



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Rilpivirine

Proprietary Product Name: Edurant

Sponsor: Janssen-Cilag Pty Ltd

March 2012

TGA Health Safety
Regulation

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I. Introduction to Product Submission

Submission Details

<i>Type of Submission</i>	New Chemical Entity
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	20 December 2011
<i>Active ingredient(s):</i>	Rilpivirine (as hydrochloride)
<i>Product Name(s):</i>	Edurant
<i>Sponsor's Name and Address:</i>	Janssen-Cilag Pty Ltd 1-5 Khartoum Rd, Macquarie Park NSW 2113
<i>Dose form(s):</i>	Tablet
<i>Strength(s):</i>	25 mg
<i>Container(s):</i>	High density polyethylene (HDPE) bottle with polypropylene cap
<i>Pack size(s):</i>	30 tablets
<i>Approved Therapeutic use:</i>	Edurant, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment naïve adult patients with viral load \leq 100,000 copies/mL at baseline.
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	25 mg/day
<i>ARTG Number (s)</i>	AUST R 176666

Product Background

This AusPAR describes an application by the sponsor, Janssen-Cilag Pty Ltd, to register a new chemical entity, rilpivirine (TMC278) 25 mg tablets for the treatment of human immunodeficiency virus type 1 (HIV-1) infection. Rilpivirine is a diarylpyrimidine non nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1.

The proposed indication is that rilpivirine, in combination with other antiretroviral (ARV) medicinal products, is indicated for the treatment of HIV-1 infection in antiretroviral treatment naïve adult patients. The sponsor has stated in this submission that the above indication is based on the Week 48 safety and efficacy analyses of two randomised double blind, controlled Phase III trials (Studies C209 and C215) in treatment naïve adult patients, and on the Week 96 safety and efficacy analyses of a Phase IIb trial (Study C204) in treatment naïve adult patients.

Regulatory Status

Registration applications for rilpivirine were submitted in the United States of America (USA), the European Union (EU), Canada, and Switzerland on 23 July 2010, 2 September 2010, 12 August 2010, and 14 September 2010, respectively. Marketing approval was granted in the US on 20 May 2011, Canada on 21 July 2011, in the European Union (EU) on 28 November 2011.

Product Information

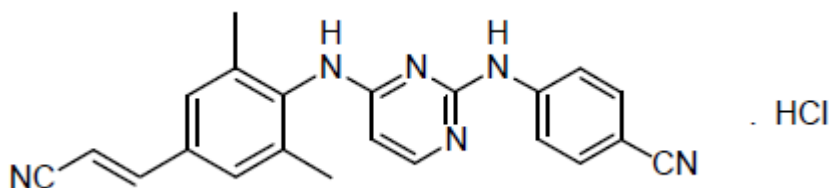
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

The drug substance has the chemical structure shown in Figure 1.

Figure 1: Chemical structure of rilpivirine hydrochloride.



It contains no chiral centres, but *cis/trans* isomerism is possible about the cyanoethenyl double bond. The drug substance is the *E (trans)* isomer.

Rilpivirine hydrochloride is practically insoluble over the entire physiological pH range. Multiple polymorphic forms are known; each are distinguishable from the other polymorphs by IR spectroscopy. The pKa of rilpivirine hydrochloride is 5.6 and the log P (octanol/pH 7 phosphate buffer) is 4.86.

The drug substance is micronised, and particle size limits are applied. Process validation experiments have demonstrated that the milling process is sufficiently robust.

The limits proposed for two specified impurities in the drug substance exceed the applicable International Conference on Harmonisation (ICH) qualification threshold and have been referred to the Medicines Toxicology Evaluation Section at TGA for comment. A third impurity was identified to be potentially genotoxic. The company proposes controlling this impurity in the intermediate, rather than in the final active pharmaceutical ingredient.

Drug Product

The tablets are film coated tablets in which the drug substance and a number of excipients are wet-granulated, dried and milled then mixed with other excipients prior to compression. The tablets are packaged in HDPE bottles with child resistant polypropylene closures.

Assay limits are applied at both release and expiry, and no impurities are specified above the ICH identification threshold.

The dissolution method shows adequate discriminatory power.

A shelf life of two years below 30°C has been approved.

Bioavailability

Two bioavailability studies were evaluated. Study C137 showed that exposure to rilpivirine is increased by about 70% when the tablets are taken with a high fat or standard meal. Hence, the product information (PI) stipulates that the tablets should be taken with a meal.

Study C145 showed that the area under the plasma concentration time curve (AUC) of the tablet is about 75% of that of an oral solution of the drug in macrogol when both are given with food.

The tablet proposed for registration is identical to the 25 mg Phase 3 clinical trial tablet apart from the embossing. The 75 mg Phase 3 tablet is a direct scale of the 25 mg Phase 3 tablet.

An absolute bioavailability study was not performed because of the lack of availability of an intravenous formulation (the drug is practically insoluble in aqueous media).

Quality Summary and Conclusions

All issues raised during the initial evaluation of this application have been satisfactorily resolved. There are now no objections in respect of Chemistry, Manufacturing and Controls to registration of this product.

The application was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) at its 138th meeting in May 2011. The subcommittee queried whether data had been provided for Active Pharmaceutical Ingredient (API) produced at two proposed manufacturing sites. Batch analysis data had been provided for both sites but stability data had been provided only for batches manufactured at one of the proposed sites. However, a commitment had been given to conduct stability studies on commercial batches manufactured at the second site. This is acceptable.

The PSC also queried whether stability studies had been conducted on batches of finished product manufactured from drug substance produced at both of the proposed sites. The primary stability batches were consecutive batches manufactured from different batches of drug substance from one site. A commitment has been sought that the company will also conduct stability studies on finished product manufactured from drug substance produced at the second site.

III. Nonclinical Findings

Introduction

The overall quality of the nonclinical data was high, with all pivotal toxicity studies conducted under Good Laboratory Practice (GLP) conditions using the proposed clinical route (PO).

Pharmacology

Mechanism of Action

Rilpivirine is a non competitive non nucleoside inhibitor of HIV-1 reverse transcriptase (RT), having no measurable activity against human DNA (deoxyribonucleic acid) polymerases α , β and γ . Crystal structures of the binding site between rilpivirine and the HIV-1 RT complex revealed that rilpivirine binds to the HIV-1 RT and adapts to changes in the non-nucleoside RT binding pocket. This is similar to other members of the diarylpyrimidine (DAPY) family of inhibitors, including etravirine, and this property might be expected to confer an increased genetic barrier to the development of resistance.

Antiviral activity *in vitro*

The *in vitro* inhibitory activity of rilpivirine against recombinant wild type HIV-1 RT showed a median half maximal inhibitory concentration (IC_{50}) value for rilpivirine of 42 nM. The median half maximal effective concentration (EC_{50}) value against HIV-1/IIIB in an acutely infected T cell line was 0.73 nM. Rilpivirine exhibited EC_{50} values against wild type

HIV-1 group M isolates A, B, C, D, E, F, and G of 0.07–1.01 nM. Comparable EC₅₀ values, were determined in human monocyte derived macrophages infected with HIV-1/Ba-L or HIV-1/ADA (0.18 and 0.22 nM, respectively). HIV-1 group O isolates were inhibited by rilpivirine with EC₅₀ values of 2.88–8.45 nM. Rilpivirine is relatively selective for HIV-1, as it was shown to exhibit antiviral activity in the micromolar range against HIV-2 and SIV. No activity for rilpivirine was observed against several non-HIV related viruses including the human hepatitis B virus, herpes simplex virus 2, human corona virus, influenza A virus, and vaccinia virus. A selectivity index (ratio of the 50% *in vitro* cytotoxic concentration to the EC₅₀) of $\pm 8,000$ was determined in MT4 cells.

Resistance

A preliminary biological cutoff of 3.7 was determined as the 97.5 percentile of fold change measurements from 2796 wild type HIV-1 recombinant clinical isolates during a three year period (February 2004 to February 2007). Rilpivirine was tested on 4786 HIV-1 recombinant clinical isolates selected based on resistance to a first generation NNRTI (efavirenz or nevirapine). *In vitro*, 62% of HIV-1 recombinant clinical isolates retained sensitivity to rilpivirine or etravirine, as compared with 11% to efavirenz and 5% to nevirapine.

Selection experiments were performed at high multiplicity of infection with varying concentrations of rilpivirine. Viral replication was inhibited with rilpivirine at ≥ 40 nM in cells infected with HIV-1 IIIB after 32 days with rilpivirine at ≥ 40 nM, and also in recombinant clinical HIV-1 isolates from group M subtypes A1, AE, AG, BG, C, D, F1, G, and H. Viral replication was also inhibited with rilpivirine at ≥ 40 nM in two HIV-1 HXB2 site directed mutants containing either of two NNRTI resistance associated mutations (RAMs), K103N or Y181C.

The rate of *in vitro* selection of rilpivirine resistant strains at low multiplicity of infection was comparable among HIV-1 group M subtypes. NNRTI resistance associated mutants emerging under selective pressure of rilpivirine included combinations of V90I, L100I, K101E, V106A/I, V108I, E138G/K/Q/R, V179F/I, Y181C/I, V189I, G190E, H221Y, F227C and M230I/L, where E138R represented a newly identified NNRTI resistance-associated mutation.

Site directed mutants were created on the basis of resistance to etravirine, and on the information on emerging reverse transcriptase mutations in patients failing rilpivirine enrolled in the Phase IIb and Phase III trials. Rilpivirine retained antiviral activity against 63.0% (136 of 216) of HIV-1/HXB2 site directed mutants carrying single, double, triple and quadruple RT mutations compared with 57.7% for etravirine, 45.8% for efavirenz and 36.2% for nevirapine. Resistance to rilpivirine was observed in three out of 67 mutants expressing single RT mutations (K101P, Y181I and Y181V), in 30 out of 79 mutants expressing double RT mutations, in 41 out of 62 mutants expressing triple RT mutations, and in 6 out of 8 mutants expressing quadruple RT mutations.

Although resistance to rilpivirine was largely associated with more than one, and usually more than two, NNRTI RAMs, the combination of specific RAMs appears to be more indicative of resistance to rilpivirine *in vitro* rather than their total number. Analysis of the double HIV-1/HXB2 site directed mutants with a combination containing V90I showed that only those with E138Q or Y181I were resistant to rilpivirine *in vitro*. Of the various combinations with K101E, only those with L100I, E138K, or M184V were sensitive to rilpivirine *in vitro*. There was considerable cross resistance between rilpivirine and etravirine among double, triple and quadruple site directed mutants.

Rilpivirine is mainly bound to albumin in human serum. The EC₅₀ ratio (EC₅₀ in the presence of 50% human serum/EC₅₀ ratio in its absence) indicates that the antiviral

activity of rilpivirine in human plasma would be expected to be reduced approximately 20 fold compared to the *in vitro* efficacy data.

Rilpivirine did not show antagonism when studied in combination with other antiretroviral agents. Low level synergy was observed in the presence of lamivudine (3TC), zidovudine (AZT), and raltegravir (RAL). All other combinations showed additive antiviral effects with rilpivirine.

The current *in vitro* data demonstrated that rilpivirine, an inhibitor of the HIV RT, is active against a wide range of wild type HIV-1 group M and NNRTI resistant HIV-1 variants that typically emerge after failing efavirenz or nevirapine containing regimens. Rilpivirine would be expected to exhibit considerable cross resistance with etravirine.

Secondary Pharmacodynamics and Safety Pharmacology

An extensive *in vitro* screening program found no evidence that rilpivirine (at a concentration of 10 μ M) had any secondary pharmacological activity on α - or β -adrenergic, dopaminergic, muscarinic, serotonergic, opioid, interleukin or chemokine receptors, nor (at 30 μ M) on histamine H₂ receptors in the guinea pig isolated right atrium. Rilpivirine (10 μ M) did not cause stimulation or inhibition of pig isolated stomach ATPase activity, and did not inhibit pentagastrin induced gastric acidity following intraperitoneal (IP) administration to rats at a dose of 10 mg/kg. Rilpivirine did not inhibit human DNA synthesis by human polymerase α , β or γ .

Secondary pharmacodynamic interactions are therefore not expected for rilpivirine in normal therapeutic use.

Rilpivirine had no effects on neurofunctional integrity in the Irwin test in male rats at oral doses \leq 400 mg/kg.

Cardiovascular Safety Studies

The cardiovascular safety studies submitted to support the current application exceeded the requirements of ICHS7B "Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals".

In the following discussion of the nonclinical data, it is necessary to have an appreciation of the rilpivirine concentrations experienced in therapeutic use. The steady state maximal plasma concentration (C_{\max}) of rilpivirine in healthy subjects ingesting a 25 mg dose was 247 ng/mL (data taken from clinical trial C152). Taking into account the extent of protein binding in humans of 99.7%, the free steady state C_{\max} with a daily dose of 25 mg is 0.74 ng/mL (or 1.84 nM) in healthy volunteers. The steady state C_{\max} in HIV-infected patients taking the same dose was generally lower. In trial C209, the steady state C_{\max} following administration of a daily rilpivirine dose of 25 mg to HIV infected subjects was 138.6 ng/mL, which corresponds to an unbound concentration of 0.42 ng/mL or 1.0 nM.

Early nonclinical screening studies were not indicative of adverse cardiac effects for rilpivirine, and in particular there was no effect at therapeutic concentrations on the potassium channels responsible for the repolarisation phase of the cardiac action potential. The effect of rilpivirine on these potassium channels was studied in the hERG assay in Chinese hamster ovary (CHO) cells *in vitro*. A dose dependent inhibition of delayed rectifier potassium currents of 10%, 33% and 80% were found with rilpivirine concentrations of 0.1, 0.3 and 3 μ M, respectively. Even allowing for an approximately 50% attenuation of rilpivirine concentration due to its propensity to stick to apparatus and tubing, the concentration range over which inhibition of delayed rectifier potassium currents was observed is approximately 250 fold higher than the maximum steady state unbound C_{\max} in HIV patients. Supporting a lack of cardiac effect for rilpivirine, a study of

the effects of rilpivirine on the rate and force of contraction of isolated, spontaneously beating guinea pig right atrium showed no effect on force of contraction or effective refractory period at concentrations up to 10 μM (approximately 5 μM allowing for attenuation of rilpivirine concentration due to binding to tissues, tubing and equipment). The rate of contraction was marginally reduced at rilpivirine concentrations $\leq 0.1 \mu\text{M}$, but this still provides a safety factor of approximately 100.

In anaesthetised guinea pigs, intravenous (IV) administration of rilpivirine at single doses up to 5 mg/kg also showed no cardiovascular effects including effects on heart rate or mean arterial blood pressure (BP), changes in electrocardiogram (ECG) morphology, or evidence of conduction disturbances. The PQ interval and QRS complex of the ECG were unchanged, but the QT interval¹ of the ECG increased by 18% (compared to 10% with vehicle); however, this effect was not apparent after correcting for heart rate according to Bazett's formula. The highest dose of rilpivirine tested in this study was associated with a safety factor of approximately 30 with respect to plasma rilpivirine concentration, allowing for interspecies differences in binding to plasma proteins. However, the usefulness of this study is limited since the animals were anaesthetised with pentobarbitone sodium, which may itself have effects on ventricular repolarisation and hence on the QT interval duration. An IV study in dogs was also confounded by the presence of anaesthetic agents (etomidate, fentanyl and succinylcholine), but showed no effects on ECG parameters and no potential for arrhythmia or conduction disturbance at plasma concentrations with a safety factor of 20. However, two studies carried out in conscious, chronically instrumented dogs showed no effects of treatment with rilpivirine (up to 160 mg/kg PO (oral administration)) on cardiovascular, ECG or respiratory parameters. Only the first of these studies was accompanied by exposure testing; single doses of 20 mg/kg PO were associated with median peak plasma rilpivirine concentrations ten times greater than the steady state C_{max} in HIV patients.

Despite these early nonclinical findings, in clinical trials with healthy volunteers, daily rilpivirine doses of 75 mg or 300 mg produced a modest, dose dependent prolongation of QT interval corrected for heart rate according to Fridericia's (QT_{CF}) formula with a delayed onset (eleven days after commencement of treatment). In clinical trial C131, these doses of rilpivirine were associated with steady state plasma C_{max} values of 605 and 1630 ng/mL, respectively, which would correspond to unbound concentrations of 1.82 and 4.89 ng/mL, respectively. These concentrations are still approximately 50-100 times lower than those found to block the hERG channel *in vitro*. It should be noted that the relationship between hERG channel blockade, QT duration and torsadogenicity is not a direct one. For example, the calcium channel blocker verapamil blocks hERG channels with an IC_{50} in the range of 100-200nM, but has no effect on QT duration².

Further nonclinical studies were conducted to investigate in more detail the effect of rilpivirine on the ion channels involved in the cardiac action potential, and to provide evidence on its torsadogenicity.

In order to investigate possible effects of rilpivirine on the human cardiac action potential, analyses were carried out in HEK293 cells expressing human cardiac ion channels. The channels studied included the fast sodium current, the slowly activating delayed rectifier potassium current (also studied in CHO cells), the transient outward potassium current, the L-type calcium current, and the inwardly rectifying potassium current. Measurable

¹ QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.

² Guth BD. Preclinical cardiovascular safety risk assessment in modern drug development. *Toxicol. Science* 2007; 97:4-20.

inhibitory effects were found on the slowly activating delayed rectifier potassium current (19% inhibition at 1 μ M rilpivirine) and on the transient outward potassium current (36% inhibition at 1 μ M), but these effects (with a safety margin in excess of 1000) are less than those on the hERG ion channel. The “hERG-Lite” assay was used to demonstrate that therapeutic concentrations of rilpivirine did not reduce the trafficking of hERG channels from the endoplasmic reticulum to the plasma membrane, which was a possible mechanism underlying a delayed effect on hERG channels.

The isolated arterially perfused rabbit ventricular wedge preparation has been shown to have a high sensitivity for detection of agents with a propensity for causing torsades de pointes (a specific type of ventricular tachycardia) with and without QT prolongation³. M cells are a unique myocardial cell found in the deeper layers of the ventricular wall, and they respond more sensitively to agents that block hERG channels, making them more likely to contribute to drug induced transmural heterogeneity of ventricular repolarisation. The transmural dispersion of repolarisation (TDR), which is approximated from the time from the peak to the end of the T wave (T_p-T_e), is widely believed to be the electrophysiological substrate for early after depolarisation (EAD) and proarrhythmia². Using this model, it was shown that treatment with rilpivirine (at concentrations up to 10 μ M) had no effect on T_p-T_e , nor on QRS duration or rate dependency, the ratio T_p-T_e/QT , or the contractile force developed by the heart muscle. No instances of EAD, torsades de pointes, ventricular tachycardia or ventricular fibrillation or myocardial inexcitability were recorded. At the highest two concentrations tested (1 and 10 μ M), the QT interval was significantly increased (by 6% and 9%, respectively). These concentrations are > 200 and 2000 times greater than the unbound C_{ss} levels associated with QT prolongation in clinical trials. While the results of the ventricular wedge study are supportive of rilpivirine not being torsadogenic in therapeutic use, they do not take into account the delayed nature of the QT prolongation seen in the clinical trials. It would be interesting to repeat this experiment using ventricular wedges prepared from rabbits that had been treated daily with rilpivirine for several weeks.

The time course for QT prolongation in humans was taken into account in a study in female guinea pigs, which were treated daily for 16 days with 10 mg/kg doses of rilpivirine, and chronically implanted with radio telemetry transmitters. There was no effect of treatment on heart rate or any aspect of ECG, including QT intervals or QT intervals corrected for heart rate according to Bazet's (QT_{cB}) or Fridericia's (QT_{cF}) formulae. Plasma concentrations of rilpivirine in this study, 4 h after administration on Day 15, were 689-911 ng/mL. Taking into account the extent of rilpivirine binding to proteins in guinea pig plasma (99.87%), this corresponds to unbound rilpivirine concentrations of 0.90-1.18 ng/mL. These levels are only slightly (1.2-1.6 times) higher than the steady state C_{max} for healthy subjects in trial C152 on a daily rilpivirine dose of 25 mg, and 2-3 times higher than the steady state C_{max} for HIV infected subjects ingesting 25 mg/day in trial C209. Most importantly, the unbound plasma concentrations of rilpivirine in the chronically telemetered guinea pigs were 75-80% lower than the unbound steady state C_{max} values reported in trial C131, in which rilpivirine doses of 300 mg were associated with prolonged QT intervals in healthy subjects (and 50% lower with respect to the 75 mg dose). The unbound concentrations of rilpivirine were not sufficient to provide a safety factor for possible adverse cardiac effects, and do not provide any insight into possible mechanisms underlying the prolongation of the QT interval seen in clinical trials with higher doses of rilpivirine.

³ Liu T, et al. Blinded validation of the isolated arterially perfused rabbit ventricular wedge in preclinical assessment of drug-induced proarrhythmias. *Heart Rhythm* 2006; 3:948-956

ECG recordings were also carried out in a 15 day repeat dose toxicity study in groups of three female cynomolgus monkeys (Study C326). After a dose ranging trial in phase I, rilpivirine was administered twice daily (bis in die; BID), at doses of 0, 100 and 250 mg eq./kg BID. Two of the monkeys dosed at 100 mg/kg BID exhibited QT and QT_c values slightly above the historical control level, but none of the monkeys dosed at 250 mg/kg BID showed any effect on QT or QT_c. The effects on QT interval seen in the LD monkeys could be unrelated to treatment, but it is also possible that there is a more complex dose-response relationship, and these effects are related to the prolongation of QT interval seen in humans at daily doses of 75 and 300 mg. In addition, the monkeys had to be restrained for ECG measurement, and their mean heart rates were in the range 226-244 bpm, which is higher than normal (mean heart rates for unrestrained female cynomolgus monkeys in a study by Gauvin⁴ were 163 bpm). As has been pointed out by the sponsor's clinical cardiology expert, elevated heart rate can obscure the known reverse frequency dependent effects of QT prolonging drugs⁵. It is thereby possible that any potential effects on QT interval were underestimated.

The plasma C_{max} values for rilpivirine on Day 14 of the repeat dose monkey toxicity study at the 250 mg/kg BID dose level were 0.50 and 0.56 ng/mL. Allowing for 99.14% of rilpivirine binding to plasma proteins in this species, this corresponds to approximately 4.56 ng/mL of free rilpivirine, which provides a safety factor of 6 compared with healthy subjects (trial C152), or 11 compared with HIV infected subjects in trial C209. The unbound C_{max} values achieved after repeat dosing in monkeys were comparable to those reported in trial C131 at a daily dose of 300 mg/kg, which was associated with QT prolongation.

Alternative potential mechanisms underlying the observed delayed QT prolongation in the clinical trials included increased exposure to rilpivirine or to one or more of its metabolites over time, or an increase of the concentration of rilpivirine, or of one or more of its metabolites in the myocardium. In healthy volunteers and HIV-1-infected subjects, exposure to rilpivirine increased over time until steady state was reached before Day 7, mainly as a consequence of the long half-life of 45-50 h. But the effect is not sufficient to account for the delayed effect on QT interval. There are no major human metabolites present in plasma at levels greater than 10% of the C_{max} of the parent compound, and no unique metabolites were detected in humans. Single dose quantitative whole body autoradiography (QWBA) studies in rats showed heart to plasma ratios of radioactivity to be two or less in the 8 h after dosing, and maximum levels of radioactivity in all tissues were reached 4-8 h after dosing. Thus, there is no evidence of any particular affinity of rilpivirine or its metabolites for heart tissue. However, it would have been informative if the distribution studies had been carried out after repeated as well as single dosing.

In summary, the nonclinical data do not provide a satisfactory explanation for possible mechanisms underlying the effects of rilpivirine on QT intervals seen in healthy subjects at daily doses of 75 mg or above. Blockade of hERG channels or other ion channels involved in the cardiac action potential would not be expected at therapeutic concentrations or at supratherapeutic doses of 75 or 300 mg. However, the validity of the *in vitro* models for predicting effects of rilpivirine on the cardiac action potential is questionable in view of the time taken for QT prolongation to develop in clinical trials. This observation is suggestive of a more complex mechanism than simple ion channel block. Alternative possible mechanisms include effects on gene expression, or delayed modulation of hERG

⁴ Gauvin DV, et al. Electrocardiogram, hemodynamics, and core body temperatures of the normal freely moving cynomolgus monkey by remote radiotelemetry. *J. Pharmacol. Toxicol. Methods* 2006; 53:140-51.

⁵ Shah AP, et al. Genetic background affects function and intracellular calcium regulation of mouse hearts. *Cardiovasc Res.* 2010; 87:683-93.

channel function through cardiac G protein coupled receptors⁶. The most appropriate studies to examine potential mechanisms underlying this effect were the repeat dose studies with telemetered guinea pigs and cynomolgus monkeys. Unfortunately, the safety margin in these studies was relatively low; unbound plasma rilpivirine concentrations in the guinea pig study were lower than those associated with QT prolongation in humans, while those in the monkey studies were comparable. However, the monkey study did provide a safety margin of 6 (for healthy subjects) or 11 (for HIV infected subjects), showing no effect on cardiac repolarisation in the species most closely related to humans.

Pharmacokinetics

Absorption

Transepithelial transport of rilpivirine was studied in human colon carcinoma derived Caco-2 cells. Based on the results of this study, the most likely mechanism for intestinal absorption of rilpivirine is by passive transcellular diffusion. The rate of absorption was characterised as intermediate.

Absorption and plasma pharmacokinetics of rilpivirine were studied in CD-1 and CB6F1-nonTgrasH2-transgenic mice, pigmented Long Evans and Sprague rats, NZW rabbits, beagle dogs, and cynomolgus monkeys after single and repeated oral administration.

The elimination half life ($t_{1/2}$) for rilpivirine was 2.8-5.7 h in rats, 12-21 h in rabbits, 18-39 h in dogs, and 7-8 h in monkeys. This compares with a $t_{1/2}$ of 45-50 h in humans. Clearance values (in L/h/kg) were 1.3 in rat, 0.03 in rabbit, 0.14 in dog, and 0.9-4.2 in monkeys.

The absolute oral bioavailability of rilpivirine free base was 21-39% in rats, 31% in dogs, and 24% in monkeys. Systemic exposure was higher when rilpivirine was administered in a formulation containing citric acid, indicating that absorption was dependent on pH. Peak plasma concentrations of either free base or hydrochloride salt were generally reached after 1-2 h, but at higher dose levels absorption was very much prolonged. Plasma rilpivirine concentrations tended to increase less than dose proportionally, due to low solubility. At very high dose levels in animals, no further increase in exposure was seen, suggesting that absorption mechanisms had become saturated.

The results of pharmacokinetic studies in dogs, and in mice at low dose levels, showed little difference between males and females, however, female exposure levels were higher in mice at higher dose levels, and in female rats at all dose levels, compared with males (up to 2 fold in mice and 2 to 4 fold in rats). In humans, no major difference in pharmacokinetics was noticed between males and females.

Exposure tended to be increased after repeated administration to mice, particularly at higher dose levels (60 to 320 mg/kg/day). In rats, the systemic exposure after repeated administration showed a gender difference. Males showed reduced exposure with repeated administration of up to 40% with the free base, and up to 76% with the HCl salt (in the carcinogenicity study). In the latter study, the decrease in exposure occurred between Day 1 and Week 27, with no further decrease observed between Weeks 27 and 39. In female rats, exposure tended to increase (up to 1.6 fold) following repeated administration of the free base, but there was no clear effect of repeated administration of the hydrochloride. Exposure of the free base and HCl salt in dogs tended to increase after repeated administration, mainly due to the long elimination half-life in this species. Similarly, exposure tended to increase in a 15 day repeat dose toxicity study with the HCl salt in female monkeys (1.6-1.7 fold). In humans, an increase in exposure was seen after repeated administration mainly due to the long half life.

⁶ Hoffmann P, Warner B. Are hERG channel inhibition and QT interval prolongation all there is in drug-induced torsadogenesis? A review of emerging trends. *J. Pharmacol. Toxicol. Methods* 2006; 53:87-105.

Comparative pharmacokinetic studies were conducted with the free base and HCl salt in rats and dogs. The two dosage forms exhibited similar exposure in rats at low doses, but at higher doses exposure was 1.7-2.7 fold higher after administrations of the free base. There was no remarkable difference noted in dogs, although there was a high level of inter individual variability.

Distribution

The plasma protein binding of rilpivirine was studied *in vitro* by equilibrium dialysis in mice, rats, rabbits, guinea pigs, dogs, monkeys and healthy adult male subjects. Binding to plasma proteins was high, ranging from 99.08% to 99.98%, and was independent of concentration. Rilpivirine bound extensively to human albumin (99.03-99.56%) and to a lesser extent to human α_1 -acid glycoprotein (11.45-72.26%). Distribution to red cells was limited in all species. The rank order of blood to plasma concentration ratio was monkey > dog > rat > man > guinea pig > rabbit > mouse. Values for steady state volume of distribution ranged from 0.32-0.56 L/kg in the rabbit to 4.2-9.1 L/kg in monkeys.

The tissue distribution of rilpivirine was studied in SD rats using LC-MS/MS analysis of a range of tissue samples after homogenisation. The peak tissue concentrations of rilpivirine in SD rats corresponded with the peak plasma concentration, and tended to decline in parallel. The highest concentrations of rilpivirine were seen in the liver and adrenal glands, reaching tissue to plasma AUC_{0-24h} (area under concentration curve from administration to 24 h post dosing) ratios of 3.4 and 2.7, and there was no evidence of retention or accumulation in any of the tissues examined.

Quantitative whole body autoradiography was carried out following single oral administration of ¹⁴C-labelled rilpivirine to Long Evans rats. Absorption of rilpivirine or its metabolites was rapid, with peak radioactivity concentrations detected at 4 h after dosing in all tissues except for the pigmented parts of the eye, where radioactivity peaked at 24 h. The highest concentration of radioactivity was detected in the liver, followed by the adrenal gland, brown fat and kidney. There was no evidence of undue retention. Radioactivity levels declined more slowly from pigmented tissues.

Metabolism

Pathways for rilpivirine metabolism were studied in mice, rats, rabbits, guinea-pigs, dogs, monkeys and humans *in vitro*, and in mice, rats, rabbits, dogs and humans *in vivo*. In each species a large number of metabolites were detected, although in quantitative terms unchanged rilpivirine was the predominant form. However, in the dog, rilpivirine appeared to be less extensively metabolised. Aromatic hydroxylation at the pyrimidyl moiety, followed by glucuronidation, was an important metabolic pathway in all species *in vitro* and *in vivo*, and was the major route of biotransformation in mice and humans *in vivo*. Aliphatic hydroxylation was another important route of metabolism, followed by glucuronidation in rabbit, dog, monkey and humans, and by glutathione conjugation in mice and rats. In mice, rats and guinea-pigs, a major metabolic route was glutathione conjugation followed by conversions leading to the mercapturic acid metabolites (M17 and M18), but this route was only a minor pathway in other species. Another route that appeared to be restricted to the mouse and rat involved hydroxylation of the glutathione conjugate (M8), followed by glucuronidation. In rabbit, guinea pig, dog and human a minor metabolic pathway involved release of the nitrile group, followed by reduction or oxidation, resulting in the formation of an alcohol metabolite (M31) and a carboxylic acid metabolite (M30). However, this pathway was not detected in mouse, rat and monkey. N glucuronidation at the pyrimidinyl moiety (M15) was an important biotransformation pathway in rabbit, and could also be detected in human, but not in the other species.

All identified metabolites of rilpivirine that were detected in human *in vitro* systems were also detected in at least one animal species. The studies on metabolic pathways thereby supported the relevance of the species used in the toxicology studies. A putative unique human metabolite was detected in a pilot comparative metabolic study in mice, rats, rabbits, dogs and humans *in vivo*. This metabolite had a molecular mass of 364 (2 daltons less than unchanged drug) and its concentration was about ten times higher after multiple dosing than after single dosing. Subsequently, this metabolite was tentatively identified as a tricyclic metabolite (M27) formed by aliphatic hydroxylation at one of the methyl groups of the cyanoethenyl-2,6-dimethylphenyl moiety (M33), followed by dehydration. This pathway has been identified in human, monkey and rabbit, but was less important in the other animal species.

Experiments designed to establish the CYP450 phenotypes involved in rilpivirine metabolism were carried out in human liver microsomes using diagnostic inhibitors, and also using a number of human CYP expression systems. The results were strongly suggestive of CYP3A involvement in the metabolism of rilpivirine, and to a lesser extent, CYP1A2, CYP2C19 and CYP2C8/9/10. A separate study confirmed the involvement of CYP3A4 and also indicated the possible involvement of CYP1A1, CYP1B1, CYP2C18 and CYP3A5. The formation of glutathione conjugates was confirmed in human liver microsomes, and studies with expressed human recombinant isoforms indicated that the μ , and to a lesser extent π , isoforms were responsible for glutathione conjugation. The results suggested a possible scavenger role for glutathione with hypothetical reactive intermediates.

In vitro studies were carried out using primary cultures from human hepatocytes to determine possible induction of hepatic enzymes by rilpivirine. Based on analysis of mRNA expression, rilpivirine appears to be a very weak inducer of CYP1A2 (6 fold less than omeprazole) and CYP2B6 (4.5 fold less than rifampicin) in human hepatocytes. In addition, the results indicate that rilpivirine appears to be a moderate inducer of CYP2C19 (1.4 fold less than rifampicin) and CYP3A4 (2 fold less than rifampicin) in human hepatocytes. Hepatic enzyme activities were also studied in microsomal fractions prepared from animals in the repeat dose toxicity studies. Repeated dosing of female and male mice with rilpivirine resulted in 20 and 25 fold increases in CYP4A activity, respectively, and up to 1.7 fold increases in the activity of CYP3A. Rilpivirine treatment induced hepatic microsomal UDP glucuronosyltransferase activity towards thyroxine in both females and males, and decreased cytosolic GST activity towards 1-chloro-2,4-dinitrobenzene in males. In the repeat dose studies in rats, rilpivirine was a mild inducer of CYP4A in males, while in females CYP3A activity was induced. Effects on thyroxine glucuronosyltransferase activity were suggestive of an interaction with thyroxine metabolism in male rats, and GST activity in females. Repeat dose studies with rilpivirine in dogs showed little effect on hepatic xenobiotic metabolism, although there was some reduction of microsomal CYP3A dependent testosterone β hydroxylase activity.

Excretion

Rilpivirine and its metabolites were rapidly eliminated in rodents, but elimination in dogs was slower with 54% of a radioactive dose eliminated within the first 24 h. Excretion was virtually complete 96 h after dosing of rodents and 168 h after dosing of dogs. In mice, rats and dogs, the predominant route of excretion was via the faeces. Faecal excretion in rats and dogs was predominantly as unchanged rilpivirine, while for mice the predominant faecal metabolites were the hydroxyl metabolite of S-methyl rilpivirine (M41) and 5-hydroxy rilpivirine (M42). Renal excretion was very limited in all species, accounting for 0.45- 4.2% of the radioactivity dose, and the amount of unchanged rilpivirine in urine was negligible. Biliary excretion studies in male rats revealed that only 18% and 25% of the

administered radioactivity was excreted in bile over 24 h in restrained and unrestrained animals, respectively. Since the amount of unchanged rilpivirine excreted in bile was negligible, this suggests that most of the faecally excreted rilpivirine is not absorbed.

A similar pattern of excretion was observed in humans with 85% of the dose excreted in faeces, and 6% in urine over 336 h (14 days). Unchanged rilpivirine accounted for 26% of the administered dose in faeces.

Pharmacokinetic drug interactions

In a study of absorption mechanisms using human colon carcinoma derived Caco-2 cells, rilpivirine was not a substrate of P-glycoprotein (P-gp), but inhibited P-gp with an apparent 50% inhibitory concentration (IC_{50}) of 9.2 μ M (3.4 μ g/mL). Taking into account the maximum unbound therapeutic concentrations of rilpivirine in clinical trials discussed above, it is unlikely that treatment with rilpivirine will have clinically relevant effects on P-gp mediated absorption.

Pharmacokinetic drug interaction studies using human liver microsomes and cytosol indicated that rilpivirine inhibited CYP2C9 mediated metabolism of warfarin with an IC_{50} of 1.35-3.02 μ M, and CYP2C8 mediated metabolism of paclitaxel with an IC_{50} = 13-19 μ M. Inhibitory effects were also observed on the metabolism of clarithromycin and sildenafil (CYP3A4; IC_{50} = 2.0 and 1.4 μ M, respectively), S-mephenytoin (CYP2C19; IC_{50} = 1.3 μ M) and norethindron (IC_{50} = 3.9 μ M), and on setraline, paroxetine (CYP2D6; IC_{50} = 5.2 & 6.6, respectively) and 17- α -ethinyloestradiol (IC_{50} = 6.5 μ M). Omeprazole metabolism (mediated by CYP2C19/2E1) was inhibited with IC_{50} = 12.0 μ M, but there was no effect on the metabolism of abacavir and chlorzoxazone. Taking into account the maximum unbound therapeutic concentrations of rilpivirine in clinical trials, inhibition of CYP enzymes is unlikely to be of major clinical relevance.

Toxicology

Acute toxicity

Acute toxicity was not examined in formal studies, but single dose evaluations were part of the initial oral dose range finding studies or, in the case of mice, part of the bone marrow micronucleus test.

In mice, no relevant effects were noted following an oral single dose of up to 1600 mg/kg of the free base in Macrogol 400 with citric acid, which was the maximum feasible dose by this route using this vehicle. Systemic exposures at 1600 mg/kg were similar as those at 400 mg/kg; this was indicative of saturation of absorption. There were no treatment-related effects in rats dosed with the maximum feasible single oral dose of 800 mg/kg free base in Macrogol 400. Treatment of dogs with the maximum feasible oral dose of 80 mg/kg free base in Macrogol 400 \pm citric acid induced more frequent vomiting and had softer stools than dogs treated with the vehicle.

The single dose data are limited as the observations were generally made only in the 24-48 h after dosing. The sponsor could have investigated acute toxicity at higher exposure levels using IV or IP dosing. However, the pharmacokinetic data suggest that absorption of higher oral doses is limited, and therefore the acute toxicity of rilpivirine by the oral route is likely to be relatively low.

Repeat dose toxicity

Single dose and repeat dose toxicity studies were up to 3 months in mice, 6 months in rats, 12 months in dogs, and 12 weeks in immature female cynomolgus monkeys. The repeat dose toxicity studies all used the same (oral) route as proposed clinically, and met the ICH guidelines in terms of species, durations and group sizes. Mouse and monkey studies were

performed using the HCl salt, but the 6 month rat and 6 and 12 month dog studies used the free base. Bridging studies and toxicokinetic studies in the rat and dog (up to 1 month duration) provided reassurance that there was no remarkable difference in toxicity for the free base and HCl salt. Further mechanistic toxicity studies were done in immature female cynomolgus monkeys. The reversibility upon repeat dosing was investigated in rats and dogs. All pivotal toxicity studies had GLP certification.

The vehicle for the rat and dogs studies with the free base was Macrogol 400, usually with citric acid to enhance absorption. Hypromellose was used in the rabbit study (since this species does not tolerate Macrogol 400) and for studies using the HCl salt (3 month mouse and monkey studies and bridging studies in rats and dogs).

Exposure ratios in Table 3 have been calculated based on the ratio of animal to human plasma AUC_{0-24h} values. Human reference values are using pooled data from clinical trials C215 and C209. The exposure ratios are relatively low at the lowest dose levels in rats and in the monkey study. A NOAEL (no observable adverse effect level) was not observed in the dog or monkey studies, so these studies do not enable a safety factor to be established for toxicities observed in these studies.

Table 3: Relative exposure in repeat dose toxicity and carcinogenicity studies.

Species	Study duration	Dose (mg/kg/day)	AUC _{0-24h} (µg·h/mL)		*Exposure ratio	
			male	female	male	female
Mouse (CD-1)	3 months (Day 86)	20	79.6	60.8	36	27
		80	210	313	94	140
		320	665	1360	297	607
	2 years [carcinogenicity] (Week 28)	20	75.6	51	34	23
		60	230	278	103	124
		160	505	766	225	346
Rat (SD)	1 month (Day 28)	10	7.2	14.0	3	6
		40	27.4	41.6	11	17
		160	50.5	88.9	21	37
	6 months (Day 83)	40	18.6	41.4	8	18
		120	41	101	18	45
		400	57	184	25	82
	2 years [carcinogenicity] (Week 39)	40	6.26	14.2	3	6
		200	8.15	41.2	4	18
		500	13.8	46.3	6	21
		1500	18.4	83.8	8	37
Dog (beagle)	6 months (Day 177)	5	21.1	17.4	9	7
		10	25.8	31.9	11	13
		40	68.3	43.1	28	18
	12 months (Day 363)	5	17.4	18.7	8	8
		10	23.8	35.8	11	16
		40	65.3	61.0	29	27
Monkey (Cynomolgus)	8 weeks	200	-	2.68	-	1
		500	-	4.62	-	2
Human (healthy volunteers)	steady state	25 mg <i>q.i.d.</i>	2.4		-	

* These values have not been corrected for small differences in protein binding; NOAEL (no observable adverse effect level) in bold. *q.i.d.* (quater in die) = four per day

Adrenal Glands

Rilpivirine had effects on the adrenal glands in repeat dose studies in mice, rats, dogs and monkeys. The dog was particularly sensitive to the effects of rilpivirine on the adrenal

glands. Increased concentrations of progesterone, the cortisol precursor 17 α -hydroxyprogesterone and adrenocorticotrophic hormone (ACTH), and reduced cortisol levels were associated with increased numbers of swollen cells with dense cytoplasm and reduced oil red O staining in the adrenal cortex at doses ≥ 5 mg/kg/day, corresponding to relative exposure levels ≥ 7 . Occasional disturbances in serum electrolytes may have been secondary to the adrenal effects. These results, together with the effects of rilpivirine on cortical biosynthesis in crude subcellular fractions of dog adrenal cortex, indicate that rilpivirine partially inhibits CYP21; this enzyme catalyses the formation of 11-deoxycorticosterone from progesterone and 11-deoxycortisol from 17 α -hydroxyprogesterone. Inhibition of CYP21 by rilpivirine results in reduced levels of 11-deoxycorticosterone and 11-deoxycortisol, which are themselves the direct precursors of corticosterone and cortisol. The resultant reduced serum levels of cortisol and corticosterone trigger an ACTH-response from the pituitary. The increased stimulus of the adrenal cortex by ACTH will partially counteract the reduction of the cortisol and corticosterone synthesis, but at the same time will increase the accumulation of the CYP21 substrates progesterone and 17 α -hydroxyprogesterone.

An additional effect of the CYP21 inhibition, notably in species that have a significant androgenic adrenal pathway, is that the increased ACTH stimulus and subsequent accumulation of progesterone and 17 α -hydroxyprogesterone may lead to increased androgen production. 17 α -hydroxypregnenolone and 17 α -hydroxyprogesterone are converted to DHEA and androstenedione, respectively, catalysed by 17,20-lyase (CYP17). To investigate the impact of the stimulation of the androgenic pathway, a study was conducted in cynomolgus monkeys since, unlike rats and dogs, this monkey strain exhibits a significant androgenic adrenal pathway that is shared with humans. In the eight week monkey study, baseline levels of progesterone were only slightly elevated in the treated animals, and 17 α -hydroxyprogesterone levels were unchanged; however, there was a marked increase in the formation of both hormones in response to an ACTH stimulus. In addition, baseline levels of androstenedione and DHEA were slightly reduced following treatment with rilpivirine. These results indicate that the influence of rilpivirine on adrenal steroidogenesis is probably mediated by inhibition of both CYP21 and CYP17 (see steroidogenesis scheme, Figure 2). The reduction of estradiol levels is also compatible with inhibition of 17,20-lyase activity leading to a depletion of precursor steroids. In the eight week repeat dose study in cynomolgus monkeys, these effects were observed at exposure levels 1-2 times the exposure levels achieved in the clinical trials. The possibility of rilpivirine affecting steroid hormone levels and hence adrenal and gonadal function in therapeutic use must therefore be considered and should be evaluated as part of the post market monitoring.

impact on Sertoli cell functioning or spermatogenesis. As with mice, the effects on steroidogenesis and gonads are probably related to inhibitory effects of CYP21 and CYP17, which regulate steroid synthesis. However, there were no effects on the male gonads in mice or rats.

The effects of rilpivirine on the female genital tract of mice and dogs and on ovulation of dogs are probably species specific and not relevant to women. Treatment effects on ovulation in dogs were not seen in immature (approximately 18 months old) cynomolgus monkeys in an eight week ovulation assessment study. However, it is noted that the monkeys were sexually immature in this study and the long term effects are unknown, so the validity of this assay is limited.

Liver

The liver was an important target organ for toxicity in mice, rats and dogs. Signs of hepatic toxicity included increased activities of liver enzymes [alkaline phosphatase (ALP), aspartate transaminase (AST) and alanine transaminase (ALT)] and increased hepatic weight associated with a dose related increase in incidence and severity of hepatocellular hypertrophy. At higher exposure levels, these effects were accompanied by hepatocellular vacuolisation, single cell necrosis, and pigmentation and proliferation of Küpffer cells, and there was evidence of peroxisome proliferation in the livers of mice under electron microscopic examination. Additional hepatic effects in dogs suggestive of cholestasis included increases in serum cholesterol and total bilirubin concentrations at doses ≥ 10 mg/kg/day, and histopathological effects including yellow pigmentation in hepatocytes and canaliculi and prominent brown pigment in the gall bladder epithelium at doses of 40 mg/kg/day. These hepatic effects are in keeping with the liver enzyme inducing effects of rilpivirine, which was documented in rats and mice. The exposure ratios for the adverse hepatic effects in the nonclinical repeat dose studies relative to exposure levels in the clinical trials in humans were ≥ 100 in mice and ≥ 10 in rats and dogs.

Kidney

Rilpivirine administration was associated with renal toxicity in mice and dogs, although the nature of this varied between species. In mice, five out of ten females dosed at 320 mg eq./kg/day in the six month study exhibited nephropathy as characterised by multifocal tubular basophilia, glomerulopathy, mononuclear cell infiltration, interstitial fibrosis, tubular dilatation and cortical mineralisation. In dogs, disturbances in ion homeostasis were observed at doses ≥ 10 mg/kg/day and there was a trend towards increased serum creatinine concentrations, while urinary output was increased in males. Histopathological examination of the kidneys revealed possible effects of treatment, including corticomedullary mineralisation in females at 40 mg/kg/day, while two males exhibited acute interstitial nephritis at this dose level. The exposure ratio for renal toxicity in the nonclinical studies compared with human exposure levels in clinical trials was ≥ 300 in mice and 10 in dogs.

Thyroid

Thyroid gland enlargement, associated with a dose-related increase in diffuse follicular hypertrophy and an increase in small follicles was observed in repeat dose toxicity studies in rats at doses ≥ 40 mg/kg/day (relative exposure ≥ 11). In addition, follicular cell hypertrophy was observed in female cynomolgus monkeys at 1-2 times the human clinical exposure level in the eight week repeat dose study. Endocrinological findings in rats included moderate decreases in T4 associated with increases in thyroid stimulating hormone (TSH). In the pituitary gland of males from all groups, the number of swollen or vacuolated cells in the *pars distalis* was increased. This effect is probably related to the thyroid effects since these cells produce TSH₃. The hepatic and thyroid effects in the rat

are associated with liver enzyme induction, predominantly the CYP3A family of isozymes, but to a lesser extent, the CYP4A family. The effects on thyroid gland and pituitary gland in rats were associated with induction of UDP-GT. This induction caused an increased clearance of thyroid hormones and subsequently increased release and synthesis of TSH by the pituitary gland. There are no data to confirm whether or not the same mechanism applies in the monkey.

Pituitary

An increase of swollen and vacuolated cells was observed in the *pars distalis* in rats, which was probably secondary to the effects on thyroxine clearance since these cells produce TSH. The reduced thyroxine levels detected in the rat repeat dose toxicity study would provide a feedback signal for the pituitary gland to produce more TSH.

The NOAEL for effects on the pituitary gland or serum concentrations of TSH was 10 mg/kg/day, corresponding to relative exposures of three in males and six in females compared with human clinical exposure levels.

Haematological Effects

In the three month mouse study, daily gavage doses of 320 mg/kg/day were associated with slightly reduced erythrocytic parameters, reduced lymphocyte numbers (in males) and increased reticulocyte count (in females), which were probably related to observations of extramedullar hematopoiesis in the thymus and an increase in the myeloid/erythroid ratio in bone marrow (in males). Similar results were observed in the six month rat study at doses ≥ 400 mg/kg/day, and the effects were shown to be reversible. There were no signs indicative of bone marrow suppression. The increased cellularity in bone marrow of female mice is probably due to an increase of erythroid elements compensatory to the decrease of red blood cells in the circulation, while the increased myeloid/erythroid ratio in bone marrow of male mice was probably due to an increase in myeloid precursor cells compensating the decrease of lymphocytes in the circulation. Importantly, no effects were observed on bone marrow and haemopoietic cells in the mouse and rat carcinogenicity studies.

In addition to the effects on red cells, increases in activated partial thromboplastin time (APTT) and prothrombin time (PT) were observed in treated male rats at all dose levels (exposure levels relative to clinical trials ≥ 8), while eosinophil numbers were reduced in females. The effects on coagulation parameters were only partially reversed after one month without dosing.

Genotoxicity

A standard battery of genotoxicity tests was carried out to establish the effects of rilpivirine on the rates of reverse mutation in bacterial strains and forward mutation in mammalian cells *in vitro*, and on chromosomal aberrations in mice *in vivo*. Experiments were carried out in accordance with ICH guidelines and under GLP conditions using the maximum feasible concentration or dose with respect to solubility, and suitable positive control substances that produced the anticipated effects. An additional Ames test was done using a human S9 mix as a metabolism enhancer, as the rat S9 mix used in the Ames test and mouse lymphoma assay had a poor capacity to generate metabolites M30 and M31. The metabolic pathway to these metabolites yields a reactive epoxide, which would not have been present in the Ames test with a rat S9 mix (the metabolites themselves do not contain any structural alerts for genotoxicity). The experiment was optimised to ensure an adequate level of M30 was produced.

