24 October 2013
EMA/725635/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eviplera

International non-proprietary name: EMTRICITABINE / RILPIVIRINE / TENOFOVIR DISOPROXIL

Procedure No. EMEA/H/C/002312/II/0021

Note

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

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Annex - List of abbreviations

3TC	lamivudine
ABC	abacavir
ADR	adverse drug reactions
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
aka	also known as
ANCOVA	analysis of covariance
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC_{24h}	area under the plasma/serum concentration versus time curve from time 0 to 24 hours after dosing
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as AUC0−last + (Clast/λz)
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing I interval
AZT	zidovudine; ZDV
BID	twice daily
BMD	bone mineral density
Caco-2	colon carcinoma-derived
CDC	Center for Disease Control and Prevention
CD4+	cluster of differentiation 4 positive
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CLcr	creatinine clearance
Cmax	maximum observed concentration of drug in plasma
Cmin	minimum observed concentration of drug in plasma (trough level)
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
DNA	deoxyribonucleic acid
DRV	darunavir
EACS	European AIDS Clinical Society
EC50 / EC90	median 50% 90% effective concentration
ECG	electrocardiogram
EFV	efavirenz (Sustiva)
eGFR	estimated glomerular filtration rate
EMA, EMEA	European Medicines Agency
ETR	etravirine
EU	European Union
FDA (US)	Food and Drug Administration

FDC	fixed-dose combination
FTC	emtricitabine (Emtriva)
FTC/EFV/TDF	emtricitabine/efavirenz/tenofovir disoproxil fumarate (Atripla, fixed-dose combination product)
FTC/RPV/TDF	emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Eviplera, fixed-dose combination product)
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate (Truvada; fixed-dose combination product)
FTC-TP	emtricitabine triphosphate
FUM	follow up measure
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)
HPLC	high-performance liquid chromatography
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
MAA (EU)	Marketing Authorization Application
MEA	Measure (type of PAM)
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
non-VF	non-virologic failure (population of patients)
PAM	Post Approval Measure
PBMC	peripheral blood mononuclear cell
P-gp	P-glycoprotein
PI	protease inhibitor
PK	pharmacokinetic
PP	per protocol
PPI	Proton Pimp Inhibitors
PNP	purine nucleoside phosphorylase
PR	Protease
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
/r	ritonavir boosted
RAM	resistance-associated mutation
REC	Recommendation (type of PAM)
RNA	ribonucleic acid
RPV	rilpivirine (27.5 mg rilpivirine hydrochloride is equivalent to 25 mg RPV)
RSI	Request for Supplementary Information
RT	reverse transcriptase
RTV	ritonavir (Norvir)
rtv	coadministered low-dose ritonavir
SAE	serious adverse event
SAWP	Scientific Advice Working Party
SD	standard deviation
SmPC	Summary of Product Characteristics
SNPs	single-nucleotide polymorphisms
SOC	system organ class
T½, t1/2,	term terminal elimination half-life
TDF	tenofovir disoproxil fumarate, (300 mg TDF is equivalent to 45 mg tenofovir disoproxil or 136 mg of tenofovir)
TFV	tenofovir
tmax	time (observed time point) of Cmax
TQT	thorough QT
US, USA	United States
VF	virologic failure
ZDV	ZIDVUDINE, AZT

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences International Ltd submitted to the European Medicines Agency on 9 January 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Eviplera	emtricitabine / rilpivirine / tenofovir disoproxil fumarate	See Annex A

The following variation type was requested:

Variation requested		**Type**
C.1.6 a)	Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for the extension of the indication for the treatment of HIV-1 infection in antiretroviral therapy (ART)-experienced adults who are virologically suppressed with no history of virologic failure based on clinical studies GS-US-264-0111 and GS-US-264-0106. Consequently, the MAH proposed the update of sections 4.1, 4.8, 5.1 and 5.2 of the SmPC.

The Package Leaflet was proposed to be updated in accordance. Furthermore, the MAH took the opportunity to perform correction of errors in the Package Leaflet (possible side effects section).

The requested variation proposed amendments to the SmPC and Package Leaflet.

The requested variation proposed amendments to the RMP.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0176/2012) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (EMEA-000774-PIP01-09-MO1) was not yet completed as all measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek scientific advice or Protocol assistance at the CHMP.

1.2. Steps taken for the assessment

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

Rapporteur: Barbara van Zwieten-Boot / Hans Hillege Co-Rapporteur: Bengt Ljungberg

Submission date:	9 January 2013
Start of procedure:	25 January 2013
CHMP Rapporteur's preliminary assessment report circulated on:	20 March 2013
CHMP Rapporteur/Co-Rapporteur updated joint assessment report circulated on:	18 April 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 April 2013
MAH's responses submitted to the CHMP on:	27 May 2013
PRAC advice on the RMP on:	16 May 2013
Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	8 July 2013
CHMP 2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	25 July 2013
MAH's responses submitted to the CHMP on:	23 Aug 2013
Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	4 Oct 2013
MAH's responses submitted to the CHMP on:	15 Oct 2013
CHMP member comments received on:	15 Oct 2013
Rapporteurs' assessment report on the MAH's responses circulated on:	18 Oct 2013
MAH's responses submitted to the CHMP on:	21 Oct 2013
Rapporteurs' final assessment report on the MAH's responses circulated on:	23 Oct 2013
CHMP Opinion	24 Oct 2013

2. Scientific discussion

2.1. Introduction

Product profile

Eviplera contains the active substances emtricitabine (FTC) 200 mg, rilpivirine (RPV) 25 mg, and tenofovir disoproxil (as fumarate) (TDF) 245 mg. In the European Union, Eviplera 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 (Commission Decision granted on 28 November 2011).

During the registration procedure questions were raised about the selection of the dose of RPV, which appeared to be motivated not by the most optimal efficacy but by fears of QT prolongation. The selected dose was sensitive to disruptions by non-adherence, concomitant use of PPIs and lack of concomitant food intake, which lowered plasma concentrations and subsequently antiretroviral activity. Also this dose appeared to be not optimal in patients with high baseline viral loads or low baseline CD4 counts. The latter number was too low to be evaluated properly. However, considering the non-inferior efficacy in comparison to comparator regimens in patients with baseline viral load ≤ 100,000 copies/ml, MA was granted.

