**Janssen Research & Development**

# Nonclinical Introduction

## MODULE 2.6.1

## Rilpivirine Long-Acting

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| CAB | cabotegravir |
| HIV-1 | human immunodeficiency virus type 1 |
| IM | intramuscular(ly) |
| LA | long-acting |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| RPV | rilpivirine |

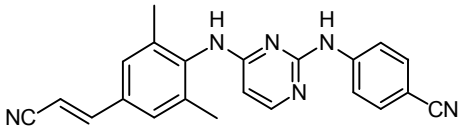
# 1. INTRODUCTION

Rilpivirine (RPV, previously known as TMC278, JNJ-16150108 or R278474), a diarylpyrimidine derivative, is a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) with *in vitro* activity against wild-type human immunodeficiency virus type 1 (HIV-1) and NNRTI-resistant mutants. Rilpivirine is available as a 25 mg oral tablet, which has been approved for the treatment of HIV-1 infection in antiretroviral treatment-naïve adult patients in multiple countries including Europe, the United States of America, Canada, and Japan as EDURANT®.

Janssen Sciences Ireland UC in partnership with ViiV Healthcare Company are developing the RPV Long-Acting (LA) + Cabotegravir (CAB) LA injectable regimen for the treatment of HIV-1 infection. The overall objective of the CAB + RPV clinical program is to develop a novel, highly effective, well tolerated 2-drug intramuscular (IM) injectable regimen LA administration for the treatment of HIV-1 infection. This Marketing Authorization Application (MAA) focuses on the RPV LA component of this 2-drug regimen. CAB will be the subject of a separate, parallel, MAA, submitted by ViiV Healthcare. Janssen is the sponsor of the RPV LA development and manufacturing program; ViiV Healthcare is the sponsor of the CAB + RPV clinical program

The active ingredient of the parenteral LA formulation is RPV as the free base. The chemical name is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino] benzonitrile. The molecular formula is $C_{22}H_{18}N_6$ and its molecular weight is 366.42 Dalton. The structural formula can be found in Figure 1.

**Figure 1: Structural Formula of RPV**




# 2. PROPOSED CLINICAL USE

The final clinical formulation G001 contains 300 mg RPV base/mL suspension and poloxamer 338 (50 mg/mL). The proposed CAB + RPV regimen for HIV-1-infected subjects is oral CAB 30 mg once daily + oral RPV 25 mg once daily for approximately 1 month (at least 28 days) followed by initial injections (one of each) of CAB LA 600 mg IM + RPV LA 900 mg IM and subsequent monthly injections of CAB LA 400 mg IM + RPV LA 600 mg IM.

**Janssen Research & Development**

**Pharmacology Written Summary**

# MODULE 2.6.2

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ATPase | adenosine triphosphatase |
| $AUC_{0-t}$ | area under the plasma concentration versus time curve from time 0 to time 't' |
| CHO | Chinese hamster ovary |
| (c)DNA | (complementary) deoxyribonucleic acid |
| $C_{max}$ | maximum plasma concentration |
| DMSO | dimethylsulfoxide |
| EADs | early afterdepolarizations |
| ECG | electrocardiogram |
| ERP | effective refractory period |
| FC | force of contraction |
| hERG | human ether à go-go |
| hERG-SM | single mutant hERG channel |
| hERG-WT | wild-type hERG channel |
| HCl | hydrochloride |
| HEK | human embryonic kidney |
| HIV | human immunodeficiency virus |
| $IC_{50}$ | median inhibitory concentration |
| $I_{Ca,L}$ | high threshold L-type calcium current |
| $I_{K1}$ | inward rectifying potassium current |
| $I_{Kr}$ | rapidly activating rectifying potassium current |
| $I_{Ks}$ | slowly activating rectifying potassium current |
| IM | intramuscular |
| $I_{Na}$ | fast sodium current |
| $I_{to}$ | transient outward potassium current |
| LA | long-acting |
| LV | left ventricular |
| MAA | Marketing Authorization Application |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| PEG400 | polyethylene glycol with molar mass between 380 and 420 |
| PQ | interval between the start of the P wave and the start of the Q wave on ECG |
| q.d. | quaque die = every day = once daily |
| QRS | part of the ECG complex comprising the Q, R, and S-waves |
| QT | interval between the start of the Q wave and the end of the T wave on ECG |
| QTc(F) | QT-interval corrected for heart rate (according to Fridericia) |
| RC | rate of contraction |
| RPV | rilpivirine |
| RR | interval between the peak of R waves of 2 consecutive ECG complexes |
| TdP | torsade de pointes |
| TDR | transmural dispersion of repolarization |
| $T_{max}$ | time after dosing at which maximum concentration was measured |
| Tp-Te interval | time between peak and end of the T wave on ECG |
| Tween 80 | polyoxyethylenesorbitan monooleate 80 |
| TQT study | thorough clinical QTc-prolongation study according to ICH E14 |
| VF | ventricular fibrillation |
| VT | ventricular tachycardia |

## DEFINITION OF TERMS

| | |
|---|---|
| Contractility index | LV dp/dt max/pd: maximum positive rate of change of isovolumic left ventricular pressure divided by the s developed pressure at maximum positive rate of change |
| Effective refractory period (ERP) | frequency of external stimulations that does not elicit continuous contractions |
| LV dp/dt max | maximum positive rate of change of isovolumic left ventricular pressure |
| LV dp/dt min | maximum negative rate of change of isovolumic left ventricular pressure |
| rTp-Te interval | Tp-Te/QT ratio; reflects the potential for phase 2 afterdepolarizations |
| Tp-Te interval | measure of transmural dispersion of repolarization (TDR) |

# 1. BRIEF SUMMARY

Rilpivirine (RPV, previously known as TMC278, JNJ-16150108 or R278474), a diarylpyrimidine derivative, is a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) with *in vitro* activity against wild-type human immunodeficiency virus type 1 (HIV-1) and NNRTI-resistant mutants. Rilpivirine is available as a 25 mg oral tablet, which has been approved for the treatment of HIV-1 infection in antiretroviral treatment-naïve adult patients in multiple countries including Europe (EMEA/H/C/002264), the United States of America, Canada, and Japan as EDURANT®.

Janssen Sciences Ireland UC in partnership with ViiV Healthcare Company are developing the RPV Long-Acting (LA) + Cabotegravir (CAB) LA injectable regimen for the treatment of HIV-1 infection. The overall objective of the CAB + RPV clinical program is to develop a novel, highly effective, well tolerated 2-drug intramuscular (IM) injectable regimen LA administration for the treatment of HIV-1 infection. This Marketing Authorization Application (MAA) focuses on the RPV LA component of this 2-drug regimen. CAB will be the subject of a separate, parallel, MAA, submitted by ViiV Healthcare. Janssen is the sponsor of the RPV LA development and manufacturing program; ViiV Healthcare is the sponsor of the CAB + RPV clinical program.

This summary provides an overview of the studies conducted with RPV in support of the approval of the current marketing authorization for RPV LA. As the active moiety for the LA formulation is essentially the same as for the oral formulation (hydrochloride (HCl) salt for the oral formulation versus base for the LA formulation), the (safety) pharmacology studies conducted for the development of oral RPV are considered relevant for RPV LA. In the RPV oral formulation development program (i.e., EDURANT® registration), an extensive package of studies was conducted including primary and secondary pharmacodynamics studies, as well as in vitro and in vivo cardiovascular safety, pulmonary safety and central nervous system safety studies.

All (safety) pharmacology studies were conducted in accordance with best scientific principles. Pivotal safety pharmacology studies outlined in the Pharmacology Written Summary were performed in compliance with the United States (US) Food and Drug Administration (FDA) Good Laboratory Practice (GLP) regulations (21 CFR Part 58) and Organization for Economic Co-operation and Development (OECD) principles of GLP (Directive 2004/10/EC) in OECD-adherent countries. Information on the GLP status of the studies and location of the test facilities is provided in Mod2.6.3.1/Pharmacology Overview Table. The dates of study conduct, and location of the raw data are mentioned in the individual study reports.

The following convention is applied throughout this Module: Reference is made to ‘RPV’ when the HCl salt was administered and to ‘RPV base’ when the free base was administered. The RPV LA formulation contains the RPV base form. The dose or concentration is always given as base equivalent.

Rilpivirine base has been applied in the early phases of development and RPV in the later phases, after selection of the final chemical form. All in vitro studies described in this section were conducted with serum-free medium. The indicated bath concentrations are therefore

considered as unbound concentrations whereas RPV base is bound more than 99% (between 99.14 and 99.97%) to plasma proteins of the species involved in nonclinical safety studies and 99.67% to human plasma proteins.

**Primary Pharmacodynamics**

The primary pharmacodynamics are discussed in Mod2.7.2/Virology Summary.