There was no evidence that rilpivirine increased the spontaneous rate of mutations or caused chromosome damage in these experiments.

Carcinogenicity

The carcinogenic potential of rilpivirine HCl was studied in two year carcinogenicity studies in rats and in mice.

As shown in the above table comparing exposure levels in the clinical trials with those achieved in the nonclinical repeat-dose studies, the exposures to rilpivirine in the mouse study were ≥ 20 -30 times the clinical exposure level. However, in the rat carcinogenicity study, the exposures in males in particular were only low multiples of the human clinical exposure levels. Nevertheless, the relative exposure in females was ≤ 37 , and the study did provide evidence of carcinogenicity, so is therefore considered to be valid.

In both species there was an increase in incidence of hepatocellular adenoma and carcinoma associated with rilpivirine at all dose levels (relative exposures were 20 in mice and 3 in rats). In view of the lack of evidence of genotoxicity for rilpivirine, together with evidence of hepatic enzyme induction (increased liver weight, induction of CYP4A in male and female mice and male rats, induction CYP3A in female rats, and electron microscopic evidence of peroxisome proliferation in mice), this is most likely due to a species specific epigenetic phenomenon and is unlikely to be relevant to humans.

The increased incidence of thyroid follicular adenomas and carcinomas in rats is similarly likely to be due to increased hepatic activity of the enzyme UDPGT. This is known to be the most important enzyme involved in the metabolism and clearance of thyroid hormones, and its induction is a well known cause of increased thyroid hormone clearance, associated with the development of follicular adenomas and carcinomas.

Reproductive toxicity

Investigation of the potential effects of rilpivirine on reproductive toxicity included GLP-compliant fertility studies in male and female rats, embryofetal development studies in rats and rabbits, and a prenatal and postnatal development study in rats. In addition, the placental transfer of ^{14}C -rilpivirine was studied by administration of the radiolabelled substance to pregnant rats. The male fertility study was carried out in view of the effects on the testes in dogs. Male rats were dosed for ten weeks prior to mating, and the HD level was the maximum feasible dose that could be administered. In addition to examining the effects of paternal treatment on mating and pregnancy, the study looked for any adverse effects (AEs) on sperm quality or quantity. The doses selected in the rat and rabbit embryofetal toxicity studies were appropriate, and dosing was administered during the period of organogenesis, as outlined in Table 4.

Table 4: Relative exposure in pivotal reproductive toxicity studies.

Species	Study	Dose (mg/kg/day)	AUC _{0-24h} (µg·h/mL)	Exposure ratio [#]
Rat (SD)	Embryofetal development (GD16)	40	36.8	15
		120	62.5	26
		400	152	63
Rabbit (NZW)	Embryofetal development (GD19)	5	105	44
		10	170	71
		20	232	97
Human (pooled data phase III trials)	steady state	25 mg <i>q.i.d.</i>	2.4	–

[#] = animal to human plasma AUC_{0-24h}, *q.i.d.* (quater in die) = four per day

The relative exposure achieved in the reproductive toxicity studies was high. Placental transfer of ¹⁴C-rilpivirine (or its metabolites) was demonstrated, indicating that the placenta is only a partial barrier to this substance. Rilpivirine administration had no effects on male or female fertility or reproductive performance. In the rat teratology study, a dose-related increased incidence of dilated renal pelvis was observed at all treatment levels, reaching statistical significance at doses ≥ 120 mg/kg/day (NOAEL at exposure ratio of 15). This effect is possibly related to treatment, and was also observed at low incidence in the prenatal and postnatal development study, associated with maternal doses of 400 mg/kg/day during GD6 to PND 20. The fetal NOAELs in these studies were 40 and 120 mg/kg/day, respectively (exposure ratio ≥ 15). In the rabbit embryofetal toxicity study, there were increased incidences of fetuses exhibiting hypoplastic interparietal bone and branching of the left subclavian artery originating from the aorta, both associated with maternal rilpivirine doses ≥ 20 mg/kg/day (NOAEL at exposure ratio of 71). These effects in rat and rabbit fetuses are relatively minor in nature, although it is unclear whether or not they are secondary to maternal toxicity.

In the prenatal and postnatal development toxicity study in rats, there was no effect of maternal treatment with rilpivirine on pregnancy outcome or pup development, including fertility and reproductive performance, at maternal doses of up to 400 mg/kg/day. In a separate pilot prenatal and postnatal toxicity study in rats, a group of F1 pups were selected for a subsequent juvenile toxicity study (dosing by gavage on Days 12-25 of lactation). Toxicokinetic data from this study showed that rilpivirine was secreted into the milk of suckling rats. On lactation Day 7, the exposure ratios for pups were approximately 0.009 to 0.01 compared with the maternal levels (based on data in non pregnant female rats in the six month repeat dose study). The exposure ratios for pups dosed through milk were 0.004 to 0.050 compared with exposure levels in F1 pups dosed directly by oral gavage on postnatal Day 25.

Pregnancy classification

The sponsor has proposed Pregnancy Category B1. This category is considered to be acceptable since the fetal variations observed in rats occurred at maternally toxic doses, and the NOAELs for both species were high multiples of the clinical exposure levels.

Local tolerance

Rilpivirine was classed as a moderate eye irritant in the *in vitro* bovine corneal opacity-permeability eye irritation test. There was no evidence of potential phototoxicity as assessed by neutral red uptake in mouse fibroblasts *in vitro*. A skin irritation test in rabbits showed no signs of skin irritation, and there was no evidence of delayed-type hypersensitivity in the mouse local lymph node assay.

Immunotoxicity

Rilpivirine did not reduce the antibody response to sheep red blood cells in the plaque forming assay, indicating that it does not possess immunotoxic potential.

Impurities

Two impurities exceed the International Conference on Harmonisation (ICH) qualification limit.

Another two impurities were considered to have been adequately qualified in one month repeat dose toxicity study in rats. On the basis of the results of this study, it is considered that the free base form of one of the impurities was also adequately qualified.

A fifth impurity has also been adequately qualified in a one month repeat-dose toxicity study in dogs.

A sixth impurity identified from an early synthesis route for rilpivirine, was investigated for genotoxicity on the basis of its chemical moieties. Three drug substance impurities contain the same chemical moiety and were for that reason evaluated for their mutagenic potential. Only one impurity increased the mutation frequency in the Ames test. This impurity contains another separate distinct chemical moiety whereas the others do not. The mutagenic potential of the shared common chemical moiety was considered to be low and the mutagenicity of this impurity is due to its distinct chemical moiety. The other impurities were not mutagenic in the Ames test.

The sponsor has proposed to use a Threshold of Toxicological Concern (TTC) approach to manage the genotoxic risk proposed by the abovementioned impurity or its hydrochloride salt. The level of this impurity is less than the maximal allowable level.

Paediatric use

Rilpivirine is not recommended for paediatric use as there are no clinical data in this population. However, it is noted that a number of the studies submitted to support the current application involved treatment of juvenile animals, including a juvenile toxicity study in rats (dosed by gavage from Days 12-25 of lactation) and an eight week study in immature female cynomolgus monkeys. In addition, in the repeat dose studies in dogs, the animals were six to eight months old at the start of dosing. In the one month dog study, the control female animals were still immature at necropsy, since they showed no signs of ovarian maturation or ovulation. The nonclinical data have not been evaluated to specifically address issues relating to juvenile toxicity since the indications preclude paediatric dosing. However, the potential endocrine effects will be of particular importance in any clinical trials in children or adolescents.

Nonclinical Summary and Conclusions

- The overall quality of the nonclinical data was high, with all pivotal toxicity studies conducted under GLP conditions using the proposed clinical route (PO).

- Rilpivirine is a non-competitive non-nucleoside inhibitor of HIV-1 reverse transcriptase (RT), with a median IC_{50} of 42 nM, and no activity against human cellular DNA polymerases α , β and γ *in vitro*.
- Antiviral activity against laboratory strains of wild type HIV-1 was demonstrated in an acutely infected T cell line *in vitro*. The median EC_{50} against HIV-1/IIIB was 0.73 nM. Rilpivirine exhibited EC_{50} values against wild type HIV-1 group M isolates A, B, C, D, E, F, and G of 0.07–1.01 nM. HIV-1 group O isolates were inhibited by rilpivirine with EC_{50} values of 2.88–8.45 nM. Rilpivirine was shown to be relatively selective for HIV-1.
- There was no evidence of any clinically relevant interaction on a broad range of neurotransmitter, interleukin or chemokine receptors or enzymes. There were no remarkable effects in safety pharmacology studies on the CNS, cardiovascular and respiratory systems.
- The mechanism underlying the QT prolongation seen in clinical trials is not explained by the nonclinical data, including a consideration of pharmacokinetic or metabolic data. QT prolongation occurred at unbound clinical C_{max} levels 50-100 times lower than the *in vitro* concentrations associated with hERG K^+ channel inhibition. Rilpivirine did not inhibit human cardiac ion channels expressed in mammalian cells, and was not torsadogenic in the rabbit ventricular wedge preparation *in vitro*. The relevance of these *in vitro* studies could be criticised on the basis of the 11 day time course of onset for the clinical effect. One possible explanation for the delayed effect on QT, the interference with the trafficking of hERG K^+ channels from the endoplasmic reticulum to the cell surface, did not occur at clinically relevant concentrations. Repeated dosing with rilpivirine had no effect on QT interval in chronically telemetered female guinea pigs, but the plasma C_{max} values were 50% lower than the clinical C_{max} values associated with prolonged QT intervals. Slight prolongation of QT or QT_c occurred in 2/3 monkeys after repeated dosing with rilpivirine at plasma C_{max} levels similar to those associated with QT prolongation in the clinical trials, but not in monkeys at a 2 fold higher dose level. The elevated HR in these restrained monkeys may have obscured a more prominent QT effect.
- The rate of absorption of rilpivirine base and HCl salt was moderate in the animal species, with T_{max} in the range of 1-2 h, although absorption was prolonged at higher doses. The proposed mechanism of absorption is passive transcellular diffusion. Absorption was increased at lower pH levels, and plasma concentrations tended to increase less than dose proportionally, due to low solubility and saturation of absorption. The elimination half life ($t_{1/2}$) was generally shorter in laboratory species (2.8-21 h in rats, rabbits and monkeys, 18-39 h in dogs, compared with 45-50 h in humans). The absolute oral bioavailability of the free base was 21-39%. Rilpivirine was extensively bound (99.08-99.98%) to plasma proteins, predominantly albumin, in all species. There was no evidence of retention or accumulation in any tissues. The major route of metabolism in animals, as in humans, was aromatic hydroxylation at the pyrimidyl moiety, followed by glucuronidation. No unique human metabolites were observed, and although there were some differences, overall the human profile of metabolites was reflected in the animal species. In each species a large number of metabolites were detected. The main route of elimination of rilpivirine and its metabolites was faecal, with unchanged rilpivirine being the predominant excreted form. Unchanged rilpivirine was not excreted in rat bile.
- *In vitro* experiments indicate that rilpivirine is predominantly metabolised by CYP3A. *In ex vivo* induction studies, rilpivirine was an inducer of CYP4A in rats and mice, and induced uridine diphosphateglucuronosyltransferase activity towards thyroxine, but

had little effect in dogs, other than to reduce CYP3A-dependent testosterone 6 β -hydroxylase activity. It is unlikely that treatment with rilpivirine will have clinically relevant effects on P-gp mediated absorption. Although rilpivirine had inhibitory effects on a range of CYP isozymes, clinically relevant effects on the metabolism of other medicines are unlikely to be significant.

- Rilpivirine has a low level of acute toxicity in animals.
- Repeat dose toxicity studies were performed in mice (up to 3 months), rats (up to 6 months), dogs (up to 12 months) and monkeys (up to 8 weeks) using the clinical route (oral). Exposure ratios based on the ratio of animal to human plasma AUC_{0-24h} values were relatively low at the lowest dose levels in rats (3-6) and in the monkey study (1-2), but were high in mice and dogs.
- Rilpivirine inhibited cortisol and corticosterone biosynthesis in mice, rats, dogs and monkeys, an effect that was probably mediated by inhibition of CYP21 (21 α -hydroxylase) and CYP17 (17 α -hydroxylase or 17,20 lyase), resulting in histological changes, and alterations in basal steroid levels and serum levels after ACTH stimulation. A no observed effect level (NOEL) was not established in dogs or monkeys, with the lowest observed effect level (LOEL) corresponding to exposure ratios of 7 and 1, respectively, compared with the clinical AUC.
- Gonadal effects were seen in mice and dogs, most probably secondary to the effects on adrenal steroidogenesis. In mice, ovarian function appeared to be suppressed, but the female genital tract and mammary glands appeared to be activated in dogs, and rilpivirine treatment may have led to earlier sexual maturation in females of this species. Increased ovarian weight and dilation of mammary gland ducts was observed in dogs at exposures ≥ 7 times the clinical AUC, with evidence of ovarian activation at ≥ 11 times the clinical AUC. Immature female cynomolgus monkeys did not show early sexual maturation at exposures comparable to the clinical AUC. Male dogs had evidence of mild testicular damage, consisting of an increase in atrophic tubuli and reduced spermiogenesis (exposure ratios ≥ 11), and Leydig cell hyperplasia and hypertrophy (exposure ratios ≥ 28), with no impact on Sertoli cell functioning or spermatogenesis. There were no effects on the male gonads in mice or rats.
- Hepatic effects of rilpivirine in rats and mice (at relative exposures ≥ 10 and 100, respectively) were in keeping with the induction of liver enzymes, including increased activities of ALP, AST and ALT, increased hepatic weight and histopathological changes, including (in mice) peroxisome proliferation. This is likely species specific, and not of clinical significance. However, in dogs, relative exposures ≥ 10 were associated with increases in serum cholesterol and total bilirubin, and histopathological changes indicative of cholestasis, with no evidence of enzyme induction.
- In dogs, renal toxicity included a trend towards increased serum creatinine concentrations, corticomedullary mineralisation in females, and acute interstitial nephritis in two males at an exposure ratio ≥ 10 .
- Thyroid and pituitary effects in rats were related to hepatic UDP-GT induction, leading to an increased clearance of thyroid hormones and subsequently increased release and synthesis of TSH by the pituitary gland (exposure ≥ 11 times clinical AUC). Follicular cell hypertrophy was also observed in female cynomolgus monkeys at 1-2 times the human clinical exposure level. There are no data to confirm whether or not the same mechanism applies in the monkey as is proposed for the rat.

- Rilpivirine was not genotoxic in a standard battery of genotoxicity tests, including reverse mutation studies in bacterial strains or forward mutation in mammalian cells *in vitro*, or chromosomal aberrations in mice *in vivo*.
- In two year carcinogenicity studies in rats and mice there was an increased incidence of hepatocellular adenoma and carcinoma associated with rilpivirine at all dose levels (relative exposures of 20 in mice and 3 in rats, compared with clinical AUC). Rats also exhibited an increased incidence of thyroid adenoma and carcinoma at relative exposures ≥ 4 . Both these types of tumour are most likely due to a species specific epigenetic phenomenon associated with hepatic enzyme induction, and are unlikely to be relevant to humans.
- There was no apparent effect of rilpivirine on fertility in male or female rats, indicating that in this species at least effects on steroid hormones were without consequence for gonadal function. Placental transfer of rilpivirine was demonstrated in rats, and it was also secreted into the milk of lactating dams in this species. Rilpivirine was not teratogenic, but a dose related increased incidence of dilated renal pelvis was observed in rats with a NOAEL at exposure levels of 15 times clinical AUC. In the rabbit embryofetal toxicity study, there were increased incidences of fetuses exhibiting hypoplastic interparietal bone and branching of the left subclavian artery originating from the aorta (NOAEL at 71 times the clinical AUC).
- Rilpivirine showed no evidence of potential phototoxicity, skin irritation, delayed type hypersensitivity or immunotoxicity, and was classed as a moderate eye irritant.
- One impurity, identified from an early synthesis route for rilpivirine on the basis of a structural alert, was found to be genotoxic in a bacterial reverse mutation assay (Ames) and an *in vitro* mammalian chromosomal aberration assay. The Threshold of Toxicological Concern (TTC) for this impurity based on a daily dose of 25 mg is 60 ppm. The level of this impurity is controlled to <5 ppm in the manufacture of rilpivirine.
- Two impurities were adequately qualified in a one month repeat dose toxicity study in rats, with exposure levels (based on a comparison of dose per unit of body surface area) > 700 times the clinical exposure level.
- Another impurity was present in a one month repeat dose toxicity study in dogs at a level of 0.61%. On the basis of dose per unit of body surface area, the exposure to this impurity was approximately 180 times the anticipated clinical exposure. It is therefore considered that this impurity have been adequately qualified in this study.

Conclusions and Recommendation

Overall, the nonclinical data support the use of rilpivirine in the treatment of HIV-1 infection in combination with other antiviral medications. The toxicological issues identified include:

- Rilpivirine is predominantly metabolised by CYP3A, and so therapeutic concentrations will be affected by medicines that affect the activity of this isozyme;
- The mechanism underlying prolongation of the QT interval seen in the clinical trials with a delayed onset is not explained by the nonclinical data;
- Possible effects on adrenal cortical function and associated steroidogenesis;
- Possible effects on ovarian function; and
- Possible interference with thyroid hormone homeostasis.

These effects have been monitored in the clinical trials, and should be included in a post market monitoring program.

There are no objections on nonclinical grounds to the registration of rilpivirine as proposed. The Product Information document should be amended as indicated.

IV. Clinical Findings

Introduction

The sponsor has stated in this submission that the data package for the Australian submission is the same as that submitted in the EU. It is also essentially the same as that submitted in Canada and the USA.

The current submission package does not contain any studies relating to the use of rilpivirine in a paediatric population. However, the sponsor has stated that a paediatric development program for rilpivirine has been developed. The paediatric investigation plan for rilpivirine was approved by the European Medicines Agency in March 2010.

All clinical studies reviewed in this evaluation were conducted according to Good Clinical Practice (GCP) guidelines.

Pharmacokinetics

Introduction

Overall, 31 studies were presented in the Clinical Pharmacology section. A total of 555 healthy subjects received rilpivirine in Phase I studies. Rilpivirine was administered as an oral solution in some studies (C101, C108, C119, CDE101, CDE 102, CDE103,). A phase IIb tablet formulation was developed and used in studies (C103, C104, C106, C105, C112, C125, C127, C116, C120, C114, C140, C109, C139, C151). The remaining studies were performed with a Phase III tablet (C130, C123, C136, C121, C131, C152). In addition, other PK data was available from studies conducted in 1052 HIV-1 infected subjects using oral solution (C201, C202), Phase IIb tablets (C204), or Phase III tablets (C209, C215). The PK/PD (pharmacokinetics/pharmacodynamics) effects of rilpivirine were evaluated over a wide dose range (12.5 to 400 mg) for both single and multiple doses.

Methods

Analytical Methods

Bioanalytic assays for rilpivirine in plasma and urine were developed at 2 different laboratories and were based on liquid chromatography with tandem mass spectrometry [LC-MS/MS]. Due to transformation of rilpivirine to another isomeric form (Z isomer) on exposure to light, PK samples in each of the trials were protected from light during processing and storage. Assays were evaluated in the range 1-2000ng/ml and demonstrated a precision and accuracy across the range <20% (coefficient of variation for repeated measurements). Valid, reliable methods with sufficient accuracy and precision were used for drug interaction studies, where other analytes were also measured.

Pharmacokinetic Data Analysis

Individual PK parameters were derived from non-compartmental methods by WinNonlin Professional® (version 3.3, statistical analysis in version 4.1; Pharsight Corporation, Mountain View, California, USA). The peak plasma concentration (C_{max}) and the time to reach the peak concentration (T_{max}) were obtained from experimental observations. The slope (λ) of the terminal phase of the plasma concentration time profile was determined by the method of least squares (log linear regression of at least three data points). The terminal half life ($t_{1/2}$) was estimated as $\ln 2/\lambda$. The AUC_{inf} was determined by summing the

areas from zero to the time of last measured concentration, calculated by using conventional trapezoidal and log trapezoidal methods and the extrapolated area. The extrapolated area was determined by dividing the last measured concentration by the slope of the terminal log linear phase. Average steady state plasma concentration ($C_{ss,av}$) was calculated by AUC/τ at steady-state (τ = dosing interval). Fluctuation index (FI), that is, percentage fluctuation (variation between maximal and minimal plasma concentration at steady-state), was calculated as $100 \times (C_{max} - C_{min}) / C_{ss,av}$.

Statistical Analysis

All statistical analyses were carried out using SAS Version 8.2. Descriptive statistics were calculated for the plasma concentrations of rilpivirine at each time point and for the derived PK parameters. Statistics included sample size (N), mean, standard deviation (SD), percentage of coefficient of variation (%CV), geometric mean, median, minimum, and maximum. To assess the dependency on dose, scatter plots of rilpivirine C_{max} , AUC_{inf} , and $AUC_{(0-t)}$ versus dose were provided where appropriate. For comparison between groups, the least square (LS) means of the primary parameters for each treatment group were estimated with a linear mixed effects model. A 90% confidence interval (CI) was constructed around the difference between the LS means of test and reference. Both the difference between the LS means and the 90% CIs were retransformed to the original scale.

Absorption

Bioavailability

The absolute bioavailability of rilpivirine was not investigated because an intravenous (IV) formulation of the drug was not available.

Bioequivalence

The bioequivalence of rilpivirine when administered as a Phase III tablet compared to Phase IIb tablet was evaluated in an open label, randomised, two period crossover study (C117). The trial population consisted of 32 healthy subjects in two parallel panels: 16 subjects each received a single, oral dose of rilpivirine on two occasions as follows: Treatment C (test): 4 X 25 mg Phase III tablets and Treatment D (reference): 1 X 100 mg Phase IIb tablet; Treatment E (test): 1 X 150 mg Phase III tablet and Treatment F (reference): 3 X 50 mg Phase IIb tablets. All treatments were taken under fed conditions within 10 minutes after completion of a standardised breakfast. Treatments were separated by a 13 day washout period. The mean C_{max} and AUC values were comparable between the Phase III and Phase IIb tablets for the 100 mg (Treatment C versus Treatment D) and 150 mg (Treatment E versus Treatment F) dose groups. In the 100 mg dose group, the 90% CIs of the LS means ratio were just outside the 0.80 to 1.25 interval for C_{max} and AUC_{∞} (area under the plasma concentration-time curve from time zero to infinity), and were within this interval for AUC_{last} (area under the plasma concentration-time curve from time zero to time of last measurable concentration). In the 150 mg dose group, the 90% CIs of the LS means ratio were within the 0.80 to 1.25 interval for all pharmacokinetic parameters evaluated. No relevant differences were observed between the Phase III and Phase IIb tablets for the t_{max} , and $t_{1/2}$. The inter individual variability within each of the test formulations was comparable to the variability within each of the reference formulations.

Influence of Food

The effect of concomitant food intake on the oral bioavailability of rilpivirine administered as a tablet was investigated in two trials (C102 using the 100 mg Phase IIb tablet; and C137 using the 75 mg Phase III tablet). In addition, the effect of food on the bioavailability

of rilpivirine administered as three oral concept formulations (solution, suspension, and granules) intended for potential use in paediatric subjects was investigated in trial C145.

The open label, randomised, three period crossover trial evaluated oral bioavailability of two solid formulations compared to a reference solution (C102). A total of 24 healthy subjects received a single, oral dose of 100 mg rilpivirine in each of three sessions as either: 4 mL of 25 mg/mL solution (reference); 2 capsules, each containing 50 mg; or 1 tablet containing 100 mg of rilpivirine. The reference formulation was given under fed conditions (that is, within 10 minutes after a standardised breakfast) and the test formulations were each given once under fed and fasted conditions. Treatments were separated by a washout period of at least two weeks. Under fed conditions, the mean exposure to rilpivirine with the capsule formulation was comparable to the mean exposure with the reference solution; the 90% CIs of the LS means ratios for C_{max} and AUC_{∞} were within the 0.80 to 1.25 interval. The mean exposure with the tablet was up to 17% lower than the mean exposure with the reference solution and the lower limits of the 90% CIs of the LS means ratios for C_{max} and AUC_{∞} values were below the lower boundary of the 0.80 to 1.25 interval. No relevant differences were observed between the reference solution and the capsule or tablet formulations for the t_{max} (time to reach maximum plasma concentration) and $t_{1/2}$ (terminal elimination half life) of rilpivirine. When administered as the capsule or tablet, the oral bioavailability of rilpivirine is improved under fed conditions compared to fasted conditions and inter- individual variability in PK parameters is lower.

The effect of different types of meals on the oral bioavailability of rilpivirine 75 mg Phase III tablet was examined in an open label, randomised, four period crossover trial in 20 healthy subjects (C137). In each of four sessions, subjects received a single, oral dose of 75 mg within 10 minutes after consumption of breakfast or under fasted conditions: Treatment A (reference): Normal fat breakfast (533 kcal, 21 g fat, 189 kcal from fat, 268 kcal from carbohydrates, and 76 kcal from proteins); Treatment B (test): Fasted conditions (subjects had to have fasted overnight for at least 10 hours); Treatment C (test): High fat breakfast (928 kcal, 56 g fat, 504 kcal from fat, 260 kcal from carbohydrates, and 164 kcal from proteins); Treatment D (test): Protein rich nutritional drink (Ensure® HP, 240 mL; 300 kcal, 7.9 g fat, 72 kcal from fat, 153 kcal from carbohydrates, and 75 kcal from proteins). Treatments were separated by a washout period of at least 13 days. The mean plasma concentration time profiles of rilpivirine were lower when administered under fasted conditions and after a protein rich nutritional drink, compared to administration after a normal fat breakfast. Mean plasma concentrations were comparable when taken after a high fat breakfast or after a normal fat breakfast. A lag time of approximately 1 to 2 hours was observed when rilpivirine was taken after the protein rich nutritional drink compared to lag times of up to 0.5 hours for the other treatments. The oral bioavailability was 40% to 50% lower when administered under fasted conditions or after a protein rich nutritional drink, compared to administration after a normal fat breakfast. Administration of rilpivirine after a high fat breakfast or after a normal fat breakfast resulted in similar exposures.

The comparative bioavailability and the influence of food on three paediatric concept formulations (a solution, a suspension, or granules) to that of a 25 mg Phase III tablet used in adults was evaluated in an open label, randomised, three period crossover trial. The effect of food on each concept formulation was also evaluated. The study was conducted in 36 healthy adults, divided over three panels of 12 subjects each, one panel for each concept paediatric formulation. In each of the three panels, subjects received three different rilpivirine treatments in a randomised fashion in three sessions separated by a washout period of at least 14 days. The different treatments were: Panel 1: single 25 mg (2.5 mL) of oral solution (10 mg/mL) given under fed (Treatment A1) and fasted

(Treatment B1) conditions; Panel 2: single 25 mg dose (5 mL) of oral suspension (5 mg/mL) given under fed (Treatment A2) and fasted (Treatment B2) conditions; Panel 3: single 25 mg dose (10 g) of oral granules (2.5 mg/g) given under fed (Treatment A3) and fasted (Treatment B3) conditions; Panels 1, 2, and 3: single 25 mg dose of the Phase III tablet under fed conditions (Treatments C1, C2, C3). When given under fed conditions, the oral bioavailability of rilpivirine with all 3 concept paediatric formulations was either comparable to (suspension) or exceeded (solution, granules) the bioavailability of rilpivirine when given as the Phase III tablet. Compared to the Phase III tablet under fed conditions, the oral bioavailability under fasted conditions was higher when given as the solution and similar when given as the suspension and granules. Compared to administration of the solution or suspension under fed conditions, the absorption of rilpivirine was more rapid under fasted conditions, with 1.32-fold higher C_{max} values attained with the solution and comparable C_{max} and AUC_{∞} values attained with the suspension. Food had no effect on the rate of absorption when rilpivirine was administered as granules, but the mean exposure (C_{max} , AUC_{∞}) was decreased by approximately 30% when the granules were administered under fasted compared to fed conditions. The granule formulation has been selected for use in future paediatric trials.

The recommendation that rilpivirine be administered with a meal to ensure optimal absorption and adequate exposure is appropriate based on the results of the above studies.

Distribution

After a single oral dose of 150 mg ^{14}C -rilpivirine in healthy adults (trial C119), the blood to plasma ratios of total ^{14}C -radioactivity were time independent, with values ranging between 0.65 and 0.75, indicating that rilpivirine and its metabolites were not distributed to blood cells to any significant extent. In whole blood, rilpivirine is predominantly distributed to plasma and to a very limited extent to water and blood cells.

Plasma protein binding was evaluated using equilibrium dialysis of plasma samples from healthy men after incubation with 3H -labelled rilpivirine. Binding was independent of drug concentration within the concentration range tested (10 to 3000 ng/mL [0.03 to 8.19 μM]), and was on average 99.7%. The results of incubations with purified human proteins at physiological concentrations indicated that rilpivirine was extensively bound to human albumin and to a lesser extent to $\alpha 1$ -acid glycoprotein. The blood to plasma concentration ratios were 0.67 and 0.66 at rilpivirine concentrations of 100 and 1000 ng/mL [0.27 and 2.73 μM], respectively. In addition, irrespective of the concentration tested, only a very limited fraction of rilpivirine was distributed to the plasma water compartment (0.003). The fraction of rilpivirine distributed to plasma proteins and blood cells was 0.773 and 0.224, respectively.

Elimination

Excretion

A mass balance trial in healthy adults (C119) showed that most of the administered ^{14}C -rilpivirine related radioactivity from a single 150 mg dose administered as an oral solution was excreted in faeces. At 7 days (168 h) after dosing, a mean of 85.1% of the administered radioactivity was recovered in faeces. Unchanged rilpivirine accounted for a mean of 25.5% of the dose in faeces. The excretion of radioactivity in urine was limited (mean 6.1% of the administered radioactive dose). Only trace amounts ($\leq 0.03\%$) of unchanged rilpivirine were detected in urine.

Metabolism

The *in vitro* metabolism of rilpivirine was studied in human hepatocytes and subcellular liver fractions of humans and various animal species. A major metabolic pathway of

rilpivirine, representing the main *in vitro* biotransformation, was aromatic hydroxylation at the pyrimidinyl moiety, followed by glucuronidation. Another major metabolic pathway was aliphatic hydroxylation at one of the methyl groups of the cyanoethenyl-2,6-dimethylphenyl moiety (hydroxymethyl rilpivirine), followed by dehydration to form a tricyclic metabolite. Aliphatic hydroxylation in combination with glucuronidation was also observed. The metabolism of ^{14}C -rilpivirine in human liver microsomes revealed that the primary rilpivirine metabolism was mainly catalysed by cytochrome CYP3A enzymes.

The metabolites of radioactive carbon labelled (^{14}C)-rilpivirine *in vivo* were determined in faeces, urine, and plasma collected from healthy adults after a single oral dose of 150 mg - ^{14}C -rilpivirine (C119). Rilpivirine was extensively metabolised, with more than 15 metabolites detected. The most abundant metabolite originated from aromatic hydroxylation at the pyrimidinyl moiety, accounting for 16.1% of the rilpivirine-related radioactivity in faeces. Three other metabolites in faeces each accounted for 2.2% to 3.0% of the dose, including a carboxylic acid metabolite and hydroxymethyl rilpivirine. In plasma, unchanged rilpivirine represented the major fraction of the absorbed radioactivity. Several minor metabolites were detected in plasma, including a direct glucuronide of rilpivirine the tricyclic metabolite, and hydroxymethyl rilpivirine.

Inter conversion

Not applicable as rilpivirine is not a chiral product.

Pharmacokinetics of metabolites

No data was presented.

Consequences of genetic polymorphisms

Although rilpivirine is subject to the potential influence of polymorphisms of CYP3A4, these were not investigated for effects on the PK of the drug.

Dose Proportionality and Time Dependency

Dose proportionality

When administered as an oral solution (CDE101, CDE103), the rate of rilpivirine absorption was not influenced by the dose; the median t_{max} was 4 h at all doses, with a range of individual values between 2 and 6 h. In the dose range 12.5 to 200 mg, the mean exposure – in terms of C_{max} and $\text{AUC}_{144\text{h}}$ (area under concentration curve from administration to 144 h post dosing) – to rilpivirine appeared to increase dose proportionally (Table 5). At doses between 200 and 300 mg, the increase was less than proportional (Table 6).

Table 5: PK data for single doses of rilpivirine (Study CDE101).

Parameters	12.5 mg	25 mg	50 mg
T_{max} h	4 (4-4)	4 (2-6)	4 (4-4)
C_{max} ng/ml	73.1 \pm 14.1	149 \pm 32.3	267 \pm 27.4
$\text{AUC}_{(0-\text{last})}$ ng.h/ml	2097 \pm 360	4496 \pm 1240	7879 \pm 973
$\text{AUC}_{(0-\infty)}$ ng.h/ml	2467 \pm 526	5210 \pm 2001	8872 \pm 1342
$t_{1/2}$ h	50.5 \pm 21.6	47.7 \pm 18.6	44.7 \pm 8.7

Table 6: PK data for single doses of rilpivirine (Study CDE103).

Parameters	50 mg	100 mg	200 mg	300 mg
T _{max} h	4 (4.2-6)	4 (4-6)	4 (4-6)	4 (4-4)
C _{max} ng/ml	226 ± 15	482 ± 121	807 ± 207	944 ± 172
AUC ₍₀₋₁₄₄₎ ng.h/ml	6118 ± 1558	13013 ± 4039	25600 ± 5621	27910 ± 7298
AUC _(0-∞) ng.h/ml	6584 ± 1881	15820 ± 4568	28669 ± 6876	32794 ± 10352
t _{1/2} h	34.2 ± 12.0	54.6 ± 17.9	43.1 ± 13.1	52.0 ± 17.2

In the multiple dose trial C103, rilpivirine was administered as 25 and 100 mg Phase IIb tablets and single dose PK data were obtained after the first administration. The rate of rilpivirine absorption was not influenced by dose; the median t_{max} was 4 h at all dose levels, and individual values ranged from 2.0 to 6.7 h. Across the dose range of 25 to 150 mg, the mean exposure – in terms of the C_{max} and AUC_{24h} (area under concentration curve from administration to 24 h post dosing) – to rilpivirine increased dose proportionally (Table 7). Statistical analysis on dose normalised PK parameters revealed no dose dependency for any of the parameters tested.

Table 7: Multiple dose PK parameters for rilpivirine (Study C103).

Parameter	25 mg/d	50 mg/d	100 mg/d	150 mg/d
Day 1				
C _{max} ng/mL	90.08 ± 44.28	138.2 ± 63.10	397.6 ± 147.3	523.8 ± 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 ± 585.6	1551 ± 596.0	4464 ± 1520	5608 ± 1902
Day 14				
C _{0h} ng/mL	89.85 ± 38.07	157.9 ± 52.23	347.8 ± 148.7	504.9 ± 174.6
C _{min} ng/mL	66.85 ± 29.53	115.7 ± 49.30	249.5 ± 90.51	362.0 ± 130.9
C _{max} ng/mL	203.8 ± 75.81	298.6 ± 98.05	685.5 ± 202.4	1019 ± 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 ± 868.8	4139 ± 1236	9278 ± 2846	13581 ± 3195
t _{1/2} h	50.92 ± 19.56	48.75 ± 16.34	46.07 ± 15.44	44.83 ± 12.31
Acc. Ratio	3.020 ± 1.966	2.880 ± 0.7982	2.071 ± 0.7491	2.503 ± 0.7211

Similar linear dose dependency was obtained with single dose administration of rilpivirine as Phase III tablets. Thus, PK data obtained after single dose administration of 25 mg (C145), 75 mg (C137) and 100 and 150 mg (C117) showed that the rate of rilpivirine absorption was not influenced by dose. The median t_{max} was 4-5 h at all doses. Across the range of 25 to 150 mg, the mean exposure (in terms of the C_{max} and AUC) to rilpivirine increased dose proportionally.

Time dependency

In trial CDE102, rilpivirine was administered as an oral solution at doses of 25 to 150 mg/day for 14 days. The rate of rilpivirine absorption at steady state was not influenced by the dose level; the median t_{max} was 4 h at all doses, and individual values ranged from 2-6 h. Across the dose range of 25 to 150 mg, the mean exposure (in terms of the C_{max} and AUC_{24h}) to rilpivirine appeared to increase dose proportionally between doses of 25 and 75 mg/day, but the increase was less than dose proportional between doses of 75 and 150 mg/day. The median t_{1/2} values after multiple dosing across the different doses (41 to 49 hours) were in the same range as those observed in single dose trials (34 to 55 hours). Steady state was achieved after 8 to 10 doses. The mean CL/F (apparent total clearance of a drug from plasma after oral administration) ranged from 6.89 to 8.66 L/h, which was comparable with the range observed in the single dose trial at doses of 50 to 200 mg (6.92 to 8.33 L/h). These findings suggest that there was no time dependent change in pharmacokinetics following multiple oral dosing. Plasma concentrations of rilpivirine

accumulated during the 14 days of multiple dosing. The mean accumulation index was 2.1 to 2.4 for C_{\max} , 2.5 to 3.5 for C_{0h} , (predose plasma concentration) and 2.6 to 3.1 for AUC_{24h} . The inter individual variability at steady state was low, varying between 10% and 25% for C_{\max} , between 13% and 24% for C_{0h} , and between 10% and 19% for AUC_{24h} .

In trial C103, rilpivirine was administered at doses of 25 to 150 mg/day with Phase IIb tablets for 14 days. The rate of rilpivirine absorption at steady state was not influenced by the dose; the median t_{\max} was 4 h at all doses, and individual values ranged from 2-6 h. Across the dose range of 25 to 150 mg/day, the increase in mean exposure (in terms of the C_{\max} and AUC_{24h}) to rilpivirine was dose proportional. The inter-individual variability was low and independent of the dose administered, ranging from 23.5% to 33.6% for AUC_{24h} . The accumulation ratio and $t_{1/2}$ were independent of the dose. The steady state AUC_{24h} was 2 to 3 fold higher on Day 14 compared to Day 1, which concurred with the mean $t_{1/2}$ of approximately 45 to 50 h across the dose levels studied (Table 6). In addition to trial C103, rilpivirine was also administered as the Phase IIb tablet at a dose of 25 mg/day for 11 days in trial C151. The multiple dose pharmacokinetics of rilpivirine in trial C151 were generally comparable to those observed in trial C103 for the dose of 25 mg/day.

In trials C130 (data from healthy, non hepatic impaired subjects) and C152, rilpivirine was administered at a dose of 25 mg/day for 11 days using a Phase III tablet. On Day 11, the median t_{\max} was 5 h in both trials and individual values ranged from 4 to 24 h. The inter individual variability for C_{\min} (steady state minimal plasma concentration), C_{\max} , and AUC_{24h} within each trial was low to moderate, with values (CV%) ranging from 24.8% to 31.0%. The observed pharmacokinetic parameters in trial C130 were significantly lower as compared to those observed in trial C152. There is no obvious explanation for the differences in exposure to rilpivirine between trials C130 and C152, for example, by differences in trial conduct and/or demographic characteristics. It is likely that the observed difference between the two trials is reflective of a relatively wide range of exposures to rilpivirine in healthy subjects.

The exposure to rilpivirine after multiple doses of rilpivirine 75 mg/day using the 75 mg Phase III tablet in trial C131 seemed to be dose proportional to the exposure to rilpivirine at a dose of 25 mg/day in trials C130 and C152 (based on average exposure from both trials). With 300 mg/day doses in trial C131, the exposure to rilpivirine seemed to be slightly less than dose proportional compared to the exposure after rilpivirine at a dose of 75 mg/day in trial C131 and at a dose of 25 mg/day in trials C130 and C152, respectively.

Intra and Inter Individual Variability

In both trials with oral solution administration (CDE101, CDE103), the inter individual variability of PK parameters was low to moderate at all doses (15% to 38%). With Phase IIB tablets a low to moderate inter individual variability was observed (24% to 34% for AUC_{24h} at Day 14) and was independent of the dose administered. When rilpivirine was administered as the Phase III tablet (C117, C137, C145), the inter individual variability of pharmacokinetic parameters was also low to moderate at all doses (20% to 49%).

Pharmacokinetics in Target Population

Single Dose

Single dose PK of rilpivirine, after administered as the oral solution across the dose range of 25 to 150 mg, were obtained after administration of the first dose in treatment naïve (C201) and treatment experienced subjects (C202). The rate of absorption was not influenced by dose: median t_{\max} was 4 h (range 1-24 h) between 25 and 100 mg and 3 h (range 2-8 h) at 150 mg. Systemic exposure (C_{\max} , AUC_{24h}) appeared to increase less than dose proportionally. When administered as a single dose of 25 mg, the mean exposure was

comparable in treatment naïve and treatment experienced subjects. For higher single doses, the mean exposure was higher in treatment experienced subjects than treatment naïve subjects. The results of cross trial comparisons should be interpreted with caution due to the large standard deviations recorded. The differences may be related to residual effects of previous antiretroviral agents.

Multiple Dose

Multiple dose PK of rilpivirine were obtained after administration of 25 to 150 mg/day for 7 days in treatment naïve subjects (C201) and in treatment experienced subjects (C202). In these trials, rilpivirine was administered as an *oral solution*. The rate of absorption was not influenced by dose: the median t_{max} was 3-4 h (range 2-23 h). After 7 days of treatment, when steady-state conditions had almost been reached, the exposure to rilpivirine (expressed as AUC_{24h}) was approximately 2 to 3 fold higher than on Day 1 across all dose levels. The inter-individual variability increased as the dose level increased in treatment naïve subjects (C201): from 22% to 64% for C_{max} and from 24% to 51% for AUC_{24h} . In treatment experienced subjects (C202), a moderate inter individual variability of PK was observed at all dose levels; from 25% to 43% for C_{max} and from 34% to 54% for AUC_{24h} . The mean PK parameters of rilpivirine appeared to increase in a less than dose proportional manner. Across all dose levels, there were no consistent differences in PK for treatment naïve and treatment experienced subjects.

The PK of rilpivirine, administered as the Phase IIb tablet (25, 50, and 100 mg) at doses of 25, 75, and 150 mg/day, was determined over 24 h in a subset of subjects at Weeks 4, 24, and 48 in the Phase IIb dose-response Study C204. The rate of absorption was not dependent on the dose: median t_{max} was 4 h (ranged from 0-24 h). Systemic exposure was comparable at Weeks 4, 24, and 48. Within each dose level, there was no difference in the mean exposure to rilpivirine over time (based on C_{24h} , C_{min} , C_{max} , and AUC_{24h} at different sampling weeks). The increase in exposure was less than dose proportional between the 25 and 75 mg/day dose levels, and dose proportional between the 75 and 150 mg/day dose levels. The inter-individual variability in PK parameters was moderate at all doses (25 mg/day: 40% to 50%; 75 mg/day: 46% to 64%; 150 mg/day: 35% to 50%).

A similar analysis was performed in a subset of patients at Week 4, Week 8, or at any time in between when rilpivirine was administered as a 25 mg Phase III tablet in the Phase III studies C209 and C215. A 24 h PK profile was determined at these weeks when subjects were treated with 25 mg/day. Mean values of C_{0h} and C_{min} were slightly higher in trial C209 compared trial C215, while the mean C_{max} and AUC_{24h} were comparable in both trials. The median t_{max} was 4 h and the interindividual variability of PK parameters was moderate (48% to 58%).

Irrespective of the oral formulation or dose of rilpivirine administered, exposure appears to be lower in HIV-1 infected subjects when retrospectively compared to that obtained in healthy subjects receiving similar doses. The reason for this lower exposure in HIV-1 infected subjects has not been identified. Elevated gastric pH in HIV-1 infected patients may have contributed to the lower exposure, as the absorption of rilpivirine is pH-dependent with decreasing oral bioavailability at higher pH (see drug interaction study with famotidine discussed below).

Special Populations

Children

Although formulations were developed for the potential use of rilpivirine in children, the PK were only evaluated in an adult population.

Age, Gender, Race

No specific PK trials were conducted in healthy volunteers to examine the influence of these factors on rilpivirine exposure. Information was available from the population PK data and a pooled analysis of data from Phase III studies in HIV infected patients. While gender appeared to be a factor influencing the clearance of rilpivirine, this was thought to be explained largely by differences in body weight between males and females. Asians may have higher exposure to rilpivirine than Caucasians but body weight differences are a likely explanation. The number of Asian subjects in the population PK analysis is relatively small compared to Caucasians. The majority of subjects in the population PK analysis were less than 65 years of age and very few subjects were over 75 years.

Impaired Renal Function

No specific studies were presented. The population PK analysis of pooled data from Phase III trials in HIV-1 infected subjects used baseline eGFR as a covariate to assess the effect on clearance of rilpivirine. It was not retained as a significant factor affecting clearance.

Impaired Hepatic Function

In Study C130, steady state exposure to rilpivirine at doses of 25 mg/day was higher in subjects with mild hepatic impairment compared to matched healthy control subjects. Mean C_{max} and AUC_{24h} were 1.27 and 1.47 fold higher than in controls, respectively. In subjects with moderate hepatic impairment, the exposure to rilpivirine after a single dose was lower compared to healthy subjects (C_{max} : 30% lower; AUC_{24h} : 24% lower). Based on the shape of the plasma concentration profiles, this appeared to be due to a difference in the absorption of rilpivirine. However, at steady state, the exposure to rilpivirine was comparable in subjects with moderate hepatic impairment and healthy subjects due to the longer $t_{1/2}$ in subjects with moderate hepatic impairment. These data suggest that no dose adjustment of rilpivirine is needed in subjects with mild or moderate hepatic impairment. The effect of severe hepatic impairment on the exposure to rilpivirine has not been studied.

Evaluator's overall comments on PK in special populations

A modest study has been undertaken to evaluate the effect of mild to moderate hepatic impairment on the PK of rilpivirine. The sample size was small and no patients with severe hepatic impairment were included. The population PK study assessed the potential effect of a number of other parameters on the PK of rilpivirine but there are some significant gaps in knowledge about the PK and the influence of such factors as ethnicity and age. Renal impairment probably is unlikely to be particularly important given the extensive metabolism of the drug; nevertheless, a study in severe renal impairment would have been informative. Some formulations were developed for potential use in children but the PK data were evaluated only in adults. The PK profile of rilpivirine in paediatric populations is yet to be evaluated.

Population PK Analysis

Three population PK studies were undertaken and utilised different populations of samples from healthy control subjects and HIV patients in Phase IIb trials or Phase III trials.

A population PK evaluation was performed using data from 107 healthy volunteers (Studies C102, C103, C104, C105, C109) and 56 HIV infected patients (Study C204) receiving single or multiple doses. The final population model comprised a two compartment with a lag time of absorption. No covariate effects were examined other than differences between patients and controls. Plasma concentration time profiles were

somewhat lower in patients compared to controls. Relative bioavailability at 75 and 150 mg was 81.3% and 70.4% respectively in patients compared to controls. Less than dose proportional exposure was observed in patients between 25 and 150 mg/day. Apparent oral clearance was estimated as 10.5 L/h. The volume of the central compartment was 173L, indicating a moderate distribution outside of the plasma compartment. Inter subject variability for was <40% for both parameters.

A similar population PK analysis was undertaken in data from 269 HIV infected patients (Study C204) on drug concentrations available to 96 weeks of treatment. The data appeared to fit a similar two compartment model as derived in previous analysis using 48 week data. The population estimates of mean oral clearance, apparent volume of distribution and lag time were only slightly different from that of the previous set.

A population PK analysis was undertaken in 679 HIV-1 infected subjects (Study C209, C215) and 57 healthy controls (Study C152). The model development was performed with a limited amount of richly sampled Phase III data and one Phase I study (C152). All the subjects included received 25 mg/day of a Phase III tablet. A two compartment model was adequate to explain steady state PK of rilpivirine. The shape of the plasma concentrations time curves were similar, although HIV patients had lower concentrations than healthy controls. Absorption was variable and characterised by a lag time followed by an almost linear increase in plasma concentrations. The final population model comprised a two compartment with a lag time of absorption. The exposure in HIV patients was estimated to be 40% lower than healthy subjects. In HIV-1 subjects, apparent oral clearance was estimated to be 11.8 L/h and the apparent volume of the central compartment 152 L, which corresponds well with the previous two population PK studies. Inter-individual variability for clearance was 39% and for volume of distribution 117%.

The model was used to evaluate the effect of continuous and categorical variables on apparent oral clearance and their clinical significance. The following covariates were tested for their effect on CL/F: age, gender, race, body mass index, body weight, creatinine clearance (as a marker of eGFR), background antiretroviral treatment, and hepatitis B and/or C co-infection status. Within the pooled trial population set, 24.5% of subjects were female and 75.5% were male. A statistically significant effect of gender on the CL/F of rilpivirine was observed, resulting in a slightly lower CL/F in females (13.6% lower) compared to males. However, this effect appeared to have no impact on the overall inter individual variability and had only a minor effect on explaining the difference between the extremes of the covariate. This covariate induced difference in CL/F is therefore considered not to be of clinical relevance and was not retained in the final population PK model. In HIV-1 infected subjects, baseline eGFR was not retained as a significant covariate in the population model affecting the CL/F of rilpivirine. Within the data set for the population analysis, the median age at baseline was 36 years (range: 18 to 78 years) There were 30 subjects \geq 55 years of age and 2 subjects > 65 years of age (74 and 78 years). Age did not have a statistically significant effect on exposure in HIV-1 infected subjects and was not retained as a significant covariate affecting the CL/F of rilpivirine. The majority of subjects included in this population PK analysis were White (61.4%); 24.1% were Black or African American and 11.4% were Asian. A statistically significant effect of race on the exposure to rilpivirine was observed with a higher exposure in Asian subjects compared to the rest of the population. Within the pooled data set, the median body weight at baseline was 70.91 kg (range: 36.2 to 200.9 kg). The median BMI at baseline was 24.01 kg/m² (range: 14.9 to 72.9 kg/m²). Body weight did not have a statistically significant effect on the CL/F of rilpivirine. None of the covariate induced differences in apparent oral clearance were considered to be clinically relevant and were not retained in the final model.