The MAH proposed to extend the indication in Section 4.1 of the SmPC to include the use of Eviplera "for the treatment of HIV-1 in adult patients with virologic suppression to replace their current antiretroviral therapy." In order to expand this indication efficacy and safety data from 2 switch studies in virologically suppressed adult HIV patients were provided:

- GS-US-264-0106 (aka MEA009, patients receiving protease inhibitors) and
- GS-US-264-0111 (aka MEA010, patients receiving efavirenz).

During the first two rounds of assessment major objections were formulated relating to:

- The defined target population which was not recognized within the current regulatory thinking and the state of the art of the HIV therapeutics as shown in evolving EMA guidelines
- The reason for switch appeared to be tolerability of the previous regimen, suggesting a better tolerability with rilpivirine (RPV) which was not demonstrated. On the contrary, more patients discontinued upon switch to RPV from PI-based regimens.
- Determination of the optimal dose of RPV after switch from EFV (see below).

In addition, several other concerns were identified during the procedure and the CHMP took also into account the data and answers provided to post authorisation measures that were assessed in parallel.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the Committee.

2.2.1. Ecotoxicity/environmental risk assessment

No ERA was initially submitted in this application.

The Committee requested an ERA in the first RSI arguing that the extension of the indication might lead to an increase in use, and therefore environmental exposure of the product. In line with the guideline in environmental risk assessment EMEA/CHMP/SWP/4447/00, an ERA was considered warranted. The MAH was therefore requested to update the ERA for Eviplera, with regard to the increase in patient population.

The applicant submitted an updated ERA and presented recalculated F_{pen} and PEC values for rilpivirine, which the CHMP considered acceptable.

2.3. Clinical aspects

2.3.1. 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.

- Tabular overview of clinical studies

Type of Study	Study Identifier	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treat-ment	Study Status; Type of Report
Controlled Clinical Study Pertinent to the Claimed Indication	GS-US-264-0111 (Synopsis)	Primary Objective: Evaluate the efficacy of FTC/RPV/TDF STR after switching from EFV/FTC/TDF at baseline in maintaining HIV-1 RNA < 50 copies/ mL at Week 12 Secondary Objectives: Evaluate the safety and tolerability of FTC/RPV/TDF STR over 24 and 48 weeks Evaluate the efficacy of FTC/RPV/TDF STR after switching from EFV/FTC/TDF at baseline in maintaining HIV-1 RNA < 50 copies/ mL at Weeks 24 and 48 Explore the pharmacokinetics of RPV after switching from EFV	Phase 2b, open-label, multicenter, pilot study	FTC 200 mg/ RPV 25 mg/ TDF 300 mg STR administered orally with a meal once daily	49 (treated)	HIV-1 infected adults receiving a first ARV regimen consisting of EFV/FTC/TDF for ≥ 3 months prior to screening who decided on a change of regimen due to EFV intolerance. Subjects must have maintained plasma HIV-1 RNA at undetectable levels while on treatment for ≥ 8 weeks prior to screening.	48 weeks	Study complete Final CSR

Type of Study	Study Identifier	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treat-ment	Study Status; Type of Report
Controlled Clinical Study Pertinent to the Claimed Indication	GS-US-264-0106 (Synopsis)	Primary Objective: Evaluate the noninferiority of FTC/RPV/TDF STR relative to regimens consisting of a PI/r and 2 NRTIs in maintaining HIV-1 RNA < 50 copies/ mL at Week 24 Secondary Objectives: Evaluate the change from baseline in fasting lipid parameters over 24 and 48 weeks Evaluate the safety and tolerability of each treatment over 24 and 48 weeks Evaluate the change from baseline in CD4+ cell count in each treatment group at 24 and 48 weeks	Phase 3b, randomized, open-label, multicenter study	FTC/RPV/TDF: FTC 200 mg/ RPV 25 mg/ TDF 300 mg STR administered orally with a meal once daily for 48 weeks Delayed Switch: Baseline ARV drug regimen consisting of a PI/r and 2 NRTIs administered orally for 24 weeks (SBR group) followed by FTC 200 mg/ RPV 25 mg/ TDF 300 mg STR administered orally with a meal once daily for 24 weeks	FTC/RPV/TDF: 317 SBR (baseline ARV regimen for 1st 24 weeks): 159 Delayed Switch: 152	Adult HIV-1 infected subjects receiving ARV therapy consisting of a PI/r and 2 NRTIs, with undetectable HIV-1 RNA for ≥ 6 months prior to screening and HIV-1 RNA < 50 copies /mL at screening.	48 weeks [a]	48-week randomized treatment period complete Final CSR

2.3.2. Pharmacokinetics

No new pharmacokinetics data have been submitted in this application.

However, for the assessment of this variation 2 PAMs for the rilpivirine component are relevant and are presented below.

2.3.2.1. Optimal RPV dose after switch from EFV

As part of MEA007 (drug interaction study with efavirenz and 50 mg rilpivirine dose) also a study with 25 mg rilpivirine after switch from efavirenz in healthy volunteers (TMC278HIV1001) was submitted. After examination of the results questions were raised by the CHMP about the prolonged decrease of concentrations of RPV when administered as 25 mg qd due to induction of EFV of hepatic enzymes (CYP3A4).

The data submitted initially showed that combined antiviral concentrations of rilpivirine and efavirenz were still above the individual EC50 of RPV and EFV.