**Secondary Pharmacodynamics**

RPV base did not cause any inhibition in vitro of α- or β-adrenergic, dopaminergic, muscarinergic, serotonergic, opioid, interleukin, or chemokine receptors (up to 10 µM, 3.7 µg/mL), or human deoxyribonucleic acid (DNA) polymerase α, β, or γ (up to 1000 µM, 366 µg/mL). RPV base showed no agonistic or antagonistic activity on histamine $H_2$ receptors in the isolated guinea pig right atrium (30 µM, 11°µg/mL) and no inhibition of adenosine triphosphatase (ATPase) in isolated pig stomach (10µM, 3.7µg/mL). In vivo, RPV base did not cause any significant inhibition of pentagastrin-induced gastric acidity in rats.

It is concluded that RPV is essentially devoid of any clinically relevant secondary pharmacodynamic effect at unbound concentrations that greatly exceed the median maximum systemic exposure to total RPV in man following an oral dose of 25 mg per day (q.d.) (0.2 µg/mL), after an initial IM dose of 900 mg on the day of the last oral dose (0.173 µg/mL), or following subsequent IM doses of 600 mg (0.143 µg/mL).

**Safety Pharmacology**

*Cardiovascular safety*

The standard battery of cardiovascular safety studies showed a concentration-dependent inhibition of RPV base on the rapidly activating rectifying potassium current ($I_{Kr}$) from 33% at 0.3 µM (0.11 µg/mL) to 80% at 3 µM (1.1 µg/mL). However, no relevant effects by RPV base were noted on other cardiovascular or electrocardiographic parameters in vitro in the right atrium of the guinea pig, in vivo in anesthetized guinea pigs and dogs given a single intravenous dose, or in conscious instrumented or telemetered dogs given a single oral dose.

Delayed onset (after 11 days of treatment) prolongation of the interval between the start of Q wave and the end of the T wave on ECG (QT) interval corrected for heart rate according to Fridericia (QTcF) was reported in the orally dosed clinical thorough QTc (TQT) study (Mod5.3.4.1/TMC278-C131). To investigate the mechanism of action of the QTc-prolongation and of the delayed onset, additional nonclinical studies were done. Moreover, the potential of RPV to induce proarrhythmic effects, in particular torsade de pointes (TdP), was evaluated.

The additional studies showed inhibition of the slowly activating rectifying potassium current ($I_{Ks}$) from 17% at 1 µM (0.37 µg/mL) up to 73% at 10 µM (3.7 µg/mL), with a median inhibitory concentration ($IC_{50}$) of 3.1 µM (1.15 µg/mL). In addition, the transient outward potassium current ($I_{to}$) was reduced for 14% at 0.3 µM (0.11 µg/mL) up to 36% at 1 µM (0.37 µg/mL).

However, no effects were observed on the inward rectifying potassium current ($I_{K1}$), the fast sodium current ($I_{Na}$) or the high threshold L-type calcium current ($I_{Ca,L}$).

In vitro, a concentration-dependent inhibition of trafficking of the human ether à go-go (hERG) channel by RPV base was observed from 1 µM (0.37 µg/mL) onwards. However, no signs of trafficking, determined as delayed onset of QT-prolongation, were noted in an in vivo model. In this model, telemetered guinea pigs were orally dosed for 16 days at 10 mg/kg/day associated with maximum plasma concentrations of RPV base ranging from 0.6 to 0.9 µg/mL. This concentration was similar to the steady state median maximum plasma concentration at 75 mg q.d. RPV, a dose that caused delayed onset QTc-prolongation in TQT study C131.

RPV base showed only a marginal potential to induce proarrhythmic effects in the rabbit arterially perfused left ventricular wedge model. Up to 10 µM (3.7 µg/mL), RPV base caused maximally 9% QT-prolongation but showed no effects on dispersion of the repolarization across the ventricular wall (TDR) or any early afterdepolarizations (EADs), resulting in a TdP score of 0.5. True arrhythmogenic drugs have a TdP score of around 5 in this model.

*Pulmonary safety*

RPV base had no effect on respiratory parameters in anesthetized dogs (single 1-hour intravenous infusion of 5 mg/kg) or conscious telemetered dogs (single oral dose of 20 mg/kg).

*Neurobehavior and motor activity*

No compound-related neurological, behavioral changes or delayed neurotoxicity were observed in a modified Irwin test in rats (single oral dose up to 400 mg/kg) or in conscious telemetered (single oral dose up to 160 mg/kg) or instrumented dogs (single oral dose of 20 mg/kg).

**Overall Conclusion**

RPV base had no effects on secondary pharmacodynamic parameters or on the core battery of safety pharmacology tests, apart from inhibitory effects on some cardiac potassium currents and channels and moderate QT-prolongation in the rabbit ventricular wedge, at concentrations exceeding the median maximum systemic concentration of total RPV in man, when dosed at 25 mg oral or at the highest proposed RPV LA dose (initial single dose of 900 mg on the day of the last oral dose), by at least 20-fold. The observed inhibition of trafficking of the hERG channel may be involved in the delayed onset of the QTcF-prolongation observed in clinical TQT study C131. However, pharmacokinetic mechanisms may be involved, also (as discussed in Section 6). Importantly, the absence of effects in nonclinical models at maximum plasma concentrations up to 0.9 µg/mL allow the conclusion that RPV has only a marginal potential to induce proarrhythmic effects, which is confirmed by the absence of any relationship between RPV administration and TdP in patients.

## 2. PRIMARY PHARMACODYNAMICS

For the primary pharmacodynamics of RPV, please refer to Mod2.7.2/Virology Summary.

# 3. SECONDARY PHARMACODYNAMICS

The potential secondary pharmacodynamic effects of RPV base were investigated in in vitro and in vivo studies in support of the already approved oral RPV (EDURANT®). The studies conducted are listed in Mod2.6.3.1/Overview Table and summarized in the Mod2.6.3.3.

## 3.1. Receptor Binding and Neurotransmitter Uptake Inhibition

The interaction of RPV base with 19 receptors in tissue or cellular preparations was studied at one concentration of 10 µM (3.7 µg/mL) in buffer containing 1% dimethylsulfoxide (DMSO) (Mod4.2.1.2/TMC278-870219). RPV base did not cause any significant inhibition of binding to α- or β-adrenergic, dopaminergic, muscarinergic, serotonergic, opioid, interleukin, or chemokine receptors.

No agonistic or antagonistic activity of RPV base was noted on histamine $H_2$ receptors in the isolated guinea pig right atrium at 30 µM (11 µg eq/mL) (Mod4.2.1.2/TMC278-NC204 (2) (TOX7649; [redacted] 1074888)). No inhibition of ATPase by RPV base was evident in isolated pig stomach at 10 µM (3.7 µg eq/mL) (Mod4.2.1.2/TMC278-NC204 (3) (TOX7649; [redacted] 1074888)). The incubation in these 2 studies was done in buffer containing 0.1% DMSO.

RPV base was evaluated for possible gastric anti-secretory activity in the pentagastrin-stimulated gastric acidity assay (Mod4.2.1.2/TMC278-NC204 (1) (TOX7649; [redacted] 1074888)). Three groups of 5 male Wistar rats fasted overnight were treated intraperitoneally at a volume of 5 mL/kg with vehicle (2% polyoxyethylenesorbitan monooleate 80 (Tween 80) in 0.9% NaCl in water), RPV base (at 9.1 mg/kg), or positive control cimetidine (10 mg/kg). Thirty minutes later, gastric acid production was stimulated by intraperitoneal injection of 5 µg/kg pentagastrin dissolved in distilled water. RPV base caused a 20%-increase in gastric acidity compared to vehicle. The positive control reduced acidity with 74%. The significance of the increased gastric acidity effect by RPV is considered limited.

## 3.2. Human DNA Polymerase Inhibition

RPV base was dissolved in a TRIS buffer with 10% DMSO and 0.7% β-octyl glucoside up to 1000 µM (366 µg/mL).

Even this very high concentration had no effects on DNA synthesis by human polymerase α, β, or γ determined by polymerase chain reaction (Mod4.2.1.2/TMC278-1646_0005343). DideoxyATP was used as the positive control for inhibition of polymerase α and β.

# 4. SAFETY PHARMACOLOGY

The effects of RPV base on a core battery of safety pharmacology parameters were evaluated in a series of in vitro and in vivo studies. The studies conducted are listed in Mod2.6.3.1/Overview Table and summarized in the Mod2.6.3.4.

## 4.1. Cardiovascular Safety

The standard battery of cardiovascular safety studies included evaluation of hERG channel inhibition, cardiac contractility in the isolated guinea pig right atrium, and evaluation of cardiovascular parameters in vivo in anesthetized guinea pigs and dogs and in conscious dogs.

Additional cardiovascular safety studies were conducted to investigate the mechanism of action of the delayed onset of the prolongation of the QTcF noted in the thorough clinical QTc-prolongation (TQT) study, TMC278-TiDP6-C131 (Mod5.3.4.1/TMC278-C131). In this study, RPV was given to healthy subjects for 11 days. Another objective of the additional nonclinical studies was to evaluate the proarrhythmic potential of RPV at doses that gave QT-prolongation.

