.

Table 6-Ritonavir pharmacokinetic parameters (administered as lopinavir/ritonavir 400 mg/100 mg twice daily and lopinavir/ritonavir 400 mg/100 mg twice daily with rilpivirine 150 mg once daily coadministration)

Pharmacokinetics of Ritonavir (mean \pm SD, t_{max} ; median [range])	Treatment B (Day 10): LPV/r 400/100 mg b.i.d	Treatment B (Day 20): LPV/r 400/100 mg b.i.d + TMC278 150 mg q.d.
n	15	15
C _{0h} , ng/mL	273.1 \pm 192.9	275.5 \pm 156.2
C _{12h} , ng/mL	192.9 \pm 103.4	198.7 \pm 102.0
C _{min} , ng/mL	168.5 \pm 96.33	177.9 \pm 100.5
t _{max} , h	4.0 (2.0 - 5.0)	4.0 (3.0 - 5.0)
C _{max} , ng/mL	1256 \pm 648.4	1070 \pm 417.7
AUC _{12h} , ng.h/mL	6331 \pm 2731	6035 \pm 2444
C _{ss,av} , ng/mL	527.6 \pm 227.6	502.9 \pm 203.6
FI, %	206.1 \pm 41.58	183.8 \pm 43.97

Table 7-Statistical analysis for ritonavir (administered as lopinavir/ritonavir 400 mg/100 mg twice daily and lopinavir/ritonavir 400 mg/100 mg twice daily with rilpivirine 150 mg once daily coadministration)

Parameter	n		Least Square Means		Least Square Means Ratio, %	90% CI, % ^a	p-value
	LPV/r Alone (Reference)	LPV/r/ TMC278 (Test)	LPV/r Alone (Reference)	LPV/r/ TMC278 (Test)			Treatment
C _{min} , ng/mL	15	15	138.6	147.7	106.6	89.1 - 128	0.5419
C _{max} , ng/mL	15	15	1101	977.9	88.81	72.8 - 108	0.3093
AUC _{12h} , ng.h/mL	15	15	5664	5459	96.38	84.0 - 111	0.6424

LPV/r = lopinavir/ritonavir.

^a 90% confidence intervals.

On Day 20 (Treatment B), with rilpivirine coadministration, a lower mean ritonavir C_{max} was observed and minimal changes were observed with C_{min} and AUC_(0-12h) in subjects compared to Day 10 (Treatment B), when lopinavir/ritonavir was administered by itself. The 90% confidence interval for ritonavir AUC_(0-12h) was within 80%-125%. The 90% confidence interval for ritonavir C_{max} and C_{min} were not within 80%-125%.

Based on evaluating the individual lopinavir and ritonavir predose or C_{24h} concentrations, steady state concentrations were achieved by Day 10 (Treatment B) and Day 20 (Treatment B) in most subjects.

10.4 Safety Issues

No deaths or other serious adverse events were reported for the trial. No grade 3 or 4 adverse events were reported. The most common adverse event that was reported for more than one subject was pain (2 subjects, 12.5%).

Table 8-Adverse event incidence reported for greater than one subject per system organ class and categorized by system organ class and preferred term

<i>System Organ Class Preferred Term n (%)</i>	TMC278 Alone (N = 15)	LPV/r Alone (N = 16)	LPV/r/ TMC278 (N = 15)	Follow-up (N = 14)	Total (N = 16)
Any Adverse Event	3 (20.0%)	6 (37.5%)	1 (6.7%)	1 (7.1%)	8 (50.0%)
Gastrointestinal Disorders	0	3 (18.8%)	0	0	3 (18.8%)
Abdominal pain upper	0	1 (6.3%)	0	0	1 (6.3%)
Flatulence	0	1 (6.3%)	0	0	1 (6.3%)
Nausea	0	1 (6.3%)	0	0	1 (6.3%)
General Disorders and Administration Site Conditions	2 (13.3%)	2 (12.5%)	0	0	4 (25.0%)
Asthenia	0	1 (6.3%)	0	0	1 (6.3%)
Fatigue	1 (6.7%)	0	0	0	1 (6.3%)
Pain	1 (6.7%)	1 (6.3%)	0	0	2 (12.5%)
Investigations	0	1 (6.3%)	0	1 (7.1%)	2 (12.5%)
Blood uric acid increased	0	0	0	1 (7.1%)	1 (6.3%)
Transaminases increased	0	1 (6.3%)	0	0	1 (6.3%)
Respiratory, Thoracic, and Mediastinal Disorders	0	1 (6.3%)	1 (6.7%)	0	2 (12.5%)
Epistaxis	0	0	1 (6.7%)	0	1 (6.3%)
Rhinitis	0	1 (6.3%)	0	0	1 (6.3%)

LPV/r: Lopinavir/ritonavir.

n = number of subjects with 1 or more events; N = number of subjects per treatment group.

No AEs were reported during the washout phases.

Table 9-Adverse event incidence possibly related to either rilpivirine or lopinavir/ritonavir categorized by system organ class and preferred term

<i>System Organ Class Preferred Term n (%)</i>	TMC278 Alone (N = 15)	LPV/r Alone (N = 16)	LPV/r/ TMC278 (N = 15)	Follow-up (N = 14)	Total (N = 16)
Any AE of any causality	3 (20.0%)	6 (37.5%)	1 (6.7%)	1 (7.1%)	8 (50.0%)
With at least 1 AE thought to be possibly related to TMC278	2 (13.3%)	0	0	0	2 (12.5%)
General Disorders and Administration Site Conditions	1 (6.7%)	0	0	0	1 (6.3%)
Fatigue	1 (6.7%)	0	0	0	1 (6.3%)
Vascular Disorders	1 (6.7%)	0	0	0	1 (6.3%)
Hot flush	1 (6.7%)	0	0	0	1 (6.3%)
With at least 1 AE thought to be possibly related to LPV/r	0	4 (25.0%)	0	0	4 (25.0%)
Gastrointestinal Disorders	0	2 (12.5%)	0	0	2 (12.5%)
Abdominal pain upper	0	1 (6.3%)	0	0	1 (6.3%)
Nausea	0	1 (6.3%)	0	0	1 (6.3%)
Investigations	0	1 (6.3%)	0	0	1 (6.3%)
Transaminases increased	0	1 (6.3%)	0	0	1 (6.3%)
Skin and Subcutaneous Tissue Disorders	0	1 (6.3%)	0	0	1 (6.3%)
Rash maculo-papular	0	1 (6.3%)	0	0	1 (6.3%)

LPV/r: Lopinavir/ritonavir.

n = number of subjects with 1 or more events; N = number of subjects per treatment group.

No AEs were thought to be probably or very likely drug related.

No AEs were reported during the washout phases.

11. Discussion and Conclusions

Based on the results from the drug-drug interaction trial, the following conclusions can be made:

- Rilpivirine exposure was increased with lopinavir/ritonavir coadministration (rilpivirine mean C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were increased by 74%, 29%, and 52%, respectively). The 90% confidence interval for all three parameters was not within 80-125%.
- With rilpivirine coadministration, the mean lopinavir C_{min} value was decreased by 11% and minimal changes were observed with lopinavir C_{max} and $AUC_{(0-12h)}$ [decrease of 4% and 1%, respectively]. The 90% confidence interval for lopinavir C_{max} and $AUC_{(0-12h)}$ was within 80%-125%, however the 90% confidence interval for C_{min} was 73%-108%.
- With rilpivirine coadministration, the mean ritonavir C_{max} value was decreased by 11% and minimal changes were observed with ritonavir C_{min} and $AUC_{(0-12h)}$ [increase of 7% and decrease of 4%, respectively]. The 90% confidence interval for ritonavir $AUC_{(0-12h)}$ was within 80%-125%, however the 90% confidence interval for C_{max} and C_{min} was 73%-108% and 89%-128%.

The increase in rilpivirine exposure may be potentially explained by lopinavir/ritonavir CYP 3A inhibition. The information from the trial supports the conclusion that with a rilpivirine 150 mg once daily dosing regimen, potential lopinavir/ritonavir CYP 3A inhibition of rilpivirine metabolism does not result in clinically relevant changes in rilpivirine exposure and therefore no dosage adjustment for rilpivirine is required (see below for further discussion regarding rilpivirine 25 mg once daily dosing).

With a 150 mg once daily rilpivirine dosage regimen, the decreases in both lopinavir and ritonavir exposure may be potentially explained by rilpivirine CYP 3A induction. The specific effects of a 25 mg once daily rilpivirine dosage regimen on lopinavir/ritonavir exposure have not been evaluated. From a mechanistic standpoint, the degree of induction with rilpivirine 25 mg once daily dosing is anticipated to be the same or less compared to 150 mg once daily dosing. The changes in lopinavir/ritonavir exposure appear to be minimal with rilpivirine coadministration based on the results from the trial and therefore no dosage adjustment for lopinavir/ritonavir is required with rilpivirine dosage regimens ranging from 25 mg once daily to 150 mg once daily. However, potential differences in the inhibitory effects of lopinavir/ritonavir when coadministered with rilpivirine 25 mg once daily compared to rilpivirine 150 mg once daily may be clinically relevant. The rationale for this statement is that under the scenario of decreased rilpivirine induction, a greater degree of lopinavir/ritonavir inhibition may occur with rilpivirine 25 mg once daily dosing. Further analysis of this issue will be conducted.

TMC278-C106

1. Title

A Phase I, open-label trial to investigate the pharmacokinetic interaction between didanosine (ddI) and TMC278 at steady-state in healthy individuals

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at (b) (4) from June 2, 2005 to December 16, 2005.

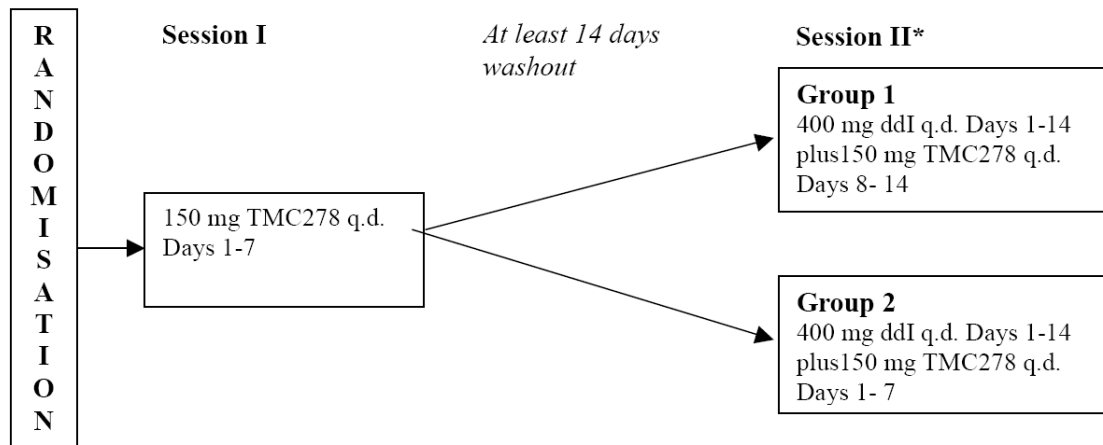
3. Objectives

The objectives of the trial were to evaluate the effect at steady state of didanosine on rilpivirine pharmacokinetics and the effect of steady state rilpivirine on didanosine pharmacokinetics.

4. Trial Design

TMC278-C106 was a Phase I, open label, randomized, clinical trial that enrolled male and female subjects between 18 and 55 years old. The trial design is displayed in Figure 1.

Figure 1-TMC278-C106 trial design



* Note: Repeat Session II (substudy) was performed in the same way as Session II after all subjects had completed the main study.

5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Use of ibuprofen was permitted up to three days before administration of trial medication in each session or treatment arm. Afterwards, ibuprofen use was permitted up to 400 mg/day until the end of each session or treatment arm. Any medications were to be

discontinued a minimum of fourteen days before the first administration of trial medication (with the exception of ibuprofen). Use of herbal medicines or dietary supplements was not permitted from fourteen days before initiation of the trial and throughout the trial. Use of hormone replacement therapy was also permitted in postmenopausal women.

Use of liquids containing alcohol or quinine was not permitted from 24 hours before the first administration of trial medication until 96 hours after the last administration of trial medication in each session or treatment arm. Intake of grapefruit and grapefruit juice was not permitted from 7 days before the first administration of trial medication until 96 hours after the last administration of trial medication in each session or treatment arm.

In the event of an adverse event, the following medications were permitted:

- A) Rash or an allergic reaction: cetirizine, topical corticosteroids, or antipruritic agents (specific medications were not included in the trial report)
- B) Nausea: antiemetics (specific medications were not included in the trial report)
- C) Diarrhea: loperamide

6. Dosage and Administration

A standard meal was administered in the morning and rilpivirine was administered within 10 minutes after completion of the meal. Didanosine was administered on an empty stomach with a meal administered 1.5 hours after didanosine administration. Rilpivirine was administered two hours after didanosine administration.

7. Rationale for Doses Used in the Trial

The rilpivirine dosage regimen that was administered to all subjects was 150 mg once daily. In contrast, the rilpivirine dosage regimen that was evaluated in the Phase 3 clinical trials and the recommended dosage regimen in the proposed prescribing information is 25 mg once daily with a meal. Across the dose range of 25 mg to 150 mg, increases in rilpivirine exposure were approximately dose proportional. However, didanosine is not anticipated to cause clinically significant changes in rilpivirine exposure.

The didanosine dosage regimen (using the delayed release capsules with enteric coated beadlets) administered in the trial (400 mg once daily) is the recommended dosage regimen for patients weighing a minimum of 60 kg in the didanosine (Videx EC) prescribing information (label) for the treatment of HIV-1 infection. Didanosine is to be administered on an empty stomach.

8. Drugs Used in the Trial

Rilpivirine 25 mg tablets (formulation F001) and 100 mg tablets (formulation F002) were administered in the trial. Both of these tablets were Phase 2b formulations that were used in the Phase 1 or 2 trials.

Didanosine (Videx[®] EC) 400 mg capsules were administered in the trial.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

For session 1 (rilpivirine administered alone), blood samples for analysis of rilpivirine concentrations were obtained on Days 7 and 8 at predose and up to 24 hours postdose. Predose rilpivirine blood samples were also obtained on Days 1, 3, 5, and 6.

For session 2, in Group 1, blood samples for analysis of rilpivirine concentrations were obtained on Days 14 and 15 at predose and up to 26 hours postdose. On Days 1, 8, 10, 12 and 13, a predose blood sample was drawn to determine rilpivirine concentrations. In Group 2, blood samples for analysis of rilpivirine concentrations were obtained on Days 7 and 8 at predose and up to 26 hours postdose. On Days 1, 3, 5, and 6, a predose blood sample was drawn to determine rilpivirine concentrations. Didanosine concentrations were obtained at Day 7 and 8 at predose and up to 24 hours postdose and on Days 14 and 15 at predose and up to 24 hours postdose for both groups. For both groups, on Days 1, 3, 5 and 6 and on Days 10, 12 and 13, a predose blood sample was drawn to determine didanosine predose concentrations.

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a validated LC/MS/MS method by Johnson and Johnson Pharmaceutical Research and Development. The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the TMC278-C106 trial, precision and accuracy were evaluated using the low (2.51 or 2.85 ng/mL), medium (50.2 or 57.1 ng/mL), and high (1550 or 1560 ng/mL) QC samples. The corresponding rilpivirine inter-run accuracy values were 2.4% and -2.8%, respectively, for the low QCs, -1% and -0.2%, respectively, for the medium QCs, and -2.6% and 1.9%, respectively, for the high QCs, and the rilpivirine inter-run precision values were 8.4% and 10.3%, respectively, for the low QCs, 4.1% and 5%, respectively, for the medium QCs, and 3.9% and 5%, respectively, for the high QCs. The submitted rilpivirine long term stability data of 1528 days at -20°C covered the duration of long term rilpivirine stability data necessary for the TMC278-C106 trial.

The method and bioanalysis of didanosine is acceptable. Plasma samples were analyzed for didanosine concentrations using a validated LC/MS/MS method by (b) (4). The lower

limit of quantification for didanosine was 10 ng/mL and the upper limit of quantification was 5000 ng/mL. There were no precision or accuracy issues identified for didanosine based on the bioanalytical report. For the TMC278-C106 trial, precision and accuracy were evaluated using plasma QC samples at 30 (low QC), 400 (medium QC) and 4000 ng/mL (high QC). In addition, in two runs, one QC out of the six QCs that were evaluated failed to meet acceptance criteria and in a third run, two QCs (one QC at 400 ng/mL and the other QC at 4000 ng/mL) out of the six QCs that were evaluated failed to meet acceptance criteria. However, in all three runs, the acceptance criterion of at least 67% of the QCs calculated to be within $\pm 15\%$ of the theoretical or nominal value was still achieved. The corresponding didanosine inter-run accuracy values were 2.9% for the low QCs, 2.5% for the medium QCs, and 2.2% for the high QCs, and the didanosine inter-run precision values were 7.2% for the low QCs, 6.1% for the medium QCs, and 6.1% for the high QCs. Long term didanosine stability data in plasma matrix at -20°C is pending and the reliability of the reported didanosine pharmacokinetic data can not be determined at this time.

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate plasma pharmacokinetic parameters, including C_{\min} , C_{\max} , and $\text{AUC}_{(0-\tau)}$. If a major difference ($> 10.00\%$ deviation from the scheduled time) was observed, the actual sampling time was used instead of the scheduled sampling time.

Statistical Analysis

Descriptive statistics were calculated for rilpivirine and didanosine plasma concentrations and pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), geometric mean, median, and the minimum and maximum values.

Statistical analysis involved comparison of plasma rilpivirine log transformed pharmacokinetic parameters for rilpivirine when administered 2 hours after didanosine (test arm) compared to rilpivirine administration by itself (reference arm). For didanosine, statistical analysis involved comparison of didanosine when administered 2 hours before rilpivirine (test arm) compared to didanosine administration by itself (reference arm). C_{0h} (the predose plasma concentrations), C_{\min} (the minimum plasma concentrations between 0 hour and the dosing interval $[\tau]$), C_{\max} , and $\text{AUC}_{(0-\tau)}$ were evaluated. Using a linear mixed effects model, least squares means were calculated and 90% confidence intervals were derived based on the difference of the pharmacokinetic parameter's least squares means for the test and reference arms. The applicant did not specify predetermined "no effect boundaries" for the 90% confidence intervals.

An assessment was performed to determine if rilpivirine (both sessions) steady state concentrations were achieved, presumably by the seventh day of dosing. An assessment was also planned to determine if didanosine steady state concentrations were achieved, however this assessment was not conducted (see 10.3 for further information).

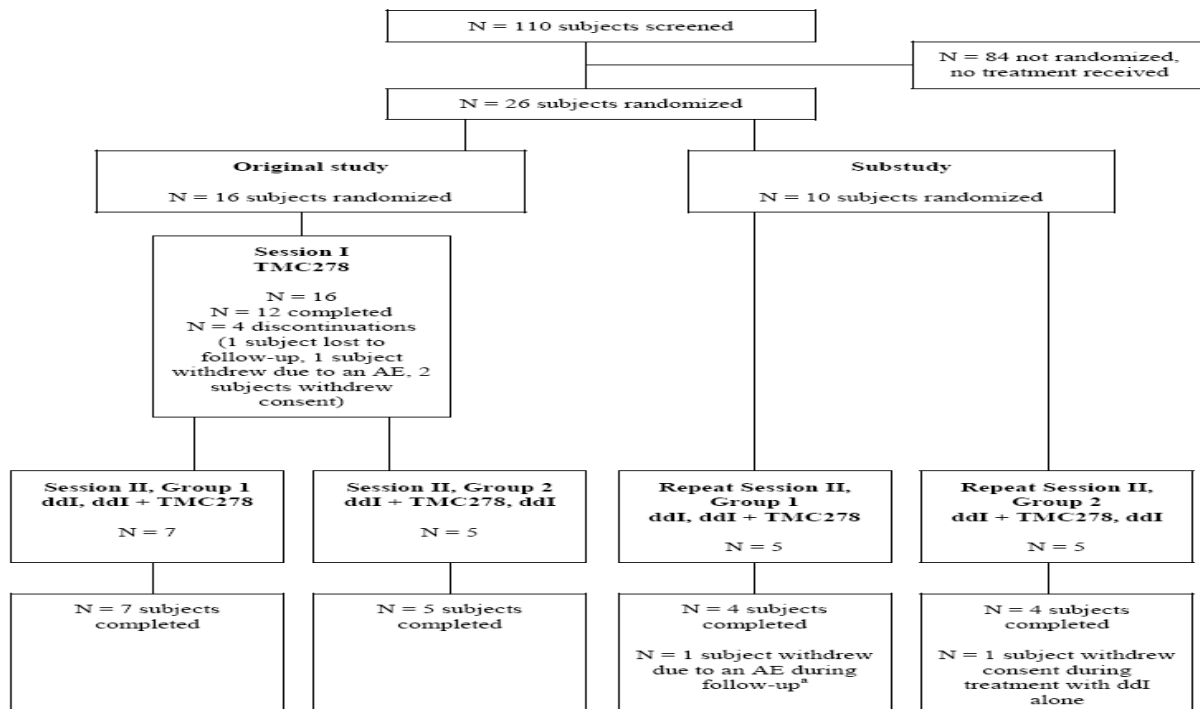
10. Results

10.1 Subject Demographics and Disposition

Table 1-TMC278-C106 subject demographics

Parameter	Group 1 N = 13	Group 2 N = 13	Total N = 26
Age, years			
Median (range)	28.0 (18-54)	24.0 (19-52)	25.5 (18-54)
Height, cm			
Median (range)	170.0 (157-174)	171.0 (151-183)	170.5 (151-183)
Weight, kg			
Median (range)	73.0 (60-87)	73.0 (62-89)	73.0 (60-89)
BMI, kg/m ²			
Median (range)	26.8 (20-30)	25.5 (21-30)	25.9 (20-30)
Sex, n (%)			
Male	10 (76.9%)	11 (84.6%)	21 (80.8%)
Female	3 (23.1%)	2 (15.4%)	5 (19.2%)
Race, n (%)			
Caucasian/White	6 (46.2%)	5 (38.5%)	11 (42.3%)
Hispanic	4 (30.8%)	2 (15.4%)	6 (23.1%)
Black	3 (23.1%)	4 (30.8%)	7 (26.9%)
Oriental / Asian	0	1 (7.7%)	1 (3.8%)
Other	0	1 (7.7%)	1 (3.8%)
Smoker, n (%)			
No	13 (100.0%)	13 (100.0%)	26 (100.0%)

Figure 2-TMC278-C106 subject disposition



^a [Subject 1060097](#) stopped taking study medication after receiving ddI on Day 7, but remained in the trial undergoing scheduled assessments without receiving study medication. The subject withdrew from the study completely at follow-up.

10.2 Prior and Concomitant Medications

One subject administered concurrent medications during the trial. The administered concurrent medication was prune juice to treat constipation. Prune juice would not be expected to alter CYP 3A metabolism.

10.3 Pharmacokinetic and Statistical Analysis

In the second session, in Group 1 (excluding replacement subjects), there were seven subjects with quantifiable rilpivirine concentrations on Day 1 and two subjects with quantifiable rilpivirine concentrations on Day 8. In the second session, in Group 2 (excluding replacement subjects), there were three subjects with quantifiable rilpivirine concentrations on Day 1. However, these concentrations were 5% or less of the subject's C_{max} for the session and no adjustments were necessary for the pharmacokinetic analyses. All subjects had didanosine concentrations that were less than the lower limit of quantification (LLOQ) on Day 1 in the second session.

In addition, 10 additional subjects were enrolled in session 2 in order to replace samples that were lost during shipment.

Rilpivirine

Table 2-Pharmacokinetic parameters for rilpivirine 150 mg once daily and rilpivirine 150 mg once daily administered two hours after didanosine 400 mg once daily [%FI=100 x $[(C_{max}-C_{min})/C_{ss,av}]$]

Pharmacokinetics of TMC278 (mean±SD, t_{max} : median [range])	TMC278 + ddI (Test)	TMC278 Alone (Reference)
n	21	14
t_{max} , h	4.0 [3.0-4.0]	4.0 [2.0-4.0] ^a
C_{0h} , ng/mL	644 ± 218	542 ± 138
C_{min} , ng/mL	527 ± 163	491 ± 107
C_{max} , ng/mL	1379 ± 463	1366 ± 384 ^a
AUC_{24h} , ng.h/mL	18429 ± 5085	18286 ± 4130
$C_{ss,av}$, ng/mL	768 ± 212	762 ± 172
FI, %	110.5 ± 30.3	115.3 ± 18.8

^a For C_{max} and t_{max} , n =15

Table 3-Statistical analysis for rilpivirine 150 mg once daily and rilpivirine 150 mg once daily administered two hours after didanosine 400 mg once daily

Parameter	Test/Ref. (n)		Least Squares Means				p-value	
			TMC278 +ddI (Test)	TMC278 Alone (Reference)	Treatment ratio, % and 90% CI ^a (Test/Reference)		Treatment	Randomization Group
C _{0h} , ng/mL	21	14	603	557	108	99 – 118	0.1223	0.7488
C _{min} , ng/mL	21	14	502	500	100	92 – 109	0.9309	0.7075
C _{max} , ng/mL	21	15	1312	1309	100	90 – 110	0.9644	0.5508
AUC _{24h} , ng.h/ml	21	14	17941	17936	100	95 – 106	0.9930	0.5648
Parameter	Test/Ref. (n)		Median		p-value (Wilcoxon Signed Rank Test)			
			TMC278 +ddI (Test)	TMC278 Alone (Reference)	Treatment		Randomization Group	
t _{max} , h	21 ^b	15 ^b	4.0	4.0	1.0000		-	

^a 90% confidence interval; ^b n = 12 for Wilcoxon signed rank test

When rilpivirine was administered two hours after didanosine, the mean rilpivirine C_{0h} value was increased, and minimal differences were observed in the mean rilpivirine C_{min}, C_{max}, and AUC_(0-24h) values compared to rilpivirine when administered by itself. The 90% confidence interval for rilpivirine C_{0h}, C_{min}, C_{max} and AUC_(0-24h) were within 80%-125%.

Based on evaluating the mean rilpivirine concentrations, steady state appears to not have been achieved by Day 7 in either the first or second session (plots of the individual rilpivirine predose concentrations were not provided). However, the conclusions drawn from the trial regarding didanosine's impact on the rilpivirine exposure would still be applicable.

Didanosine

For didanosine, the C_{0h} and C_{min} values were not reported because on Days 7 and 14 the predose concentrations were less than the lower limit of quantification (LLOQ).

Table 4-Didanosine plasma pharmacokinetic parameters (administered as didanosine 400 mg once daily and rilpivirine 150 mg once daily administered two hours after didanosine 400 mg once daily) [%FI=100 x ((C_{max} - C_{min})/ $C_{ss,av}$)]

Pharmacokinetics of ddI (mean±SD, t_{max} : median [range])	TMC278 + ddI (Test)	ddI Alone (Reference)
n	13	13
t_{max} , h	2.0 [1.0-3.0]	2.0 [1.0-3.0]
C_{0h} , ng/mL	NQ	NQ
C_{min} , ng/mL	NQ	NQ
C_{max} , ng/mL	1270 ± 426	1398 ± 538
AUC _{24h} , ng.h/mL	4140 ± 1181	3643 ± 944
$C_{ss, av}$, ng/mL	173 ± 49	152 ± 39
FI, %	747 ± 215	924 ± 313

NQ: Not Quantifiable

Table 5-Statistical analysis for didanosine in plasma (administered as didanosine 400 mg once daily and rilpivirine 150 mg once daily administered two hours after didanosine 400 mg once daily)

			Least Squares Means				p-value		
	Test/Ref. (n)		TMC278 + ddI (Test)	ddI Alone (Reference)	Treatment ratio, % and 90% CI ^a (Test/Reference)		Treatment	Period	Sequence
C_{max} , ng/mL	13	13	1260	1317	96	80 - 114	0.6669	0.7780	0.1428
AUC _{24h} , ng.h/mL	13	13	3985	3548	112	99 - 127	0.1203	0.8951	0.7819
			median		p-value (Koch Analysis)				
	Test/Ref. (n)		TMC278 + ddI (Test)	ddI Alone (Reference)	Treatment		Period	Sequence	
t_{max} , h	12	12	2.0	2.0	0.6342		0.7338	0.2424	

^a 90% confidence interval

When rilpivirine was administered two hours after didanosine, minimal differences were observed in the mean didanosine C_{max} value, and the AUC_(0-24h) value was increased compared to didanosine when administered by itself. The 90% confidence interval for didanosine C_{max} was within 80%-125% and the 90% confidence interval for didanosine AUC_(0-24h) was not within 80%-125%.

The predose didanosine concentrations were not evaluated to determine if steady state was achieved by Day 7 because the predose didanosine concentrations for Days 1, 3, 5, 6, and 7 were less than the lower limit of quantification for all subjects.

10.4 Safety Issues

No deaths or other serious adverse events were reported for the trial. One subject that withdrew from the trial reported grade 3 increased pancreatic lipase and grade 4 increased lipase during rilpivirine administration by itself. Another subject also experienced a grade 3 increase in cholesterol that was not reported as an adverse event. The most common reported adverse event was headache (see Table 6 for information regarding the number of subjects).

Table 6-Adverse event incidence categorized by system organ class and preferred term reported in more than one subject (includes original and replacement subjects)

<i>System Organ Class Preferred Term n (%)</i>	TMC278 N = 16	ddI N = 22	ddI + TMC278 N = 21	Follow-up N = 22	Total N = 26
Number (%) of Subjects with AE Data	6 (37.5%)	3 (13.6%)	6 (28.6%)	2 (9.1%)	13 (50.0%)
<i>Nervous System Disorders</i>	5 (31.3%)	1 (4.5%)	2 (9.5%)	0	9 (34.6%)
Dizziness	1 (6.3%)	0	1 (4.8%)	0	2 (7.7%)
Headache	4 (25.0%)	1 (4.5%)	1 (4.8%)	0	6 (23.1%)
<i>Gastrointestinal Disorders</i>	3 (18.8%)	2 (9.1%)	3 (14.3%)	0	7 (26.9%)
Abdominal pain	2 (12.5%)	0	0	0	2 (7.7%)
Loose stools	0	1 (4.5%)	1 (4.8%)	0	2 (7.7%)
Nausea	2 (12.5%)	0	2 (9.5%)	0	4 (15.4%)
<i>General Disorders and Administration Site Conditions</i>	1 (6.3%)	1 (4.5%)	1 (4.8%)	0	3 (11.5%)
Injection site hemorrhage	0	1 (4.5%)	1 (4.8%)	0	2 (7.7%)
<i>Renal and Urinary Disorders</i>	2 (12.5%)	0	1 (4.8%)	0	3 (11.5%)
Pollakiuria	2 (12.5%)	0	0	0	2 (7.7%)

n = number of subjects with that particular AE, % = percentage of subjects with that particular AE, computed against the total number of subjects who are still in the trial in that phase. Successive events are counted only once.

Table 7-Adverse event incidence at least possibly related to rilpivirine categorized by system organ class and preferred term (includes original and replacement subjects)

<i>System Organ Class</i> <i>Preferred Term</i> <i>n (%)</i>	TMC278 N = 16	ddI N = 22	ddI + TMC278 N = 21	Follow-up N = 22	Total N = 26
<i>Nervous System Disorders</i>	5 (31.3%)	0	1 (4.8%)	0	6 (23.1%)
Dizziness	1 (6.3%)	0	0	0	1 (3.8%)
Headache	4 (25.0%)	0	1 (4.8%)	0	5 (19.2%)
Somnolence	1 (6.3%)	0	0	0	1 (3.8%)
<i>Gastrointestinal Disorders</i>	2 (12.5%)	0	1 (4.8%)	0	3 (11.5%)
Abdominal distension	1 (6.3%)	0	0	0	1 (3.8%)
Abdominal pain	2 (12.5%)	0	0	0	2 (7.7%)
Constipation	1 (6.3%)	0	0	0	1 (3.8%)
Flatulence	1 (6.3%)	0	0	0	1 (3.8%)
Nausea	1 (6.3%)	0	1 (4.8%)	0	2 (7.7%)
<i>Investigations</i>	1 (6.3%)	0	0	1 (4.5%)	2 (7.7%)
ALT increased	0	0	0	1 (4.5%)	1 (3.8%)
AST increased	0	0	0	1 (4.5%)	1 (3.8%)
Blood amylase increased	1 (6.3%)	0	0	0	1 (3.8%)
Blood LDH increased	0	0	0	1 (4.5%)	1 (3.8%)
Lipase increased	1 (6.3%)	0	0	0	1 (3.8%)
<i>Psychiatric Disorders</i>	0	0	2 (9.5%)	0	2 (7.7%)
Anxiety	0	0	1 (4.8%)	0	1 (3.8%)
Insomnia	0	0	1 (4.8%)	0	1 (3.8%)
<i>Renal and Urinary Disorders</i>	1 (6.3%)	0	1 (4.8%)	0	2 (7.7%)
Proteinuria	0	0	1 (4.8%)	0	1 (3.8%)
Pollakiuria	1 (6.3%)	0	0	0	1 (3.8%)
<i>Musculoskeletal and</i> <i>Connective Tissue Disorders</i>	1 (6.3%)	0	0	0	1 (3.8%)
Myalgia	1 (6.3%)	0	0	0	1 (3.8%)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, LDH = lactate dehydrogenase

n = number of subjects with that particular AE, % = percentage of subjects with that particular AE, computed against the total number of subjects who are still in the trial in that phase. Successive events are counted only once.

Table 8-Adverse event incidence at least possibly related to didanosine categorized by system organ class and preferred term (includes original and replacement subjects)

<i>System Organ Class</i> <i>Preferred Term</i> <i>n (%)</i>	TMC278 N = 16	ddI N = 22	ddI + TMC278 N = 21	Follow-up N = 22	Total N = 26
<i>Gastrointestinal Disorders</i>	0	2 (9.1%)	1 (4.8%)	0	3 (11.5%)
Aphthous stomatitis	0	1 (4.5%)	0	0	1 (3.8%)
Loose stools	0	1 (4.5%)	0	0	1 (3.8%)
Nausea	0	0	1 (4.8%)	0	1 (3.8%)
<i>Investigations</i>	0	1 (4.5%)	0	1 (4.5%)	2 (7.7%)
Blood triglycerides increased	0	1 (4.5%)	0	0	1 (3.8%)
ALT increased	0	0	0	1 (4.5%)	1 (3.8%)
AST increased	0	0	0	1 (4.5%)	1 (3.8%)
Blood LDH increased	0	0	0	1 (4.5%)	1 (3.8%)
<i>Nervous System Disorders</i>	0	1 (4.5%)	1 (4.8%)	0	2 (7.7%)
Headache	0	1 (4.5%)	1 (4.8%)	0	2 (7.7%)
<i>Psychiatric Disorders</i>	0	0	2 (9.5%)	0	2 (7.7%)
Anxiety	0	0	1 (4.8%)	0	1 (3.8%)
Insomnia	0	0	1 (4.8%)	0	1 (3.8%)
<i>Renal and Urinary Disorders</i>	0	0	1 (4.8%)	0	1 (3.8%)
Proteinuria	0	0	1 (4.8%)	0	1 (3.8%)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, LDH = lactate dehydrogenase

n = number of subjects with that particular AE, % = percentage of subjects with that particular AE, computed against the total number of subjects who are still in the trial in that phase. Successive events are counted only once.

11. Discussion and Conclusions

Based on the results from the drug-drug interaction trial, the following conclusions can be made:

- When rilpivirine was administered two hours after didanosine, the mean rilpivirine C_{0h} value was increased by 8%, and minimal differences were observed in the mean rilpivirine C_{min} , C_{max} , and $AUC_{(0-24h)}$ values (0% increase in all three parameters) compared to rilpivirine when administered by itself. The 90% confidence interval for rilpivirine C_{0h} , C_{min} , C_{max} and $AUC_{(0-24h)}$ were within 80%-125%.
- When rilpivirine was administered two hours after didanosine, minimal differences were observed in the mean didanosine C_{max} value (decrease of 4%), and the $AUC_{(0-24h)}$ value was increased by 12% compared to didanosine when administered by itself. The 90% confidence interval for didanosine C_{max} was within 80%-125% and the 90% confidence interval for didanosine $AUC_{(0-24h)}$ was not within 80%-125%.

Didanosine does not result in clinically relevant changes in the exposure of rilpivirine and a dose adjustment for rilpivirine is not necessary. Didanosine is not a substrate of cytochrome P450 enzymes. The mechanism underlying the increase in didanosine exposure is unclear. Based on the results from this trial, a rilpivirine dosage regimen of 125 mg once daily does not result in clinically relevant changes in the exposure of didanosine and a dose adjustment for didanosine is not necessary. However, it is important to note that in the absence of identifying the mechanism behind the increase in didanosine exposure, an extrapolation of the effects of rilpivirine 25 mg once daily on didanosine 400 mg once daily can not be made.

In the proposed prescribing information for rilpivirine, the applicant recommends administering didanosine (b) (4). This recommendation differs from the administration of didanosine and rilpivirine in the C106 trial, where didanosine was administered two hours before rilpivirine (which is administered with a meal). The prescribing information for didanosine (Videx[®] EC) capsules does not provide specific time interval recommendations for spacing out administration of didanosine from meals. The prescribing information for didanosine (Videx[®]) pediatric powder for oral solution states that didanosine should be administered on an empty stomach a minimum of 30 minutes before or 2 hours after meals. The didanosine pediatric powder is mixed with antacid. There is no drug-drug interaction data currently available for administering a combination of didanosine pediatric powder and rilpivirine. However, in order to minimize the potential for the didanosine pediatric powder to alter the absorption of rilpivirine, a recommendation will be sent to the applicant to change the labeling information to state that didanosine should be administered at least two hours before (to minimize the effects of antacids) or four hours after rilpivirine (to account for the median occurrence of the maximum rilpivirine concentration [t_{max}] at 4 hours). This recommendation would also be applicable to the delayed release capsules (Videx[®] EC).

Trial R278474-C108

A phase I, open-label, randomized, three-way crossover trial in 16 healthy subjects to establish the two-way pharmacokinetic interaction between rilpivirine and rifampin at steady-state

Dates: May 25 – September 20, 2004

Trial Site:

Summary of Findings:

Rifampin 600 mg q.d. had a statistically and clinically significant effect on the steady-state pharmacokinetics of rilpivirine 150 mg q.d. Co-administration of rifampin and rilpivirine for 7 days decreased the steady-state rilpivirine exposures (AUC_{24h}) by about 80% when compared to reference exposures produced by rilpivirine alone. This pronounced decrease in rilpivirine exposure is likely due to the inductive effects of rifampin on CYP3A4. On the other hand, steady-state rilpivirine had no clinically significant effect on the steady-state pharmacokinetics of rifampin and its active metabolite 25-desacetylriofampin. From a safety perspective, healthy subjects were able to tolerate treatment with rilpivirine alone or in combination with rifampin. Only one patient dropped out from the trial due to a grade 3 adverse event during rifampin treatment. Based on results from this trial, rilpivirine and rifampin should not be co-administered.

Objectives:

The primary objective of the trial was to investigate the effect of steady-state rifampin on the steady-state pharmacokinetics of rilpivirine, and the effect of steady-state rilpivirine on the steady-state pharmacokinetics of rifampin and its active metabolite 25-desacetylriofampin. The secondary objective of the trial was to investigate the safety and tolerability of rilpivirine and rifampin when co-administered for 7 days in healthy subjects.

Design:

This was a phase I, open-label, randomized, 3-way crossover trial to determine the pharmacokinetic interaction between rilpivirine and rifampin at steady-state. The trial was divided into 3 sessions. In each session, subjects received one of 3 treatments (Treatment A, B, or C). Randomization was done in such a way that each subject received one different treatment in each session.

Treatment A: Rilpivirine 150 mg q.d. for 7 days

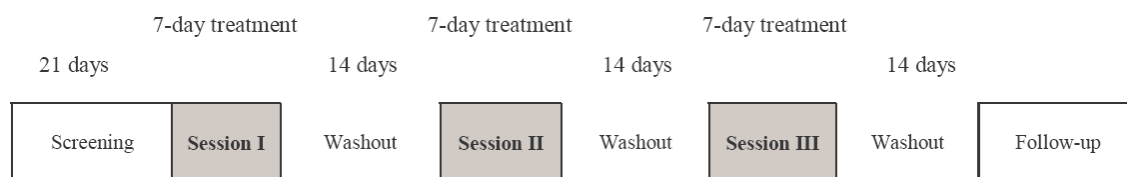
Treatment B: Rifampin 600 mg q.d. for 7 days

Treatment C: Rilpivirine 150 mg q.d. + rifampin 600 mg q.d. for 7 days

Washout: After each session for at least 14 days

Full pharmacokinetic profiles of rilpivirine, and or/rifampin and 25-desacetylriofampin were determined on day 7 of each treatment session.

Figure 1 Trial Design



The trial included 16 Caucasian healthy subjects (10 males and 6 females of non-childbearing potential). The trial enrolled subjects between 18 to 55 years with normal body weight (BMI 18.0 to 30.0 kg/m²) and cortisol levels ≥ 19.9 µg/dL at screening. Subjects were excluded from the trial if they had any current or previous adrenal illness, viral infection (HIV-1, HIV-2, HAV, HBV, HCV), or the following laboratory abnormalities considered \geq grade 1: serum creatinine, pancreatic amylase or lipase, hemoglobin, platelet count, absolute neutrophil count, total bilirubin, AST, and ALT. Subjects were also excluded if they had a history or suspicion of alcohol, barbiturate, amphetamine, or narcotic drug use.

The use of medications, herbal medications, and dietary supplements was prohibited at least 14 before the first dose of trial medication, except for ibuprofen. Subjects were not allowed to consume alcoholic or quinine-containing beverages between 24 hours before each intake of trial medication until the end of each session. Consumption of grapefruit and grapefruit juice was not allowed between 7 days before each intake of trial medication until the end of each session.

Investigational Products:

Rilpivirine was administered as a 25 mg/mL oral solution in 100% PEG400 (Formulation F002). The solution was manufactured and quality assured by J&JPRD, Beerse, Belgium. Batch numbers of rilpivirine were 04D01/F002 and 04C29/F002 (expiry date: January 2005 and December 2004, respectively). An oral dispenser was used to administer 6 mL of rilpivirine oral solution.

Rifampin was administered as a 300 mg capsule (Rifadin[®]) and was supplied and obtained by J&JPRD from the Belgian market. Batch number of rifampin was 03K24 (expiry date: November 2006).

Rationale for Trial Doses:

Rilpivirine was dosed at 150 mg q.d. (6-fold higher than the to-be-marketed dose, 25 mg q.d.) for 7 days to achieve steady state concentrations. In previous clinical trials, rilpivirine was generally safe and well tolerated after multiple oral doses of up to 150 mg q.d. for 14 days. It is noteworthy to mention that 100 mg of the oral solution of rilpivirine generally produced about ~20% greater exposure ($AUC_{[0-\infty]}$) than was achieved with a similar dose delivered with the 100 mg tablet F002 formulation in the R278474-C102 trial under fed conditions.

Rilpivirine systemic exposures generally increase in a dose proportional fashion and it is anticipated that a dose of 150 mg q.d. could deliver exposures that are ~6-fold higher than those produced by 25 mg q.d. If a drug-drug interaction occurs with 150 mg q.d., then the percentage change in rilpivirine exposure could be potentially scaled down to one produced by 25 mg q.d. (assuming similar rifampin induction effects with the two rilpivirine dosage regimens and similar rilpivirine effects on rifampin).

Rifampin (Rifadin[®]) was administered for 7 days at 600 mg q.d. This is the maximum recommended daily dose as stated in the manufacturer's package insert (Sanofi-Aventis).

Dosage and Administration:

Each subject was randomly assigned to receive 3 treatments. All treatments started on day 1 of each session after an overnight fast of at least 10 hours. Only water intake was allowed until 2 hours before drug intake. When administered alone, rilpivirine and rifampin were taken between 7 a.m. and 10 a.m. within 10 minutes after completion of a standardized breakfast at the unit. When co-administered, rifampin was taken within 10 minutes after completion of a standardized meal at the unit and rilpivirine was administered within 5 minutes after rifampin intake.

Pharmacokinetic Assessments:

Blood samples were collected to determine plasma concentrations of rilpivirine, rifampin, and 25-desacetylriofampin during all three treatment sessions as follows:

Days 1, 3, and 5 at predose (0),

Day 7 at predose (0), 0.5, 1, 2, 3, 4, 6, 8, 12, 16 hours post dose

Day 8 at predose (24 hours post dose)

Analytical Methods – Bioanalysis:

The bioanalytical methods for rilpivirine, rifampin, and 25-desacetylriofampin are acceptable. Two different laboratories performed the analysis 1) J&J PRD in Beerse, Belgium analyzed rilpivirine and 2) (b) (4) analyzed rifampin and 25-desacetylriofampin.

Rilpivirine concentrations in plasma were determined using a validated LC-MS/MS method with a lower limit of quantification (LLOQ) of 1.0 ng/mL and the upper limit of quantification (ULOQ) of 2000 ng/mL.

Rifampin and 25-desacetylriofampin concentrations in plasma were determined using a validated HPLC-UV method with LLOQ of 0.2 µg/mL for rifampin and 0.1 µg/mL for 25-desacetylriofampin. The ULOQ was 40 µg/mL for rifampin and 5 µg/mL for 25-desacetylriofampin. All standard samples were prepared using reference standards acquired from (b) (4) (rifampin) and (b) (4) (25-desacetylriofampin).

Table 1 Precision (% CV) and accuracy (% relative error) of calibration standards and QC samples for the bioanalysis of R278474-C108 rilpivirine and rifampin plasma concentrations

	Rilpivirine		Rifampin		25-Desacetylriofampin	
	Calibration Stds	QCs	Calibration Stds	QCs	Calibration Stds	QCs
% CV	0.5 – 4.2	0.3 – 8.8	1.2 – 4.9	6.1 – 7.1	1.5 – 5.7	5.4 – 6.2
% Relative error	≤2.2	≤3.2	≤1.2	≤5.7	≤4.1	≤5.4
	≥0.9997 (r value)		≥0.9995 (correlation coefficient)		≥0.9991 (correlation coefficient)	

The submitted rilpivirine long term stability data of 1528 days at -20°C covered the duration of long term rilpivirine stability data necessary for the TMC278-C108 trial.

Long-term stability of rifampin and 25-desacetylriofampin in frozen plasma was demonstrated at -20°C and -70°C in heparin human plasma for a period of 92 days. Plasma samples from this trial were stored at -20°C and analyzed within 92 days.

Pharmacokinetic Analysis:

Pharmacokinetic analysis was performed by (b) (4) using SAS System for Windows® version 8.2 (SAS Institute Inc., Cary, NC). A non-compartmental model with extravascular input was used for the pharmacokinetic analysis. Nominal sampling times were used for the calculation of all the pharmacokinetic parameters. In case major aberrations (>10.0% deviations from the scheduled time) occurred, actual sampling times were used in the PK analysis.

Statistical Analysis:

Statistical analysis was performed by (b) (4) using SAS System for Windows[®] version 8.2 (SAS Institute Inc., Cary, NC). Descriptive statistics were calculated for the plasma concentrations of rilpivirine, rifampin, and 25-desacetylrifampin at each time point and for PK parameters. The derived statistical parameters included sample size (n), mean, standard deviation, coefficient of variation, geometric mean, median, minimum and maximum.

Statistical analyses were performed using day 7 of treatment C (rilpivirine + rifampin) as test and day 7 of treatment A or B (rilpivirine or rifampin alone) as reference. The primary parameters were C_{min} , C_{max} , and AUC_{0-24h} on the logarithmic scale.

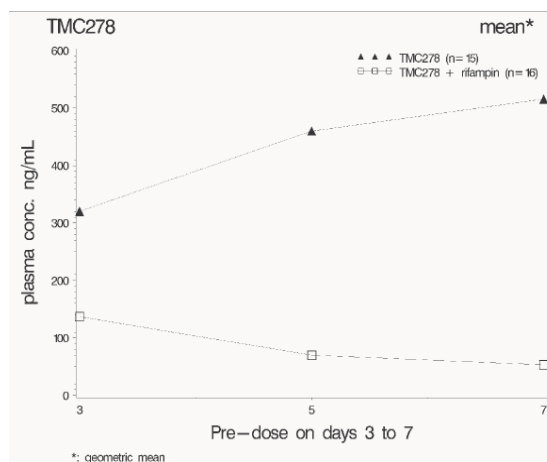
The least square means of the primary parameters for each treatment were estimated with a linear mixed effects model, controlling for treatment, sequence, and period as fixed effects and subject as random effect. A 90% confidence interval was constructed around the difference between the LS means of test and reference. Period effects were considered significant at the 5% level and sequence effects were considered significant at the 10% level.

Pharmacokinetic results, rilpivirine:

Fifteen subjects completed the trial and 1 subject dropped out during session II (rifampin treatment only) due to an adverse event.

Visual inspection of the mean predose plasma concentrations of rilpivirine revealed that steady state levels may have been achieved by Day 7 during Treatment A (rilpivirine alone) and Treatment C (rilpivirine + rifampin). There were no significant differences noted in most subjects in comparing the individual Day 7 and Day 8 24 hour values. In general, the mean predose plasma concentrations of rilpivirine were lower during combination treatment than with rilpivirine alone. See figure 2 below

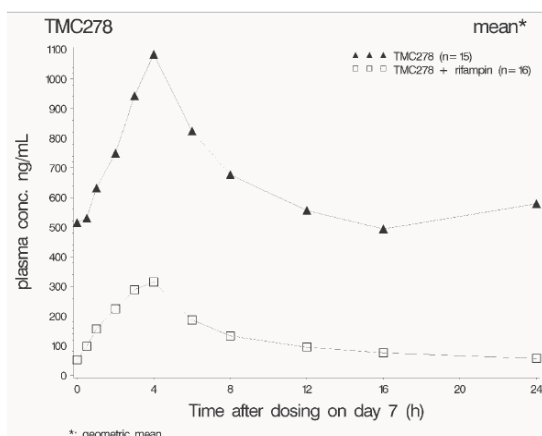
Figure 2 Geometric Mean Predose Concentrations



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Moreover, the mean steady-state concentration-time profile of rilpivirine on Day 7 was also decreased during combination treatment with rifampin. See figure 3 below

Figure 3 Mean Steady-State Plasma Concentration-Time Curve of Rilpivirine



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The statistical analysis confirmed an 80% decrease in rilpivirine exposure (AUC_{24h}) after combined treatment with rifampin. See table 3 below.

Table 3 Statistical Evaluation of the Pharmacokinetics of Rilpivirine

TMC278	Least square means				p-value		
Parameter	TMC278+ rifampin Test (C)	TMC278 Ref. (A)	ratio, % Test/Ref.	90% CI ^a	Treatment	Period	Sequence
n	16	15					
C_{oh} , (ng/mL)	53	507	10	9 - 12	<.0001	0.0522	0.6865
C_{min} , (ng/mL)	50	456	11	10 - 13	<.0001	0.1647	0.5526
C_{max} , (ng/mL)	341	1091	31	27 - 36	<.0001	0.3030	0.9614
AUC_{24h} , (ng.h/mL)	3110	15545	20	18 - 23	<.0001	0.3285	0.9567

^a 90% confidence interval of ratio

Pharmacokinetic results, rifampin and 25-desacetylriofampin:

No clinically significant differences were observed in the steady-state plasma concentrations of rifampin and 25-desacetylriofampin during co-administration with or without rilpivirine. The metabolite ratios, expressed as the ratio of the AUC of 25-desacetylriofampin over the AUC of rifampin, were similar after Treatment B (rifampin) and C (rilpivirine + rifampin). The 90% confidence intervals were within 80%-125% for both analytes, with the exception of $AUC_{(0-24h)}$ for 25-desacetylriofampin. See Table 2 below.

Table 2 Statistical Evaluation of the Pharmacokinetics of rifampin and 25-Desacetyl rifampin

rifampin	Least square means				p-value		
Parameter	TMC278+ rifampin Test (C)	rifampin Ref. (B)	ratio, % Test/Ref.	90% CI ^a	Treatment	Period	Sequence
n	16	15					
C _{max} , µg/mL	8.7	8.55	102	93 - 112	0.7411	0.0148	0.3742
AUC _{24h} , µg.h/mL	40.4	40.6	99	92 - 107	0.8873	0.0128	0.3477
AUC _{last} , µg.h/mL	38.2	38.3	100	93 - 108	0.9870	0.0138	0.3449
25-desacetyl rifampin	Least square means				p-value		
Parameter	TMC278+ rifampin Test (C)	rifampin Ref. (B)	ratio, % Test/Ref.	90% CI ^a	Treatment	Period	Sequence
n	16	15					
C _{max} , µg/mL	0.717	0.715	100	87 - 115	0.9782	0.1158	0.5690
AUC _{24h} , µg.h/mL	3.58	3.93	91	77 - 107	0.3338	0.0752	0.5586
AUC _{last} , µg.h/mL	2.94	3.07	96	83 - 110	0.5858	0.0573	0.4520

^a 90% confidence interval**Discussion and Conclusions:**

The applicant omitted C_{min} from the statistical evaluation because this parameter was frequently below the LLOQ for rifampin and its metabolite. The Day 7 LLOQs made it difficult to calculate the AUC_{24h} of rifampin and its metabolite. For instance, most subjects had rifampin and 25-desacetyl-rifampin plasma concentrations below the LLOQ for the 16 and 24 hr time points on Day 7 of Treatments B and C. The omission of C_{min} from the analysis should not impact the overall findings of the trial because the C_{max} and AUC_{last} of rifampin and 25-desacetyl-rifampin were similar in treatment C and treatment B. Therefore, it would be reasonable to assume that C_{min} values were also similar in both treatment sessions even if the actual concentrations could not be measured.

Four subjects had predose concentrations of rilpivirine ranging from 2.52 ng/mL to 11.5 ng/mL on Day 1 of treatment C (rilpivirine + rifampin). This observation suggests that the 14-day washout period prior to treatment C was insufficient to prevent carry-over concentrations of rilpivirine. Fortunately, these relatively low concentrations may not influence the steady-state pharmacokinetics of rilpivirine because they constitute <5% of the individual's C_{max} during treatment C.

All subjects reported at least 1 adverse event but most of these events were grade 1 or 2. The most commonly reported AEs during the trial were chromatemia (100%), headache (38%), and hypercholesterolemia (31%). Only one subject discontinued treatment due to an adverse event (grade 3, increased lipase) during treatment with rifampin.

In summary, rifampin 600 mg q.d. had a statistically and clinically significant effect on the steady-state pharmacokinetics of rilpivirine 150 mg q.d. Co-administration of rifampin and rilpivirine for 7 days decreased the steady-state rilpivirine exposures (AUC_{24h}) by about 80% when compared to reference exposures produced by rilpivirine alone. This pronounced decrease in rilpivirine exposure is likely due to the inductive effects of rifampin on CYP3A4. On the other hand, steady-state rilpivirine had no clinically significant effect on the steady-state pharmacokinetics of rifampin and its active metabolite 25-desacetyl-rifampin. From a safety

perspective, healthy subjects were able to tolerate treatment with rilpivirine alone or in combination with rifampin. Based on results from this trial, rilpivirine and rifampin should not be co-administered.

1. Title

A Phase I, open-label, randomized, 2-way crossover trial in 16 healthy subjects to establish the 2-way pharmacokinetic interaction between steady-state TMC278 and paracetamol

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at (b) (4) from February 14, 2005 to May 3, 2005.

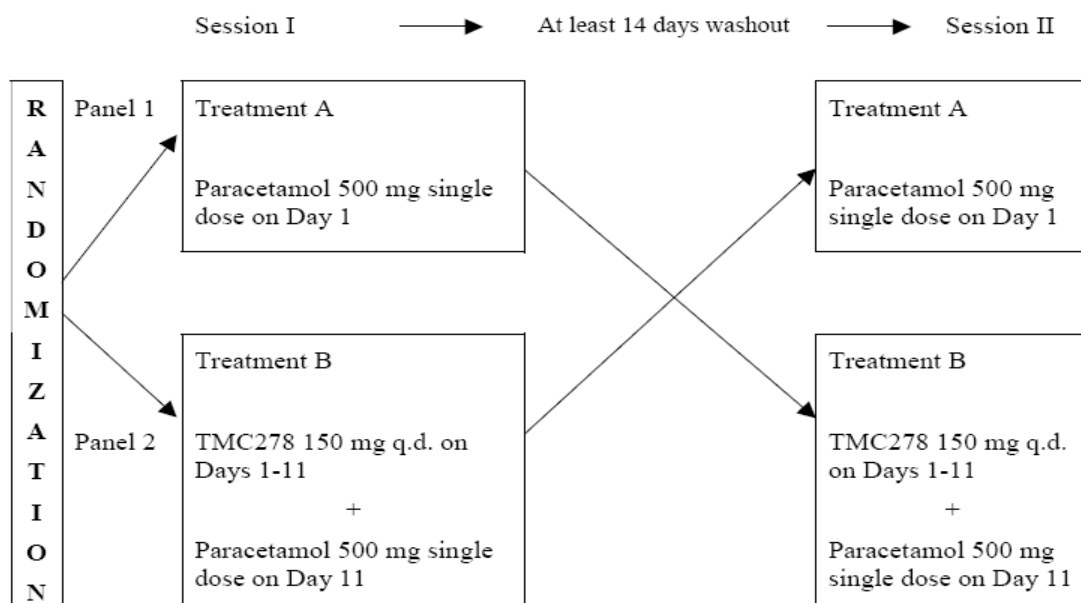
3. Objectives

The objectives of the trial were to evaluate the effect of single dose acetaminophen (paracetamol) on steady state rilpivirine pharmacokinetics and the effect of steady state rilpivirine on single dose acetaminophen pharmacokinetics.

4. Trial Design

TMC278-C109 was a Phase I, open label, randomized, 2 way crossover clinical trial that enrolled male and female subjects between 18 and 55 years old. The trial design is displayed in Figure 1.

Figure 1-TMC278-C109 trial design



5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Use of ibuprofen was permitted up to three days before administration of trial medication. Afterwards, ibuprofen use was permitted up to 400 mg/day until the end of each treatment arm. Any medications were to be discontinued a minimum of fourteen days before administration of trial medication (with the exception of ibuprofen or hormone replacement therapy in postmenopausal women). Use of herbal medicines or dietary supplements was not permitted from fourteen days before initiation of the trial and throughout the trial.

Use of liquids containing alcohol or quinine was not permitted from 24 hours before administration of trial medication until 96 hours after administration of trial medication. Intake of grapefruit and grapefruit juice was not permitted from 7 days before administration of trial medication until 96 hours after administration of trial medication.

In the event of an adverse event, the following medications were permitted:

- A) Rash or an allergic reaction: cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents (specific medications were not included in the trial report)
- B) Nausea: antiemetics (specific medications were not included in the trial report)
- C) Diarrhea: loperamide

6. Dosage and Administration

A standard meal was administered in the morning and medication was administered within 10 minutes after completion of the meal. There was no specific information in the trial report regarding whether rilpivirine and acetaminophen were coadministered or whether one medication was administered prior to the second medication.

7. Rationale for Doses Used in the Trial

The rilpivirine dosage regimen that was administered to all subjects was 150 mg once daily. In contrast, the rilpivirine dosage regimen that was evaluated in the Phase 3 clinical trials and the recommended dosage regimen in the proposed prescribing information is 25 mg once daily with a meal. Across the dose range of 25 mg to 150 mg, increases in rilpivirine exposure were approximately dose proportional. The C109 trial was conducted to evaluate the impact of coadministration of both medications on metabolism through glutathione conjugation, which is saturable. The specific effects of rilpivirine on glutathione conjugation with 25 mg once daily dosing has not been evaluated, however the C109 trial provides information on whether such a trial would be necessary.

The single dose of acetaminophen administered in the trial was 500 mg compared to the recommended dosage regimens of 1 gram every 4 to 6 hours or 650 mg every 4 to 6 hours for pain and fever.

8. Drugs Used in the Trial

Rilpivirine 25 mg tablets (formulation F001) and 100 mg tablets (formulation F002) were administered in the trial. Both of these tablets were Phase 2b formulations that were used in the Phase 1 or 2 trials.

Acetaminophen (Perdolan[®]) 500 mg tablets were administered in the trial.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

For Treatment A (acetaminophen administered alone), blood samples for analysis of acetaminophen and acetaminophen metabolite concentrations were obtained on Days 1 and 2 at predose and up to 24 hours postdose.

For Treatment B, blood samples for analysis of rilpivirine concentrations were obtained on Days 10 and 11 at predose and up to 24 hours postdose. On Days 1, 5, 6 and 7, a predose sample was drawn to determine rilpivirine concentrations. Rilpivirine, acetaminophen, and acetaminophen metabolite concentrations were obtained on Days 11 and 12 at predose and up to 24 hours postdose.

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a validated LC/MS/MS method by Johnson and Johnson Pharmaceutical Research and Development. The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the TMC278-C109 trial, precision and accuracy were evaluated using the low (2.51 ng/mL), medium (50.2 ng/mL), and high (1560 ng/mL) QC samples. The corresponding rilpivirine inter-run accuracy values were -6% for the low QCs, -6% for the medium QCs, and -1.3% for the high QCs, and the rilpivirine inter-run precision values were 5% for the low QCs, 2.7% for the medium QCs, and 3.4% for the high QCs. The submitted rilpivirine long term stability data of 1528 days at -20°C covered the duration of long term rilpivirine stability data necessary for the TMC278-C109 trial.

The method and bioanalysis of acetaminophen, acetaminophen glucuronide, and acetaminophen sulphate are acceptable. Plasma samples were analyzed for acetaminophen, acetaminophen glucuronide, and acetaminophen sulphate concentrations using a validated HPLC-UV method by (b) (4). The lower limit of quantification for acetaminophen was 0.5 ng/mL and the upper limit of quantification was 50 ng/mL. There were no precision or accuracy issues identified for acetaminophen based on the bioanalytical report. For the TMC278-C109 trial, precision and accuracy were evaluated using QC samples at 1.5 (low QC), 7.5 (medium QC) and 40 ng/mL (high QC). The corresponding acetaminophen inter-run accuracy values were

-0.4% for the low QCs, -2% for the medium QCs, and -1.4% for the high QCs, and the acetaminophen inter-run precision values were 1.4% for the low QCs, 1.6% for the medium QCs, and 0.8% for the high QCs. The lower limit of quantification for acetaminophen glucuronide was 0.5 ng/mL and the upper limit of quantification was 50 ng/mL. There were no precision or accuracy issues identified for based on the bioanalytical report. For the TMC278-C109 trial, precision and accuracy were evaluated using QC samples at 1.5 (low QC), 7.5 (medium QC) and 40 ng/mL (high QC). The corresponding acetaminophen glucuronide inter-run accuracy values were 0.6% for the low QCs, -0.5% for the medium QCs, and -1.2% for the high QCs, and the acetaminophen inter-run precision values were 1.3% for the low QCs, 1.3% for the medium QCs, and 1.2% for the high QCs. The lower limit of quantification for acetaminophen sulphate was 0.5 ng/mL and the upper limit of quantification was 50 ng/mL. There were no precision or accuracy issues identified for based on the bioanalytical report. For the TMC278-C109 trial, precision and accuracy were evaluated using QC samples at 1.5 (low QC), 7.5 (medium QC) and 40 ng/mL (high QC). The corresponding acetaminophen sulphate inter-run accuracy values were 0% for the low QCs, -0.9% for the medium QCs, and -2.9% for the high QCs, and the acetaminophen inter-run precision values were 2.5% for the low QCs, 2.4% for the medium QCs, and 2.5% for the high QCs. The submitted acetaminophen, acetaminophen glucuronide and acetaminophen sulphate long term stability data of 86 days at -20°C covered the duration of long term stability data necessary for the TMC278-C109 trial.

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate pharmacokinetic parameters, including C_{min} , C_{max} , and $AUC_{(0-\tau)}$ for rilpivirine and C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ for acetaminophen and the acetaminophen metabolites. If a major difference (> 10.00% deviation from the scheduled time) was observed, the actual sampling time was used instead of the scheduled sampling time.

Statistical Analysis

Descriptive statistics were calculated for rilpivirine, acetaminophen and the acetaminophen metabolites plasma concentrations and pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), geometric mean, median, and the minimum and maximum values.

Statistical analysis involved comparison of rilpivirine log transformed pharmacokinetic parameters for Day 11, Treatment B (test arm) compared to Day 10, Treatment B (reference arm). For acetaminophen and the acetaminophen metabolites, statistical analysis involved comparison of acetaminophen and the acetaminophen metabolites log transformed pharmacokinetic parameters for Day 11, Treatment B (test arm) compared to Treatment A (reference arm). C_{0h} (the predose plasma concentrations), C_{min} (the minimum plasma concentrations between 0 hour and the dosing interval $[\tau]$), C_{max} , and $AUC_{(0-\tau)}$ were evaluated for rilpivirine and C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ were evaluated for acetaminophen and the acetaminophen metabolites. Using a linear mixed effects model, least squares means were calculated and 90% confidence intervals were derived

based on the difference of the pharmacokinetic parameter's least squares means for the test and reference arms. The applicant did not specify predetermined "no effect boundaries" for the 90% confidence intervals.

In Treatment B, an assessment was performed to determine if rilpivirine steady state concentrations were achieved, presumably by Day 10, based on predose concentrations from Days 1, 5, 6, 7, 10, and 11.

10. Results

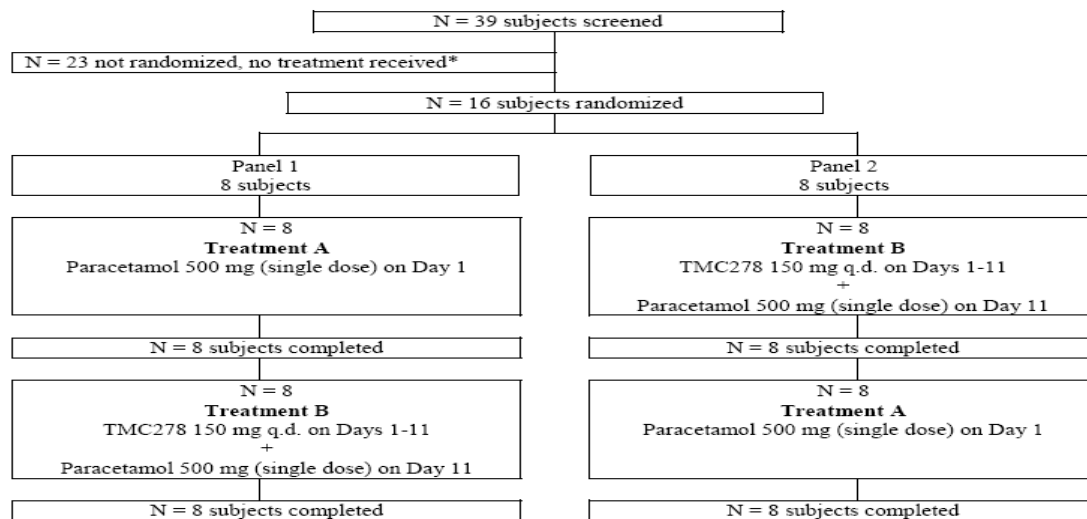
10.1 Subject Demographics and Disposition

Table 1-TMC278-C109 subject demographics

Parameter	Panel 1 N = 8	Panel 2 N = 8	All Subjects N = 16
Age, years			
Median (range)	46.5 (19 - 54)	41.0 (18 - 49)	43.5 (18 - 54)
Height, cm			
Median (range)	173.5 (159 - 181)	174.0 (161 - 185)	174.0 (159 - 185)
Weight, kg			
Median (range)	79.1 (58 - 96)	75.8 (59 - 85)	76.3 (58 - 96)
BMI, kg/m ²			
Median (range)	27.0 (21 - 30)	24.1 (23 - 28)	24.6 (21 - 30)
Race, n (%)			
Caucasian/white	8 (100.0)	8 (100.0)	16 (100.0)
Sex, n (%)			
Female	3 (37.5)	4 (50.0)	7 (43.8)
Male	5 (62.5)	4 (50.0)	9 (56.3)
Type of smoker, n (%)			
No	7 (87.5)	8 (100.0)	15 (93.8)
Yes (Light)	1 (12.5)	0	1 (6.3)

BMI: Body mass index, N: Number of subjects per panel.

Figure 2-TMC278-C109 subject disposition



N: Number of subjects per treatment group.

* Twenty-three subjects were not randomized because they did not meet all the in- and exclusion criteria (18 subjects), withdrew consent (3), or 'other' reason (2).

10.2 Prior and Concomitant Medications

Six subjects administered concurrent medications during the trial. The administered concurrent medications were amoxicillin-clavulanate, fluconazole, ibuprofen, loratidine, meloxicam, and mucopolysaccharide polysulfuric acid ester. With the exception of fluconazole, none of the coadministered medications would be expected to alter CYP 3A metabolism. However, fluconazole was only administered during follow up.

10.3 Pharmacokinetic and Statistical Analysis

All subjects had rilpivirine concentrations that were less than the lower limit of quantification (LLOQ) prior to initiation of Treatment B.

Rilpivirine

Table 2-Pharmacokinetic parameters for rilpivirine 150 mg once daily and rilpivirine 150 mg once daily with single dose acetaminophen 500 mg coadministration [%FI=100 x $([C_{\max}-C_{\min}]/C_{ss,av})$]

Pharmacokinetics of TMC278 (mean \pm SD, t_{\max} : median [range])	TMC278/Paracetamol Test	TMC278 Alone Reference
n	16	16
t_{\max} , h	3.0 [2.0 - 6.0]	4.0 [2.0 - 6.0]
C_{0h} , ng/mL	461 \pm 144	390 \pm 162
C_{\min} , ng/mL	403 \pm 111	323 \pm 111
C_{\max} , ng/mL	1015 \pm 189	937 \pm 237
AUC _{24h} , ng.h/mL	14679 \pm 3015	12799 \pm 3290
$C_{ss, av}$, ng/mL	612 \pm 126	533 \pm 137
FI, %	101.9 \pm 22.5	117.7 \pm 27.9

Both panels were combined in the pharmacokinetic analysis.

Table 3-Statistical analysis for rilpivirine 150 mg once daily and rilpivirine 150 mg once daily with single dose acetaminophen 500 mg coadministration

TMC278	n		Least Squares Means			p-value	
	Test / Ref.		TMC278/ Paracetamol	TMC278 Alone	Treatment Ratio % (90% CI) ^a		
Parameter	Test	Ref.	Test	Reference	Test / Reference	Treatment	Group
C _{0h} , ng/mL	16	16	441	370	119 (108 – 132)	0.0071	0.4409
C _{min} , ng/mL	16	16	389	308	126 (116 – 138)	0.0002	0.2156
C _{max} , ng/mL	16	16	999	914	109 (101 – 118)	0.0573	0.7172
AUC _{24h} , ng.h/mL	16	16	14401	12434	116 (110 – 122)	0.0002	0.4494

Ref. = reference.

^a 90% confidence interval.

Both panels were combined in the pharmacokinetic analysis.

On Day 11 (coadministration with single dose acetaminophen 500 mg), the mean rilpivirine C_{0h}, C_{min}, C_{max}, and AUC_(0-24h) values were increased compared to Day 10 (Treatment B), when rilpivirine was administered by itself. The 90% confidence interval for rilpivirine C_{0h} and C_{min} were not within 80%-125%. The 90% confidence interval for rilpivirine C_{max} and AUC_(0-24h) were within 80%-125%.

Based on evaluating the mean rilpivirine concentrations, steady state appears to have been achieved by Day 10 in Treatment B (plots of the individual rilpivirine predose concentrations were not provided).

Acetaminophen and acetaminophen metabolites

Table 4-Single dose acetaminophen pharmacokinetic parameters (administered as single dose acetaminophen 500 mg and single dose acetaminophen 500 mg with rilpivirine 150 mg once daily coadministration)

Pharmacokinetics of Paracetamol (mean ± SD, t _{max} : median [range])	TMC278/Paracetamol Test	Paracetamol Alone Reference
n	16	16
t _{max} , h	1.0 [0.3 - 2.0]	1.5 [0.3 - 2.0]
C _{max} , µg/mL	5.81 ± 2.08	5.93 ± 2.04
AUC _{last} , µg.h/mL	18.42 ± 4.35	19.98 ± 4.57
AUC _∞ , µg.h/mL	20.72 ± 4.63	22.63 ± 4.89
t _{1/2term} , h	2.05 ± 0.32	2.42 ± 0.37

Both panels were combined in the pharmacokinetic analysis.

Table 5-Statistical analysis for acetaminophen (administered as single dose acetaminophen 500 mg and single dose acetaminophen 500 mg with rilpivirine 150 mg once daily coadministration)

Paracetamol	n	Least Squares Means			p-value		
Parameter	Test / Ref.	TMC278/ Paracetamol Test	Paracetamol Alone Reference	Treatment Ratio, % (90% CI) ^a Test/ Reference	Treatment	Period	Sequence
C _{max} , µg/mL	16 : 16	5.48	5.65	97 (86 – 110)	0.6671	0.0056	0.8192
AUC _{last} , µg.h/mL	16 : 16	17.87	19.52	92 (85 - 99)	0.0569	0.1865	0.5728
AUC _∞ , µg.h/mL	16 : 16	20.16	22.14	91 (86 - 97)	0.0203	0.1014	0.3915
	n	median		p-value (Koch analysis)			
Parameter	Test / Ref.	TMC278/ Paracetamol Test	Paracetamol Alone Reference	Treatment	Period	Sequence	
t _{max} , h	16 : 16	1.0	1.5	0.9517	0.0438	0.9037	

Ref. = reference.

^a 90% confidence interval.

Both panels were combined in the pharmacokinetic analysis.

For Treatment B (Day 11), with single dose acetaminophen and rilpivirine coadministration, minimal differences were observed in acetaminophen C_{max}, and the acetaminophen AUC_(0-last) and AUC_(0-∞) values were decreased compared to Treatment A, when single dose acetaminophen was administered by itself. The 90% confidence interval for acetaminophen C_{max}, AUC_(0-last) and AUC_(0-∞) were within 80%-125%.

Table 6-Single dose acetaminophen glucuronide pharmacokinetic parameters (administered as single dose acetaminophen 500 mg and single dose acetaminophen 500 mg with rilpivirine 150 mg once daily coadministration)

Pharmacokinetics of Paracetamol Glucuronide (mean ± SD, t _{max} : median [range])	TMC278/Paracetamol Test	Paracetamol Alone Reference
n	16	16
t _{max} , h	3.0 [2.0 - 4.0]	3.0 [2.0 - 4.0]
C _{max} , µg/mL	8.38 ± 1.70	8.79 ± 2.05
AUC _{last} , µg.h/mL	54.82 ± 11.89	54.71 ± 12.59
AUC _∞ , µg.h/mL	61.33 ± 12.76	62.59 ± 14.23
t _{1/2term} , h	3.29 ± 0.62	3.46 ± 0.37

Both panels were combined in the pharmacokinetic analysis.

Table 7-Statistical analysis for acetaminophen glucuronide (administered as single dose acetaminophen 500 mg and single dose acetaminophen 500 mg with rilpivirine 150 mg once daily coadministration)

Paracetamol Glucuronide	n	Least Squares means			p-value		
Parameter	Test / Ref.	TMC278/ Paracetamol Test	Paracetamol Alone Reference	Treatment Ratio, % (90% CI) ^a Test/ Reference	Treatment	Period	Sequence
C _{max} , µg/mL	16 / 16	8.22	8.57	96 (90 – 103)	0.2881	0.8594	0.7236
AUC _{last} , µg.h/mL	16 / 16	53.68	53.4	101 (95 – 107)	0.8778	0.3093	0.3562
AUC _∞ , µg.h/mL	16 / 16	60.12	61.09	98 (94 – 103)	0.5635	0.3498	0.2706
	n	Median		p-value (Koch analysis)			
Parameter	Test / Ref.	TMC278/ Paracetamol Test	Paracetamol Alone Reference	Treatment	Period	Sequence	
t _{max} , h	16 / 16	3.0	3.0	0.6737	0.0457	0.3641	

Ref. = reference.

^a 90% confidence interval.

Both panels were combined in the pharmacokinetic analysis.

For Treatment B (Day 11), with single dose acetaminophen and rilpivirine coadministration, minimal differences were observed in acetaminophen glucuronide C_{max}, AUC_(0-last), and AUC_(0-∞) values compared to Treatment A, when single dose acetaminophen was administered by itself. The 90% confidence interval for acetaminophen glucuronide C_{max}, AUC_(0-last), and AUC_(0-∞) were within 80%-125%.

Table 8-Single dose acetaminophen sulphate pharmacokinetic parameters (administered as single dose acetaminophen 500 mg and single dose acetaminophen 500 mg with rilpivirine 150 mg once daily coadministration)

Pharmacokinetics of Paracetamol Sulphate (mean ± SD, t _{max} : median [range])	TMC278/Paracetamol Test	Paracetamol Alone Reference
n	16	16
t _{max} , h	2.0 [1.0 - 3.0]	2.0 [0.8 - 3.0]
C _{max} , µg/mL	3.30 ± 0.73	3.28 ± 0.69
AUC _{last} , µg.h/mL	15.63 ± 4.33	16.47 ± 4.76
AUC _∞ , µg.h/mL	19.00 ± 4.46	19.72 ± 4.93
t _{1/2term} , h	2.69 ± 0.38	2.93 ± 0.39

Both panels were combined in the pharmacokinetic analysis.

Table 9-Statistical analysis for acetaminophen sulfate (administered as single dose acetaminophen 500 mg and single dose acetaminophen 500 mg with rilpivirine 150 mg once daily coadministration)

Paracetamol Sulphate	n	Least Squares Means			p-value		
Parameter	Test / Ref.	TMC278/ Paracetamol Test	Paracetamol Alone Reference	Treatment Ratio, % (90% CI) ^a Test/ Reference	Treatment	Period	Sequence
C_{max} , µg/mL	16 : 16	3.22	3.21	100 (94 – 107)	0.9268	0.3171	0.9769
AUC_{last} , µg.h/mL	16 : 16	15.02	15.82	95 (88 – 102)	0.2408	0.5137	0.4469
AUC_{∞} , µg.h/mL	16 : 16	18.46	19.12	97 (91 – 103)	0.3279	0.8342	0.3425
	n	Median		p-value (Koch Analysis)			
Parameter	Test / Ref.	TMC278/ Paracetamol Test	Paracetamol Alone Reference	Treatment	Period	Sequence	
t_{max} , h	16 : 16	2.0	2.0	0.1936	0.0149	0.0507	

Ref. = reference.

^a 90% confidence interval.

Both panels were combined in the pharmacokinetic analysis.

For Treatment B (Day 11), with single dose acetaminophen and rilpivirine coadministration, minimal differences were observed in acetaminophen sulphate C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ values compared to Treatment A, when single dose acetaminophen was administered by itself. The 90% confidence interval for acetaminophen glucuronide C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ were within 80%-125%.

10.4 Safety Issues

No deaths or other serious adverse events were reported for the trial. No grade 3 or grade 4 adverse events were reported. The most common reported adverse events were headache and pruritus (see Table 10 for information regarding the number of subjects).

Table 10-Adverse event incidence categorized by system organ class and preferred term

System Organ Class Preferred Term n (%)	Trial Phase						
	Paracetamol Alone N = 16	Paracetamol Washout N = 16	TMC278 Alone N = 16	TMC278/ Paracetamol N = 16	TMC278/ Paracetamol Washout N = 16	Follow-up N = 16	Whole Trial N = 16
Any Adverse Event	2 (12.5)	4 (25.0)	11 (68.8)	7 (43.8)	1 (6.3)	5 (31.3)	13 (81.3)
Gastrointestinal Disorders	0	1 (6.3)	4 (25.0)	0	0	0	4 (25.0)
Abdominal distension	0	0	1 (6.3)	0	0	0	1 (6.3)
Dry mouth	0	0	1 (6.3)	0	0	0	1 (6.3)
Eructation	0	1 (6.3)	0	0	0	0	1 (6.3)
Flatulence	0	0	1 (6.3)	0	0	0	1 (6.3)
Peptic ulcer	0	0	1 (6.3)	0	0	0	1 (6.3)
General Disorders and Administration Site Conditions	0	0	0	2 (12.5)	0	0	2 (12.5)
Fatigue	0	0	0	1 (6.3)	0	0	1 (6.3)
Feeling hot	0	0	0	1 (6.3)	0	0	1 (6.3)
Investigations	0	0	3 (18.8)	1 (6.3)	1 (6.3)	1 (6.3)	6 (37.5)
ALT increased	0	0	0	0	1 (6.3)	1 (6.3)	2 (12.5)
Blood amylase increased	0	0	0	1 (6.3)	0	0	1 (6.3)
Blood triglycerides increased	0	0	1 (6.3)	0	0	0	1 (6.3)
Lipase increased	0	0	0	1 (6.3)	0	0	1 (6.3)
Neutrophil count decreased	0	0	2 (12.5)	0	0	0	2 (12.5)
Musculoskeletal and Connective Tissue Disorders	0	0	1 (6.3)	0	0	1 (6.3)	2 (12.5)
Back pain	0	0	1 (6.3)	0	0	0	1 (6.3)
Pain in extremity	0	0	0	0	0	1 (6.3)	1 (6.3)
Nervous System Disorders	2 (12.5)	2 (12.5)	6 (37.5)	5 (31.3)	0	0	9 (56.3)
Dizziness	0	0	0	1 (6.3)	0	0	1 (6.3)
Headache	2 (12.5)	2 (12.5)	6 (37.5)	4 (25.0)	0	0	8 (50.0)

System Organ Class Preferred Term n (%)	Trial Phase						
	Paracetamol Alone N = 16	Paracetamol Washout N = 16	TMC278 Alone N = 16	TMC278/ Paracetamol N = 16	TMC278/ Paracetamol Washout N = 16	Follow-up N = 16	Whole Trial N = 16
Any Adverse Event	2 (12.5)	4 (25.0)	11 (68.8)	7 (43.8)	1 (6.3)	5 (31.3)	13 (81.3)
Skin and Subcutaneous Tissue Disorders	0	1 (6.3)	4 (25.0)	1 (6.3)	0	1 (6.3)	5 (31.3)
Dry skin	0	0	2 (12.5)	0	0	0	2 (12.5)
Erythema	0	0	1 (6.3)	0	0	0	1 (6.3)
Pruritus	0	0	3 (18.8)	1 (6.3)	0	1 (6.3)	4 (25.0)
Rash papular	0	1 (6.3)	0	0	0	0	1 (6.3)
Vascular Disorders	0	0	1 (6.3)	1 (6.3)	0	0	2 (12.5)
Phlebitis	0	0	1 (6.3)	1 (6.3)	0	0	2 (12.5)

n = number of subjects with that particular adverse event; N = number of subjects per phase; ALT = alanine aminotransferase.

Note: 1 subject (6.3%) reported a grade 2 AE of lymphopenia during screening.

Table 11-Adverse event incidence possibly related to either rilpivirine or acetaminophen categorized by system organ class and preferred term

System Organ Class Preferred Term n (%)	Trial Phase						
	Paracetamol Alone N = 16	Paracetamol Washout N = 16	TMC278 Alone N = 16	TMC278/ Paracetamol N = 16	TMC278/ Paracetamol Washout N = 16	Follow-up N = 16	Whole Trial N = 16
Any AE of any causality	2 (12.5)	4 (25.0)	11 (68.8)	7 (43.8)	1 (6.3)	5 (31.3)	13 (81.3)
With at least 1 AE thought to be possibly related to TMC278	0	1 (6.3)	11 (68.8)	6 (37.5)	1 (6.3)	0	12 (75.0)
Gastrointestinal Disorders	0	0	3 (18.8)	0	0	0	3 (18.8)
Abdominal distension	0	0	1 (6.3)	0	0	0	1 (6.3)
Dry mouth	0	0	1 (6.3)	0	0	0	1 (6.3)
Flatulence	0	0	1 (6.3)	0	0	0	1 (6.3)
Investigations	0	0	3 (18.8)	1 (6.3)	1 (6.3)	0	5 (31.3)
ALT increased	0	0	0	0	1 (6.3)	0	1 (6.3)
Blood amylase increased	0	0	0	1 (6.3)	0	0	1 (6.3)
Blood triglycerides increased	0	0	1 (6.3)	0	0	0	1 (6.3)
Lipase increased	0	0	0	1 (6.3)	0	0	1 (6.3)
Neutrophil count decreased	0	0	2 (12.5)	0	0	0	2 (12.5)
Nervous System Disorders	0	0	6 (37.5)	4 (25.0)	0	0	7 (43.8)
Headache	0	0	6 (37.5)	4 (25.0)	0	0	7 (43.8)
Skin and Subcutaneous Tissue Disorders	0	1 (6.3)	4 (25.0)	1 (6.3)	0	0	5 (31.3)
Dry skin	0	0	2 (12.5)	0	0	0	2 (12.5)
Erythema	0	0	1 (6.3)	0	0	0	1 (6.3)
Pruritus	0	0	3 (18.8)	1 (6.3)	0	0	4 (25.0)
Rash papular	0	1 (6.3)	0	0	0	0	1 (6.3)
With at least 1 AE thought to be possibly related to Paracetamol	2 (12.5)	0	1 (6.3)	4 (25.0)	0	0	6 (37.5)
Nervous System Disorders	2 (12.5)	0	0	3 (18.8)	0	0	4 (25.0)
Headache	2 (12.5)	0	0	3 (18.8)	0	0	4 (25.0)

n = number of subjects with that particular AE; N = number of subjects per phase; ALT = alanine aminotransferase.

No AEs were thought to be probably or very likely drug related.

11. Discussion and Conclusions

Based on the results from the drug-drug interaction trial, the following conclusions can be made:

- With single dose acetaminophen coadministration (Day 11, Treatment B), the mean rilpivirine C_{0h} , C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were increased by 19%, 26%, 9%, and 16%, respectively, compared to Day 10 (Treatment B), when rilpivirine was administered by itself. The 90% confidence interval for rilpivirine C_{0h} and C_{min} were not within 80%-125%. The 90% confidence interval for rilpivirine C_{max} and $AUC_{(0-24h)}$ were within 80%-125%.
- With rilpivirine coadministration, the minimal differences were observed in acetaminophen C_{max} (decreased by 3%), and the acetaminophen $AUC_{(0-last)}$ and $AUC_{(0-\infty)}$ values were decreased by 8% and 9%, respectively, compared to Treatment A, when single dose acetaminophen was administered by itself. The 90% confidence interval for acetaminophen C_{max} , $AUC_{(0-last)}$ and $AUC_{(0-\infty)}$ was within 80%-125%.
- With rilpivirine coadministration, minimal differences were observed in acetaminophen glucuronide C_{max} (decreased by 4%) and $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ values were increased by 1% and decreased by 2%, respectively, compared to Treatment A, when single dose acetaminophen was administered by itself. The 90% confidence interval for acetaminophen glucuronide C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ was within 80%-125%.
- With rilpivirine coadministration, minimal differences were observed in acetaminophen sulphate C_{max} (no change), and $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ values were decreased by 5% and 3%, respectively, compared to Treatment A, when single dose acetaminophen was administered by itself. The 90% confidence interval for acetaminophen glucuronide C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ was within 80%-125%.

Single dose acetaminophen does not result in clinically relevant changes in the exposure of rilpivirine and a dose adjustment for rilpivirine is not necessary. The mechanism underlying the increase in rilpivirine exposure is unclear and does not appear to be fully explained by saturation of glutathione conjugation. However, based on the results from this trial, an additional drug-drug interaction trial does not need to be conducted to evaluate the specific effects of rilpivirine on glutathione conjugation with 25 mg once daily dosing. The changes in acetaminophen exposure with rilpivirine coadministration are not clinically relevant based on the results from the trial and therefore no dosage adjustment for acetaminophen is required with rilpivirine dosage regimens ranging from 25 mg once daily to 150 mg once daily.

TMC278-C112

1. Title

A phase I, open-label, randomized 2-way crossover trial in 16 healthy subjects to investigate the steady-state pharmacokinetic interaction between TMC278 and TMC114/ritonavir (rtv)

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at (b) (4) from December 19, 2005 to April 10, 2006.

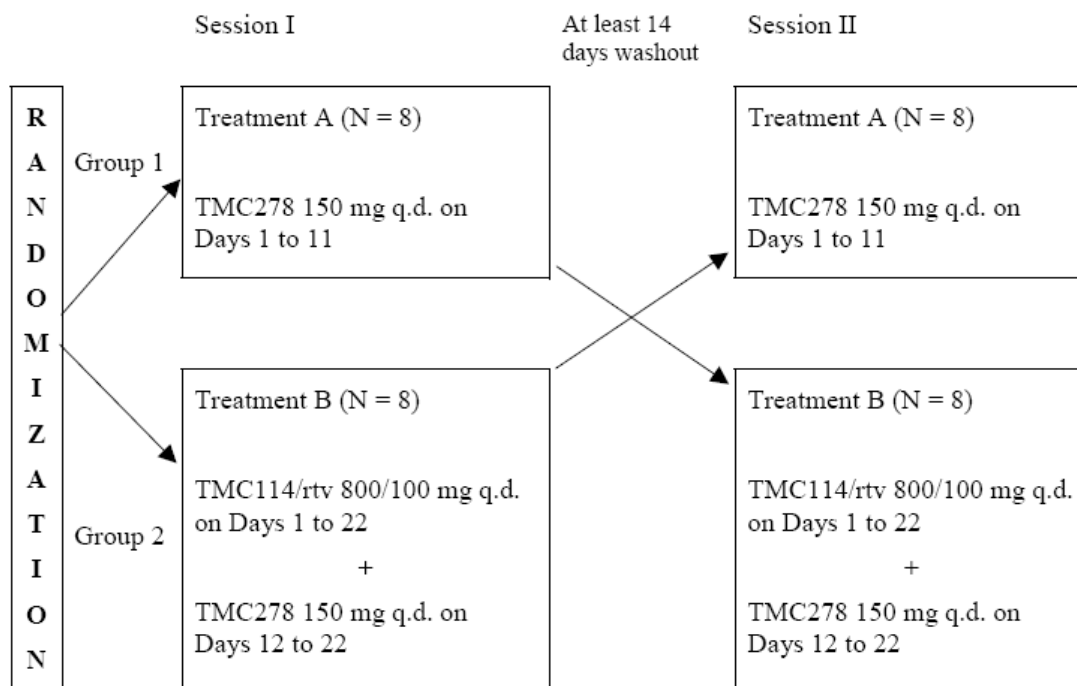
3. Objectives

The objectives of the trial were to evaluate the effect at steady state of darunavir (TMC114)/ritonavir on rilpivirine pharmacokinetics and the effect of rilpivirine on darunavir/ritonavir pharmacokinetics.

4. Trial Design

TMC278-C112 was a Phase I, open label, randomized, 2 way crossover clinical trial that enrolled male and female subjects between 18 and 55 years old. The trial design is displayed in Figure 1.

Figure 1-TMC278-C112 trial design



5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Use of ibuprofen was permitted up to three days before first dosing. From three days before first dosing until the end of the treatment arm, ibuprofen use was permitted up to 400 mg/day. Any over the counter medications were to be discontinued a minimum of 7 days before first dosing and any prescription medications were to be discontinued a minimum of fourteen days before first dosing (with the exception of ibuprofen). Use of any medication other than ibuprofen was not permitted up to fourteen days after the last administration of trial medication. Use of herbal medicines or dietary supplements was not permitted from fourteen days before first dosing up to fourteen days after the last administration of trial medication.

Use of liquids containing alcohol or quinine was not permitted from 24 hours before administration of trial medication until the end of each treatment arm. Intake of grapefruit and grapefruit juice was not permitted from 7 days before administration of trial medication until the end of the trial.

In the event of an adverse event, the following medications were permitted:

- A) Rash or an allergic reaction: cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents (specific medications were not included in the trial report)
- B) Nausea: antiemetics (specific medications were not included in the trial report)
- C) Diarrhea: loperamide

6. Dosage and Administration

On pharmacokinetic sampling days, subjects fasted overnight for a minimum of 10 hours. After a standard meal in the morning, rilpivirine was administered within 10 minutes after completion of the meal.

On pharmacokinetic sampling days, darunavir/ritonavir was administered within 10 minutes after completion of the meal in the morning. On days when both darunavir/ritonavir and rilpivirine were administered, ritonavir was administered first, followed by darunavir, and then rilpivirine.

7. Rationale for Doses Used in the Trial

The rilpivirine dosage regimen that was administered to all subjects in Session 1 and Session 2 was 150 mg once daily. On Days 11 (Treatment A) and 22 (Treatment B), rilpivirine was administered with meals as recommended in the proposed prescribing information. In contrast, the rilpivirine dosage regimen that was evaluated in the Phase 3 clinical trials and the recommended dosage regimen in the proposed prescribing information is 25 mg once daily with a meal. Across the dose range of 25 mg to 150 mg, increases in rilpivirine exposure were approximately dose proportional. Therefore, the percentage change in rilpivirine exposure that is caused by the inhibitory effects of darunavir/ritonavir should be similar with a rilpivirine dosage regimen of either 25 mg

once daily or 150 mg once daily in the absence of significant induction effects from either rilpivirine or ritonavir and if similar darunavir/ritonavir inhibition effects occur with the two rilpivirine dosage regimens.

The darunavir/ritonavir dosage regimen is the standard once daily regimen that is used to treat HIV-1 infected patients. On Days 11 and 22 (Treatment B), darunavir/ritonavir was administered with meals as recommended in the prescribing information.

8. Drugs Used in the Trial

Rilpivirine 50 mg tablets (formulation F003) and 100 mg tablets (F002) were administered in the trial. Both of these tablets were Phase 2b formulations that were used in the Phase 1 or 2 trials.

Darunavir 400 mg tablets and ritonavir 100 mg capsules were administered in the trial.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

For Treatment A, blood samples for analysis of rilpivirine concentrations were obtained on Days 11 and 12 at predose and up to 24 hours postdose. Predose rilpivirine blood samples were also obtained on Days 9 and 10. On Day 1, a predose sample was drawn to determine rilpivirine, darunavir and ritonavir concentrations.

For Treatment B, blood samples for analysis of darunavir and ritonavir concentrations were obtained on Days 11 and 12 at predose and up to 24 hours postdose. Additionally, plasma samples for analysis of rilpivirine, darunavir and ritonavir concentrations were obtained on Days 22 and 23 at predose and up to 24 hours postdose. Predose blood samples for analysis of darunavir and ritonavir concentrations were also obtained on Days 9 and 10 and predose blood samples for analysis of rilpivirine, darunavir and ritonavir concentrations were obtained on Days 20 and 21. On Day 1, a predose sample was drawn to determine rilpivirine, darunavir and ritonavir concentrations.

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a validated LC/MS/MS method by Johnson and Johnson Pharmaceutical Research and Development. The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the TMC278-C112 trial, precision and accuracy were evaluated using the low (2.77 ng/mL), medium (59.0 ng/mL), and high (1550 ng/mL) QC samples. The corresponding rilpivirine inter-run accuracy values were 1.1% for the low QCs, -4.2% for the medium QCs, and -2.6% for the high QCs, and the rilpivirine inter-run precision values were 10% for the low QCs, 10% for the medium QCs, and 10% for the high QCs.

The submitted rilpivirine long term stability data of 1528 days covered the duration of long term rilpivirine stability data necessary for the TMC278-C112 trial.

The method and bioanalysis of darunavir and ritonavir are acceptable. Plasma samples were analyzed for darunavir and ritonavir concentrations using a validated LC/MS/MS method by Johnson and Johnson Pharmaceutical Research and Development. The lower limit of quantification for darunavir was 5 ng/mL and the upper limit of quantification was 10000 ng/mL. There were no precision or accuracy issues identified for darunavir based on the bioanalytical report. For the TMC278-C112 trial, precision and accuracy were evaluated using the low (13.8 ng/mL), medium (251 ng/mL), and high (7540 ng/mL) QC samples. The corresponding darunavir inter-run accuracy values were 3.6% for the low QCs, -2.0% for the medium QCs, and 4.2% for the high QCs, and the darunavir inter-run precision values were 13.5% for the low QCs, 3.6% for the medium QCs, and 7.5% for the high QCs. The lower limit of quantification for ritonavir was 5 ng/mL and the upper limit of quantification was 10000 ng/mL. There were no precision or accuracy issues identified for ritonavir based on the bioanalytical report. For the TMC278-C112 trial, precision and accuracy were evaluated using the low (13.8 ng/mL), medium (251 ng/mL), and high (7540 ng/mL) QC samples. The corresponding ritonavir inter-run accuracy values were 8.0% for the low QCs, -1.6% for the medium QCs, and -2.5% for the high QCs, and the ritonavir inter-run precision values were 11.4% for the low QCs, 8.3% for the medium QCs, and 4.6% for the high QCs. The submitted darunavir and ritonavir long term stability data of 1597 days covered the duration of long term darunavir and ritonavir stability data necessary for the TMC278-C112 trial.

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate pharmacokinetic parameters, including C_{\max} and $AUC_{(0-\tau)}$. If a major difference ($> 10.00\%$ deviation from the scheduled time) was observed, the actual sampling time was used instead of the scheduled sampling time.

Statistical Analysis

Descriptive statistics were calculated for rilpivirine, darunavir and ritonavir plasma concentrations and pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), geometric mean, median, and the minimum and maximum values.

Statistical analysis involved comparison of rilpivirine log transformed pharmacokinetic parameters for Day 22, Treatment B (test arm) compared to Day 11, Treatment A (reference arm). For darunavir and ritonavir, statistical analysis involved comparison of darunavir and ritonavir log transformed pharmacokinetic parameters for Day 22, Treatment B (test arm) compared to Day 11, Treatment B (reference arm). C_{\min} , C_{\max} , and $AUC_{(0-\tau)}$ were evaluated. Using a linear mixed effects model, least squares means were calculated and 90% confidence intervals were derived based on the difference of the pharmacokinetic parameter's least squares means for the test and reference arms. If the

90% confidence intervals were within 80%-125%, it was concluded that a clinically relevant drug-drug interaction did not exist.

An assessment was performed to determine if rilpivirine steady state concentrations were achieved by Day 11 (Treatment A) based on predose concentrations from Days 9, 10 and 11 or by Day 22 (Treatment B) based on predose concentrations from Days 20, 21 and Day 22. For darunavir and ritonavir, an assessment was performed to determine if steady state concentrations were achieved by Day 11 (Treatment B) based on predose concentrations from Days 9, 10 and 11 or by Day 22 (Treatment B) based on predose concentrations from Days 20, 21 and 22.

10. Results

10.1 Subject Demographics and Disposition

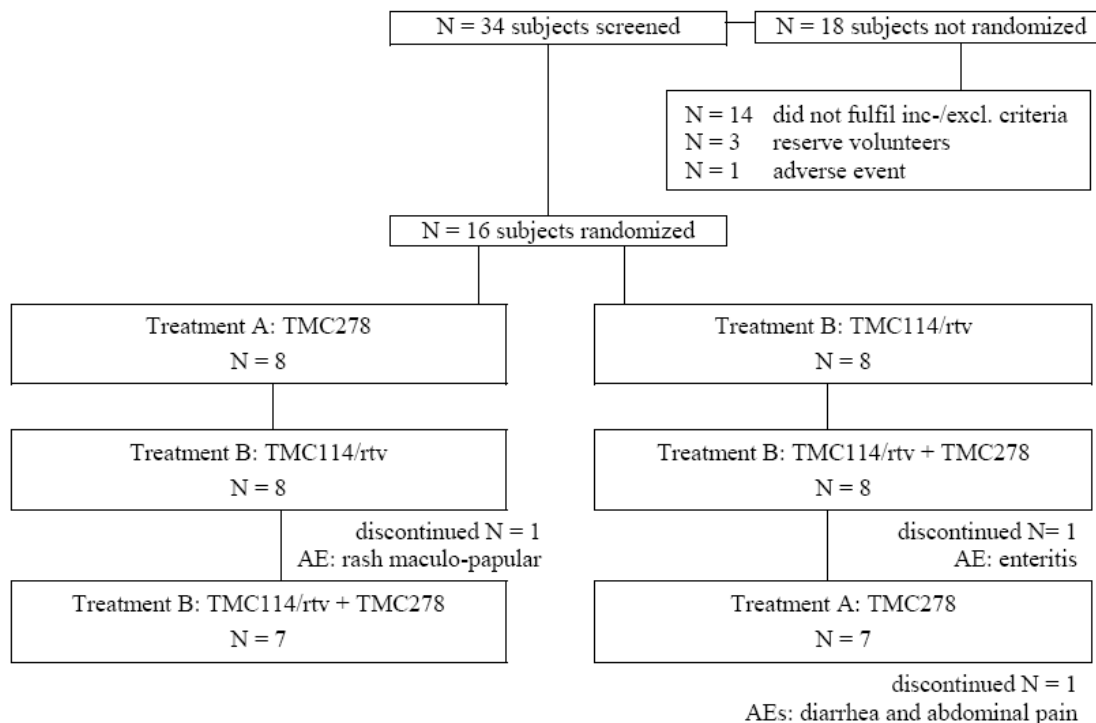
Table 1-TMC278-C112 subject demographics

Parameter	TMC278→ TMC114/rtv + TMC278 N = 8	TMC114/rtv + TMC278 → TMC278 N = 8	Total N = 16
Age, years			
Median	32.5	47.5	38.0
Range	24 - 53	37 - 51	24 - 53
Race, n (%)			
Caucasian/white	8 (100.0%)	8 (100.0%)	16 (100.0%)
Sex, n (%)			
Female		3 (37.5%)	3 (18.8%)
Male	8 (100.0%)	5 (62.5%)	13 (81.3%)
Height, cm			
Median	180.5	169.0	175.5
Range	172 - 196	154 - 190	154 - 196
Weight, cm			
Median	79.3	72.4	78.4
Range	72 - 99	53 - 92	53 - 99
BMI, kg/m ²			
Median	25.2	24.5	24.6
Range	20 - 30	20 - 30	20 - 30
Smoking, n (%)			
No	6 (75.0%)	4 (50.0%)	10 (62.5%)
Yes, light ^b	2 (25.0%)	4 (50.0%)	6 (37.5%)

^a Smoking type percentages are calculated for smokers only

^b No more than 10 cigarettes, 2 cigars or 2 pipes per day

Figure 2-TMC278-C112 subject disposition



10.2 Prior and Concomitant Medications

Seven subjects administered concurrent medications during the trial. The administered concurrent medications were domperidone, loperamide, ibuprofen, omeprazole, and Gaviscon. These medications would not be expected to alter CYP 3A metabolism.