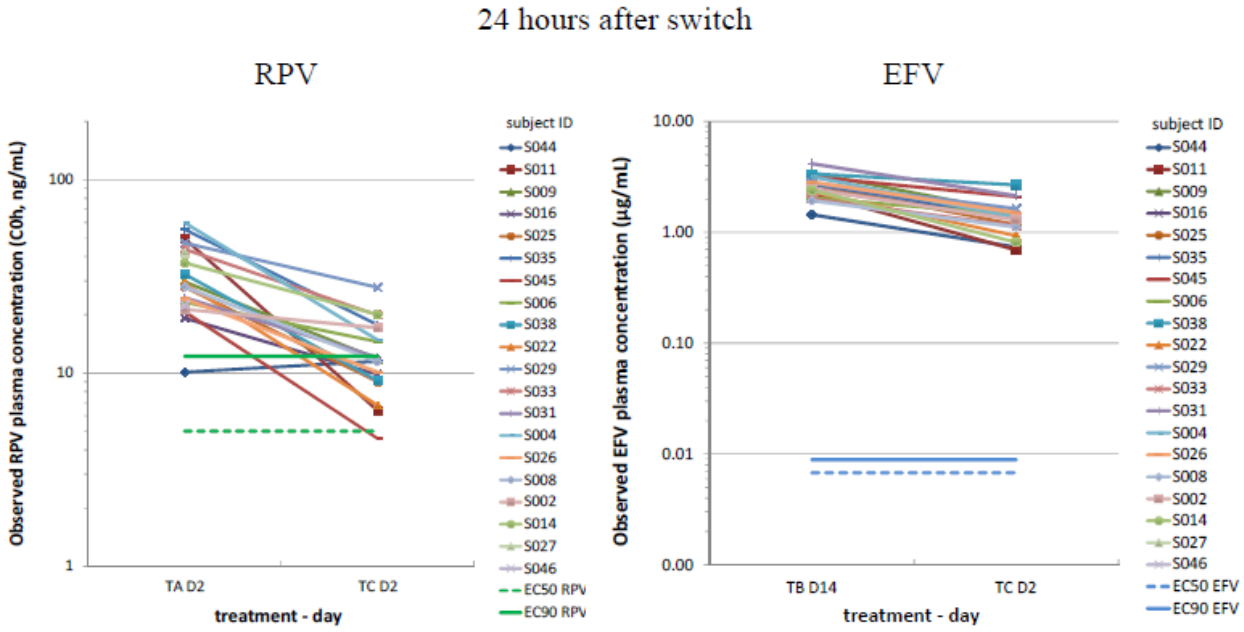
However, it remained unclear whether individual concentrations may have been decreased below the EC50 of each molecule. Therefore the CHMP requested to provide the concentrations of both EFV and RPV in relation to their respective EC50 and EC90.

As an alternative the MAH sent Figure A to Figure H, where the actual measured plasma concentrations of RPV and EFV measured by the LC/MS/MS assays were provided. The concentrations are depicted in relation to their respective plasma protein binding-adjusted EC50 and EC90 values[1]. Figure A to Figure F show, for all subjects and at the different time points, the RPV observed pre-dose plasma concentration (C0h) after the switch (Treatment C, TC) as compared to the corresponding time point in the absence of preceding EFV treatment (Treatment A, TA), and the observed plasma concentrations for EFV during Treatment C, with for each time point the last day of EFV intake as a reference (Day 14 Treatment B, TB D14). Figure G and Figure H show, for all subjects, the evolution of, respectively, the RPV and EFV observed plasma concentrations over time during Treatment C (i.e., after switch from EFV). In addition, Figure I shows scatterplots of the observed RPV and EFV plasma concentrations on the same graph (1 graph per time point). Table 1 shows the median (range) ratios of the RPV or EFV plasma concentration divided by the respective EC50 and EC90 value, for the different time points.

The scatterplots of these ratios, using EC50 and EC90, for RPV and EFV, for each subject on the same graph (1 graph per time point) are shown below. With regard to these ratios, it should be noted that the meaning of this relationship of *in vivo* concentrations with the in vitro potency (EC50 and EC90) is poorly understood for non-nucleoside reverse transcriptase inhibitors (NNRTIs). Several studies have shown that an efficacy margin predictive for virologic outcome cannot always be identified. Plasma exposure may also not be directly comparable to the in vitro potency, as additional factors may come into play in vivo, such as tissue distribution and intracellular accumulation of drug in infected cells.

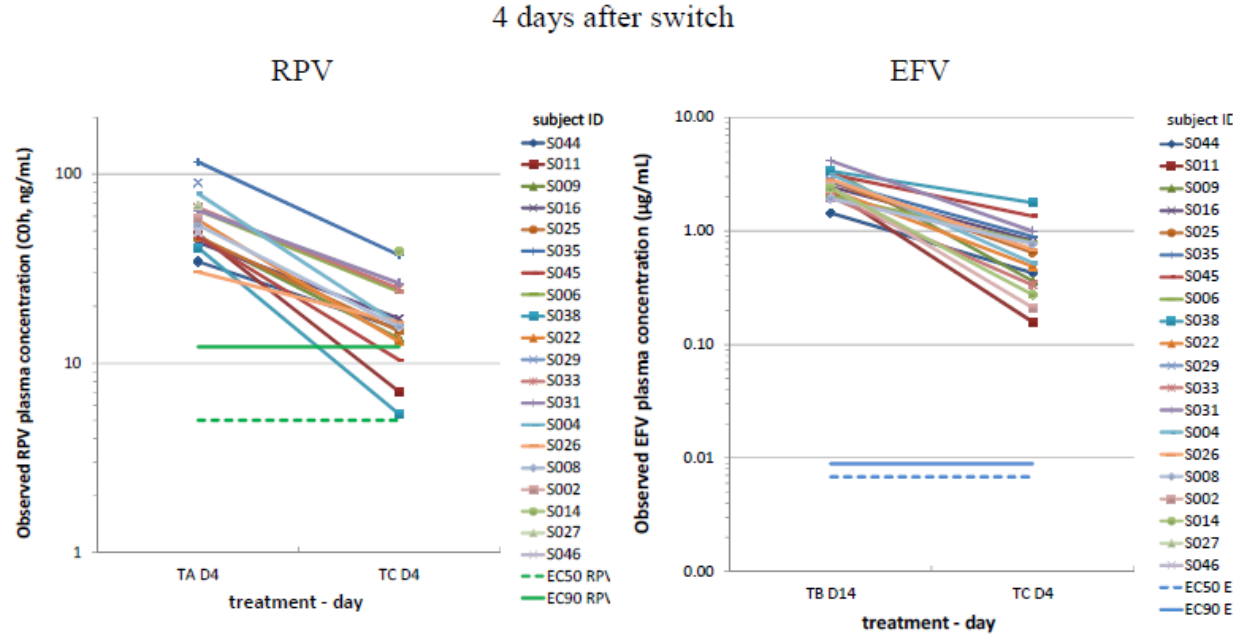
[1] The protein binding-adjusted RPV EC50 value is 5.0 ng/mL (obtained by adjusting the RPV EC50 value of 0.27 ng/mL with the functional protein binding effect in the presence of human serum which is 18.5-fold). Similarly, the adjusted RPV EC90 value is 12.2 ng/mL (0.66 ng/mL * 18.5). The protein binding-adjusted EFV EC50 value is 6.8 ng/mL (obtained by adjusting the EFV EC50 value of 0.55 ng/mL with the functional protein binding effect in the presence of human serum which is 12.3-fold). For EFV EC90, the reported value of 8.9 ng/mL was used.