As a result of duration-related reduced responses to RPV in some of the in vitro studies, recovery of freshly prepared solutions of RPV base in the buffers used in these studies was evaluated using $^{14}$C-RPV base. The radioactive concentration of a RPV base stock solution of 10 mM (10 MBq/mL) in DMSO was 99.1% of the theoretical radioactive concentration. However, the radioactive concentration of a solution of 10 µM and 3 µM of RPV base in Tyrode buffer containing 0.1% and 0.03% DMSO was 84.7% and 58.0% of the theoretical radioactive concentration, respectively (Mod4.2.1.3/TMC278-NC338 [FK6822]). Further studies showed that recovery could be significantly improved by adding 5% bovine serum albumin to the solutions indicating that the low recovery in the serum-free conditions was likely due to adsorption of RPV base to the equipment (Mod4.2.1.3/TMC278-NC381). This conclusion is in line with the high (more than 99%) degree of plasma protein binding of RPV in all species including man (see Mod2.6.4/Sec4.2). As the in vitro models were validated with protein-free incubation fluids, it was decided not to add serum albumin. The results of the studies are presented with the nominal bath concentrations.

### 4.1.1. Standard Battery Studies

#### 4.1.1.1. Inhibition of the ($I_{Kr}$)

Chinese hamster ovary (CHO) cells were stably transfected with the hERG encoding for the $I_{Kr}$ channel (Mod4.2.1.3/TMC278-CPF730). These cells were incubated with RPV base at nominal bath concentrations of 0.1, 0.3, and 3 µM (0.037, 0.111, and 1.11 µg/mL) in buffer containing 0.1% DMSO. Astemizole and terfenadine were used as positive controls.

RPV caused a concentration-dependent inhibition of $I_{Kr}$ ranging from 10% at 0.1 µM (0.037 µg/mL) to 80% at 3 µM (1.10 µg/mL).

#### 4.1.1.2. Cardiac Contractility in the Isolated Guinea pig Right Atrium

Rate and force of (spontaneous) contraction (RC and FC, respectively) and effective refractory period (ERP), defined as the frequency of external stimulations that does not elicit continuously a contraction, were evaluated in two series of experimentations with isolated spontaneously beating right atrium of guinea pigs. In the first series, incubations occurred with RPV base at subsequently 0.01, 0.03, and 0.1 µM (0.004, 0.011, and 0.037 µg/mL) in buffer containing

respectively 0.01, 0.03, 0.1% DMSO. In the second series, subsequently 1, 3 and 10 µM (0.369, 1.11, and 3.69 µg/mL) RPV base in buffer containing 1, 3, and 10% DMSO was tested (Mod4.2.1.3/TMC278-N168576). ERP was determined after the highest concentration in each of the series was applied.

RPV base caused a concentration-dependent decrease in the rate of spontaneous contractions to 86, 72, and 44% of baseline at 1, 3, and 10 µM (0.369, 1.10, and 3.69 µg/mL), respectively. The compound at 0.1 and 10 µM (0.037 and 3.69 µg/mL) had no effect on ERP compared to vehicle. RPV base did not cause any effects on the force of the spontaneous contraction compared to vehicle over the full range of concentrations.

#### 4.1.1.3. Cardiovascular Parameters in Anesthetized Guinea Pigs

Anesthetized guinea pigs were used to evaluate the effects of RPV base relative to vehicle on heart rate and mean arterial blood pressure and electrophysiological parameters (Mod4.2.1.3/TMC278-CPF643). The latter parameters comprised the duration of the part of the ECG complex comprising the Q, R, and S-waves (QRS) and of the interval between the start of the P wave and the start of the Q wave on ECG (PQ-), interval between the peak of R waves of 2 consecutive ECG complexes (RR-), and QT-interval. The duration of QTc using Bazett's formula ($QT = QT/\sqrt{RR}$) was calculated. In addition, the incidence of cardiac conduction disturbances such as type II and III atrioventricular blocks and intraventricular bundle branch block were recorded. Moreover, the occurrence of ventricular arrhythmias was evaluated on the basis of occurring ventricular premature beats, ventricular tachycardia (VT), and ventricular fibrillation (VF). A group of 7 animals received a series of 6 intravenous injections of increasing concentrations of RPV dissolved in polyethylene glycol with molar mass between 380 and 420 (PEG400) at a volume of 0.5 mL/kg with a 15-min interval between each dose. Individual animals received doses ranging from 0.16 up to 5 mg/kg (cumulative dose of 9.87 mg/kg over 75 minutes). Plasma, heart and lung tissue of the first 3 animals were sampled immediately after the last injection for determination of RPV base.

RPV base had no effect on heart rate or mean arterial blood pressure and had no statistically significant effect on the duration of the PQ and the QRS intervals of the electrocardiogram (ECG). The QT-interval tended to be increased (+18% versus +10% with vehicle) after administration of the highest dose of 5 mg/kg. After correction for heart rate using Bazett's formula, no drug-induced effect was observed on QTc. No differences in the incidence of cardiac conduction disturbances were observed. Plasma levels of RPV base reached a median value of 9.2 µg/mL, 5 min after the last injection. The concentration of RPV base in lung tissue was 4 times higher than that in heart tissue (47.7 µg/g and 11.7 µg/g, respectively).

#### 4.1.1.4. Cardiovascular Parameters in Anesthetized Dogs

Groups of 4 anesthetized beagle dogs (Mod4.2.1.3/TMC278-CPF648 and Mod4.2.1.3/TMC278-CPF648 [FK4126]) received an intravenous infusion for 1 hour at a flow of 2 mL/kg of a formulation of 2.5 mg RPV base/mL in PEG400 (dose: 5 mg RPV base/kg) or the vehicle, PEG400. The effects of RPV base were compared with those of the vehicle and evaluated during

infusion and for 3 hours following administration on general and regional cardio-hemodynamic, ECG, cardio-electrophysiological, pulmonary, and arterial blood parameters. The general hemodynamic parameters comprised heart rate, systolic and diastolic aortic and pulmonary artery pressure, systolic pressure rate product, cardiac output, and stroke volume. Moreover, left ventricular pressure parameters were determined: end diastolic pressure, maximum positive and negative isovolumic rate of change (LV dp/dt max and LV dp/dt min, respectively), contractility index (LV dp/dt max/pd), and the time constant of relaxation (Tau). The regional hemodynamic parameters were common carotid artery blood flow, systemic and pulmonary vascular resistance, common carotid arterial vascular resistance, systolic and diastolic intracranial pressure and cerebral perfusion pressure. ECG morphology was evaluated and the duration of the QRS complex and of the PQ and QT intervals were determined; the latter also corrected for heart rate according to Bazett, Fridericia, and Van de Water. Cardio-electrophysiological effects were evaluated on the morphology and the duration of the right endocardial monophasic action potential (at 90% of repolarization). The pulmonary and arterial blood parameters are presented in Section 4.2.1.

RPV had no effects on the ECG or cardio-electrophysiological parameters. From cardio-hemodynamic parameters, systemic vascular resistance (-25% versus baseline; vehicle: +29% versus baseline), pulmonary vascular resistance (-20% versus baseline; vehicle: +31% versus baseline) and cardiac output (+31% versus baseline; vehicle: -12% versus baseline) were affected at the end of the infusion. The vehicle, PEG400, had its own cardio-hemodynamic effects, opposite to those by RPV base. The mean plasma concentration of RPV base at the end of the infusion was 2.62 µg/mL and decreased to 0.484 µg/mL, 3 hours after cessation of the infusion. The results on the pulmonary and arterial blood parameters are presented in Section 4.2.1.

#### 4.1.1.5. Cardiovascular Parameters in Instrumented, Awake Dogs

Instrumented dogs were allocated to 2 groups of 7 dogs each. One group was administered a single oral dose of 20 mg/kg of RPV base dissolved in PEG400 and the second group was dosed with vehicle (PEG400) (Mod4.2.1.3/TMC278-CPF654 and Mod4.2.1.3/TMC278-CPF654 [FK4125]).

RPV had no effects on heart rate, blood pressure, systolic pressure rate product, LV dp/dt max, LV dp/dt min, and LV dp/dt max/pd, cardiac output, stroke volume, systemic vascular resistance and ECG intervals. No differences in the morphology of the ECG were observed between the 2 groups. The median maximum plasma concentration of RPV was 1.5 µg/mL.

#### 4.1.1.6. Cardiovascular Parameters in Telemetered Conscious Dogs

Four telemetered male beagle dogs were administered orally via gavage escalating doses of 0 (vehicle), 20, 80 and 160 mg/kg of RPV base dissolved in PEG400 plus citric acid (Mod4.2.1.3/Exp5555 [[redacted] 843412] and Mod4.2.1.3/Exp5555-FK4280 [[redacted] 843412]). The interval between administrations was 1 week. Cardio-hemodynamic (heart rate, systolic and diastolic blood pressure and pressure rate product) and ECG parameters (RR, PQ, and QT

intervals) recorded for 12 hours following dosing were evaluated. QTc interval was calculated according to Van de Water's formula.