10.3 Pharmacokinetic and Statistical Analysis

There were 6 subjects with a quantifiable rilpivirine drug concentration prior to starting Treatment A and 2 subjects with a quantifiable rilpivirine drug concentration prior to starting Treatment B. The applicant stated that the cause was rilpivirine administration in the previous session, despite a 14 day washout. However, these concentrations were 5% or less of the subject's C_{max} for the treatment arm and no adjustments were necessary for the pharmacokinetic analyses (there were no rilpivirine plasma concentration data available for subject 1121528 (Treatment B) after the predose concentration).

Rilpivirine

Table 2-Pharmacokinetic parameters for rilpivirine 150 mg once daily and rilpivirine 150 mg once daily with darunavir and ritonavir coadministration (800 mg/100 mg once daily) [%FI=100 x $([C_{\max}-C_{\min}]/C_{ss,av})$]

<i>Pharmacokinetics of TMC278</i> (mean ± SD, t_{\max} : median [range])	TMC278 alone (reference)	TMC278 + TMC114/rtv (test)
n	14	14
t_{\max} , h	4.0 [1.0 - 5.0]	4.0 [4.0 - 24.0]
C_{0h} , ng/mL	415.9 ± 103.7	1233 ± 474.0
C_{24h} , ng/mL	407.3 ± 109.3	1190 ± 528.2
C_{\min} , ng/mL	359.9 ± 91.55	1013 ± 407.9
C_{\max} , ng/mL	991.3 ± 208.4	1860 ± 673.0
AUC _{24h} , ng.h/mL	12740 ± 2008	30630 ± 11230
$C_{ss,av}$, ng/mL	530.9 ± 83.68	1276 ± 468.0
FI, %	121.9 ± 47.89	68.26 ± 23.38

Table 3-Statistical analysis for rilpivirine 150 mg once daily and rilpivirine 150 mg once daily with darunavir and ritonavir coadministration (800 mg/100 mg once daily)

<i>Parameter</i>	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b	P-values	
	TMC278 alone (reference)	TMC278 + TMC114/rtv (test)			Period	Sequence
C_{\min} , ng/mL	342.0	951.7	278.3	239.3 - 323.6	0.3201	0.4876
C_{\max} , ng/mL	985.0	1760	178.7	155.5 - 205.5	0.0881	0.8858
AUC _{24h} , ng.h/mL	12620	29030	229.9	197.9 - 267.2	0.7201	0.8835

^a n= 14 for Treatment A (reference) and n=14 for Treatment B (test)

^b 90% confidence intervals

On Day 22 (Treatment B), with darunavir/ritonavir coadministration, higher mean rilpivirine C_{\min} , C_{\max} , and AUC_(0-24h) values were observed in subjects compared to Day 11 (Treatment A), when rilpivirine was administered by itself. The 90% confidence interval for rilpivirine C_{\min} , C_{\max} , and AUC_(0-24h) were not within 80%-125%.

Based on evaluating the individual rilpivirine predose concentrations, steady state concentrations appear to have been achieved by Day 11 (Treatment A) and Day 22 (Treatment B) in most subjects. For Treatment A, there was a trend of increasing predose concentrations from Day 9 to Day 11 that was more pronounced for the Day 9 and 10 predose concentrations.

Darunavir/ritonavir

Table 4-Darunavir pharmacokinetic parameters (administered as darunavir/ritonavir 800 mg/100 mg once daily and darunavir/ritonavir 800 mg/100 mg twice daily with rilpivirine 150 mg once daily coadministration)

<i>Pharmacokinetics of TMC114</i> (mean \pm SD, t_{max} : median [range])	TMC114/rtv alone (reference)	TMC114/rtv + TMC278 (test)
n	15	14
t_{max} , h	2.0 [1.0 - 5.0]	3.0 [1.0 - 4.0]
C_{0h} , ng/mL	1887 \pm 1010	1890 \pm 1330
C_{24h} , ng/mL	2140 \pm 831.4	1592 \pm 764.0
C_{min} , ng/mL	1714 \pm 916.2	1388 \pm 614.6
C_{max} , ng/mL	7586 \pm 1988	6676 \pm 1374
AUC _{24h} , ng·h/mL	82780 \pm 24980	71930 \pm 21350
$C_{ss, av}$, ng/mL	3449 \pm 1041	2997 \pm 889.7
FI, %	176.5 \pm 39.47	184.8 \pm 35.06

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Table 5-Statistical analysis for darunavir (administered as darunavir/ritonavir 800 mg/100 mg once daily and darunavir/ritonavir 800 mg/100 mg once daily with rilpivirine 150 mg once daily coadministration)

<i>Parameter</i>	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b
	TMC114/rtv alone (reference)	TMC114/rtv + TMC278 (test)		
C_{min} , ng/mL	1457	1295	88.88	67.98 - 116.2
C_{max} , ng/mL	7324	6595	90.06	80.95 - 100.2
AUC _{24h} , ng·h/mL	79240	70870	89.45	80.87 - 98.94

^a n= 15 for Day 11 (reference) and n=14 for Day 22 (test)

^b 90% CIs.

On Day 22 (Treatment B), with rilpivirine coadministration, lower mean darunavir C_{min} , C_{max} , and AUC_(0-24h) values were observed in subjects compared to Day 11 (Treatment B), when darunavir/ritonavir was administered by itself. The 90% confidence interval for darunavir C_{max} and AUC_(0-24h) were within 80%-125%. The 90% confidence interval for darunavir C_{min} was not within 80%-125%.

Table 6-Ritonavir pharmacokinetic parameters (administered as darunavir/ritonavir 800 mg/100 mg once daily and darunavir/ritonavir 800 mg/100 mg once daily with rilpivirine 150 mg once daily coadministration)

<i>Pharmacokinetics of ritonavir</i> (mean \pm SD, t_{max} : median [range])	TMC114/rtv alone (reference)	TMC114/rtv + TMC278 (test)
n	15	14
t_{max} , h	4.0 [1.0 - 6.0]	4.5 [2.0 - 6.0]
C_{0h} , ng/mL	43.30 \pm 15.99	37.64 \pm 25.78
C_{24h} , ng/mL	45.23 \pm 24.53	31.06 \pm 13.42
C_{min} , ng/mL	35.74 \pm 15.08	27.67 \pm 14.26
C_{max} , ng/mL	690.3 \pm 293.1	558.3 \pm 277.3
AUC_{24h} , ng.h/mL	5201 \pm 2381	4060 \pm 1537
$C_{ss, av}$, ng/mL	216.7 \pm 99.20	169.2 \pm 64.03
FI, %	312.7 \pm 75.32	314.6 \pm 85.40

Table 7-Statistical analysis for ritonavir (administered as darunavir/ritonavir 800 mg/100 mg once daily and darunavir/ritonavir 800 mg/100 mg once daily with rilpivirine 150 mg once daily coadministration)

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<i>Parameter</i>	LSmeans ^a		LSmeans ratio, %	90% CI, %
	TMC114/rtv alone (reference)	TMC114/rtv + TMC278 (test)		
C_{min} , ng/mL	32.22	25.29	78.49	68.25 - 90.26
C_{max} , ng/mL	645.2	535.2	82.95	72.32 - 95.14
AUC_{24h} , ng.h/mL	4791	4051	84.55	78.21 - 91.41

^a n= 15 for Day 11 (reference) and n=14 for Day 22 (test)

On Day 22 (Treatment B), with rilpivirine coadministration, a lower mean ritonavir C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were observed in subjects compared to Day 11 (Treatment B), when darunavir/ritonavir was administered by itself. The 90% confidence interval for ritonavir C_{min} , C_{max} , and $AUC_{(0-24h)}$ were not within 80%-125%.

Based on evaluating the individual darunavir and ritonavir predose concentrations, steady state concentrations were achieved by Day 11 (Treatment B) and Day 22 (Treatment B) in most subjects.

10.4 Safety Issues

No deaths or other serious adverse events were reported for the trial. Grade 3 adverse events were reported (increased lipids were observed in one subject, and a second subject with gastric pain during follow up). No grade 4 adverse events were reported. There are discrepancies in the trial report regarding the number and specific occurrences of grade 3 increases in lipids. However, it appears that one subject experienced grade 3 increases in LDL on three occasions: the first occurrence with darunavir/ritonavir administration only (5 mmol/L), the second occurrence with darunavir/ritonavir and rilpivirine coadministration (5.2 mmol/L), and the third occurrence during follow up (5 mmol/L).

The most commonly reported adverse events were headache, increased cholesterol, increased lipids and pruritis (see Table 8 below for information regarding the number and percentage of subjects). Tables 9 and 10 provide information on adverse events that were possibly related to either rilpivirine or darunavir/ritonavir.

Table 8-Adverse event incidence reported for three or more subjects and categorized by system organ class and preferred term

System Organ Class Preferred Term n (%)	Trial Phase				
	TMC278 Alone N = 15	TMC114/rtv N = 16	TMC114/rtv + TMC278 N = 15	Follow-up N = 16	Total N = 16
Number (%) of Subjects with AE	13 (86.7%)	11 (68.8%)	11 (73.3%)	6 (37.5%)	16 (100.0%)
Investigations	2 (13.3%)	3 (18.8%)	6 (40.0%)	3 (18.8%)	9 (56.3%)
Lipids increased	0	1 (6.3%)	4 (26.7%)	2 (12.5%)	5 (31.3%)
Lipase increased	0	2 (12.5%)	2 (13.3%)	0	4 (25.0%)
Blood creatinine increased	1 (6.7%)	0	1 (6.7%)	1 (6.3%)	3 (18.8%)
Skin and subcutaneous tissue disorders	1 (6.7%)	6 (37.5%)	1 (6.7%)	0	8 (50.0%)
Pruritus	0	4 (25.0%)	1 (6.7%)	0	5 (31.3%)
Gastrointestinal Disorders	4 (26.7%)	5 (31.3%)	3 (20.0%)	2 (12.5%)	8 (50.0%)
Aphthous stomatitis	0	0	2 (13.3%)	1 (6.3%)	3 (18.8%)
Diarrhea	1 (6.7%)	2 (12.5%)	0	0	3 (18.8%)
Nausea	1 (6.7%)	1 (6.3%)	1 (6.7%)	0	3 (18.8%)
Metabolism and nutrition disorders	2 (13.3%)	4 (25.0%)	2 (13.3%)	0	7 (43.8%)
Hypercholesterolemia	2 (13.3%)	2 (12.5%)	2 (13.3%)	0	6 (37.5%)
Nervous system disorders	2 (13.3%)	2 (12.5%)	5 (33.3%)	0	6 (37.5%)
Headache	2 (13.3%)	2 (12.5%)	5 (33.3%)	0	6 (37.5%)
Hepatobiliary Disorders	2 (13.3%)	0	1 (6.7%)	2 (12.5%)	3 (18.8%)
Hyperbilirubinemia	2 (13.3%)	0	1 (6.7%)	2 (12.5%)	3 (18.8%)

n = number of subjects with that particular AE; N = number of subjects per phase.

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Table 9-Adverse event incidence possibly related to rilpivirine reported for more than one subject and categorized by system organ class and preferred term

System Organ Class Preferred Term n (%)	Trial Phase				
	TMC278 Alone N = 15	TMC114/rtv N = 16	TMC114/rtv + TMC278 N = 15	Follow-up N = 16	Total N = 16
<i>With at Least 1 AE that is Possibly Related to TMC278</i>	6 (40.0%)	0	10 (66.7%)	3 (18.8%)	13 (81.3%)
<i>Investigations</i>	1 (6.7%)	0	6 (40.0%)	2 (12.5%)	8 (50.0%)
Lipids increased	0	0	4 (26.7%)	2 (12.5%)	5 (31.3%)
Blood creatinine increased	1 (6.7%)	0	1 (6.7%)	0	2 (12.5%)
Lipase increased	0	0	2 (13.3%)	0	2 (12.5%)
<i>Nervous System Disorders</i>	1 (6.7%)	0	4 (26.7%)	0	4 (25.0%)
Headache	1 (6.7%)	0	4 (26.7%)	0	4 (25.0%)
<i>Gastrointestinal Disorders</i>	2 (13.3%)	0	3 (20.0%)	0	4 (25.0%)
Aphthous stomatitis	0	0	2 (13.3%)	0	2 (12.5%)
Dyspepsia	2 (13.3%)	0	0	0	2 (12.5%)
<i>Metabolism and Nutrition Disorders</i>	1 (6.7%)	0	2 (13.3%)	0	3 (18.8%)
Hypercholesterolemia	1 (6.7%)	0	2 (13.3%)	0	3 (18.8%)

n = number of subjects with that particular adverse event; N = number of subjects per phase.

* No adverse event was considered to be probably or definitely related to medication

Table 10-Adverse event incidence possibly related to darunavir/ritonavir reported for more than one subject and categorized by system organ class and preferred term

System Organ Class Preferred Term n (%)	Trial Phase				
	TMC278 Alone N = 15	TMC114/rtv N = 16	TMC114/rtv + TMC278 N = 15	Follow-up N = 16	Total N = 16
<i>With at Least 1 AE that is Possibly Related to TMC114/rtv</i>	3 (20.0%)	11 (68.8%)	11 (73.3%)	1 (6.3%)	14 (87.5%)
<i>Skin and Subcutaneous Tissue Disorders</i>	0	6 (37.5%)	1 (6.7%)	0	7 (43.8%)
Pruritus	0	4 (25.0%)	1 (6.7%)	0	5 (31.3%)
Rash Maculo-papular	0	2 (12.5%)	0	0	2 (12.5%)
<i>Investigations</i>	1 (6.7%)	3 (18.8%)	6 (40.0%)	1 (6.3%)	7 (43.8%)
Lipids increased	0	1 (6.3%)	4 (26.7%)	1 (6.3%)	4 (25.0%)
Lipase increased	0	2 (12.5%)	2 (13.3%)	0	3 (18.8%)
<i>Nervous System Disorders</i>	1 (6.7%)	2 (12.5%)	5 (33.3%)	0	6 (37.5%)
Headache	1 (6.7%)	2 (12.5%)	5 (33.3%)	0	6 (37.5%)
<i>Gastrointestinal Disorders</i>	1 (6.7%)	5 (31.3%)	3 (20.0%)	0	6 (37.5%)
Nausea	1 (6.7%)	1 (6.3%)	1 (6.7%)	0	3 (18.8%)
Aphthous stomatitis	0	0	2 (13.3%)	0	2 (12.5%)
Diarrhea	0	2 (12.5%)	0	0	2 (12.5%)
Flatulence	0	1 (6.3%)	1 (6.7%)	0	2 (12.5%)
<i>Metabolism and Nutrition Disorders</i>	0	4 (25.0%)	2 (13.3%)	0	5 (31.3%)
Hypercholesterolemia	0	2 (12.5%)	2 (13.3%)	0	4 (25.0%)

n = number of subjects with that particular AE; N = number of subjects per phase.

* No AE was considered to be probably or definitely related to medication

11. Discussion and Conclusions

Based on the results from the drug-drug interaction trial, the following conclusions can be made:

- Rilpivirine exposure was increased with darunavir/ritonavir coadministration (rilpivirine mean C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were increased by 178%, 79%, and 130%, respectively). The 90% confidence interval for all three parameters was not within 80-125%.

- With rilpivirine coadministration, the mean darunavir C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were decreased by 11, 10% and 11%, respectively. The 90% confidence interval for darunavir C_{max} and $AUC_{(0-24h)}$ was within 80%-125%, however the 90% confidence interval for C_{min} was 68%-116%.
- With rilpivirine coadministration, the mean ritonavir C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were decreased by 22%, 17% and 15%, respectively. The 90% confidence interval for all three parameters was not within 80-125%.

The increase in rilpivirine exposure may be potentially explained by darunavir/ritonavir CYP 3A inhibition. The information from the trial supports the conclusion that with a rilpivirine 150 mg once daily dosing regimen, potential darunavir/ritonavir CYP 3A inhibition of rilpivirine metabolism does not result in clinically relevant changes in rilpivirine exposure and therefore no dosage adjustment for rilpivirine is required (see below for further discussion regarding rilpivirine 25 mg once daily dosing).

With a 150 mg once daily rilpivirine dosage regimen, the decreases in both darunavir and ritonavir exposure may be potentially explained by rilpivirine CYP 3A induction. The specific effects of a 25 mg once daily rilpivirine dosage regimen on darunavir/ritonavir exposure have not been evaluated. From a mechanistic standpoint, the degree of induction with rilpivirine 25 mg once daily dosing is anticipated to be the same or less compared to 150 mg once daily dosing. The changes in darunavir/ritonavir exposure with rilpivirine coadministration do not appear to be clinically relevant based on the results from the trial and therefore no dosage adjustment for darunavir/ritonavir is required with rilpivirine dosage regimens ranging from 25 mg once daily to 150 mg once daily. However, potential differences in the inhibitory effects of darunavir/ritonavir when coadministered with rilpivirine 25 mg once daily compared to rilpivirine 150 mg once daily may be clinically relevant. The rationale for this statement is that under the scenario of decreased rilpivirine induction, a greater degree of darunavir/ritonavir inhibition may occur with rilpivirine 25 mg once daily dosing. Further analysis of this issue will be conducted.

1. Title

A Phase I, open-label trial to investigate the two-way, pharmacokinetic drug-drug interaction between single-dose and steady-state TMC278 and steady-state omeprazole in healthy volunteers

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at (b) (4) from July 12, 2005 to November 3, 2005.

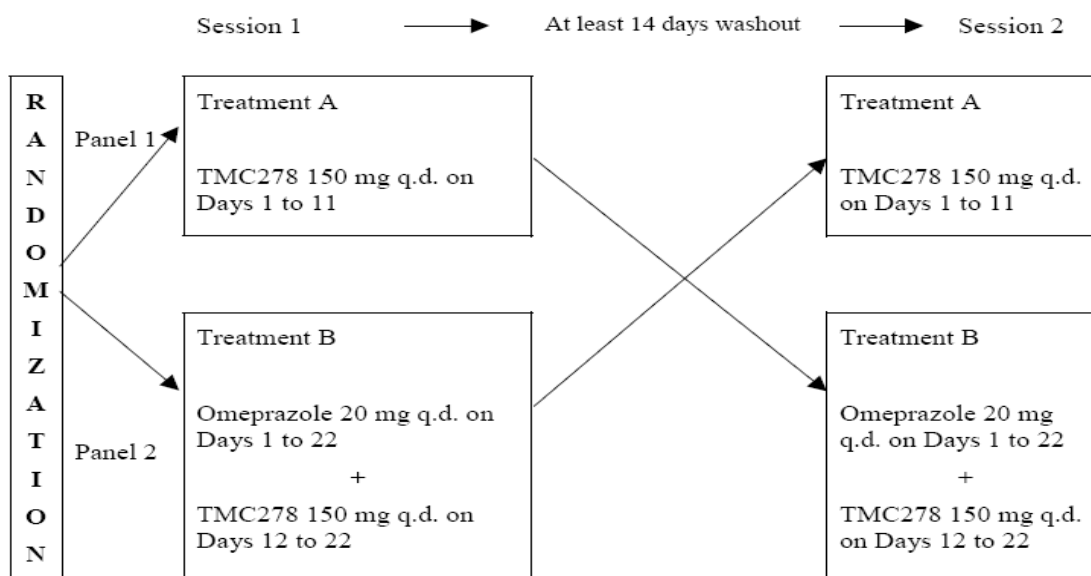
3. Objectives

The objectives of the trial were to evaluate the effect at steady state of omeprazole on rilpivirine single dose and steady state pharmacokinetics and the effect of single dose and steady state rilpivirine on omeprazole and omeprazole metabolite (5-hydroxyomeprazole and omeprazole sulfone) pharmacokinetics.

4. Trial Design

TMC278-C114 was a Phase I, open label, randomized, 2 way crossover clinical trial that enrolled male and female subjects between 18 and 45 years old. The trial design is displayed in Figure 1.

Figure 1-TMC278-C114 trial design



5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Use of ibuprofen was permitted up to three days before the first administration of trial medication. Afterwards, ibuprofen use was permitted up to 400 mg/day until the end of each session or treatment arm. Any over the counter medications were to be discontinued a minimum of seven days before the first administration of trial medication and all prescription medications were to be discontinued a minimum of fourteen days before the first administration of trial medication. Use of herbal medicines or dietary supplements was not permitted from fourteen days before the first administration of trial medication and up to fourteen days after the last administration of trial medication.

Use of liquids containing alcohol or quinine was not permitted from 24 hours before administration of trial medication until 96 hours after administration of trial medication. Intake of grapefruit and grapefruit juice was not permitted from 7 days before administration of trial medication until 96 hours after administration of trial medication.

In the event of an adverse event, the following medications were permitted:

- A) Rash or an allergic reaction: cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents (specific medications were not included in the trial report)
- B) Nausea: antiemetics (specific medications were not included in the trial report)
- C) Diarrhea: loperamide

6. Dosage and Administration

When medications were administered at the trial site, a standard meal was administered in the morning. Rilpivirine or omeprazole was administered within 10 minutes after completion of the meal. When both omeprazole and rilpivirine were coadministered, omeprazole was to be administered before rilpivirine.

7. Rationale for Doses Used in the Trial

The rilpivirine dosage regimen that was administered to all subjects was 150 mg once daily. In contrast, the rilpivirine dosage regimen that was evaluated in the Phase 3 clinical trials and the recommended dosage regimen in the proposed prescribing information is 25 mg once daily with a meal. Across the dose range of 25 mg to 150 mg, increases in rilpivirine exposure were approximately dose proportional. In vitro results indicate that CYP 2C19 may be involved in the metabolism of rilpivirine and rilpivirine may potentially induce or inhibit CYP 2C19. Therefore, the percentage change in rilpivirine exposure that is caused by the CYP 2C19 inhibitory effects of omeprazole (which is also metabolized through CYP 2C19) should be similar with a rilpivirine dosage regimen of either 25 mg once daily or 150 mg once daily under the following conditions: a) the absence of significant CYP 2C19 induction or inhibition effects from rilpivirine, b) similar omeprazole CYP 2C19 inhibition effects, and c) similar effects on the absorption of rilpivirine (which possesses pH-dependent absorption).

The omeprazole dosage regimen administered in the trial (20 mg once daily) is the recommended dosage regimen for treatment of active duodenal ulcers. Omeprazole is to be administered a minimum of one hour before meals.

8. Drugs Used in the Trial

Rilpivirine 50 mg tablets (formulation F003) and 100 mg tablets (formulation F002) were administered in the trial. Both of these tablets were Phase 2b formulations that were used in the Phase 1 or 2 trials.

Omeprazole (Losec®) 20 mg delayed release tablets were administered in the trial.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

For Treatment A (rilpivirine administered alone), blood samples for analysis of rilpivirine concentrations were obtained on Days 1 and 2 and Days 11 and 12 at predose and up to 24 hours postdose. Predose rilpivirine blood samples were also obtained on Days 9 and 10. A predose omeprazole blood sample was obtained on Day 1.

For Treatment B, blood samples for analysis of rilpivirine concentrations were obtained on Days 12 and 13 and Days 22 and 23 at predose and up to 24 hours postdose. On Days 1, 20, and 21, a predose blood sample was drawn to determine rilpivirine concentrations. Omeprazole concentrations were obtained at Day 11 at predose and up to 16 hours postdose and on Days 12 and 13 and Days 22 and 23 at predose and up to 24 hours postdose. Blood samples were drawn to determine omeprazole concentrations on Day 1 at predose and at 4 hours postdose and on Days 20 and 21 at predose.

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a validated LC/MS/MS method by (b) (4). The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the TMC278-C114 trial, precision and accuracy were evaluated using the low (3 ng/mL), medium (50 ng/mL), and high (1600 ng/mL) QC samples. The corresponding rilpivirine inter-run accuracy values were -4.5% for the low QCs, -5.7% for the medium QCs, and -0.4% for the high QCs, and the rilpivirine inter-run precision values were 4.8% for the low QCs, 5.4% for the medium QCs, and 1.9% for the high QCs. The submitted rilpivirine long term stability data of 1528 days at -20°C covered the duration of long term rilpivirine stability data necessary for the TMC278-C114 trial.

The method and bioanalysis of omeprazole, 5-hydroxyomeprazole and omeprazole sulphone is acceptable. Plasma samples were analyzed for omeprazole,

5-hydroxyomeprazole and omeprazole sulphone concentrations using a validated LC/MS/MS method by (b) (4). The lower limit of quantification for omeprazole was 1 ng/mL and the upper limit of quantification was 1000 ng/mL. There were no precision or accuracy issues identified for omeprazole based on the bioanalytical report. For the TMC278-C114 trial, precision and accuracy were evaluated using plasma QC samples at 3 (low QC), 30 (medium QC) and 750 ng/mL (high QC). The corresponding omeprazole inter-run accuracy values were 5% for the low QCs, 2.7% for the medium QCs, and 3.7% for the high QCs, and the omeprazole inter-run precision values were 4.3% for the low QCs, 3.2% for the medium QCs, and 3.8% for the high QCs. The lower limit of quantification for 5-hydroxyomeprazole was 1 ng/mL and the upper limit of quantification was 1000 ng/mL. There were no precision or accuracy issues identified for 5-hydroxyomeprazole based on the bioanalytical report. For the TMC278-C114 trial, precision and accuracy were evaluated using plasma QC samples at 3 (low QC), 30 (medium QC) and 750 ng/mL (high QC). The corresponding 5-hydroxyomeprazole inter-run accuracy values were 0.3% for the low QCs, -1% for the medium QCs, and -7.3% for the high QCs, and the 5-hydroxyomeprazole inter-run precision values were 4.8% for the low QCs, 3.1% for the medium QCs, and 3.3% for the high QCs. The lower limit of quantification for omeprazole sulphone was 1 ng/mL and the upper limit of quantification was 1000 ng/mL. There were no precision or accuracy issues identified for omeprazole sulphone based on the bioanalytical report. For the TMC278-C114 trial, precision and accuracy were evaluated using plasma QC samples at 3 (low QC), 30 (medium QC) and 750 ng/mL (high QC). The corresponding omeprazole sulphone inter-run accuracy values were -1.7% for the low QCs, 4.3% for the medium QCs, and 2.1% for the high QCs, and the omeprazole sulphone inter-run precision values were 6.3% for the low QCs, 3.7% for the medium QCs, and 5.6% for the high QCs.

The submitted omeprazole, 5-hydroxyomeprazole and omeprazole sulphone long term stability data in plasma using sodium heparin as an anticoagulant of 461 days at -20°C covered the duration of long term omeprazole, 5-hydroxyomeprazole and omeprazole sulphone stability data necessary for the TMC278-C114 trial.

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate plasma pharmacokinetic parameters, including C_{min} , C_{max} , and $AUC_{(0-\tau)}$. If a major difference (> 10.00% deviation from the scheduled time) was observed, the actual sampling time was used instead of the scheduled sampling time.

Statistical Analysis

Descriptive statistics were calculated for rilpivirine and omeprazole plasma concentrations and pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), geometric mean, median, and the minimum and maximum values.

Statistical analysis involved comparison of plasma rilpivirine log transformed pharmacokinetic parameters for rilpivirine when administered with omeprazole (test arm)

compared to rilpivirine administration by itself (reference arm) both with after a single dose of rilpivirine and with multiple dosing of both medications. For omeprazole and the omeprazole metabolites, statistical analysis involved comparison of omeprazole when administered with rilpivirine (test arm) compared to omeprazole administration by itself (reference arm) both with after a single dose of rilpivirine and with multiple dosing of both medications. C_{0h} (the predose plasma concentrations), C_{min} (the minimum plasma concentrations between 0 hour and the dosing interval $[\tau]$), C_{max} , and $AUC_{(0-\tau)}$ were the primary parameters of interest that were evaluated. Using a linear mixed effects model, least squares means were calculated and 90% confidence intervals were derived based on the difference of the pharmacokinetic parameter's least squares means for the test and reference arms. The 90% confidence intervals and the difference of the pharmacokinetic parameter's least squares means were transformed back to the original scale. The predetermined "no effect boundaries" for the 90% confidence intervals was 80%-125%.

An assessment was performed to determine if rilpivirine steady state concentrations were achieved by Day 11 (Treatment A) and Day 22 (Treatment B). An assessment was also performed to determine if omeprazole steady state concentrations were achieved by Day 22 in Treatment B.

10. Results

10.1 Subject Demographics and Disposition

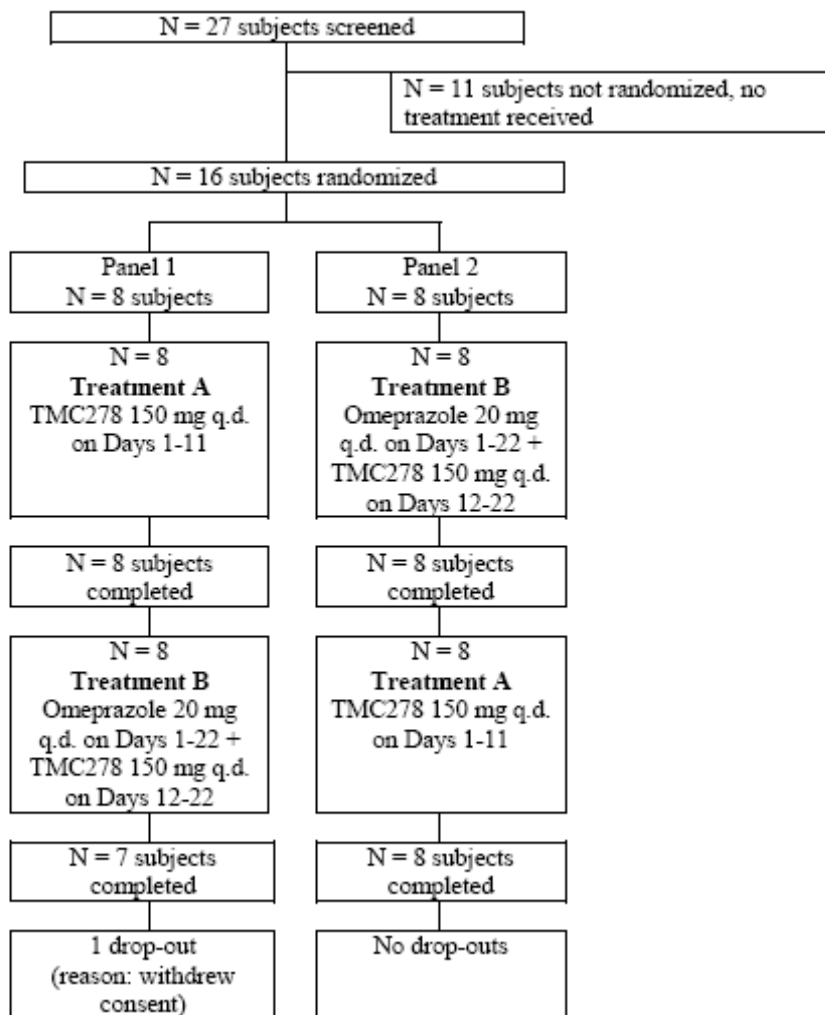
Table 1-TMC278-C114 subject demographics

Parameter	Panel 1 TMC278 → Omeprazole + TMC278 (N = 8)	Panel 2 Omeprazole + TMC278 → TMC278 (N = 8)	All Subjects N = 16
Age, years			
Median	32.0	36.0	34.5
(range)	24 - 45	20 - 43	20 - 45
Height, cm			
Median	183.0	175.5	178.5
(range)	169 - 189	161 - 193	161 - 193
Weight, kg			
Median	74.0	68.2	71.1
(range)	68 - 91	59 - 105	59 - 105
BMI, kg/m ²			
Median	23.5	22.9	23.0
(range)	19 - 28	20 - 28	19 - 28
Sex, n (%)			
Female	1 (12.5)	2 (25.0)	3 (18.8)
Male	7 (87.5)	6 (75.0)	13 (81.3)
Ethnic Origin, n (%)			
Caucasian/White	8 (100.0)	7 (87.5)	15 (93.8)
Black	0	1 (12.5)	1 (6.3)
Type of Smoker, n (%)			
No (non-smoker)	7 (87.5)	6 (75.0)	13 (81.3)
Yes (light)	1 (12.5)	2 (25.0)	3 (18.8)

BMI = body mass index.

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Figure 2-TMC278-C114 subject disposition



10.2 Prior and Concomitant Medications

Eight subjects administered concurrent medications during the trial. The most frequently administered concurrent medications were ibuprofen (administered in 6 subjects) and acetaminophen (administered in 3 subjects). Other concomitant medications that were administered include cetirizine, clobetasol, doxycycline, a heparin derivative, lidocaine, and talc. These medications would not be expected to alter CYP 3A or 2C19 metabolism.

10.3 Pharmacokinetic and Statistical Analysis

In Treatment A, there were five subjects with quantifiable rilpivirine concentrations on Day 1. However, these concentrations were 5% or less of the subject's Day 1 C_{max} for the session and no adjustments were necessary for the pharmacokinetic analyses. In Treatment B, five subjects had quantifiable predose rilpivirine concentrations on Day 1.

Of the five subjects, two subjects had quantifiable rilpivirine drug concentrations that were greater than 5% of the subject's rilpivirine C_{max} on Day 12 (a third subject did not have rilpivirine concentrations reported for Day 12). However, the overall conclusion that was derived from comparing Treatment B to Treatment A is anticipated to be valid regardless of whether rilpivirine pharmacokinetic data from two subjects is included and it would be anticipated that the predose rilpivirine concentrations would be negligible by Day 12.

All subjects had omeprazole concentrations that were less than the lower limit of quantification (LLOQ) on Day 1 in Treatment A and Treatment B.

Rilpivirine

Table 2-Pharmacokinetic parameters for rilpivirine 150 mg once daily and rilpivirine 150 mg once daily coadministered with omeprazole 20 mg once daily
 $[\%FI = 100 \times ((C_{max} - C_{min}) / C_{ss,av})]$

Pharmacokinetics of TMC278 (mean \pm standard deviation, t_{max} : median [range])	Treatment A: TMC278 Alone	Treatment B: TMC278 with Omeprazole
n	16	15
Day 1 (Treatment A)/Day 12 (Treatment B) (single dose)		
C_{max} , ng/mL	682.6 \pm 264.8	308.9 \pm 179.4
t_{max} , h	3.5 (2.0 - 6.0)	5.0 (2.0 - 6.0)
AUC_{24h} , ng.h/mL	7711 \pm 3770	3502 \pm 2092
Day 9 (Treatment A)/Day 20 (Treatment B) (multiple dose)		
C_{0h} , ng/mL	539.4 \pm 243.5	435.0 \pm 325.6
Day 10 (Treatment A)/Day 21 (Treatment B) (multiple dose)		
C_{0h} , ng/mL	541.9 \pm 248.9	427.6 \pm 266.2
Day 11 (Treatment A)/Day 22 (Treatment B) (steady-state)		
C_{0h} , ng/mL	620.5 \pm 314.5	431.4 \pm 240.5
C_{min} , ng/mL	507.1 \pm 241.0	347.0 \pm 196.2
C_{max} , ng/mL	1205 \pm 311.3	779.4 \pm 408.7
t_{max} , h	4.0 (0.0 - 6.0)	4.0 (2.0 - 9.0)
AUC_{24h} , ng.h/mL	18730 \pm 6307	11920 \pm 6573
$C_{ss,av}$, ng/mL	780.5 \pm 262.8	496.6 \pm 273.9
FI, %	94.98 \pm 31.05	87.85 \pm 25.34

Table 3-Statistical analysis for rilpivirine 150 mg once daily after a single dose and rilpivirine 150 mg once daily after a single dose coadministered with omeprazole 20 mg once daily

Parameter	LSmeans ^a		LSmeans Ratio, %	90% CI, % ^c	p-Value		
	Treatment A, Day 1 TMC278 Alone (Reference)	Treatment B, Day 12 TMC278 with Omeprazole (Test)			Treatment	Period	Sequence
C _{max} , ng/mL	620.2	259.5	41.84	32.35 - 54.12	<0.0001	0.5892	0.8828
AUC _{24h} , ng.h/mL	6852	3031	44.24	35.31 - 55.42	<0.0001	0.4517	0.9546
Parameter	Median ^b		Treatment Difference Median	90% CI, % ^c	p-Value		
	Treatment A, Day 1 TMC278 Alone (Reference)	Treatment B, Day 12 TMC278 with Omeprazole (Test)			Treatment	Period	Sequence
t _{max} , h	4.0	5.0	1.0	0.0 - 1.5	0.0738	1.000	0.8598

^a n = 16 for Treatment A (reference) and n = 15 for Treatment B (test).

^b n = 15 for t_{max} of Treatment A (reference).

^c 90% confidence intervals.

CI = confidence interval; LSmeans = least square means.

Table 4-Statistical analysis for rilpivirine 150 mg once daily and rilpivirine 150 mg once daily coadministered with omeprazole 20 mg once daily

Parameter	LSmeans ^a		LSmeans Ratio, %	90% CI, % ^c	p-Value		
	Treatment A, Day 11 TMC278 Alone (Reference)	Treatment B, Day 22 TMC278 with Omeprazole (Test)			Treatment	Period	Sequence
C _{0h} , ng/mL	552.9	388.4	70.25	59.94 - 82.35	0.0017	0.5030	0.9286
C _{min} , ng/mL	459.7	309.7	67.36	58.02 - 78.20	0.0004	0.8504	0.8603
C _{max} , ng/mL	1151	685.4	59.53	48.39 - 73.23	0.0006	0.9198	0.5513
AUC _{24h} , ng.h/mL	17595	10561	60.02	51.05 - 70.57	0.0001	0.8876	0.5022
Parameter	Median ^b		Treatment Difference Median	90% CI, % ^c	p-Value		
	Treatment A, Day 11 TMC278 Alone (Reference)	Treatment B, Day 22 TMC278 with Omeprazole (Test)			Treatment	Period	Sequence
t _{max} , h	4.0	4.0	0.75	(-0.5) - (2.5)	0.1969	0.9533	0.8610

^a n = 16 for Treatment A (reference) and n = 15 for Treatment B (test).

^b n = 15 for t_{max} of Treatment A (reference).

^c 90% confidence intervals.

CI = confidence interval; LSmeans = least square means.

Based on the statistical analysis after a single dose of rilpivirine 150 mg once daily coadministered with omeprazole, the mean rilpivirine C_{max} and AUC_(0-24h) values were

decreased compared to rilpivirine when administered by itself. The 90% confidence interval for rilpivirine C_{\max} and $AUC_{(0-24h)}$ were not within 80%-125%.

With multiple dosing, based on the statistical analysis, when rilpivirine was coadministered with omeprazole, the mean rilpivirine C_{0h} , C_{\min} , C_{\max} , and $AUC_{(0-24h)}$ values were decreased compared to rilpivirine when administered by itself. The 90% confidence interval for rilpivirine C_{0h} , C_{\min} , C_{\max} , and $AUC_{(0-24h)}$ were not within 80%-125%.

Based on evaluating the individual rilpivirine predose concentrations, steady state concentrations were achieved by Day 11 (Treatment A) and Day 22 (Treatment B) in most subjects.

Omeprazole, 5-hydroxyomeprazole and omeprazole sulphone

Table 5-Omeprazole plasma pharmacokinetic parameters (administered as omeprazole 20 mg once daily and rilpivirine 150 mg once daily coadministered with omeprazole 20 mg once daily [%FI=100 x $([C_{\max}-C_{\min}]/C_{ss,av})$]

Pharmacokinetics of Omeprazole (mean \pm standard deviation, t_{\max} : median [range])	Day 11: Omeprazole Alone	Day 12: Omeprazole and TMC278 (SD)	Day 22: Omeprazole and TMC278 (MD)
n	15 ^a	15 ^a	15 ^b
C_{0h} , ng/mL	NQ ^c	NQ ^c	NQ ^c
C_{\min} , ng/mL	NQ ^c	NQ ^c	NQ ^c
C_{\max} , ng/mL	415.5 \pm 215.3	409.8 \pm 257.8	385.1 \pm 238.6
t_{\max} , h	4.0 (1.0 - 5.0)	4.0 (1.0 - 6.0)	4.0 (2.0 - 6.0)
AUC_{24h} , ng.h/mL	1251 \pm 919.7	1271 \pm 1081	1136 \pm 1054
$t_{1/2}$, h	1.166 \pm 0.3684	1.217 \pm 0.3099	1.145 \pm 0.3191
$C_{ss,av}$, ng/mL	52.12 \pm 38.32	52.98 \pm 45.02	47.33 \pm 43.93
FI, %	987.5 \pm 383.8	925.3 \pm 337.0	978.2 \pm 374.9

^a n = 10 for $t_{1/2}$.

^b n = 12 for $t_{1/2}$.

^c NQ = Not Quantifiable (< 1.00 ng/mL).

SD = single dose; MD = multiple dose.

Table 6-Statistical analysis for omeprazole (administered as omeprazole 20 mg once daily and after a single dose of rilpivirine 150 mg once daily coadministered with omeprazole 20 mg once daily)

Parameter	LSmeans ^a		LSmeans Ratio, %	90% CI,% ^b	p-Value
	Day 11: Omeprazole Alone (Reference)	Day 12: Omeprazole and TMC278 (SD) (Test)			Treatment
C _{max} , ng/mL	367.2	345.9	94.21	74.95 - 118.4	0.6533
AUC _{24h} , ng.h/mL	961.1	955.6	99.43	89.19 - 110.8	0.9279
Parameter	Median ^a		Treatment Difference Median	90% CI,% ^b	p-Value
	Day 11: Omeprazole Alone (Reference)	Day 12: Omeprazole and TMC278 (SD) (Test)			Treatment
t _{max} , h	4.0	4.0	0.5	(-0.5) - (1.0)	0.6386

^a n = 15 for Day 11 (reference) and Day 12 (test).

^b 90% confidence intervals.

CI = confidence interval; LS means = least square means; SD = single dose.

Table 7-Statistical analysis for omeprazole (administered as omeprazole 20 mg once daily and rilpivirine 150 mg once daily coadministered with omeprazole 20 mg once daily)

Parameter	LSmeans ^a		LSmeans Ratio, %	90% CI,% ^b	p-Value
	Day 11: Omeprazole Alone (Reference)	Day 22: Omeprazole and TMC278 (MD) (Test)			Treatment
C _{max} , ng/mL	367.2	314.5	85.64	67.57 - 108.6	0.2687
AUC _{24h} , ng.h/mL	961.1	824.3	85.77	75.68 - 97.21	0.0486
Parameter	Median ^a		Treatment Difference Median	90% CI,% ^b	p-Value
	Day 11: Omeprazole Alone (Reference)	Day 22: Omeprazole and TMC278 (MD.) (Test)			Treatment
t _{max} , h	4.0	4.0	0.0	(-0.5) - (0.5)	0.7620

^a n = 15 for Day 11 (reference) and Day 22 (test).

^b 90% confidence intervals.

CI = confidence interval; LS means = least square means; MD = multiple dose.

The omeprazole statistical analysis did not include a comparison of C_{0h} (the predose plasma concentrations) and C_{min} (the minimum plasma concentrations between 0 hour and the dosing interval [τ]) because the omeprazole predose concentrations were less than the lower limit of quantification (LLOQ) on Day 11, Day 12, and Day 22 and the Day 11, Day 12, and Day 22 C_{0h} and C_{min} values for all 15 evaluable subjects was zero. For similar reasons, an evaluation regarding whether steady state omeprazole concentrations were achieved was not performed.

Based on the statistical analysis after a single dose of rilpivirine 150 mg once daily coadministered with omeprazole, the mean omeprazole C_{max} value was decreased and minimal differences were observed in the $AUC_{(0-24h)}$ value compared to omeprazole when administered by itself. The 90% confidence interval for omeprazole C_{max} was not within 80%-125%. The 90% confidence interval for omeprazole $AUC_{(0-24h)}$ was within 80%-125%.

With multiple dosing of both medications, based on the statistical analysis, when rilpivirine was coadministered with omeprazole, the mean omeprazole C_{max} and $AUC_{(0-24h)}$ values were decreased compared to omeprazole when administered by itself. The 90% confidence interval for omeprazole C_{max} and $AUC_{(0-24h)}$ were not within 80%-125%. There was no change in the omeprazole t_{max} value for Days 11 and 22.

Table 8-5-hydroxyomeprazole plasma pharmacokinetic parameters (administered as omeprazole 20 mg once daily and rilpivirine 150 mg once daily coadministered with omeprazole 20 mg once daily [%FI=100 x ($[C_{max}-C_{min}]/C_{ss,av}$)])

Pharmacokinetics of 5-hydroxyomeprazole (mean ± standard deviation, t_{max} : median [range])	Day 11: Omeprazole Alone	Day 12: Omeprazole and TMC278 (SD)	Day 22: Omeprazole and TMC278 (MD)
n	15	15 ^a	15
C_{0h} , ng/mL	NQ ^b	NQ ^b	NQ ^b
C_{min} , ng/mL	NQ ^b	NQ ^b	NQ ^b
C_{max} , ng/mL	176.6 ± 56.34	187.9 ± 73.36	192.3 ± 76.48
t_{max} , h	4.0 (1.0 - 5.0)	5.0 (1.0 - 6.0)	4.0 (2.0 - 6.0)
AUC_{24h} , ng.h/mL	594.5 ± 139.6	631.4 ± 175.5	652.5 ± 181.4
$t_{1/2}$, h	1.521 ± 0.5309	1.485 ± 0.3346	1.448 ± 0.3456
$C_{ss,av}$, ng/mL	24.77 ± 5.816	26.31 ± 7.314	27.19 ± 7.557
FI, %	739.3 ± 252.0	708.8 ± 190.6	716.2 ± 228.1
Ratio AUC_{24h} , 5-hydroxyomeprazole/omeprazole (%)	72.36 ± 42.44	78.29 ± 49.43	92.28 ± 55.46

^a n = 14 for $t_{1/2}$.

^b NQ = not quantifiable (< 1.00 ng/mL).

SD = single dose; MD = multiple dose.

Table 9-Statistical analysis for 5-hydroxyomeprazole (administered as omeprazole 20 mg once daily and after a single dose of rilpivirine 150 mg once daily coadministered with omeprazole 20 mg once daily)

Parameter	LSmeans ^a		LSmeans Ratio, %	90% CI,% ^b	p-Value
	Day 11: Omeprazole Alone (Reference)	Day 12: Omeprazole and TMC278 (SD) (Test)			Treatment
C _{max} , ng/mL	169.0	174.7	103.4	87.44 - 122.2	0.7316
AUC _{24h} , ng.h/mL	580.3	612.3	105.5	99.10 - 112.4	0.1540
Median ^a					p-Value
Parameter	Day 11: Omeprazole Alone (Reference)	Day 12: Omeprazole and TMC278 (SD) (Test)	Treatment Difference Median	90% CI,% ^b	Treatment
t _{max} , h	4.0	5.0	0.25	(-1.0) - (1.5)	0.6358

^a n = 15 for Day 11 (reference) and Day 12 (test).

^b 90% confidence intervals.

CI = confidence interval; LS means = least square means; SD = single dose.

Table 10-Statistical analysis for 5-hydroxyomeprazole (administered as omeprazole 20 mg once daily and rilpivirine 150 mg once daily coadministered with omeprazole 20 mg once daily)

Parameter	LSmeans ^a		LSmeans Ratio, %	90% CI,% ^b	p-Value
	Day 11: Omeprazole Alone (Reference)	Day 22: Omeprazole and TMC278 (MD) (Test)			Treatment
C _{max} , ng/mL	169.0	180.1	106.5	91.04 - 124.7	0.4895
AUC _{24h} , ng.h/mL	580.3	630.0	108.6	101.7 - 115.9	0.0439
Median ^a					p-Value
Parameter	Day 11: Omeprazole Alone (Reference)	Day 22: Omeprazole and TMC278 (MD.) (Test)	Treatment Difference Median	90% CI,% ^b	Treatment
t _{max} , h	4.0	4.0	0.0	(-0.5) - (0.5)	0.6296

^a n = 15 for Day 11 (reference) and Day 22 (test).

^b 90% confidence intervals.

CI = confidence interval; LS means = least square means; MD = multiple dose.

The 5-hydroxyomeprazole statistical analysis did not include a comparison of C_{0h} (the predose plasma concentrations) and C_{min} (the minimum plasma concentrations between 0 hour and the dosing interval [τ]) because the 5-hydroxyomeprazole predose concentrations were less than the lower limit of quantification (LLOQ) on Day 11, Day 12, and Day 22 and the Day 11, Day 12, and Day 22 C_{0h} and C_{min} values for all 15 evaluable subjects was zero.

Based on the statistical analysis after a single dose of rilpivirine 150 mg once daily coadministered with omeprazole, minimal differences were observed in the mean

5-hydroxyomeprazole C_{\max} and $AUC_{(0-24h)}$ values compared to omeprazole when administered by itself. The 90% confidence interval for 5-hydroxyomeprazole C_{\max} and $AUC_{(0-24h)}$ were within 80%-125%.

With multiple dosing of both medications, based on the statistical analysis, when rilpivirine was coadministered with omeprazole, the mean 5-hydroxyomeprazole C_{\max} and $AUC_{(0-24h)}$ values were increased compared to omeprazole when administered by itself. The 90% confidence interval for 5-hydroxyomeprazole C_{\max} and $AUC_{(0-24h)}$ were within 80%-125%. There was no change in the 5-hydroxyomeprazole t_{\max} value for Days 11 and 22.

Table 11-Omeprazole sulfone plasma pharmacokinetic parameters (administered as omeprazole 20 mg once daily and rilpivirine 150 mg once daily coadministered with omeprazole 20 mg once daily [%FI=100 x $([C_{\max}-C_{\min}]/C_{ss,av})$])

Pharmacokinetics of Omeprazole Sulfone (mean \pm standard deviation, t_{\max} : median [range])	Day 11: Omeprazole Alone	Day 12: Omeprazole and TMC278 (SD)	Day 22: Omeprazole and TMC278 (MD)
n	15 ^a	15	15 ^a
C_{0h} , ng/mL	7.211 \pm 12.32	6.239 \pm 9.853	5.058 \pm 8.825
C_{\min} , ng/mL	5.773 \pm 9.776	4.989 \pm 8.409	NQ ^b
C_{\max} , ng/mL	98.63 \pm 50.35	91.67 \pm 53.93	91.31 \pm 64.18
t_{\max} , h	5.0 (2.0 - 9.0)	5.0 (2.0 - 9.0)	5.0 (3.0 - 6.0)
AUC_{24h} , ng.h/mL	845.8 \pm 690.1	851.5 \pm 846.8	742.9 \pm 825.3
$t_{1/2}$, h	3.571 \pm 1.594	3.417 \pm 1.574	3.060 \pm 1.555
$C_{ss,av}$, ng/mL	35.24 \pm 28.76	35.48 \pm 35.28	30.96 \pm 34.39
FI, %	381.3 \pm 197.3	355.9 \pm 168.8	425.8 \pm 212.2
Ratio AUC_{24h} , omeprazole sulfone/omeprazole (%)	66.96 \pm 27.72	61.08 \pm 14.44	57.70 \pm 16.23

^a n = 14 for $t_{1/2}$

^b NQ = not quantifiable (< 1.00 ng/mL).

SD = single dose; MD = multiple dose.

Table 12-Statistical analysis for omeprazole sulphone (administered as omeprazole 20 mg once daily and after a single dose of rilpivirine 150 mg once daily coadministered with omeprazole 20 mg once daily)

Parameter	LSmeans ^a		LSmeans Ratio, %	90% CI,% ^b	p-Value
	Day 11: Omeprazole Alone (Reference)	Day 12: Omeprazole and TMC278 (SD) (Test)			Treatment
C _{0h} , ng/mL	8.930	8.556	95.81	81.73 - 112.3	0.6258
C _{min} , ng/mL	7.219	6.780	93.92	77.79 - 113.4	0.5480
C _{max} , ng/mL	87.54	78.57	89.75	75.20 - 107.1	0.2997
AUC _{24h} , ng.h/mL	603.6	567.7	94.05	83.12 - 106.4	0.3966
Parameter	Median ^a		Treatment Difference Median	90% CI,% ^b	p-Value
	Day 11: Omeprazole Alone (Reference)	Day 12: Omeprazole and TMC278 (SD) (Test)			Treatment
t _{max} , h	5.0	5.0	0.0	(-0.5) - (1.0)	0.7670

^a n = 8 for C_{0h} and C_{min} and n = 15 for C_{max}, AUC_{24h} and t_{max} for Day 11 (reference) and Day 12 (test).

^b 90% confidence intervals.

CI = confidence interval; LS means = least square means; SD = single dose.

Table 13-Statistical analysis for omeprazole sulphone (administered as omeprazole 20 mg once daily and rilpivirine 150 mg once daily coadministered with omeprazole 20 mg once daily)

Parameter	LSmeans ^a		LSmeans Ratio, %	90% CI,% ^b	p-Value
	Day 11: Omeprazole Alone (Reference)	Day 22: Omeprazole and TMC278 (MD) (Test)			Treatment
C _{0h} , ng/mL	8.930	5.911	66.19	57.25 - 76.53	0.0010
C _{max} , ng/mL	87.54	73.99	84.52	69.21 - 103.2	0.1605
AUC _{24h} , ng.h/mL	603.6	458.0	75.87	65.15 - 88.36	0.0065
Parameter	Median ^a		Treatment Difference Median	90% CI,% ^b	p-Value
	Day 11: Omeprazole Alone (Reference)	Day 22: Omeprazole and TMC278 (MD) (Test)			Treatment
t _{max} , h	5.0	5.0	0.0	(-0.5) - (0.5)	0.5337

^a n = 8 for C_{0h} and n = 15 for C_{max}, AUC_{24h} and t_{max} for Day 11 (reference) and Day 22 (test)

^b 90% confidence intervals.

CI = confidence interval; LS means = least square means; MD = multiple dose.

The omeprazole sulphone statistical analysis after a single dose of rilpivirine 150 mg once daily included a comparison of C_{0h} and C_{min}. The omeprazole sulphone statistical analysis after multiple dosing of both medications did not include a comparison of C_{min} because more than half of the C_{min} values were less than the lower limit of quantification (LLOQ). Plots of individual predose omeprazole sulphone concentrations were not generated.

Based on the statistical analysis after a single dose of rilpivirine 150 mg once daily coadministered with omeprazole, minimal differences were observed in the mean omeprazole sulphone C_{0h} value and the mean omeprazole sulphone C_{min} , C_{max} , and $AUC_{(0-24h)}$ C_{max} values were decreased when compared to omeprazole administered by itself. The 90% confidence interval for omeprazole sulphone C_{0h} and $AUC_{(0-24h)}$ were within 80%-125%. The 90% confidence interval for omeprazole sulphone C_{min} and C_{max} were not within 80%-125%.

With multiple dosing of both medications, based on the statistical analysis, when rilpivirine was coadministered with omeprazole, the mean omeprazole sulphone C_{0h} , C_{max} and $AUC_{(0-24h)}$ values were decreased compared to omeprazole when administered by itself. The 90% confidence interval for omeprazole sulphone C_{max} and $AUC_{(0-24h)}$ were not within 80%-125%. There was no change in the omeprazole sulphone t_{max} value for Days 11 and 22.

10.3 Pharmacodynamic Analysis

Subjects were tested for H.pylori and CYP 2C19 genotyping was performed on Day 1 of their first treatment period. An exploratory analysis was conducted to compare the least squares means omeprazole C_{max} and $AUC_{(0-\tau)}$ in subjects with and without H.pylori infection and for different CYP 2C19 genotypes. However, according to the trial report, due to the low number of subjects with a genotype other than WT/WT, definitive conclusions could not be made regarding omeprazole and omeprazole metabolite exposure either by itself or in combination with rilpivirine and CYP 2C19 genotypes. The low number of subjects that tested positive for H.pylori also precluded definitive conclusions from being made regarding the influence of the presence of H.pylori infection on rilpivirine exposure when coadministered with or without omeprazole.

10.4 Safety Issues

No deaths or other serious adverse events were reported for the trial. No grade 3 or grade 4 adverse events were reported. The most common reported adverse events were headache, fatigue and hyperbilirubinemia (see Table 14 for information regarding the number of subjects).

Table 14-Adverse event incidence categorized by system organ class and preferred term reported in more than one subject

System Organ Class Preferred Term n (%)	Trial Phase				
	TMC278 Alone N = 16	Omeprazole Alone N = 16	Omeprazole + TMC278 N = 15	Follow-up N = 16	Whole Trial N = 16
<i>Any Adverse Event</i>	10 (62.5)	14 (87.5)	11 (73.3)	5 (31.3)	15 (93.8)
<i>Gastrointestinal Disorders</i>	1 (6.3)	5 (31.3)	0	0	5 (31.3)
Bowel sounds abnormal	0	2 (12.5)	0	0	2 (12.5)
Diarrhea	1 (6.3)	1 (6.3)	0	0	2 (12.5)
<i>General Disorders and Administration Site Conditions</i>	3 (18.8)	2 (12.5)	2 (13.3)	0	5 (31.3)
Fatigue	3 (18.8)	1 (6.3)	2 (13.3)	0	5 (31.3)
<i>Hepatobiliary Disorders</i>	2 (12.5)	2 (12.5)	1 (6.7)	2 (12.5)	5 (31.3)
Hyperbilirubinaemia	2 (12.5)	2 (12.5)	1 (6.7)	2 (12.5)	5 (31.3)
<i>Investigations</i>	1 (6.3)	1 (6.3)	2 (13.3)	4 (25.0)	7 (43.8)
Blood creatinine increased	0	0	0	4 (25.0)	4 (25.0)
Hemoglobin decreased	1 (6.3)	0	1 (6.7)	0	2 (12.5)
Lipase increased	1 (6.3)	0	1 (6.7)	0	2 (12.5)
<i>Metabolism and Nutrition Disorders</i>	1 (6.3)	1 (6.3)	2 (13.3)	1 (6.3)	4 (25.0)
Hyperuricaemia	1 (6.3)	1 (6.3)	2 (13.3)	1 (6.3)	3 (18.8)
<i>Nervous System Disorders</i>	8 (50.0)	6 (37.5)	5 (33.3)	0	11 (68.8)
Headache	8 (50.0)	6 (37.5)	4 (26.7)	0	10 (62.5)
<i>Respiratory, Thoracic and Mediastinal Disorders</i>	0	1 (6.3)	1 (6.7)	0	2 (12.5)
Nasopharyngitis	0	1 (6.3)	1 (6.7)	0	2 (12.5)
<i>Skin and Subcutaneous Tissue Disorders</i>	1 (6.3)	1 (6.3)	2 (13.3)	1 (6.3)	4 (25.0)
Rash maculo-papular	0	0	1 (6.7)	1 (6.3)	2 (12.5)

n = number of subjects with that particular adverse event; N = number of subjects per phase.

Table 15-Adverse event incidence at least possibly related to rilpivirine categorized by system organ class and preferred term

System Organ Class Preferred Term n (%)	Trial Phase				
	TMC278 Alone N = 16	Omeprazole Alone N = 16	Omeprazole + TMC278 N = 15	Follow-up N = 16	Whole Trial N = 16
<i>Any Adverse Event</i>	10 (62.5)	14 (87.5)	11 (73.3)	5 (31.3)	15 (93.8)
<i>With at least 1 AE thought to be at least possibly related to TMC278</i>	9 (56.3)	0	9 (60.0)	5 (31.3)	12 (75.0)
<i>Gastrointestinal Disorders</i>	1 (6.3)	0	0	0	1 (6.3)
Diarrhea	1 (6.3)	0	0	0	1 (6.3)
Dry mouth	1 (6.3)	0	0	0	1 (6.3)
<i>General Disorders and Administration Site Conditions</i>	3 (18.8)	0	2 (13.3)	0	4 (25.0)
Fatigue	3 (18.8)	0	2 (13.3)	0	4 (25.0)
<i>Hepatobiliary Disorders</i>	2 (12.5)	0	1 (6.7)	2 (12.5)	3 (18.8)
Hyperbilirubinaemia	2 (12.5)	0	1 (6.7)	2 (12.5)	3 (18.8)
<i>Investigations</i>	1 (6.3)	0	2 (13.3)	4 (25.0)	6 (37.5)
Blood amylase increased	0	0	1 (6.7)	0	1 (6.3)
Blood creatinine increased	0	0	0	4 (25.0)	4 (25.0)
Hemoglobin decreased	1 (6.3)	0	1 (6.7)	0	2 (12.5)
Lipase increased	1 (6.3)	0	1 (6.7)	0	2 (12.5)
<i>Metabolism and Nutrition Disorders</i>	0	0	1 (6.7)	0	1 (6.3)
Hyperuricemia	0	0	1 (6.7)	0	1 (6.3)
<i>Nervous System Disorders</i>	8 (50.0)	0	4 (26.7)	0	9 (56.3)
Dizziness	1 (6.3)	0	0	0	1 (6.3)
Dizziness postural	1 (6.3)	0	0	0	1 (6.3)
Headache	8 (50.0)	0	4 (26.7)	0	9 (56.3)
<i>Skin and Subcutaneous Tissue Disorders</i>	1 (6.3)	0	2 (13.3)	1 (6.3)	4 (25.0)
Pruritus	0	0	1 (6.7)	0	1 (6.3)
Rash macular	1 (6.3)	0	0	0	1 (6.3)
Rash maculo-papular	0	0	1 (6.7)	1 (6.3)	2 (12.5)

n = number of subjects with that particular AE; N = number of subjects per phase.

Table 16-Adverse event incidence at least possibly related to omeprazole categorized by system organ class and preferred term (includes original and replacement subjects)

System Organ Class Preferred Term n (%)	Trial Phase				
	TMC278 Alone N = 16	Omeprazole Alone N = 16	Omeprazole + TMC278 N = 15	Follow-up N = 16	Whole Trial N = 16
<i>Any Adverse Event</i>	10 (62.5)	14 (87.5)	11 (73.3)	5 (31.3)	15 (93.8)
<i>With at least 1 AE thought to be at least possibly related to Omeprazole</i>	0	11 (68.8)	8 (53.3)	3 (18.8)	12 (75.0)
Gastrointestinal Disorders	0	5 (31.3)	0	0	5 (31.3)
Abdominal pain	0	1 (6.3)	0	0	1 (6.3)
Abnormal faeces	0	1 (6.3)	0	0	1 (6.3)
Bowel sounds abnormal	0	2 (12.5)	0	0	2 (12.5)
Diarrhea	0	1 (6.3)	0	0	1 (6.3)
Nausea	0	1 (6.3)	0	0	1 (6.3)
Vomiting	0	1 (6.3)	0	0	1 (6.3)
General Disorders and Administration Site Conditions	0	1 (6.3)	2 (13.3)	0	3 (18.8)
Fatigue	0	1 (6.3)	2 (13.3)	0	3 (18.8)
Hepatobiliary Disorders	0	2 (12.5)	1 (6.7)	2 (12.5)	4 (25.0)
Hyperbilirubinaemia	0	2 (12.5)	1 (6.7)	2 (12.5)	4 (25.0)
Investigations	0	1 (6.3)	1 (6.7)	2 (12.5)	3 (18.8)
ALT increased	0	1 (6.3)	0	0	1 (6.3)
Blood amylase increased	0	0	1 (6.7)	0	1 (6.3)
Blood creatinine increased	0	0	0	2 (12.5)	2 (12.5)
Lipase increased	0	0	1 (6.7)	0	1 (6.3)
Nervous System Disorders	0	6 (37.5)	4 (26.7)	0	8 (50.0)
Headache	0	6 (37.5)	4 (26.7)	0	8 (50.0)
Skin and Subcutaneous Tissue Disorders	0	1 (6.3)	2 (13.3)	0	2 (12.5)
Pruritus	0	1 (6.3)	1 (6.7)	0	1 (6.3)
Rash maculo-papular	0	0	1 (6.7)	0	1 (6.3)

n = number of subjects with that particular AE; N = number of subjects per phase; ALT = alanine aminotransferase.

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11. Discussion and Conclusions

Based on the results from the drug-drug interaction trial, the following conclusions can be made:

- After a single dose of rilpivirine 150 mg once daily coadministered with omeprazole, the mean rilpivirine C_{max} and $AUC_{(0-24h)}$ values were decreased by 58% and 56%, respectively, compared to rilpivirine when administered by itself. The 90% confidence interval for rilpivirine C_{max} and $AUC_{(0-24h)}$ were not within 80%-125%.
- With multiple dosing, when rilpivirine was coadministered with omeprazole, the mean rilpivirine C_{0h} , C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were decreased by 30%, 33%, 40%, and 40%, respectively, compared to rilpivirine when administered by itself. The 90% confidence interval for rilpivirine C_{0h} , C_{min} , C_{max} , and $AUC_{(0-24h)}$ were not within 80%-125%.
- After a single dose of rilpivirine 150 mg once daily coadministered with omeprazole, the mean omeprazole C_{max} value was decreased by 6% and minimal differences were observed in the $AUC_{(0-24h)}$ value (decreased by 0.6%) compared to omeprazole when administered by itself. The 90% confidence interval for omeprazole C_{max} was not within 80%-125%. The 90% confidence interval for omeprazole $AUC_{(0-24h)}$ was within 80%-125%.
- With multiple dosing of both medications, when rilpivirine was coadministered with omeprazole, the mean omeprazole C_{max} and $AUC_{(0-24h)}$ values were both decreased by 14% compared to omeprazole when administered by itself. The 90% confidence interval for omeprazole C_{max} and $AUC_{(0-24h)}$ were not within 80%-125%.

- After a single dose of rilpivirine 150 mg once daily coadministered with omeprazole, minimal differences were observed in the mean 5-hydroxyomeprazole C_{\max} and $AUC_{(0-24h)}$ values (increased by 3% and 6%, respectively) compared to omeprazole when administered by itself. The 90% confidence interval for 5-hydroxyomeprazole C_{\max} and $AUC_{(0-24h)}$ were within 80%-125%.
- With multiple dosing of both medications, when rilpivirine was coadministered with omeprazole, the mean 5-hydroxyomeprazole C_{\max} and $AUC_{(0-24h)}$ values were increased by 7% and 9%, respectively, compared to omeprazole when administered by itself. The 90% confidence interval for 5-hydroxyomeprazole C_{\max} and $AUC_{(0-24h)}$ were within 80%-125%.
- After a single dose of rilpivirine 150 mg once daily coadministered with omeprazole, minimal differences were observed in the mean omeprazole sulphone C_{0h} value (decreased by 4%) and the mean omeprazole sulphone C_{\min} , C_{\max} , and $AUC_{(0-24h)}$ values were decreased by 6%, 10%, and 6%, respectively, when compared to omeprazole administered by itself. The 90% confidence interval for omeprazole sulphone C_{0h} and $AUC_{(0-24h)}$ were within 80%-125%. The 90% confidence interval for omeprazole sulphone C_{\min} and C_{\max} were not within 80%-125%.
- With multiple dosing of both medications, when rilpivirine was coadministered with omeprazole, the mean omeprazole sulphone C_{0h} , C_{\max} and $AUC_{(0-24h)}$ values were decreased by 34%, 15%, and 24%, respectively, compared to omeprazole when administered by itself. The 90% confidence interval for omeprazole sulphone C_{\max} and $AUC_{(0-24h)}$ were not within 80%-125%.

Omeprazole results in clinically relevant changes in the exposure of rilpivirine with a rilpivirine dosage regimen of 150 mg once daily and the applicant's recommendation in the proposed rilpivirine prescribing information that omeprazole (and other proton pump inhibitors) and rilpivirine should not be coadministered is acceptable. The changes in rilpivirine exposure are believed to be due to an alteration or alterations in rilpivirine's pH dependent absorption. The current trial did not evaluate dosing strategies to minimize the potential for a drug-drug interaction when use of omeprazole is combined with rilpivirine. The specific impact of omeprazole on rilpivirine exposure with a rilpivirine dosage regimen of 25 mg once daily was not evaluated in the current trial, however it is anticipated that the applicant's recommendation regarding coadministration of omeprazole (and other proton pump inhibitors) and rilpivirine would still be applicable.

Coadministration of rilpivirine 150 mg once daily and omeprazole does not result in clinically relevant changes in omeprazole or 5-hydroxyomeprazole exposure. The decrease in omeprazole sulphone exposure with multiple dosing of both omeprazole and rilpivirine is not anticipated to be clinically relevant because the omeprazole sulphone metabolite has minimal antisecretory effects. Therefore, no dosage adjustment for omeprazole is necessary when coadministered with rilpivirine.

Trial TMC278-C116

A phase I, open-label, randomized, two-way crossover trial in 16 healthy subjects to investigate the potential pharmacokinetic interaction between steady-state rilpivirine and steady-state atorvastatin

Dates: October 28, 2005 – January 25, 2006

Trial Site: (b) (4)

Summary of Findings:

Rilpivirine 150 mg q.d. did not have a clinically relevant effect on the steady state pharmacokinetics of atorvastatin. Rilpivirine increased the C_{max} of atorvastatin by 35% but had no significant effect on AUC_{24h} . Conversely, rilpivirine decreased the C_{min} of atorvastatin by 15% and the 90% confidence interval was 69.4% – 103%.

Moreover, rilpivirine increased the exposures (C_{0h} , C_{max} , and $AUC_{[0-24h]}$) of the active metabolites 2-OH-atorvastatin and 4-OH-atorvastatin by 23% to 58%. Rilpivirine also increased the C_{max} and AUC_{24h} of the total HMG-CoA reductase activity (the sum of atorvastatin, 2-OH-atorvastatin and 4-OH-atorvastatin) by 39 and 21%, respectively.

Unexpectedly, rilpivirine decreased the C_{0h} , C_{min} , and AUC_{24h} of inactive atorvastatin lactone by 27%, 26%, and 18%, respectively. The 90% confidence intervals ranged from 62 to 87%.

Atorvastatin 40 mg q.d. did not have a clinically relevant effect on the steady state pharmacokinetics of rilpivirine 150 mg q.d. The magnitude of interaction is unlikely to affect the efficacy of rilpivirine.

Overall, clinicians should not adjust the dose of atorvastatin when co-administered with rilpivirine.

Trial Objectives:

The trial primarily aimed to determine the effect of steady-state atorvastatin on the steady-state pharmacokinetics (PK) of rilpivirine, and the effect of steady-state rilpivirine on the steady-state PK of atorvastatin, atorvastatin lactone, and the active metabolites 2-OH-atorvastatin and 4-OH-atorvastatin. The trial also aimed to determine the safety and tolerability of co-administration of rilpivirine and atorvastatin.

Trial Design:

This was a phase 1, open-label, randomized, two-way crossover trial to investigate the PK interaction between rilpivirine and atorvastatin at steady state. Trial subjects were divided into 2 periods. In both periods, subjects randomly received atorvastatin alone (Treatment A) or the combination of rilpivirine and atorvastatin (Treatment B). The treatments consisted of:

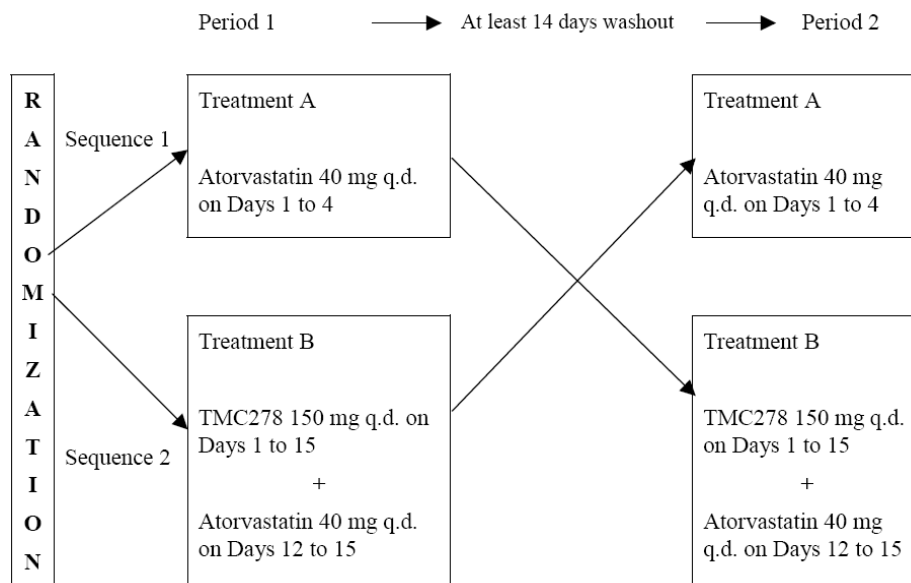
Treatment A: Atorvastatin 40 mg once daily (q.d.) from Day 1 to Day 4

Treatment B: Rilpivirine 150 mg q.d. from Day 1 to Day 15
+ atorvastatin 40 mg q.d. from Day 12 to Day 15

Washout: Between each treatment session for at least 14 days

During the trial, investigators collected full PK profiles of atorvastatin, atorvastatin lactone, 2-OH-atorvastatin, and 4-OH-atorvastatin up to 72 hours post dose beginning on Day 4 of Treatment A and on Day 15 of Treatment B. Investigators also collected full PK profiles of rilpivirine up to 24 hours post dose beginning on Day 11 and on Day 15 of Treatment B. Figure 1 illustrates the trial design.

Figure 1 Trial Design



The trial enrolled 16 male healthy Caucasian subjects ranging from 19 to 40 years of age, with BMIs ranging from 19.0 to 29.0 kg/m². Subjects were to have cortisone levels ≥ 19.9 µg/dL for at least one of the three screening timepoints.

The trial excluded subjects with any current or previous adrenal illness, viral infection (HIV-1, HIV-2, HAV, HBV, HCV), or if they had the following abnormalities \geq grade 1 at screening: serum creatinine, serum lipase, hemoglobin, platelet count, absolute neutrophil count, ALT, AST and total bilirubin. The trial also excluded subjects with a history or suspicion of alcohol, amphetamine, barbiturate, recreational or narcotic drug use.

Investigational Products:

1. Rilpivirine 150 mg q.d. dosed using 2 tablets, 50 mg (F003) and 100 mg (F002). The film-coated tablets contained the hydrochloric salt of rilpivirine (R314585) along with the fillers lactose and microcrystalline cellulose. Each tablet contained 55 mg or 110 mg of R314585, equivalent to 50 mg or 100 mg of rilpivirine, respectively. The tablet's batch numbers and expiry dates are listed below.
2. Atorvastatin 40 mg q.d. was dosed using commercially available oral tablets (Sortis® 40 mg). Tibotec Pharmaceuticals Ltd. provided the rilpivirine and atorvastatin tablets for the trial.

Table 1 Batch numbers and expiry dates of investigational products used in the trial

	Batch Number	Expiry Date
TMC278, 50 mg tablets	PD1273	12 November 2006
TMC278, 100 mg tablets	PD1268	12 November 2006
Atorvastatin	0444104D	28 September 2007

Dose Rationale:

Rilpivirine was dosed at 150 mg q.d. for 15 days to achieve steady state concentrations. This dose is 6-fold higher than the to-be-marketed dose of 25 mg q.d. In the clinical trials, subjects safely tolerated multiple doses of rilpivirine 150 mg q.d. for 14 days.

Generally, rilpivirine systemic exposures increase in a dose proportional fashion. Thus, one can anticipate 6-fold higher exposures of rilpivirine with 150 mg q.d. compared to a dose of 25 mg q.d. Similarly, if a drug-drug interaction is observed between atorvastatin and rilpivirine at 150 mg q.d., then it is reasonable to expect a 6-fold lower magnitude of the interaction at 25 mg q.d. This rationale assumes that both doses of rilpivirine produce similar rilpivirine induction effects on CYP3A4.

Atorvastatin (Sortis[®]) was dosed at 40 mg q.d for 4 days. The therapeutic range of atorvastatin is 10 to 80 mg q.d. administered with or without food. In this trial, subjects took atorvastatin within 10 minutes after ingesting a meal.

Dosage and Administration:

On days of PK assessment (Day 1, 4, and 5 for Treatment A and Days 1, 8, 11, 12, 15, and 16 for Treatment B) subjects fasted overnight for at least 10 hours. Only water was allowed until 2 hours before drug administration. Subjects were to administer rilpivirine and atorvastatin every day between 7:00 a.m. and 9 a.m. Subjects took the drugs with water (~200 mL) and within 10 minutes of breakfast (a standardized breakfast was administered in the clinic). On the days of co-administration, subjects ingested atorvastatin first, followed by rilpivirine administration.

Pharmacokinetic Assessments:

Investigators collected blood samples to determine plasma concentrations of rilpivirine, atorvastatin, and atorvastatin metabolites. The time points are listed below:

Atorvastatin and metabolites when given alone during periods 1 or 2 (Treatment A)

Days 1 to 3: Predose (0)*

Day 4: Predose (0), and 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 16 hrs postdose

Day 5: 24 hrs and 36 hrs postdose

Day 6: 48 hrs postdose

Day 7: 72 hrs post dose

*Predose rilpivirine concentrations were also evaluated on Day 1

Atorvastatin and metabolites when co-administered with rilpivirine during periods 1 or 2 (Treatment B)

Day 1: Predose (0)

Days 12 to 14: Predose (0)

Day 15: Predose (0), 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 16 hrs postdose

Day 16: 24 hrs and 36 hrs postdose
Day 17: 48 hrs postdose
Day 18: 72 hrs post dose

Rilpivirine when co-administered with or without atorvastatin during period 1 or 2 (Treatment B)

Day 1: Predose (0), and 4 hrs postdose
Days 8 to 10: Predose (0)
Day 11: Predose (0), and 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 16 hrs postdose
Day 12: Predose (24 hrs)
Days 13 to 14: Predose (0)
Day 15: Predose (0), and 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 16 hrs postdose
Day 16: 24 hrs post dose

Analytical Methods – Bioanalysis:

Two different laboratories analyzed the blood samples collected in this trial. J&J PRD, located in Beerse, Belgium analyzed rilpivirine and (b) (4) analyzed atorvastatin and its metabolites.

J&J PRD used a validated LC-MS/MS method to determine rilpivirine plasma concentrations. The method had a lower limit of quantification (LLOQ) of 1.0 ng/mL and an upper limit of quantification (ULOQ) of 2000 ng/mL.

(b) (4) used a validated LC-MS/MS method to determine plasma concentrations of atorvastatin, atorvastatin lactone, 2-OH-atorvastatin, and 4-OH-atorvastatin. The method had a LLOQ of 0.250 ng/mL and a ULOQ of 250 ng/mL for all analytes. The laboratory staff prepared the reference standards using material obtained from Syncom.

The table below displays the precision and accuracy of calibration standards and QC samples reported by both bioanalytical laboratories. Generally, all calibration standards and quality controls met the bioanalytical criteria defined as accuracy within $\pm 15\%$ ($\pm 20\%$ for LLOQ), and precision ($\%RE$) $\leq 15\%$ ($\leq 20\%$ for LLOQ).

Table 2 Precision (% CV) and accuracy (% relative error) of calibration standards and QC samples for the bioanalysis of TMC278-C116 rilpivirine and atorvastatin/atorvastatin metabolite plasma concentrations

	Rilpivirine		Atorvastatin		Atorvastatin lactone		2-OH-atorvastatin		4-OH-atorvastatin	
	Calibration SD	QCs	Calibration SD	QCs	Calibration SD	QCs	Calibration SD	QCs	Calibration SD	QCs
% CV	0.3– 8.9	3.6 – 5.2	2.3 – 7.7	4.5 – 10.5	1.9 – 7.2	4.3 – 4.9	4.1 – 8.4	6.6 – 8.3	3.3 – 6.8	5.5 – 11.2
% Relative error	≤ 5.0	≤ 0.9	≤ 2.6	≤ 4.4	≤ 3.1	≤ 2.1	≤ 5	≤ 5.0	≤ 3.0	≤ 5.6

The long-term stability of rilpivirine samples was appropriate. Tibotec investigators reported that rilpivirine is stable in frozen plasma for up to 1528 days at -20°C. The bioanalytical laboratory stored rilpivirine plasma samples at -20°C. Investigators analyzed rilpivirine plasma samples within the long-term stability period.

Long-term stability of atorvastatin, atorvastatin lactone, 2-OH-atorvastatin, and 4-OH-atorvastatin in frozen plasma was demonstrated at -70°C in heparin human plasma for a period of

209 days. The submitted atorvastatin/atorvastatin metabolite long term stability data of 209 days covered the duration of long term rilpivirine stability data necessary for the TMC278-C116 trial.

The applicant confirmed in a request for information that the atorvastatin samples were stored at $< -70^{\circ}\text{C}$.

Pharmacokinetic and Statistical Analyses:

(b) (4) performed the PK and statistical analyses using WinNonlin Professional, Microsoft Excel[®], and SAS[®]. The PK analysis assumed a non-compartmental model with extravascular input. All PK parameters were to be calculated using nominal sampling times; however, the parameters were estimated using actual sampling times when the actual sampling times deviated by $>10.0\%$ from the scheduled time.

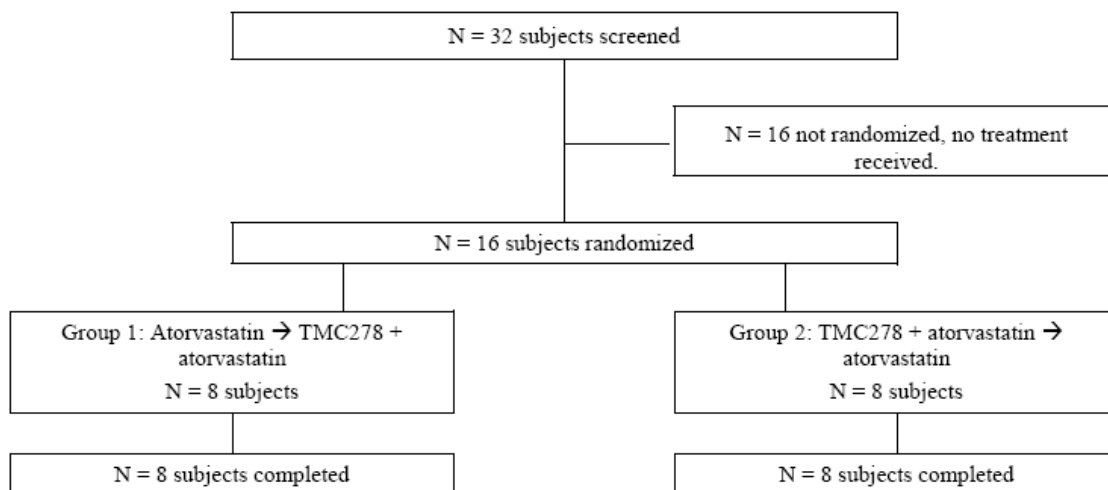
(b) (4) performed statistical analysis for rilpivirine by comparing Day 15 of Treatment B (test, rilpivirine + atorvastatin) with Day 11 of Treatment B (reference, rilpivirine alone). The primary parameters were C_{0h} , C_{min} , C_{max} , and AUC_{24h} . The least square means of the primary parameters for each treatment group were estimated with a linear mixed effects model, controlling for treatment as a fixed effect and subject as a random effect.

(b) (4) also performed statistical analysis for atorvastatin and its metabolites and for total HMG-CoA reductase activity by comparing Day 15 of Treatment B (test, rilpivirine + atorvastatin) with Day 4 of Treatment A (reference, atorvastatin alone). The primary parameters were C_{0h} , C_{min} , C_{max} , and AUC_{24h} for all analytes. The least square means of the primary parameters for each treatment group were estimated with a linear mixed effects model, controlling for treatment, sequence, and period as fixed effects and subject as random effect.

The difference between the LS means of test and reference for all primary parameters was used to derive a 90% confidence interval. Treatment and period effects were considered significant at the 5% level and sequence effects were considered significant at the 10% level. A no-effect boundary of 80% to 125% was established for the 90% confidence interval.

Disposition and demographic results:

The trial enrolled 16 male Caucasian subjects. Subjects had a median age of 32 (range 19 to 40) and a median BMI of 23 (range 19 to 29). Seventy five percent of subjects were non smokers. One subject received kanamycin during the follow-up period of the trial. This event will not affect the results from this trial. All randomized subjects successfully completed the trial.

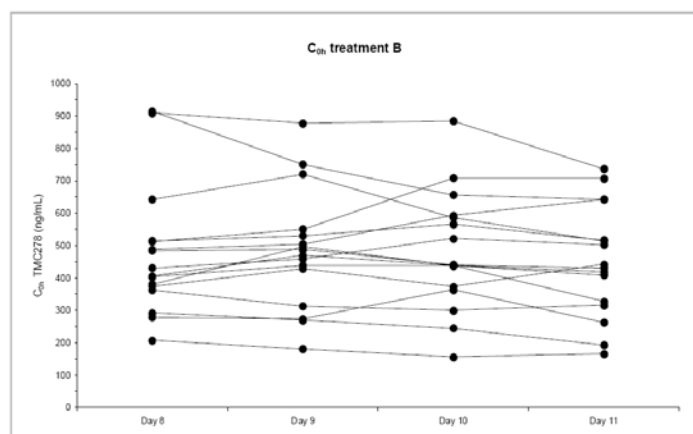


Pharmacokinetic results, rilpivirine:

This trial aimed to evaluate the drug-drug interaction between atorvastatin and rilpivirine at steady state. To verify that rilpivirine reached steady state levels, investigators collected several PK samples before drug co-administration. The figure below shows individual predose plasma concentrations of rilpivirine collected from Day 8 to 11 during Treatment B (rilpivirine alone). Visual inspection of this figure reveals that steady-state levels of rilpivirine were achieved before co-administration with atorvastatin on Day 15 in most subjects.

Seven subjects had quantifiable rilpivirine predose concentrations on Day 1, Treatment A. However, all these subjects had been randomized to Treatment B then Treatment A, and the quantifiable rilpivirine predose concentrations in Treatment A would not impact the atorvastatin /atorvastatin metabolite pharmacokinetic analysis (rilpivirine plasma samples were not collected in Treatment A).

Figure 2 Plots of individual predose concentrations (C_{0h}) of rilpivirine collected before Day 15



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During co-administration on day 15, atorvastatin minimally decreased the concentrations of rilpivirine. The two figures below show that atorvastatin did not alter the general shapes of individual and mean concentration-time profiles of rilpivirine. However, the median rilpivirine t_{max} was delayed by ~1 hour (from 4 to 5 hours) possibly due to PK variability.

Figure 3 Individual steady-state plasma concentration-time curves of rilpivirine alone (Day 11) and in combination with atorvastatin (Day 15)

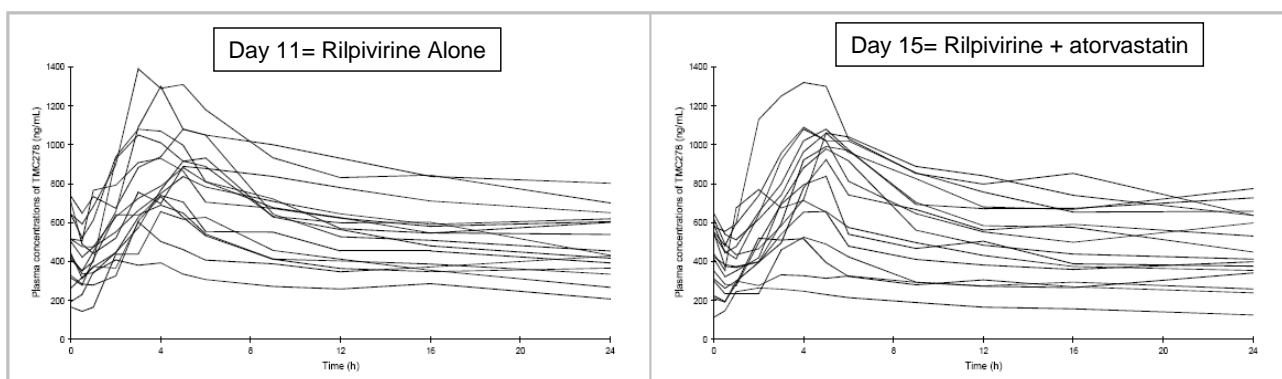
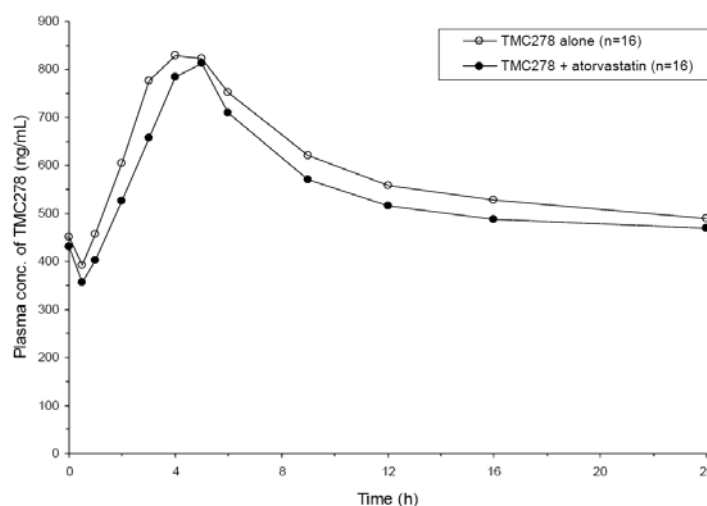


Figure 4 Combined mean steady-state plasma concentration-time curves of rilpivirine alone (Day 11) and in combination with atorvastatin (Day 15)



Atorvastatin decreased the mean C_{0h} , C_{min} , C_{max} , and AUC_{24h} of rilpivirine by 6%, 10%, 9%, and 11%, respectively. The decreases in rilpivirine concentrations are not clinically relevant and a dose adjustment for rilpivirine is not necessary. The following table summarizes the statistical results for rilpivirine alone and in the presence of atorvastatin.

Table 3 Summary of the statistical analysis of the pharmacokinetic parameters of rilpivirine alone (150 mg q.d.) and in combination with atorvastatin (40 mg q.d.)

Parameter	LS means ^a		LS means Ratio, %	90% CI, % ^b	p-Value
	TMC278 Alone (Reference)	TMC278 + Atorvastatin (Test)			Treatment
C _{0h} , ng/mL	416.5	392.0	94.13	84.86 - 104.4	0.3232
C _{min} , ng/mL	356.0	320.4	90.02	84.44 - 95.96	0.0113 ^c
C _{max} , ng/mL	850.3	776.9	91.36	78.99 - 105.7	0.2937
AUC _{24h} , ng.h/mL	13513	12094	89.50	80.66 - 99.30	0.0808
Median					p-Value
Parameter	TMC278 Alone (Reference)	TMC278 + Atorvastatin (Test)	Treatment Difference Median	90% CI, % ^b	Treatment
t _{max} , h	4.0	5.0	0.25	(-0.5) - (1.0)	0.4472

^a n=16 for TMC278 + atorvastatin (test) and TMC278 alone (reference)

^b 90% CIs

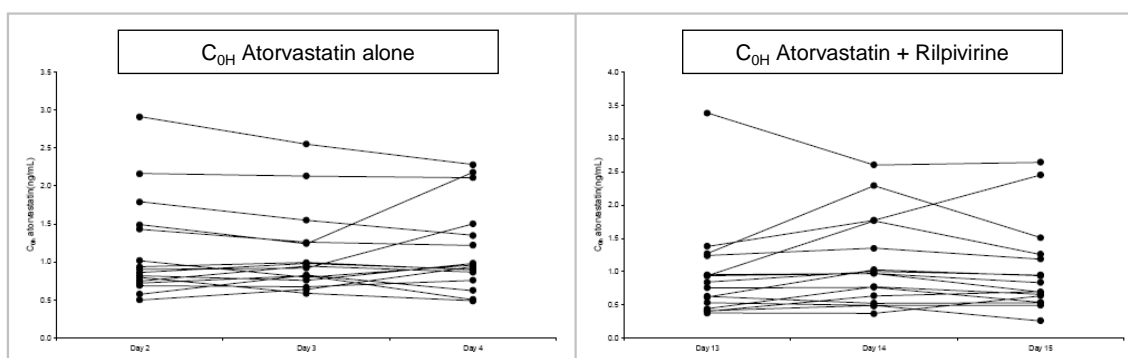
^c Statistically significant difference

Pharmacokinetic results, atorvastatin:

There were no subjects with quantifiable predose atorvastatin concentrations on Day 1 of either Treatment A or Treatment B.

The figures below indicate that atorvastatin levels were at steady state when administered alone and prior to co-administration with rilpivirine in most subjects.

Figure 5 Plots of individual predose concentrations (C_{0h}) of atorvastatin collected during monotherapy (Days 2 to 4) and co-administration with rilpivirine (Days 13 to 15)



The mean elimination phase of atorvastatin was similar in the absence (11 hours) and in the presence (10 hours) of rilpivirine. The two figures below show individual and mean concentration-time profiles of atorvastatin alone and in combination with rilpivirine.

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Figure 6 Linear and semi-logarithmic plots of individual steady-state plasma concentration-time curves of atorvastatin alone (Day 4) and in combination with rilpivirine (Day 15)

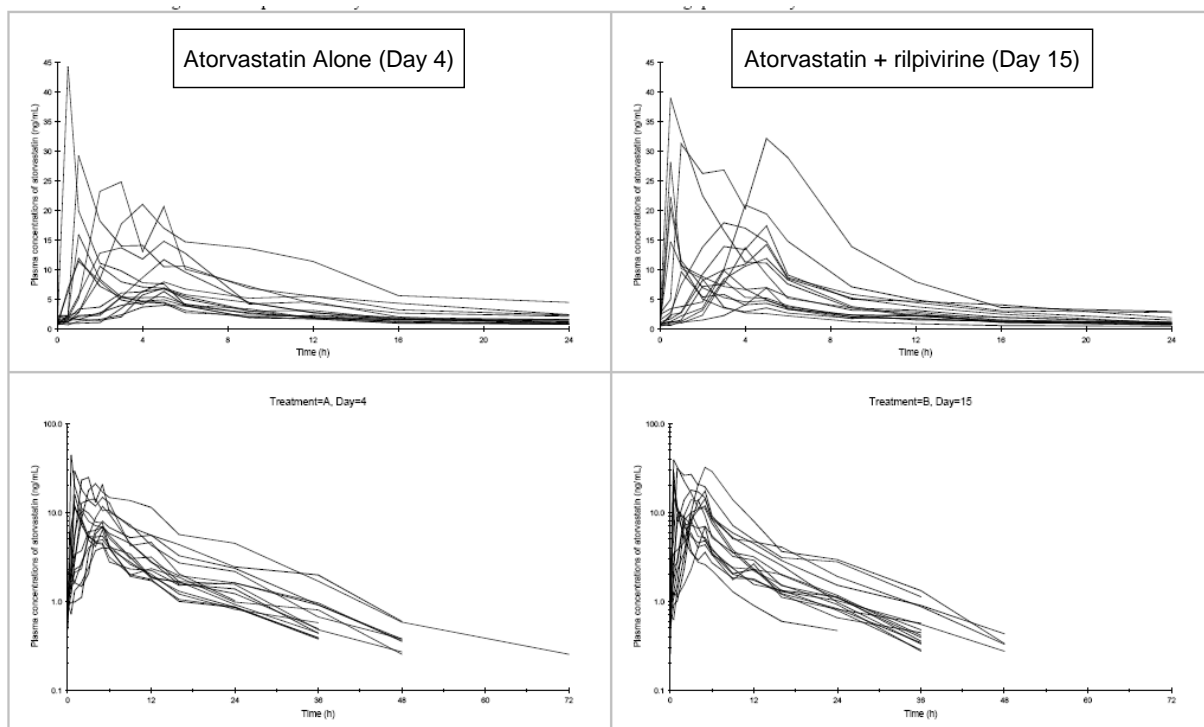
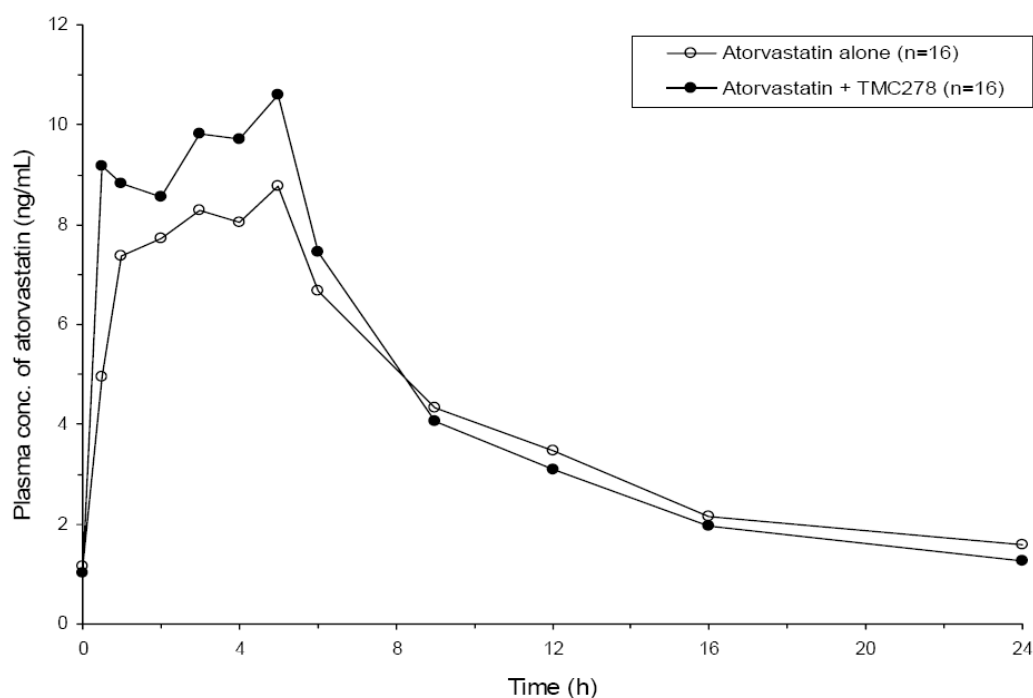


Figure 7 Mean plasma concentration-time curves of atorvastatin alone (40 mg q.d.) and in combination with rilpivirine (150 mg q.d.)



The statistical analysis revealed that rilpivirine decreased the mean C_{0h} and C_{min} of atorvastatin by 18% and 15%, respectively. Conversely, rilpivirine increased the C_{max} and AUC_{24h} of atorvastatin by 35% and 4%, respectively. The changes in the pharmacokinetic parameters of atorvastatin do not appear to be clinically relevant. The following table provides a summary of the statistical analysis.