Figure A: **Observed plasma concentrations of RPV (left) and EFV (right) 24 hours after switch from EFV versus before switch – with the addition of respective EC_{50} and EC_{90} values[2]**



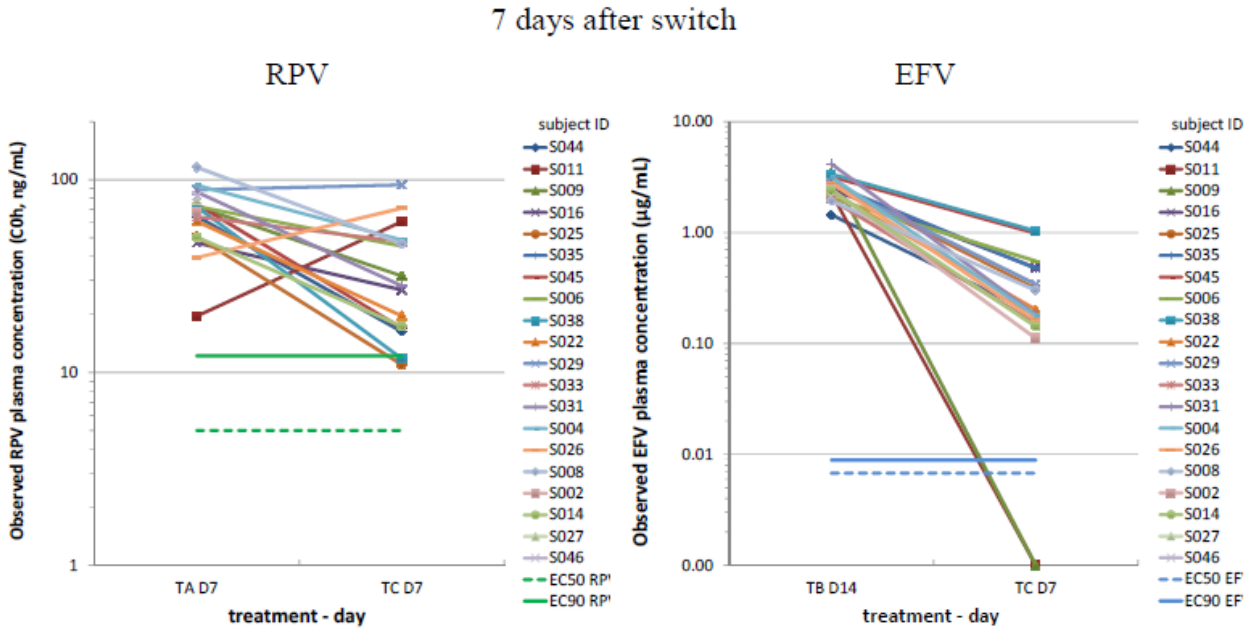
2 Note: plasma concentrations below the limit of detection (BQL) are depicted as 0.01xBQL for graphical purpose. TA: RPV 25 mg qd; TB: EFV 600 mg qd; TC: RPV 25 mg qd after EFV

Figure B: **Observed plasma concentrations of RPV (left) and EFV (right) 4 days after switch from EFV versus before switch – with the addition of respective EC_{50} and EC_{90} values[2]**



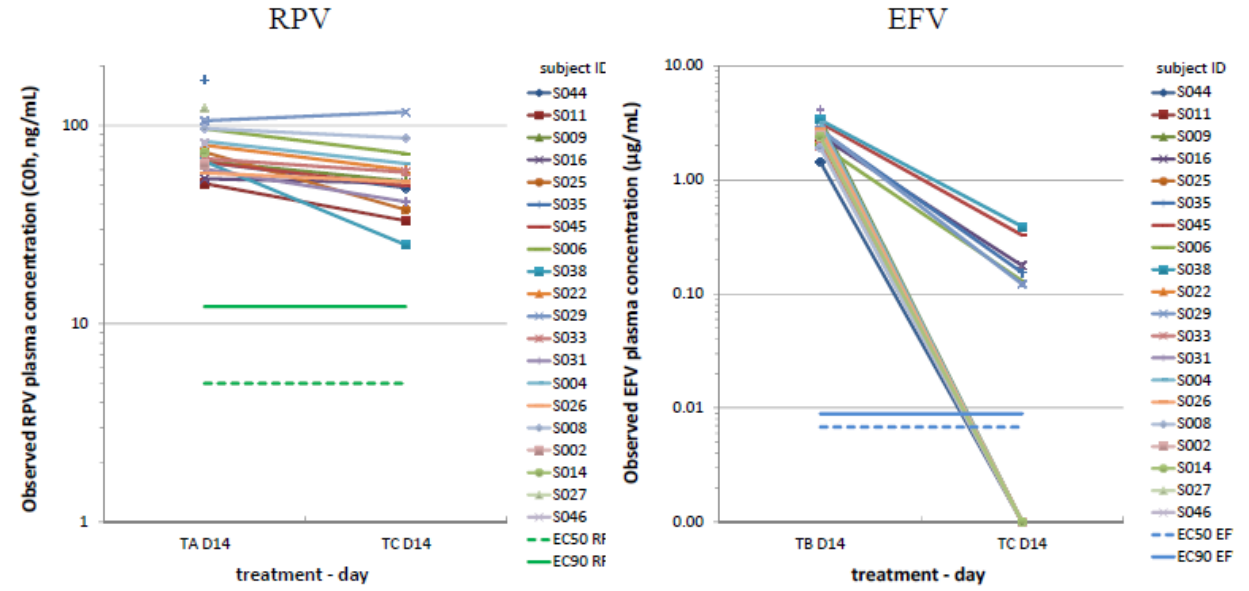
2 Note: plasma concentrations below the limit of detection (BQL) are depicted as 0.01xBQL for graphical purpose. TA: RPV 25 mg qd; TB: EFV 600 mg qd; TC: RPV 25 mg qd after EFV