Drug Interactions

In vitro Interactions

An extensive series of *in vitro* studies on the potential of other medications to interfere with metabolism of rilpivirine and of rilpivirine to interfere with the metabolism of other agents was conducted. Metabolism experiments in expressed CYP P450 *E. coli* and Supersomes® showed that rilpivirine metabolism was catalysed mainly by CYP3A enzymes for the formation of all metabolites (NC141). CYP2C19, CYP1A2 and CYP2C8/9/10 are also involved to a lesser extent for some metabolites of rilpivirine. However, evidence for involvement of CYP2C8/9/10 and CYP2C19 was less consistent throughout the different phenotyping experiments.

The *in vitro* interaction between rilpivirine and substrates of different CYP enzymes was investigated in pooled human liver microsomes (HLMs): phenacetin *O*-deethylation (CYP1A2), coumarin 7-hydroxylation (CYP2A6), tolbutamide 4-hydroxylation (CYP2C8/9/10), S-mephenytoin 4-hydroxylation (CYP2C19), dextromethorphan *O*-demethylation (CYP2D6), bufuralol hydroxylation (CYP2D6), chlorzoxazone 6-hydroxylation (CYP2E1), testosterone 6 β -hydroxylation (CYP3A4), cyclosporin A oxidation (CYP3A4), midazolam 4- and 1'-hydroxylation (CYP3A4/3A5), and lauric acid ω - and (ω -1)-hydroxylation (CYP4A and CYP2E1) (FK4123). Little to no inhibition was observed for metabolism dependent on CYP2A6 and CYP4A. The formation of metabolites dependent on CYP2D6, CYP2C8/9/10, CYP3A4/5, CYP2E1 and CYP1A2 was clearly inhibited. Rilpivirine was a strong inhibitor of metabolism dependent on CYP2C19 and CYP2E1. *In vivo* inhibition of the other CYP enzymes is unlikely considering the maximum steady state plasma concentrations of rilpivirine likely to be achieved by the therapeutic dose of 25 mg/day (approximately 0.13 μ g/mL).

The potential for rilpivirine to induce CYP isozyme activities was determined in primary human hepatocyte cultures (NC186). Based on the observed change of mRNA expression and induction of CYP isozyme activities, it can be concluded that rilpivirine may be a weak inducer of CYP1A2 and CYP2B6 in human hepatocytes. In addition, at high free drug concentrations employed in the study, rilpivirine was a moderate inducer of CYP2C19 and CYP3A4. No conclusions were possible for CYP2E1.

The inhibition of CYP2C8 mediated paclitaxel 6 α -hydroxylation and CYP2C9 mediated S-warfarin-7-hydroxylation by rilpivirine was investigated in Study NC283 that showed rilpivirine is an inhibitor of CYP2C8 and CYP2C9 activity. Taking into account maximum steady state plasma concentrations at therapeutic doses of rilpivirine, inhibition of CYP2C8 and CYP2C9 is unlikely to be clinically relevant.

The *in vitro* interaction between rilpivirine and the metabolism of sertraline, paroxetine, clarithromycin, sildenafil, omeprazole, chlorzoxazone, 17 α -ethinylestradiol, S-mephenytoin, and norethindrone was investigated in a pooled batch of human liver microsomes (HLMs) (NC194). A similar study was performed with abacavir using a pooled batch of human liver cytosol. Rilpivirine appeared to have a significant inhibitory effect on the metabolism of clarithromycin, sildenafil, S-mephenytoin, and norethindrone, and a moderate effect on sertraline, paroxetine, and 17 α -ethinylestradiol. Omeprazole metabolism was only slightly inhibited. There was no measurable effect on the metabolism of abacavir or chlorzoxazone and the metabolite formation of these compounds was not inhibited.

Rilpivirine is not a substrate of P-gp. However, it has been shown to inhibit the P-gp mediated transport of paclitaxel in Caco-2 cells with an apparent IC₅₀ value of 9.2 μ M (3371 ng/mL) (NC104). An *in vivo* effect at the intestinal absorption level is unlikely given

the therapeutic dose (25 mg/day) and the fact that *in vivo* plasma concentrations of the drug are more than 10-fold lower than the IC₅₀ value.

In vivo Interactions

Rilpivirine was studied in 17 drug interaction studies. The potential for PK or PD interactions was assessed for drugs which may be commonly co-administered with rilpivirine. Based on nonclinical data, the potential for other drugs to affect rilpivirine exposure appear to be primarily related to the inhibition or induction of CYP3A4 and perhaps CYP2C19.

Administration with Other Antiretrovirals

An open label, two period, randomised trial investigated the PK interaction between rilpivirine and tenofovir in 16 healthy volunteers (C104). Subjects received rilpivirine 150 mg/day on Days 1 to 8, followed by a washout period of at least 14 days. They then received either: tenofovir 300 mg/day on Days 1 to 16, and rilpivirine 150 mg/day on Days 9 to 16 or tenofovir 300 mg/day on Days 1 to 16, and rilpivirine 150 mg/day on Days 1 to 8. All treatments were taken under fed conditions within 10 minutes after breakfast. The mean C_{0h}, C_{min}, C_{max}, and AUC_{24h} of rilpivirine were comparable when given alone or co-administered with tenofovir. There was no change in the median t_{max} of rilpivirine. The mean C_{max} and AUC_{24h} of tenofovir were increased 1.19 and 1.23 fold, respectively, when co-administered with rilpivirine compared to administration alone. The mean C_{0h} and C_{min} were both increased 1.24-fold. There was no relevant change in the median t_{max} of tenofovir. The urinary excretion of tenofovir, as a percentage of the dose administered, was comparable when co-administered with rilpivirine (40.8%) or administered alone (36.2%). The changes in PK are not considered to be clinically relevant.

The PK interaction between rilpivirine and didanosine at steady state was evaluated in an open label, two period, trial in 16 healthy volunteers (C106). After completion of the main trial, Session 2 was repeated with an additional 10 subjects, after samples from 8 subjects in the main trial were lost during shipment. In Session 1, all subjects received rilpivirine 150 mg/day on Days 1 to 7, followed by a washout period of at least 14 days. In Session 2, subjects received one of either: didanosine 400 mg/day on Days 1 to 14, and rilpivirine 150 mg/day on Days 8 to 14; or didanosine 400 mg/day on Days 1 to 14, and rilpivirine 150 mg/day on Days 1 to 7. In Session 1, rilpivirine was taken under fed conditions within 10 minutes after breakfast. In Session 2, didanosine was taken under fasted conditions, with breakfast taken 1.5 hours thereafter. When co-administered with didanosine in Session 2, rilpivirine was taken 30 minutes after breakfast had started (that is, 2 hours after didanosine intake). The mean C_{0h}, C_{min}, C_{max}, and AUC_{24h} of rilpivirine were comparable when given alone or co-administered with didanosine. There was no change in the median t_{max} of rilpivirine. For didanosine values of C_{0h} and C_{24h} were below the lower limit of quantification in all subjects. The mean C_{max} of didanosine was comparable, and AUC_{24h} was slightly increased (1.12 fold) when co-administered with rilpivirine compared to administration alone. There was no change in the median t_{max} of didanosine. No relevant changes were observed in the steady state pharmacokinetics of either drug during co-administration as compared to their administration alone.

The PK interaction of rilpivirine with the combination of lopinavir (LPV) and ritonavir (r) was investigated in 16 healthy subjects in an open label, randomised, two period crossover trial (C105). The two sessions were separated by a washout period of at least 14 days. Subjects received either rilpivirine alone (150 mg/day for 10 days) or combined LPV/r (400 mg/100 mg twice daily for 20 days) alone followed by the combination of rilpivirine and LPV/r (combined treatment on the last 10 days of a 20 day treatment period). Treatments were taken under fed conditions within 10 minutes after a meal. The

mean C_{max} and AUC_{24h} of rilpivirine were increased 1.29 and 1.52 fold, respectively, when co-administered with LPV/r, compared to administration alone (Table 8). The mean C_{min} was increased 1.74 fold. There was no relevant change in the median t_{max} of rilpivirine. Rilpivirine did not significantly affect the PK of lopinavir or ritonavir.

Table 8: PK parameters for rilpivirine (TMC278) with and without coadministration of lopinavir (LPV)/ritonavir (Study C105).

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
$C_{12h,ss}$, ng/mL	823.9 \pm 351.5	1250 \pm 537.3
FL, %	104.5 \pm 37.94	68.02 \pm 20.75

q.d. (quaque die) = one per day

b.i.d. (bis in die) = two per day

In a similarly designed study, the PK interaction of rilpivirine with the combination of darunavir and ritonavir at steady state was studied in 16 healthy volunteers (C112). The darunavir/ritonavir combination was 800 mg/100 mg administered once daily for 22 days. Rilpivirine was given as 150 mg/day for 11 days either alone or in combination with the other two antiretrovirals. The mean C_{max} and AUC_{24h} of rilpivirine were increased 1.79 and 2.30 fold, respectively, when coadministered with a darunavir/ritonavir combination compared to administration alone (Table 9). The mean C_{min} was increased 2.78 fold. There was no relevant change in the median t_{max} of rilpivirine. Rilpivirine did not affect the mean exposure (AUC_{24h}) to darunavir or ritonavir (AUC_{24h}).

Table 9: PK Parameters for rilpivirine (TMC278) with and without coadministration of darunavir (TMC114)/ritonavir (Study C112).

Pharmacokinetics of TMC278 (mean \pm SD, t_{max} : median [range])	TMC278 alone (reference)	TMC278 + TMC114/riv (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 \pm 103.7	1233 \pm 474.0
C_{24h} , ng/mL	407.3 \pm 109.3	1190 \pm 528.2
C_{min} , ng/mL	359.9 \pm 91.55	1013 \pm 407.9
C_{max} , ng/mL	991.3 \pm 208.4	1860 \pm 673.0
AUC_{24h} , ng h/mL	12740 \pm 2008	30630 \pm 11230
$C_{12h,ss}$, ng/mL	530.9 \pm 83.68	1276 \pm 468.0
FL, %	121.9 \pm 47.89	68.26 \pm 23.38

The effect of multiple antiretroviral treatments on the single dose PK of rilpivirine was studied in 15 HIV-1 infected male subjects (C101). Rilpivirine was administered as a 50 mg dose using a 25 mg/mL oral solution. The subjects were taking at least two nucleoside/tide reverse transcriptase inhibitors N(t)RTIs in addition to either efavirenz or nevirapine. The mean C_{max} , AUC_{last} , and AUC_{∞} of rilpivirine were lower in the efavirenz group compared to the nevirapine group (Table 10). The median t_{max} was the same in both groups, but the mean $t_{1/2}$ was shorter in the efavirenz group. Mean PK parameters for

rilpivirine in the nevirapine group were comparable to PK parameters when administered alone in healthy subjects (studies CDE101 and CDE103). Compared to PK parameters for rilpivirine in healthy subjects, C_{max} was decreased by 29%, AUC_{last} by 67%, AUC_{∞} by 71%, and $t_{1/2}$ by 51% in the efavirenz group.

Table 10: PK parameters of rilpivirine (R278474) with concomitant multiple antiviral therapies (Study C101).

Pharmacokinetics of R278474 (mean \pm SD, t_{max} : median [range])	R278474 and Efavirenz (n=7)	R278474 and Nevirapine (n=8)
t_{max} , h	4.0 (4.0 - 4.0)	4.0 (4.0 - 8.0)
C_{max} , ng/mL	176 \pm 36.5	222 \pm 40.9
AUC_{last} , ng·h/mL	2179 \pm 734	6402 \pm 1343
AUC_{∞} , ng·h/mL	2246 \pm 765	7144 \pm 1696
$t_{1/2term}$, h	19.4 \pm 8.23	40.1 \pm 15.9
Pharmacokinetics of NNRTI (mean \pm SD)	Efavirenz (n=7)	Nevirapine (n=8)
n	2	8
C_{0h} , ng/mL	1003	4531 \pm 1023
n	5	-
C_{12h} , ng/mL	3466 \pm 2148	-

Administration with Other Agents

An open label crossover study was conducted in 16 healthy subjects to examine the effect of rifampin on rilpivirine PK at steady state of both drugs (C108). Subjects received either 150 mg/day rilpivirine alone for 7 days (Treatment A), 600 mg/day rifampin alone for 7 days (Treatment B), or a combination of rilpivirine and rifampin for 7 days (Treatment C). The mean C_{max} and AUC_{24h} of rilpivirine were decreased by 69% and 80%, respectively, when co-administered with rifampin. At steady state mean C_{0h} and C_{min} of rilpivirine were decreased by 90% and 89%, respectively (Table 11). There was no effect of rilpivirine on the PK of rifampin or its metabolite 25-desacetyl-rifampin.

Table 11: PK parameters for rilpivirine (TMC278) with and without coadministration of rifampin (Study C108).

Pharmacokinetics of TMC278 (mean \pm SD, t_{max} : median [range])	Treatment C TMC278 + rifampin	Treatment A TMC278
Day 7	n=16	n=15
t_{max} (h)	4.0 [1.0-6.0]	4.0 [3.0-6.0]
C_{0h} (ng/mL)	56.7 \pm 21.7	544.7 \pm 207.6
C_{min} (ng/mL)	53.0 \pm 17.4	478.4 \pm 161.4
C_{max} (ng/mL)	356 \pm 96	1123 \pm 261
AUC_{24h} (ng·h/mL)	3218 \pm 865	16051 \pm 4764
Fluctuation index (%)	225.9 \pm 46.8	100.2 \pm 25.7

A similar open label crossover study was conducted in 18 healthy subjects to examine the effect of rifabutin on rilpivirine PK at steady state of both drugs (C125). Subjects received either 150 mg/day rilpivirine alone for 11 days (Treatment A), 300 mg/day rifabutin alone for 11 days (Treatment B), or a combination of rilpivirine and rifabutin for 11 days (Treatment C). The mean C_{max} and AUC_{24h} of rilpivirine were decreased by 35% and 46%, respectively, when co-administered with rifabutin. At steady state mean C_{0h} and C_{min} of rilpivirine were decreased by 47% and 49%, respectively (Table 12). There was no effect of rilpivirine on the PK of rifabutin and its metabolite 25-O-desacetyl-rifabutin.

Table 12: PK Parameters for rilpivirine (TMC278) with and without rifabutin (Study C125).

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

An open label crossover study was conducted in 16 healthy subjects to examine the effect of ketoconazole on rilpivirine PK at steady state of both drugs (C127). Subjects received either 150 mg/day rilpivirine alone for 11 days, 400 mg/day ketoconazole for 22 days with rilpivirine added on Days 11-22. The mean C_{max} and AUC_{24h} of rilpivirine were increased by 1.3 and 1.49 fold, respectively, when co-administered with ketoconazole. At steady state mean C_{0h} and C_{min} of rilpivirine were increased by 1.8 and 1.76 fold, respectively (Table 13). There was no effect of rilpivirine on the PK of ketoconazole.

Table 13: PK parameters for rilpivirine (TMC 278) with and without ketoconazole (Study C127).

Pharmacokinetics of TMC278 (mean \pm SD, t_{max} : median [range])	Treatment A, Day 11: TMC278 alone	Treatment B, Day 22: Ketoconazole + TMC278
n	15	14
t_{max} , h	5.0 (3.0 - 12.0)	7.0 (3.0 - 12.0)
C_{0h} , ng/mL	462.2 \pm 142.8	843.7 \pm 304.2
C_{min} , ng/mL	378.5 \pm 115.1	674.1 \pm 255.9
C_{max} , ng/mL	1015 \pm 215.8	1385 \pm 523.8
AUC _{24h} , ng.h/mL	14960 \pm 3248	23590 \pm 8779
$C_{ss, av}$, ng/mL	623.3 \pm 135.3	983.1 \pm 365.8
FI, %	103.9 \pm 24.94	71.64 \pm 17.15

The PK drug interaction between steady state rilpivirine and a single dose of sildenafil was evaluated in 16 healthy subjects as a two way crossover study (C123). Subjects received either 50 mg of sildenafil on Day 1 followed by rilpivirine 75 mg/day for 12 days with a repeat single dose of sildenafil on Day 12. The mean C_{0h} , C_{min} , C_{max} , t_{max} and AUC_{24h} of rilpivirine were comparable when taken alone or with sildenafil (Table 14). There was no effect of rilpivirine on the single dose PK of sildenafil or *N*-desmethyl sildenafil.

Table 14: PK Parameters for sildenafil with and without coadministration of rilpivirine (TMC278) (Study C123).

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_{min} , ng/mL	143.8 ± 43.91	131.5 ± 41.08
AUC_{last} , ng.h/mL	560.6 ± 208.4	530.9 ± 159.6
AUC_{inf} , ng.h/mL	572.4 ± 212.7	553.4 ± 160.6
λ_z , 1/h	0.2087 ± 0.1067	0.2015 ± 0.06758
$t_{1/2elim}$, h	3.813 ± 1.163	3.770 ± 1.109

^a n=15 for AUC_{inf} , λ_z , and $t_{1/2elim}$

An open label crossover study was conducted in 16 healthy subjects to examine the potential PK interaction between rilpivirine and atorvastatin at steady state of both drugs (C116). Subjects received 40 mg/day atorvastatin for 4 days and after a 14 day washout commenced rilpivirine 150 mg/day for 15 days with atorvastatin 40 mg/day added from day 12-15. The mean C_{0h} , C_{min} and AUC_{24h} of rilpivirine were comparable in the presence and absence of atorvastatin. The mean C_{max} was decreased by ~9% (Table 15). The mean C_{max} and C_{min} values of atorvastatin were increased 1.35 fold and decreased by 15%, respectively, during coadministration with rilpivirine. The mean AUC_{24h} of the inactive metabolite atorvastatin lactone was decreased by 18% while the AUC_{24h} of the total HMG-CoA reductase activity (calculated as the sum of atorvastatin and the active metabolites 2-hydroxy- and 4-hydroxy-atorvastatin) was increased 1.21 fold when coadministered with rilpivirine, as compared to atorvastatin alone. The changes in total HMG-CoA reductase activity during coadministration of atorvastatin and rilpivirine were not considered to be clinically relevant. The 1.34 fold increase in the ratio of 2-hydroxy-atorvastatin to atorvastatin during coadministration with rilpivirine may be explained by a modest induction of the CYP3A4 mediated metabolism of atorvastatin.

Table 15: PK parameters for rilpivirine (TMC278) with and without coadministration of atorvastatin (Study C116).

Pharmacokinetics of TMC278 (mean ± SD, t_{max} : median [range])	TMC278 Alone (Reference)	TMC278 + Atorvastatin (Test)
n	16	16
C_{0h} , ng/mL	451.8 ± 173.4	429.8 ± 163.7
C_{min} , ng/mL	382.4 ± 141.5	345.9 ± 126.3
C_{max} , ng/mL	886.5 ± 255.3	843.7 ± 302.7
t_{max} , h	4.0 [2.0 - 5.0]	5.0 [2.0 - 24.0]
AUC_{24h} , ng.h/mL	14130 ± 4202	13110 ± 4908
$C_{ss, av}$, ng/mL	588.8 ± 175.1	546.3 ± 204.5
FI, %	88.12 ± 26.23	90.75 ± 22.54

Two studies were conducted to examine the effect of rilpivirine on the PK of the constituents of the oral contraceptive pill in healthy women who were willing to continue or initiate treatment with an oral contraceptive, specifically 35 µg ethinylestradiol and 1 mg norethindrone (the components of Ortho-Novum® 1/35). Subjects received treatment for two cycles separated by 7 days without OC treatment. In the first cycle the women received the contraceptive alone for 21 days, and in the second cycle received rilpivirine for the final 7 days of the cycle. The dose of rilpivirine differed between studies: 25 mg/day

in Study C136 and 150 mg/day in Study C120. The PK parameters of ethinylestradiol were not affected by co-administration with rilpivirine. The mean exposure (AUC_{24h}) to norethindrone was decreased by 41% when coadministered with rilpivirine at a dose of 150 mg/day while C_{max} of ethinylestradiol was increased 17% with 25 mg/day rilpivirine. There were no marked effects of coadministration on Luteinizing hormone, follicle stimulating hormone, and progesterone levels.

The PK interaction between rilpivirine and methadone at steady state was investigated in 13 HIV-negative subjects on stable methadone maintenance therapy (C121). Subjects received individualised methadone maintenance therapy throughout the trial. For 11 days they also received 25 mg/day rilpivirine. PK parameters for rilpivirine were comparable to historical controls after administration of rilpivirine alone. The mean PK parameters of R(-) methadone were lower when methadone was co-administered with rilpivirine (Table 16). Mean C_{min} , C_{max} , and AUC_{24h} of R(-) methadone were decreased by 22%, 14%, and 16%, respectively. The mean AUC_{24h} ratio of S(+) methadone and R(-) methadone was comparable between both treatments. There was no change in the median t_{max} of R(-) methadone. The mean pharmacokinetic parameters of S(+) methadone were lower when methadone was co-administered with rilpivirine (Table 15). Mean C_{min} , C_{max} , and AUC_{24h} of R(-) methadone were decreased by 21%, 13%, and 16%, respectively. There was no change in the median t_{max} of S(+) methadone. Co-administration of rilpivirine and methadone did not have a clinically relevant effect on withdrawal symptoms.

Table 16: PK parameters for R- and S-methadone in the presence of rilpivirine (Study 121).

<i>PK Parameters</i>	<i>R-methadone</i>		<i>S-methadone</i>	
	<i>Day -1</i>	<i>Day 11</i>	<i>Day -1</i>	<i>Day 11</i>
C_{0h} , ng/mL	216.3 ± 101.9	177.3 ± 83.15	200.4 ± 99.49	157.5 ± 84.86
C_{min} , ng/mL	195.9 ± 86.66	159.4 ± 81.25	179.9 ± 90.59	146.1 ± 85.02
C_{max} , ng/mL	315.8 ± 122.8	279.3 ± 109.2	358.1 ± 145.2	316.1 ± 123.2
t_{max} , h	2.5 (1.5 - 4.0)	2.5 (1.15 - 6.0)	2.5 (1.5 - 4.0)	2.5 (1.2 - 6.0)
AUC_{24h} , ng.h/mL	5578 ± 2343	4811 ± 2106	5610 ± 2515	4815 ± 2275
$C_{ss,av}$, ng/mL	232.4 ± 97.61	200.5 ± 87.74	233.7 ± 104.8	200.7 ± 94.77

An open label crossover study was conducted in 16 healthy subjects to examine the effect of omeprazole on rilpivirine PK at steady state of both drugs (C114). Subjects received either 150 mg/day rilpivirine alone for 11 days, 20 mg/day omeprazole for 22 days with rilpivirine added on days 12-22. The mean PK parameters for rilpivirine were decreased when administered with single or repeated doses of omeprazole (Table 17). The decreases were larger for single doses than for multiple doses for C_{max} (58% versus 40%) and AUC_{24h} (56% versus 40%). The median t_{max} of rilpivirine was later when a single dose of rilpivirine was coadministered with omeprazole. There was no change in the median t_{max} of rilpivirine when multiple doses were coadministered with omeprazole. A single dose of 150 mg rilpivirine did not have a relevant influence on the AUC_{24h} of omeprazole or its metabolites 5-hydroxy-omeprazole and omeprazole sulfone. Multiple doses of rilpivirine decreased the AUC_{24h} of omeprazole and omeprazole sulfone by 14% and 24%, respectively, suggesting a modest induction of CYP2C19-mediated metabolism.

Table 17: PK Parameters for rilpivirine (TMC278) with and without coadministration of omeprazole (Study 114).

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

The PK drug interaction between steady state rilpivirine and a single dose of paracetamol was studied in 16 healthy subjects as a two way crossover study (C109). Subjects received 500 mg of paracetamol on Day 1 followed by rilpivirine 75 mg/day for 11 days with a repeat single dose of paracetamol on Day 11. The mean C_{0h} , C_{min} , C_{max} , t_{max} and AUC_{24h} of rilpivirine were comparable when taken alone or with paracetamol (Table 18). There was no effect of rilpivirine on the single dose PK of paracetamol or paracetamol glucuronide and paracetamol sulphate.

Table 18: PK parameters for rilpivirine (TMC278) with and without coadministration of paracetamol (Study C109).

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

An open label trial investigated the PK interaction between rilpivirine and chlorzoxazone (C139). Subjects received a single dose of 500 mg chlorzoxazone on Days 1, 4, and 15, and rilpivirine 150 mg/day on Days 4 to 15. The mean exposure (AUC_{24h}) to rilpivirine was increased 1.25 fold after a single dose of chlorzoxazone (Table 19). The mean exposures to chlorzoxazone and its metabolite 6-hydroxychlorzoxazone were unaffected by a single dose or multiple doses of rilpivirine, as was the ratio of 6-hydroxy-chlorzoxazone to chlorzoxazone AUC_{last} values. These data indicate that rilpivirine does not inhibit or induce CYP2E1 activity *in vivo*.

Table 19: PK parameters for rilpivirine (TMC 278) with and without chlorzoxazone (Study C139).

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

A randomised, crossover trial investigated the PK interaction between single doses of rilpivirine and famotidine (C140). The relationship between intragastric pH and the PK of rilpivirine was assessed. The study consisted of 24 healthy subjects treated in of 4 sessions separated by a washout period of 14 days. Subjects received a 150 mg single dose of rilpivirine taken alone or with 12 h after, 2 h after, or 4 h before a 40 mg single dose of famotidine. When rilpivirine was administered 2 h after famotidine, the mean C_{max} , AUC_{last} , and AUC_{∞} were decreased by 85%, 77%, and 76%, respectively, compared to administration of rilpivirine alone (Table 20). When administered 4 h before famotidine the mean C_{max} , AUC_{last} , and AUC_{∞} were increased 1.21, 1.12 and 1.13 fold, respectively, compared to administration alone. There was no relevant change in the median t_{max} of rilpivirine. When rilpivirine was administered 12 h after famotidine, the mean AUC_{last} and AUC_{∞} were slightly decreased (by 9%), and there was no change in the mean C_{max} compared to administration alone. There was no change in the median t_{max} of rilpivirine. The results of this study demonstrate that the absorption of rilpivirine is pH-dependent.

Table 20: PK parameters for rilpivirine (TMC 278) with and without famotidine (Study C140).

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.

The results suggest that there should be an appropriate gap between intake of rilpivirine and famotidine (and probably other H2 antagonists) (for example, famotidine 4 h after rilpivirine or rilpivirine 12 h after famotidine). Such a regimen should prevent reduced absorption of rilpivirine due to effects on intragastric pH and so allow combined use of the two agents. There was minimal effect of rilpivirine on famotidine PK.

Evaluator's overall comments on PK drug interactions

A comprehensive assessment of the potential for other liver enzyme inducers and inhibitors to alter the PK of rilpivirine has been performed. The in vitro studies showed rilpivirine to be a moderate inducer as well as an inhibitor of CYP3A enzymes. Further, it was shown that rilpivirine is also a moderate inducer and potent inhibitor of CYP2C19 and an inhibitor of

CYP2E1, CYP2C8 and CYP2C9. Because of these effects on liver enzymes, rilpivirine has the potential to alter the PK of other co-administered agents. Most of the clinical drug-drug interaction trials were performed with a dose of 150 mg/day, which was the highest dose studied in the Phase IIb dose-finding trial (C204), to assess the maximal effect of rilpivirine on other drugs. With a dose of 25 mg/day (the recommended clinical dose), any observed effect on the PK of other drugs would either be similar or, more likely, lower than that observed with 150 mg/day due to lower exposure to rilpivirine. Given the dependence of rilpivirine's metabolism on CYP3A enzymes, it is not surprising that in vivo the PK of the drug is altered by inducers and inhibitors. Thus the inducers rifampin and rifabutin markedly reduced systemic exposure to rilpivirine while inhibitors ketoconazole and ritonavir boosted protease inhibitors increased exposure.

There was no clinically relevant interaction between rilpivirine and either tenofovir or didanosine other agents commonly used in the treatment of HIV. Consistent with effects on CYP3A4, the combination treatments lopinavir/ritonavir and darunavir/ritonavir increased exposure to rilpivirine. If administered in combination with these medications, the dose of rilpivirine may require adjustment. In HIV-1 infected subjects, the exposure to rilpivirine was decreased when coadministered with efavirenz and at least two N(t)RTIs. Co-administration of rilpivirine with nevirapine and at least two N(t)RTIs did not affect the systemic exposure to rilpivirine.

Rilpivirine showed evidence for modest induction of CYP3A enzymes, for example in the study with atorvastatin, but there was no effect on omeprazole PK. In contrast to the in vitro data, the in vivo studies showed modest evidence for induction of CYP2C19 (omeprazole), equivocal results for CYP2E1 (chlorzoxazone), and no effect on CYP2C9 and CYP3A4 (ethinylestradiol). Effects on the PK of norethindrone (CYP3A4) were apparent only at the higher dose (150 mg/day). It would seem the rilpivirine has a relatively low potential for PK drug-drug interactions when administered at the recommended doses. On the other hand the risk of interactions is increased when higher doses of the drug are used.

Exposure relevant for safety evaluation

A statistically significant and positive relationship was seen between rilpivirine plasma concentration and change from baseline in QT_{cf} (C131), which was gender dependent (plasma concentration-gender interaction was statistically significant, $p < 0.001$): the estimated slope of that relationship was 0.0122 and 0.0183 for males and females respectively, meaning that for every 100 ng/mL increase in exposure, the change in QT_{cf} versus baseline increases on average by 1.2 ms for males and 1.8 ms for females. Higher plasma concentrations lead to a larger difference between gender for the change in QT_{cf}. Predictions based on this PK/PD relationship for mean C_{max} concentrations of rilpivirine 75 mg/day and 300 mg/day and anticipated average C_{max} for rilpivirine 25 mg/day are presented in Table 21.

Table 21: Model based predictions (LSMeans + 90% CI) for change from baseline in QT_{cf} (Day 11) at various plasma concentrations of rilpivirine (TMC 278), overall and by gender (Study C131).

Mean C _{max}	Overall		Female (mean baseline QT _{cf} =409 ms)		Male (mean baseline QT _{cf} =398 ms)	
	LSMean	90%CI	LSMean	90%CI	LSMean	90%CI
75 mg q.d.: 636 ng/mL ^a	7.42	[3.47, 11.4]	10.4	[5.01, 15.8]	6.16	[0.36, 12.0]
300 mg q.d.: 1665 ng/mL ^a	23.1	[19.1, 27.2]	29.3	[23.8, 34.7]	18.7	[12.8, 24.7]
25 mg q.d.: 220 ng/mL ^b	1.06	[-2.89, 5.01]	2.77	[-2.62, 8.17]	1.08	[-4.72, 6.88]

a, from this study; b, anticipated value based on data from TMC278-C103 in healthy volunteers and PK substudy of TMC278-C204 in HIV-infected subjects

The relationship between rilpivirine plasma concentrations and effect on the QT_{cf} interval was confirmed in an independent study (C151). A positive correlation (slope = 0.038, $p < 0.001$) was found between plasma rilpivirine and QT_{cf} change, meaning that for every 100 ng/mL increase in rilpivirine concentration there was an increased change in QT_{cf} of 3.8 ms on average. The relationship, however, was not significant when placebo data with corresponding zero concentration were included (slope = 0.007, $p = 0.39$). The results should be interpreted with caution, given the small number of subjects, the data suggest that there is a gender-specific relationship between change in QT_{cf} and rilpivirine plasma concentrations, with higher plasma concentrations leading to a larger difference between females and males.

In a study using the recommended dose of rilpivirine (25 mg/day) (C152), no linear relationship between rilpivirine plasma concentration and change in QT_{cf} interval from baseline was observed. In order to further characterise the plasma concentration response relationship of rilpivirine on the QT/QT_c interval, data obtained in an earlier trial (rilpivirine 75 mg/day and 300 mg/day doses from C131) were included in the analysis. This resulted in a positive relationship between rilpivirine plasma concentration and change in QT_{cf} interval from baseline, suggesting a rilpivirine concentration effect relationship for change in QT_c.

Evaluator's overall conclusions on PK

Rilpivirine is orally bioavailable with maximum plasma concentrations achieved about 4 h after the dose. Absorption rate is not influenced by the dose. In healthy subjects, systemic exposure after tablet formulations increases dose proportionally across a dose range of 25 to 150 mg/day. In HIV-1 infected subjects, a less than dose-proportional increase was observed. Under fasting conditions exposure is ~40% lower than fed conditions. It is recommended that the drug be given with a meal to ensure optimal absorption and exposure. The inter-individual variability of PK parameters is generally low or moderate, and independent of the dose administered. The mean terminal elimination half life is approximately 45 to 50 h. On average the drug is highly protein bound (~99.7%), mainly to albumin. Rilpivirine is predominantly excreted in faeces (85.1%). There is negligible renal excretion. The exposure to rilpivirine was generally lower in HIV-1 infected subjects than in healthy subjects. There is no clinically relevant effect of intrinsic factors (age, gender, race, body weight, estimated glomerular filtration rate [eGFR], and hepatitis B and/or C co-infection status) on the PK of rilpivirine. No dose adjustment is needed in subjects with mild or moderate hepatic impairment. The effect of severe hepatic impairment on the exposure was not studied. Oral bioavailability decreases with increasing intragastric pH. Drugs that alter intragastric pH should not be co-administered with rilpivirine. If the combination of medications is clinically indicated then alternative dosing regimens should be considered, for example, administration of rilpivirine 12 h after a H2-antagonist. Cytochrome P450 (CYP) 3A enzymes have a predominant role in the metabolism of the drug. At a 25 mg/day dose, rilpivirine does not have a clinically relevant effect on the exposure to co-administered drugs. Mild induction of CYP3A and CYP2C19 is observed at higher doses but is unlikely to be of clinical importance at the recommended dose of 25 mg/day. Exposure to rilpivirine is increased by inhibition of CYP3A enzyme activity however, drug-drug interaction trials showed the effect to be relatively modest and the two can be co-administered without dose adjustments. Rilpivirine exposure is decreased by induction of CYP3A enzyme activity and CYP3A inducers should not be co-administered.

Pharmacodynamics

Introduction

The efficacy of the drug as an antiviral agent was evaluated *ex vivo* in healthy volunteer studies as well as *in vivo* in HIV-1 infected patients by assessment of viral load.

Mechanism of action

Rilpivirine is a potent NNRTI selected for its high *in vitro* potency against wild-type HIV-1 and NNRTI-resistant mutants.

Primary pharmacology

The *ex vivo* antiviral activity of rilpivirine was evaluated in three studies in healthy volunteers. An escalating single oral dose study was performed in three groups of nine subjects (six active drug and three placebo) in the dose range 12.5 to 50 mg of rilpivirine as an oral solution (CDE101). Antiviral activity was determined in an *ex vivo* validated cell culture assay. Antiviral activity of serum samples increased in a concentration dependent manner (Table 22). Antiviral activity was linearly related to dose ($r^2 = 0.687$). The maximum *ex vivo* antiviral effect occurred at 4 h post dose.

Table 22: Ex vivo antiviral activity for single doses of rilpivirine (TMC 278) (Study CDE101).

Parameters	12.5mg	25mg	50mg
T _{max} h	3.6 ± 0.9	3.3 ± 0.8	3.7 ± 0.8
E _{max} ng/ml	26.6 ± 6.0	103 ± 80.0	205 ± 43.6
AUEC _{12h} ng.h/ml	578 ± 145	1745 ± 1357	4279 ± 1225

A similar ascending dose study was conducted in four groups of nine subjects (six active drug and three placebo) in the dose range of 50 to 300 mg of rilpivirine administered as an oral solution (CDE103). The *ex vivo* antiviral activity time profiles were consistent with the concentration time profiles over the 12 h post dose period in most subjects (Table 23). The maximal *ex vivo* antiviral effect occurred at a median of 4 h post dose at all dose levels. The *ex vivo* activity showed a linear correlation with plasma concentrations of rilpivirine ($r^2 = 0.5935$). However inspection of median antiviral activity suggests that both the 50 and 100 mg/day doses had similar activity (E_{max} 249 ± 191 ng/ml versus 207 ± 110 ng/ml; that is, no doubling of effect for doubling of the dose). Similarly, the results for 200 and 300 mg/day doses was less than dose proportional (E_{max} 463 ± 121 ng/ml versus 557 ± 140 ng/ml).

Table 23: Ex vivo antiviral activity for single doses of rilpivirine (TMC 278) (Study CDE103).

Parameters	50mg	100mg	200mg	300mg
T _{max} h	5 ± 3	5 ± 1	4 ± 2	5 ± 4
E _{max} ng/ml	249 ± 191	207 ± 110	463 ± 121	557 ± 140
AUEC _{12h} ng.h/ml	1230 ± 310	1279 ± 632	3176 ± 538	3918 ± 1586

A double blind, randomised, placebo controlled in healthy subjects to investigated the *ex vivo* antiviral activity of rilpivirine (CDE102). Subjects received escalating multiple doses of 25 to 150 mg for 14 days. In each of three sequential dose groups, 6 subjects received rilpivirine at a dose of 25, 75, or 150 mg/day (as an oral solution) and 3 subjects received placebo. The maximum *ex vivo* antiviral activity occurred between a median of 4 and 6 h post dose (Table 24). The E_{max} (concentration for maximum antiviral effect) and AUEC_{24h} (area under the effect-time curve from administration to 24 h after dosing) increased by 2

to 3 fold over the 14 day dosing schedule. The *ex vivo* antiviral activity-time profiles were similar to the concentration time profiles over the dosing interval on both Day 1 and Day 14. The *ex vivo* antiviral activity was significantly correlated with plasma concentration ($r^2 = 0.799$).

Table 24: Ex vivo antiviral activity for multiple doses of rilpivirine (TMC 278) (Study CDE102).

	Day 1			Day 14		
Parameters	25mg	75mg	150mg	25mg	75mg	150mg
T_{max} h	5 (4-24)	5 (4-12)	4 (4-6)	6 (4-6)	5 (4-12)	4 (4-24)
E_{max} ng/ml	43 ± 27	186 ± 38	288 ± 166	83 ± 32	502 ± 87	549 ± 51
AUEC _T ng.h/ml	469 ± 195	2641 ± 727	3418 ± 1318	1268 ± 523	7555 ± 1188	9770 ± 3132

Although the magnitude of increase was similar to that of the C_{max} and AUC_{24h} levels in plasma, for repeated dosing over 14 days the increase in *ex vivo* antiviral activity between 75 and 150 mg/day was not dose proportional (Table 24). These results are at odds with data from the *in vivo* studies in patients with HIV infection, which tend to show no increase in antiviral activity for doses greater than 25 mg/day. The differences may reflect either: the small sample size in the *ex vivo* studies versus the larger sample sizes in the proof of principle trials; the use of healthy volunteers versus HIV infected individuals; or the difference between activity *in vivo* versus activity assessed *ex vivo*. It is unlikely to reflect PK differences as exposure in patients is generally lower than healthy subjects for the same dose so it might be expected that antiviral activity is lower in patients.

The *in vivo* antiviral activity of rilpivirine was evaluated in the Phase IIa proof of principle trials C201 and C202 and the efficacy in the Phase IIb dose finding trial C204. In trial C201, rilpivirine was administered to treatment naïve, HIV-1 infected subjects at doses of 25 to 150 mg/day for 7 days as a monotherapy, a decrease in log₁₀ viral load from baseline was seen for all dose groups throughout the treatment period. There was no clear difference in change of viral load between the dose groups. The decrease from baseline in plasma log₁₀ viral load on Day 8 was statistically significant in all 4 dose groups but not in the placebo group. In trial C202, rilpivirine was administered to treatment experienced, HIV-1 infected subjects at doses of 25 to 150 mg/day for 7 days as a monotherapy. Significant antiviral activity of rilpivirine was observed in all treatment groups. There was no statistically significant difference between the three dose levels. In trial C204, rilpivirine was administered to treatment naïve, HIV-1 infected subjects at doses of 25 to 150 mg/day. The proportion of subjects with confirmed and sustained virologic response (that is, viral load < 50 HIV-1 RNA copies/mL, time to loss of virologic response (TLOVR)) after 48 weeks were 80%, 80%, and 77% in the 25 mg/day, 75 mg/day and 150 mg/day groups, respectively, and 81% in the control group (efavirenz). The efficacy of the different rilpivirine doses was maintained over time: the proportion of subjects with confirmed and sustained virologic response after 96 weeks was 76%, 72%, and 71% in the 25, 75, and 150 mg/day groups, respectively, and 71% in the control group. There was no clear dose response for the different doses nor were there differences in response between the rilpivirine and control groups.

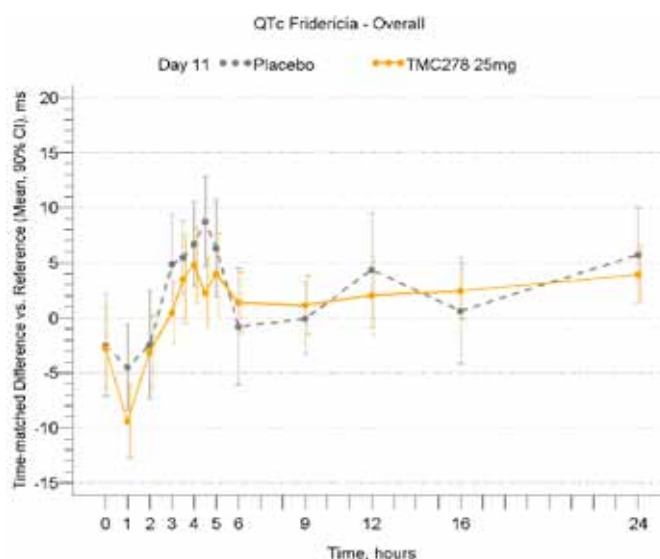
In each of these trials the antiviral response did not appear to be different across the dose range evaluated, that is, from 25 mg to 150 mg/day. The issue of whether a lower dose of rilpivirine might have been as effective remains unanswered. Indeed the minimum effective dose of rilpivirine was not established in these trials.

Secondary pharmacology

The effect of rilpivirine on the QT_{cf} interval was initially evaluated in a QT/QT_c trial (C131) in healthy subjects, with rilpivirine at doses of 75 mg and 300 mg/day. At these doses rilpivirine caused prolongations in QT_{cf} interval. After a single dose (Day 1), the upper limit of the 90% CIs of the difference versus placebo in QT_{cf} interval was below 10 ms at all time points. However, at steady state (Day 11), nearly all 90% CIs for 75 mg crossed the 10 ms threshold value of regulatory concern, with a peak at 16 h (+10.7 ms; 90% CI [6.1, 15.3]). For 300 mg, differences from placebo were larger, with a peak at 4.5 h (+23.3 ms; 90% CI [18.1, 28.4]). At this time, the differences versus placebo in QT_{cf} interval for females were higher than for males, and the difference between genders was dependent on the dose, suggesting a dose gender interaction effect. Similar trends were observed for the differences in QT_{cf} interval versus baseline. With moxifloxacin, the lower limit of the 97.5% CI of the differences versus placebo in QT_{cf} interval exceeded 5 ms at the majority of time points, confirming the trial sensitivity.

The effect on the QT_{cf} interval at the recommended dose of 25 mg/day was first assessed in a pilot trial (C151) in healthy subjects. The largest increase from baseline in mean time matched QT_{cf} interval for rilpivirine was +4.8 ms (90% CI: [1.4, 8.2]) at 4 h post dose on Day 11. The largest increase from baseline in mean QT_{cf} interval seen during placebo administration was +8.7 ms (90% CI: [4.6, 12.9]) on Day 11 at 4.5 h post dose (Figure 3). The maximum mean difference in QT_{cf} interval between rilpivirine and placebo was 2.2 ms (90% CI: [-3.0, 7.4]) at 6 h post dose, suggesting that there is no clinically relevant effect of rilpivirine on QT_{cf} interval. For moxifloxacin, the largest increase from reference in mean time matched QT_{cf} interval was +7.4 ms (90% CI: [4.2, 10.6]) at 3 h post dose, which is an expected outcome after a single dose of moxifloxacin. Trial sensitivity was not established according to the requirements of ICH E14 not only due to the small sample size, but since the comparison with placebo was not appropriate (that is, single dose of active moxifloxacin on Day 12 following placebo treatment).

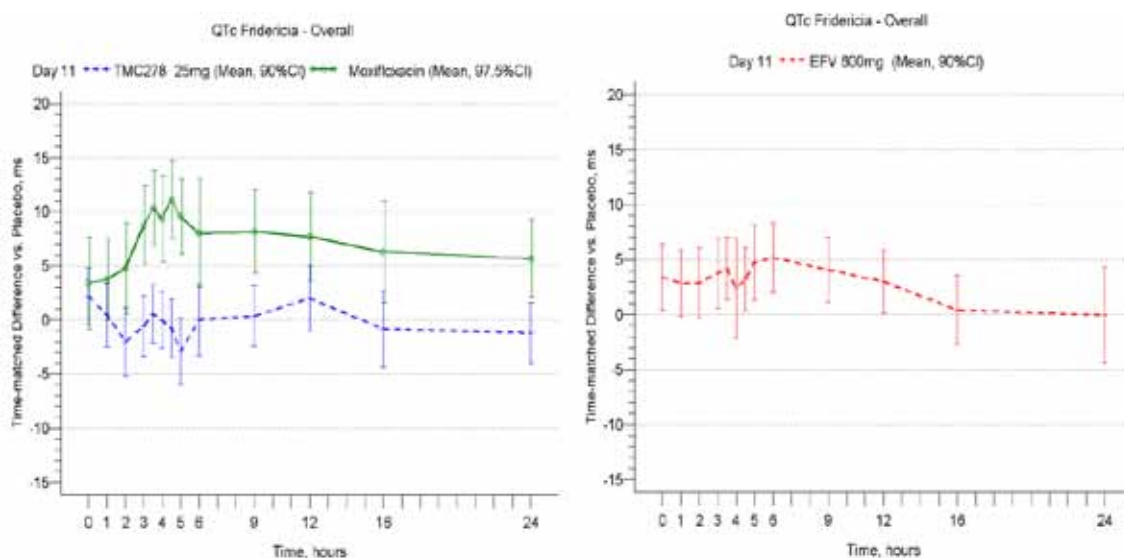
Figure 3: Time matched change from placebo (Mean, 90% CI) in QT_{cf} for rilpivirine 25 mg/d (Study C151).



In a later QT/QT_c trial, that also evaluated the effect of efavirenz 600 mg/day in the same setting, the effect of repeated doses of rilpivirine 25 mg/day was evaluated in healthy volunteers (C152). At steady state (Day 11) on rilpivirine 25 mg/day, the 90% CIs of the observed time-matched difference versus placebo in QT_{cf} interval did not cross the

10 ms threshold at any time point (Figure 4). The highest upper limit of the 90% CI was observed at 12 h post dose (90% CI [-1.0, 5.0]). For efavirenz, none of the 90% CIs of the observed time matched difference versus placebo in QT_{cF} interval exceeded 10 ms. The highest upper limit of the 90% CI was observed at 6 h post dose (90% CI [2.0, 8.4]). The trial sensitivity was proven by showing that the positive control (moxifloxacin) had a statistically significant mean effect on QT_{cF} interval exceeding 5 ms for at least one time point.

Figure 4: Time matched change from placebo (Mean, 90% CI) in QT_{cF} for rilpivirine 25 mg/d (Study C152).



Study population exposure response analysis

In an analysis using Generalised Additive Models (GAM) to evaluate the impact of possible predictive factors of virologic response as observed in the pooled Phase III trials, treatment adherence was found to be the most important predictor of response (< 50 HIV-1 RNA copies/mL and < 400 HIV-1 RNA copies/mL, TLOVR non virologic failure (VF) censored), followed by exposure to rilpivirine and baseline viral load (the latter mostly for < 50 HIV-1 RNA copies/mL and to a lesser extent for < 400 HIV-1 RNA copies/mL, TLOVR non VF censored). Also, the probability of virologic response increased with a decreasing baseline phenotypic fold change in EC_{50} for rilpivirine and an increasing CD4+ cell count at baseline. Even though pharmacokinetic exposure to rilpivirine in the presence of two N(t)RTIs was found to be predictive, the likelihood of virologic response as a function of C_{0h} and AUC_{24h} showed a high likelihood of response (median of 76.4% and 76.6%, respectively) at the lowest simulated values of 25 ng/mL for C_{0h} and 800 ng.h/mL for AUC_{24h} , respectively. These values are comparable to the observed response rate (78.3%) in the lowest quartile of exposure (AUC_{24h} < 1633 ng.h/mL). Data on the efficacy of a treatment regimen with two N(t)RTIs alone, looking at similar virologic endpoints, are relatively scarce. A series of historical clinical trials in treatment naïve HIV-1 infected subjects evaluated the efficacy and safety of different triple combination treatment regimens as compared to treatment with two NRTIs (AZT plus 3TC). In these trials, the proportions of subjects treated with AZT and 3TC alone reaching plasma HIV-1 RNA levels below a certain cut off at Week 52 was 8% (< 500 HIV-1 RNA copies/mL) 18% (< 500 HIV-1 RNA copies/mL) and 17% (< 400 HIV-1 RNA copies/mL). The efficacy of this regimen and likely other N(t)RTI regimens is thus likely significantly lower compared to what has been observed in combination with rilpivirine, including the observed response rate in the

low exposure range. This indicates that rilpivirine is already effective at the low end of the plasma concentrations that are achieved with 25 mg/day in this population.

Pharmacodynamic interactions with other medicinal products or substances

No PD interaction effects such as *in vivo* or *ex vivo* antiviral effects were assessed. With respect to the two interaction studies with oral contraceptives (C136, C120), the effect on Luteinizing hormone (LH), follicle stimulating hormone (FSH) and serum progesterone were examined. There were no significant effects on any of these hormones suggesting that rilpivirine may not comprise the efficacy of the contraceptive pill. The results of these studies cannot discount that the efficacy of OCs may be compromised when combined with rilpivirine at a high doses as exposure to norethindrone is reduced.

Genetic differences in pharmacodynamic response

No studies were presented.