Table 4 Summary of the statistical analysis of pharmacokinetic parameters of atorvastatin alone and in combination with rilpivirine

Parameter	LS means ^a		LS means Ratio, %	90% CI, % ^b	p-Value		
	Atorvastatin Alone (Reference)	Atorvastatin + TMC278 (Test)			Treatment	Period	Sequence
C_{0h} , ng/mL	1.041	0.8537	81.98	67.25 - 99.94	0.0991	0.6104	0.0745 ^c
C_{min} , ng/mL	0.9916	0.8386	84.57	69.44 - 103.0	0.1561	0.7195	0.0759 ^c
C_{max} , ng/mL	11.54	15.56	134.9	108.3 - 168.1	0.0311 ^c	0.6661	0.9425
AUC_{24h} , ng.h/mL	88.44	91.99	104.0	96.55 - 112.1	0.3680	0.6286	0.5389
Median			Treatment Difference Median	90% CI, % ^b	p-Value		
Parameter	Atorvastatin Alone (reference)	Atorvastatin + TMC278 (Test)			Treatment	Period	Sequence
t_{max} , h	4.0	3.0	-0.25	(-1.25) - (0.5)	0.5525	0.6264	0.5246

^a n=16 for atorvastatin + TMC278 (test) and atorvastatin alone (reference)

^b 90% CIs

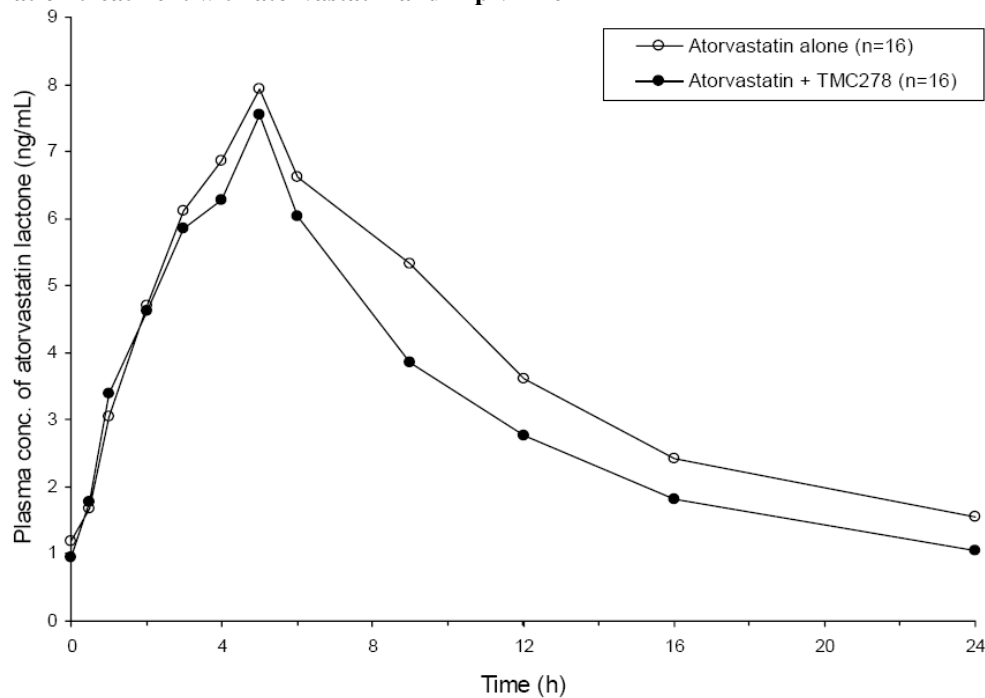
^c Statistically significant difference

Pharmacokinetic results, atorvastatin lactone:

There were no subjects with quantifiable predose atorvastatin lactone concentrations on Day 1 of either Treatment A or Treatment B. There were no individual or mean predose plots generated for atorvastatin lactone.

Rilpivirine decreased the mean steady state plasma concentrations of atorvastatin lactone. The figures below display the individual and mean concentration-time profiles of atorvastatin lactone in the absence and presence of rilpivirine.

Figure 8 Mean plasma concentration-time curves of atorvastatin lactone prior to and during combination treatment with atorvastatin and rilpivirine



The statistical analysis revealed that rilpivirine decreased the C_{0h} , C_{min} , C_{max} , and AUC_{24h} of atorvastatin lactone by 27%, 26%, 7%, and 18%, respectively. The following table summarizes the statistical analysis for atorvastatin lactone.

Table 5 Summary of the statistical analysis of pharmacokinetic parameters of atorvastatin lactone after administration of atorvastatin alone and in combination with rilpivirine

Parameter	LS means ^a		LS means Ratio, %	90% CI, % ^b	p-Value		
	Atorvastatin Alone (Reference)	Atorvastatin + TMC278 (Test)			Treatment	Period	Sequence
C_{0h} , ng/mL	1.061	0.7772	73.28	62.57 - 85.81	0.0038 ^c	0.7748	0.3314
C_{min} , ng/mL	1.000	0.7398	73.95	63.46 - 86.18	0.0037 ^c	0.5452	0.3761
C_{max} , ng/mL	7.159	6.672	93.19	84.33 - 103.0	0.2343	0.1085	0.4189
AUC_{24h} , ng.h/mL	80.18	65.81	82.08	76.73 - 87.80	0.0001 ^c	0.1095	0.4010
Median					p-Value		
Parameter	Atorvastatin Alone (Reference)	Atorvastatin + TMC278 (Test)	Treatment Difference Median	90% CI, % ^b	Treatment	Period	Sequence
t_{max} , h	5.0	5.0	-0.5	(-1.0) - (0.0)	0.1925	0.3861	1.0000

^a n=16 for atorvastatin + TMC278 (test) and atorvastatin alone (reference)

^b 90% CIs

^c Statistically significant difference

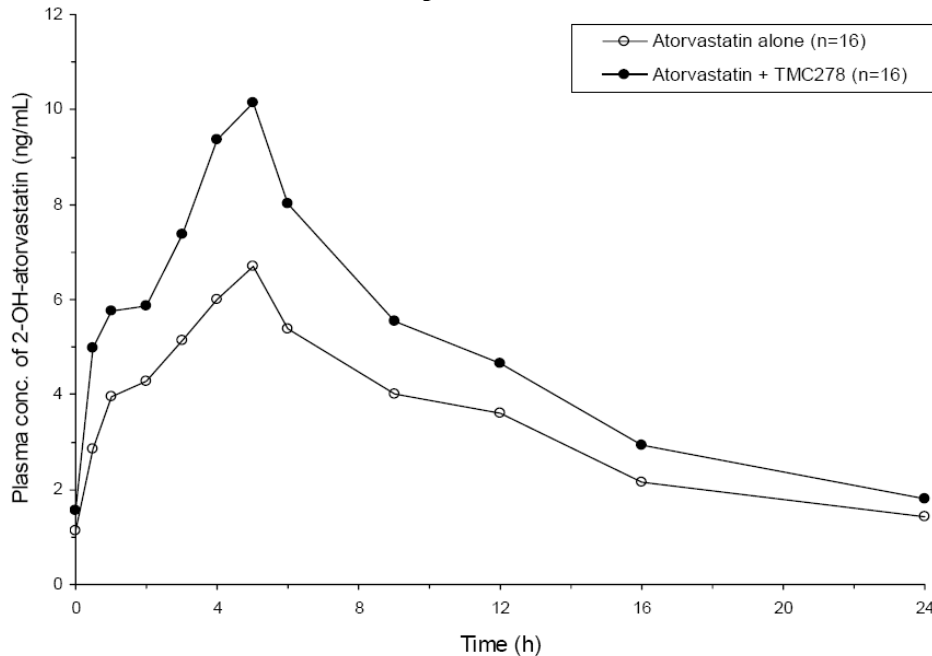
Pharmacokinetic results, 2-OH-atorvastatin:

There were no subjects with quantifiable predose 2-OH-atorvastatin concentrations on Day 1 of either Treatment A or Treatment B. There were no individual or mean predose plots generated for predose 2-OH-atorvastatin.

Rilpivirine increased the mean steady state plasma concentrations of 2-OH-atorvastatin. The shapes of the mean concentration-time profiles of 2-OH-atorvastatin look similar, but the profile obtained during co-administration with rilpivirine is higher than the reference profile. The mean $t_{1/2\text{term}}$ of 2-OH-atorvastatin was decreased by ~4 hours (from 15 to 11 hours) when combined with rilpivirine.

The increase of 2-OH-atorvastatin concentrations may be a result of rilpivirine's inductive effect on CYP3A4 independent of changes in the metabolism of atorvastatin. Figure 9 below displays the mean concentration-time profiles of 2-OH-atorvastatin in the presence and absence of rilpivirine.

Figure 9 Mean plasma concentration-time curves of 2-OH-atorvastatin after administration of atorvastatin alone and in combination with rilpivirine



The statistical analysis revealed that rilpivirine increased the C_{0h} , C_{min} , C_{max} , AUC_{24h} , and metabolite formation ratio of 2-OH-atorvastatin by 31%, 32%, 58%, 39%, and 34%, respectively. The table below summarizes the statistical results for 2-OH-atorvastatin.

Table 6 Summary of the statistical analysis of the pharmacokinetic parameters of 2-OH-atorvastatin after administration of atorvastatin alone and in combination with rilpivirine

Parameter	LS means ^a		LS means Ratio, %	90% CI, % ^b	p-Value		
	Atorvastatin Alone (Reference)	Atorvastatin + TMC278 (Test)			Treatment	Period	Sequence
C _{0h} , ng/mL	1.029	1.349	131.0	107.8 - 159.2	0.0284 ^c	0.6439	0.0630 ^c
C _{min} , ng/mL	0.9271	1.219	131.5	109.5 - 158.1	0.0199 ^c	0.5161	0.1914
C _{max} , ng/mL	7.269	11.46	157.6	132.6 - 187.2	0.0004 ^c	0.6464	0.6390
AUC _{24h} , ng.h/mL	74.26	103.3	139.1	128.9 - 150.1	<0.0001 ^c	0.0752	0.6926
Ratio AUC _{24h,2-OH-atorvastatin/atorvastatin} , %	83.97	112.3	133.7	128.5 - 139.2	<0.0001 ^c	0.5659	0.0164 ^c
Parameter	Median		Treatment Difference Median	90% CI, % ^b	p-Value		
	Atorvastatin Alone (Reference)	Atorvastatin + TMC278 (Test)			Treatment	Period	Sequence
t _{max} , h	5.0	5.0	-0.25	(-1.0) - (0.75)	0.4923	0.3410	0.0997 ^c

^a n=16 for atorvastatin + TMC278 (test) and atorvastatin alone (reference)

^b 90% CIs

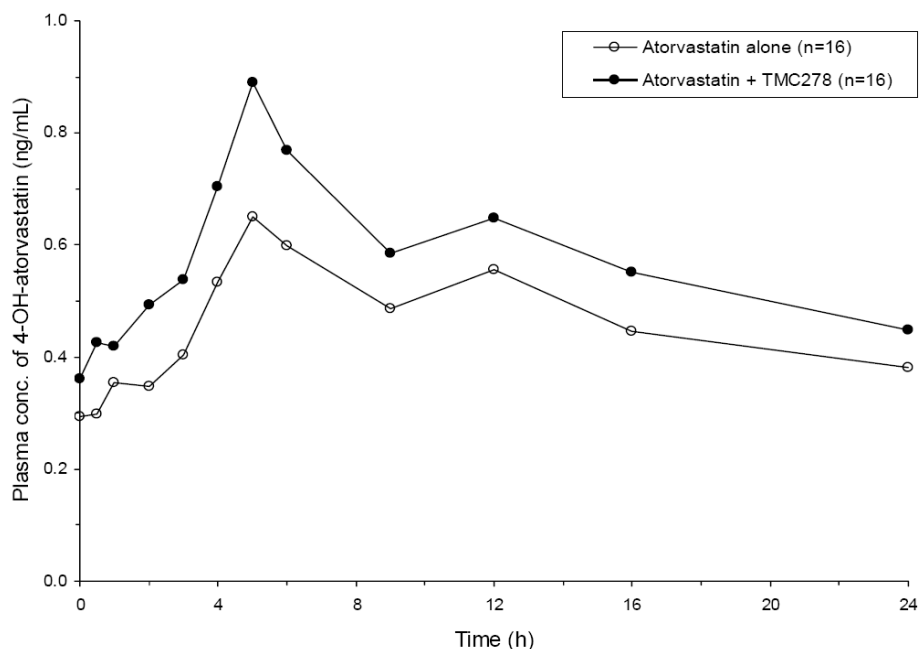
^c Statistically significant difference

Pharmacokinetic results, 4-OH-atorvastatin:

There were no subjects with quantifiable predose 4-OH-atorvastatin concentrations on Day 1 of either Treatment A or Treatment B. There were no individual or mean predose plots generated for predose 4-OH-atorvastatin.

Rilpivirine increased the mean steady state plasma concentrations of 4-OH-atorvastatin. The shapes of the concentration-time profiles of 4-OH-atorvastatin look similar, but the profile obtained during co-administration with rilpivirine was higher than the reference profile. Figure 10 below shows the mean plasma concentration-time profiles of 4-OH-atorvastatin in the absence and presence of rilpivirine.

Figure 10 Mean Plasma concentration-time curves of 4-OH-atorvastatin after administration of atorvastatin alone and in combination with rilpivirine



The statistical analysis revealed that rilpivirine increased the C_{0h} , C_{max} , and AUC_{24h} of 4-OH-atorvastatin by 25%, 28%, and 23%, respectively. Investigators could not evaluate the C_{min} of 4-OH-atorvastatin because more than half the subjects in Treatment A had C_{min} concentrations that were below the LLOQ. 9 out of 16 subjects in Treatment A and 5 out of 16 subjects in Treatment B had one or more concentrations up to 24 hours of 4-OH-atorvastatin that were below the LLOQ. Even though C_{min} was unavailable, the overall trend in C_{max} and AUC_{24h} indicates that rilpivirine also increased the C_{min} levels of 4-OH-atorvastatin. The table below summarizes the statistical results for 4-OH-atorvastatin.

Table 7 Summary of the statistical analysis of the pharmacokinetic parameters of 4-OH-atorvastatin after administration of atorvastatin alone and in combination with rilpivirine

Parameter	LS means ^a		LS means Ratio, %	90% CI, % ^b	p-Value		
	Atorvastatin Alone (Reference)	Atorvastatin + TMC278 (Test)			Treatment	Period	Sequence
C _{0h} , ng/mL	0.3349	0.4175	124.7	104.3 - 149.1	0.0485 ^c	0.9835	0.1490
C _{max} , ng/mL	0.6819	0.8742	128.2	114.7 - 143.4	0.0015 ^c	0.4822	0.2227
AUC _{24h} , ng.h/mL	9.289	11.42	122.9	113.4 - 133.1	0.0005 ^c	0.7408	0.3485
Median					p-Value		
Parameter	Atorvastatin Alone (Reference)	Atorvastatin + TMC278 (Test)	Treatment Difference Median	90% CI, % ^b	Treatment	Period	Sequence
t _{max} , h	5.0	5.0	-1.75	(-3.5) - (1.5)	0.3314	0.4500	0.8320

^a n=16 for atorvastatin + TMC278 (test) and atorvastatin alone (reference), n=13 for C_{0h}

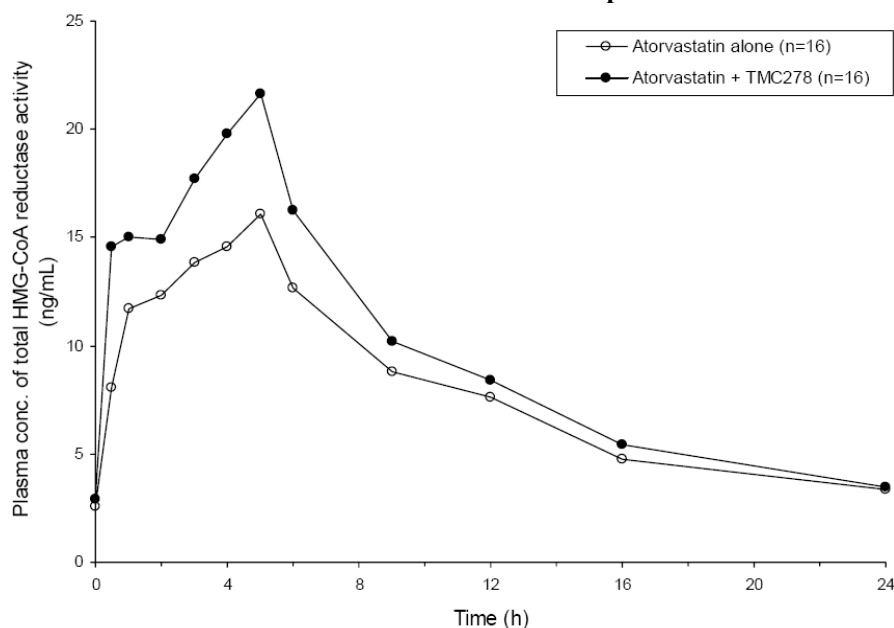
^b 90% CIs

^c Statistically significant difference

Pharmacokinetic results, total HMG-CoA reductase activity:

Investigators measured the total activity of HMG-CoA reductase by calculating the sum of the individual concentrations of atorvastatin, 2-OH-atorvastatin, and 4-OH-atorvastatin per time point. The total concentrations of atorvastatin and its active metabolites in the absence and presence of rilpivirine were then compared. Overall, rilpivirine increased mean total plasma concentrations of the total HMG-CoA reductase activity over the entire dosing period. The figure below depicts the mean plasma concentration-time profiles of the total HMG-CoA reductase activity.

Figure 11 Mean plasma concentration-time curves of the total HMG-CoA reductase activity after administration of atorvastatin alone and in combination with rilpivirine



The statistical analysis revealed that rilpivirine increased the ratios of the LS means of C_{0h} , C_{min} , C_{max} , and AUC_{24h} of the total HMG-CoA reductase activity 8%, 13%, 39%, and 21%, respectively. The table below summarizes the statistical results for the total activity of HMG-CoA activity.

Table 8 Summary of the statistical analysis of the pharmacokinetic parameters of the total HMG-CoA reductase activity after administration of atorvastatin alone and in combination with rilpivirine

Parameter	LS means ^a		LS means ratio, %	90% CI, % ^b	p-Value		
	Atorvastatin alone (reference)	Atorvastatin + TMC278 (test)			Treatment	Period	Sequence
C_{0h} , ng/mL	2.330	2.525	108.4	89.03 - 131.9	0.4833	0.6406	0.0674 ^c
C_{min} , ng/mL	2.151	2.433	113.1	92.24 - 138.8	0.3051	0.7068	0.1263
C_{max} , ng/mL	19.34	26.94	139.3	114.2 - 169.9	0.0107 ^c	0.8422	0.8776
AUC_{24h} , ng.h/mL	173.8	209.3	120.5	112.1 - 129.5	0.0004 ^c	0.2333	0.5682

^a n=16 for atorvastatin + TMC278 (test) and atorvastatin alone (reference)

^b 90% CIs

^c Statistically significant difference

Safety and tolerability:

All randomized subjects completed the trial. Overall, 9 subjects (53.6%) experienced at least 1 adverse event (AE) during the trial. Headache was the most commonly reported adverse event. One subject reported two grade 2 adverse events (pharyngitis during rilpivirine treatment alone, and conjunctivitis during combination treatment). No AEs were considered probably or very likely treatment related to rilpivirine or atorvastatin according to the trial report.

Discussion and Conclusions:

This trial evaluated the potential drug-drug interaction between steady state levels of atorvastatin and rilpivirine. Atorvastatin decreased the rilpivirine exposure by approximately 10% or less. On the other hand, rilpivirine increased the $AUC_{(0-24h)}$ and C_{max} of atorvastatin by 4% and 35%, respectively, and decreased C_{min} , and C_{0h} by 20% or less. A dosage adjustment is not required for atorvastatin or rilpivirine when coadministered together.

TMC278-C121

1. Title

A Phase I, open-label, single-sequence drug-drug interaction trial in subjects on stable methadone maintenance therapy, to investigate the potential interaction between TMC278 25 mg q.d. and methadone, at steady-state

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at [REDACTED] (b) (4) from October 31, 2008 to June 15, 2009.

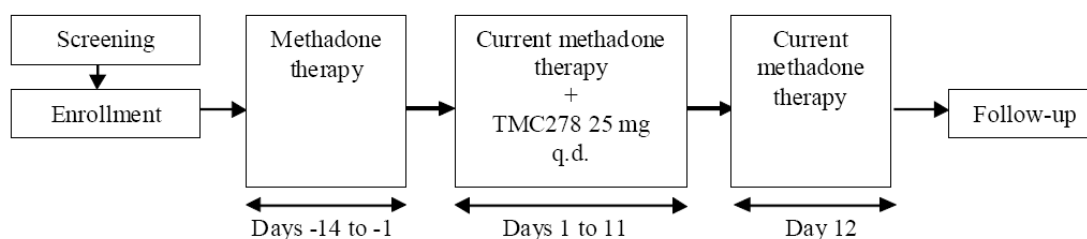
3. Objectives

The objective of the trial was to evaluate the effect at steady state of rilpivirine on R and S methadone pharmacokinetics.

4. Trial Design

TMC278-C121 was a Phase I, open label clinical trial that enrolled male and female subjects receiving chronic methadone maintenance treatment between 18 and 55 years old. The trial design is displayed in Figure 1. The trial population consisted of thirteen subjects. The duration of chronic methadone maintenance treatment required for enrollment in the trial was not specified in the trial report or protocol. However, all subjects received a minimum of thirteen days of methadone prior to pharmacokinetic sampling in Day -1 which should be sufficient duration to reach steady state based on a methadone terminal elimination half life of 8 to 59 hours.

Figure 1-TMC278-C121 trial design



5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Medications that were not permitted during the trial included clinically relevant inhibitors and inducers of CYP 3A, the primary metabolism pathway for rilpivirine. CYP 3A metabolism is involved in methadone metabolism. Specific CYP 3A substrates were also excluded, including cyclosporine, tacrolimus, and calcium channel blockers (amlodipine,

diltiazem, felodipine, nifedipine, and verapamil), among others. Use of medications that were not permitted within the 14 days prior to the first dose of rilpivirine was listed as an exclusion criterion. All other medications that were not specifically excluded were to be reviewed on a case by case basis (with the exception of acetaminophen and ibuprofen). Changes to permitted concomitant medications from Day -14 to Day 11 were not permitted unless the changes were discussed with the applicant. Ibuprofen and acetaminophen were permitted up to three days before the first dose of rilpivirine. Subsequently, ibuprofen use was permitted up to 400 mg/day and acetaminophen was permitted up to 1 gram/day.

Use of liquids containing alcohol or quinine was not permitted from 24 hours before admission to the clinical trial site (Day -4) until Day 12. Intake of grapefruit and grapefruit juice was not permitted from 7 days before the first supervised administration of methadone (Day -14) until Day 12.

In the event of an adverse event, the following medications were permitted:

- A) Rash or an allergic reaction: cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents (specific medications were not included in the trial report)
- B) Nausea: antiemetics (specific medications were not included in the trial report)
- C) Diarrhea: loperamide

6. Dosage and Administration

On pharmacokinetic sampling days, a standard meal was administered in the morning. Both methadone and rilpivirine were administered within 10 minutes after completion of the meal and on days when both methadone and rilpivirine were administered, methadone was administered immediately after rilpivirine.

7. Rationale for Doses Used in the Trial

The rilpivirine dosage regimen that was administered to all subjects was 25 mg once daily. The trial report states that methadone was administered after rilpivirine (if applicable) on Days -3 to Day 11 after consuming breakfast (on Day -14 to Day -4, methadone was administered before noon). The rilpivirine dosage regimen that was evaluated in the Phase 3 clinical trials and the recommended dosage regimen in the proposed prescribing information is 25 mg once daily with a meal.

The methadone dosage regimen was individualized and the actual dosage regimen ranged from 60 mg to 100 mg once daily. Methadone dose adjustments were prohibited from Day -14 to Day 11 unless a dose adjustment was immediately required.

8. Drugs Used in the Trial

Rilpivirine 25 mg tablets (formulation F006) were administered in the trial. These tablets were developed for use in the Phase 3 trials.

Methadone (Symoron[®]) tablets were administered in the trial.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Blood samples for analysis of R and S methadone were obtained on Days -1 and 1 at predose (0 hour) and up to 24 hours postdose. Predose blood samples for analysis of R and S methadone were also obtained on Days -3 and -2.

Blood samples for analysis of rilpivirine, and R and S methadone concentrations were obtained on Days 11 and 12 at predose (0 hour) and up to 24 hours postdose. Predose blood samples for analysis of rilpivirine and R and S methadone concentrations were also obtained on Days 8, 9 and 10.

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a validated LC/MS/MS method by Johnson and Johnson Pharmaceutical Research and Development. The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the TMC278-C136 trial, precision and accuracy were evaluated using the low (2.71 or 2.77 ng/mL), medium (54.3 or 55.3 ng/mL), and high (1570 ng/mL) QC samples. The corresponding rilpivirine intra-run accuracy values were 1.5% and -4% for the low QCs, 1.1% and -6.9% for the medium QCs, and 7% for the high QCs, and the rilpivirine intra-run precision values were 2.6% and 7.4% for the low QCs, 9.7% and 15.3% for the medium QCs, and 11.1% for the high QCs. The submitted rilpivirine long term stability data of 1528 days at -20°C covered the duration of long term rilpivirine stability data necessary for the TMC278-C121 trial.

The method and bioanalysis of R and S methadone are acceptable. Plasma samples were analyzed for R and S methadone concentrations using a validated LC/MS/MS method by (b) (4). Of note, the majority of the analytical runs were run using calibration standards and quality control samples prepared in K₃EDTA plasma while the blood samples for analysis of R and S methadone concentrations from the TMC278-C121 trial were drawn in K₂EDTA plasma. The methadone bioanalytical report for the TMC278-C121 trial states that a partial validation run was conducted comparing K₃EDTA plasma to K₂EDTA plasma; however the data was not submitted for review. Overall, the discrepancy is expected to have a minimal impact on the validity of the reported R and S methadone concentrations.

The lower limit of quantification for R methadone was 5 ng/mL and the upper limit of quantification was 1000 ng/mL. There were no precision or accuracy issues identified for R methadone based on the bioanalytical report. For the TMC278-C121 trial, precision and accuracy were evaluated using QC samples at the following concentrations: 10, 25,

70, 200, and 750 ng/mL. The corresponding R methadone inter-run accuracy values were separated out by the analytical runs that used calibration standards and quality control samples prepared in K₃EDTA plasma (1HPT-A-1 through 7HPT-A-1) versus the analytical runs that used calibration standards and quality control samples prepared in K₂EDTA plasma (8HPT-A-1 through 10HPT-A-1). For analytical runs 1HPT-A-1 through 7HPT-A-1, the R methadone inter-run accuracy values were -1.6%, -1.1%, -2.1%, -0.4%, and -1.3%. For analytical runs 8HPT-A-1 through 10HPT-A-1, the R methadone inter-run accuracy values were -1.5%, -4.6%, -7%, 5%, and -1.9%. For analytical runs 1HPT-A-1 through 7HPT-A-1, the R methadone inter-run precision values were 3.08%, 2.83%, 2.36 %, 3.55%, and 3.06% . For analytical runs 8HPT-A-1 through 10HPT-A-1, the R methadone inter-run precision values were 4.81%, 2.95%, 5.16%, 4.02%, and 3.73%.

The lower limit of quantification for S methadone was 5 ng/mL and the upper limit of quantification was 1000 ng/mL. There were no precision or accuracy issues identified for S methadone based on the bioanalytical report. For the TMC278-C121 trial, precision and accuracy were evaluated using QC samples at the following concentrations: 10, 25, 70, 200, and 750 ng/mL. The corresponding S methadone inter-run accuracy values were separated out by the analytical runs that used calibration standards and quality control samples prepared in K₃EDTA plasma (1HPT-A-2 through 7HPT-A-2) versus the analytical runs that used calibration standards and quality control samples prepared in K₂EDTA plasma (8HPT-A-2 through 10HPT-A-2). For analytical runs 1HPT-A-2 through 7HPT-A-2, the S methadone inter-run accuracy values were -2.4%, -1.2%, -1.8%, -0.4%, and -1.8%. For analytical runs 8HPT-A-2 through 10HPT-A-2, the S methadone inter-run accuracy values were -1.7%, -4.6%, -8.6%, 4%, and -3.6%. For analytical runs 1HPT-A-2 through 7HPT-A-2, the S methadone inter-run precision values were 6.48%, 3.51%, 2.99%, 3.61%, and 2.91%. For analytical runs 8HPT-A-2 through 10HPT-A-2, the S methadone inter-run precision values were 5.80%, 6.28%, 4.25%, 3.66%, and 3.87%.

The submitted R and S methadone long term stability data of 219 days at -20°C covered the duration of long term R and S methadone stability data necessary for the TMC278-C121 trial. The TMC278-C121 R and S methadone bioanalytical report states that 190 days of long term stability data is necessary for the trial.

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate pharmacokinetic parameters, including C_{\max} and $AUC_{(0-\tau)}$. If a major difference (> 10% deviation from the scheduled time) was observed, the actual sampling time was used instead of the scheduled sampling time.

Statistical Analysis

Descriptive statistics were calculated for rilpivirine, R and S methadone plasma concentrations and pharmacokinetic parameters, including the number of subjects (n),

mean, standard deviation, the coefficient of variation (CV%), geometric mean, median, and the minimum and maximum values.

For R and S methadone, statistical analysis involved comparison of methadone log transformed pharmacokinetic parameters for Day 11 (test arm consisting of methadone and rilpivirine) compared to Day -1 (reference arm consisting of methadone only). C_{min} (the minimum plasma concentrations between 0 hour and the dosing interval $[\tau]$), C_{max} , and $AUC_{0-\tau}$ were evaluated. Using a linear mixed effects model, least squares means were calculated and 90% confidence intervals were derived based on the difference of the pharmacokinetic parameter's least squares means for the test and reference arms. The applicant did not specify predetermined "no effect boundaries" for the 90% confidence intervals.

An assessment was performed to determine if rilpivirine steady state concentrations were achieved by Day 11 based on predose concentrations from Days 8, 9, 10 and 11. For R and S methadone, an assessment was performed to determine if steady state concentrations were achieved by Day -1 based on predose concentrations from Days -4, -3, -2 and -1 and by Day 11 from Days 8, 9, 10 and 11.

10. Results

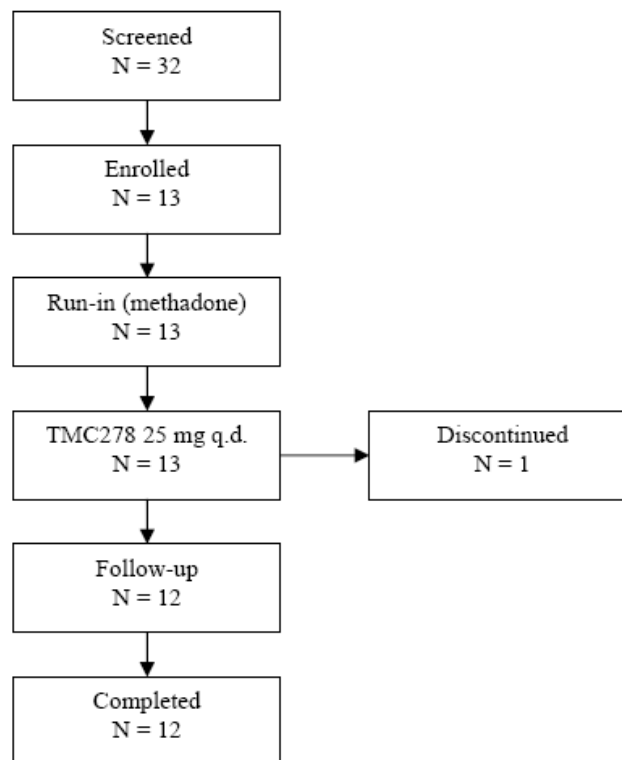
10.1 Subject Demographics and Disposition

Table 1-TMC278-C121 subject demographics

Parameter	All Subjects N = 13
Age, years Median (range)	41.0 (31-54)
Height, cm Median (range)	181.0 (165-198)
Weight, kg Median (range)	84.0 (57-112)
BMI, kg/m ² Median (range)	26.42 (20.3-33.4)
Sex, n (%)	
Male	13 (100.0)
Race, n (%)	
Asian	2 (15.4)
Black or African American	1 (7.7)
White	10 (76.9)
Type of Smoker, n (%)	
Light	6 (46.2)
Moderate	6 (46.2)

BMI = body mass index

Figure 2-TMC278-C121 subject disposition



Note: Run-in phase = Day -14 until 1 minute before the first intake of TMC278 on Day 1.
TMC278 25 mg q.d. phase = time of first intake of TMC278 on Day 1 until 1 minute before the first follow-up assessment.

10.2 Prior and Concomitant Medications

Ten subjects administered concurrent medications during the trial. The administered concurrent medications included diazepam, ibuprofen and acetaminophen. None of the coadministered medications would be expected to alter CYP 3A metabolism.

10.3 Pharmacokinetic and Statistical Analysis

The methadone pharmacokinetic parameters and statistical analyses presented in Tables 2 to 5 do not appear to be dose normalized. This should not affect the validity of the trial results because ratios are being derived for the statistical analyses. The trial report also states that there was one subject (subject 121-0001) that had the methadone dosage regimen adjusted. However the adjustment occurred on Day 13 after the completion of rilpivirine dosing for the trial.

Rilpivirine

Table 2-Pharmacokinetic parameters for rilpivirine 25 mg once daily with coadministration of individualized methadone dosage regimens

$$[\%FI=100 \times ([C_{\max}-C_{\min}]/C_{ss,av})]$$

Pharmacokinetics of TMC278 (mean ± SD, t _{max} : median [range])	25 mg TMC278 q.d. on Days 1-11 + individualized methadone therapy (TMC278-TiDP6-C121, healthy volunteers)	25 mg TMC278 q.d. on Days 1-11 (TMC278-TiDP6-C152, healthy volunteers)	25 mg TMC278 q.d. on Days 1-11 (TMC278-TiDP6-C130, healthy volunteers)
n	12	57	16
Day 8			
C _{0h} , ng/mL	66.62 ± 24.00	-	-
Day 9			
C _{0h} , ng/mL	72.57 ± 29.94 ^a	114.6 ± 36.42	71.86 ± 22.51
Day 10			
C _{0h} , ng/mL	83.48 ± 31.67	113.0 ± 33.55	77.67 ± 22.56
Day 11			
C _{0h} , ng/mL	81.98 ± 35.09	132.3 ± 40.60	79.69 ± 19.53
C _{min} , ng/mL	67.63 ± 25.08	95.23 ± 29.07	66.48 ± 16.29
C _{max} , ng/mL	156.3 ± 65.20	246.8 ± 74.36 ^b	145.5 ± 31.97
t _{max} , h	4.0 (2.5 - 24.0)	5.0 (4.0 - 24.0) ^b	5.0 (5.0 - 12.0)
AUC _{24h} , ng.h/mL	2174 ± 759.2 ^a	3324 ± 884.0 ^b	2235 ± 460.4
C _{ss,av} , ng/mL	90.63 ± 31.68 ^a	138.5 ± 36.83 ^b	93.13 ± 19.18
FI, %	89.48 ± 27.33 ^a	111.1 ± 32.47 ^b	86.77 ± 29.20

AUC_{24h} = area under the plasma concentration time curve over 24 hours, C_{0h} = predose plasma concentration, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, C_{ss,av} = average steady-state plasma concentration, FI = fluctuation index, SD = standard deviation, t_{max} = time to maximum plasma concentration.

^a n = 11
^b n = 56

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Comparative data for rilpivirine without methadone coadministration was not obtained in the TMC278-C121 trial. However, the applicant provided a comparison of the C_{min}, C_{max}, and AUC_(0-24h) values obtained from the TMC278-C152 (thorough QT) and TMC278-C130 (hepatic impairment) trials that evaluated the 25 mg Phase 3 tablet formulation (F006) in healthy subjects. The data from the hepatic impairment trial for the two separate groups of healthy subjects that were matched to subjects with mild and moderate hepatic impairment appears to have been averaged together.

Lower rilpivirine exposure was observed in the TMC278-C121 trial compared to the TMC278-C152 trial and minimal differences were observed compared to the TMC278-C130 trial. The mean C_{min}, C_{max}, and AUC_(0-24h) values in the TMC278-C121 trial were 29%, 37%, and 35% lower, respectively compared to the mean values from the TMC278-C152 trial. In comparison to the mean values from the TMC278-C130 trial, in the TMC278-C121 trial, the mean C_{min} and C_{max} values were 2% and 7% higher, respectively and the AUC_(0-24h) value was 3% lower.

Based on evaluating the individual rilpivirine predose concentrations, steady state concentrations were achieved by Day 11 in most subjects.

R and S methadone

Table 3-R methadone pharmacokinetic parameters (administered as individualized methadone dosage regimens and individualized methadone dosage regimens with rilpivirine 25 mg once daily coadministration)

<i>Pharmacokinetics of R-methadone</i> (mean \pm SD, t_{max} : median [range])	Individualized methadone therapy (reference)	Individualized methadone therapy + 25 mg TMC278 q.d. on Days 1-11 (test)
n	13	12
Day -4/Day 8		
C_{0h} , ng/mL	253.0 \pm 107.1 ^a	178.2 \pm 80.61
Day -3/Day 9		
C_{0h} , ng/mL	230.1 \pm 118.8	176.1 \pm 79.77
Day -2/Day 10		
C_{0h} , ng/mL	229.7 \pm 115.3 ^a	176.8 \pm 79.97
Day -1/Day 11		
C_{0h} , ng/mL	216.3 \pm 101.9	177.3 \pm 83.15
C_{min} , ng/mL	195.9 \pm 86.66	159.4 \pm 81.25
C_{max} , ng/mL	315.8 \pm 122.8	279.3 \pm 109.2
t_{max} , h	2.5 (1.5 - 4.0)	2.5 (1.15 - 6.0)
AUC _{24h} , ng.h/mL	5578 \pm 2343	4811 \pm 2106
Ratio AUC _{24h} , S-/R-methadone, %	101.5 \pm 17.17	99.84 \pm 11.67
$C_{ss,av}$, ng/mL	232.4 \pm 97.61	200.5 \pm 87.74
FI, %	54.63 \pm 15.19	63.86 \pm 22.61

AUC_{24h} = area under the plasma concentration time curve over 24 hours, C_{0h} = predose plasma concentration, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, $C_{ss,av}$ = average steady-state plasma concentration, FI = fluctuation index, SD = standard deviation, t_{max} = time to maximum plasma concentration.

^a n = 12

Table 4-Statistical analysis for R methadone (administered as individualized methadone dosage regimens and individualized methadone dosage regimens with rilpivirine 25 mg once daily coadministration)

<i>Parameter</i>	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b
	Individualized methadone therapy (reference)	Individualized methadone therapy + 25 mg TMC278 q.d. (test)		
C_{min} , ng/mL	176.8	138.0	78.05	66.86 - 91.10
C_{max} , ng/mL	291.8	250.6	85.86	77.53 - 95.08
AUC _{24h} , ng.h/mL	5092	4268	83.82	73.93 - 95.03
Ratio AUC _{24h} , S-/R-methadone, %	100.1	100.7	100.6	96.49 - 104.8

AUC_{24h} = area under the plasma concentration time curve over 24 hours, CI = confidence interval, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, LS = least squares.

^a n = 13 for reference and n = 12 for test

^b 90% CIs

With rilpivirine coadministration, lower mean R methadone C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were observed in subjects compared to methadone use by itself. The 90% confidence interval for R methadone C_{min} , C_{max} and $AUC_{(0-24h)}$ was not within 80%-125%. The S methadone/R methadone ratio for $AUC_{(0-24h)}$ was within 80%-125%.

Table 5-S methadone pharmacokinetic parameters (administered as individualized methadone dosage regimens and individualized methadone dosage regimens with rilpivirine 25 mg once daily coadministration)

<i>Pharmacokinetics of S-methadone (mean \pm SD, t_{max}: median [range])</i>	Individualized methadone therapy (reference)	Individualized methadone therapy + 25 mg TMC278 q.d. on Days 1-11 (test)
n	13	12
Day -4/Day 8		
C_{0h} , ng/mL	244.7 \pm 114.4 ^a	160.2 \pm 91.22
Day -3/Day 9		
C_{0h} , ng/mL	226.3 \pm 124.5	159.9 \pm 88.81
Day -2/Day 10		
C_{0h} , ng/mL	221.6 \pm 118.8 ^a	159.6 \pm 84.03
Day -1/Day 11		
C_{0h} , ng/mL	200.4 \pm 99.49	157.5 \pm 84.86
C_{min} , ng/mL	179.9 \pm 90.59	146.1 \pm 85.02
C_{max} , ng/mL	358.1 \pm 145.2	316.1 \pm 123.2
t_{max} , h	2.5 (1.5 - 4.0)	2.5 (1.2 - 6.0)
AUC_{24h} , ng.h/mL	5610 \pm 2515	4815 \pm 2275
$C_{ss,av}$, ng/mL	233.7 \pm 104.8	200.7 \pm 94.77
FI, %	81.25 \pm 22.61	92.78 \pm 32.29

AUC_{24h} = area under the plasma concentration time curve over 24 hours, C_{0h} = predose plasma concentration, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, $C_{ss,av}$ = average steady-state plasma concentration, FI = fluctuation index, SD = standard deviation, t_{max} = time to maximum plasma concentration.

^a n = 12

Table 6-Statistical analysis for S methadone (administered as individualized methadone dosage regimens and individualized methadone dosage regimens with rilpivirine 25 mg once daily coadministration)

<i>Parameter</i>	LSmeans^a		LSmeans ratio, %	90% CI, %^b
	Individualized methadone therapy (reference)	Individualized methadone therapy + 25 mg TMC278 q.d. (test)		
C_{min} , ng/mL	159.4	125.2	78.57	67.45 - 91.52
C_{max} , ng/mL	330.8	287.5	86.91	77.64 - 97.28
AUC_{24h} , ng.h/mL	5100	4299	84.30	74.16 - 95.84

AUC_{24h} = area under the plasma concentration time curve over 24 hours, CI = confidence interval, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, LS = least squares.

^a n = 13 for reference and n = 12 for test

^b 90% CIs

With rilpivirine coadministration, lower mean S methadone C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were observed in subjects compared to methadone use by itself. The 90% confidence interval for S methadone C_{min} , C_{max} and $AUC_{(0-24h)}$ was not within 80%-125%.

Based on evaluating the individual R methadone and S methadone predose concentrations, steady state concentrations were achieved by Day -1 and by Day 11.

10.4 Pharmacodynamic Analysis

Assessments were conducted during the trial evaluating the symptoms of methadone withdrawal, including the Short Opiate Withdrawal Scale (SOWS), the Desires for Drugs Questionnaire (DDQ), and pupillometry. The trial report states that there were no clinically relevant changes over time using the Short Opiate Withdrawal Scale and the Desires for Drugs Questionnaire and minimal changes were observed using pupillometry. Overall, the trial reports concluded that methadone withdrawal was not observed during the trial.

10.5 Safety Issues

No deaths or other serious adverse events were reported for the trial. No grade 3 or grade 4 adverse events were reported for the trial. The most common adverse events included nausea and hyperhidrosis (see Table 7 below for information regarding the number and percentage of subjects).

Table 7-Adverse event incidence reported for two or more subjects and categorized by system organ class and preferred term

System Organ Class Preferred Term n (%)	Run-in ^a (N = 13)	TMC278 25 mg q.d. (N = 13)
Any AE	9 (69.2)	12 (92.3)
Gastrointestinal Disorders	5 (38.5)	7 (53.8)
Nausea	0	3 (23.1)
Constipation ^b	3 (23.1)	2 (15.4)
Diarrhea	0	2 (15.4)
General Disorders and Administration Site Conditions	2 (15.4)	7 (53.8)
Drug withdrawal syndrome	0	2 (15.4)
Fatigue	0	2 (15.4)
Nervous System Disorders	6 (46.2)	7 (53.8)
Dizziness	0	2 (15.4)
Dysgeusia	0	2 (15.4)
Headache	6 (46.2)	2 (15.4)
Skin and Subcutaneous Tissue Disorders	2 (15.4)	6 (46.2)
Hyperhidrosis	1 (7.7)	3 (23.1)
Pruritus	0	2 (15.4)
Musculoskeletal and Connective Tissue Disorders	1 (7.7)	2 (15.4)
Pain in extremity	0	2 (15.4)

AE = adverse event, n = number of subjects with AE, N = number of subjects per phase.

^a Run-in = Day -14 to Day 1, 1 minute before TMC278 administration.

^b Subject 121-0008 experienced an AE of constipation during the TMC278 25 mg q.d. phase that was not captured in the trial database because the investigational site did not send the information about the occurrence of the AE for inclusion in the trial database. The AE was considered probably related to TMC278 and doubtfully related to methadone.

Table 8 provides information on adverse events that were possibly or probably related to rilpivirine. The applicant did not include comparative information for methadone in the same table. In the trial report, the adverse events that were possibly related to methadone were classified as grade 1 adverse events and included constipation (1 subject during the Day -14 to Day 1 phase, 1 subject during the Days 1 to Day 11 phase and 1 subject during both of these phases), and dry throat (1 subject during the Day -14 to Day 1 phase and 1 subject during the Day 1 to Day 11 phase).

Table 8-Adverse event incidence possibly or probably related to rilpivirine reported for two or subjects and categorized by system organ class and preferred term

System Organ Class Preferred Term n (%)	TMC278 25 mg q.d. (N = 13)	
	Possible	Probable
Gastrointestinal Disorders	5 (38.5)	2 (15.4)
Nausea	3 (23.1)	0
Nervous System Disorders	5 (38.5)	0
Dizziness	2 (15.4)	0
Headache	2 (15.4)	0
Skin and Subcutaneous Tissue Disorders	5 (38.5)	0
Hyperhidrosis	3 (23.1)	0
Pruritus	2 (15.4)	0
General Disorders and Administration Site Conditions	3 (23.1)	0
Drug withdrawal syndrome	2 (15.4)	0

AE = adverse event, n = number of subjects with AE, N = number of subjects per phase.

Note: only the TMC278 25 mg q.d. phase had AEs considered at least possibly related to TMC278.

The trial also collected information on the worst changes in QTcF or QTcB that were observed in the trial. One subject (subject 121-0001) experienced an abnormal increase of 30-60 ms from baseline resulting in a QTcF value of greater than 450 to 480 ms (see Table 9). The specific timing of the ECG abnormality was not provided in the trial report. The available Day 11 C_{max} value of 129 ng/mL for subject 121-0001 was less than the mean Day 11 C_{max} value of 156 ng/mL.

Table 9-Worst treatment emergent ECG abnormalities and worst QTcF and QTcB changes during rilpivirine treatment

Parameter n (%)	Abnormal result	TMC278 25 mg q.d. (N = 13)	Follow-up (N = 12)
QTcF	Any treatment-emergent abnormality	2 (15.4)	1 (8.3)
	Abnormal actual value of > 450 - 480 ms	1 (7.7)	1 (8.3)
	Abnormal increase of 30 - 60 ms	2 (15.4)	0
	Abnormal increase of 30 - 60 ms leading to abnormal value of > 450 - 480 ms	1 (7.7)	0
QTcB	Any treatment-emergent abnormality	5 (38.5)	2 (16.7)
	Abnormal actual value of > 450 - 480 ms	3 (23.1)	1 (8.3)
	Abnormal increase of 30 - 60 ms	5 (38.5)	1 (8.3)
	Abnormal increase of 30 - 60 ms leading to abnormal value of > 450 - 480 ms	3 (23.1)	0

N = number of subjects, n = number of subjects with treatment-emergent worst abnormalities.

% = percentage relative to the total number of subjects with the indicated test.

Note: only data for abnormal changes as defined in the Statistical Analysis Plan (see Appendix 7.1.8) are presented above.

11. Discussion and Conclusions

Based on the results from the drug-drug interaction trial, the following conclusions can be made:

- With rilpivirine coadministration, lower R methadone exposure was observed. The mean R methadone C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were decreased by 22%, 14%, and 16%, respectively. The 90% confidence interval for R methadone C_{min} , C_{max} , and $AUC_{(0-24h)}$ was not within 80%-125%.
- With rilpivirine coadministration, lower S methadone exposure was observed. The mean S methadone C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were decreased by 21%, 13%, and 16%, respectively. The 90% confidence interval for S methadone C_{min} , C_{max} , and $AUC_{(0-24h)}$ was not within 80%-125%.
- When coadministered with methadone, lower rilpivirine exposure was observed in the TMC278-C121 trial compared to the TMC278-C152 trial and minimal differences were observed compared to the TMC278-C130 trial.
- Methadone withdrawal was not observed based on the information from the Short Opiate Withdrawal Scale (SOWS), the Desires for Drugs Questionnaire (DDQ), and pupillometry.

The trial report states that the R isomer is responsible for methadone's activity and the S isomer is responsible for the QT prolongation. With a 25 mg once daily rilpivirine dosage regimen, the decreases in both R and S methadone exposure may be potentially explained by rilpivirine CYP 3A induction. The decrease in the exposure of R methadone when coadministered with rilpivirine was similar to the decrease in the exposure of S methadone when coadministered with rilpivirine.

The changes in R and S methadone exposure with rilpivirine coadministration do not appear to be clinically relevant based on the results from the trial and therefore no recommendation to monitor for withdrawal effects or to dose adjust the methadone regimen is necessary.

TMC278-C123

1. Title

A Phase I, open-label, randomized, 2-way crossover trial in 16 healthy subjects to investigate the potential pharmacokinetic interaction between TMC278 and sildenafil

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at [REDACTED] (b) (4)
[REDACTED] from October 16, 2007 to January 15, 2008.

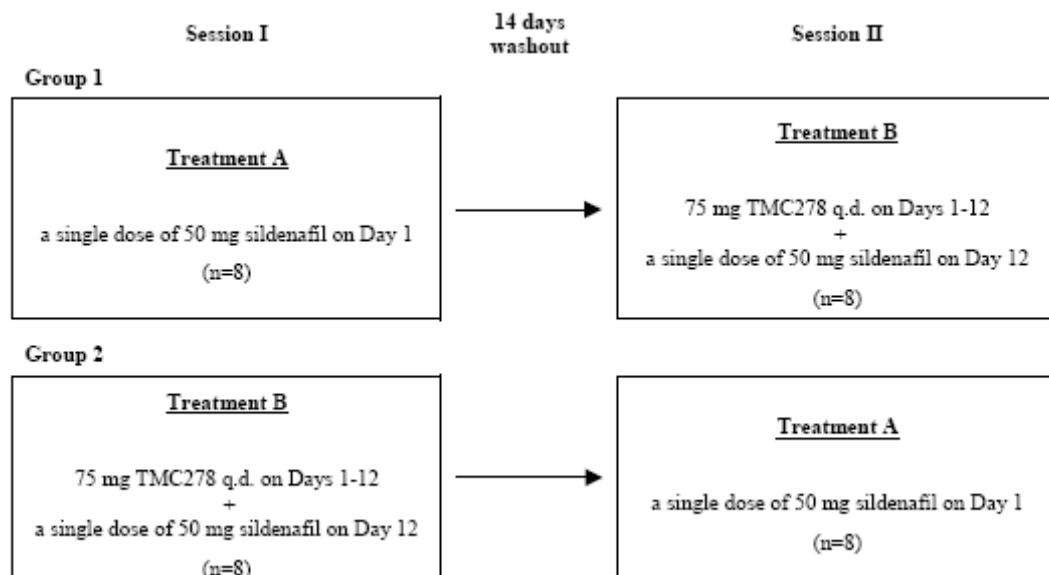
3. Objectives

The objectives of the trial were to evaluate the effect at steady state of single dose sildenafil and N-desmethyl sildenafil on rilpivirine pharmacokinetics and the effect of rilpivirine on single dose sildenafil and N-desmethyl sildenafil pharmacokinetics.

4. Trial Design

TMC278-C123 was a Phase I, open label, randomized, 2 way crossover clinical trial that enrolled male subjects between 19 and 55 years old. The trial design is displayed in Figure 1.

Figure 1-TMC278-C123 trial design



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5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Use of ibuprofen and acetaminophen was permitted up to three days before first dosing. Afterwards, ibuprofen use was permitted up to 400 mg/day and acetaminophen use was permitted up to 1 gram/day. Any over the counter medications were to be discontinued a minimum of 7 days before first dosing and any prescription medications were to be discontinued a minimum of fourteen days before first dosing (with the exception of ibuprofen or acetaminophen). Use of any medication other than ibuprofen or acetaminophen was not permitted up to fourteen days after the last administration of trial medication. Use of herbal medicines or dietary supplements was not permitted from fourteen days before first dosing up to fourteen days after the last administration of trial medication.

Caffeine containing beverages were not permitted from 10 hours before administration of trial medication on Day 1 (Treatment A) and Days 11 and 12 (Treatment B) until 24 hours after dosing. Use of liquids containing alcohol or quinine was not permitted from 24 hours before Day -1 of each treatment arm until Day 2 of Treatment A or Day 13 of Treatment B. Intake of grapefruit and grapefruit juice was not permitted from 7 days before Day -1 of each treatment arm until Day 2 of Treatment A or Day 13 of Treatment B.

In the event of an adverse event, the following medications were permitted:

- A) Rash or an allergic reaction: cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents (specific medications were not included in the trial report)
- B) Nausea: antiemetics (specific medications were not included in the trial report)
- C) Diarrhea: loperamide

6. Dosage and Administration

On pharmacokinetic sampling days, subjects fasted overnight for a minimum of 10 hours. A standard meal was administered in the morning and medication was administered within 10 minutes after completion of the meal. When both sildenafil and rilpivirine were coadministered, rilpivirine was administered first and sildenafil was administered within five minutes.

7. Rationale for Doses Used in the Trial

The rilpivirine dosage regimen that was administered to all subjects was 75 mg once daily. In contrast, the rilpivirine dosage regimen that was evaluated in the Phase 3 clinical trials and the recommended dosage regimen in the proposed prescribing information is 25 mg once daily with a meal. Across the dose range of 25 mg to 150 mg, increases in rilpivirine exposure were approximately dose proportional. Therefore, the percentage change in rilpivirine exposure that is caused by the inhibition effects of sildenafil (if any) should be similar with a rilpivirine dosage regimen of either 25 mg once daily or 75 mg once daily. However two important assumptions are: a) the absence

of significant CYP 3A induction effects from rilpivirine that could affect sildenafil CYP 3A metabolism, and b) similar sildenafil inhibition effects (if any) occurring with the two rilpivirine dosage regimens.

The single dose of sildenafil administered in the trial (50 mg) is the recommended dose in the sildenafil (Viagra) prescribing information (label) for the treatment of erectile dysfunction. There are no specific recommendations in the sildenafil (Viagra) label to administer sildenafil with food.

8. Drugs Used in the Trial

Rilpivirine 75 mg tablets (formulation F008) were administered in the trial. These tablets were developed for use in the Phase 3 trials.

Sildenafil (Viagra[®]) 50 mg tablets were administered in the trial.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

For Treatment A (sildenafil administered alone), blood samples for analysis of sildenafil and N-desmethyl sildenafil concentrations were obtained on Days 1 and 2 at predose and up to 24 hours postdose. Predose rilpivirine blood samples were also obtained on Day 1.

For Treatment B, blood samples for analysis of rilpivirine concentrations were obtained on Days 11 and 12 at predose and up to 24 hours postdose. Rilpivirine, sildenafil and N-desmethyl sildenafil concentrations were obtained on Days 12 and 13 at predose and up to 24 hours postdose. Predose blood samples for analysis of rilpivirine, sildenafil and N-desmethyl sildenafil concentrations were also obtained on Day 1. On Days 8, 9, and 10, a predose sample was drawn to determine rilpivirine concentrations.

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a validated LC/MS/MS method by Johnson and Johnson Pharmaceutical Research and Development. The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the TMC278-C123 trial, precision and accuracy were evaluated using the low (2.77 ng/mL), medium (55.3 ng/mL), and high (1570 ng/mL) QC samples. The corresponding rilpivirine inter-run accuracy values were -3.2% for the low QCs, -2.9% for the medium QCs, and 0.6% for the high QCs, and the rilpivirine inter-run precision values were 6.5% for the low QCs, 4.1% for the medium QCs, and 3.0% for the high QCs. The submitted rilpivirine long term stability data of 1528 days at -20°C covered the duration of long term rilpivirine stability data necessary for the TMC278-C123 trial.

The method and bioanalysis of sildenafil and N-desmethyl sildenafil are acceptable. Plasma samples were analyzed for sildenafil and N-desmethyl sildenafil concentrations using a validated LC/MS/MS method by (b) (4). The lower limit of quantification for sildenafil was 1 ng/mL and the upper limit of quantification was 1000 ng/mL. There were no precision or accuracy issues identified for sildenafil based on the bioanalytical report. For the TMC278-C123 trial, precision and accuracy were evaluated using QC samples at 3, 8, 30, 125 and 750 ng/mL. The corresponding sildenafil inter-run accuracy values were 5%, 1.7%, 0%, 1%, and 0.1% and the sildenafil inter-run precision values were 6.58%, 3.44%, 3.39%, 3%, and 3.79%. The lower limit of quantification for N-desmethyl sildenafil was 1 ng/mL and the upper limit of quantification was 1000 ng/mL. There were no precision or accuracy issues identified for N-desmethyl sildenafil based on the bioanalytical report. For the TMC278-C123 trial, precision and accuracy were evaluated using QC samples at 3, 8, 30, 125 and 750 ng/mL. The corresponding N-desmethyl sildenafil inter-run accuracy values were 3%, -1%, -2.9%, 1%, and 10% and the N-desmethyl sildenafil inter-run precision values were 7.25%, 7.95%, 5.35%, 5.10% and 3.40%.

The long-term stability data for sildenafil and N-desmethyl sildenafil for 85 and 97 days, respectively, at -80°C is pending. The applicant response in a request for information stated that the sildenafil and N-desmethyl sildenafil plasma samples were stored at -80°C or lower at the clinical trial site (the specific storage temperature at the bioanalytical laboratory was not specified and requires further follow up).

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate pharmacokinetic parameters, including C_{min} , C_{max} , and $AUC_{(0-\tau)}$ for rilpivirine and C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ for sildenafil and N-desmethyl sildenafil. If a major difference (> 10.00% deviation from the scheduled time) was observed, the actual sampling time was used instead of the scheduled sampling time.

Statistical Analysis

Descriptive statistics were calculated for rilpivirine, sildenafil and N-desmethyl sildenafil plasma concentrations and pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), geometric mean, median, and the minimum and maximum values.

Statistical analysis involved comparison of rilpivirine log transformed pharmacokinetic parameters for Day 12, Treatment B (test arm) compared to Day 11, Treatment B (reference arm). For sildenafil and N-desmethyl sildenafil, statistical analysis involved comparison of sildenafil and N-desmethyl sildenafil log transformed pharmacokinetic parameters for Day 12, Treatment B (test arm) compared to Day 1, Treatment A (reference arm). C_{min} (the minimum plasma concentrations between 0 hour and the dosing interval $[\tau]$), C_{max} , and $AUC_{(0-\tau)}$ were evaluated for rilpivirine and C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ were evaluated for sildenafil and N-desmethyl sildenafil. Using a linear mixed effects model, least squares means were calculated and 90% confidence intervals

were derived based on the difference of the pharmacokinetic parameter's least squares means for the test and reference arms. The applicant did not specify predetermined "no effect boundaries" for the 90% confidence intervals.

An assessment was performed to determine if rilpivirine steady state concentrations were achieved, presumably by Day 11, based on predose concentrations from Days 8, 9, 10 and 11.

10. Results

10.1 Subject Demographics and Disposition

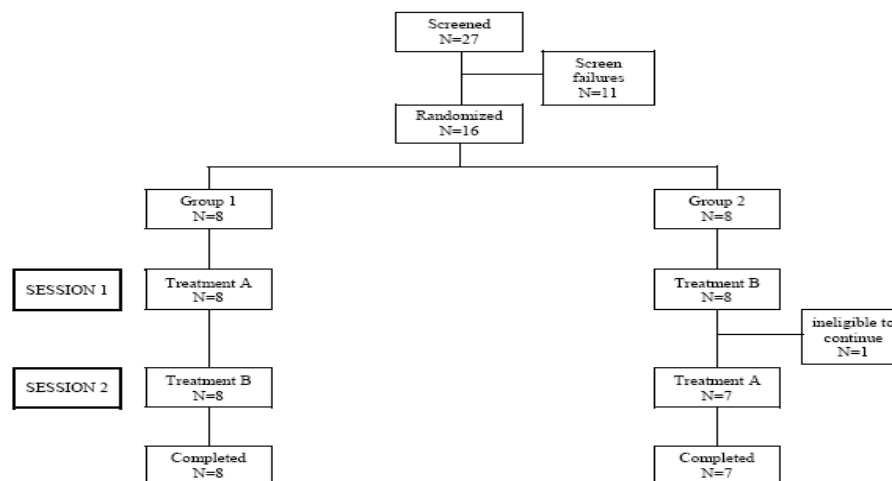
Table 1-TMC278-C123 subject demographics

Parameter	50 mg sildenafil → 75 mg TMC278 q.d. + 50 mg sildenafil (Group 1) N=8	75 mg TMC278 q.d. + 50 mg sildenafil → 50 mg sildenafil (Group 2) N=8	All Subjects N=16
Age, years Median (range)	38.0 (22-45)	42.0 (23-55)	38.5 (22-55)
Height, cm Median (range)	174.0 (160-183)	180.0 (171-189)	178.0 (160-189)
Weight, kg Median (range)	79.5 (69-101)	87.0 (63-101)	82.5 (63-101)
BMI, kg/m ² Median (range)	28.30 (20.9-31.9)	26.53 (21.5-29.5)	27.54 (20.9-31.9)
Sex, n (%) Male	8 (100.0)	8 (100.0)	16 (100.0)
Ethnic Origin, n (%) Caucasian Hispanic Black Oriental	1 (12.5) 2 (25.0) 4 (50.0) 1 (12.5)	1 (12.5) 3 (37.5) 4 (50.0) 0	2 (12.5) 5 (31.3) 8 (50.0) 1 (6.3)
Type of Smoker, n (%) Non-smoker	8 (100.0)	8 (100.0)	16 (100.0)

N = number of subjects per group; BMI = body mass index.

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Figure 2-TMC278-C123 subject disposition



N = number of subjects per group; Treatment A = 50 mg sildenafil on Day 1; Treatment B = 75 mg TMC278 q.d. on Days 1-12 plus 50 mg sildenafil on Day 12.

10.2 Prior and Concomitant Medications

Two subjects administered concurrent medications during the trial. The administered concurrent medications were bacitracin and terbinafine. None of the coadministered medications would be expected to alter CYP 3A metabolism.

10.3 Pharmacokinetic and Statistical Analysis

All subjects had sildenafil concentrations that were less than the lower limit of quantification (LLOQ) prior to initiation of Treatment A or Treatment B.

Two subjects had quantifiable rilpivirine concentrations prior to initiation of Treatment A, which were 5% or less of the subject's rilpivirine C_{max} without sildenafil coadministration on Day 11, Treatment B. In Treatment B, subjects 123001 through 123006 and 123013 through 123016 had predose rilpivirine concentrations on Day 1 that were less than the LLOQ (1 ng/mL). However, subjects 123007 through 123012 had predose rilpivirine concentrations that were less than 2 ng/mL on Day 1 that were 5% or less of the subject's rilpivirine C_{max} without sildenafil coadministration on Day 11, Treatment B.

Rilpivirine

Table 2-Pharmacokinetic parameters for rilpivirine 75 mg once daily and rilpivirine 75 mg once daily with single dose sildenafil 50 mg coadministration
[%FI=100 x $([C_{max}-C_{min}]/C_{ss,av})$]

Pharmacokinetics of TMC278 (mean \pm SD, t_{max} : median [range])	75 mg TMC278 q.d. (reference)	75 mg TMC278 q.d. + 50 mg sildenafil (test)
n	16	16
t_{max} , h	5.0 (2.0 - 5.0)	4.0 (1.0 - 9.0)
C_{0h} , ng/mL	201.7 \pm 63.08	210.2 \pm 76.30
C_{min} , ng/mL	176.9 \pm 58.32	187.3 \pm 70.80
C_{max} , ng/mL	459.8 \pm 120.7	427.5 \pm 137.8
AUC _{24h} , ng.h/mL	6517 \pm 1778	6504 \pm 2035
$C_{ss,av}$, ng/mL	271.6 \pm 74.00	270.8 \pm 84.58
FI, %	106.5 \pm 32.91	92.51 \pm 32.48

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Table 3-Statistical analysis for rilpivirine 75 mg once daily and rilpivirine 75 mg once daily with single dose sildenafil 50 mg coadministration

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b
	75 mg TMC278 q.d. (reference)	75 mg TMC278 q.d. + 50 mg sildenafil (test)		
C _{min} , ng/mL	166.9	172.7	103.5	98.11 - 109.1
C _{max} , ng/mL	444.2	407.1	91.65	84.89 - 98.94
AUC _(0-24h) , ng.h/mL	6281	6162	98.11	92.11 - 104.5
Parameter	Median ^a		Treatment difference median	90% CI, % ^b
	75 mg TMC278 q.d. (reference)	75 mg TMC278 q.d. + 50 mg sildenafil (test)		
t _{max} , h	5.0	4.0	0.0	(-1.0) - (0.0)

^a n=16 for reference and n=16 for test.

^b 90% confidence intervals.

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On Day 12 (Treatment B), with single dose coadministration, the mean rilpivirine C_{min} was decreased and minimal changes were observed in mean rilpivirine C_{max} and AUC_(0-24h) values compared to Day 11 (Treatment B), when rilpivirine was administered by itself. The 90% confidence interval for rilpivirine C_{min}, C_{max}, and AUC_(0-24h) were within 80%-125%.

Based on evaluating the individual rilpivirine predose concentrations, steady state concentrations were achieved by Day 11 in Treatment B in most subjects.

Sildenafil and N-desmethyl sildenafil

Table 4-Single dose sildenafil pharmacokinetic parameters (administered as single dose sildenafil 50 mg and single dose sildenafil 50 mg with rilpivirine 75 mg once daily coadministration)

Pharmacokinetics of sildenafil (mean ± SD, t _{max} : median [range])	50 mg sildenafil alone (reference)	75 mg TMC278 q.d. + 50 mg sildenafil (test)
n	15	16 ^a
t _{max} , h	1.5 (0.5 - 5.0)	2.0 (0.5 - 3.0)
C _{max} , ng/mL	143.8 ± 43.91	131.5 ± 41.08
AUC _{last} , ng.h/mL	560.6 ± 208.4	530.9 ± 159.6
AUC _{0-∞} , ng.h/mL	572.4 ± 212.7	553.4 ± 160.6
λ _z , 1/h	0.2087 ± 0.1067	0.2015 ± 0.06758
t _{1/2term} , h	3.813 ± 1.163	3.770 ± 1.109

^a n=15 for AUC_{0-∞}, λ_z, and t_{1/2term}.

Table 5-Statistical analysis for sildenafil (administered as single dose sildenafil 50 mg and single dose sildenafil 50 mg with rilpivirine 75 mg once daily coadministration)

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b	p-value	
	50 mg sildenafil alone (reference)	75 mg TMC278 q.d. + 50 mg sildenafil (test)			Period	Sequence
C _{max} , ng/mL	134.8	125.0	92.74	80.03 – 107.5	0.9806	0.1570
AUC _{last} , ng.h/mL	524.0	508.1	96.96	87.34 – 107.6	0.3829	0.6055
AUC _∞ , ng.h/mL ^c	535.1	518.0	96.81	86.62 – 108.2	0.3832	0.5961
Median ^d						
Parameter	50 mg sildenafil alone (reference)	75 mg TMC278 q.d. + 50 mg sildenafil (test)	Treatment difference median	90% CI, % ^b	Period	Sequence
t _{max} , h	1.5	2.0	0.0	(-0.5) - (0.5)	0.5986	0.9086

^a n=15 for reference and n=16 for test.

^b 90% confidence intervals.

^c n=15 for test AUC_∞.

^d n=15 for reference and test.

On Day 12 (Treatment B), with single dose sildenafil and rilpivirine coadministration, sildenafil C_{max} was decreased and minimal changes were observed for single dose sildenafil AUC_(0-last) and AUC_(0-∞) values compared to Day 1 (Treatment A), when single dose sildenafil was administered by itself. The 90% confidence interval for sildenafil C_{max}, AUC_(0-last) and AUC_(0-∞) were within 80%-125%.

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Table 6-Single dose N-desmethyl sildenafil pharmacokinetic parameters (administered as single dose sildenafil 50 mg and single dose sildenafil 50 mg with rilpivirine 75 mg once daily coadministration)

Pharmacokinetics of N-desmethyl sildenafil; (mean ± SD, t _{max} ; median [range])	50 mg sildenafil alone (reference)	75 mg TMC278 q.d. + 50 mg sildenafil (test)
n	15	16 ^a
t _{max} , h	1.5 (0.5 - 4.0)	2.0 (0.5 - 3.0)
C _{max} , ng/mL	98.77 ± 39.53	87.49 ± 43.76
AUC _{last} , ng.h/mL	365.1 ± 151.2	326.8 ± 156.1
AUC _∞ , ng.h/mL ^b	380.3 ± 158.2	355.3 ± 168.5
λ _z , 1/h ^b	0.1359 ± 0.05884	0.1342 ± 0.06480
t _{1/2term} , h ^b	5.934 ± 2.236	6.146 ± 2.318

^a n=15 for AUC_∞, λ_z, and t_{1/2term}.

^b Accurate determination not possible for > 50% of subjects; AUC_∞ not used for statistical evaluations

Table 7-Statistical analysis for N-desmethyl sildenafil (administered as single dose sildenafil 50 mg and single dose sildenafil 50 mg with rilpivirine 75 mg once daily coadministration)

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b	p-value	
	50 mg sildenafil alone (reference)	75 mg TMC278 q.d. + 50 mg sildenafil (test)			Period	Sequence
C _{max} , ng/mL	88.19	79.60	90.26	79.75 – 102.1	0.6535	0.0420*
AUC _{last} , ng.h/mL	324.7	297.7	91.68	85.13 – 98.74	0.5443	0.0845
Median ^c						
Parameter	50 mg sildenafil alone (reference)	75 mg TMC278 q.d. + 50 mg sildenafil (test)	Treatment difference median	90% CI, % ^b	Period	Sequence
t _{max} , h	1.5	2.0	0.375	(-0.25) - (0.75)	0.9529	0.6803

^a n=15 for reference and n=16 for test.

^b 90% confidence intervals.

^c n=15 for reference and test.

* Statistically significant difference.

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On Day 12 (Treatment B), with rilpivirine coadministration, lower mean N-desmethyl sildenafil C_{max} and AUC_(0-last) values were observed compared to Day 1 (Treatment A), when single dose sildenafil was administered by itself. The 90% confidence interval for N-desmethyl sildenafil C_{max} was not within 80%-125%. The 90% confidence interval for N-desmethyl sildenafil AUC_(0-last) was within 80%-125%. Statistical analysis for N-desmethyl sildenafil AUC_(0-∞) was not conducted because the N-desmethyl sildenafil AUC_(0-∞) could not be derived in more than half the subjects.

10.4 Safety Issues

No deaths or other serious adverse events were reported for the trial. No grade 3 or grade 4 adverse events were reported. The only adverse event that was reported in more than one subject was pruritus. Pruritus was reported in two subjects as a grade 1 adverse event. There were no adverse events that were attributed to rilpivirine, and only one adverse event (nasal congestion) that was classified as “probably related” to sildenafil.

Table 8-Adverse event incidence categorized by system organ class and preferred term

<i>System Organ Class Preferred Term n (%)</i>	<i>50 mg sildenafil alone (Treatment A) N = 15</i>	<i>75 mg TMC278 q.d. (Treatment B, Days 1-11) N=16</i>	<i>75 mg TMC278 q.d. + 50 mg sildenafil (Treatment B, Day 12) N=16</i>	<i>Follow-up N = 16</i>
<i>Any Adverse Event</i>	1 (6.7)	4 (25.0)	2 (12.5)	1 (6.3)
<i>Eye Disorders</i>	0	1 (6.3)	0	0
Vision Blurred	0	1 (6.3)	0	0
<i>Gastrointestinal Disorders</i>	0	2 (12.5)	0	0
Flatulence	0	1 (6.3)	0	0
Nausea	0	1 (6.3)	0	0
Vomiting	0	1 (6.3)	0	0
<i>Infections and Infestations</i>	0	1 (6.3)	0	0
Body Tinea	0	1 (6.3)	0	0
<i>Injury, Poisoning and Procedural Complications</i>	1 (6.7)	0	0	1 (6.3)
Excoriation	0	0	0	1 (6.3)
Skin Laceration	1 (6.7)	0	0	0
<i>Nervous System Disorders</i>	0	1 (6.3)	1 (6.3)	0
Headache	0	0	1 (6.3)	0
Somnolence	0	1 (6.3)	0	0
<i>Respiratory, Thoracic and Mediastinal Disorders</i>	1 (6.7)	0	0	0
Nasal Congestion	1 (6.7)	0	0	0
<i>Skin and Subcutaneous Tissue Disorders</i>	0	1 (6.3)	1 (6.3)	0
Pruritus	0	1 (6.3)	1 (6.3)	0
Skin Ulcer	0	0	1 (6.3)	0

n = number of subjects with that particular AE; N = number of subjects per treatment.

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11. Discussion and Conclusions

Based on the results from the drug-drug interaction trial, the following conclusions can be made:

- The mean rilpivirine C_{min} was decreased by 4% and minimal changes were observed in rilpivirine C_{max} and $AUC_{(0-24h)}$ with sildenafil coadministration (the mean C_{max} and $AUC_{(0-24h)}$ values were decreased by 8% and 2%, respectively). The 90% confidence interval for all three parameters was within 80-125%.
- With rilpivirine coadministration, the single dose mean sildenafil C_{max} was decreased by approximately 7% and minimal changes were observed in single dose sildenafil $AUC_{(0-last)}$ and $AUC_{(0-\infty)}$ (the single dose sildenafil $AUC_{(0-last)}$ and $AUC_{(0-\infty)}$ values were both decreased by 3%). The 90% confidence interval for C_{max} , $AUC_{(0-last)}$ and $AUC_{(0-\infty)}$ values was within 80%-125%.
- With rilpivirine coadministration, the mean N-desmethyl sildenafil C_{max} and $AUC_{(0-last)}$ values were decreased by 10% and 8%, respectively. The 90% confidence interval for N-desmethyl sildenafil C_{max} was not within 80%-125%. The 90% confidence interval for N-desmethyl sildenafil $AUC_{(0-last)}$ was within 80%-125%.

Single dose sildenafil does not result in clinically relevant changes in the exposure of rilpivirine and no dosage adjustment for rilpivirine is required. The decrease in single dose sildenafil and N-desmethyl sildenafil exposure may be potentially explained by rilpivirine CYP 3A induction. The specific effects of a 25 mg once daily rilpivirine dosage regimen on sildenafil exposure have not been evaluated. From a mechanistic standpoint, the degree of induction with rilpivirine 25 mg once daily dosing is anticipated to be the same or less compared to 75 mg once daily dosing. The changes in sildenafil exposure with rilpivirine coadministration do not appear to be clinically relevant based on the results from the trial and therefore no dosage adjustment for sildenafil is required with rilpivirine dosage regimens ranging from 25 mg once daily to 75 mg once daily.

TMC278-C125

1. Title

A Phase I, open label, randomized, three-way crossover trial in 18 healthy subjects to investigate the pharmacokinetic interaction between steady-state TMC278 and steady-state rifabutin

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at the (b) (4) from November 18, 2005 to March 16, 2006.

3. Objectives

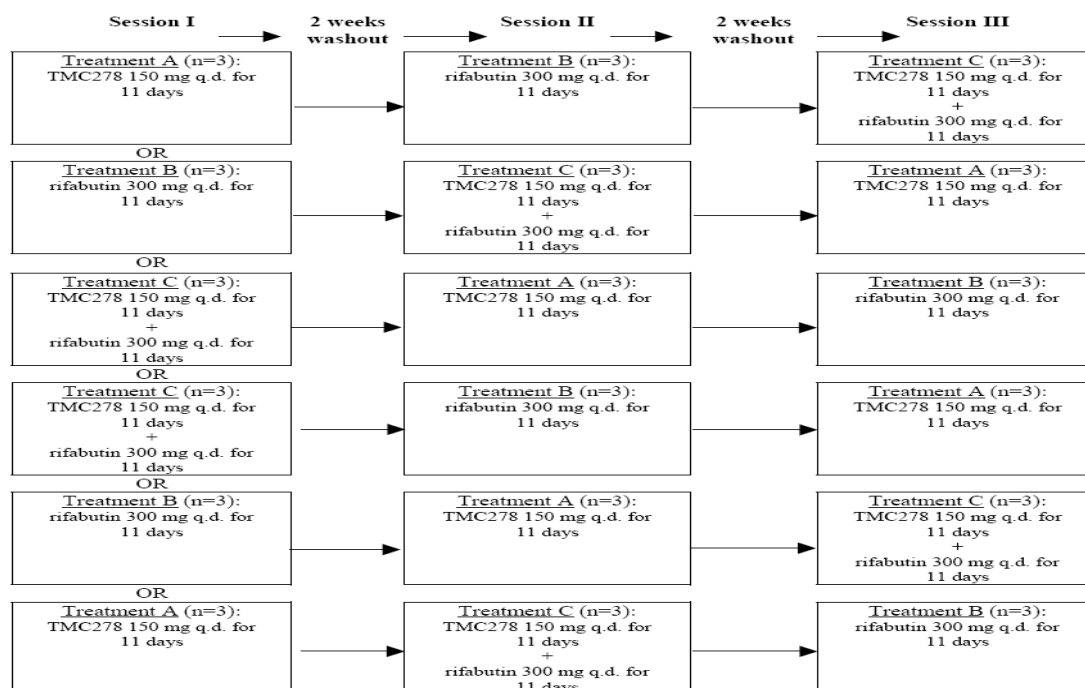
The objectives of the trial were to evaluate the effect at steady state of rifabutin and 25-O-desacetyl-rifabutin on rilpivirine pharmacokinetics and the effect of rilpivirine on rifabutin and 25-O-desacetyl-rifabutin pharmacokinetics.

4. Trial Design

TMC278-C125 was a Phase I, open label, randomized, 3 way crossover clinical trial that enrolled male and female subjects between 18 and 55 years old. The trial design is displayed in Figure 1.

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Figure 1-TMC278-C125 trial design



5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Use of ibuprofen was permitted up to three days before first dosing. Afterwards, ibuprofen use was permitted up to 400 mg/day. Any medications were to be discontinued a minimum of 14 days before first dosing (with the exception of ibuprofen). Use of herbal medicines or dietary supplements was not permitted from a minimum of fourteen days before first dosing until the last trial visit.

Use of liquids containing alcohol or quinine was not permitted from 24 hours before administration of trial medication until 96 hours after administration of medication. Intake of grapefruit and grapefruit juice was not permitted from 7 days before administration of trial medication until 96 hours after administration of medication.

In the event of an adverse event, the following medications were permitted:

- A) Rash or an allergic reaction: cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents (specific medications were not included in the trial report)
- B) Nausea: antiemetics (specific medications were not included in the trial report)
- C) Diarrhea: loperamide

6. Dosage and Administration

On days when trial medication was administered at the clinical trial site (including pharmacokinetic sampling days), a standard meal was administered in the morning and medication was administered within 10 minutes after completion of the meal. When both rifabutin and rilpivirine were coadministered, rifabutin was administered first and rilpivirine was administered within five minutes.

7. Rationale for Doses Used in the Trial

The rilpivirine dosage regimen that was administered to all subjects for Treatments A, B and C was 150 mg once daily. On days when rilpivirine (with or without rifabutin) was administered at the clinical site, breakfast was consumed prior to dose administration (the proposed rilpivirine prescribing information recommends administering rilpivirine with a meal). In contrast, the rilpivirine dosage regimen that was evaluated in the Phase 3 clinical trials and the recommended dosage regimen in the proposed prescribing information is 25 mg once daily with a meal. Across the dose range of 25 mg to 150 mg, increases in rilpivirine exposure were approximately dose proportional. Therefore, the percentage change in rilpivirine exposure that is caused by the induction effects of rifabutin should be similar with a rilpivirine dosage regimen of either 25 mg once daily or 150 mg once daily. However two important assumptions are: a) the absence of significant CYP 3A induction effects from rilpivirine that could affect rifabutin CYP 3A metabolism, and b) similar rifabutin induction effects occurring with the two rilpivirine dosage regimens.

The rifabutin dosage regimen (300 mg once daily) is the recommended regimen in the rifabutin prescribing information (label). There are no specific recommendations in the rifabutin label to administer rifabutin 300 mg once daily with food.

8. Drugs Used in the Trial

Rilpivirine 50 mg tablets (formulation F003) and 100 mg tablets (F002) were administered in the trial. Both of these tablets were Phase 2b formulations that were used in the Phase 1 or 2 trials.

Rifabutin (Mycobutin[®]) 150 mg capsules were administered in the trial.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

For Treatment A (rilpivirine administered alone), blood samples for analysis of rilpivirine concentrations were obtained on Days 11 and 12 at predose and up to 24 hours postdose. Predose rilpivirine blood samples were also obtained on Days 9 and 10. On Day 1, a predose sample was drawn to determine rilpivirine, rifabutin and 25-O-desacetyl-rifabutin concentrations and a 4 hour postdose blood sample was drawn to determine rilpivirine concentrations.

For Treatment B, blood samples for analysis of rifabutin and 25-O-desacetyl-rifabutin concentrations were obtained on Days 11 and 12 at predose and up to 24 hours postdose. Predose blood samples for analysis of rifabutin and 25-O-desacetyl-rifabutin concentrations were also obtained on Days 9 and 10. On Day 1, a predose sample was drawn to determine rilpivirine, rifabutin and 25-O-desacetyl-rifabutin concentrations and a 4 hour postdose blood sample was drawn to determine rifabutin and 25-O-desacetyl-rifabutin concentrations. On Day 5, a predose sample was drawn to determine rifabutin and 25-O-desacetyl-rifabutin concentrations.

For Treatment C, blood samples for analysis of rilpivirine, rifabutin and 25-O-desacetyl-rifabutin concentrations were obtained on Days 11 and 12 at predose and up to 24 hours postdose. Predose blood samples for analysis of rilpivirine, rifabutin and 25-O-desacetyl-rifabutin concentrations were also obtained on Days 9 and 10. On Day 1, a predose and a 4 hour postdose sample was drawn to determine rilpivirine, rifabutin and 25-O-desacetyl-rifabutin concentrations. On Day 5, a predose sample was drawn to determine rilpivirine, rifabutin and 25-O-desacetyl-rifabutin concentrations.

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a validated LC/MS/MS method by Johnson and Johnson Pharmaceutical Research and Development. The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There

were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the TMC278-C125 trial, precision and accuracy were evaluated using the low (2.77 ng/mL), medium (59.0 ng/mL), and high (1550 ng/mL) QC samples. The corresponding rilpivirine inter-run accuracy values were 1.1% for the low QCs, -4.1% for the medium QCs, and -0.6% for the high QCs, and the rilpivirine inter-run precision values were 5.2% for the low QCs, 2.3% for the medium QCs, and 3.5% for the high QCs. The submitted rilpivirine long term stability data of 1528 days covered the duration of long term rilpivirine stability data necessary for the TMC278-C125 trial.

The method and bioanalysis of rifabutin and 25-O-desacetyl-rifabutin are acceptable. Plasma samples were analyzed for rifabutin and 25-O-desacetyl-rifabutin concentrations using a validated LC/MS/MS method by (b) (4). The lower limit of quantification for rifabutin was 2 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rifabutin based on the bioanalytical report. For the TMC278-C125 trial, precision and accuracy were evaluated using the low (6 ng/mL), medium (75 ng/mL), and high (1500 ng/mL) QC samples. The corresponding rifabutin inter-run accuracy values were 0.8% for the low QCs, 1.2% for the medium QCs, and 1.3% for the high QCs, and the rifabutin inter-run precision values were 6.2% for the low QCs, 6.6% for the medium QCs, and 5.5% for the high QCs. The lower limit of quantification for 25-O-desacetyl-rifabutin was 2 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for 25-O-desacetyl-rifabutin based on the bioanalytical report. For the TMC278-C125 trial, precision and accuracy were evaluated using the low (6 ng/mL), medium (75 ng/mL), and high (1500 ng/mL) QC samples. The corresponding 25-O-desacetyl-rifabutin inter-run accuracy values were 6.7% for the low QCs, 6.9% for the medium QCs, and 8.3% for the high QCs, and the 25-O-desacetyl-rifabutin inter-run precision values were 4% for the low QCs, 7.4% for the medium QCs, and 5.2% for the high QCs.

Both rifabutin and 25-O-desacetyl-rifabutin failed to demonstrate stability at -20°C when long term stability was evaluated for approximately 12 months. The applicant has been requested to provide long term stability data for rifabutin and 25-O-desacetyl-rifabutin covering approximately 5 months at the appropriate storage temperature (-20°C) to support the inclusion of rifabutin pharmacokinetic data from the TMC278-C125 trial in the proposed rilpivirine label.

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate pharmacokinetic parameters, including C_{\max} and $AUC_{(0-\tau)}$. If a major difference (> 10.00% deviation from the scheduled time) was observed, the actual sampling time was used instead of the scheduled sampling time.

Statistical Analysis

Descriptive statistics were calculated for rilpivirine, rifabutin and 25-O-desacetyl-rifabutin plasma concentrations and pharmacokinetic parameters, including the number of

subjects (n), mean, standard deviation, the coefficient of variation (CV%), geometric mean, median, and the minimum and maximum values.

Statistical analysis involved comparison of rilpivirine log transformed pharmacokinetic parameters for Day 11, Treatment C (test arm) compared to Day 11, Treatment A (reference arm). For rifabutin and 25-O-desacetyl-rifabutin, statistical analysis involved comparison of rifabutin and 25-O-desacetyl-rifabutin log transformed pharmacokinetic parameters for Day 11, Treatment C (test arm) compared to Day 11, Treatment B (reference arm). C_{0h} (predose plasma concentrations), C_{min} (the minimum plasma concentrations between 0 hour and the dosing interval $[\tau]$), C_{max} , and $AUC_{0-\tau}$ were evaluated. Using a linear mixed effects model, least squares means were calculated and 90% confidence intervals were derived based on the difference of the pharmacokinetic parameter's least squares means for the test and reference arms. The applicant did not specify predetermined "no effect boundaries" for the 90% confidence intervals.

An assessment was performed to determine if rilpivirine steady state concentrations were achieved by Day 11 (Treatment A or C) based on predose concentrations from Days 9, 10 and 11. For rifabutin and 25-O-desacetyl-rifabutin, an assessment was performed to determine if steady state concentrations were achieved by Day 11 (Treatment B or C) based on predose concentrations from Days 9, 10 and 11.

10. Results

10.1 Subject Demographics and Disposition

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Table 1-TMC278-C125 subject demographics

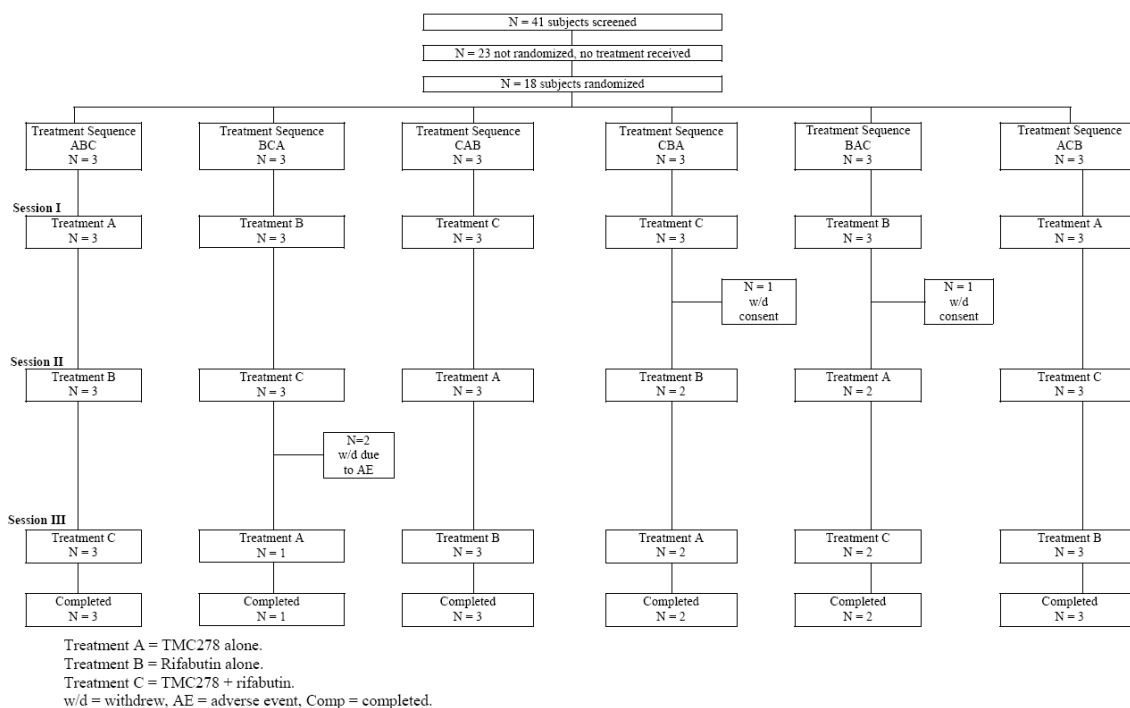
Parameter	Treatment Sequence ABC N = 3	Treatment Sequence BCA N = 3	Treatment Sequence CAB N = 3	Treatment Sequence CBA N = 3	Treatment Sequence BAC N = 3	Treatment Sequence ACB N = 3	Total N = 18
Age, years							
Median (range)	42.0 (40-49)	47.0 (43-48)	47.0 (40-48)	29.0 (22-47)	41.0 (30-52)	42.0 (34-45)	42.5 (22-52)
Height, cm							
Median (range)	175.0 (172-184)	177.0 (176-179)	179.0 (177-181)	173.0 (172-175)	173.0 (167-173)	175.0 (169-191)	175.0 (167-191)
Weight, cm							
Median (range)	73.0 (70-74)	81.0 (71-84)	83.0 (73-86)	69.0 (66-75)	70.0 (68-79)	80.0 (64-92)	73.5 (64-92)
BMI, kg/m ²							
Median (range)	23.7 (22-24)	25.3 (23-27)	25.3 (23-27)	23.3 (22-25)	24.4 (23.26)	25.2 (22-26)	24.3 (22-27)
Sex, n (%)							
Male	3 (100)	3 (100)	3 (100)	3 (100)	2 (66.7)	2 (66.7)	16 (88.9)
Female	0	0	0	0	1 (33.3)	1 (33.3)	2 (11.1)
Ethnic Origin, n (%)							
Caucasian	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)	18 (100)
Type of Smoker, n (%)							
Nonsmoker	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)	18 (100)

Treatment A = TMC278 alone.

Treatment B = rifabutin alone.

Treatment C = TMC278 + rifabutin.

BMI = body mass index.

Figure 2-TMC278-C125 subject disposition

10.2 Prior and Concomitant Medications

Eight subjects administered concurrent medications during the trial. The administered concurrent medications were carbocysteine, ibuprofen, loperamide, silver sulfadiazine and a combination miconazole and hydrocortisone topical formulation (Daktacort). None of the coadministered medications would be expected to alter CYP 3A metabolism.

10.3 Pharmacokinetic and Statistical Analysis

All subjects had rilpivirine concentrations that were less than the lower limit of quantification (LLOQ) prior to initiation of Treatment A. There were five subjects with a quantifiable rilpivirine drug concentration prior to starting Treatment B and four subjects with a quantifiable rilpivirine drug concentration prior to starting Treatment C. The applicant did not specifically state a reason for the quantifiable rilpivirine concentrations. Quantifiable rilpivirine drug concentrations have been observed in other drug-drug interaction trials despite a washout period. However, in Treatment C, these concentrations were less than 5% or less of the subject's C_{max} and for treatment B (where rilpivirine concentrations were not analyzed), these concentrations were 5% or less of the subject's C_{max} for Treatment A (where rilpivirine was administered alone) and no adjustments were necessary for the pharmacokinetic analyses.

There were also subjects with quantifiable rifabutin predose concentrations. In Treatments A, B and C, there were 3, 2 and 1 subject, respectively that had quantifiable Day 1 predose concentrations. The applicant did not specifically state a reason for the quantifiable rifabutin concentrations. However, the mean elimination half life of

rifabutin is 45 hours and the washout period may not have been sufficient in subjects with quantifiable rifabutin concentrations. For all three treatment arms, these concentrations were 5% or less of the subject's C_{max} for Treatment B (where rifabutin was administered alone) and no adjustments were necessary for the pharmacokinetic analyses.

There were no subjects with quantifiable 25-O-desacetyl-rifabutin predose concentrations.

Rilpivirine

Table 2-Pharmacokinetic parameters for rilpivirine 150 mg once daily and rilpivirine 150 mg once daily with rifabutin 300 mg once daily coadministration
[%FI=100 x $([C_{max}-C_{min}]/C_{ss,av})$]

Pharmacokinetics of TMC278 (mean \pm SD, t_{max} : median [range])	Treatment A, TMC278 alone (reference)	Treatment C, TMC278 + rifabutin (test)
n	14	16
t_{max} , h	5.0 [4.0 - 9.0]	5.0 [2.0 - 9.0]
C_{0h} , ng/mL	433.9 \pm 112.1	229.3 \pm 76.66
C_{min} , ng/mL	363.8 \pm 80.28	187.0 \pm 57.03
C_{max} , ng/mL	991.6 \pm 240.6	682.5 \pm 227.0
AUC _{24h} , ng.h/mL	15184 \pm 3254	8692 \pm 2564
$C_{ss, av}$, ng/mL	632.7 \pm 135.6	362.1 \pm 106.8
FI, %	97.85 \pm 21.28	134.3 \pm 32.56

Table 3-Statistical analysis for rilpivirine 150 mg once daily and rilpivirine 150 mg once daily with rifabutin 300 mg once daily coadministration

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI,% ^b	p-value	
	Treatment A, TMC278 alone (reference)	Treatment C, TMC278 + rifabutin (test)			Period	Sequence
C_{0h} , ng/mL	421.8	221.9	52.60	47.46 - 58.30	0.1255	0.0719
C_{min} , ng/mL	354.3	180.7	50.99	48.04 - 54.13	0.0059	0.0872
C_{max} , ng/mL	982.6	641.8	65.31	57.84 - 73.74	0.2902	0.3345
AUC _{24h} , ng.h/mL	15423	8324	53.97	50.04 - 58.22	0.0776	0.2664

^a n= 14 for Treatment A (reference) and n=16 for Treatment C (test).

^b 90% confidence intervals.

On Day 11 (Treatment C), with rifabutin coadministration, lower mean rilpivirine C_{0h} , C_{min} , C_{max} , and AUC_(0-24h) values were observed in subjects compared to Day 11 (Treatment A), when rilpivirine was administered by itself. The 90% confidence interval for rilpivirine C_{min} , C_{max} , and AUC_(0-24h) were not within 80%-125%.

Based on evaluating the individual rilpivirine predose concentrations, steady state concentrations were achieved by Day 11 for both Treatment A and Treatment C in most subjects.

Rifabutin and 25-O-desacetyl-rifabutin

Table 4-Rifabutin pharmacokinetic parameters (administered as rifabutin 300 mg once daily and rifabutin 300 mg once daily with rilpivirine 150 mg once daily coadministration)

Pharmacokinetics of rifabutin (mean \pm SD, t_{max} : median [range])	Treatment B, Rifabutin alone (reference)	Treatment C, TMC278 + rifabutin (test)
n	17	16
t_{max} , h	3.0 [2.0 - 6.0]	4.5 [2.0 - 6.0]
C_{0h} , ng/mL	66.83 \pm 19.38	71.45 \pm 27.11
C_{min} , ng/mL	62.16 \pm 17.58	64.33 \pm 25.24
C_{max} , ng/mL	415.6 \pm 136.9	420.7 \pm 111.6
AUC_{24h} , ng.h/mL	3943 \pm 982.1	4109 \pm 1083
$C_{ss, av}$, ng/mL	164.3 \pm 40.92	171.2 \pm 45.14
FI, %	212.2 \pm 40.34	209.9 \pm 32.95

Table 5-Statistical analysis for rifabutin (administered as 300 mg once daily and rifabutin 300 mg once daily with rilpivirine 150 mg once daily coadministration)

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b	p-value	
	Treatment B, Rifabutin alone (reference)	Treatment C, TMC278 + rifabutin (test)			Period	Sequence
C_{0h} , ng/mL	62.69	65.87	105.1	94.58 - 116.8	0.8077	0.9359
C_{min} , ng/mL	58.53	59.37	101.4	94.03 - 109.4	0.6322	0.9427
C_{max} , ng/mL	396.1	408.1	103.0	93.47 - 113.6	0.0254	0.5993
AUC_{24h} , ng.h/mL	3895	3999	102.7	96.56 - 109.1	0.0583	0.9572

^a n=17 for Treatment B (reference) and n=16 for Treatment C (test).

^b 90% confidence intervals.

On Day 11 (Treatment C), with rilpivirine coadministration, similar mean rifabutin C_{0h} , C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were observed in subjects compared to Day 11 (Treatment B), rifabutin was administered by itself. The 90% confidence interval for rifabutin C_{0h} , C_{min} , C_{max} , and $AUC_{(0-24h)}$ were within 80%-125%.

Table 6- 25-O-desacetyl-rifabutin (metabolite) pharmacokinetic parameters (administered as rifabutin 300 mg once daily and rifabutin 300 mg once daily with rilpivirine 150 mg once daily coadministration)

Pharmacokinetics of 25- <i>O</i> -desacetyl-rifabutin (mean \pm SD, t_{max} : median [range])	Treatment B, Rifabutin alone (reference)	Treatment C, TMC278 + rifabutin (test)
n	17	16
t_{max} , h	4.0 [2.0 - 5.0]	5.0 [3.0 - 5.0]
C_{0h} , ng/mL	3.939 \pm 1.444	4.734 \pm 2.393
C_{min} , ng/mL	3.427 \pm 1.491	3.956 \pm 1.862
C_{max} , ng/mL	27.66 \pm 7.368	32.41 \pm 13.91
AUC_{24h} , ng.h/mL	259.9 \pm 77.78	315.3 \pm 172.6
$C_{ss, av}$, ng/mL	10.83 \pm 3.241	13.14 \pm 7.191
FI, %	227.7 \pm 32.81	223.8 \pm 35.03

Table 7-Statistical analysis for 25-O-desacetyl-rifabutin (administered as rifabutin 300 mg once daily and rifabutin 300 mg once daily with rilpivirine 150 mg once daily coadministration)

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b	p-value	
	Treatment B, Rifabutin alone (reference)	Treatment C, TMC278 + rifabutin (test)			Period	Sequence
C_{0h} , ng/mL	3.706	4.192	113.1	97.06 - 131.9	0.4891	0.9549
C_{min} , ng/mL	3.500	3.917	111.9	102.7 - 121.9	0.5866	0.7347
C_{max} , ng/mL	27.88	29.85	107.1	97.82 - 117.2	0.0264	0.4695
AUC_{24h} , ng.h/mL	266.8	284.1	106.5	101.8 - 111.4	0.0030	0.7586

^a for C_{0h} , C_{max} , and AUC_{24h} : n=16 for Treatment C (test) and n=17 for Treatment B (reference), for C_{min} : n=15 for Treatment C (test) and n=16 for Treatment B (reference).

^b 90% confidence intervals.

On Day 11 (Treatment C), with rilpivirine coadministration, higher mean 25-O-desacetyl-rifabutin C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were observed in subjects compared to Day 11 (Treatment B), when rifabutin was administered by itself. The 90% confidence interval for 25-O-desacetyl-rifabutin C_{0h} was not within 80%-125%. The 90% confidence interval for 25-O-desacetyl-rifabutin C_{min} , C_{max} , and $AUC_{(0-24h)}$ were within 80%-125%.

Based on evaluating the individual rifabutin and 25-O-desacetyl-rifabutin predose concentrations, steady state concentrations were achieved by Day 11 for both Treatment B and Treatment C in most subjects.

10.4 Safety Issues

No deaths or other serious adverse events were reported for the trial. Two grade 3 adverse events were reported (one subject with increased triglycerides and one subject with increased lipase). No grade 4 adverse events were reported. The most commonly reported adverse events were chromaturia and headache (see Table 8 below for information regarding the number and percentage of subjects). Tables 9 and 10 provide information on adverse events that were at a minimum possibly related to either rilpivirine or rifabutin.

Table 8-Adverse event incidence reported for two or more subjects and categorized by system organ class and preferred term

System Organ Class Preferred Term n (%)	Trial Phase			
	Treatment A, TMC278 alone N = 14	Treatment B, Rifabutin alone N = 17	Treatment C, TMC278 + rifabutin N = 17	Total N = 18
<i>Any Treatment-emergent Adverse Event</i>	10 (71.4)	12 (70.6)	14 (82.4)	17 (94.4)
<i>Renal and Urinary Disorders</i>	0	7 (41.2)	6 (35.3)	10 (55.6)
Chromaturia	0	7 (41.2)	6 (35.3)	10 (55.6)
<i>Gastrointestinal Disorders</i>	3 (21.4)	0	5 (29.4)	7 (38.9)
Diarrhoea	1 (7.1)	0	3 (17.6)	4 (22.2)
Nausea	1 (7.1)	0	2 (11.8)	3 (16.7)
<i>General Disorders and Administration Site Conditions</i>	1 (7.1)	2 (11.8)	6 (35.3)	7 (38.9)
Fatigue	1 (7.1)	2 (11.8)	2 (11.8)	4 (22.2)
Pyrexia	0	1 (5.9)	2 (11.8)	3 (16.7)
Influenza like illness	0	0	2 (11.8)	2 (11.1)
<i>Musculoskeletal and Connective Tissue Disorders</i>	0	3 (17.6)	4 (23.5)	7 (38.9)
Back pain	0	1 (5.9)	4 (23.5)	5 (27.8)
<i>Nervous System Disorders</i>	5 (35.7)	4 (23.5)	3 (17.6)	7 (38.9)
Headache	5 (35.7)	4 (23.5)	2 (11.8)	6 (33.3)
<i>Investigations</i>	1 (7.1)	0	2 (11.8)	5 (27.8)
Lipase increased	1 (7.1)	0	2 (11.8)	4 (22.2) ^a
<i>Respiratory, Thoracic and Mediastinal Disorders</i>	0	1 (5.9)	4 (23.5)	4 (22.2)
Pharyngolaryngeal pain	0	0	2 (11.8)	2 (11.1)
<i>Skin and Subcutaneous Tissue Disorders</i>	3 (21.4)	1 (5.9)	0	4 (22.2)
Rash	2 (14.3)	0	0	2 (11.1)

^a including 1 subject with lipase increased during the follow-up period

N = number of subjects with that particular AE; N= number of subjects per phase.