Figure C: **Observed plasma concentrations of RPV (left) and EFV (right) 7 days after switch from EFV versus before switch – with the addition of respective EC_{50} and EC_{90} values[2]**



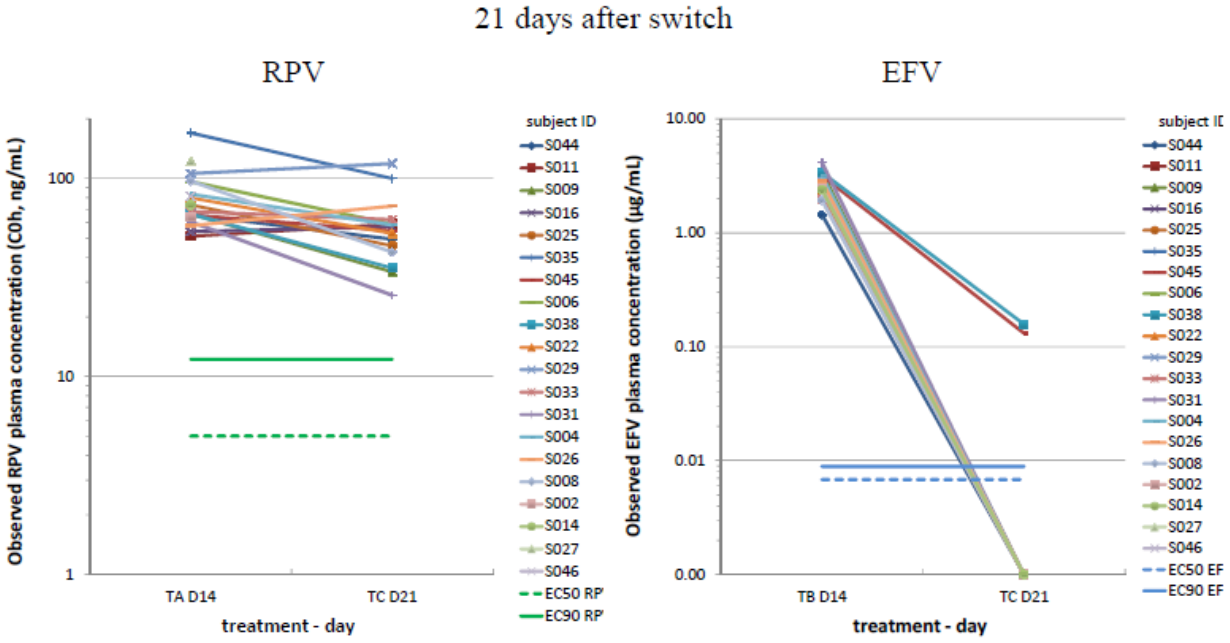
2 Note: plasma concentrations below the limit of detection (BQL) are depicted as 0.01xBQL for graphical purpose. TA: RPV 25 mg qd; TB: EFV 600 mg qd; TC: RPV 25 mg qd after EFV

Figure D: **Observed plasma concentrations of RPV (left) and EFV (right) 14 days after switch from EFV versus before switch – with the addition of respective EC_{50} and EC_{90} values[2]**



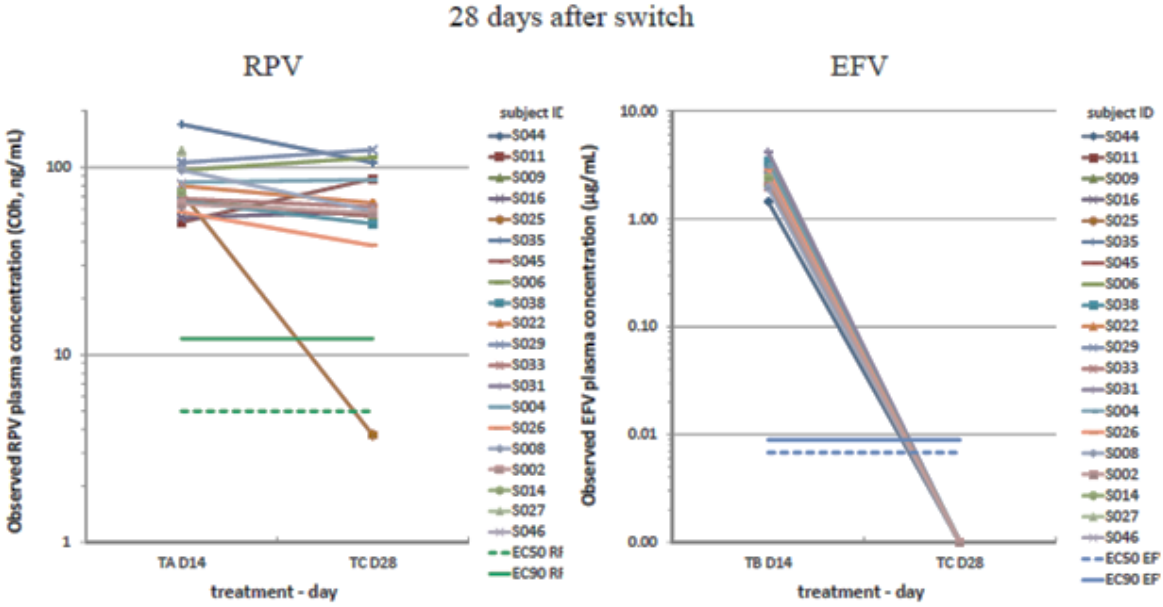
2 Note: plasma concentrations below the limit of detection (BQL) are depicted as 0.01xBQL for graphical purpose. TA: RPV 25 mg qd; TB: EFV 600 mg qd; TC: RPV 25 mg qd after EFV