RPV base did not show any effects on cardio-hemodynamic or ECG parameters. Plasma samples taken during the days of dosing were rejected following erroneous processing. Exposure to RPV base was evaluated on the basis of oral single dose toxicokinetic data from a separate dog study (Mod4.2.3.2/FK4244) with the same formulation at oral doses of 20, 40, and 80 mg RPV base/kg. The mean maximal plasma concentrations of RPV base were fairly comparable between the different dose groups: 1.5, 1.7 and 1.5 µg/mL, respectively. Time after dosing at which maximum concentration was measured ($T_{max}$) values were variable occurring up to 24 h after dosing. $AUC_{0-24h}$ values also did not differ between the three dose levels: 18.1, 26.8, and 18.8 µg.h/mL, respectively.

### 4.1.2. Additional Mechanistic Studies

#### 4.1.2.1. Membrane Currents Involved in Cardiac Action Potential Depolarization and Repolarization

The effects of RPV base were studied on ion channels involved in the depolarization and repolarization phase of the cardiac action potential. The parameters evaluated included the $I_{Ks}$, the $I_{to}$, the $I_{K1}$, the $I_{Na}$ and the high threshold L-calcium current ($I_{Ca,L}$). The effects on the currents were studied at single cell level using the single-electrode-whole-cell configuration of the patch clamp technique. Positive controls were used in each study.

The effect of RPV base at nominal bath concentrations of 0.3 to 10 µM (0.11 - 3.7 µg/mL) in a buffer containing 0.1% DMSO was studied in a CHO cell line transfected with human KvLQT1 and minK, two subunits encoding for the $I_{Ks}$ channel (Mod4.2.1.3/TMC278-NC342). The positive control was HMR 1556. RPV caused a concentration-dependent block of $I_{Ks}$ from 1 µM (0.37 µg/mL) onwards with an $IC_{50}$ of 3.1 µM (1.15 µg/mL).

In addition, RPV base was tested in the human embryonic kidney (HEK) 293 cells (Mod4.2.1.3/TMC278-NC331) transfected with human cDNA, encoding for channels for $I_{Na}$, $I_{Ks}$, $I_{to}$, $I_{Ca,L}$, and $I_{K1}$. The positive controls used were lidocaine for $I_{Na}$, chromanol 293B for $I_{Ks}$, flecinide for $I_{to}$, nifedipine for $I_{Ca,L}$ and $BaCl_2$ for $I_{K1}$.

RPV base at nominal concentrations of 0.1, 0.3, and 1 µM (0.037, 0.11 and 0.37 µg/mL) caused 19.1% inhibition of $I_{Ks}$ at 1 µM (0.37 µg/mL) and 13.6 and 35.5% inhibition of $I_{to}$ at 0.3 and 1 µM (0.1 and 0.37 µg/mL), respectively. RPV had no biologically relevant effects on $I_{K1}$, $I_{Na}$, or $I_{Ca,L}$ at 1 µM.

#### 4.1.2.2. Trafficking of the hERG Channel

One of the mechanisms possibly responsible for the delayed onset QTcF-prolongation observed in clinical TQT study C131 is inhibition by RPV of the synthesis, assembly in the endoplasmic reticulum, and/or transport of the hERG channel proteins to the cell membrane. This effect - also known as trafficking - on the most prominent ion channel involved in the repolarization of the

cardiac action potential was assessed in the hERG-Lite® test (Mod4.2.1.3/TMC278-NC330 and 4). In this test, the effects of RPV on the expression of the wild-type hERG channel (hERG-WT) or a single mutant channel (hERG-SM) at the surface of HEK293 cells transfected with these channels were determined, following overnight incubation. The mildly misfolded mutant channels show reduced trafficking. However, hERG channel blockers have been shown to act as pharmacological chaperones for the mutant channels in stabilizing their correct conformation and rescuing their expression by allowing their export from the endoplasmic reticulum and movement to the cell surface. So, in this test the potential of RPV to inhibit trafficking of the hERG-WT channel has been evaluated in parallel with its potential to behave as a hERG blocker by rescuing the surface expression of the hERG-SM channel. RPV base was incubated at nominal bath concentrations of 1, 10, and 30 μM (0.37, 3.7, and 11.1 μg/mL) in 0.1% DMSO in aqueous buffer. Geldanamycin (1 μM) served as positive control for trafficking of hERG-WT. Astemizole (1 μM) was used as positive control hERG blocker.

On the basis of the reduced expression of the hERG-WT on the cell membrane of 29 and 36% from control expression at 10 and 30 μM (3.7 and 11.0 μg/mL), respectively, it is concluded that RPV has the potential to reduce trafficking of the hERG channel. The overexpression of hERG-SM on the cell membrane of 146, 155, and 213% of control values at RPV base concentrations of 1, 10, and 30 μM (0.37, 3.7 and 11.0 μg/mL), respectively, is an indication of the potential of RPV to inhibit the hERG channel. This result is in line with that of the patch clamp study with CHO cells expressing the hERG channel (see Section 4.1.2.1).

#### 4.1.2.3. Electrophysiological Parameters of the Isolated Arterially Perfused Rabbit Left Ventricular Wedge

Electrophysiological and other cardiophysiological parameters were studied in isolated arterially perfused rabbit left ventricular wedge preparations (Mod4.2.1.3/TMC278-NC341). The effects of RPV base at concentrations increasing from 10 nM to 10 μM (3.7 ng/mL to 3.7 μg/mL) were evaluated relative to vehicle control (buffer containing 0.1% DMSO). The parameters measured were: the duration of the QT and QRS intervals, the time between the peak and the end of the T wave (Tp-Te), as a measure of transmural dispersion of repolarization (TDR), and the rTp-Te-interval (Tp-Te/QT ratio), as indicator of the potential to induce phase 2 EADs. Moreover, FC, in-excitability (inability of the preparation to follow the stimulation) and the occurrence of VT and VF were recorded. The potential to induce TdP was assessed semiquantitatively on the basis of QT duration, TDR measured as (Tp-Te)/QT, and the occurrence of phase 2 EADs.

RPV caused 6 and 9% prolongation of the QT-interval from baseline at nominal bath concentrations of 1 and 10 μM (0.37 and 3.7 μg/mL), respectively. Only at 10 μM (3.7 μg/mL), the assessment of the potential to induce TdP resulted in a marginal score of 0.5. No other significant or physiologically relevant changes were noted in any of the other parameters.

#### 4.1.2.4. Cardiovascular Parameters in Telemetered Guinea Pig

The potential of orally administered RPV to inhibit in vivo trafficking of the hERG channel was evaluated through the occurrence of delayed onset QT-prolongation in a 16-day repeat-dose

telemetered guinea pig model (Mod4.2.1.3/TMC278-NC327 and 3). The dose of RPV was selected in a preliminary kinetics study as that giving a maximum plasma concentration ($C_{max}$) value of approximately 2 times the human $C_{max}$ at 75 mg RPV q.d., 466 ng/mL, in clinical phase IIb study C204. This 75mg-dose gave approximately 10 ms QT-prolongation in the TQT study C131, at a steady state median maximum plasma concentration of 636 ng/mL. RPV was suspended in an aqueous mixture of hydroxypropylmethylcellulose (0.5%) and Tween 80 (in demineralized water) and dosed by gavage at 10 mg/kg for 16 consecutive days. Recordings of heart rate, body temperature, and ECG made for 4 hours after dosing were evaluated. From ECGs, the durations of the QRS complex, and the PQ and QT-interval (with or without correction for heart rate according to Bazett or Fridericia were reported every 30 minutes.

RPV at a dose of 10 mg/kg/day for 16 consecutive days which gave mean $C_{max}$ values of 0.689 – 0.911 µg/mL throughout the dosing period, had no notable effects on the measured ECG parameters, heart rate, or body temperature.

## 4.2. Pulmonary Safety

### 4.2.1. Respiratory Parameters in Anesthetized Dog

Respiration pressure and flow, tidal volume, expiratory airway resistance, dynamic lung compliance, and arterial blood parameters (pH, oxygen tension and saturation, $CO_2$ tension, and concentration of electrolytes, hemoglobin, glucose, lactate, chloride, and bicarbonate) were studied in CPF648 (FK4126) in groups of 4 anesthetized beagle dogs (Mod4.2.1.3/TMC278-CPF648 and Mod4.2.1.3/TMC278-CPF648 [FK4126]). The animals received an intravenous infusion for 1 hour at a flow of 2 mL/kg of 2.5 mg RPV base/mL in PEG400, resulting in a dose of 5 mg/kg, or the vehicle PEG400. Parameters were recorded during the infusion and for 3 hours after the end of the administration.

None of the respiratory or arterial blood parameters were affected during or for 3 hours after the 1-hour intravenous infusion. The mean plasma concentration of RPV at the end of the infusion was 2.62 µg/mL and decreased to 0.484 µg/mL, 3 hours after cessation of the infusion.