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Table 9-Adverse event incidence at a minimum possibly related to rilpivirine and categorized by system organ class and preferred term

System Organ Class Preferred Term n (%)	Trial Phase			
	Treatment A, TMC278 alone N = 14	Treatment B, Rifabutin alone N = 17	Treatment C, TMC278 + rifabutin N = 17	Total N = 18
<i>Any Adverse Event</i>	10 (71.4)	12 (70.6)	14 (82.4)	17 (94.4)
<i>With at Least 1 AE Thought to be at Least Possibly Related to TMC278</i>	7 (50.0)	0	8 (47.1)	10 (55.6)
<i>Gastrointestinal Disorders</i>	3 (21.4)	0	5 (29.4)	7 (38.9)
Diarrhoea	0	0	3 (17.6)	3 (16.7)
Nausea	1 (7.1)	0	2 (11.8)	3 (16.7)
Abdominal pain upper	1 (7.1)	0	0	1 (5.6)
Dyspepsia	1 (7.1)	0	0	1 (5.6)
Enteritis	1 (7.1)	0	0	1 (5.6)
Tongue ulceration	1 (7.1)	0	0	1 (5.6)
<i>General Disorders and Administration Site Conditions</i>	1 (7.1)	0	2 (11.8)	2 (11.1)
Fatigue	1 (7.1)	0	2 (11.8)	2 (11.1)
Feeling cold	1 (7.1)	0	0	1 (5.6)
<i>Infections and Infestations</i>	2 (14.3)	0	0	2 (11.1)
Folliculitis	1 (7.1)	0	0	1 (5.6)
Gastroenteritis	1 (7.1)	0	0	1 (5.6)
<i>Investigations</i>	1 (7.1)	0	2 (11.8)	3 (16.7)
Lipase increased	1 (7.1)	0	2 (11.8)	3 (16.7)
<i>Nervous System Disorders</i>	3 (21.4)	0	2 (11.8)	4 (22.2)
Headache	3 (21.4)	0	2 (11.8)	4 (22.2)
<i>Psychiatric Disorders</i>	0	0	1 (5.9)	1 (5.6)
Sleep disorders	0	0	1 (5.9)	1 (5.6)
<i>Skin and Subcutaneous Skin Disorders</i>	1 (7.1)	0	0	1 (5.6)
Rash	1 (7.1)	0	0	1 (5.6)
Pruritus	1 (7.1)	0	0	1 (5.6)

n = number of subjects with that particular AE; N = number of subjects per phase.

Only one event of rash was considered to be probably related to TMC278. No subjects had an AE considered to be very likely related to TMC278.

Table 10-Adverse event incidence at a minimum possibly related to rifabutin and categorized by system organ class and preferred term

System Organ Class Preferred Term n (%)	Trial Phase			
	Treatment A, TMC278 alone N = 14	Treatment B, Rifabutin alone N = 17	Treatment C, TMC278 + rifabutin N = 17	Total N = 18
<i>Any Adverse Event</i>	10 (71.4)	12 (70.6)	14 (82.4)	17 (94.4)
<i>With at Least 1 AE Thought to be at Least Possibly Related to Rifabutin</i>	0	9 (52.9)	10 (58.8)	14 (77.8)
<i>Renal and Urinary Disorders</i>	0	7 (41.2)	6 (35.3%)	10 (55.6)
Chromaturia	0	7 (41.2)	6 (35.3%)	10 (55.6)
<i>Gastrointestinal Disorders</i>	0	0	5 (29.4)	5 (27.8)
Diarrhoea	0	0	3 (17.6)	3 (16.7)
Nausea	0	0	2 (11.8)	2 (11.1)
<i>General Disorders and Administration Site Conditions</i>	0	2 (11.8)	2 (11.8)	4 (22.2)
Fatigue	0	2 (11.8)	2 (11.8)	4 (22.2)
Pyrexia	0	1 (5.9)	0	1 (5.6)
<i>Investigations</i>	0	0	2 (11.8)	2 (11.1)
Lipase increased	0	0	2 (11.8)	2 (11.1)
<i>Musculoskeletal and Connective Tissue Disorders</i>	0	1 (5.9)	0	1 (5.6)
Back pain	0	1 (5.9)	0	1 (5.6)
<i>Nervous System Disorders</i>	0	2 (11.8)	2 (11.8)	3 (16.7)
Headache	0	2 (11.8)	2 (11.8)	3 (16.7)
<i>Psychiatric Disorders</i>	0	0	1 (5.9)	1 (5.6)
Sleep disorder	0	0	1 (5.9)	1 (5.6)

n = number of subjects with that particular AE; N = number of subjects per phase.

Only the events of chromaturia were considered to be probably related to rifabutin. No subjects had an AE considered to be very likely related to rifabutin.

11. Discussion and Conclusions

Based on the results from the drug-drug interaction trial, the following conclusions can be made:

- Rilpivirine exposure was decreased with rifabutin coadministration (rilpivirine mean C_{0h} , C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were decreased by 47%, 49%, 35% and 46%, respectively). The 90% confidence interval for all three parameters was not within 80-125%.
- With rilpivirine coadministration, minimal changes were observed in rifabutin exposure. The mean rifabutin C_{0h} , C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were increased by 5%, 1%, 3%, and 3%, respectively. The 90% confidence interval for rifabutin C_{0h} , C_{min} , C_{max} , and $AUC_{(0-24h)}$ was within 80%-125%.
- With rilpivirine coadministration, the mean 25-O-desacetyl-rifabutin C_{0h} , C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were increased by 13%, 12%, 7% and 7%, respectively. The 90% confidence interval for C_{0h} was 97%-132% and was not within 80%-125%. The 90% confidence interval C_{min} , C_{max} , and $AUC_{(0-24h)}$ was within 80%-125%.

The decrease in rilpivirine exposure may be potentially explained by rifabutin CYP 3A induction. The information from the trial supports the conclusion that with a rilpivirine 150 mg once daily dosing regimen, potential rifabutin CYP 3A induction of rilpivirine metabolism results in clinically relevant changes in rilpivirine exposure and therefore either a dosage adjustment for rilpivirine or a recommendation in the rilpivirine prescribing information that rifabutin and rilpivirine should not be coadministered is required.

With a 150 mg once daily rilpivirine dosage regimen, the decreases in both rifabutin and 25-O-desacetyl-rifabutin exposure may be potentially explained by rilpivirine CYP 3A induction. The specific effects of a 25 mg once daily rilpivirine dosage regimen on rifabutin and 25-O-desacetyl-rifabutin exposure have not been evaluated. From a mechanistic standpoint, the degree of induction with rilpivirine 25 mg once daily dosing is anticipated to be the same or less compared to 150 mg once daily dosing. The changes in rifabutin and 25-O-desacetyl-rifabutin exposure with rilpivirine coadministration do not appear to be clinically relevant based on the results from the trial and therefore no dosage adjustment for rifabutin is required with rilpivirine dosage regimens ranging from 25 mg once daily to 150 mg once daily. A greater degree of rifabutin induction may occur with rilpivirine 25 mg once daily dosing. However the same conclusions that were reached for rilpivirine 150 mg once daily dosing would still apply: either a dosage adjustment for rilpivirine or a recommendation in the rilpivirine prescribing information that that rifabutin and rilpivirine should not be coadministered is required.

Trial TMC278-C127

A phase I, open-label, randomized, two-way crossover trial in 16 healthy subjects to investigate the potential pharmacokinetic interaction between steady-state rilpivirine and steady-state ketoconazole

Dates: July 04 - October 19, 2005

Trial Site: (b) (4)

Summary of Findings:

When co-administered at steady state, rilpivirine exposure (AUC_{24h}) increased by 49% while ketoconazole exposure (AUC_{24h}) decreased by 24%. The applicant considers this increase in rilpivirine exposure to be safe and does not recommend any dose adjustments; especially because the dose tested in this trial is 6-fold higher than the proposed recommended dose (25 mg q.d.) of rilpivirine. The decrease in ketoconazole exposure was anticipated because rilpivirine was an inducer of enzymes in the CYP3A-family *in vitro* (the *in vitro* CYP induction study did not evaluate rilpivirine concentrations below 2.5 μ M (the C_{max} for 150 mg once daily dosing] and for 25 mg once daily dosing, the C_{max} value is approximately 0.5 μ M). It is unknown if the decrease in exposure will impact the clinical efficacy of ketoconazole.

Objectives:

To investigate the effect of steady-state ketoconazole on the steady-state pharmacokinetics of rilpivirine, and vice versa and to investigate the short-term safety and tolerability of co-administration of rilpivirine and ketoconazole

Design:

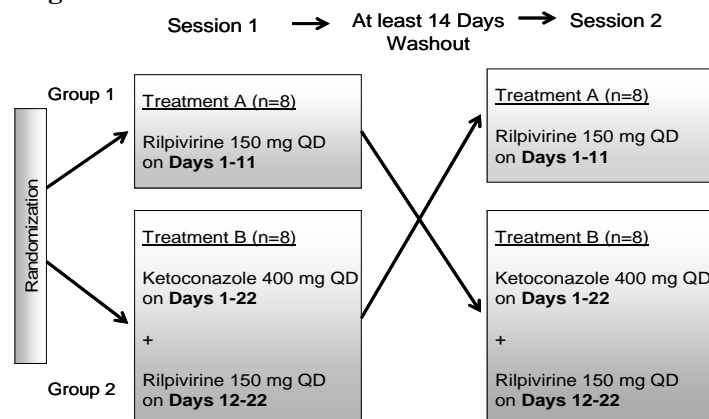
This was a phase 1, open-label, randomized, two-way crossover trial to investigate the pharmacokinetic interaction between rilpivirine and ketoconazole at steady-state. A total of 16 healthy male subjects (8 Caucasian/White, 8 Black) received in a randomized order, rilpivirine alone (Treatment A) or ketoconazole alone followed by a combination of rilpivirine and ketoconazole (Treatment B) during session 1. After a 14-day washout period, a cross over occurred and subjects received a different treatment in session 2.

Treatment A: Rilpivirine 150 mg QD on Days 1 – 11

Treatment B: Ketoconazole 400 mg QD on Days 1 – 22

Rilpivirine 150 mg QD + ketoconazole 400 mg QD on Days 12 – 22

Figure 1 Trial Design



The trial's inclusion criteria specified enrolling healthy males and females 18 to 45 years old with normal body weight (BMI 18.0 to 30.0 kg/m²) and cortisol levels ≥ 19.9 µg/dL at screening. Subjects were excluded from the trial if they had any current or previous adrenal illness, viral infections (HIV-1, HIV-2, and Hep A, B, or C infection), or any of the following abnormal laboratory parameters: SCr ≥ 1.1 X ULN, hemoglobin ≤ 10.9 g/dL, and AST or ALT ≥ 1.25 X ULN. Subjects were also excluded if they had a history or suspicion of using alcohol, barbiturates, amphetamines, recreational drugs, and/or narcotic drugs. The use of prescription medications, herbal medications, and dietary supplements were discontinued 14 days before the first administration of trial medication. All over-the-counter products (OTC) were discontinued at least 7 days prior to the first administration of trial medication. The only medications permitted during the trial were ibuprofen (no more than 400 mg/day), antipruritic agents including cetirizine, levocetirizine or topical corticosteroids (in case of rash/allergic reactions), antiemetics (if nausea), and loperamide (if diarrhea).

Investigational Products:

The hydrochloric acid salt of rilpivirine, R314585, was formulated as an oral film-coated tablet with lactose and microcrystalline cellulose as fillers. Each tablet contained 55 mg or 110 mg of R314585, equivalent to 50 mg (F003) or 100 mg (F002) of rilpivirine, respectively.

- Rilpivirine 50 mg tablet (Batch ID: PD1273), Rilpivirine 100 mg tablet (Batch ID: PD1268)
- Ketoconazole (Nizoral[®]) 200 mg tablet (Badge ID: 02GB749/A)

Rationale for Trial Doses:

Rilpivirine was given at 150 mg q.d. (6-fold higher than the to-be-marketed dose, 25 mg q.d.) for 11 days to achieve steady state concentrations. In previous clinical trials, rilpivirine was generally safe and well tolerated after multiple oral doses of up to 150 mg q.d. for 14 days.

Rilpivirine systemic exposures generally increase in a dose proportional fashion and it is anticipated that a dose of 150 mg q.d. could deliver exposures that are ~6-fold higher than those produced by 25 mg q.d. If a drug-drug interaction (via ketoconazole CYP3A inhibition and/or rilpivirine CYP3A inhibition/induction) occurs with 150 mg q.d., then the magnitude interaction could be scaled down to one produced by 25 mg q.d. (assuming similar magnitude of inhibition or induction effects). The effect of rilpivirine on CYP3A4 enzyme activity was explored in terms of the urinary 6-β-OH-cortisol/cortisol ratio in a clinical trial (TMC278-C131). Thirty nine subjects were given rilpivirine at 75 mg q.d. and thirty nine subjects were given rilpivirine at 300 mg q.d. After steady-state administration of rilpivirine, the average day 1/day 11 ratio was increased, compared to placebo, to a mean of 1.146 (95% CI 1.032 – 1.260) and 1.389 (95% CI 1.212 – 1.566) for the 75 mg q.d. and 300 mg q.d. dose groups, respectively. The applicant states the results from this trial indicate that rilpivirine had mild inducing effects on CYP3A4, which appeared to be dose related. The applicant believes that the rilpivirine at the recommended dose of 25 mg q.d. is unlikely to cause a clinically significant impact on medications combined with rilpivirine.

Ketoconazole (Nizoral[®]) was administered for 22 days at 400 mg q.d. This is the recommended dosage regimen for ketoconazole as stated in the FDA guidance for drug-drug interaction trials.

Dosage and Administration:

During days of PK assessments, subjects were instructed to fast overnight for at least 10 hours prior to the next morning's clinic visit. At the testing facility, subjects ingested their medications with food. At home, subjects were instructed to ingest trial medication with food.

Pharmacokinetic Assessments:

Blood samples were collected at the following time points for evaluation of rilpivirine and ketoconazole plasma concentrations:

- Rilpivirine for Treatment A
 - Day 1: predose (0) and 4 hours post dose
 - Days 9 and 10: Predose (0)
 - Days 11 and 12: A total of 12 samples starting from predose (0) to 24 hours post dose
- Rilpivirine for Treatment B
 - Day 1: predose (0) and 4 hours post dose
 - Day 12: predose (0) and 4 hours post dose
 - Days 20 and 21: predose (0)
 - Days 22 and 23: A total of 12 samples starting from predose (0) to 24 hours post dose
- Ketoconazole for Treatment A
 - Day 1: predose (0)
- Ketoconazole for Treatment B
 - Day 1: predose (0) and 4 hours post dose
 - Days 9 and 10: Predose (0)
 - Days 11 and 12: A total of 12 samples starting from predose (0) to 24 hours post dose. On Day 12, an additional time point was collected at 4 hours post dose for determination of ketoconazole concentration
 - Days 20 and 21: Predose (0)
 - Days 22 and 23: A total of 12 samples starting from Predose (0) to 24 hours post-dose

Analytical Methods – Bioanalysis:

The bioanalytical methods for rilpivirine and ketoconazole are acceptable. Two different laboratories performed the analysis: (b) (4) in The (b) (4) analyzed rilpivirine plasma concentrations and (b) (4) analyzed ketoconazole plasma concentrations.

Rilpivirine concentrations in plasma were determined using a validated LC-MS/MS method with a lower limit of quantification (LLOQ) of 1.0 ng/mL and the upper limit of quantification (ULQ) of 2000 ng/mL. A $1/x^2$ weighted least squares linear regression analysis was used for all calibration curves.

Ketoconazole concentrations in plasma were determined using a validated LC-MS/MS method with LLOQ of 50 ng/mL and ULQ of 5000 ng/mL. All standard samples were prepared using ketoconazole supplied by USP.

Table 1-Precision (% CV) and accuracy (% relative error) of calibration standards and QC samples for the bioanalysis of TMC278-C127 rilpivirine and ketoconazole plasma concentrations

	Rilpivirine		Ketoconazole	
	Calibration Stds	QCs	Calibration Stds	QCs
% CV	0.8 – 4.3	2.7 – 6.0	0.7 – 6.0	3.8 – 4.6
% Relative error	≤ 5.7	≤ 4.7	≤ 2.0	≤ 1.6
R	≥ 0.9979		≥ 0.9992	

Rilpivirine was unstable in daylight therefore, all samples, QC and calibration solutions were processed under a sodium lamp light source. Throughout the trial and during shipping, plasma samples were stored at <-18°C except during bioanalysis. The contract lab (b) (4) did not report long-term storage stability tests for rilpivirine in human plasma. A rilpivirine post preparative stability test for 120 hours was included in the TMC278-C127 bioanalytical report for rilpivirine that was conducted to evaluate whether the rilpivirine plasma samples degraded while awaiting bioanalysis (samples sat in the auto sampler for 120 hours under regular conditions). The (b) (4) rilpivirine method validation report included a rilpivirine post preparative stability test for 48 hours. Test results revealed no apparent deviations from the regular levels of rilpivirine, indicating that the plasma samples were stable during the period of bioanalysis. The long term stability data generated from Tibotec indicated that rilpivirine was stable for up to 1528 days at -20°C.

Long-term stability of ketoconazole in frozen human plasma was demonstrated at -20°C for up to 691 days. The actual storage time of the trial samples was 115 days from the first sample taken to the last date of sample analysis. Therefore, the ketoconazole plasma samples were considered stable.

Pharmacokinetic Analysis:

Plasma concentrations of rilpivirine and ketoconazole were analyzed by non-compartmental analysis model 200 (extravascular input, plasma data) using WinNonlin Professional® (version 4.1; Pharsight Corporation, Mountain View, CA) and/or Microsoft Excel® (version 2000; Microsoft, Redmond, Washington). Nominal sampling times were used for the calculation of all the pharmacokinetic parameters. In case major aberrations (>10.0% deviations from the scheduled time) occurred, actual sampling times were used in the PK analysis.

Statistical Analysis:

Statistical analysis for pharmacokinetic analysis was performed by (b) (4) using SAS® (version 9.1.3). Descriptive statistics were calculated for the plasma concentrations of rilpivirine and ketoconazole at each time point and for the derived PK parameters. Statistics included sample size (n), mean, standard deviation, percentage of coefficient of variation, geometric mean, median, minimum, and maximum.

The least square means (LSmeans) of the primary parameters of rilpivirine for each treatment group were estimated with a linear mixed effects model, controlling for treatment, sequence, and period as fixed effects and subject as random effect.

The LSmeans of the primary parameters of ketoconazole for each treatment were estimated with a linear fixed effects model, controlling for treatment as fixed effect and subject as a random effect. As the treatments of ketoconazole were not given in a randomized crossover design, controlling for sequence and period as fixed effects was not possible.

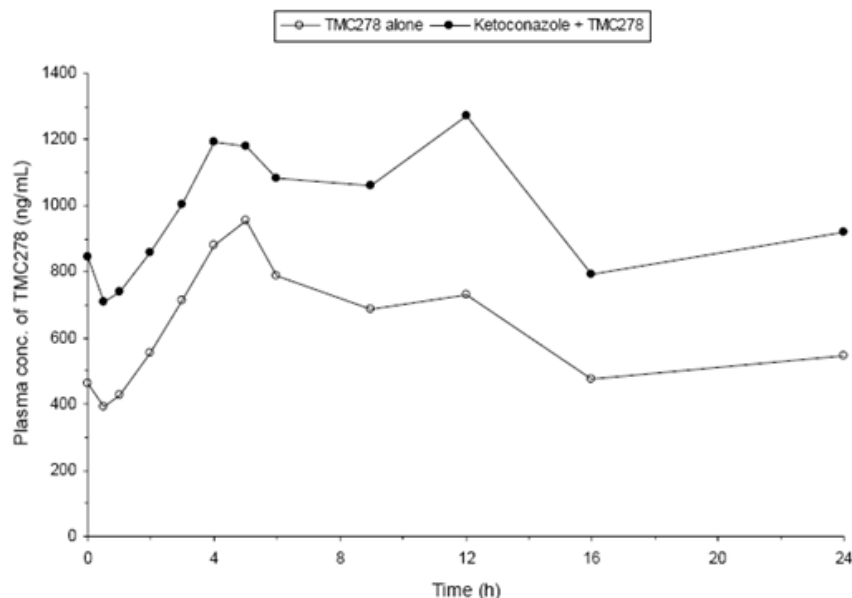
A 90% confidence interval was constructed around the difference between the LS means of test (Treatment B, ketoconazole + rilpivirine) and reference (Treatment A, rilpivirine or Treatment B, ketoconazole alone).

Pharmacokinetic results, rilpivirine:

Based on evaluating the individual rilpivirine C_{0h} concentrations, steady state concentrations were achieved by Day 11 (Treatment A) or Day 22 (Treatment B) in most subjects.

The steady state co-administration of rilpivirine and ketoconazole (Treatment B, Day 22) resulted in higher mean plasma concentrations of rilpivirine compared to administration of rilpivirine alone (Treatment A, Day 11). Visual inspection of the mean steady state concentration-time profile of rilpivirine revealed double peaks, the first higher peak occurred at approximately 4 to 5 hours and the second lower peak occurred around approximately 9 to 12 hours post dose. Co-administration with ketoconazole seemed to influence the rilpivirine plasma concentration-time profile. Without ketoconazole, the first rilpivirine peak was higher than the second, while with ketoconazole the second peak was higher than the first. The mean profile also showed higher rilpivirine plasma concentrations at 24 hours than at 16 hours post dose for both treatments. Refer to Figure 2 below.

Figure 2 Mean Steady State Plasma Concentration-Time Curves of TMC278 With and Without Co-administration of Ketoconazole



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A summary of the statistical analysis is listed below.

Table 2 Summary of the Statistical Analysis of the pharmacokinetic parameters of rilpivirine 150 mg once daily with and without co-administration of ketoconazole 400 mg once daily

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b	p-value		
	Treatment A, Day 11: TMC278 alone (reference)	Treatment B, Day 22: Ketoconazole + TMC278 (test)			Treatment	Period	Sequence
C _{0h} , ng/mL	439.1	791.9	180.3	161.3 - 201.6	<0.0001	0.2911	0.6216
C _{min} , ng/mL	360.3	633.2	175.7	156.9 - 196.7	<0.0001	0.5428	0.5638
C _{max} , ng/mL	993.9	1287	129.5	113.2 - 148.2	0.0049	0.8594	0.5908
AUC _{24h} , ng.h/mL	14676	21923	149.4	130.9 - 170.4	0.0001	0.6121	0.4971

^a n = 15 for Treatment A (reference) and n = 14 for Treatment B (test).

^b 90% confidence intervals.

Pharmacokinetic results, ketoconazole:

Based on evaluating the individual ketoconazole C_{0h} concentrations, steady state concentrations were achieved by Day 11 in most subjects.

The steady state co-administration of rilpivirine and ketoconazole (Treatment B, Day 22) resulted in lower mean plasma concentrations of ketoconazole compared to administration of ketoconazole alone (Treatment B, Day 11). For both treatments, there was no delay in absorption of ketoconazole and the t_{max} was 4 hours.

Mean values for all pharmacokinetic parameters, except fluctuation index, of ketoconazole were higher when ketoconazole was co-administered with rilpivirine (Treatment B, Day 22) compared to ketoconazole alone (Treatment B, Day 11). The fluctuation index with combination was 71.64% versus 103.9% with rilpivirine alone. A summary of the statistical analysis is listed below.

Table 3 Summary of the statistical analysis of the pharmacokinetic parameters of ketoconazole 400 mg once daily with and without co-administration of rilpivirine 150 mg once daily

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b	p-value
	Treatment B, Day 11 Ketoconazole alone (reference)	Treatment B, Day 22 Ketoconazole + TMC278 (test)			Treatment
C _{0h} , µg/mL	0.3516	0.1183	33.66	24.74 - 45.78	<0.0001
C _{min} , µg/mL	0.3346	0.1134	33.90	24.94 - 46.06	<0.0001
C _{max} , µg/mL	8.825	7.507	85.06	80.06 - 90.37	0.0004
AUC _{24h} , µg.h/mL	82.08	62.37	75.98	70.40 - 82.01	<0.0001

^a n = 14 for Treatment B, Day 11 (reference) and for Treatment B, Day 22 (test).

^b 90% confidence intervals.

Discussion and Conclusions:

The applicant failed to report the impact of ketoconazole on the half-life of rilpivirine and vice versa. In the presence of ketoconazole, the half-life of rilpivirine may be prolonged in some subjects, and the washout period did not prevent carryover concentrations of rilpivirine into the next treatment session. Five out of sixteen subjects in Treatment B (rilpivirine + ketoconazole) had quantifiable plasma concentrations of rilpivirine at predose and six out of sixteen subjects had in Treatment A (rilpivirine alone) had quantifiable plasma concentrations of rilpivirine at predose on Day 1. Fortunately, these carryover concentrations were too low (<5% of the individual's C_{max}) to have a relevant influence on rilpivirine exposure in Session 2, Treatment A. There were no subjects with quantifiable predose ketoconazole concentrations on Day 1.

Seven subjects had a treatment-emergent ECG abnormality, none of which was reported as an AE. Three subjects showed QT interval change (> 60 ms change during the trial) that was at least borderline and no new ECG abnormalities were reported during follow-up.

Based on trial results, no dose adjustment of rilpivirine is required when given concurrently with ketoconazole. At steady state, rilpivirine exposure (AUC_{24h}) increased by 49%. The applicant considers this increase in exposure safe and does not recommend any dose adjustment; especially because the dose tested in this trial is 6-fold higher than the recommended dose of 25 mg q.d. Even so, one question still remains: Could the inhibitory effect of ketoconazole be greater than 49% when rilpivirine is given at 25 mg q.d.? At higher doses, rilpivirine appears to induce the 3A enzymes (based on observed decreases in ketoconazole exposure). If the magnitude of 3A induction is dose related, then lower doses of rilpivirine could produce less induction and potentiate the inhibitory effects of ketoconazole.

In regard to the effect of rilpivirine on ketoconazole, it is unknown if the 24% decrease in ketoconazole exposures is clinically significant. A drug-drug interaction trial between ketoconazole and nevirapine showed marked decreases in ketoconazole exposures by as much as ~72% for AUC (Viramune[®] package insert, Boehringer-Ingelheim). This trial's applicant recommended avoiding concomitant administration of ketoconazole and nevirapine. Similarly, the package insert of etravirine reports a drug-drug interaction with ketoconazole but does not provide a magnitude of interaction. The applicant suggests adjusting the dose of ketoconazole depending on the other co-administered drugs (Intelence[®] package insert, Tibotec). It is unlikely that the applicant in this trial will recommend ketoconazole dose adjustments primarily because it appears that the 25 mg q.d. dose of rilpivirine may not induce 3A enzymes as much as the 150 mg q.d. dose.

TMC278-C136

1. Title

A Phase I, open-label drug-drug interaction trial to investigate the effect of TMC278 25 mg q.d. on the steady-state pharmacokinetics of ethinylestradiol and norethindrone, in healthy women

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at the (b) (4) from July 18, 2008 to December 2, 2008.

3. Objectives

The objective of the trial was to evaluate the effect at steady state of rilpivirine on ethinyl estradiol and norethindrone pharmacokinetics.

4. Trial Design

TMC278-C125 was a Phase I, open label clinical trial that enrolled female subjects between 18 and 45 years old that were either already receiving oral contraceptives containing ethinyl estradiol 35 µg ethinyl estradiol and 1 mg norethindrone or were receptive to switching to or initiating an oral contraceptive containing ethinyl estradiol 35 µg ethinyl estradiol and 1 mg norethindrone. The trial design is displayed in Figure 1.

Figure 1-TMC278-C136 trial design

Stabilizing treatment First OC cycle				Treatment A Second OC cycle				Treatment B Third OC cycle			
Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4
Day -28- -8			Day -7- -1	Day 1-21			Day 22-28	Day 29-49			Day 50-56
Treatment: Ovysmen® q.d.				Treatment: Ovysmen® q.d.				Treatment: Ovysmen® q.d.			
Tablets			Pill-free period	Tablets			Pill-free period	Tablets			Pill-free period
								Day 29-43			
								Treatment: TMC278 25 mg q.d.			
				Day 15: full PK profile of ethinylestradiol and norethindrone				Day 43: full PK profile of ethinylestradiol, norethindrone, and TMC278			

PK =pharmacokinetic

5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Use of ibuprofen was permitted up to three days before the start of the second oral contraceptive cycle. Afterwards, ibuprofen use was permitted up to 400 mg/day. Any over the counter medications were to be discontinued a minimum of 7 days before the second oral contraceptive cycle and any prescription medications were to be discontinued a minimum of fourteen days before the start of the second oral contraceptive cycle (with the exception of ibuprofen and oral contraceptives [Ovysmen[®]]). Use of any medication other than ibuprofen was not permitted up to fourteen days after the last administration of rilpivirine on Day 43. Use of herbal medicines or dietary supplements was not permitted from fourteen days before the second oral contraceptive cycle up to fourteen days after the last administration of rilpivirine on Day 43.

Use of liquids containing alcohol or quinine was not permitted from 24 hours before administration of the oral contraceptive on Day 1 until 24 hours after administration of the oral contraceptive on Day 15 and from 24 hours before administration of rilpivirine on Day 29 until 24 hours after administration of rilpivirine on Day 43. Intake of grapefruit and grapefruit juice was not permitted from 7 days before administration of the oral contraceptive on Day 1 until 24 hours after administration of the oral contraceptive on Day 15 and from seven days before administration of rilpivirine on Day 29 until 96 hours after administration of rilpivirine on Day 43.

In the event of an adverse event, the following medications were permitted:

- A) Rash or an allergic reaction: cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents (specific medications were not included in the trial report)
- B) Nausea: antiemetics (specific medications were not included in the trial report)
- C) Diarrhea: loperamide

6. Dosage and Administration

On Day 15 (Treatment A) and Day 43 (Treatment B), subjects fasted overnight for a minimum of 8 hours. After a standard meal in the morning, the oral contraceptive was administered alone or in combination with rilpivirine within 10 minutes after completion of the meal.

7. Rationale for Doses Used in the Trial

The rilpivirine dosage regimen that was administered to all subjects for Treatment B was 25 mg once daily. The trial report states that the oral contraceptive was administered with or without rilpivirine after consuming breakfast. The rilpivirine dosage regimen that was evaluated in the Phase 3 clinical trials and the recommended dosage regimen in the proposed prescribing information is 25 mg once daily with a meal.

The oral contraceptive dosage regimen (35 µg ethinyl estradiol and 1 mg norethindrone) is one of the available oral contraceptive dosage regimens that are used in oral contraceptive combinations.

8. Drugs Used in the Trial

Rilpivirine 25 mg tablets (formulation F006) were administered in the trial. These tablets were developed for use in the Phase 3 trials.

Ethinyl estradiol 35 µg and norethindrone 1 mg (Ovysmen[®]) tablets were administered in the trial. The Ovysmen oral contraceptive formulation is not commercially available in the United States but appears to be similar to other monophasic combination oral contraceptive products consisting of ethinyl estradiol 35 µg and norethindrone 1 mg that utilize 21 days of active treatment with or without seven days of placebo.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection for Pharmacokinetic Assessments

For Treatment A (ethinyl estradiol and norethindrone administered alone), blood samples for analysis of ethinyl estradiol and norethindrone concentrations were obtained on Days 15 and 16 at predose and up to 24 hours postdose. Predose blood samples for analysis of ethinyl estradiol and norethindrone concentrations were also obtained on Days 13 and 14.

For Treatment B, blood samples for analysis of rilpivirine, ethinyl estradiol and norethindrone concentrations were obtained on Days 43 and 44 at predose and up to 24 hours postdose. Predose blood samples for analysis of rilpivirine, ethinyl estradiol and norethindrone concentrations were also obtained on Days 41 and 42.

Sample Collection for Pharmacodynamic Assessments

Serum concentrations of progesterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were collected on Days 1 and 14 (Treatment A), and on Days 29 and 42 (Treatment B).

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a validated LC/MS/MS method by Johnson and Johnson Pharmaceutical Research and Development. The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. There was only one analytical run that was performed for the trial. For the TMC278-C136 trial, precision and accuracy were evaluated using the low (2.77 ng/mL), medium (55.3 ng/mL), and high (1570 ng/mL) QC samples. The corresponding rilpivirine intra-run accuracy values were -0.4% for the low QCs, 1.6% for the medium

QCs, and 0% for the high QCs, and the rilpivirine intra-run precision values were 3.6% for the low QCs, 1.3% for the medium QCs, and 3.3% for the high QCs. The submitted rilpivirine long term stability data of 1528 days covered the duration of long term rilpivirine stability data necessary for the TMC278-C136 trial.

The method and bioanalysis of ethinyl estradiol and norethindrone are acceptable. Plasma samples were analyzed for ethinyl estradiol and norethindrone concentrations using a validated LC/MS/MS method by (b) (4). The lower limit of quantification for ethinyl estradiol was 2 pg/mL and the upper limit of quantification was 500 pg/mL. There were no precision or accuracy issues identified for ethinyl estradiol based on the bioanalytical report. For the TMC278-C136 trial, precision and accuracy were evaluated using QC samples at the following concentrations: 5, 10, 30, 100 and 400 pg/mL. The corresponding ethinyl estradiol inter-run accuracy values were 2%, 6%, 5%, 6% and 5%, respectively, and the ethinyl estradiol inter-run precision values were 2.94%, 3.67%, 1.7%, 1.64%, and 1.54%, respectively. The lower limit of quantification for norethindrone was 50 pg/mL and the upper limit of quantification was 25000 pg/mL. There were no precision or accuracy issues identified for norethindrone based on the bioanalytical report. For the TMC278-C136 trial, precision and accuracy were evaluated using QC samples at the following concentrations: 125, 300, 1200, 4000 and 20000 pg/mL. The corresponding norethindrone inter-run accuracy values were 0%, 5%, 5%, 4%, and 2% and the norethindrone inter-run precision values were 6.37%, 4.04%, 2.21%, 2.55%, and 1.98%. The submitted ethinyl estradiol and norethindrone long term stability data of 160 days at -20°C covered the duration of long term ethinyl estradiol and norethindrone stability data necessary for the TMC278-C136 trial.

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate pharmacokinetic parameters, including C_{max} and $AUC_{(0-\tau)}$. If a major difference (> 10% deviation from the scheduled time) was observed, the actual sampling time was used instead of the scheduled sampling time. In addition, plasma concentrations for actual sampling times that deviated > 30% from the scheduled sampling time were excluded from the descriptive statistics.

Pharmacodynamic Assessments

For progesterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), descriptive statistics were calculated for the actual values, the change from predose values, and the change from predose values to mid-cycle values. In addition, descriptive statistics were derived for intra subject changes in predose values over the two cycles, changes from predose values to mid-cycle values, and the difference in change from predose values between Treatment B and Treatment A.

Statistical Analysis

Descriptive statistics were calculated for rilpivirine, ethinyl estradiol and norethindrone plasma concentrations and pharmacokinetic parameters, including the number of subjects

(n), mean, standard deviation, the coefficient of variation (CV%), geometric mean, median, and the minimum and maximum values.

For ethinyl estradiol and norethindrone, statistical analysis involved comparison of ethinyl estradiol and norethindrone log transformed pharmacokinetic parameters for Treatment B (test arm) compared to Treatment A (reference arm). C_{\min} (the minimum plasma concentrations between 0 hour and the dosing interval $[\tau]$), C_{\max} , and $AUC_{0-\tau}$ were evaluated. Using a linear mixed effects model, least squares means were calculated and 90% confidence intervals were derived based on the difference of the pharmacokinetic parameter's least squares means for the test and reference arms. Upper and lower limits for the 90% confidence interval of 80% and 125%, respectively were defined for comparison purposes.

An assessment was performed to determine if rilpivirine steady state concentrations were achieved by Day 43 (Treatment B) based on predose concentrations from Days 41, 42 and 43. For ethinyl estradiol and norethindrone, an assessment was performed to determine if steady state concentrations were achieved by Day 15 (Treatment A) based on predose concentrations from Days 13, 14, and 15 and by Day 43 (Treatment B) from Days 41, 42 and 43.

10. Results

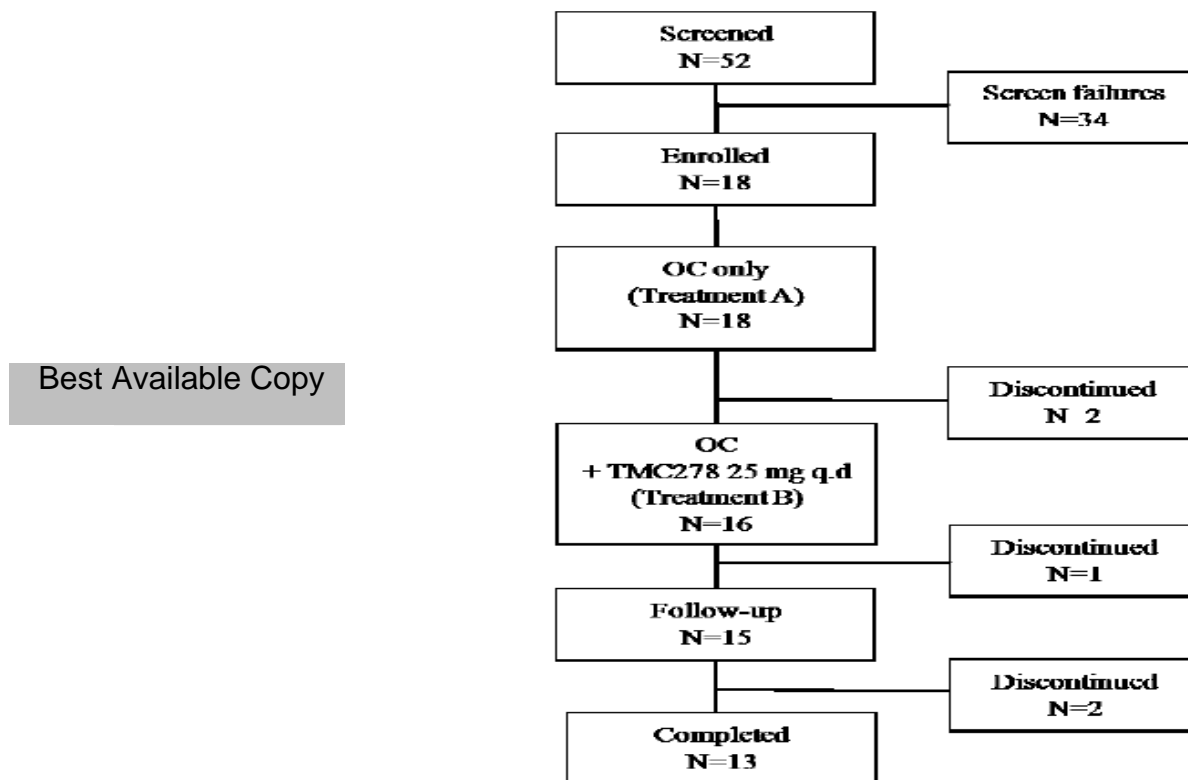
10.1 Subject Demographics and Disposition

Table 1-TMC278-C136 subject demographics

Parameter	All Subjects N=18
Age, years Median (range)	26.0 (20-38)
Height, cm Median (range)	166.0 (153-177)
Weight, kg Median (range)	69.5 (52-85)
BMI, kg/m ² Median (range)	24.56 (18.9-29.4)
Sex, n (%) Female	18 (100)
Race, n (%) American Indian or Alaska native / white Asian Black or African American White	1 (5.6) 2 (11.1) 3 (16.7) 12 (66.7)
Ethnicity Hispanic or Latino Not Hispanic or Latino	1 (5.6) 17 (94.4)
Smoking in last 3 months Yes No	4 (22.2) 14 (77.8)
Type of Smoker, n (%) Light	4 (22.2)

N = number of subjects, BMI = body mass index.

Figure 2-TMC278-C136 subject disposition



N = number of subjects, OC = oral contraceptives

10.2 Prior and Concomitant Medications

Nine subjects administered concurrent medications during the trial. The administered concurrent medications were unspecified antiseptics, clarithromycin, clotrimazole, unspecified cough and cold medications, ibuprofen, oxymetazoline, acetaminophen and a combination miconazole and hydrocortisone formulation (Brentan). Of these medications, clarithromycin and clotrimazole (both medications were administered concurrently with oral contraceptives only) could potentially alter CYP 3A metabolism. However, because only a limited number of subjects received medications that would be expected to alter CYP 3A metabolism (one subject received clarithromycin and one subject received clotrimazole), the impact on the trial results is anticipated to be minimal.

10.3 Pharmacokinetic and Statistical Analysis

The trial report states that there were subjects that had predose concentrations drawn postdose and predose samples that were drawn greater than 10 minutes postdose were excluded from the analysis.

Rilpivirine

Table 2-Pharmacokinetic parameters for rilpivirine 25 mg once daily with coadministration of ethinyl estradiol 35 µg and norethindrone 1 mg once daily
 $[\%FI=100 \times ([C_{\max}-C_{\min}]/C_{ss,av})]$

Pharmacokinetics of TMC278 (mean ±SD, t _{max} : median [range])	Treatment B: 1 mg norethindrone / 35 µg ethinylestradiol q.d. + 25 mg TMC278 q.d		
n	15		
Day 41			
C _{0h} , ng/mL ^a	113.6	±	55.08
Day 42			
C _{0h} , ng/mL	121.2	±	45.65
Day 43			
C _{0h} , ng/mL	121.2	±	51.70
C _{min} , ng/mL	89.49	±	38.04
C _{max} , ng/mL	172.1	±	37.91
t _{max} , h	4.0 (2.0-24.0)		
C _{24h} , ng/mL	126.2	±	52.95
AUC _{24h} , ng.h/mL	3028	±	941.4
C _{ss,av} , ng/mL	126.2	±	39.22
FI, %	71.24	±	23.65

^a n=14

Comparative data for rilpivirine without ethinyl estradiol and norethindrone coadministration was not obtained in the TMC278-C136 trial. However, based on a comparison of the C_{min}, C_{max}, and AUC_(0-24h) values obtained from the TMC278-C209 and TMC278-C215 trials that evaluated the 25 mg Phase 3 tablet formulation in HIV-1 infected subjects, higher rilpivirine exposure was observed in the TMC278-C136 trial. The mean Day 43 C_{min}, C_{max}, and AUC_(0-24h) values in the TMC278-C136 trial were 44%-77%, 24%-30%, and 42%-55% higher, respectively compared to the mean values from the TMC278-C209 and TMC278-C215 trials. In addition, the 25 mg Phase 3 tablet formulation was also administered to healthy subjects in two thorough QT trials (C151 and C152). The mean Day 43 C_{min} value was 2% higher and the C_{max} and AUC_(0-24h) values were 25% and 4% lower, respectively in the TMC278-C136 trial compared to the mean values from the TMC278-C151 trial. The mean Day 43 C_{min}, C_{max} and AUC_(0-24h) values were 6%, 30% and 9% lower, respectively in the TMC278-C136 trial compared to the mean values from the TMC278-C152 trial.

Based on evaluating the individual rilpivirine predose concentrations, steady state concentrations were achieved by Day 43 (Treatment B) in most subjects.

Ethinyl estradiol and norethindrone

Table 3-Ethinyl estradiol pharmacokinetic parameters (administered as ethinyl estradiol 35 µg and norethindrone 1 mg once daily and ethinyl estradiol 35 µg and norethindrone 1 mg once daily with rilpivirine 25 mg once daily coadministration)

Pharmacokinetics of ethinylestradiol (mean ± SD, t _{max} ; median [range])	Treatment A: 1 mg norethindrone / 35 µg ethinylestradiol q.d. (reference)	Treatment B: 1 mg norethindrone / 35 µg ethinylestradiol q.d. + 25 mg TMC278 q.d. (test)
Day 13/ Day 41		
n	16	14
C _{0h} , pg/mL	23.88 ± 6.144	28.86 ± 18.47
Day 14/ Day 42		
n	16	15
C _{0h} , pg/mL	24.29 ± 6.343	27.85 ± 10.38
Day 15/ Day 43		
n	17 ^a	15 ^b
C _{0h} , pg/mL	23.56 ± 10.06	23.83 ± 7.279
C _{min} , pg/mL	23.56 ± 10.06	23.77 ± 7.340
C _{max} , pg/mL	82.22 ± 26.74	94.65 ± 28.36
t _{max} , h	1.5 (1.0-6.0)	1.5 (1.0-4.0)
C _{24h} , pg/mL	27.38 ± 10.60	27.24 ± 8.396
AUC _{24h} , pg.h/mL	1015 ± 292.5	1093 ± 271.7
C _{ss,av} , pg/mL	42.28 ± 12.19	45.53 ± 11.32
FI, %	153.9 ± 39.05	149.6 ± 49.47

^a n=15 for AUC_{24h}, C_{ss,av} and FI

^b n=14 for C_{24h}, AUC_{24h}, C_{ss,av} and FI

Table 4-Statistical analysis for ethinyl estradiol (administered as ethinyl estradiol 35 µg and norethindrone 1 mg once daily and ethinyl estradiol 35 µg and norethindrone 1 mg once daily with rilpivirine 25 mg once daily coadministration)

Parameter	LSmeans ^a		LS means ratio, %	90% CI, % ^b
	Treatment A: 1 mg norethindrone / 35 µg ethinylestradiol q.d. (reference)	Treatment B: 1 mg norethindrone / 35 µg ethinylestradiol q.d. + 25 mg TMC278 q.d. (test)		
C _{min} , pg/mL	21.96	23.97	109.2	102.9 – 115.8
C _{max} , pg/mL	77.95	91.37	117.2	106.1 - 129.5
AUC _{24h} , pg.h/mL ^c	959.4	1096	114.2	109.8 - 118.8

^a n=17 for reference and n=15 for test

^b 90% confidence intervals.

^c n=15 for reference and n=14 for test

With rilpivirine coadministration (Treatment B), higher mean ethinyl estradiol C_{min}, C_{max}, and AUC_(0-24h) values were observed in subjects compared to Treatment A, when ethinyl estradiol and norethindrone were administered without rilpivirine. The 90% confidence

interval for ethinyl estradiol C_{min} and $AUC_{(0-24h)}$ were within 80%-125%. The 90% confidence interval for ethinyl estradiol C_{max} was not within 80%-125%.

Table 5-Norethindrone pharmacokinetic parameters (administered as ethinyl estradiol 35 µg and norethindrone 1 mg once daily and ethinyl estradiol 35 µg and norethindrone 1 mg once daily with rilpivirine 25 mg once daily coadministration)

Pharmacokinetics of norethindrone (mean ± SD, t_{max} : median [range])	Treatment A: 1 mg norethindrone / 35 µg ethinylestradiol q.d. (reference)	Treatment B: 1 mg norethindrone / 35 µg ethinylestradiol q.d. + 25 mg TMC278 q.d. (test)
Day 13/ Day 41		
n	16	14
C_{0h} , pg/mL	2382 ± 1269	2791 ± 2388
Day 14/ Day 42		
n	16	15
C_{0h} , pg/mL	2520 ± 1276	2499 ± 1453
Day 15/ Day 43		
n	17 ^a	15 ^b
C_{0h} , pg/mL	2268 ± 1226	2066 ± 1093
C_{min} , pg/mL	2268 ± 1226	2055 ± 1084
C_{max} , pg/mL	14520 ± 5120	13150 ± 4042
t_{max} , h	1.0 (0.5-6.0)	1.5 (1.0-4.0)
C_{24h} , pg/mL	3040 ± 1592	2377 ± 1253
AUC_{24h} , pg.h/mL	152800 ± 52350	128700 ± 40240
$C_{ss,av}$, pg/mL	6369 ± 2181	5365 ± 1676
FI, %	209.8 ± 54.35	217.7 ± 71.55

^a n=15 for AUC_{24h} , $C_{ss,av}$ and FI

^b n=14 for C_{24h} , AUC_{24h} , $C_{ss,av}$ and FI

Table 6-Statistical analysis for norethindrone (administered as ethinyl estradiol 35 µg and norethindrone 1 mg once daily and ethinyl estradiol 35 µg and norethindrone 1 mg once daily with rilpivirine 25 mg once daily coadministration)

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b
	Treatment A: 1 mg norethindrone / 35 µg ethinylestradiol q.d. (reference)	Treatment B: 1 mg norethindrone / 35 µg ethinylestradiol q.d. + 25 mg TMC278 q.d. (test)		
C_{min} , pg/mL	1894	1870	98.72	90.04 – 108.2
C_{max} , pg/mL	13710	12900	94.10	83.37 - 106.2
AUC_{24h} , pg.h/mL	142800	126900	88.92	83.77 - 94.38

^a n=17 for reference and n=15 for test

^b 90% confidence intervals.

^c n=15 for reference and n=14 for test

With rilpivirine coadministration (Treatment B), minimal changes were observed with norethindrone C_{min} and C_{max} , and a lower mean norethindrone $AUC_{(0-24h)}$ value was

observed in subjects compared to Treatment A, when ethinyl estradiol and norethindrone were administered without rilpivirine. The 90% confidence interval for norethindrone C_{min} , C_{max} , and $AUC_{(0-24h)}$ were within 80%-125%.

Based on evaluating the individual ethinyl estradiol and norethindrone predose concentrations, steady state concentrations were achieved by Day 15 (Treatment A) and by Day 43 (Treatment B) in most subjects.

10.4 Pharmacodynamic Analysis

Minimal changes were observed in follicle stimulating hormone (FSH), luteinizing hormone (LH) and progesterone when rilpivirine was coadministered with ethinyl estradiol and norethindrone (see Table 6 below).

Table 7-Assessment of follicle stimulating hormone (FSH), luteinizing hormone (LH) and progesterone values for Treatment A and Treatment B

Treatment Period	Time Point	FSH (IU/L)	LH (IU/L)	Progesterone (nmol/L)
Treatment A: OC q.d. alone	n Day 1	15 6.50 (4.6, 15.0)	15 4.30 (0.4, 9.7)	15 1.50 (0.4, 4.1)
	n Day 14	18 2.00 (0.3, 5.9)	18 1.35 (0.0, 9.2)	18 1.70 (0.5, 4.1)
	n Day 14 change from reference	15 -5.20 (-13.9, -1.1)	15 -2.90 (-6.8, 0.5)	15 0.10 (-0.3, 0.4)
	n Day 29	16 6.65 (1.3, 12.5)	16 3.00 (1.4, 14.1)	16 1.70 (0.4, 3.1)
Treatment B: OC q.d. + TMC278 25 mg q.d.	n Day 42	15 1.60 (0.5, 6.4)	15 1.40 (0.0, 8.1)	15 1.80 (0.4, 3.9)
	n Day 42 change from reference	15 -4.50 (-11.7, -0.3)	15 -1.90 (-6.6, 4.3)	15 0.00 (-0.9, 1.4)

FSH = follicle stimulating hormone, LH = luteinizing hormone, N = number of subjects

Note: All samples were taken at 2 hours predose

For the OC alone treatment period, the reference time point was the Day 1 predose measurement. For the Ovysmen® and TMC278 treatment period, the reference time point was the Day 29 predose measurement.

10.5 Safety Issues

No deaths or other serious adverse events were reported for the trial. No grade 3 or grade 4 adverse events were reported for the trial. The most common adverse events that were reported included headache in a total of ten subjects and nasopharyngitis that was reported in eight subjects.

Table 8-Adverse event incidence categorized by system organ class and preferred term

<i>System Organ Class Preferred Term n (%)</i>	<i>Treatment A: OC q.d. alone N=18</i>	<i>Treatment B: OC q.d. + TMC278 25 mg q.d. N=16</i>	<i>Follow-up N=15</i>
<i>Any Adverse Event</i>	14 (77.8)	12 (75.0)	3 (20.0)
<i>Ear and Labyrinth Disorders</i>	0	1 (6.3)	0
Vestibular ataxia	0	1 (6.3)	0
<i>Eye Disorders</i>	0	1 (6.3)	0
Vision blurred	0	1 (6.3)	0
<i>Gastrointestinal Disorders</i>	1 (5.6)	7 (43.8)	0
Diarrhea	0	3 (18.8)	0
Nausea	1 (5.6)	2 (12.5)	0
Toothache	0	1 (6.3)	0
Vomiting	0	3 (18.8)	0
<i>General Disorders and Administration Site Conditions</i>	1 (5.6)	2 (12.5)	0
Fatigue	0	2 (12.5)	0
Pyrexia	1 (5.6)	0	0
<i>Infections and Infestations</i>	6 (33.3)	2 (12.5)	1 (6.7)
Nasopharyngitis	5 (27.8)	2 (12.5)	1 (6.7)
Skin infection	1 (5.6)	0	0
<i>Metabolism and Nutrition Disorders</i>	1 (5.6)	0	0
Food craving	1 (5.6)	0	0
<i>Musculoskeletal, Connective Tissue and Bone Disorders</i>	2 (11.1)	0	0
Back pain	1 (5.6)	0	0
Myalgia	1 (5.6)	0	0
<i>Nervous System Disorders</i>	6 (33.3)	7 (43.8)	0
Dizziness	2 (11.1)	0	0
Headache	4 (22.2)	6 (37.5)	0
Migraine	1 (5.6)	0	0
Paresthesia	0	2 (12.5)	0
<i>Psychiatric Disorders</i>	2 (11.1)	2 (12.5)	0
Depressed mood	1 (5.6)	0	0
Insomnia	1 (5.6)	0	0
Panic attack	0	1 (6.3)	0
Sleep disorder	0	1 (6.3)	0
<i>Renal and Urinary Disorders</i>	0	1 (6.3)	0
Micturition urgency	0	1 (6.3)	0
<i>Reproductive System and Breast Disorders</i>	2 (11.1)	0	1 (6.7)
Breast pain	1 (5.6)	0	0
Dysmenorrhea	1 (5.6)	0	0
Menstruation delayed	0	0	1 (6.7)
<i>Respiratory, Thoracic and Mediastinal Disorders</i>	0	0	1 (6.7)
Rhinorrhea	0	0	1 (6.7)

n = number of subjects with 1 or more events, N = number of subjects

Table 9-Adverse event incidence at a minimum possibly related to either rilpivirine or oral contraceptives categorized by system organ class and preferred term

System Organ Class Preferred Term n (%)	TMC278		OC	
	Treatment A: OC q.d. alone (N=18)	Treatment B: OC q.d. + TMC278 25 mg q.d. (N=16)	Treatment A: OC q.d. alone (N=18)	Treatment B: OC q.d. + TMC278 25 mg q.d. (N=16)
<i>Any AE at least possibly related</i>	4 (22.2) ^a	9 (56.3)	7 (38.9)	9 (56.3)
<i>Ear and Labyrinth Disorders</i>	0	1 (6.3)	0	1 (6.3)
Vestibular ataxia	0	1 (6.3)	0	1 (6.3)
<i>Eye Disorders</i>	0	1 (6.3)	0	1 (6.3)
Vision blurred	0	1 (6.3)	0	1 (6.3)
<i>Gastrointestinal Disorders</i>	1 (5.6) ^a	6 (37.5)	1 (5.6)	6 (37.5)
Diarrhea	0	3 (18.8)	0	3 (18.8)
Nausea	1 (5.6)	2 (12.5)	1 (5.6)	2 (12.5)
Vomiting	0	3 (18.8)	0	3 (18.8)
<i>General Disorders and Administration Site Conditions</i>	0	2 (12.5)	0	2 (12.5)
Fatigue	0	2 (12.5)	0	2 (12.5)
<i>Metabolism and Nutrition Disorders</i>	0	0	1 (5.6)	0
Food craving	0	0	1 (5.6)	0
<i>Musculoskeletal and Connective Tissue Disorders</i>	0	0	1 (5.6)	0
Myalgia	0	0	1 (5.6)	0
<i>Nervous System Disorders</i>	2 (11.1) ^a	7 (43.8)	5 (27.8)	6 (37.5)
Dizziness	0	0	1 (5.6)	0
Headache	2 (11.1) ^a	6 (37.5)	4 (22.2)	5 (31.3)
Paresthesia	0	2 (12.5)	0	2 (12.5)
<i>Psychiatric Disorders</i>	1 (5.6) ^a	2 (12.5)	1 (5.6)	1 (6.3)
Depressed mood	1 (5.6) ^a	0	1 (5.6)	0
Panic attack	0	1 (6.3)	0	1 (6.3)
Sleep disorder	0	1 (6.3)	0	0
<i>Renal and Urinary Disorders</i>	0	1 (6.3)	0	1 (6.3)
Micturition urgency	0	1 (6.3)	0	1 (6.3)
<i>Reproductive System and Breast Disorders</i>	0	0	1 (5.6)	0
Breast pain	0	0	1 (5.6)	0

^a The start date was equal to the Day 29 date but no time was recorded for these events and therefore they were assigned to both Treatment A (OC alone) and Treatment B (OC + TMC278).

n = number of subjects with 1 or more events, N = number of subjects

11. Discussion and Conclusions

Based on the results from the drug-drug interaction trial, the following conclusions can be made:

- With rilpivirine coadministration, higher ethinyl estradiol exposure was observed. The mean ethinyl estradiol C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were increased by 9%, 17%, and 14%, respectively. The 90% confidence interval for ethinyl estradiol C_{min} and $AUC_{(0-24h)}$ was within 80%-125%. The 90% confidence interval for ethinyl estradiol C_{max} was not within 80%-125%.
- With rilpivirine coadministration, minimal changes were observed with norethindrone C_{min} and C_{max} and a lower mean norethindrone $AUC_{(0-24h)}$ value was observed. The mean norethindrone C_{max} , and $AUC_{(0-24h)}$ values were

decreased by 1%, 6%, and 11%, respectively. The 90% confidence interval for norethindrone C_{min} , C_{max} , and $AUC_{(0-24h)}$ was within 80%-125%.

- When coadministered with ethinyl estradiol and norethindrone, higher rilpivirine exposure was observed in the TMC278-C136 trial compared to the observed rilpivirine exposure in the TMC278-C209 and TMC278-C215 trials in HIV-1 infected subjects.
- In healthy subjects, when coadministered with ethinyl estradiol and norethindrone, lower rilpivirine exposure (with the exception of C_{min}) was observed in the TMC278-C136 trial compared to the observed rilpivirine exposure in the TMC278-C151 trial and lower exposure was observed in the TMC278-C136 trial compared to the observed rilpivirine exposure in the TMC278-C152 trial.
- Minimal changes were observed in FSH, LH and progesterone when rilpivirine was coadministered with ethinyl estradiol and norethindrone

When coadministered with ethinyl estradiol, with a 25 mg once daily rilpivirine dosage regimen, the increase in ethinyl estradiol exposure and the decrease in norethindrone exposure may be potentially explained by rilpivirine CYP 3A inhibition and induction, respectively. However, the changes in ethinyl estradiol and norethindrone exposure with rilpivirine coadministration do not appear to be clinically relevant based on the results from the trial and therefore no recommendation to use additional or alternative oral contraceptive therapies is necessary.

TMC278-C139

1. Title

A Phase I, open label trial in 16 healthy subjects to investigate the effect of single-dose and steady-state TMC278 on the pharmacokinetics of chlorzoxazone

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at [REDACTED] (b) (4) from September 19, 2005 to March 17, 2006.

3. Objectives

The objectives of the trial were to evaluate the effect after a single dose and at steady state of rilpivirine on chlorzoxazone and 6-hydroxy-chlorzoxazone single dose pharmacokinetics and the effect of a single dose of chlorzoxazone on rilpivirine steady state pharmacokinetics.

4. Trial Design

TMC278-C139 was a Phase I, open label, clinical trial that enrolled male and female subjects between 18 and 55 years old. The trial design is displayed in Figure 1. A subtrial that enrolled 9 additional subjects were included as part of the overall trial because of the high discontinuation rate in the main trial that was caused by a hurricane.

Figure 1-TMC278-C139 trial design

<u>Treatment (main protocol):</u> A single dose of 500 mg chlorzoxazone on Days 1, 4, and 15 + TMC278 150 mg q.d. on Days 4-15 <u>Treatment (substudy protocol):</u> A single dose of 500 mg chlorzoxazone on Days 1, 4, and 19 + TMC278 150 mg q.d. on Days 4-19
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Note: Due to extreme weather conditions (hurricane) some subjects under the main protocol also received 4 additional days of TMC278 dosing and were therefore dosed on Days 1, 4, and 19.

5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Use of ibuprofen was permitted up to three days before the first administration of trial medication. Afterwards, ibuprofen use was permitted up to 400 mg/day until the end of each session or treatment arm. Any over the counter medications were to be discontinued a minimum of seven days before the first administration of trial medication and all prescription medications were to be discontinued a minimum of fourteen days before the first administration of trial medication. Use of herbal medicines or dietary supplements was not permitted from fourteen days before the first administration of trial medication and up to fourteen days after the last administration of trial medication.

Use of liquids containing alcohol or quinine was not permitted from 24 hours before the first administration of trial medication until Day 16 (for subjects in the main trial) or Day 20 (for subjects in the subtrial). Intake of grapefruit and grapefruit juice was not permitted from 7 days before the first administration of trial medication until Day 16 (for subjects in the main trial) or Day 20 (for subjects in the subtrial).

In the event of an adverse event, the following medications were permitted:

- A) Rash or an allergic reaction: cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents (specific medications were not included in the trial report)
- B) Nausea: antiemetics (specific medications were not included in the trial report)
- C) Diarrhea: loperamide

6. Dosage and Administration

On Days 1, 4, 5, 12, 13, 14 and 15 for subjects in the main trial and on Days 1, 4, 5, 16, 17, 18, and 19 for subjects in the subtrial, a standard meal was administered in the morning. Rilpivirine was administered within 10 minutes after completion of the meal. Chlorzoxazone was administered two hours after breakfast (Day 1) or two hours after breakfast and administration of rilpivirine (Days 4 and 15 for subjects in the main trial and Days 4 and 19 for subjects in the subtrial). Dosing in the main trial was extended to Day 19 for seven subjects in the main trial because of the hurricane. The rationale for spacing out administration of chlorzoxazone and rilpivirine was to ensure that there was sufficient exposure to rilpivirine prior to chlorzoxazone administration.

7. Rationale for Doses Used in the Trial

The rilpivirine dosage regimen that was administered to all subjects was 150 mg once daily. In contrast, the rilpivirine dosage regimen that was evaluated in the Phase 3 clinical trials and the recommended dosage regimen in the proposed prescribing information is 25 mg once daily with a meal. Across the dose range of 25 mg to 150 mg, increases in rilpivirine exposure were approximately dose proportional. However, chlorzoxazone is not anticipated to cause clinically significant changes in rilpivirine exposure.

The chlorzoxazone dosage regimen administered in the trial (a single dose of 500 mg) is within the recommended range of dosage regimens for treatment of musculoskeletal disorders (250 mg to 750 mg three to four times a day).

8. Drugs Used in the Trial

Rilpivirine 50 mg tablets (formulation F003) and 100 mg tablets (formulation F002) were administered in the trial. Both of these tablets were Phase 2b formulations that were used in the Phase 1 or 2 trials.

Chlorzoxazone (Parafon Forte[®] DSC) 500 mg caplets were administered in the trial.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Blood samples for analysis of rilpivirine plasma concentrations were obtained on Days 4 and 5, Days 18 and 19, and Days 19 and 20 at predose and up to 24 hours postdose. The Day 18 24 hour concentration and the Day 19 predose concentration were derived from the same plasma sample. Predose rilpivirine blood samples were also obtained either on Days 12 and 13 or Days 16 and 17.

Blood samples for analysis of chlorzoxazone concentrations were obtained on Days 1, 4 and 19 at predose and up to 14 hours postdose.

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a validated LC/MS/MS method by (b) (4). The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the TMC278-C139 trial, precision and accuracy were evaluated using the low (3 ng/mL), medium (50 ng/mL), and high (1600 ng/mL) QC samples. The corresponding rilpivirine inter-run accuracy values were -0.8% for the low QCs, -1.3% for the medium QCs, and -3% for the high QCs, and the rilpivirine inter-run precision values were 9% for the low QCs, 5.3% for the medium QCs, and 7.1% for the high QCs. The submitted rilpivirine long term stability data of 1528 days at -20°C covered the duration of long term rilpivirine stability data necessary for the TMC278-C139 trial.

The method and bioanalysis of chlorzoxazone and 6-hydroxychlorzoxazone is acceptable. Plasma samples were analyzed for chlorzoxazone concentrations using a validated LC/MS/MS method by (b) (4). In response to a request for information, the applicant stated that the 6-hydroxychlorzoxazone method was a “qualified” method. The applicant did not provide specific information regarding the difference between a qualified method and a validated method. The lower limit of quantification for chlorzoxazone was 0.005 µg/mL and the upper limit of quantification was 10 µg/mL. There were no precision or

accuracy issues identified for chlorzoxazone based on the bioanalytical report. For the TMC278-C139 trial, precision and accuracy were evaluated using plasma QC samples at the following concentrations: 0.01, 0.02, 2, and 8 µg/mL. (For the method validation, plasma QC samples at the following concentrations were evaluated: 0.01, 0.02, 0.4, and 8 µg/mL). The corresponding chlorzoxazone inter-run accuracy values for subjects in the main trial were 0%, -0.5%, 3%, and -4.2%, respectively, and the chlorzoxazone inter-run precision values were 8.62%, 5.08%, 5.54%, and 4.47%, respectively. The corresponding chlorzoxazone inter-run accuracy values for subjects in the subtrial were 2%, 1%, 2%, and -2.8%, respectively, and the chlorzoxazone inter-run precision values were 7.55%, 5.46%, 3.70%, and 6.48%, respectively. The lower limit of quantification for 6-hydroxychlorzoxazone was 0.005 µg/mL and the upper limit of quantification was 0.5 µg/mL. For 6-hydroxychlorzoxazone, there were multiple batches where the majority of QCs samples failed at one concentration level based on the bioanalytical report.

(b) (4)

The submitted chlorzoxazone and 6-hydroxychlorzoxazone long term stability data in plasma using sodium heparin as an anticoagulant of 405 days at -70°C covered the duration of long term chlorzoxazone and 6-hydroxychlorzoxazone stability data necessary for the TMC278-C139 trial (the specific storage temperature at the bioanalytical laboratory and at the clinical trial site requires further follow up).

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate plasma pharmacokinetic parameters, including C_{min} , C_{max} , and $AUC_{(0-\tau)}$ for rilpivirine, and C_{max} , $AUC_{(0-last)}$ and $AUC_{(0-\infty)}$ for chlorzoxazone and 6-hydroxychlorzoxazone. If a major difference (> 10.00% deviation from the scheduled time) was observed, the actual sampling time was used instead of the scheduled sampling time.

Statistical Analysis

Descriptive statistics were calculated for rilpivirine, chlorzoxazone, and 6-hydroxychlorzoxazone plasma concentrations and pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), geometric mean, median, and the minimum and maximum values.

Statistical analysis involved comparison of plasma rilpivirine log transformed pharmacokinetic parameters for rilpivirine when administered with chlorzoxazone on Day 19 (test arm) compared to rilpivirine administration by itself on Day 18 (reference arm). Initially, Day 15 (test arm) instead of Day 19 versus Day 14 (reference arm) was to be compared for subjects in the main trial, however all seven subjects who completed the main trial had rilpivirine dosing extended by four days. For chlorzoxazone and 6-hydroxychlorzoxazone, statistical analysis involved comparison of chlorzoxazone when administered with rilpivirine (test arm) on Days 4 and 19 compared to chlorzoxazone administration by itself (reference arm) on Day 1 both after a single dose of rilpivirine and with multiple dosing of rilpivirine with a single dose of chlorzoxazone. Initially, Day

15 (test arm) instead of Day 19 versus Day 1 (reference arm) was to be compared for subjects in the main trial, however all seven subjects who completed the main trial had rilpivirine dosing extended by 4 days. C_{0h} (the predose plasma concentrations), C_{min} (the minimum plasma concentrations between 0 hour and the dosing interval $[\tau]$), C_{max} , and $AUC_{0-\tau}$ were evaluated for rilpivirine, and C_{max} , AUC_{0-last} and $AUC_{0-\infty}$ were evaluated for chlorzoxazone and 6-hydroxychlorzoxazone. Using a linear mixed effects model, least squares means were calculated and 90% confidence intervals were derived based on the difference of the pharmacokinetic parameter's least squares means for the test and reference arms. The 90% confidence intervals and the difference of the pharmacokinetic parameter's least squares means were transformed back to the original scale.

An assessment was performed to determine if rilpivirine steady state concentrations were achieved by Day 19. For subjects in the main trial, predose concentrations on Days 12, Day 13, Day 18, and Day 19 were compared and for subjects in the subtrial, predose concentrations on Days 16, Day 17, Day 18, and Day 19 were compared.

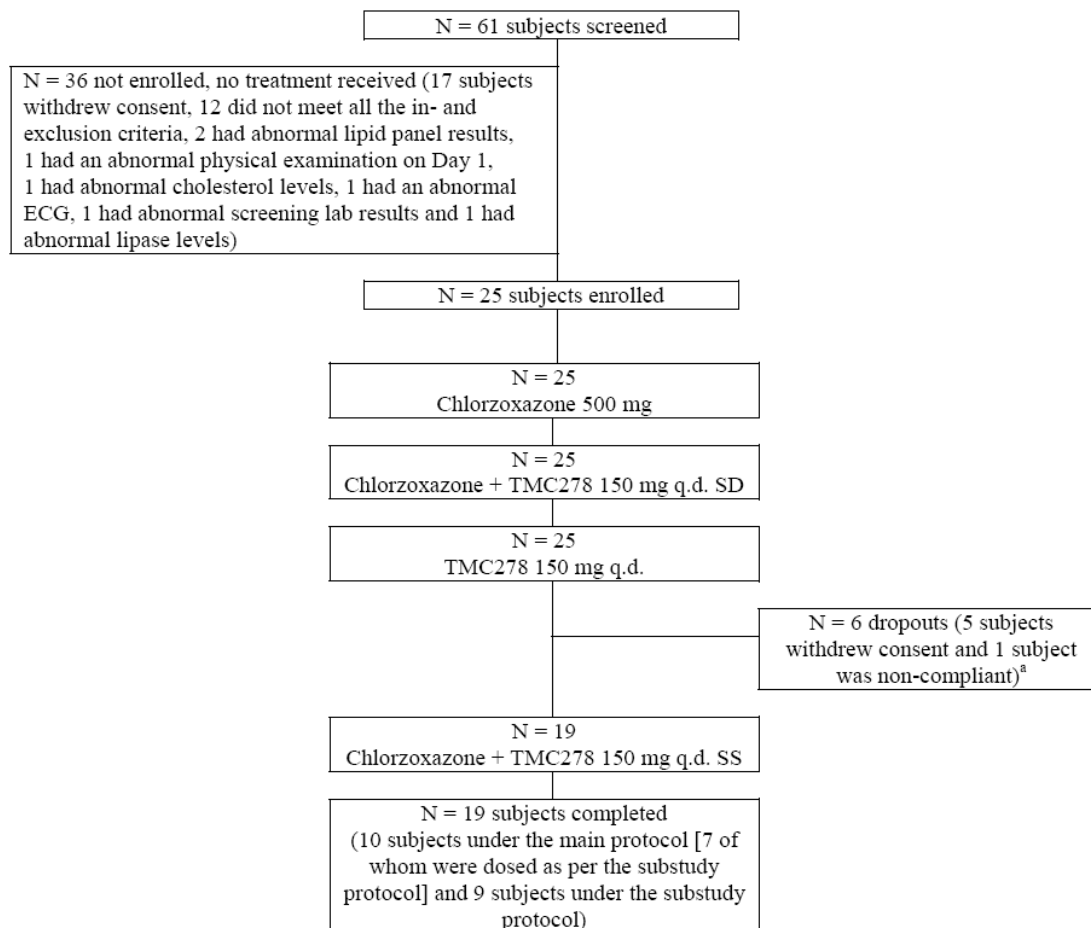
10. Results

10.1 Subject Demographics and Disposition

Table 1-TMC278-C139 subject demographics

Parameter	Main Protocol N = 16	Substudy Protocol N = 9	All Subjects (Main Protocol + Substudy Protocol Combined) N = 25
Age, years Median (range)	43.0 (23 - 53)	49.0 (31 - 55)	45.0 (23 - 55)
Height, cm Median (range)	165.0 (155 - 190)	165.0 (151 - 177)	165.0 (151 - 190)
Weight, kg Median (range)	73.5 (58 - 96)	74.0 (55 - 81)	74.0 (55 - 96)
BMI, kg/m ² Median (range)	26.1 (19 - 30)	25.6 (23 - 29)	25.6 (19 - 30)
Sex, n (%)			
Male	8 (50.0)	5 (55.6)	13 (52.0)
Female	8 (50.0)	4 (44.4)	12 (48.0)
Race, n (%)			
Black	2 (12.5)	0	2 (8.0)
Caucasian	1 (6.3)	0	1 (4.0)
Hispanic	13 (81.3)	9 (100.0)	22 (88.0)

Figure 2-TMC278-C139 subject disposition



N = Number of subjects per treatment phase; SD = single dose; SS = steady-state.

^a High number of subjects withdrawing consent occurred during the period of extreme weather (hurricane) at the investigational site

10.2 Prior and Concomitant Medications

Nine subjects administered concurrent medications during the trial. The medications that were administered included acyclovir, gatifloxacin, Caladryl[®], CoTylenol, Pedialyte[®], tocopherol, Neosporin[®], hydrogen peroxide, and irofol C. These medications would not be expected to alter CYP 3A or CYP 2E1 metabolism.

10.3 Pharmacokinetic and Statistical Analysis

There were no subjects with quantifiable predose rilpivirine concentrations on Day 4.

There was one subject with a quantifiable predose chlorzoxazone drug concentration that was less than 5% of the subject's rilpivirine C_{max} on Day 1. It is unclear why a quantifiable predose chlorzoxazone drug concentration was observed prior to initiation of dosing for the trial.

Subjects enrolled in the subtrial had pharmacokinetic parameters derived for rilpivirine, chlorzoxazone and 6-hydroxychlorzoxazone but statistical analyses were not performed. In the trial report, the applicant did not present all the pharmacokinetic data for subjects in the subtrial and the results below pertain to subjects in the main trial only (with the exception of the discussion of rilpivirine predose concentrations).

Rilpivirine

Table 2-Pharmacokinetic parameters for rilpivirine 150 mg once daily and with single doses of chlorzoxazone 500 mg administered 2 hours after rilpivirine 150 mg once daily for subjects in the main trial [%FI=100 x $([C_{\max}-C_{\min}]/C_{ss,av})$]

Pharmacokinetics of TMC278 (mean \pm SD, t_{max} : median [range])	TMC278 (Single Dose) + Chlorzoxazone (Day 4)	TMC278 (Multiple Dose) alone (reference) (Day 18)	TMC278 (Multiple Dose) + Chlorzoxazone (test) (Day 19)
n	16	16	16
C_{0h} , ng/mL	-	403.1 \pm 154.1	505.6 \pm 188.4
C_{min} , ng/mL	-	349.8 \pm 138.0	401.5 \pm 121.2
C_{max} , ng/mL	579.6 \pm 219.6	946.4 \pm 325.0	1107 \pm 329.9
t_{max} , h	4.0 [3.0 - 9.0]	4.0 [3.0 - 5.0]	4.5 [4.0 - 5.0]
AUC _{24h} , ng.h/mL	6026 \pm 2409	13010 \pm 4757	15950 \pm 4303
$C_{ss,av}$, ng/mL	-	542.0 \pm 198.0	664.7 \pm 179.3
FI, %	-	112.2 \pm 24.42	104.7 \pm 19.75

Table 3-Statistical analysis for rilpivirine 150 mg once daily and single doses of chlorzoxazone 500 mg administered 2 hours after rilpivirine 150 mg once daily for subjects in the main trial

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Parameter	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b
	TMC278 (Multiple Dose) alone (reference) (Day 18)	TMC278 (Multiple Dose) + Chlorzoxazone (test) (Day 19)		
C_{0h} , ng/mL	371.2	464.1	125.0	115.4 - 135.4
C_{min} , ng/mL	318.6	375.9	118.0	108.5 - 128.3
C_{max} , ng/mL	877.8	1028	117.2	107.8 - 127.4
AUC _{24h} , ng.h/mL	11990	15010	125.2	116.4 - 134.7

^a n=16 for TMC278 alone (reference) and for TMC278 + chlorzoxazone (test).

^b 90% confidence intervals.

Based on the statistical analysis after a single dose of chlorzoxazone 500 mg administered 2 hours after rilpivirine 150 mg once daily for subjects in the main trial, the mean rilpivirine C_{0h} , C_{min} , C_{max} , and AUC_(0-24h) values were increased compared to rilpivirine when administered by itself. The 90% confidence interval for rilpivirine C_{0h} , C_{min} , C_{max} , and AUC_(0-24h) were not within 80%-125%.

Based on evaluating the individual rilpivirine predose concentrations, steady state concentrations were achieved by Day 19 for most subjects in the subtrial. For subjects in the main trial, an increase in C_{0h} from Day 18 to Day 19 was observed in all subjects. The specific reasons for the increase are unknown and do not appear to be attributed to a drug-drug interaction because an increase in rilpivirine predose concentrations was not observed from Day 18 to Day 19 for subjects in the subtrial. However, it appears that steady state was achieved for most subjects in the main trial.

Chlorzoxazone and 6-hydroxychlorzoxazone

Table 4-Chlorzoxazone pharmacokinetic parameters (administered as single doses of chlorzoxazone 500 mg and single doses of chlorzoxazone 500 mg administered 2 hours after rilpivirine 150 mg once daily for subjects in the main trial)

Pharmacokinetics of chlorzoxazone (mean \pm SD, t_{max} : median [range])	Chlorzoxazone alone (reference) (Day 1)	Chlorzoxazone + TMC278 (Single Dose) (test 1) (Day 4)	Chlorzoxazone + TMC278 (Multiple Dose) (test 2) (Day 19)
n	16	16	16
C_{max} , $\mu\text{g/mL}$	15.19 \pm 3.683	14.89 \pm 4.789	14.70 \pm 2.775
t_{max} , h	1.5 [0.5 - 3.0]	1.5 [1.0 - 3.0]	1.5 [0.5 - 3.0]
AUC_{last} , $\mu\text{g.h/mL}$	36.29 \pm 9.404	35.19 \pm 9.372	36.87 \pm 6.381
AUC_{∞} , $\mu\text{g.h/mL}$	36.31 \pm 9.410	35.21 \pm 9.369	36.89 \pm 6.390
$t_{1/2term}$, h	1.099 \pm 0.1525	1.135 \pm 0.2192	1.120 \pm 0.1980

Table 5-Statistical analysis for chlorzoxazone (administered as single doses of chlorzoxazone 500 mg and chlorzoxazone 500 mg administered 2 hours after a single dose of rilpivirine 150 mg once daily)

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Parameter	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b
	Chlorzoxazone alone (reference) (Day 1)	Chlorzoxazone + TMC278 (Single Dose) (test) (Day 4)		
C_{max} , $\mu\text{g/mL}$	14.78	14.14	95.69	82.01 - 111.7
AUC_{last} , $\mu\text{g.h/mL}$	35.22	34.00	96.53	87.49 - 106.5
AUC_{∞} , $\mu\text{g.h/mL}$	35.24	34.02	96.55	87.51 - 106.5

^a n=16 for chlorzoxazone alone (reference) and for chlorzoxazone + TMC278 (test).

^b 90% confidence intervals.

Table 6-Statistical analysis for chlorzoxazone (administered as single doses of chlorzoxazone 500 mg and chlorzoxazone 500 mg administered 2 hours after rilpivirine 150 mg once daily)

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b
	Chlorzoxazone alone (reference) (Day 1)	Chlorzoxazone + TMC278 (Multiple Dose) (test) (Day 19)		
C _{max} , µg/mL	14.78	14.45	97.81	84.67 - 113.0
AUC _{last} , µg.h/mL	35.22	36.36	103.2	94.59 - 112.7
AUC _∞ , µg.h/mL	35.24	36.38	103.3	94.59 - 112.7

^a n=16 for chlorzoxazone alone (reference) and for chlorzoxazone + TMC278 (test).

^b 90% confidence intervals.

Based on the statistical analysis after a single dose of chlorzoxazone 500 mg administered 2 hours after a single dose of rilpivirine 150 mg once daily for subjects in the main trial, minimal differences were observed in the mean chlorzoxazone C_{max}, AUC_(0-last), and AUC_(0-∞) values compared to chlorzoxazone when administered by itself. The 90% confidence interval for chlorzoxazone C_{max}, AUC_(0-last), and AUC_(0-∞) were within 80%-125%.

With multiple dosing of both medications, based on the statistical analysis, when chlorzoxazone was administered 2 hours after rilpivirine, minimal differences were observed in the mean chlorzoxazone C_{max}, AUC_(0-last), and AUC_(0-∞) values compared to chlorzoxazone when administered by itself. The 90% confidence interval for chlorzoxazone C_{max}, AUC_(0-last), and AUC_(0-∞) were within 80%-125%.

Table 7-6-hydroxychlorzoxazone pharmacokinetic parameters (administered as single doses of chlorzoxazone 500 mg and single doses of chlorzoxazone 500 mg administered 2 hours after rilpivirine 150 mg once daily for subjects in the main trial)

Pharmacokinetics of 6-hydroxy-chlorzoxazone (mean ± SD, t _{max} : median [range])	Chlorzoxazone alone (reference) (Day 1)	Chlorzoxazone + TMC278 (Single Dose) (test 1) (Day 4)	Chlorzoxazone + TMC278 (Multiple Dose) (test 2) (Day 19)
n	16	16	16
C _{max} , µg/mL	0.3025 ± 0.09440	0.2998 ± 0.09370	0.2934 ± 0.08432
t _{max} , h	2.0 [1.0 - 3.0]	2.0 [1.0 - 3.0]	1.75 [0.5 - 3.0]
AUC _{last} , µg.h/mL	1.101 ± 0.3604	1.040 ± 0.3646	1.062 ± 0.3279
AUC _∞ , µg.h/mL	1.119 ± 0.3613	1.060 ± 0.3639	1.081 ± 0.3308
t _{1/2term} , h	1.504 ± 0.1975	1.602 ± 0.3966	1.679 ± 0.3466
Ratio AUC _{last} , 6-OH-CLX/CLX, (%)	3.214 ± 1.321	3.127 ± 1.267	2.931 ± 0.8889

Table 8-Statistical analysis for 6-hydroxychlorzoxazone (administered as single doses of chlorzoxazone 500 mg and chlorzoxazone 500 mg administered 2 hours after a single dose of rilpivirine 150 mg once daily)

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI,% ^b
	Chlorzoxazone alone (reference) (Day 1)	Chlorzoxazone + TMC278 (Single Dose) (test) (Day 4)		
C _{max} , µg/mL	0.2892	0.2863	98.97	94.35 - 103.8
AUC _{last} , µg.h/mL	1.047	0.9794	93.50	89.11 - 98.11
AUC _∞ , µg.h/mL	1.066	1.001	93.89	89.76 - 98.21
Ratio AUC _{last} , 6-OH-CLX/CLX (%)	2.974	2.881	96.86	87.10 - 107.7

^a n=16 for chlorzoxazone alone (reference) and for chlorzoxazone + TMC278 (test).

^b 90% confidence intervals.

Table 9-Statistical analysis for 6-hydroxychlorzoxazone (administered as single doses of chlorzoxazone 500 mg and chlorzoxazone 500 mg administered 2 hours after rilpivirine 150 mg once daily)

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI,% ^b
	Chlorzoxazone alone (reference) (Day 1)	Chlorzoxazone + TMC278 (Multiple Dose) (test) (Day 19)		
C _{max} , µg/mL	0.2892	0.2817	97.38	90.19 - 105.1
AUC _{last} , µg.h/mL	1.047	1.013	96.70	87.21 - 107.2
AUC _∞ , µg.h/mL	1.066	1.032	96.81	87.44 - 107.2
Ratio AUC _{last} , 6-OH-CLX/CLX (%)	2.974	2.786	93.66	81.03 - 108.3

^a n=16 for chlorzoxazone alone (reference) and for chlorzoxazone + TMC278 (test).

^b 90% confidence intervals.

Based on the statistical analysis after a single dose of chlorzoxazone 500 mg administered 2 hours after a single dose of rilpivirine 150 mg once daily for subjects in the main trial, minimal differences were observed in the mean 6-hydroxychlorzoxazone C_{max} value and the mean AUC_(0-last), and AUC_(0-∞) values were decreased compared to chlorzoxazone when administered by itself. The 90% confidence interval for 6-hydroxychlorzoxazone C_{max}, AUC_(0-last), and AUC_(0-∞) were within 80%-125%. Additionally, minimal differences were observed in the AUC_(0-last) 6-hydroxychlorzoxazone/chlorzoxazone ratio and the 90% confidence interval for the AUC_(0-last) 6-hydroxychlorzoxazone/chlorzoxazone ratio was within 80%-125%.

With multiple dosing of both medications, based on the statistical analysis, when chlorzoxazone was administered 2 hours after rilpivirine, minimal differences were observed in the mean 6-hydroxychlorzoxazone C_{max}, AUC_(0-last), and AUC_(0-∞) values compared to chlorzoxazone when administered by itself. The 90% confidence interval for 6-hydroxychlorzoxazone C_{max}, AUC_(0-last), and AUC_(0-∞) were within 80%-125%. Additionally, the AUC_(0-last) 6-hydroxychlorzoxazone/chlorzoxazone ratio was decreased but the 90% confidence interval for the AUC_(0-last) 6-hydroxychlorzoxazone/

chlorzoxazone ratio was within 80%-125%.

10.4 Safety Issues

No deaths or other serious adverse events were reported for the trial. No grade 3 or grade 4 adverse events were reported. The most common reported adverse events were headache, pruritus, and dizziness (see Table 10 for information regarding the number of subjects).

Table 10-Adverse event incidence categorized by system organ class and preferred term reported in more than one subject

System Organ Class Preferred Term n (%)	Trial Phase					Total N = 25
	Chlorzoxazone Alone N = 25	Chlorzoxazone + TMC278 (Single Dose) N = 25	TMC278 Alone N = 25	Chlorzoxazone + TMC278 (Steady-state) N = 19	Follow-up N = 25	
Any AE	9 (36.0)	7 (28.0)	15 (60.0)	8 (42.1)	2 (8.0)	19 (76.0)
Nervous System Disorders	6 (24.0)	5 (20.0)	7 (28.0)	5 (26.3)	0	11 (44.0)
Headache	3 (12.0)	4 (16.0)	5 (20.0)	4 (21.1)	0	8 (32.0)
Dizziness	3 (12.0)	2 (8.0)	2 (8.0)	1 (5.3)	0	5 (20.0)
Gastrointestinal Disorders	5 (20.0)	1 (4.0)	4 (16.0)	0	0	10 (40.0)
Abdominal pain upper	0	1 (4.0)	2 (8.0)	0	0	3 (12.0)
Diarrhea	1 (4.0)	0	2 (8.0)	0	0	3 (12.0)
Vomiting	2 (8.0)	0	1 (4.0)	0	0	3 (12.0)
Nausea	1 (4.0)	0	1 (4.0)	0	0	2 (8.0)
Skin and Subcutaneous Tissue Disorders	2 (8.0)	1 (4.0)	7 (28.0)	0	0	7 (28.0)
Pruritus	1 (4.0)	1 (4.0)	4 (16.0)	0	0	5 (20.0)
Skin lesion	1 (4.0)	0	4 (16.0)	0	0	4 (16.0)
Investigations	0	0	2 (8.0)	1 (5.3)	2 (8.0)	6 (24.0)
AST abnormal	0	0	0	0	1 (4.0)	2 (8.0)*
General Disorders and Administration Site Conditions	1 (4.0)	0	0	2 (10.5)	0	3 (12.0)
Influenza like illness	0	0	0	2 (10.5)	0	2 (8.0)

n = number of subjects with that particular adverse event; N = number of subjects per phase; AE = adverse event; AST = aspartate aminotransferase.

* Also reported for 1 subject during screening.

Note: AEs were reported for 3 subjects (12.0%) during screening: grade 1 thermal burn and grade 1 arthralgia were each reported for 1 subject and grade 1 AST abnormal and ALT abnormal were reported for 1 subject.

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Table 11-Adverse event incidence at least possibly related to rilpivirine categorized by system organ class and preferred term

System Organ Class Preferred Term n (%)	Trial Phase					Total N = 25
	Chlorzoxazone Alone N = 25	Chlorzoxazone + TMC278 (Single Dose) N = 25	TMC278 Alone N = 25	Chlorzoxazone + TMC278 (Steady-state) N = 19	Follow-up N = 25	
Any AE of any causality	9 (36.0)	7 (28.0)	15 (60.0)	8 (42.1)	2 (8.0)	19 (76.0)
With at least 1 AE thought to be at least possibly related to TMC278	1 (4.0)	7 (28.0)	13 (52.0)	6 (31.6)	2 (8.0)	17 (68.0)
Nervous System Disorders	1 (4.0)	5 (20.0)	7 (28.0)	5 (26.3)	0	10 (40.0)
Headache	1 (4.0)	4 (16.0)	5 (20.0)	4 (21.1)	0	8 (32.0)
Dizziness	0	2 (8.0)	2 (8.0)	1 (5.3)	0	4 (16.0)
Aura	0	1 (4.0)	0	0	0	1 (4.0)
Somnolence	0	1 (4.0)	0	0	0	1 (4.0)
Gastrointestinal Disorders	1 (4.0)	1 (4.0)	4 (16.0)	0	0	6 (24.0)
Abdominal pain upper	0	1 (4.0)	2 (8.0)	0	0	3 (12.0)
Diarrhea	0	0	2 (8.0)	0	0	2 (8.0)
Vomiting	1 (4.0)	0	1 (4.0)	0	0	2 (8.0)
Dyspepsia	0	0	1 (4.0)	0	0	1 (4.0)
Nausea	0	0	1 (4.0)	0	0	1 (4.0)
Skin and Subcutaneous Tissue Disorders	0	1 (4.0)	6 (24.0)	0	0	6 (24.0)
Pruritus	0	1 (4.0)	3 (12.0)	0	0	4 (16.0)
Skin lesion	0	0	2 (8.0)	0	0	2 (8.0)
Pruritus generalized	0	0	1 (4.0)	0	0	1 (4.0)
Investigations	0	0	0	1 (5.3)	2 (8.0)	3 (12.0)
AST abnormal	0	0	0	0	1 (4.0)	1 (4.0)
Lipase abnormal	0	0	0	1 (5.3)	0	1 (4.0)
Lipase increased	0	0	0	0	1 (4.0)	1 (4.0)
Renal and Urinary Disorders	0	1 (4.0)	0	0	0	1 (4.0)
Pollakiuria	0	1 (4.0)	0	0	0	1 (4.0)

n = number of subjects with that particular adverse event; N = number of subjects per phase; AE = adverse event; AST = aspartate aminotransferase.

Table 12-Adverse event incidence at least possibly related to chlorzoxazone categorized by system organ class and preferred term (includes original and replacement subjects)

System Organ Class Preferred Term n (%)	Trial Phase					Total N = 25
	Chlorzoxazone Alone N = 25	Chlorzoxazone + TMC278 (Single Dose) N = 25	TMC278 Alone N = 25	Chlorzoxazone + TMC278 (Steady-state) N = 19	Follow-up N = 25	
Any AE of any causality	9 (36.0)	7 (28.0)	15 (60.0)	8 (42.1)	2 (8.0)	19 (76.0)
<i>With at least 1 AE thought to be at least possibly related to chlorzoxazone</i>	7 (28.0)	5 (20.0)	1 (4.0)	6 (31.6)	1 (4.0)	13 (52.0)
<i>Nervous System Disorders</i>	6 (24.0)	4 (16.0)	0	5 (26.3)	0	10 (40.0)
Headache	3 (12.0)	3 (12.0)	0	4 (21.1)	0	7 (28.0)
Dizziness	3 (12.0)	2 (8.0)	0	1 (5.3)	0	4 (16.0)
Aura	0	1 (4.0)	0	0	0	1 (4.0)
<i>Gastrointestinal Disorders</i>	4 (16.0)	0	0	0	0	4 (16.0)
Vomiting	2 (8.0)	0	0	0	0	2 (8.0)
Diarrhea	1 (4.0)	0	0	0	0	1 (4.0)
Nausea	1 (4.0)	0	0	0	0	1 (4.0)
<i>Investigations</i>	0	0	0	1 (5.3)	1 (4.0)	2 (8.0)
Lipase abnormal	0	0	0	1 (5.3)	0	1 (4.0)
Lipase increased	0	0	0	0	1 (4.0)	1 (4.0)
<i>Renal and Urinary Disorders</i>	0	1 (4.0)	0	0	0	1 (4.0)
Pollakiuria	0	1 (4.0)	0	0	0	1 (4.0)
<i>Skin and Subcutaneous Tissue Disorders</i>	0	0	1 (4.0)	0	0	1 (4.0)
Skin lesion	0	0	1 (4.0)	0	0	1 (4.0)

n = number of subjects with that particular adverse event; N = number of subjects per phase; AE = adverse event; AST = aspartate aminotransferase.

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11. Discussion and Conclusions

Based on the results from the drug-drug interaction trial, the following conclusions can be made:

- After a single dose of chlorzoxazone 500 mg administered 2 hours after rilpivirine 150 mg once daily for subjects in the main trial, the mean rilpivirine C_{0h} , C_{min} , C_{max} , and $AUC_{(0-24h)}$ values were increased by 25%, 18%, 17%, and 25%, respectively, compared to rilpivirine when administered by itself. The 90% confidence interval for rilpivirine C_{0h} , C_{min} , C_{max} , and $AUC_{(0-24h)}$ were not within 80%-125
- When a single dose of chlorzoxazone 500 mg was administered 2 hours after a single dose of rilpivirine 150 mg once daily for subjects in the main trial, minimal differences were observed in the mean chlorzoxazone C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ values (decreased by 4%, 3%, and 3%, respectively) compared to chlorzoxazone when administered by itself. The 90% confidence interval for chlorzoxazone C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ were within 80%-125%.
- With multiple dosing of both medications, when chlorzoxazone was administered 2 hours after rilpivirine, minimal differences were observed in the mean chlorzoxazone C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ values (C_{max} decreased by 2% and $AUC_{(0-last)}$ and $AUC_{(0-\infty)}$ both increased by 3%) compared to chlorzoxazone when administered by itself. The 90% confidence interval for chlorzoxazone C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ were within 80%-125%.
- After a single dose of chlorzoxazone 500 mg administered 2 hours after a single dose of rilpivirine 150 mg once daily for subjects in the main trial, minimal differences were observed in the mean 6-hydroxychlorzoxazone C_{max} value (decreased by 1%) and the mean $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ values were decreased by 7% and 6%, respectively) compared to chlorzoxazone when administered by

- itself. The 90% confidence interval for 6-hydroxychlorzoxazone C_{\max} , $AUC_{(0-\text{last})}$, and $AUC_{(0-\infty)}$ were within 80%-125%.
- With multiple dosing of both medications, when chlorzoxazone was administered 2 hours after rilpivirine, minimal differences were observed in the mean 6-hydroxychlorzoxazone C_{\max} , $AUC_{(0-\text{last})}$, and $AUC_{(0-\infty)}$ values (all three parameters decreased by 3%) compared to chlorzoxazone when administered by itself. The 90% confidence interval for 6-hydroxychlorzoxazone C_{\max} , $AUC_{(0-\text{last})}$, and $AUC_{(0-\infty)}$ were within 80%-125%.

Chlorzoxazone does not result in clinically relevant changes in the exposure of rilpivirine with a rilpivirine dosage regimen of 150 mg once daily and no dosage adjustment for rilpivirine is required.

Administration of single doses of chlorzoxazone 500 mg administered 2 hours after rilpivirine 150 mg once daily does not result in clinically relevant changes in chlorzoxazone or 6-hydroxychlorzoxazone exposure and no dosage adjustment for chlorzoxazone is required. The specific effects of a 25 mg once daily rilpivirine dosage regimen on chlorzoxazone exposure have not been evaluated. However, there was no clinically relevant potential rilpivirine CYP 2E1 inhibitory effects on chlorzoxazone or 6-hydroxychlorzoxazone exposure with a dosage regimen of 150 mg one daily, and from a mechanistic standpoint, the results would be anticipated to be applicable to a rilpivirine dosage regimen of 25 mg once daily.

TMC278-C140

1. Title

A Phase I, open-label, randomized, 4-way, crossover trial in 24 healthy subjects to investigate the pharmacokinetic interaction between single doses of TMC278 and famotidine in 3 different dosing regimens

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at (b) (4) from March 13, 2006 to July 3, 2006.

3. Objectives

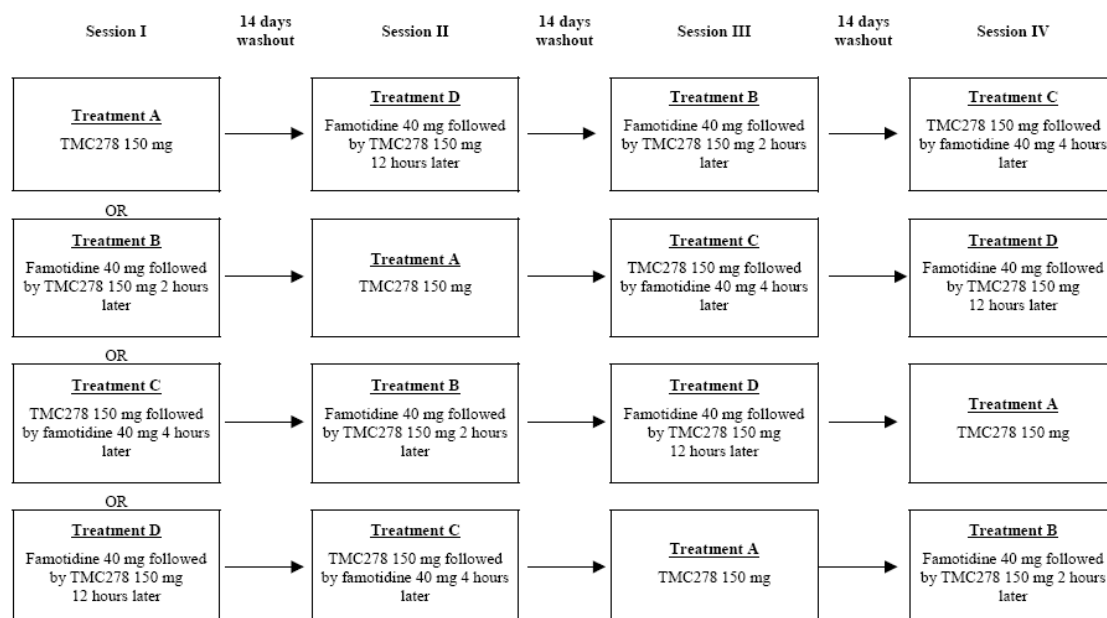
The objectives of the trial were to evaluate the effect of a single dose of famotidine on the single dose pharmacokinetics of rilpivirine and to evaluate the relationship between intragastric pH and the pharmacokinetics of rilpivirine.

4. Trial Design

TMC278-C140 was a Phase I, open label, randomized, 4 way crossover clinical trial that enrolled male and female subjects between 18 and 55 years old. The trial design is displayed in Figure 1.

Figure 1-TMC278-C140 trial design

Best Available Copy



5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Use of ibuprofen was permitted up to three days before first dosing. Afterwards, ibuprofen use was permitted up to 400 mg/day until Day 8 of each treatment arm. Any over the counter medications were to be discontinued a minimum of 7 days before first dosing and any prescription medications were to be discontinued a minimum of fourteen days before first dosing (with the exception of ibuprofen). Use of any medication other than ibuprofen was not permitted up to fourteen days after the last administration of trial medication. Use of herbal medicines or dietary supplements was not permitted from fourteen days before first dosing up to fourteen days after the last administration of trial medication.

Use of liquids containing alcohol or quinine was not permitted from 24 hours before administration of trial medication until Day 8 of each treatment arm. Intake of grapefruit and grapefruit juice was not permitted from 7 days before administration of trial medication until Day 8 of each treatment arm.