Figure E: **Observed plasma concentrations of RPV (left) and EFV (right) 21 days after switch from EFV versus before switch – with the addition of respective EC_{50} and EC_{90} values[2]**



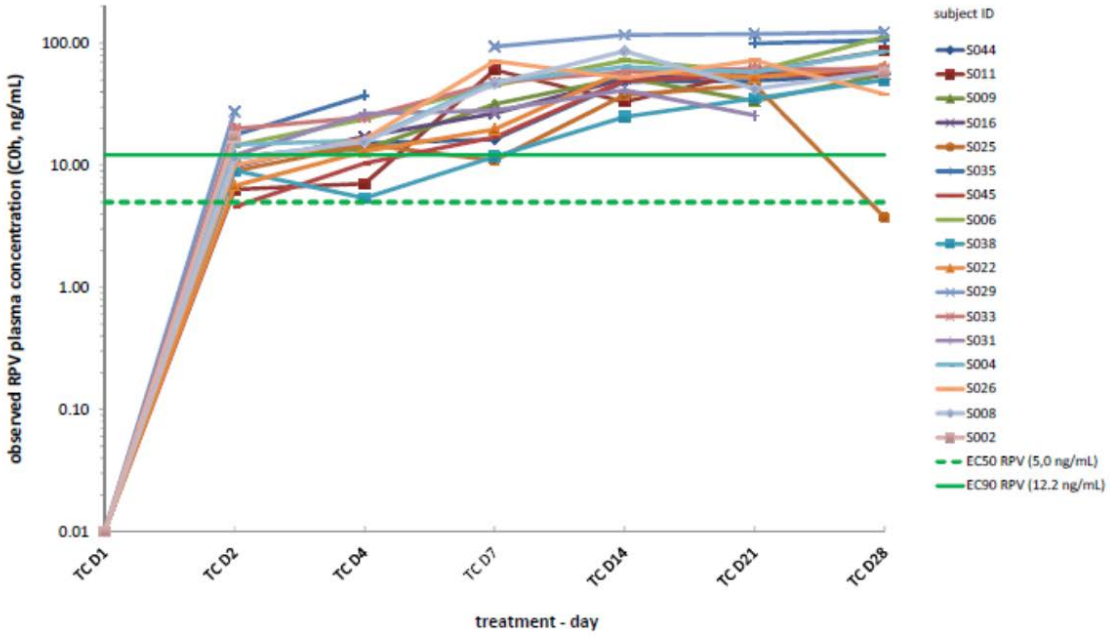
2 Note: plasma concentrations below the limit of detection (BQL) are depicted as 0.01xBQL for graphical purpose. TA: RPV 25 mg qd; TB: EFV 600 mg qd; TC: RPV 25 mg qd after EFV

Figure F: **Observed plasma concentrations of RPV (left) and EFV (right) 28 days after switch from EFV versus before switch – with the addition of respective EC_{50} and EC_{90} values[2]**



2 Note: plasma concentrations below the limit of detection (BQL) are depicted as 0.01xBQL for graphical purpose. TA: RPV 25 mg qd; TB: EFV 600 mg qd; TC: RPV 25 mg qd after EFV Note: The Treatment C Day 28 RPV plasma concentration for subject S025 is an outlier value, as previously described

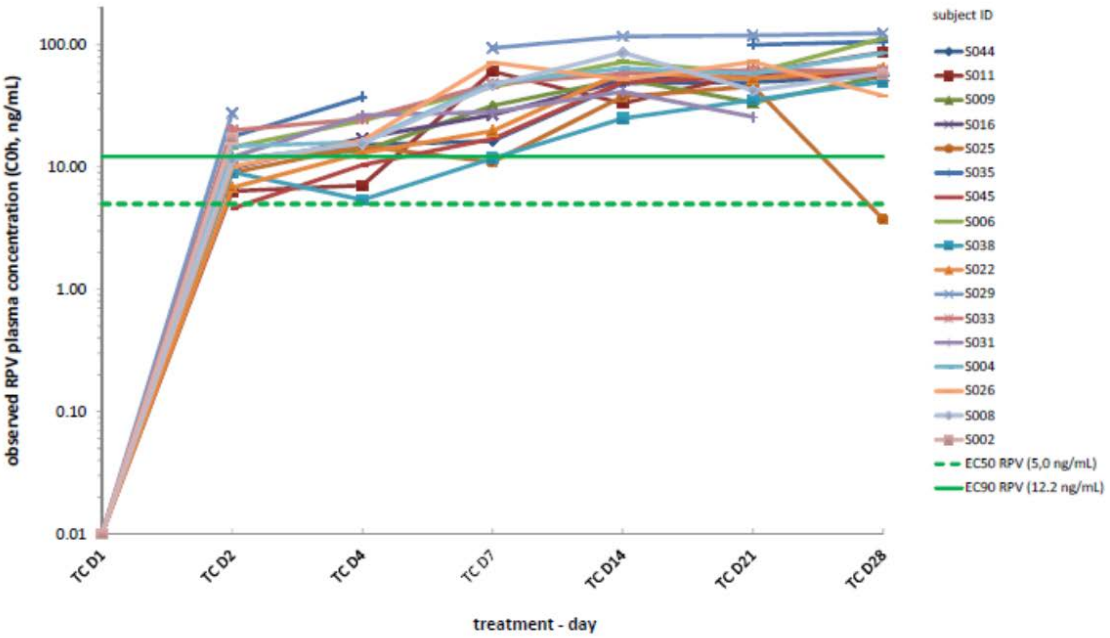
Figure G: **Observed plasma concentrations (C0h) of RPV over time after switch from EFV – with the addition of RPV EC_{50} and EC_{90} values[2]**



2 Note: plasma concentrations below the limit of detection (BQL) are depicted as 0.01xBQL for graphical purpose. TA: RPV 25 mg qd; TB: EFV 600 mg qd; TC: RPV 25 mg qd after EFV

Note: The Treatment C Day 28 RPV plasma concentration for subject is an outlier value, as previously described

