Assessment report

Edurant

International non-proprietary name: **rilpivirine**

Procedure No. **EMEA/H/C/002264**

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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22 September 2011
EMA/CHMP/576493/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

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An agency of the European Union

Product information

Name of the medicinal product:	Edurant
Applicant:	Janssen-Cilag International N.V. Turnhoutseweg 30 BE-2340 Beerse Belgium
Active substance:	rilpivirine hydrochloride
International Nonproprietary Name/Common Name:	rilpivirine
Pharmaco-therapeutic group (ATC Code):	DIRECT ACTING ANTIVIRALS (J05AG05)
Therapeutic indication(s):	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 a viral load ≤ 100,000 HIV 1 RNA copies/ml. This indication is based on week 48 safety and efficacy analyses from two randomised, double blind, controlled, Phase III trials in treatment naïve patients and week 96 safety and efficacy analyses from a Phase IIb trial in treatment naïve patients (see section 5.1). As with other antiretroviral medicinal products, genotypic resistance testing should guide the use of Edurant (see sections 4.4 and 5.1).
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	25 mg
Route(s) of administration:	Oral use
Packaging:	bottle (HDPE)
Package size(s):	30 tablets

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List of abbreviations

3TC	lamivudine
ABC	abacavir
ACTG	AIDS Clinical Trials Group
ACTH	adrenocorticotropic hormone
ADR	adverse drug reactions
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC24h	area under the plasma/serum concentration versus time curve from time 0 to 24 hours after dosing
AUCinf	area under the concentration versus time curve extrapolated to infinite time, calculated as AUC0−last + (Clast/λz)
AUClast	rea under the concentration versus time curve from time zero to the last quantifiable concentration
AUCtau	area under the concentration versus time curve over the dosing I interval
AVMR	antiviral microbiology report
AZT	zidovudine; ZDV
BCO	biological cut-off
BID	twice daily
BMD	bone mineral density
Caco-2	colon carcinoma-derived
CBV	Combivir (lamivudine/zidovudine)
CCO	clinical cut-off
CDC	Center for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CLcr	creatinine clearance
CL/F	apparent clearance
Cmax	maximum observed concentration of drug in plasma
Cmin	minimum observed concentration of drug in plasma (trough level)
CPT	Child-Pugh-Turcotte (classification system for hepatic impairment)
CRR or CSR	clinical research report or study report
CV	coefficient of variation
CYP	cytochrome P450
d4T	stavudine
dATP	deoxyadenosine triphosphate
dCTP	deoxycytidine triphosphate
ddI	didanosine
DHEAS	dehydroepiandrosterone sulphate
DHHS	Department of Human Health and Services
DNA	deoxyribonucleic acid
DLV	delavirdine
DRV	darunavir
EACS	European AIDS Clinical Society
EC	enteric coated
EC50	median 50% effective concentration
ECG	electrocardiogram
EFV	efavirenz (Sustiva®)
eGFR	estimated glomerular filtration rate
eGFRcreat	estimated glomerular filtration rate for creatinine as calculated by modification of diet in renal disease (MDRD) formula
eGFRcyst	estimated glomerular filtration rate for cystatin C
EMA, EMEA	European Medicines Agency
EOI	event of interest
ESRD	end-stage renal disease

ETR	etravirine
EU	European Union
FC	fold change
FDA (US)	Food and Drug Administration
FDC	fixed-dose combination
FTC	emtricitabine (Emtriva)
FTC/RPV/TDF	emtricitabine/rilpivirine/tenofovir disoproxil fumarate (fixed-dose combination product)
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate (Truvada; fixed-dose combination product)
FTC-TP	emtricitabine triphosphate
GAM	generalized additive models
GFR	glomerular filtration rate
GLS	geometric least squares
H2	histamine-2
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV-1 (-2)	human immunodeficiency virus type 1 (-2)
hOAT (1, 3)	human organic anion transporter (type 1, type 3)
HOMA-IR	homeostasis model assessment insulin resistance
HPLC	high-performance liquid chromatography
IAS-USA	International AIDS Society-United States of America
ICH	International Conference on Harmonization
IC50	50% inhibitory concentration
IDV	indinavir
ITT	intent-to-treat
Ki	inhibition constant
LDL	low-density lipoprotein
LOCF	last observation carried forward
LPV	lopinavir
LPV/r	lopinavir/ritonavir
M = F	missing = failure
MAA (EU)	Marketing Authorization Application
MCS	mental component summary
MDCK	Madin-Darby canine kidney
MDRD	modification of diet in renal disease
MITT	modified intent-to-treat
MRP (2,4)	multidrug resistance protein (type 2, type 4)
mtDNA	mitochondrial DNA
NC = F	noncompleter = failure
NNRTI	nonnucleoside reverse transcriptase inhibitor
non-VF	non-virologic failure
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI, N(t)RTI	nucleotide reverse transcriptase inhibitor
NVP	nevirapine
PBMC	peripheral blood mononuclear cell
PCS	Physical Component Summary
P-gp	P-glycoprotein
PI	protease inhibitor
PK	pharmacokinetic
PMPA	9-R-2-(phosphonomethoxy)propyl]adenine
PP	per protocol
PNP	purine nucleoside phosphorylase
PSUR	periodic safety update report
QT	interval representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected by Fridericia's formula
/r	itonavir boosted
RAM	resistance-associated mutation
RNA	ribonucleic acid

RPTEC	renal proximal tubule cell
RPV	rilpivirine (27.5 mg rilpivirine hydrochloride is equivalent to 25 mg RPV)
RT	reverse transcriptase
RTV	ritonavir (Norvir)
rtv	coadministered low-dose ritonavir
SAE	serious adverse event
SAWP	Scientific Advice Working Party
SD	standard deviation
SF-36v2®	Short Form-36 version 2
SmPC	Summary of Product Characteristics
SNPs	single-nucleotide polymorphisms
SOC	system organ class
T½, t1/2,	term terminal elimination half-life
TAM	thymidine analogue-associated mutation
TDF	tenofovir disoproxil fumarate (Viread), (300 mg TDF is equivalent to 45 mg tenofovir disoproxil or 136 mg of tenofovir)
TFV	tenofovir
TLOVR	time to loss of virologic response
TMC	Tibotec Medicinal Compound
tmax	time (observed time point) of Cmax
TQT	thorough QT
US, USA	United States
VF	virologic failure
ZDV	ZIDOVUDINE, AZT

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 2 September 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Edurant, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 December 2009.

The applicant applied for the following indication: Rilpivirine, 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.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/43/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance rilpivirine (hydrochloride) contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19 July 2007, 24 April 2008 and 22 October 2009. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

In the first Scientific Advice (EMEA/H/SA/919/1/2007/III) the CHMP remarked that a non-inferiority margin of 10% is regarded as more appropriate in studies in antiretroviral naïve patients, despite this remark the company chose for a non-inferiority margin of 12%. However, as the results of the pivotal phase III studies also demonstrate non-inferiority within the 10% margin this considered acceptable. Furthermore based upon non-clinical safety signals the CHMP considered that the effect on cortisol as well as on coagulation parameters should be assessed in the phase III studies. This was done for cortisol however not for coagulation parameters.

The second Scientific Advice (EMEA/H/SA/919/1/FU/1/2008/II) concerned a new dose selection. In this advice in view of preclinical data obtained so far and the results of the TQT-study conduct of an electrophysiology study (APD-study) in accordance with ICH S 7 B was highly recommended. Such a specific APD-study has not been performed but as the safety pharmacology has been extensively studied in other ways this is considered acceptable.

In the third Scientific Advice (EMEA/H/SA/919/1/FU/2/2009/III it was remarked that it should be ensured that all failing patients in phase III studies were followed with regard to development of resistance. This has thoroughly been done in the phase II and III studies. Concerning the QTc study C152 the requests of CHMP with regard to presentation of results were partly fulfilled.

In addition based upon the clinical and non-clinical data the CHMP concluded that rilpivirine may have a proarrhytmic effect. The request for special attention for potential effects on QTc was addressed by the applicant.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Barbara van Zwieten-Boot** Co-Rapporteur: **Kristina Dunder**

- The application was received by the EMA on 2 September 2010.
- The procedure started on 22 September 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 December 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 December 2010.
- During the meeting on 20 January 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 January 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 8 April 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 1 June 2011.
- During the CHMP meeting on 23 June 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 8 August 2011.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 September 2011.
- The Rapporteurs circulated the revised Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 16 September 2011.
- During the meeting on 19-22 September 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Edurant on 22 September 2011.

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Infection with human immunodeficiency virus (HIV) and the resulting Acquired Immunodeficiency Syndrome (AIDS) are having a significant human and socio-economic impact.

Introduction of combination antiretroviral therapy (ART) has led to a dramatic reduction in mortality and morbidity in treated HIV-infected individuals. Further improvements in therapy and outcome have been challenged by limitations of the commercially available antiretroviral (ARV) agents, including safety and tolerability, dosing complexity, and the emergence of viral resistance resulting in reduced ARV activity.

Current treatment guidelines recommend a combination of 2 nucleoside/tide reverse transcriptase inhibitor (N(t)RTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) for first line therapy in HIV infected individuals. Improved tolerability, safety, and simple dosing regimens are important drivers of good adherence and hence lessen risk of development of drug resistance and should, therefore, be considered as major elements in the development of new potent ARV compounds, especially for the ARV treatment-naïve population.
NNRTIs play an important role and are widely used in the treatment of HIV infection, most commonly in first line therapy. The currently approved NNRTIs in the United States of America (USA) and/or Europe for use in treatment-naïve adult patients are nevirapine (NVP), delavirdine [DLV) and efavirenz (EFV). These NNRTIs can be associated with safety/tolerability problems (mainly hepatotoxicity, central nervous system symptoms, and/or rash). Currently one novel NNRTI, etravirine (ETR), is approved for use in HIV-1 infected, treatment-experienced adult patients, including those with NNRTI resistance.

2.1.2. About the product

Rilpivirine (TMC278; formerly known as R278474) is a di-amino pyrimidine derivative. It is a novel NNRTI with in vitro activity against wild-type HIV-1 and NNRTI-resistant mutants. It has been developed for treatment of ARV naïve HIV-1 infected individuals with the aim to have a better safety/tolerability profile compared to other NNRTIs (such as nevirapine and efavirenz and etravrine). Furthermore, the pharmacokinetic profile allows a once daily (q.d.) dosing.

There are currently no data available from clinical studies with RPV in treatment-experienced or in heavily pretreated patients.

The applicant applied for the following indication: Rilpivirine, 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. The recommended dose of EDURANT is one 25 mg tablet taken once daily.

Rilpivirine at the time of submission was not registered in any country in the world.

2.2. Quality aspects

2.2.1. Introduction

Rilpivirine is presented as film-coated tablets for immediate release containing rilpivirine hydrochloride equivalent to 25 mg rilpivirine as active substance. The other ingredients are povidone, polysorbate 20, lactose monohydrate, croscarmellose sodium, silicified microcrystalline cellulose, croscarmellose sodium and magnesium stearate. The ingredients of the coating are hypromellose, lactose monohydrate, macrogol, triacetin and titanium dioxide. The medicinal product is packaged in HDPE bottles with polypropylene (PP) child-resistant closure with an aluminium induction seal liner.

2.2.2. Active Substance

Rilpivirine is a white to almost white powder, is soluble in N,N-dimethylformamide and N,N-dimethylacetamide, sparingly soluble in sulfinylbismethane, slightly soluble in methanol, propylene glycol and 1-methoxy-2-propanol. The active substance does not have chiral centres and is not considered hygroscopic.
Three polymorphic forms of rilpivirine have been observed and a number of solvates can also be formed in various solvents. Polymorph form A is routinely produced by the synthetic process described in the dossier and is used in the manufacture of the finished product.

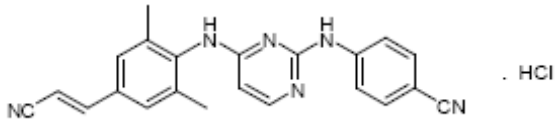


Figure 1: Rilpivirine hydrochloride

Manufacture

At the time of the CHMP opinion, the active substance used is supplied by two active substance manufacturers. Detailed information about the manufacturing process, control of starting materials, reagents and solvents, control of critical steps and intermediates and process development and process validation of the active substance has been supplied in the form of an active substance master file (ASMF). The manufacturing process of the active substance consists of five steps synthesis. The purified active substance is packed in double, antistatic, low-density polyethylene (LDPE) bags, both the inner and the outer bag are appropriately closed and placed in a fibreboard container. The chemical structure of rilpivirine has been confirmed by spectroscopy (UV, IR, ^{1}H-NMR, ^{13}C-NMR, and MS) and XRD. In addition the molecular weight was determined by elemental analysis.

Specification

Rilpivirine specifications include tests for appearance, identification (IR), identification of chloride (Ph Eur), assay (HPLC), impurities (HPLC), residual solvents (GC), water content, particle size, sulphated

ash, and heavy metals. A detailed description for all analytical methods was provided. Full method validation data was provided for the in-house analytical methods and are in accordance with the relevant ICH Guidelines. In general, the analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety. Batch analysis data of 10 production scaled batches of active substance are provided. The tests and limits in the specifications are considered appropriate for controlling the quality of this active substance.

Stability

Stability data are presented for three batches of rilpivirine hydrochloride, stored for 36 months at 5°C, 25 °C / 60% RH, 30°C/ 65% RH and 30°C/ 75% RH and 6 months at 40 °C / 75% RH. A photostability study and a forced degradation study were also performed according to ICH guidelines. The packaging used in stability trials is identical to that proposed for storage and distribution.

The test parameters evaluated in these studies were appearance, assay, chromatographic purity, water content, particle size, microbiological purity and identification of polymorph. The testing was performed in accordance with the tests in the specifications for the drug substance. In the stability studies additional tests for microbiological purity and, polymorphism are also included.

The active substance remained unchanged at all time points and under all conditions tested. No trends have been observed for any test parameter under any conditions with the exception for ICH light conditions. The results justify the retest period proposed when the active substance is stored in the original packing material protected from light.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The choice of the active substance and the excipients are sufficiently justified. The main aim of the pharmaceutical development was to formulate a conventional film-coated tablet, with a relatively rapid drug release. Prior to the selection of the final formulation and strength for commercial development, several earlier formulation and dosage strengths were investigated. An oral solution 25 mg/ml of the active substance as free base was developed. For additional clinical studies and commercialisation a solid dosage forms were considered for ease of administration. The first dosage form to be developed was a 50 mg hard capsule with the active substance free base. A 100 mg film-coated tablet was developed from the micronised hydrochloric acid salt of rilpivirine using standard wet granulation technology. Both the capsule and tablet formulations provided significant exposure to the active substance, which was either comparable to (capsule) or slightly lower than (tablet) the exposure obtained with the oral solution formulation. Following further experimental studies the tablet manufactured with the micronised hydrochloride salt was selected for further development because it provided sufficient bioavailability and a less complex manufacturing process. The initial 100 mg tablet was maintained for further use in clinical studies, and two additional strengths for use in the Phase 2b clinical study were considered (25 mg and 50 mg).
For these tablets as the active substance concentration increased, the amount of lactose was decreased in order to maintain constant tablet weight (350 mg). This change was not adequate to provide the required lubricity for all strengths.
Further pharmaceutical development was done before the phase 3 clinical trials in order to ensure ease of manufacturability. The qualitative composition of the phase 3 formulation was very similar to the

formulation used at the start of Phase 2b. This formulation was manufactured by means of a common blend that allowed the compression of dose-proportional tablets of different strengths and proportional tablet weights. The bioavailability study results demonstrated that both formulations (Phase 3 formulation and Phase 2b formulation) are bioequivalent. Base on the results of pharmaceutical development and clinical trials the phase 3 formulation (25 mg) was selected as the final formulation.

Adventitious agents

As regards excipients of human or animal origin, the following applies. The lactose monohydrate is sourced from cow's milk that is fit for human consumption. A letter of confirmation in respect of this matter from the supplier has been submitted. The magnesium stearate is of vegetable origin which also has been confirmed by supplier statement.

Manufacture of the product

The proposed commercial manufacturing process for the film-coated tablets involves standard technology and it is divided into the following steps: mixing, granulation, drying, milling, blending, compression, film coating, and packaging. The equipment used is commonly available in the pharmaceutical industry. The manufacturing process has been adequately described and some steps have been identified as critical and optimised during the drug development (granulation and compression of tablets). The manufacturing process is adequately validated by three production scale batches. Furthermore, the validation protocol proposed for the full scale batches has been provided and the quality of the production batches will be evaluated through the results of in process testing as well as the results of finished product testing.

Product Specification

The product specification is standard for film-coated tablets and contains tests with suitable limits for appearance, identification (IR), assay (HPLC), impurities (HPLC), uniformity of dosage (Ph.Eur), dissolution, and microbiological purity (Ph.Eur). Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. It was noted that no new impurities were observed during the manufacturing of the finished product. All analytical procedures that were used for testing the finished product were properly described and satisfactorily validated in accordance with the relevant ICH guidelines. The batch analysis data for seven commercial batches confirm that the film-coated tablets can be manufactured reproducibly according to the agreed finished product specifications.

Stability of the product

Stability studies under ICH long-term, intermediate and accelerated conditions (i.e. 25°C/60% RH, 30°C/65% RH, 30°C/75% RH and 40°C/75% RH) have been carried out on three batches of the finished product. The following parameters were monitored during the stability studies: appearance, assay, related compounds, dissolution, and water content (Ph.EUR). During the stability studies the product did not show any significant change in its quality. All the results remained well within the specification limits during all the stability studies. A photostability testing programme was conducted on three batches in accor rl Fischer) and microbiological purity dance with the recommendations of ICH guideline Q1B. The results were found to meet the specifications. The finished product requires light protection. Based on available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The pharmaceutical development of the formulation, the manufacturing process, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The manufacturing flow-chart was provided with suitable in-process controls. The manufacturing process is adequately validated for three production scale batches at the proposed manufacturing site. Furthermore, the validation protocol proposed for the full scale batches has been provided and the quality of the production batches will be evaluated through the results of in process testing as well as the results of finished product testing. The routine specifications and tests methods proposed for the active substance and finished product will adequately control the quality of the active substance and finished product. Analytical methods were well described and validated in agreement with relevant guidelines.

Batch analyses were presented and the results showed that the finished product meets the specifications proposed.

The container-closure system for the finished product was found to be suitable to ensure the quality of the finished product as shown by the stability data.

The conditions used in the stability studies comply with the ICH stability guideline. The control tests and specifications for the finished product were adequately established.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the medicinal product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, all quality issues have been resolved.

2.3. Non-clinical aspects

2.3.1. Introduction

A comprehensive nonclinical programme was conducted to evaluate pharmacology, pharmacokinetics and toxicology of rilpivirine. The studies were conducted considering European and international guidelines.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Rilpivirine is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. It binds to reverse transcriptase separately from the polymerase active site, inhibiting reverse transcriptase allosterically. Rilpivirine had no effect on human DNA synthesis up to 1000 µM.

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).

Rilpivirine demonstrated antiviral activity against a broad panel of HIV-1 group M and O. EC50 for rilpivirine against HIV-1 group M (subtype A, B, C, D, F, G, H) was 0.07 – 1.01 nM (0.03 to 0.37 ng/ml). Against group O, EC50 was 2.88 – 8.45 nM (1.06 to 3.10 ng/ml). EC90 against HIV-1 was 1.12 – 1.79 nM (0.41 – 0.66 ng/mL).

Rilpivirine demonstrated limited *in vitro* activity against HIV-2 with EC_{50} values ranging from 2,510 to 10,830 nM (920 to 3,970 ng/ml).

A reduction in antiviral activity was observed in the presence of human serum proteins. The protein binding correction factor was experimentally determined to be 39.2 in the presence of 45 mg/mL human serum albumin. This corresponds to a high protein binding of rilpivirine.

Resistance

In fixed-dose selection experiments at high MOI (multiplicity of infection), the concentration of rilpivirine to prevent viral replication was lower (40 nM) than that of efavirenz, etravirine and nevirapine (at least 200 nM). Experiments in wild-type and NNRTI resistant strains showed that the in vitro resistance profile of rilpivirine may include the mutations V90I, L100I, K101E, V106A/I, V108I, E138G/K/Q/R, V179F/I, Y181C/I, V189I, G190E, H221Y, F227C, and M230I/L. It was shown crystallographically that rilpivirine is capable of conformational changes to mutations in the reverse transcriptase, thus providing protection to at least some of the potential mutations. Among a large amount of recombinant clinical isolates resistant to at least 1 first generation NNRTI, 62% remained susceptible to rilpivirine, which was similar to etravirine (62%) and better than efavirenz (11.3%) and nevirapine (4.6%). Experiments with site-directed mutants showed that M184V/I did not induce resistance to rilpivirine.

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.

No in vivo studies were performed with rilpivirine. Considering the sufficient presence of in vitro data and the limited relevance of in vivo animal data in this case (in animal studies, animal variants of the virus are investigated instead of the human HIV), this is endorsed.

Secondary pharmacodynamic studies

Rilpivirine has no antiviral activity against various human viruses other than HIV and no potential off-target activity, but might have low cytotoxic potential in various human cell lines.

Safety pharmacology programme

Except for the dog cardiovascular study Exp5555 and the rat CNS study Exp5560, safety pharmacology studies were not GLP compliant. However, at least one study per vital organ system was performed under GLP and results of the GLP-compliant studies were consistent with those obtained in the non-GLP studies.

Results of the *in vitro* hERG test reveal that rilpivirine has the potential to prolong the QT-interval. Delayed QT prolongation was also observed in a thorough QT study, in which healthy subjects were exposed to 75 and 300 mg rilpivirine. This QT prolonging potential and its delayed onset was confirmed by the results of the additional *in vitro* cardiovascular safety studies. However, none of the studies do explain the mechanism behind the (delayed) onset of QT prolongation observed in man. It might be

concentration-related since it was only observed following exposure to concentrations exceeding the clinically relevant concentrations in man. QT prolongation might also be highly species-specific, since it was only observed in man and not in any of the animal models used, not even following exposure to supratherapeutic concentrations. The role of accumulation can not be excluded either. The applicant indicates that a steady-state plasma concentration of rilpivirine was reached at day 7 after starting treatment. The occurrence of accumulation following long-term treatment with the intended dose of 25 mg rilpivirine needs to be followed up. Overall, due to the results of the performed cardiovascular safety studies, the potential of rilpivirine to induce QT prolongation can still not be disregarded. Since the potential to induce QT prolongation was only observed in a human channel model and occurred after a certain time of delay, the applicant is requested as a post authorisation measure to investigate the whether species-specific metabolites maybe responsible for the QT prolongation of rilpivirine in man and the mechanism behind the QT prolongating and proarrhythmic potential of rilpivirine in man.

Rilpivirine appears not to affect the respiratory and central nervous system when administered at therapeutic concentrations.

Pharmacodynamic drug interactions

The applicant did not conduct specific pharmacodynamic drug interaction studies.

2.3.3. Pharmacokinetics

The non-clinical pharmacokinetics of rilpivirine was investigated in a series of in vitro and in vivo studies. In vivo studies were conducted in CD 1 and CB6F1-nonTgrasH2-transgenic mice, pigmented Long Evans and Sprague Dawley rats, New Zealand white rabbits, beagle dogs and Cynomolgus monkeys. With the exception of pigmented rats, all species and strains were the same as those used in the non clinical pharmacology and toxicology studies.

The drug substance, rilpivirine, has been used in 2 forms in the non-clinical studies, in base form and as the HCl salt form. The latter was used in a limited number of preclinical studies and in the clinical tablet formulations.

Absorption

In vitro experiments showed a medium permeability of rilpivirine. Passive transcellular diffusion was proposed as a mechanism for rilpivirine absorption. However, the solubility, and in case of suspension and solid dosage forms, also dissolution may limit the rate and extent of absorption. Rilpivirine is no substrate for P-gp, but has an inhibitory effect on P-gp. However, the IC50 is 26-fold higher than the Cmax in HIV-1 infected subjects (0.13 µg/ml) and therefore clinical effects are not likely.

The studies were performed after single and repeated oral administration either as specific pharmacokinetic studies or as toxicokinetic evaluations of toxicology studies. Oral bioavailability of rilpivirine base appeared to be moderate in all species examined. After oral administration of rilpivirine base, the absolute oral bioavailability of rilpivirine was 32%, 54%, 31% and 24% to rats, rabbits, dogs and monkeys, respectively. Adding citric acid (CA) in the formulation administered to rats and dogs usually increased the exposure showing that the absorption of rilpivirine is pH-dependent in these species as in humans.

Distribution

Maximum blood concentrations of rilpivirine in rat and dog showed a plateau after an initial rapid absorption until ~8 hours. A higher exposure to rilpivirine was observed in mice compared to the other

species. The volume of distribution is high in rat, dog and monkey, while it was low in rabbits. The clearance is moderate in rats, whereas in rabbits, dogs and monkeys the clearance is low. Species differences in t½ following iv administration were also observed between rat (4.4 h), rabbit (12-21 h), dog (31 h) and monkey (7.1 h). Exposure increased less than dose-proportionally in mice, rats, rabbits, dogs and immature monkeys after both single and repeated dose. Only in female mice a more than dose proportionate increase was observed after repeated dose. In monkeys, a dose-proportional increase in exposure was observed after single and repeated dosing. Toxicokinetic studies showed evidence of some accumulation of rilpivirine in female mouse and rat, dog and monkey plasma after repeated dosing.

The binding of rilpivirine to human, monkey, dog, rat, rabbit and mouse plasma proteins is high in all species (>99%) and is concentration independent. Rilpivirine was highly bound to human albumin (99.5%) and to lesser extent to α1-acid glycoprotein (25-55%). In human plasma, the protein binding of rilpivirine appeared to be pH-dependent. The distribution of rilpivirine to red blood cells is limited in all species. Absorption of radioactivity was rapid with highest levels of radioactivity in all tissues at 4 h post-dose, except the uveal tract (24 h post-dose). This is in line with the high volume of distribution of rilpivirine and limited clearance. The highest tissue concentrations of radioactivity were observed in the uveal tract, liver and adrenal gland. Rilpivirine-related material crosses the blood-brain barrier. There appeared to be binding to melanin in the pigmented parts of the eye, meninges, skin and uveal tract. Although the concentrations in these tissues are low, accumulation is expected since radioactivity is still present 14 days post-dose. Rilpivirine-related material crosses the placenta barrier in rats. The AUC0-8h for total radioactivity in whole fetus was 0.64 times that in maternal blood. Placental transfer in humans is expected based on these results in rat and this information is reflected in section 4.6 of the SmPC.

Metabolism

Rilpivirine is metabolised via Phase I and Phase II reactions and a large number of metabolites were detected in all species. The most important pathway is oxidation and hydroxylation and to a minor extent conjugation with glutathione and glucuronide. Overall, identified metabolites that were detected in human matrices were also detected in at least one animal species. However, a unique metabolite (M15) formed by N glucuronidation of rilpivirine, was observed in human plasma (8.7%) and faeces (0.6%). This metabolite is expected to be inactive and non-toxic due to the glucuronidation.

Rilpivirine metabolism as well as formation of all its metabolites was mainly catalysed by CYP3A4. CYP1A1, CYP1A2, CYP1B1, CYP2C8/9/10, CYP2C18, CYP2C19, and CYP3A5 are also involved, but to a lesser extent. Also CYP3A7 is involved in the metabolism of rilpivirine. The applicant is recommended to further elaborate on the impact of CYP3A5 on the exposure of rilpivirine.

Reactive intermediate(s) of rilpivirine formed by phase I enzymes were scavenged by glutathione. Conjugation with glutathione was more dependent on the mu than the pi isoform of GST, although both isoforms were involved. GST mu and GST pi are subjected to genetic polymorphisms, leading to an absence or decreased isozyme activity. Thus, genetic polymorphisms of GST could influence the pharmacokinetics of rilpivirine in humans. However, conjugation with glutathione was a minor biotransformation route and therefore it is unlikely that GST will influence the pharmacokinetics of rilpivirine in humans.