In the event of an adverse event, the following medications were permitted:

- A) Rash or an allergic reaction: cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents (specific medications were not included in the trial report)
- B) Nausea: antiemetics (specific medications were not included in the trial report)
- C) Diarrhea: loperamide

6. Dosage and Administration

On Day 1, subjects fasted overnight for a minimum of 10 hours. A standard meal was administered in the morning and rilpivirine was administered within 10 minutes after completion of the meal. Famotidine was administered on an empty stomach between 5:30 AM and 7:30AM and rilpivirine was administered 2 hours after famotidine for Treatment B. For Treatment C, famotidine was administered four hours after rilpivirine. Rilpivirine was administered 12 hours after famotidine for Treatment D.

7. Rationale for Doses Used in the Trial

The rilpivirine dosage regimen that was administered to all subjects was a single 150 mg dose of rilpivirine. In contrast, the rilpivirine dosage regimen that was evaluated in the Phase 3 clinical trials and the recommended dosage regimen in the proposed prescribing information is 25 mg once daily with a meal. Because the primary objective of the trial was to evaluate the effect of famotidine on the absorption of rilpivirine (which possesses pH-dependent absorption), the results of the trial are expected to be applicable for rilpivirine at 25 mg once daily.

The single dose of famotidine administered in the trial (40 mg) is the highest total daily dose recommended in the famotidine (Pepcid) prescribing information for the treatment of duodenal ulcers.

8. Drugs Used in the Trial

Rilpivirine 50 mg tablets (formulation F003) and 100 mg tablets (F002) were administered in the trial. Both of these tablets were Phase 2b formulations that were used in the Phase 1 or 2 trials.

Famotidine (Pepcid) 40 mg tablets were administered in the trial.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

For Treatment A (rilpivirine administered alone), blood samples for analysis of rilpivirine concentrations were obtained on Days 1 through 8 at predose and up to 168 hours postdose. Predose famotidine blood samples were also obtained on Day 1.

For Treatment B and C, blood samples for analysis of rilpivirine concentrations were obtained on Days 1 through 8 at predose and up to 168 hours postdose. Famotidine concentrations were obtained on Days 1 and 2 at predose and up to 24 hours postdose.

For Treatment D, blood samples for analysis of rilpivirine concentrations were obtained on Days 1 through 8 at predose and up to 168 hours postdose. Famotidine concentrations were obtained on Days -1 and 1 at predose and up to 24 hours postdose. Predose rilpivirine concentrations were also obtained on Day -1 for rilpivirine.

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a validated LC/MS/MS method by Johnson and Johnson Pharmaceutical Research and Development. The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the TMC278-C140 trial, precision and accuracy were evaluated using the low (2.77 ng/mL), medium (59 ng/mL), and high (1550 ng/mL) QC samples. The corresponding rilpivirine inter-run accuracy values were -1.8% for the low QCs, -0.5% for the medium QCs, and -0.6% for the high QCs, and the rilpivirine inter-run precision values were 4.6% for the low QCs, 4% for the medium QCs, and 3.6% for the high QCs. The submitted rilpivirine long term stability data of 1528 days at -20°C covered the duration of long term rilpivirine stability data necessary for the TMC278-C140 trial.

The method and bioanalysis of famotidine are acceptable. Plasma samples were analyzed for famotidine concentrations using a validated LC/MS/MS method by (b) (4). The lower limit of quantification for famotidine was 1 ng/mL and the upper limit of quantification was 200 ng/mL. There were no precision or accuracy issues identified for famotidine based on the bioanalytical report. For the TMC278-C140 trial, precision and accuracy were evaluated using QC samples at 3, 15, and 150 ng/mL. The corresponding

famotidine inter-run accuracy values were 4.7%, 6.1%, and 3.1% and the famotidine inter-run precision values were 10.4%, 6.7% and 7.2%.

The long-term stability data for famotidine was not submitted. Therefore, the stability of the samples from the day the first sample was collected to the day the last sample was analyzed is unknown and the reliability of the reported famotidine pharmacokinetic data can not be guaranteed.

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate pharmacokinetic parameters, including C_{\max} , $AUC_{(0-\text{last})}$, and $AUC_{(0-\infty)}$. If a major difference ($> 10.00\%$ deviation from the scheduled time) was observed, the actual sampling time was used instead of the scheduled sampling time.

Statistical Analysis

Descriptive statistics were calculated for rilpivirine and famotidine plasma concentrations and pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), geometric mean, median, and the minimum and maximum values.

Statistical analysis for rilpivirine involved comparison of Treatments B, C and D (test arms) to Treatment A (reference arm). C_{\max} , $AUC_{(0-\text{last})}$, and $AUC_{(0-\infty)}$ were evaluated. Using a linear mixed effects model, least squares means were calculated and 90% confidence intervals were derived based on the difference of the pharmacokinetic parameter's least squares means for the test and reference arms. The applicant did not specify predetermined "no effect boundaries" for the 90% confidence intervals.

For famotidine, statistical analysis involved an ANOVA analysis of famotidine log transformed $AUC_{(0-\text{last})}$ and $AUC_{(0-\infty)}$ for Treatments B, C and D. If a p value less than 5% was observed, multiple comparison testing using Bonferoni adjustment was to be conducted.

In Treatments A and B, monitoring of intragastric pH was performed. An exploratory analysis was conducted to evaluate the effect of intragastric pH on rilpivirine pharmacokinetics.

10. Results

10.1 Subject Demographics and Disposition

Table 1-TMC278-C140 subject demographics

Parameter	Treatment Sequence ADBC N = 6	Treatment Sequence BACD N = 6	Treatment Sequence CBDA N = 6	Treatment Sequence DCAB N = 6	Total N = 24
Age, years					
Median (range)	31.0 (22-48)	24.0 (21-37)	31.0 (20-53)	26.5 (21-49)	26.5 (20-53)
Height, cm					
Median (range)	178.5 (168-187)	180.5 (168-189)	180.0 (175-184)	177.5 (172-185)	179.0 (168-189)
Weight, kg					
Median (range)	74.5 (66-78)	74.0 (59-88)	69.0 (61-80)	75.0 (67-92)	75.0 (59-92)
BMI, kg/m ²					
Median (range)	23.4 (22-24)	22.7 (19-28)	21.4 (19-24)	23.7 (20-30)	23.0 (19-30)
Sex, n (%)					
Male	6 (100)	6 (100)	6 (100)	6 (100)	24 (100)
Race, n (%)					
Black	1 (16.7)	0	1 (16.7)	2 (33.3)	4 (16.7)
Caucasian	4 (66.7)	3 (50.0)	4 (66.7)	3 (50.0)	14 (58.3)
Oriental/Asian	0	1 (16.7)	0	0	1 (4.2)
Other ^a	1 (16.7)	2 (33.3)	1 (16.7)	1 (16.7)	5 (20.8)
Type of Smoker, n (%)					
No	4 (66.7)	5 (83.3)	2 (33.3)	4 (66.7)	15 (62.5)
Yes	2 (33.3)	1 (16.7)	4 (66.7)	2 (33.3)	9 (37.5)

Treatment A = TMC278 alone.

Treatment B = Famotidine followed by TMC278 2 hours later.

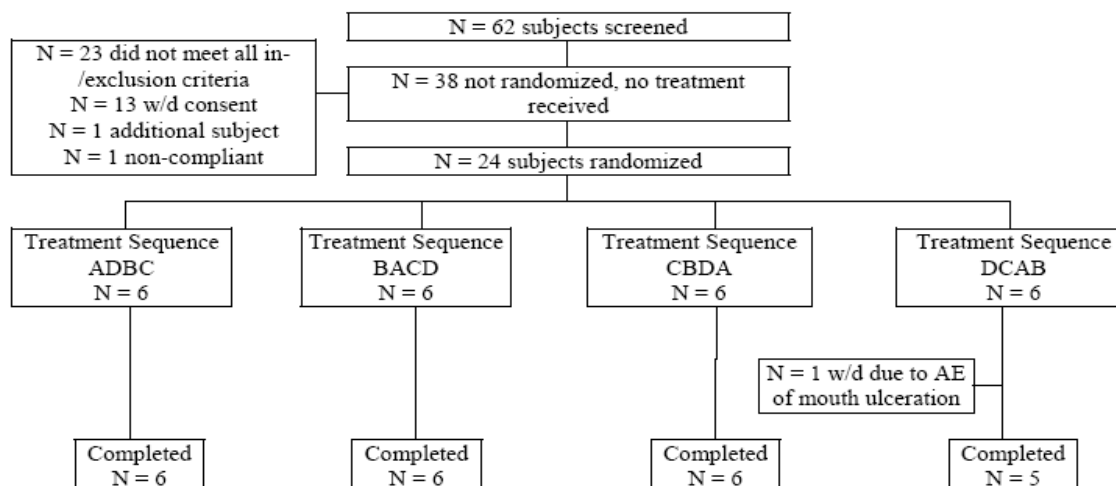
Treatment C = TMC278 followed by famotidine 4 hours later.

Treatment D = Famotidine followed by TMC278 12 hours later.

^a Five subjects from the West Indies.

BMI = body mass index.

Figure 2-TMC278-C140 subject disposition



Treatment A = TMC278 alone.

Treatment B = Famotidine followed by TMC278 2 hours later.

Treatment C = TMC278 followed by famotidine 4 hours later.

Treatment D = Famotidine followed by TMC278 12 hours later.

W/d = withdrew, AE = adverse event.

10.2 Prior and Concomitant Medications

All subjects were administered concurrent medications during the trial. The administered concurrent medications were lidocaine in twenty three subjects (as prophylaxis for esophageal pain from the intragastric pH procedure) and one subject received acetaminophen. None of the coadministered medications would be expected to alter CYP 3A metabolism.

10.3 Pharmacokinetic and Statistical Analysis

One subject had a quantifiable famotidine concentration in Treatment B. The predose concentration was 5% or less of the subject's C_{max} for the treatment arm and no adjustments were necessary for the pharmacokinetic analysis. All other subjects had famotidine concentrations that were less than the lower limit of quantification (LLOQ) prior to initiation of Treatments A, B, C and D.

For Treatments A, B, C and D, 7, 7, 4 and 6 subjects, respectively, had predose quantifiable rilpivirine concentrations. In Treatments A, C and D, the predose quantifiable rilpivirine drug concentrations were 5% or less of the subject's rilpivirine C_{max} for the treatment arm. In Treatment B, four subjects had quantifiable rilpivirine drug concentrations that were greater than 5% of the subject's rilpivirine C_{max} for the treatment arm. These subjects were included in the pharmacokinetic analysis. However, the overall conclusion that was derived from comparing Treatment B to Treatment A is anticipated to be valid regardless of whether pharmacokinetic data from the four subjects is included.

Rilpivirine

Table 2-Pharmacokinetic parameters for single dose rilpivirine 150 mg (Treatment A) and single dose rilpivirine 150 mg with different combinations of administration with single dose famotidine 40 mg

Pharmacokinetics of TMC278 (mean \pm SD, t_{max} : median [range])	Treatment A TMC278 Alone	Treatment B Famotidine + TMC278 2 h Later	Treatment C TMC278 + Famotidine 4 h Later	Treatment D Famotidine + TMC278 12 h Later
n	23	23 ^a	24	24
C_{max} , ng/mL	563.6 \pm 211.8	108.0 \pm 109.6	665.0 \pm 221.0	552.8 \pm 193.6
t_{max} , h	5.0 (1.0 - 12.0)	5.0 (4.0 - 48.0)	4.0 (3.0 - 6.0)	5.0 (2.0 - 6.0)
AUC _{last} , ng.h/mL	19920 \pm 9562	4819 \pm 2963	20790 \pm 7754	17200 \pm 6734
AUC _{∞} , ng.h/mL	21630 \pm 11070	5349 \pm 3221	22660 \pm 9306	18470 \pm 7217
$t_{1/2term}$, h	40.98 \pm 14.73	44.54 \pm 18.57	40.59 \pm 21.52	39.04 \pm 14.60

^a For AUC _{∞} and $t_{1/2term}$, n=22.

Table 3-Statistical analysis for single dose rilpivirine 150 mg (Treatment A) and single dose rilpivirine 150 mg administered two hours after single dose famotidine 40 mg (Treatment B)

Parameter	LSmeans		LSmeans Ratio, %	90% CI,% ^c	p-value	
	TMC278 Alone (Reference)	Famotidine + TMC278 2 h Later (Test 1)			Period	Sequence
C_{max} , ng/mL ^a	523.9	80.36	15.34	12.31 - 19.12	0.9819	0.4836
AUC_{last} , ng.h/mL ^a	17850	4140	23.19	19.65 - 27.37	0.9752	0.8050
AUC_{∞} , ng.h/mL ^b	19130	4588	23.99	20.31 - 28.34	0.9725	0.7995
Parameter	Median		Treatment Difference Median	90% CI,% ^c	p-value	
	TMC278 Alone (Reference)	Famotidine + TMC278 2 h Later (Test 1)			Period	Sequence
t_{max} , h ^a	5.0	5.0	1.5	0.5 - 3.0	0.1595	0.5755

^a n=23 for TMC278 alone (reference) and famotidine + TMC278 2 h later (test 1).

^b n=23 for TMC278 alone (reference), n=22 for famotidine + TMC278 2 h later (test 1).

^c 90% confidence intervals.

In Treatment B, when single dose rilpivirine 150 mg was administered two hours after single dose famotidine 40 mg, the mean rilpivirine C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ values were decreased when compared to Treatment A, when rilpivirine was administered by itself. The 90% confidence interval for rilpivirine C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ were not within 80%-125%.

Table 4-Statistical analysis for single dose rilpivirine 150 mg (Treatment A) and single dose famotidine 40 mg administered four hours after single dose rilpivirine 150 mg (Treatment C)

Parameter	LSmeans		LSmeans Ratio, %	90% CI,% ^c	p-value	
	TMC278 Alone (Reference)	TMC278 + Famotidine 4 h Later (Test 2)			Period	Sequence
C_{max} , ng/mL ^a	522.7	632.6	121.0	105.6 - 138.7	0.4326	0.6070
AUC_{last} , ng.h/mL ^a	17390	19510	112.2	99.49 - 126.5	0.4789	0.9791
AUC_{∞} , ng.h/mL ^a	18500	20950	113.2	100.7 - 127.4	0.5764	0.9591
Parameter	Median		Treatment Difference Median	90% CI,% ^c	p-value	
	TMC278 Alone (Reference)	TMC278 + Famotidine 4 h Later (test 2)			Period	Sequence
t_{max} , h ^b	5.0	4.0	0.0	-0.5 - 0.5	0.9742	0.4874

^a n=23 for TMC278 alone (reference), n=24 for TMC278 + famotidine 4 h later (test 2).

^b n=23 for TMC278 alone (reference) and famotidine 4 h later (test 2).

^c 90% confidence intervals.

In Treatment C, when single dose famotidine 40 mg was administered four hours after single dose rilpivirine 150 mg, the mean rilpivirine C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ values were increased when compared to Treatment A, when rilpivirine was administered by

itself. The 90% confidence interval for rilpivirine C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ were not within 80%-125%.

Table 5-Statistical analysis for single dose rilpivirine 150 mg (Treatment A) and single dose rilpivirine 150 mg administered twelve hours after single dose famotidine 40 mg (Treatment D)

Parameter	LSmeans		LSmeans Ratio, %	90% CI,% ^c	p-value	
	TMC278 Alone (Reference)	Famotidine + TMC278 12 h Later (Test 3)			Period	Sequence
C_{max} , ng/mL ^a	524.2	517.0	98.64	84.27 - 115.5	0.2776	0.2689
AUC_{last} , ng.h/mL ^a	17680	16040	90.74	77.06 - 106.9	0.6155	0.6978
AUC_{∞} , ng.h/mL ^a	18880	17250	91.40	78.14 - 106.9	0.5978	0.6640
Parameter	Median		Treatment Difference Median	90% CI,% ^c	p-value	
	TMC278 Alone (Reference)	Famotidine + TMC278 12 h Later (Test 3)			Period	Sequence
t_{max} , h ^b	5.0	5.0	0.0	-0.5 - 1.0	0.5458	0.5674

^a n= 23 for TMC278 alone (reference), n=24 for famotidine + TMC278 12 h later (test 3).

^b n= 23 for TMC278 alone (reference) and famotidine + TMC278 12 h later (test 3).

^c 90% confidence intervals.

In Treatment D, when single dose rilpivirine 150 mg was administered twelve hours after single dose famotidine 40 mg, minimal change was observed in the mean rilpivirine C_{max} , and the mean rilpivirine $AUC_{(0-last)}$ and $AUC_{(0-\infty)}$ values were decreased when compared to Treatment A, when rilpivirine was administered by itself. The 90% confidence interval for rilpivirine C_{max} was within 80%-125%. The 90% confidence interval for rilpivirine $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ were not within 80%-125%.

Famotidine

Table 6-Pharmacokinetic parameters for single dose famotidine 40 mg pharmacokinetic parameters with different combinations of administration with single dose rilpivirine 150 mg

Pharmacokinetics of Famotidine (mean \pm SD, t_{max} : median [range])	Treatment B Famotidine + TMC278 2 h Later	Treatment C TMC278 + Famotidine 4 h Later	Treatment D Famotidine + TMC278 12 h Later
n	23	24 ^a	24 ^a
C_{max} , ng/mL	125.0 \pm 35.29	105.9 \pm 31.98	91.16 \pm 28.98
t_{max} , h	3.0 (1.0 - 4.0)	2.0 (1.0 - 7.88)	4.0 (2.0 - 8.0)
AUC_{last} , ng.h/mL	840.6 \pm 213.6	723.5 \pm 205.3	792.5 \pm 223.3
AUC_{∞} , ng.h/mL	860.2 \pm 215.3	742.6 \pm 211.7	815.7 \pm 234.9
$t_{1/2term}$, h	3.890 \pm 0.6077	4.365 \pm 0.5376	4.046 \pm 0.4966

^a For AUC_{∞} and $t_{1/2term}$, n=23.

Table 7-Statistical analysis for single dose famotidine 40 mg pharmacokinetic parameters with different combinations of administration with single dose rilpivirine 150 mg

Parameter	LSmeans			p-value		
	Famotidine + TMC278 2 h Later	TMC278 + Famotidine 4 h Later	Famotidine + TMC278 12 h Later	Treatment	Period	Sequence
AUC _{last} , ng.h/mL ^a	806.7	698.1	764.7	0.0616	0.4817	0.8686
AUC _∞ , ng h/mL ^b	826.1	717.2	790.7	0.0684	0.4568	0.8487

^a n=23 for famotidine + TMC278 2 h later and n=24 for TMC278 + famotidine 4 h later and Famotidine + TMC278 12 h later.

^b n=23 for all treatments.

Based on the ANOVA analysis, there were no statistically significant differences (p value less than 5%) that were observed among the different treatment arms for famotidine AUC_(0-last), and AUC_(0-∞).

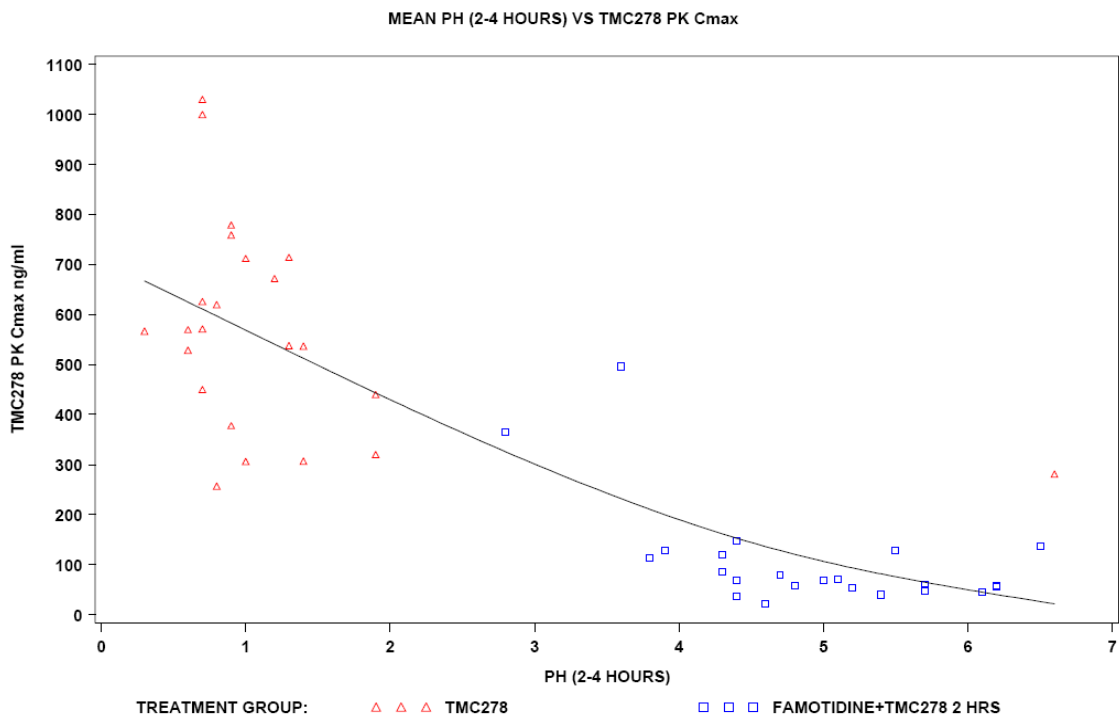
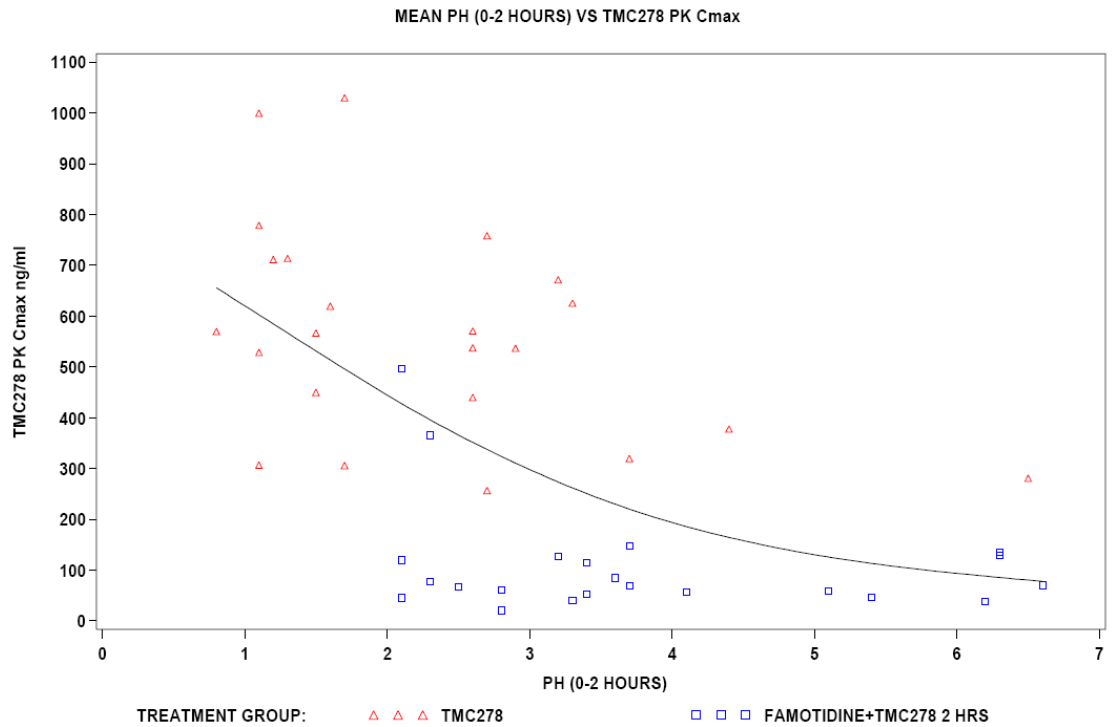
Intragastric pH monitoring

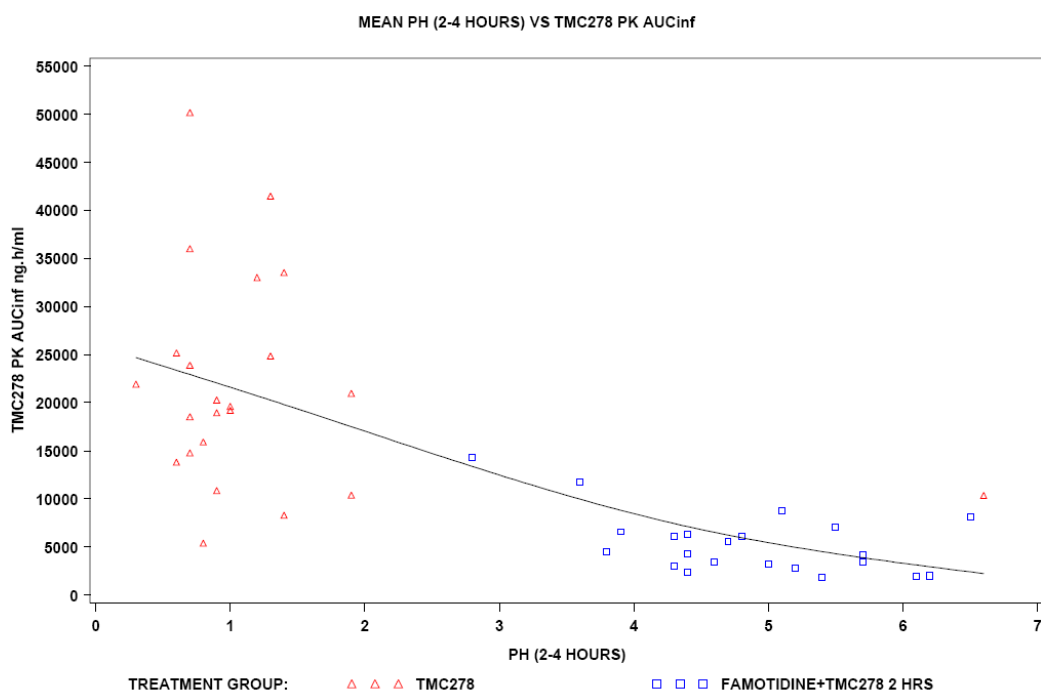
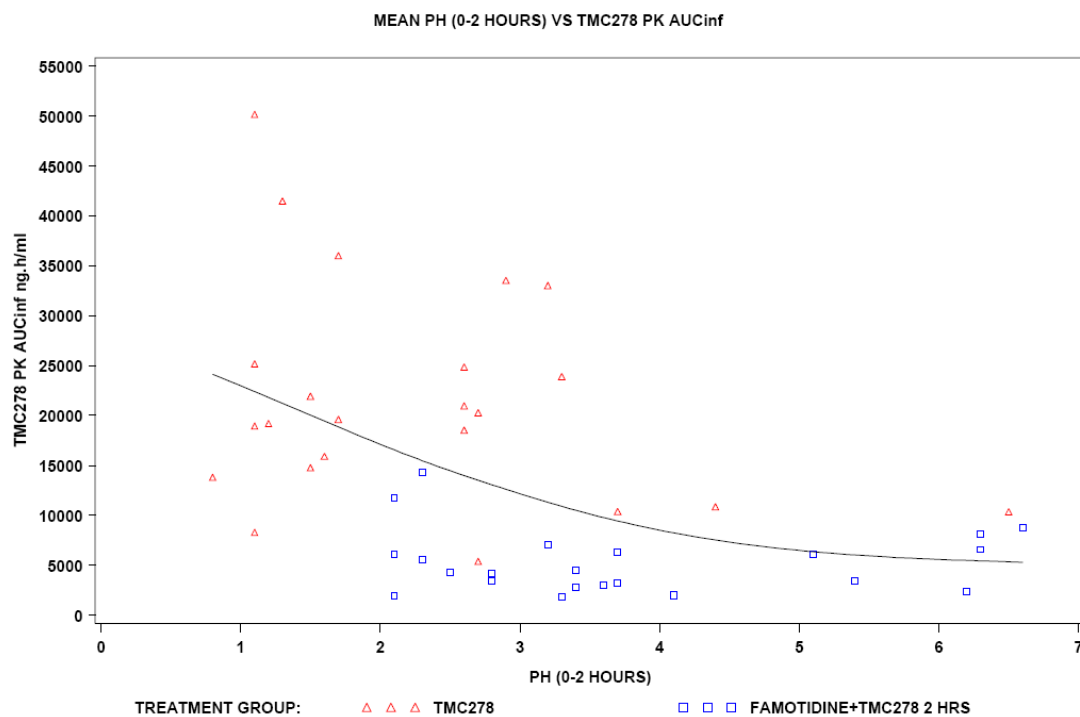
Table 8-Intragastric pH information for percent time above a gastric pH threshold ranging from >3 to >6 for Treatments A and B at 0-2 and 2-4 hours postdose

Parameter	Treatment A TMC278 Alone N = 23	Treatment B Famotidine + TMC278 2 h Later N = 23
Time pH > 3, %		
0-2 h Mean (range)	27.99 (0.0-100.0)	93.04 (35.9-100.0)
2-4 h Mean (range)	8.12 (0.0-100.0)	71.85 (0.2-100.0)
Time pH > 4, %		
0-2 h Mean (range)	17.76 (0.0-100.0)	83.72 (2.6-100.0)
2-4 h Mean (range)	6.12 (0.0-100.0)	64.07 (0.0-100.0)
Time pH > 5, %		
0-2 h Mean (range)	6.71 (0.0-100.0)	48.54 (0.0-100.0)
2-4 h Mean (range)	5.15 (0.0-100.0)	47.26 (0.0-100.0)
Time pH > 6, %		
0-2 h Mean (range)	3.84 (0.0-88.1)	15.83 (0.0-81.8)
2-4 h Mean (range)	3.90 (0.0-88.2)	25.32 (0.0-84.7)
Mean pH		
0-2 h Mean (range)	2.30 (0.8-6.5)	4.90 (2.8-6.5)
2-4 h Mean (range)	1.23 (0.3-6.6)	4.30 (1.2-6.6)
Median pH		
0-2 h Median (range)	1.50 (0.7-6.6)	4.80 (2.7-6.5)
2-4 h Median (range)	0.80 (0.3-6.7)	4.80 (1.0-6.6)
Minimum pH		
0-2 h Mean (range)	0.82 (0.0-5.1)	3.45 (0.0-5.3)
2-4 h Mean (range)	0.43 (0.0-5.1)	1.62 (0.0-5.5)
Maximum pH		
0-2 h Mean (range)	4.64 (1.8-7.3)	6.55 (4.8-9.0)
2-4 h Mean (range)	4.79 (1.1-8.3)	6.63 (3.3-9.0)

In Treatment B, there were a higher percent time above a gastric pH threshold ranging from >3 to >6 compared to Treatment A. In both Treatment A and Treatment B, as the pH threshold increased from >3 to >6, the percent time decreased.

Figures 3-6-Graphical analysis of intragastric pH versus C_{max} and $AUC_{(0-\infty)}$ for Treatment A and B at 0-2 and 2-4 hours postdose





At both 0-2 hours and 2-4 hours postdose, for both C_{max} and $AUC_{(0-\infty)}$, a trend was observed of decreasing rilpivirine C_{max} and $AUC_{(0-\infty)}$ as intragastric pH increased.

10.4 Safety Issues

No deaths or other serious adverse events were reported for the trial. No grade 3 or grade 4 adverse events were reported. Three subjects reported an adverse event during the trial. One subject reported grade 2 nasopharyngitis during Treatment D. A second subject reported grade 1 dyspepsia and upper abdominal pain during Treatment C. The third subject reported grade 1 dizziness with Treatment D and grade 1 headache and grade 2 mouth ulceration with Treatment C. The grade 2 mouth ulceration resulted in premature discontinuation of the subject from the trial. No adverse events were reported during follow up.

The applicant did not provide tables describing adverse events by system organ class.

11. Discussion and Conclusions

Based on the results from the drug-drug interaction trial, the following conclusions can be made:

- With single dose rilpivirine 150 mg administered two hours after single dose famotidine 40 mg (Treatment B), the mean rilpivirine C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ values were decreased by 85%, 77%, 76%, respectively, when compared to Treatment A, when rilpivirine was administered by itself. The 90% confidence interval for rilpivirine C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ was not within 80%-125%.
- With single dose famotidine 40 mg administered four hours after single dose rilpivirine 150 mg (Treatment C), the mean rilpivirine C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ values were increased by 21%, 12%, and 13%, respectively, when compared to Treatment A, when rilpivirine was administered by itself. The 90% confidence interval for rilpivirine C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ was not within 80%-125%.
- With single dose rilpivirine 150 mg administered twelve hours after single dose famotidine 40 mg (Treatment D), minimal change was observed in the mean rilpivirine C_{max} (decrease of 1%), and the mean rilpivirine $AUC_{(0-last)}$ and $AUC_{(0-\infty)}$ values were both decreased by 9% when compared to Treatment A, when rilpivirine was administered by itself. The 90% confidence interval for rilpivirine C_{max} was within 80%-125%. The 90% confidence interval for rilpivirine $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ was not within 80%-125%.
- For famotidine, based on the ANOVA analysis, there was no statistically significant differences (p value less than 5%) that were observed among the different treatment arms for famotidine $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$.

Based on the information obtained from intragastric pH monitoring during Treatment A and Treatment B, the following results were observed:

- In Treatment B, there were a higher percent time above a gastric pH threshold ranging from >3 to >6 compared to Treatment A. In both Treatment A and

Treatment B, as the pH threshold increased from >3 to >6, the percent time decreased.

- At both 0-2 hours and 2-4 hours postdose, for both C_{\max} and $AUC_{(0-\infty)}$, a trend was observed of decreasing rilpivirine C_{\max} and $AUC_{(0-\infty)}$ as intragastric pH increased.

The changes in rilpivirine exposure are believed to be due to changes in gastric pH caused by famotidine. When single dose rilpivirine 150 mg was administered twelve hours after single dose famotidine 40 mg or single dose famotidine 40 mg was administered four hours after single dose rilpivirine 150 mg, clinically relevant changes in the exposure of rilpivirine were not observed. When single dose rilpivirine 150 mg was administered two hours after single dose famotidine 40 mg, clinically relevant changes in the exposure of rilpivirine were observed. Therefore, rilpivirine should be administered twelve hours after famotidine or famotidine should be administered four hours after rilpivirine. This is consistent with the applicant's recommendations for rilpivirine administration with H_2 receptor antagonists in the proposed rilpivirine prescribing information.

Food effect trial

Trial Number	Title	Page Number
TMC278-C137	The effect of food on the bioavailability of TMC278 after a single oral dose of 75 mg, formulated as the Phase III tablet, in healthy subjects	253

TMC278-C137

1. Title

The effect of food on the bioavailability of TMC278 after a single oral dose of 75 mg, formulated as the Phase III tablet, in healthy subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at [REDACTED] (b) (4)
from July 11, 2007 to October 23, 2007.

3. Objectives

The objectives of the trial were to evaluate the effect of different types of meals on the bioavailability of rilpivirine and to evaluate the bioavailability of rilpivirine under fasted conditions using the Phase 3 tablets.

4. Trial Design

TMC278-C137 was a Phase I, open label, randomized, 4 way crossover, clinical trial that enrolled male and female subjects between 18 and 55 years old. The trial design is displayed in Figure 1 and the treatments that were administered are displayed in Table 1.

Figure 1-TMC278-C139 trial design

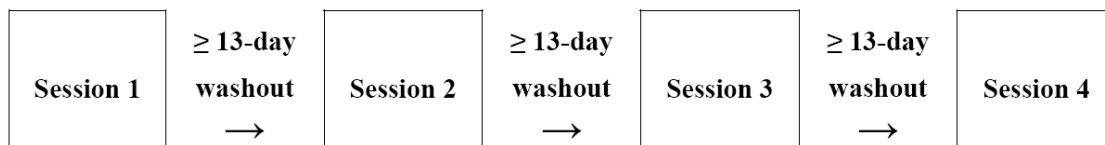


Table 1-Treatments administered in the C137 trial

	Treatment A	Treatment B	Treatment C	Treatment D
TMC278, 75 mg tablet (F008)	Day 1: 1 tablet orally in the morning after a standard breakfast	Day 1: 1 tablet orally in the morning under fasting conditions	Day 1: 1 tablet orally in the morning after a high-fat breakfast	Day 1: 1 tablet orally in the morning after a nutritional drink rich in proteins

5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Use of ibuprofen and acetaminophen was permitted up to three days before the first administration of trial medication. Afterwards, ibuprofen use was permitted up to 400 mg/day and acetaminophen was permitted up to 1 gram/day. Any over the counter

medications were to be discontinued a minimum of seven days before the first administration of trial medication and all prescription medications were to be discontinued a minimum of fourteen days before the first administration of trial medication, except for ibuprofen and acetaminophen. Use of herbal medicines or dietary supplements was not permitted from fourteen days before the first administration of trial medication and up to fourteen days after the last administration of trial medication.

Use of liquids containing alcohol or quinine was not permitted from 24 hours before administration of trial medication until Day 8 in each session or treatment arm. Intake of grapefruit and grapefruit juice was not permitted from 7 days before administration of trial medication in the first session or treatment arm until Day 8 in the last session or treatment arm.

In the event of an adverse event, the following medications were permitted:

- A) Rash or an allergic reaction: cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents (specific medications were not included in the trial report)
- B) Nausea: antiemetics (specific medications were not included in the trial report)
- C) Diarrhea: loperamide

6. Dosage and Administration

Information regarding the fat and calorie content for the treatment administered in the C137 trial are displayed in Table 2. The total calorie content for high fat, high calorie meals is consistent with the recommendations in the FDA guidance document for food effect trials.

Table 2-Fat and calorie content for the treatments administered in the C137 trial

Treatment	Fat (g)	Total Kcal	Kcal from fat	Kcal from carbohydrates	Kcal from proteins
A (standard breakfast)	21	533	189	268	76
B (fasted)	0	0	0	0	0
C (high-fat breakfast)	56	928	504	260	164
D (protein-rich drink)	7.9	300	72	153	75

All subjects were to fast overnight for a minimum of 10 hours before administration of rilpivirine with approximately 240 mL of water. Water was allowed up to two hours before and two hours after rilpivirine administration. All breakfast meals with Treatments A, C, and D were to be consumed in 30 minutes or less. Rilpivirine was subsequently administered within 10 minutes after the meal was completed (this differs from the recommendation in the FDA guidance document for food effect trials which

recommends that medication should be administered 30 minutes after initiation of the meal). The specific impact of this deviation is unknown.

7. Rationale for Doses Used in the Trial

The rilpivirine dosage regimen that was administered to all subjects was a single 75 mg dose of rilpivirine. In contrast, the rilpivirine dosage regimen that was evaluated in the Phase 3 clinical trials and the recommended dosage regimen in the proposed rilpivirine prescribing information is 25 mg once daily with a meal. Across the dose range of 25 mg to 150 mg, increases in rilpivirine exposure were approximately dose proportional. It is anticipated that the change in rilpivirine exposure for the different types of meals and under fasted conditions would be applicable for rilpivirine 25 mg once daily with a meal.

8. Drugs Used in the Trial

Rilpivirine 75 mg tablets (formulation F008) were administered in the trial. The 75 mg tablets (formulation F008) that were administered in the trial was designed to be proportional in terms of the active and inactive ingredients to the 25 mg (formulation F006) tablets that were administered in the Phase 3 trials.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Blood samples for analysis of rilpivirine plasma concentrations were obtained on Days 1 through 8 at predose and up to 168 hours postdose.

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a validated LC/MS/MS method by Tibotec. The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the TMC278-C137 trial, precision and accuracy were evaluated using the low (2.77 ng/mL), medium (59 ng/mL), and high (1550 ng/mL) QC samples. The corresponding rilpivirine inter-run accuracy values were 7.6% for the low QCs, 5.6% for the medium QCs, and 2.6% for the high QCs, and the rilpivirine inter-run precision values were 5.2% for the low QCs, 5% for the medium QCs, and 7% for the high QCs. The submitted rilpivirine long term stability data of 1528 days at -20°C covered the duration of long term rilpivirine stability data necessary for the TMC278-C137 trial.

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate plasma pharmacokinetic parameters, including C_{max} , AUC_{0-last} and $AUC_{0-\infty}$ for rilpivirine. If a major difference ($> 10.00\%$ deviation from the scheduled time) was observed, the actual sampling time was used instead of the scheduled sampling time.

Statistical Analysis

Descriptive statistics were calculated for rilpivirine plasma concentrations and pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), geometric mean, median, and the minimum and maximum values.

Statistical analysis involved the following comparisons of plasma rilpivirine log transformed pharmacokinetic parameters: a) Treatment B (test arm) versus Treatment A (reference arm), b) Treatment C (test arm) versus Treatment A (reference arm), and c) Treatment D (test arm) versus Treatment A (reference arm). In contrast to the recommendations in the FDA guidance document for food effect trials, the fed arms served as the reference instead of the fasted arm. A formal statistical analysis was not conducted comparing rilpivirine exposure with high fat meals compared to fasted conditions. Using a linear mixed effects model, least squares means were calculated and 90% confidence intervals were derived based on the difference of the pharmacokinetic parameter's least squares means for the test and reference arms. The 90% confidence intervals and the difference of the pharmacokinetic parameter's least squares means were transformed back to the original scale.

10. Results

10.1 Subject Demographics and Disposition

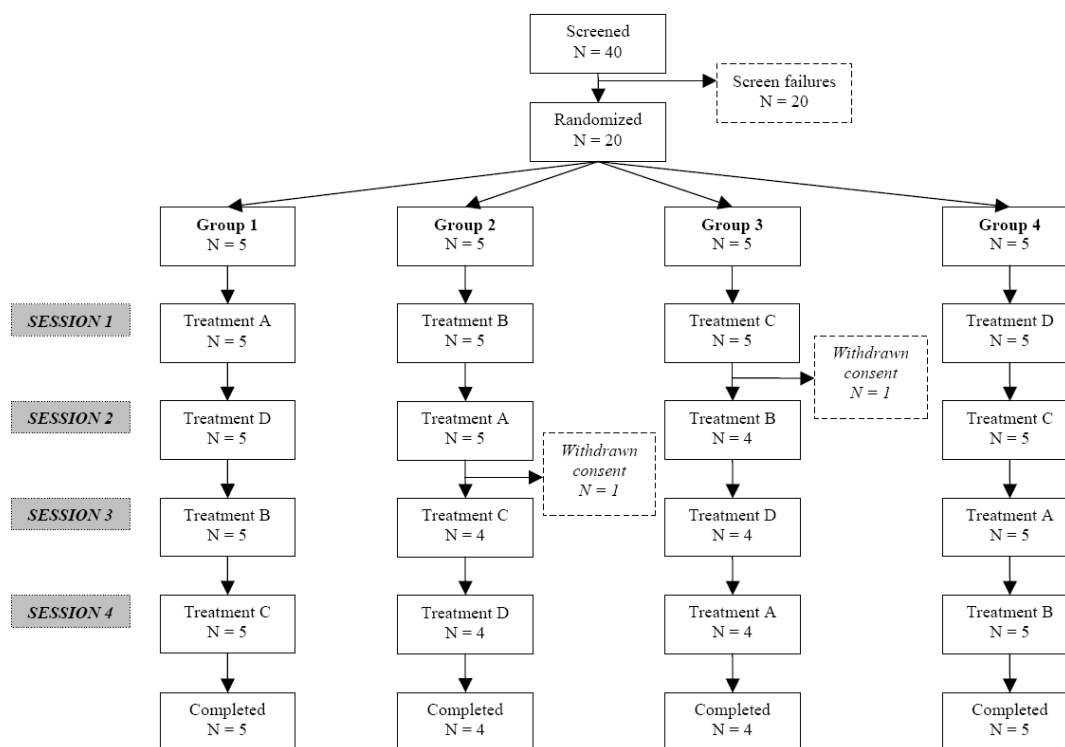
Table 3-TMC278-C137 subject demographics

Parameter	Group 1 N = 5	Group 2 N = 5	Group 3 N = 5	Group 4 N = 5	All Subjects N = 20
Age, years Median (range)	38.0 (36-55)	31.0 (21-50)	31.0 (23-34)	35.0 (31-54)	34.5 (21-55)
Height, cm Median (range)	170.0 (158-185)	173.0 (166-177)	175.0 (173-182)	180.0 (166-183)	173.5 (158-185)
Weight, kg Median (range)	71.0 (50-88)	74.0 (58-90)	67.0(66-68)	75.0 (66-93)	69.5 (50-93)
BMI, kg/m ² Median (range)	24.57 (20.0-26.8)	25.31 (21.0-28.7)	21.55 (20.2-22.5)	25.40 (19.7-28.7)	23.95 (19.7-28.7)
Sex, n (%)					
Male	3 (60.0)	5 (100.0)	5 (100.0)	5 (100.0)	18 (90.0%)
Ethnic Origin, n (%)					
Caucasian	4 (80.0)	4 (80.0)	5 (100.0)	2 (40.0)	15 (75.0)
Black	0	0	0	1 (20.0)	1 (5.0)
Asian/Oriental	0	0	0	1 (20.0)	1 (5.0)
Other	1 (20.0)	1 (20.0)	0	1 (20.0)	3 (15.0)
Type of Smoker, n (%)					
Non-smoker	5 (100.0)	3 (60.0)	3 (60.0)	3 (60.0)	14 (70.0)

Table 4-TMC278-C137 treatment sequences

	Session 1	Session 2	Session 3	Session 4
Group 1	A	D	B	C
Group 2	B	A	C	D
Group 3	C	B	D	A
Group 4	D	C	A	B

Figure 2-TMC278-C137 subject disposition



10.2 Prior and Concomitant Medications

There were no subjects that administered concurrent medications during the trial.

10.3 Pharmacokinetic and Statistical Analysis

There were 6, 5, 6 and 6 subjects in Treatments A, B, C and D, respectively, with a quantifiable predose rilpivirine drug concentration that was less than 5% of the subject's rilpivirine C_{max} on Day 1.

Rilpivirine

Table 5-Pharmacokinetic parameters for single doses of rilpivirine 75 mg once daily with Treatments A, B, C and D

<i>Pharmacokinetics of TMC278</i> (mean \pm SD, t_{max} : median [range])	Standard breakfast (reference)	Fasting conditions (Test 1)	High-fat breakfast (Test 2)	Protein-rich nutritional drink (Test 3)
n	19	19	19 ^a	18
t_{max} , h	5.0 (2.0 - 9.0)	4.0 (2.0 - 24.0)	5.0 (3.0 - 9.0)	5.0 (4.0 - 9.0)
C_{max} , ng/mL	296.4 \pm 117.6	170.2 \pm 65.61	279.8 \pm 102.6	156.0 \pm 59.66
AUC_{last} , ng h/mL	10340 \pm 3894	6230 \pm 2339	9717 \pm 3535	5437 \pm 2421
AUC_{∞} , ng h/mL	11450 \pm 4431	7202 \pm 3024	10670 \pm 4331	6094 \pm 3047
$t_{1/2term}$, h	47.98 \pm 22.08	54.84 \pm 28.25	43.05 \pm 17.28	47.29 \pm 22.89

^a n=18 for AUC_{last} , AUC_{∞} and $t_{1/2term}$

Table 6-Statistical analysis for rilpivirine with a standard meal (reference arm) and fasted conditions (test arm)

<i>Parameter</i>	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b	p-value	
	Treatment A (reference)	Treatment B (Test 1)			Period	Sequence
C_{max} , ng/mL	275.8	150.2	54.45	42.92 - 69.07	0.8372	0.5425
AUC_{last} , ng h/mL	9683	5546	57.27	45.72 - 71.75	0.8452	0.4668
AUC_{∞} , ng h/mL	10620	6269	59.02	46.87 - 74.32	0.9196	0.3921
	Median				p-value	
<i>Parameter</i>	Treatment A (reference)	Treatment B (Test 1)	Treatment difference median	90% CI, % ^b	Period	Sequence
t_{max} , h	5.0	4.0	1.00	(0.50) - (2.00)	0.3494	0.2968

^a n=19 for Reference and n=19 for Test

^b 90% confidence intervals.

Based on the statistical analysis after a single dose of rilpivirine 75 mg administered under fasted condition, the mean rilpivirine C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ values were decreased compared to rilpivirine administered with a standard meal. The 90% confidence interval for rilpivirine C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ were not within 80%-125%.

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Table 7-Statistical analysis for rilpivirine with a standard meal (reference arm) and a high fat meal (test arm)

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b	p-value	
	Treatment A (reference)	Treatment C (Test 2)			Period	Sequence
C_{max} , ng/mL	272.5	251.2	92.20	80.97 - 105.0	0.2852	0.4456
AUC_{last} , ng h/mL	9705	8950	92.21	79.81 - 106.5	0.7911	0.2659
AUC_{∞} , ng h/mL	10650	9685	90.94	78.52 - 105.3	0.7408	0.3431
Median					p-value	
Parameter	Treatment A (reference)	Treatment C (Test 2)	Treatment difference median	90% CI, % ^b	Period	Sequence
t_{max} , h	5.0	5.0	0.50	(-0.50) - (2.00)	0.1662	1.000

^a n=19 for Reference and n=19 for Test (C_{max}) and n=18 for Test (AUC_{last} and AUC_{∞})

^b 90% confidence intervals.

Based on the statistical analysis after a single dose of rilpivirine 75 mg administered with a high fat meal, the mean rilpivirine C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ values were decreased (less than a 10% decrease) compared to rilpivirine administered with a standard meal. The 90% confidence interval for rilpivirine C_{max} was within 80%-125%. The 90% confidence interval for rilpivirine $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ were not within 80%-125%, with the lower limit of the 90% confidence interval for both parameters falling below 80% by less than 5%.

Table 8-Statistical analysis for rilpivirine with a standard meal (reference arm) and a protein containing drink (test arm)

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI, % ^b	p-value	
	Treatment A (reference)	Treatment D (Test 3)			Period	Sequence
C_{max} , ng/mL	275.8	138.4	50.17	39.66 - 63.46	0.5312	0.7872
AUC_{last} , ng h/mL	9683	4866	50.25	41.36 - 61.05	0.8845	0.6008
AUC_{∞} , ng h/mL	10620	5369	50.55	41.50 - 61.56	0.8593	0.5990
Median					p-value	
Parameter	Treatment A (reference)	Treatment D (Test 3)	Treatment difference median	90% CI, % ^b	Period	Sequence
t_{max} , h	5.0	5.0	0.50	(-0.50) - (1.50)	0.1135	0.5852

^a n=19 for Reference and n=18 for Test

^b 90% confidence intervals.

Based on the statistical analysis after a single dose of rilpivirine 75 mg administered with a protein containing drink, the mean rilpivirine C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ values

were decreased compared to rilpivirine administered with a standard meal. The 90% confidence interval for rilpivirine C_{\max} , $AUC_{(0-\text{last})}$, and $AUC_{(0-\infty)}$ were not within 80%-125%.

The applicant did not compare the changes in rilpivirine exposure with high fat meals compared to fasted conditions or vice versa. Based on the 90% confidence intervals, similar C_{\max} and lower $AUC_{(0-\text{last})}$, and $AUC_{(0-\infty)}$ values were observed with high fat meals compared to standard meals. Therefore, the percent change in rilpivirine exposure with fasted conditions compared to high fat meals is anticipated to be similar for C_{\max} and greater for $AUC_{(0-\text{last})}$ and $AUC_{(0-\infty)}$ compared to the changes in rilpivirine exposure in Table 6. However, the difference in rilpivirine exposure when administered with a high fat meal compared to a standard meal is not clinically significant. The applicant's statement in the proposed rilpivirine prescribing information that there is a 40% change in rilpivirine exposure with either standard or high fat meals (presumably referring to the change in $AUC_{(0-\text{last})}$, and $AUC_{(0-\infty)}$ values) compared to fasted conditions is acceptable.

10.4 Safety Issues

No deaths or other serious adverse events were reported for the trial. No grade 3 or grade 4 adverse events were reported. There were no grade 1 or grade 2 adverse events that were possibly, probably, or very likely related to rilpivirine. Information regarding the adverse events that were reported in the trial is summarized in Table 9.

Table 9-Adverse event incidence categorized by system organ class and preferred term

System Organ Class Preferred Term n (%)	Treatment A (N = 19)	Treatment B (N = 19)	Treatment C (N = 19)	Treatment D (N = 18)	Total (N = 20)
<i>Any AE</i>	3 (15.8)	1 (5.3)	2 (10.5)	0	5 (25.0)
<i>Gastrointestinal Disorders</i>					
Diarrhea	0	1 (5.3)	0	0	1 (5.0)
<i>General Disorders and Administration Site Conditions</i>					
Puncture site pain	1 (5.3)	0	0	0	1 (5.0)
<i>Infections and Infestations</i>	1 (5.3)	0	1 (5.3)	0	2 (10.0)
Gastroenteritis	0	0	1 (5.3)	0	1 (5.0)
Rhinitis	1 (5.3)	0	0	0	1 (5.0)
<i>Nervous System Disorders</i>					
Headache	0	0	1 (5.3)	0	1 (5.0)
<i>Vascular Disorders</i>					
Hot flush	1 (5.3)	0	0	0	1 (5.0)

n = number of subjects with 1 or more events; N = number of subjects per treatment.

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11. Discussion and Conclusions

Based on the results from the trial, the following conclusions can be made:

- After a single dose of rilpivirine 75 mg administered under fasted condition, the mean rilpivirine C_{\max} , $AUC_{(0-\text{last})}$, and $AUC_{(0-\infty)}$ values were decreased by 46%,

43%, and 41%, respectively, compared to rilpivirine administered with a standard meal. The 90% confidence interval for rilpivirine C_{\max} , $AUC_{(0-\text{last})}$, and $AUC_{(0-\infty)}$ were not within 80%-125%.

- After a single dose of rilpivirine 75 mg administered with a high fat meal, the mean rilpivirine C_{\max} , $AUC_{(0-\text{last})}$, and $AUC_{(0-\infty)}$ values were decreased by 8%, 8%, and 9%, respectively, compared to rilpivirine administered with a standard meal. The 90% confidence interval for rilpivirine C_{\max} was within 80%-125%. The 90% confidence interval for rilpivirine $AUC_{(0-\text{last})}$, and $AUC_{(0-\infty)}$ were not within 80%-125%.
- After a single dose of rilpivirine 75 mg administered with a protein containing drink, the mean rilpivirine C_{\max} , $AUC_{(0-\text{last})}$, and $AUC_{(0-\infty)}$ values were decreased by 50%, 50%, and 49%, respectively, compared to rilpivirine administered with a standard meal. The 90% confidence interval for rilpivirine C_{\max} , $AUC_{(0-\text{last})}$, and $AUC_{(0-\infty)}$ were not within 80%-125%.

A food effect exists for rilpivirine when administered at 75 mg once daily. Higher rilpivirine exposure are observed when rilpivirine is administered with a standard and high fat meals compared to fasted conditions. The percent change in rilpivirine exposure with fasted conditions compared to high fat meals is anticipated to be similar for C_{\max} and greater for $AUC_{(0-\text{last})}$ and $AUC_{(0-\infty)}$ compared to the changes in rilpivirine exposure with fasted versus standard meals. However, the difference in rilpivirine exposure when administered with a high fat meal compared to a standard meal is not clinically significant and both types of meals may be administered with rilpivirine.

Across the dose range of 25 mg to 150 mg, increases in rilpivirine exposure were approximately dose proportional and the results of the C137 trial are anticipated to be applicable to administration of rilpivirine 25 mg once daily with a meal. The applicant's recommendation in the proposed rilpivirine prescribing information that rilpivirine 25 mg once daily should be administered with a meal is acceptable.

Hepatic impairment trial

Trial Number	Title	Page Number
TMC278-C130	Pharmacokinetics, safety and tolerability of TMC278 in subjects with mildly or moderately impaired hepatic function	263

TMC278-C130

1. Title

Pharmacokinetics, safety and tolerability of TMC278 in subjects with mildly or moderately impaired hepatic function

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at [REDACTED] (b) (4) from June 18, 2008 to November 16, 2009.

2. Objectives

The objective of the trial was to evaluate the rilpivirine single and steady state pharmacokinetics and safety in mild or moderate hepatically impaired subjects compared to healthy subjects

3. Trial Design

TMC278-TiDP6-C130 was a Phase I, open label, parallel, clinical trial that enrolled 32 male and female subjects between 18 and 65 years old. In Panel A, two groups (8 subjects in each group) were enrolled: the first group was subjects with mild hepatic impairment (Panel A1) and the second group were healthy subjects (Panel A2). In Panel B, two groups (8 subjects in each group) were enrolled: the first group was subjects with moderate hepatic impairment (Panel B1) and the second group was healthy subjects (Panel B2). The degree of hepatic impairment (mild or moderate) was categorized using the Child-Pugh classification. The total duration of treatment for both Panel A and Panel B was 11 days. For Panels A2 and B2, healthy subjects were matched for gender, age (± 5 yrs), and body mass index (BMI) ($\pm 15\%$) to subjects with mild and moderate hepatic impairment, respectively.

5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Subjects with hepatic impairment were permitted to continue using medications for managing hepatic impairment, including albumin, diuretics, lactulose, beta blockers, and vitamins. Use of proton pump inhibitors was not permitted. All other medications were to be reviewed on a case by case basis (with the exception of acetaminophen and ibuprofen).

For healthy subjects, use of ibuprofen and acetaminophen was permitted up to three days before first dosing. Afterwards, ibuprofen use was permitted up to 400 mg/day and acetaminophen use was permitted up to 1000 mg/day. Any over the counter medications were to be discontinued a minimum of 7 days before first dosing and any prescription medications were to be discontinued a minimum of fourteen days before first dosing

(with the exception of ibuprofen and acetaminophen). Use of any medication other than trial medication, ibuprofen, acetaminophen, and medications for the treatment of adverse events was not permitted up to fourteen days after the last administration of trial medication. Use of herbal medicines or dietary supplements was not permitted from fourteen days before first dosing up to fourteen days after the last administration of trial medication.

Use of liquids containing alcohol or quinine was not permitted from 24 hours before the first administration of trial medication until Day 18. Intake of grapefruit and grapefruit juice was not permitted from 7 days before the first administration of trial medication until Day 18.

In the event of an adverse event, the following medications were permitted:

- A) Rash or an allergic reaction: cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents (specific medications were not included in the trial report)
- B) Nausea: antiemetics (specific medications were not included in the trial report)
- C) Diarrhea: loperamide

6. Dosage and Administration

Prior to obtaining blood samples for pharmacokinetic analysis on Days 1 and 11, subjects fasted overnight for a minimum of 10 hours. After a standard meal in the morning, rilpivirine was administered within 10 minutes after completion of the meal.

7. Rationale for Doses Used in the Trial

The rilpivirine dosage regimen that was administered to all subjects in both Panel A and Panel B was 25 mg once daily with a meal. This is the dosage regimen that was evaluated in the Phase 3 clinical trials and is the recommended dosage regimen in the proposed prescribing information.

8. Drugs Used in the Trial

Rilpivirine 25 mg tablets (formulation F006) were administered in the trial. This is the tablet that is to be commercially marketed.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Blood samples for analysis of rilpivirine concentrations were obtained on Day 1 and Day 11.

In Panel A, on Day 1, blood samples were obtained at predose (0 hour), and 0.5, 1, 2, 3, 4, 5, 6, 9, 12, and 16 hours postdose, and a 24 hour postdose sample was drawn on Day 2.

On Days 9 and 10, trough concentrations were obtained. On Day 11, blood samples were obtained at predose (0 hour), and 0.5, 1, 2, 3, 4, 5, 6, 9, 12, and 16 hours postdose. 24, 48, 72, 120, and 168 hour postdose samples were drawn on Days 12, 13, 14, 16, and 18, respectively.

In Panel B, on Day 1, blood samples were obtained at predose (0 hour), and 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 14, 16, 18, 20 and 22 hours postdose, and a 24 hour postdose sample was drawn on Day 2. On Days 9 and 10, trough concentrations were obtained. On Day 11, blood samples were obtained at predose (0 hour), and 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 14, 16, 18, 20, 22 hours postdose. 24, 48, 72, 120 and 168 hour postdose samples were drawn on Days 12, 13, 14, 16, and 18, respectively.

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a validated LC/MS/MS method by Johnson and Johnson Pharmaceutical Research and Development. The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the TMC278-TiDP6-C130 trial, precision and accuracy were evaluated using the low (either 2.71 or 2.77 ng/mL), medium (54.3 or 55.3 ng/mL), and high (1570 ng/mL) QC samples. The corresponding rilpivirine inter-run accuracy values were 1.1%, or 4.3% for the low QCs, -0.2% or 0.9% for the medium QCs, and -1.9% for the high QCs, and the rilpivirine inter-run precision values were 5.5% or 4.5% for the low QCs, 3.5% or 7.2% for the medium QCs, and 6.5% for the high QCs.

The submitted rilpivirine long term stability data of 1528 days covered the duration of long term rilpivirine stability data necessary for the hepatic impairment trial.

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate pharmacokinetic parameters, including C_{max} and $AUC_{(0-24h)}$. Rilpivirine clearance and volume of distribution parameters were not evaluated. If a major difference (> 10.00% deviation from the scheduled time) was observed, the actual sampling time was used instead of the scheduled sampling time.

The applicant did not evaluate protein binding of rilpivirine in healthy and hepatically impaired subjects.

Statistical Analysis

Descriptive statistics were calculated for rilpivirine plasma concentrations and pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), geometric mean, median, and the minimum and maximum values.

Statistical analysis involved comparison of rilpivirine log transformed pharmacokinetic parameters for mild or moderate hepatic impairment subjects (test arms) compared to healthy subjects (reference arm). On Day 1 C_{max} , and $AUC_{(0-24h)}$, were evaluated, and on Day 7, C_{24h} , C_{max} , $AUC_{(0-24h)}$ were evaluated. Using a linear mixed effects model, least squares means were calculated and 90% confidence intervals were derived based on the difference of the pharmacokinetic parameter's least squares means for the test and reference arms. The applicant did not specify predetermined "no effect boundaries" for the 90% confidence intervals.

An assessment was performed to determine if rilpivirine steady state concentrations were achieved by Day 11 based on predose concentrations from Days 9, 10 and 11.

10. Results

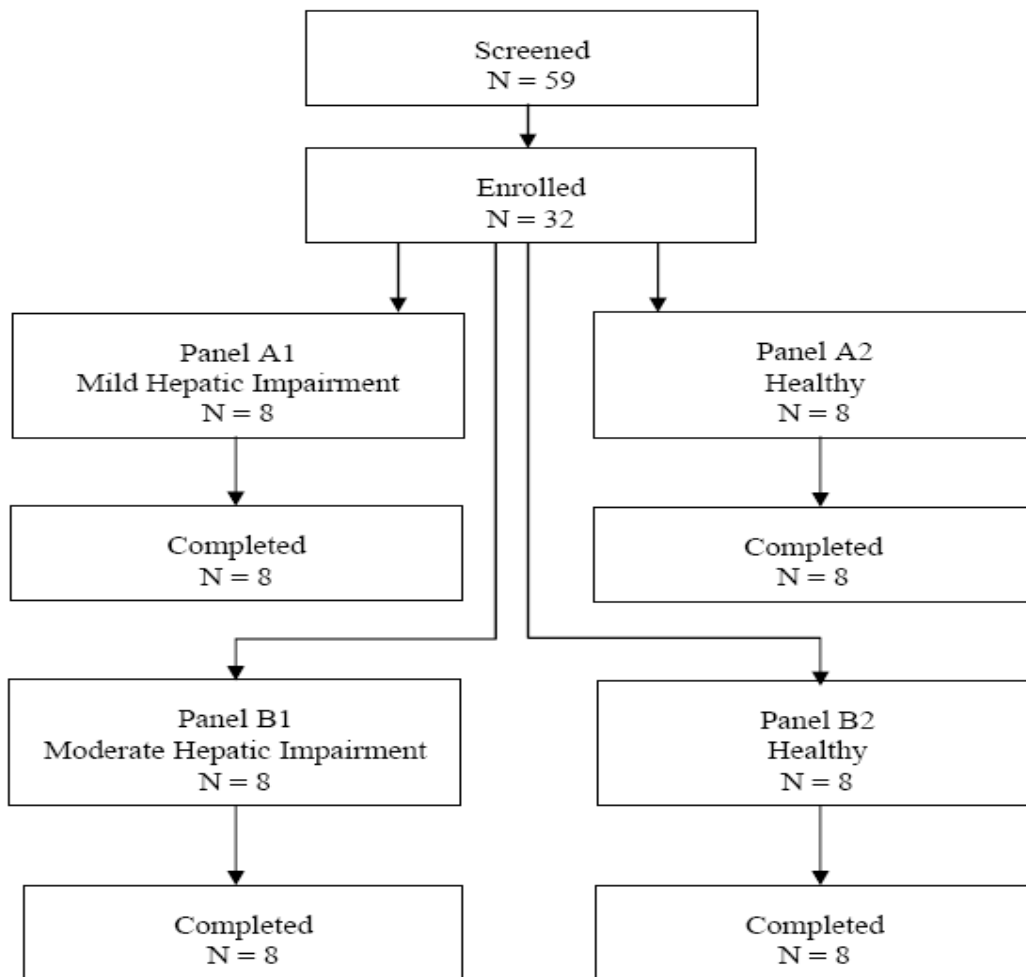
10.1 Subject Demographics and Disposition

Table 1-TMC278-C130 subject demographics

Parameter	Panel A		Panel B	
	Healthy N = 8	Mild Hepatic Impairment N = 8	Healthy N = 8	Moderate Hepatic Impairment N = 8
Age, years				
Median (range)	48.0 (36-61)	47.5 (41-57)	52.0 (45-65)	53.0 (47-64)
Height, cm				
Median (range)	172.0 (158-189)	172.5 (160-190)	175.5 (155-184)	171.5 (158-182)
Weight, kg				
Median (range)	80.5 (61-100)	77.0 (61-100)	81.0 (55-107)	81.0 (59-98)
BMI, kg/m ²				
Median (range)	26.30 (21.0-31.4)	26.96 (21.6-30.6)	26.98 (22.5-31.6)	26.77 (21.2-31.8)
Gender, n (%)				
Male	4 (50.0%)	4 (50.0%)	6 (75.0%)	6 (75.0%)
Race, n (%)				
White	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)
Type of Smoker, n (%)				
Light	5 (62.5%)	6 (75.0%)	3 (37.5%)	3 (37.5%)

Specific Child Pugh scores for hepatically impaired subjects were not reported and subjects were only classified into general Child Pugh categories of mild (5 to 6) or moderate (7 to 9) hepatic impairment.

Figure 2-TMC278-C130 subject disposition



10.2 Prior and Concomitant Medications

Medications that were taken by greater than 2 subjects per panel were evaluated for the potential to alter CYP 3A metabolism. The medications that meet this criterion were spironolactone, furosemide, and lactulose. None of these medications would be expected to alter CYP 3A metabolism.

10.3 Pharmacokinetic and Statistical Analysis

Subjects with mild hepatic impairment

Table 2-Pharmacokinetic parameters for mild hepatic impairment subjects and matched healthy subjects [%FI=100 x ((C_{max}-C_{min})/C_{ss,av})]

Pharmacokinetics of TMC278 (mean ± SD, t _{max} : median [range])	Panel A	
	Healthy (reference)	Mild Hepatic Impairment (test)
n	8	8 ^b
Day 1		
C _{max} , ng/mL	81.73 ± 20.01	90.29 ± 31.96
t _{max} , h	4.0 (3.0 - 9.0)	4.5 (2.0 - 5.0)
AUC _{24h} , ng.h/mL	890.2 ± 169.0	1071 ± 266.3
Ratio C _{max} , hepatic/healthy, % ^a	-	110.5
Ratio AUC _{24h} , hepatic/healthy, % ^a	-	120.3
Day 9		
C _{0h} , ng/mL	64.04 ± 18.79	126.8 ± 46.17
Day 10		
C _{0h} , ng/mL	69.08 ± 25.75	126.3 ± 49.95
Day 11		
C _{0h} , ng/mL	77.56 ± 22.12	137.8 ± 62.25
C _{min} , ng/mL	65.65 ± 18.58	84.13 ± 20.72
C _{24h} , ng/mL	82.09 ± 20.87	147.1 ± 50.20
C _{max} , ng/mL	144.3 ± 35.70	187.0 ± 66.31
t _{max} , h	5.0 (3.0 - 12.0)	5.0 (2.0 - 24.0)
AUC _{24h} , ng.h/mL	2152 ± 538.1	3206 ± 1080
t _{1/2term} , h	60.59 ± 20.03	80.82 ^c ± 33.17 ^c
C _{ss,av} , ng/mL	89.68 ± 22.42	133.6 ± 45.00
FI, %	89.91 ± 29.74	74.40 ± 22.04
Ratio C _{min} , hepatic/healthy, % ^a	-	128.1
Ratio C _{24h} , hepatic/healthy, % ^a	-	179.2
Ratio C _{max} , hepatic/healthy, % ^a	-	129.6
Ratio AUC _{24h} , hepatic/healthy, % ^a	-	149.0

^a Ratio of mean pharmacokinetic parameter values

^b n = 7 for t_{1/2term}

^c Accurate determination not possible

^d n = 6 for Day 1 and n = 5 for t_{1/2term}

Table 3-Statistical analysis of mild hepatic impairment subjects (test arm) compared to matched healthy subjects (reference arm)

Parameter	Panel A			
	LSmeans ^a		LSmeans ratio	90% CI ^b
	Healthy (reference)	Mild Hepatic Impairment (test)		
Day 1				
C _{max} , ng/mL	79.58	84.38	1.060	0.7834 - 1.435
AUC _{0-24h} , ng.h/mL	876.0	1031	1.177	0.9315 - 1.487
Day 11				
C _{min} , ng/mL	62.73	81.97	1.307	1.004 - 1.702
C _{0h} , ng/mL	79.62	139.9	1.758	1.343 - 2.301
C _{max} , ng/mL	140.4	178.0	1.268	0.9804 - 1.641
AUC _{0-24h} , ng.h/mL	2093	3070	1.467	1.144 - 1.881
Parameter	Median ^a		Treatment difference median	90% CI ^b
	Healthy (reference)	Mild Hepatic Impairment (test)		
Day 1				
t _{max} , h	4.0	4.5	1.00	(-1.00) - (1.00)
Day 11				
t _{max} , h	5.0	5.0	0.00	(-2.00) - (12.00)

^a n = 8 for reference and test

^b 90% CIs

On Days 1 and Day 11, higher mean C_{max} and AUC_(0-24h) values were observed in subjects with mild hepatic impairment compared to matched healthy subjects. Higher C_{0h}, C_{24h}, and C_{min} values on Day 11 were also observed in subjects with mild hepatic impairment compared to matched healthy subjects. The change in the mean C_{max} and AUC_(0-24h) ratio was higher on Day 11 compared to Day 1 when subjects with mild hepatic impairment were compared to matched healthy subjects.

On Day 1, the intersubject variability for C_{max} and AUC_(0-24h) was 24.5% and 19%, respectively, in the matched healthy subjects and the intersubject variability for C_{max} and AUC_(0-24h) was 35.4% and 24.9%, respectively, in mild hepatic impairment subjects. On Day 11, the intersubject variability for C_{min}, C_{0h}, C_{max} and AUC_(0-24h) was 28.3%, 28.5%, 24.8% and 25%, respectively, in the matched healthy subjects and the intersubject variability for C_{min}, C_{0h}, C_{max} and AUC_(0-24h) was 24.6%, 45.2%, 35.5%, and 33.7%, respectively, in mild hepatic impairment subjects.

Subjects with moderate hepatic impairment

Table 4-Pharmacokinetic parameters for moderate hepatic impairment subjects and matched healthy subjects

Pharmacokinetics of TMC278 (mean ± SD, t _{max} : median [range])	Panel B	
	Healthy (reference)	Moderate Hepatic Impairment (test)
n	8	8 ^d
Day 1		
C _{max} , ng/mL	62.99 ± 22.31	44.43 ± 17.69
t _{max} , h	5.0 (3.0 - 5.0)	5.0 (2.0 - 22.0)
AUC _{24h} , ng.h/mL	726.9 ± 214.0	569.6 ± 227.5
Ratio C _{max} , hepatic/healthy, % ^a	-	70.54
Ratio AUC _{24h} , hepatic/healthy, % ^a	-	78.36
Day 9		
C _{0h} , ng/mL	79.68 ± 24.35	98.31 ± 24.73
Day 10		
C _{0h} , ng/mL	86.26 ± 16.08	118.9 ± 53.73
Day 11		
C _{0h} , ng/mL	81.83 ± 17.81	122.2 ± 51.53
C _{min} , ng/mL	67.31 ± 14.88	76.55 ± 26.24
C _{24h} , ng/mL	88.75 ± 23.56	121.7 ± 62.22
C _{max} , ng/mL	146.8 ± 30.21	143.5 ± 49.69
t _{max} , h	5.0 (3.0 - 5.0)	20.0 (2.0 - 24.0)
AUC _{24h} , ng.h/mL	2318 ± 385.9	2525 ± 851.2
t _{1/2term} , h	56.01 ± 21.31	90.56 ^c ± 37.04 ^c
C _{ss,av} , ng/mL	96.58 ± 16.08	105.2 ± 35.47
FI, %	83.63 ± 30.34	65.26 ± 13.20
Ratio C _{min} , hepatic/healthy, % ^a	-	113.7
Ratio C _{24h} , hepatic/healthy, % ^a	-	137.1
Ratio C _{max} , hepatic/healthy, % ^a	-	97.75
Ratio AUC _{24h} , hepatic/healthy, % ^a	-	108.9

^a Ratio of mean pharmacokinetic parameter values

^b n = 7 for t_{1/2term}

^c Accurate determination not possible

^d n = 6 for Day 1 and n = 5 for t_{1/2term}

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Table 5-Statistical analysis of moderate hepatic impairment subjects (test arm) compared to matched healthy subjects (reference arm)

Parameter	Panel B			
	LSmeans^a		LSmeans ratio	90% CI^b
	Healthy (reference)	Moderate Hepatic Impairment (test)		
Day 1				
C _{max} , ng/mL	59.10	41.74	0.7062	0.4835 - 1.031
AUC _{24h} , ng.h/mL	697.8	532.7	0.7635	0.5426 - 1.074
Day 11				
C _{min} , ng/mL	65.78	73.05	1.111	0.8671 - 1.423
C _{24h} , ng/mL	86.05	109.8	1.276	0.9079 - 1.792
C _{max} , ng/mL	144.2	136.9	0.9496	0.7514 - 1.200
AUC _{24h} , ng.h/mL	2290	2409	1.052	0.8379 - 1.320
Parameter	Median^a		Treatment difference median	90% CI^b
	Healthy (reference)	Moderate Hepatic Impairment (test)		
Day 1				
t _{max} , h	5.0	5.0	0.00	(-1.00) - (2.00)
Day 11				
t _{max} , h	5.0	20.0	16.00	(1.00) - (19.00)

^a n = 8 for reference and test, except n = 6 for test C_{max}, t_{max} and AUC_{24h} of Day 1

^b 90% CIs

On Day 1, lower mean C_{\max} , and $AUC_{(0-24h)}$ values were observed, and on Day 11 lower mean C_{\max} , and higher $AUC_{(0-24h)}$ values were observed in subjects with moderate hepatic impairment compared to matched healthy subjects. Higher C_{0h} , C_{24h} , and C_{\min} values were observed on Day 11 in subjects with moderate hepatic impairment compared to matched healthy subjects.

On Day 1, the intersubject variability for C_{\max} and $AUC_{(0-24h)}$ was 35.4% and 29.4%, respectively, in the matched healthy subjects and the intersubject variability for C_{\max} and $AUC_{(0-24h)}$ was 39.8% and 39.9%, respectively, in moderate hepatic impairment subjects. On Day 11, the intersubject variability for C_{\min} , C_{0h} , C_{\max} and $AUC_{(0-24h)}$ was 22.1%, 21.8%, 20.6%, and 16.7%, respectively, in the matched healthy subjects and the intersubject variability for C_{\min} , C_{0h} , C_{\max} and $AUC_{(0-24h)}$ was 34.3%, 42.2%, 34.6% and 33.7%, respectively, in moderate hepatic impairment subjects.

Other pharmacokinetic information

Based on evaluating the individual rilpivirine predose concentrations, steady state concentrations were achieved by Day 11 for mildly and moderately hepatically impaired subjects and for healthy subjects.

While the mean elimination half life in hepatically impaired subjects appeared to be longer when compared to healthy subjects, a definitive conclusion regarding the half life comparison for hepatically impaired versus healthy subjects could not be made based on the available data. The trial report states that in all but one subject with hepatic impairment an accurate estimation of the half life could not be made either because the available time period for estimating the half life was less than twice the derived half life or the regression coefficient was less than 0.9. In three out of eight healthy subjects, the half life could not be accurately estimated.

10.4 Safety Issues

No deaths were reported for the trial. During follow up, in subjects with moderate hepatic impairment, one grade 3 adverse event (inguinal hernia) and one grade 4 adverse event (increased bilirubin) were reported for the trial.

Table 6-Adverse event incidence reported categorized by system organ class and preferred term

System Organ Class Preferred Term n (%)	Panel A		Panel B	
	Healthy N = 8	Mild Hepatic Impairment N = 8	Healthy N = 8	Moderate Hepatic Impairment N = 8
Any AE	2 (25.0)	4 (50.0)	3 (37.5)	3 (37.5)
Nervous System Disorders	1 (12.5)	2 (25.0)	1 (12.5)	1 (12.5)
Dizziness	0	1 (12.5)	0	1 (12.5)
Headache	0	1 (12.5)	1 (12.5)	0
Migraine	1 (12.5)	0	0	0
General Disorders and Administration Site Conditions	0	1 (12.5)	1 (12.5)	1 (12.5)
Asthenia	0	0	0	1 (12.5)
Fatigue	0	0	1 (12.5)	0
Thirst	0	1 (12.5)	0	0
Musculoskeletal and Connective Tissue Disorders	0	1 (12.5)	0	2 (25.0)
Back pain	0	1 (12.5)	0	1 (12.5)
Muscle spasms	0	0	0	1 (12.5)
Eye Disorders	0	0	1 (12.5)	1 (12.5)
Conjunctivitis	0	0	1 (12.5)	1 (12.5)
Gastrointestinal Disorders	1 (12.5)	2 (25.0)	0	0
Abdominal discomfort	0	1 (12.5)	0	0
Diarrhea	1 (12.5)	0	0	0
Dyspepsia	0	1 (12.5)	0	0
Nausea	0	1 (12.5)	0	0
Vomiting	0	1 (12.5)	0	0
Infections and Infestations	0	1 (12.5)	0	1 (12.5)
Nasopharyngitis	0	1 (12.5)	0	1 (12.5)
Skin and Subcutaneous Tissue Disorders	0	0	1 (12.5)	1 (12.5)
Pruritus	0	0	1 (12.5)	1 (12.5)
Psychiatric Disorders	1 (12.5)	0	0	0
Nervousness	1 (12.5)	0	0	0
Sleep disorder	1 (12.5)	0	0	0
Renal and Urinary Disorders	0	1 (12.5)	0	0
Nocturia	0	1 (12.5)	0	0
Pollakiuria	0	1 (12.5)	0	0
Reproductive and Breast Disorders	1 (12.5)	0	0	0
Post menopausal hemorrhage	1 (12.5)	0	0	0

Table 7-Adverse event incidence possibly related to rilpivirine categorized by system organ class and preferred term

System Organ Class Preferred Term n (%)	Panel A		Panel B	
	Healthy N = 8	Mild Hepatic Impairment N = 8	Healthy N = 8	Moderate Hepatic Impairment N = 8
Nervous System Disorders	0	1 (12.5)	1 (12.5)	1 (12.5)
Dizziness	0	0	0	1 (12.5)
Headache	0	1 (12.5)	1 (12.5)	0
General Disorders and Administration Site Conditions	0	1 (12.5)	1 (12.5)	1 (12.5)
Asthenia	0	0	0	1 (12.5)
Fatigue	0	0	1 (12.5)	0
Thirst	0	1 (12.5)	0	0
Gastrointestinal Disorders	1 (12.5)	1 (12.5)	0	0
Diarrhea	1 (12.5)	0	0	0
Nausea	0	1 (12.5)	0	0
Vomiting	0	1 (12.5)	0	0
Skin and Subcutaneous Tissue Disorders	0	0	1 (12.5)	1 (12.5)
Pruritus	0	0	1 (12.5)	1 (12.5)
Renal and Urinary Disorders	0	1 (12.5)	0	0
Nocturia	0	1 (12.5)	0	0
Pollakiuria	0	1 (12.5)	0	0

One important safety issue that was noted in reviewing the trial was the ECG abnormalities (see Table 5 below) that occurred in subjects with mild or moderate hepatic impairment but not in the matched healthy subjects. The trial also collected information on the worst changes in QTcF or QTcB that were observed in the trial. Two subjects (one subject with mild hepatic impairment and one subject with moderate hepatic impairment) experienced an abnormal increase of 30-60 ms from baseline resulting in a QTcF value of greater than 450 to 480 ms (see Table 8) during treatment. The specific subjects are not identified in the trial report or in the accompanying listings.

Table 8-Worst treatment emergent ECG abnormalities and worst QTcF and QTcB changes during rilpivirine treatment

Parameter Abnormal result n (%)	Panel A		Panel B	
	Healthy N = 8	Mild Hepatic Impairment N = 8	Healthy N = 8	Moderate Hepatic Impairment N = 8
QTcF				
Any treatment-emergent abnormality	0	1 (12.5)	0	1 (12.5)
Abnormal actual value of > 450 - 480 ms	0	1 (12.5)	0	1 (12.5)
QTcB				
Any treatment-emergent abnormality	0	2 (25.0)	0	1 (12.5)
Abnormal actual value of > 450 - 480 ms	0	1 (12.5)	0	1 (12.5)
Abnormal increase of 30 - 60 ms	0	1 (12.5)	0	0

N = number of subjects, n = number of subjects with treatment-emergent worst abnormalities.

11. Discussion and Conclusions

In subjects with mild hepatic impairment, the greatest change in rilpivirine exposure occurred on Day 11 with C_{24h} and $AUC_{(0-24h)}$ increasing by 76% (90% CI: 134.3%-230.1%) and 47% (90% CI: 114.4%-188.1%), respectively, compared to matched healthy subjects. For the other pharmacokinetic parameters, on Day 1, C_{max} and $AUC_{(0-24h)}$ were higher by 6% (90% CI: 78.34%-143.5%) and 18% (90% CI: 93.15%-148.7%), respectively and on Day 11, C_{min} and C_{max} were higher by 31% (90% CI: 100.4%-170.2%) and 27% (90% CI: 98.04%-164.1%), respectively compared to matched healthy subjects. Overall, low to moderate variability was observed for the above pharmacokinetic parameters.

In subjects with moderate hepatic impairment, on Day 1, C_{max} and $AUC_{(0-24h)}$ were lower by 29% (90% CI: 48.35%-103.1%) and 24% (90% CI: 54.26%-107.4%), respectively and on Day 11, C_{min} , C_{24h} , $AUC_{(0-24h)}$ were higher by 11% (90% CI: 86.71%-142.3%), 28%, (90% CI: 90.79%-179.2%) and 5% (90% CI: 83.79%-132%), respectively and C_{max} were lower by 5% (90% CI: 75.14%-120%). Overall, low to moderate variability was observed for the above pharmacokinetic parameters.

For both mild and moderate hepatic impairment, there appeared to be an increase in the rilpivirine half life; however accurate estimations were not obtained for the trial. Based on the differences in $AUC_{(0-24h)}$ for mild hepatic impairment subject compared to the matched healthy control group, with multiple dosing it appears that an increase in the half life decreased the clearance of rilpivirine with mild hepatic impairment. A greater change was observed in the mean C_{max} and $AUC_{(0-24h)}$ ratio on Day 11 compared to Day 1 when subjects with mild hepatic impairment were compared to matched healthy subjects. For moderate hepatic impairment subjects, based on the differences in $AUC_{(0-24h)}$ compared to the healthy matched control group, with multiple dosing an increase in the half life did not result in a substantial impact on the clearance of rilpivirine in moderate hepatic impairment.

The reasons for a greater magnitude of change in rilpivirine exposure, as measured through $AUC_{(0-24h)}$ on Day 11, for mild hepatic impairment subjects compared to moderate hepatic impairment subjects are unclear. There were no specific subjects identified that could result in anomalous results. In vitro, rilpivirine is highly protein bound (99.7%) predominately to albumin. Decreased plasma protein concentrations and increased volume of distribution, which is observed with hepatic impairment, can result in decreased total plasma concentrations and no change in free plasma concentrations. However, rilpivirine plasma protein binding was not evaluated in the trial and the elimination half life could not be accurately estimated in both mild and moderate hepatic impairment subjects, so further conclusions can not be made. The volume of distribution was also not reported. In addition, alterations in the fraction absorbed of rilpivirine may also have contributed to the lower exposure with moderate hepatic impairment compared to the matched healthy control subjects on Day 1.

Based on the magnitude of change in rilpivirine C_{\max} and $AUC_{(0-24h)}$ in the trial compared to matched control subjects, no dose adjustment is necessary for rilpivirine in mild and moderate hepatic impairment patients. The pharmacokinetics of rilpivirine in subjects with severe hepatic impairment was not evaluated in the trial.

Mass balance trial

Trial Number	Title	Page Number
TMC278-C119	A Phase I, open label, single dose, mass-balance trial with ¹⁴ C-labeled TMC278	277

TMC278-C119

1. Title

A Phase I, open label, single dose, mass-balance trial with ^{14}C -labeled TMC278

2. Objectives

The objectives of the trial were to obtain information on the excretion and metabolic profile subsequent to administering a single dose of ^{14}C -labeled TMC278 (rilpivirine) in humans.

3. Trial Design

TMC278-C119 was a Phase I, open label trial that enrolled six male subjects between 40 and 60 years old.

4. Rationale for Doses Used in the Trial

A single dose of rilpivirine 150 mg (6 mL) was administered. 150 mg once daily was the highest rilpivirine dosing regimen evaluated in the clinical trials (other than the thorough QTc trial).

5. Drugs Used in the Trial

An oral rilpivirine solution (FK5343) was administered to subjects containing ^{14}C -labeled and unlabeled rilpivirine in PEG 400 at a concentration of 25 mg/mL. ^{14}C -labeled rilpivirine was labeled with ^{14}C on the nitrile carbon of the benzonitrile. The radioactivity amount that each subject received was 1.85 MBq or less (or 50 μCi or less).

6. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Blood samples were collected on Day 1 at predose, and 0.5, 1, 2, 3, 4, 6, 8, 12, and 16 hours postdose. Blood samples were also collected on Day 2 (24 and 32 hours), Day 3 (48 hours), Day 4 (72 hours), Day 5 (96 hours), Day 6 (120 hours), Day 7 (144 hours), and Day 8 (168 hours). Additional samples were also collected after Day 8 if the discharge criteria on Day 8 were not met. Secondly, blood samples were also collected to measure whole blood and plasma radioactivity and to quantify metabolites and determine metabolite structures on Day 1 at 1, 2, 4, 8, and 12 hours postdose and on Day 2 (24 hours), and Day 3 (48 hours).

Urine samples were collected at 3 intervals on Day 1 (0-4, 4-8, and 8-24 hours) and on other days, urine was collected at 24 hour intervals.

Feces were collected on all trial days from Day -1 to Day 7.

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a validated LC/MS/MS method by Johnson and Johnson Pharmaceutical Research and Development. The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the TMC278-C119 trial, precision and accuracy were evaluated using the low (2.51 ng/mL), medium (50.1 ng/mL), and high (1550 ng/mL) QC samples. The corresponding rilpivirine inter-run accuracy values were -9.6% for the low QCs, -3.4% for the medium QCs, and 5.2% for the high QCs, and the rilpivirine inter-run precision values were 0.3% for the low QCs, 2.5% for the medium QCs, and 0.9% for the high QCs. The submitted rilpivirine long term stability data of 1528 days covered the duration of long term rilpivirine stability data necessary for the TMC278-C119 trial.

One discrepancy that was noted in the bioanalytical report for the TMC278-C119 trial was the lack of a current certificate of analysis for the rilpivirine reference standard. The bioanalysis was conducted in April 2005 and the certificate of analysis included in the report listed a retest date of (b) (4) (the text of the report listed a retest date of (b) (4)).

The total radioactivity (^{14}C) analysis was conducted by Johnson and Johnson Pharmaceutical Research and Development using liquid scintillation counting. Concentrations were converted from disintegrations per minute (dpm)/mL to ng.eq./mL. For each sample, the lower limit of quantification (LLOQ) was individually selected but was generally set at 134 ng.eq./mL.

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate pharmacokinetic parameters, including C_{\max} , $\text{AUC}_{(0-\text{last})}$ and $\text{AUC}_{(0-\infty)}$. If a major difference ($> 10.00\%$ deviation from the scheduled time) was observed, the actual sampling time was used instead of the scheduled sampling time.

The following ratios were also calculated for each subject:

- For each time point, the ratio of rilpivirine (RPV) and total radioactivity in plasma (ratio C_t , RPV/total)
- The ratio of rilpivirine (RPV) and total radioactivity in plasma (ratio RPV/total) for C_{\max} , $\text{AUC}_{(0-\text{last})}$ and $\text{AUC}_{(0-\infty)}$.
- For each time point, the ratio of total radioactivity in whole blood and plasma (ratio C_t , $\text{blood}/\text{plasma}$).

Statistical Analysis

For rilpivirine and the total radioactivity, descriptive statistics were calculated for plasma concentrations and pharmacokinetic parameters. Descriptive statistics were also calculated for the ratio of total radioactivity in whole blood and plasma at each time point. The descriptive statistics that were calculated included the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), geometric mean, median, and the minimum and maximum values.

7. Results

7.1 Demographics

Table 1-TMC278-C119 subject demographics

Parameter	All Subjects (N = 6)
Age, years Median (range)	47.5 (45-51)
Height, cm Median (range)	175.5 (165-183)
Weight, kg Median (range)	84.5 (67-96)
BMI, kg/m ² Median (range)	27.05 (22.6-28.6)
Sex, n (%) Male	6 (100%)
Ethnic Origin, n (%) Caucasian/White	6 (100%)
Smoking, n (%) Yes (Light) ^a No	1 (16.7%) 5 (83.3%)

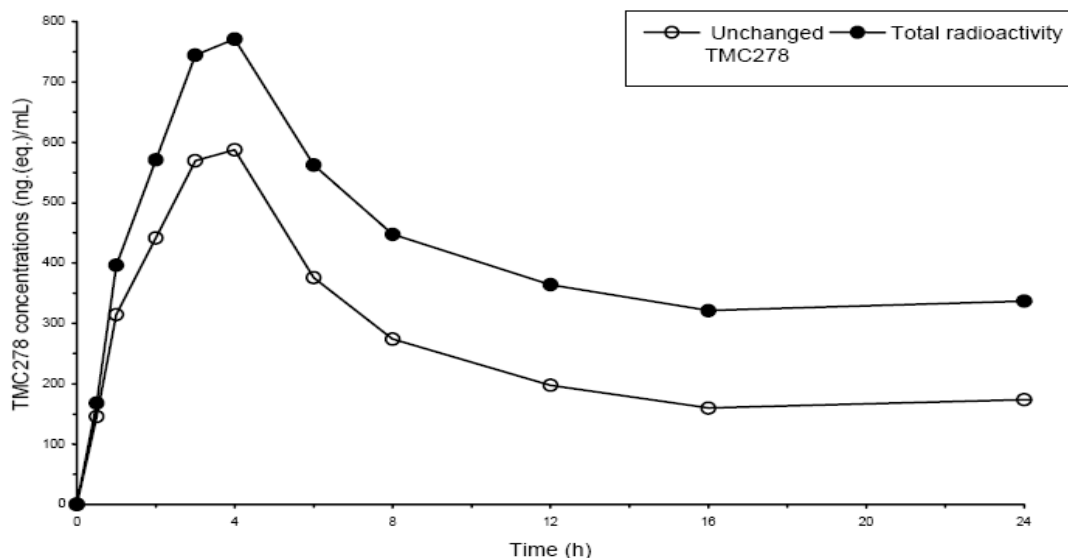
^a Light smoking was defined as no more than 10 cigarettes or 2 cigars or pipes per day

7.2 Pharmacokinetic and Statistical Analysis

For all six subjects, data for plasma concentrations, whole blood concentrations and pharmacokinetic parameters was analyzed for unchanged rilpivirine and total radioactivity (¹⁴C) [unchanged rilpivirine and metabolites].

Figure 1 below displays the mean concentration time profiles of unchanged rilpivirine and total radioactivity (¹⁴C) after a single 150 mg dose of rilpivirine containing ¹⁴C-labeled and unlabeled rilpivirine.

Figure 1- Mean concentration time profiles of unchanged rilpivirine and total radioactivity (^{14}C) after a single 150 mg dose of rilpivirine



At 168 hours postdose, all subjects had quantifiable unchanged rilpivirine concentrations. In contrast, only two subjects had measurable total radioactivity at 168 hours.

Table 2-Pharmacokinetic parameters of unchanged rilpivirine and total radioactivity

Pharmacokinetic of TMC278 (mean \pm SD, t_{\max} : median [range])	TMC278 (N = 6)	^{14}C -Total Radioactivity (N = 6)
t_{\max} , h	3.5 (3.0-4.0)	4.0 (3.0-4.0)
C_{\max} , ng(eq.)/mL	602.8 \pm 126.1	794.7 \pm 170.7
AUC_{last} , ng(eq.)h/mL	16240 \pm 4186	33040 \pm 11160
AUC_{∞} , ng(eq.)h/mL	18520 \pm 4709	56620 ^a \pm 14090 ^a
λ_z , 1/h	0.01283 \pm 0.003019	0.006796 ^a \pm 0.001735 ^a
$t_{1/2\text{term}}$, h	56.56 \pm 12.98	107.7 ^a \pm 27.45 ^a

^a Accurate determination was not possible

Tables 3, 4, and 5 display the following information: ratio C_t , RPV/total , ratio RPV/total for C_{\max} , $\text{AUC}_{(0-\text{last})}$ and $\text{AUC}_{(0-\infty)}$, and ratio C_t , $\text{blood}/\text{plasma}$, respectively.

Table 3-Individual ratios of rilpivirine (RPV) and total radioactivity in plasma (ratio C_t , RPV/total) at each concentration time point after a single 150 mg rilpivirine (^{14}C labeled and unlabeled) dose

Parameter	Subject						Descriptive statistics							
	119001	119002	119003	119004	119005	119006	N	Mean	SD	Min	Median	Max	CV(%)	Geometric mean
Ratio TMC278/Total radioactivity														
C_{0h} , TMC278/Total	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA
$C_{0.5h}$, TMC278/Total	64.25	NA	76.25	70.14	NA	73.33	4	70.99	5.140	64.25	71.74	76.25	7.240	70.85
C_{1h} , TMC278/Total	70.59	75.90	84.56	82.93	83.87	71.89	6	78.29	6.294	70.59	79.42	84.56	8.039	78.08
C_{2h} , TMC278/Total	71.22	72.46	83.94	72.65	73.82	86.95	6	76.84	6.783	71.22	73.24	86.95	8.828	76.60
C_{3h} , TMC278/Total	72.03	76.21	77.23	83.33	73.45	74.66	6	76.15	3.981	72.03	75.43	83.33	5.228	76.07
C_{4h} , TMC278/Total	72.47	78.73	77.66	70.25	76.34	83.65	6	76.52	4.751	70.25	77.00	83.65	6.209	76.39
C_{6h} , TMC278/Total	61.33	61.57	65.52	71.09	67.52	74.34	6	66.89	5.189	61.33	66.52	74.34	7.758	66.73
C_{8h} , TMC278/Total	56.40	60.48	60.17	64.77	57.24	69.77	6	61.47	5.019	56.40	60.32	69.77	8.165	61.30
C_{12h} , TMC278/Total	52.42	49.53	57.30	52.70	52.72	59.29	6	53.99	3.596	49.53	52.71	59.29	6.660	53.89
C_{16h} , TMC278/Total	40.28	53.79	53.83	43.53	55.25	53.36	6	50.01	6.391	40.28	53.58	55.25	12.78	49.65
C_{24h} , TMC278/Total	52.90	46.36	61.94	42.02	51.07	50.18	6	50.75	6.720	42.02	50.62	61.94	13.24	50.38
C_{32h} , TMC278/Total	50.00	47.99	49.41	45.02	49.32	56.12	6	49.64	3.642	45.02	49.37	56.12	7.337	49.54
C_{48h} , TMC278/Total	39.67	39.04	46.89	31.77	46.96	54.50	6	43.14	7.947	31.77	43.28	54.50	18.42	42.51
C_{72h} , TMC278/Total	38.70	38.76	40.07	27.33	40.37	58.85	6	40.68	10.16	27.33	39.41	58.85	24.98	39.68
C_{96h} , TMC278/Total	28.48	28.99	39.13	17.18	30.77	47.43	6	32.00	10.31	17.18	29.88	47.43	32.22	30.53
C_{120h} , TMC278/Total	NA	23.70	27.63	17.01	27.51	NA	4	23.96	4.984	17.01	25.61	27.63	20.80	23.53
C_{144h} , TMC278/Total	NA	NA	25.21	9.600	28.60	NA	3	21.14	10.14	9.600	25.21	28.60	47.95	19.06
C_{168h} , TMC278/Total	NA	NA	21.70	NA	26.84	NA	2	NA	NA	21.7	NA	26.84	NA	NA

NA: Not Assessable

Table 4-Individual ratios of rilpivirine (RPV) and total radioactivity in plasma (ratio $RPV/total$) for C_{max} , $AUC_{(0-last)}$ and $AUC_{(0-\infty)}$ after a single 150 mg rilpivirine (^{14}C labeled and unlabeled) dose

Parameter	Subject						Descriptive statistics							
	119001	119002	119003	119004	119005	119006	N	Mean	SD	Min	Median	Max	CV(%)	Geometric mean
Ratio TMC278/Total radioactivity														
Ratio C_{max} , TMC278/Total (%)	72.47	76.21	77.23	70.70	76.34	83.65	6	76.10	4.489	70.70	76.27	83.65	5.898	75.99
Ratio AUC_{last} , TMC278/Total (%)	57.70	49.25	46.40	37.77	42.96	74.67	6	51.46	13.17	37.77	47.83	74.67	25.60	50.19
Ratio AUC_{∞} , TMC278/Total (%)	29.04*	33.95*	36.23*	22.38*	29.95*	52.27*	6	33.97*	10.15*	22.38*	31.95*	52.27*	29.87*	32.83*

* Accurate determination not possible

Table 5-Individual ratios of rilpivirine (RPV) and total radioactivity in whole blood and plasma (ratio C_t , blood/plasma) after a single 150 mg rilpivirine (^{14}C labeled and unlabeled) dose

Parameter	Subject						Descriptive statistics							
	119001	119002	119003	119004	119005	119006	N	Mean	SD	Min	Median	Max	CV(%)	Geometric mean
Ratio Blood/Plasma														
C_{1h} , blood/plasma	67.89	64.66	70.34	70.19	75.27	100.0	6	74.72	12.86	64.66	70.26	100.0	17.21	73.92
C_{2h} , blood/plasma	73.35	60.33	67.88	63.53	62.30	63.17	6	65.09	4.745	60.33	63.35	73.35	7.289	64.96
C_{4h} , blood/plasma	67.05	64.23	71.86	62.22	63.36	73.88	6	67.10	4.790	62.22	65.64	73.88	7.139	66.96
C_{8h} , blood/plasma	70.34	62.86	67.60	69.41	69.46	72.38	6	68.68	3.243	62.86	69.43	72.38	4.722	68.61
C_{12h} , blood/plasma	64.85	58.68	63.06	66.32	76.36	63.21	6	65.41	5.945	58.68	64.03	76.36	9.088	65.20
C_{24h} , blood/plasma	88.74	62.68	76.72	63.19	68.93	66.32	6	71.10	10.04	62.68	67.62	88.74	14.12	70.55
C_{48h} , blood/plasma	83.61	59.36	77.40	64.62	80.87	73.50	6	73.23	9.487	59.36	75.45	83.61	12.96	72.69

7.2 Mass balance and metabolite identification

Information regarding the total radioactivity after a single 150 mg rilpivirine dose (recovered in urine up to 168 hours and in feces [up to 168 hours and 366 hours]) is presented in Table 6 below. The majority of the radioactivity is recovered in the feces (at 336 hours, the percentage in the six subjects ranged from 78.81% to 90.71% with a mean

of 85.05%. The percentage recovered in urine at 168 hours ranged from 3.69% to 8.84% for the six subjects with a mean of 6.13%.