Evaluator's overall conclusions on pharmacodynamics

Rilpivirine is a NNRTI with apparent effects against the HIV-1 virus. After single doses of rilpivirine administered in healthy volunteers, the ex vivo activity showed a linear correlation with plasma concentrations of the drug. Similarly after repeated doses in healthy volunteers the ex vivo antiviral activity appeared to increase with plasma concentration. The magnitude of increase was similar to that of the C_{max} and AUC_{24h} levels in plasma. These ex vivo studies in healthy subjects stand in sharp contrast to the in vivo results obtained in patients with HIV-1 infection. Doses of 25 mg/day of rilpivirine in HIV-1 infected patients were effective in reducing viral load. Higher doses did not appear to be any more effective (based on determination of plasma viral load expressed in HIV-1 RNA copies/mL or immunologic changes determined by changes in CD4+ and CD8+ counts) than 25 mg/day. Thus the minimum effective dose of rilpivirine has not been established by these studies. The differences observed in apparent effectiveness against the virus for volunteers and patient studies may be due to intrinsic differences in testing ex vivo versus in vivo, that is, the cell culture system used for ex vivo testing may not adequately reflect the in vivo situation. Other factors such as the nature of the populations studied (patients versus controls) may also be important. Nevertheless in HIV-1 patient populations 25 mg/day has been shown to be effective in reducing viral load either alone or in concert with other antiretroviral treatments. This is despite the fact the systemic exposure in HIV-1 infected patients appears to be lower than in controls. Further data are necessary to better establish the dose response effect in the patient population and whether lower doses might not be as effective as 25 mg/day. From the data presented it would appear that increases in doses above 50 mg/day are not associated with any significant further decrease in viral load than 25 mg/day.

Efficacy

Introduction

Efficacy data for rilpivirine is based on the 48 week data in treatment naïve HIV-1 infected adult patients from the 2 Phase III trials (C209 and C215). The efficacy data was supplemented by that from a Phase IIb trial (C204), which had an initial dose finding part (Week 96 analysis). This study had an extended part with an additional analysis at Week 192 in order to assess the long term safety profile of rilpivirine.

In this evaluation report, the 2 Phase III trials (C209 and C215) will be the main studies upon which the clinical efficacy will be evaluated. The Phase IIb trial (C204) will be evaluated with regards to preliminary efficacy and dose selection for the Phase III trials.

Dose response studies and main clinical studies

Dose response study

Study C204 was a Phase IIb, randomised, partially blinded, dose finding trial of rilpivirine in 368 antiretroviral treatment naïve HIV-1 infected adult subjects. It was an international multi centre study involving centres in fourteen countries.

- Methods: The primary objective of the study was to evaluate the dose response relationship of antiviral efficacy after 48 weeks of treatment with three different doses of rilpivirine: 25 mg/day, 75 mg/day and 150 mg/day. Secondary objectives included:

- Evaluating the antiviral efficacy of the 3 rilpivirine doses over 96 weeks
- Evaluating the antiviral efficacy of rilpivirine from Week 96 onwards
- Comparing the safety and efficacy of rilpivirine with the control drug efavirenz

The main inclusion criteria were subjects with a HIV-1 viral load of > 5,000 copies/mL, who had previously received \geq 2 weeks of treatment with a N(t)RTI or Protease Inhibitor (PI), and who had no prior use of NNRTIs. The main exclusion criteria were a life expectancy of less than six months, any currently active acquired immunodeficiency syndrome (AIDS) defining illness, any use of NNRTIs, having acute hepatitis A, B, or C infection, or having documented genotypic evidence of NNRTI resistance at screening or from historical data available in the source documents.

Subjects were randomised in a 1:1:1:1 ratio to 1 of the three rilpivirine dose regimens (25 mg/day, 75 mg/day, or 150 mg/day) or to the control drug efavirenz 600 mg/day. Subjects received rilpivirine or efavirenz plus a background regimen containing two investigator selected N(t)RTIs. Randomisation was stratified by geographical region and the selected background regimen. The study was partially blinded: the three rilpivirine doses were blinded to each other while the administration of efavirenz in the control group was open label.

The primary efficacy endpoint was the proportion of subjects achieving virologic response. Virologic response was defined as a viral load of < 50 HIV-1 copies/mL, according to the Time to Loss Of Virologic Response (TLOVR) algorithm. The TLOVR algorithm defines a confirmed virologic response as two consecutive viral load values below the threshold. The Intent to Treat (ITT) population was used. Differences between treatment groups were tested for statistical significance using logistic regression model with factors of treatment, geographical region, and N(t)RTIs used, and covariate baseline viral load.

Comments:

As the study was mainly a dose finding study, the partial blinding design was appropriate. Due to this aspect of the study design, comparison of the efficacy data would be more robust between the three rilpivirine dose groups than between the rilpivirine dose groups and the control group. However, this is attenuated by the fact that the primary efficacy endpoint was an objective laboratory measure. The definition of virologic response in the primary efficacy endpoint is consistent with current HIV research guidelines and recommendations.

Results: Overall, 368 HIV-1 infected, treatment naïve subjects were randomised: 93, 95, and 91 subjects in the rilpivirine 25 mg/day, 75 mg/day, and 150 mg/day dose groups, respectively, and 89 subjects in the control (efavirenz) group. In order to collect long term safety and efficacy data for the treatments administered in the trial, an optional open label extension to the treatment period until Week 144 was provided for subjects who reached Week 96, and who, in the opinion of the investigator, would still benefit from

antiretroviral therapy. In this extension period, all subjects who were originally randomised to 1 of the 3 rilpivirine groups were treated with rilpivirine 75 mg/day plus the investigator selected N(t)RTIs background regimen. rilpivirine 75 mg/day dose was used in this extension as this was the initial selected dose for further development based on the Week 48 primary analysis. All subjects who were originally randomised to the control group continued to be treated with efavirenz plus the investigator selected N(t)RTIs in this extension period.

Later in the study, based on results obtained in a thorough QT (TQT) trial, the selected dose for further development of rilpivirine was changed to 25 mg/day (this change in selected dose will be described later in this section). The subjects were then switched to rilpivirine 25 mg/day upon approval of the amended protocol, and continued on this dose for the remainder of the trial. In order to continue to collect further long term safety and efficacy data, a second optional open label extension to the treatment period up to a total treatment duration of 240 weeks was provided for subjects who reached Week 144, and who, in the opinion of the investigator, would still benefit from antiretroviral therapy.

The overall virologic response rate of rilpivirine was similar to that of the control drug efavirenz (78.9% and 80.9%, respectively, at Week 48; and 73.1% and 70.8%, respectively, at Week 96). However, there was no dose efficacy relationship observed for rilpivirine across the dose range from 25 mg/day to 150 mg/day. The sponsor performed a logistic regression model with factors of treatment, geographical region, and N(t)RTIs used, and covariate baseline viral load. It showed that there were no statistically significant differences observed among the rilpivirine dose groups, and with the control group at either Week 48 or Week 96 (overall p-value = 0.94 and 0.81, respectively).

- Dose selection for Phase III trials: Based on the above results, and that there was no significant dose safety relationship seen over the dose range tested, the initial selection of rilpivirine dose for Phase III trials was 75 mg/day. The sponsor stated that the initial selection of rilpivirine 75 mg/day after the Week 48 analysis was due to some safety observations supporting the selection of a 75 mg/day dose instead of the higher dose of 150 mg/day (for example, AEs leading to discontinuation and rash).

Comments:

A review through these AEs showed that there was an increasing incidence of rash and AEs leading to permanent discontinuation, with increasing doses of rilpivirine. The incidence of rash was 5.4%, 9.5% and 13.2% in the rilpivirine 25 mg/day, 75 mg/day, and 150 mg/day groups, respectively. AEs led to treatment discontinuation in 8.6%, 11.6%, and 14.3% of subjects in the rilpivirine 25 mg/day, 75 mg/day, and 150 mg/day groups, respectively. Based on this, there would be inadequate justification for the selection of 75 mg/day instead of 25 mg/day at this point. However, the selected dose for use in Phase III trials was later changed to 25 mg/day due to the results of a Thorough QT study.⁷ This would be described below.

Prior to the start of the Phase III trials, a then ongoing Thorough QT trial (TQT) trial (Study C131) showed a dose and concentration dependent QT_c prolongation effect. In this study, rilpivirine was studied in healthy subjects at doses of 75 mg/day (the initially selected therapeutic dose) and 300 mg/day (a suprathreshold dose). The QT_c prolongation exceeded the ICH E14⁸ threshold of clinical concern at both doses of

⁷ See FDA Guidance for Industry. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. October 2005. URL: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129357.pdf>

⁸ Guidelines for Industry: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

rilpivirine. The sponsor applied PK/PD modeling, which predicted that rilpivirine 25 mg/day would not have an effect on the QT_c interval.

These results led to the selection of rilpivirine 25 mg/day as the final dose for further development. Prior to the start of the Phase III trials, a pilot QT trial (Study C151) was performed in healthy adult subjects to evaluate the potential effect of rilpivirine 25 mg/day dose on the QT/QT_c interval. In this pilot trial, the change in QT_{cf} with the administration of rilpivirine 25 mg/day did not exceed the threshold as defined by ICH E14. On the basis of the results of this pilot QT trial, a TQT trial (Study C152) using rilpivirine dose of 25 mg/day and the two Phase III trials evaluating rilpivirine 25 mg/day were started. The results of the TQT trial C152 later showed that the change in QT_{cf} with the administration of rilpivirine 25 mg/day did not exceed the threshold as defined by ICH E14.

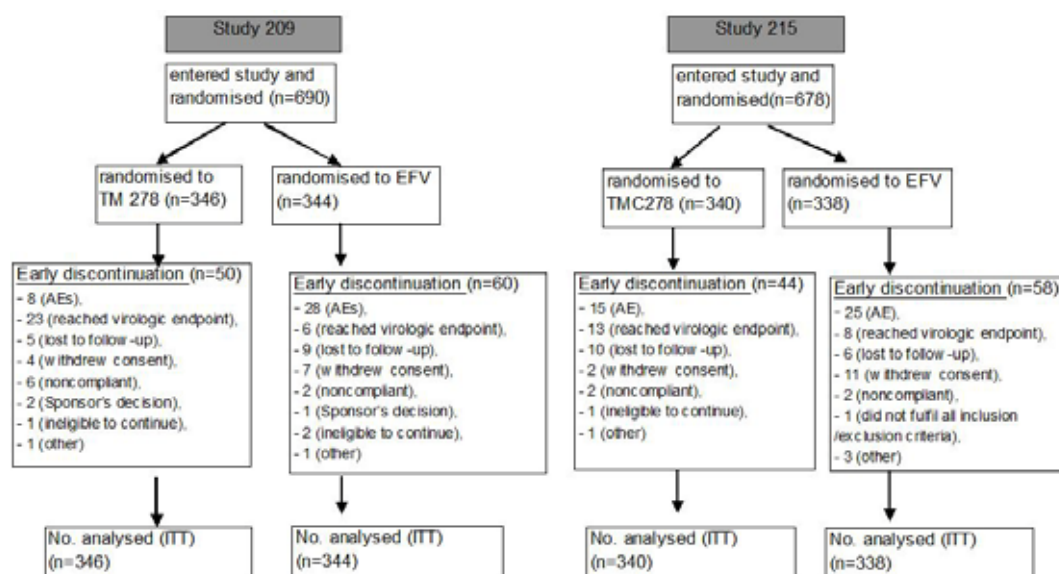
Comments:

The selection of the dose of 25 mg/day of rilpivirine for use in Phase III trials and for further development was appropriate based on the above results. However, the dose range explored in the Phase IIb trials did not show any efficacy dose relationship. There is therefore no clinical information regarding whether a lower dose of rilpivirine would have been more appropriate. The dose range explored failed to elicit the minimum clinically efficacious dose.

Main (pivotal) studies

The main studies from which the efficacy data was derived were the two Phase III studies (C209 and C215) outlined in Figure 5. The sponsor had made separate analysis of each study as well as a pooled analysis of the efficacy data of both studies. The study designs of the two studies were similar, and will be summarised together below, with the differences highlighted.

Figure 5: Participant Flow of the Intent to Treat (ITT) population.



Study Titles and Acronyms

C209: A Phase III, randomised, double blind trial of rilpivirine 25 mg/day versus efavirenz 600 mg/day in combination with a fixed background regimen consisting of tenofovir disoproxil fumarate and emtricitabine in antiretroviral naïve HIV-1 infected subjects.

Study Acronym: ECHO

C215: A Phase III, randomised, double blind trial of rilpivirine 25 mg/day versus efavirenz 600 mg/day in combination with a background regimen containing two NNRTIs in antiretroviral naïve HIV-1 infected subjects.

Study Acronym: THRIVE

Methods

Both studies C209 and C215 were randomised, controlled, and double blind studies. The control drug used in both studies was efavirenz 600 mg/day.

Objectives

The stated objectives of both aforementioned studies were the same. The primary objective was to demonstrate non inferiority of treatment with multiple doses of rilpivirine compared to the control efavirenz, with regards to the proportion of virologic responders (plasma viral load < 50 HIV-1 RNA copies/mL, according to the TLOVR algorithm) at 48 weeks, with a maximum allowable difference of 12%.

The main secondary objectives of both studies were to:

- demonstrate non inferiority of rilpivirine compared to efavirenz, with regards to the proportion of virologic responders (plasma viral load < 50 HIV-1 RNA copies/mL, according to the TLOVR algorithm) at 48 weeks, with a maximum allowable difference of 10%;
- evaluate superiority in efficacy of rilpivirine compared to efavirenz, in case non inferiority was established;
- evaluate and compare the safety and tolerability of rilpivirine when administered as 25 mg/day compared to efavirenz 600 mg/day over 48 and 96 weeks;
- evaluate and compare the antiviral activity of rilpivirine when administered as 25 mg/day versus efavirenz 600 mg/day over 48 and 96 weeks;
- evaluate and compare immunologic changes (as measured by CD4+ cell count) in the rilpivirine group versus those in the efavirenz group over 48 and 96 weeks;
- assess the evolution of the viral genotype and phenotype over 48 and 96 weeks;
- evaluate the population PK and the PK/PD relationships for efficacy and safety of rilpivirine;
- assess treatment adherence as measured by the Modified Medication Adherence Self-Report Inventory (M-MASRI).

Sites

Both studies were international, multicentre studies, each involving 21 countries.⁹ The study start dates for studies C209 and C215 were 21 April 2008 and 22 May 2008, respectively.

⁹ Study C209 was conducted in Argentina, Australia, Austria, Brazil, Canada, Denmark, France, Italy, Mexico, Portugal, Puerto Rico, Romania, Russia, South Africa, Spain, Sweden, Taiwan, Thailand, The Netherlands,

Treatments

The control drug used in both studies was efavirenz 600 mg/day. Patients were randomised in a 1:1 ratio into the study drug arm (rilpivirine 25 mg/day) or the control drug arm (efavirenz 600 mg/day). In addition to rilpivirine or efavirenz, all patients in both groups received a background regimen of two N(t)RTIs. In trial C209, the background N(t)RTIs regimen was fixed and all patients received tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) (denoted as TDF/FTC) in addition to rilpivirine or efavirenz. In trial C215, patients in both groups received abacavir (ABC) and lamivudine (3TC) (denoted as ABC/3TC), zidovudine (AZT) and lamivudine (3TC) (denoted as AZT/3TC), or TDF/FTC as background regimen, in addition to rilpivirine or efavirenz. The choice of background regimen in trial C215 was based on investigator's selection. The treatment duration in both studies was for 96 weeks for the complete trial. However, the data cut off time frame for primary analysis was at Week 48 after commencement of treatment.

Comments:

The study design that involves a positive control instead of a placebo is appropriate in HIV trials as placebo controlled trials are not considered ethical in the HIV-1 infected patient population. The use of the study drug or control with a background regimen of N(t)RTIs is appropriate as the current guideline and recommendation for initiating treatment in treatment naïve HIV-1 infected patients is the combined use of at least three antiretroviral drugs due to the high mutation rate of the HIV causing issues with resistance. The proposed indication of rilpivirine is for use in combination with other antiretroviral drugs, and hence testing it together with other antiretroviral drug combinations that are likely to be used in clinical settings is appropriate. The combinations of ABC with 3TC, AZT with 3TC, and TDF with FTC, are common N(t)RTI regimens for first line use together with other antiretroviral drugs. The choice of positive control drug efavirenz is in agreement with current treatment guidelines on the use of efavirenz and two N(t)RTIs as a first line treatment regimen for HIV-1 infected patients.¹⁰

Inclusion and exclusion criteria

In both studies the main *inclusion criteria* were male or female subjects, aged 18 years or older, with HIV-1 plasma viral load at screening of $\geq 5,000$ copies/mL, who had never been treated with a therapeutic HIV vaccine or an antiretroviral drug prior to screening, and in whom, in the judgement of the investigator, it was appropriate to initiate antiretroviral therapy based on the subject's medical condition and taking into account guidelines for the treatment of HIV-1 infection.

In addition, subjects were eligible only if there was demonstrated sensitivity to the respective background regimen of N(t)RTIs to be used. In Study C209, subjects were eligible only if there was demonstrated sensitivity to TDF and FTC based on results at screening or based on available historical data. In Study C215, subjects were eligible only if there was demonstrated sensitivity to ABC and 3TC, AZT and 3TC, and/or TDF and FTC based on results at screening or based on available historical data.

United Kingdom, and the United States of America. Study C215 was conducted in Australia, Belgium, Brazil, Canada, Chile, China, Costa Rica, France, Germany, India, Italy, Mexico, Panama, Portugal, Puerto Rico, Russia, South Africa, Spain, Thailand, United Kingdom, and the United States of America.

¹⁰ National Institutes of Health, Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, 10 January 2011. URL: http://aidsinfo.nih.gov/contentfiles/AA_Recommendations.pdf (accessed 2 April 2011).

The *exclusion criteria* in both studies were the same. The main exclusion criteria were: having documented genotypic evidence of NNRTI resistance at screening or from historical data available in the source documents, that is, having at least one of the NNRTI Resistance-Associated Mutations (RAMs) from a list of RAMs based on the list of International AIDS Society (IAS)-United States of America (USA) NNRTI RAMs¹¹; previously documented HIV-2 infection; life expectancy of less than six months; any currently active AIDS-defining illness; having one or more of the specified risk factors for QT_c prolongation¹² and renal impairment: estimated glomerular filtration rate based on creatinine (eGFR_{creat}) < 50 mL/min.

Primary endpoint

The primary endpoint was the proportion of subjects with virologic response at 48 weeks. Virologic response was defined as a viral load of < 50 HIV-1 copies/mL, according to the TLOVR algorithm. The TLOVR algorithm defines a confirmed virologic response as two consecutive viral load values below the threshold.

Secondary endpoints

The secondary efficacy endpoints assessed included the

- proportion of subjects with a viral load of < 50 and < 400 copies/mL at each time point
- proportion of subjects with a viral load of < 200 copies/mL at each time point (observed and TLOVR algorithm)
- time to first virologic response, where virologic response was defined as viral load < 50 copies/mL (TLOVR algorithm only)
- time to virologic failure for plasma viral load measurements of <50 and <400 HIV-1 copies/mL
- Change from baseline in log₁₀ plasma viral load
- Change in CD4+ cells (that is, immunologic changes)
- Genotypic and phenotypic pattern of the virus
- Pharmacokinetic, safety and tolerability evaluations
- Treatment adherence evaluation, as measured by the M-MASRI

Sample size

The sample size of both studies was determined based on the results of previous clinical trials with efavirenz, which gave an anticipated proportion of virologic responders in the

¹¹ The RAMS tested were A098G, E138A, E138G, E138K, E138Q, E138R, F227C, G190A, G190C, G190E, G190Q, G190S, G190T, K101E, K101P, K101Q, K103H, K103N, K103S, K103T, K238N, K238T, L100I, M230I, M230L, P225H, P236L, V106A, V106M, V108I, V179D, V179E, Y181C, Y181I, Y181V, Y188C, Y188H, Y188L, Y318F

¹² The risk factors specified in the exclusion criteria were a confirmed prolongation of QT/QT_c interval, pathological Q-waves (defined as Q-wave > 40 ms or depth > 0.4-0.5 mV), evidence of ventricular pre excitation, electrocardiographic evidence of complete or incomplete left bundle branch block or right bundle branch block, evidence of second or third degree heart block, intraventricular conduction delay with QRS duration > 120 ms, bradycardia as defined by sinus rate < 50 beats per minute, personal or family history of long QT syndrome, personal history of cardiac disease, symptomatic or asymptomatic arrhythmias, with the exception of sinus arrhythmia, syncopal episodes or risk factors for torsades de pointes (for example, heart failure, hypokalemia, hypomagnesemia).

efavirenz group of 70% to 80%. The sponsor assumed a response rate of 75% at 48 weeks in both treatment groups (rilpivirine and efavirenz). Based on this, it was calculated that 340 subjects were needed per treatment group to establish non inferiority of rilpivirine versus efavirenz with a maximum allowable difference of 12%, to yield 95% power.

Randomisation, Blinding

Randomisation to the treatment groups (rilpivirine or control) was stratified according to screening plasma viral load (strata were $\leq 100,000$, $> 100,000$ to $\leq 500,000$, and $> 500,000$ copies/mL) in both trials, and the selected background regimen in trial C215.

As optimal administration schedule for rilpivirine was with food, and that for efavirenz was without food, blinding in both studies was carried out by the use of a double dummy design. This means that subjects receiving active rilpivirine also took placebo efavirenz (and vice versa) in addition to their background regimen, such that all subjects have the daily dosing regimen of rilpivirine (or placebo) with food, and efavirenz (or placebo) on an empty stomach, and the background regimen.

Statistical methods

The population included in the efficacy analysis is the ITT population, that is, all randomised subjects who received at least one dose of study medication. The ITT population was the primary analysis population for the comparison between the rilpivirine and the control group. In addition an analysis based on the per protocol (PP) population was performed to supplement the results of the ITT population.

Primary efficacy endpoint analysis

The primary efficacy endpoint was the proportion of subjects with a viral load < 50 copies/mL at Week 48 according to the TLOVR algorithm. To be a virologic responder in this algorithm, 2 consecutive viral load values < 50 copies/mL were required.

Non-responders or virologic failures were defined as subjects who

- were never virologically suppressed (that is, never achieved two consecutive viral load values of < 50 copies/mL), or
- were a rebounder (that is, subject responded, then had two consecutive viral load values above the threshold value of 50 copies/mL), or
- discontinued prematurely while being a responder.

Missing viral load values were imputed according to a “time to” approach, that is, a missing response was imputed as “response = yes” when both preceding and subsequent virologic responses indicated “response = yes”; responses were imputed with “response = no” in all other cases. The primary efficacy endpoint was analysed in different ways, in accordance to the primary and secondary objectives of the studies:

- to demonstrate non inferiority of rilpivirine versus control for the primary efficacy parameter, using a maximum allowable non inferiority margin of 12% (primary objective) and 10% (secondary objective)
- primary efficacy endpoint was also analysed to try to establish superiority of rilpivirine over control

The test for non inferiority and superiority was based on response rates predicted by a logistic regression analysis on the primary efficacy parameter, adjusting for the stratification factors (that is, baseline \log_{10} viral load for both Phase III trials, and background regimen for trial C215 only). Predicted response rates and the two sided 95%

CI of the difference between the treatment groups were derived using the delta method. In addition, the 95% CI of the difference between treatments in the observed proportion of responders was reported using a normal approximation of the binomial distribution.

Additional analyses

(i) "Snapshot approach" analysis

In addition to the primary efficacy endpoint analysis (< 50 copies/mL, TLOVR), virologic response rates at Week 48 were also tabulated by treatment group according to the "snapshot approach". In this analysis, the single last available viral load value in the Week 48 time point window (Week 44 to 54) was used. This differed from the primary efficacy endpoint analysis which used the TLOVR algorithm, where two consecutive viral loads of < 50 copies/mL were needed to define virologic responders. In this snapshot approach, "missing equals failure" imputation was applied. Non-responders included virologic failures¹³: as well as "non-responders"¹⁴ with no viral load data in the Week 48 window".

(ii) Additional sensitivity analysis

Additional sensitivity analyses were performed on the primary efficacy endpoint (< 50 copies/mL TLOVR) to test the robustness of the primary analysis result. This includes a non VF censored analysis of the primary efficacy endpoint, as well as analyses of the primary efficacy endpoint using different imputations for missing data.

A non VF censored analysis was performed on the primary efficacy parameter (< 50 copies/mL TLOVR), whereby all subjects who discontinued early and were not considered virologic failures were censored at the time of discontinuation (that is, excluded from the analysis). For this non ITT analysis, "virologic failures" were defined as subjects who first achieved two consecutive viral load values < 50 copies/mL, followed by two consecutive viral load values of \geq 50 copies/mL, or first achieved two consecutive viral load values < 50 copies/mL and then discontinued with a last observed viral load value on treatment of \geq 50 copies/mL, or never achieved two consecutive viral load values of < 50 copies/mL and having an increase in viral load of at least 0.5 log₁₀ above the nadir.

Analyses were also done with missing data handled using different imputations: an observed case analysis (without imputation), imputed analysis using non-completer = failure (NC = F) imputed analysis using missing = failure (M = F).

Comment:

The definition of virologic response in the primary endpoint and the use of the TLOVR algorithm are consistent with current HIV treatment and research guidelines. The choice of a non inferiority design over a superiority design as a primary objective is in line with current HIV drug development trends, where trials are designed to demonstrate that a new treatment is not worse in efficacy than the current standard antiretroviral drugs¹⁵. The benefit of the new treatment being investigated may be

¹³ Subjects who had \geq 50 copies/mL in the Week 48 window, subjects who discontinued early due to lack or loss of efficacy, subjects who discontinued for reasons other than adverse events, death or lack or loss of efficacy, and at the time of discontinuation had a viral load value of \geq 50 copies/mL (or missing), or subjects who had a switch in background regimen that was not permitted by the protocol (that is, for reasons other than tolerability).

¹⁴ Subjects with missing viral load data in the Week 48 window, subjects who discontinued due to adverse event or death, and subjects who discontinued due to other reasons than adverse event or death and with viral load < 50 copies/mL.

¹⁵ Hill A, Sabin C. Designing and interpreting HIV noninferiority trials in naïve and experienced patients. *AIDS* 2008; 22:913-921.

simplified dosing regimen or a better safety profile, rather than better efficacy than the current standard antiretroviral drugs. The use of the non inferiority margin of 12% is consistent with current ICH guidelines for HIV drug development, which suggest a margin ranging from 10% to 12%. In these two Phase III trials, the more stringent margin of 10% margin was pre defined as a secondary objective to test the robustness of the primary objective results.

Results

The 48 week data cut off date for studies C209 and C215 were 1 February 2010 and 28 January 2010, respectively.

Baseline data

Demographic characteristics were similar between the two studies, and between the two treatment groups in each study and in the pooled analysis. In the pooled analysis, the median age was 36.0 years in both the rilpivirine group and control group, with an age range of 18-78 years and 19-69 years, respectively. The proportion of female subjects was approximately 24% in each treatment group. Approximately 60% of subjects were White.

The baseline HIV disease characteristics of the trial population were similar between the two studies and between the two treatment groups. In the pooled analysis of both studies, the median baseline viral load was 90,450 copies/mL and 104,500 copies/mL in the rilpivirine and control groups, respectively, and the median baseline CD4+ cell count was 249 cells/ μ L and 260 cells/ μ L, respectively. The majority of subjects (53.6% in the rilpivirine group and 48.4% in the control group) were in the $\leq 100,000$ copies/mL baseline viral load category, followed by the $> 100,000$ to $\leq 500,000$ copies/mL category. Only about 10% of the subjects were in the highest baseline viral load category of $> 500,000$ copies/mL. The proportions of subjects per baseline viral load category were similar between the two studies and between the treatment groups. The majority of subjects (45.7% in the rilpivirine group and 45.0% in the control group) were in the ≥ 200 to < 350 cells/ μ L baseline CD4+ cell count category, followed by the ≥ 50 to < 200 cells/ μ L category. Only about 5% of the subjects were in the lowest baseline CD4+ cell count category of < 50 cells/ μ L. The proportions of subjects per baseline CD4+ cell count category were similar between the two studies and between the treatment groups. At screening, the median time since diagnosis of HIV was 1.4 years and 1.3 years in the pooled rilpivirine and control groups, respectively. Approximately 70% of subjects in both treatment groups had HIV disease CDC category A.

Treatment Duration: In the pooled analysis, the median study treatment duration was similar between the treatment groups: 55.7 weeks in the rilpivirine group and 55.6 weeks in the control group. The median treatment duration was also similar between the two studies, and between the treatment groups within each study.

Subject disposition: Overall, a similar proportion of subjects in the pooled rilpivirine and control groups had early discontinuation at the time of the Week 48 analysis (13.7% and 16.4%, respectively). In the pooled analysis, the most frequent reason for discontinuation in the rilpivirine group was subjects reaching a virologic endpoint (that is, virologic failures) (5.2% versus 2.1% in the control group), while in the control group, it was discontinuation due to an AE (7.8% versus 3.4% in the rilpivirine group).

The difference in the proportion of subjects discontinuing due to reaching a virologic endpoint between the rilpivirine group and the control group was larger in Study C209 (6.6% in rilpivirine group versus 1.7% in control group) than in Study C215 (3.8% in rilpivirine group versus 2.4% in control group). In addition, the difference in the

proportion of subjects discontinuing due to adverse events between the rilpivirine group and the control group was also larger in Study C209 (2.3% in rilpivirine group versus 8.1% in control group) than in Study C215 (4.4% in rilpivirine group versus 7.4% in control group).

Concomitant antiretroviral therapies: As defined in the protocol, in trial C209, the initial background N(t)RTIs regimen was fixed and all patients received TDF/FTC in addition to rilpivirine or efavirenz. In trial C215, patients received ABC/3TC, AZT/3TC, or TDF/FTC as initial background regimen, in addition to rilpivirine or efavirenz. The choice of background regimen in trial C215 was based on investigator's selection. The majority of subjects in the C215 trial took TDF/FTC as their initial background regimen. In the pooled analysis, the proportion of subjects taking TDF/FTC, AZT/3TC and ABC/3TC were similar between the treatment groups.

Numbers analysed: The ITT population was the primary analysis population for the comparison between the rilpivirine and the control group. In addition, an analysis based on the PP population was performed to investigate the impact of exclusion of subjects with major protocol violations. The number of subjects analysed was similar in both treatment groups for both the ITT and PP populations.

Outcomes and estimation: Efficacy comparisons and non-inferiority objectives were evaluated within each individual Phase III trial, as well as on the pooled data set. The sponsor has stated that it was not the intention of the sponsor to make a non-inferiority claim based solely on the pooled results. In view of the above, in this evaluation report, the results of each study will be presented as well as that of the pooled analysis.

Primary endpoints

The proportion of subjects with virologic response (< 50 copies/mL, TLOVR) was about 80% in the individual Phase III trials for both the rilpivirine and control groups. In the pooled analysis, the proportions of subjects with virologic response (< 50 copies/mL, TLOVR) in the rilpivirine and control groups were 84.3% and 82.3%, respectively.

Comments:

This result was consistent with that in the Phase IIb trial (described in the earlier sections of this report) where the proportion of virologic responders in the rilpivirine 25 mg/day group was 79.6%.

Primary endpoint non inferiority analyses using normal approximation of binomial distribution:

(i) Study C209

In the ITT population, the difference in virologic response [95% CI] between the rilpivirine and control groups was 0.1 [-5.5; 5.7]. The lower limit of the 95% CI of the difference between the treatment groups (-5.5%) was above the set non inferiority margins of -12% and -10%. Therefore, non inferiority of rilpivirine versus the control efavirenz was demonstrated. The result of analysis in the PP population was consistent with the result in the ITT population.

(ii) Study C215

In the ITT population, the difference in virologic response [95% CI] between the rilpivirine and control groups was 3.9 [-1.6; 9.5]. The lower limit of the 95% CI of the difference between the treatment groups (-1.6%) was above the set non inferiority margins of -12% and -10%. Therefore, non inferiority of rilpivirine versus the control efavirenz was demonstrated. The result of analysis in the PP population was consistent with the result in the ITT population.

(iii) Pooled analysis

In the pooled ITT population, the difference in virologic response [95% CI] between the rilpivirine and control groups was 2.0 [-2.0; 6.0]. The lower limit of the 95% CI of the difference between the treatment groups (-2.0%) was above the set non-inferiority margins of -12% and -10%. Therefore, non inferiority of rilpivirine versus the control efavirenz was demonstrated. The result of analysis in the PP population was consistent with the result in the ITT population.

Comments:

Comparing the results of Study C215 with those of Study C209 showed that the calculated difference [95% CI] between treatments in favour of rilpivirine was greater in Study C215 (3.9, [-1.6; 9.5]) than in Study C209 (0.1, [-5.5; 5.7]). However, looking at the results from Study C209 (the study with the lesser difference between treatment groups), the lower limit of the 95% CI of the difference between the treatment groups (-5.5%) was still well above the set non inferiority margins of -12% and -10%. The conclusion of non-inferiority of rilpivirine compared with efavirenz based on the margins of -12% and -10% was therefore appropriate.

Primary endpoint non-inferiority and superiority analyses: using logistic regression:

The difference [95% CI] in virologic response at Week 48 in the ITT population between the rilpivirine and control groups predicted by logistic regression was -0.4 [-5.9; 5.2] in Study C209, 3.5 [-1.7; 8.8] in Study C215, and 1.6 [-2.2; 5.3] in the pooled analysis.

In the individual studies as well as the pooled analysis, the lower limit of the 95% CI of the difference between treatment groups was above the set non inferiority margins of -12% and -10% (p-value < 0.05). Non inferiority was demonstrated at the -12% and -10% margins. However superiority of rilpivirine over control was not demonstrated at the 5% significance level (p = 0.4114 in the pooled analysis).

"Snapshot" approach analysis: using normal approximation of binomial distribution.

(i) Study C209

In the ITT population, the difference in virologic response [95% CI] between the rilpivirine and control groups was 0.7 [-5.1; 6.4]. The lower limit of the 95% CI of the difference between the treatment groups (-5.1%) was above the set non inferiority margins of -12% and -10%. Therefore, non inferiority of rilpivirine versus the control efavirenz was demonstrated. The result of the PP population was consistent with the result of the ITT population.

(ii) Study C215

In the ITT population, the difference in virologic response [95% CI] between the rilpivirine and control groups was 4.2 [-1.7; 10.2]. The lower limit of the 95% CI of the difference between the treatment groups (-1.7%) was above the set non inferiority margins of -12% and -10%. Therefore, non-inferiority of rilpivirine versus the control efavirenz was demonstrated. The result of the PP population was consistent with the result of the ITT population.

(iii) Pooled analysis

In the ITT population, the difference in virologic response [95% CI] between the rilpivirine and control groups was 2.4 [-1.7; 6.6]. The lower limit of the 95% CI of the difference between the treatment groups (-1.7%) was above the set non inferiority margins of -12% and -10%. Therefore, non inferiority of rilpivirine versus the control efavirenz was demonstrated. The result of the PP population was consistent with the result of the ITT population.

"Snapshot" approach analyses using logistic regression

The difference [95% CI] in virologic response at Week 48 in the ITT population between the rilpivirine and control groups, using the snapshot approach and predicted by logistic regression was 0.3 [-5.4; 5.9] in Study C209, 3.9 [-1.9; 9.6] in Study C215, and 2.0 [-2.1; 6.1] for in the pooled analysis.

In the individual studies as well as the pooled analysis, the lower limit of the 95% CI of the difference between treatment groups was above the set non inferiority margins of -12% and -10% (p-value <0.05). Non inferiority was demonstrated at the -12% and -10% margins. However superiority of rilpivirine over control was not demonstrated at the 5% significance level (p = 0.3314 in the pooled analysis).

Comments:

The snapshot approach utilised a different definition of virologic responders and non responders from the primary endpoint analysis approach. The result of the snapshot approach was comparable to that of the primary endpoint analysis in both the pooled analysis, as well as in the individual studies.

Non virologic failure censored (non VF censored) analysis and other additional sensitivity analyses:

In the pooled analysis, the results of the different sensitivity analyses showed that the lower limits of the 95% CI of the difference between treatment groups were above the set non-inferiority margins of -12% and -10%, thus demonstrating non inferiority of rilpivirine versus the control efavirenz.

In the individual studies, the lower limits of the 95% CI of the difference between treatment groups were also above the set non inferiority margins of -12% and -10%, except for the TLOVR non VF censored analysis in Study C209. In Study C209, the difference in the response rate for the TLOVR non VF censored analysis was -7.9, 95% CI: [-12.5; -3.2], based on the results using normal approximation. The lower limit of the 95% CI (-12.5%) was below the set non inferiority margins of -12% and -10%.

Comments

Overall, the primary endpoint analysis demonstrated non inferiority of rilpivirine 25 mg/day compared with efavirenz 600 mg/day at the set non inferiority margins of -12% and -10%, in both studies individually as well as in the pooled analysis. The additional analyses using the "snapshot" approach and the different imputation methods generally supported the results of the primary endpoint analysis.

However, the results from Study C209 were not as robust as those from Study C215. When the non VF censored analysis was applied to Study C209, non-inferiority at -12% and -10% was not demonstrated. The non VF censored analysis excluded subjects who were treatment failures for reasons other than virologic failure (for example, subjects who were discontinued due to AEs). The number of subjects excluded from this analysis was imbalanced between treatment groups and this was more so in Study C209 than C215. In Study C209, 13 subjects in the rilpivirine group and 41 subjects in the control group were excluded in this analysis, while in Study C215 there were 21 subjects in the rilpivirine group and 42 subjects in the control group who were excluded.

However, the overall conclusion from the primary efficacy analysis that there was non inferiority in the virologic efficacy of rilpivirine 25 mg/day compared with efavirenz 600 mg/day was appropriate.

Secondary endpoints

For the purpose of this evaluation report, evaluation and review will be restricted to the main secondary endpoints analyses that have relevance in the assessment of this submission.

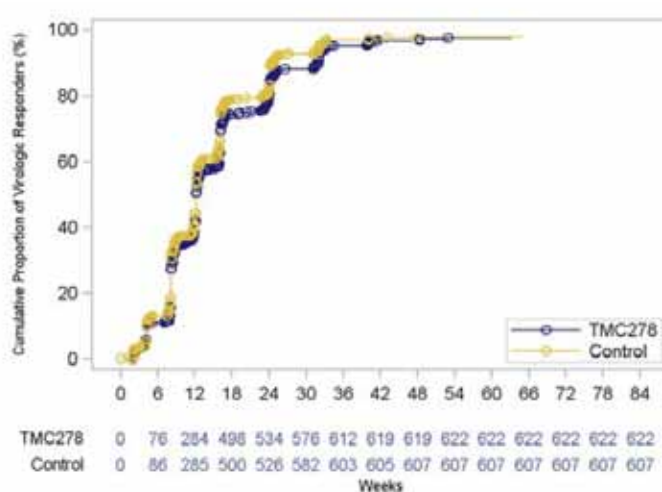
Virologic response over time

Virologic response over time for the TLOVR analysis in the Phase III pooled analysis showed that the proportions of responders over time in the rilpivirine and control groups were similar up to Week 48.

Time to virologic response

In the pooled analysis, the median time to response for both treatment groups was approximately 12 weeks. Some separation between the treatment groups was seen from Week 18 onwards indicating that subjects in the control group were responding earlier than those in the rilpivirine group (Figure 6). However, this difference narrowed from approximately Week 36 onwards.

Figure 6: Time to virologic response (<50 HIV-1 copies/mL, TLOVR), pooled phase III studies.



- Immunological response: In the pooled analysis, the mean increase in the absolute CD4+ cell count (imputed) from baseline was 192.1 cells/ μ L in the rilpivirine group and 176.2 cells/ μ L in the control group. This difference was found to be statistically significant in favour of rilpivirine for ($p = 0.0263$, ANCOVA (analysis of covariance)). However, in Phase III trials C209 and C215, analysed individually at Week 48, the difference between the rilpivirine and control groups for the mean change from baseline in absolute CD4+ cell count was found to be not statistically significant ($p = 0.1307$ and 0.0915 for studies C209 and C215, respectively, ANCOVA).

Clinical studies in special populations

There were no pivotal efficacy studies involving the use of rilpivirine in special populations. There were two small Phase I studies (C121 and C130) involving special populations. In Study C121, 13 subjects were receiving a stable methadone therapy, and in Study C130, 16 subjects had mild or moderate hepatic impairment and 16 were matched healthy control subjects. These studies would be briefly described with respect to safety data under the clinical safety section of this evaluation report.

Evaluator's overall conclusions on clinical efficacy

Overall, in the Phase III registration trials, the conclusion from the primary efficacy analysis that there was non inferiority in the virologic efficacy of rilpivirine 25 mg/day compared with efavirenz 600 mg/day was appropriate. The study designs of both Phase III registration trials were sound, and utilised primary endpoints that were in agreement with current HIV research guidelines and recommendations. The sample sizes of each trial

were adequate for the primary endpoint. Pooled analysis was appropriate as the study designs of both trials were identical apart from the background regimen used.

However, the dose range explored in the Phase IIb trials (rilpivirine 25 mg/day to rilpivirine 150 mg/day) did not show any efficacy dose relationship. The dose range explored failed to elicit the minimum clinically efficacious dose, and there is no clinical information regarding whether a lower dose of rilpivirine would have been more appropriate as a therapeutic dose. This would be discussed further in Section 6 of this evaluation report.

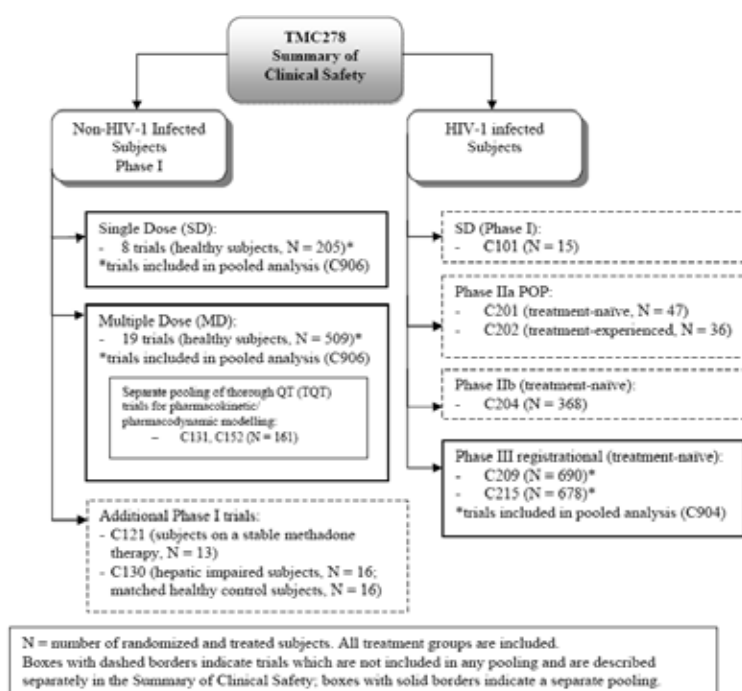
Safety

Introduction

Overall, the clinical safety data for rilpivirine was collected from 35 trials: thirty Phase I trials, two Phase IIa trials, one Phase IIb trial, and two Phase III trials. The cut off date for inclusion of the safety information was 1 February 2010.

The population included in all safety analyses was the ITT population, and they were analysed as treated (that is, on the treatment they actually received, irrespective of their compliance with the trial protocol) (Figure 7).

Figure 7: Intent to Treat (ITT) population included in safety analyses of rilpivirine (TMC278).



In this evaluation report, the main safety data evaluated and presented will be that of the two phase III studies. The safety data from the other studies will be summarised and evaluated with regards to the occurrences of any significant variations from the Phase III safety data, or any safety concerns that were not subsequently addressed by the Phase III trials.

Patient exposure

Overview: At the time of the cut off date of the Phase III Week 48 analysis (28 January 2010 for C215 and 1 February 2010 for C209), the clinical safety database consisted of 1712 subjects treated with rilpivirine: 1052 HIV-1 infected subjects, and 660 non-HIV infected subjects.

Phase III trials (studies C209 and C215): The study design of the two phase III trials has been presented in the clinical efficacy section of this report. Overall in these two trials, 686 HIV-1 infected patients had at least one dose of rilpivirine. rilpivirine was taken for at least 48 weeks by 611 subjects (89.1%).

Phase IIb trial (Study C204): Overall, a total of 279 HIV-1 infected patients had at least one dose of rilpivirine. Rilpivirine was taken for at least 48 weeks by 236 subjects (84.6%), for at least 96 weeks by 218 subjects (78.1%) and for at least 144 weeks by 193 subjects (69.2%).

Phase IIa trials (studies C201 and C202) and Phase I trial involving HIV-1-infected subjects (Study C101): Two Phase IIa proof of concept trials (C201 and C202) and one Phase I trial (C101) involving HIV-1 infected subjects were conducted. A total of 98 HIV-1 infected subjects were enrolled and treated in these trials: 47 in Study C201, 36 in Study C202 and 15 in Study C101.

In Study C201, a total of 47 HIV-1 infected, treatment-naïve subjects were randomised into 1 of 4 rilpivirine groups (25 mg/day, n = 9; 50 mg/day, n = 9; 100 mg/day, n = 9; 150 mg/day, n = 9) or the placebo group (n = 11). All 47 subjects completed the 7 day monotherapy period. A total of 36 subjects received rilpivirine for 7 days, 9 in each dose level.

In Study C202, a total of 36 HIV-1 infected treatment experienced subjects were randomised into one of three rilpivirine groups (25 mg/day, n = 13; 50 mg/day, n = 12; 150 mg/day, n = 11). Thirty-three subjects completed 7 day rilpivirine daily dose. Three subjects in the 150 mg/day group discontinued the trial prematurely: two subjects withdrew their consent on Day 5 and Day 7, respectively, and one subject discontinued due to AEs on Day 3.

In Study C101, a total of 15 HIV-1 infected subjects received a single oral dose of rilpivirine 50 mg/day, together with their current NNRTI regimens.

Phase 1 studies involving non HIV infected subjects: In total, 660 non HIV infected healthy subjects received rilpivirine in the Phase I trials: 431 in 19 multiple dose (MD) studies, 184 in 8 single dose (SD) studies, and 45 in studies C212 and C130 that involved special populations.

The data from 27 of the Phase I trials in healthy subjects were analysed by the sponsor in two pooled safety analyses: one with 19 MD trials, and one with 8 SD trials. The two trials C121 and C130 that involved special populations were not included in the pooled analyses.

In the C121 trial, 13 subjects were receiving a stable methadone therapy, and in the C130 trial, 16 subjects had mild or moderate hepatic impairment and 16 were matched healthy control subjects. Of the 13 subjects enrolled in C121, 12 subjects received rilpivirine 25 mg/day for 11 days, added to their current methadone therapy, and one subject discontinued rilpivirine after 6 days. Of the 32 subjects enrolled in C130, all 32 received rilpivirine 25 mg/day for 11 days.

Comments:

Overall, the amount of exposure to the drug is adequate to evaluate the safety profile of rilpivirine. In the 2 Phase III trials, 611 HIV1-infected patients were exposed to rilpivirine for between 8 weeks and 96 weeks. Longer term safety profile was derived from the extended period of Phase IIb trial C204, where subjects were exposed to rilpivirine beyond 96 weeks.

Adverse Events (AEs)

Phase III studies (C209 and C215)

In the pooled analysis, the proportions of subjects who experienced at least one AE were similar between the rilpivirine group and the control group (89.8% and 92.2% of subjects, respectively ($p = 0.1304$)). In each treatment group, the majority of subjects who experienced AEs had AEs of Grade 1 or 2 in severity (88.5% and 90.6% in the rilpivirine and control group, respectively). In the pooled analysis, a smaller proportion of subjects experienced at least one treatment related AE in the rilpivirine group (46.4% of subjects) compared with in the control group (64.1% of subjects). This was also reflected in a comparison between treatment groups within each individual study.

Commonly occurring AEs are tabulated in Table 25. By System Organ Class (SOC) classification, the two most common AEs in the pooled rilpivirine group were *Infections and infestations* (rilpivirine versus control; 58.6% versus 58.2%) and *Gastrointestinal disorders* (40.2% versus 37.0%). By preferred term, the most commonly reported AEs in the rilpivirine group were headache (13.8% versus 13.5%), nausea (13.4% versus 14.2%), diarrhoea (11.4% versus 13.8%) and nasopharyngitis (10.1% versus 11%). The sponsor had performed statistical testing comparing rilpivirine and control in the incidence of AEs reported in more than 10% of subjects (by preferred term, using the Fisher's Exact test). It showed statistically significant differences in favour of rilpivirine for dizziness ($p < 0.0001$), abnormal dreams/nightmare ($p = 0.0093$) and rash ($p < 0.0001$). No statistically significant differences were found in favour of control for the AEs tested.

Table 25: Adverse events in at least 5% of subjects (by System Organ Class or preferred term) in the rilpivirine (TMC278) or control group (Phase III Week 48 pooled analysis, C209 and C215).