In vitro and in vivo data indicate that gender differences might be present for the biotransformation of rilpivirine. In addition, interspecies differences in metabolism were observed both in vitro and in vivo (e.g. glutathione conjugation was a major conjugation route in rat whereas in humans glucuronidation was the major conjugation route), making it more difficult to compare the different species.

Elimination

The predominant route of elimination of radioactivity in all species following oral administration was via faeces (>85%), with a small contribution eliminated in urine (<6.2%). The majority of the eliminated radioactivity is unchanged rilpivirine (25-47% of the dose). In rats, biliary excretion is limited (18-25%). Concentrations of rilpivirine were quantifiable in blood samples from rat pups, demonstrating that pups were exposed to rilpivirine via the milk.

At therapeutic levels of rilpivirine, rilpivirine may inhibit the metabolism of clarithromycin (CYP3A4), sildenafil (CYP3A4), S-mephenytoin (CYP2C19) and norethindron (CYP2C19), but also, although less likely, the metabolism of sertraline (multiple CYPS, MAO, UGT), paroxetine (CYP2D6) and 17α ethinyloestradiol (Phase II metabolism). Rilpivirine could influence cortisol and aldosterone levels in vivo by a direct inhibition of the enzymes involved in the biosynthesis of those hormones. Furthermore, rilpivirine is primarily metabolised by CYP3A, and medicinal products that induce or inhibit CYP3A may thus affect the clearance of rilpivirine. Rilpivirine at a dose of 25 mg is not likely to have a clinically relevant effect on the exposure of medicinal products metabolised by CYP enzymes. Rilpivirine resulted in an induction of CYP4A enzyme activity and to some extent of CYP3A. In addition, rilpivirine may induce UGT and GST, but the preclinical results were contradictory.

A toxicity study in dogs showed changes in the liver accompanied by gall bladder pigmentation which suggest cholestasis. This study indicates that rilpivirine may mediate causative and adaptive transporter changes leading to cholestasis. Cholestasis can be caused by alterations of transporter function in the liver, such as sodium taurocholate cotransporting polypeptide (NTCP), organic anion-transporting polypeptides (OATPs) or multidrug resistance–associated proteins (MRPs). It can not be excluded that OATP transporters may be involved in the observed cholestasis in dogs. However, as cholestasis was not observed in clinical studies, it is unlikely that the recommended therapeutic dose of rilpivirine will lead to systemic interaction via P-gp or OATPs (no effect on atorvastatin in vivo).

Based on in vitro data, rilpivirine metabolism as well as formation of all its metabolites was mainly catalysed by CYP3A4. CYP1A1, CYP1A2, CYP1B1, CYP2C8/9/10, CYP2C18, CYP2C19, and CYP3A5 are also involved, but to a lesser extent. Also CYP3A7 is involved in the metabolism of rilpivirine. The apparent Michaelis-Menten constant Km and Vmax values for the metabolism of 14C-rilpivirine in human liver microsomes were 4.17 µM and 381 pmol/mg/min, respectively. CYP3A5 is inactive in the majority of the population. However, due to an SNP in 20-30% of the population, in this group, CYP3A5 may be more active than CYP3A4. Evidence regarding involvement of CYP3A4 and CYP3A5 is inconsistent throughout several experiments. The applicant is recommended to further elucidate the impact of CYP3A5 on exposure of rilpivirine.

2.3.4. Toxicology

The Applicant has performed a full program of non-clinical toxicity studies including repeated dose toxicity testing, genotoxic and carcinogenicity testing, reproductive and developmental studies, supplemented with studies on local tolerance, studies for the toxicological qualification of impurities and supportive mechanistical studies. In all in vivo studies rilpivirine was administered orally with the exception of the sensitization and dermal irritation studies. All pivotal studies were performed according to GLP.

Single dose toxicity

The 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 rilpivirine base in PEG400 + CA, the maximum feasible dose in this vehicle for this species. Exposures at 1600 mg/kg were similar as those at 400 mg/kg indicating saturation of absorption (TMC278-Exp5538).

Rats dosed with an oral maximum feasible single dose of 800 mg/kg rilpivirine base in PEG400 showed no treatment-related effects (TMC278-EXP5559).
Dogs that received an oral maximum feasible dose of 80 mg/kg rilpivirine base in PEG400 or PEG400 + CA vomited more frequently and had softer stool than dogs treated with the vehicle. No other effects were noted (TMC278-EXP5461).

In single dose toxicity evaluation it was concluded that the single dose toxicity of rilpivirine at the maximal feasible dose is low.

Repeat dose toxicity

Systemic toxicity of rilpivirine base or rilpivirine after repeat dosing was studied in mice, rats, rabbits, dogs and cynomolgus monkeys. Pivotal repeat dose studies were conducted in mice (3 months), rats (1 and 6 months), dogs (1, 3, 6, and 12 months), and cynomolgus monkeys (8 weeks). as listed in Table 1 below; these included a number of non-pivotal studies in mice, rats and dogs.

The mouse study served as dose range finder for the carcinogenicity study in that species. The 5-day rabbit study was a pilot for the rabbit embryo-fetal toxicity study. The studies in rats and dogs were designed to investigate the toxicity profile of rilpivirine and to support clinical studies and marketing authorization. A further mechanistic juvenile toxicity study was done in immature female cynomolgus monkeys. The reversibility upon repeat dosing was investigated in rats and dogs.

In all studies high exposure multiples were reached varying from 2 in the monkey to >500 in the mice at the highest dose.

Table 1: Repeated dose toxicity studies.

Study ID (duration)	**Species Number/ Sex/ Group**	**Dose** (mg/kg/day)	**NOAEL** (mg/kg/ day)	**Major findings**
NC101 6 months + 1 month recovery	SPF-SD rats 20+10[h]+6[a] /sex/group a: TK satellite group h: recovery	0[b], 40, 120, 400 base/CA b: vehicle	n.d.	**Death** None **In life observations** **≥40:** salivation, ↑APTT (m), ↑PT (m) ↓eos (f), ↓trig, ↓bili, ↑creat (m), ↑phos (f), ↓T4, ↑TSH **≥ 120:** ↓MCV (f), ↓MCH (f), ↑phos (m), ↑alb, ↑ALP (m), ↑urea (m), ↑creat (m),↓gluc (f), ↓ cort, ↑prog. (m) **400:** wet urogenital region, ↓RBC (m), ↓Hb (m), ↓Hct (m), ↓Ca (m), ↓prot (f), ↑alb (f), ↑ACTH (f) **Necropsy/pathology** **≥ 20:** *Pituitary:* swollen-vacuolated cells (m) *Thyroid*: ↑ small follicles **≥ 40:** *Thyroid*: ↑weight, diffuse follicular hypertrophy, focal follicular hyperplasia (m). *Liver:* ↑weight *Pituitary* (m): ↑swollen-vacuolated cells

				≥ 120: *Thyroid*: swollen, *Liver:* ↑weight, ↑ pronounced lobulation, swollen, dark, hepatocellular hypertrophy *Kidney:* ↑weight (m) **400:** *Mesenteric lymph node:* swollen-vacuolated small aggregates Mϕ *Kidney:* ↑weight (f)
NC115 6 month	Beagle dogs 4+2[i] /sex/group i: 3 month interim kill	0[b], 5, 10, 40 base/CA b: vehicle	n.d.	**Death** None **In life observations** **≥ 5:** soft feces, vomiting, ↑ALP (f), ↑bili (f), ↑ACTH (f), ↓cort (m), ↑17α-OH-prog (m), **≥ 10:**↑ALP, ↑ACTH (m), ↓cort, ↑prog **40:** salivation (f), mucous/pale feces , ↓BW, ↓FC, ↑chol, blood in urine (m) **Necropsy/pathology** **≥ 5:** *Ovaries:* ↑weight, ↑tertiary follicles, **≥10:** *Liver*: brown pigmented macrophages (m). *Adrenals*: swollen cells/dense staining zona reticularis/ fasciculate, ↓fat deposition, *Gall bladder*: prominent bile/brown pigment in the epithelial cells. *Ovaries:* ↑atretic follicles, *Testes*: Leydig cell hyperplasia/ hypertrophy, ↓spermiogenesis + ↓sperm count. *Epididymis*: cellular debris **40:** *Liver*: brown pigmented macrophages (f), *Thymus*: ↑thymic involution, *Ovaries*:, swollen, ↑corpora lutea *Uterus/Vagina*: swollen *Testes*: atrophic tubuli
NC107 12 month	Beagle dogs 4/sex/group	0[b], 5, 10, 40 base/CA b: vehicle	n.d.	**Death** None **In life observations** **≥ 5:** liquid feces, colored mucus in feces, salivation, ↓BWG., ↓Ca, ↑prog (m), ↑17α-OH-prog (m), bili in urine (m), ↑urine volume, ↓urine gravity **≥ 10:** ↑ALP, ↑ALT,↑bili, ↓cort, ,↑creat **40:** ↓BW (f),, ↓BWG (m) ↓RBC, ↓Hb, ↓Hct (m), ↓ PCV, ↓K (f), ↑Cl, ↓Phos (f), **Necropsy/pathology** **≥ 5:***Thyroid* ↓weight (m), ↑weight (f), *Adrenals*: dense staining zona reticularis/fasciculate, ↓fat deposition *Ovaries*: ↑ antral follicles **≥10:** *Liver:* yellow pigmentation in hepatocytes, canaliculi and Kupffer cells *Ovaries:* ↑weight, cystic areas, prominent corpora lutea **40:** *Kidney*: interstitial nephritis (m), mineralization (f), *Adrenals*: ↑weight, enlarged (f), pigment deposits in cortex (m) *Spleen*: ↓weight (m) *Gall bladder*: brown pigment in the epithelial cells. *Prostate*: ↓weight, *Testes*: hypertrophy of Leydig cells, *Ovaries*: prominent early luteinized follicles
NC248 8 weeks	Cynomolgus monkeys 8 females/ group	0[c], 200, 500 (bid) c: water	n.d.	**Death** None **In life observations** **≥ 200:** ↑17α-OH-prog, ↑prog, ↓androstenedione , ↓estradiol **500:** ↓DHEA, **Necropsy/pathology** **≥ 200:** *Thyroid*: ↑follicular cell hypertrophy **500:** *Ovaries*: cysts

m: males, f: females, BWG: body weight gain, FC: food consumption, WBC: white blood cell count, RBC: red blood cell count, lymph; lymphocytes, mono: monocytes, neutr: neutrophils, retic: reticulocytes, Hb: hemaglobin, hct,: hematocrit, PCV: packed cell volume, MCV: mean cell volume, eos: eosiniphils, bili: bilirubin, trig: triglycerides, ALP: alkalic phosphatase, AST: aspartate aminotransferase, ALT: alanine aminotransferase ,prot: total protein, Ca: calcium, Phos: phosphorus, alb: albumin, chol: cholesterol, extramed. hem.: extramedullary hematopoeisis, triPh.

cryst.: triple phosphate crystals, APTT: activated partial thrombine time, PT: prothrombine time, creat: creatinine, MCH: mean cell hemoglobin, corti: corticosterone, cort : cortisol, prog: progesterone, Мф: macrophage, GGT: gamma glutamyl transferase PKC assay (plaque forming cell assay, sheep red blood cell test)

Adverse effects on the liver and blood liver enzymes were noted in all test species, but differed between rodents and dogs. In rodents predominantly hepatocellular hypertrophy was noted, while in dogs initial perivascular inflammatory reactions were followed by pigmentation of the liver and gall bladder suggestive of cholestasis was noted. No sign of liver toxicity was seen in the lowest tested dose (AUC ≥20 mice, ≥2 rat, ≥5 dog). The mechanism of the observed effects and why different effects were noted in rodents versus dogs has been fully clarified. A possible explanation for the liver pathology seen in rodents may be induction of liver enzymes (see pharmacokinetic section). Enzyme induction is generally rodent specific, and thus not relevant to humans. The cause for cholestasis in dogs may be more related to a treatment-related effect on drug transporters. A safety margin for the effect in dogs is present (≥ 5). Cholestasis was not observed in clinical studies. Because a minor potentially reactive metabolite of rilpivirine was observed in humans (2.7% of dose in feces) and evidence of liver toxicity in non-clinical species, (idiosyncratic) liver toxicity can not be completely excluded and are included in the risk management plan.

Effects on the kidney were noted in mice (pale and enlarged/swollen kidneys, (necrotic) nephropathy), dogs (acute interstitial nephritis, corticomedullar mineralization) and possibly also rats (reduced weight, changes in urine parameters) at the highest dose level with a sufficient safety margin (≥80 mice, ≥6 dogs, ≥14 rats).

An effect on the adrenal gland and steroid hormone levels has been demonstrated in all species in studies of sufficient duration. The Applicant has performed additional mechanistical studies to explain these observations. From these studies it was concluded that most likely rilpivirine partially inhibits cytochrome CYP21 and CYP17 (enzymes are involved in the adrenal steroid synthesis). In the clinic the potential effect of rilpivirine treatment on steroid synthesis has been investigated, and no effect was noted.

In the rat treatment-related hypertrophy and hyperplasia of the thyroid was seen. This is most likely caused by species-specific liver enzyme induction. In juvenile female monkeys rilpivirine induced minimal follicular cell hypertrophy in thyroid already at the lowest dose tested.

A treatment-related induction of swollen and vacuolated cells in the pars distalis of the pituitary gland in rats is most likely secondary to the species-specific liver enzyme induction.

In dogs, rilpivirine treatment appeared to induce early sexual maturation (1 month study) and activation (6 and 12 month study) of ovaries as suggested by the increases in the numbers of tertiary follicles, (cystic) luteinized follicles, and in some dogs by corpora lutea in the ovaries, and the changes in the other parts of the female genital tract and with the prominent activation of the mammary glands in the 1 month study. An opposite effect on the female genital tract was also noted in mice (i.e. reduced weight/size of ovaries/uterus, absence of ovulation, uterus atrophy and hyperkeratosis/mucification of vaginal epithelium). Some effects on the testes were seen in dogs, these included atrophic tubuli and hypertrophy of Leydig cells. The cause of these effects on the reproductive organs is unclear but they may be caused by the effect of rilpivirine on the hormonal balance due to partial CYP21 and CYP17 inhibition. In the clinic no effect on these hormones was detected.

In mice, rat and dogs, small reduction in red blood cell parameters were noted. In rats increases in coagulation parameters were noted, which did not completely recovered following 1 month recovery period. Both effects may be due to rilpivirine induced liver pathology. Clinically no effects on the red blood cell parameters were noted.

Genotoxicity

Rilpivirine was studied in the standard battery of in vitro and in vivo tests (in vitro test on bacteria (Ames test), and on mammalian cells (mouse lymphoma) and in vivo micronucleus in roedents. Rilpivirine did not show a genotoxic potential, at the highest feasible concentration or dose.

Carcinogenicity

No short or medium term studies were conducted. Long term carcinogenicity studies were performed in mice and rat.

Rilpivirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. 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 once daily). In rats, there were no drug related neoplasms. In mice, rilpivirine was positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent specific.

Table 2: Overview of carcinogenicity studies

Study ID	Species	Dose (mg/kg/day)/ Duration	No. of animals	Major findings
NC120	Crl: CD-1™ (ICR) mice	0, 22, 66, 176[a] 104 weeks	60+24[b]/sex/group	**≥ 20**:↑hepatocellular tumours, liver findings ↑ BWG (m), **≥ 66:** ↓survival (m), ↑ BWG **176:** ↑ FC
NC123	SD Rats	0, 44, 220, 550, 1650[c] 104 weeks	65+9[b]/sex/group	**≥ 44:** ↑ hepatocellular tumours, ↑thyroid follicular cell tumours, thyroid findings, lung pathology ungroomed (m), pale/white feces, **≥220:** ↑survival (f), ↑creatine, ↓trig, disturbance plasma proteins, disturbance urine parameters **≥ 550:** ↑liver enzymes, ↑urea, ↓Ca **1650:** ↑hair loss, brown staining and encrustation on head (f), yellow/brown staining body surface(m), ↑palpable swelling (m), nasal pathology

a: equivalent to 20, 60 or 160 mg free base/kg/day
b: TK group
c: equivalent to 40, 200, 500 and 1500 mg free base/kg/day

Reproduction Toxicity

The reproductive toxicity of rilpivirine was studied in line with the requirements of the S5 ICH guideline.

The main reproductive and developmental studies and their findings are summarised in table 3.

Table 3: Overview of reproductive toxicity studies

Study type Study ID	Species Number/sex/ group	Dose (mg/kg/ day)	Dosing period	Major findings	NOAEL (mg/kg/ day)
Male fertility NC124	SD rats 25 m/group	0, 100, 400, 1600	10 wk prior and 4 wk after mating	≥100 ↑ weight liver and thyroid 1600: salivation	1600
Female fertility NC125	SD rats 25 f/group	0, 40, 120, 400	14 d prior and 7 d after mating	400: ↑BW, FC	400
Embryo-foetal development NC127 (non-GLP)	SD rats 8 f/group	0, 40, 120, 400	GD6-17	*Maternal* ≥ 120 ↑BWG, FC *Foetal* -	
Embryo-foetal development NC105	SD rats 24+6[a] f/group	0, 40, 120, 400	GD6-17	*Maternal* ≥ 120: ↓ BWG, FC, ↑ thyroid weight *Foetal*: ≥ 120 ↑ dilated renal pelvis	F0: 40 F1: 40
Embryo-foetal development NC128 (non-GLP)	NZW rabbits 6 f/group	0, 25, 75, 150	GD6-19	150: ↓ BW, FC, faecal output	
Embryo-foetal development NC129 (non-GLP)	NZW rabbits 6 f/group	0, 5, 20, 60	GD6-19	*Maternal* 60: ↓ BW *Foetal* 60: ↓ survival, weight	
Embryo-foetal development NC130	NZW rabbits 20+3[a] f/group	0, 5, 10, 20	GD6-19	*Maternal* - *Foetal* 20: ↑ branches of left subclavian artery, hypoplastic interparietal bone	F0: 20 F1: 10
Peri & postnatal NC168 (TOX6847) (non-GLP)	SD rats 6 f/group	0, 0, 40, 120, 400	GD6-LD7	*Maternal* - *F1* 120: 1/16 dead 400:2/16 dead	F0: 400 F1: 120
Peri & postnatal NC131	SD rats 25 f/group	0, 40, 120, 400	GD6-LD20	*Maternal* - *F1pre-weaning* - *F1 post-weaning* -	400

a: toxicokinetic satellite group

No effect on male or female fertility was noted in fertility studies in rats.

Effects on embryo-foetal development were seen at maternal toxic doses in rats and below maternally toxic doses in rabbit. In the rat embryo-foetal development study a dose-related increase in the incidence of dilated renal pelvis increased dose related (0/140, 2/155, 5/149, 7/149) was noted. However all incidences were below the maximal historical control, and high exposure multiples were reached in this study. It was thus concluded that this effect is most likely not of toxicological relevance. In rabbits the incidence of branches of left subclavian artery and hypoplastic interparietal bone was increased. No marked effects were noted in the peri/post-natal development study in the rat.

Local Tolerance

No local tolerance studies were performed.

Other toxicity studies

No specific immunotoxicity or dependence studies were conducted.

Three drug substance impurities (R600682, R600683, R289932) were specified at levels equal to or exceeding 0.15%. These impurities were adequately qualified regarding general toxicity and genotoxicity. In addition, there is an impurity with a genotoxic alert (T002594). The level of this genotoxic impurity has been restricted to below the TTC, in line with the Guideline on the limits of genotoxic impurities (EMEA/CHMP/QWP/251344/2006).

2.3.5. Ecotoxicity/environmental risk assessment

The following table shows the results of the environmental risk assessment study.

Table 4: Summary of main study results

2.3.5.1.1.1. Substance (INN/Invented Name): Rilpivirine			
2.3.5.1.1.2. CAS-number (if available): 500287-72-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 123	Log K_{OW} = 4.9(study report to be submitted)	Potential PBT – Yes
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	184	Not B
Persistence	DT50 or ready biodegradability	$DT_{50,\ sediment}$ = 307 / 321 days in aerobic sediment, not degraded during 100 days in anaerobic sediment	P and vP
Toxicity	NOEC or CMR	NOEC ≥ 0.02 mg/L; CMR not reported.	T not clear
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$,	0.125	µg/L	> 0.01 threshold (Y)

Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	*Study to be resubmitted*			
Ready Biodegradability Test	OECD 301	Not reported, compound is not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 1.2 / 4.6 days $DT_{50, sediment}$ = 307 / 321 days in aerobic sediment, not degraded during 100 days in anaerobic sediment % shifting to sediment = upto 95%			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	NOEC	≥ 22	µg/L	*Scenedesmus subspicatus*
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥ 32	µg/L	
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC	≥ 20	µg/L	*Danio rerio*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥ 1000	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	184	L/kg	%lipids: 3.73
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	212; 151; 168; 191 17.3; 31.5; 20.5; 0.6	Days %	Recalculated to 12 ºC; for all 4 soils tested
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	6.9	%	At 100 mg/kg
Terrestrial Plants, Growth Test	OECD 208	NOEC	≥ 1000	mg/kg	*Beta vulgaris; Brassica oleracea; Lolium perenne; Lycopersicon esculentum; Triticum aestivum; Vigna radiata*
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	≥ 1000	mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC	≥ 1000	mg/kg	

Rilpivirine is very persistent in the environment ((v)P). However the bioconcentration study showed that rilpivirine is not B, thus the compound is not PBT nor vPvB. Since PECsurfacewater is above 0.01 µg/L, a phase II assessment has been performed. Results from phase IIa studies do not indicate any risk for the surface water, groundwater and STP.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed:

The MAH should submit studies in accordance with OECD 123 (regarding the determination of log Kow) and OECD 106 (regarding sediment and soil compartment).

2.3.6. Discussion on non-clinical aspects

Rilpivirine is a NNRTI of HIV-1. 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). Rilpivirine also demonstrated antiviral activity against a broad panel of HIV-1 group M and group O primary isolates.

The most commonly observed resistance-associated mutations that emerged in cell culture from wild-type HIV-1 of different origins and subtypes as well as NNRTI resistant HIV-1included L100I, K101E, V108I, E138K, V179F, Y181C, H221Y, F227C and M230I.

These data is reflected in section 5.1 on Pharmacodynamic properties of the SmPC.

As part of the safety pharmacology programme, results revealed that rilpivirine has the potential to prolong the QT-interval. However, the mechanism behind the (delayed) onset of QT prolongation observed in man is not clear. It might be concentration-related or be highly species-specific, since it was only observed in man and not in any of the animal models used, not even following exposure to supratherapeutic concentrations. The role of accumulation can not be excluded either. Overall the potential of rilpivirine to induce QT prolongation can still not be disregarded. Since the potential to induce QT prolongation was only observed in a human channel model and occurred after a certain time of delay, the applicant is requested in accordance to the measure in the RMP to investigate whether species-specific metabolites maybe responsible for the QT prolongation of rilpivirine in man and the mechanism behind the QT prolongating and proarrhythmic potential of rilpivirine in man.

Pharmacokinetics studies showed that the absorption of rilpivirine is pH-dependent in these species as in humans.

Based on in vitro data, rilpivirine metabolism as well as formation of all its metabolites was mainly catalysed by CYP3A4. Evidence regarding involvement of CYP3A4 and CYP3A5 is inconsistent throughout several experiments. Therefore, the applicant is recommended to further elucidate the impact of CYP3A5 on exposure of rilpivirine.

Studies in animals have shown no evidence of relevant embryonic or foetal toxicity or an effect on reproductive function. There was no 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 70 times higher than the exposure in humans at the recommended dose of 25 mg once daily. Studies in animals have shown limited placenta passage.

Rilpivirine is excreted in the milk of rats.
No clinically relevant effects on fertility were seen in animal studies.

These data were reflected in sections 4.6 on Fertility, pregnancy and lactation and 5.3 on Preclinical safety data of the SmPC.

Repeated dose toxicity showed liver toxicity associated with liver enzyme induction in rodents. In dogs, cholestasis-like effects were noted. The cause for cholestasis in dogs may be more related to a

treatment-related effect on drug transporters. A safety margin for the effect in dogs is present (≥ 5). Cholestasis was not observed in clinical studies. Because a minor potentially reactive metabolite of rilpivirine was observed in humans (2.7% of dose in feces) and evidence of liver toxicity in non-clinical species, (idiosyncratic) liver toxicity can not be completely excluded and are included in the risk management plan.

Carcinogenicity long-term studies showed that Rilpivirine induced increases in liver tumours in mice and rat and in the thyroid in the rat. These tumours were linked to species/rodent-specific enzyme induction in the liver. This is a well-known mechanism for induction of liver tumours and secondary thyroid tumours in rats and does not occur in humans.

Rilpivirine has tested negative in the absence and presence of a metabolic activation system in the in vitro Ames reverse mutation assay and the in vitro clastogenicity mouse lymphoma assay. Rilpivirine did not induce chromosomal damage in the in vivo micronucleus test in mice.

These data were reflected in section 5.3 on Preclinical safety data of the SmPC.

Assessment of paediatric data on non-clinical aspects

Not applicable

2.3.7. Conclusion on the non-clinical aspects

The CHMP considers the following measures necessary to address the non clinical issues:

Since the potential to induce QT prolongation was only observed in a human channel model and occurred after a certain time of delay, the applicant will investigatre in accordance with the measures in the RMP to investigate whether species-specific metabolites maybe responsible for the QT prolongation of rilpivirine in man and the mechanism behind the QT prolongating and proarrhythmic potential of rilpivirine in man.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following point to be addressed:

With respect to the Environmental Risk Assessment, the Applicant should submit studies in accordance with OECD 123 (regarding the determination of log Kow) and OECD 106 (regarding sediment and soil compartment).

The applicant was recommended based on available samples from patients, to further elaborate on the impact of CYP3A5 on the exposure of rilpivirine.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 5: Studies providing key efficacy and safety data

Trial	Design	Treatment Groups
C204 (N=368)	Dose finding phase IIb: Randomized to 3 doses of rilpivirine or control. Blinded with regards to dose of rilpivirine up to wk 96.	rilpivirine in doses 25 mg or 75 mg or 150 mg q.d. or EFV 600 mg q.d. (1:1:1:1) All in combination with AZT/3TC (around 25%) or TDF/FTC (around 25%). After 96 weeks all rilpivirine patients to be changed to selected dose for extension phase (total 240 weeks).
C209 (N=690)	Phase III, randomized, double blind	rilpivirine 25 mg q.d. Or EFV 600 mg q.d. (1:1) **All in combination with TDF/FTC** Duration: 96 weeks
C215 (N=678)	Phase III, randomized, double blind	rilpivirine 25 mg q.d.Or EFV 600 mg q.d. (1:1) **All in combination with TDF/FTC (around 60%) or AZT/3TC (around 30%) or abacavir/3TC (around 10%).** Duration: 96 weeks

2.4.2. Pharmacokinetics

Rilpivirine pharmacokinetics has been studied as primary or secondary objective in 33 conducted Phase I, II and III trials. Four validated bioanalytical assays LC-MS/MS were used during development. When exposed to light the drug is transformed to another isomeric form (Z- isomer). Selectivity towards the Z-isomer has been demonstrated.

Absorption

Rilpivirine is a poorly soluble (even less at pH above 2) drug with intermediate permeability *in vitro.*

After oral administration, the maximum plasma concentration of rilpivirine is generally achieved within 4-5 hours.

Efflux data indicate that rilpivirine may be a substrate for P-gp. There is no indication of increased bioavailability with increasing dose above 25 mg hence the impact of active efflux for rilpivirine absorption seems not relevant at the chosen dose level.

Absolute bioavailability of rilpivirine was not studied because of its low solubility. Comparable bioavailability is obtained with phase II and Phase III tablet forms.

The influence of food is substantial where normal fat and high fat meal result in similar exposure while if taken in fasting state the AUC is reduced by about 40%. If taken with only a protein rich nutritional drink the exposure is reduced by 50% as compared to a normal fat meal. Rilpivirine should be taken with a meal to ensure optimal absorption. This information is reflected in section 4.2 of the SmPC.

Distribution

Animal data indicate that rilpivirine distributes over the whole body, but high concentrations were observed in liver, adrenal gland, brown fat and kidney. In addition, rilpivirine crosses blood-brain barrier, but to a small extent, and crosses the placenta.