Table 6-Cumulative radioactivity recovered in urine (up to 168 hours) and feces (up to 168 hours and 336 hours) after a single 150 mg rilpivirine (¹⁴C labeled and unlabeled) dose

Subject number	Subject 119001	Subject 119002	Subject 119003	Subject 119004	Subject 119005	Subject 119006	Mean ± SD
Urine 168 hours	5.01	5.61	8.84	8.70	4.92	3.69	6.13 ± 2.14
Feces 168 hours	76.89	82.89	69.54	83.12	73.42	71.35	76.20 ± 5.81
Feces 336 hours	84.84	90.71	82.82	87.35	85.74	78.81	85.05 ± 4.04
Total	89.85	96.32	91.66	96.04	90.66	82.50	91.17 ± 5.05

The major metabolites that were identified and the method of identification are listed in Table 7 below.

Table 7-Rilpivirine and rilpivirine metabolites identified in TMC278-C119

Metabolite code	Identification method	Identity
2	-	unknown
3	-	unknown
11	LC-MS/MS	carboxylic acid metabolite on the cyanoethenyl moiety of metabolite 27
13,14	LC-MS/MS	glycine conjugates of TMC278
15	LC-MS/MS, co-elution with isolated rabbit metabolite, NMR on isolated rabbit metabolite.	N-glucuronide at the N1-position of the pyrimidinyl moiety of TMC278
18	LC-MS/MS	mercapturic acid conjugate of TMC278 (R378523)
19	LC-MS/MS	glucuronide of metabolite 33
23	LC-MS/MS	oxidized metabolite of metabolite 27
25	LC-MS/MS, enzymatic hydrolysis in vitro samples	glucuronide of metabolite 42
27	LC-MS/MS, NMR on isolated rabbit metabolite.	tricyclic metabolite, originating from oxidation and dehydration most probably of metabolite 33
30	LC-MS/MS, NMR	carboxylic acid metabolite on the cyanoethenyl moiety
33	Co-chromatography LC-MS/MS	hydroxymethyl TMC278 (R419763)
35	LC-MS/MS	unknown (+ 2 mass units)
39		cis 5-hydroxy pyrimidinyl TMC278 (cis isomer of metabolite 42)
42	LC-MS/MS, NMR	hydroxyl metabolite at the 5-position of the pyrimidinyl moiety of TMC278
43	Co-chromatography LC-MS/MS	cis TMC278
UD	Co-chromatography LC-MS/MS	TMC278
46	LC-MS/MS	unknown, most probably originating from a glutathione-derived metabolite on the cyanoethenyl moiety

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The metabolic pathways after a single 150 mg rilpivirine (¹⁴C labeled and unlabeled) dose are displayed in Figure 2 below. In feces, unchanged rilpivirine represented 25.5% on average of the dose (range: 12.1%-33.4%). The major metabolite that was identified in the feces was metabolite 42 that is formed through oxidation. Metabolite 42 represented 16.1% on average of the dose (range: 10.2%-20.5%). Other metabolites

identified in the feces included metabolites 30, 33 and 35 that represented 2.2%-3% on average of the dose and metabolites 3, 11, 23, 27 and 46 that represented 0.3%-1.6% on average of the dose.

Unchanged rilpivirine was present in trace amounts in the urine. In the proposed rilpivirine prescribing information, the amount of unchanged rilpivirine present in the urine is stated to be <1% of the dose, which is reasonable based on the information presented in Figure 3. In the urine, a carboxylic acid metabolite (metabolite 30) was identified that represented 0.03% on average of the dose. The other metabolites identified in urine were Phase 2 metabolites. The Phase 2 metabolites that were identified are listed below:

- A) Metabolites derived from glutathione conjugation: two glycine conjugates (metabolites 13 and 14) and a mercapturic acid conjugate (metabolite 18) that represented 1.2% on average of the dose.
- B) Metabolite 15, a rilpivirine N-glucuronide that represented 0.6% on average of the dose.
- C) Glucuronides of hydroxylated metabolites: metabolites 19 and 25 that represented 0.3% and 0.6% on average, respectively of the dose.

Figure 2-Metabolic pathways of rilpivirine after a single 150 mg rilpivirine (¹⁴C labeled and unlabeled) dose

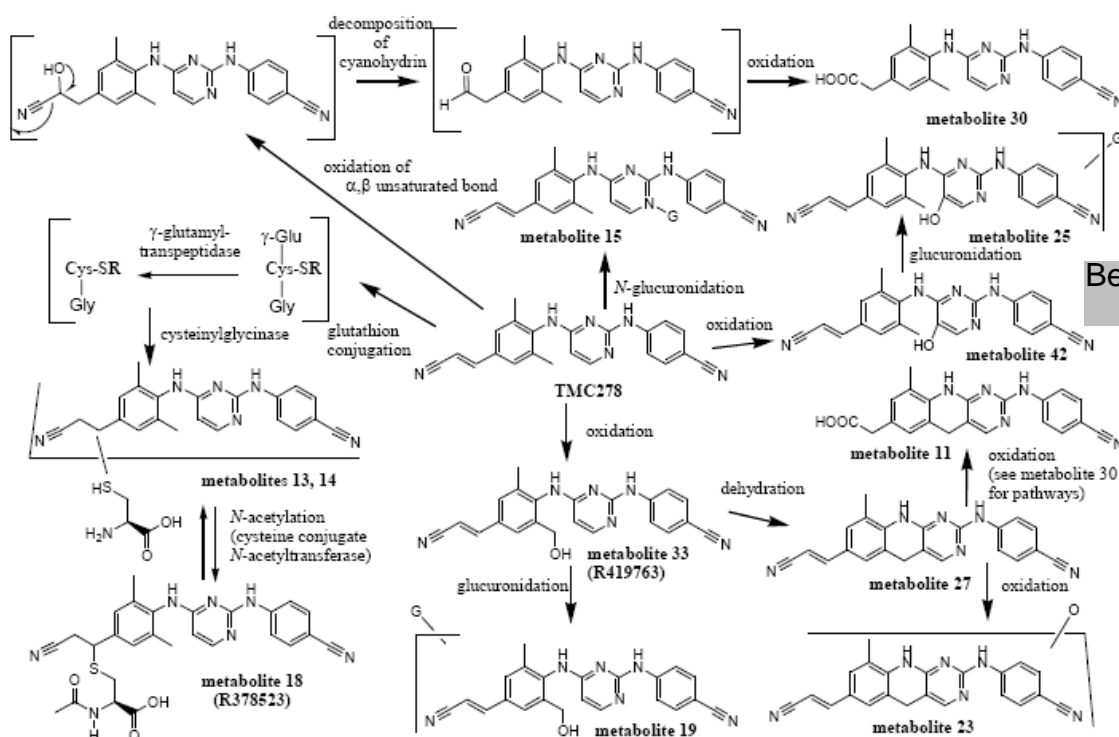
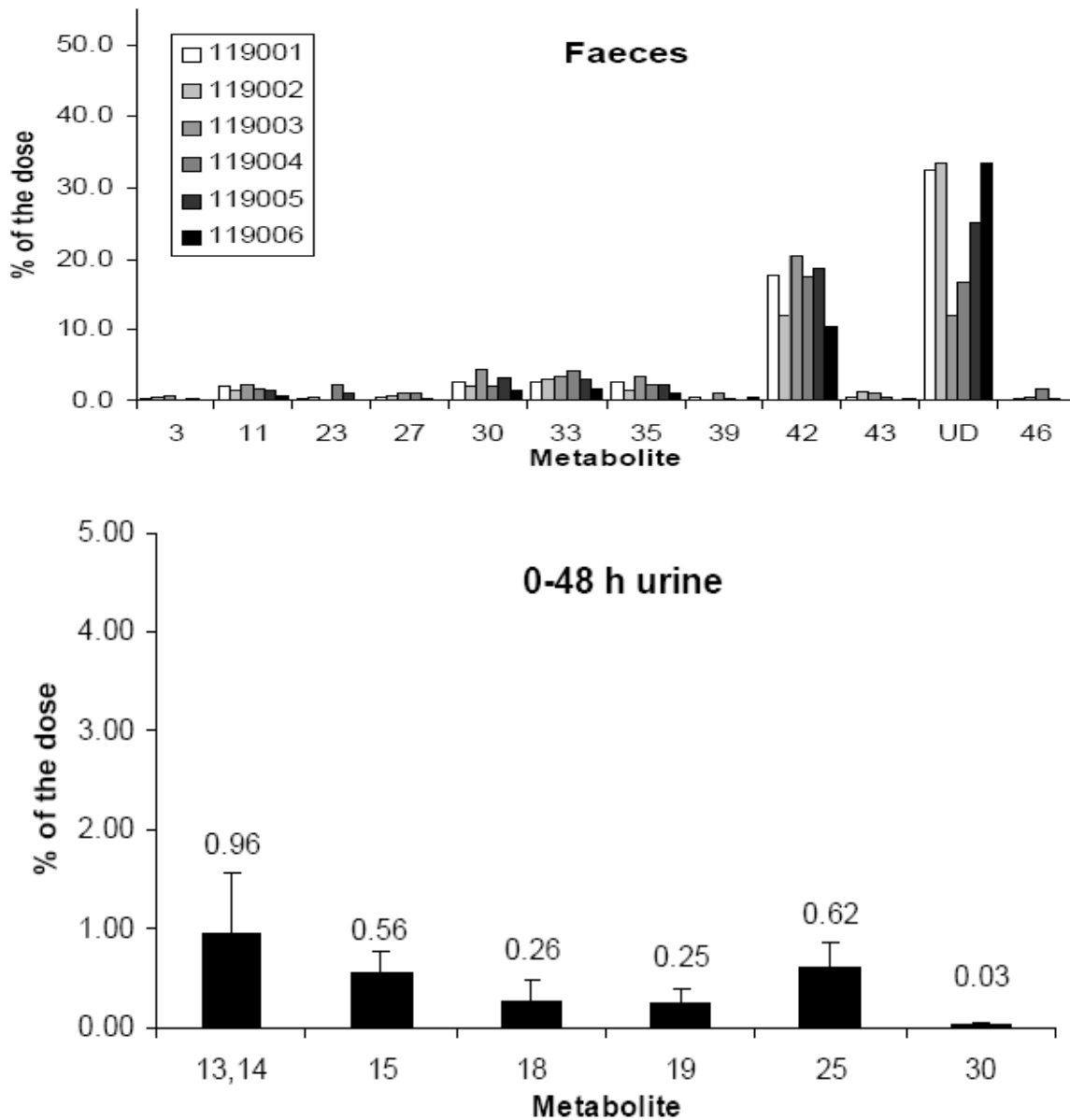


Figure 3 below displays the mass balance of rilpivirine and its metabolites after a single 150 mg rilpivirine (¹⁴C labeled and unlabeled) dose.

Figure 3 -Mass balance of rilpivirine and its metabolites in individual subjects after a single 150 mg rilpivirine (^{14}C labeled and unlabeled) dose in feces and urine



7.3 Safety Issues

No deaths or other serious adverse events were reported for the trial. There were no grade 2, 3 or 4 adverse events that were reported for the trial

8. Discussion and conclusions

After 336 hours, $91 \pm 5\%$ of a single 150 mg rilpivirine (^{14}C labeled and unlabeled) dose was recovered based on radioactivity. In the feces, $85 \pm 4\%$ was recovered after 336 hours, and unchanged rilpivirine represented 25.5% on average of the dose.

In the urine, $6 \pm 2\%$ was recovered after 168 hours, and unchanged rilpivirine was present in trace amounts.

The highest mean percentage of $C_{t, \text{RPV/total}}$ was observed at 1 hour postdose. Based on the ratio of rilpivirine (RPV) and total radioactivity in plasma (ratio RPV/total) for C_{max} and $\text{AUC}_{(0-\text{last})}$, the mean percentage of unchanged rilpivirine that accounted for the total radioactivity was 76.1% and 51.5%, respectively. It appears that the ratio of rilpivirine (RPV) and total radioactivity in plasma (ratio RPV/total) for $\text{AUC}_{(0-\infty)}$ could not be accurately estimated because the higher lower limit of quantification for the total radioactivity method prevented an accurate half life estimation. The mean ratio of total radioactivity in whole blood and plasma (ratio $C_{t, \text{blood/plasma}}$) that was evaluated from 1 to 48 hours postdose ranged from 65.1% to 74.7%. The ratios were less than 100%, indicating that rilpivirine does not extensively bind to blood cells.

The major metabolite that was identified in the feces was metabolite 42 that is formed through oxidation. Two other metabolites have been definitely identified that are formed from rilpivirine in minor amounts (metabolite 15 [0.6% on average of the dose in the urine], and metabolite 33 [3% on average of the dose in the feces]). In the urine, with the exception of metabolite 30 (a carboxylic acid metabolite), the other metabolites identified in urine were Phase 2 metabolites. In plasma, unchanged rilpivirine accounted for the majority of the total radioactivity based on the C_{max} and $\text{AUC}_{(0-\text{last})}$ comparisons.

Multiple dosing trial

Trial Number	Title	Page Number
TMC278-C103	A Phase I, open label, randomized, multiple dose ranging trial in four parallel panels of 12 healthy subjects each, to determine the pharmacokinetics, safety and tolerability of once daily dosing of TMC278 formulated as a solid formulation	287

TMC278-C103

1. Title

A Phase I, open label, randomized, multiple dose ranging trial in four parallel panels of 12 healthy subjects each, to determine the pharmacokinetics, safety and tolerability of once daily dosing of TMC278 formulated as a solid formulation

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at (b) (4) from August 25, 2004 to November 29, 2004.

3. Objectives

The objective of the trial was to evaluate rilpivirine single dose and multiple dose pharmacokinetics with multiple dosing of rilpivirine.

4. Trial Design

TMC278-C103 was a Phase I, open label, clinical trial that enrolled healthy male and female subjects between 18 and 55 years old. Subjects were randomized to one of four parallel arms. Twelve subjects were to be enrolled in each arm. The treatments that were administered are displayed in Table 1.

Table 1-Treatments administered in the C103 trial

Panel	Treatment	Number of Subjects	Days	Dose	Volume
1	A	12	Days 1-14	25 mg q.d.	1 tablet containing 25 mg of TMC278
2	B	12	Days 1-14	50 mg q.d.	2 tablets each containing 25 mg of TMC278
3	C	12	Days 1-14	100 mg q.d.	1 tablet containing 100 mg of TMC278
4	D	12	Days 1-14	150 mg q.d.	1 tablet containing 100 mg of TMC278 and 2 tablets each containing 25 mg of TMC278

5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Use of ibuprofen was permitted up to three days before administration of trial medication. Afterwards, ibuprofen use was permitted up to 400 mg/day. Any medications were to be discontinued a minimum of fourteen days before the first administration of trial medication, except for ibuprofen. Use of herbal medicines or dietary supplements was not permitted from fourteen days before the first administration of trial medication and up to nine days after the last administration of trial medication.

Use of liquids containing alcohol or quinine was not permitted from 24 hours before administration of the first trial medication until nine days after the last administration of trial medication. Intake of grapefruit and grapefruit juice was not permitted from 7 days before the first administration of trial medication until nine days after the last administration of trial medication.

In the event of an adverse event, the following medications were permitted:

- A) Rash or an allergic reaction: cetirizine, topical corticosteroids, or antipruritic agents (specific medications were not included in the trial report)
- B) Nausea: antiemetics (specific medications were not included in the trial report)
- C) Diarrhea: loperamide

6. Dosage and Administration

On the evening of Day -1 and Day 13, subjects were admitted to the clinical trial site and fasted overnight for a minimum of 10 hours. A standard meal was consumed within 30 minutes on the morning of Day 1 and Day 14 and rilpivirine was subsequently administered with approximately 200 mL of water within 10 minutes after the meal was completed.

7. Rationale for Doses Used in the Trial

The rilpivirine dosage regimens that were administered to all subjects are displayed in Table 1.

8. Drugs Used in the Trial

Rilpivirine 25 mg (formulation F001) or 100 mg tablets (formulation F002) were administered in the trial. Both of these tablets were Phase 2b formulations that were used in the Phase 1 or 2 trials.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Blood samples for analysis of rilpivirine plasma concentrations were obtained on Days 1 and 2 at predose and up to 24 hours postdose and Days 14 through 23 at predose and up to 216 hours postdose. Predose rilpivirine blood samples were obtained on Days 7, 10, 12, and 13.

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a validated LC/MS/MS method by Tibotec. The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000

ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the TMC278-C103 trial, precision and accuracy were evaluated using the low (2.51 or 2.52 ng/mL), medium (50.1 or 50.4 ng/mL), and high (1510 or 1550 ng/mL) QC samples. The corresponding rilpivirine inter-run accuracy values were 0.4% and 1.6%, respectively, for the low QCs, -1% and -1.2 %, respectively, for the medium QCs, and -2.6% and 1.9%, respectively, for the high QCs, and the rilpivirine inter-run precision values were 6% and 4.6%, respectively, for the low QCs, 5.7% and 3.9%, respectively, for the medium QCs, and 8.2% and 5.5%, respectively, for the high QCs. The submitted rilpivirine long term stability data of 1528 days at -20°C covered the duration of long term rilpivirine stability data necessary for the TMC278-C103 trial.

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate plasma pharmacokinetic parameters, including C_{\max} and AUC_{0-24h} after a single dose of rilpivirine, and C_{0h} , C_{\min} , C_{\max} and AUC_{0-24h} with multiple dosing. If a major difference (> 10.00% deviation from the scheduled time) was observed, the actual sampling time was used instead of the scheduled sampling time.

Statistical Analysis

Descriptive statistics were calculated for rilpivirine plasma concentrations and pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), geometric mean, median, and the minimum and maximum values.

Rilpivirine dose proportionality was evaluated graphically by comparing the dose normalized C_{\max} and AUC_{0-24h} values after a single dose of rilpivirine, and dose normalized C_{0h} , C_{\min} , C_{\max} and AUC_{0-24h} with multiple dosing. Additionally, a statistical analysis for rilpivirine dose proportionality was conducted to determine if a statistically significant difference existed among the treatment groups. If a statistically significant difference was observed, individual treatment groups were evaluated. For single dosing, the Day 1 C_{\max} and AUC_{0-24h} were evaluated, and the Day 14 C_{0h} , C_{\min} , C_{\max} and AUC_{0-24h} were evaluated for multiple dosing. Using a linear mixed effects model, least squares means were calculated and 90% confidence intervals were derived based on the difference of the pharmacokinetic parameter's least squares means for the test and reference arms. The 90% confidence intervals and the difference of the pharmacokinetic parameter's least squares means were transformed back to the original scale.

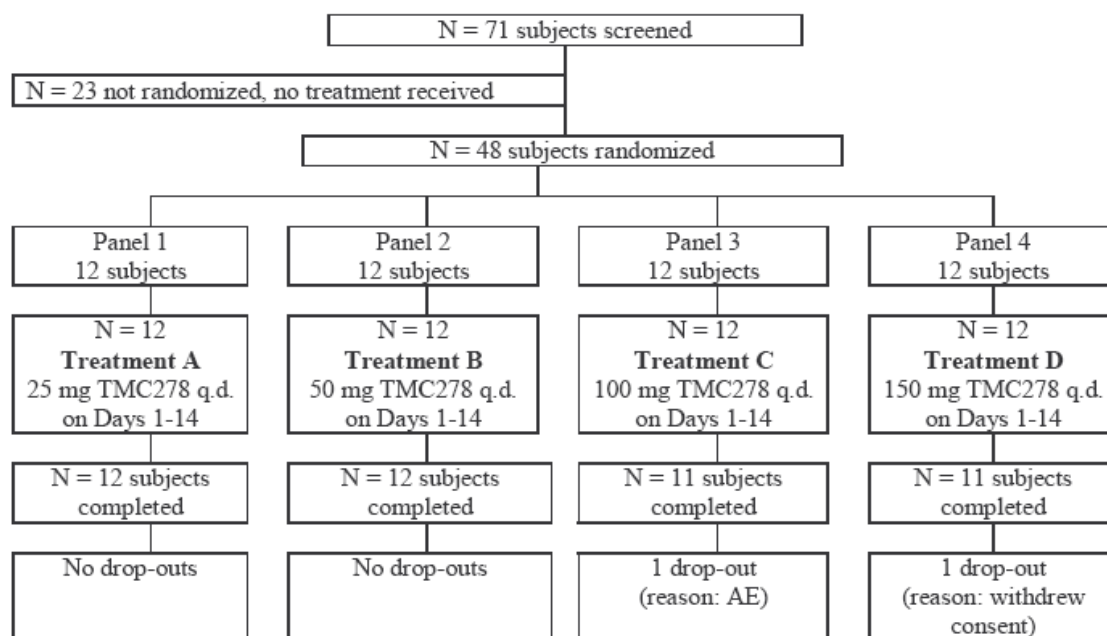
10. Results

10.1 Subject Demographics and Disposition

Table 2-TMC278-C103 subject demographics

Parameter	25 mg q.d. TMC278 (N=12)	50 mg q.d. TMC278 (N=12)	100 mg q.d. TMC278 (N=12)	150 mg q.d. TMC278 (N=12)	All Subjects N = 48
Age, years					
Median	39.0	39.0	43.0	38.0	39.5
(range)	21 - 54	26 - 52	22 - 52	21 - 53	21 - 54
Height, cm					
Median	179.0	181.0	172.0	182.0	180.0
(range)	164 - 192	161 - 192	157 - 186	169 - 198	157 - 198
Weight, kg					
Median	81.0	81.0	75.0	78.0	79.0
(range)	67 - 97	57 - 90	58 - 92	65 - 102	57 - 102
BMI, kg/m ²					
Median	26.1	24.5	24.9	24.2	24.5
(range)	20 - 30	21 - 29	21 - 27	22 - 30	20 - 30
Sex, n (%)					
Female	1 (8.3)	2 (16.7)	2 (16.7)	1 (8.3)	6 (12.5)
Male	11 (91.7)	10 (83.3)	10 (83.3)	11 (91.7)	42 (87.5)
Ethnic Origin, n (%)					
Caucasian	12 (100.0)	11 (91.7)	12 (100.0)	12 (100.0)	47 (97.9)
Black		1 (8.3)			1 (2.1)
Type of Smoker, n (%)					
No (non-smoker)	9 (75.0)	10 (83.3)	10 (83.3)	10 (83.3)	39 (81.3)
Yes (light)	3 (25.0)	2 (16.7)	2 (16.7)	2 (16.7)	9 (18.8)

Figure 1-TMC278-C103 subject disposition



10.2 Prior and Concomitant Medications

Thirteen subjects administered concurrent medications during the trial. The most frequently administered concomitant medications were ibuprofen in 7 subjects and acetaminophen in 3 subjects. The other concomitant medications that were administered included dexamethasone, fluticasone propionate, mucopolysaccharide polysulfuric acid, miconazole, naproxen, tramadol, and flucloxacillin sodium. None of these medications would be expected to alter CYP 3A metabolism.

10.3 Pharmacokinetic and Statistical Analysis

There were no subjects in Treatments A, B, C or D with a quantifiable predose rilpivirine drug concentration on Day 1.

Rilpivirine

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Figure 2- Dose normalized rilpivirine pharmacokinetic parameters with Treatments A, B, C and D

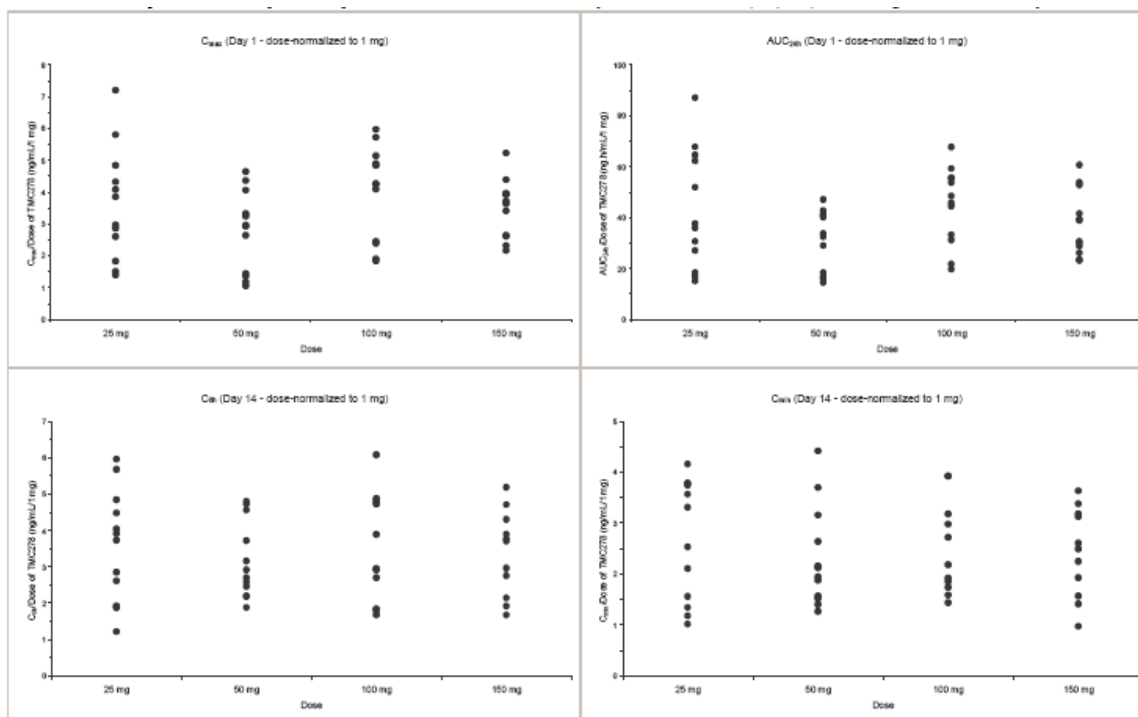


Table 3-Rilpivirine pharmacokinetic parameters with Treatments A, B, C and D

Pharmacokinetics of TMC278 (mean \pm SD; t _{max} : median (range))	25 mg q.d. TMC278	50 mg q.d. TMC278	100 mg q.d. TMC278	150 mg q.d. TMC278
n	12	12	12 ^a	12 ^b
Day 1				
C _{max} , ng/mL	90.08 \pm 44.28	138.2 \pm 63.10	397.6 \pm 147.3	523.8 \pm 136.9
t _{max} , h	4.0 (2.0 - 6.0)	4.0 (3.0 - 4.0)	4.0 (2.0 - 6.65)	4.0 (3.0 - 6.0)
AUC _{24h} , ng.h/mL	1072 \pm 585.6	1551 \pm 596.0	4464 \pm 1520	5608 \pm 1902
Day 7				
C _{0h} , ng/mL	79.13 \pm 30.22	169.7 \pm 61.44	353.6 \pm 111.4	431.4 \pm 133.7
Day 10				
C _{0h} , ng/mL	90.43 \pm 39.36	161.8 \pm 85.20	312.3 \pm 105.3	482.4 \pm 178.0
Day 12				
C _{0h} , ng/mL	91.72 \pm 38.43	149.7 \pm 52.83	336.5 \pm 116.4	449.4 \pm 198.0
Day 13				
C _{0h} , ng/mL	83.64 \pm 38.23	168.6 \pm 74.71	326.8 \pm 129.3	459.5 \pm 178.6
Day 14				
C _{0h} , ng/mL	89.85 \pm 38.07	157.9 \pm 52.23	347.8 \pm 148.7	504.9 \pm 174.6
C _{min} , ng/mL	66.85 \pm 29.53	115.7 \pm 49.30	249.5 \pm 90.51	362.0 \pm 130.9
C _{max} , ng/mL	203.8 \pm 75.81	298.6 \pm 98.05	685.5 \pm 202.4	1019 \pm 222.0
t _{max} , h	4.0 (2.0 - 4.0)	4.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	4.0 (3.0 - 6.0)
AUC _{24h} , ng.h/mL	2589 \pm 868.8	4139 \pm 1236	9278 \pm 2846	13581 \pm 3195
t _{1/2term} , h	50.92 \pm 19.56	48.75 \pm 16.34	46.07 \pm 15.44	44.83 \pm 12.31
C _{ss,av} , ng/mL	107.8 \pm 36.20	172.5 \pm 51.48	386.6 \pm 118.6	565.9 \pm 133.1
FI, %	128.5 \pm 41.71	107.8 \pm 45.20	113.7 \pm 35.59	121.7 \pm 46.55
Acc. Ratio	3.020 \pm 1.966	2.880 \pm 0.7982	2.071 \pm 0.7491	2.503 \pm 0.7211

^a for the parameters of Day 10 until Day 14: n=11^b for the parameters of Day 7 until Day 14: n=11**Table 4-Statistical analysis for dose normalized rilpivirine pharmacokinetic parameters for Treatments A, B, C and D**

Parameter	Least square means dose-normalized PK parameters				Least square means PK parameters				p-value ^a
	25	50	100	150	25	50	100	150	
Day 1									
C _{max} , ng/mL	3.201	2.460	3.683	3.379	80.03	123.0	368.3	506.8	0.1641
AUC _{24h} , ng.h/mL	36.87	28.61	41.82	35.53	921.8	1430	4182	5329	0.2351
Day 14									
C _{0h} , ng/mL	3.256	3.008	3.182	3.167	81.39	150.4	318.2	475.1	0.9720
C _{min} , ng/mL	2.393	2.147	2.353	2.248	59.83	107.4	235.3	337.2	0.9265
C _{max} , ng/mL	7.550	5.666	6.498	6.636	188.7	283.3	649.8	995.4	0.2820
AUC _{24h} , ng.h/mL	97.06	79.60	88.39	88.21	2426	3980	8839	13231	0.5297

^a Obtained after an overall statistical analysis on dose effect. P-value is testing for a difference between doses.

For both Day 1 and Day 14, based on the statistical analysis, none of the dose normalized pharmacokinetic parameters demonstrated a statistically significant difference ($p < .05$) among the treatment groups.

Based on evaluating the individual rilpivirine predose concentrations, steady state concentrations were achieved by Day 14 for most subjects.

10.4 Safety Issues

No deaths or other serious adverse events were reported for the trial. Five grade 3 adverse events that were reported that included increased blood amylase, three reports of increased lipase, and a lumbar vertebral fracture. No grade 4 adverse events were reported. Information regarding the adverse events that were reported in the trial is summarized in Table 9A and 9B.

Table 9A-Adverse event incidence categorized by system organ class and preferred term reported in more than one subject

System Organ Class Preferred Term	Panel 1 (N = 12)	
	25 mg q.d. TMC278	Posttreatment
	n (%)	n (%)
<i>Any Adverse Event</i>	8 (66.7)	3 (25.0)
<i>Nervous System Disorders</i>	4 (33.3)	0
Dizziness	2 (16.7)	0
Headache	2 (16.7)	0
Migraine	0	0
<i>Gastrointestinal Disorders</i>	4 (33.3)	0
Bowel Sounds Abnormal	2 (16.7)	0
Diarrhoea	1 (8.3)	0
Dyspepsia	1 (8.3)	0
<i>Hepatobiliary Disorders</i>	2 (16.7)	1 (8.3)
Hyperbilirubinaemia	2 (16.7)	1 (8.3)
<i>General Disorders and Administration Site Conditions</i>	2 (16.7)	0
Fatigue	1 (8.3)	0
Influenza Like Illness	1 (8.3)	0
<i>Respiratory, Thoracic and Mediastinal Disorders</i>	0	2 (16.7)
Nasopharyngitis	0	2 (16.7)
System Organ Class Preferred Term	Panel 2 (N = 12)	
	50 mg q.d. TMC278	Posttreatment
	n (%)	n (%)
<i>Any Adverse Event</i>	8 (66.7)	1 (8.3)
<i>Nervous System Disorders</i>	5 (41.7)	0
Dizziness	1 (8.3)	0
Headache	4 (33.3)	0
<i>Gastrointestinal Disorders</i>	3 (25.0)	0
Abdominal Pain	1 (8.3)	0
Aphthous Stomatitis	1 (8.3)	0
Bowel Sounds Abnormal	1 (8.3)	0
Flatulence	1 (8.3)	0
<i>Hepatobiliary Disorders</i>	2 (16.7)	0
Hyperbilirubinaemia	2 (16.7)	0
<i>Investigations</i>	2 (16.7)	0
Lipase Increased	1 (8.3)	0
Neutrophil Count Decreased	1 (8.3)	0
<i>Skin and Subcutaneous Tissue Disorders</i>	2 (16.7)	0
Pruritus	1 (8.3)	0
Rash Pustular	1 (8.3)	0
<i>Metabolism and Nutrition Disorders</i>	1 (8.3)	1 (8.3)
Hypercholesterolaemia	1 (8.3)	1 (8.3)

n = number of subjects with that particular AE, % = percentage of subjects with that particular AE

Table 9B-Adverse event incidence categorized by system organ class and preferred term reported in more than one subject

System Organ Class Preferred Term	Panel 3 (N = 12)	
	100 mg q.d. TMC278	Posttreatment
	n (%)	n (%)
<i>Any Adverse Event</i>	7 (58.3)	3 (25.0)
<i>Investigations</i>	3 (25.0)	1 (8.3)
Alanine Aminotransferase Increased	1 (8.3)	0
Blood Amylase Increased	1 (8.3)	0
Blood Triglycerides Increased	0	0
Eosinophil Count Increased	0	0
Lipase Increased	2 (16.7)	1 (8.3)
<i>Skin and Subcutaneous Tissue Disorders</i>	3 (25.0)	1 (8.3)
Erythema	1 (8.3)	0
Hyperhidrosis	1 (8.3)	0
Pruritus	1 (8.3)	0
Seborrheic Dermatitis	0	1 (8.3)
<i>Hepatobiliary Disorders</i>	2 (16.7)	0
Hyperbilirubinaemia	2 (16.7)	0
<i>Nervous System Disorders</i>	2 (16.7)	0
Headache	2 (16.7)	0
<i>Gastrointestinal Disorders</i>	2 (16.7)	0
Abdominal Pain Upper	1 (8.3)	0
Bowel Sounds Abnormal	1 (8.3)	0
<i>Metabolism and Nutrition Disorders</i>	1 (8.3)	1 (8.3)
Hypercholesterolaemia	1 (8.3)	1 (8.3)
Hyperuricaemia	0	0
System Organ Class Preferred Term	Panel 4 (N = 12)	
	150 mg q.d. TMC278	Posttreatment
	n (%)	n (%)
<i>Any Adverse Event</i>	5 (41.7)	4 (33.3)
<i>Gastrointestinal Disorders</i>	2 (16.7)	0
Dyspepsia	1 (8.3)	0
Flatulence	1 (8.3)	0
<i>Nervous System Disorders</i>	2 (16.7)	0
Dizziness	1 (8.3)	0
Headache	2 (16.7)	0
<i>Skin and Subcutaneous Tissue Disorders</i>	3 (25.0)	0
Herpes Simplex	1 (8.3)	0
Hyperhidrosis	1 (8.3)	0
Skin Irritation	1 (8.3)	0
<i>Musculoskeletal and Connective Tissue Disorders</i>	1 (8.3)	2 (16.7)
Back Pain	0	1 (8.3)
Neck Pain	0	1 (8.3)
Sensation of Heaviness	1 (8.3)	0
<i>Hepatobiliary Disorders</i>	1 (8.3)	0
Hyperbilirubinaemia	1 (8.3)	0

n = number of subjects with that particular AE, % = percentage of subjects with that particular AE

11. Discussion and Conclusions

Based on the results from the trial, dose proportionality is observed both after a single dose and with multiple doses of rilpivirine when the Phase 1 or 2 tablets were observed. There were no safety trends identified that require further evaluation with multiple dosing of rilpivirine ranging from 25 mg once daily to 150 mg once daily.

In vitro studies

Study Number	Title	Page Number
FK4123	A pilot study on the interaction of R278474 on CYP1A2, CYP2A6, CYP2C8, 9, 10, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5 and CYP4A in human liver microsomes	298
TMC278-NC102	The <i>in-vitro</i> metabolism of ¹⁴ C-TMC278 in hepatocytes and liver subcellular fractions of male and female Swiss albino mice, male and female black Agouti rasH2 microinjected mice, male and female rats, female rabbit, male dog and man	300
TMC278-NC104	Determination of the <i>in vitro</i> transport characteristics of TMC278, evaluation of the possible role of P-glycoprotein in TMC278 transport and assessment of possible inhibition of P-glycoprotein activity by TMC278: a study in Caco-2 monolayers	306
TMC278-NC112	The plasma protein binding and blood distribution of TMC278 in animals and man	312
TMC278-NC141	An in vitro study to (a) identify the microsomal cytochrome P-450 iso-enzymes mediating TMC278 metabolism (reaction phenotyping) and to (b) determine the kinetics of TMC278 metabolism in human liver microsomes	317
TMC278-NC186	An in vitro study to assess the potential of TMC278 to	323

	induce CYP enzyme activities in cryopreserved human hepatocytes	
TMC278-NC194	An <i>in vitro</i> study on the possible inhibitory effect of TMC278 on the metabolism of sertraline, paroxetine, clarithromycin, sildenafil, 17 α -ethinyloestradiol, omeprazole, S-mephenytoin, abacavir, norethindrone and chlorzoxazone in human liver microsomes	327
TMC278-NC283	An <i>in-vitro</i> study on the inhibition of paclitaxel (CYP2C8-mediated) and S-warfarin (CYP2C9-mediated) metabolism by TMC278	330

1. Title

A pilot study on the interaction of R278474 on CYP1A2, CYP2A6, CYP2C8,9,10, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5 and CYP4A in human liver microsomes

2. Objectives

The primary objective of the study was to determine effect of rilpivirine on cytochrome P450 enzymes.

3. Methods

The effect of rilpivirine on cytochrome P450 substrates was evaluated in pooled liver microsomes. Information on the incubation conditions for the substrates that were evaluated is displayed in Table 1.

Table 1-Incubation conditions for cytochrome P450 substrates evaluated in human liver microsomes

P-450 Substrate	Human CYP-form	Substrate concentration (μ M)	Protein concentration (mg/ml)	Incubation time (min)	Incubation volume (ml)	Analytical method
Phenacetin	CYP1A2	100	0.5	15	1	LC-UV
Coumarin	CYP2A6	50	0.1	10	1	Fluorimetry
Tolbutamide	CYP2C8/9/10	100	1.0	30	0.5	LC-MSMS
S-Mephenytoin	CYP2C19	100	0.5	30	0.5	Radio-HPLC
Dextromethorphan	CYP2D6	3	0.2	20	0.25	LC-MSMS
Bufuralol	CYP2D6	100	0.5	20	1	LC-UV
Chlorzoxazone	CYP2E1	50	0.5	20	1	LC-UV
Testosterone	CYP3A4	100	0.5	25	0.5	LC-MSMS
Cyclosporin A	CYP3A4	5	1	30	1	Radio-HPLC
Midazolam	CYP3A4/5	50	0.5	10	1	LC-UV
Lauric acid	CYP4A and CYP2E1	100	1	10	1	Radio-HPLC

0, 0.03, 0.1, 0.3, 1, 3, 10, 30 and 100 μ M were the final rilpivirine inhibitory concentrations that were evaluated. Incubations were conducted in triplicate.

4. Results

The results of the experiment are displayed in Table 2.

Table 2-IC₅₀ values for cytochrome P450 substrates evaluated in human liver microsomes

Substrate	CYP involved	I ₅₀ -values in μ M or % inhibition at 100 μ M	I ₅₀ -values in μ g/ml or % inhibition at highest concentration tested
Phenacetin phenacetin <i>O</i> -deethylation	CYP1A2	34.0	12.5
Coumarin coumarin 7-hydroxylation	CYP2A6	>100 (15.7)	>36.6 (15.7)
Tolbutamide tolbutamide 4-hydroxylation	CYP2C8/9/10	3.99	1.46
S-Mephenytoin S-mephenytoin 4-hydroxylation	CYP2C19	<0.06 (69.6) ¹⁾	<0.02 (69.6) ¹⁾
Dextromethorphan dextrophan	CYP2D6	3.88	1.42
Bufuralol bufuralol hydroxylation	CYP2D6	12.0	4.40
Chlorzoxazone chlorzoxazone 6-hydroxylation	CYP2E1	<0.03 (86.0) ²⁾	<0.01 (86.0) ²⁾
Testosterone 6 β -hydroxy-testosterone formation	CYP3A4	6.29	2.30
Cyclosporin A overall metabolism	CYP3A4	16.8	6.16
Midazolam 4-OH midazolam formation	CYP3A4/5	4.20	1.54
1'-OH midazolam formation	CYP3A4/5	18.3	6.70
Lauric acid ω -hydroxylated acids (ω -1)-hydroxylated acids	CYP4A CYP2E1	>100 (15.9) 9.79	>36.6 (15.9) 3.59

1) The S-mephenytoin metabolism was already inhibited for 70 % at the lowest tested final concentration of R278474 (0.06 μ M or 0.02 μ g/ml).

2) Chlorzoxazone 6-hydroxylation was constantly \pm 85 % inhibited, starting from the lowest concentration tested (0.03 μ M or 0.01 μ g/ml).

5. Conclusions

Based on the experiment's results, the applicant concluded that rilpivirine inhibits CYP 1A2, CYP 2C8/9/10, CYP 2C19, CYP 2D6, CYP 2E1, and CYP 3A4/5.

1. Title

The *in-vitro* metabolism of ^{14}C -TMC278 in hepatocytes and liver subcellular fractions of male and female Swiss albino mice, male and female black Agouti rasH2 microinjected mice, male and female rats, female rabbit, male dog and man

2. Objectives

The primary objective of the study was to evaluate the *in vitro* metabolism of rilpivirine in hepatocytes and liver subcellular fractions of male and female Swiss albino mice, male and female Sprague-Dawley rats, female rabbit, male dog and man.

3. Methods

All experiments and sample analyses were protected from light. The experimental system used hepatocytes derived from the freshly prepared whole livers of male and female Swiss albino mice, male and female black agouti rasH2 microinjected mice (wild type) and male and female SPF Sprague-Dawley rats. For female New Zealand white rabbits and male beagle dogs, hepatocytes were prepared from liver pieces. Freshly prepared human hepatocytes, were supplied by (b) (4)

. Liver subcellular fractions (microsomes and 12,000 x g supernatants) of Swiss albino mice (male and female), Sprague-Dawley rats (male and female), rabbit (female), dogs (male) and humans and freshly prepared liver subcellular fractions from male and female black agouti rasH2 microinjected mice (wild type) were also used.

Primary hepatocyte cell cultures were incubated in 6 well plates with 10^6 cells per well. 5 μM of ^{14}C -rilpivirine was placed into wells containing 2 mL of RPMI medium (without fetal calf serum) and the plates were incubated at 37 °C for approximately 12 and 24 hours with 4 wells per time point. For the liver subcellular fractions, microsome incubations used a protein concentration of 1 mg/mL in a total volume of 1.0 mL. The 12,000 x g supernatants used a cytochrome P-450 concentration equivalent to that of the microsomes of the respective species. The cofactors used were 0.5 mg of glucose-6-phosphate, 0.25 units of glucose-6-phosphate dehydrogenase (only for incubations with microsomes), 0.125 mg of NADP and 0.5 mg of $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ in 0.5 mL of 0.5 M Na, K phosphate buffer pH 7.4. For Aroclor 1254-pretreated rats, incubations of ^{14}C -rilpivirine under the conditions of the Ames test were performed with S9 liver subcellular fractions (the results of this incubation will not be discussed).

The cytochrome P450 content of liver subcellular fractions and in the cell lysates of hepatocyte suspensions was derived based on the Omura and Sato method. The incubation conditions for evaluating the functional activity of liver microsomes are displayed in Table 1.

Table 1-Incubation conditions for evaluating the functional activity of liver microsomes

<u>Substrate</u>	<u>final substrate concentration (μM)</u>	<u>protein concentration (mg/mL)</u>	<u>incubation time (min)</u>
7-ethoxycoumarin	100	0.015	10
Dextromethorphan*	3	0.2	20
Midazolam*	50	0.5	10

*Only for human liver microsomes.

The formation of dextromethorphan O-desmethyl and hydroxyl-midazolam was determined using LC/MS/MS.

Table 2-Incubation conditions for evaluating the functional activity of 7-ethoxycoumarin O-deethylase activity in hepatocyte suspensions

Substrate concentration	Cell concentration (cells/mL)	Incubation time	Deconjugation	Analytical method
100 μM	0.5 10 ⁶	10 min	β-glucuronidase/ arylsulphatase	Fluorimetric

After incubation, 10 μL samples were withdrawn and diluted with methanol and 10 mL of scintillation cocktail (Ultima Gold™ Packard). Liquid scintillation counting was then performed with samples counted in duplicate.

Two methods were used to identify metabolites: a) unlabeled compounds (monitored using UV detection at 306 nm) were compared with metabolites of ¹⁴C- rilpivirine (monitored using radioactivity) using HPLC co-chromatography, and b) LC/MS/MS.

Unchanged rilpivirine and its metabolites in a sample were determined based on the percentage of radioactivity relative to the total injected radioactivity of the sample.

4. Results

Reviewer note: only the mass balance and metabolite profile results for humans are displayed below.

Table 3-Human mass balance and metabolite profile for rilpivirine in hepatocyte suspensions, primary cell cultures, microsomes, and 12,000 x g supernatant fractions

	Hepatocytes (Donor 1)		Hepatocytes (Donor 2)		Hepatocytes (Donor 3)		Hepatocytes (Donor 4)		Hepatocytes (Mean of Donors 1-4)		Liver subcellular fractions	
	SK	PCK	SK	PCK	SK	PCK	SK	PCK	SK	PCK	12,000 g	MICR
2	-	-	-	-	-	-	-	-	-	-	4.8	1.6
3	0.7	1.7	-	2.0	-	1.2	-	1.0	0.2	1.5	-	-
7	0.5	2.2	1.0	2.1	-	1.5	-	1.4	0.4	1.8	2.3	1.3
13	2.0	1.9	4.3	5.5	2.3	10.0	-	1.8	2.2	4.8	-	-
14	1.0	3.0	3.8	9.7	-	3.9	1.0	3.0	1.5	4.9	-	-
15	2.6	3.8	1.3	3.4	-	6.2	0.6	4.8	1.1	4.6	-	-
17	0.7	2.7	1.2	14.4	-	7.5	-	2.5	0.5	6.8	-	-
22	-	-	-	-	-	-	-	-	-	-	3.6	7.8
18	-	-	-	6.9	-	-	-	-	-	1.7	-	-
19	0.8	3.4	-	T	-	2.2	-	2.8	0.2	2.1	-	-
27	4.6	6.8	1.6	3.3	1.6	7.6	1.8	11.1	2.4	7.2	5.6	4.9
25	22.2	48.3	9.2	15.8	6.8	27.4	8.9	32.5	11.8	31.0	-	-
30 (+ 31*)	2.3	1.3	1.3	1.0	-	1.1	-	2.8	0.9	1.6	3.6*	0.5
33	2.5	1.8	1.3	-	0.7	1.1	1.0	1.6	1.4	1.1	2.5	2.9
35 + 36	1.6	-	-	-	-	-	-	-	0.4	-	9.8	7.9
38	-	-	-	-	-	-	-	-	-	-	3.8	-
42	1.2	2.0	-	-	-	0.9	0.9	0.9	0.5	1.0	6.6	6.0
43	1.3	-	2.1	1.4	2.0	-	1.6	0.8	1.8	0.6	T	-
UD	57.7	15.5	75.0	28.5	80.3	18.4	90.3	29.9	75.8	23.1	34.8	43.5
Sum	101.7	94.4	102.1	94.0	93.7	89.0	106.1	96.9	100.9	93.6	73.8	76.4

* The figure represent the sum of the percentages of metabolites 30 and 31.

T: below limit of quantification

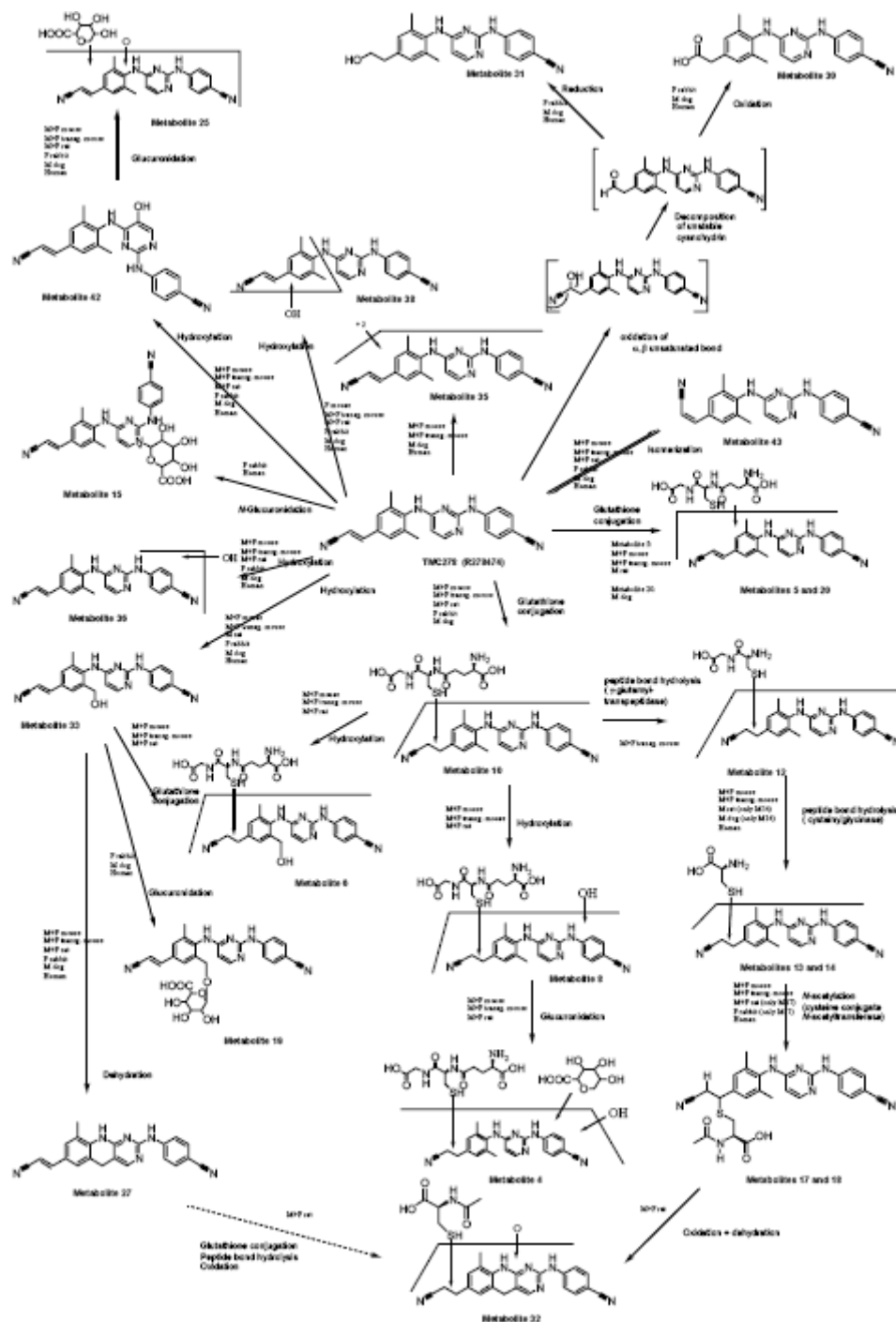
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Table 4-Summary of metabolites identified in the TMC278-NC102 study

Metabolite code	Identification method	Identity
4	LC-MS/MS	glucuronide of metabolite 8
5	LC-MS/MS	glutathione conjugate of TMC278
6	LC-MS/MS	glutathione conjugate of metabolite 33
8	LC-MS/MS	hydroxylated metabolite of metabolite 10
10	LC-MS/MS	glutathione conjugate of TMC278
12	LC-MS/MS	glycine-cysteine conjugate of TMC278
13,14	LC-MS/MS	cysteine conjugates of TMC278
15	LC-MS/MS, co-elution with isolated rabbit metabolite, NMR on isolated rabbit metabolite, enzymatic hydrolysis.	<i>N</i> -glucuronide at the <i>N</i> ₁ -position of the pyrimidinyl moiety of TMC278
17,18	LC-MS/MS Co-chromatography	mercapturic acid conjugates of TMC278 (R378523)
19	LC-MS/MS enzymatic hydrolysis	glucuronide of metabolite 33
20	LC-MS/MS	glutathione conjugate of TMC278
25	LC-MS/MS Enzymatic hydrolysis	glucuronide of metabolite 42
27	LC-MS/MS, NMR on isolated rabbit metabolite.	tricyclic metabolite, originating from oxidation and dehydration most probably of metabolite 33
30	LC-MS/MS	carboxylic acid metabolite on the cyanoethenyl moiety
31	LC-MS/MS	hydroxylated metabolite on the cyanoethenyl moiety
32	LC-MS/MS	tricyclic mercapturic acid conjugate metabolite, originating from oxidation and dehydration most probably of metabolites 17 or 18
33	LC-MS/MS	hydroxymethyl TMC278 (R419763)
35	LC-MS/MS	unknown (+ 2 mass units)
36	LC-MS/MS	hydroxylated metabolite of TMC278
38	LC-MS/MS	hydroxyl metabolite at the cyanoethenyl-2,6-dimethylphenyl moiety of TMC278
42	LC-MS/MS	hydroxyl metabolite at the 5-position of the pyrimidinyl moiety of TMC278
43	Co-chromatography	cis TMC278 (R289932)
	LC-MS/MS	
UD	Co-chromatography LC-MS/MS	TMC278

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Figure 1-In vitro metabolic pathways for humans and various animal species



5. Conclusions

Metabolites 25, 27, 36, 42, and 43 were identified in all species. The major in vitro metabolic route that was identified in humans (as well as in dogs and rabbits) was aromatic hydroxylation at the pyrimidinyl moiety of rilpivirine followed by

glucuronidation. Both aromatic hydroxylation at the pyrimidinyl moiety of rilpivirine followed by glucuronidation and aliphatic hydroxylation at one of the methyl groups of the cyanoethenyl-2,6- dimethylphenyl moiety of rilpivirine followed by dehydration to the ring-closed metabolite 27 were identified in all species. There were no unique human metabolites that were identified.

1. Title

Determination of the *in vitro* transport characteristics of TMC278, evaluation of the possible role of P-glycoprotein in TMC278 transport and assessment of possible inhibition of P-glycoprotein activity by TMC278: a study in Caco-2 monolayers

2. Objectives

The objectives of the study were to evaluate the transport of rilpivirine across Caco-2 cells, both in the apical to basolateral direction and vice versa at concentrations ranging from 3 to 300 μ M and to evaluate the P-gp inhibitory effects of rilpivirine.

3. Methods

Transepithelial transport of rilpivirine across Caco-2 cell monolayers

Caco-2 cells (passage #29) were placed on 24-well cell culture inserts (Millicell[®]-PCF) at 63,000 cells/cm². The cell culture medium consisted of the following: DMEM, 5% FCS, 1% NEAA, 1% L-glutamine and 100 U/mL penicillin/streptomycin. The medium was replaced the day after seeding and every other day afterwards. A pre-incubation period was not specified as recommended in the draft FDA drug interaction guidance document. At 21 to 23 days after seeding, the cell monolayer integrity was evaluated by measuring transepithelial electrical resistance (TEER) and determining the leakage of ¹⁴C- or ³H-mannitol before the experiments. Each batch of Caco-2 cells was validated using reference compounds for low, medium, and high transepithelial permeation (¹⁴C-alniditan (R091274), ³H-levocabastine (R050547) and ³H-theophylline (R076771)).

The incubation buffers used were Hank's Balanced Salt Solution (HBSS) at pH 6.5 [containing 25 mM 2-(N-morpholino) ethanesulfonic acid; MES] and HBSS at pH 7.4, both containing 10 % Fetal Calf Serum (FCS). An ethanol solution of ¹⁴C-rilpivirine was evaporated and reconstituted in DMSO to achieve a radioactive stock solution of 4.06 MBq/ml (2.0 mM). Stock solutions containing unlabeled rilpivirine were prepared at 118, 38, 10 and 2 mM. Both HBSS buffers were spiked with radioactive and unlabeled rilpivirine stock solutions using 2.5 μ L/mL (except for the 3 μ M rilpivirine dosing solution that was spiked with 1.5 μ L/mL of radiolabeled stock solution and 3.5 μ L/mL of DMSO). The final total (labeled + unlabelled) rilpivirine concentrations were 3, 10, 30, 100 and 300 μ M. The final radioactivity concentrations were 10.2 kBq/mL (or 6.1 kBq/mL for the 3 μ M solution). The final concentration in the dosing solutions for the ¹⁴C-alniditan, ³H-levocabastine and ³H-theophylline reference compounds solutions was 20 μ M (radioactive concentration of 15, 10 and 5 kBq/mL, respectively). The final mannitol concentration was 1.45 μ M (radioactive concentration of about 3.1 kBq/mL) for dosing solutions spiked with ¹⁴C- or ³H-mannitol stock solution.

The transport experiments were conducted in quadruplicate. The dosing solutions were applied to the apical (AP; 0.4 mL; HBSS pH 6.5 + 10% FCS) or to the basolateral (BL;

0.6 mL; HBSS pH 7.4 + 10% FCS) side of the cell monolayer for the experiments evaluating absorptive (AP to BL) or secretory (BL to AP) transport, respectively. The cell culture inserts were incubated at 37°C in a humidified incubator containing 5% CO₂ for 120 min. At time 0, dosing solution samples were obtained in duplicate to measure initial concentrations. Afterwards, 100 µL samples were obtained at 15 min, 45 min, 90 min and 120 min from the acceptor compartment and the volume was corrected by adding 100 µL of the appropriate buffer solution. At the end of incubation (120 minutes), a sample was obtained from the donor compartment.

Evaluation of the P-gp inhibitory effects of rilpivirine on taxol transport across Caco-2 cell monolayers

An ethanol solution of ³H-taxol was evaporated and reconstituted in DMSO to achieve a radioactive stock solution of 30.3 µM and 5.6 MBq/mL (specific activity of 185 MBq/µmol) in addition to making a stock solution of 40 mM verapamil in DMSO. HBSS at pH 7.4 was spiked with rilpivirine stock solution to obtain rilpivirine concentrations of 0, 1, 3, 10, 30, and 100 µM. These solutions were spiked with ³H-taxol stock solution to achieve a taxol concentration of 75.8 nM at 14.0 kBq/mL. For the positive control, HBSS was combined with verapamil stock solution and ³H-taxol stock solution to achieve a final verapamil concentration of 100 µM. The final mannitol concentration was 1.45 µM (radioactive concentration of about 3.1 kBq/ml) for dosing solutions spiked with ¹⁴C mannitol stock solution.

The transport experiments were conducted in triplicate. The dosing solutions in HBSS at pH 7.4 were applied to the apical (0.4 mL) or to the basolateral (0.6 mL) side of the cell monolayer for the experiments to evaluate apical to basolateral or basolateral to apical transport, respectively. HBSS at pH 7.4 was added to the acceptor compartments. The cell culture inserts were incubated at 37°C in a humidified incubator (Hera cell) containing 5% CO₂. The incubation time was not specified. At time 0, dosing solution samples were obtained in duplicate to measure concentrations using liquid scintillation counting. 100 µL samples were obtained from the acceptor and donor compartments after incubating for 120 minutes.

¹⁴C-TMC278, ¹⁴C-alniditan, ³H-levocabastine, ³H-theophylline, ³H-taxol, and ¹⁴C-mannitol or ³H-mannitol were analyzed for total ³H- and ¹⁴C-associated radioactivity using a liquid scintillation spectrometer.

The calculation of the amount of compound that was transported across the Caco-2 cell monolayers was based on the radioactivity from the acceptor compartment samples during and at the end of incubation. Apparent permeability coefficients (P_{app}) were calculated for the initial permeation rate (using data from the 15 minute time point) or for the 15-45-90 minute steady state permeation rate (using the linear slope range). Graphical displays were generated for the amount of transport (nmol) versus time. Mannitol and taxol apparent permeability coefficients were derived based on the slope of the regression line through the 15-45-90 minute and 0 through 120 minute time points, respectively. Apparent permeability coefficients were calculated using the following equation (the

equation does not include the volume of medium in the donor compartment as recommended in the draft FDA drug interaction guidance document and it is not clear how this is accounted for):

$$P_{app} = \frac{dQ}{dt} \cdot \frac{1}{A \cdot C_0}$$

where:

dQ/dT=the slope of the regression line through the time points of interest

A=surface area of the monolayers (0.6 cm²)

C₀=initial measured concentration in the dosing solution (μM)

Rilpivirine's absorption potential was determined based on comparing the Papp values for the reference compounds.

Rilpivirine's P-gp inhibitory effect was determined based on the percent inhibition of secretory taxol transport in the presence of rilpivirine compared to taxol transport under control conditions.

The IC₅₀ value for rilpivirine's inhibition of taxol transport was using the following equation:

$$Y = E_0 - \frac{E_{max} \cdot C^n}{IC_{50} + C^n}$$

where:

Y=relative P-gp mediated transport activity (expressed as percent of average control activity)

E₀=calculated control value for P-gp mediated transport activity (after fitting)

E_{max}=calculated maximum decrease in P-gp mediated transport activity

IC₅₀=calculated concentration of rilpivirine causing half-maximal reduction in

P-gp-mediated transport activity

n=Hill coefficient

4. Results

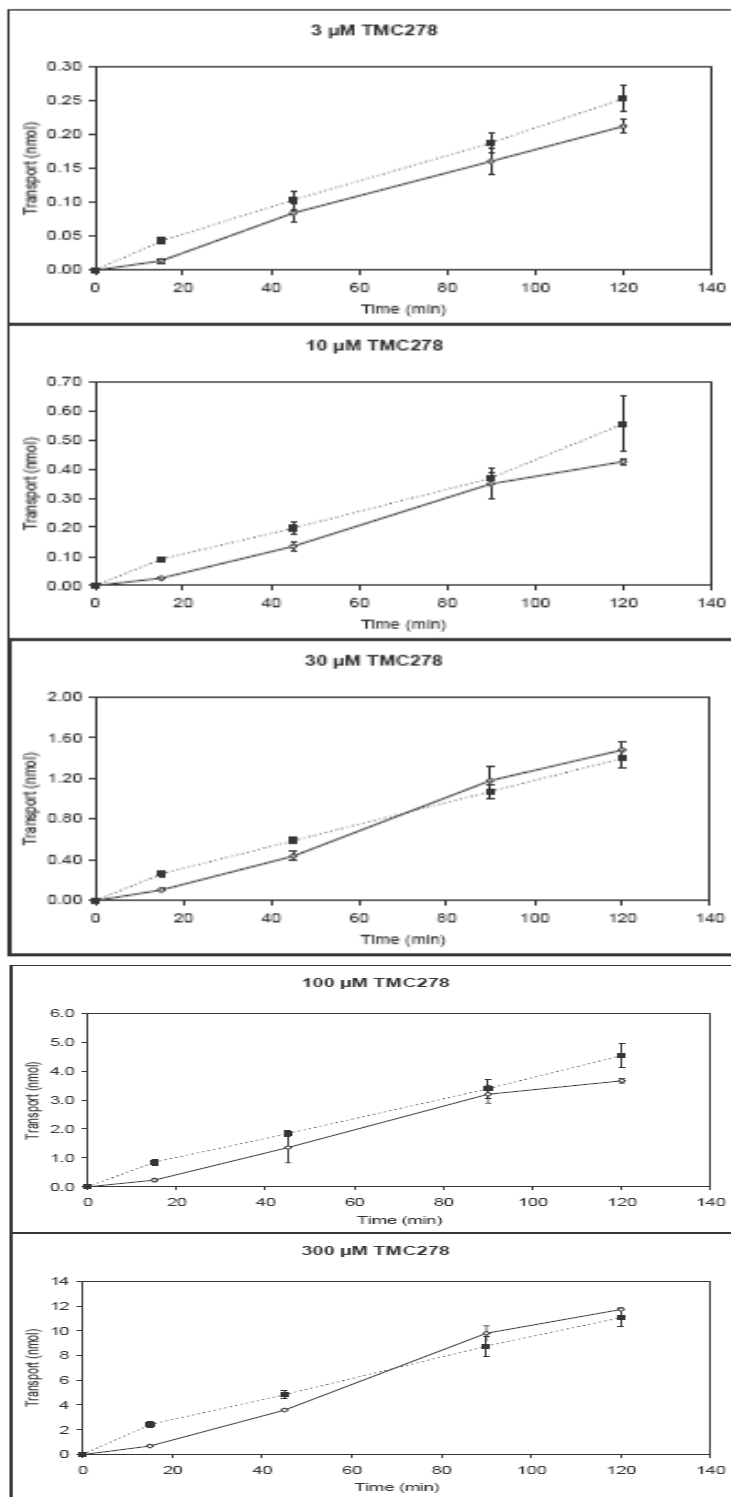
Transepithelial transport of rilpivirine across Caco-2 cell monolayers

Initially, efflux ratio values (secretory Papp/absorptive Papp) of up to 10 were observed, however, efflux ratios decreased to at most 2 when steady-state Papp values were derived. The report states that steady-state Papp values are the most relevant since transport occurs at intermediate rates with maintaining of sink conditions (< 15 % of initial amount transported to acceptor compartment) until the end of the incubation period.

Table 1-Average apparent permeability coefficient (Papp) values for rilpivirine and reference compounds

P _{app} values in 10 ⁻⁶ cm/s	AP-BL TRANSPORT		BL-AP TRANSPORT	
	0-15 min	15-45-90 min	0-15 min	15-45-90 min
TMC278 3 µM	5.0 ± 1.2	11.1 ± 2.0	51.3 ± 10.5	22.8 ± 3.3
TMC278 10 µM	4.8 ± 0.6	12.5 ± 2.2	46.7 ± 10.3	19.0 ± 3.9
TMC278 30 µM	6.2 ± 0.9	13.4 ± 1.1	63.5 ± 9.0	26.5 ± 5.7
TMC278 100 µM	4.9 ± 1.2	12.8 ± 1.8	40.1 ± 4.5	16.1 ± 2.3
TMC278 300 µM	3.6 ± 0.6	9.8 ± 0.8	43.1 ± 9.5	15.1 ± 3.7
TMC278 30 µM + 100 µM verapamil	3.1 ± 0.5	11.8 ± 1.6	67.8 ± 16.3	27.1 ± 4.8
Alniditan 20 µM	0.6 ± 0.3	0.6 ± 0.3	3.0 ± 0.2	0.7 ± 0.0
Levocabastine 20 µM	15.1 ± 2.9	20.2 ± 4.2	92.8 ± 0.8	24.8 ± 0.9
Theophylline 20 µM	38.6 ± 8.4	28.4 ± 2.4	119.0 ± 23.1	31.4 ± 5.6

Figure 1-Time course for average secretory (closed symbols) and absorptive (open symbols) transport of rilpivirine across Caco-2 cells

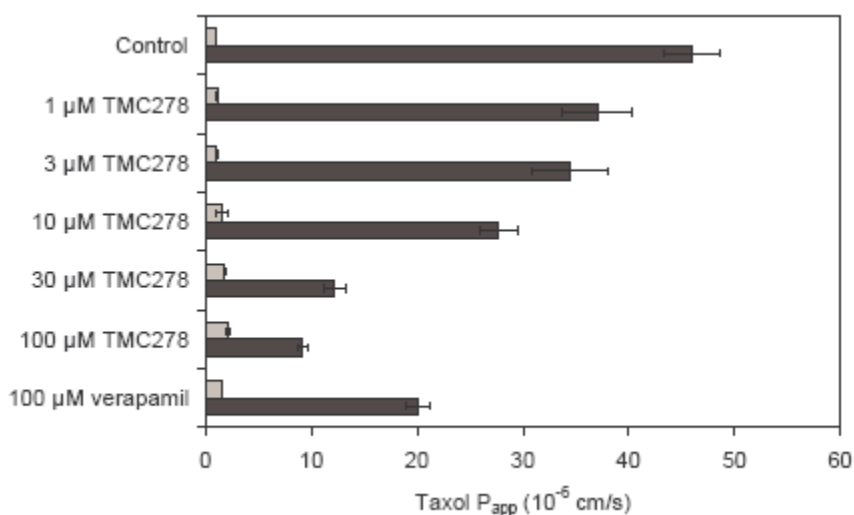


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Evaluation of the P-gp inhibitory effects of rilpivirine on taxol transport across Caco-2 cell monolayers

The IC₅₀ value for rilpivirine P-gp inhibition is 9.2 μ M. Rilpivirine demonstrates competitive inhibition as demonstrated by a notable decrease in secretory transport and a slight increase in absorptive transport of taxol. These effects decrease as the concentration of rilpivirine decreases.

Figure 2-Effect of different concentrations of rilpivirine on the secretory and absorptive transport of ³H-taxol across Caco-2 monolayers (bars represent ³H-taxol permeability coefficients obtained following 120-min incubation periods)



5. Conclusions

Based on comparing rilpivirine's permeation rate to the reference compounds (¹⁴C-alniditan, ³H-levocabastine and ³H-theophylline), rilpivirine is an intermediate transepithelial permeability compound. Rilpivirine is not significantly transported by P-gp under steady state conditions. Rilpivirine also has the potential to inhibit P-gp with an IC₅₀ value for P-gp inhibition of 9.2 μ M.

1. Title

The plasma protein binding and blood distribution of TMC278 in animals and man

2. Objectives

The objectives of the study were to evaluate the plasma protein binding and distribution of rilpivirine in healthy male adult subjects, male beagle dogs, male and female SPF Sprague-Dawley rats, male and female Swiss CD-1 mice and female SPF New Zealand white rabbits.

3. Methods

³H-rilpivirine solutions were prepared at concentrations of 2, 20, 60, 200, 600, 2000 and 20000 µg/mL. 5 µL of the solution per mL of sample were spiked into blood samples, plasma samples or protein solutions. An additional ³H-rilpivirine solution was prepared to cross-validate the use of DMSO and ethanol for the study. In all solutions, the radioactivity was approximately 4.4 MBq/mL, and the final radioactivity concentrations was approximately 22 kBq/mL in plasma, blood and protein solutions.

Rilpivirine protein binding

The time to achieve dialysis equilibrium was determined using blank pooled plasma from five healthy male adult subjects with ³H-rilpivirine added at 1000 ng/mL (22 kBq/mL). Ten aliquots subsequently underwent equilibrium dialysis. The equilibrium dialysis utilized a 0.067 M phosphate buffer, pH 7.17, at 37 °C in a Dianorm system with identical macro-1 Teflon cells and Diachema 10.17 membranes. After 1, 2, 3, 4, and 6 hours, the dialysis was stopped and the buffer and plasma compartment contents were collected (2 dialysis cell for each time point).

The stability of the tritium labeled rilpivirine in human plasma was determined using blank human plasma with ³H-rilpivirine added at 1000 ng/mL (22 kBq/mL) and incubated for 3 hours in a water bath maintained at 37°C. Plasma aliquots (n=10 per time point) were collected at time 0 and at the end of incubation. For each time point, half the samples were analyzed for radioactivity and the rest were analyzed after freeze drying.

The effect of pH on rilpivirine's binding to plasma proteins in human plasma was evaluated using pooled blank plasma from 5 healthy male adult subjects with rilpivirine added at 1000 ng/mL (22 kBq/mL). Twenty aliquots (two aliquots per buffer pH) underwent equilibrium dialysis. Using the same system utilized in the experiments evaluating the time to achieve dialysis equilibrium, the equilibrium dialysis used either an isotonic 0.04 M phosphate buffer with a pH of approximately 5.10, 5.81, 6.14, 6.55, 6.96, 7.19, 7.42, 7.79 or 8.37, or a 0.067 M phosphate buffer, pH 7.17. The pH in the plasma compartments collected at the end of the dialysis was evaluated using a Beckman Φ45 pH meter.

The concentration dependence of the protein binding was evaluated in blank, pooled plasma at the following rilpivirine concentrations in all species except for human plasma: 10, 100, 1000, 10000 and 100000 ng/mL. Blank pooled human plasma was fortified at 10, 100, 300, 1000 and 3000 ng/mL. The concentrations of 100000, 3000 and 300 ng/mL had a radioactivity concentration of about 220, 66 and 66 kBq/mL sample, respectively. All other concentrations had a radioactivity of approximately 22 kBq/mL sample. Samples for each species underwent equilibrium dialysis in triplicate (for dogs, samples were dialyzed in duplicate) using the same system utilized in the experiments evaluating the time to achieve dialysis equilibrium.

The total protein, albumin and α 1-acid glycoprotein concentrations were analyzed using the colorimetric biuret test, the colorimetric bromocresol green method and the immunoturbidimetric method, respectively, using a Roche Hitachi Modular analyzer.

Blood distribution

100 ng/mL and 1000 ng/mL (approximately 22 kBq/mL) of ^3H -rilpivirine was added to whole blood samples in duplicate in all species. Hematocrit values were also obtained. Whole blood samples were incubated at 37 °C for 30 min in a GRANT incubation shaking water bath. After incubation, five 100 μL whole blood samples were used to determine blood radioactivity levels. The remaining whole blood samples were used to determine the total radioactivity in duplicate 100 μL plasma samples.

Binding of rilpivirine to purified human proteins

Albumin was dissolved in 0.067 M Sørensen phosphate buffer (pH 7.40) to obtain the following concentrations: 2.0 %, 3.0 %, 4.3% and 5.0 % (w/v). α 1-acid glycoprotein was dissolved in 0.067 M Sørensen phosphate buffer (pH 7.40) to obtain the following concentrations: 0.02 %, 0.05 %, 0.07 % and 0.15 % (w/v). At physiologic protein concentrations (4.3% albumin or 0.07% α 1-acid glycoprotein), ^3H -rilpivirine was added at the following concentrations: 10, 30, 100, 300, 1000, and 3000 ng/mL. At non physiologic protein concentrations, ^3H -rilpivirine was added at 1000 ng/mL. The radioactivity concentration at 3000, 300 and 30 ng/mL was approximately 66 kBq/mL sample and for all other concentrations, the radioactivity concentration was approximately 22 kBq/mL. Samples underwent equilibrium dialysis in duplicate for 3 hours at 37 °C using 0.067 M Sørensen phosphate buffer (pH 7.40).

For the protein binding studies, radioactivity was measured in duplicate 100 μL samples of the plasma or protein solutions before and after equilibrium dialysis, and in 1000 μL duplicate samples of the buffer compartments after dialysis using a Packard Tri-Carb 2100 TR liquid scintillation spectrometer with automatic conversion from counts per minute (cpm) into disintegrations per minute (dpm).

For the blood distribution studies, whole blood samples were combusted using a Packard Sample Oxidizer 307 and the released $^3\text{H}_2\text{O}$ was measured using liquid scintillation counting. A similar procedure was used for the plasma samples.

The unbound fraction of rilpivirine ($f_u = C_u/C$) was derived based on the radioactivity in the buffer ($C_u \times$ the dilution factor) and plasma compartments (C) of the dialysis cells.

The blood to plasma concentrations (C_b/C) was derived based on the blood distribution experiments. The distribution of rilpivirine for blood into plasma water [$f_{ub}(1-H)$], plasma proteins [$f_{pP}(1-H)$] and blood cells [$f_{BC.H}$] was derived using the following equations:

$$f_{ub}(1-H) = \frac{C_{BDD} \times f_u \times (1-H)}{C_{bl}}$$

with H = haematocrit value

C_{BDD} = Concentration in plasma after blood distribution

C_{bl} = Concentration in blood

$$f_{pP}(1-H) = \frac{C_{BDD} \times f_b \times (1-H)}{C_{bl}}$$

with $f_b = 1 - f_u$

$$f_{BC.H} = 1 - \frac{C_{BDD} \times (1-H)}{C_{bl}}$$

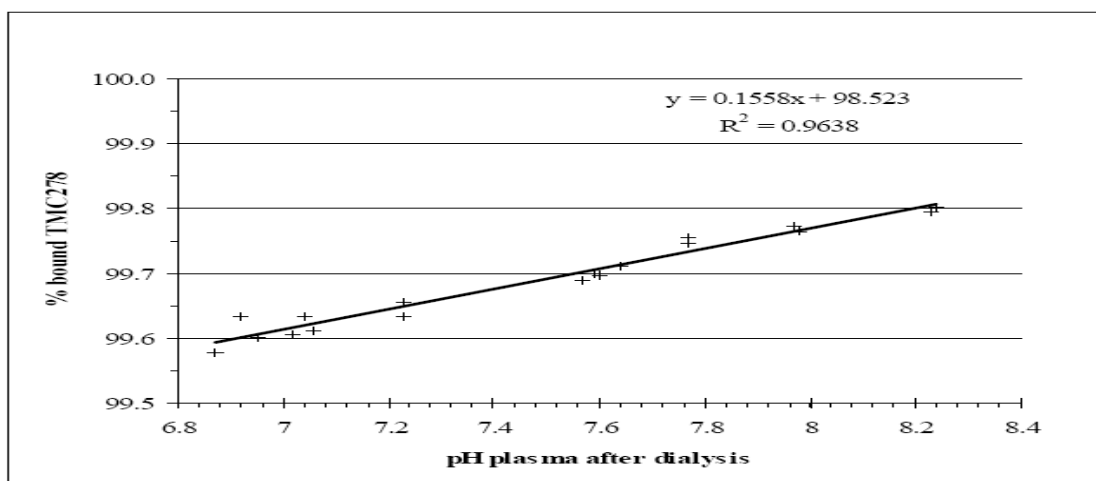
4. Results

Rilpivirine protein binding

The percentage of unbound rilpivirine at 100 ng/mL after 1, 2, 3, 4, and 6 h of dialysis was 0.28 %, 0.30 %, 0.30 %, 0.31 % and 0.35 %, respectively. A dialysis time of 3 hours was selected for the experiments.

Both the use of DMSO in the experiments and the stability of the 3H -rilpivirine were determined to be acceptable. pH-dependent effects were observed (see Figure 1).

Figure 1-Plasma protein binding for 100 ng/mL of rilpivirine at various pH values



The results of the experiments evaluating the concentration dependence of rilpivirine's protein binding are displayed in Table 1. Across all species, at a concentration range of 10 ng/mL to 100000 ng/mL, the protein binding of rilpivirine was >99% and was concentration independent.

Table 1-Plasma protein binding of rilpivirine in humans and animal species (each value=mean \pm SD of three determinations)

Species	Test Concentrations (ng/ml)				
	10	100	1000	10000	100000
	% Protein bound (Mean \pm S.D)				
Mouse (m)	99.93 \pm 0.01	99.89 \pm 0.04	99.93 \pm 0.00	99.92 \pm 0.01	99.84 \pm 0.01
Mouse (f)	99.94 \pm 0.01	99.94 \pm 0.00	99.94 \pm 0.01	99.94 \pm 0.01	99.89 \pm 0.00
Rat (m)	99.80 \pm 0.01	99.83 \pm 0.01	99.84 \pm 0.04	99.82 \pm 0.01	99.80 \pm 0.01
Rat (f)	99.85 \pm 0.01	99.86 \pm 0.01	99.86 \pm 0.01	99.82 \pm 0.02	99.71 \pm 0.02
Rabbit (f)	99.98 \pm 0.01	99.98 \pm 0.00	99.97 \pm 0.01	99.97 \pm 0.00	99.96 \pm 0.01
Dog (m)	99.31 \pm 0.04	99.32 \pm 0.01	99.35 \pm 0.01	99.32 \pm 0.07	99.23 \pm 0.03
Human (m)	Test Concentrations (ng/ml)				
	10	100	300	1000	3000
	% Protein bound (Mean \pm S.D)				
	99.66 \pm 0.00	99.64 \pm 0.01	99.62 \pm 0.02	99.67 \pm 0.02	99.70 \pm 0.02

(m): male; (f): female

The results of the experiments evaluating the binding of rilpivirine at various concentrations of albumin and α 1-acid glycoprotein are displayed in Table 2. Overall, a greater percentage of rilpivirine was bound to albumin compared to α 1-acid glycoprotein.

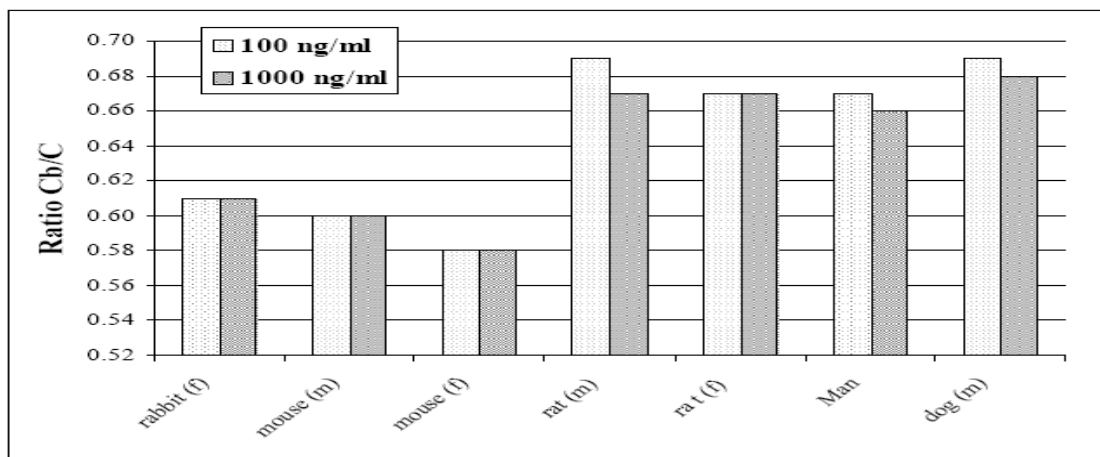
Table 2-Rilpivirine binding to various concentrations of albumin and α 1-acid glycoprotein

Human serum albumin (g/100 ml)	Concentration of TMC278 (ng/ml)	Percentage bound (%)	Percentage unbound (%)
5.0	1000	99.56	0.45
4.3	3000	99.51	0.50
4.3	1000	99.50	0.50
4.3	300	99.50	0.51
4.3	100	99.50	0.50
4.3	30	99.50	0.51
4.3	10	99.52	0.48
3	1000	99.32	0.68
2	1000	99.03	0.97

α 1-acid-glycoprotein (g/100 ml)	Concentration of TMC278 (ng/ml)	Percentage bound (%)	Percentage unbound (%)
0.15	1000	72.26	27.75
0.07	3000	54.99	45.02
0.07	1000	48.76	51.25
0.07	300	39.02	60.98
0.07	100	25.92	74.08
0.07	30	30.36	69.65
0.07	10	42.10	53.27
0.05	1000	25.89	74.11
0.02	1000	11.45	88.56

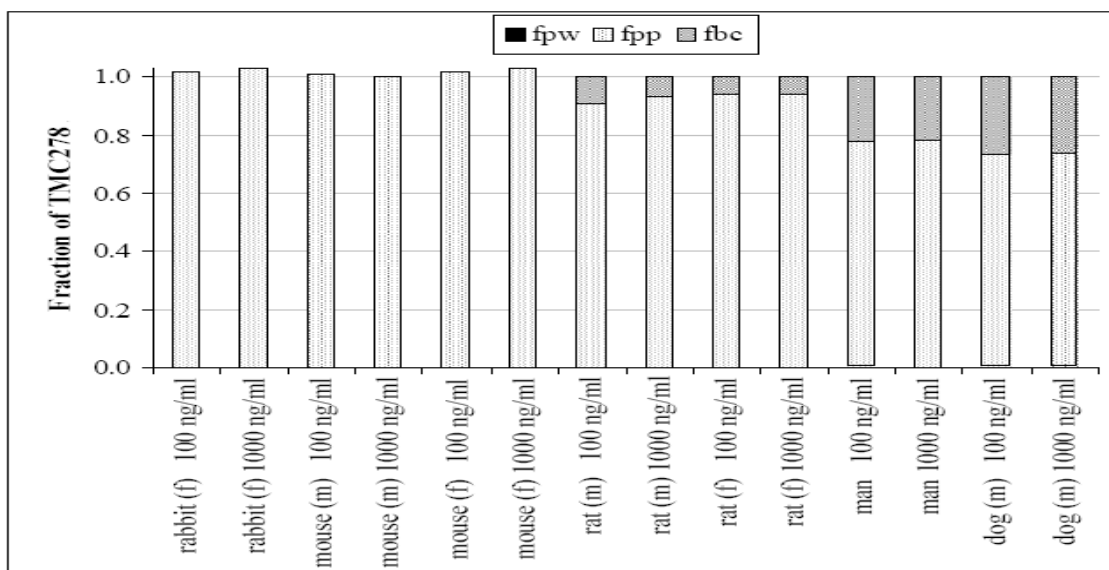
Based on the results of the experiments evaluating the distribution of rilpivirine in blood that are displayed in Figures 2 and 3, rilpivirine binds extensively to plasma proteins in humans and other species.

Figure 2-Rilpivirine blood to plasma ratios in humans and animal species



(m): male; (f): female

Figure3-Fraction of rilpivirine distributed to plasma water, plasma proteins and blood cells



(m): male; (f): female; in all species: f_{pw} is < 0.005

5. Conclusions

The protein binding of rilpivirine was $>99\%$ and was concentration independent. A greater percentage of rilpivirine was bound to albumin compared to $\alpha 1$ -acid glycoprotein. Rilpivirine extensively binds to plasma proteins in humans and other species.

TMC278-NC141

1. Title

An in vitro study to (a) identify the microsomal cytochrome P-450 iso-enzymes mediating TMC278 metabolism (reaction phenotyping) and to (b) determine the kinetics of TMC278 metabolism in human liver microsomes

2. Objectives

The primary objective of the study was to determine the microsomal cytochrome P450 enzymes involved in rilpivirine's metabolism and to evaluate the kinetics of rilpivirine's metabolism in human liver microsomes (HLMs).

3. Methods

Rilpivirine metabolism enzyme kinetics

Two experiments were conducted to derive the kinetics (K_m and V_{max}) for rilpivirine's metabolism. The first experiment involved incubating HLMs with different concentrations of ^{14}C -rilpivirine [0.5 μM (1.03 kBq/mL), 1 μM (2.06 kBq/mL), 3 μM (6.18kBq/mL), 5 μM (7.25 kBq/mL), 10 μM (7.25 kBq/mL), 30 μM (7.25 kBq/mL) and 50 μM (7.25 kBq/mL)]. A protein concentration of 0.25 mg/mL with 15 min incubation time was used for the experiment. A second experiment was subsequently conducted based on the results from the first experiment and the lower than desired radioactivity from the first experiment.

CYP P450 reaction phenotyping

Use of CYP P450 inhibitors in HLMs

^{14}C -rilpivirine incubations in HLMs (in triplicate) were conducted with CYP specific inhibitors. 1-aminobenzotriazole was used as a nonspecific CYP P450 inhibitor for evaluating the potential role of microsomal CYP P450 enzymes in rilpivirine's metabolism. Troleandomycin, furafylline or clarithromycin were used as mechanism based inhibitors. When either mechanism-based or nonspecific inhibitors were evaluated, microsomes were incubated with the inhibitor and a NADPH-generating system (containing NADP) for 15 minutes before adding rilpivirine. The experimental conditions included a rilpivirine concentration of 5 μM (7.25 kBq/mL), a microsomal protein concentration of 0.25 mg/mL (pooled batch of HLMs,) and a 15 minute incubation time. After preincubating for 5 minutes, the reactions were initiated by adding 0.1 ml of the NADP-solution to obtain a final incubate concentration of 0.125 mg/mL.

Use of heterologously expressed recombinant enzymes

In E.coli systems, E coli expressing human reductase were combined with one of the following CYPs: CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP2E1, CYP2C8 or CYP2B6. The cofactors used were 0.5 mg of glucose-6-phosphate, 0.25 units of glucose-6-phosphate dehydrogenase, 0.125 mg of NADP and 0.5 mg of MgCl₂.6H₂O in 0.5 ml of 0.5 M Na, K phosphate buffer pH 7.4. After preincubating for 5 minutes, the reactions were started by adding ¹⁴C-rilpivirine (final concentration in incubation: 5 µM, 7.25 kBq/mL) and incubating in triplicate for 60 minutes. Similar procedures were performed for recombinant CYP P450 enzymes (Baculovirus expressed insect cell lines-Supersomes[®] [BD]).

Correlation analysis in different HLM batches

The metabolism of ¹⁴C-rilpivirine was evaluated in 10 different batches of individual human liver microsomes. The experimental conditions included a rilpivirine concentration of 5 µM (7.25 kBq/mL), a microsomal protein concentration of 0.25 mg/mL and a 15 minute incubation time. After preincubating for 5 minutes, the reactions were started by adding ¹⁴C-rilpivirine.

In vitro covalent binding experiments

Multiple experiments were conducted to evaluate rilpivirine's covalent binding,

Samples from the rilpivirine metabolism enzyme kinetics, the CYP P450 reaction phenotyping experiments, and some of the in vitro covalent binding experiments were analyzed using radio-HPLC analysis. Other methods used to analyze samples from the in vitro covalent binding experiments included LC/MS/MS or radioactivity).

If feasible, metabolites were identified using unlabeled compounds (monitored using UV detection at 306 nm). Alternatively, the metabolites were identified based on comparing the radio-HPLC profile from the in vitro species comparison study (TMC278-NC102) study and the human mass balance trial.

Unchanged rilpivirine and its metabolites in a sample were determined based on the percentage of radioactivity relative to the total injected radioactivity of the sample.

The Michaelis-Menten equation was used to derive the K_m and V_{max} values for rilpivirine. For the experiments involving CYP P450 inhibitors, the percent inhibition was derived using the equation below. The major (M42) and minor (M27, M33 and M35+M36) metabolites in HLMs were evaluated.

$$\text{Percent inhibition} = 100 - [C_{(+\text{inhibitor})}/C_{(\text{control})}] * 100]$$

where:

C_(+inhibitor)=the percentages of the metabolite formed with the addition of the inhibitor to the incubations

$C_{(control)}$ = the percentages of the metabolite formed without the addition of the inhibitor to the incubations.

For the correlation analysis (using pair-wise correlation), the rate of rilpivirine metabolism and the forming of the major and minor metabolites (M2, M33, M35+M36 and M42) were obtained from the 10 individual batches of HLMs and were correlated with the CYP P450 specific activities of the HLMs.

4. Results

Rilpivirine metabolism enzyme kinetics

A protein concentration of 0.25 mg/mL with a 15 minute incubation time was used in evaluating rilpivirine enzyme kinetics. At the concentration range evaluated (0.5 μ M to 50 μ M) monophasic Michaelis Menten kinetics was observed and mean apparent K_m and V_{max} values for rilpivirine metabolism were $4.17 \pm 1.06 \mu$ M and 381 ± 26 pmol/mg/min, respectively.

CYP P450 reaction phenotyping

Use of CYP P450 inhibitors in HLMs

The in vitro results displayed in Tables 1 and 2 and Figure 1 indicate that CYP 3A is the major pathway of rilpivirine metabolism and an important metabolic pathway for rilpivirine metabolites. No significant effect on the formation of rilpivirine was observed with inhibitors of other CYP enzymes. The CYP 2C9 inhibitor sulphaphenazole decreased the forming of the M33 metabolite by 30%.

Table 1-Impact of CYP specific inhibitors on 14 C-rilpivirine in human liver microsomes including the major (M42) and minor (M27, M33 and M35+M36) metabolites

Diagnostic CYP inhibitor (CI)	CYP P450 Isoform selectivity	Final Conc. CI in the incubate (µM)	Substrate turnover/product formation rate (pmol/min.mg protein)														
			TMC278			M27			M33			M35 + NB6			M42		
			Mean	±	S.D	Mean	±	S.D	Mean	±	S.D	Mean	±	S.D	Mean	±	S.D
Furafylline	CYP1A2	10	172	±	20	30.1	±	1.9	17.4	±	1.9	5.08	±	5.08	128	±	20
Coumarin	CYP2A6	100	170	±	26	33.9	±	7.0	22.0	±	1.9	3.81	±	6.61	119	±	13
Sulphaphenazole	CYP2C9	10	160	±	28	27.1	±	6.5	10.6	±	9.4	2.12	±	3.67	131	±	19
Quinidine	CYP2D6	10	149	±	24	26.7	±	2.2	16.1	±	0.7	4.66	±	8.07	108	±	15
4-methylpyrazole	CYP2E1	20	166	±	42	26.7	±	4.6	16.5	±	7.6	5.51	±	9.54	127	±	25
Ticlopidine HCl	CYP2C19/D6	5	168	±	20	29.7	±	5.1	19.5	±	2.6	10.2	±	8.9	116	±	21
Ketoconazole	CYP3A4	1	-10.6	±	0.0	0.0	±	0.00	0.0	±	0.0	0.0	±	0.00	0.0	±	0.00
Troleandomycin	CYP3A4	200	-10.6	±	0.0	0.0	±	0.00	0.0	±	0.0	0.0	±	0.00	0.0	±	0.00
Clarithromycin	CYP3A	15	66.5	±	13.8	14.8	±	1.9	9.32	±	2.65	6.36	±	2.54	44.9	±	4.8
Ritonavir	CYP3A4	0.15	13.6	±	5.5	0.0	±	0.0	0.0	±	0.0	0.0	±	0.00	20.8	±	0.7
1-aminobenzotriazole	CYP P450	1000	-6.36	±	3.88	0.0	±	0.0	0.0	±	0.0	0.0	±	0.00	0.0	±	0.00
Control (+ methanol)	-	-	156	±	40	27.1	±	6.3	15.3	±	3.4	15.3	±	4.4	105	±	30
Control (+ water)	-	-	163	±	44	28.8	±	12.2	15.3	±	4.6	13.6	±	5.1	107	±	32

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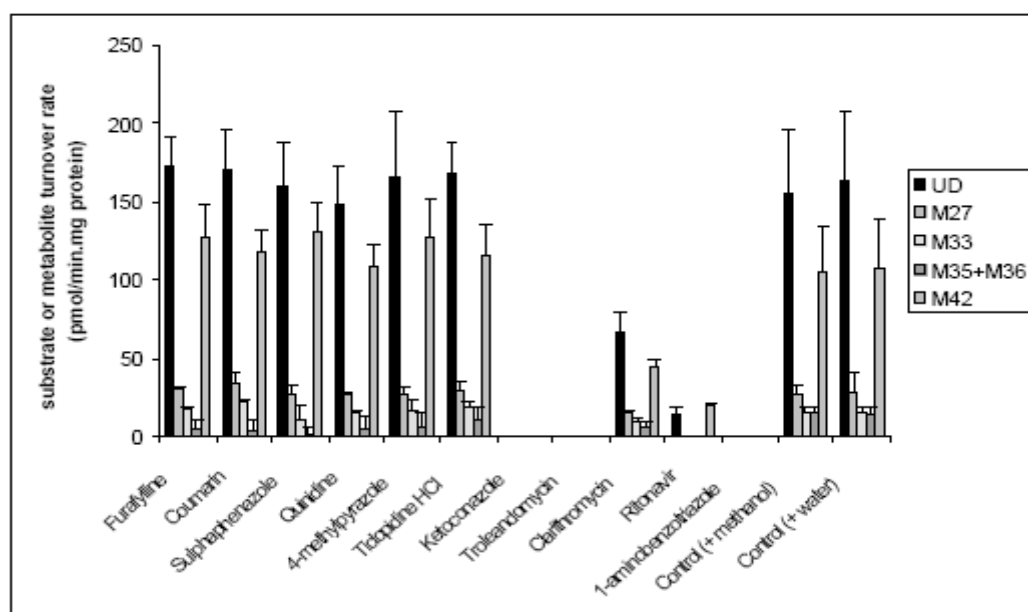
Table 2-Percentage inhibition in evaluating the impact of CYP specific inhibitors on ¹⁴C-rilpivirine in human liver microsomes including the major (M42) and minor (M27, M33 and M35+M36) metabolites

Test Article: TMC278

Type of Study: CYP reaction phenotyping- Effect of diagnostic CYP inhibitors on the metabolism of TMC278		Study no : TMC278/FK5300				
Method: Inhibition of the metabolism of TMC278 in human liver microsomes by diagnostic inhibitors was carried out with ¹⁴ C-TMC278 (5 µM) for 15 minutes at a protein concentration of 0.25 mg/ml. The amounts of unchanged TMC278 and its metabolites (M27, M33, M35+M36 and M42 ¹) were determined by radio-HPLC. The values represent the percentage of inhibition obtained for each inhibitor in comparison to a control incubate (without inhibitor). Each value represents mean of three observations.						
Results:						
Diagnostic Inhibitor	CYP P450 Form	% Inhibition of Metabolism ²				
		Overall ³	M27 ³	M33 ³	M35+M36	M42 ^{3,4}
Furafylline (10 µM)	CYP1A2	-10.9	-10.9	-13.9	66.7	-22.3
Coumarin (100 µM)	CYP1A6	-9.3	-25.0	-44.4	75.0	-13.4
Sulphaphenazole (10 µM)	CYP2C8/9/10	-3.0	0.0	30.6	86.1	-25.1
Quinidine (10 µM)	CYP2D6	4.4	1.56	-5.56	69.4	-3.24
4-methylpyrazole (20 µM)	CYP2E1	-6.5	1.56	-8.33	63.9	-21.1
Ticlopidine (5 µM)	CYP2C19/D6	-3.1	-2.94	-27.8	25.0	-7.91
Ketoconazole (1 µM)	CYP3A4	107	100	100	100	100
Troleandomycin (200 µM)	CYP3A4	107	100	100	100	100
Clarithromycin (15 µM)	CYP3A	57.2	45.3	38.9	58.3	57.1
Ritonavir (0.15 µM)	CYP3A	91.3	100	100	100	80.2
1-aminobenzotriazole (1000 µM)	CYP P450	104	100	100	100	100
Additional Information						
1. Major metabolite in human liver microsomes (> 5 % of the sample radioactivity)						
2. Calculated from control incubation (without inhibitor); higher the positive value and higher the extent of inhibition						
3. Negative values indicates higher % product formation in test sample compared to the control. This was more prominent with the minor metabolites. For all qualitative purposes, all negative values were considered as no inhibition.						

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Figure 1-Impact of CYP specific inhibitors on ¹⁴C-rilpivirine in human liver microsomes including the major (M42) and minor (M27, M33 and M35+M36) metabolites



Use of heterologously expressed recombinant enzymes

In E.coli systems, the results indicate that CYP 3A4 was the major metabolic pathway for rilpivirine and rilpivirine metabolites. M22 and M35+M36 were the major metabolites that were formed based on the formation rate information.

In Supersome systems, the results indicate that CYP 3A4, CYP 3A5 and CYP 3A7 were the major metabolic pathways for rilpivirine and rilpivirine metabolites.

Table 3-CYP P450 reaction phenotyping using an E.coli system to evaluate the metabolism of ¹⁴C-rilpivirine

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Test Article: TMC278

Type of Study: CYP reaction phenotyping- Metabolism of ¹⁴ C-TMC278 in <i>E. coli</i> expressed CYP isoforms									
Study no : TMC278/FK5300									
Method: The metabolism of TMC278 in <i>E. coli</i> expressed CYP systems (prepared in-house) was carried out with ¹⁴ C-TMC278 (5 µM) for 60 minutes at a CYP P450 concentration of 100 pmol/ml of incubation. The amounts of unchanged TMC278 and its metabolites (M50, M2, M22, M27, M33, M35+M36, M51, M42 ¹ and M43) were determined by radio-HPLC. Each value represents mean ± S.D of three observations.									
Results:									
Cytochrome P-450 Form (100 pmol/ml)	Overall % Metabolism ²	M50	M2	Product formation rate (pmol/min.100 pmol P450)					
				M22	M27	M33	M35+M36	M51	M42
CYP1A2	1.40 ± 0.26	-	-	-	-	-	0.83 ± 0.17	-	-
CYP2A6	1.07 ± 1.44	-	-	-	-	-	-	-	-
CYP2B6	1.30 ± 1.76	-	-	-	-	-	-	-	-
CYP2C8	0.43 ± 0.38	-	-	-	-	-	-	-	-
CYP2C9	0.47 ± 0.42	-	-	-	-	-	-	-	-
CYP2C19	0.37 ± 0.32	-	-	-	-	-	-	-	-
CYP2D6	1.07 ± 1.85	-	-	-	-	-	-	-	-
CYP2E1	0.00 ± 0.00	-	-	-	-	-	-	-	-
CYP3A4	86.87 ± 1.40	4.11 ± 0.35	9.03 ± 0.71	15.6 ± 1.30	2.58 ± 0.95	3.00 ± 0.58	20.4 ± 2.95	-	6.28 ± 0.75
CYP3A5	0.53 ± 0.68	-	-	-	-	-	-	-	0.31 ± 0.34
Additional Information									
1. Major metabolite of human liver microsomes (> 5 % of the sample radioactivity)									
2. Overall % metabolism of TMC278 calculated from % drug that remained in the sample at the end of the incubation									
- No measurable product observed in radio-HPLC profile (LLOQ= 211 dpm)									

Table 4-CYP P450 reaction phenotyping using a Supersome system to evaluate the metabolism of ¹⁴C-rilpivirine

Test Article: TMC278

Type of Study: CYP reaction phenotyping- Metabolism of ¹⁴ C-TMC278 in CYP isoforms (Supersomes [®])									
Study no : TMC278/FK5300									
Method: The metabolism of TMC278 in expressed CYP systems (Supersomes [®]) was carried out with ¹⁴ C-TMC278 (5 µM) for 60 minutes at a CYP P450 concentration of 100 pmol/ml of incubation. The amounts of unchanged TMC278 and its metabolites (M50, M22 ¹ , M27 ¹ , M33 ¹ , M35+M36 ¹ , M51, M42 ¹ and M43) were determined by radio-HPLC. Each value represents mean ± S.D of three observations.									
Results:									
CYP-450 Form (100 pmol/ml)	Overall % Metabolism ²	M50	M2	Product formation rate (pmol/min.100 pmol P450)					
				M22	M27	M33	M35+M36	M51	M42
CYP1A2	1.17 ± 0.64	-	-	-	-	0.47 ± 0.41	-	-	-
CYP2A6	0.37 ± 0.32	-	-	-	-	-	-	-	-
CYP2B6	0.50 ± 0.44	-	-	-	-	-	-	-	-
CYP2C8	0.00 ± 0.00	-	-	-	-	-	-	-	-
CYP2C9	0.43 ± 0.38	-	-	-	-	-	-	-	-
CYP2C19	0.43 ± 0.40	-	-	-	-	-	-	-	-
CYP2D6	2.37 ± 2.45	-	-	-	-	-	-	-	-
CYP2E1	0.23 ± 0.40	-	-	-	-	-	-	-	-
CYP3A4	39.5 ± 2.1	0.97 ± 0.84	4.44 ± 0.86	3.39 ± 0.32	4.14 ± 0.68	4.00 ± 0.46	7.72 ± 1.73	-	5.19 ± 1.13
CYP3A5	28.3 ± 2.7	0.61 ± 0.21	1.64 ± 0.21	5.00 ± 0.52	0.25 ± 0.43	5.08 ± 0.36	2.56 ± 0.21	2.61 ± 0.91	3.81 ± 1.14
CYP3A7	26.3 ± 3.3	-	1.17 ± 0.14	3.50 ± 1.39	-	4.33 ± 1.15	6.14 ± 0.60	-	6.39 ± 0.59
Additional Information									
3. Major metabolites of human liver microsomes									
4. Overall % metabolism of TMC278 calculated from % drug that remained in the sample at the end of the incubation									
- No measurable product observed in radio-HPLC profile (LLOQ= 211 dpm)									

Correlation analysis in different HLM batches

Based on the correlation analysis, for rilpivirine metabolism and for the M27 and M42 metabolites, CYP 3A and CYP 2C19 generated r^2 values >0.5. For M33, CYP 2C19 and at least one of the CYP 1A2 and CYP 3A markers generated r^2 values >0.5.