### 4.2.2. Respiratory Parameters in Telemetered Conscious Dog

Respiratory rate and tidal volume were not affected in 4 telemetered conscious male beagle dogs at 1, 2 and 4 hours after single oral (gavage) escalating doses of 0 (vehicle), 20, 80 and 160 mg RPV base/kg dissolved in PEG400 plus citric acid (Mod4.2.1.3/Exp5555 [[redacted] 843412]), with a dosing interval of 1 week. For exposure data, see Section 4.1.1.6.

## 4.3. Central Nervous System Safety

### 4.3.1. Neurobehavior and Motor Activity in Rat

RPV was tested in a modified test according to Irwin in Sprague Dawley rats (5 males/group) in order to evaluate their neurofunctional integrity (Mod4.2.1.3/TMC278-Exp5560). RPV base dissolved in PEG400 with citric acid was administered orally by gavage in a volume of

10 mL/kg at 40, 120, and 400 mg/kg. Mortality, observations of motor-affective and sensori-motor behavior and neurologic and autonomic functioning upon manipulation and made at cage-side, general clinical signs, and body weight were evaluated during a 7-day observation period following the single oral administration.

No mortality was seen in any group and no adverse clinical signs were noted up to 400 mg/kg. Neurofunctional integrity of rats was not affected at 40 or 120 mg/kg and there were no signs of neurotoxic effects recorded up to Day 7 after dosing. At a dose of 400 mg/kg, occasionally animals showed a single slightly abnormal behavioral parameter, 8 hours after dosing, and all animals showed a slightly reduced pupil size, 2 hours after dosing. These parameters returned to normal 24 hours after dosing. No compound-related neurological changes or delayed neurotoxicity were noted.

Data from a separate toxicokinetic study in male rats (Mod4.2.3.2/FK4243 [Addendum to the Toxicology Report EXP5535]) with the same formulation and oral doses, indicated that $T_{max}$ values were reached within 3 h (40 mg/kg) or within 8 h (120 and 400 mg/kg) after dosing. Mean $C_{max}$ values were 1.6, 2.8, and 9.9 µg/ml at 40, 120, and 400 mg/kg, respectively.

### 4.3.2. Neurobehavior Assessment in the Instrumented, Awake Dog

Behavioral effects of a single oral dose of 20 mg/kg RPV base dissolved in PEG400 were assessed upon cage-side observations in instrumented awake dogs (Mod4.2.1.3/TMC278-CPF654 and Mod4.2.1.3/TMC278-CPF654 [FK4125]).

RPV had no overt effects on behavior. The median maximum plasma concentration of RPV was 1.5 µg/mL.

### 4.3.3. Locomotor Activity in the Telemetered Conscious Dog

Four telemetered male beagle dogs were dosed orally via gavage at escalating doses of 0 (vehicle), 20, 80 and 160 mg/kg of RPV base dissolved in PEG400 plus citric acid (Mod4.2.1.3/TMC-278-Exp5555 [[redacted] 843412] and Mod4.2.1.3/TMC-278-Exp5555-FK4280 [[redacted] 843412]), with 1-week dosing intervals.

RPV did not influence locomotor activity at cage-side observations over 12 hours following dosing. For exposure data, see Section 4.1.1.6.

## 5. PHARMACODYNAMIC DRUG INTERACTIONS

For the pharmacodynamic drug interactions, please refer to Mod2.7.2/Virology Summary.

## 6. DISCUSSION AND CONCLUSIONS

As the active moiety for the LA formulation is essentially the same as for the oral formulation (HCl salt for the oral formulation versus base for the LA formulation), therefore (safety) pharmacology studies conducted for the development of oral RPV are deemed relevant for RPV LA as well.

In the RPV oral formulation development program, an extensive package of studies was conducted including primary and secondary pharmacodynamics studies, and in vitro and in vivo cardiovascular safety, pulmonary safety and central nervous system safety studies.

**Secondary Pharmacodynamics**

The testing on a variety of receptors, human DNA polymerases, stomach ATPase, and gastric acidity did not reveal any significant effects secondary to the primary anti-HIV effect of RPV. Therefore, and in line with ICH guideline S7A, safety pharmacology evaluations focused on the battery of core vital systems (cardiovascular, pulmonary and nervous).

**Cardiovascular Safety Pharmacology**

The standard battery of cardiovascular safety studies indicates that RPV has the potential to inhibit partially the hERG channel at the unbound concentration of 37 ng/mL and higher. Even the lowest concentration of RPV base that caused significant potassium current reduction in protein-free medium (37 ng/mL) is much higher than the unbound concentration that can be achieved in the in vivo cardiovascular safety studies in guinea pigs and dogs at the highest dose administered. These species have only 0.14% and 0.65% unbound RPV base, respectively. No other cardiovascular or cardio-electrophysiological parameters were affected by RPV. The relevance of the decreased vascular resistance and increased cardiac output noted in the anesthetized dog study (Section 4.1.1.4) is questionable as the vehicle PEG400 appeared to have a clear effect on these parameters, opposite to that of RPV base.

In a thorough QT study for the oral program (Mod5.3.4.1/TMC278-C131), a QTc-prolongation was noted and considered unexpected in view of the results of the standard battery studies. This study in which doses of 75 and 300 mg RPV q.d. were given for 11 days, showed dose-related clinically relevant QTcF-prolongation which became manifest after 11 days of treatment.

In order to investigate the mechanism of action of the clinical QTc-prolongation, additional nonclinical cardiovascular safety studies were done (as described below), as well as additional clinical studies. No QT-prolongation was observed with the 25 mg once daily dose of RPV, marketed as EDURANT®. Also, no clinically significant QTc prolongation was noted in the RPV LA development program (Mod2.7.4/Sec5.3.5.3).

**Mechanism of QT-prolongation**

The potential of RPV to inhibit potassium currents $I_{Kr}$, $I_{Ks}$, and $I_{to}$ involved in the repolarization phase of the cardiac action potential is likely a contributing factor but cannot explain some aspects of the QTcF-prolongation seen in TQT study C131. The inhibition of these potassium currents in the cells expressing their channels is a direct concentration-related effect. For that reason, this effect cannot explain for the delayed onset of the QTc-prolongation in the TQT study. Moreover, in TQT study C131, the median maximum plasma concentration on Day 1 in subjects treated with 300 mg was higher than that on Day 11 with 75 mg. On Day 1, 300 mg did not elicit a clinically relevant QTc-prolongation whereas 75 mg did so on Day 11. Unfortunately, due to the adsorption of RPV to the in vitro equipment, the margin between the unbound

concentrations of RPV at which the inhibition of the potassium currents occurred in the serum-free in vitro conditions (nominally 0.11 µg/mL and higher) and the free $C_{max}$ values associated with QTcF-prolongation in TQT study C131 (see Table 1) cannot be accurately determined but is likely significant.

**Mechanism Delayed Onset**

Several drugs (e.g., pentamidine, As2O3) are now known to prolong the QT-interval in man by interfering with hERG trafficking [1] and this can be demonstrated in repeat-dose animal models. The concentration-related inhibition of trafficking of the hERG channel seen in the hERG-Lite® test could contribute to the delayed onset of the QTcF-prolongation seen in TQT study C131. However, it is to be noted that the in vitro inhibition of trafficking becomes manifest after hours whereas the QTc-prolongation by RPV needs days to develop in the TQT study. In addition, the repeat-dose study with telemetered guinea pigs failed to induce QT-prolongation even after treatment for 16 days. So, the trafficking inhibition seen in vitro did not occur in vivo whereas delayed onset QTcF-prolongation occurred in subjects treated with 75 mg in the TQT study at the median maximum plasma concentration (636 ng/mL) of RPV that was similar as that in the repeat-dose guinea pig study. Moreover, ECG recordings in a repeat-dose study with cynomolgus monkeys (Mod4.2.3.2/TMC278-NC326 [FK6541]) and in the repeat-dose general toxicity studies with RPV base in dogs (see Mod2.6.6/Sec3.1.4) did not indicate any QT-prolongation. The highest $C_{max}$ value in the 12-month study in male dogs was 4.1 µg/mL with a plasma protein binding of 99.3%. This value was approximately 6 times higher than that in man at 75 mg RPV q.d. in C131, after 11 days of administration.

Non-cardio-electrophysiological mechanisms to explain for the delayed onset of the QTc-prolongation comprise an increase over time of the exposure to RPV or to one or more of its metabolites or an increase of the concentration of RPV or of one or more of its metabolites in the myocardium.