Blood to plasma ratio was 0.65-0.75 indicating limited distribution to blood cells. Plasma protein binding was on average 99.7%. Rilpivirine was extensively bound to albumin and to a lesser extent to alpha acid glycoprotein. Apparent volume of distribution was estimated to be 152 l in the Phase III population analysis.

The distribution of rilpivirine into compartments other than plasma (e.g., cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

Elimination

The terminal half-life was around 45-50 hours across trials.

Rilpivirine is metabolised by hydroxylation, oxidation, glucuronidation and conjugation with glutathion. At 14 days after the administration of a single oral dose of radiolabelled rilpivirine, on average 85.1% ± 4.0% of the administered radioactivity had been excreted via the faeces. The average recovery in urine was 6.1% ± 2.1% with only trace amounts (≤ 0.03%) of unchanged rilpivirine. The total radioactivity recovered was about 91.2 ± 5.1%. Only sixty % of the excreted radioactivity was identified. The major loss in radioactivity appears to be caused by the fact that late faeces samples were not analysed for metabolites, some during extraction and some not identified. Unchanged drug was excreted in faeces and accounted for 25.5% of the dose on average (range 12.1-33.4%). No quantitative conclusion can be made on the origin but some of the unchanged drug may originate from poor absorption (solubility issue at higher doses). It can also not be excluded that biliary excretion of rilpivirine exists as an elimination pathway.

In plasma, unchanged drug accounted for a major part of the total radioactivity (76% based on Cmax and 51% based on AUClast). Fifty nine - 84 % of the drug related plasma exposure has been identified. Several metabolites were detected in plasma (glucuronides, direct and following oxidation, tricyclic and hydroxymethyl metabolite). Two metabolites were tested for antiviral activity M33 (hydroxymethyl-rilpivirine, which constituted 4-11% of parent exposure in plasma) had similar activity on wild type virus while metabolite 42 (oxidation at the pyrimidinyl moiety, main metabolite in faeces, 16% of dose) had 36 times lower activity. Neither is active on resistant strains.

In vitro data suggest that CYP3A4 is the major pathway involved in metabolism of rilpivirine.

Dose proportionality and time dependencies

Less than dose proportional increase in exposure at higher doses was observed, which is likely due to the limited solubility of the substance. The assessment of dose proportionality at lower doses was hampered by the fact that parallel group design was applied in all studies. Approximately dose

proportional increase was observed in healthy subjects up to 200 mg while in patients some studies indicated less than proportional increase already at lower doses while others suggested dose proportional increase. Since the applicant applied for only one dose with no dose adjustment the assessment of dose proportionality in patients is currently not essential.

No time dependency was obvious however no comparison of CL/F between first dose and steady state dose within study was provided. Based on interaction data limited induction is expected at a dose of 25 mg, hence this issue will not be further pursued.

Special populations

Interindividual variability was about 40%CV in oral clearance. No estimate on interoccasion variability in CL/F has been provided.

In the population PK study of the Phase IIb trial 20-30% lower exposure was observed in patients as compared to healthy volunteers. In the Phase III studies comparison was made with on study C152 (second thorough QT study). The exposure was 40 % lower in patients. Other data in healthy subjects suggest that Study C152 was at the higher end of exposures observed in healthy subjects.

- **Impaired renal function**

Renal elimination of rilpivirine is negligible. No study has been performed in patients with renal impairment. Since severe renal impairment may affect also drugs that are eliminated through hepatic elimination a cautious approach is recommended especially when combined with potent inhibitors of CYP3A.

- **Impaired hepatic function**

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 multiple dose exposure of rilpivirine was 47% higher in patients with mild hepatic impairment and 5% higher in patients with moderate hepatic impairment.

No data on unbound exposure has been submitted and the applicant claims it impossible to measure due to insensitivity of the assay. In the group with Child Pugh B very few subjects appear by score to have an affected metabolic capacity. Hence it cannot be excluded that the effect on unbound exposure would be larger in other subjects with moderate hepatic impairment and there is very limited safety data in this group. Therefore a more cautious approach is proposed in these groups of patients.

- **Gender, race, weight**

No clinically relevant impact of sex, race (White, Black or Asian), weight or BMI on rilpivirine PK was identified in the population PK analysis.

- **Elderly**

There is essentially no data in elderly (2 subjects above 65) hence no conclusions regarding elderly can be made.

The above information is reflected in section 4.2 and 5.2 of the SmPC.

- **Children**

The pharmacokinetics of rilpivirine in pediatric patients are not part of this procedure.

- **Pregnancy**

There are no pharmacokinetic studies in pregnant women submitted in this application.

Pharmacokinetic interaction studies

- **In vitro**

In vitro data suggest that rilpivirine may inhibit CYP2C19 and CYP2E1 at a systemic level and 3A4 at an intestinal level. Furthermore time dependent inhibition of CYP2C9 by rilpivirine cannot be excluded. Therefore the applicant will further investigate inhibitory properties (time dependent) of rilpivirine on CYP2C9 according to the measures in the RMP.

The in vitro induction data shows that rilpivirine is an inducer. The enzyme pattern induced (CYP3A4, CYP1A2 and possibly CYP2B6) fits PXR/CAR mediated induction hence several enzymes and transport proteins may be induced. The CYP2E1 results were inconclusive.

In vitro data suggest that rilpivirine may inhibit P-gp in the gut. Systemic inhibition of P-gp is not expected.

- **In vivo**

In vivo data with atorvastatin suggests that rilpivirine is not an inhibitor of OATP. There is no data on interaction potential with other transport proteins.
In vivo interaction data was to a large extent obtained with rilpivirine at a higher dose (150 mg) in healthy subjects. Steady state conditions for the interactions were aimed for See Table 6.

Table 6: Some main DDI studies for rilpivirine

Coadministered Drug (Trial)	Dose/Schedule		N	PK Effect	Mean Ratio (90% CI) of TMC278 Pharmacokinetic Parameters with/Without Coadministered Drug No Effect = 1		
	Coadministered Drug	TMC278			C_{max}	AUC	C_{min}
N(t)RTIs							
TDF (C104)	300 mg q.d. 16 days	150 mg q.d. 8 days	16	↔	0.96 (0.81 - 1.13)	1.01 (0.87 - 1.18)	0.99 (0.83 - 1.16)
ddI (C106)	400 mg q.d. 14 days	150 mg q.d. 7 days	21	↔	1.00 (0.90 - 1.10)	1.00 (0.95 - 1.06)	1.00 (0.92 - 1.09)
PIs							
LPV/rtv (C105)	400/100 mg b.i.d. 20 days	150 mg q.d. 10 days	15	↑	1.29 (1.18 - 1.40)	1.52 (1.36 - 1.70)	1.74 (1.46 - 2.08)
DRV/rtv (C112)	800/100 mg q.d. 22 days	150 mg q.d. 11 days	14	↑	1.79 (1.56 - 2.06)	2.30 (1.98 - 2.67)	2.78 (2.39 - 3.24)
Drugs other than Antiretrovirals							
Rifampin (C108)	600 mg q.d. 7 days	150 mg q.d. 7 days	16	↓	0.31 (0.27 - 0.36)	0.20 (0.18 - 0.23)	0.11 (0.10 - 0.13)
Rifabutin (C125)	300 mg q.d. 11 days	150 mg q.d. 11 days	16	↓	0.65 (0.58 - 0.74)	0.54 (0.50 - 0.58)	0.51 (0.48 - 0.54)
Ketoconazole (C127)	400 mg q.d. 22 days	150 mg q.d. 11 days	15	↑	1.30 (1.13 - 1.48)	1.49 (1.31 - 1.70)	1.76 (1.57 - 1.97)
Omeprazole (C114)	20 mg q.d. 12 days	150 mg single dose	16	↓	0.42 (0.32 - 0.54)	0.44 (0.35 - 0.55)	-
		150 mg q.d. 11 days	16	↓	0.60 (0.48 - 0.73)	0.60 (0.51 - 0.71)	0.67 (0.58 - 0.78)
Famotidine (C140)	40 mg single dose 2 hours before TMC278	150 mg single dose	23	↓	0.15 (0.12 - 0.19)	0.24 (0.20 - 0.28)	-
Famotidine (C140)	40 mg single dose 4 hours after TMC278	150 mg single dose	24	↔	1.21 (1.06 - 1.39)	1.13 (1.01 - 1.27)	-
Famotidine (C140)	40 mg single dose 12 hours before TMC278	150 mg single dose	24	↔	0.99 (0.84 - 1.16)	0.91 (0.78 - 1.07)	-
Paracetamol (C109)	500 mg single dose	150 mg q.d. 11 days	16	↔	1.09 (1.01 - 1.18)	1.16 (1.10 - 1.22)	1.26 (1.16 - 1.38)
Chlorzoxazone (C139)	500 mg single dose	150 mg q.d. 16 days	16	↑	1.17 (1.08 - 1.27)	1.25 (1.16 - 1.35)	1.18 (1.09 - 1.28)

N = maximum number of subjects with data; - = no information available.
* Comparison based on historic controls.
Source: Section 2.8

No effect of tenofovir, didanosine, sildenafil, atorvastatin, anticontraceptives or methadone on rilpivirine exposure was observed.

Inducers of CYP3A affected the exposure of rilpivirine and can affect as such the efficacy. Therefore the anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin; the antimycobacterials: rifabutin, rifampicin, rifapentine; the systemic glucocorticoid dexamethasone, except as a single dose treatment and St John's wort (*Hypericum perforatum*) are contra-indicated.

Drugs affecting the gastric pH substantially also affected the exposure of rilpivirine. Therefore proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole are contra-indicated.

Staggered dosing is suggested for H2 antagonists and antacids.

No dose adjustments are suggested for CY3A inhibitors.

Further data on interaction studies with raltegravir and rifabutin will be provided according to the measures mentioned in the RMP.

Rilpivirine exhibit a dose dependent induction in vivo with limited or no effect observed at lower doses than 150 mg q.d. At a dose of 25 mg no relevant impact on substrates of CYP3A, CYP2E1 and CYP2C19 is expected. Tenofovir exposure was increased by 23% when co-administered with rilpivirine (150 mg). The mechanism is not fully clear; the clinical relevance of this interaction is further discussed under safety.

Rilpivirine inhibits creatinine secretion in vivo. Inhibition of creatinine secretion has been suggested to be due to OCT-2 inhibition, but later publications also indicate that creatinine secretion as well as metformin secretion may involve MATE as a main transporter. There is a risk of a clinically relevant interaction with metformin. Therefore, an interaction study with metformin will be performed, which also includes investigations of the MATE inhibitory potential of rilpivirine (see corresponding measures in the RMP).

After a 25 mg dose mean Cmax in healthy subjects (QTc study C152) mean Cmax at day 11 was 247 ng/ml and AUCtau about 3300 ngh/ml. The exposure in this study was at the higher end of observed exposure.

A clear relation between concentration and QTc prolongation was observed after administration of 75 and 300 mg rilpivirine day 11. Women were more sensitive to QTc prolongation than men. The mean maximum prolongation appeared to coincide with the mean time of maximum concentration. It was noted that the QTc prolongation at day 11 was substantially higher than expected based on exposure of the parent compound (75 mg q.d. had lower exposure day 11 then 300 mg day 1 but higher QTc prolongation). Given the large exposure margin for the parent compound in preclinical studies and longer half-life of radioactivity in the mass-balance study, any contribution by metabolites to the QTc effect needs to be further elucidated. Therefore the applicant agreed to submit a report of the metabolite profiling and decision on synthesis of disproportional metabolites in relation to QT prolongation (see corresponding measures in the RMP).

2.4.3. 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).

Primary and Secondary pharmacology

Resistance

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.

- In sequential passages of different fixed doses of rilpivirine, no virus was seen using 40 nM or higher.

- Passages with gradually increasing dose, starting low, suggested the in vitro genotypic profile for rilpivirine to be: V90I, L100I, K101E, V106A/I, V108I, E138G/K/Q/R, V179F/I, Y181C/I, V189I, G190E, H221Y, F227C, and M230I/L.

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, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, H221Y, F227C, M230I, and M230L. The basis for this list of rilpivirine-associated mutations is discussed in more detail in section Failure and Resistance development in the clinical part. The fold changes seen with the most common rilpivirine-associated single mutations are low to modest.

It is of major importance to understand that this list only refers to treatment naïve patients, prior to starting therapy, and previously treatment naïve patients failing therapy with rilpivirine. In contrast, this list is not sufficient for a safe use in patients with prior virological failure with another NNRTI-based regimen. This is because a large number of NNRTI-associated mutations were used as exclusion criteria in the clinical studies. In addition to in vitro selection studies, that list of excluding mutations was based on data from the literature, and also included mutations not known to be associated to rilpivirine (or efavirenz).

Hence, the efficacy of rilpivirine in patients with virus showing the NNRTI mutations listed as exclusion criteria, but not selected for within the in vitro studies (or in vivo), has in fact not been studied. It is not straightforward to rely on in vitro sensitivity to make extrapolated assumptions about clinical activity against the excluded mutants/polymorphisms, since the in vitro fold changes are relatively low also for mutations clearly associated with virological failure on rilpivirine.

In addition to the mutations included in the list above, mutation M184I (intermediate mutation in the development of typical lamivudine/emtricitabine resistance) doubles the fold change of the most common rilpivirine-associated mutation E138K, and is in practice directly involved in the resistance score. This double mutation, E138K+M184I, was indeed the most common mutation pattern in patients failing rilpivirine in the phase 3 studies. Interestingly this pair of mutations were found in patients with the tenofovir/FTC backbone - but not in those treated with zidovudine/3TC (true for both phase 3 and phase 2b studies), and in only 1 patient treated with abacavir (low numbers), table 7 below.

Table 7: Frequency of 184 mutations and NNRTI mutation E138K by treatment arms (C209, 215 pooled).

NRTI-arm	rilpivirine Number of failures n/N, (%)	Control Number of failures n/N, (%)
tdf	55/550 (10%) M184I1+E138K: 21/55 1 M184I + other: 8/55 M184V+ E138K: 3/55 2 M184V+ other: 3/55	20/546 (3.7%) M184I +/- other: 1/20 M184V +/- other: 2/20 M184I/V (mix) +/- other: 1/20
azt	6/101 (6.9%) M184I+E138K: 0/7 M184I + other: 0/7 M184V+E138K: 2/7 M184V+(/-) other: 1/7	6/103 (5.8%) M184I +/- other: 0/6 M184V +/- other: 2/6 M184I/V (mix) +/- other: 0/6

1 Including mix of M184I/M184V. 2 Not including mix with M184I.

2.4.4. Discussion on clinical pharmacology

Discussion on clinical pharmacokinetics

The influence of food is substantial where normal fat and high fat meal result in similar exposure while if taken in fasting state the AUC is reduced by about 40%. Rilpivirine should be taken with a meal to ensure optimal absorption. This information is reflected in section 4.2 of the SmPC.

rilpivirine crosses blood-brain barrier, but to a small extent, and crosses the placenta.

Inhibitors and inducers of CYP3A as well as drugs affecting the gastric pH substantially affected the exposure of rilpivirine. Co-administration with inducers and PPIs (drugs affecting the gastric pH) are contraindicated (section 4.3), as these may decrease the plasma levels of rilpivirine and as such the efficacy. Staggered dosing is suggested for H2 antagonists and antacids.
All relevant information on pharmacokinetic interactions is adequately reflected in the SmPC.

The information on pharmacokinetics is reflected in sections 4.2, 4.5, 4.6 and 5.2 of the SmPC. Additional information on interactions and on the contribution of metabolites in QT prolongation will be performed according to the relevant measures in the RMP (see below).

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. 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, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, H221Y, F227C, M230I, and M230L. The basis for this list of rilpivirine-associated mutations is discussed in more detail in section Failure and Resistance development in the clinical part.

2.4.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology data submitted are considered satisfactory.
The CHMP considers the following measures as part of the RMP necessary to further characterise the pharmacology of the product:
- To further investigate inhibitory properties (time dependent) of rilpivirine on CYP2C9
- To provide further data on interaction studies with raltegravir and rifabutin
- To perform an interaction study with metformin, which also includes investigations of the MATE inhibitory potential of rilpivirine
- To submit a report of the metabolite profiling and decision on synthesis of disproportional metabolites in relation to QT prolongation.

2.5. Clinical efficacy

To determine clinical efficacy, the submitted clinical dossier consist of (see Figure 2):

- 2 phase IIa studies proof-of-principle (functional) monotherapy studies in ARV-naïve (C201) and ARV-experienced (C202) HIV-1 infected patients to confirm its antiviral activity.
- 1 phase IIb dose finding study in ARV naïve HIV-1 infected adults with rilpivirine 25 mg, 75mg or 150 mg q.d.
- 2 pivotal phase III randomized trials (C209 and C215) in ARV naïve HIV-1 infected adults comparing rilpivirine 25 mg q.d. plus 2 N(t)RTIs to efavirenz 600 mg q.d. plus 2 N(t)RTIs.

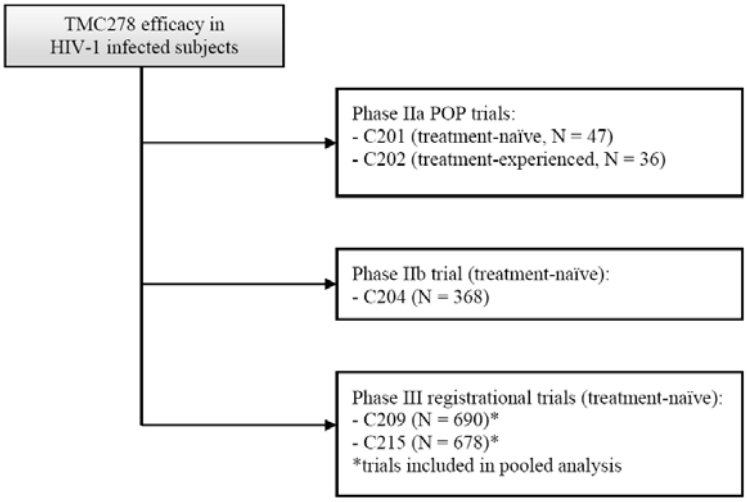


Figure 2.

2.5.1. Dose response studies

Phase IIa studies

Two phase IIa proof-of-principle studies were performed with rilpivirine in HIV-1 infected patients to confirm its antiviral activity. One study (C201) explored the efficacy of different dosages of rilpivirine mono-therapy in treatment-naïve patients (n = 36 received rilpivirine) while the other study (C202) explored the efficacy of different dosages of rilpivirine in treatment-experienced patients (n = 36 received rilpivirine) as a substitute for a failing NNRTI or protease inhibitor (PI) (= functional mono-therapy). The treatment duration in both studies was limited to 7 days to minimize the risk of emergence of mutations. Both studies confirmed a significant in vivo activity to HIV-1 of different dosages (25 mg – 150 mg q.d.) of rilpivirine. Based on these results a final dose-finding phase IIb study was performed (C204).

A 1.2 $\log_{10}$ reduction of HIV-RNA was seen, with no relevant difference between doses tested. This means that the potency of rilpivirine is low compared to other agents (raltegravir > 2$\log_{10}$ reduction, PI/r around -2$\log_{10}$, efavirenz -1.6 $\log_{10}$; tenofovir and abacavir around 1.6 $\log_{10}$ reduction in monotherapy).

No emerging resistance in the RT gene was detected at any time during treatment, using population sequencing.

Phase IIb study

C204 is a randomized, active controlled, partially blinded (to dose of rilpivirine) trial in treatment-naïve HIV-1 patients to evaluate the dose-response, efficacy, tolerability, and safety of a 96-week regimen with 3 doses (25mg, 75 mg and 150mg) of rilpivirine. The active comparator was EFV 600 q.d. and all patients received a background regimen of 2 N(t)RTIs selected by the investigators (tenofovir/emtricitabie, abacavir/lamivudine or zidovudine/lamivudine). After 96 weeks all patients were offered to continue or switch their study medication to rilpivirine 75 q.d. After 144 weeks, based on the evaluation of the 96 weeks data, they were switched to rilpivirine 25 q.d. This trial is still ongoing to obtain long-term (up to 240 weeks) efficacy and safety data.

It should be noted that the rilpivirine 25 mg formulation (F001) used in this trial is different from the formulation (F006) used in the pivotal phase III trials The current request for marketing authorization concerns the latter rilpivirine 25 mg q.d. formulation (F006). The different formulations are considered to be bioequivalent.

Inclusion/exclusion criteria were those commonly used for treatment naïve patients. Two specific issues are considered particularly relevant. 1) An extensive number of NNRTI-associated mutations constituted exclusion criteria (n=37); 2) A cortisol level on the screening assessment requested for inclusion. This criterion was the major reason for screening failures (around 8% of screened patients). The reason for this and for endocrine monitoring performed, were effects on the steroid hormones seen pre-clinically.

The study included HIV-1 infected ARV treatment naïve adults with a plasma viral load of > 5,000 copies/mL who were appropriate to initiate ART according to the investigator's judgment, who were susceptible to the selected ARV regimen (according to baseline genotyping).

As defined by exclusion criteria all subjects were relatively healthy (e.g. life expectancy > 6 months, absence of AIDS defining illness, absence of renal impairment or other significant coexisting illness).

Of 515 screened subjects, 368 (71%) were randomized and received treatment (≈ n = 90 per treatment arm). The most common reasons for screen failures were cortisol levels outside the required levels, abnormal lab values and viral load values ≤ 5,000 copies/mL. The proportion of screen failures excluded because of NNRTI RAMs from the exclusion list was 3.5% (5/142); this represented 1.0% of the total screened population (5/515). The mutations observed at screening in these 5 subjects were K101E, K103N, Y181C, and G190A. All of these mutations are listed in the most recent IAS-USA December 2010 Resistance Mutations Update as associated with resistance to NNRTIs.

The demographics were quite representative of today's patients, including race other than white and non-B subtypes being well represented. Discontinuations were rather common with around 25% of patients stopping therapy prior to week 96 for various reasons. However, reasons for stopping were not markedly different between the treatment arms, including the control.

The primary efficacy variable was the proportion of subjects achieving virologic response (< 50 copies/mL, TLOVR) at 96 weeks which demonstrated rilpivirine to be efficacious across different dosages.

Results are presented in table 8 below.

Table 8: Outcomes at week 48 and 96 in numbers and (%), study 204.

	25 mg (n=93)	75 mg (n=95)	150 mg (n=91)	TMC pooled (n=220)	Control (n=89)
Wk 48, < 50 cps/mL	(79.6)	(80.0)	(76.9)	(78.9)	(80.9)
BL VL <100.000	51/61 (84)	48/59 (82)	46/58 (79)	145/178 (82)	46/56 (82)
BL VL >100.000	23/32 (72)[#]	28/36 (78)	29/31 (94)[#]	75/101 (75)	26/33 (79)
Non-responders					
Virologic failure	9 (9.7)	5 (5.3)	6 (6.6)	20 (7.2)	5 (5.6)
Discont. for AE	6 (6.5)	5 (5.3)	9 (9.9)	20 (7.2)	5 (5.6)
Wk 96, < 50 cps/mL	(76.3)	(71.6)	(71.4)	(73.1)	(70.8)
Non-responders					
Virologic failure	8	9	6	23 (8.2)	7 (7.9)
Discont. for AE	8	8	13	29 (10.4)	7 (7.9)

[#] comparing 25 mg vs 150 mg for high BL VL: 23/32 vs 29/31 (CI95: -39 to -4)

Numbers are small for proper sub analyses regarding dose dependency according to baseline VL. However, the difference between doses 25 mg and 150 mg in patients with a baseline VL >100000 (94% vs 72%) is significant at week 48.

The majority of patients were taking zidovudine/lamivudine in this study (75%), in contrast to the pivotal studies.

rilpivirine seems to be doing better when combined with zidovudine/3TC (given in low income regions) than with tenofovir/FTC (given in EU/US) and it is not expected that EU and US study sites yield worse outcomes than sites in the other regions of this study (this trend is further discussed in the main clinical studies).

The efficacy of rilpivirine was maintained up to 192 weeks of treatment. By Week 144, 64.5% of subjects had maintained virologic response (< 50 copies/mL, TLOVR) (note that all rilpivirine recipients used 75 mg q.d. between week 96 and 144). By Week 192, a total of 58.8% of subjects taking rilpivirine had maintained virologic response (note that all rilpivirine recipients used 25 mg q.d. between week 144 and 192). These long term outcomes were similar to the results in the control group (EFV 600 mg q.d.).

Thirty-one of 279 subjects (11.1%) randomized in the rilpivirine group and 8 of 89 subjects (9.0%) randomized in the control (EFV) group experienced virological failure at the time of the Week 192 analysis. For 21/30 patients treated with TCM278 and with available genotypic and phenotypic data, emergence of reverse transcriptase mutations was observed. The most frequently emerging reverse transcriptase mutations were: L74V, K101E, V108I, E138K, E138R, I178L, Y181C, M184V, M184I, M230L, and N348I. Thirteen of the 30 subjects had emerging nucleoside/tide reverse transcriptase inhibitor resistance associated mutations. Emergence of M184V or M184I (associated to the development of resistance to lamivudine and emtricitabine) was observed in the rilpivirine group but not in the control (EFV) group. In the control (EFV) group, the emerging non-nucleoside reverse transcriptase inhibitor resistance-associated mutations observed in the subjects experiencing virological failure were K103N and V106M.

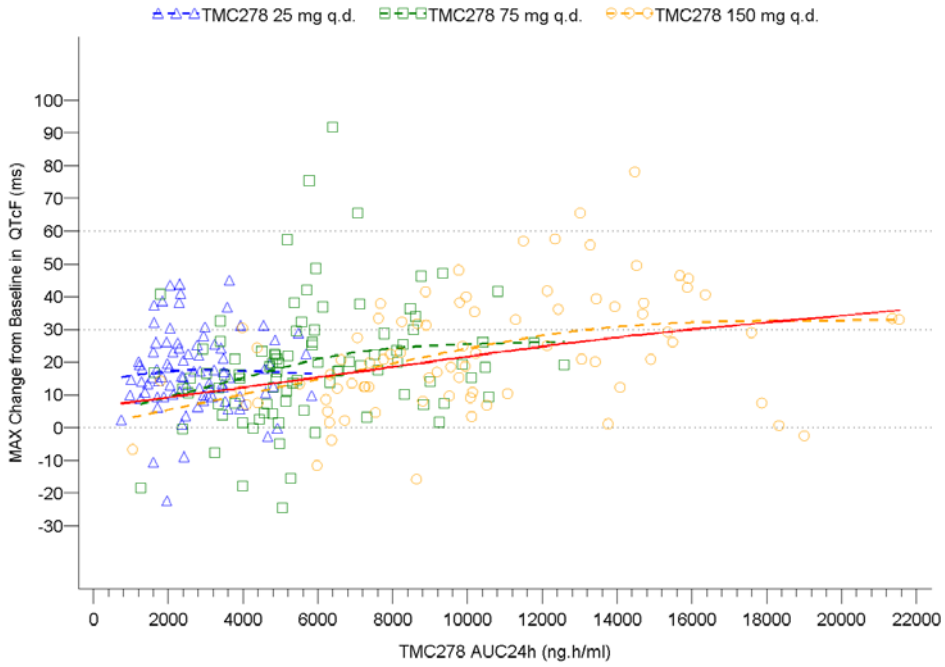
Subjects experiencing virological failure in the rilpivirine group with phenotypic resistance to rilpivirine were generally cross-resistant to etravirine and efavirenz, and subjects from the control (EFV) group with phenotypic resistance to EFV retained sensitivity to rilpivirine and etravirine.

Dose selection

A dose-response relationship could not be demonstrated. However, initially the 75 mg q.d. dose was selected for the Phase III trials and further development of rilpivirine because, though not statistically significant, the proportion of virologic failures in the rilpivirine 25 mg q.d. group was 8.6% compared to 5.3% and 6.6% in the 75 mg q.d. and 150 mg q.d. dose groups, respectively. Furthermore, there was a trend towards lower efficacy of the 25 mg q.d group among those with a high baseline viral load. Later, data became available demonstrating a possible dose-response relationship with respect to AEs (see below and safety assessment).