System Organ Class Preferred Term, n (%)	C209		C215		Pooled	
	TMC278 N = 346	Control N = 344	TMC278 N = 340	Control N = 338	TMC278 N = 686	Control N = 682
Infections and Infestations	208 (60.1)	212 (61.6)	194 (57.1)	185 (54.7)	402 (58.6)	397 (58.2)
Nasopharyngitis	28 (8.1)	42 (12.2)	41 (12.1)	33 (9.8)	69 (10.1)	75 (11.0)
Upper respiratory tract infection	33 (9.5)	36 (10.5)	28 (8.2)	31 (9.2)	61 (8.9)	67 (9.8)
Influenza	26 (7.5)	29 (8.4)	21 (6.2)	25 (7.4)	47 (6.9)	54 (7.9)
Gastrointestinal disorders	135 (39.0)	118 (34.3)	141 (41.5)	134 (39.6)	276 (40.2)	252 (37.0)
Nausea	37 (10.7)	33 (9.6)	55 (16.2)	64 (18.9)	92 (13.4)	97 (14.2)
Diarrhea	36 (10.4)	53 (15.4)	42 (12.4)	41 (12.1)	78 (11.4)	94 (13.8)
Vomiting	13 (3.8)	17 (4.9)	20 (5.9)	23 (6.8)	33 (4.8)	40 (5.9)
Nervous system disorders	92 (26.6)	148 (43.0)	120 (35.3)	173 (51.2)	212 (30.9)	321 (47.1)
Headache	43 (12.4)	38 (11.0)	52 (15.3)	54 (16.0)	95 (13.8)	92 (13.5)
Dizziness	26 (7.5)	88 (25.6)	42 (12.4)	106 (31.4)	68 (9.9)	194 (28.4)
Somnolence	12 (3.5)	23 (6.7)	16 (4.7)	28 (8.3)	28 (4.1)	51 (7.5)
Psychiatric disorders	81 (23.4)	112 (32.6)	84 (24.7)	86 (25.4)	165 (24.1)	198 (29.0)
Insomnia	23 (6.6)	32 (9.3)	31 (9.1)	20 (5.9)	54 (7.9)	52 (7.6)
Abnormal dreams	28 (8.1)	41 (11.9)	18 (5.3)	25 (7.4)	46 (6.7)	66 (9.7)
Depression	22 (6.4)	17 (4.9)	18 (5.3)	15 (4.4)	40 (5.8)	32 (4.7)
Anxiety	4 (1.2)	21 (6.1)	12 (3.5)	14 (4.1)	16 (2.3)	35 (5.1)
Skin and subcutaneous tissue disorders	76 (22.0)	107 (31.1)	78 (22.9)	107 (31.7)	154 (22.4)	214 (31.4)
Rash	24 (6.9)	41 (11.9)	12 (3.5)	49 (14.5)	36 (5.2)	90 (13.2)
Musculoskeletal and connective tissue disorders	63 (18.2)	58 (16.9)	59 (17.4)	59 (17.5)	122 (17.8)	117 (17.2)
Back pain	16 (4.6)	15 (4.4)	14 (4.1)	21 (6.2)	30 (4.4)	36 (5.3)
Investigations	51 (14.7)	51 (14.8)	69 (20.3)	60 (17.8)	120 (17.5)	111 (16.3)
General disorders and administration site conditions	55 (15.9)	79 (23.0)	47 (13.8)	61 (18.0)	102 (14.9)	140 (20.5)
Fatigue	15 (4.3)	26 (7.6)	16 (4.7)	27 (8.0)	31 (4.5)	53 (7.8)
Respiratory, thoracic and mediastinal disorders	38 (11.0)	46 (13.4)	63 (18.5)	33 (9.8)	101 (14.7)	79 (11.6)
Cough	14 (4.0)	10 (2.9)	26 (7.6)	10 (3.0)	40 (5.8)	20 (2.9)
Blood and lymphatic system disorders	24 (6.9)	19 (5.5)	35 (10.3)	26 (7.7)	59 (8.6)	45 (6.6)
Metabolism and nutrition disorders	24 (6.9)	36 (10.5)	27 (7.9)	39 (11.5)	51 (7.4)	75 (11.0)
Injury, poisoning and procedural complications	23 (6.6)	30 (8.7)	27 (7.9)	23 (6.8)	50 (7.3)	53 (7.8)
Renal and urinary disorders	25 (7.2)	17 (4.9)	25 (7.4)	21 (6.2)	50 (7.3)	38 (5.6)
Reproductive system and breast disorders	26 (7.5)	18 (5.2)	20 (5.9)	25 (7.4)	46 (6.7)	43 (6.3)
Cardiac disorders	18 (5.2)	26 (7.6)	22 (6.5)	21 (6.2)	40 (5.8)	47 (6.9)
Vascular disorders	16 (4.6)	21 (6.1)	23 (6.8)	18 (5.3)	39 (5.7)	39 (5.7)
Ear and labyrinth disorders	9 (2.6)	27 (7.8)	5 (1.5)	11 (3.3)	14 (2.0)	38 (5.6)

N = number of subjects per treatment group; n = number of observations.

Treatment related AEs are tabulated in Table 26. The incidence of treatment related AEs was lower in the pooled rilpivirine group (46.4%) than in the pooled control group (64.1%). By SOC, the most common treatment related AEs in the rilpivirine group were *Gastrointestinal disorders* (rilpivirine versus control; 19.2% versus 17.7%) and *Nervous system disorders* (17.2% versus 36.7%). By preferred term, the most frequently reported treatment-related AEs in the rilpivirine group were nausea (10.1% versus 11.3%), dizziness (8.0% versus 26.2%), abnormal dreams (6.3% versus 9.4%) and headache (6.1% versus 6.2%).

Table 26: Adverse events at least possibly related to rilpivirine (TMC278) or control in at least 2% of subjects (by System Organ Class or preferred term) in the rilpivirine or control group (Phase III Week 48 pooled analysis, C209 and C215).

System Organ Class Preferred Term, n (%)	C209		C215		Pooled	
	TMC278 N = 346	Control N = 344	TMC278 N = 340	Control N = 338	TMC278 N = 686	Control N = 682
<i>Any AE at least possibly related</i>	<i>147 (42.5)</i>	<i>214 (62.2)</i>	<i>171 (50.3)</i>	<i>223 (66.0)</i>	<i>318 (46.4)</i>	<i>437 (64.1)</i>
Gastrointestinal disorders	56 (16.2)	46 (13.4)	76 (22.4)	75 (22.2)	132 (19.2)	121 (17.7)
Nausea	30 (8.7)	24 (7.0)	39 (11.5)	53 (15.7)	69 (10.1)	77 (11.3)
Diarrhea	13 (3.8)	20 (5.8)	15 (4.4)	11 (3.3)	28 (4.1)	31 (4.5)
Vomiting	7 (2.0)	9 (2.6)	6 (1.8)	15 (4.4)	13 (1.9)	24 (3.5)
Nervous system disorders	52 (15.0)	117 (34.0)	66 (19.4)	133 (39.3)	118 (17.2)	250 (36.7)
Dizziness	22 (6.4)	85 (24.7)	33 (9.7)	94 (27.8)	55 (8.0)	179 (26.2)
Headache	22 (6.4)	15 (4.4)	20 (5.9)	27 (8.0)	42 (6.1)	42 (6.2)
Somnolence	12 (3.5)	21 (6.1)	13 (3.8)	28 (8.3)	25 (3.6)	49 (7.2)
Disturbance in attention	2 (0.6)	10 (2.9)	3 (0.9)	7 (2.1)	5 (0.7)	17 (2.5)
Psychiatric disorders	50 (14.5)	86 (25.0)	52 (15.3)	69 (20.4)	102 (14.9)	155 (22.7)
Abnormal dreams	26 (7.5)	39 (11.3)	17 (5.0)	25 (7.4)	43 (6.3)	64 (9.4)
Insomnia	14 (4.0)	23 (6.7)	20 (5.9)	16 (4.7)	34 (5.0)	39 (5.7)
Nightmare	7 (2.0)	10 (2.9)	8 (2.4)	15 (4.4)	15 (2.2)	25 (3.7)
Depression	6 (1.7)	9 (2.6)	6 (1.8)	6 (1.8)	12 (1.7)	15 (2.2)
Sleep disorder	2 (0.6)	11 (3.2)	7 (2.1)	9 (2.7)	9 (1.3)	20 (2.9)
Anxiety	2 (0.6)	8 (2.3)	2 (0.6)	6 (1.8)	4 (0.6)	14 (2.1)
Skin and subcutaneous tissue disorders	21 (6.1)	61 (17.7)	27 (7.9)	49 (14.5)	48 (7.0)	110 (16.1)
Rash	11 (3.2)	30 (8.7)	6 (1.8)	31 (9.2)	17 (2.5)	61 (8.9)
Pruritus	1 (0.3)	10 (2.9)	9 (2.6)	6 (1.8)	10 (1.5)	16 (2.3)
General disorders and administration site conditions	23 (6.6)	42 (12.2)	20 (5.9)	30 (8.9)	43 (6.3)	72 (10.6)
Fatigue	10 (2.9)	13 (3.8)	9 (2.6)	13 (3.8)	19 (2.8)	26 (3.8)
Asthenia	4 (1.2)	7 (2.0)	2 (0.6)	7 (2.1)	6 (0.9)	14 (2.1)
Investigations	20 (5.8)	19 (5.5)	21 (6.2)	20 (5.9)	41 (6.0)	39 (5.7)
Metabolism and nutrition disorders	10 (2.9)	22 (6.4)	6 (1.8)	23 (6.8)	16 (2.3)	45 (6.6)
Cardiac disorders	5 (1.4)	9 (2.6)	4 (1.2)	9 (2.7)	9 (1.3)	18 (2.6)
Ear and labyrinth disorders	2 (0.6)	16 (4.7)	1 (0.3)	4 (1.2)	3 (0.4)	20 (2.9)
Vertigo	2 (0.6)	13 (3.8)	0	3 (0.9)	2 (0.3)	16 (2.3)

N = number of subjects per treatment group; n = number of observations.

The sponsor had performed statistical testing comparing rilpivirine and control in the incidence of treatment related AEs reported in more than 10% of subjects (by preferred term, using the Fisher's Exact test). It showed statistically significant differences in favour of rilpivirine for dizziness ($p < 0.0001$) and for abnormal dreams/nightmare ($p = 0.0061$). No statistically significant differences were found in favour of control for the AEs tested.

The incidence of treatment related AEs with a severity of at least Grade 2 was lower in the rilpivirine group than in the control group (15.9% versus 31.1%). The difference in incidence was statistically significant in favour of rilpivirine ($p < 0.0001$; Fisher's Exact test). In the rilpivirine group, the most common treatment related AEs with a severity grade of at least 2 (preferred term) were insomnia (1.7% versus 2.3%), headache (1.6% versus 2.2%) and abnormal dreams (1.0% versus 2.3%).

Events of interest are tabulated in Table 27. Skin, neurological, psychiatric and hepatic events of interest were reported in a smaller proportion of subjects in the rilpivirine group than in the control group, as was the incidence of events of interest potentially related to QT_c interval prolongation. Endocrine events of interest were reported in a higher proportion of subjects in the rilpivirine group than in the control (5.0% versus 3.8%). The sponsor had performed statistical testing comparing rilpivirine and control in the incidence of events of interest. However, the difference in the proportion of subjects reporting at least one endocrine event of interest between the rilpivirine group and control group was not included in this analysis and hence the difference was not analysed for statistical significance.

Table 27: Adverse events of interest following treatment with rilpivirine (TMC278) or control (Phase III trials C209, C215 and Pooled Phase III trials).

AE Summary, n (%)	C209		C215		Pooled	
	TMC278 N = 346	Control N = 344	TMC278 N = 340	Control N = 338	TMC278 N = 686	Control N = 682
Any skin event of interest ^{d,e}	57 (16.5)	89 (25.9)	39 (11.5)	88 (26.0)	96 (14.0)	177 (26.0)
Rash (grouped term)	33 (9.5)	77 (22.4)	18 (5.3)	73 (21.6)	51 (7.4)	150 (22.0)
Any neuropsychiatric event of interest ^{d,f}	128 (37.0)	190 (55.2)	148 (43.5)	198 (58.6)	276 (40.2)	388 (56.9)
Any neurologic event of interest	80 (23.1)	145 (42.2)	104 (30.6)	163 (48.2)	184 (26.8)	308 (45.2)
Any psychiatric event	81 (23.4)	112 (32.6)	83 (24.4)	86 (25.4)	164 (23.9)	198 (29.0)
Any hepatic event of interest ^{d,g}	17 (4.9)	24 (7.0)	21 (6.2)	21 (6.2)	38 (5.5)	45 (6.6)
Any event of interest potentially related to QTc interval prolongation ^{d,g}	1 (0.3)	2 (0.6)	2 (0.6)	6 (1.8)	3 (0.4)	8 (1.2)
Any endocrine event of interest ^{d,g}	16 (4.6)	10 (2.9)	18 (5.3)	16 (4.7)	34 (5.0)	26 (3.8)

N = number of subjects per treatment group; n = number of observations

^d AEs of interest were not identified from single relevant SOC, but were based on selected AE preferred terms from a number of relevant SOC.

^e Presented overall for event of interest category and by grouped term (see Section 1.3.2.4.1).

^f Presented overall for neuropsychiatric events of interest and by neurologic/psychiatric event of interest categories.

^g Presented overall for event of interest category.

Comments on endocrine events of interest:

Among the events of interest presented by the sponsor, only the endocrine events of interest had a higher incidence in the rilpivirine group compared to the control group (pooled analysis, as well as in individual studies). This was not tested for statistical significance.

It is noted by this evaluator that in the pre clinical animal toxicity studies, the potential target organs and systems of toxicity identified for rilpivirine included the endocrine organs and system: adrenal function, reproductive organs, thyroid and pituitary function.

A detailed breakdown of the endocrine events showed that the main SOC under "endocrine events of interest" that had a higher proportion of subjects in the rilpivirine group than in the control group was Investigations (2.6% and 1.2 % respectively). Within this SOC, the main preferred term AE that had a higher proportion of subjects in the rilpivirine group than in the control group was "Blood cortisol decreased" (2.2% and 1.0% respectively). These investigations pertaining to endocrine function will be evaluated and presented in the "Laboratory Findings" section of this report.

Phase IIb study (C204)

The safety data from the Phase IIb trial (C204) were analysed by the sponsor in 2 parts: one for the dose finding part of the trial (that is, the Week 96 analysis) and the other for the long term safety part of the trial (that is, the Week 192 analysis). The cutoff date for the Week 96 analysis was 3 October 2007, and that for the Week 192 analysis was 7 August 2009.

(i) Week 96 analysis

The incidence of AEs and treatment related AEs showed no obvious dose relationship, and was not higher in the rilpivirine groups compared to the control group. In the Week 96 analysis, the most commonly reported AEs by SOC for the rilpivirine 25 mg/day group were *Infections and infestations* (62.4%) and *Gastrointestinal disorders* (51.6%). Similar proportions of subjects reported *Infections and infestations* in all 3 rilpivirine dose groups

and in the control group (67.4%, 63.7% and 64% for the rilpivirine 75 mg/day group, rilpivirine 150 mg/day group and control group respectively). Adverse events in the SOC of *Gastrointestinal disorders* were reported in a greater proportion of subjects in the rilpivirine 75 mg/day group (70.5%) than in the rilpivirine 25 mg/day group (51.6%), the rilpivirine 150 mg/day group (58.2%) or the control group (59.6%). No consistent pattern or dose relationship was observed across the three rilpivirine dose groups in any SOC.

The most commonly reported AEs by preferred term in the rilpivirine 25 mg/day group were nausea (33.3% versus 29.2%), upper respiratory tract infection (18.3% versus 7.9%) and headache (17.2% versus 15.7%). No dose relationship was observed for these AEs.

The incidence of treatment related AEs that were Grade 2 or more in severity was similar in each of the 3 rilpivirine dose groups (approximately 21%) and was lower than that in the control group (38.2%). By SOC, the most commonly reported of these AEs in the rilpivirine 25 mg/day group were *Investigations* (10.8% versus 9.0%), and *Gastrointestinal disorders* (5.4% versus 7.9%). No dose relationship was observed in the 3 rilpivirine dose groups. By preferred term, the most frequently reported overall were nausea (3.2% versus 5.6%) and Alanine Transaminase (ALT) increased (5.4% versus 2.2%).

No dose relationship was observed in the overall incidence of neurological, psychiatric, hepatic, potential QTc interval-prolongation related, or endocrine events of interest in the 3 rilpivirine dose groups. A possible dose-relationship was observed in the incidence of the grouped term "rash" under skin events of interest, which increased in incidence with increasing rilpivirine dose.

Comments:

This trial was only partially blinded up to Week 96: the three rilpivirine doses were blinded to each other but the administration of efavirenz in the control group was open-label. This means that in looking at the safety data, the comparison analyses would be more robust between the three rilpivirine dose groups than between the rilpivirine dose groups and the control group.

There was no obvious dose relationship in the adverse events data of this study except for the grouped term of "rash" under skin events of interest. However the number involved was small, making interpretation difficult. In addition, the overall incidence of this AE in the pooled rilpivirine group (9.3%) was lower than that in the control group (21.3%). The incidence of this AE in the highest dose group of rilpivirine (150 mg/day) was also lower than that in the control group (13.2% versus 21.3%, respectively). This was supported by the results in the Phase III trials in which the incidence of the grouped AE term of "rash" was lower in the pooled rilpivirine 25 mg/day group (7.4%) compared with that in the pooled control group (22.0%).

The most commonly occurring AEs by preferred term in the rilpivirine 25 mg/day group had higher incidences in the rilpivirine 25 mg/day group than in the control group: nausea (33.3% versus 29.2%), upper respiratory tract infection (18.3% versus 7.9%) and headache (17.2% versus 15.7%). However, this pattern was not found in the Phase III trials.

(ii) Week 192 analysis

In Study C204, all rilpivirine treated subjects who consented to participate in the open-label extensions to the trial switched their dose after Week 96, first to 75 mg/day, then, at approximately Week 144, to 25 mg/day. Safety data were therefore presented for the combined rilpivirine group across 48-week periods, rather than by dose.

The majority of AEs in both the rilpivirine and control groups appeared in the first 48 weeks of the trial. After the first 48 weeks of the trial, the incidence of any AEs in the rilpivirine group declined.

In the Week 192 analysis, the AE most frequently reported by SOC in the combined rilpivirine group were *Infections and infestations* (68.5%) and *Gastrointestinal disorders* (61.3%). Similar proportions of subjects experienced events in these SOC in the control group (66.3% and 61.8%, respectively). In the rilpivirine group, the incidence of AEs in the SOC of *infections and infestations* was greatest in the first 48 weeks of the trial (56.3%) after which the incidence fell to 39.0% in Week 48 to 96, and then stabilised (32.1% and 30.6% in Week 96 to 144 and Week 144 to 192, respectively). The incidence of AEs in the SOC of *gastrointestinal disorders* in the rilpivirine group was also the greatest in the first 48 weeks (55.9%) and declined to 17.8%, 10.6% and 9.3% in Week 48 to 96, Week 96 to 144 and Week 144 to 192, respectively.

The most commonly reported AEs by preferred term in the combined rilpivirine group in the Week 192 analysis were nausea (35.8% versus 29.2%), headache (20.8% versus 16.9% on control) and upper respiratory tract infection (15.8% versus 9.0% on control). Most cases of nausea, headache and upper respiratory tract infection in the rilpivirine group occurred in the first 48 weeks of the trial (34.8%, 18.3% and 10.8%, respectively), after which the incidence of these AEs in the rilpivirine group declined.

Most treatment-related AEs in both the rilpivirine and control groups were reported in the first 48 weeks of the trial. After Week 48, the incidence of treatment-related AEs declined.

In the Week 192 analysis, the most frequent treatment-related AEs were nausea (rilpivirine versus control; 20.8% versus 18.0%), and headache (8.2% versus 7.9%). Twenty-four percent (24.0%) of subjects in the combined rilpivirine group had treatment-related AEs that were at least Grade 2 in severity, compared with 43.8% of subjects in the control group. The most frequent of these AEs in the rilpivirine group were in the SOC of *Investigations*, reported in 10.4% of subjects, and *Gastrointestinal disorders*, reported in 5.7% of subjects. By preferred term, the most frequently reported treatment-related AEs that were at least Grade 2 in severity were nausea (3.2% on rilpivirine versus 5.6% on control) and ALT (alanine transaminase) increased (5.4% versus 2.2%)

Comment:

The Week 192 analysis provided some long term safety data for rilpivirine beyond 96 weeks. The overall incidences of any AEs, any treatment related AEs, and any treatment related AEs with severity of at least Grade 2, decreased with time beyond 48 weeks. In addition, the most commonly occurring AEs and treatment related AEs were comparable between the Week 96 analysis and the Week 192 analysis, suggesting that use of rilpivirine beyond 96 weeks to 192 weeks was not found to be associated with new or increasing AEs.

(iii) Comparison of safety data between phase III trials and IIb trials

The incidence of any AEs and treatment related AEs were similar between the Phase IIb Week 48 analysis and the Phase III pooled Week 48 analysis. There was a higher incidence of any Grade 3 or 4 AE in the rilpivirine group compared to the control group in the Phase IIb trial at Week 48, but this was not detected in the Phase III trials.

The most commonly occurring AEs by SOC were *Infections and infestations* and *Gastrointestinal disorders* in both Study C204 and the pooled Phase III trials. The incidence of these AEs was similar between the rilpivirine 25 mg/day group in the Phase IIb trial and that in the pooled Phase III trials.

Phase IIa studies (C201 and C202)

Overall, safety results in the Phase IIa studies were similar to the safety data profile seen in the Phase III and IIb studies.

(i) C201 HIV-1 infected, treatment naïve subjects

In Study C201, a total of 47 HIV-1 infected, treatment naïve subjects were randomised into one of four rilpivirine groups (25 mg/day, N = 9; 50 mg/day, N = 9; 100 mg/day, N = 9; 150 mg/day N = 9) or the placebo group (N = 11). All 47 subjects completed the seven day monotherapy period. A total of 36 subjects received rilpivirine. Overall, 22 subjects (61.1%) on rilpivirine experienced at least one AE during treatment. By SOC, the commonest AEs were *Gastrointestinal disorders* (25.0% versus 18.2% in the combined rilpivirine and placebo groups, respectively), and *Nervous system disorders* (19.4% versus 18.2%). By preferred term, headache was the most commonly reported event: this was reported in five subjects (13.9%) in the combined rilpivirine group compared with two subjects (18.2%) in the placebo group. Adverse events were mostly Grade 1 or Grade 2 in severity. No Grade 4 AEs were reported during the treatment phase. One subject in the rilpivirine 50 mg/day had Grade 3 nausea during the treatment phase, which was reported to be possibly related to study medication by the investigator.

(ii) C202 HIV-1 infected, treatment experienced subjects

In Study C202, a total of 36 HIV-1 infected subjects were randomised into one of three rilpivirine groups (25 mg/day, N = 13; 50 mg/day, N = 12; 150 mg/day, N = 11). Thirty-three subjects completed the seven day rilpivirine dose. Three subjects in the 150 mg/day group discontinued the trial prematurely: two subjects withdrew their consent on Day 5 and Day 7, respectively, and one subject discontinued due to adverse events (AEs) on Day 3. Overall, 14 subjects (39%) experienced at least one AE during treatment with rilpivirine. The most commonly reported AEs by SOC were *Nervous system disorders* (17%) and *Gastrointestinal disorders* (17%). The most commonly reported AE by preferred term was headache (14%). Adverse events were mostly Grade 1 in severity. One (9.1%) subject in the rilpivirine 150 mg/day group experienced two Grade 4 AEs (increased lipase and pancreatic amylase) and discontinued treatment on Day 3. These two AEs were judged by the investigator to be not related to the study medication. One (8.3%) subject in the rilpivirine 50 mg/day group experienced a Grade 3 AE of Gamma Glutamyl Transferase (GGT) increased during treatment. This was judged by the investigator to be doubtfully related to study medication.

Phase I Multiple-Dose (MD) and Single-Dose (SD) studies: Overall, adverse events were reported in 68.2% and 63.6% of subjects treated with rilpivirine in the MD trials and SD trials, respectively. Safety data in the pooled MD and SD analyses were generally similar to the safety data profile seen in the Phase III and IIb studies.

Deaths, SAEs and discontinuations due to AEs

Phase III studies (C209 and C215): An overview of deaths, serious adverse event (SAEs) and AEs leading to permanent discontinuation in studies C209 and C215 is tabulated in Table 28.

Table 28: Deaths, SAEs, and AEs leading to permanent discontinuation following treatment with rilpivirine (TMC278) or control (C209, C215 and pooled Phase III trials).

AE Summary, n (%)	C209		C215		Pooled	
	TMC278 N = 346	Control N = 344	TMC278 N = 340	Control N = 338	TMC278 N = 686	Control N = 682
Death	0	1 (0.3)	1 (0.3)	3 (0.9)	1 (0.1)	4 (0.6)
Any SAEs	23 (6.6)	31 (9.0)	22 (6.5)	24 (7.1)	45 (6.6)	55 (8.1)
AE leading to permanent discontinuation	8 (2.3)	27 (7.8)	15 (4.4)	25 (7.4)	23 (3.4)	52 (7.6)

N = number of subjects per treatment group; *n* = number of observations

In total, five subjects died during the course of the two Phase III trials: one in the rilpivirine group (trial C215) and four in the control group (one in trial C209 and three in trial C215). The subject who died while on rilpivirine died of bronchopneumonia. This AE leading to death was assessed by the investigator as not related to the study medication.

In the pooled analysis, 45 subjects (6.6%) in the rilpivirine group and 55 subjects (8.1%) in the control group had at least one SAE during the treatment period. In the rilpivirine group, the highest incidence of SAEs was observed in the SOC of *Infections and infestations* (2.6% in the rilpivirine group and 2.5% in the control group). The incidence of SAEs in the rilpivirine group was less than 1.0% in all the other SOCs. The only notable difference in incidence of SAEs between rilpivirine and control, where the incidence was higher in the rilpivirine group than the control group, was seen in the SOC of *Hepatobiliary disorders* (0.9% on rilpivirine versus 0.1% on control). In the rilpivirine group, six subjects had SAEs in the SOC of hepatobiliary disorders (three with acute cholecystitis, two with cholelithiasis and one with hyperbilirubinemia), compared with one subject in the control group (cholecystitis and cholelithiasis). However, none of these events were judged to be at least possibly related to study medication or led to permanent treatment discontinuation. Seven subjects (1.0%) in the rilpivirine group and six subjects (0.9%) in the control group experienced at least one treatment related SAE. The only SOC in which more than one subject in the rilpivirine group had a treatment related SAE was in the SOC of *Psychiatric disorders* (three subjects on rilpivirine [0.4%] versus two subjects on control [0.3%]). Out of these three subjects in the rilpivirine group with treatment related SAEs in the SOC of *Psychiatric disorder*, two had suicidal attempts and one had sleep disorder.

Overall, 23 subjects (3.4%) in the rilpivirine group and 52 subjects (7.6%) in the control group had at least one AE leading to permanent discontinuation. By SOC, the commonest AEs leading to permanent discontinuation on rilpivirine were *Psychiatric disorders* (1.5% versus 2.2% on control).

Phase IIb study (C204) Week 96 analysis: In the Week 96 analysis, one subject in the rilpivirine 75 mg/day group died in a car accident after 100 weeks of treatment. Another subject in the rilpivirine 75 mg/day group died of cardio-respiratory arrest on Day 4 of the follow up period after 35 weeks of treatment. The investigator assessed the causality relationship between the AEs leading to death and rilpivirine or the background antiretroviral drugs as not related.

In the Week 96 analysis, there was no obvious dose relationship in the incidence of SAEs: 12.9%, 13.7% and 9.9% of subjects in the rilpivirine 25 mg/day, 75 mg/day and 150 mg/day groups, respectively were reported with at least one SAE. The incidence of subjects with at least one SAE in the Week 96 analysis was similar between the combined rilpivirine group (12.2%) and the control group (14.6%). In the Week 96 analysis, overall

five subjects (1.8%) in the three rilpivirine dose groups reported treatment related SAEs compared with one subject in the control group (1.1%). In the rilpivirine 25 mg/day group, the treatment related SAEs were cytolytic hepatitis, ALT increased and AST (aspartate transaminase) increased (in one subject), blood amylase increased (in one subject) and abdominal pain and constipation (in one subject). One subject in the rilpivirine 75 mg/day group had SAEs of maculopapular rash, hepatitis, and allergic alveolitis. In the rilpivirine 150 mg/day group, the treatment related SAEs were suicide attempt (in one subject) and anaemia (in one subject).

The proportion of subjects experiencing AEs leading to permanent discontinuation increased with increasing rilpivirine dose: 8.6% (N = 8), 11.6% (N = 11), and 14.3% (N = 13) of subjects in the rilpivirine 25 mg/day, 75 mg/day, and 150 mg/day groups, respectively. However the number of subjects involved was small, making interpretation of dose relationship difficult. In the control group, 9.0% (N = 8) of subjects experienced AEs leading to permanent discontinuation. In the pooled rilpivirine group, the commonest AE leading to permanent discontinuation was under the SOC of *Investigations*: 20 AEs under this SOC was reported by 12 patients in the pooled rilpivirine group compared to none in the efavirenz group. There was no dose relationship observed. Within this SOC, the commonest AEs by preferred term were ALT increased and AST increased (six and five AEs, respectively).

Phase IIb study (C204) Week 192 analysis: An overview of deaths, SAEs and AEs leading to permanent discontinuation in Study C204 Week 192 analysis is tabulated in Table 29.

Table 29: Deaths, SAEs, and AE leading to permanent discontinuation following treatment with rilpivirine (TMC278) or control (Study C204 Week 192 analysis).

AE Summary, n (%)	Week [0; 48]	Week [48; 96]	Week [96; 144]	Week [144; 192]	Week 192 Analysis	
	All TMC278 N = 279	All TMC278 N = 236	All TMC278 N = 218	All TMC278 N = 193	All TMC278 N = 279	Control N = 89
Death ^c	0	0	3 (1.4)	0	3 (1.1)	0
Any SAE ^c	29 (10.4)	5 (2.1)	8 (3.7)	8 (4.1)	44 (15.8)	15 (16.9)
AE leading to permanent discontinuation	22 (7.9)	8 (3.4)	7 (3.2)	2 (1.0)	39 (14.0)	11 (12.4)

N = number of subjects per treatment group; n = number of observations

Two subjects in the combined rilpivirine group died after the Week 96 analysis. Neither of these deaths was reported to be related to treatment with rilpivirine by the investigator.

In the Week 192 analysis, the incidence of SAEs was 15.8% in the combined rilpivirine group compared with 16.9% in the control group. Most SAEs were reported in the first 48 weeks of the trial, with SAE incidence in the rilpivirine group of 10.4%. After Week 48, the incidence of SAEs in the rilpivirine group was 2.1%, 3.7% and 4.1% in Week 48-96, Week 96-144 and Week 144-192, respectively.

The incidence of AEs leading to permanent discontinuation in the Week 192 analysis was 14.0% for the combined rilpivirine group compared with 12.4% for the control group. Most AEs leading to permanent discontinuation were reported in the first 48 weeks of the trial with incidence of 7.9% in the combined rilpivirine. After Week 48, the incidence of AEs leading to permanent discontinuation was 3.4%, 3.2% and 1.0% in Week 48-96, Week 96-144 and Week 144-192, respectively. Overall, in the Week 192 analysis, the common AEs leading to permanent discontinuation were similar to the results in the Week 96 analysis. In the Week 192 analysis, the most common AE leading to permanent discontinuation was under the SOC of *Investigations*. 22 AEs were reported by 14 patients

in the pooled rilpivirine group compared to one AE reported by one patient in the efavirenz group.

Within this SOC, the commonest AEs by preferred term were ALT increased and AST increased (six and five AEs, respectively).

Phase IIa Study C201: There were no deaths reported in trial C201. Three SAEs (Grade 3 herpes zoster, and Grade 3 anal fissure and hemorrhoids) were reported in two subjects during the screening period, all of which were judged by the investigator to be not related to study medication. There were no AEs leading to permanent discontinuation.

Phase IIa Study C202: There were no deaths reported in Study C202. Four SAEs were reported in one subject in the rilpivirine 50 mg/day group during the follow up period (Grade 2 vertigo, Grade 2 headache, Grade 1 vomiting and Grade 1 dyspnoea). All SAEs were judged by the investigator to be not related to study medication. One subject discontinued due to two Grade 4 laboratory related AEs (increased lipase and amylase). Neither event was reported to be related to study medication by the investigator.

Phase I studies: There were no deaths reported in the Phase I trials. One SAE of nephrolithiasis was reported during treatment with rilpivirine alone (> 25 mg) in the MD trials. This SAE was reported to be doubtfully related to study medication by the investigator and led to permanent discontinuation of the subject from the trial. No SAEs were reported in the SD trials.

In the MD trials, seven subjects (1.6%) discontinued treatment with rilpivirine due to AEs. The most commonly reported AEs by preferred term that led to permanent discontinuation during rilpivirine alone treatment were increased lipase and increased blood amylase (two subjects for each AE preferred term, 0.5%). The only AE that led to permanent discontinuation in the SD trials was maculopapular rash during treatment with rilpivirine alone (1 subject, 0.5%).

Comments:

There were no obvious concerns detected with regards to the incidence of deaths or SAEs with rilpivirine. In the dose finding Phase IIb study, there was no obvious dose relationship in the incidence of SAEs and of treatment related SAEs from doses of rilpivirine 25 mg/day to rilpivirine 150 mg/day. Consistent with the finding in the Phase III trials, the overall incidence of subjects with at least one SAE in the Week 96 analysis was not higher in the combined rilpivirine group (12.2%) than in the control group (14.6%). In the Week 96 analysis of the Phase II trial, there were five subjects (1.8%) across the three rilpivirine dose groups who reported treatment related SAEs compared with only one subject in the control group (1.1%). However, these treatment related SAEs did not show any particular concentration within a particular preferred term AE.

Laboratory findings

In the nonclinical animal toxicity studies, the target organs and systems of toxicity identified for rilpivirine were the adrenal cortex and the associated steroid biosynthesis (mouse, rat, dog, cynomolgus monkey), the reproductive organs (female mouse, male and female dog), the thyroid and pituitary gland (rat), the liver (mouse, rat, dog), the kidney (mouse, dog), and the haematopoietic system (mouse, rat, dog).

Safety laboratory tests in the Phase IIb and III trials therefore included haematology, renal parameters, hepatic parameters, as well as endocrine monitoring (including gonadal, adrenal and thyroid parameters).

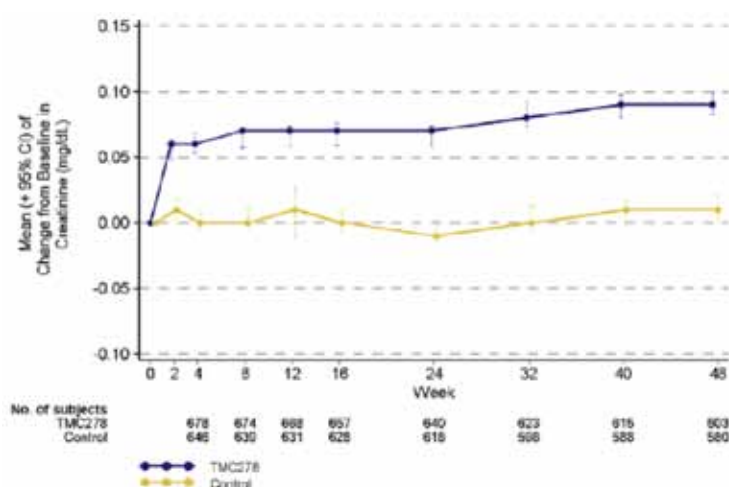
This evaluation report will concentrate on laboratory findings of significance in the safety data from the 2 Phase III trials and the Phase IIb trial. In the evaluation of the Phase IIa

and Phase I trials, there were no significant variations from the laboratory data of the Phase III and IIb trials, and no significant abnormalities which were not addressed subsequently by the laboratory data from the Phase III and IIb trials.

(i) Safety laboratory tests

Phase III studies (C209 and C215): The only notable finding in the safety laboratory tests results in the Phase III trials is that serum creatinine in the pooled rilpivirine group showed a mean increase of about 0.06 mg/day from baseline at Week 2. The subsequent increase throughout the rest of the 48 week treatment period was smaller, reaching an increase from baseline of about 0.09 mg/day at Week 48. In control subjects, serum creatinine fluctuated around the baseline level over the treatment period (Figure 8).

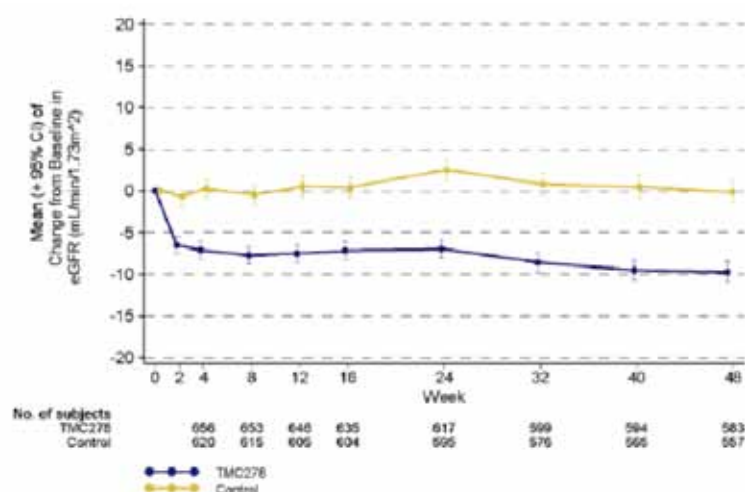
Figure 8: Mean change (+/- 95% CI) from baseline in creatinine over time following treatment with rilpivirine (TMC278) or control (Phase III Week 48 pooled analysis of C209 and C215).



When the serum creatinine profile was analysed according to the background regimen, it was found that this increase in serum creatinine was observed for rilpivirine treated subjects in all of the background regimen subgroups, although it was greater in the TDF/FTC and ABC/3TC subgroups (about 0.10 mg/day) than in the AZT/3TC subgroup (about 0.04 mg/day). This increase was not detected in the control group in each background regimen subgroup. This data suggested that the serum creatinine increase that was observed was due to rilpivirine rather than the background regimen.

This increase in serum creatinine was reflected in a corresponding decrease in the estimated glomerular filtration rate (GFR) calculated from the serum creatinine (eGFR_{creat}) of about 10mL/min/1.73m² from the baseline, at Week 48, for subjects in the pooled rilpivirine group (Figure 9).

Figure 9: Mean Change (+/- 95% CI) from baseline in eGFR_{creat} over time following treatment with rilpivirine (TMC278) or control (Phase III Week 48 pooled analysis of C209 and C215).



Phase IIb study (C204): This decrease in eGFR_{creat} was also present in the Phase IIb study Week 96 analysis, and showed a possible dose-relationship up to Week 48. Mean decreases from baseline in the eGFR_{creat} were observed in all three rilpivirine dose groups and were first detected at the first on treatment visit, after which the eGFR_{creat} stabilised. Maximum mean decreases in eGFR_{creat} of between 6 to 10 mL/min/1.73m² were seen in the three rilpivirine dose groups. In the control group, no decrease in eGFR_{creat} was observed. There was a possible dose relationship pattern up to first 12 weeks.

The Phase IIb Week 192 analysis showed that after Week 108, eGFR_{creat} gradually increased back towards baseline levels.

Phase III trial C215 additional renal laboratory parameter: The sponsor stated that the possibility of rilpivirine induced nephrotoxicity was investigated further by measuring cystatin C in Study C215. Cystatin C was measured in order to further evaluate whether the effect of rilpivirine on serum creatinine reflected a true change in GFR or could have an alternative explanation, such as an interaction with the tubular secretion of creatinine. The sponsor stated that cystatin C is accepted to be a better marker of GFR than creatinine because it is freely filtered by the glomeruli without proximal tubular secretion. Cystatin C was measured in subjects in the C215 trial at baseline, Week 2 and Week 24, and eGFR_{cyst} was calculated using the Larsson formula. The results of this analysis showed there was an increase in eGFR_{cyst} at Week 2 and at Week 24 in both treatment groups. This data led the sponsor to conclude that there was no rilpivirine induced nephrotoxicity.

Comment:

The use of cystatin C to measure GFR compared to the use of serum creatinine is still a matter of debate and research¹⁶. The advantage of cystatin C over creatinine is that creatinine can be affected by multiple other factors such as muscle mass, diet, gender and age. In addition, creatinine undergoes both renal glomerular filtration as well as tubular secretion, and some drugs (for example, cimetidine) have been known to lead to

¹⁶ Stevens LA, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis*. 2008; 51:395-406.

increased measured serum creatinine by inhibiting tubular secretion of creatinine. Cystatin C does not undergo tubular secretion and is freely filtered by the glomeruli.

The above results need to be studied further in the context of whether the pharmacokinetics of rilpivirine has suggested an effect on tubular secretion. Nonetheless, the maximum observed decrease in eGFR_{creat} was 10 mL/min/1.73m² from the baseline. This drop in GFR is not of clinical significance if the subjects had normal baseline GFR. In addition, the long term safety data showed that the GFR did not continue to drop, but returned back towards normal from Week 108 onwards.

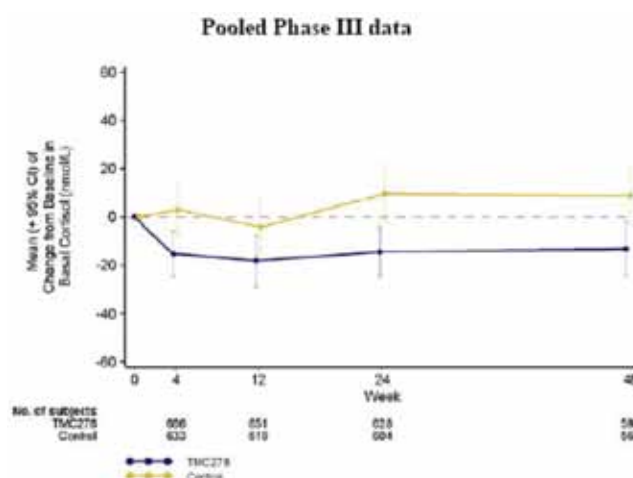
(ii) Adrenal function

- Phase III studies (C209 and C215): The concern with regards to adrenal toxicity was the potential inhibition of 17-hydroxylase and hence inhibition of steroidogenesis. Adrenal function tests done in the Phase III trials included the levels of basal cortisol, 17-OH-progesterone, aldosterone, androstenedione, DHEAS, progesterone and testosterone. In addition, an ACTH stimulation test was also performed at baseline and at Week 48. Inhibition of 17-hydroxylase would result in a decrease in basal cortisol, increases in 17-OH-progesterone and aldosterone, and an impaired ACTH stimulation test.

As presented in the earlier sections, endocrine events of interest were reported in a higher proportion of subjects in the pooled rilpivirine group than in the control (5.0% versus 3.8%). The main SOC under “Endocrine events of interest” with a higher proportion of subjects in the rilpivirine group than in the control group was *Investigations* (2.6% and 1.2 % respectively). Within this SOC, the main preferred term AE that had a higher proportion of subjects in the rilpivirine group than in the control group was “blood cortisol decreased” (2.2% (N = 15) and 1.0% (N = 7), respectively).

In the pooled data, there was a decrease from baseline in basal cortisol levels in the first four weeks of rilpivirine treatment. No notable change from baseline was observed in the control group (Figure 10). This drop in basal cortisol levels at Week 4 in the rilpivirine group was present in both studies C209 and C215. Later, at Week 48, the overall mean change from baseline in basal cortisol level showed a decrease of -13.1 nmol/L in the pooled rilpivirine group, and an increase of +9.0 nmol/L in the control group. This drop in basal cortisol level in the rilpivirine group at Week 48 was driven mainly by trial C215. In trial C209 at Week 48, there was no change from baseline in basal cortisol with rilpivirine and the change was +22.8nmol/L with control. In trial C215 at Week 48, the mean change from baseline in basal cortisol was -25.7 nmol/L with rilpivirine and -5.3 nmol/L with control.

Figure 10: Mean Change (\pm 95% CI) from basal cortisol (nmol/L) over time following treatment with rilpivirine (TMC278) or control (Phase III Week 48 pooled analysis).



In addition, in the pooled analysis, the mean increase in aldosterone at Week 48 was higher in the rilpivirine group than in the control group (+18.7 pmol/L and +6.9 pmol/L, respectively). However, the mean increases in the 17-OH progesterone levels at Week 48 in the rilpivirine group was less than that in the control group (+0.20 nmol/L and +0.4 nmol/L, respectively). Changes in the other parameters measured (androstenedione, DHEAS, progesterone and testosterone) were also inconclusive for inhibition of steroidogenesis.

In the ACTH stimulation test done at Week 48, the mean change from baseline in the maximum change in cortisol after ACTH stimulation was lower in the rilpivirine group ($+16.5 \pm 6.14$ nmol/L) than in the control group ($+58.1 \pm 6.66$ nmol/L). The incidence of a treatment emergent abnormal cortisol response to ACTH stimulation was higher in the rilpivirine group than the control group, both at Week 48 (3.9% with rilpivirine compared to 1.4% with control) as well as during the entire treatment period (5.9% with rilpivirine compared to 2.1% with control). The incidence of at least two consecutive abnormal cortisol responses (< 500 nmol/L) to ACTH stimulation was 1.7% in the rilpivirine group compared to none in the control group. This higher incidence of treatment emergent abnormal cortisol response to ACTH stimulation in the rilpivirine group than the control group was present in each individual study as well.

Phase IIb trial (C204): The adrenal parameters in the Phase IIb trial showed similar results to those in the two Phase III trials. There was a mean decrease in basal cortisol level in the rilpivirine groups (25 mg/day: -27nmol at Week 48, -28nmol at Week 96; 75 mg/day: -9nmol at Week 48, -15nmol at Week 96; 150 mg/day: -16nmol at Week 48, -26nmol at Week 96), which was more than that in the control group (+36nmol at Week 48, -7nmol at Week 96). There was no obvious dose relationship.

The incidence of abnormal ACTH test was higher in all three rilpivirine dose groups compared to control. There was no definite dose relationship, but the incidence of abnormal ACTH test was higher in the rilpivirine 75 mg/day and rilpivirine 150 mg/day groups compared to that in rilpivirine 25 mg/day group (Table 30).

Table 30: Abnormal cortisol response to ACTH stimulation following treatment with rilpivirine (TMC278) or control (Phase IIb trial C204).

Adrenal testing parameter Category, n (%)	TMC278 25 mg q.d. N = 93	TMC278 75 mg q.d. N = 95	TMC278 150 mg q.d. N = 91	All TMC278 N = 279	Control N = 89
Any abnormal ACTH test	12 (13.2)	20 (21.3)	20 (22.5)	52 (19.0)	6 (7.1)
< 450 nmol/L	4 (4.4)	12 (12.8)	8 (9.0)	24 (8.8)	5 (6.0)
450 to 500 nmol/L	8 (8.8)	8 (8.5)	12 (13.5)	28 (10.2)	1 (1.2)
At least 2 consecutive abnormal ACTH tests	N' = 91 2 (2.2)	N' = 94 6 (6.4)	N' = 89 7 (7.9)	N' = 274 15 (5.5)	N' = 84 2 (2.4)

N = number of subjects per treatment group; N' = number of subjects with data; n = number of observations

Note: Only treatment-emergent abnormalities are considered, i.e., where baseline cortisol response was ≥ 500 ng/mL (the cut-off for a normal response). Percentages are calculated relative to the number of subjects with on-treatment ACTH data.

In the Week 192 analysis, at Week 144, mean decreases from baseline for cortisol was similar in the combined rilpivirine and control groups (26 and 28 nmol/L, respectively).

Comments:

The results of the ACTH stimulation test in the Phase III and IIb trials suggested a possibility of adrenal suppression at Week 48. However, the number of subjects involved was small and this makes interpretation of the difference between the rilpivirine and control groups difficult. The decrease from baseline in basal cortisol levels in the rilpivirine group at Week 48 was more than that in the control group, in the Phase III as well as Phase IIb trials. However, the results of the other adrenal parameters (aldosterone, 17-OH progesterone, androstenedione, DHEAS, progesterone and testosterone) were inconclusive for inhibition of steroidogenesis. A look through the physical findings in the Phase III and IIb trials also showed that there were no clinical signs or symptoms suggestive of an adrenal or gonadal dysfunction in the subjects.

The sponsor had stated that a subgroup analysis was performed on the pooled Phase III data of the ACTH stimulation tests on subjects using ketoconazole or corticosteroids as concomitant medication. There were no subjects using ketoconazole concomitantly while an ACTH stimulation test was being performed in either treatment group in the Phase III trials. Eight subjects in the rilpivirine group and 6 subjects in the control group had an ACTH stimulation test while taking concomitant corticosteroids. One of the eight subjects in the rilpivirine group with an ACTH stimulation test while taking corticosteroids had an abnormal cortisol response to ACTH stimulation, compared to none of the six such subjects in the control group. While these subject numbers were too small to draw definite conclusions, this subgroup analysis suggested that the ACTH stimulation test results were unlikely to be due to the confounding effect of concomitant corticosteroids on the outcome of the ACTH stimulation test, or of drug interaction between rilpivirine and corticosteroids.

In the Week 192 analysis, the mean decreases from baseline for cortisol was similar in the combined rilpivirine and control groups at Week 144. However, no ACTH stimulation test was performed in the long term analysis.

Overall, the results for possible inhibition of steroidogenesis were inconclusive. While the results did not point to a definite inhibitory effect on steroidogenesis, they did not conclusively exclude the possibility. It is suggested that further clinical evaluation of this be carried out.

(iii) QT interval

The sponsor had stated that a TQT trial (C131) in healthy subjects on rilpivirine doses of 75 mg/day and 300 mg/day showed a dose and concentration dependent QT_c.

prolongation effect. The QT_c prolongation exceeded the ICH E14 threshold of clinical concern at both doses of rilpivirine. However, the results of another TQT trial (C152) showed that the change in QT_{cF} with the administration of rilpivirine 25 mg/day did not exceed the threshold as defined by ICH E14⁷.

Phase III trials (C209 and C215): There was an increase over time in the mean QT_{cF} interval in both treatment groups. The mean maximum change from baseline in QT_{cF} interval was similar between the pooled rilpivirine group (+17.9ms) and the pooled control group (+19.2 ms). The incidence of prolonged QT_{cF} interval (> 480 ms) was also similar between rilpivirine group (0.3%) and control group (0.2%). There were no QT_{cF} intervals greater than 500 ms. No AEs suggestive of ventricular tachyarrhythmia were reported in either Phase III trials.

Phase IIb trial (C204): The QT_{cF} changes with rilpivirine 25 mg/day in the Phase IIb trial were comparable to those of the Phase III trials, with an increase of about 6ms above baseline at Week 48. Mean change in QT_{cF} interval was maximal at Week 72 for rilpivirine 25 mg/day (+7.8ms). At Week 96, the increase in QT_{cF} appeared to have a dose relationship.

In the Phase IIb trial Week 192 analysis, both treatment groups had mean QT_{cF} interval increases from baseline to Week 48, remained stable up to Week 144, then showed a further increase from baseline at Week 192, when maximum mean increases from baseline of 16.4 ms and 14.4 ms were observed in the combined rilpivirine and control groups, respectively.

Comments:

The results of the QT_{cF} prolongation in HIV-1 infected subjects in the Phase III and IIb trials were consistent with those of the TQT studies involving healthy subjects. There was no clinically significant QT prolongation effect with rilpivirine 25 mg/day, but the results suggested a dose relationship with QT prolongation.