Table 5-Correlation analysis to evaluate the metabolism of ¹⁴C-rilpivirine

Type of Study: CYP reaction phenotyping- Correlation analysis of TMC278 metabolites with CYP activities			Study no : TMC278/FK5300		
Method: The metabolism of ¹⁴ C-TMC278 (5 µM) was examined with a characterized panel of 10 human liver microsomal preparations. The protein concentration of the samples was 0.25 mg/ml and the time of incubation was 15 min. The amounts of unchanged TMC278 and its metabolites (M27, M33, M35+M36 and M42 ¹) were determined by radio-HPLC. The rate of product formation was calculated for TMC278 metabolites and were correlated (pair-wise) with the CYP isoform dependent enzyme activities of corresponding batches of human liver microsomes.					
Results:					
Enzyme activities (CYP isoform)	Overall TMC278 metabolism Correlation (r ²)	M27	M33	TMC278 Metabolite Correlation coefficient (r ²) M35+M36	M42 ¹
7-ethoxycoumarin O-deethylase (1A2)	0.119	-0.050	0.523	0.093	0.073
Phenacetin O-deethylase (1A2)	0.052	-0.186	0.347	0.102	0.047
Coumarin 7-hydroxylase (2A6)	-0.071	0.055	-0.297	0.201	-0.080
Taxol 6- α -hydroxylase (2C8)	-0.437	-0.613	-0.324	-0.660	-0.289
Tolbutamide methyl hydroxylase (2C9,10)	-0.711	-0.842	-0.530	-0.468	-0.608
S-mephenytoin 4-hydroxylase (2C19)	0.748	0.704	0.878	0.107	0.790
Dextromethorphan O-demethylase (2D6)	-0.413	-0.538	-0.310	-0.611	-0.306
Bufuralol hydroxylase (2D6)	-0.442	-0.578	-0.348	-0.659	-0.325
Chlorzoxazone 6-hydroxylase (2E1)	0.030	-0.098	-0.303	-0.389	0.215
Lauroic acid ω -1 hydroxylase (2E1)	-0.543	-0.709	-0.393	-0.450	-0.424
Testosterone 6- β -hydroxylase (3A4)	0.819	0.749	0.485	-0.003	0.881
Cyclosporine oxidase (3A)	0.716	0.744	0.336	0.015	0.746
Taxol 3'-hydroxylase (3A4)	0.889	0.938	0.503	0.383	0.872
Midazolam 4-hydroxylase (3A4/A5)	0.864	0.817	0.611	0.055	0.876
Midazolam 1'-hydroxylase (3A5/A4)	0.577	0.594	0.329	-0.310	0.638
Lauroic acid ω -hydroxylase (4A)	-0.001	-0.207	-0.185	-0.499	0.173
Additional Information					
1. Major metabolite in human liver microsomes					
Bolded numbers: Positive correlations higher than 0.500					

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In vitro covalent binding experiments

The information obtained from the in vitro covalent binding experiments included the following:

- Rilpivirine or rilpivirine metabolites demonstrated covalent binding after incubation of the compound in human liver microsomes in the presence of NADPH and cofactor
- Metabolic activation of rilpivirine to reactive metabolites was necessary for the observed covalent binding.
- Glutathione is at least partially capable of recovering the reactive intermediate(s) that cause covalent binding of rilpivirine related radioactivity

5. Conclusions

Overall, CYP 3A is the major pathway of rilpivirine metabolism and an important metabolic pathway for rilpivirine metabolites. In E.coli systems, M22 and M35+M36 were the major metabolites that were formed based on the formation rate information. In Supersome systems, CYP 3A4, CYP 3A5 and CYP 3A7 were the major metabolic pathways for rilpivirine. Based on the correlation analysis, in addition to CYP 3A, CYP 2C19 may also be involved in rilpivirine's metabolism.

1. Title

An in vitro study to assess the potential of TMC278 to induce CYP enzyme activities in cryopreserved human hepatocytes

2. Objectives

The primary objective of the study was to determine the induction effects of rilpivirine on cytochrome P450 enzymes.

3. Methods

CYP 1A2, CYP 2B6, CYP 2C19, CYP 2E1, and CYP 3A4 enzyme activity in hepatocytes was evaluated after the addition of rilpivirine and representative enzyme inducers (rifampicin [CYP 3A4, CYP 2B6, CYP 2C19 inducer], omeprazole [1A2 inducer], and ethanol [CYP 2E1 inducer]). Three rilpivirine concentrations (2.5, 10, and 25 μ M) were used in the induction experiments. 50 μ M of rifampicin, 25 μ M of omeprazole, 100 mM of ethanol and a vehicle control (0.1% DMSO) were evaluated in the induction experiments.

Hepatocytes were seeded into 48-well plates coated with collagen and incubations were performed in a CO₂-incubator at 37 °C (5% CO₂ in humidified air). After 24 hours, the hepatocyte incubation medium was switched to (b) (4) and 0.1 μ M dexamethasone and 1 % penicillin-streptomycin solution were added. After a 2 day adaption period, the hepatocytes were examined to verify that they were suitable for the induction experiments.

Rilpivirine, omeprazole, rifampicin, ethanol, or DMSO was added to the hepatocytes daily for 48 hours. Three separate batches of hepatocytes were used with treatments added in duplicate. Fresh media was also added every day. At the end of the 48 hour period, the hepatocytes were examined for changes in morphology or possible toxicity.

To determine the CYP P450 activity, the wells were rinsed with 0.200 mL of Hank's Balanced Salt Solution (HBSS) [pH 7.4] and 0.200 mL of HBSS (pH 7.4) with probe substrate was added to all the wells. The incubation conditions at 37 \pm 1°C are outlined in Table 1.

Table 1-Incubation conditions for evaluating CYP P450 activity

CYP Enzyme	Probe Substrate	Incubation Time	Analytical Method	Analyte of Interest
CYP1A2	Phenacetin (200 μ M)	1 h	LC-MS/MS	Paracetamol
CYP2B6	S-mephenytoin (100 μ M)	1 h	LC-MS/MS	N-desmethyl-S-mephenytoin
CYP2C19	S-mephenytoin (100 μ M)	1 h	LC-MS/MS	4-hydroxy-S-mephenytoin
CYP2E1	Chlorzoxazone (300 μ M)	1 h	LC-MS/MS	6-hydroxy chlorzoxazone
CYP3A4	Testosterone (125 μ M)	1 h	LC-MS/MS	6- β -hydroxy testosterone

After incubation, the supernatants were stored for future analysis using LC/MS/MS and the hepatocytes were processed to determine the protein content.

To determine the mRNA concentrations, after the 48 hour incubation period, hepatocytes were washed once with 0.200 mL of HBSS (pH 7.4) and lysed with 400 μ L RLT buffer containing 10 μ L of β mercaptoethanol per mL of RLT buffer. The total RNA from the hepatocytes was extracted using an RNeasy Mini Protect kit. mRNA expression in total RNA samples was determined using a TaqMan realtime reverse transcription-polymerase chain reaction (RT-PCR) and a Applied Biosystems ABI Prism 7900HT Sequence Detection System.

The concentrations of the substrates that were evaluated in the induction experiments were determined using LC/MS/MS.

4. Results

Based on the results presented below, it appears that rilpivirine may potentially induce CYP 2C19 and CYP 3A4 with lesser induction effects on CYP 1A2 and 2B6. Conclusions could not be made regarding CYP 2E1 because induction effects were not observed with ethanol, the positive control. The conclusions from the study are based on changes in mRNA activity.

Conclusions could not be drawn based on the results of changes in enzyme activity. At higher concentration of rilpivirine, for some of the CYP enzymes, lower enzyme activity was observed. The applicant believes that a potential causative factor is residual rilpivirine inhibition effects in hepatocytes and a possible reason for the greater CYP enzyme activity at 2.5 μ M compared to 25 μ M for some of the CYP enzymes could be attributed to differences in the occupying of rilpivirine binding sites at different concentrations.

Table 2-Fold induction of different CYP enzymes for 2.5, 10 and 25 μ M of rilpivirine and positive controls relative to DMSO in human hepatocytes

CYP	Treatment	Fold induction				
		082	KCT	NPV	Mean	SD
CYP1A2	25 μ M TMC278	0.15	NC	0.87	0.51	0.51
	10 μ M TMC278	0.29	NC	0.96	0.62	0.47
	2.5 μ M TMC278	1.12	NC	1.00	1.06	0.09
	DMSO	1.00	NC	1.00	1.00	0.00
	OM	2.99	NC	6.90	4.95	2.77
	OM+25 μ M TMC278	2.35	NC	NC	2.35*	0.00
CYP2B6	25 μ M TMC278	0.28	0.45	1.01	0.58	0.38
	10 μ M TMC278	0.40	0.52	1.21	0.71	0.44
	2.5 μ M TMC278	1.68	0.78	1.36	1.28	0.46
	DMSO	1.00	1.00	1.00	1.00	0.00
	RIF	3.32	1.53	2.94	2.60	0.94
	RIF+25 μ M TMC278	0.58	0.42	0.29	0.43	0.15
CYP2C19	25 μ M TMC278	0.13	0.81	2.82	1.25	1.40
	10 μ M TMC278	0.48	0.90	2.22	1.20	0.91
	2.5 μ M TMC278	1.75	0.99	1.57	1.44	0.40
	DMSO	1.00	1.00	1.00	1.00	0.00
	RIF	2.71	1.50	4.99	3.07	1.77
	RIF+25 μ M TMC278	0.55	0.23	0.05	0.28	0.25
CYP2E1	25 μ M TMC278	0.61	1.26	0.91	0.93	0.32
	10 μ M TMC278	0.69	1.99	1.42	1.37	0.65
	2.5 μ M TMC278	1.05	0.90	0.98	0.98	0.07
	DMSO	1.00	1.00	1.00	1.00	0.00
	EtOH	0.83	1.54	1.36	1.24	0.37
	EtOH+25 μ M TMC278	0.49	1.28	0.51	0.76	0.45
CYP3A4	25 μ M TMC278	0.01	NC	0.09	0.05	0.06
	10 μ M TMC278	0.02	NC	0.06	0.04	0.03
	2.5 μ M TMC278	0.29	0.12	0.31	0.24	0.10
	DMSO	1.00	1.00	1.00	1.00	0.00
	RIF	21.13	5.43	16.74	14.43	8.10
	RIF+25 μ M TMC278	0.10	NC	NC	0.10*	0.00

NC – not calculated (metabolites levels were below detection limit)

* indicates a single value rather than a mean

Table 3-Mean fold change in CYP P450 mRNA expression in human hepatocytes

Treatment	Mean Fold Change \pm SD				
	CYP1A2	CYP2B6	CYP2C19	CYP2E1	CYP3A4
25 μ M TMC278	3.58 \pm 3.44	1.18 \pm 0.48	0.60 \pm 0.20	1.12 \pm 0.49	5.08 \pm 4.42
10 μ M TMC278	3.17 \pm 1.07	2.96 \pm 1.60	1.12 \pm 0.24	0.56 \pm 0.25	25.95 \pm 18.60
2.5 μ M TMC278	2.55 \pm 0.18	2.89 \pm 0.12	1.19 \pm 0.47	0.81 \pm 0.14	27.12 \pm 17.83
25 μ M Omeprazole, 50 μ M Rifampicin, or 100 mM Ethanol	15.07 \pm 5.74	6.80 \pm 5.12	1.69 \pm 0.63	1.01 \pm 0.18	54.88 \pm 29.45
0.1 % DMSO	1.00 \pm 0.00	1.00 \pm 0.00	1.00 \pm 0.00	1.00 \pm 0.00	1.00 \pm 0.00

5. Conclusions

Based on the information from the in vitro induction study, it appears that rilpivirine may potentially induce CYP 2C19 and CYP 3A4 with lesser induction effects on CYP 1A2 and 2B6.

1. Title

An *in vitro* study on the possible inhibitory effect of TMC278 on the metabolism of sertraline, paroxetine, clarithromycin, sildenafil, 17 α -ethinyloestradiol, omeprazole, S-mephenytoin, abacavir, norethindrone and chlorzoxazone in human liver microsomes

2. Objectives

The primary objective of the study was to evaluate *in vitro* the potential inhibitory effects of rilpivirine on the metabolism of sertraline, paroxetine, clarithromycin, sildenafil, 17 α -ethinyl estradiol, omeprazole, S-mephenytoin, abacavir, norethindrone, and chlorzoxazone in human liver microsomes or liver cystols.

3. Methods

Rilpivirine and the incubation experiments were protected from light. Pooled, human liver microsomes with and without various rilpivirine concentrations and at various microsomal protein concentrations (abacavir was evaluated in pooled human liver cytosols). The final rilpivirine concentrations that were evaluated in the inhibition experiments were 0, 0.3, 1, 3, 10 and 30 μ M. Incubations were conducted in triplicate at 37°C. Table 1 provides information regarding the experiment's incubation for the substrates that were evaluated

Table 1-Incubation information for the substrates evaluated in TMC278-NC194

Interacting drugs	Unique identifier	Batch Ref No.	Molecular weight (g/mol)	Solvent	Stock conc. (μ M)	Stock conc. (μ g-base- μ g/mL)	Incubation time (min)	Protein conc. (mg/mL)	Final conc. (μ M)	Final conc. (μ g-base- μ g/mL)	Method of analysis
sertraline	R060102	EXTE_0201_177_4	306.23	Milli Q water	200	61.25	40	0.50	1.0	0.31	LC-MS/MS
paroxetine	R047209	EXTE_0001_457_4	329.37	Milli Q water	200	65.87	20	0.50	1.0	0.33	LC-MS/MS
clarithromycin	R101296	EXTE_0101_474_4	747.96	Methanol	200	149.6	20	0.50	1.0	0.75	LC-MS/MS
sildenafil	R122978	PLUY_0084_046_1	474.58	Methanol	200	94.92	5	0.25	1.0	0.47	LC-MS/MS
omeprazole	R058208	EXTE_0001_736_1	345.42	10% DMSO	200	69.08	20	0.5	1.0	0.35	LC-MS/MS
chlorzoxazone	R007274	EXTE_0001_557_1	169.57	0.1 M NaOH	200	33.91	10	0.5	1.0	0.17	LC-MS/MS
17 α -ethinyloestradiol	R104230	EXTE_0001_627_1	297.19	Acetonitrile	600	177.8	30	0.5	3.0	0.89	LC-MS/MS
S-mephenytoin	R170681	EXTE_0201_198_1	204.23	Propylene glycol 2%	2000	436.5	30	0.5	10	2.18	LC-MS/MS
Abacavir*	TJ35807564-AAA	Lot 10	286.33	Milli Q water	2095	600.0	1200*	1.0*	10.5	3.00	Radio-HPLC
[³ H]-Abacavir	Moravsek MT-1736	#244-172-0006, batch 1984	286.33 (unlabelled)								
norethindrone	R016045	EXTE_0001_544_1	298.42	Methanol	10,000	2984	30	0.50	50	14.9	LC-MS/MS

* Abacavir metabolism was studied in cytosol fractions (see Table 7-4) in 0.05 M Na,K-phosphate buffer pH8.8, containing 7.5 mM NAD.

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Each incubation sample contained 390 μL microsomes, 5 μL of the various rilpivirine stock solutions, 5 μL of the substrate and 500 μL of a NADPH generating system (buffered glucose-6-phosphate and glucose-6-phosphate-dehydrogenase). In the absence of NADP, 0.5M Na,K phosphate buffer (pH 7.4) was used. After pre incubating for 5 minutes, 100 μL of NADP was used to initiate the experiments for a final concentration of 0.125 mg/mL. For abacavir, instead of microsomes and NADPH, the incubation used 390 μL of cytosolic fraction and 500 μL of 50 mM Na pyrophosphate (pH 8.8), respectively, and the incubation was initiated with 100 μL of 75 mM NAD dissolved in 50 mM Na pyrophosphate (pH 8.8). For 17α -ethinyl estradiol only, L-ascorbic acid was added, resulting in a 1 mM final concentration. Samples were frozen in dry ice to terminate the enzyme reaction.

IC_{50} values were calculated for substrate depletion data and metabolite formation data according to the equations below:

Substrate depletion data

$$S = S_{\text{boiled}} - \frac{S_{\text{boiled}} - S_0}{\left(1 + \frac{I}{\text{IC}_{50}}\right)}$$

S=measured concentration of drug substrate

S_{boiled} =concentration of test drug when microsomes/cytosol was boiled

S_0 =concentration of test drug in the absence of rilpivirine

I = concentration of rilpivirine

IC_{50} = rilpivirine concentration resulting in a 50% reduction of substrate depletion

Metabolite formation data

$$M = \frac{100}{\left(1 + \frac{I}{\text{IC}_{50}}\right)}$$

M=percent of control activity

I=concentration of rilpivirine

IC_{50} =rilpivirine concentration resulting in a 50% reduction of control activity for the metabolite

4. Results

Based on the IC_{50} values, rilpivirine potentially inhibits sertraline, paroxetine, clarithromycin, sildenafil, 17α -ethinyl estradiol, S-mephenytoin, and norethindrone. Significant inhibition of chlorzoxazone, abacavir, and omeprazole was not observed. The results are displayed in Table 2.

Table 2-IC₅₀ values for rilpivirine's inhibitory effects on selected substrates

Type of Study: Inhibition of metabolism by TMC278 of interacting drugs was investigated				Study No.	FK5568	Location in CTD:	
Method: The interaction of TMC278 with the metabolism of interacting drugs was investigated in a pooled batch of human liver microsomes. The inhibitory potential of TMC278 on the overall metabolism and/or the formation of their major metabolites is shown. The IC ₅₀ -values represent the concentration in µM or µg-base-eq./mL of TMC278 inhibiting the metabolism by 50%.							
FK5568							
Interacting drugs	IC ₅₀ (95% confidence interval)			Positive control			
	µM		µg-base-eq./mL	µM	inhibitor	% inhibition	
S-mephenytoin ^a	1.3 ^a	(0.74 – 1.8)	0.46 ^a	(0.27 – 0.65)	1	3-benzyl-phenobarbital	81
Sildenafil	1.4	(-0.13 – 3.0)	0.53	(-0.047 – 1.1)	1	ketocanazole	125
Clarithromycin	2.0	(0.042 – 4.0)	0.74	(0.015 – 1.46)	1	ketocanazole	93
Norethindron	3.9	(2.6 – 5.3)	1.44	(0.93 – 1.95)	1	ketocanazole	84
Sertraline	5.2	(-3.1 – 14)	1.9	(-1.1 – 4.9)	10 ^b	1-aminobenzotriazole	167 ^b
Paroxetine	6.6	(-1.2 – 14)	2.4	(-0.42 – 5.3)	3	quinidine	91
17α-Ethinylestradiol ^c	6.5 ^c	(4.2 – 8.7)	2.4 ^c	(1.5 – 3.2)	1	ketocanazole	56 / 59 ^d
Omeprazole	12.0	(7.0 – 17)	4.4	(2.6 – 6.2)	1 /	3-benzyl-phenobarbital /	
Abacavir ^{e,f}	>30 ^f		>11 ^f		1	ketocanazole	92
Chlorzovazone ^g	>30 ^g		>11 ^g		600	4-methylpyrazole	95
					100	diethyldithiocarbamate	-184 ^h
Additional Information							
a) As determined by the formation of the 4-hydroxy metabolite only.							
b) This inhibition is not significantly different from the boiled fraction.							
c) As determined by the formation of a hydroxy metabolite.							
d) 56 / 59 % inhibition of metabolism of unchanged drug and inhibition of formation of a hydroxy metabolite, respectively.							
e) Tested in cytosol fractions (see Table 7-4), not in microsomes.							
f) As determined by disappearance from the unchanged abacavir, as well as the formation of its carboxylic acid metabolite.							
g) As determined by disappearance from the unchanged chlorzovazone, as well as the formation of its 6-hydroxy metabolite.							
h) No inhibition was observed.							

5. Conclusions

Based on the information from this study, rilpivirine potentially inhibits sertraline, paroxetine, clarithromycin, sildenafil, 17α-ethinyloestradiol, S-mephenytoin, and norethindrone. The cytochrome P450 enzymes that rilpivirine may potentially inhibit are CYP 3A, CYP 2C19, and CYP 2D6.

1. Title

An *in-vitro* study on the inhibition of paclitaxel (CYP2C8-mediated) and S-warfarin (CYP2C9-mediated) metabolism by TMC278

2. Objectives

The primary objective of the study was to evaluate *in vitro* the potential inhibitory effects of rilpivirine on the metabolism of paclitaxel and S-warfarin in human liver microsomes.

3. Methods

The incubations for paclitaxel and S-warfarin were protected from light. Human liver microsomes (at 1 mg protein/mL) were incubated with paclitaxel concentrations (final concentrations of 5, 10, 20, 40 and 80 μ M) in the presence of rilpivirine (final concentrations of 0 [negative, solvent control], 0.1, 0.3, 1, 3, 10, 30, 100 and 300 μ M). After pre incubating for 5 minutes at 37°C and 100 oscillations/min, the 30 minute incubations (conducted in triplicate) were initiated by adding NADPH (3 mM final concentration). Dry ice was used to terminate the enzyme reaction. Montelukast, the positive control inhibitor, was evaluated at 0 (solvent control, 1% methanol in total, v/v), 0.01, 0.03, 0.1, 0.3, 1, 3, and 10 μ M with a paclitaxel concentration of 25 μ M.

Human liver microsomes (at 0.2 mg protein/mL) were incubated with S-warfarin concentrations (final concentrations of 1.25, 2.5, 5, 10, 20 and 50 μ M) in the presence of rilpivirine (final concentrations of 0 [negative, solvent control], 0.1, 0.3, 1, 3, 10, 30, 100 and 200 μ M). After pre incubating for 5 minutes at 37°C and 100 oscillations/min, the 15 minute incubations (conducted in triplicate) were initiated by adding NADPH (3 mM final concentration). Dry ice was used to terminate the enzyme reaction. Sulphaphenazole, the positive control inhibitor was evaluated at 0 (solvent control, 1% methanol in total, v/v), 0.01, 0.03, 0.1, 0.3, 1, 3, and 10 μ M with an S-warfarin concentration of 4 μ M.

A LC/UV analytical method was used in the analysis of the 6 α -hydroxypaclitaxel conversion and a LC/MS/MS analytical method was used in the analysis of the 7-hydroxy-S-warfarin conversion.

IC₅₀ values for paclitaxel 6 α -hydroxylation and S-warfarin-7-hydroxylation inhibition were derived from semilog plots with log [inhibitor] and percent inhibition on the X axis and Y axis, respectively. For evaluating the type of inhibition, Sigmaplot Enzyme Kinetics software was used in analyzing the velocity data for paclitaxel and S-warfarin metabolism at the highest rilpivirine concentrations with usable rilpivirine data (up to 30 μ M and 10 μ M of rilpivirine, respectively). The corrected Akaike Information Criterion (AIC_c) was used as the primary criteria along with the r^2 value in selecting the appropriate inhibition model. The Enzyme Kinetics software was also used

to derive K_i (apparent inhibition constant) values for rilpivirine's inhibition of paclitaxel 6 α -hydroxylation and S-warfarin-7-hydroxylation.

4. Results

Paclitaxel

Based on the C_{max} value for a 25 mg once daily dose of rilpivirine of approximately 0.5 μ M, the rilpivirine IC_{50} values in Table 1, and the rilpivirine K_i value of $10.0 \pm 3.22 \mu$ M, the potential for a drug-drug interaction for CYP 2C8 substrates with rilpivirine is not likely or "remote". A mixed inhibition model was determined to be the most appropriate inhibition model.

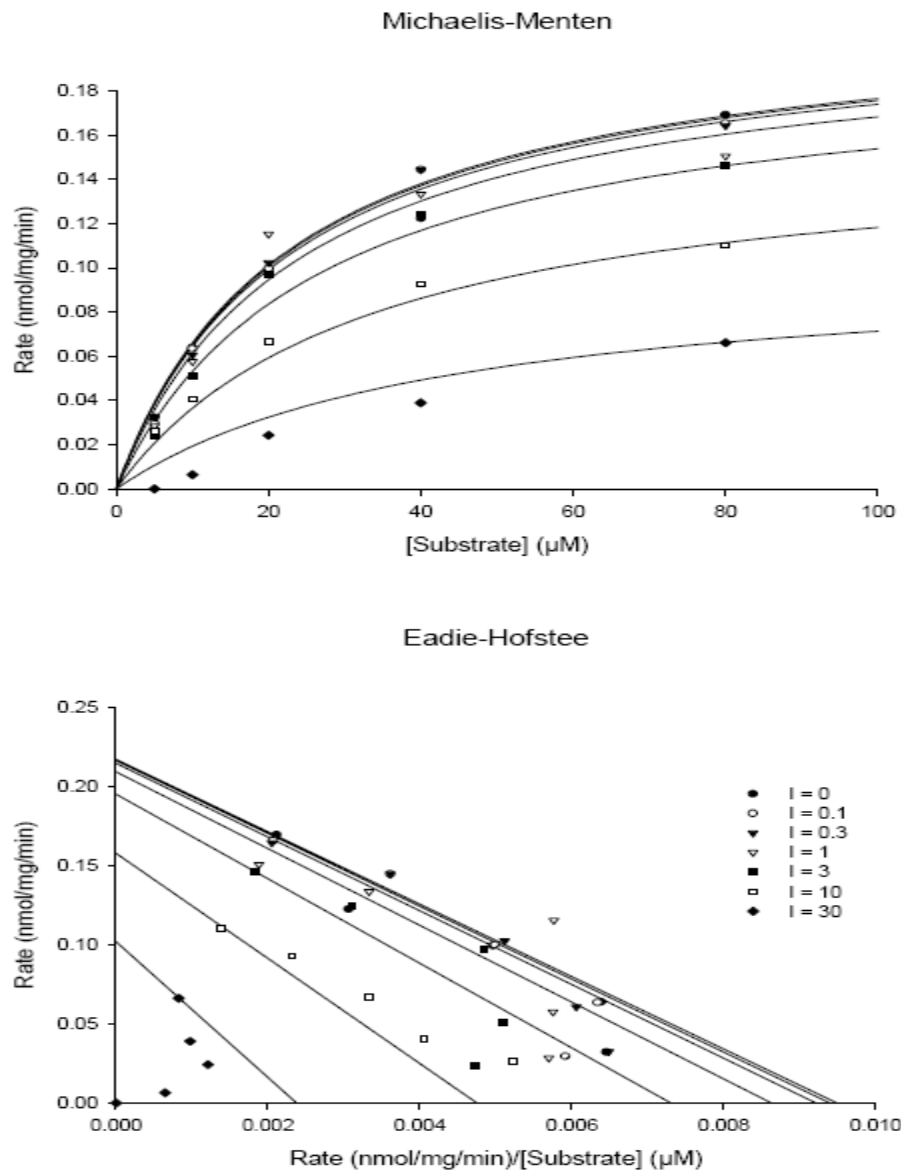
Table 1-Rilpivirine IC_{50} values for various paclitaxel concentrations with the addition of rilpivirine (0.1 μ M-300 μ M)

Paclitaxel concentration	I_{50} -values in μ M	I_{50} -values in μ g/ml	C_{max}/I_{50} ratio (at a C_{max} plasma concentration of 0.22 μ g/ml at a target dose of 25 mg^3)
5.00 μ M	15.2	5.57	0.040 (remote)
10.0 μ M	13.2	4.84	0.046 (remote)
20.0 μ M	15.5	5.68	0.039 (remote)
40.0 μ M	19.1	7.00	0.031 (remote)
80.0 μ M	18.7	6.85	0.032 (remote)

Table 2-Velocity data for paclitaxel 6 α -hydroxylation formation with the addition of rilpivirine

Effect of TMC278 on 2C8-mediated metabolism of paclitaxel					
Type of inhibition	Vmax	Km	Ki	R^2	AICc
Mixed (full)	0.217	22.8	10.0	0.97619	-328.719
Mixed (partial)	0.217	22.8	10.0	0.97619	-325.788
Noncompetitive (full)	0.223	24.7	16.7	0.97418	-328.625
Noncompetitive (partial)	0.223	24.7	16.7	0.97418	-325.890
Competitive (full)	0.209	20.8	5.51	0.97024	-323.655
Competitive (partial)	0.209	20.8	5.51	0.97024	-320.919
Uncompetitive (full)	0.233	28.0	9.86	0.95644	-310.314
Uncompetitive (partial)	0.233	28.0	9.85	0.95644	-307.579

Figure 1-Michaelis-Menten and Eadie-Hofstee plots for inhibition of paclitaxel 6 α -hydroxylation by rilpivirine



S-warfarin

Based on the C_{\max} value for a 25 mg once daily dose of rilpivirine of approximately 0.5 μM , the rilpivirine IC_{50} values in Table 3, and the rilpivirine K_i value of 1.70 ± 0.301 μM , the potential for a drug-drug interaction for CYP 2C9 substrates with rilpivirine is “possible”. A noncompetitive model was determined to be the most appropriate inhibition model.

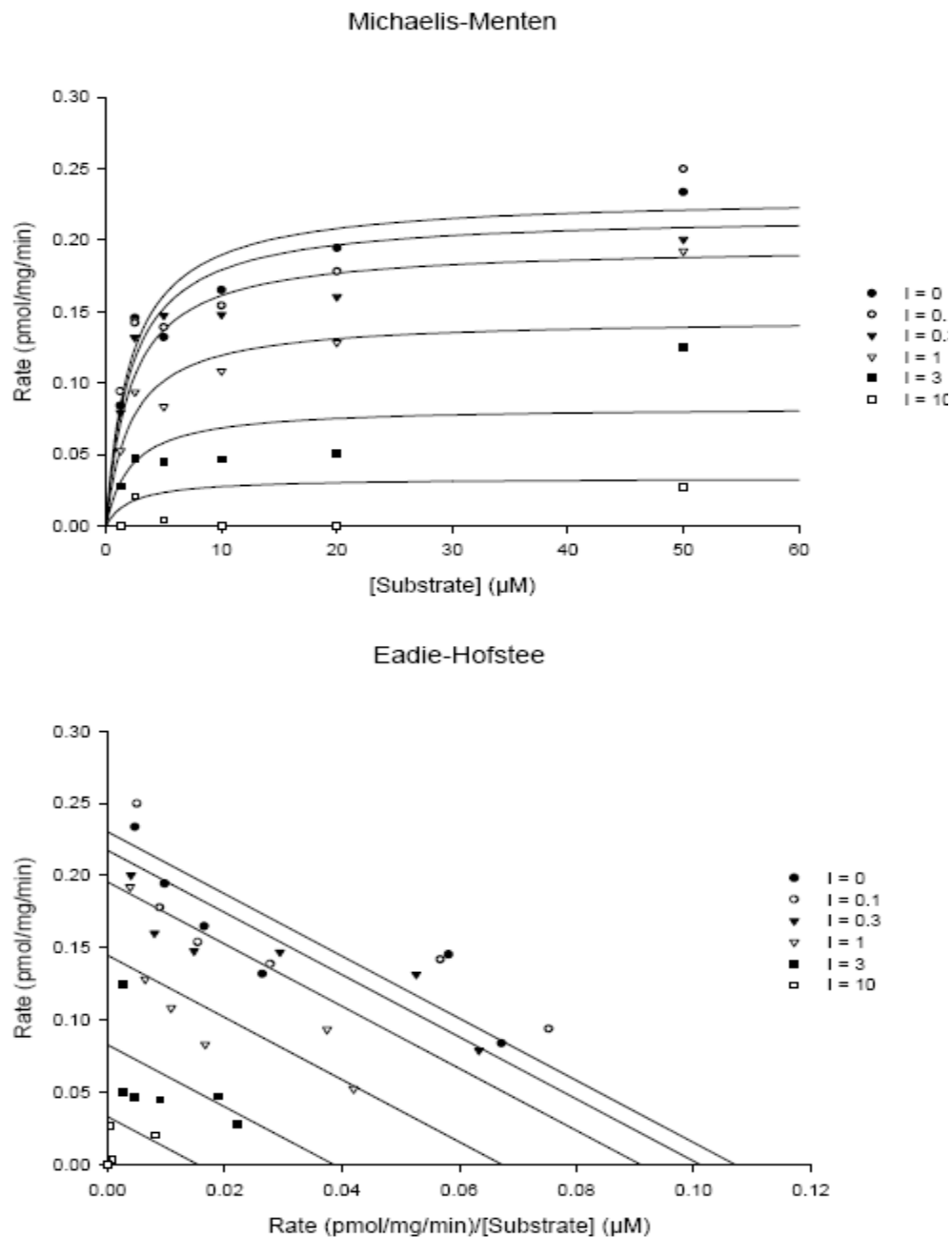
Table 3-Rilpivirine IC₅₀ values for various S-warfarin concentrations with the addition of rilpivirine (0.1 µM-200 µM)

S-warfarin concentration	IC ₅₀ -values in µM	IC ₅₀ -values in µg/ml	C _{max} /IC ₅₀ ratio (at a C _{max} plasma concentration of 0.22 µg/ml at a target dose of 25 mg ³)
1.25 µM	1.35	0.495	0.444 (possible)
2.50 µM	1.59	0.583	0.377 (possible)
5.00 µM	1.95	0.715	0.308 (possible)
10.0 µM	1.74	0.638	0.345 (possible)
20.0 µM	1.64	0.601	0.366 (possible)
50.0 µM	3.02	1.11	0.198 (possible)

Table 4-Velocity data for 7-hydroxy-S-warfarin formation with the addition of rilpivirine

Effect of TMC278 on 2C9-mediated metabolism of warfarin					
Type of inhibition	V _{max}	K _m	K _i	R ²	AICc
Mixed (partial)	0.224	1.81	0.680	0.90511	-263.354
Mixed (full)	0.224	1.81	0.690	0.90511	-266.250
Noncompetitive (partial)	0.230	2.15	1.70	0.90136	-264.853
Noncompetitive (full)	0.230	2.15	1.70	0.90136	-267.563
Uncompetitive (partial)	0.235	2.41	1.34	0.88776	-260.205
Uncompetitive (full)	0.235	2.41	1.34	0.88776	-262.915
Competitive (full)	0.211	1.27	0.147	0.86151	-255.348
Competitive (partial)	0.211	1.27	0.147	0.86151	-252.638

Figure 2-Michaelis-Menten and Eadie-Hofstee plots for inhibition of 7-hydroxy-S-warfarin by rilpivirine



5. Conclusions

Based on the information from this study, the potential for a drug-drug interaction for CYP 2C8 substrates with rilpivirine is not likely or “remote” and the potential for a drug-drug interaction for CYP 2C9 substrates with rilpivirine is “possible”.

4.2 DCP4 Division Director's Concurrence on PMR

Au, Stanley

From: Lazor, John A
Sent: Friday, March 25, 2011 6:54 AM
To: Au, Stanley; Reynolds, Kellie S
Cc: Robertson, Sarah
Subject: RE: NDA 202022-rilpivirine PMR concurrence

Concur

From: Au, Stanley
Sent: Tuesday, March 22, 2011 12:42 PM
To: Lazor, John A; Reynolds, Kellie S
Cc: Robertson, Sarah
Subject: NDA 202022-rilpivirine PMR concurrence

At your earliest convenience, for NDA 202022, please provide your concurrence on the proposed digoxin DDI trial as a PMR for rilpivirine as outlined in the attached PMC/PMR template. The deadline for DARRTS sign off is Monday, March 28. Thanks.

<< File: PMR-PMC Development Template 031811.doc >>

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4.3 Consult Reviews

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Pharmacometrics Reviewer: Jeffry Florian

Pharmacometrics Team Leader: Pravin Jadhav

Clinical Pharmacology Reviewer: Stanley Au

Clinical Pharmacology Team Leader: Sarah Robertson

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1 SUMMARY OF FINDINGS

1.1 Key Review Questions

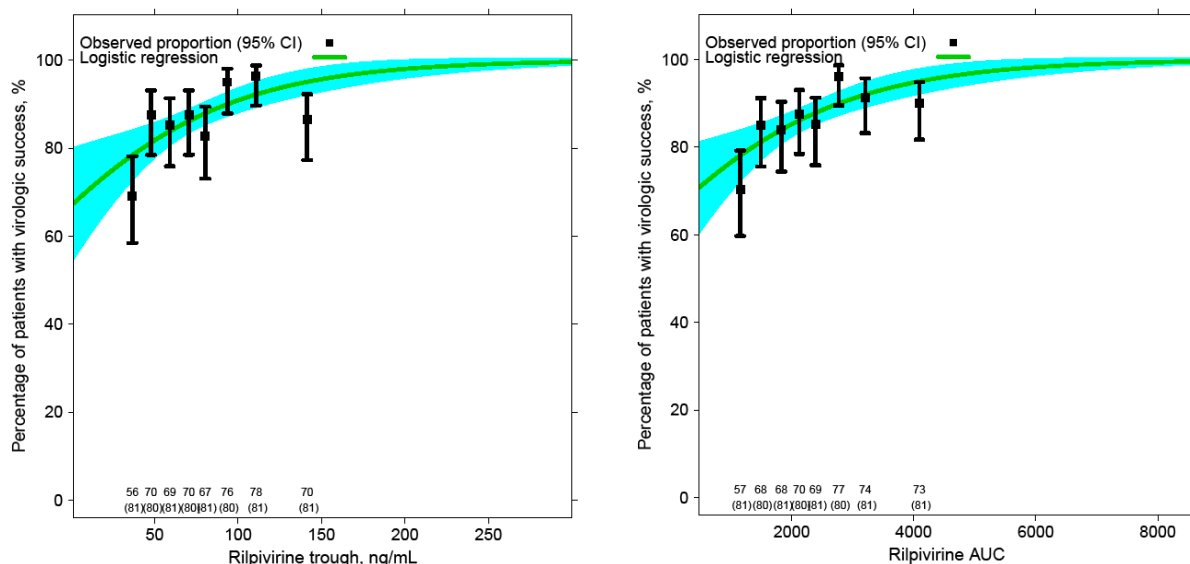
The purpose of this review is to address the following key questions.

1.1.1 Is there evidence of an exposure-response relationship for rilpivirine (TMC278) for virologic outcome?

A decrease in the percentage of subjects achieving virologic success (plasma viral load <50 HIV-1 RNA copies/mL) at Week 48 was observed in patients with the lowest rilpivirine C_{0h} quantile from the two pivotal Phase III trials (C209 and C215) with 25 mg rilpivirine q.d.

While patient compliance was identified as the most important modeling component during generalized additive models (GAM) analysis based on AIC, this was driven by a <4% of the treatment population with <90% compliance. Patient with self-reported compliance <90% were removed from the subsequent exposure-response analysis as these patients are assumed to have lower rilpivirine exposure that is driven by a failure to properly follow the dosing schedule as opposed to pharmacokinetic variability. After removing the non-compliant patients from the analysis an exposure-response relationship between rilpivirine exposure (C_{0h} and AUC_{τ}) and virologic success is still present (Figure 1). Median exposure values for C_{0h} and AUC_{τ} were 80 ng/mL and 2397 (ng·h/mL) and correspond to 87% of patients achieving virologic success.

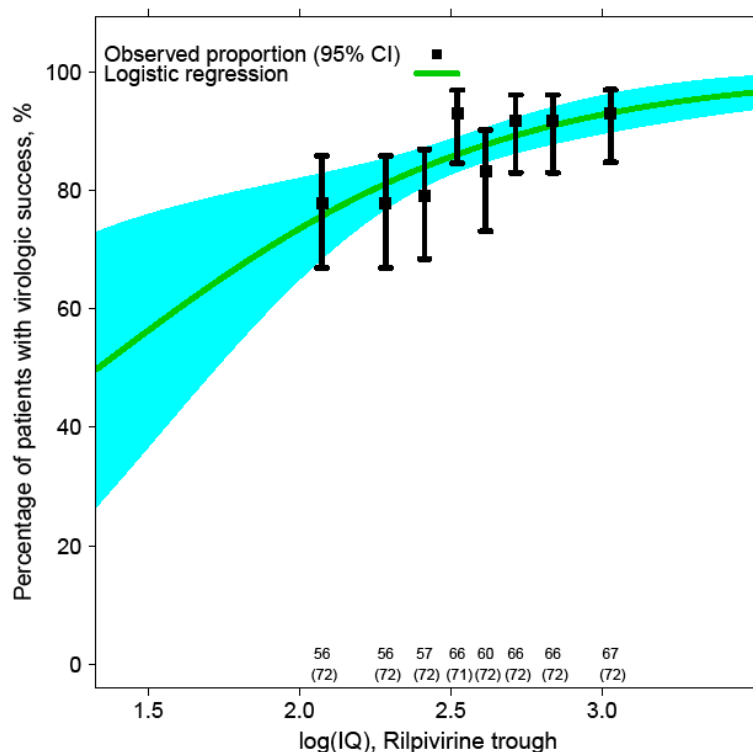
Figure 1: Percentage of Patients Achieving Virologic Success (<50 Copies/mL) Versus Rilpivirine C_{0h} (left) and AUC_{τ} (right) from C209 and C215.



Based on the significant factors identified from the applicant's GAM analysis (self-reported adherence, rilpivirine trough concentration, baseline viral load), a relationship between inhibitory quotient (IQ) and probability of virologic success was evaluated. IQ,

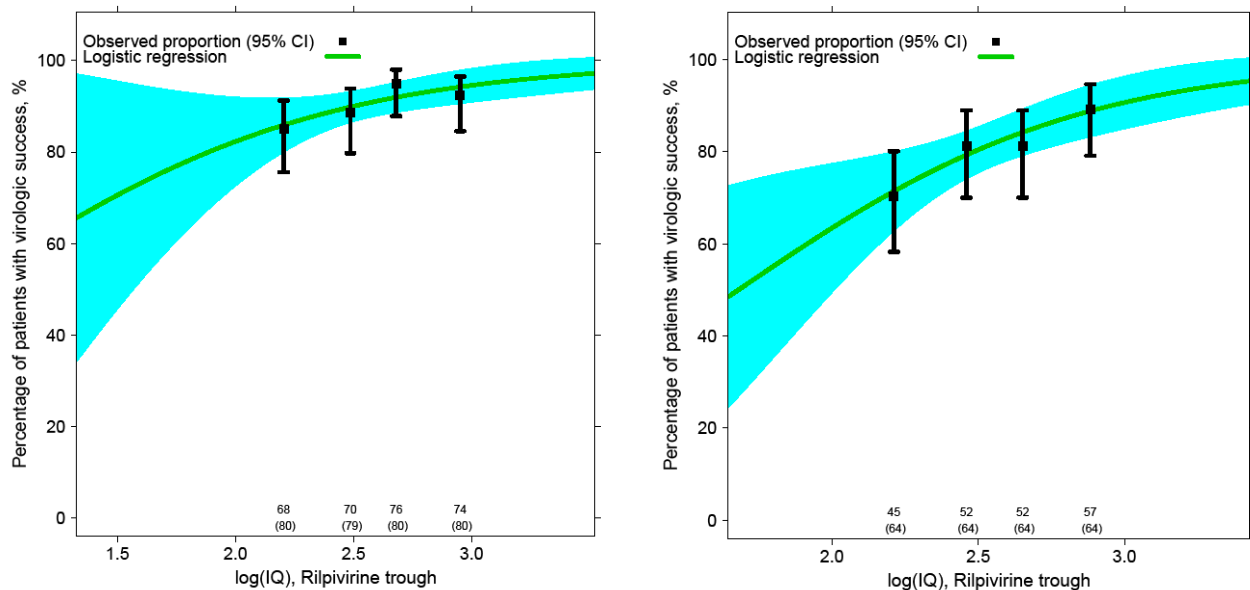
a ratio of drug exposure (C_{0h}) to a patient-specific viral phenotypic IC_{50} (a measurement of the ability of rilpivirine to inhibit HIV-1 virus), was calculated for both Phase III trials. IQ calculations are expected to provide more accurate predictions of population response as it combines information regarding a subject's drug exposure in addition to the expected exposure necessary based on a patient's specific viral phenotype. Indeed, when the relationship between \log_{10} (IQ) and the percentage of patients achieving virologic success is evaluated a steeper exposure-response relationship is identified (Figure 2). The evaluation was only performed for C_{0h} as phenotype IC_{50} is reported as a concentration. Median exposure values for \log_{10} (IQ) was 2.57 corresponds to 88% of patients achieving virologic success.

Figure 2: Percentage of Patients Achieving Virologic Success (<50 Copies/mL) Versus \log_{10} (IQ) from C209 and C215.



If the results in Figure 2 are further divided based on baseline viral load (patients with baseline viral load <100,000 copies/mL or \geq 100,000 copies/mL), a significant relationship is still identified for both populations (Figure 3). However, the exposure-response relationship is flat for patients with viral load <100,000 copies/mL (percentage of patients achieving virologic success was 89% in the lowest exposure quartile compared to 94% in the highest exposure quartile). By comparison, a more pronounced relationship was seen for patients with baseline viral load \geq 100,000 copies/mL (percentage of patients achieving virologic success was 68% in the lowest exposure quartile compared to 92% in the highest exposure quartile). Median exposure values for \log_{10} (IQ) was 2.57 for both subgroups.

Figure 3: Percentage of Patients Achieving Virologic Success (<50 Copies/mL) Versus $\log_{10}(\text{IQ})$ for Patients with Baseline Viral Load <100,000 (left) and $\geq 100,000$ Copies/mL (right) from the Phase 3 (C209 and C215) trials.



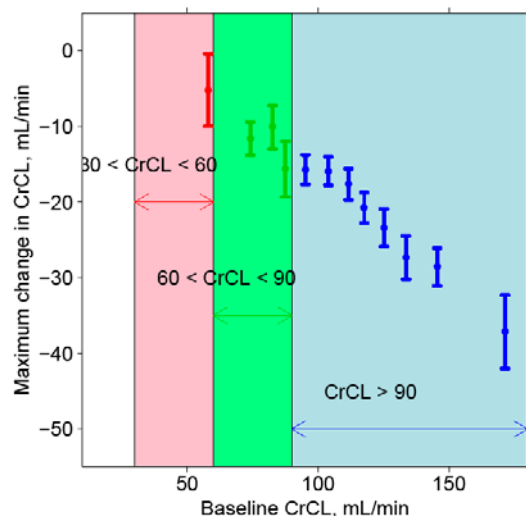
Those patients who were virologic failures were not limited to patients with lower rilpivirine trough exposures or with higher IC_{50} values. Instead, baseline viral load appears to be the primary factor in determining response in patients treated with rilpivirine. The rilpivirine label should be updated to reflect this decreased likelihood of achieving virologic success in patients with baseline viral load >100,000 copies/mL.

1.1.2 What is the effect of rilpivirine treatment on creatinine clearance?

Rilpivirine affects creatinine clearance (CrCL) depending on baseline status with smaller changes in patients with lower baseline CrCL and vice versa (Figure 4). The CrCL in almost all patients returned to baseline after the treatment was stopped (Figure 5). CrCL and serum creatinine in a subset of patients (n=59) who discontinued rilpivirine treatment returned to baseline after 2-4 week follow-up. Also, data supports the sponsor's assertion that rilpivirine inhibits tubular secretion of creatinine. Based on these evidences, additional monitoring of serum creatinine is not supported.

To assess effect of rilpivirine on CrCL depending on baseline, all rilpivirine-treated patients from the two Phase 3 pivotal trials (C209 and C215) were pooled. The relationship between on-treatment maximum decrease in CrCL and baseline CrCL was explored in 683 patients (out of 686). Three patients were excluded due to discontinuation prior to the first on treatment serum creatinine assessment. Figure 4 shows the relationship between on treatment maximum on-treatment decrease in CrCL and baseline CrCL. A trend of smaller maximum decreases in CrCL dependent on baseline CrCL was observed for baseline CrCL values ranging from 41–180 mL/min. Patients with baseline moderate renal function had an on-treatment mean maximum decreases in CrCL of 6 mL/min compared to mean maximum decreases of 13 mL/min and 22 mL/min for patients with mild or normal renal function, respectively (Table 1).

Figure 4: Maximum on Treatment Change in CrCL Versus Baseline CrCL in Patients Administered Rilpivirine 25 mg q.d. from C209 and C215.



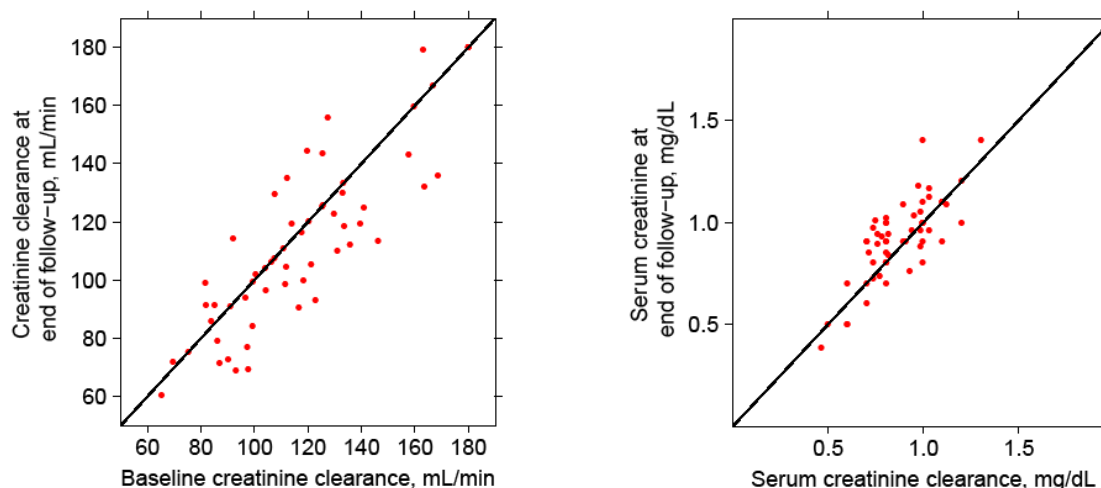
An outlier assessment of patients transitioning across renal function category (i.e. from mild to moderate) was also performed using all patient visit information through Week 48. A patient was considered to transition in renal function category if two consecutive CrCL measurements indicated a transition in renal function. A total of 15% (87/596) and 9% (7/80) patients with normal and mild baseline renal function, respectively, transitioned to mild and moderate renal impairment, respectively. Most importantly, none of the 7 moderate renal function patients transitioned to severe during treatment with rilpivirine.

Table 1: Mean Maximum Change in CrCL Grouped by Baseline Renal Function for Patients Treated with Rilpivirine 25 mg q.d. from C209 and C215			
CrCL Category, mL/min	Count, n	Mean max change in CrCL, mL/min	Percent of Patients with two consecutive CrCL measurements indicating transition to worse renal function category
30-60 (moderate)	7	-5.9	0 (0/7)
60-90 (mild)	80	-12.5	9 (7/80)
>90 (normal)	596	-22.2	15 (87/596)

A total of 59 subjects who discontinued rilpivirine treatment during C209 and C215 were available for follow-up CrCL assessment to determine if CrCL returned to baseline after cessation of rilpivirine therapy. Nine subjects had mildly impaired baseline renal

function, and 50 had normal renal function. Typical time to follow-up in all the subjects was 2-4 weeks. Of the 59 subjects, 29 were below baseline CrCL at follow-up, 14 were above, and 16 had returned to baseline. In addition, mild renal impairment patients had a mean difference of 1.1 mL/min from baseline CrCL at follow-up while normal renal function patients were -5.7 mL/min lower than baseline. The overall deviation from baseline CrCL in these follow-up patients is driven by normal patients, which are also those patients with the largest deviation from baseline. The failure of this group to return to baseline may be suggestive of insufficient time between follow-up or random variability in measurement.

Figure 5: 2-4 Week Follow-up CrCL Versus Baseline CrCL (left) and Follow-up Serum Creatinine Versus Baseline Serum Creatinine (left) in Patients Who Stopped Rilpivirine Treatment from C209 and C215. A Line of Unity is Shown on Both Graphs.



In order to assess the sponsor's assertion that rilpivirine inhibits tubular secretion of creatinine, eleven subjects on cimetidine or trimethoprim were identified. Of these 11 patients, 5 were on background tenofovir/emtricitabine and 6 were on zidovudine/lamivudine. Maximum on-treatment decrease in CrCL for this subset of patients was for a period during which the patient was receiving trimethoprim (range: 2-48 weeks). A comparison between baseline CrCL and maximum on treatment decrease in CrCL for patients on these concomitant medications and the remaining portion of the population are shown in Table 2. Mean baseline CrCL in these patients was 116 mL/min. These patients had a mean maximum decrease in CrCL of -8 mL/min compared to -20 mL/min in overall patient population with similar baseline CrCL. This analysis supports the sponsor's proposed mechanism of action of rilpivirine inhibition of tubular secretion of creatinine. This analysis does not rule out small changes on CrCL resulting from rilpivirine treatment, however, further investigation of the mechanism of action of rilpivirine on inhibition of tubular secretion of creatinine does not seem necessary due to the small effect size.

Table 2: Comparison in Mean Maximum Change in CrCL Versus Baseline Renal Function for Patients Treated with Rilpivirine 25 mg q.d. with Concomitant

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Trimethoprim at Baseline from C209 and C215			
	CrCL, mL/min	Maximum on- treatment decrease in CrCL, mL/min	Count, n
Moderate	58	-6	
Mild	74	-11	27
	83	-11	27
	87	-16	26
Normal	95	-16	74
	104	-17	73
	112	-17	73
	118	-21	73
	126	-23	73
	134	-27	73
	146	-28	73
	171	-26	73
Concomitant Medications (cimetidine or trimethoprim)	116	-8	11

1.1.3 Is there evidence of exposure-safety relationships for psychiatric, skin, dizziness, and hepatobiliary adverse events?

An exposure-response relationship could not be established for psychiatric, skin, dizziness, or hepatobiliary adverse events. Logistic regression models were evaluated for rilpivirine C_{0h} and AUC_{τ} with no significant relationships identified. Modeling results for adverse event rates versus rilpivirine AUC_{τ} are shown below in Figure 14 and Figure 15 of the reviewer's analysis.

1.1.4 Are the PK parameters reported in the label supported by the population PK analysis submitted by the applicant?

The pharmacokinetic parameters for 25 mg rilpivirine q.d. in adults reported in section 12.3 (Pharmacokinetics) of the proposed rilpivirine label are supported by the population PK analysis (Table 3). AUC_{τ} and C_{0h} means, standard deviations, medians, and ranges were in good agreement with the applicant's results.

Table 3: Population Pharmacokinetic Estimates of Rilpivirine 25 mg q.d. in Antiretroviral Treatment Naïve HIV-1-Infected Patients (Comparison of Applicant's Label Claims and Reviewer Analyses)		
Parameter	Rilpivirine 25 mg q.d. (N=679), Applicant*	Rilpivirine 25 mg q.d. (N=679), Reviewer
AUC_τ (ng·h/mL)		
Mean ± Standard Deviation	2397 ± 1032	2287 ± 877
Median (Range)	2204 (482 – 8601)	2152 (192 – 7523)
C_{0h} (ng/mL)		
Mean ± Standard Deviation	80 ± 37	82 ± 33
Median (Range)	74 (1 – 300)	74 (14 – 304)

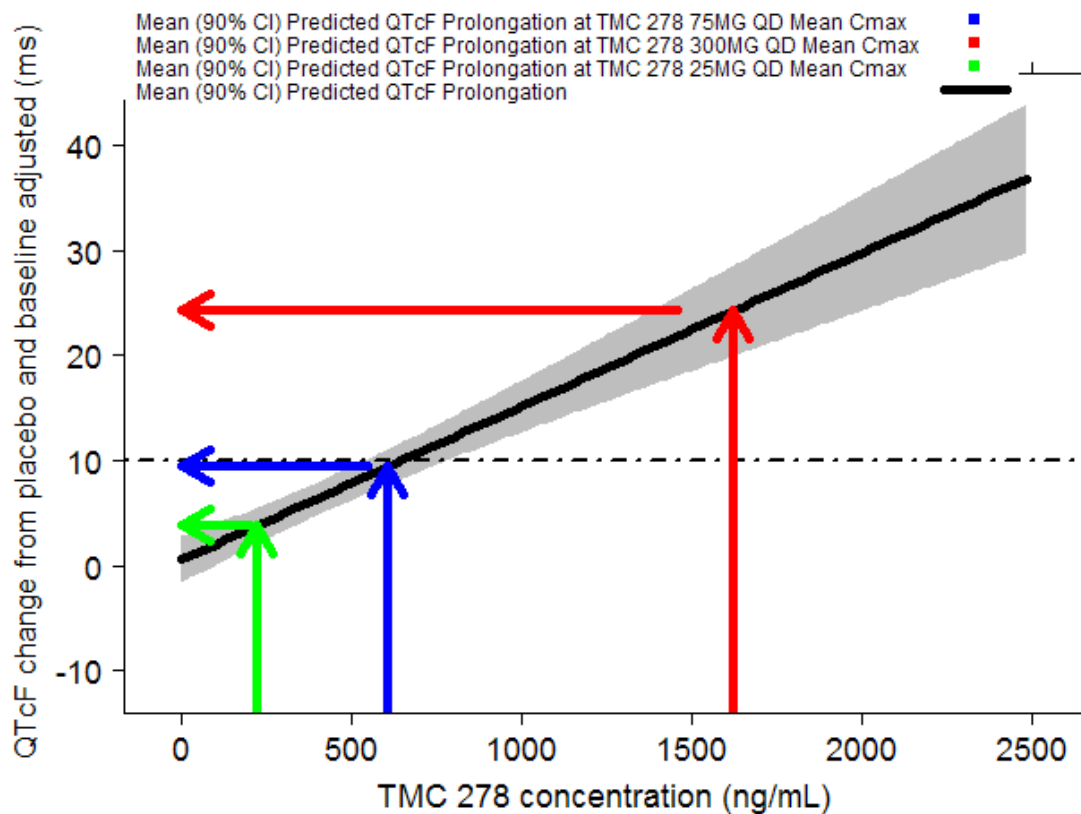
*Sponsor's tmc278-20100709-uspi.pdf, (section 12.3 [Pharmacokinetics]) (does not include Reviewer's summary of parameters)

In addition, the applicant claims that gender, hepatitis B/C infection, race, and age have no impact on the rilpivirine exposure is supported by population PK analysis. However, only 3 patients in the Phase III population were 65 years or older. (b) (4)

1.1.5 Are there drug-drug interactions that result in QTc prolongation >10 ms for 25 mg rilpivirine q.d.?

Drug-drug interactions may result in QTc prolongation >10 ms for 25 mg rilpivirine q.d. The QT prolongation potential of rilpivirine was assessed by combining data from two thorough QT trials: TMC278-TiDP6-C131 (doses of 75 and 300 mg q.d.) and TMC278-TiDP6-C151 (dose of 25 mg q.d.). A significant concentration-QTc relationship was identified with a mean predicted placebo- and baseline-adjusted change in QT interval corrected using Fridericia's method ($\Delta\Delta\text{QTcF}$) of 4 ms (upper bound of two-sided 90% confidence interval (CI): 6 ms) at 25 mg q.d. rilpivirine (C_{max} 220 ng/mL). Supratherapeutic doses of 75 and 300 mg q.d. resulted in mean QTc prolongation of 9 and 23 ms, respectively (upper 90% CI: 11 and 27 ms) (Figure 6).

Figure 6: Mean (90% CI) Predicted $\Delta\Delta$ QTcF at Geometric Mean C_{max} for 25, 75, and 300 mg Q.D. Rilpivirine



From the sponsor's drug-drug interaction tables, the largest increase in C_{max} resulted from coadministration with darunivir/ritonavir (DRV/rtv) with a C_{max} increase of 80% (C_{max} of 400 ng/mL based on a C_{max} of 220 ng/mL for rilpivirine 25 mg q.d.; upper 90% CI $\Delta\Delta$ QTcF 8 ms). Likewise, the greatest impact from intrinsic factors (mild hepatic impairment) resulted in a 30% increase in C_{max} (C_{max} 290 ng/mL; upper 90% CI $\Delta\Delta$ QTcF 6 ms) for patients with mild impairment (no change in C_{max} was observed in patients with moderate impairment). Rilpivirine is predominantly hepatically eliminated (CYP3A4), and coadministration with a potent inhibitor, such as DRV/rtv, may not result in higher exposures in patients with hepatic impairment. However, assuming that these two interactions could independently contribute to increases in rilpivirine exposure, a hepatically impaired patient coadministered DRV/rtv may have a 2.3-fold increase in rilpivirine concentration for 25 mg q.d. (C_{max} 510 ng/mL; upper 90% CI $\Delta\Delta$ QTcF 10 ms). In addition, the QT prolongation from TMC278-TiDP6-C131 may have been underestimated as the moxifloxacin assay sensitivity for this study was not established (i.e. largest lower bound of the two-sided 90% confidence interval did not exceed 5 ms), and the upper bound of the two-sided 90% CI of $\Delta\Delta$ QTcF predictions for the high exposure scenarios may exceed the QT prolongation values reported above. However, as the subset of patients with mild hepatic impairment also taking darunivir/ritonavir is anticipated to be small and the upper bound of the 90% CI for the high exposure scenario was 10 ms, the rilpivirine label does not require additional revisions beyond the sponsor's

currently proposed language (i.e. caution against the use of rilpivirine with known Torsadegenic agents).

1.2 Recommendations

- Rilpivirine provides acceptable efficacy and safety in the treatment naïve patients, particularly in HIV-infected patients who may be contraindicated from other therapies. The submitted information supports approval of the application.
- Patients with higher baseline viral load (>100,000 copies/mL) were less likely to achieve virologic success on 25 mg q.d., and the label should be amended to acknowledge the difference in response rates in treatment naïve patients. The label should caution against the use of rilpivirine in patients with baseline viral load >100,000 copies/mL due to increased likelihood of treatment failure and subsequently developing resistance.
- Rilpivirine demonstrates modest effect on creatinine clearance. The effect is lowest in patients with renal impairment (moderate<mild<normal) with renal function returning to baseline after treatment discontinuation. Data support the mechanism proposed by the sponsor that rilpivirine potentially inhibits tubular secretion of creatinine. Therefore, additional studies of rilpivirine's mechanism of action that affect serum creatinine are not necessary.

1.3 Label Statements

Labeling statements to be removed are shown in ~~red-strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

(b) (4)



2 PERTINENT REGULATORY BACKGROUND

Rilpivirine, a diarylpyrimidine derivative, is a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) selected for clinical development based on its high in vitro potency against wildtype human immunodeficiency virus type 1 (HIV-1) and NNRTI-resistant strains and its potential for once-daily dosing.

Based on the efficacy, safety, pharmacokinetic and pharmacokinetic/pharmacodynamic assessments obtained from the primary analysis (48 week data) of the Phase IIb dose finding trial (C204), the dose of rilpivirine 75 mg q.d. was initially selected for further development. All of the rilpivirine dosage regimens studied in this trial (25, 75, and 150 mg q.d.) demonstrated substantial and sustained clinical efficacy that was comparable to control (EFV), and at the time the 75 mg q.d. dose was considered to provide the most favorable benefit/risk ratio. Prior to the start of the Phase III trials, additional information became available affecting the benefit/risk profile of rilpivirine, which led to the re-evaluation of the dose selection. The TQT trial (C131), where rilpivirine was studied in healthy subjects at dosage regimens of 75 mg q.d. and 300 mg q.d. demonstrated dose- and concentration-dependent QTc prolongation at steady-state. The QTc prolongation exceeded the ICH E14 threshold of clinical concern (>10 ms QTc prolongation) at both doses of rilpivirine. Based on pharmacokinetic/pharmacodynamic modeling, it was anticipated that rilpivirine 25 mg q.d. would not have an effect on the QTc interval. The potential suitability of the 25 mg q.d. dose for further clinical development was assessed with respect to efficacy, in particular on the basis of the Week 96 analysis of trial C204 that had become available. This analysis indicated that the 25 mg q.d. dose provided substantial and sustained virologic response after 96 weeks of therapy in treatment-naïve HIV-1 infected subjects, regardless of the baseline viral load. The response rate with 25

mg q.d. was not different from the response rate with the higher doses, indicating that the exposures associated with the 25 mg q.d. dose of rilpivirine are as effective as those achieved with higher doses. Based on these findings the dose of 25 mg q.d. was thus selected for the Phase III trials and further development.

This application is being submitted with a proposed indication for the treatment of HIV-1 infection in antiretroviral treatment-naïve adult patients. The current submission to support full marketing authorization of TMC278 25 mg tablets q.d. with a background regimen of 2 nucleoside/nucleotide reverse transcriptase inhibitors is based on the 48-week data from the double blind, double dummy registrational Phase III trials C209 and C215 with the recommended dose and tablet formulation. The key efficacy and safety data were obtained from the Week 48 primary analyses of these Phase III trials, which were performed when all subjects had completed at least 48 weeks of treatment or had discontinued earlier (i.e. up to the cut-off date of 01 February 2010 for C209 and 28 January 2010 for C215). Further comprehensive data from the 96-week efficacy and safety analysis of the dose-finding Phase IIb trial (C204) and long-term data up to 192 weeks of that same trial also support this application.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Introduction

The applicant developed a population pharmacokinetic model to explore the impact of intrinsic and extrinsic factors on rilpivirine exposure. In addition, pharmacokinetic parameters were used by the applicant to explore exposure-response analyses between rilpivirine and selected efficacy (e.g. HIV-1 plasma viral load <50 copies/mL) and safety (e.g. QT prolongation) endpoints.

3.2 Population Pharmacokinetic Model

Report tmc278-0016435-w48-poppk.pdf: TMC278 Phase III (48 weeks) Population Pharmacokinetic Modelling, Empirical Bayesian Feedback, and Covariate Analysis

3.2.1 Data

The data included in the population pharmacokinetic model development for empirical Bayesian predictions of TMC278 exposure in the Phase III trials were from the 2 Phase III trials in HIV-1 infected subjects (C209 and C215) and from one of the recent Phase I thorough QT/QTc trials in healthy subjects (C152). All three trials used the Phase III tablet using a dosage regimen of 25 mg q.d.. No other pharmacokinetic data were included in this analysis for the Phase III trials as previous data were generated using a wider dose range and different formulations of TMC278. An outline of these studies is summarized below in Table 5.

Table 5: Summary of Trials Used in Phase III Population PK Model Development

Item	Study 1	Study 2	Study 3
Tibotec Code	TMC278-TiDP6-C209	TMC278-TiDP6-C215	TMC278-TiDP6-C152
Population	HIV-1 infected subjects	HIV-1 infected subjects	healthy subjects
No of subjects for analysis	13 with rich sampling 329 with sparse sampling	34 with rich sampling 303 with sparse sampling	57 subjects
Dose	25 mg q.d. for 96 wks	25 mg q.d. for 96 wks	25 mg q.d. for 11 days
Background regimen	TDF/FTC	AZT/3TC, ABC/3TC or TDF/FTC	-
Single/Multiple dose	Multiple dose	Multiple dose	Multiple dose
Formulation	Oral tablet F006	Oral tablet F006	Oral tablet F006
Food	With a meal	With a meal	With a meal
Data used ⁽¹⁾	All available data from the TMC278 treated arm	All available data from the TMC278 treated arm	Treatment A (TMC278 25 mg)
Sampling time windows/ no. of samples	week 4 and 24: pre- and post-dose sample week 8: two post-dose samples week 12, 48, 72, 96: 1 sample any time post-dose PK substudy: at one time point between week 4-8 frequent sampling 0-24 h (9 samples)	week 4 and 24: pre- and post-dose sample week 8: two post-dose samples week 12, 48, 72, 96: 1 sample any time post-dose PK substudy: at one time point between week 4-8 frequent sampling 0-24h (9 samples)	Day 9 and 10: 1 pre-dose sample Day 11: frequent sampling between 0-24 h (14 samples)
Assay (LLOQ)	LC-MS/MS (1 ng/mL)	LC-MS/MS (1 ng/mL)	LC-MS/MS (1 ng/mL)

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The final analysis dataset consisted of 736 subjects, with 5945 records containing TMC278 plasma concentrations. Richly sampled concentration-time profiles were available in 104 subjects (57 healthy subjects (C152) and 47 HIV-1 infected patients (C209 and C215)). Sparse data was available in 632 patients (C209 and C215). The TMC278 dosage regimen was 25 mg q.d. for all subjects, and the longest exposure was for 514 days.

3.2.2 Methods

Structural Model Development

Although different structural models were tested earlier, the analyses suggested that a two-compartment model for drug disposition was appropriate and was used as a starting point. The main parameters of the final model were apparent clearance (CL/F), central and peripheral volume of distribution, rate constants, and absorption parameters.

Parameter estimation was performed using the First Order Condition Estimation (FOCE) with the INTERACTION option. Comparison between potential models used a likelihood ratio test based on the difference in the NONMEM provided objective function value for two hierarchical competing models.

Empirical Bayes' Estimation

The empirical Bayes' estimation was performed using NONMEM with MAXEVAL=0 in the \$ESTIMATION record. The model parameters were used, including estimates for the fixed and random effects. Goodness-of-fit plots were generated to evaluate the overall fit of the fixed and random parameters, and shrinkage for the random parameters were

calculated. These estimated parameters were used to obtain exposure estimates (i.e., AUC_{τ} , C_{0h})

After an assessment of the predictive performance, the model developed from the dense PK sampling were used to predict TMC278 exposure in the sparsely sampled subjects of the Phase III studies. For these sparse data, steady-state dosing were assumed unless patient records indicate otherwise.

Covariate Model Development

The final model including all Phase III data included a thorough covariate analysis. Covariate effects were evaluated for CL/F and V/F. The following covariates were tested in the model: age, body weight, creatinine clearance, sex, race, background HIV treatment, HIV infection, hepatitis B/C coinfection, and study region. Potential covariate relationships were included in the model if they are statistically significant and clinically relevant. A covariate relationship was deemed significant and clinically relevant if the following three conditions were met:

1. The covariate effect relationship showed statistical significance ($p < 0.01$ for forward selection and $p < 0.001$ for backward deletion).
2. There was a reduction in the extent of inter-individual variability (IIV) of CL/F or V/F compared to the reduced model.
3. There was a clinical relevance for the covariate to be included. Here, clinical relevance was defined as an increase in CL/F of more than 25% or a decrease in CL/F of more than 40% from the typical value for covariates.

3.2.3 Software

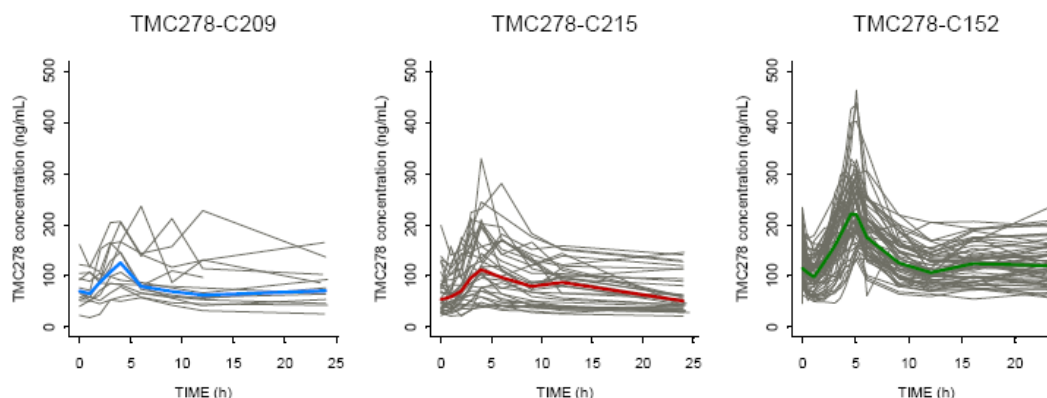
For data management, processing, and graphical analysis, S-Plus 6-2 was used. NONMEM VI level 2.0 was used for the population pharmacokinetic analysis using Compaq Visual Fortran version 6.6a. The computing environment was a Dell Precision 670 Workstation with dual Xeon Processors at 2.8 GHz, running on Windows XP. Analyses were performed in accordance with appropriate guidelines.

3.2.4 Results

3.2.4.1 Observed Concentration-Time Profiles

An overlay of the median and individual concentration-time profiles within a dose interval for the two Phase III trials (C209 and C215) and one Phase I (C152) trial are shown in Figure 7.

Figure 7: Individual Plasma Concentration-Time Profiles of TMC278 in C209, C215, and C152. Thick Lines are the Medians.

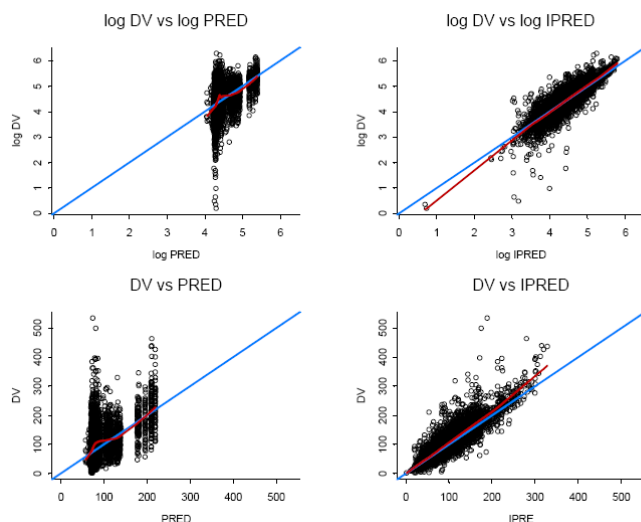


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3.2.4.2 Population PK Model Results

The final population model that best described the pharmacokinetics of TMC278 was a two-compartment disposition model. Absorption of TMC278 with food was described by a lag-time followed by sequential zero- and first-order absorption processes. The model appeared to have adequate predictive performance (Figure 8). A summary of the final model parameters are shown in Table 6.

Figure 8: Goodness of Fit Plots for the Applicant's Final Population PK Model



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**Table 6: TMC278 Population PK NONMEM
Parameter Estimates**

Parameter	Estimate	SE (%) ⁽¹⁾
Structural model		
CL/F (L/h)	11.8	2.2
V2/F (L)	152	21
Q/F (L/h)	87.9	8.3
V3/F (L)	912	15
Ka (1/h)	1.49	23
D1 (h)	3.10	3.7
Tlag (h) ⁽²⁾	1.27	9.8
F1, healthy subjects	1.67	6.3
F1, HIV-1 infected subjects	1.0 (fixed)	
Statistical model		
	IIV (%)	SE (%)
CL/F	39	8.2
V2/F	117	43
Tlag	43	32
Proportional residual error, Phase I data	16%	5.4
Proportional residual error, Phase III data	33%	3.8

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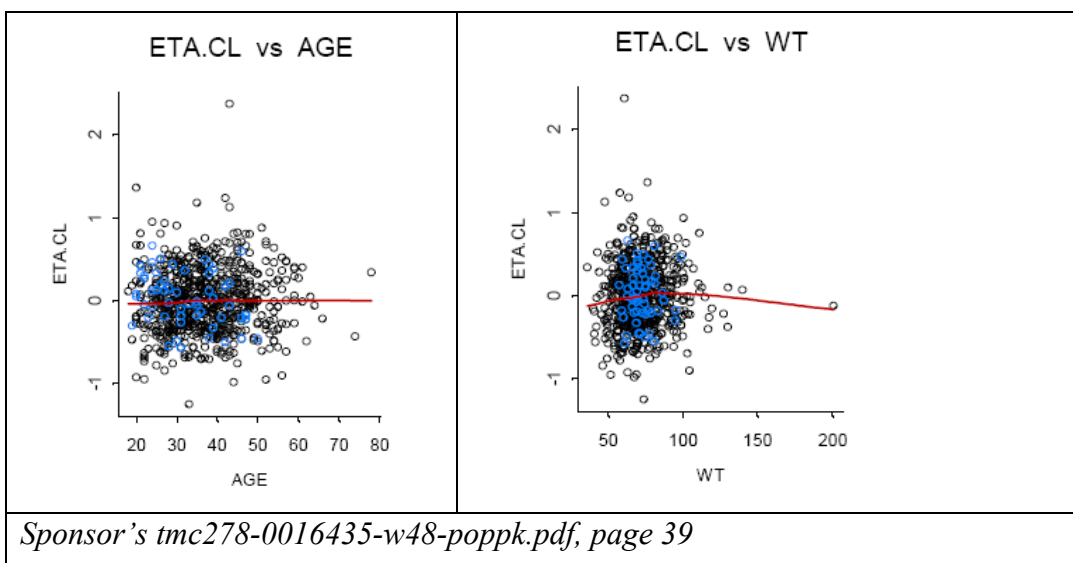
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In HIV-1 infected subjects, CL/F of TMC278 was estimated to be 11.8 L/h and the apparent volume of the central compartment was estimated to be 152 L with the Phase III population pharmacokinetic model. These values correspond very well to the previous population pharmacokinetic analysis for the Phase IIb study in which CL/F was estimated to be 10.5 L/h and the apparent volume of the central compartment was estimated to be 173 L in HIV-1 infected subjects. The inter-individual variability (IIV) for CL/F and V2/F was 39% and 117%, respectively. Likewise, shrinkage was 4% for CL/F and 62% for V2/F.

In HIV-1 infected subjects, intrinsic factors that have been considered for their potential effect on the pharmacokinetics of TMC278 include age, gender, race, body weight, estimated glomerular filtration rate (eGFR), and hepatitis B and/or C virus co-infection status. The effect of these factors was explored using covariate analysis in the population pharmacokinetic analysis of TMC278 for the pooled data from the Phase III trials.

The relationship between IIV on CL/F and age and body weight is shown in Figure 9. No clear relationship was evident between IIV and any of these covariates.

Figure 9: Continuous Covariate Relationships for Random Effect on TMC278 Apparent Oral Clearance (black symbols – Phase III; blue symbols – Phase I).



In addition, the univariate covariate evaluation results for effects on oral clearance are summarized in Table 7. Of the evaluated intrinsic factors only sex and race were identified as having a statistically significant effect on CL/F. Female subjects were found to have a slightly lower CL/F (13.6%) compared to males while CL/F in Asians was lower (17.2%) compared to the rest of the population. However, inclusion of these covariates had no impact on CL/F inter-individual variability and was considered not to be clinically relevant.

Table 7: Univariate Covariate Analysis Results for the Overall Dataset

Run	Covariate tested	Implementation	DF	\$COVAR step?	OFV	Δ OFV vs. reference	p	IIV	Factor	Difference High-Low	Keep covariate in model?
Reference Run:	COV062		---	yes	-6338.4	---	---	38		0	---
COV062WT1	weight	(WT/70)** θ	1	yes	-6340.9	-2.509	0.1132	38			no
COV062AGE1	age	(AGE/36)** θ	1	yes	-6339.1	-0.699	0.4031	38			no
COV062BMI1	BMI	(BMI/24)** θ	1	no	-6338.0	0.362	0.5474	38			no
COV062CRCL1	CRCL	(CRCL/120)** θ	1	no	-6338.3	0.153	0.6957	38			no
COV062SEX1	SEX	$\theta^{**}(\text{SEX})$	1	yes	-6357.3	-18.940	<0.0001	38	0.964	13.6%	no
COV062RACE3	Asian race	$\theta^{**}\text{RAC1}$	1	yes	-6354.0	-15.573	<0.0001	38	0.828	17.2%	no
COV062RACE4	Black race	$\theta^{**}\text{RAC1}$	1	yes	-6344.4	-5.968	0.0146	38	1.09	8.3%	no
COV062RACE5	White race	$\theta^{**}\text{RAC1}$	1	yes	-6340.5	-2.086	0.1487	38			no
COV062RACE6	Other race	$\theta^{**}\text{RAC1}$	1	yes	-6346.7	-8.300	0.0040	38	0.787	21.3%	no
COV062BB1	Backbone	$\theta^{**}\text{BB1}*\theta^{**}\text{BB2}*\theta^{**}\text{BB3}*\theta^{**}\text{B4}$	4	no	-6340.1	-1.685	0.7934	38			no
COV062STU1	Study	$\theta^{**}\text{ST1}*\theta^{**}\text{ST2}*\theta^{**}\text{ST3}$	3	no	-6342.8	-4.430	0.2186	38			no
COV062HEP1	HEP B/C inf.	FIX1**HEPBC (reference)	---		-6276.8	---	---	39			
COV062HEP2	HEP B/C inf.	$\theta^{**}\text{HEPBC}$	1	no	-6276.9	-0.051	0.8213	38			no

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The empirical Bayes' pharmacokinetic parameter estimates based on the final model were used to predict AUC_τ and C_{0h} for all Phase III subjects with PK samples available ($n = 679$). Summary statistics of these results are shown in Table 8.

Table 8: Applicant's Reported AUC_τ and C_{0h} Based on Population PK Modeling

Table 5: Population Pharmacokinetic Estimates of Rilpivirine 25 mg once daily in Antiretroviral Treatment-Naïve HIV-1-Infected Subjects (Pooled Data from Phase 3 Trials at Week 48)	
Parameter	Rilpivirine 25 mg once daily N = 679
AUC _{24h} (ng•h/mL)	
Mean ± Standard Deviation	2397 ± 1032
Median (Range)	2204 (482 - 8601)
C _{0h} (ng/mL)	
Mean ± Standard Deviation	80 ± 37
Median (Range)	74 (1 - 300)

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Reviewer's Comments: The population pharmacokinetic model development by the applicant was sufficient to describe the time course of rilpivirine exposure. The applicant's label claims of no clinically relevant impact of gender, race, age (between 18 and 75 years), and hepatitis infection status on rilpivirine exposure is supported by their population PK modeling results.

Steady-state rilpivirine AUC and C_{0h} predictions for the Phase III trials were obtained using empirical Bayes' estimates of the final population PK model. The applicant demonstrated that AUC and C_{0h} predictions from sparse versus rich data sets using this approach had good agreement, while C_{max} estimates from sparse data sets showed shrinkage to the population value and were not considered reliable. This population PK modeling approach and subsequent estimation of rilpivirine AUC and C_{0h} (and exclusive of C_{max} estimates) is reasonable, and the summary pharmacokinetic parameters presented by the applicant are supported by the applicant's population PK analysis.

3.3 Efficacy of Rilpivirine in HIV-1 Treatment Naïve Patients

Report tmc278-0016436-w48-gam.pdf: Modelling of the 48 week decrease in viral load and increase in CD4 count to explore the relationship with TMC278 exposure and other prognostic factors for the phase-III studies of TMC278

3.3.1 Data Sets

The pooled 48-week efficacy data in 652 treatment-naïve HIV-1 infected subjects from the TMC278 arms of the Phase III studies TMC278-TiDP6-C209 and TMC278-TiDP6-C215 were made available for the current analysis. This was based on the intent-to-treat population, but excluded subjects that discontinued without evidence of virologic failure (e.g. subjects who discontinued from the trial, lost to follow up).

3.3.2 Methods

3.3.2.1 Generalized Additive Modeling

The effect of TMC278 exposure and other potential prognostic factors on the virologic response parameters were analysed as a binary variable (success/failure) using logistic

regression applying generalized additive models (GAM). In the case of the CD4 counts, absolute change from baseline was analyzed using generalized additive models. In the generalized additive logistic regression model, it is assumed that the log-odds of the probability of an event given prognostic factors $x_{i1}, x_{i2}, \dots, x_{ip}$ is:

$$\log \frac{p(y_i | x_{i1}, x_{i2}, \dots, x_{ip})}{1 - p(y_i | x_{i1}, x_{i2}, \dots, x_{ip})} = \beta_0 + f_1(x_{i1}) + \dots + f_p(x_{ip})$$

where each f_j is an unspecified (“non-parametric”) function. The functions f_j are estimated in a flexible manner, using an algorithm whose basic building block is a scatter plot smoother.

A univariate GAM analysis was initially undertaken, separately exploring the relationship between each of the potential prognostic factors (TMC278 exposure and the other prognostic factors) and the primary endpoint using the GAM. To develop the final GAM models, the automated step-wise search was used. This automated step-wise search selects the best GAM using forward selection and backwards deletion given the range of possible models being considered. Generalized additive models (GAM) were fitted to the data using the statistical software R version 2.10.0. The Akaike Information Criterion (AIC) was used to select the best model during the step-wise search process.

Efficacy parameters

The primary efficacy endpoint virologic response was defined as a confirmed viral load less than 50 copies/mL at Week 48 (TLOVR non-VF censored). Subjects who discontinued without signs of virologic failure are excluded from this analysis.

Prognostic factors

The following potential prognostic factors for the efficacy parameters were evaluated by the GAM analyses:

- TMC278 C_{trough} and AUC_{τ} at 48 weeks
- Baseline phenotype for TMC278 (fold-change in TMC278 EC50, FC)
- Compliance (COMP), based on self reported 48-week pill count
- Baseline viral load, CD4 count, hepatitis B/C co-infection, and Phenotypic Sensitivity Score according to Antivirogram®
- Patient demographics (age, body weight, sex, and race)
- Background regimen
-

GAM Model selection

In the initial univariate GAM analyses, all prognostic factors were independently evaluated for their potential relationship with the primary endpoint.

In this multivariate analysis, the Akaike Information Criterion (AIC) was used to select the best model. The step-wise search ended when the default maximum number of steps was used (1000) or when the AIC could not be decreased further by any of the remaining eligible steps.

As the pharmacokinetic exposure parameters of TMC278 were highly correlated, C_{0H} and AUC_{τ} of TMC278 were each separately analyzed with all other prognostic factors in the automated step-wise GAM search. Based on a comparison of the AIC values, the most informative pharmacokinetic exposure parameter of TMC278 was selected in the final model.

3.3.2.2 Exposure-effect Relationship

After a successful evaluation of the predictive performance of the GAM models, simulations of the exposure-effect relationship including model parameter uncertainty (but not the residual error) were performed for the probability of virologic response at Week 48 (confirmed viral load < 50 copies/mL). TMC278 pharmacokinetic exposure values covering the observed exposure range were assigned to each subject in the original database while keeping all other data as originally recorded. The likelihood of virologic response was subsequently predicted based on the corresponding 1000 sets of GAM parameters obtained in a bootstrap step. For each of the 1000 replicates, the overall likelihood of response in the investigated population was calculated. Finally, the calculated median and 2.5th and 97.5th percentiles for the predictions from the replicates were presented graphically, as a function of TMC278 exposure.

3.3.3 Exposure-response Results

3.3.3.1 Exposure-response Summary Statistics

For the primary endpoints of virologic response, C_{0H} as well as AUC_{τ} of TMC278 were generally somewhat lower in subjects without a virologic response as compared to subjects with a virologic response. Also, the compliance was generally somewhat lower in subjects without a virologic response. A quartile analysis of the virologic response as a function of the pharmacokinetic exposure of TMC278 is listed in Table 9 for a viral load < 50 copies/mL.

Table 9: Quartile Analysis of Percentage Virologic Response (Viral Load <50 Copies/mL) Versus C_{0H} and AUC_{τ} of TMC278

C_{0H} of TMC278	Virologic response	AUC_{τ} of TMC278	Virologic response
C_{0H} < lower quartile	78.5%	AUC_{τ} < lower quartile	78.5%
lower quartile $\geq C_{0H}$ < median	88.3%	lower quartile $\geq AUC_{\tau}$ < median	87.7%
median $\geq C_{0H}$ < upper quartile	92.0%	median $\geq AUC_{\tau}$ < upper quartile	92.6%
C_{0H} \geq upper quartile	95.7%	AUC_{τ} \geq upper quartile	95.7%

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3.3.3.2 GAM Analysis

The potential relationship between the TMC278 pharmacokinetic exposure parameters and the other prognostic factors was evaluated using the gam function of the R software with a loess fitting (using the 'lo' function) for the continuous variables, and a fit by category for the categorical variables. The results of the automated step-wise searches

for the prognostic factors of virologic response defined as a viral load below 50 copies/mL are given in Table 10.

Table 10: GAM Models and AIC Obtained at the End of Automated Step-wise Searches for Prognostic Factors of Virologic Response (Viral Load <50 Copies/mL)

Analysis	TMC278 exposure parameter included in the analysis	GAM model	AIC
0	-	-	437.82
1	C _{0h}	VR50 ~ log(BCD4) + log(BVL) + log(C _{0h}) + s(COMP, 2) + FC + BLQ + STD	307.61
2	AUC	VR50 ~ log(BCD4) + log(BVL) + log(AUC) + s(COMP, 3) + FC + BLQ + STD	313.92

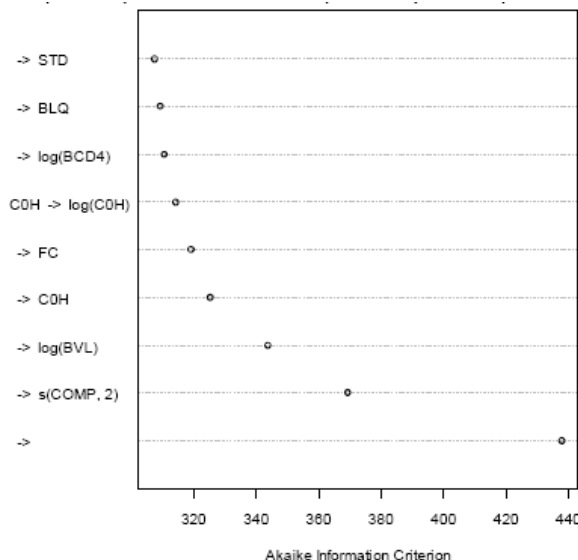
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Based on the lowest AIC, baseline CD4 count, baseline viral load (BVL), pre-dose plasma concentration of TMC278, compliance, phenotypic fold change for TMC278, absence or presence of BLQ value(s), and study (TMC278-TiDP6-C209 *versus* TMC278-TiDP6-C215) were the prognostic factors retained in the final model explaining the virologic response (viral load < 50 copies/mL). Based on a comparison of the AIC values, AUC_τ appeared to be slightly less informative as compared to the C_{0h} of TMC278. However, as C_{0h} and AUC_τ of TMC278 were found to be highly correlated, the data do not allow the conclusion to be made that AUC_τ of TMC278 is clearly inferior to C_{0h} as a prognostic factor for virologic response.

The results of the step-wise search for the final GAM model including the prognostic factors of virologic response (viral load < 50 copies/mL) are depicted in Figure 10. Compliance was the prognostic factor that was selected first during the automated step-wise GAM search resulting in the biggest drop in AIC. Subsequently, baseline viral load was selected, followed by C_{0h} of TMC278, fold change, log(C_{0h}) instead of C_{0h}, baseline CD4 count, BLQ and study.

Figure 10: Results of the Automated GAM Search for Prognostic Factors of Virologic Response (<50 Copies/mL)

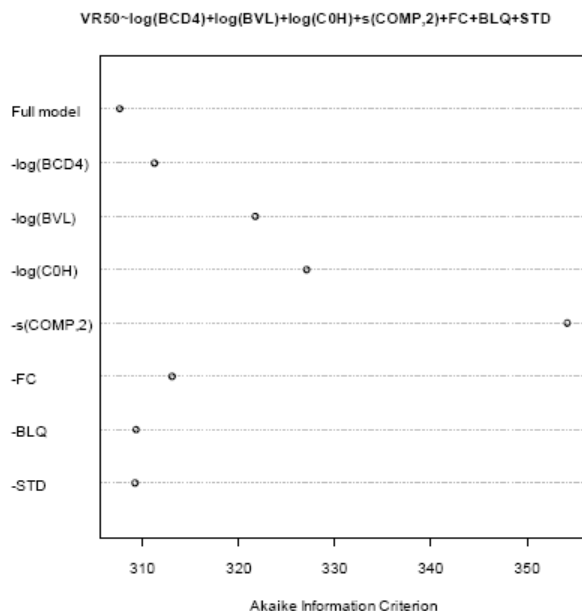


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The relative importance of the retained prognostic factors in explaining the likelihood of virologic response (viral load < 50 copies/mL) is evaluated in Figure 11. The higher the increase in AIC when one of the prognostic factors is deleted from the final model, the more important this prognostic factor is in explaining the likelihood of response.

Compliance could be considered to be the most important prognostic factor, followed by the trough plasma concentration of TMC278, baseline viral load, phenotypic fold change for TMC278 at baseline and baseline CD4 count. The other retained prognostic factors were considered to be less important in explaining the likelihood of virologic response as the increase in AIC was found to be minor when these factors were deleted from the final model.

Figure 11: Increase in AIC from the Full Model of Virologic Response Virologic Response (<50 Copies/mL) as a Result of Deleting One by One Each of the Prognostic Factors

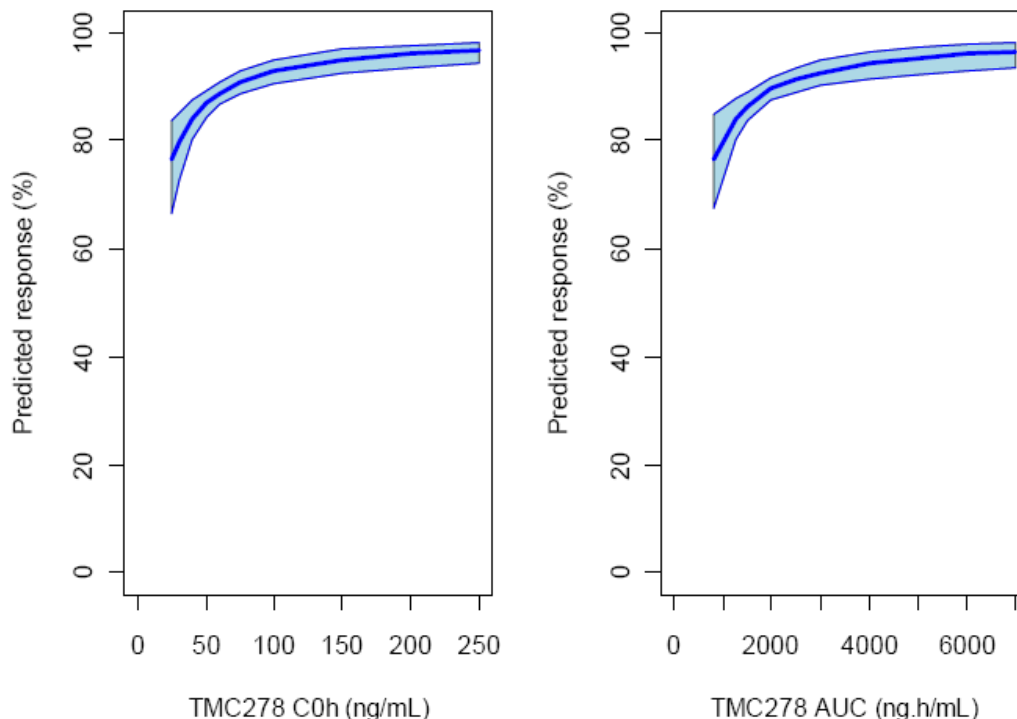


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3.3.3.3 Exposure-response Simulation Results

Figure 12 shows the median (2.5th-97.5th percentiles) prediction of percentage of virologic response at Week 48 (HIV-1 viral load < 50 copies/mL) as a function of the pre-dose plasma concentration (C_{0h}) and AUC_{τ} of TMC278. The predicted likelihood of virologic response at Week 48 (viral load < 50 copies/mL) slightly increased between a C_{0h} of 25 and 50 ng/ml and between 50 and 100 ng/ml (left panels of Figure 12), representing respectively approximately 20% and 53% of the total number of subjects. From a C_{0h} of approximately 100 ng/mL onwards, the predicted likelihood of virologic response seemed to reach a plateau, representing approximately 26% of the total number of subjects.

Figure 12: Median (2.5th-97.5th percentiles) prediction of the likelihood of response (HIV-1 viral load <50 copies/mL) as a function of TMC278 C_{0h} (left panel) and AUC_τ (right panel), based on the final GAM models fitted to 1000 bootstrap samples of the original data set.



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Reviewer's comments: The applicant's GAM analysis identifies key patient factors and pharmacokinetic parameters associated with virologic success. The simulation exposure-response relationship depicts a flat relationship for rilpivirine trough concentrations >100 ng/mL. However, the median C_{0h} for the combined Phase III trials was 80 ng/mL, indicating that more than 50% of the subjects did not achieve exposures that would result in maximum virologic response. The average response rate in the lowest quartile was 78.5% and is not fully explained by a lack of compliance because the self reported compliance was >90% in 95% of the population. The impact of different covariates on the probability of virologic success is explored further in the reviewer's analysis.

3.4 Safety (QTc Prolongation) of Rilpivirine in HIV-1 Treatment Naïve Patients

Report tmc278-0015283-pkpd-qt.pdf: Pharmacokinetic/pharmacodynamic modeling and simulation of the effect of TMC278 on QTcF prolongation, based on pooled data from clinical trials TMC278-TiDP6-C152 and TMC278-TiDP6-C131 in healthy volunteers

In 3 rilpivirine thorough QT trials in healthy subjects (C131 that evaluated 75 mg and 300 mg; C151 and C152 that evaluated 25 mg), the effect of TMC278 on cardiac rhythm and ECG parameters, especially QTc interval, was evaluated. In all 3 trials, a single dose of moxifloxacin 400 mg was used as a positive control to assess trial sensitivity.

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C131 was conducted in accordance with ICH E14 guideline. In this trial, healthy subjects received TMC278 at doses of 75 mg q.d. (the TMC278 dose originally selected for further development) and 300 mg q.d. (supratherapeutic dose), to evaluate the effect of TMC278 75 mg q.d. and TMC278 300 mg q.d. both after a single dose and at steady-state on the QT/QTc interval. In this trial, a mean increase in QTcF was observed at steady-state plasma concentrations with the higher doses of TMC278 (75 mg q.d. and 300 mg q.d.). The upper limit of the 2-sided 90% CI of the mean time-matched effect of TMC278 on the QTcF exceeded the 10 ms ICH threshold for at least at 1 time point for both the TMC278 75 mg q.d. and 300 mg q.d. dose. This relevant QTc prolongation was dose and concentration-dependent. Based on pharmacokinetic/pharmacodynamic modeling of the data, it was expected that TMC278 25 mg q.d. would not have an effect on the QTc interval. These results led to the selection of TMC278 25 mg q.d. as the final dose for Phase III development.

Following the selection of the TMC278 25 mg q.d. dose and prior to the start of the Phase III trials, a pilot QT trial (C151) was performed in healthy adult subjects to evaluate the potential effect of the lower TMC278 25 mg q.d. dose at steady-state on the QT/QTc interval. In this pilot trial, administration of TMC278 25 mg q.d. was not associated with prolongation of the QTc as the change in QTcF did not exceed the threshold as defined by ICH E14. These results provided clinical support for the predictions of the pharmacokinetic/pharmacodynamic modeling, indicating that the TMC278 25 mg q.d. dose was not associated with a clinically relevant effect on QTcF at steady-state.