A statistically significant positive correlation was observed between change from baseline in QTcF interval and exposure (AUC24h) to rilpivirine ($p < 0.001$) as illustrated by the following scatterplot (Figure 3).

Figure 3. Scatter-plot of rilpivirine AUC24h vs the Maximum Change in QTcF Interval From Baseline (Phase IIb Trial C204)



Thus rilpivirine 25 mg q.d. formulation was finally chosen for further evaluation in phase III studies as well as the prolonged arm of this phase IIb study.

A concern was raised on the possible suboptimal dose of 25 mg q.d. in terms of efficacy, especially among patients with high baseline viral load, and the applicant was requested to further clarifiy the relation between dosage, exposure, efficacy, virologic failure and emergence of resistance stratified by baseline viral load. The phase IIb study did not show a dose-response in terms of virologic response for both low and high baseline viral load categories, however, there was a tendency towards a lower reponse in patients with lower AUC, although there was a large overlap in AUC values between

responders and non-responders. This trend was also observed within the phase 3 studies using the 25 mg dose based on population PK. Also within the dose-finding study there appeared a trend for higher rates of emerging resistance in the lowest dose group of 25 mg TCM278 q.d. and especially for patients with baseline viral load > 100,000 copies/ml. Analyses of phase 3 studies stratified by baseline viral load showed lower virologic response, higher rate of virologic failure, and increased risk of resistance for patients with baseline viral load > 100,000 copies/ml compared to control group and compared to patients with lower baseline viral load. It remains unknown whether an intermediate dose of 50 mg rilpivirine q.d. would allow enhancing the virological suppression at the level of efavirenz without exposing to a critical risk of QT prolongation.

2.5.2. Main studies

C209 and C215

The two phase III studies (C209 and C215) are both randomized, double-blind, double-dummy, trials of rilpivirine 25 mg q.d. versus EFV 600 mg q.d. in combination with a fixed background regimen consisting of tenofovir disoproxil fumarate and emtricitabine (C209) or with a background regimen containing 2 investigator initiated N(t)RTIs (either ABC/3TC, AZT/3TC or TDF/FTC) (C215) in ARV-naïve HIV-1 infected subjects.

The design of these trials were similar and therefore there is a common description. The outcomes are presented separately together with the pooled data.

Methods

Study Participants

Included HIV-1 infected adults with a plasma viral load of > 5,000 copies/mL who were appropriate to initiate ART according to the investigator's judgment, had never received ARV treatment, who were susceptible to the selected background regimen at screening, and who had no NNRTI RAMs from a predefined list were eligible for this trial (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).

Exclusion criteria were the use of disallowed concomitant therapy, life expectancy < 6 months, presence of AIDS defining illness except cutaneous Kaposi sarcoma and HIV wasting syndrome, acute HIV-1 infection, HIV-2 coinfection, any active clinically significant disease, subjects with a risk factor for QTc prolongation, pregnancy or breastfeeding, absence of effective birth control methods, estimated glomerular filtration rate < 50mL/min.

Both trials are conducted in USA, Canada, Europe, Australia, Asia, Africa and Latin America with some differences seen in the proportions of subjects recruited per region and country between the two trials.

Treatments

Subjects were randomized in a 1:1 ratio to receive either rilpivirine 25 mg q.d or to EFV 600 mg q.d. (control) plus a background regimen containing TDF/FTC (C209) or 2 investigator-selected N(t)RTIs (either ABC/3TC, AZT/3TC or TDF/FTC) (C215).

rilpivirine (or placebo) q.d. should have been taken with food, preferably breakfast, each dose separated by approximately 24 hours. EFV (or placebo) q.d., was taken on an empty stomach, preferably at bedtime, each dose separated by approximately 24 hours. The background regimen was recommended to be taken at the same time as rilpivirine (or placebo). Due to the differences in administration with or without food, a double-dummy design was chosen so subjects receiving active rilpivirine also took placebo EFV (and vice versa) in addition to their background regimen.

Objectives

The primary objective was to demonstrate non-inferiority of treatment with rilpivirine 25 mg q.d compared to control (EFV 600 mg q.d.) in regard to the proportion of virologic responders (plasma viral load < 50 human immunodeficiency virus [HIV]-1 ribonucleic acid [RNA] copies/mL, according to the TLOVR algorithm at 48 weeks, with a maximum allowable difference of 12%.

Secondary objectives included:
- demonstrate non-inferiority of rilpivirine compared to EFV with a maximum allowable difference of 10% at 48 weeks for the primary efficacy endpoint;
- evaluate superiority in efficacy of rilpivirine compared to EFV, in case non-inferiority was established;
- evaluate and compare the safety and tolerability of rilpivirine when administered as 25 mg q.d. versus (vs.) EFV over 48 and 96 weeks;
- evaluate and compare the antiviral activity of rilpivirine when administered as 25 mg q.d. vs. EFV over
48 and 96 weeks;
- evaluate and compare immunologic changes (as measured by CD4+ cell count) in the rilpivirine group vs. those in the EFV group over 48 and 96 weeks;
- assess the evolution of the viral genotype and phenotype over 48 and 96 weeks;
- evaluate the population pharmacokinetics and the pharmacokinetic/pharmacodynamic relationships for efficacy and safety of rilpivirine.

Outcomes/endpoints

The primary efficacy parameter was the proportion of subjects with virologic response, i.e. a viral load < 50 HIV-1 copies/mL at Week 48, according to the time to loss of virologic response (TLOVR) algorithm.

Sample size

The primary efficacy parameter was the proportion of subjects with virologic response, i.e., a plasma viral load < 50 copies/mL, according to the FDA's TLOVR algorithm. Based on previous trials with EFV, the proportion of virologic responders (response rate) in the control group was expected to be approximately 70–80%. Assuming a response rate of 75% at 48 weeks for both treatment options, it was calculated that 340 subjects would be needed per treatment group (rilpivirine or control) to establish non-inferiority of rilpivirine vs. EFV with a maximum allowable difference of 12%, at 95% power.

Randomisation

Subjects were randomized in a 1:1 ratio to either rilpivirine or EFV. Randomization was stratified by screening viral load (strata were ≤ 100,000; > 100,000 - ≤ 500,000; and > 500,000 copies/mL) and

for trial C215 also by background regimen (ABC/3TC, AZT/3TC, TDF/FTC).
Predefined randomization schedules using permuted blocks were applied to ensure balance across treatment groups in the strata and random treatment assignment.

Blinding (masking)

After randomization on Day 1, neither Tibotec Pharmaceuticals, the investigator, nor the subjects who had been allocated to one of the double-blind NNRTI treatments (rilpivirine or EFV) were aware of the identity of their treatment. In addition to the investigator-selected N(t)RTIs, subjects assigned to one of the double-blind treatments took 2 tablets daily, either:
- Active rilpivirine and EFV placebo
- Active EFV and rilpivirine placebo
The placebo tablets were identical in appearance to their respective active treatments.

The primary analysis was performed once all randomized subjects had been treated for 48 weeks, or had been withdrawn earlier (cut-off date 28 January 2010). For this analysis, the blind was broken for Tibotec Pharmaceuticals but not for subjects, investigators, and monitors who interact with site personnel.

Once the trial is completed (96-week data and follow-up visits) and the database is locked, a final analysis will be performed on all available data. The investigator will receive a copy of the randomization codes for the subjects participating in his/her center, clearly identifying the treatment numbers and the corresponding treatment group (rilpivirine or control).

A DSMB was installed to monitor the safety of the subjects included in the trial. Blinded data was sent to the DSMB every 16 weeks. A summary of SAEs, grade 3 and grade 4 AEs, and AEs leading to discontinuation was provided on a monthly basis. Two formal DSMB analyses were performed: the first when 340 randomized subjects (50% of the planned number of subjects) had reached ≥12 weeks of treatment or discontinued, and the second when almost all randomized subjects had reached 24 weeks of treatment or discontinued. Data of these analyses were shared with the DSMB but not with Tibotec Pharmaceuticals (other than the Sponsor Review Committee) or site personnel directly involved in trial conduct. In these analyses, the treatment code was partially unblinded (up to code level) to the DSMB, but not revealed to Tibotec Pharmaceuticals (other than the Sponsor Review Committee). Involvement of the Sponsor Review Committee in these analyses was according to the DSMB Charter. Although full unblinding did not occur, if deemed necessary by the DSMB, treatment codes could be fully unblinded to the DSMB members only. Based on these analyses, the DSMB recommended that the trial could continue without modification.

Statistical methods

The intent-to treat (ITT) population was defined as the set of all subjects who were randomized and who took at least 1 dose of study medication, regardless of their adherence with the protocol or their eligibility.

The per protocol (PP) population was defined as the set of all randomized subjects who took at least 1 dose of study medication and experienced no major protocol violations during the trial.

The primary population was the ITT population. However, since an analysis on the ITT population may not be conservative in a non-inferiority setting, an analysis based on the PP population was also

performed to investigate the impact of exclusion of subjects with major protocol violations and to evaluate the robustness of the primary analysis results.

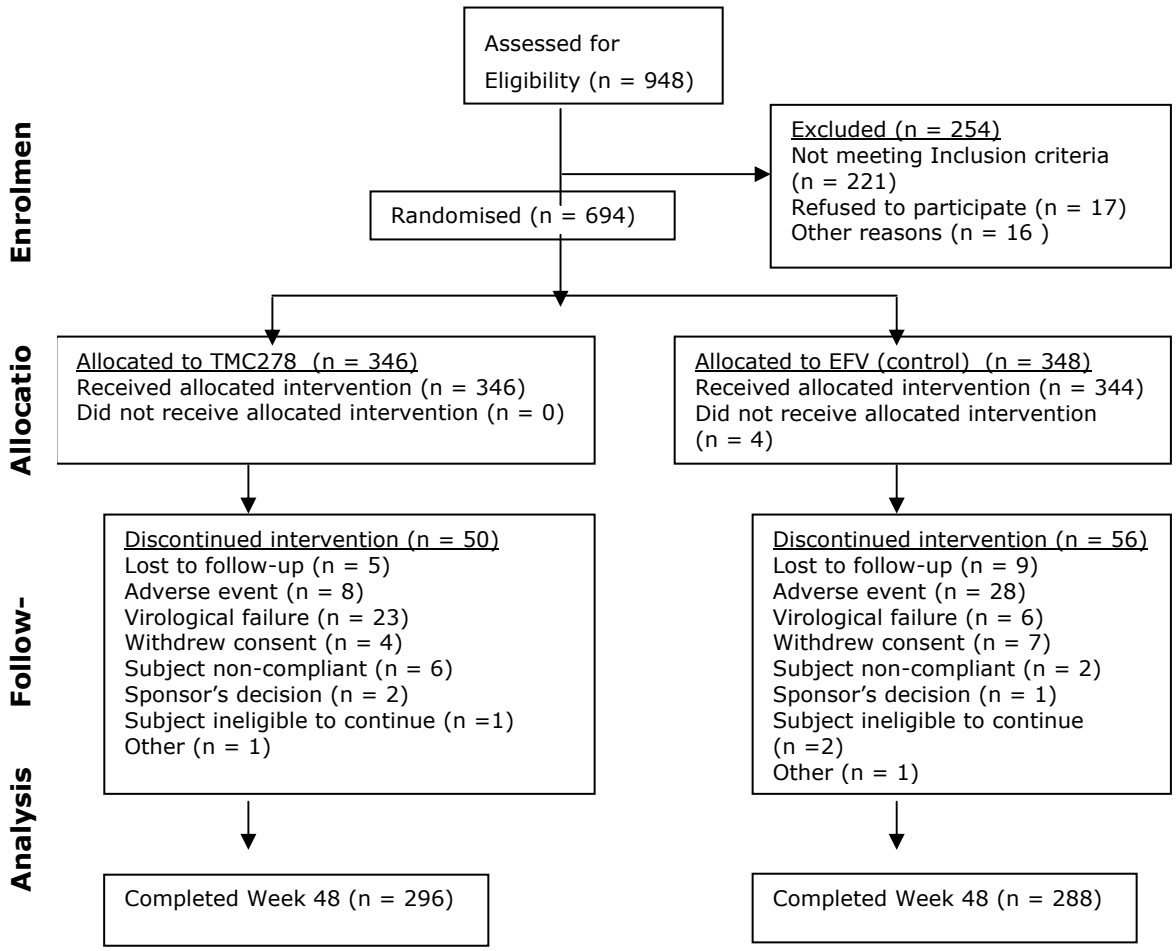
The safety analyses were performed on the ITT population.

The primary efficacy variable in the primary population (ITT) was compared between rilpivirine and control at the Week 48 time point, adjusted for factors treatment group and background regimen (C215), and using baseline log10 plasma viral load as a continuous variable. The model-based odds ratio for rilpivirine relative to control was presented along with the associated 95% CI. The predicted proportion of responders with 95% CI as well as the differences in these proportions with 95% CI, based on the above logistic regression model, for the rilpivirine and control was calculated. A p-value for non-inferiority of rilpivirine compared with control was provided for a maximum allowable difference of 12% (the primary efficacy analysis) and 10% (secondary efficacy analysis). A p-value for superiority of rilpivirine compared with control was also provided where non-inferiority was achieved.

Results

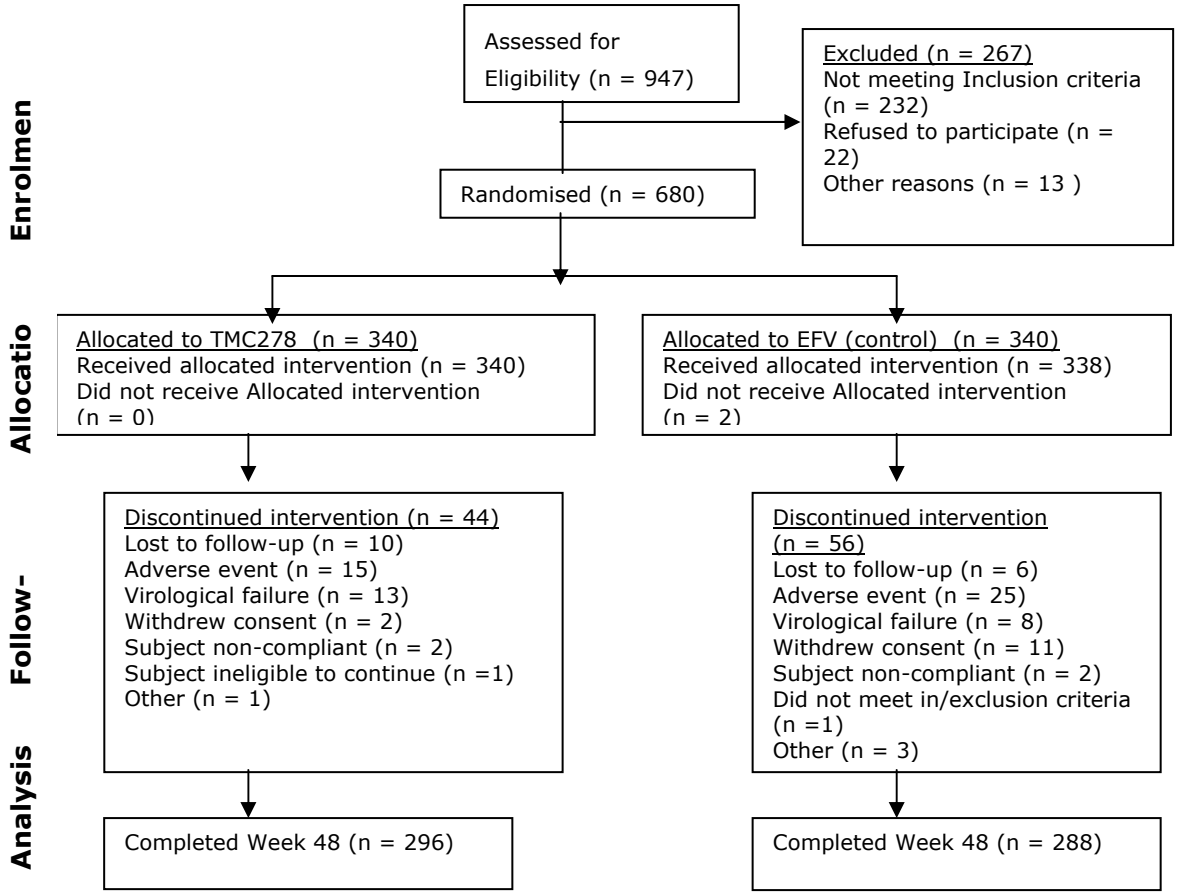
Participant flow

Figure 4: Study C209



Note: Those who received the allocated intervention is the ITT population.

Figure 5: Study C215



Screening failures

The reasons for screening failures are displayed in the following Table 9 (of note: as subjects could have more than one reason for screening failure these numbers outweigh the number of patients):

Table 9.

Number of subjects failing in- or exclusion criteria[a], n (%)	Screen Failures		
	C209 N' = 258	C215 N' = 269	Pooled N' = 527
Inclusion Criteria			
HIV-1 viral load at screening < 5,000 copies/mL	79 (30.6)	86 (32.0)	165 (31.3)
Inability to comply with protocol requirements	8 (3.1)	24 (8.9)	32 (6.1)
Having decreased sensitivity to at least 1 of the background N(t)RTIs	9 (3.5)	16 (5.9)	25 (4.7)
Exclusion Criteria			
Presence of at least 1 NNRTI RAM from the protocol list[b]	74 (28.7)	74 (27.5)	148 (28.1)
Having 1 or more risk factors for QTc prolongation	28 (10.9)	30 (11.2)	58 (11.0)
Having any of the specified grade 3 or 4 laboratory toxicities	13 (5.0)	18 (6.7)	31 (5.9)

Of 1895 screened patients, 1368 (72%) were randomized and received allocated treatment (686 rilpivirine versus 682 EFV). The reasons for screening failure (n = 527) were low baseline viral load (< 5.000 copies/mL), presence of at least NNRTI RAM or having risk factors for QTc prolongation or laboratory toxicities.

A considerable part (165/1895; 8.7%=35% of screening failures) of the population failed inclusion because of baseline viral load of < 5,000 copies/ml, and the applicant was asked to justify this threshold (Q62). In their response, the applicant argued that this threshold was chosen to allow for a measureable decrease in viral load of ≥ 1.0 log10 copies/mL, given the detection limit of 50 copies/ml. This is considered acceptable.

In the overall screened population with genotypic data, 156 (8.7%) out of 1,796 subjects had at least 1 NNRTI RAM of the protocol list. To what extent this 8.7% primary genotypic resistance implicates phenotypic resistance to either rilpivirine or EFV is unclear. The most frequent mutation was E138A that is associated with resistance to rilpivirine and not to EFV.

Recruitment

Primary analyses were performed when all subjects completed 48 weeks of treatment or discontinued earlier (cut-off date of 01 February 2010 for C209 and 28 January 2010 for C215). The final analysis of the two Phase III trials will be performed when all subjects have completed 96 weeks of treatment, or discontinued earlier.

Baseline data

The baseline demographic characteristics are the following:

Table 10.

	C209		C215		Pooled	
Parameter	**TMC278 N = 346**	**Control N = 344**	**TMC278 N = 340**	**Control N = 338**	**TMC278 N = 686**	**Control N = 682**
Gender (n [%]), N'	**346**	**344**	**340**	**338**	**686**	**682**
Female	78 (22.5)	69 (20.1)	90 (26.5)	94 (27.8)	168 (24.5)	163 (23.9)
Male	268 (77.5)	275 (79.9)	250 (73.5)	244 (72.2)	518 (75.5)	519 (76.1)
Age (years), N'	**346**	**344**	**310**	**310**	**656**	**654**
Median	36.0	36.0	36.0	35.5	36.0	36.0
(Min - Max)	(18 - 78)	(19 - 67)	(19 - 62)	(19 - 69)	(18 - 78)	(19 - 69)
Body Mass Index (kg/m^2), N'	**345**	**341**	**337**	**336**	**682**	**677**
Median	24.2	23.7	23.9	23.4	24.0	23.5
(Min - Max)	(16 - 44)	(16 - 42)	(15 - 73)	(16 - 44)	(15 - 73)	(16 - 44)
Race (n [%]), N'	**346**	**344**	**338**	**338**	**684**	**682**
White	214 (61.8)	206 (59.9)	206 (60.9)	204 (60.4)	420 (61.4)	410 (60.1)
Black/African American	89 (25.7)	80 (23.3)	76 (22.5)	76 (22.5)	165 (24.1)	156 (22.9)
Asian	33 (9.5)	48 (14.0)	45 (13.3)	49 (14.5)	78 (11.4)	97 (14.2)
Other	3 (0.9)	4 (1.2)	11 (3.3)	8 (2.4)	14 (2.0)	12 (1.8)
Not allowed to ask per local regulations	7 (2.0)	6 (1.7)	0	1 (0.3)	7 (1.0)	7 (1.0)

The median age was 36 years (range 18-78), 76% were men. The number of patients aged above 65 years was low (4 subjects).

The background regimens were:

Table 11.

NRTI background regimen, n (%)	C209		C215		Pooled	
	TMC278 N = 346	Control N = 344	TMC278 N = 340	Control N = 338	TMC278 N = 686	Control N = 682
N'	346	344	340	338	686	682
TDF/FTC	346 (100)	344 (100)	204 (60.0)	202 (59.8)	550 (80.2)	546 (80.1)
AZT/3TC	0	0	101 (29.7)	103 (30.5)	101 (14.7)	103 (15.1)
ABC/3TC	0	0	35 (10.3)	33 (9.8)	35 (5.1)	33 (4.8)

About 9% of the included population had active hepatitis B or C infection, well balanced between the two treatment arms.

The baseline disease characteristics are:

Table 12.

Baseline Disease Parameters	C209		C215		Pooled	
	TMC278 N = 346	Control N = 344	TMC278 N = 340	Control N = 338	TMC278 N = 686	Control N = 682
Viral Load (copies/mL), N'	**346**	**344**	**340**	**338**	**686**	**682**
Median (Min - Max)	94,950.0 (156 – 3,300,000)	105,000.0 (1,010 – 3,360,000)	83,950.0 (836 – 20,800,000)	102,500.0 (1,140 – 4,550,000)	90,450.0 (156 – 20,800,000)	104,500.0 (1,010 – 4,550,000)
Log_{10} Viral Load (copies/mL), N'	**346**	**344**	**340**	**338**	**686**	**682**
Median (Min - Max)	5.0 (2 - 7)	5.0 (3 - 7)	4.9 (3 - 7)	5.0 (3 - 7)	5.0 (2 - 7)	5.0 (3 - 7)
$CD4^+$ Cell Count (cells/µL), N'	**346**	**344**	**339**	**338**	**685**	**682**
Median (Min - Max)	240.0 (1 - 888)	257.0 (1 - 757)	263.0 (2 - 744)	263.0 (1 - 1137)	249.0 (1 - 888)	260.0 (1 - 1137)
$CD4^+$ Cell Count (%,) N'	**346**	**344**	**339**	**338**	**685**	**682**
Median (Min - Max)	18.7 (0 - 42)	17.8 (0 - 43)	17.6 (0 - 45)	17.0 (0 - 44)	18.3 (0 - 45)	17.5 (0 - 44)
Duration of Known HIV Infection at Screening (years), N'	**346**	**344**	**340**	**338**	**686**	**682**
Median (Min - Max)	1.2 (0 - 22)	1.3 (0 - 25)	1.7 (0 - 24)	1.3 (0 - 28)	1.4 (0 - 24)	1.3 (0 - 28)
Clinical Stage of HIV Infection at Screening (n [%]), N'	**346**	**344**	**340**	**338**	**686**	**682**
CDC Category A	249 (72.0)	242 (70.3)	237 (69.7)	232 (68.6)	486 (70.8)	474 (69.5)
CDC Category B	83 (24.0)	79 (23.0)	82 (24.1)	90 (26.6)	165 (24.1)	169 (24.8)
CDC Category C	14 (4.0)	23 (6.7)	21 (6.2)	16 (4.7)	35 (5.1)	39 (5.7)
Clade (n [%]), N'	**346**	**344**	**340**	**338**	**686**	**682**
B	247 (71.4)	243 (70.6)	238 (70.0)	219 (64.8)	485 (70.7)	462 (67.7)
C	40 (11.6)	41 (11.9)	36 (10.6)	48 (14.2)	76 (11.1)	89 (13.0)
CRF01_AE	34 (9.8)	27 (7.8)	42 (12.4)	43 (12.7)	76 (11.1)	70 (10.3)
CRF02_AG	4 (1.2)	11 (3.2)	6 (1.8)	5 (1.5)	10 (1.5)	16 (2.3)
F1	6 (1.7)	8 (2.3)	4 (1.2)	6 (1.8)	10 (1.5)	14 (2.1)
A1	4 (1.2)	6 (1.7)	7 (2.1)	2 (0.6)	11 (1.6)	8 (1.2)
CRF12_BF	4 (1.2)	4 (1.2)	0	2 (0.6)	4 (0.6)	6 (0.9)
D	3 (0.9)	0	1 (0.3)	3 (0.9)	4 (0.6)	3 (0.4)
CRF07_BC	0	0	3 (0.9)	3 (0.9)	3 (0.4)	3 (0.4)
CRF14_BG	2 (0.6)	2 (0.6)	0	1 (0.3)	2 (0.3)	3 (0.4)
CRF03_AB	1 (0.3)	0	1 (0.3)	1 (0.3)	2 (0.3)	1 (0.1)
A1/CRF01_AE	0	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.1)	2 (0.3)
CRF08_BC	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)
F2	1 (0.3)	0	0	0	1 (0.1)	0
CRF06_CPX	0	1 (0.3)	0	0	0	1 (0.1)
CRF16_A2D	0	0	0	1 (0.3)	0	1 (0.1)
CRF18_CPX	0	0	0	1 (0.3)	0	1 (0.1)
K	0	0	0	1 (0.3)	0	1 (0.1)

Dividing the CD4 T-cell count and viral load into different categories revealed the following:

Figure 6.

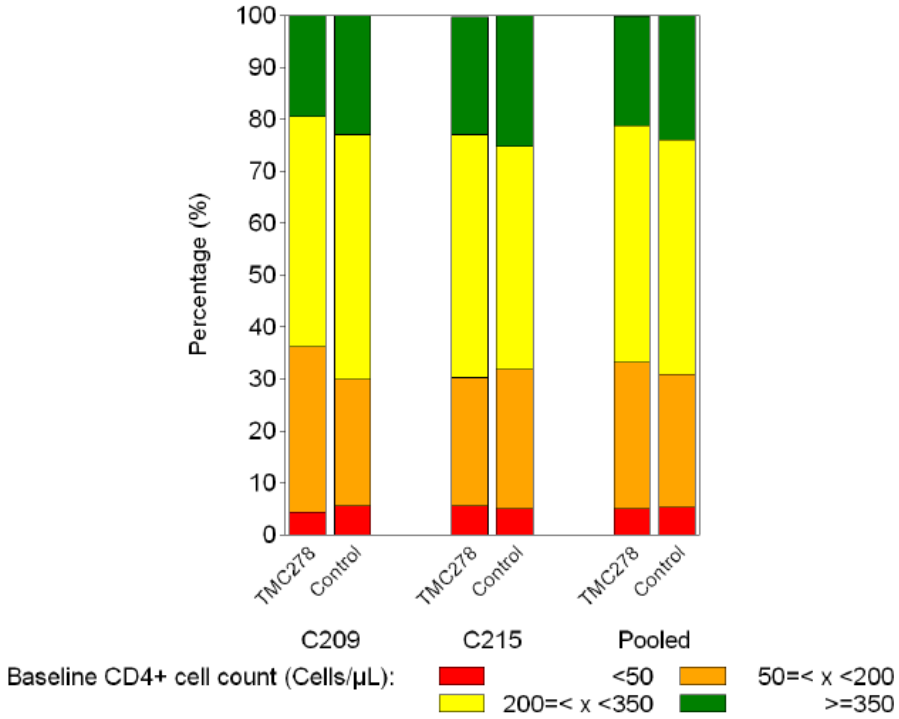
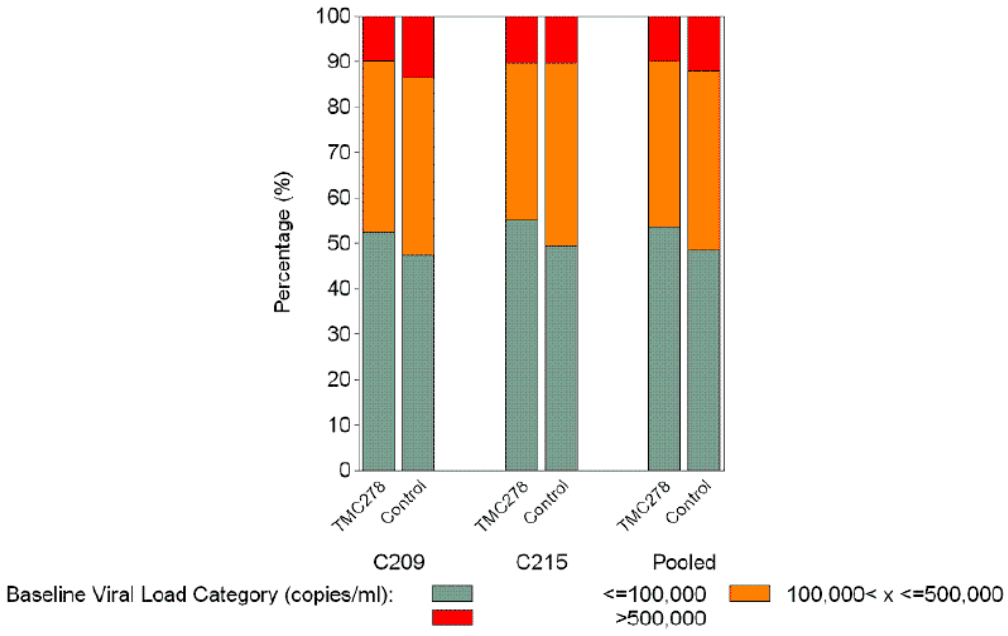


Figure 7.