Resistance determination analysis

Phase III trials: At baseline, subjects in both treatment groups in trials C209 and C215 were characterised by the near absence of NNRTI resistance associated mutations (RAMs) due to the study inclusion and exclusion criteria.

The median time to virologic failure in the rilpivirine group was shorter than in the control group (113.5 versus 188 days, respectively). Overall, the proportion of subjects who met the definition of virologic failure adopted for the resistance analysis¹⁷ was larger in the pooled rilpivirine group than in the control group (10.5% and 5.7%, respectively). Among these virologic failures on rilpivirine, 62.9% developed treatment emergent NNRTI mutations, and 67.7% developed treatment emergent N(t)RTI mutations. In the control group, the corresponding proportions were 53.6% and 32.1%, respectively.

Among the 62 virologic failures in the pooled rilpivirine group, 31 (50.0%) lost susceptibility to rilpivirine. Among the 28 virologic failures in the pooled control (efavirenz) group, 12 (42.9%) lost susceptibility to efavirenz. Among the 31 rilpivirine

¹⁷ Virologic failure for resistance determination was defined differently than that for efficacy analysis. For resistance determination, virologic failure was defined as subjects who either (a) first achieved two consecutive viral load values < 50 copies/mL, followed by 2 consecutive viral load values of ≥ 50 copies/mL (also called a 'rebounder'); (b) first achieved two consecutive viral load values < 50 copies/mL and stopped treatment with a last observed viral load value on treatment of ≥ 50 copies/mL (also called a 'stopped treatment while not suppressed'); or (c) never achieved two consecutive viral load values of < 50 copies/mL and having an increase in viral load of at least 0.5 log₁₀ copies/mL above the nadir (also called a 'never suppressed').

virologic failures resistant to rilpivirine at failure, 27 (87.1%), 28 (90.3%) and 14 (45.2%) developed cross resistance to efavirenz, etravirine and nevirapine, respectively. Among the twelve control virologic failures resistant to efavirenz at failure, none developed cross resistance to rilpivirine or etravirine, but all twelve demonstrated cross resistance to nevirapine.

The frequency of resistance to 3TC/FTC used in the background regimen was approximately twice as high among rilpivirine virologic failures compared to control virologic failures. Resistance to FTC and 3TC was observed in 42 subjects (67.7%) and 41 subjects, (67.2%), respectively among the rilpivirine virologic failures, compared to 7 subjects, (25.0%) and 8 subjects (28.6%), respectively among the control virologic failures. However, more than 90.0% of the rilpivirine and control virologic failures retained susceptibility to TDF, ABC, and AZT at failure.

Phase IIb trial: The results of the resistance determination analysis in the Phase IIb trial were generally later supported by that of the Phase III trials. Consistent with the results later found in the Phase III trials, in the Week 192 analysis in the Phase IIb trial, virologic failures from the rilpivirine group with phenotypic resistance to rilpivirine were generally cross-resistant to ETR and efavirenz, and virologic failures from the control group with phenotypic resistance to efavirenz retained sensitivity to ETR and rilpivirine.

Safety in special populations

No pivotal studies were done to investigate the safety of rilpivirine in special populations. A small single dose Phase I trial (C130) was conducted to compare the short term safety and tolerability of rilpivirine dose in 8 subjects with mild hepatic impairment (Child-Pugh A) and 8 subjects with moderate hepatic impairment (Child-Pugh B) to that of 16 healthy matched control subjects with normal hepatic function. All 32 subjects were without HIV-1 infection. All 32 subjects received rilpivirine 25 mg/day for eleven days. There were no major clinical safety concerns that had arisen from this study, but the number of subjects involved was too small for clinical interpretation.

Safety related to drug-drug interactions and other interactions

Drug interaction studies conducted for rilpivirine were Phase I studies involving clinical pharmacological endpoints and analyses (PK/PD).

Evaluator's overall conclusions on clinical safety

Overall, the safety profile of rilpivirine in terms of commonly occurring AEs was comparable across the Phase III and IIb trials (Table 31). Across the Phase III and IIb trials, the most commonly occurring AEs by SOC were *Infections and infestations* and *Gastrointestinal disorders*. By preferred term, they were nausea and headache.

Table 31: Summary of adverse effects (AEs) across Phase III and IIB trials of rilpivirine.

AEs (%)	Pooled Phase III trials (C209 and C215)	Phase IIB (C204): Week 96 analysis (combined rilpivirine group)	Phase IIB (C204): Week 192 analysis (combined rilpivirine group)
Any AEs	89.8%	93.2%	95%
Commonest AEs by SOC	- infections and infestations (58.6%) - gastrointestinal disorders (40.2%)	- infections and infestations (62.4%) - gastrointestinal disorders (51.6%)	- infections and infestations (68.5%) - gastrointestinal disorders (61.3%)
Commonest AEs by preferred term	- headache (13.8%) - nausea (13.4%) - diarrhoea (11.4%) - nasopharyngitis (10.1%)	- nausea (33.3%) - upper respiratory tract infection (18.3%) - headache (17.2%)	- nausea (35.8%) - headache (20.8%) - upper respiratory tract infection (15.8%)
Commonest treatment related AEs with severity grade of at least 2, by preferred term	- insomnia (1.7%) - headache (1.6%) - abnormal dreams (1.0%)	- nausea (3.2%) - ALT increased (5.4%)	- nausea (3.2%) - ALT increased (5.4%)

There were no adverse events that stood out as a particular concern with rilpivirine 25 mg/day. In the statistical tests comparing rilpivirine and control in the incidence of AEs reported in more than 10% of subjects (by preferred term, using the Fisher's Exact test), statistically significant differences in favour of rilpivirine were found for dizziness, abnormal dreams/nightmare, and rash. No statistically significant differences were found in favour of control for the AEs tested.

There were no particular safety concerns with regards to the incidence of deaths or SAEs. Overall, five deaths occurred in subjects on rilpivirine across all trials from Phase I to Phase III: four in the Phase IIB trial (C204) and one in the Phase III trial (C215). All involved HIV-1 infected patients. None of the AEs leading to the deaths were judged to be related to rilpivirine. No deaths occurred in healthy non HIV1-infected subjects who had taken at least one dose of rilpivirine. No obvious concerns stood out in the evaluation of incidence of SAEs across the trials. In the two Phase III registration trials, the proportion of subjects reporting at least one SAE was not higher in the pooled rilpivirine group (6.6%) than in the control group (8.1%). In these two Phase III trials, the proportion of subjects reporting at least one treatment related SAE was similar between the pooled rilpivirine group (1.0%) and the control group (0.9%).

In the long term safety analysis, there was no increase in the incidence of any AEs or any treatment related AEs with time beyond 48 weeks to 192 weeks. Continued exposure to rilpivirine beyond 96 weeks to 192 weeks was also not associated with increased incidence of SAEs, with the incidence of SAEs being the highest in the first 48 weeks, and then dropped beyond 48 weeks. Overall in the long term safety analysis, the incidence of SAEs between the rilpivirine group and the control group was comparable (15.8% versus 16.9%; combined rilpivirine group versus control group), and was consistent with the result in the dose finding part of the Phase IIB trials, and in the two Phase III trials.

In terms of safety dose relationships, there appeared to be a dose relationship with the grouped AE term of “rash” under skin events of interest. However the number involved was small making interpretation difficult, and the overall incidence of this AE in the pooled rilpivirine group (9.3%) was lower than that in the control group (21.3%). In addition, the safety results also suggested a dose relationship with QT prolongation, although there was no clinically significant QT prolongation effect with rilpivirine 25 mg/day. These results of the QT_{cf} prolongation in HIV-1 infected subjects in the Phase III and IIb trials were consistent with those of the TQT studies involving healthy subjects.

The results for possible inhibition of steroidogenesis were inconclusive. While the results did not point to a definite effect on steroidogenesis, they did not conclusively exclude the possibility. It is suggested that further clinical evaluation of this be carried out.

Resistance analysis results showed that rilpivirine had a resistance profile that appeared to be somewhat worse than that of the control efavirenz. The median time to virologic failure in the rilpivirine group was shorter than that in the control group. The proportion of subjects who met the definition of virologic failure adopted for the resistance analysis was also larger in the rilpivirine group than in the control group (10.5% and 5.7%, respectively). Among the virologic failures on rilpivirine, approximately twice the proportion of subjects (67.7%) developed treatment emergent N(t)RTI mutations compared to those in the control virologic failure group (32.1%). In addition, among virologic failures on rilpivirine, 87.1% and 90.3% developed cross resistance to efavirenz and etravirine (ETR), respectively. In contrast, among the control virologic failures resistant to efavirenz at failure, none were cross-resistant to rilpivirine and ETR. However, among virologic failures on rilpivirine, 45.2% demonstrated cross-resistance to nevirapine, compared to 100% of the virologic failures on the control. The frequency of resistance to 3TC/FTC used in the background regimen was approximately twice as high among rilpivirine virologic failures compared to control virologic failures. However, more than 90.0% of both the rilpivirine and control virologic failures retained susceptibility to TDF (tenofovir disoproxil fumarate), ABC (abacavir), and AZT (zidovudine) at failure.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Pharmacokinetics

- (i) Are there any PK studies with severe hepatic impairment or better powered studies mild/moderate impairment?
- (ii) In patients with hepatitis C infection are there any studies on the potential interaction with interferon treatment?
- (iii) Does rilpivirine interfere with the PK of commonly administered benzodiazepine/non benzodiazepine sedative hypnotic agents either at a PK or PD level?
- (iv) Some *in vitro* studies on the potential interaction with antidepressants are not included in the PI. Are there clinical interaction studies and what might be expected across the range of antidepressant medications? Similarly antipsychotic medications may be used in this population for HIV induced mania. What are the interaction potentials with this class of medications (particularly atypical antipsychotics)?

Pharmacodynamics

- (i) The issue of the minimum effective dose in HIV-1 populations needs to be clarified. Are there dose- response trials in patients at doses lower than 25 mg/day? Is there a

corresponding dose response (or plasma concentration) relationship to the decrease in viral load from baseline in these studies?

- (ii) What is the explanation for the reasonably good dose/plasma concentration relationship and antiviral effect measured *ex vivo* yet there is no apparent relationship when determined *in vivo*?
- (iii) With respect to hypnotic sedative agents including alcohol, what is the potential for interference with psychomotor/cognitive function if taken with rilpivirine?

Efficacy

- (i) The dose range explored in the Phase IIb trials (rilpivirine 25 mg/day to rilpivirine 150 mg/day) did not show any efficacy dose relationship and failed to elicit the minimum clinically efficacious dose. There is no clinical information regarding whether a lower dose of rilpivirine would have been more appropriate as a therapeutic dose.

On the other hand, the safety results suggested that the therapeutic margin of rilpivirine for clinically significant QT prolongation by ICH E14 definition is not wide. TQT studies involving healthy subjects showed there was clinically significant QT prolongation by ICH E14 definition for rilpivirine 75 mg, but not for rilpivirine 25 mg, and that there was a dose and concentration dependent QT_c prolongation effect. The safety results from the Phase III studies supported the presence of a dose relationship for QT prolongation effect in HIV-1 infected subjects. Pharmacokinetics analysis showed that steady state administration of 75 mg/day of rilpivirine resulted in a mean C_{max} of only approximately 2.6 fold higher than the mean steady state C_{max} observed with the 25 mg/day dose of rilpivirine.

Overall, the benefit-risk profile of rilpivirine may be improved if a lower therapeutic dose was found to be as efficacious, and would be able to widen the therapeutic margin for QT prolongation.

- (ii) What other clinical data was there that would support the selection of rilpivirine 25 mg/day as the therapeutic dose instead of a lower dose?

Safety

Clinical safety results suggested a dose relationship with QT prolongation, although there was no clinically significant QT prolongation effect with rilpivirine 25 mg/day. TQT studies involving healthy subjects showed there was clinically significant QT prolongation by ICH E14 definition for rilpivirine 300 mg and rilpivirine 75 mg but not for rilpivirine 25 mg. However, no information was available with regards to doses between 25 mg and 75 mg. If an intermediate dose of rilpivirine (*for example*, 50 mg) is likely to lead to clinically significant QT prolongation, this would narrow the therapeutic margin and would be clinically relevant in view of drug interactions or overdose, and would affect the benefit-risk profile of rilpivirine.

What is the therapeutic margin for clinically significant QT prolongation with the use of rilpivirine?

Clinical Summary and Conclusions

Clinical aspects

Pharmacokinetics

Rilpivirine is orally bioavailable with the maximum plasma concentrations achieved about 4 hours after the dose. Absorption rate is not influenced by the dose. In healthy subjects, systemic exposure after tablet formulations increases dose proportionally across a dose range of 25 to 150 mg/day. In HIV-1 infected subjects, a less than dose proportional

increase was observed. Exposure under fasting conditions is ~40% lower than fed conditions. It is recommended that the drug be given with a meal to ensure optimal absorption and exposure. The inter-individual variability of PK parameters is generally low or moderate, and independent of the dose administered. The mean terminal elimination half life is approximately 45 to 50 hours. On average the drug is highly protein bound (~99.7%), mainly to albumin. Rilpivirine is predominantly excreted in faeces (85.1%). There is negligible renal excretion. The exposure to rilpivirine was generally lower in HIV-1 infected subjects than in healthy subjects. There is no clinically relevant effect of intrinsic factors (age, gender, race, body weight, estimated glomerular filtration rate [eGFR], and hepatitis B and/or C co-infection status) on the PK of rilpivirine.

With respect to the PK data in special populations, it might be useful to stress that the lack of effects in elderly sample populations and between race and genders are derived from population PK and not from studies specifically designed to investigate these factors. Further, the numbers of elderly patients included in the population PK is relatively limited and differences may be obscured because of the lack of sufficient sample size.

No dose adjustment is needed in subjects with mild or moderate hepatic impairment. The effect of severe hepatic impairment on rilpivirine exposure was not studied. An important caveat for the hepatic impairment study is the larger PK effect for mild compared to moderate impairment. This is clearly counterintuitive: the opposite might have been expected. This probably reflects inter subject variability due to small sample sizes rather than any clinically relevant difference. Further studies would be required to more fully investigate the effects of hepatic impairment on the PK of rilpivirine. The PI should be more circumspect with recommendations in moderate hepatic impairment.

Oral bioavailability decreases with increasing intragastric pH. Drugs that alter intragastric pH should not be co-administered with rilpivirine. If the combination of medications is clinically indicated, then alternative dosing regimens should be considered, for example, administration of rilpivirine 12 hours after a H2-antagonist. Only famotidine was investigated not other H2-antagonists so recommendations about separation of doses in the PI are only based on this drug. Larger (or smaller effects) may apply with other H2-antagonists while presumably the effect is dose dependent.

Cytochrome P450 (CYP)3A enzymes have a predominant role in the metabolism of the drug. At a dose of 25 mg/day rilpivirine does not have a clinically relevant effect on the exposure to co-administered drugs. Mild induction of CYP3A and CYP2C19 is observed at higher doses but is unlikely to be of clinical importance at the recommended dose of 25 mg/day. Exposure to rilpivirine is increased by inhibition of CYP3A enzyme activity; however, drug-drug interaction trials showed the effect to be relatively modest and the two can be co-administered without dose adjustments. Rilpivirine exposure is decreased by induction of CYP3A enzyme activity and CYP3A inducers should not be co-administered.

Pharmacodynamics

Rilpivirine is a NNRTI with apparent effects against the HIV-1 virus. It shows additive antiviral activity in combination with a number of N(t)RTIs. After single doses of rilpivirine administered in healthy volunteers, the *ex vivo* activity showed a linear correlation with plasma concentrations of the drug. Similarly, after repeated doses in healthy volunteers, the *ex vivo* antiviral activity appeared to increase with plasma concentration. The magnitude of increase was similar to that of the C_{max} and AUC_{24h} levels in plasma. These *ex vivo* studies in healthy subjects stand in sharp contrast to the *in vivo* results obtained in patients with HIV-1 infection. Doses of 25 mg/day of rilpivirine in HIV-1 infected patients were effective in reducing viral load. Higher doses did not appear to be

any more effective than 25 mg/day (based on determination of plasma viral load expressed in HIV-1 RNA copies/mL or immunologic changes determined by changes in CD4+ and CD8+ counts).

The minimum effective dose of rilpivirine has not been established by these studies. The differences observed in apparent effectiveness against the virus for volunteers and patient studies may be due to intrinsic differences in testing *ex vivo* versus *in vivo*, that is, the cell culture system used for *ex vivo* testing may not adequately reflect the *in vivo* situation. Other factors such as the nature of the populations studied (patients versus controls) may also be important. Nonetheless, in HIV-1 patient populations 25 mg/day has been shown to be effective in reducing viral load either alone or in concert with other antiretroviral treatments. This is despite the fact the systemic exposure in HIV-1 infected patients appears to be lower than in controls. Further data are necessary to better establish the dose response effect in the patient population and to explore whether lower doses (less than 25 mg/day) may be effective. From the data presented it would appear that increases in doses above 50 mg/day are not associated with any significant further decrease in viral load than 25 mg/day. At the recommended dose of 25 mg/day, rilpivirine is not associated with a clinically relevant effect on QT_c. When higher doses (75 mg/day and 300 mg/day) of rilpivirine were studied in healthy adults, clinically significant differences in QT_{cF} interval were noted.

In the PI it should be noted that when administered with potent CYP3A4 inhibitors, rilpivirine might achieve plasma concentrations seen after these higher doses, thereby leading to QT_c prolongation.

Clinical efficacy

Dose-response studies: The dose range explored in the Phase IIb trials (rilpivirine 25 mg/day to 150 mg/day) did not show any efficacy dose relationship. The dose range explored failed to elicit the minimum clinically efficacious dose, and there is no clinical information regarding whether a lower dose of rilpivirine would have been more appropriate as a therapeutic dose. The Phase III studies were conducted using the dose of rilpivirine 25 mg/day. While the results from the Phase III trials supported the claim of non inferiority of rilpivirine 25 mg/day compared with efavirenz 600 mg/day, there remains the question of whether a lower dose of rilpivirine would have given the same non inferiority results with a better safety profile.

Main clinical studies: Overall, in the Phase III registration trials, the conclusion from the primary efficacy analysis that there was non inferiority in the virologic efficacy of rilpivirine 25 mg/day compared with efavirenz 600 mg/day was appropriate.

The study designs of both Phase III registration trials were sound, and utilised primary endpoints that were in agreement with current HIV research guidelines and recommendations. The study design involving a positive control instead of a placebo is appropriate in HIV trials as placebo-controlled trials are not considered ethical in the HIV-1 infected patient population. The use of the study drug or control with a background regimen of N(t)RTIs is appropriate as the current guideline and recommendation for initiating treatment in treatment-naïve HIV-1 infected patients is the combined use of at least three antiretroviral drugs due to the high mutation rate of the HIV causing issues with resistance. The proposed indication of rilpivirine is for use in combination with other antiretroviral drugs, and hence testing it together with other antiretroviral drug combinations that are likely to be used in clinical settings is appropriate. The combinations of ABC with 3TC, AZT with 3TC, and TDF with FTC, are approved N(t)RTI regimens for first-line use together with other antiretroviral drugs. The choice of positive

control drug efavirenz is in agreement with current treatment guidelines on the use of efavirenz and two N(t)RTIs as a first-line treatment regimen for HIV-1 infected patients.

The definition of virologic response in the primary endpoint and the use of the TLOVR algorithm are consistent with current HIV treatment and research guidelines. The choice of a non-inferiority design over a superiority design as a primary objective is in line with current HIV drug development trends, where trials are designed to demonstrate that a new treatment is not worse in efficacy than the current standard antiretroviral drugs. The benefit of the new treatment being investigated may be simplified dosing regimen or a better safety profile, rather than better efficacy than the current standard antiretroviral drugs. The use of the non-inferiority margin of 12% is consistent with current ICH guidelines for HIV drug development, which suggest a margin ranging from 10% to 12%.

Overall, the primary endpoint analysis demonstrated non inferiority of rilpivirine 25 mg/day compared with efavirenz 600 mg/day at the set non inferiority margins of -12% and -10%, in both studies individually as well as in the pooled analysis. The additional analyses using the “snapshot” approach and the different imputation methods generally supported the results of the primary endpoint analysis.

However, the results from Study C209 were not as robust as those from Study C215. When the non VF censored analysis was applied to Study C209, non inferiority at -12% and -10% was not demonstrated. The non VF censored analysis excluded subjects who were treatment failures for reasons other than VF (for example, subjects who were discontinued due to AEs).

Clinical safety

Patient exposure: Overall, the amount of exposure to the drug is adequate to evaluate the safety profile of the drug. In the two Phase III trials, 611 HIV1-infected patients were exposed to rilpivirine for 48 to 96 weeks. Longer term safety profile was derived from the extended period of Phase IIb trial C204, where subjects were exposed to rilpivirine beyond 96 weeks.

Adverse events: Overall, the safety profile of rilpivirine in terms of commonly occurring AEs was comparable across the Phase III and IIb trials. Across the Phase III and IIb trials, the most commonly occurring AEs by SOC were *Infections and infestations* and *Gastrointestinal disorders*. By preferred term, they were nausea and headache.

There were no adverse events that stood out as a particular concern with rilpivirine 25 mg/day. In the statistical tests comparing rilpivirine and control in the incidence of AEs reported in more than 10% of subjects (by preferred term, using the Fisher’s Exact test), statistically significant differences in favour of rilpivirine was found for dizziness, abnormal dreams/nightmares, and rash. No statistically significant differences were found in favour of control for the AEs tested.

In the long term safety analysis, there was no increase in the incidence of any AEs or any treatment related AEs with time from between 48 to 192 weeks. In addition, the most commonly occurring AEs and treatment related AEs were comparable between the Week 48 analysis and the Week 192 analysis, suggesting that use of rilpivirine from between 48 to 192 weeks had not been found to be associated with new or increasing AEs.

In terms of safety dose relationships, there appeared to be a dose relationship with the grouped AE term of “rash” under skin events of interest. However the number involved was small, making interpretation difficult. The overall incidence of this AE in the pooled rilpivirine group (9.3%) was lower than that in the control group (21.3%).

Serious adverse events and deaths: There were no obvious concerns detected with regards to the incidence of deaths or SAEs with rilpivirine. Overall, five deaths occurred in subjects on rilpivirine across all trials from Phase I to Phase III: four in the Phase IIb trial (C204) and one in the Phase III trial C215. All involved HIV-1 infected patients. None of the AEs leading to the deaths were judged to be related to rilpivirine. No deaths occurred in healthy non HIV1-infected subjects who had taken at least one dose of rilpivirine.

No obvious concerns stood out in the evaluation of incidence of SAEs across the trials. In the two Phase III registration trials, the proportion of subjects reporting at least one SAE was not higher in the pooled rilpivirine group (6.6%) than in the control group (8.1%). In these two Phase III trials, the proportion of subjects reporting at least one treatment related SAE was similar between the pooled rilpivirine group (1.0%) and the control group (0.9%).

In the dose finding Phase IIb study, there was no obvious dose relationship in the incidence of SAEs and of treatment related SAEs from doses of rilpivirine 25 mg/day to rilpivirine 150 mg/day. Consistent with the finding in the Phase III trials, the overall incidence of subjects with at least one SAE in the Week 96 analysis was not higher in the combined rilpivirine group (12.2%) than in the control group (14.6%). In the Week 96 analysis of the Phase II trial, there were five subjects (1.8%) across the three rilpivirine dose groups who reported treatment related SAEs compared with only one subject in the control group (1.1%). However, the treatment related SAEs did not show any particular concentration within a particular preferred term AE.

The long term safety analysis (Week 192 analysis of the Phase IIb trial) showed that the continued exposure to rilpivirine from between 96 to 192 weeks was not associated with increased incidence of SAEs, with the incidence of SAEs being the highest in the first 48 weeks, and then dropped beyond 48 weeks. Overall in the Week 192 analysis, the incidence of SAEs between the rilpivirine group and the control group was comparable (15.8% in the combined rilpivirine group versus 16.9% in the control group), and was consistent with the result in the dose finding part of the Phase IIb trials, and in the two Phase III trials.

Laboratory findings: The results of the ACTH stimulation test in the Phase III and IIb trials suggested a possibility of adrenal suppression at Week 48. However, the number of subjects involved was small and this makes interpretation of the difference between the rilpivirine and control groups difficult. The decrease from baseline in basal cortisol levels in the rilpivirine group at Week 48 was more than that in the control group, in the Phase III as well as Phase IIb trials. However, the results of the other adrenal parameters (aldosterone, 17-OH progesterone, androstenedione, DHEAS, progesterone and testosterone) were inconclusive for inhibition of steroidogenesis. A look through the physical findings in the Phase III and IIb trials also showed that there were no clinical signs or symptoms suggestive of an adrenal or gonadal dysfunction in the subjects.

In the Week 192 analysis, the mean decreases from baseline for cortisol was similar in the combined rilpivirine and control groups at Week 144. However, no ACTH stimulation test was performed in the long term analysis.

Overall, the results for possible inhibition of steroidogenesis were inconclusive. While the results did not point to a definite effect on steroidogenesis, they did not conclusively exclude the possibility. It is suggested that further clinical evaluation of this be carried out.

Safety results also suggested a dose relationship with QT prolongation, although there was no clinically significant QT prolongation effect with rilpivirine 25 mg/day. These results of the QT_{CF} prolongation in HIV-1 infected subjects in the Phase III and IIb trials were consistent with those of the TQT studies involving healthy subjects. TQT studies involving

healthy subjects showed there was clinically significant QT prolongation by ICH E14 definition for rilpivirine 300 mg and rilpivirine 75 mg but not for rilpivirine 25 mg. However, no information was available for doses between 25 mg and 75 mg. The sponsor has stated that pharmacokinetics analysis showed that steady state administration of 75 mg/day and 300 mg/day of rilpivirine resulted in a mean C_{max} of approximately 2.6 fold and 6.7 fold, respectively, higher than the mean steady state C_{max} observed with the 25 mg/day dose of rilpivirine. This result suggested that the therapeutic margin of rilpivirine for clinically significant QT prolongation by ICH E14⁸ definition is not wide. This would have significance in terms of drug interactions and overdose.

Resistance analysis results showed that rilpivirine had a resistance profile that appeared to be somewhat worse than that of the control efavirenz. Subjects on rilpivirine had a shorter median time to virologic failure than those in the control group. Approximately twice the proportion of subjects on rilpivirine developed VF compared to those in the control group. Among these virologic failures on rilpivirine, approximately twice the proportion of subjects developed treatment emergent N(t)RTI resistance mutations compared to those in the control VF group. In addition, among the VFs on rilpivirine, 87.1% and 90.3% developed cross resistance to efavirenz and etravirine (ETR), respectively. In contrast, among the control VFs resistant to efavirenz at failure, none were cross resistant to rilpivirine and ETR. The frequency of resistance to 3TC/FTC used in the background regimen was also approximately twice as high among rilpivirine VFs compared to the control VFs.

Benefit risk assessment

Benefits

Clinical efficacy data for rilpivirine was based on the 48 week data in 1368 treatment naïve HIV-1 infected adult patients from the 2 Phase III trials (C209 [N = 690] and C215 [N = 678]). In the two Phase III trials, the primary objective was to demonstrate non inferiority of treatment with rilpivirine 25 mg/day compared to the control efavirenz 600 mg/day with regards to the primary endpoint, which was the proportion of subjects with virologic response at 48 weeks. Virologic response was defined as a viral load of < 50 HIV-1 copies/mL, according to the TLOVR algorithm. In both studies, the primary objective has a set maximum allowable non inferiority margin of 12%, while a margin of 10% was set as a secondary objective. As the study design for the two studies were identical apart from the background antiretroviral regimen used, a pooled analysis of the data from the two studies was done, and was appropriate.

Results showed that demographic characteristics and baseline diseases characteristics were similar between the two studies, and between the two treatment groups in each study and in the pooled analysis. Primary endpoint analysis showed that the proportion of subjects with virologic response (< 50 copies/mL, TLOVR) was similar between the pooled rilpivirine and control groups (84.3% and 82.3%, respectively). Using normal approximation of binomial distribution, the difference in virologic response [95% CI] between the pooled rilpivirine and control groups was 2.0 [-2.0; 6.0]. Using logistic regression, the difference [95% CI] in virologic response at Week 48 between the pooled rilpivirine and control groups was predicted to be 1.6 [-2.2; 5.3]. The lower limits of the 95% CI of the difference between the treatment groups in both methods of statistical analysis were above the set non inferiority margins of -12% and -10%. Additional analyses using the “snapshot” approach and the different imputation methods generally supported the results of the primary endpoint analysis.

The study designs of both Phase III registration trials were sound, and utilised primary endpoints that were in agreement with current HIV research guidelines and

recommendations. The use of the non inferiority margin of 12% is consistent with current ICH guidelines for HIV drug development, which suggest a margin ranging from 10% to 12%. Overall, the primary endpoint analysis demonstrated non-inferiority of rilpivirine 25 mg/day compared with efavirenz 600 mg/day at the set non-inferiority margins of -12% and -10%.

The choice of a non inferiority design as a primary objective is in line with current HIV drug development trends. The long term rationale of conducting a non inferiority trial for a new treatment is that the new treatment is not less efficacious than the pre existing drugs, but may have other benefits over currently available drugs such as a better safety profile, a more convenient dosing regimen, or lower costs. However, this means that in the case of rilpivirine, while the sponsor has demonstrated non inferiority of efficacy compared to efavirenz 600 mg/day, the safety profile has a significant weight in the relative benefit risk assessment.

Risks

Clinical safety data for rilpivirine was based on the Week 48 data in 1368 treatment naïve HIV-1 infected adult patients from the two Phase III trials (C209 [N = 690] and C215 [N = 678]). This safety data was supplemented by that from a Phase IIb trial (C204 [N = 368]), which had an initial dose finding part (Week 96 analysis) that provided dose safety relationship data. This study had an extended part with an additional analysis at Week 192 that provided the long -term safety profile of rilpivirine beyond 96 weeks.

Across the Phase III and IIb trials, the most commonly occurring AEs by SOC were *Infections and infestations* and *Gastrointestinal disorders*. By preferred term, they were nausea and headache. The proportion of subjects in the pooled Phase III trials that reported at least one AE was similar between the rilpivirine and control groups (89.8% and 92.2%, respectively). The proportion of subjects in the Phase IIb trials (Week 96 analysis) that reported at least one AE was also similar between the pooled rilpivirine group and the control group (93.2% and 93.3%, respectively). In the pooled safety analysis of the two Phase III trials, statistical tests comparing rilpivirine and control in the incidence of AEs reported in more than 10% of subjects (by preferred term, using the Fisher's Exact test) showed statistically significant differences in favour of rilpivirine for dizziness, abnormal dreams/nightmares and rash. No statistically significant differences were found in favour of the control (efavirenz) for the AEs tested.

Overall, five deaths occurred in subjects on rilpivirine across all trials from Phase I to Phase III: four in the Phase IIb trial (C204) and one in the Phase III trial C215. All involved HIV-1 infected patients. None of the AEs leading to the deaths were judged to be related to rilpivirine. No deaths occurred in healthy non HIV1-infected subjects who had taken at least one dose of rilpivirine. In the two Phase III registration trials, the proportion of subjects reporting at least 1 SAE was lower in the pooled rilpivirine group (6.6%) than in the control group (8.1%). In these two Phase III trials, the proportion of subjects reporting at least one treatment related SAE was similar between the pooled rilpivirine group (1.0%) and the control group (0.9%).

In terms of safety dose relationship analysis in the Phase IIb trial, there appeared to be a dose relationship with the grouped AE term of "rash" under skin events of interest. However the number involved was small, making interpretation difficult, and the overall incidence of this AE in the pooled rilpivirine group (9.3%) was lower than that in the control group (21.3%). In addition, the safety results also suggested a dose relationship with QT prolongation, although there was no clinically significant QT prolongation effect with rilpivirine 25 mg/day. These results of the QT_{cf} prolongation in HIV-1 infected subjects in the Phase III and IIb trials were consistent with those of the TQT studies

involving healthy subjects, which showed clinically significant QT prolongation effect with rilpivirine 75 mg and 300 mg, but not with rilpivirine 25 mg.

The dose range explored in the Phase IIb trials (rilpivirine 25 mg/day to rilpivirine 150 mg/day) did not show any efficacy dose relationship and failed to elicit the minimum clinically efficacious dose. This is of significance in evaluating the safety dose relationship, especially with regards to the effect of rilpivirine on QT interval prolongation. PK analysis showed that steady state administration of 75 mg/day of rilpivirine resulted in a mean C_{max} of only approximately 2.6 fold higher than the mean steady state C_{max} observed with the 25 mg/day dose of rilpivirine, suggesting that the therapeutic margin of rilpivirine for clinically significant QT prolongation by ICH E14 definition is not wide. There is no clinical information regarding whether a lower dose of rilpivirine would have been more appropriate as a therapeutic dose and which would be able to widen the therapeutic margin for QT prolongation.

In the long term safety analysis in the Phase IIb trial, there was no increase in the incidence of any AEs or any treatment related AEs with time beyond 48 weeks to 192 weeks. Continued exposure to rilpivirine beyond 96 weeks to 192 weeks was also not associated with increased incidence of SAEs.

With regards to laboratory safety findings in the two Phase III trials, the results for possible inhibition of steroidogenesis were inconclusive. The results of the ACTH stimulation test in the Phase III and IIb trials suggested a possibility of adrenal suppression at Week 48. However, the number of subjects involved was small and this makes interpretation of the difference between the rilpivirine and control groups difficult. The decrease from baseline in basal cortisol levels in the rilpivirine group at Week 48 was more than that in the control group, in the Phase III as well as Phase IIb trials. However, the results of the other adrenal parameters (aldosterone, 17-OH progesterone, androstenedione, DHEAS, progesterone and testosterone) were inconclusive for inhibition of steroidogenesis. Overall, while the results did not point to a definite effect on steroidogenesis, they did not conclusively exclude the possibility.

Resistance analysis results in the pooled Phase III trials showed that the median time to VF in the rilpivirine group was shorter than that in the control group. The proportion of subjects who met the definition of VF adopted for the resistance analysis was also larger in the rilpivirine group than in the control group (10.5% and 5.7%, respectively). Among the virologic failures on rilpivirine, approximately twice the proportion of subjects (67.7%) developed treatment emergent N(t)RTI mutations compared to those in the control VF group (32.1%). In addition, among VFs on rilpivirine, 87.1% and 90.3% developed cross resistance to efavirenz and etravirine, respectively. In contrast, among the control virologic failures resistant to efavirenz at failure, none were cross resistant to rilpivirine and ETR. The frequency of resistance to 3TC/FTC used in the background regimen was approximately twice as high among rilpivirine virologic failures compared to control VFs. However, more than 90.0% of both the rilpivirine and control VFs retained susceptibility to TDF, ABC, and AZT at failure.

Overall, the safety profile of rilpivirine 25 mg/day is comparable to that of efavirenz 600 mg/day. The key safety concern is the dose relationship with QT prolongation and the resistance profile.

Safety specifications

“No nonclinical potential safety concerns that have not been adequately addressed by clinical data were identified.”

Nonclinical potential safety concerns included a potential inhibitory effect of rilpivirine on adrenal steroidogenesis. The clinical safety results for possible inhibition of steroidogenesis were inconclusive, and did not adequately address this concern.

“The impact of drug-drug interactions that increase the exposure to rilpivirine (based on C_{max}) by no more than 85% (1.85-fold) is not expected to be of clinical relevance or cause safety concerns, and does therefore not result in the need for dose adjustment”

There was insufficient clinical data available with regards to the effect of rilpivirine on QT prolongation to make the above statement. Clinical safety results suggested a dose relationship with QT prolongation in HIV-1 infected subjects and healthy subjects. TQT studies involving healthy subjects showed there was clinically significant QT prolongation by ICH E14 definition for rilpivirine 300 mg and rilpivirine 75 mg but not for rilpivirine 25 mg. The sponsor has stated that pharmacokinetics analysis showed that steady state administration of 75 mg/day of rilpivirine resulted in a mean C_{max} of only approximately 2.6 fold higher than the mean steady state C_{max} observed with the 25 mg/day dose of rilpivirine. No information was available with regards to doses between 25 mg and 75 mg, and hence there was no clinical information available for the effect on QT prolongation of a C_{max} of 1.85 fold higher than that observed with the 25 mg/day dose of rilpivirine.

“Additional safety data will be collected and evaluated through routine pharmacovigilance activities and from ongoing and future planned clinical trials.”

It is recommended that it be specified that an intermediate dose between rilpivirine 25 mg and 75 mg will be tested with regards to effect on clinically significant QT interval prolongation, in order to better define the therapeutic margin.

Balance

Evaluation of the benefit risk balance of rilpivirine showed that rilpivirine has a benefit risk profile comparable with efavirenz. In the treatment of HIV-1 infected patients in combination with other antiretroviral drugs, rilpivirine 25 mg/day led to approximately 80% of patients achieving virologic levels of < 50 HIV-1 copies/mL. When benchmarked against commonly used antiretroviral drug efavirenz 600 mg/day, this proportion of virologic response of rilpivirine 25 mg/day was not inferior to efavirenz.

The safety profile showed that there were no major safety concerns and was comparable to that of efavirenz. The therapeutic margin for QT interval prolongation was not wide, but this safety issue is monitorable, and can be managed with appropriate information in the PI regarding care in drug interactions and use of ECG monitoring in cases of drug overdose. The therapeutic margin can also be more clearly defined in other clinical trials post-registration. The resistance profile also showed that among virologic failures on rilpivirine, 87.1% and 90.3% developed cross resistance to efavirenz and etravirine, respectively. This means that in clinical practice, virologic failure to a rilpivirine containing regimen can result in the loss of treatment options in other drug classes of the antiretroviral regimen. However, this development of cross resistance to other antiretroviral drugs is a concern with all antiretroviral drugs.

The presence of different RAMs decreases the susceptibility to different antiretroviral drugs. Most antiretroviral treatment guidelines recommend testing a patients' drug susceptibility via the detection of RAMs in order to guide the selection of a first line combination antiretroviral treatment. In the resistance determination analysis done for rilpivirine, ten RAMs were identified as potential determinants of decreased susceptibility to rilpivirine. Other RAMs are associated with reduced susceptibility to other antiretroviral

drugs. With a benefit risk balance that is comparable with efavirenz, a recognised reference antiretroviral drug for treatment of HIV-1 infection, rilpivirine has a role as an additional treatment option for HIV-1 infected treatment-naïve adult patients, where the patients may have RAMs that would decrease the susceptibility to another antiretroviral drug. It is unclear if it would offer other nonclinical benefits over existing antiretrovirals, such as lower costs, which would tip the benefit-risk balance in its favour when compared to other antiretrovirals.

Overall, the benefit risk balance of rilpivirine 25 mg is positive, and meets the EMEA guideline on the clinical development of medicinal products for the treatment of HIV infection, which recommended that a “convincingly demonstrated non-inferior benefit-risk at 48 weeks versus a well recognised reference product may serve as a basis for approval”¹⁸.

Conclusions

It is recommended that the application for registration of rilpivirine 25 mg for the proposed indication of treatment of HIV-1 infection in antiretroviral treatment naïve adult patients in combination with other antiretroviral medicinal products, be approved, subject to a satisfactory response to the list of questions and comments in this evaluation report.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA’s Office of Product Review (OPR).

Safety Specification

There are no Important identified risks specified by the sponsor. The Important potential risks and Missing information are tabulated in Table 32.

Table 32: Important identified and potential risks and missing information for rilpivirine.

Important identified risks	None
Important potential risks	<ul style="list-style-type: none"> • QT prolongation • Hepatotoxicity • Severe skin reactions • Depression • Development of drug resistance
Important missing information	<ul style="list-style-type: none"> • Children and adolescents (under age of 18 years) • Pregnant or breastfeeding women • Elderly (65 years and above): limited information is available • Patients with severe hepatic impairment (Child-Pugh score C)

¹⁸ European Medicines Agency. Guideline on the clinical development of medicinal products for the treatment of HIV infection. 20 Nov 2008.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003460.pdf
 (accessed 4 April 2011)

OPR reviewer comment:

Pursuant to the evaluation of the clinical aspects of the safety specifications, inhibition of steroidogenesis should be added to the Ongoing Safety Concerns as an Important potential risk, unless adequate contrary justification can be provided by the sponsor. This conclusion is based on the clinical evaluator's assessment that the results from the clinical trials for possible inhibition of steroidogenesis were inconclusive. This conclusion is based on the following evidence:

- The results of the adrenocorticotrophic hormone (ACTH) stimulation test in the Phase III and IIb trials suggested a possibility of adrenal suppression at Week 48. It was acknowledged that the number of subjects involved was small. The decrease from baseline in basal cortisol levels in the rilpivirine group was more than that in the control group; however, the results of the other adrenal parameters (aldosterone, 17-OH progesterone, androstenedione, DHEAS, progesterone and testosterone) were inconclusive for inhibition of steroidogenesis.
- In the Week 192 analysis, Week 144 mean decreases from baseline for cortisol were similar in the combined rilpivirine and control groups. However, no ACTH stimulation test was performed in the long-term analysis.

While adrenal insufficiency is known to be a complication of HIV infection, the aetiology can include medications (for example, ketoconazole, withdrawal of chronic corticosteroid use). Undiagnosed, adrenal insufficiency is associated with significant morbidity and is potentially fatal. It was therefore recommended that the sponsor put in place an adequate Pharmacovigilance (PhV) action plan to further evaluate and characterise whether patients treated with rilpivirine are at greater risk of adrenal suppression. The RMP (or the Australian specific annex) should be updated to reflect this.

As there have been no pivotal studies to investigate rilpivirine in patients with mild-moderate hepatic impairment and there are limitations on the clinical relevance of the results from the C130 trial, it is recommended that the use of rilpivirine in patients with mild to moderate hepatic impairment be included as important missing information, unless the sponsor can provide adequate justification why this is not required.

Subject to the evaluation of the nonclinical safety specifications, the remaining Ongoing Safety Concerns as specified by the sponsor were considered acceptable.

Pharmacovigilance Plan

For the all important potential risks, the sponsor proposes routine PhV¹⁹ and the additional collection and evaluation of safety data from the ongoing and future planned trials. The sponsor intends to present an analysis of the respective important potential risks in each periodic safety update report (PSUR). Annex 3 provides a synopsis of the ongoing and completed clinical trial program. There are three clinical trials that are identified as ongoing and planned trials on efficacy and safety:

¹⁹ Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

1. TMC278-TiDP6-C209 (ECHO)

- A Phase III randomised controlled and double blinded study of rilpivirine versus efavirenz 600 mg once daily in combination with a fixed background regimen consisting of tenofovir disoproxil fumarate and emtricitabine in antiretroviral naïve HIV-1 infected subjects.
- Primary objective: to demonstrate non inferiority to treatment with rilpivirine compared to efavirenz in regard to the proportion of virologic responders.
- Secondary objectives include safety and tolerability analyses.
- Duration 96 weeks. Week 48 primary analysis provided to support this application.
- 690 subjects entered the study and were randomised.
- Milestone for completion and reporting of final safety analysis not provided.

2. TMC278-TiDP6-C215 (THRIVE)

- A Phase III randomised, controlled and double blinded study of rilpivirine versus efavirenz 600 mg once daily in combination with a fixed background regimen consisting of two N(t)RTIs in antiretroviral naïve HIV-1 infected subjects.
- Primary objective: to demonstrate non inferiority to treatment with rilpivirine compared to efavirenz in regard to the proportion of virologic responders.
- Secondary objectives include safety and tolerability analyses.
- Duration 96 weeks. Week 48 primary analysis provided to support this application.
- 678 subjects entered the study and were randomised.
- Milestone for completion and reporting of final safety analysis not provided.

3. TMC278-C204

- A Phase IIb randomised, partially blinded, active controlled study.
- This study had an initial dose-finding part (Week 96 analysis) with an optional open label trial extension up to 240 weeks to assess the long term safety profile of rilpivirine.
- Rilpivirine was administered to treatment naïve, HIV-1 infected subjects at doses of 25 to 150 mg/d.
- 368 subjects enrolled: The intent to treat population was 279 subjects. A total of 278 subjects received 825 person years exposure to rilpivirine.
- Stated as ongoing in annex 3 but no milestone for reporting of the final safety analysis is provided.

No postmarketing trials are proposed as part of the PhV plan although rilpivirine-related pregnancy data from spontaneous reporting will be submitted to the US Antiretroviral Pregnancy Registry (APR). The sponsor states that the Registry will provide a 6 monthly report, which will be discussed in the PSUR.

The sponsor also describes the Highly Active Antiretroviral Therapy Oversight Committee (HAART-OC). The HAART-OC was formed in May 1999 in response to the European Medicines Agency's (EMA) request to evaluate the incidence and prevalence of long-term

complications, as well as to characterise the short-term effects of body composition and metabolic abnormalities that have occurred with concurrent use of HAART. The attention of the EMA and the work of the HAART-OC initially focused on cardiovascular risk. Subsequently, in June 2004, the EMA tasked the HAART-OC with a further directive to obtain information from observational databases on hepatic safety. A third directive from the EMA requested evaluation of the association between ART and non AIDS defining malignancies, chronic/end stage renal disease, nonfatal liver disease and all cause mortality. Participating cohorts include, the Data Collection on AEs of Anti-HIV Drugs (D:A:D) which is a prospective multi cohort study of HIV-infected persons under active follow up.

OPR evaluator's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

Background rate estimates provided by the sponsor for the important potential risks are summarised in Table 33. While the baseline incidence in HIV patients for these safety concerns is not well known, it is possible that the ongoing Phase III trials (C209 and C215) can detect increases in events above the background rate. These studies are less likely to inform the risk of serious skin reactions such as Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) which are rare events (rate in the general population is around 1 to 2 cases per million person years).

In the context of the clinical evaluation report and the clinical evaluator's assessment of the safety specifications section of the RMP, it is recommended that the therapeutic margin with respect to QT_c prolongation is further characterised. Routine PhV measures would not be sufficient to clarify this potential risk. It is therefore recommended that additional PhV activities be proposed by the sponsor that will adequately examine this issue. Specifically, an intermediate dosed of rilpivirine between 25 and 75 mg should be tested with regards to clinically significant QT interval prolongation, in order to better define the therapeutic margin.

With regard to the important potential risks, including the development of drug resistance, the sponsor was requested to provide Week 96 analysis of safety and resistance data from the ongoing Phase III trials (TMC278-C209 and TMC278-C215) in the 1st PSUR. If the final analysis is not expected to be available for reporting at this time, the sponsor should provide an alternate milestone for reporting.

With regard to the potential risk of adrenal suppression it is recommended that unless the sponsor can provide adequate justification, a PhV action plan should be implemented to evaluate and characterise whether patients treated with rilpivirine are at a greater risk of adrenal suppression. An analysis of Week 96 results from Phase III studies (TMC278-C209 and TMC278-C215) may be sufficient if ACTH stimulation testing, or at least cortisol and other adrenal parameter readings, were taken after the Week 48 analysis.

With regard to limited data on the safety of rilpivirine in subjects with hepatic impairment, it is recommended that the sponsor propose appropriate PhV activities that will adequately inform this safety concern; for example, a sufficiently powered pharmacokinetic study of rilpivirine in subjects with mild to moderate hepatic impairment.

The milestones for reporting from the ongoing and planned clinical trials, that will inform the Ongoing Safety Concerns, should be provided and included in an updated RMP (or amended Australian specific annex).

Table 33: Epidemiology of important potential risks in the background population unexposed to rilpivirine.

QT prolongation	<p><u>Incidence</u></p> <p>Unknown</p> <p><u>Prevalence</u></p> <p>The prevalence of QT interval prolongation in a cohort of asymptomatic HIV positive patients who were not taking any drug known to cause QT interval prolongation was estimated to be 28%.²⁰</p>
Hepatotoxicity	<p><u>Incidence</u></p> <p>In a retrospective cohort study of 560 treatment-naïve patients receiving HAART therapy for the first time, 44 (7.9%) developed Grade 4 liver enzyme elevations (LEE); and 95 (17%) developed Grade 3+4 LEE. Symptoms occurred in less than 20% of the patients with Grade 4 abnormalities</p>
Severe skin reactions	<p><u>Incidence</u></p> <p>Patients with AIDS have up to 1000-fold higher risk of developing SJS and TEN. Commonly caused by trimethoprim-sulfamethoxazole (TMP-SMX). TMP-SMX-related TEN in AIDS patients is 980 per 1 million. NVP is the ARV most frequently associated with SJS/TEN²¹</p>
Depression	<p><u>Prevalence</u></p> <p>Estimates of the prevalence of depression among HIV infected patients range from 0% to 47.8%. It has been estimated that HIV-infected individuals are twice as likely to be diagnosed with major depression compared to sero-negative patients.²²</p>
Drug resistance	<p><u>Prevalence</u></p> <p>An analysis using sequence data from VARHS (Variant, Atypical, and Resistant HIV Surveillance) of study data showed transmitted drug resistance associated mutation (TDRM) occurred in 14.6% of patients. TDRM associated with NNRTI occurred in 7.8%, in 5.6% for NRTI, and 4.5% for protease inhibitors.²³</p>

A search of the ClinicalTrials.gov website for rilpivirine studies was undertaken by the evaluator (search criteria: rilpivirine; Phase II/III/IV trials; sponsored by industry; safety outcome measure). This identified an additional clinical trial that could not be found in the RMP or annex 3. The NCT ID is NCT01266902, also identified as TMC278-TiDP6-C222:

- A Phase III open label trial of rilpivirine in HIV-1 infected patients.
- Number enrolled: 720. Possibly still recruiting.
- Estimated completion in March 2015.

²⁰ Sani MU, Okeahialam BN. QTc interval prolongation in patients with HIV and AIDS. *J. Nat. Med. Assoc.* 2005; 12:1657-1661.

²¹ Khambaty MM, Hsu SS. Dermatology of the patient with HIV. *Emerg. Med. Clin. North Am.* 2010; 28:355-368.

²² Chander G, Himelhoch S, Moore RD. Substance abuse and psychiatric disorders in HIV-positive patients: epidemiology and impact on antiretroviral therapy. *Drugs* 2006; 66:769-789.