In man, exposure to RPV increased over time until steady state was reached before Day 11. However, in C131 this increase in exposure from Day 1 to Day 11 at the dose of 75 mg q.d. was less than the difference in exposure between 75 and 300 mg on Day 1 (see Table 1). Therefore, concentration alone cannot explain the delayed onset of the QTcF-prolongation noted at 300 mg in TQT study C131 and likely also not that at 75 mg. RPV is metabolized in man predominantly by oxidation to metabolites that are likely to have a shorter residence time than the parent compound. After a single radiolabelled dose, 76% of the radioactivity in plasma on the basis of $C_{max}$ is unchanged drug whereas it is 51% on the basis of AUC. There are no major human metabolites (>10% of $C_{max}$ of the parent compound) (see Mod2.7.2/Summary of Clinical Pharmacology for human exposure data and Mod2.6.4/Sec5.1 for the metabolism data). After repeated oral administration of RPV for 11 days in healthy subjects (Mod5.3.4.1/TMC278-C131) at 75 and 300 mg qd, there was no disproportionate increase in exposure of any of the relevant metabolites compared to the parent compound exposure (Mod4.2.2.4/TMC278-FK10104). The most relevant metabolites detected in this study have been already detected in previous studies in human or in animals. RPV accumulated 2-3-fold from Day 1 to Day 11 in TQT study C131.

These increases in exposure over time probably contributed to the longer QT intervals on Day 11 than Day 1, but do not entirely explain them.

**Potential to Induce TdP**

The perfused rabbit ventricular wedge study indicated that RPV has at most a marginal potential to induce arrhythmogenic effects like TdP (ie. mild QT and borderline TdP proarrhythmia score) at very high concentrations of essentially free drug equivalent (10 µM). QTc-prolongation as such does not lead necessarily to TdP. The dispersion of the repolarization of the cardiac action potential over the ventricular wall plays an equally important role as QT-prolongation whereas the occurrence of EADs adds even more weight in the assessment of the potential to induce TdP, according to Liu et al. [2]. RPV did not induce EADs, TdP, VT or VF or any other proarrhythmic effects and caused no increase in TDR. So, only the QT-prolongation contributed to the TdP score of 0.5. Compounds with a history of TdP such as clarithromycin, erythromycin, and cisapride typically have a score of around 5 in this model [2]. The margin between the concentration of RPV that caused a marginal TdP score of RPV and the unbound $C_{max}$ at 75 mg RPV q.d., 0.3% of 636 ng/mL (see Table 1), after 11 days of treatment in TQT study C131, cannot be determined accurately due to the loss in the test system. However, it is likely that the margin is very high, almost 1000 based on nominal bath concentrations. The median $C_{max}$ values in HIV-infected treatment-naïve subjects treated for 48 weeks with 25 mg q.d. in clinical phase III studies C209 and C215 are 139 and 133 ng/mL, respectively; again 5 times lower compared to the 75 mg dose. As the human $C_{max}$ values after 600 mg or an initial dose of 900 mg (on the day of last oral dose) RPV LA are comparable to the values after 25 mg RPV orally, the conclusion also applies to the LA application.

**Pulmonary Safety Pharmacology**

RPV tested up to a maximum plasma concentration of 2.6 µg/mL in anesthetized dogs or conscious instrumented dogs showed no potential to affect respiratory parameters. So, the margin of exposure for respiratory effects by RPV at a clinical dose of 25 mg q.d. is 13, and similar for RPV LA at an initial clinical dose of 900 mg (on the day of last oral dose).

**Nervous System Safety Pharmacology**

At the level of the nervous system, RPV had no effects in dogs, up to a maximum plasma concentration of 1.5 µg/mL. In rats, incidental motor-affective and sensori-motor behavior parameters were affected and pupil size (autonomic parameter) was slightly reduced on the day of dosing, at an estimated maximum plasma concentration of 10 µg/mL. The repeat-dose general toxicity studies have not indicated any effect of RPV on the nervous system (see Mod2.6.6). It is concluded that the margin of exposure for effects of RPV on the nervous system at a clinical dose of 25 mg q.d. is at least 7 and similar for RPV LA at an initial clinical dose of 900 mg (on the day of last oral dose).

**Overall Conclusion**

RPV had no effects on secondary pharmacodynamic parameters or on the core battery of safety pharmacology tests, apart from inhibitory effects on some cardiac potassium currents and channels and mild QT-prolongation in the rabbit ventricular wedge. The observed inhibition of trafficking of the hERG channel in vitro, but not confirmed in vivo in guinea pigs may be involved in the delayed onset of the QTcF-prolongation observed in clinical TQT study C131. However, kinetic mechanisms may be involved, also. Importantly, the effects in nonclinical models allow concluding that RPV has only a marginal potential to induce proarrhythmic effects.

As the $C_{max}$ values with the highest proposed RPV LA dose (initial single dose of 900 mg on the day of last oral dose) are similar to those after 25 mg RPV, these conclusions are also applicable for RPV LA.

**Table 1 Exposure and QTcF-Data in QTc-Prolongation Studies With RPV**

| | 25 mg q.d. | | | | 75 mg q.d. | | | | 300 mg q.d. | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day 1 | | Day 11 | | Day 1 | | Day 11 | | Day 1 | | Day 11 | |
| | ΔQTcF | $C_{max}$ | ΔQTcF | $C_{max}$ | ΔQTcF | $C_{max}$ | ΔQTcF | $C_{max}$ | ΔQTcF | $C_{max}$ | ΔQTcF | $C_{max}$ |
| TQT | | | | | 1.0 | 0.867 | 10.4 | 1.908 | 3.9 | 2.514 | 23.8 | 4.995 |
| C131 | | | | | | (289) | | (636) | | (838) | | (1665) |
| Pilot | | | 2.2 | 0.687 | | | | | | | | |
| C151 | | | | (229) | | | | | | | | |
| TQT | | | 2.0 | 0.741 | | | | | | | | |
| C152 | | | | (247) | | | | | | | | |

ΔQTcF: median increase compared to baseline of QT-interval corrected for heart rate according to Fridericia in ms; $C_{max}$: maximum unbound plasma concentration of RPV in ng/mL (0.3% of measured $C_{max}$; measured $C_{max}$ within parentheses); q.d.: per day; TQT: thorough QTc-prolongation study according to ICH E14.

## 7. TABLES AND FIGURES

Supplemental tables and figures are included at appropriate points throughout the summary within the text; additional information is provided within the Pharmacology Tabulated Summaries, located in Mod2.6.3.

## 8. LIST OF LITERATURE CITATIONS

Literation citations are located in Mod4.3.

1. Dennis A, Wang L, Wan X, Ficker E. hERG-channel trafficking: novel targets in drug-induced long QT syndrome. Biochemical Society Transactions 35: 1060-1063 (2007).
2. Liu T, Brown B, Wu Y, et al. Blinded validation of the isolated arterially perfused rabbit ventricular wedge in preclinical assessment of drug-induced proarrhythmias. Heart Rhythm 3: 948-956 (2006).
3. Robinson S, Worton S, Simecek N, et al. Effect of pentamidine on QT interval in the conscious guinea-pig and hERG trafficking. Journal of Pharmacological and Toxicological Methods 58: 162 (2008).
4. Wible BA, Hawryluk P, Ficker E, et al. HERG-Lite: A novel comprehensive high-throughput screen for drug-induced hERG risk. Journal of Pharmacological and Toxicological Methods 52: 136-145 (2005).

**Janssen Research & Development**

**Pharmacology Tabulated Summary**

# MODULE 2.6.3

# Rilpivirine Long-Acting

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## 2.6.3.1 Pharmacology: Overview

**Test Article:** Rilpivirine[a]

| Type of Study | Test System | Route (Vehicle/Formulation) | GLP | Test Facility | Study No. Location in CTD |
|---|---|---|---|---|---|
| **Primary Pharmacodynamics:** Please refer to Mod2.7.2/Virology Summary[b] | | | | | |
| **Secondary Pharmacodynamics** | | | | | |
| Receptor binding | Cells & enzymes | In vitro | N | [redacted], France | TMC278-870219 Mod4.2.1.2 |
| Receptor binding | Guinea pig right atrium | In vitro | N | [redacted], Taiwan | TMC278 NC204 (2) (TOX7649; [redacted] 1074888) Mod4.2.1.2 |
| Receptor binding | Pig stomach | In vitro | N | [redacted], Taiwan | TMC278 NC204 (3) (TOX7649; [redacted] 1074888) Mod4.2.1.2 |
| Gastric acidity | Rat/Wistar | Intraperitoneal injection | N | [redacted], Taiwan | TMC278 NC204 (1) (TOX7649; [redacted] 1074888) Mod4.2.1.2 |
| Polymerase inhibition | Human Polymerase α, β, γ | In vitro | N | [redacted], USA | TMC278-1646_0005343 Mod4.2.1.2 |
| **Safety Pharmacology: In Vitro** | | | | | |
| Chemical stability in hERG medium | Radioactivity determination | In vitro | N | J&J PRD, Belgium | TMC278-NC338 (FK6822) Mod4.2.1.3 |
| Dummy runs | Langendorff-perfused rabbit heart | In vitro | N | J&J PRD, Belgium | TMC278-NC381 Mod4.2.1.3 |
| Cardiovascular safety (cardiac membrane potassium current) | $I_{Kr}$ in transfected CHO cells expressing hERG | In vitro | N | [redacted] Germany | TMC278-CPF730 Mod4.2.1.3 |
| Cardiovascular safety (cardiac action potential) | Guinea pig isolated atrium | In vitro | N | Janssen Research Foundation, Belgium | TMC278- N168576 Mod4.2.1.3 |
| Cardiovascular safety (cardiac membrane potassium current) | $I_{Ks}$ in transfected CHO cells expressing KvLQT1/minK | In vitro | N | J&J PRD, Belgium | TMC278-NC342 Mod4.2.1.3 |