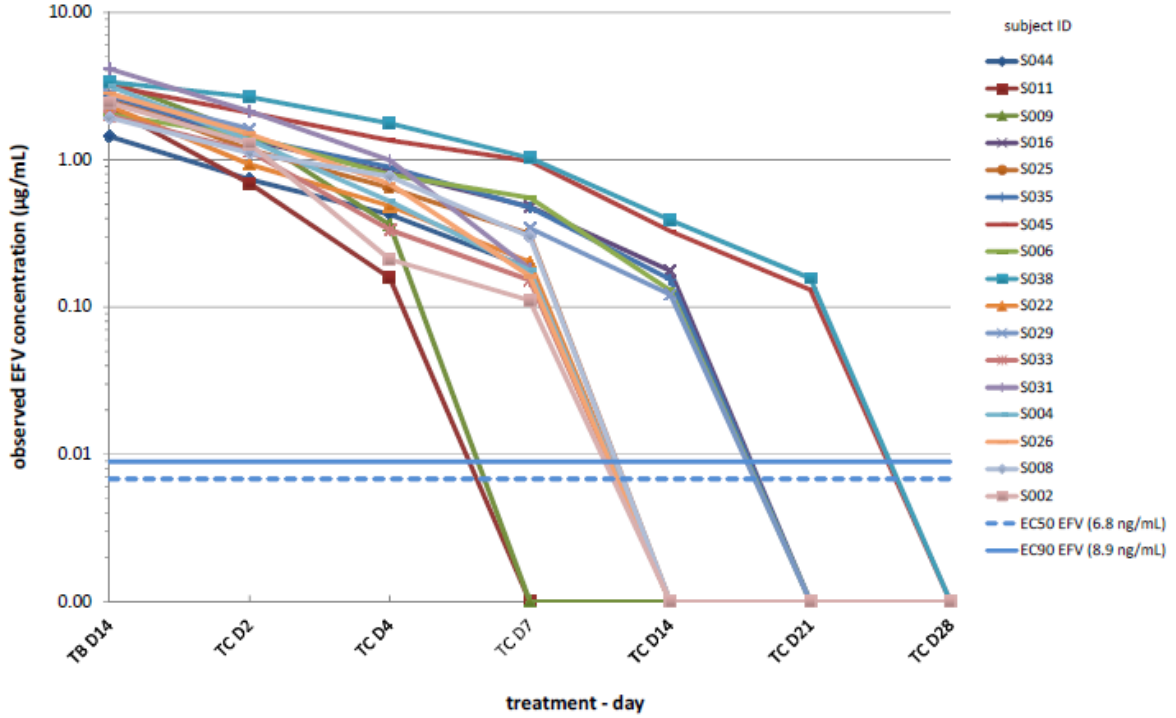
Figure G: **Observed plasma concentrations (C0h) of RPV over time after switch from EFV – with the addition of RPV EC_{50} and EC_{90} values[2]**



2 Note: plasma concentrations below the limit of detection (BQL) are depicted as 0.01xBQL for graphical purpose. TA: RPV 25 mg qd; TB: EFV 600 mg qd; TC: RPV 25 mg qd after EFV

Note: The Treatment C Day 28 RPV plasma concentration for subject S025 is an outlier value, as previously described

Figure H: Observed plasma concentrations of EFV over time after cessation of EFV intake – with the addition of EFV EC_{50} and EC_{90} values[2]



2 Note: plasma concentrations below the limit of detection (BQL) are depicted as 0.01xBQL for graphical purpose. TA: RPV 25 mg qd; TB: EFV 600 mg qd; TC: RPV 25 mg qd after EFV

Figure I: **Observed plasma concentrations of RPV (X-axis) and EFV (Y-axis) after switch from EFV, in relation to the respective EC_5 and EC_{90} values.**