²³ Gazzard BG, on behalf of the BHIVA Treatment Guidelines Writing Group British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy. *HIV Medicine* 2008; 9:563-608.

- Safety outcome measures include the incidence of AEs considered at least possible related to rilpivirine; serious AEs; AEs leading to discontinuation; any division of AIDS Severity Grade 3/4 rash; HIV RNA levels; CD4+ cell count.

The sponsor should clarify whether this study is intended to inform the PhV plan and if so identify what safety concerns will be addressed in the study. The study protocol, or a synopsis if the study has already commenced, should be provided for review.

It is recommended that the sponsor provide clarifying information with regard to the HAART-OC and participating cohorts to include but not necessarily restricted to:

- Whether it is anticipated that patients treated with rilpivirine will be included in any HAART study cohorts and if so will Australian patients be included?
- How this will inform the ongoing safety concerns?
- How will any outcomes, once available to the sponsor, be reported to the TGA and what are the anticipated milestones for reporting?

While the APR is presumably only open to patients in the US, the sponsor should clarify whether Australian data can be included in the Registry.

Finally, the FDA post marketing requirement of a drug interaction study (steady state rilpivirine and single dose digoxin pharmacokinetics) should be included in the RMP (or the Australian specific annex) with milestones for reporting identified.

Risk Minimisation Activities

The sponsor has concluded that routine risk minimisation, by way of the product information document, is sufficient to manage the important potential risks and important missing information.

OPR evaluator comment:

At this stage this evaluation of the need for risk minimisation activities was considered acceptable, subject to any additional safety concerns identified in the nonclinical evaluation.

Summary of Recommendations

The following is a summary of the recommendations made to the Delegate. It is suggested that the sponsor update the RMP with respect to the recommended amendments and additional activities, or include these in an updated Australian annex to the RMP. If the sponsor does not accept any of the particular recommendations, adequate justification should be provided. It was recommended that if any additional safety concerns are raised by the nonclinical evaluator the sponsor address these in the RMP.

1. Safety specifications – Clinical

- With regard to the clinical evaluators assessment of this section of the RMP, the sponsor should amend the safety specifications section relating to:
 - Possible inhibition of steroidogenesis.
 - C_{max} and QT prolongation.

1. Summary – Ongoing Safety Concerns

- Adrenal suppression should be included as a potential risk that requires further characterisation.

- Safety in patients with mild to moderate hepatic impairment should be included as important missing information.

2. Pharmacovigilance plan

- For the potential risk of QT prolongation, additional pharmacovigilance should be implemented by the sponsor to test intermediate doses of rilpivirine between 25 and 75 mg with regard to clinically significant QT prolongation in order to better define the therapeutic margin.
- For the potential risk of developing drug resistance, Week 96 analysis of safety and resistance data from the ongoing Phase III trials (C209 and C215) should be provided, preferably in the 1st PSUR.
- For the recommended inclusion of the potential risk of adrenal suppression, a pharmacovigilance action plan should be implemented to further evaluate whether patients treated with rilpivirine are at greater risk of adrenal suppression.
- For the recommended inclusion of missing information on the safety in patients with mild to moderate hepatic impairment, a pharmacovigilance action plan should be implemented to further inform this safety concern
- The RMP should be updated with milestones for reporting analyses from the ongoing and planned clinical trials that are intended to inform the ongoing safety concerns.
- The sponsor should clarify whether the clinical trial TMC278-TiDP6-C222 (ClinicalTrials.gov) is intended to inform the PhV plan and if so identify what safety concerns will be addressed in the study. The study protocol, or a synopsis if the study has already commenced, should be provided for review.
- With regard to the HAART-OC, the sponsor should provide clarifying information as to whether patients treated with rilpivirine are anticipated to be included in any HAART cohort studies, how this would inform the safety concerns and anticipated milestones for reporting.
- The sponsor should clarify whether Australian patients can be included in the APR.
- Provide a milestone for reporting results from the FDA postmarket requirement for a drug interaction study (single dose digoxin pharmacokinetics).

3. Potential for medication errors

- An assessment of the potential for medication errors should be provided by the sponsor taking into consideration drug, labelling, physician and patient related factors.

4. Risk minimisation plan

- Updates to the proposed PI and CMI as outlined by the RMP evaluator.
- Justification should be provided why dosage adjustment is not required in patients with mild to moderate hepatic impairment.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Rilpivirine hydrochloride is an E-isomer. It contains no chiral centre but cis/trans isomerism is possible. The drug substance is micronised and particle size limits are applied. The tablets are film coated manufactured by wet granulation followed by compression. A shelf life of two years below 30°C is proposed.

The Medicines Toxicology Evaluation Section has cleared the limits proposed for two specified impurities in the API. A third impurity is potentially genotoxic. The applicable Threshold of Toxicological Concern (TTC) is 60ppm. The sponsor has proposed controlling this impurity in the intermediate rather than in the final API. The sponsor has agreed to test one batch of API per year for the presence of the impurity as part of stability testing program.

In addition, the abovementioned impurity has been shown to form in small amounts during storage of the API or the finished product. Available data indicate that the level of this impurity remains at least an order of magnitude below the TTC of 60 ppm. Based on these data, test for this impurity is not included in the finished product release or expiry specifications. The final specifications have been mutually agreed.

The application was considered at the 138th meeting of the PSC. The sponsor has been asked to provide a commitment that stability studies on finished product produced at the second manufacturing site, one of the two sites for which data were not presented, will be conducted.

There are no outstanding objections with respect to Chemistry/Quality/Manufacture.

Nonclinical

Rilpivirine is a non competitive non nucleoside reverse transcriptase inhibitor (NRTI) of HIV-1 reverse transcriptase. *In vitro* antiviral activity against laboratory strains of wild type HIV-1 was demonstrated in an acutely infected T cell line.

The major route of metabolism in animals, as in humans, was aromatic hydroxylation at the pyrimidyl moiety followed by glucuronidation. Overall the human profile of metabolites was reflected in animal species with no unique human metabolites. A large number of metabolites were detected.

Absolute bioavailability of 39% was reported in animal studies. The main route of elimination of rilpivirine and its metabolites was faecal predominantly in unchanged form. *In vitro* data show that rilpivirine is predominantly metabolised by CYP3A.

Repeat dose toxicity studies were performed in mice (3 months), rats (6 months), dogs (12 months) and monkeys (8 weeks) using oral route. AUC_{0-24h} exposure ratios (animal/human) were relatively low in rats and monkey but were high in mice and dogs.

Rilpivirine inhibited cortisol & corticosterone synthesis in animal species resulting in histological changes as well as changes in basal and post ACTH stimulation levels of these steroids.

Gonadal effects seen in mice & dogs were likely secondary to adrenal effects. In mice, ovarian function was suppressed. In dogs, female genital tract and mammary glands appeared to be activated and rilpivirine may have led to earlier sexual maturation in females. Increased ovarian weight and dilation of mammary gland ducts was observed in

dogs at exposures ≥ 7 times clinical AUC, with evidence of ovarian activation at ≥ 11 times clinical AUC. Immature female cynomolgus monkeys did not show early sexual maturation at exposures comparable to clinical AUC. Male dogs showed evidence of mild testicular damage, consisting of increase in atrophic tubuli and reduced spermatogenesis at exposure ratios ≥ 11 , and Leydig cell hyperplasia & hypertrophy at exposure ratios ≥ 28 , with no impact on Sertoli cell functioning or spermatogenesis. There were no effects on the male gonads in mice or rats.

Hepatic effects of rilpivirine in rats and mice, at relative exposures ≥ 10 & 100 respectively, included increased hepatic weight and histopathological changes including (in mice) peroxisome proliferation. The effects were in keeping with the induction of liver enzymes, including increased activities of ALP, AST and ALT. In dogs, relative exposures ≥ 10 were associated with increases in serum cholesterol and total bilirubin, and histopathological changes indicative of cholestasis with no evidence of enzyme induction.

In dogs, renal toxicity included a trend towards increased serum creatinine concentration, corticomedullary mineralisation in females, and acute interstitial nephritis in two males at exposure ratio ≥ 10 .

Thyroid and pituitary effects in rats were related to hepatic uridine 5'-diphospho-glucuronosyltransferase (UDP-GT) induction leading to an increased clearance of thyroid hormones and subsequently increased release and synthesis of thyroid stimulating hormone (TSH) by the pituitary gland at exposure ratio ≥ 11 times clinical AUC. Follicular cell hypertrophy was also observed in female cynomolgus monkeys at 1-2 times the human clinical exposure level.

Rilpivirine was not genotoxic in a standard battery of genotoxicity tests, including reverse mutation studies in bacterial strains or forward mutation in mammalian cells *in vitro*, or chromosomal aberrations in mice *in vivo*.

In carcinogenicity (two years) studies conducted in rats and mice, there was an increased incidence of hepatocellular adenoma and carcinoma associated with rilpivirine at all dose levels at relative exposures 20 in mice and 3 in rats compared to clinical AUC. Rats also exhibited an increased incidence of thyroid adenoma and carcinoma at relative exposures ≥ 4 . These are considered species specific effects and not relevant to human species.

There was no apparent effect of rilpivirine on fertility in male or female rats. Placental transfer of rilpivirine was demonstrated in rats. It was also secreted in milk of lactating dams in this species. Rilpivirine was not teratogenic but a dose related increased incidence of dilated renal pelvis was observed in rats with a NOAEL at exposure levels 15 times clinical AUC. In the rabbit embryofetal toxicity study, there were increased incidences of foetuses exhibiting hypoplastic interparietal bone and branching of the left subclavian artery originating from the aorta (NOAEL at 71 times clinical AUC).

Rilpivirine did not show evidence indicative of potential phototoxicity, skin irritation, delayed-type hypersensitivity or immunotoxicity and was classed as a moderate eye irritant.

The mechanism underlying the QT prolongation seen in clinical trials was not explained in the nonclinical data which included consideration of pharmacokinetic and metabolic data.

Overall there were no objections on nonclinical grounds to the registration of rilpivirine as proposed. The proposed pregnancy classification is B1.

Clinical

Pharmacokinetics

Absolute bioavailability could not be determined due to lack of intravenous formulation as the drug is insoluble in aqueous media over the physiological pH range.

Study C145 showed that the AUC of tablet is 75% of an oral solution of the drug in macrogol when both were given with food.

Food effect was evaluated in Study C102 using 100 mg tablet under fed & fasted states and indicated comparative C_{max} 171.3% (90% CI: 129.2, 227.0), AUC 144.5% (90% CI: 124.1, 168.2).

Food effect was also evaluated in Study C137 using 75 mg tablet given with standard breakfast, high fat, high protein drink or fasting. These results are shown in Table 34.

Table 34: Effect of food on pharmacokinetic parameters following rilpivirine (TMC278) (trial C137).

<i>Parameter</i>	<i>Fasted v Ref</i>	<i>High fat v Ref</i>	<i>Protein rich drink v Ref</i>
C_{max}	54.45 (42.92 - 69.07)	92.20 (80.97 - 105.0)	50.17 (39.66 - 63.46)
AUC _(0-last)	57.27 (45.72 - 71.75)	92.21 (79.81 - 106.5)	50.25 (41.36 - 61.05)
AUC _(0-∞)	59.02 (46.87 - 74.32)	90.94 (78.52 - 105.3)	50.55 (41.50 - 61.56)

The results were consistent with the previous Study C102 whereby administering rilpivirine with food increases the bioavailability by about 50%.

The formulation effect was evaluated in Study C145 using 25 mg commercial table under fed state and oral solution under fed and fasting states. In the absence of absolute bioavailability study, this study provides best estimate of bioavailability of the oral tablet relative to oral solution. Note the tablet was not administered under fasting conditions but this is considered acceptable given the food effect and the recommendation that the table be taken with meals. These results are shown in Table 35.

Table 35: Effect of formulation effect on pharmacokinetic parameters following rilpivirine (TMC278) (trial C145).

<i>Parameter</i>	<i>Oral sol fed v Tab fed</i>	<i>Oral sol fasted v Tab fed</i>	<i>Oral sol fasted v Oral sol fed</i>
C_{max}	122.6 (102.8 - 146.3)	169.7 (153.3 - 187.8)	131.6 (119.2 - 145.3)
AUC _(0-last)	138.7 (118.9 - 161.7)	129.5 (114.7 - 146.3)	92.94 (86.71 - 99.61)
AUC _(0-∞)	129.8 (111.5 - 151.1)	125.6 (110.9 - 142.1)	92.72 (85.74 - 100.3)

The drug is 99.7% protein (albumin) bound in plasma.

Following oral administration, 85% radioactivity was recovered in faeces at 7 days (168 h) with unchanged rilpivirine accounting for 25% radioactivity in faeces. Rilpivirine is mainly metabolised by CYP3A4 enzyme and by CYP2C19, CYP1A2 & CYP2C8/9/10 to a lesser and variable extent. More than 15 metabolites of rilpivirine have been detected of which the most abundant (16%) originates from aromatic hydroxylation of pyrimidinyl moiety.

Rilpivirine has linear kinetics in the dose range 25 to 200 mg as determined in the study CDE103. The single dose PK parameters are shown in Table 36.

Table 36: Single dose pharmacokinetic parameters following rilpivirine (TMC278) (trial CDE103).

Parameters	50 mg	100 mg	200 mg	300 mg
T _{max} h	4 (4.2-6)	4 (4-6)	4 (4-6)	4 (4-4)
C _{max} ng/ml	226 ± 15	482 ± 121	807 ± 207	944 ± 172
AUC ₍₀₋₁₄₄₎ ng.h/ml	6118 ± 1558	13013 ± 4039	25600 ± 5621	27910 ± 7298
AUC _(0-∞) ng.h/ml	6584 ± 1881	15820 ± 4568	28669 ± 6876	32794 ± 10352
t _{1/2} h	34.2 ± 12.0	54.6 ± 17.9	43.1 ± 13.1	52.0 ± 17.2

The steady state PK parameters based on the Study C103 are shown in Table 37.

Table 37: Steady state pharmacokinetic parameters following rilpivirine (TMC278) (trial C103).

Parameter	25 mg/day	50 mg/day	100 mg/day	150 mg/day
Day 1				
C _{max} , ng/mL	90.08 ± 44.28	138.2 ± 63.10	397.6 ± 147.3	523.8 ± 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 ± 585.6	1551 ± 596.0	4464 ± 1520	5608 ± 1902
Day 14				
C ₀ , ng/mL	89.85 ± 38.07	157.9 ± 52.23	347.8 ± 148.7	504.9 ± 174.6
C _{min} , ng/mL	66.85 ± 29.53	115.7 ± 49.30	249.5 ± 90.51	362.0 ± 130.9
C _{max} , ng/mL	203.8 ± 75.81	298.6 ± 98.05	685.5 ± 202.4	1019 ± 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 ± 868.8	4139 ± 1236	9278 ± 2846	13581 ± 3195
t _{1/2} , h	50.92 ± 19.56	48.75 ± 16.34	46.07 ± 15.44	44.83 ± 12.31
Accumulation Ratio	3.020 ± 1.966	2.880 ± 0.7982	2.071 ± 0.7491	2.503 ± 0.7211

Overall, the PK parameters estimated in HIV patients (solution formulation in studies C201/C202; Phase II formulation in Study C204 & Phase III formulation in studies C209/C215) were similar to the above in healthy volunteers except somewhat lower AUCs in HIV population. This latter effect may be due to altered gastric pH or concomitant medications in this population.

Special population pharmacokinetics included a multiple dose study in mild and moderate hepatic impairment. These findings are shown in Table 38.

Table 38: Multiple dose study in mild and moderate hepatic impairment following rilpivirine (TMC278).

Pharmacokinetics of TMC278 (mean \pm SD, t_{max} : median [range])	Panel A		Panel B	
	Healthy (reference)	Mild Hepatic Impairment (test)	Healthy (reference)	Moderate Hepatic Impairment (test)
n	8	8 ^b	8	8 ^d
Day 1				
C_{max} , ng/mL	81.73 \pm 20.01	90.29 \pm 31.96	62.99 \pm 22.31	44.43 \pm 17.69
t_{max} , h	4.0 (3.0 - 9.0)	4.5 (2.0 - 5.0)	5.0 (3.0 - 5.0)	5.0 (2.0 - 22.0)
AUC_{24h} , ng.h/mL	890.2 \pm 169.0	1071 \pm 266.3	726.9 \pm 214.0	569.6 \pm 227.5
Day 9				
C_{0h} , ng/mL	64.04 \pm 18.79	126.8 \pm 46.17	79.68 \pm 24.35	98.31 \pm 24.73
Day 10				
C_{0h} , ng/mL	69.08 \pm 25.75	126.3 \pm 49.95	86.26 \pm 16.08	118.9 \pm 53.73
Day 11				
C_{0h} , ng/mL	77.56 \pm 22.12	137.8 \pm 62.25	81.83 \pm 17.81	122.2 \pm 51.53
C_{min} , ng/mL	65.65 \pm 18.58	84.13 \pm 20.72	67.31 \pm 14.88	76.55 \pm 26.24
C_{24h} , ng/mL	82.09 \pm 20.87	147.1 \pm 50.20	88.75 \pm 23.56	121.7 \pm 62.22
C_{max} , ng/mL	144.3 \pm 35.70	187.0 \pm 66.31	146.8 \pm 30.21	143.5 \pm 49.69
t_{max} , h	5.0 (3.0 - 12.0)	5.0 (2.0 - 24.0)	5.0 (3.0 - 5.0)	20.0 (2.0 - 24.0)
AUC_{24h} , ng.h/mL	2152 \pm 538.1	3206 \pm 1080	2318 \pm 385.9	2525 \pm 851.2
$t_{1/2term}$, h	60.59 \pm 20.03	80.82 ^c \pm 33.17 ^c	56.01 \pm 21.31	90.56 ^c \pm 37.04 ^c
$C_{ss,av}$, ng/mL	89.68 \pm 22.42	133.6 \pm 45.00	96.58 \pm 16.08	105.2 \pm 35.47
FI, %	89.91 \pm 29.74	74.40 \pm 22.04	83.63 \pm 30.34	65.26 \pm 13.20

AUC_{24h} = area under the plasma concentration-time curve over 24 hours, C_{0h} = predose plasma concentration, C_{24h} = plasma concentration after 24 hours, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, $C_{ss,av}$ = average steady-state plasma concentration over 24 hours, FI = fluctuation index, SD = standard deviation, t_{max} = time to maximum plasma concentration, $t_{1/2term}$ = terminal elimination half-life.

^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 $t_{1/2term}$

There was discordance between the results for mild & moderately impaired groups (steady state C_{max} and AUC nearly 50% & 30% higher respectively in mild impairment compared to negligible effect in moderate impairment) on account of small sample size and individual patient variability.

Population PK

Three analyses were conducted on separate datasets. First, based on 48 weeks data from various studies, the plasma concentration time profiles were somewhat lower (81% with 75 mg and 70% with 150 mg dose) in patients compared to healthy volunteers. Less than dose proportional exposures were observed in patients between 25-150 mg per day. Apparent oral clearance was 10.5 L/h. Second, based on 96 weeks data, the population PK values were similar to the previous analysis. Third, another population analysis was based on patients and healthy volunteers in studies C209, C215 and C152 who had all received commercial 25 mg formulation. The exposure to rilpivirine in HIV patients was 40% lower than healthy volunteers. The apparent oral clearance was 11.8 L/h. No covariates were found to be clinically significant in any analyses.

Drug interactions

For *in vitro* studies please see the CER. A total seventeen clinical drug interaction studies were provided. Most were performed with the 150 mg dose which was the highest dose studied in the dose finding trial C204.

Interaction studies with nucleoside or nucleotide RTIs (NRTIs) included: Tenofovir (Study C104): The rilpivirine PK parameters were comparable when given alone or on coadministration with tenofovir whereas the mean tenofovir C_{max} and AUC_{24h} were about 1.2 fold higher on coadministration with rilpivirine compared to administration alone.

Didanosine (Study C106): No clinical relevant changes were observed in PK of either drug during coadministration compared to administration alone.

Interaction studies with boosted Protease Inhibitors included lopinavir/ritonavir (Study C105): The mean C_{min} , C_{max} & AUC_{24h} of rilpivirine were increased by 74%, 29% and 52% respectively on coadministration. Rilpivirine did not significantly affect PK of lopinavir/ritonavir. Darunavir/ritonavir (Study C112): The mean C_{min} , C_{max} & AUC_{24h} of rilpivirine were increased by 178%, 79% and 130% respectively on coadministration. Rilpivirine did not significantly affect PK of darunavir/ritonavir.

Interaction studies with multiple ARTs included: Study C101 in which patients were on current antiretroviral treatment with at least two nucleoside reverse transcriptase inhibitors (NRTIs) and efavirenz or nevirapine (non NRTIs). Both groups received a single oral dose of 50 mg rilpivirine. The mean PK parameters for rilpivirine in the nevirapine group were comparable to PK parameters when administered alone in healthy subjects. The mean PK parameters of rilpivirine in the efavirenz group showed decrease in C_{max} and AUC_{∞} of 29% and 71% respectively compared to PK of rilpivirine alone in healthy subjects.

Interaction studies with other medicines included: Rifampin (rifampicin) (Study C108): The mean C_{min} , C_{max} , and AUC_{24h} of rilpivirine decreased by 89%, 69% & 80% respectively on coadministration with rifampicin. There was no effect on PK of rifampicin. Rifabutin (Study C125): The mean C_{min} , C_{max} and AUC_{24h} of rilpivirine were decreased by 49%, 35% and 46%, respectively on coadministration with rifabutin. There was no effect on PK of rifabutin. Ketoconazole (Study C127): The mean C_{min} , C_{max} & AUC_{24h} of rilpivirine were increased by 76%, 30% and 49% respectively on coadministration. The mean C_{min} and AUC_{24h} of ketoconazole were reduced by 66% and 24% respectively on coadministration whereas C_{max} was not affected. Sildenafil (Study C123): The PK of rilpivirine were comparable when taken alone or with sildenafil. There was no effect of rilpivirine on single dose PK of sildenafil. Atorvastatin (Study C116): The PK of rilpivirine were comparable with or without atorvastatin. The mean C_{max} of atorvastatin was increased by 1.35 fold and AUC_{24h} of total HMG-CoA reductase activity (sum of atorvastatin & active metabolites) was increased by 1.2 fold on coadministration with rilpivirine. Oral Contraceptive Pill (studies C136 & C120): The mean exposure (AUC) to norethindrone was decreased by 41% on coadministration with rilpivirine (150 mg/day). The C_{max} of ethinylestradiol was increased by 17% on coadministration with rilpivirine (25 mg/day). Methadone (Study C121): The mean C_{min} , C_{max} , and AUC_{24h} of R-methadone decreased by 22%, 14%, and 16% respectively on coadministration. The mean AUC_{24h} ratio of S/R methadone remained comparable. The mean C_{min} , C_{max} and AUC_{24h} of S-methadone decreased by 21%, 13% and 16%, respectively. Omeprazole (Study C114): The mean PK parameters for rilpivirine were significantly decreased when administered with single or multiple doses of omeprazole (C_{max} 40-58% & AUC 40-56%). Paracetamol (Study C109): The PK parameters of rilpivirine were comparable when taken with or without paracetamol. There was no effect on single dose PK of paracetamol. Chlorzoxazone (Study C139): The mean rilpivirine was increased by 1.25 fold after a single dose of chlorzoxazone. The mean exposures to chlorzoxazone and its metabolite were unaffected by a single dose or multiple doses of rilpivirine. Famotidine (Study C140): When rilpivirine was administered 2 hours after famotidine, the mean C_{max} and AUC_{∞} were decreased by 85% and 76%, respectively, compared to administration of rilpivirine alone. When rilpivirine was administered 4 h before famotidine, the mean C_{max} and AUC_{∞} were increased 21% and 13%, respectively, compared to administration alone. When rilpivirine was administered 12 h after famotidine, the mean AUC_{∞} was only slightly affected.

Pharmacodynamics

Please see the Clinical Evaluation Report for details. Only QT studies are noted here. The effect of rilpivirine on QT prolongation was evaluated in healthy volunteers in two Thorough QT (TQT) studies C131 & C152.

The Study C131 employed rilpivirine 75 mg and 300 mg/day doses. After a single dose, the UL of 90% CIs of the placebo corrected difference in QT_{cf} interval was below 10ms at all time points. At steady state (Day 11), the 90% CIs for 75 mg breached the 10ms threshold with a peak at 16 h (+10.7ms; 90% CI 6.1, 15.3). For 300 mg at steady state, the peak effect occurred at 4.5 h (+23.3ms; 90% CI 18.1, 28.4). Moxifloxacin was included as standard active control. Significant female gender effect was noted.

In Study C152, repeated doses of rilpivirine 25 mg/day were evaluated in healthy volunteers. Efavirenz 600 mg/day was also tested. At steady state (Day 11) on rilpivirine, the 90% CIs of the observed time matched difference versus placebo in QT_{cf} interval did not cross the 10ms threshold at any time point. The highest UL of 90% CI was observed at 12 h postdose (90% CI -1.0, 5.0). For efavirenz also the UL of 90% CIs of the observed time-matched difference versus placebo in QT_{cf} interval did not exceed 10ms. The highest UL of the 90% CI was observed at 6 h postdose (90% CI 2.0, 8.4). Moxifloxacin was included as standard active control.

The currently proposed clinical dose of 25 mg/day rilpivirine was also evaluated in an earlier pilot Study C151. The largest increase from baseline in mean QT_{cf} interval was +4.8ms (90% CI 1.4, 8.2) at 4 h on Day 11 compared to placebo (+8.7ms; 90% CI 4.6, 12.9) at 4.5 h on Day 11. The maximum mean placebo-corrected difference in QT_{cf} interval was 2.2ms (90% CI: -3.0, 7.4) at 6 h.

Clinical Efficacy

The rilpivirine clinical efficacy is based on one Phase II dose response study (C204) and two pivotal Phase III studies (C209 & C215) with 48 weeks data in treatment naive adult HIV-1 patient population.

The dose response Study C204 evaluated 25, 75 and 150 mg rilpivirine and efavirenz 600 mg per day treatments allocated by randomisation to the four groups with primary assessment at 48 weeks. These results are shown in Table 39.

The efficacy response (viral load < 50 copies/L TLOVR) rates across all groups were similar at 48 weeks. The dose response between groups was statistically not significant.

Based on this result, rilpivirine 75 mg/day was selected for extended treatment beyond 48 weeks in this study. However, during this time the results of TQT Study C131 became available and a decision was made to switch to 25 mg/day rilpivirine for further treatment in this trial and for development through the Phase 3 trials.

The pivotal Phase 3 studies C209 (ECHO) & C215 (THRIVE) were identical in design but differed in background antiviral regimens. Both trials investigated rilpivirine (25 mg/day) versus efavirenz (600 mg/day), that is, two parallel treatment groups.

The background NRTI was fixed to tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in Study C209, whereas the background ART consisted of investigator-selected abacavir/lamivudine (ABC/3TC), zidovudine/lamivudine (AZT/3TC) or TDF/FTC.

Both trials were multinational, randomised, double blind, non inferiority trials in antiretroviral treatment naive adult HIV-1 patients (viral load \geq 5000copies/mL at baseline; susceptible to background ART; excluded patients with documented genotypic resistance to NNRTI) with primary efficacy assessment at 48 weeks. The groups were broadly comparable at baseline.

Table 39: Virologic outcome (< 50 HIV-1 RNA copies/ml, TLOVR) following rilpivirine (TMC278) (Weeks 48 and 96, Phase IIb Trial C204).

Grouping, Specification, n (%)	TMC278				Control N = 89
	25 mg q.d. N = 93	75 mg q.d. N = 95	150 mg q.d. N = 91	All TMC278 N = 279	
Week 48					
Viral load < 50 HIV-1 RNA copies/mL (TLOVR)	74 (79.6)	76 (80.0)	70 (76.9)	220 (78.9)	72 (80.9)
Non-responders	19 (20.4)	19 (20.0)	21 (23.1)	59 (21.1)	17 (19.1)
Virologic failure ^a	9 (9.7)	5 (5.3)	6 (6.6)	20 (7.2)	5 (5.6)
Death	0	1 (1.1)	0	1 (0.4)	0
Discontinuation for AE	6 (6.5)	5 (5.3)	9 (9.9)	20 (7.2)	5 (5.6)
Discontinuation for other reasons	4 (4.3)	8 (8.4)	6 (6.6)	18 (6.5)	7 (7.9)
Week 96					
Viral Load < 50 HIV-1 RNA copies/mL (TLOVR)	71 (76.3)	68 (71.6)	65 (71.4)	204 (73.1)	63 (70.8)
Non-responders	22 (23.7)	27 (28.4)	26 (28.6)	75 (26.9)	26 (29.2)
Virologic Failure ^a	8 (8.6)	9 (9.5)	6 (6.6)	23 (8.2)	7 (7.9)
Death	0	1 (1.1)	0	1 (0.4)	0
Discontinuation for AE	8 (8.6)	8 (8.4)	13 (14.3)	29 (10.4)	7 (7.9)
Discontinuation for other reasons	6 (6.5)	9 (9.5)	7 (7.7)	22 (7.9)	12 (13.5)

N = number of subjects per treatment group, n = number of observations

^a Rebound (loss of virologic response: 2 consecutive viral load values \geq 50 copies/mL, TLOVR after having been a responder), were never virologically suppressed, and discontinued due to virologic failure as assessed by the investigator are considered as virologic failure.

The primary efficacy results indicative of non inferiority (LL of 95% CI for the Treatment Difference to be no worse than -10%) for rilpivirine versus efavirenz (control) comparison at 48 weeks are shown in Table 40.

Table 40: Proportion of virologic responders (< 50 HIV-1 RNA copies/ml, TLOVR) following rilpivirine (TMC278) (C209, C215 and pooled Phase III trials).

Proportion of Virologic Responders (< 50 HIV-1 RNA Copies/mL, TLOVR) at Week 48, ITT and PP Populations (Phase III Trial C209)

Virologic response < 50 HIV-1 RNA copies/mL	TMC278	Control	Difference* [95% CI] TMC278-Control
TLOVR (ITT), N	346	344	
n (%)	287 (82.9)	285 (82.8)	0.1 [-5.5, 5.7]
TLOVR (PP), N	335	330	
n (%)	282 (84.2)	275 (83.3)	0.8 [-4.8, 6.5]

N = number of subjects per treatment group, n = number of responders

* 95% CI of the difference in proportion is calculated using normal approximation of binomial distribution.

Proportion of Virologic Responders (< 50 HIV-1 RNA copies/mL, TLOVR) at Week 48, ITT and PP Populations (Phase III Trial C215)

Virologic response < 50 HIV-1 RNA copies/mL	TMC278	Control	Difference* [95% CI] TMC278-Control
TLOVR (ITT), N	340	338	
n (%)	291 (85.6)	276 (81.7)	3.9 [-1.6, 9.5]
TLOVR (PP), N	334	332	
n (%)	287 (85.9)	273 (82.2)	3.7 [-1.9, 9.3]

N = number of subjects per treatment group, n = number of responders

* 95% CI of the difference in proportion is calculated using normal approximation of binomial distribution.

Proportion of Virologic Responders (< 50 HIV-1 RNA Copies/mL, TLOVR) at Week 48, ITT and PP Populations (Pooled Phase III Trials)

Virologic response < 50 HIV-1 RNA copies/mL	TMC278	Control	Difference* [95% CI] TMC278-Control
TLOVR (ITT), N	686	682	
n (%)	578 (84.3)	561 (82.3)	2.0 [-2.0, 6.0]
TLOVR (PP), N	669	662	
n (%)	569 (85.1)	548 (82.8)	2.3 [-1.7, 6.2]

N = number of subjects per treatment group, n = number of responders

* CIs were calculated using the normal approximation of the binomial distribution.

Based on pooled data from both studies, there were 9.0% virologic failures in rilpivirine group compared to 4.8% virologic failures in efavirenz group.

Clinical safety

Overall, five deaths were reported in rilpivirine-treated patients. These included four in the Phase II Study C204 and one in the Phase III trial C215.

In the two Phase III trials, 611 patients were exposed to rilpivirine for at least 48 weeks. Longer-term safety data was derived from the extended period of Phase II trial C204.

The proportion of patients reporting at least 1 SAE was 6.6% in the pooled rilpivirine group compared to 8.1% in the control group.

Overall in the long term safety analysis, the incidence of SAEs between the rilpivirine group and the control group was comparable (15.8% versus 16.9% respectively) and was consistent with the safety profile based on first 48 weeks of treatment from studies C204, C209 and C215.

Notable adverse drug effects associated with rilpivirine treatment in dose related manner included rash and QT prolongation.

The results of the ACTH stimulation test in the Phase II/III studies suggested possibility of adrenal suppression at Week 48.

Resistance analyses indicated rilpivirine resistance profile to be more adverse than efavirenz resistance profile. Patients on rilpivirine had shorter median time to virologic failure than those in efavirenz group. Approximately twice the proportion of patients on rilpivirine developed virologic failures compared to those in the efavirenz group.

Among virologic failures on rilpivirine, approximately twice the proportion of patients developed treatment emergent NRTI resistance mutations compared to patients in the efavirenz virologic failure group. In addition, among virologic failures on rilpivirine, 87.1% & 90.3% developed cross-resistance to efavirenz and etravirine respectively.

Among the control virologic failures resistant to efavirenz at failure, none were cross-resistant to rilpivirine and etravirine. The frequency of resistance to 3TC/FTC used in the background regimen was also approximately twice as high among rilpivirine virologic failures compared to the control virologic failures in efavirenz.

Risk Management Plan

The RMP evaluation report, sponsor's reply to RMP evaluation and the RMP evaluator's Minute to the clinical delegate has been included in the papers for consideration by the ACPM. The Advisory Committee on the Safety of Medicines (ACSOM) advice was also sought. The issues considered by ACSOM included:

Inhibition of adrenal steroidogenesis. ACSOM view was that there was no clear indication of a clinically significant effect on adrenal function.

QT prolongation. ACSOM believed that sponsor should justify not investigating doses below 25 mg in the pre-registration phase. The RMP evaluator considered the proposed labelling acceptable.

Hepatic impairment. ACSOM noted that data are not extensive in patients with mild to moderate hepatic impairment and were lacking in patients with severe hepatic impairment. The committee has not requested any measures beyond routine PhV.

Virologic failure and drug resistance. The committee noted evidence of a shorter time to failure, more failures in general, and more failures associated with resistance for rilpivirine when compared to efavirenz. The committee felt that practitioners with clinical experience in the treatment of HIV would be able to identify problems associated with resistant or cross-resistance and integrate these into their clinical decision making.

Inadequate evaluation of the potential for medication error. The sponsor has provided an acceptable response.

A roll over study in patients who benefited from rilpivirine treatment in Phase II/III trials is ongoing. The study will provide further data on drug resistance and adverse events relating to hepatotoxicity, severe skin reactions, major depressive disorder and lipodystrophy. Analyses from this study and the results from a US post approval digoxin interaction study will be reported in rilpivirine PSUR.

The RMP evaluator recommended registration with condition that *Risk Management Plan, Version 1.0, dated 1 July 2010 and the Australian Annex* will be fully implemented.

Risk-Benefit Analysis

Delegate Considerations

Rilpivirine is a NNRTI proposed for the treatment of HIV-1 infection in treatment naive adult patients in combination with other antiretroviral agents.

The dossier consisted of full developmental program covering chemistry, quality, manufacture, toxicology and clinical data.

Extensive pharmacokinetic and drug interaction data was included although absolute bioavailability could not be determined. Further issues were raised in the clinical evaluation report with respect to lack of drug interaction data with interferon, sedatives and anti psychotics. The sponsor has provided justification for these in its response which is considered acceptable.

Based on drug interaction studies, no dose adjustment of rilpivirine is proposed with NRTIs including emtricitabine. This is considered satisfactory. Note that a fixed dose triple combination tablet containing rilpivirine (25 mg), emtricitabine (200 mg) and tenofovir DF (300 mg) is the subject of a concurrent application for registration by another sponsor.

There is no recommendation for dose adjustment of rilpivirine with protease inhibitors (boosted or unboosted). This is considered satisfactory based on data.

It is not anticipated that rilpivirine will be administered with other NNRTIs. The proposed PI contains statement to that effect.

No interaction studies were available with CCR5 inhibitor (maraviroc), HIV integrase strand transfer inhibitor (raltegravir), or fusion inhibitor (enfuvirtide). With respect to the first two, the proposed PI contains statement that such interaction is not expected.

A small hepatic study was the basis for recommendation of no change in rilpivirine dose in mild and moderate impairment. Rilpivirine should not be given to patients with severe hepatic impairment.

The sponsor in its response to the CER noted that *'it cannot be excluded that the absorption of rilpivirine is impacted in some of these subjects, possibly by a reduction in bile salt micelles which facilitate rilpivirine solubilisation. The observed inter individual variability in C_{max} and AUC_{24h} in hepatic impaired subjects was moderate, and not different between mild and moderate hepatic impairment (35.5% and 33.7% in mild, and 34.6% and 33.7% in moderate, respectively).*

Clearly more data are required, although I agree with the current proposed dosing recommendation. Please see comment below with respect to the proposed PI.

Rilpivirine has dose related effect on QT prolongation but this is not likely to be clinically significant at the proposed 25 mg daily dose. Please also see sponsor's comment in reply to the Clinical Evaluation Report.

The two pivotal efficacy trials were well designed, conducted in appropriate patient population, and used accepted comparator drug on background of commonly used antiviral therapies. I consider the results internally valid and robust. The non inferiority with respect to efficacy (viral load < 50copies/mL at 48 weeks) was satisfactorily demonstrated although the results showed higher virologic failure in rilpivirine treated patients.

I understand however that there was an issue with the viral load assay in Phase III studies which involved abandoning a new assay for an old assay. The sponsor is requested to include a comprehensive summary for the Committee's information in its pre ACPM response with respect to any influence on the efficacy outcomes.

The clinical evaluator also raised the issue of suitability of 25 mg dose because the minimum effective dose had not been defined. The ACSOM has also commented on the matter. I agree that initial selection of the 75 mg daily dose based on the Study C204 was not fully supported due to lack of dose response discrimination between the three tested doses (25, 75, 150 mg) in this study.

This likely represented sponsor bias towards selecting higher doses which has otherwise also been noted in other cases. In this instance, the error could only be corrected because results of a TQT study incidentally became available before the subsequent Phase III trials.

With respect to the suitability of the 25 mg daily dose itself, I note that virologic failure rate was nearly twice in rilpivirine group (9.0%) compared to virologic failures in efavirenz group (4.8%) based on pooled data from the two pivotal studies. This finding, along with the resistance development data that showed relatively adverse profile with rilpivirine treatment compared to efavirenz treatment, supports the argument that a lower rilpivirine dose will be less likely to improve risk benefit ratio. I do not consider lack of data for 50 mg dose as an issue due to dose related QT prolongation effect.

Delegate's Proposed Action

The Delegate opined that sufficient premarket data had been presented to allow registration. Pending advice from ACPM, I propose to approve this submission to register 25 mg rilpivirine oral tablets for the following therapeutic indication:

Rilpivirine, in combination with other antiretroviral medicinal products, is indicated for the treatment of HIV-1 infection in antiretroviral treatment naïve adult patients.

The indication is based on Week 48 safety and efficacy analyses from two randomised, double-blind, controlled Phase III trials in treatment naïve adult patients and Week 96 safety and efficacy analyses from the Phase IIb trial in treatment naïve adult patients (see CLINICAL TRIALS section).

The recommended dose is 25 mg daily taken with meals.

A statement was recommended for inclusion in the rilpivirine PI with respect to rilpivirine in hepatic impairment:

It is expected that further changes will need to be negotiated following consideration by the ACPM and prior to finalisation of the submission.

Advice from the ACPM was requested.

Response from sponsor

The sponsor agreed with the Delegate's recommendation to approve rilpivirine 25 mg tablets for the following indication:

Rilpivirine, in combination with other antiretroviral medicinal products, is indicated for treatment of HIV-1 infection in antiretroviral treatment naïve adult patients.

The indication is based on Week 48 safety and efficacy analyses from 2 randomised, double blind, controlled Phase III trials in treatment naïve adult patients and Week 96 safety and efficacy analyses from the Phase IIb trial in treatment naïve adult patients (see Clinical Trials section).

However, the sponsor commented on the following items.

Delegate's Comment 1:

Viral load assay:

The Delegate was made aware of an issue with the viral load assay in Phase III studies which involved abandoning a new assay for an old assay. The sponsor was requested to include a comprehensive summary for the Committee's information in its pre ACPM response with respect to any influence on the efficacy outcomes.

Sponsor Response:

As indicated in the sponsor's Summary of Clinical Efficacy issues were identified with regards to the viral load assay, namely the Roche Cobas HIV-1 TaqMan assay version 1.0 (TaqMan® assay), initially selected for the viral load measurements in the Phase III trials. These issues were identified from the literature and from the blinded viral load data of the rilpivirine Phase III trials.

Background information:

Several scientific articles²⁴ were published indicating that the TaqMan® assay was associated with a higher number of persistent low level viremia (PLLV)²⁵ cases compared with the Amplicor assay. To date, the clinical relevance of this increased sensitivity leading to detection of lower levels of human immunodeficiency virus type 1 (HIV-1) ribonucleic acid (RNA) by the TaqMan® assay is unknown and there is no proof that this is linked to or predictive of a worse clinical outcome.

²⁴ Damond F, et al. Human immunodeficiency virus type 1 (HIV-1) plasma load discrepancies between the Roche COBAS AMPLICOR HIV-1 MONITOR Version 1.5 and the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 assays. *J. Clin. Microbiol.* 2007; 45:3436-3438. Oliver A, et al. Comparative evaluation of the automated Roche TaqMan real-time quantitative human immunodeficiency virus type 1 RNA PCR assay and the Roche AMPLICOR Version 1.5 conventional PCR assay. *J. Clin. Microbiol.* 2007; 45:3616-3619. Montaner JSG, et al. (on behalf of the international AIDS Society – USA Antiretroviral Guidelines Panel). Poor agreement between 2 assays for measuring low levels of HIV-1 viral load. *Clin. Infect Dis.* 2009; 49:1283-1284. Pozniak A, et al. Causes and consequences of incomplete HIV RNA suppression in clinical trials. *HIV Clin. Trials* 2009; 10:289-298. Gatanaga H, et al. Detection of HIV type 1 load by the Roche Cobas TaqMan assay in patients with viral loads previously undetectable by the Roche Cobas Amplicor Monitor. *Clin. Infect Dis.* 2009; 48: 260-261. Smit E, et al. Increased frequency of HIV-1 viral load blip rate observed after switching from Roche Cobas Amplicor to Cobas TaqMan assay. *J. AIDS* 2009; 51:364-365. Manavi K. The significance of low-level plasma HIV viral load on COBAS TaqMan HIV-1 assays for patients with undetectable plasma viral load on COBAS Amplicor monitor version 1.5. *HIV Clin. Trials* 2008; 9:283-286. Lima V, et al. Increased reporting of detectable plasma HIV-1 RNA levels at the critical threshold of 50 copies per millilitre with the TaqMan assay in comparison to the Amplicor Assay. *J AIDS* 2009; 51:3-6. Willig JH, et al. The Taqman Cometh: hidden costs of a new viral load assay. *Infectious Diseases Society of America* 2009, poster 268. Ribaud H, et al. Virologic failure endpoint definition in clinical trials. Is using HIV-1 RNA threshold < 200 copies/mL better than < 50 copies/mL? An analysis of ACTG studies. *Conference on Retroviruses and Opportunistic Infections* 2009, poster 580. AIDS Clinical Trials Group. Annual Progress Report 2008-2009. Lee PK, et al. HIV-1 viral load blips are of limited clinical significance. *J. Antimicrob. Chemother.* 2006; 57:803-805.

²⁵ PLLV is defined as a viral load profile in which a confirmed viral load <50 copies/mL is never achieved and where the lowest viral load lingers between 50 and 1,000 copies/mL.

In line with these literature data, blinded viral load results in the Phase III trials showed more subjects with viral load blips²⁶ or PLLV than expected based on the results with the rilpivirine 25 mg/day dose and efavirenz in the Phase IIb trial (data on file). The different viral load assay was the likely source of these observations.

The primary efficacy endpoint of the Phase III trials follows the time to loss of virologic response (TLOVR) algorithm. Therefore, subjects with PLLV are counted as treatment failures in the analysis. The same is true for responders with at least two consecutive viral load blips. Thus, as a result of the increased rate of viral load blips and PLLV, it was likely that the overall response rates could be lower than expected, consequently reducing the power of each Phase III trial.

Moreover, comparison of the Phase III results with historical controls (using the Amplicor assay) would become more difficult. In the absence of a clear relationship between PLLV and clinical outcome, this effect on virologic success rates in the context of the TLOVR algorithm could be considered an artifact of the assay itself.

In view of the above, a decision was made to re-assess the baseline and all on treatment viral load samples of both Phase III trials with the Amplicor assay.

The Phase III efficacy analyses presented in the submission were based on the Amplicor assay viral load data. Certain efficacy analyses were also performed based on the TaqMan® assay viral load data, as specified in the statistical analysis plans (SAPs) and are presented below.

Phase III Week 48 TaqMan® results (database lock: March 2010):

Overall response rates in both treatment groups in trials C209 and C215 were lower with the TaqMan® assay than those obtained with the Amplicor assay, for the reasons outlined in our rationale for using the Amplicor assay (see above). Like the Amplicor assay data, the TaqMan® assay results for the proportion of virologic responders (<50 HIV-1 RNA copies/mL²⁷, TLOVR) at Week 48 showed similar proportions of virologic responders between treatment groups in the pooled Phase III analysis (78% versus 78.4% for rilpivirine and control) as well as in the individual trials (76.6% versus 79.9%, respectively in C209, and 79.45 versus 76.9%, respectively, in C215).

In the Phase III trials, statistical comparison using the logistic regression model showed a predicted difference [95% CI] in virologic response (<50 copies/mL, TLOVR) at Week 48 between the rilpivirine and control group of -4.1 [-10.2; 1.9] in the C209 trial and 1.5 [-4.6; 7.6] in the C215 trial. The lower limit of the 95% CI of the difference between treatment groups was greater than -12%, establishing non-inferiority of rilpivirine at the 12% margin in both the C209 trial ($p = 0.0108$) and the C215 trial ($p < 0.0001$).

There were a greater number of virologic failures using the TaqMan® compared with the Amplicor assay. Most of these virologic failures were never suppressed, regardless of the assay used. As indicated in the virology summary viral load blips or PLLV observed with the Taqman® assay were not associated with the emergence of resistance. For further details on the subjects with viral load blips and PLLV based on TaqMan® assay viral load, see the antiviral microbiology report (AVMR). In conclusion, the primary efficacy results of the trials confirming non-inferiority of rilpivirine versus control were the same, irrespective of the assay used to determine virologic response.

²⁶ Viral load blips are defined as intermittent episodes of detectable low-level HIV-1 viremia ≥ 50 copies/mL which are preceded and followed by undetectable plasma viral load without any change in therapy. Episodes of persistently detectable or high-level viremia are not considered as viral load blips.

²⁷ For brevity, hereafter 'copies/mL' will be used instead of 'HIV-1 RNA copies/mL'.

Delegate's Comment 2:***Minimum effective dose, virologic failure and QT prolongation.***

The clinical evaluator also raised the issue of suitability of 25 mg dose because the minimum effective dose had not been defined. The ACSOM has also commented on the matter. The Delegate agreed that the initial selection of the 75 mg daily dose based on the Study C204 was not fully supported due to lack of dose response discrimination between the three tested doses (25, 75, 150 mg) in this study.

This likely represented sponsor bias towards selecting higher doses which has otherwise also been noted in other cases. In this instance the error could only be corrected because results of a thorough QT study incidentally became available before subsequent Phase III trials.

With respect to the suitability of the 25 mg daily dose itself, the Delegate noted that the virologic failure rate was nearly twice in the rilpivirine group (9.0%) compared to virologic failures in the efavirenz group (4.8%) based on pooled data from the two pivotal studies. This finding, along with the resistance development data which showed a relatively adverse profile with rilpivirine treatment compared to efavirenz treatment, supports the argument that a lower rilpivirine dose will be less likely to improve risk benefit ratio. The Delegate did not consider lack of data for 50 mg dose as an issue due to dose related QT prolongation.

Sponsor Response:

The data from the Phase IIb dose-finding trial C204 (96 weeks) and from the TQT trial C131 combined, indicated that the best benefit risk ratio for the use of rilpivirine in HIV-1 infected subjects was provided by a dose of 25 mg/day, which was selected for the Phase III trials and further development.

The favorable benefit risk ratio of the rilpivirine 25 mg dose (combined with an active background regimen) was confirmed in the Phase III trials by the significant and durable efficacy as well as the safety/tolerability profile in populations representative of HIV-1 infected antiretroviral (ARV) treatment naïve adult patients .

In conclusion, the sponsor agreed with the above mentioned statement from the ACSOM committee that rilpivirine 25 mg/day is the most appropriate dose.

Delegate's Comment 3:***Virologic failure and drug resistance.***

The ACSOM noted evidence of a shorter time to failure, more failures in general, and more failures associated with resistance of rilpivirine when compared to efavirenz. The committee felt that practitioners with clinical experience in the treatment of HIV would be able to identify problems associated with resistant or crossresistance and integrate these into their clinical decision making.

Sponsor Response:

In the pooled analysis from the Phase III trials, rilpivirine treated subjects with a baseline viral load >100,000 copies/mL had a greater risk of virologic failure compared with subjects with a baseline viral load ≤100,000 copies/mL. Subjects with a baseline viral load >100,000 copies/mL who experienced virologic failure exhibited a higher rate of treatment emergent resistance to the non nucleoside reverse transcriptase inhibitor (NNRTI) class. More subjects who failed virologically on rilpivirine, than who failed virologically on EFV, developed lamivudine (3TC)/emtricitabine (FTC) associated

resistance. This information should be taken into consideration when initiating therapy with rilpivirine.

In view of these results, the sponsor added a statement in the "Precautions" section of the proposed Australian PI to advise Australian prescribers about the risk of virologic failure and cross resistance in patients with a high viral load. On the basis of these results, prescribers can make an informed decision about prescribing rilpivirine. In light of this, the sponsor agreed with the decision made by the ACSOM committee and considers that the proposed statement in the PI sufficiently highlights this issue to Australian prescribers.