(Continued)

## 2.6.3.1 Pharmacology: Overview (Continued)

**Test Article:** Rilpivirine[a]

| Type of Study | Test System | Route (Vehicle/Formulation) | GLP | Test Facility | Study No. Location in CTD |
|---|---|---|---|---|---|
| Cardiovascular safety (cardiac membrane ion currents) | $I_{Ks}$ in transfected HEK293 cells expressing KvLQT1/minK<br>$I_{to}$ in transfected HEK293 cells expressing $hK_v4.3$<br>$I_{K1}$ in transfected HEK293 cells expressing $hK_{ir}2.1$<br>$I_{Na}$ in transfected HEK293 cells expressing $hNa_v1.5$<br>$I_{Ca,L}$ in transfected HEK293 cells expressing $hCa_v1.2$ | In vitro | N | [redacted], USA | TMC278-NC331<br>Mod4.2.1.3 |
| Cardiovascular safety (cardiac membrane potassium current) | Surface expression of hERG channels in HEK293 cells | In vitro | N | [redacted], USA | TMC278-NC330<br>Mod4.2.1.3 |
| Cardiovascular safety (cardiac action potential) | Arterially perfused rabbit ventricular wedge | In vitro | N | J&J PRD, Belgium | TMC278-NC341<br>Mod4.2.1.3 |
| **Safety Pharmacology: In Vivo** | | | | | |
| Cardiovascular safety (ECG and cardio-hemodynamic parameters) | Anesthetized Guinea pig/ Dunkin Hartley | Intravenous/bolus (PEG400) | N | J&J PRD, Belgium | TMC278-CPF643<br>Mod4.2.1.3 |
| Cardiovascular safety (ECG, cardio-hemodynamic and respiratory parameters) | Anesthetized dog/beagle | Intravenous/infusion (PEG400) | N | J&J PRD, Belgium | TMC278-CPF648 and TMC278-CPF648 (FK4126)<br>Mod4.2.1.3 |
| Cardiovascular safety (ECG and cardio-hemodynamic parameters) | Conscious instrumented dog/ beagle | Oral/gavage (PEG400) | N | J&J PRD, Belgium | TMC278-CPF654 and TMC278-CPF654 (FK4125)<br>Mod4.2.1.3 |
| Cardiovascular and respiratory safety (ECG, cardio-hemodynamic and respiratory parameters) | Conscious telemetered dog/ beagle | Oral/gavage (citric acid in PEG400) | Y | [redacted], Switzerland | TMC278-Exp5555 ([redacted] 843412) and TMC278-Exp5555-FK4280 ([redacted] 843412)<br>Mod4.2.1.3 |
| Cardiovascular safety (ECG, cardio-hemodynamic and respiratory parameters) | Telemetered Guinea pig/ Dunkin Hartley | Oral/gavage (0.5% Methocel, 0.2% Tween 80 and water) | N | J&J PRD, Belgium | TMC278-NC327<br>Mod4.2.1.3 |
| Neurobehavior and motor activity (modified Irwin test) | Rat/Sprague Dawley | Oral/gavage (citric acid in PEG400) | Y | J&J PRD, Belgium | TMC278-Exp5560<br>Mod4.2.1.3 |

(Continued)

## 2.6.3.1 Pharmacology: Overview (Continued)

**Test Article:** Rilpivirine[a]

| Type of Study | Test System | Route (Vehicle/Formulation) | GLP | Test Facility | Study No. Location in CTD |
|---|---|---|---|---|---|
| **Pharmacodynamic Drug Interactions:** Please refer to Mod2.7.2/Virology Summary | | | | | |

[a] all secondary pharmacodynamic or safety pharmacology studies were conducted with rilpivirine (oral compound), and not with rilpivirine LA. As the active ingredient for the LA application is the same as for the oral application (HCl salt for the oral formulation versus base for the LA formulation), no dedicated (safety) pharmacology studies were conducted in support of the rilpivirine LA development.
[b] no Mod2.6.3.2 Primary Pharmacodynamics table is included therefore.

ECG: electrocardiogram; hERG: human ether-à-go-go related gene, CHO: Chinese hamster ovary, HEK293: human embryonic kidney cell line; $I_{Ca.L}$: high threshold calcium current; $I_{Ki}$; inward rectifying potassium current; $I_{Kr}$: rapidly activating rectifying potassium current; $I_{Ks}$: slowly activating rectifying potassium current; $I_{Na}$: fast sodium current; $I_{to}$: transient outward potassium current; J&J PRD: Johnson and Johnson pharmaceutical research and development; LA: long-acting; N: no; Y: yes

## 2.6.3.3 Secondary Pharmacodynamics

**Test Article:** Rilpivirine[a]

| Type of Study | In vitro System or Species/Strain | Route/ Method of Administration | Dose (Conc.)[b] (Controls) | Noteworthy Findings | GLP | Study Number Location in CTD |
|---|---|---|---|---|---|---|
| Receptor binding | Cells & enzymes | In vitro | 10 µM TMC278 base (3.7 µg/mL) (1% DMSO in aqueous buffer) | No inhibition of α- or β-adrenergic, dopaminergic, muscarinergic, serotonergic, opoid, interleukin, or chemokine receptors | N | TMC278-870219 Mod4.2.1.2 |
| Receptor binding | Guinea pig right atrium | In vitro | 30 µM TMC278.HCl (11 µg/mL) (0.1% DMSO in aqueous buffer) | No agonistic or antagonistic activity on histamine $H_2$ receptors | N | TMC278-NC204 (2) Mod4.2.1.2 |
| Receptor binding | Pig stomach | In vitro | 10 µM TMC278.HCl (3.7 µg/mL) (0.1% DMSO in aqueous buffer) | No inhibition of ATPase | N | TMC278-NC204 (3) Mod4.2.1.2 |
| Gastric acidity | Rat/Wistar 5M | Intraperitoneal injection | 10 mg TMC278.HCl/kg (9.1 mg/kg) (Positive control: 10 mg cimetidine/kg) (2% Tween 80 in 0.9% aqueous NaCl) | No inhibition of pentagastrin-stimulated gastric acidity | N | TMC278-NC204 (1) Mod4.2.1.2 |
| Polymerase inhibition | Human polymerase α, β, γ | In vitro | Up to 1000 µM TMC278 base (370 µg/mL) (Positive control for pol α, β: DideoxyATP) (TRIS buffer with 10% DMSO and 0.7% β-octyl glucoside) | No inhibition of polymerase α, β, γ | N | TMC278-1646_0005343 Mod4.2.1.2 |

[a] all secondary pharmacodynamic studies were conducted with rilpivirine (oral compound), and not with rilpivirine LA. As the active ingredient for the LA application is the same as for the oral application (HCl salt for the oral formulation versus base for the LA formulation), no dedicated secondary pharmacology studies were conducted in support of the rilpivirine LA development.

[b] dose of HCl-salt presented as base equivalents

ATP(ase): adenosine triphosphate(ase); DMSO: dimethyl sulfoxide; M: male; NA: not applicable; NaCl: sodium chloride; LA: long-acting

## 2.6.3.4 Safety Pharmacology

**Test Article:** Rilpivirine[a]

| Organ Systems Evaluated | Species/Strain Sex/No. Per Group | Route (Vehicle/ Formulation) | Doses (Concentrations) | Noteworthy Findings | GLP | Study No./ Location in CTD |
|---|---|---|---|---|---|---|
| **In Vitro Studies** | | | | | | |
| Chemical stability in hERG medium | Radioactivity determination | In vitro (DMSO in Tyrode buffer) | 3, 10 µM | The radioactive concentration of the TMC278 stock solution of 10 mM in DMSO was 99.1% of the theoretical radioactive concentration.<br>The radioactive concentration of 10 µM TMC278 and 3 µM TMC278 in Tyrode buffer was 84.7% and 58.0% of the theoretical radioactive concentration, respectively. | No | TMC278-NC338 (FK6822) Mod4.2.1.3 |
| Cardiovascular safety (cardiac membrane potassium current) | $I_{Kr}$ in transfected CHO cells expressing hERG | In vitro (0.1% DMSO in aqueous buffer) | 0.1, 0.3, 3 µM (0.037, 0.111, 1.11 µg/mL) | **0.1 µM**: 10% inhibition<br>**0.3 µM**: 33% inhibition<br>**3 µM**: 80% inhibition | No | TMC278-CPF730 Mod4.2.1.3 |
| Cardiovascular safety (cardiac action potential) | Isolated Guinea pig right atrium | In vitro (0.01 – 10% DMSO in aqueous buffer) | 0.01, 0.03, 0.1, 1, 3, 10 µM (0.004, 0.011, 0.037, 0.37, 1.11, 3.7 µg/mL | **1 µM:** RC 86% of baseline<br>**3 µM:** RC 72% of baseline<br>**10 µM**: RC 44% of baseline<br>No effects on force of contraction compared to vehicle<br>No effects on ERP compared to vehicle at 0.1 and 10 µM | No | TMC278-N168576 Mod4.2.1.3 |
| Cardiovascular safety (cardiac membrane potassium current) | $I_{Ks}$ in transfected CHO cells expressing KvLQT1/minK | In vitro (0.3% DMSO in aqueous buffer) | 0.3, 1, 3, 10 µM (0.111, 0.370, 1.11, 3.7 µg/mL) | **1 µM**: 17% inhibition<br>**3 µM**: 47% inhibition<br>**10 µM:** 73% inhibition<br><br>$IC_{50}$: 3.1 µM (1.15 µg/mL) | No | TMC278-NC342 Mod4.2.1.3 |