The median baseline CD4 T-cell count was around 250 cells/uL. The proportion of subjects with CD4-cell count ≥ 500 cells/uL was low (4.1% and 6.7%, respectively).

About 10% of the randomized population had a CD4 T-cell count <50 cells/uL and 5% had a high baseline viral load above 500,000 copies/mL.

The distribution per region was follows:

Table 13.

Number of Subjects n (%)	C209		C215		Pooled	
	TMC278 N = 346	Control N = 344	TMC278 N = 340	Control N = 338	TMC278 N = 686	Control N = 682
Region 1: USA, Canada, Europe, Australia	**207 (59.8)**	**193 (56.1)**	**172 (50.6)**	**154 (45.6)**	**379 (55.2)**	**347 (50.9)**
USA	106 (30.6)	91 (26.5)	74 (21.8)	69 (20.4)	180 (26.2)	160 (23.5)
Germany	-	-	30 (8.8)	28 (8.3)	30 (4.4)	28 (4.1)
Canada	10 (2.9)	13 (3.8)	15 (4.4)	15 (4.4)	25 (3.6)	28 (4.1)
United Kingdom	16 (4.6)	15 (4.4)	9 (2.6)	7 (2.1)	25 (3.6)	22 (3.2)
France	15 (4.3)	20 (5.8)	5 (1.5)	4 (1.2)	20 (2.9)	24 (3.5)
Spain	9 (2.6)	8 (2.3)	8 (2.4)	11 (3.3)	17 (2.5)	19 (2.8)
Belgium	-	-	16 (4.7)	13 (3.8)	16 (2.3)	13 (1.9)
Portugal	14 (4.0)	10 (2.9)	2 (0.6)	3 (0.9)	16 (2.3)	13 (1.9)
Italy	8 (2.3)	10 (2.9)	6 (1.8)	3 (0.9)	14 (2.0)	13 (1.9)
Australia	5 (1.4)	7 (2.0)	7 (2.1)	1 (0.3)	12 (1.7)	8 (1.2)
Denmark	7 (2.0)	11 (3.2)	-	-	7 (1.0)	11 (1.6)
Austria	6 (1.7)	4 (1.2)	-	-	6 (0.9)	4 (0.6)
Romania	4 (1.2)	3 (0.9)	-	-	4 (0.6)	3 (0.4)
Netherlands	4 (1.2)	0	-	-	4 (0.6)	0
Sweden	3 (0.9)	1 (0.3)	-	-	3 (0.4)	1 (0.1)
Region 2: Africa	**32 (9.2)**	**31 (9.0)**	**19 (5.6)**	**38 (11.2)**	**51 (7.4)**	**69 (10.1)**
South Africa	32 (9.2)	31 (9.0)	19 (5.6)	38 (11.2)	51 (7.4)	69 (10.1)
Region 3: Asia	**47 (13.6)**	**51 (14.8)**	**59 (17.4)**	**61 (18.0)**	**106 (15.5)**	**112 (16.4)**
Thailand	16 (4.6)	23 (6.7)	18 (5.3)	20 (5.9)	34 (5.0)	43 (6.3)
Russian Federation	18 (5.2)	13 (3.8)	19 (5.6)	14 (4.1)	37 (5.4)	27 (4.0)
China	-	-	20 (5.9)	24 (7.1)	20 (2.9)	24 (3.5)
Taiwan	13 (3.8)	15 (4.4)	-	-	13 (1.9)	15 (2.2)
India	-	-	2 (0.6)	3 (0.9)	2 (0.3)	3 (0.4)
Region 4: Latin America	**60 (17.3)**	**69 (20.1)**	**90 (26.5)**	**85 (25.1)**	**150 (21.9)**	**154 (22.6)**
Brazil	31 (9.0)	32 (9.3)	35 (10.3)	38 (11.2)	66 (9.6)	70 (10.3)
Mexico	9 (2.6)	13 (3.8)	13 (3.8)	12 (3.6)	22 (3.2)	25 (3.7)
Argentina	19 (5.5)	21 (6.1)	-	-	19 (2.8)	21 (3.1)
Chile	-	-	13 (3.8)	15 (4.4)	13 (1.9)	15 (2.2)
Panama	-	-	17 (5.0)	11 (3.3)	17 (2.5)	11 (1.6)
Costa Rica	-	-	11 (3.2)	8 (2.4)	11 (1.6)	8 (1.2)
Puerto Rico	1 (0.3)	3 (0.9)	1 (0.3)	1 (0.3)	2 (0.3)	4 (0.6)

The most notable differences in baseline characteristics between C209 and C215 were differences in region of origin (region 1 = western countries 55-60% versus 45-50%), gender (male sex 78-80% versus 72-73%) and HIV- 1 subtype (clade B ≈71% versus ≈68%).

Outcomes and estimation

The primary objective was to establish non-inferiority in efficacy of rilpivirine vs. control with regard to the proportion of subjects achieving a confirmed viral load of < 50 copies/mL at 48 weeks of treatment, according to the TLOVR algorithm, with a maximum allowable difference of 12%.

The proportion of subjects demonstrating virologic response was as follows:

ITT population:

Figure 8.

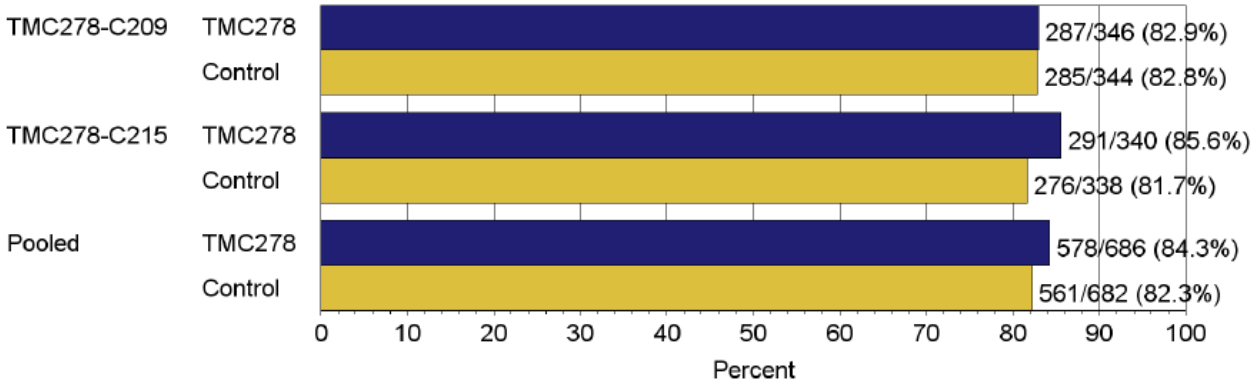
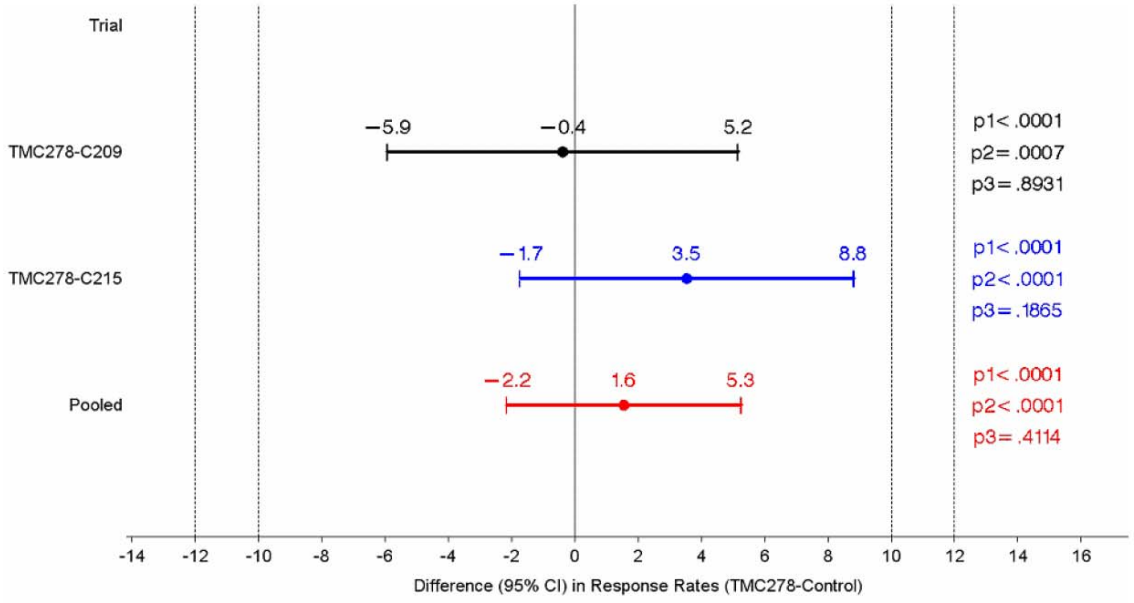


Figure 9.



Difference in response rates predicted by logistic regression model including factors treatment, baseline viral load (continuous variable), background regimen (for trial C215 and the pooled analysis only) and trial (for pooled analysis only). p1= noninferiority at 12% margin p2 = noninferiority at 10% margin, p3 = p-value for superiority.

The proportion of subjects that achieved a viral load < 50 copies/mL according to the TLOVR algorithm at Week 48 was similar between the rilpivirine group (84.3%) and the control group (82.3%).

Statistical comparison using a logistic regression model showed a predicted difference [95% CI] in virologic response (viral load < 50 copies/mL, TLOVR) at Week 48 between the pooled rilpivirine and control treatment groups of 1.6 [-2.2; 5.3] (p-value < 0.0001), demonstrating non-inferiority at both the 12% (primary endpoint) and 10% (secondary endpoint) margins.

Superiority of rilpivirine compared to control was not established. In both trials C209 and C215 individually, there was no notable difference in response rate (< 50 copies/mL, TLOVR, ITT population) between the rilpivirine group and the control group (82.9% vs 82.8% in C209, and 85.6% vs 81.7% in C215, see Figure 8) and the primary endpoint of non-inferiority at the 12% margin was met in each trial independently. Based on the ITT and PP population, non-inferiority was also demonstrated at the 10% margin in both trials.

The proportion of virologic responders seen in the control group in the Phase III trials was greater than or comparable to that seen for the same EFV-based combination ARTs in previous trials. In light of this and the non-inferiority of rilpivirine to control established in the Phase III trials, the efficacy of rilpivirine in respect of the proportion of virologic responders can be considered comparable to efavirenz.

With respect to differences in response rates, the logistic regression model shown in the above figure was not adjusted for age, sex, CDC class category, HIV clade or baseline CD4 T-cell count.

The percentages of patients with treatment failure were similar between rilpivirine and EFV (13% vs 9%) but the reasons were different; for rilpivirine this predominantly was virological failure and for EFV adverse events (see table 14).

Table 14: Response and main reasons for non-response, studies C209 and C215.

	C209		**C215**		**pooled**	
	rilpivirine (346)	**Control (344)**	**rilpivirine (340)**	**Control (338)**	**rilpivirine (686)**	**Control (682)**
Responders	82.4	81.7	82.6	78.4	82.5	80.1
Non-responders	17.6	18.3	17.4	21.6	17.5	19.9
Virologic Failure	13.6	7.0	12.1	11.2	12.8	9.1
Non-virologic failure[#]	4.0	11.3	5.3	10.4	4.7	10.9

[#]discontinued due to AE/death, for other reasons but last HIV-RNA < 50 copies/mL, or missing data but on study.

Both treatment groups showed a reconstitution of absolute and relative (%) CD4+ cell count at Week 48. The mean change from baseline in imputed absolute CD4+ cell count at Week 48 was 192.1 cells/µL; 95% CI [181.30;202.94] in the rilpivirine group and 176.2 cells/µL; 95% CI [164.63;187.76] in the control group.

Subgroup analysis revealed that the efficacy of rilpivirine was comparable to EFV across gender, race, region of origin, HIV clade and background regimen.

However, though the subgroups were small, there was a trend towards lower virological efficacy of rilpivirine compared to EFV for subjects with high viral load (>500.000 copies/mL; 70% vs 76%) and low CD4 T-cell count (< 50 cells/uL; 59% vs 81%) (see table 15).

Table 15: Proportion of Responders at Week 48 by VL and CD4-count (pooled studies)

	rilpivirine	**Control**	**Difference (CI95%)**
Baseline viral load			
≤ 100,000	90.2 (332/368)	83.6 (276/330)	
> 100,000 - ≤ 500,000	79.5 (198/249)	82.6 (223/270)	
> 500,000	69.6 (48/69)	75.6 (62/82)	(-20 to +8%)
Baseline CD4$^+$ count			
< 50	58.8 (20/34)	80.6 (29/36)	(-43 to -1%)
≥ 50 - < 200	80.4 (156/194)	81.7 (143/175)	
≥ 200 - < 350	86.9 (272/313)	82.4 (253/307)	
≥ 350	90.3..(130/144)	82.9 (136/164)	

(Viral Load < 50 HIV-1 RNA copies/mL, TLOVR)

The different backbones used were highly associated with region. Hence, comparing outcomes between for example zidovudine and tenofovir subsets will also include such large differences (social structures, adherence etc). However, within NRTI subsets (stratification factor) it seems reasonable to make comparisons, see table 16 below.

16: Frequency of virological failures[1] by NNRTI and NRTI backbone (C209 + 215).

NRTI backbone	rilpivirine	Control	Difference (CI95%)
tdf	55/550 (10%)	20/546 (3.7%)	6.3 (3.4-9.3)
azt	6/101 (6.9%)	6/103 (5.8%)	
abc	1/35	2/33	

[1] Including patients with paired genotypes successfully analyzed. (Figures from rilpivirine-C209-C215-C904-W48-AVWR, table 15)

Outcomes in the tenofovir subsets of patients are of particular importance since this is by far the most commonly used first line NRTI backbone in EU. As seen above, the incidence of virological failure was more than twice as common with rilpivirine as with control in the tenofovir subset of patients but not for the other NRTI subsets. However, numbers are low in the non-tdf subsets, and should be interpreted cautiously.

The failure rate was driven by patients with a high baseline viral load as seen in the table 17 below.

Table 17: Outcome (ITT TLOVR) at Week 48 in the pooled Phase III studies.

	rilpivirine		**Control**	
n (%)	**≤100,000**	**>100,000**	**≤100,000**	**>100,000**
Overall population	N=368	N=318	N=330	N=352
Responder	332 (90.2)	246 (77.4)	276 (83.6)	285 (81.0)
Virological failure (efficacy)	14 (3.8)	48 (15.1)	11 (3.3)	22 (6.3)
Rebounder	8 (2.2)	16 (5.0)	8 (2.4)	7 (2.0)
Never suppressed	6 (1.6)	32 (10.1)	3 (0.9)	15 (4.3)
TDF Subset	N=288	N=262	N=256	N=290
Responder	258 (89.6)	201 (76.7)	217 (84.8)	233 (80.3)
Virological failure (efficacy)	12 (4.2)	**40 (15.3)**	6 (2.3)	**17 (5.9)**
Rebounder	7 (2.4)	13 (5.0)	6 (2.3)	5 (1.7)
Never suppressed	5 (1.7)	27 (10.3)	0	12 (4.1)
Non-TDF Subset	***AZT/3TC (n=101)*** ***ABC/3Tc (n=35)***		***AZT/3TC (n=103)*** ***ABC/3TC (n=33)***	
	N=80	N=56	N=74	N=62
Responder	74 (92.5)	45 (80.4)	59 (79.7)	52 (83.9)
Virological failure (efficacy)	2 (2.5)	8 (14.3)	5 (6.8)	5 (8.1)
Rebounder	1 (1.3)	3 (5.4)	2 (2.7)	2 (3.2)
Never suppressed	1 (1.3)	5 (8.9)	3 (4.1)	3 (4.8)

These data show that efficacy was high for rilpivirine-treated patients with baseline VL<100,000 copies/ml, but considerably lower in patients with baseline VL ≥ 100,000 copies/ml regardless of NRTI backbone used. As a consequence of suboptimal virologic response when baseline viral load is high, the number of patients ending up with resistance is much higher for the rilpivirine-treated patients compared to the control group (discussed in the next section). Outcomes in patients with baseline viral load <100,000 copies/ml are comparable to that of the control group.

Failure and Resistance development

Regardless of failure population looked at (those with protocol defined virological failure, and successfully paried genotypes - as well as the broader population of all patients with a viral load possible to genotype at time of failure), the absolute number of patients ending up with resistance was considerably higher for those treated with rilpivirine (2-3 fold higher for NNRTI-resistance, 3-4 for NRTI resistance), table 18 below.

The table below shows the number of patients ending up with resistance by baseline viral load category for the overall population and the TDF subset.

Table 18.

	Rilpivirine		**Control**	
≤100,000 copies/mL				
	All (n=368)	**TDF Subset (n=288)**	**All (n=330)**	**TDF Subset (n=256)**
NRTI RAM	7	5	2	0
NNRTI RAM	6	4	5	2
>100,000 copies/mL				
	All (n=318)	**TDF Subset (n=262)**	**All (n=352)**	**TDF Subset (n=290)**
NRTI RAM	33 (10.4)	30 (11.5)	8 (2.3)	7 (2.4)
NNRTI RAM	32 (10.1)	29 (11.1)	12 (3.4)	10 (3.4)

The emerging NRTI RAMs are in the vast majority of cases resistance to cytidine analogues (emtricitabine/lamivudine). These drugs are important for the patient, with a low toxicity. Subsequently to selecting for a M184V/I mutation (i.e. resistance to FTC and 3TC), there will not be any obvious non-toxic dual NRTI backbone. Thus, 3TC/FTC resistance has more consequences as regards future therapy than just those related to cytidine analogue activity.

The emerging NNRTI RAMs in patients failing with rilpivirine were associated with cross-resistance to all other NNRTIs (efavirenz, nevirapine, etravirine). In contrast, those failing efavirenz therapy and with emerging NNRTI RAMs would generally still be able to use etravirine.

It is of interest comparing resistance outcomes in studies C209/C215 with those of studies for other first line agents. The amount of resistance seen in patients treated with rilpivirine (in this example always combination with tenofovir/FTC) is high also in such a comparison, see table 19 below.

Table 19: Emerging resistance in patients treated over 48 weeks - comparison of studies.

Name of study, and NRTIs used	**C209/C215** tdf/FTC subset		**STARTMRK** tdf/FTC		**CASTLE** tdf/FTC	
Study regimen	rilpivirine (n=550)	efavirenz (n=682)	raltegravir (n=281)	efavirenz (n=282)	lpv/r (n=443)	atv/r (n=443)
Successfully analyzed paired genotypes, n (%)	55 (10)	28 (4)	8 (3)	5 (2)	15 (3)	17 (4)

Name of study, and NRTIs used	C209/C215 tdf/FTC subset		STARTMRK tdf/FTC		CASTLE tdf/FTC	
Study regimen	rilpivirine (n=550)	efavirenz (n=682)	raltegravir (n=281)	efavirenz (n=282)	lpv/r (n=443)	atv/r (n=443)
Successfully analyzed paired genotypes, n (%)	55 (10)	28 (4)	8 (3)	5 (2)	15 (3)	17 (4)
Resistance to 3TC, n/N (%)	35/550 (6)	7/682 (1)	3/281 (1)	1/281 (<1)	3/443 (1)	3/440 (1)
Resistance to studied agent	34/550 (6)	15/682 (2)	4/281 (1)	3/282 (1)	0	0

CHMP's table: figures from ongoing report, Lancet 2009, and Reyataz AR respectively. "Virological failure" not necessarily standardized between studies.

Post-hoc analyses showed that the following factors increased chance of virologic response (in decreasing order of importance): 1. higher adherence, 2. higher rilpivirine exposure (C_{0h}), 3. lower baseline viral load, 4. lower fold change in EC_{50} (FC) for rilpivirine at baseline, and higher baseline $CD4^+$ cell count.

Analyses of risk of virological failure and emerging resistance stratified by adherence indicate that risk of virologic failure was about twice as high in patients with less perfect adherence in both treatment arms. Still, risk of virologic failure in patients on rilpivirine with optimal adherence was higher than that in patients on efavirenz with low adherence, confirming that rilpivirine is indeed not a "forgiving agent" and adherence needs to be high.

In conclusion, the data indicate that, compared to EFV, rilpivirine is associated with a 2-fold higher risk to develop NNRTI RAMs (10.5*64% = 6% absolute risk versus 5.7*54% = 3%) and a 3 to 4-fold higher risk to develop resistance to N(t)RTIs (10.5*63% = 6.6% absolute risk versus 5.7*32% = 1.8%). Additional analyses stratified for baseline viral load confirm that this increased risk of emerging resistance is driven by patients with high baseline viral load which show lower virologic response rates and higher rates of virologic failure compared to control. For patients with baseline viral load <100,000 copies/ml TCM278 shows comparable efficacy to EVF with low risk of emerging resistance and in the same order of magnitude as observed for EFV. Furthermore, in case of rilpivirine resistance, second line therapy with etravirine is no option due to cross-resistance whereas etravirine is still efficacious in case of EFV resistance.

Summary of main studies

The following tables 20 and 21 summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 20: Summary of Efficacy for trial TMC278-TiDP6-C209(ECHO study)

Title: A Phase III, randomized, double-blind trial of rilpivirine 25 mg q.d. versus efavirenz 600 mg q.d. in combination with a fixed background regimen consisting of tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naïve HIV-1 infected subjects.			
Study identifier	rilpivirine-TiDP6-C209		
Design	rilpivirine-TiDP6-C209 is an ongoing, 96-week, randomized, double-blind, double dummy, active-controlled, international Phase III trial in human immunodeficiency virus (HIV)-1 infected, treatment-naïve adult subjects. The trial was designed to evaluate the long-term efficacy, safety, and tolerability of rilpivirine 25 mg q.d. compared with efavirenz (EFV) 600 mg q.d. (control), each in combination with a background regimen containing tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). Adult subjects with an HIV-1 viral load of ≥ 5,000 HIV-1 ribonucleic acid (RNA) copies/mL, who were treatment-naïve, susceptible to their background regimen at screening, and had no non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance associated mutations (RAMs) in their screening genotype, were eligible for the trial. Approximately 680 HIV-1 infected subjects were to be randomized in a 1:1 ratio to rilpivirine 25 mg q.d. or to EFV 600 mg q.d. The trial was designed to consist of a maximum screening period of 6 weeks, a 96-week treatment period, a post 96-week treatment period (until all subjects in the trial who had not discontinued earlier had been treated for at least 96 weeks and the Week 96 database had been locked), followed by a 4-week follow-up period.		
	Duration of main phase:	96 weeks	
	Duration of Run-in phase:	Maximum of 6 weeks	
	Duration of Extension phase:	Maximum of 9 months	
Hypothesis	Non-inferiority of rilpivirine vs. EFV		
Treatments groups	Investigational treatment group	rilpivirine 25 mg q.d. plus TDF/FTC Number randomized and treated = 346	
	Control group	EFV 600 mg q.d. plus TDF/FTC Number randomized and treated = 344	
Endpoints and definitions	Primary endpoint	Virologic response < 50 copies/ml (TLOVR); non-inferiority testing with a pre-defined non-inferiority margin of 12%	To demonstrate non-inferiority of rilpivirine vs. control in regard to virologic response, defined as 2 consecutive viral load results < 50 copies/mL (TLOVR, time to loss of virologic response) at Week 48 (primary efficacy parameter) with a pre-defined non-inferiority margin of 12%
	Secondary endpoints (main ones)	Non-inferiority testing of virologic response (see above) at a pre-defined margin of 10%	To demonstrate non-inferiority of rilpivirine compared to control (EFV) with a maximum allowable difference of 10% at 48 weeks for the primary efficacy endpoint (proportion of subjects achieving confirmed virologic response, defined as a confirmed plasma viral load < 50 HIV-1 RNA copies/mL [TLOVR] at 48 weeks treatment)
		Superiority testing	To evaluate superiority in efficacy of rilpivirine compared to control (EFV), in case non-inferiority is established
		Antiviral activity	To evaluate and compare the antiviral activity of rilpivirine when administered as 25 mg q.d. versus control (EFV)

		Change from baseline in CD4+ counts	To evaluate and compare immunologic changes (as measured by CD4+ cell count) in the rilpivirine group versus those in the control group (EFV)
		Genotypic evolution	To assess the evolution of the viral genotype
		Safety and tolerability	To evaluate and compare the safety and tolerability of rilpivirine when administered as 25 mg q.d. versus control (EFV)
Database lock	01 February 2010		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	**Intent to treat – 48 Weeks**		
Descriptive statistics and estimate variability	Treatment group	**Rilpivirine**	**Control**
	Number of subject	N=346	N=344
	Predicted response rate [95% CI] (%)*	83.2 [78.9, 86.8]	83.6 [79.3, 87.2]
Effect estimate per comparison	Primary endpoint	Comparison groups	rilpivirine-Control
		% Difference rilpivirine-Control	-0.4
		[95% CI]*	[-5.9; 5.2]
		P-value for non-inferiority with 12% margin	< 0.0001
Notes	*Predicted by logistic regression (TLOVR <50 copies/mL) including factors treatment, and baseline viral load. P-value for non-inferiority with 10% margin is 0.0007; P-value for superiority is 0.89.		