Sponsor Conclusion:

The sponsor believed that an adequate application has been provided to support the quality, safety, and efficacy of rilpivirine 25 mg tablets and agreed with the Delegate's recommendation to approve the application in line with the proposed indication.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

Efficacy

The ACPM agreed with the Delegate that there was sufficient evidence of efficacy in the submitted data to support the application; nonetheless, the predefined subgroup with >100,000 cp/mL HIV RNA at baseline had a higher incidence of virological failure and consequent resistance to this product, as well as for background nucleoside reverse transcriptase inhibitors therefore cross resistance within the classes. Therefore, in this population EDURANT does not meet benefit-risk threshold.

Safety

The ACPM agreed with the Delegate that the safety profile of this product was sufficiently defined to support the application. In addition, the committee noted that the single trial investigating hepatic impairment included only small numbers and was inadequate to determine risk. Hepatic adverse effects, small increase in serum creatinine in neuropsych adverse events and unexpected cortisol reduction should be considered for periodic monitoring.

Indication

The ACPM considered this product to have a positive benefit-risk profile for the indication of:

Rilpivirine, in combination with other antiretroviral medicinal products, is indicated for the treatment of HIV-1 infection in antiretroviral treatment-naïve adult patients with viral load < 100,000 copies per mL at baseline.

The indication is based on Week 48 safety and efficacy analyses from two randomised, double-blind, controlled phase III trials in treatment-naïve adult patients and week 96 safety and efficacy analyses from the Phase IIb trial in treatment-naïve adult patients (see *Clinical Trials* section of PI).

PI/ CMI

The ACPM advised additional amendments to the Product Information (PI) and Consumer Medicines Information (CMI) in addition to the changes proposed by the Delegate.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided for EDURANT tablet, 25 mg, would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Edurant film-coated tablets (oral administration) containing rilpivirine 25 mg (as hydrochloride). The approved indication reads as follows:

Edurant, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients with viral load $\leq 100,000$ copies/mL at baseline.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia

Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605

www.tga.gov.au

Reference/Publication #

EDURANT[®]

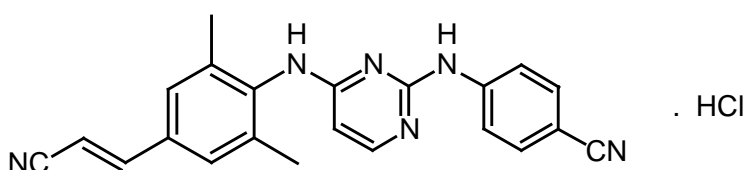
rilpivirine

PRODUCT INFORMATION

NAME OF THE MEDICINE

The chemical name of rilpivirine is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino-2-pyrimidinyl]amino]benzonitrile monohydrochloride.

Rilpivirine hydrochloride has the following chemical structure:



Molecular formula: C₂₂H₁₈N₆.HCl

Molecular weight: 402.88

CAS Registry Number: 700361-47-3

DESCRIPTION

Rilpivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type-1 (HIV-1).

Rilpivirine hydrochloride is a white to off-white powder. Rilpivirine hydrochloride is practically insoluble in water over a wide pH range, its pKa is 5.6 (pyrimidine moiety) and log P between 1-octanol and a phosphate solution (pH 7.0) is 4.86 (at 21°C).

EDURANT rilpivirine is available as 25 mg tablets. Each film-coated tablet contains rilpivirine hydrochloride equivalent to 25 mg rilpivirine. It also contains the following inactive ingredients: lactose monohydrate, croscarmellose sodium, povidone, polysorbate 20, silicified microcrystalline cellulose (a combination of microcrystalline cellulose and silicon dioxide), magnesium stearate, hypromellose, titanium dioxide, macrogol 3000 and glycerol triacetate. Each tablet contains 56 mg lactose monohydrate.

PHARMACOLOGY

Pharmacodynamics

Mechanism of action

Rilpivirine is a diarylpyrimidine NNRTI of HIV-1. Rilpivirine activity is mediated by non competitive inhibition of HIV-1 reverse transcriptase (RT). Rilpivirine does not inhibit the human cellular DNA polymerases α , β and γ .

Antiviral activity *in vitro*

Rilpivirine exhibited activity against laboratory strains of wild type HIV-1 in an acutely infected T-cell line with a median EC₅₀ value for HIV-1/IIIB of 0.73 nM (0.27 ng/ml). Although rilpivirine demonstrated limited *in vitro* activity against HIV-2 with EC₅₀ values ranging from 2,510 to 10,830 nM (920 to 3,970 ng/ml), treatment of HIV-2 infection with rilpivirine is not recommended in the absence of clinical data.

Rilpivirine also demonstrated antiviral activity against a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC₅₀ values ranging from 0.07 to 1.01 nM (0.03 to 0.37 ng/ml) and group O primary isolates with EC₅₀ values ranging from 2.88 to 8.45 nM (1.06 to 3.10 ng/ml).

Rilpivirine showed additive antiviral activity in combination with the N(t)RTIs: abacavir, didanosine, emtricitabine, stavudine and tenofovir; the protease inhibitors: amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir; the NNRTIs: efavirenz, etravirine and nevirapine; the fusion inhibitor enfuvirtide; and the entry inhibitor maraviroc. Rilpivirine shows additive to synergistic antiviral activity in combination with the NRTIs lamivudine and zidovudine, and the integrase inhibitor raltegravir.

Resistance

In cell culture

Rilpivirine-resistant strains were selected in cell culture starting from wild type HIV-1 of different origins and subtypes as well as NNRTI-resistant HIV-1. The most commonly observed amino acid substitutions that emerged included: L100I, K101E, V108I, E138K, V179F, Y181C, H221Y, F227C and M230I.

A biological cut off (BCO) for rilpivirine was determined at the fold change in EC₅₀ value (FC) of 3.7, on the basis of the analysis of the susceptibility of a large panel of HIV-1 wild type recombinant clinical isolates.

In treatment-naïve subjects

In the pooled resistance analysis from the phase III trials, 62 (of a total of 72) virologic failures in the rilpivirine arm had resistance data at baseline and time of failure. The amino acid substitutions associated with NNRTI resistance that developed most commonly in these subjects were: V90I, K101E, E138K, E138Q, Y181C, V189I and H221Y. However, in the trials, the presence of the substitutions V90I and V189I, at baseline, did not affect response.

Considering all of the available *in vitro* and *in vivo* data, the following amino acid substitutions, when present at baseline, are likely to affect the activity of rilpivirine: K101E, K101P, E138G, E138K, E138R, E138Q, Y181C, Y181I, Y181V and H221Y.

Cross resistance

Site directed NNRTI mutant virus

In a panel of 67 HIV-1 recombinant laboratory strains with one amino acid substitution at RT positions associated with NNRTI resistance, including the most commonly found K103N and Y181C, rilpivirine showed antiviral activity against 64 (96%) of these strains. The single amino acid substitutions associated with a loss of susceptibility to rilpivirine were: K101P, Y181I and Y181V.

Recombinant clinical isolates

Rilpivirine retained sensitivity (FC ≤ BCO) against 62% of 4786 HIV-1 recombinant clinical isolates resistant to efavirenz and/or nevirapine.

Treatment naïve HIV 1 infected patients

In the pooled analysis of the phase III trials ECHO and THRIVE, 31 of the 62 subjects with virologic failure on rilpivirine with phenotypic resistance data lost susceptibility to rilpivirine. Of these, 28 were resistant to etravirine, 27 to efavirenz, and 14 to nevirapine.

Effects on electrocardiogram

The effect of rilpivirine at the recommended dose of 25 mg q.d. on the QTcF interval was evaluated in a randomised, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 60 healthy adults, with 13 measurements over 24 hours at steady state. Rilpivirine at the recommended dose of 25 mg q.d. is not associated with a clinically relevant effect on QTc.

When supratherapeutic doses of 75 mg q.d. and 300 mg q.d. of rilpivirine were studied in healthy adults, the maximum mean time matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline correction were 10.7 (15.3) and 23.3 (28.4) ms, respectively. Steady state administration of rilpivirine 75 mg q.d. and 300 mg q.d. resulted in a mean C_{max} approximately 2.6 fold and 6.7 fold, respectively, higher than the mean steady state C_{max} observed with the recommended 25 mg q.d. dose of rilpivirine.

Pharmacokinetics

The pharmacokinetic properties of rilpivirine have been evaluated in adult healthy subjects and in adult antiretroviral treatment naïve HIV 1 infected patients. Exposure to rilpivirine was generally lower in HIV-1 infected patients than in healthy subjects.

Absorption

After oral administration, the maximum plasma concentration of rilpivirine is generally achieved within 4-5 hours. The absolute bioavailability of rilpivirine is unknown.

Effect of food on absorption

The exposure to rilpivirine was approximately 40% lower when rilpivirine was taken in a fasted condition as compared to a normal caloric meal (533 kcal) or high fat high caloric meal (928 kcal). When rilpivirine was taken with only a protein rich nutritional drink, exposures were 50% lower than when taken with a meal (see DOSAGE and ADMINISTRATION).

Distribution

Rilpivirine is approximately 99.7% bound to plasma proteins *in vitro*, primarily to albumin. The distribution of rilpivirine into compartments other than plasma (e.g., cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

Metabolism

In vitro experiments indicate that rilpivirine primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP) 3A system. It is possible that different populations of patients have faster or slower rilpivirine metabolism because of the various isoenzymes within the CYP3A system.

Elimination

The terminal elimination half life of rilpivirine is approximately 45 hours. After single dose oral administration of ^{14}C rilpivirine, on average 85% and 6.1% of the radioactivity could be retrieved in faeces and urine, respectively. In faeces, unchanged rilpivirine accounted for on average 25% of the administered dose. Only trace amounts of unchanged rilpivirine (< 1% of dose) were detected in urine.

Additional information on special populations

Paediatric population

The pharmacokinetics of rilpivirine in paediatric patients are under investigation. Dosing recommendations for paediatric patients cannot be made due to insufficient data (see PRECAUTIONS and DOSAGE and ADMINISTRATION).

Elderly

Population pharmacokinetic analysis in HIV infected patients showed that rilpivirine pharmacokinetics are not different across the age range (18 to 78 years, with only 2 patients aged above 65 years) evaluated. No dose adjustment of rilpivirine is required in elderly patients.

Gender

Population pharmacokinetic analysis in HIV infected patients showed no clinically relevant differences in the pharmacokinetics of rilpivirine between men and women.

Race

Population pharmacokinetic analysis of rilpivirine in HIV infected patients indicated that race had no clinically relevant effect on the exposure to rilpivirine.

Hepatic impairment

Rilpivirine is primarily metabolised and eliminated by the liver. In a study comparing 8 patients with mild hepatic impairment (Child Pugh score A) to 8 matched controls, and 8 patients with moderate hepatic impairment (Child Pugh score B) to 8 matched controls. The mean steady-state exposure to rilpivirine was higher in subjects with mild hepatic impairment (27% higher for C_{max} and 47% higher for AUC) than in healthy controls. However, rilpivirine exposure in subjects with moderate hepatic impairment (5% lower for C_{max} and 5% higher for AUC) was similar to healthy controls. The mean apparent elimination half-life of rilpivirine was longer in subjects with mild (81 hours versus 61 hours respectively) and moderate (91 hours versus 56 hours, respectively) hepatic impairment compared to healthy controls. No dose adjustment is required in patients with mild or moderate hepatic impairment. Rilpivirine has not been studied in patients with severe hepatic impairment (Child Pugh score C) (see PRECAUTIONS).

Hepatitis B and/or hepatitis C virus co infection

Population pharmacokinetic analysis indicated that hepatitis B and/or C virus co infection had no clinically relevant effect on the exposure to rilpivirine.

Renal impairment

The pharmacokinetics of rilpivirine have not been studied in patients with renal insufficiency. Renal elimination of rilpivirine is negligible. Therefore, the impact of renal impairment on rilpivirine elimination is expected to be minimal. As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis.

CLINICAL TRIALS

The evidence of efficacy of rilpivirine is based on the analyses of 48 week data from 2 randomised, double-blinded, active-controlled, phase III trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE). The trials were identical in design, with the exception of the background regimen (BR). At 48 weeks, the virologic response rate [confirmed undetectable viral load (< 50 HIV-1 RNA copies/ml)] according to the time to loss of virologic response (TLOVR) algorithm was evaluated in patients receiving rilpivirine 25 mg q.d. in addition to a BR versus patients receiving efavirenz 600 mg q.d. in addition to a BR. The TLOVR imputation algorithm was used to define confirmed virologic response i.e., two consecutive viral load values below the threshold are needed to count as a response. Non-responders or failures were defined as those subjects who never responded i.e. never achieved 2 consecutive viral load values of < 50 copies/ml, or who were a rebounder (subject responded, then has two consecutive viral load values above the threshold value of 50 copies/ml), or discontinued prematurely.

Similar efficacy for rilpivirine was seen in each trial demonstrating non-inferiority to efavirenz.

Antiretroviral treatment-naïve HIV-1 infected patients were enrolled who had a plasma HIV-1 RNA \geq 5000 copies/ml and were screened for susceptibility to N(t)RTI and for absence of specific NNRTI RAMs. In ECHO, the BR was fixed to the N(t)RTIs, tenofovir disoproxil fumarate plus emtricitabine. In THRIVE, the BR consisted of 2 investigator-selected N(t)RTIs: tenofovir disoproxil fumarate plus emtricitabine or zidovudine plus lamivudine or abacavir plus lamivudine. In ECHO, randomisation was stratified by screening viral load. In THRIVE, randomisation was stratified by screening viral load and by N(t)RTI BR.

This analysis included 690 patients in ECHO and 678 patients in THRIVE who had completed 48 weeks of treatment or discontinued earlier.

In the pooled analysis for ECHO and THRIVE, demographics and baseline characteristics were balanced between the rilpivirine arm and the efavirenz arm. Table 1 displays selected demographic and baseline disease characteristics of the patients in the rilpivirine and efavirenz arms. 53.3% of patients in the rilpivirine arm and 48.2% of patients in the efavirenz arm were in the \leq 100,000 copies/ml baseline viral load category. The proportion of patients with baseline viral load $>$ 100,000 copies/ml was 46.7% and 51.8% in the rilpivirine arm and efavirenz arm, respectively.

Table 1: Demographic and baseline disease characteristics of antiretroviral treatment-naïve HIV-1 infected adult subjects in the ECHO and THRIVE trials (pooled analysis)		
	Pooled data from the ECHO and THRIVE trials	
	rilpivirine + BR N=686	efavirenz + BR N=682
Demographic characteristics		
Median Age, years (range)	36 (18-78)	36 (19-69)
Sex		
Male	76%	76%
Female	24%	24%
Race		
White	61%	60%
Black/African American	24%	23%
Asian	11%	14%
Other	2%	2%
Not allowed to ask per local regulations	1%	1%
Baseline disease characteristics		
Median baseline plasma HIV-1 RNA (range), log ₁₀ copies/ml	5.0 (2-7)	5.0 (3-7)
Median baseline plasma HIV-1 RNA (range), copies/ml	90,450.0 (156 – 20,800,000)	104,500.0 (1,010 – 4,550,000)
Median baseline CD4+ cell count (range), x 10 ⁶ cells/l	249 (1-888)	260 (1-1137)
Percentage of subjects with: hepatitis B/C virus co-infection	7.3%	9.5%
Percentage of Subjects with the following background regimens:		
tenofovir disoproxil fumarate plus emtricitabine	80.2%	80.1%
zidovudine plus lamivudine	14.7%	15.1%
abacavir plus lamivudine	5.1%	4.8%

BR=background regimen

Table 2 below shows the efficacy results at 48 weeks for patients treated with rilpivirine and patients treated with efavirenz from the pooled data from the ECHO and THRIVE trials.

Table 2: Virologic Outcome of Randomized Treatment in the ECHO and THRIVE Trials (Pooled Analysis at Week 48; ITT-TLOVR*)		
%	rilpivirine + BR N=686	efavirenz + BR N=682
Outcome at Week 48		
Confirmed Undetectable Viral Load (< 50 HIV-1 RNA copies/ml) ^{§#}	84.3	82.3
Virologic Failure [†]	9.0	4.8
Death	0.1	0.4
Discontinued due to adverse event (AE)	2.0	6.7
Discontinued for non-AE reason [¶]	4.5	5.7

N = number of subjects per treatment group

* intent-to-treat time to loss of virologic response

§ Subjects achieved virologic response (two consecutive viral loads < 50 copies/ml) and maintained it through Week 48.

Predicted difference of response rates (95% CI): 1.6% (-2.2%; 5.3%); p-value < 0.0001 (non-inferiority at 12% margin) from logistic regression model, including stratification factors and study.

† Includes subjects who were rebounder (confirmed viral load ≥ 50 copies/mL after being responder) or who were never suppressed (no confirmed viral load < 50 copies/mL, either ongoing or discontinued due to lack or loss of efficacy).

¶ e.g. lost to follow-up, non-compliance, withdrew consent

The mean change from baseline in CD4+ cell count was +192 x 10⁶ cells/l in the rilpivirine arm and +176 x 10⁶ cells/l in the efavirenz arm in the pooled analysis of the ECHO and THRIVE trials [estimated treatment difference (95% CI): 17.9 (2.1; 33.6)].

A subgroup analysis of the virologic response (< 50 HIV-1 RNA copies/ml) at 48 weeks and virologic failure by baseline viral load and by background NRTIs (pooled data from the ECHO and THRIVE trials) is presented in table 3.

Table 3: Virologic response (< 50 HIV-1 RNA copies/ml) at 48 weeks and virologic failure by baseline viral load, by baseline CD4 count, and by background NRTIs (pooled data from the ECHO and THRIVE trials)				
	EDURANT + BR N=686		Efavirenz + BR N=682	
	N	n (%)	N	n (%)
Proportion of subjects with HIV-1 RNA < 50 copies/ml at week 48* by baseline plasma viral load (copies/ml)				
≤ 100,000	368	332 (90.2%)	330	276 (83.6%)
> 100,000	318	246 (77.4%)	352	285 (81.0%)
Virologic Failure[†] by baseline plasma viral load (copies/ml)				
≤ 100,000	368	14 (3.8%)	330	11 (3.3%)
> 100,000	318	48 (15.1%)	352	22 (6.3%)
Proportion of subjects with HIV-1 RNA < 50 copies/ml at week 48* by baseline CD4 count (cells/μl)				
< 50	34	20 (58.8%)	36	29 (80.6%)
≥ 50 - < 200	194	156 (80.4%)	175	143 (81.7%)
≥ 200 - < 350	313	272 (86.9%)	307	253 (82.4%)
≥ 350	144	130 (90.3%)	164	136 (82.9%)
Proportion of subjects with HIV-1 RNA < 50 copies/ml at week 48* by background NRTI				
tenofovir disoproxil fumarate plus emtricitabine	550	459 (83.5%)	546	450 (82.4%)
zidovudine plus lamivudine	101	88 (87.1%)	103	83 (80.6%)
abacavir plus lamivudine	35	31 (88.6%)	33	28 (84.8%)

N=number of subjects per treatment group

n=number of observations

* Imputations according to the TLOVR algorithm.

† Includes subjects who were rebounder (confirmed viral load ≥ 50 copies/mL after being responder) or who were never suppressed (no confirmed viral load < 50 copies/mL, either ongoing or discontinued due to lack or loss of efficacy).

Response rates (< 50 copies/ml [TLOVR]) in the pooled Phase III trial population were 90.2% in the EDURANT arm and 83.6% in the efavirenz arm in subjects with a baseline viral load ≤ 100,000 copies/ml versus 77.4% and 81.0%, respectively, in subjects with a baseline viral load > 100,000 copies/ml. The proportion of virologic failures according to TLOVR in the pooled Phase III trial population was 3.8% in the EDURANT arm and 3.3% in the efavirenz arm, for subjects with a baseline viral load ≤ 100,000 copies/ml. The proportion of virologic failures was higher for subjects with a baseline viral load > 100,000 copies/ml, especially in the EDURANT arm (15.1% EDURANT-treated subjects vs. 6.3% efavirenz-treated subjects).

The incidence of emergence of N(t)RTI and NNRTI RAMs in the virologic failures (according to the resistance analysis criteria) was lower in the ≤ 100,000 copies/ml category than in the > 100,000 copies/ml category. This difference was observed in both treatment groups but with a lower incidence of emerging mutations in the efavirenz arm. This difference in incidence of

emerging mutations between treatment groups was greater for N(t)RTI mutations. Among patients with baseline viral load $\leq 100,000$ copies/ml (16 patients in the rilpivirine arm and 12 patients in the efavirenz arm), 7 and 6 rilpivirine virologic failures and 2 and 5 efavirenz virologic failures had emerging N(t)RTI RAMs and NNRTI RAMs, respectively. Among patients with baseline viral load $> 100,000$ copies/ml (46 patients in the rilpivirine arm and 16 patients in the efavirenz arm), 35 and 33 rilpivirine virologic failures and 7 and 10 efavirenz virologic failures had emerging N(t)RTI RAMs and NNRTI RAMs, respectively.

Study TMC278-C204 is a randomised, active-controlled, phase IIb trial in antiretroviral treatment-naïve HIV-1 infected adult patients consisting of 2 parts: an initial partially blinded dose-finding part [rilpivirine doses blinded] up to 96 weeks, followed by a long-term, open label part. In the open label part of the trial, patients originally randomised to one of the 3 doses of rilpivirine were all treated with rilpivirine 25 mg once daily in addition to a BR, once the dose for the phase III studies was selected. Patients in the control arm received efavirenz 600 mg once daily in addition to a BR in both parts of the study. The BR consisted of 2 investigator-selected N(t)RTIs: zidovudine plus lamivudine or tenofovir disoproxil fumarate plus emtricitabine.

Study TMC278-C204 enrolled 368 HIV-1 infected treatment-naïve adult patients who had a plasma HIV-1 RNA ≥ 5000 copies/ml, previously received ≤ 2 weeks of treatment with an N(t)RTI or protease inhibitor, had no prior use of NNRTIs, and were screened for susceptibility to N(t)RTI and for absence of specific NNRTI RAMs.

At 96 weeks, the proportion of patients with < 50 HIV-1 RNA copies/ml receiving rilpivirine 25 mg (N=93) compared to patients receiving efavirenz (N=89) was 76% and 71%, respectively. The mean increase from baseline in CD4+ counts was 146×10^6 cells/l in patients receiving rilpivirine 25 mg and 160×10^6 cells/l in patients receiving efavirenz.

Of those patients who were responders at week 96, 80% of patients remained with undetectable viral load (< 50 HIV-1 RNA copies/ml) at week 192. There were no safety concerns identified in the week 192 analyses.

INDICATIONS

EDURANT, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients with viral load $\leq 100,000$ copies/ml at baseline.

This indication is based on Week 48 safety and efficacy analyses from 2 randomised double-blind, controlled Phase III trials in treatment-naïve adult patients and on Week 96 safety and efficacy analyses from the Phase IIb trial TMC278-C204 in treatment-naïve adult patients (see CLINICAL TRIALS section).

CONTRAINDICATIONS

Hypersensitivity to rilpivirine or to any of the excipients.

EDURANT should not be co-administered with the following medicinal products, as significant decreases in rilpivirine plasma concentrations may occur (due to CYP3A enzyme induction or gastric pH increase), which may result in loss of therapeutic effect of EDURANT:

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifabutin, rifampicin, rifapentine
- proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole
- the glucocorticoid systemic dexamethasone, except as a single dose treatment
- St John's wort (*Hypericum perforatum*).

PRECAUTIONS

Patients should be advised that current antiretroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV to others through blood or sexual contact. Appropriate precautions to prevent the transmission of HIV should continue to be employed.

Virologic Failure and Development of Resistance

In the pooled analysis from the phase III trials, patients treated with EDURANT with a baseline viral load > 100,000 HIV-1 RNA copies/ml had a greater risk of virologic failure (15.1% with EDURANT versus 6.3% efavirenz arm) compared to patients with a baseline viral load ≤100,000 HIV-1 RNA copies/ml (3.8% with EDURANT versus 3.3% efavirenz arm). Patients with a baseline viral load > 100,000 HIV-1 RNA copies/ml who experienced virologic failure exhibited a higher rate of treatment emergent resistance to the NNRTI class. More patients who failed virologically on EDURANT than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance. This information should be taken into consideration when initiating therapy with EDURANT (see CLINICAL TRIALS section).

Interactions with medicinal products

Caution should be given to prescribing rilpivirine with medicinal products that may reduce the exposure of rilpivirine. For information on interactions with medicinal products (see CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES).

Medicines that suppress gastric acid

Use of proton pump inhibitors is contraindicated as significant decreases in EDURANT plasma concentrations may occur (see CONTRAINDICATIONS).

The combination of EDURANT and H₂-receptor antagonists or antacids should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). H₂-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after EDURANT and antacids should only be administered at least 2 hours before or at least 4 hours after EDURANT (see INTERACTIONS WITH OTHER MEDICINES).

Fat redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long term consequences of these events are currently unknown. A causal relationship has not been established (see ADVERSE EFFECTS).

Immune reconstitution syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including rilpivirine. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, and tuberculosis), which may necessitate further evaluation and treatment (see ADVERSE EFFECTS).

Hepatic impairment

There is limited information regarding the use of EDURANT in patients with mild or moderate hepatic impairment, resulting in unexpected variability in the available data. EDURANT has not been studied in patients with severe hepatic impairment (see Pharmacokinetics and DOSAGE and ADMINISTRATION). EDURANT should be used with caution in patients with moderate to severe hepatic impairment (see Pharmacokinetics and DOSAGE and ADMINISTRATION).

CYP3A Metabolism

Rilpivirine is a CYP3A substrate. It is possible that different populations of patients have faster or slower rilpivirine metabolism because of the various isoenzymes within the CYP3A system.

Effects on fertility

No human data on the effect of rilpivirine on fertility are available. In a study conducted in rats, there were no effects on mating or fertility with rilpivirine up to 400 mg/kg/day, a dose of rilpivirine that showed maternal toxicity. This dose is associated with an exposure that is approximately 40 times higher than the exposure in humans at the recommended dose of 25 mg q.d.

Use in Pregnancy

Category B1

There are no adequate and well controlled or pharmacokinetic studies with rilpivirine in pregnant women. Placental transfer of rilpivirine or its metabolites from dam to fetus was demonstrated in rats. Studies in animals have shown no evidence of relevant embryonic or foetal toxicity or an effect on reproductive function. There was no clinically relevant teratogenicity with rilpivirine in rats and rabbits. The exposures at the embryo foetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 15 and 71 times higher than the exposure in humans at the recommended dose of 25 mg q.d.

EDURANT should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

It is not known whether rilpivirine is secreted in human milk. In nonclinical studies, rilpivirine was detected in the plasma of suckling rats following maternal dosing. Because of both the potential for HIV transmission and the potential for adverse events in nursing infants, mothers should be instructed not to breastfeed if they are receiving EDURANT.

Children

Treatment with EDURANT is not recommended in paediatric patients (<18 years) due to insufficient data in this patient population.

Elderly

No dose adjustment of EDURANT is required in elderly patients.

Carcinogenicity

Rilpivirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 20, 60 and 160 mg/kg/day were administered to mice and doses of 40, 200, 500 and 1500 mg/kg/day were administered to rats. An increase in the incidences of hepatocellular adenomas and carcinomas was observed in mice and rats. An increase in the incidences of follicular cell adenomas and/or carcinomas in the thyroid gland was observed in rats. Administration of rilpivirine did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular findings in mice and rats are considered to be rodent specific, associated with liver enzyme induction. A similar mechanism does not exist in humans; hence, these tumors are not relevant for humans. The follicular cell findings are considered to be rat specific, associated with increased clearance of thyroxine and are not considered to be relevant for humans. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21 fold (mice) and 3 fold (rats), relative to those observed in humans at the recommended dose (25 mg q.d.).

Genotoxicity

Rilpivirine has tested negative in the *in vitro* Ames reverse mutation assay, *in vitro* chromosomal aberration assay in human lymphocyte and *in vitro* clastogenicity mouse lymphoma assay, tested in the absence and presence of a metabolic activation system. Rilpivirine did not induce chromosomal damage in the *in vivo* micronucleus test in mice.

INTERACTIONS WITH OTHER MEDICINES

Medicinal products that affect rilpivirine exposure

Rilpivirine is primarily metabolised by cytochrome P450 CYP3A, and medicinal products that induce or inhibit CYP3A may thus affect the clearance of rilpivirine. Co-administration of EDURANT and medicinal products that induce CYP3A may result in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of rilpivirine. Co-administration of EDURANT and medicinal products that inhibit CYP3A may result in increased plasma concentrations of rilpivirine.

Co administration of EDURANT with medicinal products that increase gastric pH may result in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of rilpivirine.

Medicinal products that are affected by the use of rilpivirine

EDURANT at a dose of 25 mg q.d. is not likely to have a clinically relevant effect on the exposure of medicinal products metabolised by CYP enzymes.

Established and theoretical interactions with selected antiretrovirals and non antiretroviral medicinal products are listed in Table 4 and Table 5, respectively.

Interactions between rilpivirine and co-administered medicinal products are listed in the tables below (increase is indicated as “↑”, decrease as “↓”, no change as “↔”, not applicable as “NA”, once daily as “q.d.” and twice daily as “b.i.d.”).

Table 4: Drug interactions – Rilpivirine co-administered with antiretroviral and antiviral medicinal products

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C _{max}	AUC	C _{min}
NUCLEOSIDE OR NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs/N[t]RTIs)					
Didanosine* [#]	400 mg q.d.	didanosine	↔	↑ 12%	NA
		rilpivirine	↔	↔	↔
No dose adjustment is required when EDURANT is co-administered with didanosine. As didanosine is administered on an empty stomach, didanosine should be administered at least one hour before or two hours after EDURANT (which should be administered with a meal).					
Tenofovir disoproxil fumarate* [#]	300 mg q.d.	tenofovir	↑ 19%	↑ 23%	↑ 24%
		rilpivirine	↔	↔	↔
No dose adjustment is required when EDURANT is co-administered with tenofovir disoproxil fumarate.					
Other NRTIs (abacavir, emtricitabine, lamivudine, stavudine and zidovudine)	Based on the different elimination routes for rilpivirine and these other NRTIs, no clinically relevant drug-drug interactions are expected between these medicinal products and EDURANT.				
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)					
NNRTIs (delavirdine, efavirenz, etravirine, nevirapine)	It is not recommended to co-administer EDURANT with NNRTIs.				
PROTEASE INHIBITORS (PIs) - with co-administration of low dose ritonavir					
Darunavir/ritonavir* [#]	800/100 mg q.d.	darunavir	↔	↔	↓ 11%
		rilpivirine	↑ 79%	↑ 130%	↑ 178%
Concomitant use of EDURANT with darunavir/ritonavir may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when EDURANT is co-administered with darunavir/ritonavir.					
Lopinavir/ritonavir (soft gel capsules)* [#]	400/100 mg b.i.d.	lopinavir	↔	↔	↓ 11%
		rilpivirine	↑ 29%	↑ 52%	↑ 74%
Concomitant use of EDURANT with lopinavir/ritonavir may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when EDURANT is co-administered with lopinavir/ritonavir.					
Other boosted PIs (atazanavir/ritonavir, fosamprenavir/ritonavir, saquinavir/ritonavir, tipranavir/ritonavir)	Concomitant use of EDURANT with boosted PIs may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). EDURANT is not expected to affect the plasma concentrations of co-administered PIs.				
PROTEASE INHIBITORS (PIs) - without co-administration of low dose ritonavir					
Unboosted PIs (atazanavir, fosamprenavir, indinavir, nelfinavir)	Concomitant use of EDURANT with unboosted PIs may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). EDURANT is not expected to affect the plasma concentrations of co-administered PIs.				
CCR5 ANTAGONISTS					
Maraviroc	No clinically relevant drug-drug interaction is expected when EDURANT is co-administered with maraviroc.				
INTEGRASE STRAND TRANSFER INHIBITORS					

Raltegravir No clinically relevant drug-drug interaction is expected when EDURANT is co-administered with raltegravir.

OTHER ANTIVIRAL AGENTS

Ribavirin No clinically relevant drug-drug interaction is expected when EDURANT is co-administered with ribavirin.

* The interaction between EDURANT and the drug was evaluated in a clinical study. All other drug interactions shown are predicted.

This interaction study has been performed with a dose higher than the recommended dose for EDURANT assessing the maximal effect on the co-administered drug. The dosing recommendation is applicable to the recommended dose of EDURANT 25 mg q.d.

Table 5: Drug interactions – Rilpivirine co-administered with non-antiretroviral medicinal products

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C _{max}	AUC	C _{min}
ANTICONVULSANTS					
Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	EDURANT should not be used in combination with these anticonvulsants as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT.				
AZOLE ANTIFUNGAL AGENTS					
Ketoconazole* [#]	400 mg q.d.	ketoconazole	↔	↓ 24%	↓ 66%
		rilpivirine	↑ 30%	↑ 49%	↑ 76%
Fluconazole Itraconazole Posaconazole Voriconazole	Concomitant use of EDURANT with azole antifungal agents may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when EDURANT is co-administered with azole antifungal agents.				
ANTIMYCOBACTERIALS					
Rifabutin* [#]	300 mg q.d.	rifabutin	↔	↔	↔
		25- O-desacetyl-rifabutin	↔	↔	↔
		rilpivirine	↓ 35%	↓ 46%	↓ 49%
	EDURANT should not be used in combination with rifabutin as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT				
Rifampicin* [#]	600 mg q.d.	rifampicin	↔	↔	NA
		25-desacetyl-rifampicin	↔	↓ 9%	NA
		rilpivirine	↓ 69%	↓ 80%	↓ 89%
Rifapentine	EDURANT should not be used in combination with rifampicin or rifapentine as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT.				
MACROLIDE ANTIBIOTICS					
Clarithromycin Erythromycin Troleandomycin	Concomitant use of EDURANT with clarithromycin, erythromycin and troleandomycin may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Where possible, alternatives such as azithromycin should be considered.				
GLUCOCORTICOIDS					
Dexamethasone (systemic)	EDURANT should not be used in combination with systemic dexamethasone as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT. Alternatives should be considered, particularly for long-term use.				
PROTON PUMP INHIBITORS					
Omeprazole* [#]	20 mg q.d.	omeprazole	↓ 14%	↓ 14%	NA

Lansoprazole		rilpivirine	↓ 40%	↓ 40%	↓ 33%
Rabeprazole	EDURANT should not be used in combination with proton pump inhibitors as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). This may result in loss of therapeutic effect of EDURANT.				
Pantoprazole					
Esomeprazole					
H₂-RECEPTOR ANTAGONISTS					
Famotidine* [#]	40 mg single dose taken 12 hours before rilpivirine	rilpivirine	↔	↓ 9%	NA
	40 mg single dose taken 2 hours before rilpivirine	rilpivirine	↓ 85%	↓ 76%	NA
	40 mg single dose taken 4 hours after rilpivirine	rilpivirine	↑ 21%	↑ 13%	NA
Cimetidine	The combination of EDURANT and H ₂ -receptor antagonists should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). H ₂ -receptor antagonists should only be administered at least 12 hours before or at least 4 hours after EDURANT.				
Nizatidine					
Ranitidine					
ANTACIDS					
Antacids (e.g., aluminium or magnesium hydroxide, calcium carbonate)	The combination of EDURANT and antacids should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). Antacids should only be administered either at least 2 hours before or at least 4 hours after EDURANT.				
NARCOTIC ANALGESICS					
Methadone*	60-100 mg q.d., individualised dose	R(-) methadone	↓ 14%	↓ 16%	↓ 22%
		S(+) methadone	↓ 13%	↓ 16%	↓ 21%
	No dose adjustments are required when initiating co-administration of methadone with EDURANT. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.				
HERBAL PRODUCTS					
St John's wort (<i>Hypericum perforatum</i>)	EDURANT should not be used in combination with products containing St John's wort as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT.				
ANALGESICS					
Acetaminophen* [#] (paracetamol)	500 mg single dose	acetaminophen	↔	↔	NA
		rilpivirine	↔	↔	↑ 26%
	No dose adjustment is required when EDURANT is co-administered with acetaminophen (paracetamol).				
ESTROGEN-BASED CONTRACEPTIVES					
Ethinylestradiol*	0.035 mg q.d.	ethinylestradiol	↑ 17%	↔	↔
Norethindrone*	1 mg q.d.	norethindrone	↔	↔	↔
	No dose adjustment is required for the concomitant use of EDURANT and estrogen- and/or progesterone-based contraceptives.				
HMG CO-A REDUCTASE INHIBITORS					
Atorvastatin* [#]	40 mg q.d.	atorvastatin	↑ 35%	↔	↓ 15%
		rilpivirine	↓ 9%	↔	↔
Fluvastatin	No dose adjustment is required when EDURANT is co-administered with an HMG Co-A reductase inhibitor.				
Lovastatin					
Pitavastatin					
Pravastatin					
Rosuvastatin					
Simvastatin					
PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITOR					

Sildenafil**	50 mg single dose	sildenafil	↔	↔	NA
		rilpivirine	↔	↔	↔
Vardenafil Tadalafil	No dose adjustment is required when EDURANT is co-administered with a PDE-5 inhibitor.				

* The interaction between rilpivirine and the drug was evaluated in a clinical study. All other drug-drug interactions shown are predicted.

This interaction study has been performed with a dose higher than the recommended dose for EDURANT assessing the maximal effect on the co-administered drug. The dosing recommendation is applicable to the recommended dose of rilpivirine 25 mg q.d.

QT prolonging drugs

There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and other medicinal products that prolong the QTc interval of the electrocardiogram. In a study of healthy subjects, supratherapeutic doses of rilpivirine (75 mg q.d. and 300 mg q.d.) have been shown to prolong the QTc interval of the electrocardiogram (see Pharmacodynamics). EDURANT at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc. EDURANT should be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes.

Effect on Ability to Drive or Operate Machinery

EDURANT has no or negligible influence on the ability to drive and use machines.

ADVERSE EFFECTS

Adverse Drug Reactions from Clinical Trials

The safety assessment is based on pooled data from 1368 patients in the phase III controlled trials TMC278 C209 (ECHO) and TMC278 C215 (THRIVE) in antiretroviral treatment naïve HIV 1 infected adult patients, 686 of whom received EDURANT (25 mg q.d.) (see section 5.1). The median duration of exposure for patients in the EDURANT arm and efavirenz arm was 55.7 and 55.6 weeks, respectively.

In the phase III controlled trials ECHO and THRIVE, the most frequently reported adverse drug reactions (ADRs) $\geq 2\%$ that were at least grade 2 in severity were depression (3.5% in the EDURANT arm and 2.2% in the efavirenz arm), insomnia (2.9% in the EDURANT arm and 3.2% in the efavirenz arm), headache (2.6% in the EDURANT arm and 3.4% in the efavirenz arm), rash (2.2% in the EDURANT arm and 9.4% in the efavirenz arm), abnormal dreams (1.5% in the EDURANT arm and 3.8% in the efavirenz arm), nausea (1.2% in the EDURANT arm and 2.6% in the efavirenz arm) and dizziness (0.7% in the EDURANT arm and 6.6% in the efavirenz arm) (see table 6 for the complete list of ADRs).

The majority of the ADRs reported during treatment with EDURANT 25 mg once daily were grade 1 to 2 in severity. Grade 3 or 4 ADRs were reported in 3.1% and 5.6% of the EDURANT and efavirenz treated patients, respectively. The most commonly reported grade 3 or 4 ADRs were transaminases increased (1.5% in the EDURANT arm and 2.8% in the efavirenz arm), depression (0.3% in the EDURANT arm and 0.6% in the efavirenz arm), dizziness (0.3% in the EDURANT arm and 0.4% in the efavirenz arm) and rash (0.3% in the EDURANT arm and 0.6% in the efavirenz arm). 1.6% of patients in the EDURANT arm discontinued treatment due to ADRs compared to 4.0% of patients in the efavirenz arm. In the EDURANT arm, all ADRs leading to discontinuation had an incidence $< 0.5\%$. In the efavirenz arm, the most common ADRs leading to discontinuation were rash (1.5%), transaminases increased (0.7%), depression (0.6%) and abnormal dreams (0.6%).

The most common ADRs were identified in the system organ classes (SOC) of nervous system disorders (24.1% in the EDURANT arm and 41.2% in the efavirenz arm), psychiatric disorders (21.3% in the EDURANT arm and 24.2% in the efavirenz arm) and gastrointestinal disorders (20.8% in the EDURANT arm and 19.8% in the efavirenz arm). The difference between EDURANT and the efavirenz arms observed in the SOC nervous system disorders was mainly due to the difference in dizziness experienced by patients.

Clinical ADRs of at least moderate intensity (\geq grade 2) reported in adult patients treated with EDURANT are summarised in Table 6. The ADRs are listed by system organ class (SOC) and frequency. Selected treatment emergent laboratory abnormalities, considered as ADRs, are included in Table 7.

Table 6: ADRs of at least moderate intensity (\geq grade 2) reported in antiretroviral treatment-naïve HIV-1 infected adult patients treated with rilpivirine			
System Organ Class (SOC) Adverse drug reaction, %	Pooled data from the ECHO and THRIVE trials		
	rilpivirine + BR N=686	efavirenz + BR N=682	Treatment Difference (95%CI)
Skin and subcutaneous tissue disorders	2.2%	9.4%	ND
Rash ^{**}	2.2%	9.4%	-7.2 (-9.6; -4.8)
Psychiatric disorders	8.3%	8.5%	ND
Depression	3.5%	2.2%	1.3 (-0.5; 3.1)
Insomnia	2.9%	3.2%	-0.3 (-2.1; 1.5)
Abnormal dreams ^{*†}	1.5%	3.8%	-2.4 (-4; -0.7)
Sleep disorders	1.2%	0.7%	0.4 (-0.6; 1.5)
Depressed mood	0.4%	0.3%	0.1 (-0.5; 0.8)
Nervous system disorders	3.4%	10.3%	ND
Headache ^{*†}	2.6%	3.4%	-0.8 (-2.6; 1.1)
Dizziness ^{**}	0.7%	6.6%	-5.9 (-7.8; -3.9)
Somnolence	0.6%	1.3%	-0.7 (-1.8; 0.3)
Gastrointestinal disorders	2.8%	4.8%	ND
Abdominal pain	1.3%	1.6%	-0.3 (-1.6; 1)
Nausea ^{*§}	1.2%	2.6%	-1.5 (-2.9; 0)
Vomiting	0.9%	1.6%	-0.7 (-1.9; 0.4)
Abdominal discomfort	0.4%	0.1%	0.3 (-0.3; 0.9)
Metabolism and nutrition disorders	1.2%	0.6%	ND
Decreased appetite	1.2%	0.6%	0.6 (-0.4; 1.6)
General disorders and administration site conditions	1.3%	1.8%	ND
Fatigue	1.3%	1.8%	-0.4 (-1.8; 0.9)
Investigations	2.5%	3.2%	ND
Transaminases increased	2.5%	3.2%	-0.7 (-2.5; 1)

BR=background regimen; CI=confidence interval

N=total number of subjects per treatment group; ND=not determined.

* Treatment comparison was pre-specified for these ADRs (Fisher's Exact Test)

† p-value < 0.01

p-value < 0.0001

§ p-value < 0.05

There were no additional ADR terms identified in adult patients in the phase IIb TMC278-C204 trial through 192 weeks.

Laboratory abnormalities

Selected treatment emergent clinical laboratory abnormalities (grade 3 or grade 4), considered as ADRs, reported in EDURANT-treated patients are shown in Table 7.

Table 7: Selected treatment emergent laboratory abnormalities (grade 3 or grade 4) observed in antiretroviral treatment-naïve HIV-1 infected adult patients			
Laboratory parameter abnormality, %	DAIDS toxicity range	Pooled data from the ECHO and THRIVE trials	
		rilpivirine + BR N=686	efavirenz + BR N=682
HEMATOLOGY			
Decreased hemoglobin	< 4.5 mmol/L < 74 g/L	0.1%	0.3%
Decreased platelet count	< 49999/mm ³ < 49999 x 10 ⁹ /L	0.1%	0.3%
Decreased white blood cell count	< 1499/mm ³ < 1.499 10 ⁹ /L	1.0%	0.9%
BIOCHEMISTRY			
Increased creatinine	> 1.8 x ULN	0%	0.1%
Increased AST	> 5.0 x ULN	2.0%	2.8%
Increased ALT	> 5.0 x ULN	1.5%	3.4%
Increased bilirubin	> 2.5 X ULN	0.6%	0.1%
Increased pancreatic amylase	> 2 x ULN	2.9%	4.0%
Increased lipase	> 3 x ULN	0.4%	1.3%
Increased total cholesterol (fasted)*	> 7.77 mmol/L > 300 mg/dl	0.1%	2.5%
Increased LDL cholesterol (fasted)*	> 4.91 mmol/L ≥ 191 mg/dl	0.7%	4.1%
Increased Triglycerides (fasted)*	≥ 8.49 mmol/L ≥ 751 mg/dl	0.3%	2.2%

BR=background regimen; ULN=upper limit of normal

N=number of subjects per treatment group

* p ≤ 0.001 according to Fisher's Exact test (difference in grade 3 plus 4 abnormalities between the two treatment groups).

Note: Percentages were calculated for the number of subjects with results for the analyte.

Adrenal Function

In the pooled Phase 3 trials, at Week 48, the overall mean change from baseline in basal cortisol showed a decrease of -13.1 nmol/L in the EDURANT group, and an increase of +9.0 nmol/L in the efavirenz group. At Week 48, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the EDURANT group (+16.5 ± 6.14 nmol/L) than in the efavirenz group (+58.1 ± 6.66 nmol/L). Mean values for both basal and ACTH-stimulated cortisol values at Week 48 were within the normal range. Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency.

Serum Creatinine

Increases in serum creatinine occurred within the first four weeks of treatment and remained stable through 48 weeks. A mean change of 0.09 mg/dL (range: -0.20 mg/dL to 0.62 mg/dL) was observed after 48 weeks of treatment. In subjects who entered the trial with mild or moderate renal impairment, the serum creatinine increase observed was similar to that seen in subjects with normal renal function. These changes are not considered to be clinically relevant and no subject discontinued treatment due to increases in serum creatinine. Creatinine increases were comparable by background N(t)RTIs.

Serum lipids

Changes from baseline in total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides are presented in Table 8. The mean changes from baseline were smaller in the EDURANT arm versus the efavirenz arm. The impact of such findings has not been demonstrated.

Table 8: Lipid values, mean change from baseline						
	Pooled data from the ECHO and THRIVE Trials					
	rilpivirine + BR N=686			efavirenz + BR N=682		
	Baseline	Week 48		Baseline	Week 48	
Mean (95% CI)	Mean (mg/dl)	Mean (mg/dl)	Mean change* (mg/dl)	Mean (mg/dl)	Mean (mg/dl)	Mean change* (mg/dl)
Total cholesterol (fasted) [†]	161	163	2	161	189	27
HDL-cholesterol (fasted) [†]	41	45	4	40	50	10
LDL-cholesterol (fasted) [†]	96	95	-1	96	110	14
Triglycerides (fasted) [†]	124	116	-7	133	149	13

N=number of subjects per treatment group

* The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and week 48 values.

† p-value < 0.001, Wilcoxon rank-sum test for treatment comparison of change from baseline

Lipodystrophy

Combination antiretroviral therapy (CART) has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (see PRECAUTIONS).

Immune reconstitution syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (immune reconstitution syndrome) (see PRECAUTIONS).

Additional information on special populations

Patients co-infected with hepatitis B and/or hepatitis C virus

In patients co-infected with hepatitis B or C virus receiving EDURANT, the incidence of hepatic enzyme elevation was higher than in patients receiving EDURANT who were not co-infected. This observation was the same in the efavirenz arm. The pharmacokinetic exposure of rilpivirine in co-infected patients was comparable to that in patients without co-infection.

DOSAGE AND ADMINISTRATION

EDURANT must always be given in combination with other antiretroviral medicinal products.

Adults

The recommended dose of EDURANT is one 25 mg tablet once daily taken orally with a meal (see Pharmacokinetics).

Elderly

No dose adjustment of EDURANT is required in elderly patients (see Pharmacokinetics).

Paediatric Population

The safety and efficacy of EDURANT in adolescents and children are under investigation (see Pharmacokinetics). No data are available patients <18 years of age. Treatment with EDURANT is not recommended in these populations.

Hepatic impairment

No dose adjustment of EDURANT is required in patients with mild or moderate hepatic impairment (Child Pugh score A or B). EDURANT has not been studied in patients with severe hepatic impairment (Child Pugh score C). EDURANT should be used with caution in patients with moderate to severe hepatic impairment (see Pharmacokinetics and PRECAUTIONS).

Renal impairment

No dose adjustment of EDURANT is required in patients with renal impairment (see Pharmacokinetics).

Timing of dosing

If the patient misses a dose of EDURANT within 12 hours of the time it is usually taken, the patient should take EDURANT with a meal as soon as possible and then take the next dose of EDURANT at the regularly scheduled time. If a patient misses a dose of EDURANT by more than 12 hours, the patient should not take the missed dose, but resume the usual dosing schedule.

OVERDOSAGE

There is no specific antidote for overdose with EDURANT. Human experience of overdose with rilpivirine is limited. Treatment of overdose with rilpivirine consists of general supportive measures including monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance may be achieved by gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since rilpivirine is highly bound to plasma protein, dialysis is unlikely to result in significant removal of the active substance.

PRESENTATION AND STORAGE CONDITIONS

EDURANT 25 mg tablets are white to off-white, film coated, round, biconvex, tablet, debossed with "TMC" on one side and "25" on the other side.

EDURANT tablets are provided in a high density polyethylene (HDPE) bottle with a polypropylene (PP) child resistant closure and induction seal liner. One bottle contains 30 tablets.

Store below 30°C. Store in the original bottle. Protect from light.

NAME AND ADDRESS OF SPONSOR

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Tibotec, a division of JANSSEN-CILAG Pty Ltd

POISON SCHEDULE OF THE DRUG

Prescription Only Medicine

Date of TGA approval: 21 December 2011

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