(Continued)

## 2.6.3.4 Safety Pharmacology (Continued)

**Test Article:** Rilpivirine[a]

| Organ Systems Evaluated | Species/Strain Sex/No. Per Group | Route (Vehicle/ Formulation) | Doses (Concentrations) | Noteworthy Findings | GLP | Study No./ Location in CTD |
|---|---|---|---|---|---|---|
| **In Vitro Studies (continued)** | | | | | | |
| Cardiovascular safety (cardiac membrane ion currents) | $I_{Ks}$ in transfected HEK293 cells expressing KvLQT1/minK<br>$I_{to}$ in transfected HEK293 cells expressing $hK_V4.3$<br>$I_{Ki}$ in transfected HEK293 cells expressing $hK_{ir}2.1$<br>$I_{Na}$ in transfected HEK293 cells expressing $hNa_v1.5$<br>$I_{Ca,L}$ in transfected HEK293 cells expressing $hCa_v1.2$ | In vitro (0.3% DMSO in aqueous buffer) | 0.1, 0.3, 1 µM (0.037, 0.11, 0.37 µg/mL) | **1 µM**: 19.1% inhibition<br>**0.3 µM**: 13.6% inhibition<br>**1 µM**: 35.5% inhibition<br>No effects<br>No effects<br>No effects | No | TMC278-NC331 Mod4.2.1.3 |
| Cardiovascular safety (cardiac membrane potassium current) | transfected HEK293 cells[b] | In vitro (0.1% DMSO in aqueous buffer) | 1, 10, 30 µM (0.37, 3.7, 11.1 µg/mL) | **1 µM:** 146% expression hERG-SM<br>**10 µM**: 155% expression hERG-SM<br>29% block hERG-WT<br>**30 µM:**213% expression hERG-SM<br>36% block hERG-WT | No | TMC278-NC330 Mod4.2.1.3 |
| Cardiovascular safety (cardiac action potential) | Isolated arterially perfused rabbit left ventricular wedge | In vitro (0.1% DMSO in aqueous buffer) | 0.01, 0.1, 1, 10 µM (0.004, 0.037, 0.37, 3.7 µg/mL) | **1 µM**: QT-interval 106% of baseline<br>**10 µM**: QT-interval 109% of baseline. TdP score 0.5.<br>No EADs, TdP, VT, VF, or in-excitability over the whole conc. range | No | TMC278-NC341 Mod4.2.1.3 |
| **In Vivo Studies** | | | | | | |
| Cardiovascular safety | Anesthetized Guinea pig/Dunkin Hartley 7F | Intravenous escalating doses 15 min interval (PEG400) | 0.16, 0.32, 0.64, 1.25, 2.5, 5 mg/kg | No effects on HR, MABP, or ECG<br>Plasma conc.:9.2 µg/mL<br>Heart conc.: 47.7 µg/g<br>Lung conc.: 11.7 µg/g<br>All conc. 5 min after dosing at 5 mg/kg | No | TMC278-CPF643 Mod4.2.1.3 |

(Continued)

## 2.6.3.4 Safety Pharmacology (Continued)

**Test Article:** Rilpivirine[a]

| Organ Systems Evaluated | Species/Strain Sex/No. Per Group | Route (Vehicle/ Formulation) | Doses (Concentrations) | Noteworthy Findings | GLP | Study No./ Location in CTD |
|---|---|---|---|---|---|---|
| Cardiovascular and pulmonary safety | Anesthetized dog/beagle 4 | Intravenous infusion 1 hour (PEG400) | 5 mg/kg | **5 mg/kg:** SVR: -25% to BL; vehicle: +29% to BL PVR: -20% to BL; vehicle: +31% to BL Cardiac output: +31% to BL; vehicle: -12% to BL No effect on other parameters Plasma $C_{end\ of\ inf.}$ = 2.62 µg/mL. Plasma $C_{3h\ after\ inf.}$ = 0.721 µg/mL | No | TMC278-CPF648 and TMC278-CPF648 (FK4126) Mod4.2.1.3 |
| Cardiovascular safety | Conscious instrumented dogs/beagle 3M/11F | Oral/gavage Single dose (PEG400) | 20 mg/kg | No effects Median $C_{max}$ = 1.5 µg/mL (at 240 min) | No | TMC278-CPF654 and TMC278-CPF654 (FK4125) Mod4.2.1.3 |
| Cardiovascular and pulmonary safety and locomotor activity | Conscious telemetered dog/beagle 4M | Oral/gavage Single dose (PEG400) | 20, 80, 160 mg/kg | No effects on cardiac hemodynamic, electrophysiological, respiratory, or locomotor activity parameters. | Yes | TMC278-Exp5555 ([redacted] 843412) and TMC278-Exp5555-FK4280 ([redacted] 843412) Mod4.2.1.3 |
| Cardiovascular safety | Telemetered Guinea pig/Dunkin Hartley 6F | Oral/gavage for 16 days (HPMC 0.5% + 0.11 – 0.2% tween 80 in water) | 10 mg/kg | No effects on HR; ECG, BT Plasma $C_{max}$ = 0.689 – 0.911 µg/mL throughout the dosing period | No | TMC278-NC327 Mod4.2.1.3 |

(Continued)

## 2.6.3.4 Safety Pharmacology (Continued)

**Test Article:** Rilpivirine[a]

| Organ Systems Evaluated | Species/Strain Sex/No. Per Group | Route (Vehicle/ Formulation) | Doses (Concentrations) | Noteworthy Findings | GLP | Study No./ Location in CTD |
|---|---|---|---|---|---|---|
| Behavior and neurologic and autonomic functioning | Rat/ Sprague Dawley 5M | Oral/gavage Single dose (PEG400) | 40, 120, 400 mg/kg | **400 mg/kg**: Slightly abnormal single behavioral parameter, 8 hrs after dosing Slightly reduced pupil size, 2 hrs after dosing. | Yes | TMC278-Exp5560 Mod4.2.1.3 |

[a] all safety pharmacology studies were conducted with rilpivirine (oral compound), and not with rilpivirine LA. As the active ingredient for the LA application is the same as for the oral application (HCl salt for the oral formulation versus base for the LA formulation), no dedicated (safety) pharmacology studies were conducted in support of the rilpivirine LA development.

[b] Direct blocking of wild type hERG(-WT) channel and blocking of trafficking of hERG channel on the basis of overexpression at cell membrane of chaperone-resistant single mutant hERG-SM channel over hERG-WT in transfected HEK293 cells

BL = baseline; BT: body temperature; $C_{max}$: maximal concentration; DMSO: dimethylsulfoxide; CHO: Chinese hamster ovary; DMSO: dimethylsulfoxide; EAD: early afterdepolarization; ECG = electrocardiogram; ERP: effective refractory period (= maximal frequency of stimulations not followed by contraction); F: female; HEK293: human embryonic kidney cell line; hERG: human-ether-à-go-go related gene; hERG-WT: wild type hERG channel; hERG-SM: chaperone resistant single mutant hERG channel; HPMC: hydroxypropylmethylcellulose, HR: heart rate; $IC_{50}$: median inhibitory concentration; $I_{Ca,L}$: high threshold calcium current; $I_{Ki}$: inward rectifying potassium current; $I_{Kr}$: rapidly activating rectifying potassium current; $I_{Ks}$: Slowly activating rectifying potassium current; $I_{Na}$: fast sodium current, $I_{to}$: transient outward potassium current; L: long-acting; M: male; MABP: mean arterial blood pressure; NA: not applicable; PEG: polyethylene glycol; PVR: peripheral vascular resistance; QT-interval: time between peak Q wave and end T wave; RC: rate of spontaneous contraction; SVR: systemic vascular resistance; TdP: torsade des pointes; VT: ventricular tachycardia; VF: ventricular fibrillation