Analysis description	**Secondary analyses**		
Analysis population and time point description	**Per protocol – 48 weeks**		
Descriptive statistics and estimate variability	Treatment group	**Rilpivirine**	**Control**
	Number of subject	N=335	N=330
	Predicted response rate [95% CI] (%)*	84.6 [80.2, 88.1]	84.3 [79.9, 87.9]
Effect estimate per comparison	Primary endpoint	Comparison groups	rilpivirine-Control
		% Difference rilpivirine-Control	0.2
		[95% CI]*	[-5.2; 5.7]
		P-value for non-inferiority with 12% margin	< 0.0001

Notes	*Predicted by logistic regression (TLOVR <50 copies/mL) including factors treatment, and baseline viral load on Per protocol population. P-value for non-inferiority with 10% margin is 0.0003; P-value for superiority is 0.93.		
Analysis population and time point description	**Intent to treat – 48 Weeks**		
Descriptive statistics	**Antiviral activity**	Rilpivirine	Control
Overall	Number of subjects	N=346	N=344
	Virologic response <50 copies/mL (TLOVR)	287 (82.9%)	285 (82.8%)
	VFeff	38 (11.0%)	15 (4.4%)
Baseline viral load <=100,000 copies/mL	Number of subjects	N=181	N=163
	Virologic response <50 copies/mL (TLOVR)	162 (89.5%)	136 (83.4%)
	VFeff	9 (5.0%)	5 (3.1%)
Baseline viral load >100,000 copies/mL	Number of subjects	N=165	N=181
	Virologic response <50 copies/mL (TLOVR)	125 (75.8%)	149 (82.3%)
	VFeff	29 (17.6%)	10 (5.5%)
Notes	VFeff 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).		
Analysis population and time point description	**Intent to treat – 48 Weeks**		
Descriptive statistics and estimate variability	**Change from baseline in CD4+ count**	Rilpivirine N=346	Control N=344
	Absolute CD4+ cell count (cells/µL) - Mean	195.5	181.6
	[95% CI]	[179.5–211.6]	[165.0–198.3]
	Relative CD4+ cell count (%) - Mean	8.6	8.7
	[95% CI]	[7.9–9.2]	[8.0–9.3]

Effect estimate per comparison	Change from baseline in CD4+ count	Comparison groups	rilpivirine-Control
		P-value for absolute CD4+ cell count*	0.1307
		P-value for relative CD4+ cell count*	0.8514
Notes	* from ANCOVA		

Table 21: Summary of Efficacy for trial TMC278-TiDP6-C215(THRIVE study)

Title: A Phase III, randomized, double-blind trial of rilpivirine 25 mg q.d. versus efavirenz 600 mg q.d. in combination with a background regimen containing 2 nucleoside/nucleotide reverse transcriptase inhibitors in antiretroviral-naïve HIV-1 infected subjects.			
Study identifier	TMC278-TiDP6-C215		
Design	TMC278-TiDP6-C215 is an ongoing 96-week, randomized, double-blind, double-dummy, active-controlled, international Phase III trial in human immunodeficiency virus (HIV)-1 infected, treatment-naïve adult subjects. The trial was designed to evaluate the long-term efficacy, safety and tolerability of rilpivirine 25 mg q.d. compared with efavirenz (EFV) 600 mg q.d. (control). Each of these non-nucleoside reverse transcriptase inhibitors (NNRTIs) was given in combination with a background regimen containing two nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs). The investigator-selected N(t)RTIs were either abacavir (ABC)/lamivudine (3TC), zidovudine (AZT)/3TC, or tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC). Adult subjects with an HIV-1 viral load of ≥ 5000 HIV-1 ribonucleic acid (RNA) copies/mL, who were treatment-naïve, susceptible to their background regimen at screening, and had no NNRTI resistance-associated mutations (RAMs) in their screening genotype, were eligible for the trial. Approximately 680 HIV-1 infected subjects were to be randomized in a 1:1 ratio to rilpivirine 25 mg q.d. or to EFV 600 mg q.d. after the investigator had selected the N(t)RTI background regimen. The trial was designed to consist of a maximum screening period of 6 weeks, a 96 week treatment period, a post 96-week treatment period (until all subjects in the trial who had not discontinued earlier had been treated for at least 96 weeks and the Week 96 database had been locked), followed by a 4-week follow-up period.		
	Duration of main phase:	96 weeks	
	Duration of Run-in phase:	Maximum of 6 weeks	
	Duration of Extension phase:	Maximum of 9 months	
Hypothesis	Non-inferiority of rilpivirine vs. EFV		
Treatments groups	Investigational treatment group	rilpivirine 25 mg q.d plus investigator-selected N(t)RTIs. Number randomized and treated = 340	
	Control group	EFV 600 mg q.d. plus investigator-selected N(t)RTIs Number randomized and treated = 338	
Endpoints and definitions	Primary endpoint	Virologic response < 50 copies/ml (TLOVR); non-inferiority testing with a pre-defined non-inferiority margin of 12%	To demonstrate non-inferiority of rilpivirine vs. control in regard to virologic response, defined as 2 consecutive viral load results < 50 copies/mL (TLOVR, time to loss of virologic response) at Week 48 (primary efficacy parameter) with a pre-defined non-inferiority margin of 12%
	Secondary endpoints (main ones)	Non-inferiority testing of virologic response (see above) at a pre-defined margin of 10%	To demonstrate non-inferiority of rilpivirine compared to control (EFV) with a maximum allowable difference of 10% at 48 weeks for the primary efficacy endpoint (proportion of subjects achieving confirmed virologic response, defined as a confirmed plasma viral load < 50 HIV-1 RNA copies/mL [TLOVR] at 48 weeks treatment)
		Superiority testing	To evaluate superiority in efficacy of rilpivirine compared to control (EFV), in case non-inferiority is established

		Antiviral activity	To evaluate and compare the antiviral activity of rilpivirine when administered as 25 mg q.d. versus control (EFV)
		Change from baseline in CD4+ counts	To evaluate and compare immunologic changes (as measured by CD4+ cell count) in the rilpivirine group versus those in the control group (EFV)
		Genotypic evolution	To assess the evolution of the viral genotype
		Safety and tolerability	To evaluate and compare the safety and tolerability of rilpivirine when administered as 25 mg q.d. versus control (EFV)
Database lock	28 January 2010		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	**Intent to treat – 48 Weeks**		
Descriptive statistics and estimate variability	Treatment group	**rilpivirine**	**Control**
	Number of subject	N=340	N=338
	Predicted response rate [95% CI] (%)*	86.8 [82.1, 90.4]	83.2 [77.9, 87.5]
Effect estimate per comparison	Primary endpoint	Comparison groups	rilpivirine-Control
		% Difference rilpivirine-Control	3.5
		[95% CI]*	[-1.7; 8.8]
		P-value for non-inferiority with 12% margin	< 0.0001
Notes	*Predicted by logistic regression (TLOVR <50 copies/mL) including factors treatment, background regimen, and baseline viral load. P-value for non-inferiority with 10% margin is <0.0001; P-value for superiority is 0.19.		

Analysis description	**Secondary analyses**		
Analysis population and time point description	**Per protocol – 48 weeks**		
Descriptive statistics and estimate variability	Treatment group	**rilpivirine**	**Control**
	Number of subject	N=334	N=332
	Predicted response rate [95% CI] (%)*	87.3 [82.5, 90.9]	84.0 [78.7, 88.2]
Effect estimate per comparison	Primary endpoint	Comparison groups	rilpivirine-Control
		% Difference rilpivirine-Control	3.2
		[95% CI]*	[-1.9; 8.4]

		P-value for non-inferiority with 12% margin	< 0.0001
Notes	*Predicted by logistic regression (TLOVR <50 copies/mL) including factors treatment, background regimen, and baseline viral load on Per protocol population. P-value for non-inferiority with 10% margin is <0.0001; P-value for superiority is 0.22.		
Analysis population and time point description	**Intent to treat – 48 Weeks**		
Descriptive statistics	**Antiviral activity**	rilpivirine	Control
Overall	Number of subjects	N=340	N=338
	Virologic response < 50 copies/ml (TLOVR)	291 (85.6%)	276 (81.7%)
	VFeff	24 (7.1%)	18 (5.3%)
Baseline viral load <=100,000 copies/mL	Number of subjects	N=187	N=167
	Virologic response < 50 copies/ml (TLOVR)	170 (90.9%)	140 (83.8%)
	VFeff	5 (2.7%)	6 (3.6%)
Baseline viral load >100,000 copies/mL	Number of subjects	N=153	N=171
	Virologic response < 50 copies/ml (TLOVR)	121 (79.1%)	136 (79.5%)
	VFeff	19 (12.4%)	12 (7.0%)
Background regimen: tenofovir/emtricitabine	Number of subjects	N=204	N=202
	Virologic response < 50 copies/ml (TLOVR)	172 (84.3%)	165 (81.7%)
	VFeff	14 (6.9%)	8 (4.0%)
Background regimen: zidovudine/lamivudine	Number of subjects	N=101	N=103
	Virologic response < 50 copies/ml (TLOVR)	88 (87.1%)	83 (80.6%)
	VFeff	9 (8.9%)	7 (6.8%)
Background regimen: abacavir/lamivudine	Number of subjects	N=35	N=33
	Virologic response < 50 copies/ml (TLOVR)	31 (88.6%)	28 (84.8%)
	VFeff	1 (2.9%)	3 (9.1%)
Notes	VFeff 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).		
Analysis population and time point description	**Intent to treat – 48 Weeks**		
Descriptive statistics and estimate variability	**Change from baseline in CD4+ count**	rilpivirine N=339[#]	Control N=338

	Absolute CD4+ cell count (cells/µL) - Mean	188.6	170.7
	[95% CI]	[174.1–203.2]	[154.5–186.8]
	Relative CD4+ cell count (%) - Mean	8.3	8.0
	[95% CI]	[7.7–8.9]	[7.4–8.6]
Effect estimate per comparison	Change from baseline in CD4+ count	Comparison groups	rilpivirine-Control
		P-value for absolute CD4+ cell count*	0.0915
		P-value for relative CD4+ cell count*	0.4266
Notes	# Baseline CD4+ cell count was not available for 1 subject. * from ANCOVA		

Clinical studies in special populations

Not applicable

Supportive studies

Not applicable

2.5.3. Discussion on clinical efficacy

The applicant has performed one phase IIb study and two phase III studies.

The phase IIb study was a dose-finding study.

Based on this study, initially a 75 mg q.d. dosage was chosen for further development as the 25 mg q.d. formulation was associated with lower exposure and a trend towards lower efficacy especially among subjects with high baseline viral load. However, a dose-relationship could not be demonstrated. Later, when additional safety data became available suggesting a dose-safety relationship, the 25 mg q.d was selected for further evaluation in clinical studies.

The two pivotal phase III (C209 and C215) studies are ongoing randomized, double-blind, double-dummy, trials of rilpivirine 25 mg q.d. versus EFV 600 mg q.d. in combination with a fixed background regimen in ARV treatment-naïve HIV-1 infected subjects. The efficacy of rilpivirine for the treatment of HIV-1 infection in ARV treatment-naïve adult patients is based on efficacy data of the Week 48 analysis. The results of the Week 96 analysis are expected by 1Q2012.

The chosen treatments are appropriate and EFV is the preferred NNRTI in first-line ARV regimens. Both trials do reflect daily clinical practice of a general relatively healthy population of HIV-1 individuals with an indication to start ARV according to accepted HIV treatment guidelines. The design of the studies are similar and in accordance with the CHMP guideline (EMEA/CPMP/EWP/633/02/Rev.1) for marketing authorisation application.

With respect to generalisability of the trial finding, it should be noted that the studied population consisted of ARV-naïve HIV-1 infected subjects, who had no NNRTI associated resistance mutations at baseline.However, few of these subjects had AIDS-defining or clinically significant coexisting illness, or CD4 T-cell counts below 50 cells/µl. Therefore, the results can not be extrapolated to individuals with significant comorbidities. The median age was 36 years (range 18-78), 76% were male and 95% had a CDC category A or B stage of HIV infection.

Only a minority of subjects did use ABC/3TC as their background regimen (n = 35 rilpivirine versus n = 33 Control) or AZT/3TC (n = 101 rilpivirine versus n = 103 Control). The results obtained rather showed a better outcome with these agents, than with tenofovir/FTC. Hence, although numbers are low, there is no reason to believe that these NRTI backbones should be avoided in combination with rilpivirine. Patents with non-B subtypes were well represented in comparison to trials done with other agents. The applicant was recommended to follow up on this issue and to submit the experiments planned for assessing outcomes with rilpivirine in combination with zidovudine and abacavir.

With respect to selection bias, the most relevant issue is the baseline screening for potential resistance as this might not be a routine screening tool across all countries. However, according to European treatment guidelines, resistance testing is always recommended prior to starting HIV therapy.

Up to 10% of the screened population indeed had NNRTI-associated mutations, which could lower the effect of rilpivirine - although it is unclear to what extent those mutations actually would lead to treatment failure. About 3.3% of the patients would have been excluded based on the currently selected list of mutations, the way these actually affect outcome is not known. Use of therapy should be guided by resistance testing which is considered current good clinical practice and addressed in section 4.1 of the SmPC.

The baseline demographic and disease characteristics are well balanced between the two treatment arms. The vast majority of subjects were male, originated in western countries, infected with HIV-1 clade B, using TDF/TFC as the background regimen, had CD-4 T-cell counts > 50/mm3 and viral load < 500.000 copies/mL.

The differences in baseline data of the two studies are considered minor and allow the performance of a pooled analysis.

The median age was 36 years (range 18-78 years). The number of patients aged above 65 years was low (4 subjects). A caution statement for elderly patients was included in section 4.2 and 5.2 of the SmPC.

In total 686 patients were randomized to rilpivirine and 682 to EFV. The primary endpoint was the proportion of patients with viral loads <50 copies/mL at 48 weeks in an ITT, TLOVR analysis. Both groups had high rates of success at 48 weeks; 84.3% in the rilpivirine group versus 82.3% in the EFV group meeting the non-inferiority objective. The per protocol analysis showed similar results. The difference in response rate (rilpivirine versus EFV) was minus 0.4 (95% CI: minus 5.9 – 5.2) and 3.5 (95% CI: minus 1.7 – 8.8) for the C209 and C215 trial respectively; both meeting the margins of non-inferiority.

The selected non-inferiority margin of 12% difference was chosen according to the FDA guideline while 10% was recommended in a previous Scientific Advice. The observed CI is acceptable as it meets also the CHMP requested 10% delta value.

The obtained response rates are comparable to previous trials with EFV used for first line ARV.

Subgroup analysis demonstrated that rilpivirine seems to be less efficacious in subjects with high baseline viral load or low CD4 T-cell count. For subjects with a viral load > 100.000 - ≤ 500.000 copies/mL the virologic response at week 48 was 79.5% vs 82.6% and for subjects with a viral load > 500.000 copies/mL this was 69.6% vs 75.6% (n = 69 vs n = 89) for TMC78 and EFV recipients respectively. For subjects with CD4+ T-cells <50 cells/uL (n = 34 versus n = 36) the response rate was 58.8% vs 80.6%. Definite conclusions of inferiority of rilpivirine for these subgroups can not be made due to limited sample size but the possible lower efficacy is of concern. There were no

differences in efficacy across subgroups with respect to gender, age, region, HIV clade or background regimen.

In addition to this it is of special interest to know the virological efficacy among the different strata of adherence as non-adherence is associated with virological failure. Post-hoc analyses showed that virologic response rates were about 20% lower in patients with less perfect adherence compared to patients with optimal adherence whereas the proportion of virologic failures roughly doubled in this group for both treatment arms. However, since there appears to be an efficacy problem per se with rilpivirine, the risk for virological failure was actually lower with efavirenz taken with low adherence, than with rilpivirine taken with optimal adherence. Therefore, rilpivirine appears not to be a "forgiving agent" and adherence needs to be very high.

The rilpivirine group had a lower rate of discontinuation due to AEs (2% versus 7%), but the EFV group had a lower rate of virological failure (10.5% versus 5.7%, 4.7% versus 1.8% leading to discontinuation). Among the subjects with virological failure, NNRTI resistance mutations emerged in 63% of the rilpivirine recipients (most commonly E138K leading to cross-resistance to etravirine) versus 54% of the EFV recipients (most commonly K103N) and resistance to NRTIs emerged in 68% versus 32%, respectively.

Thus, rilpivirine is associated with a two-fold higher absolute risk than EFV for the development of resistance associated mutations and, moreover, in case of emergent resistance mutations the clinical impact is greater leaving fewer alternatives for sensitive second line ARVs.

Post-hoc multivariate analyses showed that the following factors increase chance of virologic response (in decreasing order of importance): 1. higher adherence, 2. higher rilpivirine exposure (C_{0h}), 3. lower baseline viral load, 4. lower fold change in EC_{50} (FC) for rilpivirine at baseline, and higher baseline $CD4^+$ cell count. From a labelling point of view, baseline viral load and CD4 count are the only parameters that can be affected. rilpivirine is approvable provided the indication is restricted to patients with low baseline viral load ≤ 100,000 copies/ml. Although response rate appears lower in patients with low baseline viral load and CD4 count < 50 cells/µl, numbers are too low to draw conclusions on the impact of low CD4 count.

The 25 mg dose appeared suboptimal in terms of efficacy (lower virologic response) for the population in general. Whereas there appeared no dose-relationship in terms of virologic response (phase 2b), lower AUC tended towards a lower response within the phase 3 studies using population PK. Hence, the exposure achieved with the 25 mg dose is just at the edge, or slightly below the Emax of RPV - which gives efficacy problems mainly in patients with a high baseline viral load. The applicant does not have the intention to continue to develop the 50 mg dose due to the safety concerns.
Any concomitant drugs that would lower the rilpivirine exposure, as well as intake in fasted state, is likely related to a risk of lower efficacy, and the development of resistance. It is crucial that the need for correct intake (fed state) and the risk associated with certain interacting drugs is emphasized in the SmPC (contraindication). However, the latter restrictions might be difficult to handle in clinical and daily practice, with the potential risk of lower virologic response and emergence of resistance. The applicant was requested to perform a drug utilisation study to evaluate how the drug is used in clinical practice (see corresponding measure in the RMP) to be followed up in the PSURs.

It remains to be seen whether an increased dose of this order would make a substantial difference in the numbers of virological failure in those patients with a high baseline viral load; although the low potency of rilpivirine might be the main obstacle with regards the risk of resistance development (1.2 $\log_{10}$ reduction in monotherapy, regardless of dose used).

In clinical practice rilpivirine might be considered a potential option for switch once viral load has been broken with more potent drugs, especially for patients who do not tolerate efavirenz. Although the drug might be an effective option, there is currently no data available in support of such use. Such use should be monitored in clinical practice and new studies on use in patients switching from other therapies to RPV (See corresponding measures in the RMP). In addition to this, the applicant will perform a drug interaction study with efavirenz and 50 mg rilpivirine dose as metabolic induction by efavirenz holds for quite some time (See corresponding measures in the RMP). This study is aimed to investigate the concerns that further lowering exposure of the 25 mg dose rilpivirine might increase the risk of virological failure.

Furthermore, the available limited data upon individuals with high viral load, do suggest that rilpivirine is less virological efficacious than EFV. Together with the previous noted higher risk for development of resistance special caution should be warranted for rilpivirine use in such individuals. The concern that rilpivirine is less virological efficacious than EFV in patients with high viral load was further confirmed by the post-hoc analyses stratified for baseline viral load. Overall the lower virologic response, the higher number of patients with virologic failure and the 3 times increased risk of emerging resistance compared with EFV, precludes use of rilpivirine in the patient population with baseline viral load >100,000 copies/ml).

The impact of the above addressed concerns will likely become clearer once the 96-weeks become available (see corresponding sections of the RMP). Thus these 96-week data are required for definite assessment of the benefits and risks.

Assessment of paediatric data on clinical efficacy

Not applicable

2.5.4. Conclusions on the clinical efficacy

Based on two pivotal phase III studies, it can be concluded that rilpivirine is non-inferior to the golden standard comparator EFV for treatment of ARV-naïve HIV-1 infected individuals.

However, to generalise the conclusion to subjects with baseline low CD4 counts and high viral load is disputable. Furthermore, the higher rate of virological failure and the development of resistance associated mutations is a major concern, especially as this hampers available second line treatment options.

Post-hoc analyses confirmed that the observed increased risk of emerging resistance with TCM278 is driven by patients with high baseline viral load; these patients show lower virologic response rates and higher rates of virologic failure compared to EFV. On the other hand, for patients with baseline viral load ≤100,000 copies/ml TCM278 shows comparable efficacy to EVF with low risk of emerging resistance and in the same order of magnitude as observed for EFV. Therefore, rilpivirine is approvable for a restricted indication to patients with low baseline viral load ≤100,000 copies/ml. Interaction with drugs that could lower TCM278 exposure should be contraindicated as this might lead to a potentially lower response and increased risk of resistance with a possible loss of treatment options and the product must be taken with a meal.

The CHMP considers the following measures necessary in the risk management plan to address issues related to efficacy:

-To provide the 96 weeks clinical study report of study C209 and C215 by 1Q 2012

-To submit the results of the ongoing switch studies GS-US-264-011 by 1Q 2013 and GS-US-264-0106 by 4Q 2012

Additionally the CHMP recommended the applicant to submit the experiments planned for assessing outcomes with rilpivirine in combination with zidovudine and abacavir (to be compared to the results in the Gilead PC-264-2003 study).

2.6. Clinical safety

Patient exposure

There were 6 trials in HIV-1 infected subjects. 1 phase I, 2 phase IIa trials, 1 phase IIb trial and 2 phase III trials. All studies except study phase I and phase IIa C202 were conducted in treatment naïve HIV-1 infected subjects. In total 1052 HIV-infected subjects of which 1001 treatment naïve HIV-1 infected subjects were exposed to rilpivirine. In addition 660 non-HIV infected subjects were exposed to rilpivirine in phase I studies.

The number of treatment naive HIV-1 infected subjects treated with at least 25 mg rilpivirine is 1001, 611 of these subjects were included in the phase III studies. This number is sufficient to explore adverse events which occur with a frequency of approximately 1%. The proposed dose of 25 mg q.d. was given in the phase III studies. The Phase IIb study was a dose-finding study with 25, 75 or 150 mg rilpivirine q.d. More than 84% of the subjects from the phase IIb and phase III studies were treated for at least 48 weeks. This is in line with HIV guideline that safety data of at least 48 weeks treatment should be submitted.

The safety assessment is based on pooled data from 1,368 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 rilpivirine 25 mg once daily. The median duration of exposure for patients in the rilpivirine arm and efavirenz arm was 55.7 and 55.6 weeks, respectively.

Based on non-clinical and early clinical findings QTc interval and adrenal function effects were given particular attention in clinical trials. In addition special attention was given to skin events, neurologic events, psychiatric events and hepatic event.

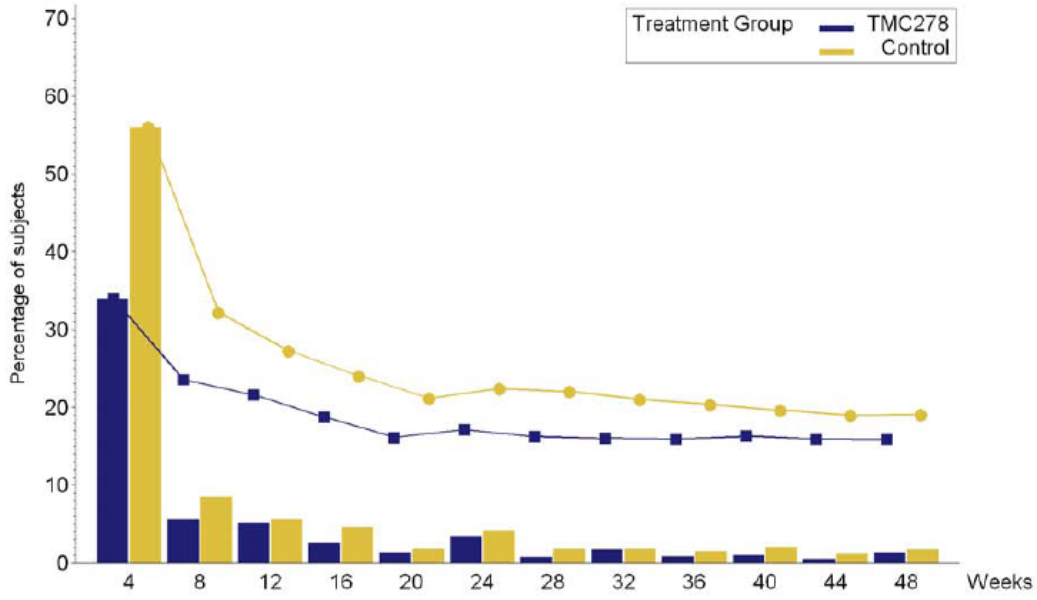
Adverse events

Phase I
Overall, rilpivirine appeared to be generally safe and well tolerated. The main finding in the phase I studies was the dose-dependent increase in QTcF interval observed in study C131 at doses of 75 mg q.d. and 300 mg q.d. This finding led to the selection of the 25 mg q.d. for further development.

Phase III
Based upon the week 48 analyses of the pooled phase III studies any treatment related adverse event occurred less frequent in the rilpivirine group compared to control (46.4% versus 64.1%) For any treatment AE at least grade 2 this was 15.9% versus 31.1%, indicating that in both groups most of the treatment related adverse events were mild. This difference was mainly driven by the differences in treatment related AEs which occurred within the first four weeks of treatment.

See figure 10 below.

Figure 10



Incidence: bar chart, Prevalence: line plot

At week four the incidence of adverse events in the rilpivirine group is approximately 35%, while it is approximately 55% in the control group. When treatment continues the differences become less.

This picture is seen for all treatment related adverse events but also for the individual adverse events like skin events (rash) and neurological events.

By SOC, the most observed treatment-related AEs in the rilpivirine group were gastrointestinal disorders (19.2% on rilpivirine vs 17.7% on control), nervous system disorders (17.2% on rilpivirine vs 36.7% on control), psychiatric disorders (14.9% vs 22.7%) skin and subcutaneous disorders (7.0% vs 16.1%). By preferred term, the most frequently reported treatment-related AEs in the rilpivirine group were nausea (10.1% vs 11.3% on control), dizziness (8.0% vs 26.2% on control), abnormal dreams (6.3% vs 9.4% on control) and headache (6.1% vs 6.2% on control). Dizziness and rash (2.5% versus 8.9%) occurred significantly more often in the control group (see table 22 below).

Table 22: Adverse Events at Least Possibly Related to rilpivirine/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)

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
Any AE at least possibly related	*147 (42.5)*	*214 (62.2)*	*171 (50.3)*	*223 (66.0)*	*318 (46.4)*	*437 (64.1)*
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.

With regard to grade 3 or more AE, these were observed in 13.3% of the rilpivirine group versus 18.0% in the control group. The most reported grade 3 or 4 events in the rilpivirine group were AST increased (1.0% vs 1.2% on control), blood amylase increased (1.0% vs 1.0% on control), neutrophil count decreased (1.0% vs 1.8% on control) and neutropenia (1.0% vs 1.0% on control).None of these AEs were considered at least possibly related to treatment.

The overall AE profile was similar in the Phase IIb and Phase III trials, except for grade 3 or 4 AEs which were reported more frequently in the Phase IIb trial (25.8% for 25 mg q.d. and 24.7 % for all rilpivirine) than in the pooled Phase III trials (13.3%) with rilpivirine 25 mg q.d.

For the Phase IIb study there were also safety analyses at week 96 and at week 192.
At week 96 there was no dose relationship in the overall incidence of AEs reported in the 3 rilpivirine dose groups. Although there appeared to be a trend towards a higher discontinuation rate due to AEs with increasing dose, there is no specific SOC or preferred term level which contributes to this phenomenon. A dose trend was observed in the incidence of the skin event of interest, the grouped term "rash", which increased in incidence with increasing rilpivirine dose (5.4%, 9.5% and 13.2% versus 21.3% for control).

Adverse events of special interest

Effects on QTc

In phase I studies the dose-dependent increase in QTcF interval observed in study C131 at doses of 75 mg q.d. and 300 mg q.d led to the selection of the 25 mg q.d. for further development.

In phase II studies at week 192 the main observation was that following the gradual mean increase from baseline in QTcF up to week 48, this interval remained stable up to week 144, but showed a further increase thereafter.

Mean increases in QTcF interval after Week 96 continued to be more pronounced in subjects treated with AZT/3TC compared with those treated with TDF/FTC, regardless of treatment group (rilpivirine or control), with greater increases in QTcF interval observed for females than for males.

Figure 11.