On the basis of the results of pilot QT trial C151, a TQT trial (C152) evaluating TMC278 25 mg q.d. was started. TQT trial C152, designed in accordance with the ICH E14, evaluated the effect of the TMC278 25 mg q.d. dose at steady-state on the QT/QTc interval. The results of TQT trial C152 show that the upper limits of the 2-sided 90% CIs of the mean time-matched effect of TMC278 on the QTcF were below the 10 ms threshold at all time points, indicating that the TMC278 25 mg q.d. dose is not associated with a clinically relevant effect on QTcF.

Finally, data from the 2 thorough QT trials (C131 and C152) were pooled for a pharmacokinetic/pharmacodynamic analysis of the relationship between TMC278 plasma concentration and change in QTc interval. A positive TMC278 plasma concentration-relationship with changes in the QTcF interval was seen with TMC278 75 mg q.d. and 300 mg q.d, but not with TMC278 at the recommended dose of 25mg q.d., indicating that the potential for prolongation of the QTcF interval is dose- and plasma concentration-dependent.

Reviewer's comments: A significant concentration- $\Delta\Delta$ QTcF (the placebo- and baseline-adjusted change in QT interval using Fridericia QT correction method) relationship was identified for rilpivirine. $\Delta\Delta$ QTcF from the supratherapeutic doses of 75 and 300 mg q.d. results in $\Delta\Delta$ QTcF >10 ms; however, the 25 mg q.d. dose had an upper 95% CI $\Delta\Delta$ QTcF of 8 ms (mean $\Delta\Delta$ QTcF of 4 ms). The impact of drug-drug interactions on potential high exposure scenarios will be further explored by the IRT-QT team.

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No relationship between the most common adverse events (depression, insomnia, headache, and rash) or changes in laboratory parameters with rilpivirine AUC_t were observed by the applicant. Potential relationships with psychiatric, skin, dizziness, and hepatobiliary adverse events are further evaluated in the reviewer's analysis.

4 REVIEWER'S ANALYSIS

4.1 Introduction

The aim of this review to examine whether the label claims and proposed dose are justified by the existing PK, efficacy, and safety data using both population PK and exposure-response analyses.

4.2 Objectives

Analysis objectives are:

1. Determine if the label claims regarding population PK parameters and covariates are accurate
2. Determine the impact of rilpivirine exposure on common adverse events
3. Evaluate exposure-response relationship for the primary endpoint (<50 HIV-1 RNA copies/mL) using inhibitor quotient as an explanatory variable and also identify different determinants of virologic success

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 11.

Table 11: Analysis Data Sets

Study Number	Name	Link to EDR
C209	ae.xpt, dm.xpt, vlad.xpt, cm.xpt, c209vir.xpt, ppad.xpt, pp.xpt, mmasri.xpt, lbad01.xpt, sn48tad.xpt	\\cdsesub1\evsprod\NDA20222\0000\m5\datasets\tmc278-tidp6-c209
C215	ae.xpt, dm.xpt, vlad.xpt, cm.xpt, c215vir.xpt, ppad.xpt, pp.xpt, mmasri.xpt, lbad01.xpt, sn48tad.xpt	\\cdsesub1\evsprod\NDA20222\0000\m5\datasets\tmc278-tidp6-c209
C152	ae.xpt, dm.xpt, ppad.xpt, pp.xpt	\\cdsesub1\evsprod\NDA20222\0000\m5\datasets\tmc278-tidp6-c152
popPK*	tmc278phase3cov2.xpt databf204w96_071102.xpt	\\cdsesub1\evsprod\NDA20222\0003\m5\datasets

*The popPK dataset included information from studies C152, C209, and C215.

4.3.2 Software

Estimation and simulation were performed NONMEM VI on the Pharmacometrics Group Linux cluster using the front end manager Perl Speaks NONMEM (PsN). Diagnostic graphs, model comparison, and statistical analysis were performed in R (version 10.1).

4.3.3 Models

4.3.3.1 Population Pharmacokinetics

A two-compartment model for drug disposition with lag-time and zero and first order absorption were used for describing rilpivirine plasma concentrations. This population PK model was used for evaluating rilpivirine exposures in the Phase III population administered 25 mg q.d.

4.3.3.2 Linear-Mixed Effects: Rilpivirine Concentration- $\Delta\Delta QTcF$

The QT prolongation potential of rilpivirine was assessed by combining data from two thorough QT trials: TMC278-TiDP6-C151 (doses of 75 and 300 mg q.d.) and TMC278-TiDP6-C131 (dose of 25 mg q.d.). Only steady-state, day 11 data was used from both trials for model development. The selected dependent variable, time-matched change from placebo- and baseline-adjusted change in Fridericia corrected QT interval ($\Delta\Delta QTcF$), was calculated using Equations (1)-(3) below:

$$\Delta QTcF_{drug}(t) = QTcF_{drug}(t) - QTcF_{drug}(t_{baseline}) \quad (1)$$

$$\Delta QTcF_{placebo}(t) = QTcF_{placebo}(t) - QTcF_{placebo}(t_{baseline}) \quad (2)$$

$$\Delta\Delta QTcF_{drug}(t) = \Delta QTcF_{drug}(t) - \Delta QTcF_{placebo}(t) \quad (3)$$

Baseline data was obtained one day prior to the start of treatment (day -1), and on treatment data was obtained at steady state on day 11. A linear mixed-effects modeling approach was used to quantify the relationship between rilpivirine concentration and $\Delta\Delta QTcF$:

$$\Delta\Delta QTcF_{ij} = Intercept_i + Slope_i \cdot Conc_{ij} + \varepsilon_{ij} \quad (4)$$

Here, $\Delta\Delta QTcF_{ij}$ is the time- matched change in $\Delta\Delta QTcF$ for subject i at time j for rilpivirine concentration $Conc_{ij}$, ε_{ij} is additive residual error for subject i at time j , and $Intercept_i$ (or $Slope_i$) is the intercept (or slope) estimate for subject i . In addition to the presented linear model, additional model structures (loglinear, fixed intercept) were also evaluated during model development.

4.3.3.3 Logistic Regression: Efficacy and Safety Exposure-Response Relationships

Logistic regression models for virologic success (HIV-1 RNA <50 copies/mL) and common adverse events (psychiatric, skin, dizziness, and hepatobiliary) were performed using the applicant's Phase III trial data. Two independent variables were used for developing logistic regression plots: steady-state AUC (AUC_{τ}) and trough concentration (C_{0h}). AUC_{τ} and C_{0h} were calculated for each patient using empirical Bayes' estimates from the population PK model.

4.3.3.4 Impact of Rilpivirine on Renal Function

All rilpivirine-treated patients from the two Phase 3 pivotal trials (C209 and C215) were pooled for assessing the relationship between on-treatment maximum decrease in CrCL and baseline CrCL (datasets lbad01.xpt). A total of 683 patients (out of 686) were included in this analysis and 3 were excluded due to discontinuation prior to the first on treatment serum creatinine assessment.

Maximum on Treatment Change in CrCL

Patients were binned first according to renal function (moderate: n=7; mild: n=80; normal: n=596), and then within renal function category to convey a trend of decrease with changes in CrCL. CrCL for patients were obtained using the Cockcroft-Gault formula. Maximum on-treatment changes in CrCL were obtained in reference to patient baseline CrCL.

CrCL Return to Baseline Assessment

A total of 59 subjects who discontinued rilpivirine treatment during C209 and C215 were available for follow-up creatinine clearance assessment to determine if creatinine clearance returned to baseline after cessation of rilpivirine therapy. Nine subjects had mild baseline renal function, and 50 had normal function. Typical time to follow-up in all the subjects was 2-4 weeks. CrCL return to baseline was assessed graphically comparing baseline and follow-up CrCL.

Mechanism of Action Assessment

Eleven subjects were on concomitant medications at baseline that also inhibit tubular secretion of creatinine (trimethoprim). Of these 11 patients, 5 were on background tenofovir/emtricitabine and 6 were on zidovudine/lamivudine. Maximum on-treatment decrease in CrCL for this subset of patients was limited to the interval over which the patient was receiving trimethoprim (range: 2-48 weeks).

4.4 Results

4.4.1 Population Pharmacokinetics

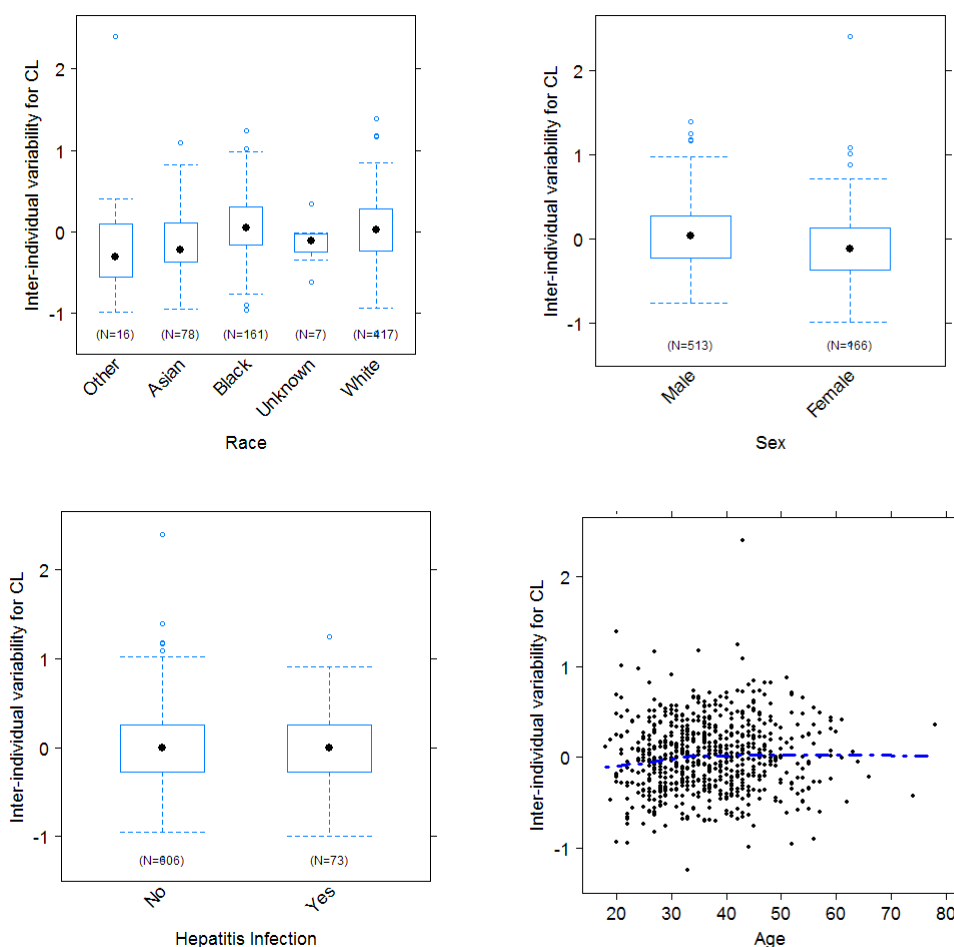
The pharmacokinetic models and concentration data for rilpivirine was evaluated to determine if the labels claims based on the population PK model was justified. Two different labels claims were investigated:

1. No clinically relevant effect on exposure from race, gender, hepatitis B/C coinfection, or age (range 18 to 75 years)
2. C_{0h} and AUC_{τ} in Phase III patients administered 25 mg q.d.

Figure 13 shows the relationship between the inter-individual variability for apparent oral clearance and the categorical covariates race, gender, hepatitis B/C coinfection, and continuous covariate age. In all cases the distributions of the inter-individual variability of clearance were centered about zero and not influenced by these covariates. While no trend was evident in the inter-individual variability for clearance with respect to age, it should be noted that only 3 patients were >65 years. No trend was evident in the inter-individual variability for clearance distribution for the 3 patients >65 years of age, but the

small sample size makes it difficult to support the labeling claim of no impact of age on clearance in patients >65 years. The label claim should be revised as indicated in Section 1.3.

Figure 13: Continuous and Categorical Covariate Relationships for Random Effect on TMC278 Apparent Oral Clearance



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In Table 12, the estimates of AUC_{τ} and C_{0h} obtained from the pharmacometrics reviewer's analysis are compared to those obtained from the applicant's analysis. For rilpivirine, AUC_{τ} and C_{0h} from studies C209 and C215, representing 25 mg q.d. in treatment-naïve patients were compared to estimates obtained in this Bayesian feedback analysis. The estimates of AUC_{τ} and C_{0h} were similar between both analyses.

Table 12: Population Pharmacokinetic Estimates of Rilpivirine 25 mg q.d. in Antiretroviral Treatment Naïve HIV-1-Infected Patients (Comparison of Applicant's Label Claims and Reviewer Analyses)		
Parameter	Rilpivirine 25 mg q.d. (N=679), Applicant	Rilpivirine 25 mg q.d. (N=679), Reviewer
AUC_τ (ng·h/mL)		
Mean ± Standard Deviation	2397 ± 1032	2287 ± 877
Median (Range)	2204 (482 – 8601)	2152 (192 – 7523)
C_{0h} (ng/mL)		
Mean ± Standard Deviation	80 ± 37	82 ± 33
Median (Range)	74 (1 – 300)	74 (14 – 304)

Impact of Renal Impairment on Rilpivirine Exposure

Creatinine clearance was calculated from the Phase III patients using the Cockcroft-Gault equation and available patient covariate data. Of the Phase III patients with rilpivirine exposure data available, 7 subjects had calculated CrCl ranging from 30-<60 mL/min (moderate renal impairment), including 1 subject with CrCl<50 mL/min: 42 mL/min and 6 subjects with CrCl between 50 and 60 mL/min. 80 subjects had CrCl between 60 and less than 90 mL/min (mild renal impairment). No clinically significant differences in rilpivirine exposure was observed between patients with normal or mild renal impairment. The limited number of subjects with moderate renal impairment precluded a definitive comparison from being made regarding whether the rilpivirine exposure in this group differs from subjects with normal renal function or subjects with mild renal impairment. No patients with severe renal impairment or end-stage renal disease were included in the Phase III trials.

Table 13: Population Pharmacokinetic Estimates of Rilpivirine 25 mg q.d. in Antiretroviral Treatment Naïve HIV-1-Infected Patients (Comparison of Patients with CrCL ≥ 90 mL/min, 60< CrCL<90 mL/min, and CrCL<60 mL/min)			
Parameter	Rilpivirine 25 mg q.d. (N=592), CrCl ≥ 90 mL/min (normal renal function)	Rilpivirine 25 mg q.d. (N=80), 60<CrCL< 90 mL/min (mild renal impairment)	Rilpivirine 25 mg q.d. (N=7), CrCL < 60 mL/min (moderate renal impairment)
AUC_τ (ng·h/mL)			
Mean ± Standard Deviation	2278 ± 886	2390 ± 821	1819 ± 614
Median (Range)	2143 (194 – 7523)	2323 (917 – 5613)	1659 (1114 – 2838)
C_{0h} (ng/mL)			
Mean ± Standard Deviation	82 ± 33	86 ± 33	69 ± 24
Median (Range)	74 (13 – 304)	78 (30 – 215)	73 (30 – 117)

In addition, estimated glomerular filtration rate was calculated using the following equation:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{S}_{\text{cr, std}})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

where $\text{S}_{\text{cr, std}}$ is serum creatinine measured with a standardized assay. Of the studied Phase III patients with rilpivirine exposure data available, 1 patient had $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ (moderate renal impairment) and 142 had $60 < \text{eGFR} < 90 \text{ mL/min/1.73 m}^2$ (mild renal impairment) (Table 14). Similar to the results from Table 13, no difference in rilpivirine exposure was observed between patients with normal and mild renal impairment. As noted before, no definitive comparisons could be made regarding comparing subjects with moderate renal impairment to subjects with normal renal function or subjects with mild renal impairment

Table 14: Population Pharmacokinetic Estimates of Rilpivirine 25 mg q.d. in Antiretroviral Treatment Naïve HIV-1-Infected Patients (Comparison of Patients with $\text{eGFR} \geq 90 \text{ mL/min/1.73 m}^2$, $60 < \text{eGFR} < 90 \text{ mL/min/1.73 m}^2$, and $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$)			
Parameter	Rilpivirine 25 mg q.d. (N=536), $\text{eGFR} \geq 90 \text{ mL/min/1.73 m}^2$ (normal renal function)	Rilpivirine 25 mg q.d. (N=142), $60 < \text{eGFR} < 90 \text{ mL/min/1.73 m}^2$ (mild renal impairment)	Rilpivirine 25 mg q.d. (N=1), $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ (moderate renal impairment)
AUC_τ (ng·h/mL)			
Mean ± Standard Deviation	2440 ± 1061	2232 ± 906	2202
Median (Range)	2210 (194 – 7523)	2176 (810 – 5822)	–
C_{0h} (ng/mL)			
Mean ± Standard Deviation	81 ± 38	74 ± 32	75
Median (Range)	74 (13 – 304)	71 (20 – 224)	–

4.4.2 Rilpivirine Concentration- $\Delta\Delta\text{QTcF}$

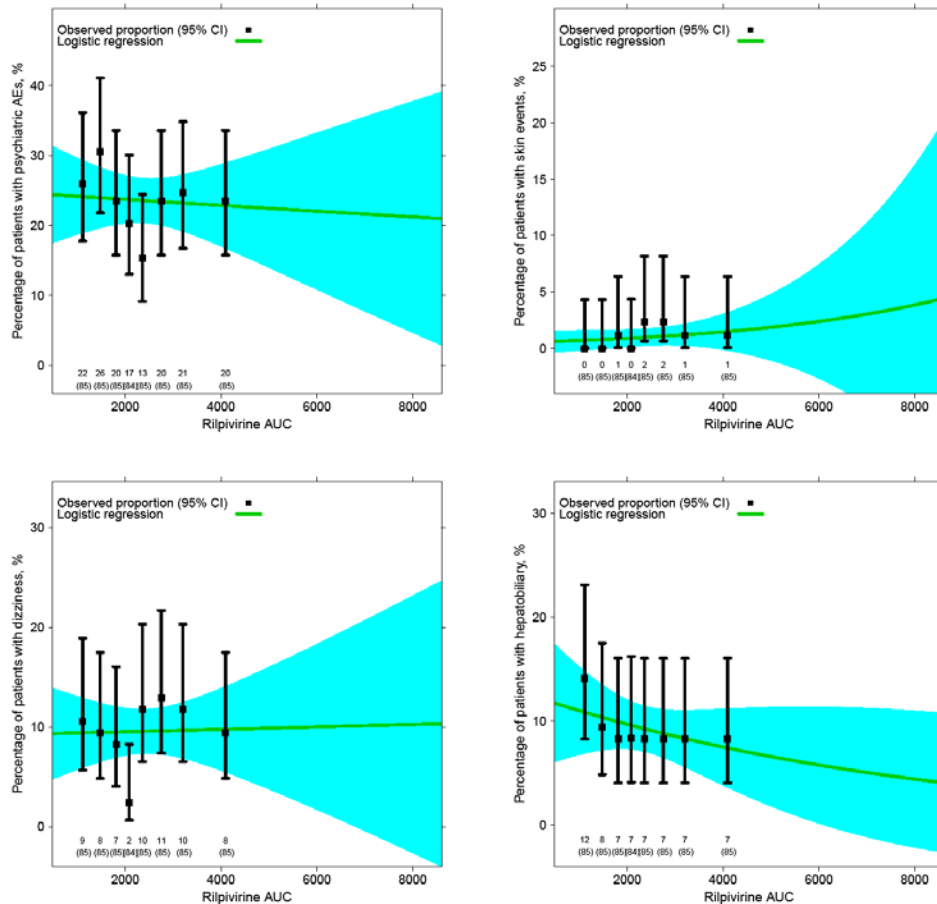
Mixed-effects modeling results indicate a significant and linear relationship between rilpivirine concentration and $\Delta\Delta\text{QTcF}$. Prolongation of the QT interval was greatest for rilpivirine supratherapeutic dose of 300 mg q.d., resulting in a mean predicted $\Delta\Delta\text{QTcF}$ of 24 ms. Similarly, QT prolongation for rilpivirine 75 mg q.d. and 25 mg q.d. was 10 and 4 ms. The mean ($\pm 90\%$ confidence interval) concentration- $\Delta\Delta\text{QTcF}$ relationship along with predicted prolongation at C_{max} for rilpivirine 25, 75, and 300 mg q.d. is shown in Figure 6.

4.4.3 Exposure-Response for Safety: Other Adverse Events

Logistic regression models were evaluated for rilpivirine C_{0h} and AUC_{τ} with no significant relationships identified. Modeling results for adverse event rates versus

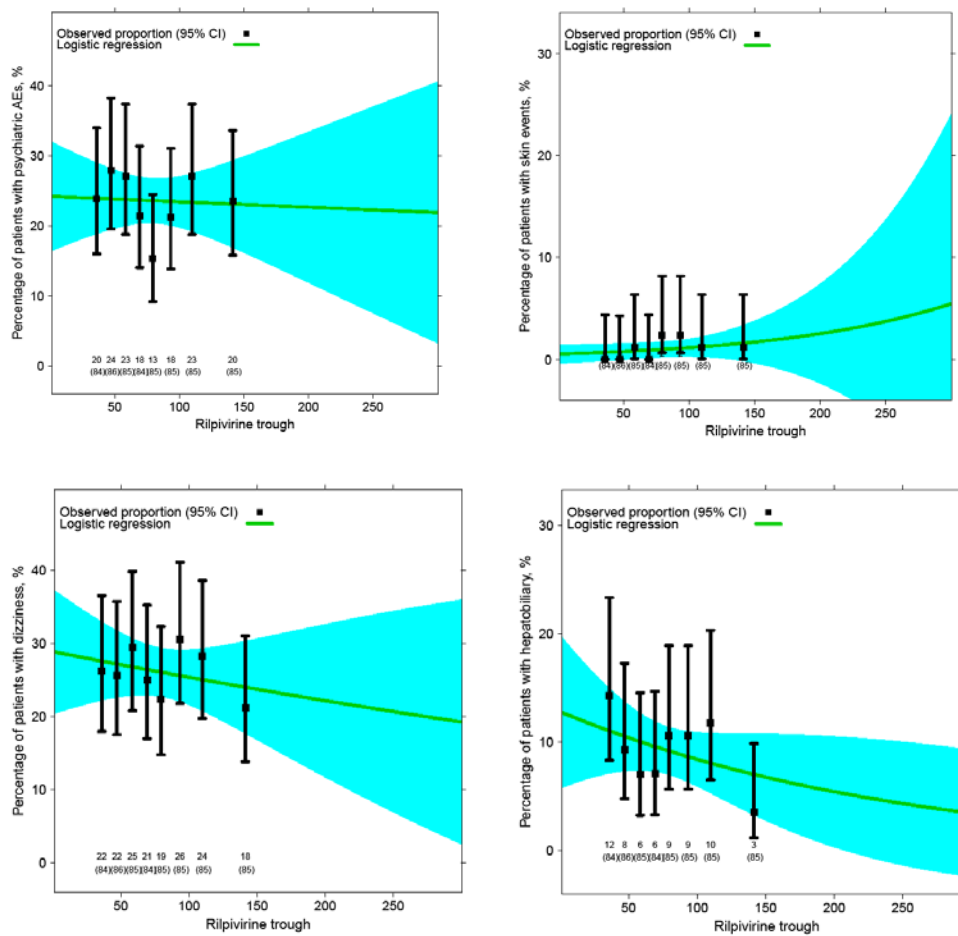
rilpivirine AUC_{τ} (Figure 14) and C_{0h} (Figure 15) indicate no significant relationship. Of the skin-related adverse events, 6 of 7 occurred in patients above the median rilpivirine exposure. However, given the overall small number of events a relationship between adverse event rate and exposure can not be confirmed.

Figure 14: Percentage of Patients with Psychiatric (top left), Skin (top right), Dizziness (bottom left), and Hepatobiliary (bottom right) Adverse Events Versus Rilpivirine AUC_{τ} for All Treatment Naïve Patients Administered 25 mg Rilpivirine Q.D.



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Figure 15: Percentage of Patients with Psychiatric (top left), Skin (top right), Dizziness (bottom left), and Hepatobiliary (bottom right) Adverse Events Versus Rilpivirine C_{0h} for All Treatment Naïve Patients Administered 25 mg Rilpivirine Q.D.



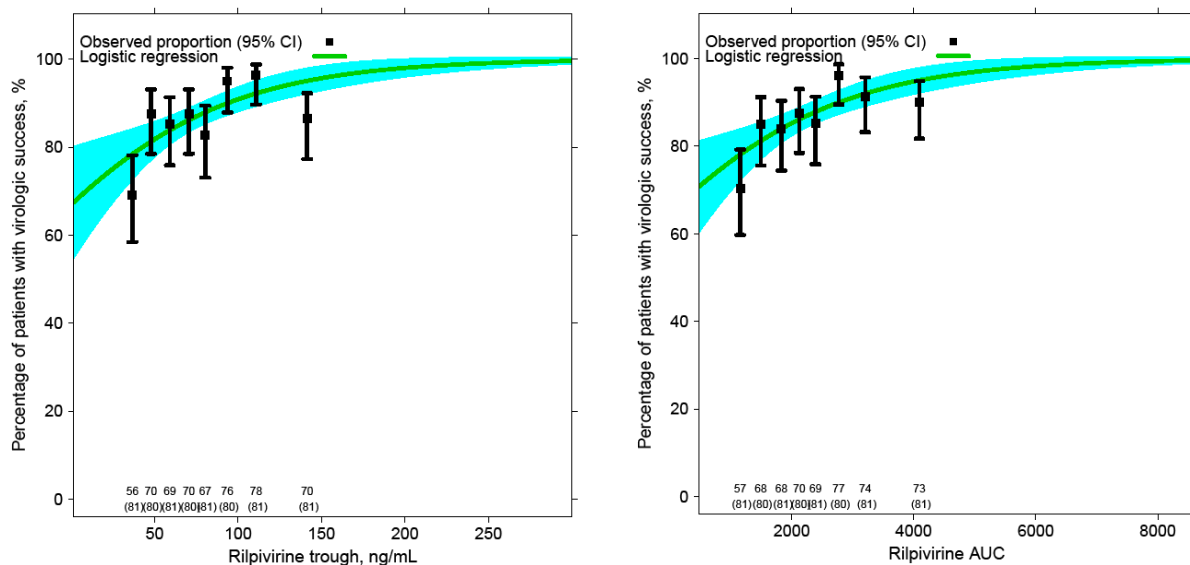
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4.4.4 Exposure-Response for Efficacy (Virologic Response)

A decrease in percentage of patients achieving virologic success (plasma viral load <50 HIV-1 RNA copies/mL) at Week 48 was observed in patients with the lowest rilpivirine C_{0h} quantile? from the two pivotal Phase III trials (C209 and C215) administered 25 mg rilpivirine q.d.

While patient compliance was identified as the most important modeling component during GAM analysis based on AIC, this was driven by a $<4\%$ of the treatment population with $<90\%$ compliance. After removing the non-compliant patients from the analysis, a significant (p value <0.05) exposure-response relationship between rilpivirine exposure (C_{0h} and AUC_{τ}) and virologic success is still present (Figure 16).

Figure 16: Percentage of Patients Achieving Virologic Success (<50 Copies/mL) Versus Rilpivirine C_{0h} (left) and AUC_{τ} (right) from C209 and C215.



Similar but steeper relationships are identified between percentage of patients achieving virologic success versus inhibitory quotient (IQ) (Figure 2). A more pronounced relationship was identified for patients with baseline viral load >100,000 copies/mL compared to patients with <100,000 copies/mL (Figure 3).

As IQ depends on baseline phenotype IC_{50} that may not be readily available from typical clinical practice the relationship between trough rilpivirine concentration C_{0h} and baseline viral load was also evaluated (Figure 17). Similar to the $\log_{10}(IQ)$ results in Figure 3, a flatter exposure-response relationship was identified for percentage of patients achieving virologic success for patients with viral load <100,000 copies/mL (predicted percentage of patients achieving virologic success was 87% in the lowest exposure quartile compared to 94% in the highest exposure quartile; Table 15). By comparison, a more pronounced relationship was seen for patients with baseline viral load $\geq 100,000$ copies/mL (predicted percentage of patients achieving virologic success was 68% in the lowest exposure quartile compared to 88% in the highest exposure quartile; Table 15). The median predicted percentage of patients achieving virologic success for the two subpopulations was 91% and 82%, respectively. The estimated odds ratio for both subpopulations was 1.2 for a change in C_{0h} of 7.5 ng/mL, implying that increasing baseline viral load results in a “shift” of the rilpivirine exposure-response relationship. As such, patients with higher baseline viral load may require increased rilpivirine exposures to achieve virologic success rates similar to those patients with lower baseline viral loads.

Figure 17: Percentage of Patients Achieving Virologic Success (<50 Copies/mL) Versus Rilpivirine C_{0h} for Patients with Baseline Viral Load <100,000 (left) and ≥100,000 Copies/mL (right) from C209 and C215.

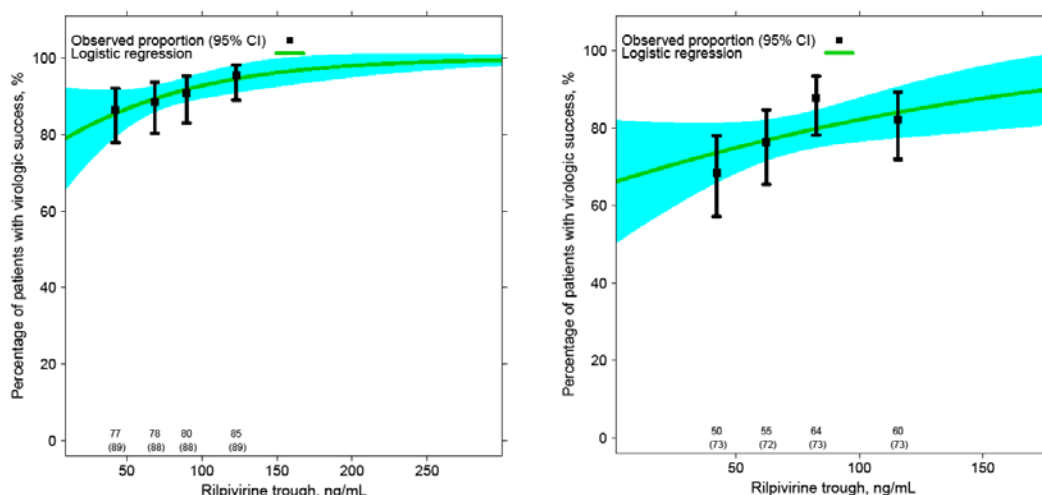


Table 15: Treatment-Naïve Subjects with Virologic Success by C_{0h} Quartile (Q1-Q4) (remove patients with adherence <90%)

	Baseline viral load <100,000 copies/mL			Baseline viral load ≥100,000 copies/mL		
	n	Median C _{0h}	% subjects with virologic success	n	Median C _{0h}	% subjects with virologic success
Q1	89	43	87	73	42	68
Q2	88	69	89	72	62	76
Q3	88	90	91	73	83	88
Q4	89	123	96	73	116	82

For the previous analysis, non-successes included both those patients that discontinued treatment due to adverse events and those resulting in virologic failure. As this is a treatment naïve population, the relationship between exposure and virologic failure is of particular concern as resistance developed from virologic failures may reduce future treatment options in these patients. Figure 18 shows the exposure-response relationship between percentages of patients with virologic failure

Figure 18: Percentage of Patients With Virologic Failure Versus Rilpivirine C_{0h} for Patients with Baseline Viral Load <100,000 (left) and ≥100,000 Copies/mL (right) from C209 and C215.

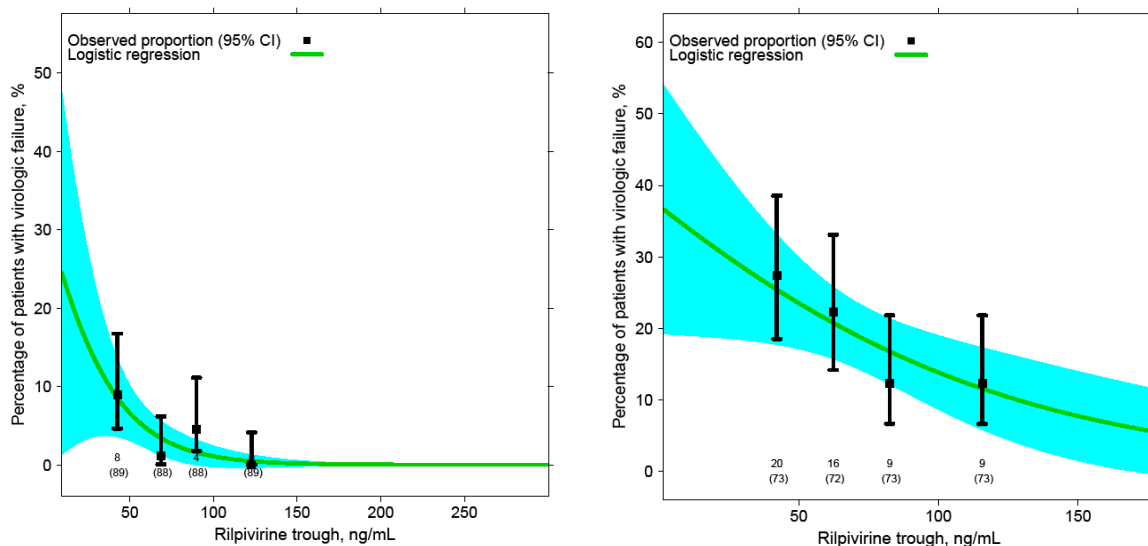


Table 16: Treatment-Naïve Subjects with Virologic Failure by C_{0h} Quartile (Q1-Q4) (remove patients with adherence <90%)

Baseline viral load <100,000 copies/mL				Baseline viral load ≥100,000 copies/mL		
	n	Median C _{0h}	% subjects with virologic success	n	Median C _{0h}	% subjects with virologic success
Q1	89	43	9	73	42	27
Q2	88	69	1	72	62	22
Q3	88	90	5	73	83	12
Q4	89	123	0	73	116	12

As with virologic success, significant relationships (p-value: <0.001 (<100,000 copies/mL) and 0.009 (>100,000 copies/mL) were identified between likelihood of virologic failure and rilpivirine trough concentrations. For baseline viral load <100,000 copies/mL 9% of patients had virologic failure in the lowest exposure quartile compared to 0% in the highest exposure quartile. Likewise, 27% of subjects in the lowest exposure quartile had virologic failure compared to 12% in the highest exposure quartile for baseline viral loads >100,000 copies/mL (Table 16). The median predicted percentage of patients with virologic failure was 3% and 18% for baseline viral loads <100,000 copies/mL and >100,000 copies/mL, respectively. The estimated odds ratio for baseline viral load <100,000 copies/mL was 0.70 compared to 0.9 for baseline viral load >100,000 copies/mL and reflects that a minimum failure rate may have been obtained in patients with low baseline viral load in the higher exposure quartiles.

4.4.5 Impact of Rilpivirine on Renal Function

Rilpivirine impact on renal function based upon on treatment changes in CrCL was described in detail under Section 1.1.2. Analyses indicate that the impact of CrCL was more pronounced in those patients with higher baseline CrCL and that those Phase III patients with baseline moderate renal function experienced the smallest changes from baseline with the addition of rilpivirine. In addition, patients returned to baseline CrCL and serum creatinine 2-4 weeks after cessation of rilpivirine treatment. Finally, a subset analysis of patients administered trimethoprim at baseline (also a inhibitor of tubular secretion of creatinine) support the mechanism proposed by the sponsor that rilpivirine potentially inhibits tubular secretion of creatinine.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
AUC_vs_dose.R AUC_vs_dose_day1.R AUC_vs_dose_day14.R	AUC calculations for evaluating dose proportionality	\Reviews\Ongoing PM Reviews\Rilpivirine_NDA202022_JAF\ER Analyses
Combine_PP_files.R	Combine population PK parameter files for analysis	Reviews\Ongoing PM Reviews\Rilpivirine_NDA202022_JAF\ER Analyses
Combine_AE_files.R	Combine adverse events for assessment of ER relationships	\Reviews\Ongoing PM Reviews\Rilpivirine_NDA202022_JAF\ER Analyses
Plots_MidCycle.R	Figures and plots for the mid-cycle	\Reviews\Ongoing PM Reviews\Rilpivirine_NDA202022_JAF\ER Analyses
functionsR.R	Generic function list that I've written to aid in analyses	\Reviews\Ongoing PM Reviews\Rilpivirine_NDA202022_JAF\ER Analyses
popPKRun1.R	Population PK tool file for generating plots and tables	\Reviews\Ongoing PM Reviews\Rilpivirine_NDA202022_JAF\PPK Analyses\Model\Run1
Fold_Change_Virology.R	Classification and Regression Tree code for Virology Fold-change and baseline viral load	\Reviews\Ongoing PM Reviews\Rilpivirine_NDA202022_JAF\ER Analyses
Plots_FinalPMReview.R	Figures and plots for the final PM review	\Reviews\Ongoing PM Reviews\Rilpivirine_NDA202022_JAF\ER Analyses
Creatinine_TimeCourse.R	Combine labs datasets for assessing serum creatinine and CrCL time course for Phase III patients	\Reviews\Ongoing PM Reviews\Rilpivirine_NDA202022_JAF\ER Analyses
Combine_Datasets_CM.R	Combine conmeds datasets for rilpivirine mechanism of action on tubular secretion assessment	\Reviews\Ongoing PM Reviews\Rilpivirine_NDA202022_JAF\ER Analyses

6 APPENDICES

6.1 Differences in the Full Phase 3 Analysis Data Set and Exposure-Response Analysis Data Set

A total of 686 patients received rilpivirine during the Phase III trials. Of these patients, 679 patients had PK samples available for determining rilpivirine exposures from the developed population pharmacokinetic model. The exposure response analysis conducted by the reviewer could not include these patients as exposure data was not collected from these patients.

Of those 7 patients without PK samples, 4 patients were from C209 and 3 were from C215. Baseline viral load for these patients included 1 patient <100,000 copies/mL, 4 patients between 100,000-500,000 copies/mL, and 2 patients >500,000 copies/mL. None of these patients achieved virologic success, and 4 of these patients were classified as virologic failures (2 with baseline viral load 100,000-500,000 copies/mL and 2 with baseline viral load >500,000 copies/mL). As all of these patients did not achieve virologic success and as a disproportionate number were also virologic failures (4/7), the total numbers for virologic success and virologic failure on rilpivirine presented in analyses in this review are slightly higher and lower, respectively, than are presented in the label. The overall virologic success and failure rates from C209 and C215 combined are shown in Table 17 and Table 18. Patients are grouped according to baseline viral load, and the results for the active comparator (efavirenz) are included to illustrate performance of a comparator drug across baseline viral load. While the overall success rate of rilpivirine and efavirenz were similar for patients with baseline viral load >100,000 copies/mL, it is observed that the rate at which virologic success declines is greater for rilpivirine. More importantly, it is essential to evaluate whether non-successes are due to adverse events or virologic failure, the latter of which is of primary concern in treatment naïve patients. Indeed, it is observed that overall failure rates and the rate of increase in failure rate is greater for rilpivirine compared to efavirenz for patients with baseline viral load >100,000 copies/mL.

Table 17: Treatment-Naïve Virologic Success by Baseline Viral Load and Treatment Arm from C209 and C215		
HIV-1 RNA < 50 copies/mL (copies/mL)	Rilpivirine	Efavirenz
All	83%	80%
≤ 100,000	89%	83%
> 100,000 to ≤ 500,000	78%	78%
> 500,000	65%	73%

Table 18: Treatment-Naïve Virologic Failures by Baseline Viral Load and Treatment Arm from C209 and C215

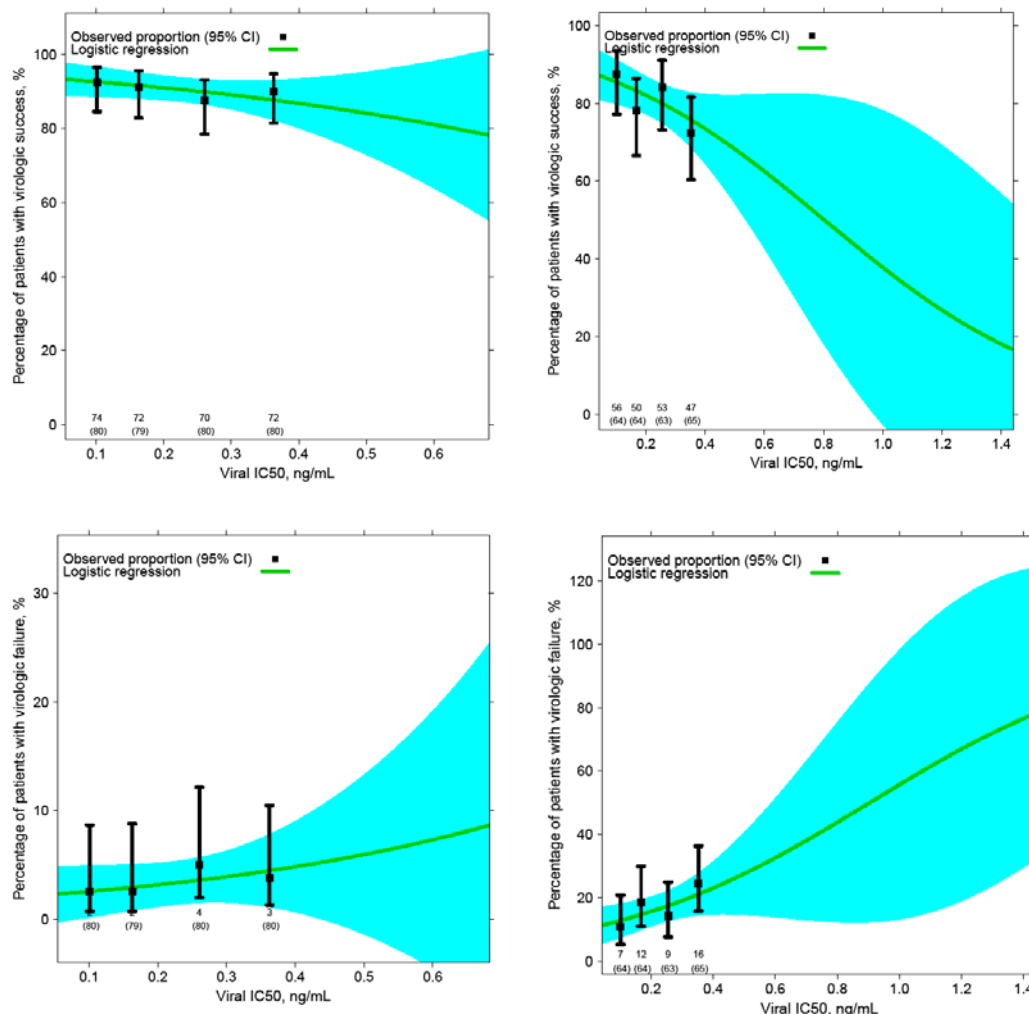
Virologic failure (copies/mL)	Rilpivirine	Efavirenz
≤ 100,000	5%	5%
> 100,000 to ≤ 500,000	20%	11%
> 500,000	29%	17%

6.2 IC₅₀ Analysis

The relationship between baseline HIV-1 IC₅₀ to rilpivirine and virologic success/failure was investigated similarly to the inhibitory quotient and rilpivirine trough concentration analyses presented previously in the review. This analysis provides evidence that trough concentration is a better predictor of virologic success/failure (combination of trough and IC₅₀ as inhibitory quotient, of course, provides additional information and is a better predictor of both outcomes).

Figure 20 shows the exposure-response relationship for patients with baseline viral load <100,000 copies/mL (left) and >100,000 copies/mL (right). Both populations had similar median (0.22 versus 0.21 ng/mL) and upper quartile (0.30 versus 0.30 ng/mL) IC₅₀, however, the virologic success and failure rate decrease and increase, respectively, in the highest quartile for patients with baseline viral load >100,000 copies/mL. Also, only the subgroup with baseline viral load >100,000 copies/mL had significant relationships between virologic success/failure and IC₅₀. As the IC₅₀ between the two populations are similar, this suggests that another factor (i.e. exposure) is the driving factor behind lower responses in patients with baseline viral loads >100,000 copies/mL.

Figure 19: Percentage of Patients Achieving Virologic Success (<50 Copies/mL) (top) or Virologic Failure (bottom) Versus IC₅₀ for Patients with Baseline Viral Load <100,000 (left) and ≥100,000 Copies/mL (right) from the Phase 3 (C209 and C215) trials.



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6.3 Full Patient Analysis (Include All Patients Regardless of Adherence)

All previous exposure-response analyses subset those patients with self-reported adherence <90% to minimize confounding factors in the inhibitory quotient, rilpivirine trough, and IC₅₀ analyses. However, it can be argued, particularly for the rilpivirine exposure analysis that inclusion of patients with low adherence provides additional information on response rates at lower exposures that should be included for understanding how responses rates may drop off in lowest exposure quartiles. The analyses were repeated, this time using the entire population with baseline HIV-1 rilpivirine IC₅₀ and rilpivirine trough concentrations available. Results for rilpivirine trough, log-transformed inhibitory quotient, and IC₅₀ are shown below. Similar trends were observed for all independent variables (Figure 20 and Figure 21), however, the odds ratio for rilpivirine trough exposure were slightly lower (0.85 compared to 0.90 for NDA 202202 Rilpivirine (TMC278)

baseline viral load >100,000 copies/mL and 0.67 compare to 0.70 for baseline load <100,000 copies/mL).

Figure 20: Percentage of Patients Achieving Virologic Success (<50 Copies/mL) Versus Rilpivirine Trough (top), $\log_{10}(\text{IQ})$ (middle), and IC_{50} (bottom) for Patients with Baseline Viral Load <100,000 (left) and $\geq 100,000$ Copies/mL (right) from the Phase 3 (C209 and C215) trials.

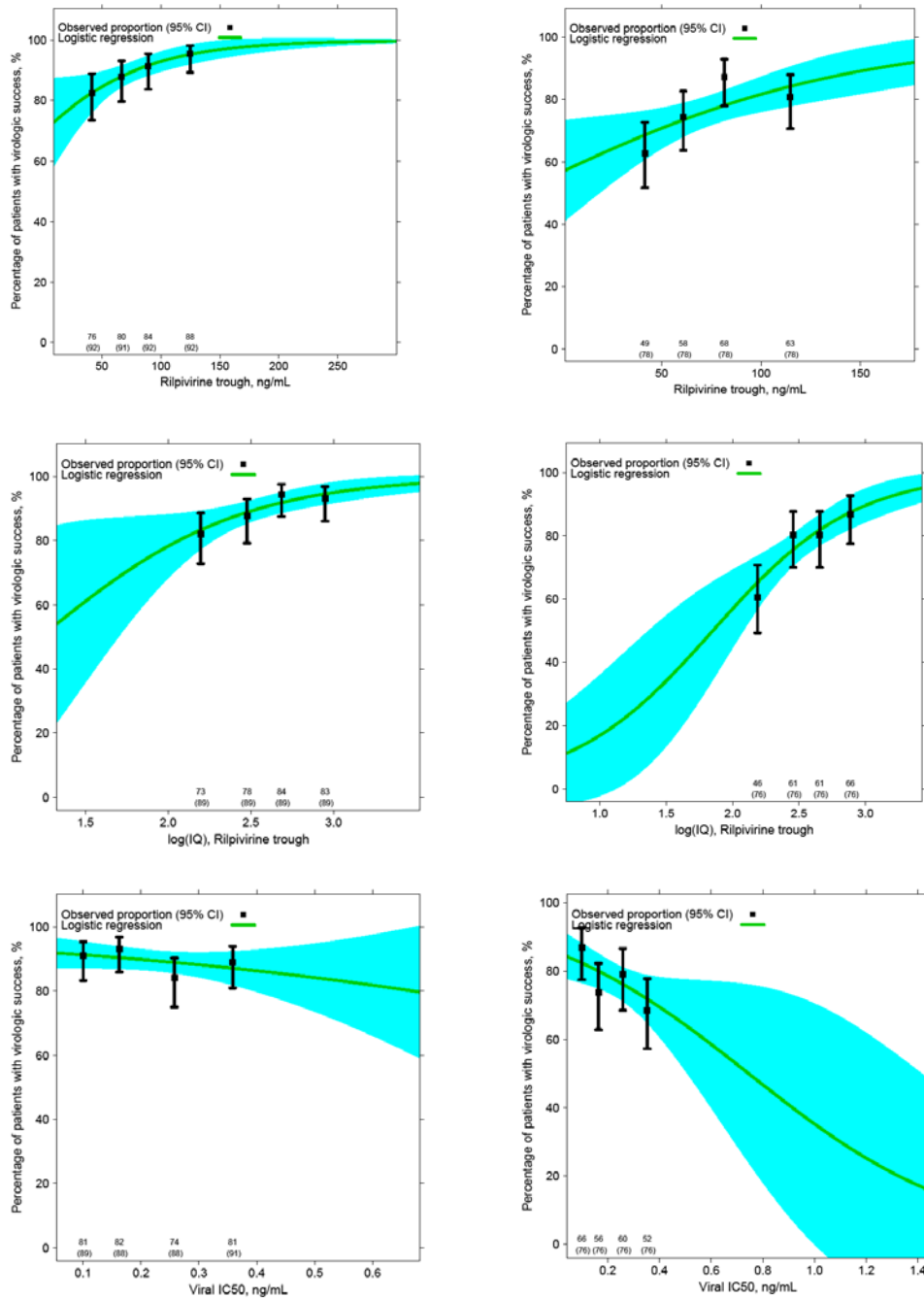
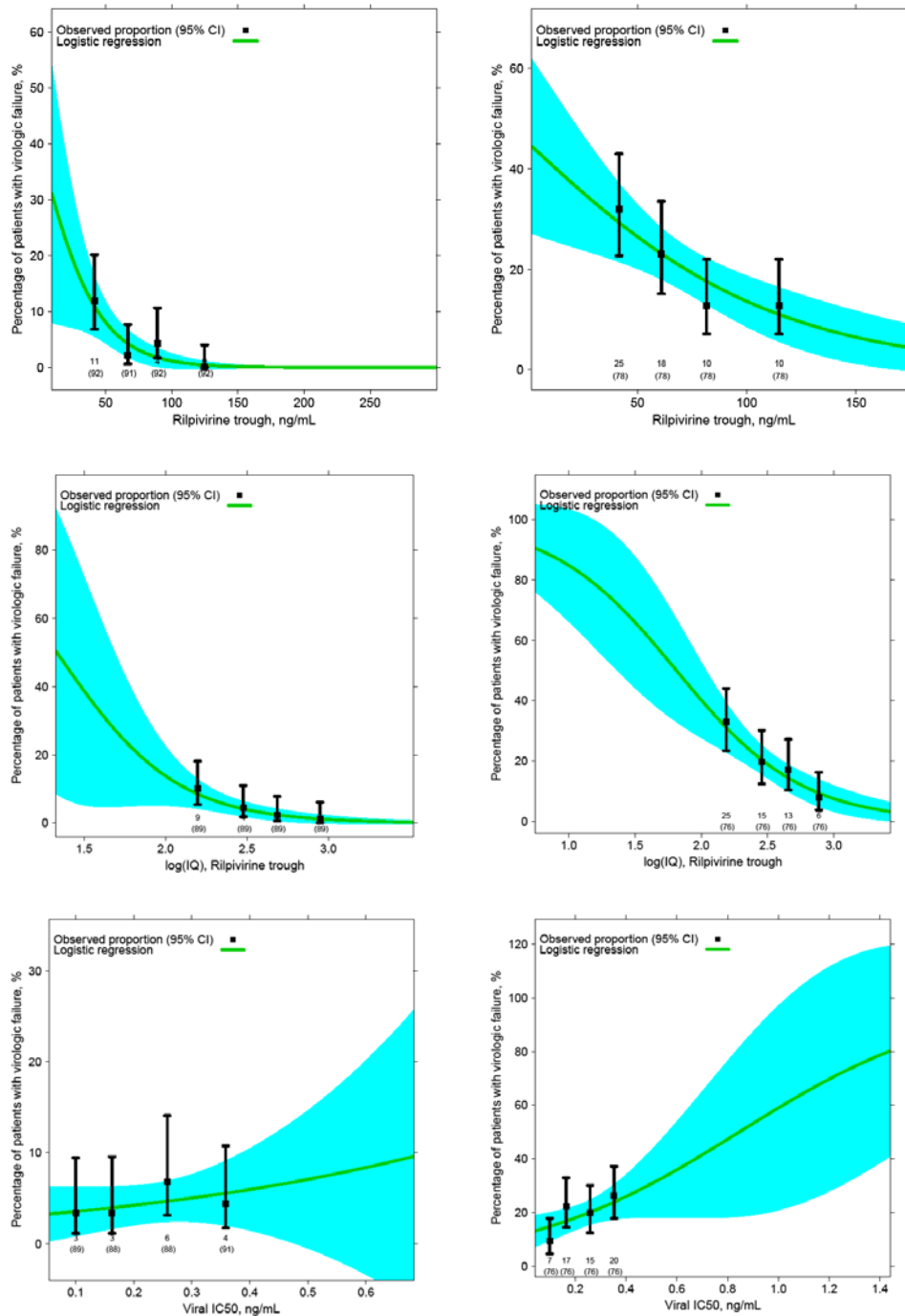


Figure 21: Percentage of Patients with Virologic Failure Versus Rilpivirine Trough (top), \log_{10} (IQ) (middle), and IC_{50} (bottom) for Patients with Baseline Viral Load <100,000 (left) and $\geq 100,000$ Copies/mL (right) from the Phase 3 (C209 and C215) trials.

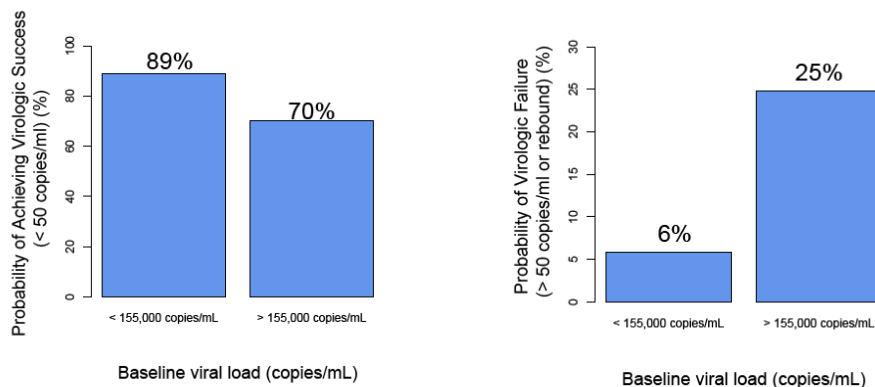


6.4 Classification and Regression Tree Analysis for Baseline Viral Load and Rilpivirine Fold-Change

The sponsor stratified patients within C209 and C215 based on baseline viral loads of <100,000 copies/mL, 100,000–500,000 copies/mL, and >500,000 copies/mL. Based on these stratifications, virologic success/failure analyses were performed to support labeling recommendations cautioning against the use of rilpivirine in patients with baseline viral load >100,000 copies/mL. However, a secondary analysis was performed to determine if 100,000 copies/mL was an accurate representation of the inflection point separating virologic successes from non-successes (and failures from non-failures).

This classification and regression tree analysis was limited to Phase III patients from C209 and C215 treated with rilpivirine 25 mg q.d. (n=675; excludes those missing PK and 4 additional patients with missing baseline viral load data). The analysis was performed in R using the *tree* function from the *tree* library with minimum cut sizes of 10% of the population. Median baseline viral load was 90,000 copies/mL with 25th and 75th percentiles at 34,300 copies/mL and 215,000 copies/mL, respectively. A cut point at 155,000 copies/mL was selected as the baseline viral load associated with the greatest change between groups for virologic success and virologic failure. Based on this cut point, 89% (398/446) of patients with baseline viral load <155,000 copies/mL achieved virologic success while 72% (164/229) of patients with baseline viral load >155,000 copies/mL. Similarly, 6% (25/446) of patients with baseline viral load <155,000 copies/mL had virologic failure compared to 24% (55/229) of patients with baseline viral load >155,000 copies/mL. The identified baseline viral load cut point supports including cautionary language of an increased incidence of virologic failure in the rilpivirine label for patients with baseline viral load >100,000 copies/mL.

Figure 22: Classification Tree Analysis of Virologic Success (left) and Virologic Failure (right) Based on Baseline Viral Load from C209 and C215.

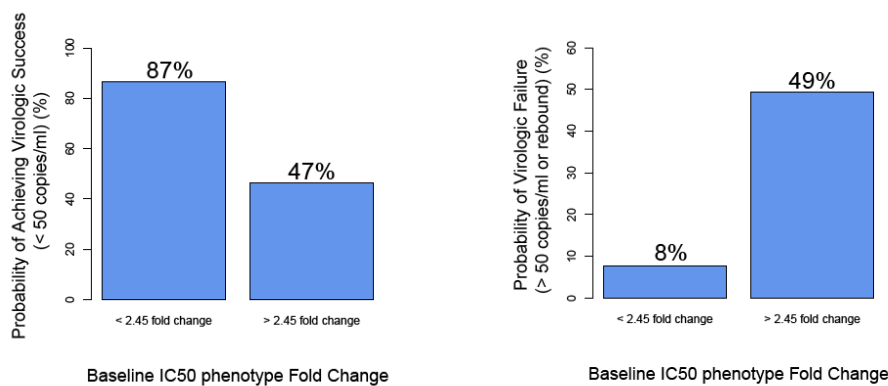


A similar analysis was performed to determine the rilpivirine fold-change over baseline phenotype associated with the development of resistance. For patients achieving virologic success, fold-change from baseline was used in the analysis (assume that fold-change in these patients did not change as no additional information is available NDA 202202 Rilpivirine (TMC278)

regarding the phenotype). In all other patients, last known fold-change in the patients (discontinued due to adverse event) or fold-change at the time of virologic failure was used for assessing the impact of fold-change on virologic success/failure. Median fold-change for this analysis data set was 1.1 with a 25th and 75th percentile of 0.7 and 1.7, respectively. A total of 670 patients were available with baseline fold-change values for rilpivirine.

Based on this analysis, a 2.45 fold-change was associated with the greatest separation between virologic success and virologic failure. 87% (519/599) of patients with lower fold-change achieved virologic success while only 46% (33/71) of patients with higher fold-changed achieved virologic success. Likewise, 8% (47/599) and 49% (35/71) of patients with fold-change < 2.45 and >2.45, respectively, had virologic failure. This identified fold-change agrees with the value identified by Dr. Naeger's analysis as indicative of increased failure rates when treated with rilpivirine.

Figure 23: Classification Tree Analysis of Virologic Success (left) and Virologic Failure (right) Based on Rilpivirine Fold-Change from C209 and C215.



***Physiologically-based pharmacokinetic modeling (PBPK) and
Simulation Memo***

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Reviewed by Shiew Mei Huang, Ph.D., Deputy Director, Office of Clinical
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Drug Name: rilpivirine (TMC278)

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1. Recommendations

NA.

2. Objectives

This memo presents the use of physiologically-based pharmacokinetic (PBPK) modeling and simulations in supporting the clinical pharmacology review of rilpivirine (TMC278).

3. Background

Rilpivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of HIV infection. Elimination of rilpivirine is predominantly via liver metabolism. *In vitro* metabolism and *in vivo* mass balance studies indicate significant contribution of CYP3A4 to the metabolism of rilpivirine (>50%). *In vitro*, rilpivirine is a CYP3A inhibitor (study NC194) and a CYP3A inducer (study NC186). According to study NC194, the IC₅₀ toward CYP3A4 (using a probe CYP3A substrate sildenafil) in human liver microsomes was 0.47 µg/mL. Assuming competitive inhibition mechanism, a K_i value of 0.23 (0.47/2) µg/mL can be calculated [1]. The maximum plasma concentration (I) of rilpivirine after multiple dosing is approximately 0.2 µg/mL. Based on FDA draft guidance for industry on drug-drug interaction studies [2;3], the I/K_i is around 1 (10-fold of the cut-off value of 0.1), and rilpivirine is likely a CYP3A inhibitor *in vivo*. According to study NC186 evaluating the CYP induction effect by rilpivirine *in vitro*, CYP3A4 activity (using a CYP3A substrate testosterone) was not increased in cryopreserved human hepatocytes incubated with rilpivirine. However the mRNA level of CYP3A4 increased by 27-fold at 2.5 µM rilpivirine (as compared to a 55-fold increase by 50 µM rifampin as a positive control). It appears that the activity data may be confounded by concurrent inhibition effect by rilpivirine.

Several *in vivo* drug-drug interaction studies were conducted with either 75 or 150 mg daily doses of rilpivirine (NDA 202022-2.7.2 Summary of Clinical Pharmacology Studies). The drug-drug interaction potential of rilpivirine as a substrate of CYP3A4 and

an inhibitor or an inducer of CYP3A4 at the therapeutic dose of rilpivirine (25 mg once daily) has not been evaluated in humans.

In vivo human inhibition studies with strong CYP3A/P-gp inhibitors confirmed that rilpivirine is significantly eliminated by CYP3A. The effect of ketoconazole (400 mg once daily) and the effect of HIV protease inhibitors darunavir/ritonavir (800 mg/100 mg once daily) on the steady state pharmacokinetics of rilpivirine (150 mg once daily) were evaluated in study TMC278-C127 and study TMC278-C112, respectively. The least square mean AUC ratios were 1.5 and 2.3 by ketoconazole and darunavir/ritonavir, respectively.

The *in vivo* effect of rilpivirine as either an inhibitor or an inducer of CYP3A appears inconclusive. Multiple dosing of rilpivirine 150 mg once daily resulted in a 24% decrease in ketoconazole exposure (Study TMC278-C127, Table 1). In a study with a sensitive CYP3A substrate sildenafil, rilpivirine 75 mg given once daily had no effect on sildenafil exposure (Study TMC278-C123, Table 2). Because rilpivirine inhibits sildenafil metabolism *in vitro* (study TMC278-NC194), and induces CYP3A in hepatocytes (study TMC278-NC186), it can be hypothesized that both inhibition and induction of CYP3A may have happened simultaneously after multiple dosing of rilpivirine at 75 or 150 mg once daily, resulting in a net null effect on the pharmacokinetics of sildenafil, a sensitive CYP3A substrate, and an apparent induction of CYP-mediated metabolism of ketoconazole, a potential substrate of multiple CYPs including CYP3A.

Table 1. Summary of pharmacokinetic drug-drug interactions between rilpivirine and ketoconazole (Study TMC278-C127)

	Least Square Mean AUC Ratios	
Rilpivirine	Day 22 (B)/Day 11 (A) ^[a]	1.49
Ketoconazole	Day 22 (B)/Day 11 (B) ^[a]	0.76
^[a] Two-way crossover design. Treatment A: Rilpivirine 150 mg once daily for 11 days; and Treatment B: ketoconazole 400 mg once daily for 22 days + rilpivirine 150 mg once daily from days12 to 22. Washout period: at least 14 days.		

Table 2. Effect of 75 mg rilpivirine once daily on pharmacokinetics of single oral dose of sildenafil (50 mg) (Trial C123)

	Least Square Mean AUC Ratio	
Sildenafil	Day 12 (B)/Day 1 (A) ^[a]	0.97
^[a] Two-way crossover design. Treatment A: sildenafil 50 mg single dose; and Treatment B: TMC278 75 mg once daily for 12 days and sildenafil 50 mg single dose on the twelfth day. Washout period: at least 14 days.		

Because rilpivirine is predominantly eliminated via hepatic metabolism, its pharmacokinetics is likely to be altered in subjects with hepatic impairment. In study TMC278-TiDP6-C130, the sponsor evaluated the pharmacokinetics of rilpivirine in subjects with mild (Child-Pugh score, CP-A) or moderate (CP-B) hepatic impairment. Study subjects received 25 mg rilpivirine once daily. Single-dose and steady state pharmacokinetics of rilpivirine in hepatic impaired subjects (CP-A and CP-B subjects) were compared to those for healthy subjects. Table 3 summarizes the AUC ratios between subjects with hepatic impairment and subjects with normal hepatic function. Rilpivirine pharmacokinetics appeared to be influenced to a greater extent by mild hepatic impairment than by moderate hepatic impairment (e.g., the steady state AUC ratios are 1.5 and 1.1 by mild and moderate hepatic impairment, respectively). Rilpivirine has a low oral clearance (CL_{po} , ~5-6 L/h) and is highly bound to plasma proteins (unbound fraction <1%). According to Equation 1 [4;5], a drug's oral clearance is influenced by both its unbound fraction in plasma (f_p) and its organ intrinsic clearance (CL_{int}):

$$CL_{po} = f_p \times CL_{int} \quad \text{Equation 1}$$

Therefore, when f_p is simultaneously affected by hepatic impairment (as it could in this case for a highly bound drug), CL_{po} may not decrease proportionally with CL_{int} [5]. Often, an increase in f_p by hepatic impairment is expected especially for highly bound drugs because of decreased levels of binding proteins in the plasma and/or altered binding affinity for the investigational drugs [5]. Consequently, increase in f_p may

compensate for the decrease in CL_{int} , resulting in a lesser extent of decrease in CL_{po} , as compared to that for CL_{int} . The AUC ratios calculated without consideration of protein binding may partially explain the unchanged total rilpivirine exposure in subjects with moderate hepatic impairment. However, as the protein binding data were not available from the study report of TMC278-C130, ratios of unbound AUC adjusting f_p changes by hepatic impairment can not be estimated.

Table 3. Effect mild and moderate hepatic impairment on single and steady state pharmacokinetics of rilpivirine (25 mg once daily) (Study TMC278-C130)

	Least square mean AUC ratio	
	Mild (CP-A)	Moderate (CP-B)
Single dose: $AUC_{0-24, D1}$	1.2	0.8
Steady State: $AUC_{0-24, D11}$	1.5	1.1

In this study, PBPK modeling and simulation was conducted to (1) predict the effect of ketoconazole on the exposure of rilpivirine when rilpivirine is administered at the planned therapeutic dose of 25 mg once daily and (2) predict the effect of hepatic impairment on the exposure of rilpivirine in mild and moderate hepatic impairment considering the effect of protein binding (f_p) changes in hepatic impairment.

4. **Results: Question-based review**

4.1. Based on observed drug-drug interaction between rilpivirine at high doses (150 mg once daily) and ketoconazole (400 mg once daily), what is the exposure change of rilpivirine by ketoconazole at low dose rilpivirine (25 mg once daily)?

The effect of ketoconazole at various dosing regimens (300 mg once daily, 400 mg once daily, 200 mg twice daily) on the pharmacokinetics of rilpivirine was simulated using PBPK model (Table 4). First, due to the lack of information on ketoconazole elimination, the PBPK model did not consider the induction of ketoconazole metabolism by rilpivirine in a dynamic manner. Instead, the model used 300 mg once daily to achieve a ketoconazole exposure similar to that obtained using 400 mg ketoconazole once daily in the presence of rilpivirine, a condition showing a 24% reduction in ketoconazole exposure. Second, because rilpivirine has a relatively long half-life and a presumably near complete bioavailability in the gut and liver during drug absorption (low oral clearance), simulation was conducted using 200 mg ketoconazole twice daily to evaluate the effect of sustained inhibition after more frequent dosing of ketoconazole, whose half-life is short [6]. Scenario A simulates the effect of 300 mg ketoconazole once daily on the steady state pharmacokinetics of rilpivirine (150 mg once daily). The simulated rilpivirine C_{max} and AUC ratios are 1.53 and 1.64, respectively. These values are comparable to those observed in a clinical study when 400 mg of ketoconazole was used (Study TMC278-C127, rilpivirine least mean square ratios of 1.30 and 1.49 for C_{max} and AUC, respectively). Scenarios B and C were intended to study the effect of ketoconazole at 300 or 400 mg once daily on rilpivirine exposure at a lower, 25 mg once daily dose, which has not been tested in clinical drug-drug interaction studies. For scenario B, 300 mg ketoconazole once daily was used by assuming the same effect of rilpivirine on ketoconazole exposure (24% reduction after 400 mg once daily due to enzyme induction) with 25 mg rilpivirine once daily. For scenario C, no induction effect with 25 mg once daily of rilpivirine is assumed. The simulated exposure changes appear similar as the exposure changes of scenarios A and B. In addition, the effect of more sustained inhibition of CYP3A using 200 mg twice daily ketoconazole was evaluated in

Scenario D, assuming no induction of CYP3A by rilpivirine. In Scenario D, 50% greater exposure changes of rilpivirine by co-administration of ketoconazole were simulated (1.91 and 2.17 for C_{max} and AUC ratios, Table 4). The greater inhibition effect under Scenario D is consistent with a long half-life of rilpivirine, which requires more frequent dosing of ketoconazole [6].

Table 4. Evaluation of the effect of various dosing regiments of ketoconazole on rilpivirine exposure using PBPK modeling and simulation

	Scenarios	Assumptions	Rilpivirine Day 12-22	Ketoconazole Day 1-22	Rilpivirine C _{max} Ratio (Day 22/Day 11)	Rilpivirine AUC ratio (Day 22/Day 11)
Observed			150 mg once daily	400 mg once daily	1.30	1.49
Simulated	A		150 mg once daily	300 mg once daily	1.53	1.64
	B	Similar induction of ketoconazole metabolism by 25 mg and 150 mg of rilpivirine	25 mg once daily	300 mg once daily	1.52	1.63
	C	No induction of ketoconazole metabolism by 25 mg of rilpivirine	25 mg once daily	400 mg once daily	1.56	1.69

	D	No induction of ketoconazole metabolism by 25 mg of rilpivirine; Ketoconazole provides sustained inhibition on the systemic clearance of rilpivirine [6]	25 mg once daily	200 mg twice daily	1.91	2.17
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4.2. To what extent the change in the unbound fraction of rilpivirine by hepatic impairment contribute to the observed total exposure change in rilpivirine?

When the protein binding effect (f_p) by hepatic impairment was not considered in the PBPK model, the model over-predicted the exposure change of total (free plus protein-bound) rilpivirine in subjects with mild and moderate hepatic impairment (AUC ratios of 1.41 and 1.69 on day 1, and 1.81 and 2.51 on day 11, respectively, as compared with the observed values of 1.2 and 0.8 on day 1, and 1.5 and 1.1 on day 11, respectively. Table 5). When protein binding changes in hepatic impairment was considered by assuming a 2-fold increase in f_p , the modified PBPK model made a better prediction for subjects with moderate hepatic impairment (Table 5, simulated versus observed AUC ratios were 0.99 versus 0.8 on day 1 and 1.06 versus 1.1 on day 11, respectively).

The simulations demonstrate the sensitivity of the model toward unbound fraction change potentially caused by hepatic impairment and indicate the hypothesis that increased f_p by hepatic impairment may contribute to the observed pharmacokinetic alteration of rilpivirine in subjects with moderate hepatic impairment. However, predictions of rilpivirine in subjects with mild hepatic impairment using both the initial model and the modified model (with a 2-fold increase in f_p) were not satisfactory. The initial model with unchanged f_p predicted a slightly higher AUC ratio of rilpivirine (Table 5, simulated versus observed AUC ratios were 1.41 versus 1.2 on day 1 and 1.81 versus 1.5 on day 11,

respectively); whereas the model with 2-fold increase in f_p resulted in a lower AUC ratio (Table 5, simulated versus observed AUC ratios were 0.82 versus 1.2 on day 1 and 0.78 versus 1.5 on day 11, respectively). It is possible that the increase in f_p of rilpivirine depends on the degree of hepatic impairment. A smaller increase in f_p by mild hepatic impairment is expected to compensate for the decreases in CL_{int} to result in the observed rilpivirine AUC change in subjects with mild hepatic impairment.

Besides the possible decrease in f_p , a decrease in drug absorption, which has been suggested for subjects with hepatic impairment [5], may also have contributed to the apparently unchanged total exposure of rilpivirine in subjects with moderate hepatic impairment in this study.

Table 5: Evaluation of the effect of hepatic impairment on total rilpivirine exposure using PBPK modeling and simulation

	Mild (CP-A)			Moderate (CP-B)		
	Observed [a]	Simulation [b] (f_p unchanged)	Simulation [b] (f_p increased by 2- fold) [c]	Observed [a]	Simulation [b] (f_p unchanged)	Simulation [b] (f_p increased by 2- fold) [c]
Day 1 (AUC _{0-24h} , D1)	1.2	1.41	0.82	0.8	1.69	0.99
Day 11 (Steady State AUC _{0-24h})	1.5	1.81	0.78	1.1	2.51	1.06
<p>[a] Least square mean AUC ratios (Study TMC278-C130)</p> <p>[b] Simulation using healthy volunteers, mild and moderate hepatic impairment population built in PBPK software (Appendix)</p> <p>[c] Assuming f_p of rilpivirine increased by 2-fold by mild and moderate hepatic impairment</p>						

In summary, a PBPK model of rilpivirine was developed using *in vitro* and *in vivo* drug disposition data from the NDA submission. After the model was qualified further with *in*

vivo drug-drug interaction between ketoconazole and rilpivirine at a higher rilpivirine dosage regimen (150 mg daily), it was used to predict the effect of ketoconazole on rilpivirine at its therapeutics dose of 25 mg once daily, which was not evaluated in clinical drug-drug inhibition studies. Based on the simulations, minimal CYP3A induction and inhibition at the rilpivirine 25 mg once daily dosing are anticipated. Therefore, rilpivirine 25 mg once daily is not expected to significantly decrease ketoconazole exposure. The simulations further predict a stronger effect of ketoconazole 200 mg twice daily on rilpivirine exposure. Finally, a modified PBPK model of rilpivirine with increased f_p was able to simulate the change in total exposure of rilpivirine in subjects with moderate hepatic impairment, and indicated that a lesser degree of increase in f_p by mild hepatic impairment may result in the apparent higher degree of change in the total exposure of rilpivirine in subjects with mild hepatic impairment than the moderate hepatic impairment.

5. **Appendix – PBPK Modeling Building and Simulations**

Abbreviations: ADME: absorption, distribution, metabolism, and excretion; B/P: blood to plasma ratio; CL: clearance; CL_{int} : intrinsic clearance; F, bioavailability; f_a : fraction absorbed; f_p : fraction unbound in plasma; $f_{u,mic}$: fraction unbound in microsomes; $f_{u,gut}$: apparent unbound fraction in enterocytes; Ind_{slope} : linear slope between inducer concentration and the extend of enzyme induction; K_a : first order absorption rate constant; K_i : reversible inhibition constant; LogP: logarithm of the octanol-water partition coefficient; P_{app} : apparent passive permeability; V_{ss} : volume of distribution.

A PBPK model of rilpivirine was developed using SimCYP® software (Version 10.10, SimCYP Ltd, Sheffield, UK). Drug dependent parameters of rilpivirine are summarized in Appendix Table 1, along with assumptions and source data for model building. Model building and simulations were conducted in a virtual healthy volunteer population with system-dependent parameters (such as organ blood flow, tissue content, enzyme abundance, renal functions, and demographic distribution) that is built in the PBPK software [7;8]. For the simulation of drug interaction with ketoconazole, the drug-model for ketoconazole in the compound library of the software was utilized. For the simulation of drug interaction with sildenafil, the drug model for sildenafil in the compound library of the software was used with minor modifications:

(http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022473s000_ClinPharmR.pdf). Simulations were conducted according to the trial design of the *in vivo* pharmacokinetic and drug-drug interaction trials using population representative approach.

Appendix Table 1. Drug-dependent parameters of rilpivirine for PBPK modeling and simulations

Parameter (Unit)	Value	comments
Mol Weight (g/mol)	366.4	
log P	4.32	ADMET Predictor ^a
Compound Type	Monoprotic Base	ADMET Predictor ^a
pKa 1	3.26	ADMET Predictor ^a
B/P	0.67	Sponsor Study NC112
f _p	0.003	Sponsor Study NC112
f _a	0.88	Predicted from Caco-2 data (see below)
K _a (1/h)	0.3	Input based on compartmental analysis
f _{u,gut}	0.003	Assumed and tested to be plausible
P _{app} Caco-2(10 ⁻⁶ cm/s)	12	Steady state measurement using Caco-2 cells (Sponsor report NC104)
V _{ss} (L/kg)	2.532	Predicted using full PBPK model ^b
Elimination		
CYP3A4 intrinsic clearance (uL/min/pmol)	2.04	From in vivo data ^c . Assuming 75% CYP3A4 (Sponsor Report C119 and NC141)
Non-CYP intrinsic clearance (ul/min/mg microsomes)	93.2	From in vivo data ^c . Assuming 25% non-CYP (Sponsor Report C119 and NC141)
K _i of CYP3A4 (μM)	0.700	IC ₅₀ is 1.4 μM (Sponsor Report NC194).

		Assuming competitive inhibition and using calculated $f_{u,mic}$ of 0.542
$f_{u,mic}$	0.542	Predicted by the software
Ind _{Slope} (1/ μ M)	63.6	Parameter estimation ^d

^a : ADMET Predictor (Simulations Plus Inc, Lancaster, CA, USA)

^b: Rowland YK, Jamei M, Yang J, Tucker GT, Rostami-Hodjegan A. Physiologically based mechanistic modelling to predict complex drug-drug interactions involving simultaneous competitive and time-dependent enzyme inhibition by parent compound and its metabolite in both liver and gut - the effect of diltiazem on the time-course of exposure to triazolam. *Eur.J.Pharm.Sci.* 2010; **39**: 298-309; Rodgers T. Tissue distribution of basic drugs: Accounting for enantiomeric, compound and regional differences amongst beta-blocking drugs in rat. 2005; and Rodgers T. Physiologically based pharmacokinetic modeling 1: Predicting the tissue distribution of moderate-to-strong bases. 2005.

^c: Hepatic intrinsic clearance (CL_{int}) at the level of enzyme was back-calculated from oral clearance values after oral administration of the using retro-grade calculator in SimCYP® (Single dose escalation studies, CDE101 and 103)

^d: Using parameter estimation function of SimCYP®. Data are the mean plasma concentration versus time from multiple dose, dose escalation study (CDE-102)

Several lines of evidence suggest the need to incorporate an enzyme induction mechanism in the PBPK model of rilpivirine. Overall, incorporation of CYP3A induction mechanism results in a pharmacokinetic profile comparable to those observed in subjects taking the drug for 14 days at 150 mg once daily, but appears to underestimate the maximum concentrations for rilpivirine solution at 25 mg once daily (Figure 1). The source of the rilpivirine pharmacokinetic data after oral solution and tablet were from the CDE-102 and TMC278-C103 trials, respectively. The auto-induction effect is minimal at 25 mg dose (Figure 1, upper panel), which becomes more apparent at 150 mg (Figure 1, lower panel). The model with linear CYP3A induction mechanism is further used to simulate a drug-drug interaction trial between rilpivirine and sildenafil (Appendix Table 2). Assuming no induction effect, a net increase (4%) in sildenafil AUC is predicted with coadministration of rilpivirine 75 mg once daily. Assuming concurrent induction and

inhibition, a net decrease (7%) in sildenafil AUC is predicted with coadministration of rilpivirine 75 mg once daily. These simulations suggest that a modest inhibition and a modest induction may happen simultaneously at doses higher than the therapeutic dose of rilpivirine (25 mg once daily). Appendix Table 2 also indicates a minimal effect for either inhibition or induction on CYP3A activity with rilpivirine using the sensitive CYP3A substrate sildenafil (25 mg once daily). The model incorporating CYP3A induction and inhibition effects was used for the simulation of the effect of ketoconazole on rilpivirine and the simulation of rilpivirine pharmacokinetics in subjects with hepatic impairment.

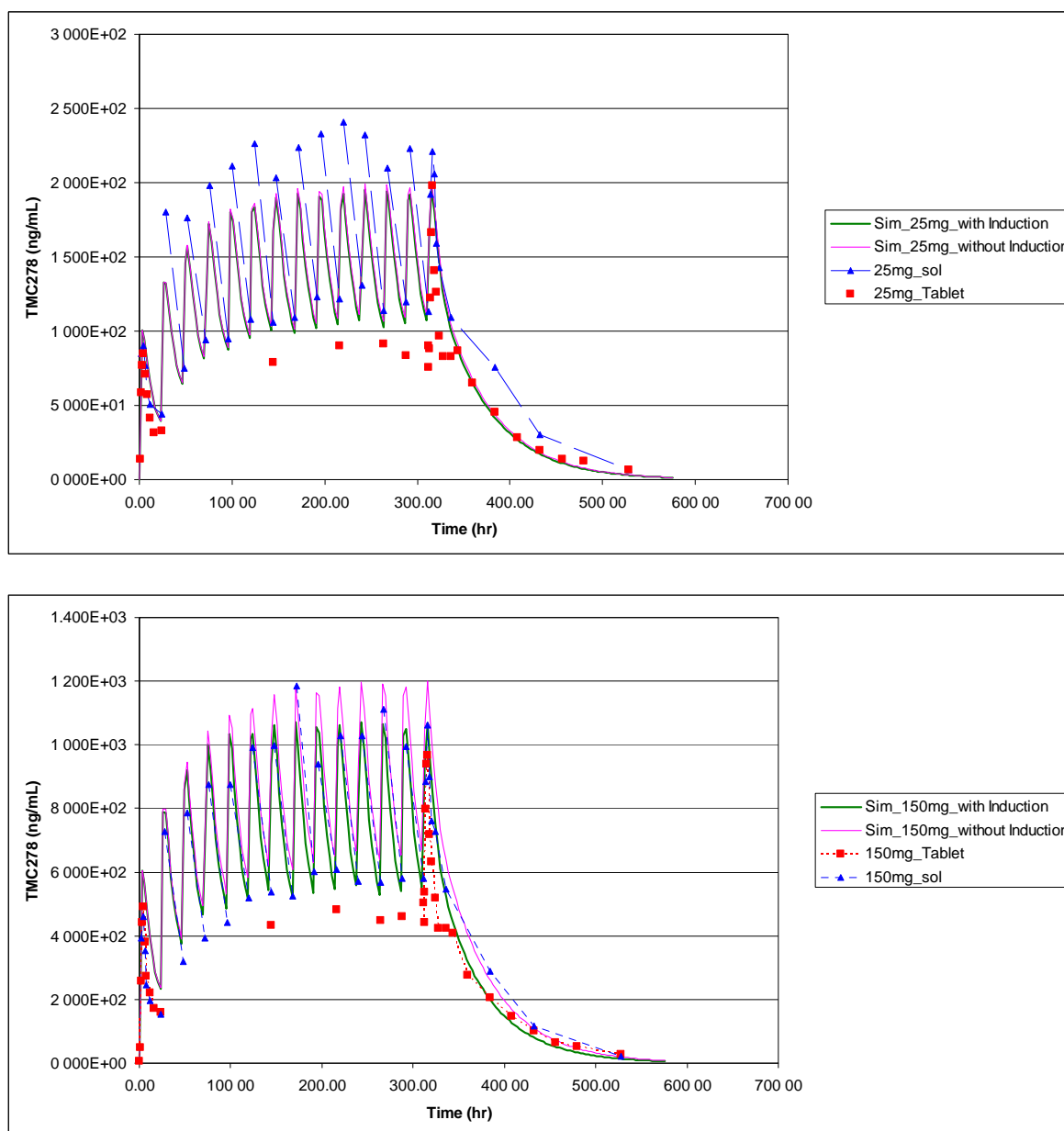
Appendix Table 2. Simulation of drug interaction study between sildenafil and rilpivirine.

		rilpivirine 12 days at 75 mg once daily	rilpivirine 12 days at 25 mg once daily
Simulated ^a	Assuming no CYP3A induction by rilpivirine (CYP 3A inhibition effects only)	1.04	1.02
	Assuming CYP3A induction by rilpivirine (CYP 3A inhibition and induction effects)	0.93	0.98
Observed ^b		0.97	Not determined
^a Mean AUC Ratio using population representative			
^b Least square mean ratio (Study C123)			

The drug model (Appendix Table 1) was used to simulate the pharmacokinetic changes of rilpivirine in mild and moderate hepatic impairment populations built in SimCYP®

(V10.1). The virtual populations incorporate the known physiological changes including enzyme expression in the liver and small intestine, organ blood flow, tissue composition, and levels of plasma proteins [9]. To evaluate the model sensitivity toward f_p , drug model was modified by doubling f_p (from 0.003 to 0.006) and simulations conducted in mild and moderate hepatic impairment populations. The study design follows those reported in study TMC278-C130 to obtain AUC_{0-24h} on day 1 and AUC_{0-24h} on day 11. All simulations used population representatives. The simulated mean AUC values using hepatic impairment populations were compared with those simulated using the healthy volunteer population (SimCYP®) to obtain AUC ratios for each study day.

Appendix **Figure 1.** Simulated plasma concentration versus time profiles of rilpivirine. Upper panel: 25 mg rilpivirine for 14 days, and lower panel: 150 mg rilpivirine for 14 days. Purple and green solid lines: assuming induction and no induction of CYP3A in the PBPK model. Blue and red dotted lines and symbols: observed data for solution and tablet formulations of rilpivirine, respectively.



Reference List

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7. Jamei M, Dickinson GL, Rostami-Hodjegan A. A framework for assessing inter-individual variability in pharmacokinetics using virtual human populations and integrating general knowledge of physical chemistry, biology, anatomy, physiology and genetics: A tale of 'bottom-up' vs 'top-down' recognition of covariates. *Drug Metab Pharmacokinet.* 2009; 24: 53-75.
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9. Johnson TN, Boussery K, Rowland-Yeo K, Tucker GT, Rostami-Hodjegan A. A semi-mechanistic model to predict the effects of liver cirrhosis on drug clearance. *Clin.Pharmacokinet.* 2010; 49: 189-206.

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/s/

STANLEY AU
03/28/2011

JEFFRY FLORIAN
03/28/2011

PING ZHAO
03/28/2011
Reviewed by Dr. Shiew Mei Huang

PRAVIN R JADHAV
03/28/2011

SARAH M ROBERTSON
03/28/2011

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	202-022/N-000
Submission Date:	07/23/10, 12/22/10, and 02/25/11
Brand Name:	To be determined
Generic Name:	Rilpivirine HCl
Formulation:	Oral immediate release (IR) tablets
Strength:	One strength only, 25 mg
Sponsor:	Tibotec
Type of submission:	Original
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

TMC278 (rilpivirine) is a new molecular entity (NME) which was developed under IND 67,699. On 07/23/10, Tibotec filed NDA 202-022 under 505(b)(1) seeking approval for TMC278 (rilpivirine) 25 mg IR tablet dosage form (only one strength proposed). TMC278 is a human immunodeficiency virus type 1 (HIV-1) specific, non-nucleoside reverse transcriptase inhibitor (NNRTI). It is to be indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve adult patients. A 25 mg IR tablet is to be taken orally with a meal once daily.

The to-be-marketed (TBM) composition/formulation (No. R314585-F006) has also been employed in the Phase 3 clinical studies. There is no biowaiver issue since there is only one strength proposed. The dissolution data on three primary stability (debossed) batches were submitted, however, these primary stability batches had not been tested clinically.

The proposed TBM tablet formulation is to be debossed, whereas the clinically tested biolots were not debossed. The comparative dissolution data to link the TBM (debossed) tablet batches and the clinical (non-debossed) biolots were requested on 11/10/10 and the sponsor responded on 12/22/10 and further on 02/25/11.

The above dissolution data are reviewed here. During the IND stage, the sponsor provided the dissolution development report to the Agency for review on 03/03/10. The Agency reviewed and agreed with the sponsor's proposed dissolution methodology in a letter dated 05/20/10.

The sponsor's proposed dissolution method and specifications are shown below.

Parameter	Condition
Apparatus	USP Type 2 (Paddle) Apparatus
Dissolution medium	0.5% polysorbate 20 in 0.01 N HCl (pH = 2.0)
Volume	900 mL
Temperature	37± 0.5°C
Rotation speed	75 rpm
Assay	HPLC with UV detection

Specifications: Q= (b) (4) at 45 min

RECOMMENDATION

From the Biopharmaceutics perspective, the sponsor's proposed dissolution method is acceptable, but the proposed dissolution specification needs to be revised. The following comment needs to be conveyed to the sponsor.

COMMENT: (Needs to be sent to the sponsor)

Your proposed dissolution method as shown below is acceptable.

Parameter	Condition
Apparatus	USP Type 2 (Paddle) Apparatus
Dissolution medium	0.5% polysorbate 20 in 0.01 N HCl (pH = 2.0)
Volume	900 mL
Temperature	37± 0.5°C
Rotation speed	75 rpm
Assay	HPLC with UV detection

However, your proposed dissolution specifications need to be tightened as shown below since the mean of rilpivirine dissolution (n=6 tablets/batch) is (b) (4) (mean values ranged from (b) (4) at 45 minutes for the batches tested.

Change from $Q = \text{(b) (4)}$ at 45 minutes
 $Q = \text{(b) (4)}$ at 45 minutes

Prior to approval, you should update your specifications to reflect the newly recommended dissolution specifications.

BACKGROUND

TMC 278 (rilpivirine) is a new molecular entity (NME) which was developed under IND 67,699. During the IND stage, the sponsor provided the dissolution development report to the Agency for review on 03/03/10. The Agency reviewed and agreed with the sponsor's proposed dissolution methodology in a letter dated 05/20/10.

CURRENT SUBMISSION

On 07/23/10, Tibotec filed NDA 202-022 under 505(b)(1) seeking approval for TMC (rilpivirine) 25 mg IR tablet dosage form (one strength proposed only). TMC278 is a human immunodeficiency virus type 1 (HIV-1) specific, non-nucleoside reverse transcriptase inhibitor (NNRTI). It is to be indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve adult patients. A 25 mg IR tablet is to be taken orally with a meal once daily.

The dissolution data on three primary stability (debossed) batches were submitted and the dissolution specifications were proposed, however, these primary stability batches have not been tested clinically. The above dissolution data are reviewed here.

The TBM tablet formulation is to be debossed, whereas the clinically tested tablets were not debossed. The comparative dissolution data to link the clinical (non-debossed) biolots and the TBM (debossed) tablet batches were requested on 11/10/10 and the sponsor responded on 12/22/10 and further on 02/25/11. The above comparative dissolution testing/data are also reviewed here.

FORMULATION COMPARISONS

The formulation/composition of the TMC (rilpivirine) 25 mg IR tablet is shown below.

Table 1. The Formulation/Composition of TMC278 (Rilpivirine) 25 mg IR Tablet

Component	Quality Standard ^a	Function	Amount	
			(mg/tablet)	(% w/w)
(b) (4)				
Povidone (K30)	USP/Ph.Eur.	(b) (4)		
Polysorbate 20	USP/Ph.Eur.			
	NF/Ph.Eur.			
(b) (4)				
TMC278	CS	Active	27.50 ^c	25.00
Lactose Monohydrate	NF/Ph.Eur.	(b) (4)		
Croscarmellose Sodium	NF/Ph.Eur.			
(b) (4)				
Silicified Microcrystalline Cellulose	NF			
Croscarmellose Sodium	NF/Ph.Eur.			
Magnesium Stearate	NF/Ph.Eur.			
Core Tablet Weight:	-			
Film Coating				
Coating Powder White ^d	CS			
(b) (4)	USP/Ph.Eur.			
Total Tablet Weight:	NA	NA	114.40	NA

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

^b (b) (4)

^c Quantity of TMC278 equivalent to the labeled amount TMC278 free base.

^d A commercially available mixture consisting of Hypromellose 2910 6mPa.s, USP/Ph.Eur.; Lactose Monohydrate, NF/Ph.Eur.; PEG 3000, NF (b) (4); Triacetin, USP/Ph.Eur.; and Titanium Dioxide, USP/Ph.Eur.

CS = Company Standard

NA = Not Applicable

The TBM formulation (No. R314585-F006) have also been employed in the Phase 3 clinical studies. There is no biowaiver issue since only one strength is proposed.

DISSOLUTION METHODOLOGY AND SPECIFICATIONS

The dissolution development report had been submitted previously on 03/03/10 to IND 67,699 and reviewed by Dr. Angelica Dorantes. An Agency's letter was sent to the sponsor on 05/20//10 indicating that the sponsor's proposed dissolution methodology is acceptable. Therefore, the dissolution development report will not be reviewed again here.

The dissolution methodology for TMC278 (Rilpivirine) IR 25 mg tablets has been optimized for the following parameters: medium, pH, surfactant concentration, paddle speed, and the HPLC method for the quantification of TMC278. The sponsor reported that the parameters selected have been shown to provide the discriminative capabilities needed to discern drug substance particle size and process changes, as well as changes on stability.

The sponsor's proposed dissolution method and specifications are shown below.

Table 1. The Proposed Dissolution Methodology for Rilpivirine 25 mg IR Tablets

Parameter	Condition
Apparatus	USP Type 2 (Paddle) Apparatus
Dissolution medium	0.5% polysorbate 20 in 0.01 N HCl (pH = 2.0)
Volume	900 mL
Temperature	37± 0.5°C
Rotation speed	75 rpm
Assay	HPLC with UV detection

Specifications: Q= (b) (4) at 45 min.

The mean dissolution profiles and data (n=6 tablets/batch) for the three primary stability batches are shown below.

Figure 1. Mean Dissolution Profiles (n=6 Tablets/Batch) of the Three Primary Stability Batches at Initial Time (t=0)



Table 1. Mean Dissolution Data (n=6 Tablets/Batch) of The Three Primary Stability Batches

Usage	Batch No.	Debossing Condition	Mean % Dissolved at the Sampling Time Points (min)	
				(b) (4)
Stability	8JL3K	Debossed		
	8JL3H			
	8JL3S			

These primary stability batches were debossed and made in full production batch size (b) (4) but had not been tested clinically. The individual dissolution data, however, were not located in the NDA. Upon request, the sponsor submitted the needed individual data on 02/25/11. Please see individual and mean dissolution data in Appendix 2 for details.

The sponsor reported that the TBM tablet formulation will be debossed. However, the clinical biolots were non-debossed. A link between the clinical biolots (non-debossed) and the TBM tablet formulation (debossed) was not provided in the NDA. On 11/10/10, the Agency sent an IR asking for the comparative dissolution data to support the above linkage. The sponsor submitted the requested data on 12/22/10 (Appendix 1) and further on 02/25/11 (Appendix 2). The submitted comparative dissolution data are shown below.

Figure 2. Mean Comparative Dissolution Profiles (n=6 Tablets/Batch) of Rilpivirine IR Tablets between the Clinically Tested and the TMB (Process Validation) Batches



Table 3. Dissolution Results for the Clinically Tested and the TBM (Process Validation) Batches

Purpose	Debossing	Batch	% Dissolved at Sampling Intervals (min)
Clinical	No debossing	9CL1F ^a	(b) (4)
		8BL2H ^b	
Process Validation (to-be-marketed)	Debossed with "TMC" on one side and "25" on the other ^c	AJL2K	
		AJL2L	
		AJL2M	
	(b) (4)		
^a Batch tested with proposed regulatory methods following conditions			(b) (4)
^b Batch tested with proposed regulatory methods following			(b) (4)
^c Debossing for the US market			
^d			(b) (4)

The clinical biolot No. 9CL1F was a full production batch (b) (4) and the other biolot No. 8BL2H was made with (b) (4) of a full production batch).

The batch information on the above three process validation (TBM) batches and the individual dissolution data, however, were not included in the 12/22/10 response. Upon request, the sponsor submitted the batch information and the individual data on 02/25/11. Please see the batch information and individual and mean dissolution data in Appendix 2 for details.

The batch information on the above three process validation batches are shown below.

Table 3. Batch Information on the Three Process Validation Batches (Debossed)

Batch	Batch Size (kg / tablets)	Drug Product Manufacturing Site	Manufacturing date
AJL2K		(b) (4)	Oct 2010
AJL2L			Oct 2010
AJL2M			Oct 2010

Reviewer's Comment:

Since the mean of rilpivirine dissolution (n=6 tablets/batch) is (b) (4) at 45 min (means ranged from (b) (4) it is recommended that the proposed specifications Q= (b) (4) at 45 min be tightened to Q= (b) (4) at 45 min.

Tien-Mien Chen, Ph.D.
Reviewer
ONDQA Biopharmaceutics

03/02/11

Date

Patrick Marroum, Ph.D.
ONDQA Biopharmaceutics

03/02/11

Date

CC: NDA
Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

**NDA 202-022/N-000 for TMC278
(Rilpivirine) IR Tablet, 25 mg**

Appendix 1

**Comparative Dissolution Data Submitted
on 12/22/10**

3. FDA QUESTION #3:

Please provide the comparative dissolution data/profile between the clinically tested and the TBM (to-be-marketed) formulations to address the difference in de-bossing between the two formulations.

Response

Data provided in [Table 8](#) and presented in [Figure 6](#) demonstrate that there is no observable difference in dissolution profiles at 30, 45, and 60 minutes resulting from the addition of debossing.

Table 8: Dissolution Results for Clinical and Process Validation Batches

Purpose	Debossing	Batch	% Dissolved at Sampling Intervals (min)	
				(b) (4)
Clinical	No debossing	9CL1F ^a		
		8BL2H ^b		
Process Validation (to-be-marketed)	Debossed with “TMC” on one side and “25” on the other ^c	AJL2K		
		AJL2L		
		AJL2M		
	(b) (4)			
^a Batch tested with proposed regulatory methods following conditions			(b) (4)	
^b Batch tested with proposed regulatory methods following			(b) (4)	
^c Debossing for the US market				
^d			(b) (4)	

Figure 6: Comparative Dissolution Profiles for Clinical and Commercial Tablets, Demonstrating No Effect of Debossing on Dissolution



Conclusion

The data provided above confirm that the addition of debossing does not produce a difference in dissolution values at the specified criterion of "Q is (b) (4) at 45 minutes."

**NDA 202-022/N-000 for TMC278
(Rilpivirine) IR Tablet, 25 mg**

Appendix 2

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**Batch Information and Individual
Dissolution Data Submitted on 02/25/11**

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/s/

TIEN MIEN CHEN
03/02/2011

PATRICK J MARROUM
03/02/2011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	202-022	Brand Name	To be determined
OCP Division (I, II, III, IV, V)	DCP4	Generic Name	Rilpivirine
Medical Division	DAVP	Drug Class	NNRTI
OCP Reviewer	Stanley Au	Indication(s)	Treatment of HIV-1 infection
OCP Team Leader	Sarah Robertson	Dosage Form	Oral tablet
Pharmacometrics Reviewer	Jeff Florian	Dosing Regimen	25 mg once daily
Date of Submission	July 23, 2010	Route of Administration	Oral
Estimated Due Date of OCP Review	March 28, 2011	Sponsor	Tibotec
Medical Division Due Date	April 11, 2011	Priority Classification	Standard
PDUFA Due Date	May 23, 2011		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Critical Comments If any
STUDY TYPE			
Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies			
HPK Summary	X		
Labeling	X		
Reference Bioanalytical and Analytical Methods		1) Rilpivirine validation reports: 4 2) Validation reports for other analytes: 21 (excluding additional reports for the same analyte) 3) Bioanalytical reports: 39 total (excluding reports for ECG trials)	
I. Clinical Pharmacology			
Mass balance:	X	1 (includes the trial report and the pharmacokinetics report)	
Isozyme characterization:	X	1 in vitro metabolism report; 1 CYP metabolism report	
Blood/plasma ratio:			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Plasma protein binding:	X	1	
Pharmacokinetics (e.g., Phase I) -			
Healthy Volunteers-			
single dose:	X	2	
multiple dose:	X	2	
Patients-			
single dose:			
multiple dose:			
Dose proportionality -			
fasting / non-fasting single dose:			
fasting / non-fasting multiple dose:	X	1 (under fed conditions)	
Drug-drug interaction studies -			
In-vivo effects on primary drug:			
In-vivo effects of primary drug:	X	17 (all evaluated two way drug interaction trials)	
In-vitro:	X	4 in vitro drug-drug interaction reports	
Subpopulation studies -			
ethnicity:			
gender:			
pediatrics:			
geriatrics:			
renal impairment:			
hepatic impairment:	X	1	
PD -			
Phase 2:			
Phase 3:			
PK/PD -			
Phase 1 and/or 2, proof of concept:	X	3	
Phase 3 clinical trial:	X	2	
Population Analyses -			
Data rich:			
Data sparse:			
II. Biopharmaceutics			
Absolute bioavailability			
Relative bioavailability -			
solution as reference:	X	1	
alternate formulation as reference:	X	2 (1 trial comparing Phase 2b tablets vs. Phase 3 tablets and 1 trial comparing the 25 mg Phase 3 tablet formulation to various pediatric formulations in adults)	
Bioequivalence studies -			
traditional design; single / multi dose:			
replicate design; single / multi dose:			
Food-drug interaction studies	X	1	
Bio-waiver request based on BCS			
BCS class			
Dissolution study to evaluate alcohol induced dose-dumping			
III. Other CPB Studies			
Genotype/phenotype studies			
Chronopharmacokinetics			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Pediatric development plan			
Literature References			
Total Number of Studies		44	

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?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
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)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
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)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
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 pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
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?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

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.

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-202022	ORIG-1	TIBOTEC INC	TMC278

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/s/

STANLEY AU
09/02/2010

SARAH M ROBERTSON
09/02/2010