QTcF INTERVAL OVER TIME IN THE PHASE IIB TRIAL LONG-TERM SAFETY (WEEK 192 ANALYSIS)

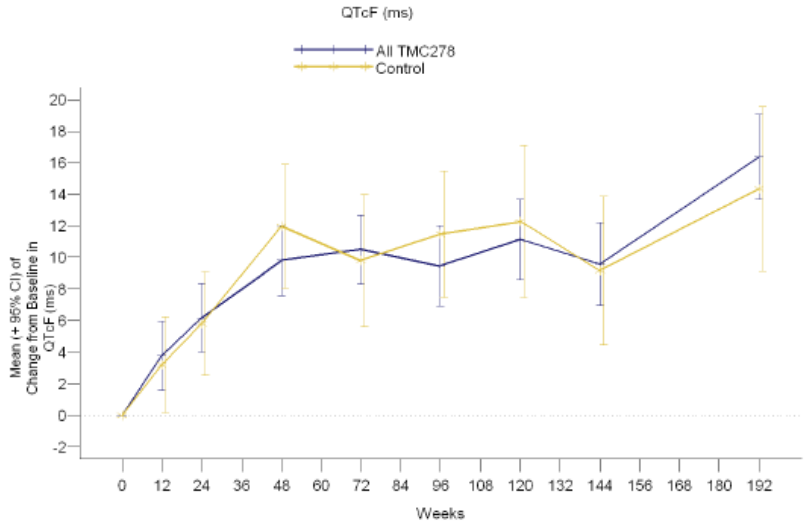


Table 23: QTcF interval abnormalities over time (worst case) (Trial C204)

Abnormality, n (%)	Week 12	Week 24	Week 48	Week 96	Week 144	Week 192	Overall[a]	
	All TMC278 N = 259	All TMC278 N = 247	All TMC278 N = 236	All TMC278 N = 218	All TMC278 N = 192	All TMC278 N = 183	All TMC278 N = 279	Control N = 89
N'	**251**	**243**	**236**	**212**	**180**	**166**	**264**	**85**
QTcF abnormality[b]	**3 (1.2)**	**4 (1.6)**	**3 (1.3)**	**2 (0.9)**	**2 (1.1)**	**5 (3.0)**	**18 (6.8)**	**7 (8.2)**
]450 ms,480 ms]	3 (1.2)	3 (1.2)	2 (0.8)	1 (0.5)	2 (1.1)	5 (3.0)	15 (5.7)	6 (7.1)
]480 ms,500 ms]	-	1 (0.4)	1 (0.4)	1 (0.5)	-	-	3 (1.1)	-
> 500 ms	-	-	-	-	-	-	-	1 (1.2)
Abnormal QTcF Increase	**10 (4.0)**	**17 (7.0)**	**27 (11.4)**	**29 (13.7)**	**26 (14.4)**	**34 (20.5)**	**84 (31.8)**	**28 (32.9)**
Increase by [30,60] ms	8 (3.2)	16 (6.6)	27 (11.4)	27 (12.7)	25 (13.9)	32 (19.3)	74 (28.0)	25 (29.4)
Increase by > 60 ms	2 (0.8)	1 (0.4)	-	2 (0.9)	1 (0.6)	2 (1.2)	10 (3.8)	3 (3.5)
Abnormal increase resulted in an abnormal actual value	**2 (0.8)**	**3 (1.2)**	**2 (0.8)**	**2 (0.9)**	**2 (1.1)**	**5 (3.0)**	**16 (6.1)**	**5 (5.9)**
]450 ms,480 ms]	2 (0.8)	2 (0.8)	2 (0.8)	1 (0.5)	2 (1.1)	5 (3.0)	14 (5.3)	4 (4.7)
]480 ms,500 ms]	-	1 (0.4)	-	1 (0.5)	-	-	2 (0.8)	-
> 500 ms	-	-	-	-	-	-	-	1 (1.2)

Overall, similar proportions of subjects in the combined rilpivirine and control groups had a QTcF interval abnormality, an abnormal increase in QTcF interval during the trial, or an abnormal increase in QTcF interval that resulted in an abnormal QTcF value. No pattern was observed at the different time points in the number of subjects with increases in QTcF interval of > 60 ms, and only a small proportion of subjects with an abnormal increase in QTcF interval had an abnormal actual value. Therefore, the clinical relevance of the obtained QT-prolongation at a dose of 75 mg is currently unclear.

in phase 3 studies the ECG data were included in 5 planned subgroup analyses: by background N(t)RTI regimen, by gender, by race, by race-by-gender, and by co-medication with a potential impact on QT interval.
Overall there was an increase over time in the mean QTcF interval in both rilpivirine and control groups. The increase was gradual and numerically higher in the control group. The mean maximum change from baseline in QTcF interval in the overall population was +17.9 ms in the rilpivirine group and +19.2 ms in the control group.

A summary of the incidence of treatment-emergent ECG abnormalities (worst abnormality) is presented in the table 24 below.

Table 24: Treatment-emergent ECG abnormalities (phase III week 48 pooled analysis)

ECG Parameter Abnormality, n (%)	C209		C215		Pooled	
	TMC278 N = 346	Control N = 344	TMC278 N = 340	Control N = 338	TMC278 N = 686	Control N = 682
HR (beats/min), N'	**345**	**338**	**340**	**321**	**685**	**659**
Abnormally low	32 (9.3)	16 (4.7)	23 (6.8)	15 (4.7)	55 (8.0)	31 (4.7)
Abnormally high	0	1 (0.3)	2 (0.6)	0	2 (0.3)	1 (0.2)
PR (ms), N'	**345**	**338**	**340**	**321**	**685**	**659**
Abnormally high	5 (1.4)	6 (1.8)	1 (0.3)	5 (1.6)	6 (0.9)	11 (1.7)
QRS (ms), N'	**345**	**338**	**340**	**321**	**685**	**659**
Abnormally high	2 (0.6)	0	0	0	2 (0.3)	0
QTcF (ms), N'	**345**	**338**	**340**	**321**	**685**	**659**
]450 ms, 480 ms]	3 (0.9)	2 (0.6)	7 (2.1)	12 (3.7)	10 (1.5)	14 (2.1)
]480 ms, 500 ms]	1 (0.3)	0	1 (0.3)	1 (0.3)	2 (0.3)	1 (0.2)
QTcF (ms), N'	**344**	**338**	**338**	**319**	**682**	**657**
Increase by [30, 60] ms	57 (16.6)	64 (18.9)	70 (20.7)	67 (21.0)	127 (18.6)	131 (19.9)
Increase by > 60 ms	4 (1.2)	2 (0.6)	4 (1.2)	4 (1.3)	8 (1.2)	6 (0.9)
QTcB (ms), N'	**345**	**338**	**340**	**321**	**685**	**659**
]450 ms, 480 ms]	19 (5.5)	19 (5.6)	22 (6.5)	33 (10.3)	41 (6.0)	52 (7.9)
]480 ms, 500 ms]	1 (0.3)	2 (0.6)	0	5 (1.6)	1 (0.1)	7 (1.1)
> 500 ms	0	0	1 (0.3)	0	1 (0.1)	0
QTcB (ms), N'	**344**	**338**	**338**	**319**	**682**	**657**
Increase by [30, 60] ms	81 (23.5)	104 (30.8)	91 (26.9)	92 (28.8)	172 (25.2)	196 (29.8)
Increase by > 60 ms	5 (1.5)	7 (2.1)	9 (2.7)	12 (3.8)	14 (2.1)	19 (2.9)

N = Overall number of subjects, N' = number of subjects per test and treatment group; n = number of observations.

There were no clinically relevant differences between the rilpivirine and control groups in the incidence of treatment-emergent ECG abnormalities overall. In both treatment groups, the most frequent (in at least 2.0% of rilpivirine-treated subjects) treatment-emergent ECG abnormalities were abnormally low HR (8.0% with rilpivirine vs 4.7% in the control group), QTcB interval > 450 ms (6.3% vs 9.0%), and abnormal increases in QTcF and QTcB interval (QTcF: 19.8% vs 20.9%, QTcB: 27.3% vs 32.7%). Abnormalities in the QRS and PR intervals were infrequent in both treatment groups.

The QTcF interval increase was lower in the TDF/FTC subgroup than in the AZT/3TC subgroup, with a QTcF interval increase at Week 48 of +10.6 ms and +12.1 ms in the rilpivirine group and +12.1 ms and +17.8 ms and in the control group, respectively. No differences were found for gender and race or co medication.

Subjects with pre-existing risk factors for QTc prolongation were excluded in the phase III trials. Post-hoc analyses showed that about 3% of the screened subjects failed screening for this reason. The most frequently reported ECG finding was incomplete right bundle branch block occurring in 28 subjects, followed by complete right bundle branch block in seven subjects. Given the low incidence at screening, the fact that the most frequently observed ECG finding is of limited clinical relevance and the fact that the 25 mg dose was not associated with QT interval prolongation, there is no need to screen with ECG before starting treatment with rilpivirine.

Adverse events of special interest for an NNRTI

Skin events (rash), neurological events (headache, dizziness and somnolence) and psychiatric events (insomnia, abnormal dreams and depression) occurred more frequently in the first four weeks of treatment with a lower incidence of events in the rilpivirine group compared to control. After the first four weeks the incidence decreased but remained somewhat lower for the rilpivirine group compared to control.

The incidence of hepatic events of interest was low in the pooled Phase III trials (2.2% out of 5.5% were considered treatment related in the rilpivirine groups versus 2.1% out of 6.6% in the control groups).

With regard to hepatic events (AST, ALT) incidence seems to be comparable between the two groups; also for this kind of adverse events the occurrence is somewhat higher in the first four weeks but overall low.

With regard to the adverse events of special interest, the safety profile of rilpivirine appears to be in favour compared to the safety profile of the control (efavirenz).

Serious adverse event and deaths

In total there were 9 deaths, all were considered not related to the study medication. Five subjects died (with 6 AEs leading to death) during the course of the 2 Phase III trials, 1 in the rilpivirine group in trial C215 and 4 in the control group (1 in trial C209 and 3 in trial C215). Causes of death were bronchopneumonia for the subject on rilpivirine and Burktt's lymphoma, cerebral toxoplasmosis and respiratory failure, dysentery, cerebrovascular accident for the 4 subjects in control group. In the phase IIb study up to week 192 in total four subjects died. Up to the week 96 analysis of the phase IIb study it is described that one subject died in a car accident and another died of cardio-respiratory arrest both were on rilpivirine 75 mg. After the week 96 analysis two subjects died. One of unknown cause, the other died from acute infarction of the intestines following multiple drug intoxication.

Overall, 45 subjects (6.6%) in the rilpivirine group and 55 subjects (8.1%) in the control group had at least 1 SAE during the treatment period. The highest incidence of Seas was in the SOC of infections and infestations (2.6% for rilpivirine versus 2.5% versus control). The only notable difference was seen in the SOC of hepatobiliary disorders (0.9% on rilpivirine vs 0.1% on control).

Most SAEs were considered not related to treatment. Seven subjects (1.0%) in the rilpivirine group and 6 subjects (0.9%) in the control group experienced at least 1 treatment-related SAE. Thus no difference between the two groups, also psychiatric disorders (0.4% versus 0.3%), skin disorders (0.1% versus 0.1%) and nervous system disorders (0.1% versus 0.1%) were comparable between the two groups.

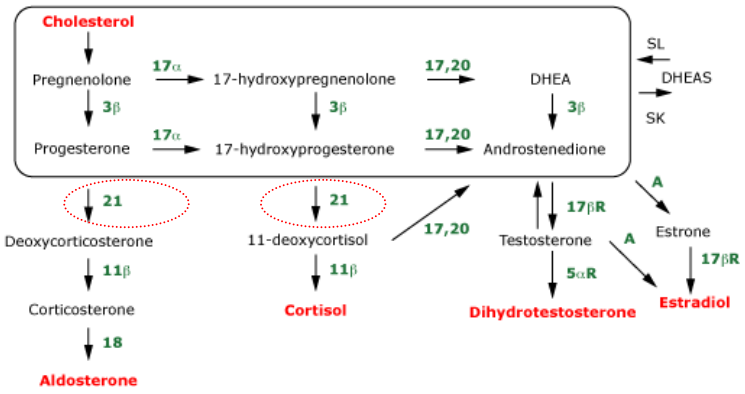
Laboratory findings

The most frequently reported treatment-emergent graded laboratory abnormalities of at least grade 2 in the rilpivirine group were hypophosphatemia (9.1%), increased pancreatic amylase (6.1%), hyperglycemia (5.4%), and elevated LDL cholesterol (5.5%). There were no apparent differences between treatment groups in the frequency of at least grade 2 hypophosphatemia, increased pancreatic amylase or hyperglycemia.

With regard to haemoglobin, hepatic parameters (ALT, AST) and pancreatic parameters (amylase, lipase) overall the pattern between TMC 278 and control appear comparable.

Adrenal hormones
Effects on adrenal glands were seen preclinically in all species except rabbits. This is considered to be related to partial inhibition of the CYP21 enzyme - which catalyzes major steps in the aldosterone and cortisol pathways, figure below.

Figure. 11.



Therefore basal cortisol, 17-OH-progesterone, aldosterone, androstenedione, DHEAS, progesterone and testosterone were monitored in both phase 2b and phase 3. In addition an ACTH stimulation test was also performed at baseline, at Week 48, and at unscheduled visits if based on basal cortisol results or an abnormal ACTH test.

In study C204 cortisol levels of ≥ 550 nmol/ at least at one of the 3 time points (i.e., morning cortisol, 30 or 60 minutes after 250 µg ACTH stimulation) on the screening assessment was an inclusion criterion. However, in phase 3 there were no such restrictions.

Changes of adrenal hormones in the phase 3 study (rilpivirine dosed 25 mg) were small, and varied inconsistently between treatments. In study C204 25mg, 75 mg, 150 mg), there was a tendency for a slightly lower cortisol response to ACTH-stimuli in patients with the higher TMC-doses (table 25 below), while morning values were not affected. No clinical symptoms related to cortisol deficiency were noted.

Table 25: Cortisol levels (nmol/L) up to week 48, morning and *30 minutes* after ACTH-stimuli. C204.

Mean, (range)	**25 mg**	**75 mg**	**150 mg**	**control**
BL +30 min Actual Δ Δ change fr BL	373 (128-774) 614 (249-979) 241 0 (n=93)	341 (54-669) 608 (83-856) 267 0 (n=94)	367 (91-1043) 612 (166-1180) 245 0 (n=91)	333 (110-552) 617 (390-985) 284 0 (n=89)
V 24 + 30 min Actual Δ Δ change fr BL	337 (60-1104) 604 (442-1104) 267 26 (n=81)	306 (17-774) 577 (351-908) 271 4 (n=85)	330 (98-682) 612 (261-800) 282 37 (n=79)	334 (54-779) 660 (367-912) 326 42 (n=79)
V 48 + 30 min Actual Δ Δ change fr BL	337 (110-635) 624 (439-883) 287 46 (n=80)	330 (69-662) 606 (335-1049) 276 9 (n=78)	340 (54-828) 579 (138-966) 239 -6 (n=75)	350 (126-662) 678 (468-1057) 328 44 (n=75)

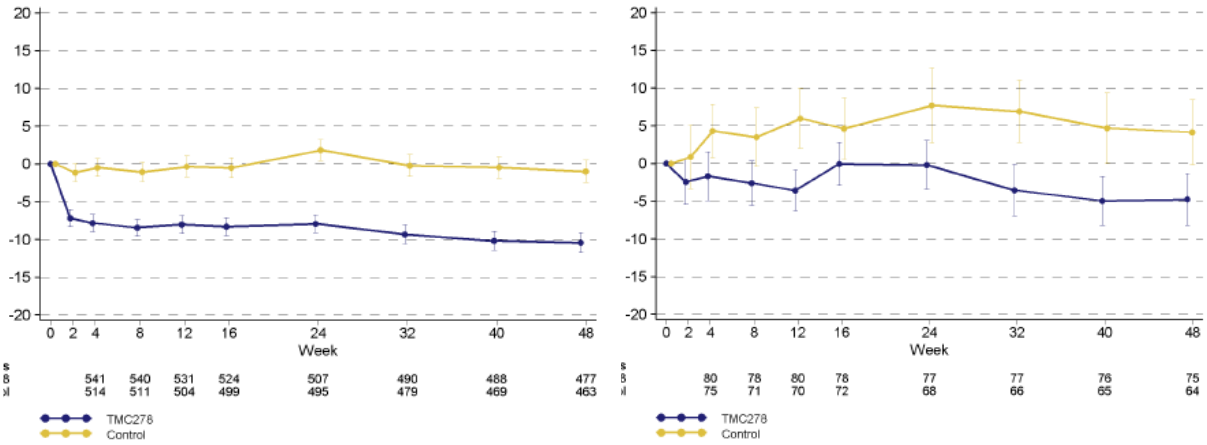
Note: Delta and delta change (i.e. the difference between actual delta at a specific week and the delta seen at baseline) after ACTH stimulation, are presented as the difference between group level means - not an average performed on each individual delta.

No significant changes were seen in levels of androstenedione, progesterone, testosterone and LH. Likewise, not symptoms related to impaired levels of these hormones were reported to occur.

Renal parameters

In patients treated with rilpivirine there was an immediate increase of serum creatinine - causing a decrease in calculated clearance, not seen with the control regimen. In the phase 3 studies (25 mg), this decrease in clearance was more pronounced with tenofovir (left) than with zidovudine (right).

Figure 12. Change in calculated creatine clearance in studies C209 + C215 pooled.
Left: tenofovir/FTC subset; right: zidovudine/3TC subset



In the tenofovir subset of patient in study C204 (3 doses of rilpivirine), this change in creatinine clearance seen with rilpivirine was, however, not dose dependent (data shown in Clinical report).

The immediate change in creatinine clearance is likely to be caused by an inhibition of creatinine secretion on the tubular level. In contrast, cystatin C is freely filtered by the glomeruli without any proximal tubular secretion. Therefore, also cystatin clearance was calculated in study C215 - where the different NRTI back bones made this analysis more interesting. Although, increases of cystatin clearance was seen from baseline to week 48 for all dose groups (an effect of controlling HIV-infection), smaller increases were obtained in rilpivirine-treated patients regardless of NRTI backbone used. Also a lower increase, not only a decrease, could be indicative of a slight renal toxicity.

Considering the pre-clinical data (kidney target organ) and renal effects seen in patients, it is clear that long term renal toxicity should be monitored also with parameters adequate for determining tubular dysfunction.

It is of particular interest to see such data by tenofovir and non-tenofovir subsets for both rilpivirine and control; as tenofovir per se carries a, dose dependent, risk for that kind of toxicity. It is important to verify that rilpivirine and tenofovir given in combination, does not give an additive/synergistic risk for the tubular toxicity already described for tenofovir, which in turn causes phosphate loss with bone loss as perhaps the most important outcome measure. Such data was requested as part of the primary LoQ (urine-protein, urine-β2-microglobulin etc). For the issue of possible tubular toxicity, DEXA-scanning for bone mineral density (BMD) is of major interest, particularly comparing the tenofovir subsets of rilpivirine treated vs control, for reasons outlined above.

To be noted, long term bone safety with tenofovir was only shown for tenofovir in combination with efavirenz - in practice as Atripla, which given in a fasted state. It is therefore a concern that, based on

the data presented the tenofovir exposure is increased around 50% compared to the Atripla combination, when given with rilpivirine (+25%) and food (+25%) (rilpivirine needs to be taken with food).

The phase 3 studies included an optional DEXA sub study looking at BMD progress from baseline to weeks 48 and 96.

The applicant could not provide additional safety data on parameters adequate for monitoring tubular injury, as these were not collected during the studies. However, other available data do not point toward tubular toxicity with rilpivirine. There was no difference in bone parameters in the DEXA substudy for rilpivirine and EFV, regardless of NRTI backbone. Also, rates of hypophosphatemia were quite the same between treatment arms.

Given the fact that tenofovir exposure is highly dependent on renal clearance the effect of rilpivirine on renal clearance and creatinine levels should however be reflected in the SmPC, as well that rilpivirine was only studied in patients with normal renal function.

Adverse drug reactions

The company describes a methodology used to identify Adverse Drug Reactions (ADR). The first step was the generation of a list of preferred terms to be considered as potential ADRs, the second step (review of individual and multiple cases) to generate a draft ADR list and finally this draft list was discussed in a broader group leading to the Final ADR list. In some cases, MedDRA preferred terms related to a common pathology or symptom were grouped to a single common preferred term. These are called 'grouped terms' and were assigned to the primary SOC associated with the preferred term which corresponds to the term used as an ADR grouped term. This methodology was considered appropriate.

All ADRs of at least grade 2 identified from the Phase III pooled database are listed in the table 26.

Table 26: Adverse Drug Reactions (Excluding Laboratory Abnormalities) with Severity at Least Grade 2 (Phase III Week 48 Analysis)

System Organ Class ADR Grouped Term/Preferred Term, n (%)	C209		C215		Pooled		
	TMC278 N = 346	Control N = 344	TMC278 N = 340	Control N = 338	TMC278 N = 686	Control N = 682	p-value*
Psychiatric disorders	***29 (8.4)***	***36 (10.5)***	***28 (8.2)***	***22 (6.5)***	***57 (8.3)***	***58 (8.5)***	-
Depression	15 (4.3)	7 (2.0)	9 (2.6)	8 (2.4)	24 (3.5)	15 (2.2)	-
Insomnia	9 (2.6)	13 (3.8)	11 (3.2)	9 (2.7)	20 (2.9)	22 (3.2)	-
Abnormal dreams[a]	6 (1.7)	19 (5.5)	4 (1.2)	7 (2.1)	10 (1.5)	26 (3.8)	0.0067
Sleep disorders[b]	2 (0.6)	4 (1.2)	6 (1.8)	1 (0.3)	8 (1.2)	5 (0.7)	-
Depressed mood[c]	1 (0.3)	2 (0.6)	2 (0.6)	0	3 (0.4)	2 (0.3)	-
Nervous system disorders	**12 (3.5)**	**34 (9.9)**	**11 (3.2)**	**36 (10.7)**	**23 (3.4)**	**70 (10.3)**	-
Headache	9 (2.6)	8 (2.3)	9 (2.6)	15 (4.4)	18 (2.6)	23 (3.4)	0.43
Dizziness	4 (1.2)	24 (7.0)	1 (0.3)	21 (6.2)	5 (0.7)	45 (6.6)	< 0.0001
Somnolence	2 (0.6)	5 (1.5)	2 (0.6)	4 (1.2)	4 (0.6)	9 (1.3)	
Gastrointestinal disorders	**9 (2.6)**	**18 (5.2)**	**10 (2.9)**	**15 (4.4)**	**19 (2.8)**	**33 (4.8)**	-
Abdominal pain[d]	5 (1.4)	6 (1.7)	4 (1.2)	5 (1.5)	9 (1.3)	11 (1.6)	-
Nausea	6 (1.7)	9 (2.6)	2 (0.6)	9 (2.7)	8 (1.2)	18 (2.6)	0.05
Vomiting	1 (0.3)	5 (1.5)	5 (1.5)	6 (1.8)	6 (0.9)	11 (1.6)	-
Abdominal discomfort[e]	1 (0.3)	1 (0.3)	2 (0.6)	0	3 (0.4)	1 (0.1)	-
Dry mouth	0	1 (0.3)	0	0	0	1 (0.1)	-
Skin and subcutaneous tissue disorders	**11 (3.2)**	**30 (8.7)**	**4 (1.2)**	**34 (10.1)**	**15 (2.2)**	**64 (9.4)**	-
Rash[f]	11 (3.2)	30 (8.7)	4 (1.2)	34 (10.1)	15 (2.2)	64 (9.4)	< 0.001
General disorders and administration site conditions	**2 (0.6)**	**8 (2.3)**	**7 (2.1)**	**4 (1.2)**	**9 (1.3)**	**12 (1.8)**	-
Fatigue	2 (0.6)	8 (2.3)	7 (2.1)	4 (1.2)	9 (1.3)	12 (1.8)	-
Metabolism and nutrition disorders	**3 (0.9)**	**4 (1.2)**	**5 (1.5)**	**0**	**8 (1.2)**	**4 (0.6)**	-
Decreased appetite[g]	3 (0.9)	4 (1.2)	5 (1.5)	0	8 (1.2)	4 (0.6)	-

N = number of subjects per treatment group; n = number of subjects with ADR(s).

[a] Grouped term 'abnormal dreams' includes preferred terms with severity of at least grade 2: 'abnormal dreams' and 'nightmare'.

[b] Grouped term 'sleep disorders' includes preferred terms with severity of at least grade 2: 'sleep disorder', 'initial insomnia', and 'poor quality sleep'.

[c] Grouped term 'depressed mood' includes preferred terms with severity of at least grade 2: 'depressed mood' and 'mood altered'.

[d] Grouped term 'abdominal pain' includes preferred terms with severity of at least grade 2: 'abdominal pain' and 'abdominal pain upper'.

[e] Grouped term 'abdominal discomfort' includes preferred terms with severity of at least grade 2: 'abdominal discomfort' and 'abdominal distension'.

[f] Grouped term 'rash' includes preferred terms with severity of at least grade 2: 'rash', 'rash pruritic', 'rash papular', 'rash macular' and 'rash maculo-papular'.

[g] Grouped term 'decreased appetite' includes preferred terms with severity of at least grade 2: 'anorexia' and 'decreased appetite'.

Safety in special populations

Hepatitis B or Hepatitis C Co-infection
In the Phase III pooled analysis, approximately 9% of subjects were reported to be co-infected with hepatitis B and/or C at baseline or on-treatment. As expected, in both treatment groups, elevated hepatic parameters were observed at a higher incidence in subjects who were co-infected with hepatitis B and/or C than in subjects who were not co-infected. The incidence in co-infected subjects was comparable in both the rilpivirine and control groups.

Safety related to drug-drug interactions and other interactions

Not applicable

Discontinuation due to adverse events

Phase III: Overall, 23 subjects (3.4%) in the rilpivirine group and 52 subjects (7.6%) in the control group had at least 1 AE leading to discontinuation. Psychiatric disorders (1.5% vs 2.2% on control) were the most frequent. rilpivirine-treated subjects who discontinued because of AEs did so later than subjects in the control group and this difference was sustained throughout the treatment period. Overall the discontinuation rate due to AEs was 2.2% the rilpivirine group versus 7.2% on the control.

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

TMC 278 appeared to be generally safe and well tolerated. The most frequently reported treatment-related AEs in the rilpivirine group were nausea, dizziness, abnormal dreams and headache. Especially within the first four weeks of treatment rilpivirine the safety profile of rilpivirine seemed in favor compared to control. After the first four weeks the occurrence of adverse events decreased but there remained somewhat difference in safety profile in favor of TMC although to a lesser extend.

With regards to AEs frequently discussed for approved NNRTIs Neurological AEs often experienced during the first weeks of treatment for the preferred NNRTI efavirenz (control), was less frequently seen with rilpivirine. Psychiatric AEs, often discussed as a problem with efavirenz, were rather uncommon for both regimens; anxiety and abnormal dreams were somewhat more common with control, while depression was slightly more frequently reported in rilpivirine treated patients. Rash, commonly seen with efavirenz (but only causing 1 patient from each treatment arm to permanently stop therapy in phase 3), was less frequent with rilpivirine. However, dermatitis/eczema appearing later during treatment was more common. Lipid parameters are not significantly affected by rilpivirine.

Hepatic events were uncommon and mild for both treatments, Three subjects had grade 4 hepatic events while on rilpivirine, none of which were reported as SAEs. Those 3 patients all had hepatitis co-infection.

Renal function was lowered with rilpivirine compared to control, regardless if using creatinine (lowered from baseline value) or cystatin C (somewhat less improvement from baseline vs control) as the parameter used to calculate GFR. This did not seem to be dose related when looking at the phase 2 b study (cystatin C data only presented for the 25 mg dose). Since kidney was a target organ in rats and dogs, primarily with tubular toxicity the company was asked to provide safety data on parameters adequate for tubular injury. This is particularly important having in mind that rilpivirine is used in combination with tenofovir; an agent with well known risk for tubular toxicity. Post-hoc analyses provided did not point toward tubular toxicity with rilpivirine. There was no difference in bone parameters in the DEXA substudy for rilpivirine and EFV, regardless of NRTI backbone, and rates of hypophosphatemia were similar between treatment arms. These data are therefore reassuring. The effect of rilpivirine on renal clearance and creatinine levels is reflected in sections 4.2 and 4.8 of the SmPC, as well as that rilpivirine was only studied in patients with normal renal function.

Due to QT results, during the phase 2b study, the dose for further development was lowered from 75 mg q.d. to 25 mg q.d.. The clinical relevance of the QT-prolongation seen with 75 mg is currently not clear. Long term safety in this regard is of interest. Although the 25 mg q.d. does not show QT prolongation, a warning was included in section 4.4 of the SmPC that QT prolongation was observed at doses of 75 mg q.d.

Inhibition of adrenal hormone-axis does not seem to be a relevant issue for rilpivirine dosed 25 mg q.d.

2.6.2. Conclusions on the clinical safety

The safety of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. The safety conclusions are further discussed in the context of the overall benefit-risk balance.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan.

Table 27: Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Important Identified Risks:		
1) Development of Drug Resistance	- **Routine pharmacovigilance** - **Discussed in separate section of the PSUR** - **Surveillance through national and international collaborative programs** - **Guided questionnaire for postmarketing cases** - **Follow-up on development of drug resistance in subjects failing rilpivirine in trials TMC278-C204, TMC278-TiDP6-C209/C215, and the roll-over trial TMC278-TiDP6-C222** - **Follow-up on second line ARV treatment in subjects failing TMC278 in the observational part of trials TMC278-TiDP6-C209/C215** - **Follow-up on the development of resistance in paediatric subjects failing TMC278 in trials TMC278-TiDP38-C213/C220** - **Drug Utilisation Study Including a Nested Case-Control Study** - **Follow-up on development of drug resistance in subjects switching from other therapies to TMC278 in trial TMC278HIV4001 and the Gilead sponsored trials GS-US-264-0106 and GS-US-264-0111.** - **Experiments to assess the emergence of resistance following in vitro selection with TMC278 in combination with zidovudine and abacavir.**	The proposed SmPC (Section 4.1: Therapeutic Indications, Section 4.4: Special Warnings and Precautions for Use and Section 5.1: Pharmacodynamic Properties) discusses emergence of resistance (mutations) and effects of baseline resistance on virologic response and states that resistance testing should guide the use of rilpivirine.
Important Potential Risks:		
1) QT Interval Prolongation	- **Routine pharmacovigilance** - **Discussed in separate section of the PSUR** - **Participation to the HAART Oversight Committee** - **Long-term follow-up in adults in trials TMC278-C204 and TMC278-TiDP6-C209/C215** - **Collection of safety data in the paediatric trials TMC278-TiDP38-C213/C220** - **Nonclinical metabolite profiling study TMC278/FK10104**	The proposed SmPC (Section 4.4: Special Warnings and Precautions for Use and 4.5: Interaction With Other Medicinal Products and Other Forms of Interaction) states that 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 ECG and QT prolongation has been observed with supra-therapeutic doses of rilpivirine.rilpivirine should, therefore, be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes. The proposed SmPC (Section 4.9 Overdose) states that treatment of overdose should include monitoring of vital signs and ECG (QT interval).

2) Hepatotoxicity	- **Routine pharmacovigilance** - **Discussed in separate section of the PSUR** - **Participation to the HAART Oversight Committee** - **Long-term follow-up in adults in trials TMC278-C204, TMC278-TiDP6-C209/C215, and the roll-over trial TMC278-TiDP6-C222** - **Collection of safety data in the paediatric trials TMC278-TiDP38-C213/C220**	The proposed SmPC (Section 4.8: Undesirable Effects) includes 'transaminase increased' in the Tabulated summary of adverse reactions. Additionally in the proposed SmPC Section 4.8, information is provided on patients co-infected with hepatitis B and/or hepatitis C virus to reflect that increased hepatic enzymes are noted in patients co-infected with hepatitis B and/or C.
3) Severe Skin Reactions	- **Routine pharmacovigilance** - **Discussed in separate section of the PSUR** - **Long-term follow-up in adults in trials TMC278-C204, TMC278-TiDP6-C209/C215, and the roll-over trial TMC278-TiDP6-C222** - **Collection of safety data in the paediatric trials TMC278-TiDP38-C213/C220**	The proposed SmPC (Section 4.8: Undesirable Effects) includes 'rash' in the Tabulated summary of adverse reactions.
4) Major Depressive Disorder	- **Routine pharmacovigilance** - **Discussed in separate section of the PSUR** - **Long-term follow-up in adults in trials TMC278-C204, TMC278-TiDP6-C209/C215, and the roll-over trial TMC278-TiDP6-C222** - **Collection of safety data in the paediatric trials TMC278-TiDP38-C213/C220**	The proposed SmPC (Section 4.8: Undesirable Effects) includes 'depression' in the Tabulated summary of adverse reactions.
Lipodystrophy	- **Routine pharmacovigilance** - **Discussed in separate section of the PSUR** - **Participation to the HAART Oversight Committee** - **Substudy of trials TMC278-TiDP6-C209/C215 (dual energy X-ray absorptiometry substudies)** - **Long-term follow-up in adults in trials TMC278-C204, TMC278-TiDP6-C209/C215, and the roll-over trial TMC278-TiDP6-C222** - **Collection of safety data in the paediatric trials TMC278-TiDP38-C213/C220**	The proposed SmPC Section 4.4 Special Warnings and Precautions for Use includes a section on fat redistribution associated with cART in HIV-infected patients.
5) Overdose	- **Routine pharmacovigilance** - **Discussed in separate section of the PSUR**	The proposed SmPC Section 4.2 Posology and Method of Administration contains clear instructions on dosing regimen and Section 4.9 contains information on general supportive measures in case of overdose, which include monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient.

6) Off-label Use (in adult and paediatric subjects)	- **Routine pharmacovigilance** - **Discussed in separate section of the PSUR** - **Clinical trials TMC278-TiDP38-C213 in HIV-1 infected ARV naïve adolescents (≥ 12 to < 18 years) and TMC278-TiDP38-C220 in HIV-1 infected ARV naïve children less than 12 years old** - **Drug Utilisation Study Including a Nested Case-Control Study**	Information to Healthcare Professionals and/or Patients on the appropriate use of rilpivirine is contained within the proposed SmPC and Package Leaflet Sections 4.1. (Therapeutic Indications) and 4.2 (Posology and Method of Administration) and aims to reduce off-label use in patient populations for which the safety and efficacy have not been established and patient populations at higher risk of treatment failure.
7) Bleeding Disorders	- **Routine pharmacovigilance** - **Discussed in separate section of the PSUR**	No information with regard to bleeding disorders is included in the SmPC.
Important Missing Information		
1) Children and Adolescents (under age of 18 years)	- **Routine pharmacovigilance** - **Discussed in separate section of the PSUR** - **Clinical trials TMC278-TiDP38-C213 in HIV-1 infected ARV naïve adolescents (≥ 12 to < 18 years) and TMC278-TiDP38-C220 in HIV-1 infected ARV naïve children less than 12 years old**	The proposed SmPC (Section 4.2: Posology and Method of Administration) states that the safety and efficacy of rilpivirine in children aged < 18 years have not yet been established. No data are available.
2) Pregnancy and Breast Feeding Women	- **Routine Pharmacovigilance** - **Discussed in separate section of the PSUR** - **Participation to the US APR** Post-authorisation in-utero exposure will also be captured within the US APR. The Registry will provide a 6-monthly report, which will be discussed in the PSURs. - **Rilpivirine Women's Cohort Study (TMC278HIV4001)**	The proposed SmPC (Section 4.6: Fertility, Pregnancy and Lactation) states that rilpivirine should not be used during pregnancy unless clearly needed and that mothers should be instructed not to breastfeed if they are receiving rilpivirine.
3) Elderly (65 years and above)	- **Routine pharmacovigilance** - **Discussed in separate section of the PSUR**	The proposed SmPC (Section 4.2: Posology and Methods of Administration) indicates that no dose adjustment of rilpivirine is required in elderly patients. rilpivirine should be used with caution in this population.
4) Use in Severe Hepatic Impairment (Child-Pugh score C)	- **Routine pharmacovigilance** - **Discussed in separate section of the PSUR**	- There is limited information regarding the use of rilpivirine in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). The proposed SmPC (Section 4.2: Posology and Methods of Administration) states that no dose adjustment of rilpivirine is required in patients with mild or moderate hepatic impairment. rilpivirine should be used with caution in patients with moderate hepatic impairment. rilpivirine has not been studied in patients with severe hepatic impairment (Child-Pugh score C) and is therefore not recommended in this population. -
5) Patients with eGFRcreat < 50 mL/min/ 1.73 m²	- **Routine pharmacovigilance** - **Discussed in separate section of the PSUR**	rilpivirine has mainly been studied in patients with normal renal function. The proposed SmPC (Section 4.2: Posology and Methods of Administration) states that no dose adjustment is needed for

		patients with mild or moderate renal impairment. No clinical data are available in patients with severe renal impairment. rilpivirine should be used with caution in subjects with severe renal impairment or end-stage renal disease and that the combination with a strong CYP3A inhibitor should only be used if the benefit outweighs the risk.
6) Drug-drug Interaction	- **Routine pharmacovigilance** - **Continued evaluation through planned and ongoing drug-drug interaction trials of rilpivirine in combination with raltegravir, rifabutin, digoxin, and metformin.** - **Evaluation through a planned drug-drug interaction trial of rilpivirine 50 mg q.d. after a switch from EFV.** - **Evaluation through a planned in vitro study to evaluate the potential for time-dependent inhibition of CYP2C9 by rilpivirine.** - **Evaluation through a planned in vitro study to evaluate the MATE inhibitory potential of rilpivirine.**	The proposed SmPC (Section 4.3: Contraindications) lists drugs for which co-administration with rilpivirine is contraindicated. The proposed SmPC (Section 4.5: Interactions With Other Medicinal Products and Other Forms of Interactions) lists drugs for which co-administration with rilpivirine is contraindicated; should be used with caution; should be avoided; or requires specific monitoring; and provides a tabular summary of established and other potentially significant drug interactions with dosing recommendations and/or clinical comments.
7) Patients Taking Unstudied Background Regimens	- **Routine pharmacovigilance** - **Drug Utilisation Study Including a Nested Case-Control Study** - **Rilpivirine Women's Cohort Study (TMC278HIV4001)**	The proposed SmPC (Section 5.1: Pharmacodynamic Properties) lists the virologic outcome of randomised treatment in the ECHO and THRIVE trials for each studied background regimen. The proposed SmPC (Section 4.4: Interaction With Other Medicinal Products and Other Forms of Interaction) lists interactions and dose recommendation with other ARVs. No additional risk minimisation activities are considered needed for patients taking unstudied background regimens.

The below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Table 28: Pharmacovigilance activities in addition to the routine pharmacovigilance

Description	Due date
To investigate whether species-specific metabolite(s) may be responsible for the QT prolongation that was observed particularly in humans.	04Q2011
To perform an interaction study with raltegravir	June 2012
To further investigate inhibitory properties (time dependent) of rilpivirine on CYP2C9.	March 2012
To perform an interaction study with rifabutin	June 2013
To submit a report of the metabolite profiling and decision on synthesis of disproportional metabolites in relation to QT prolongation.	December 2011
To perform an interaction study with metformin, which also includes investigations of the MATE inhibitory potential of rilpivirine.	3Q2013
Perform a drug interaction study with efavirenz and 50 mg rilpivirine dose	1Q2013

Provide the 96 weeks clinical study report of study C209 and C215 upon completion.	1Q 2012
To submit the results of the ongoing switch studies GS-US-264-011 and GS-US-264-0106	GS-US-264-0106 1Q 2013 GS-US-264-0111 4Q 2012
To perform a drug utilization study: Observational Cohort Study Including a Nested Case-Control Study to Assess Rilpivirine (RPV) Utilization According to the European SmPC	To be followed up in the PSURs and the RMP updates
Women´s study: USA cohort study in women	To be followed up in the PSURs and the RMP updates

Drug utilisation study (DUS)

The Applicant provided a protocol for a drug utilisation study (DUS) implicating the use of the already existing European HIV cohorts: Observational Cohort Study Including a Nested Case-Control Study to Assess Rilpivirine (RPV) Utilization According to the SmPC.

The development of resistance and the utilization of RPV-containing products according to the products' SmPC will be assessed through a drug utilization study (DUS) conducted in existing HIV observational cohorts within Europe. Additionally, the DUS will provide context to the observed rates of virologic failure and development of resistance for patients initiating RPV treatment by describing the treatment outcomes of patients initiating efavirenz (EFV). The relative risk of virologic failure and resistant-associated mutations (RAMs) after initiating RPV-containing regimens will be estimated separately by comparing the incidence rates of virologic failure and RAMs among RPV-treated patients to the incidence of virologic failure and RAMs among EFV-treated patients. For all study objectives, frequency and rates will be reported for the RPV and EFV-treated groups separately, as well as for RPV relative to EFV.

A minimum of 600 HIV-positive patients are to be included. Additionally, a comparator cohort of a minimum of 600 EFV-treated patients will be included.

A nested case-control study will be conducted to assess the effects of ARV treatment adherence and pill intake with food on the risk of virologic failure with RPV will be assessed.

Primary objectives include: to describe the proportion of patients treated with RPV in accordance with the SmPC, to describe treatment emergent RAMs in patients treated with RPV or EFV-containing regimens and to describe virologic failure in patients treated with RPV or EFV-containing regimens.

The final protocol of the DUS study, including the nested case control study protocol, is agreed by the CHMP. The Applicant should report on this study as well in the PSURs and the RMP updates.

USA cohort study in women

In the USA a cohort study in women will be conducted, which will provide additional data on the use of rilpivirine-containing regimens for treatment of HIV-infected women, in everyday clinical practice. The primary objective of this cohort study is to characterize the population and treatment outcomes of ARV-naïve women (including switches) in routine clinical practice initiating rilpivirine-containing regimens. The Applicant has submitted the protocol of this study. The Applicant should report on this study as well in the PSURs and the RMP updates.

Switch studies GS-US-264-011 and GS-US-264-0106
The two ongoing Gilead FDC switch studies are:

A Phase III randomized, open-label study to evaluate switching from regimens consisting of a ritonavir-boosted PI and two nucleoside reverse transcriptase inhibitors (NRTIs) to FTC/rilpivirine/TDF fixed-dose regimen in virologically-suppressed, HIV-1 infected patients (study GS-US-264-0106)

A Phase IIb open-label pilot study to evaluate switching from a regimen consisting of an EFV/FTC/TDF single tablet regimen to FTC/rilpivirine/TDF single tablet regimen in virologically-suppressed, HIV-1 infected subjects (study GS-US-264-0111)

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

In European Union, Rilpivirine is the fourth representative of the Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI) after nevirapine, efavirenz (EFV) and etravirine. The applicant applied for the indication in treatment of HIV-1 infection in antiretroviral (ARV) treatment-naïve adults. As such, according to current HIV treatment guidelines, it could be considered an alternative to EFV as the first choice NNRTI agent in first line ARV regimens.

Benefits

Beneficial effects

The beneficial virological effects of RPV is clearly demonstrated in two pivotal phase III randomized trials, comparing RPV to EFV, both in combination with 2 NRTIs, in treatment-naïve HIV-1 infected adults. NRTI backbones used were tenofovir/FTC (major part), abacavir/lamivudine or zidovudine/lamuvidine. Both studies demonstrated non-inferiority of RPV to EFV; at 48 weeks follow-up, the overall response rate (< 50 copies/mL) for pooled results was 84% and 82% for RPV and EFV respectively. Such response rates are similar to previous studies with EFV.

RPV has a favourable tolerability profile compared to EFV, as relatively common skin disorders and neuro-psychiatric side effects were reported less frequently.

Uncertainty in the knowledge about the beneficial effects.

The beneficial effects in individuals with high baseline viral load (and low CD4 T-cell counts, often associated with high viral loads) are questionable. Post-hoc analyses stratified for baseline viral load (≤100,000 versus >100,000 copies/ml) for the overall population and the tenofovir/emtricitabine

subset confirmed the trend towards lower efficacy in patients with high baseline viral load (77% with TCM278 versus 81% with EFV) whereas efficacy was comparable (numerically higher) for patients with baseline viral load ≤100,000 copies/ml (90% versus 84%). Although response rate appears lower in patients with CD4 count < 50 cells/µl, numbers are too low to draw conclusions on the impact of low CD4 count per se.

In phase 2b three doses of RPV were tested: 25 mg, 75 mg and 150 mg. There was not an obvious difference in overall efficacy between doses, although a trend for higher incidence of virological failure with the lowest dose was noted. Due to concerns of QT-effects with the higher doses in a thorough QT study, the lowest dose was chosen for phase 3. Within phase 3, using the 25 mg dose, outcomes were associated to RPV exposure (using population PK data); the response rate was significantly lower for RPV patients belonging to AUC quartile 1 compared to AUC quartile 3. Hence, the exposure achieved with the 25 mg dose is just at the edge , or slightly below the Emax of RPV - which gives efficacy problems mainly in patients with a high baseline viral load, but less so in patients with lower viral loads. Hence, any concomitant drugs that would lower the RPV exposure, as well as intake an intake in fasted state, is likely related to a risk of lower efficacy, and the development of resistance. It is uncertain whether these issues will be handled as carefully in clinical practice as within a well controlled trial. It is crucial that the need for correct intake (fed state) and the risk associated with certain interacting drugs is emphasized in the SmPC. However, the later restrictions might be difficult to handle in clinical and daily practice, with the potential risk of lower virologic response and emergence of resistance. Whether restrictions like low baseline viral load and dosing instructions can be met in daily clinical practice or that the somewhat suboptimal dose is more fragile here than within clinical trials, needs to be confirmed by the drug utilisation study and subsequent PSURs.

It remains to be seen whether an increased dose of this order would make a substantial difference in the numbers of virological failure in those patients with a high baseline viral load. The rather low potency of rilpivirine might be the main obstacle with regards the risk of resistance development (1.2 $\log_{10}$ reduction in monotherapy, regardless of dose used).

In clinical practice rilpivirine might be considered a potential option for switch once viral load has been broken with more potent drugs. Although the drug might be an effective option, there is currently no data available in support of such use. The applicant will monitor such use in clinical practice and studies are ongoing in patients switching from other therapies to RPV. In addition to this, the applicant is requested to perform a drug interaction study with efavirenz and 50 mg rilpivirine dose as metabolic induction by efavirenz holds for quite some time. Further lowering exposure of the 25 mg dose rilpivirine might increase the risk of virological failure.

Patients with a number of baseline HIV resistance associated mutations, an estimated glomerular filtration rate < 50 ml/min, AIDS defining illness or any significant co-existing illness were excluded from the phase III trials.

The number of HIV patients aged over 65 years treated with RPV is too low to draw any conclusions for this subgroup. However, based on the mechanism of action there is no reason to expect a less beneficial effect of RPV among the elderly or those with co morbidity including renal insufficiency.

There are currently no data available from clinical studies with RPV to support the combination of RPV with other antiretroviral agents than tenofovir/emtricitabine, abacavir/lamivudine or zidovudine/lamivudine.

Finally, the beneficial effect (non-inferiority of RPV to EFV) has been demonstrated in the phase III trials for 48 weeks of follow-up. The 96-weeks data of these trials are expected to become available by 1Q 2012.

Risks

Unfavourable effects

As with all ARVs, once there is virological failure there is a risk of emerging resistance. The extensiveness of this determines the available alternative ARVs left for 2nd line treatment.

In the pivotal studies there was overall a 2-fold risk for virological failure for RPV-treated patients compared to those treated with for EFV; 10.5% versus 5.7%. About half of the patients with virological failure (both with RPV and EFV) developed resistance associated mutations; thus RPV was also associated with a 2-fold higher risk to develop resistance. Moreover, RPV resistance was associated with cross-resistance to the 2nd line NNRTI (etravirine) whereas in case of resistance to EFV, susceptibility to etravirine remained. In addition, patients failing RPV therapy more frequently developed resistance to the NRTI backbone (particularly emtricitabine/lamivudine) than did patients failing with efavirenz.

Post-hoc analyses demonstrated that this increased risk of virologic failure was driven by patients with high baseline viral load (i.e >100,000 copies/ml) , 15% with RPV versus 6% with EFV, whereas virologic failure rates were comparably low for patients with low baseline viral load, 3.8% versus 3.3%, regardless of NRTI backbone used. Hence, for the high viral load strata, the risk for emerging resistance (NNRTI and/or NRTI) was 3-4 times higher for those treated with RPV compared to those treated with EFV. In contrast, the number of patients developing resistance was low and similar to that seen for efavirenz-treated patients within the low viral load strata.

The most frequently reported treatment-related AEs in the patients treated with RPV were nausea, dizziness, abnormal dreams and headache. These AEs were mild and occurred less frequently with RPV than with EFV.

Tenofovir carries a, dose dependent, risk for renal tubular toxicity which in turn causes phosphate loss with bone loss as perhaps the most important outcome measure. Post-hoc analyses of the optional DEXA sub study within the phase 3 studies showed that there was no difference in bone parameters for rilpivirine and EFV at week 96, regardless of NRTI backbone. Also, rates of hypophosphatemia were quite the same between treatment arms. Therefore, there are no suggestions for a possible additive/synergistic risk for tubular toxicity when rilpivirine is given in combination with tenofovir.

Uncertainty in the knowledge about the unfavourable effects

An extensive list of NNRTI-associated mutations (n= 39) constituted exclusion criteria in both phase 2b and phase 3 (around 10% of all screening failures). Many of these NNRTI-associated mutations were quite infrequent though, and were neither seen in the in vitro resistance profile of RPV, nor in patients failing RPV therapy in the trials. In the final analyses of all data a list of 15 RPV-associated mutations is proposed to constitute those baseline mutations precluding RPV therapy in treatment naïve patients. This list covers the majority of the population not included in the trials, and the analyses behind it are endorsed. The combined frequency of these 15 mutations is high enough in untreated patients to

request that resistance testing should be done prior to the use of RPV. This is reflected in the indication: as with other antiretroviral medicinal products, genotypic resistance testing should guide the use of rilpivirine and cross reference is made to the relevant sections 4.4 and 5.1.

To perform resistance testing prior to the use of RPV is in line with the general recommendation in Europe - which implies that a baseline resistance testing should be done prior to starting HIV therapy (Vandamme et al, 2011). The other mutations used as exclusion criteria, not included in this list, were deselected by the company after final analyses of pre-clinical and clinical data; they were not found to affect activity in vitro and were not seen in any significant numbers in those failing RPV. Although they were formally not properly studied in vivo, the impact in response rates of the phase 3 studies would not have been significantly affected by their presence in the list of exclusion criteria. Future follow-up of resistance should be provided according to the proposed pharmacovigilance measures and the correctness of associated mutations should be confirmed.

In a thorough QT-study a somewhat unexpected QTc increase above the threshold (just above 10 ms for female subjects) was seen at doses 75 mg or higher. As consequence any risk factor for QT prolongation was an exclusion criterion in the phase III trials giving an uncertainty about the safety of RPV in individuals with such risk factors. However, no difference in QTc increase was seen for the 75 mg dose compared to and efavirenz in the phase 2b study (using common 12-lead ECGs). Also no significant QTc change was noted in an interaction study with RPV 150 mg qd in combination with darunavir/r, which further doubles the exposure. Therefore, the clinical relevance of the QT-prolongation observed at a dose of 75 mg is currently unclear.
Furthermore, post-hoc analyses showed a low incidence for patients with risk of QTc prolongation at screening to phase 3, and observed risk factors were of limited clinical relevance. Therefore, as the 25 mg dose was not associated with QTc interval prolongation, no special warnings are required for the moment. A warning on QT prolongation with supratherapeutic dose (75 mg and higher) was included in section 4.4 of the SmPC.

The applicant could not provide additional safety data on parameters adequate for monitoring tubular injury (urine-protein, urine-β2-microglobulin etc), as these were not collected during the studies. However, other available data do not point toward tubular toxicity with rilpivirine. Still, given the fact that tenofovir exposure is highly dependent on renal clearance the effect of rilpivirine on renal clearance and creatinine levels is reflected in sections 4.2 and 4.8 of the SmPC, as well that rilpivirine was only studied in patients with normal renal function.

Benefit Risk Balance

Importance of favourable and unfavourable effects

As the targeted indication is the treatment of HIV-1 infection in ARV-naïve individuals, both tolerability and efficacy of the ARV regimen are of high importance; this is the start of a potential life-long treatment. In this light, the noted better tolerability of RPV compared to the golden standard EFV, is considered of clinical relevance. Also the qd dosage and low pill burden are advantages that can make it easier for patients to comply with therapy.

A prerequisite of the ARV regimen is its virological potency. Any inability to suppress HIV replication is considered of clinical concern as this may lead to resistance hampering 2nd line ARV treatment options. Virological failure due to resistance should therefore be considered of greater clinical relevance than the tolerability of the regimen.

Benefit-risk balance

Overall, it can be concluded that RPV was non-inferior to the active comparator EFV with respect to the most relevant clinical endpoint (<50 copies/mL). The potential extra benefit over EFV relies in a better tolerability, all be it predominantly the first four weeks of treatment, and the patients convenience having one tablet, once daily as ARV regimen.

This benefit, together with the non-inferior efficacy, should be balanced against an overall 2-fold higher risk of RPV for developing virological failure and emerging resistance of which the latter has greater clinical consequences, as resistance to RPV was also more frequently associated with resistance development to the backbone NRTIs.

In the pivotal phase III studies, the overall risk of emergence of resistance appeared to be about 6% versus 3% for RPV and EFV, respectively. In further analyses it was shown that, the increased risk of emerging resistance with TCM278 is driven by patients with high baseline viral load (>100,000 copies/ml); these patients show lower virologic response rates and higher rates of virologic failure compared to EFV. On the other hand, for patients with baseline viral load ≤100,000 copies/ml TCM278 showed numerically higher response rate and a low risk of emerging resistance and in the same order of magnitude as observed for EFV. It can be expected that the ongoing studies up to 96 weeks will confirm the observed comparative efficacy and safety profiles of RPV.

Based on these arguments the limited benefit of better tolerability does not weigh against the higher risk for emerging resistance for treatment naïve patients at large - the risk of failure and its consequences are not acceptable for patients with a high baseline viral load, taking into account the performance of other available first line options for such patients. Therefore, the CHMP considers that the benefits outweigh the risks when RPV is restricted to patients with low baseline viral load.

Since the 25 mg dose is at the edge of being suboptimal, it is crucial that the exposure is not lowered (concomitant drugs, need for intake in fed state); there is always a risk that these issues are handled less strict in clinical practice than within a clinical trial, where everything is closely monitored. This risk was emphasized in the respective sections of the SmPC. Therapy should be guided by resistance testing as it is considered current good clinical practice in line with the general recommendation according to updated European treatment guidelines.

In clinical practice rilpivirine might be considered a potential option for switch once viral load has been broken with more potent drugs. Although the drug might be an effective option, there is currently no data available in support of such use. The applicant will monitor such use in clinical practice and new studies are on going on use in patients switching from other therapies to RPV.

Discussion on the Benefit Risk Balance

From an individual patient perspective, the reason for judging an ARV agent to be abandoned from the 1st line regimen, either intolerability or insufficient virological effect, is not so relevant as long as alternate future, 2nd line, options are still available. Rilpivirine presents a higher risk for emerging resistance limiting 2nd line options, although nevertheless available 2nd line options in general still remain. However, whenever possible, avoidance of emerging resistance is considered more critical than tolerability.

The restriction of the indication to patients with low baseline viral load resolves the major concern on increased risk of emerging resistance compared to efavirenz. As mentioned above although the potential consequences of developing resistance are of greater concern with RPV given the potential loss of treatment options, the absolute risk is low and available 2nd line options still remain. Interaction with drugs that lower RPV exposure is contraindicated given the potential lower efficacy and subsequent emergence of resistance and RPV must be taken in fed state. Within these restrictions, in patients with low viral load the risks are outweighted by the benefits of RPV showing a comparable high virologic response rate with a better tolerability profile to efavirenz and a favourable once-daily dosing regimen.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of 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 a viral load ≤ 100,000 HIV 1 RNA copies/ml. This indication is based on week 48 safety and efficacy analyses from two randomised, double blind, controlled, Phase III trials in treatment naïve patients and week 96 safety and efficacy analyses from a Phase IIb trial in treatment naïve patients (see section 5.1). As with other antiretroviral medicinal products, genotypic resistance testing should guide the use of EDURANT (see sections 4.4 and 5.1)." is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Obligation to complete post-authorisation measures

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that rilpivirine (hydrochloride) is to be qualified as a new active substance.