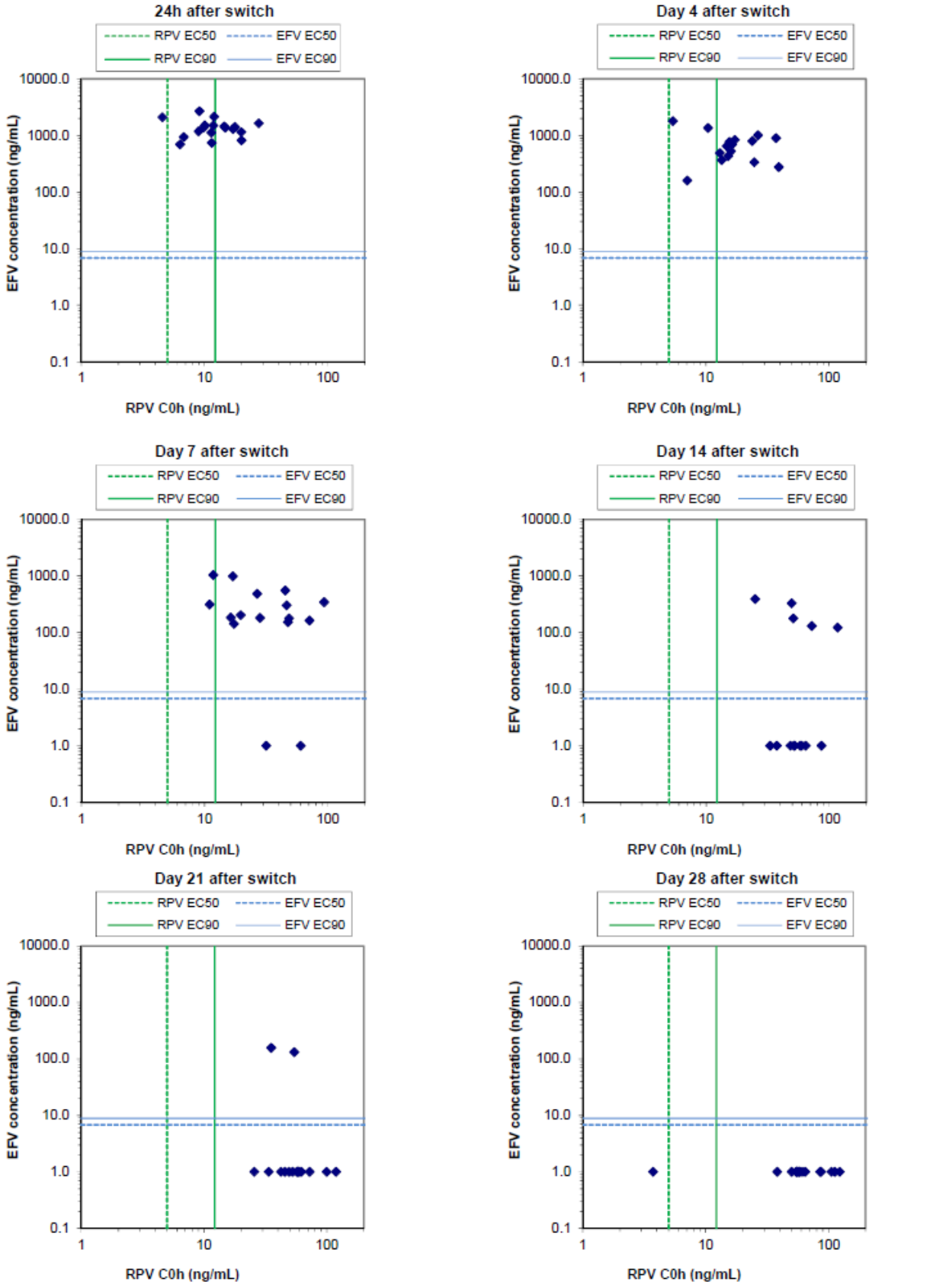


Table 1. Median (range) ratios of the RPV or EFV plasma concentration divided by the respective EC50 and EC 90 value, for the different timepoints after switch

Time Point after switch	plasma concentration/EC_{50}		plasma concentration/EC_{90}	
	EFV Median (Range)	RPV Median (Range)	EFV Median (Range)	RPV Median (Range)
24 hours	201 (102 – 393)	2.33 (0.91 – 5.54)	153 (78 – 300)	0.95 (0.37 – 2.27)
Day 4	95 (23 – 260)	3.16 (1.08 – 7.84)	73 (18 – 199)	1.30 (0.44 – 3.21)
Day 7	28 [a] (0 – 151)	5.99 (2.20 – 18.78)	22 [a] (0 – 116)	2.45 (0.90 – 7.70)
Day 14	0 [a] (0 – 57)	10.40 (5.00 – 23.40)	0 [a] (0 – 44)	4.26 (2.05 – 9.59)
Day 21	0 [a] (0 – 23)	11.13 (5.14 – 23.80)	0 [a] (0 – 18)	4.56 (2.11 – 9.75)
Day 28	0 [a] (0 – 0)	11.67 (7.66 – 24.80) [b]	0 [a] (0 – 0)	4.78 (3.14 – 10.16) [b]

a EFV plasma concentration BQL (and hence ratio = 0) for 2/18 subjects on Day 7, for 11/17 subjects on Day 14, for 16/18 subjects on Day 21 and for all subjects (17/17) on Day 28 after switch.

b Range excludes the outlier value on Day 28, which was 0.75 and 0.31 for EC_{50} and EC_{90}, respectively

According to the MAH, the data in the figures clearly demonstrated that as RPV is building up to steady-state after the switch from EFV, plasma concentrations are above the RPV EC50 as of 24 hours (17/18 subjects) to Day 4 (16/16) after the start of dosing, and continue to increase further above the EC50 thereafter. The values are also above the RPV EC90 for most subjects as of Day 4 (13/16) and Day 7 (14/16) and for all subjects as of Day 14 after the switch from EFV. EFV plasma concentrations start to decline after cessation of EFV intake, but remain well above the EFV EC50 and the EFV EC90 in all but two subjects until at least 7 days after cessation of EFV intake. At this time (Day 7 after switch), RPV plasma concentrations are well above the RPV EC90 in these two subjects. In Figure I, the lower left quadrant is always empty. There is only 1 subject (S025) with an observed RPV plasma concentration below the EC90 on Day 28 after the switch from EFV, which is the outlier. According to the RPV plasma concentration data observed for this subject on the days before and after Day 28, which are well above the EC50 as of 24 hours after the switch, this low value on Day 28 cannot be explained by prolonged cytochrome P450 (CYP) 3A induction by EFV.

2.3.2.2. RPV exposure and CD4+ cell count

Baseline viral load >100,000 copies/ml increase the rate of virologic failure in Rilpivirine compared to efavirenz. In addition low baseline CD4 counts seemed to influence outcome, but numbers were too small to determine a clear relationship. Whether lower CD4 counts also influence RPV exposures (C0h and AUC_{24h}) has been determined by the MAH upon request by the CHMP. Since RPV exposure is influenced by gastric uptake, i.e. acidity, a possible association between lower CD4 counts and poorer gastric acid production was postulated. In this context, it was questioned whether lower CD4+ cell counts, potentially associated with gastric hypoacidity, would influence RPV absorption (which is pH dependent).

Estimated RPV exposure as a function of CD4+ cell count

Using a population pharmacokinetic model, pharmacokinetic parameters (as measures of exposure to RPV) were derived from RPV concentrations in sparse plasma samples at pre-defined time points

during treatment. As a result, one value for each pharmacokinetic parameter was derived for each subject with pharmacokinetic samples during the treatment period.

The MAH has explored the correlation between CD4+ cell counts at baseline, at Week 48, and at Week 96 with pharmacokinetic parameter values. Note that for the figures (**Figure 1** and following) with CD4+ cell count at Week 48 and Week 96, the observed CD4+ values at these respective time points are used, and hence subjects who did not reach either time point are not included in the analysis for the concerned time point.

The MAH also conducted a multivariable analysis (ANCOVA using log10 transformed AUC24h) to explore the effect of baseline CD4+ on RPV exposure, while controlling for factors that are known to affect RPV exposure (i.e., race, gender, and adherence). The effect of baseline CD4+ cell count observed in this analysis was small, not statistically significant and not considered to be clinically relevant (for every 10 cell increase in CD4+ cell count, the RPV AUC24h increases 1.0016-fold; p=0.13).

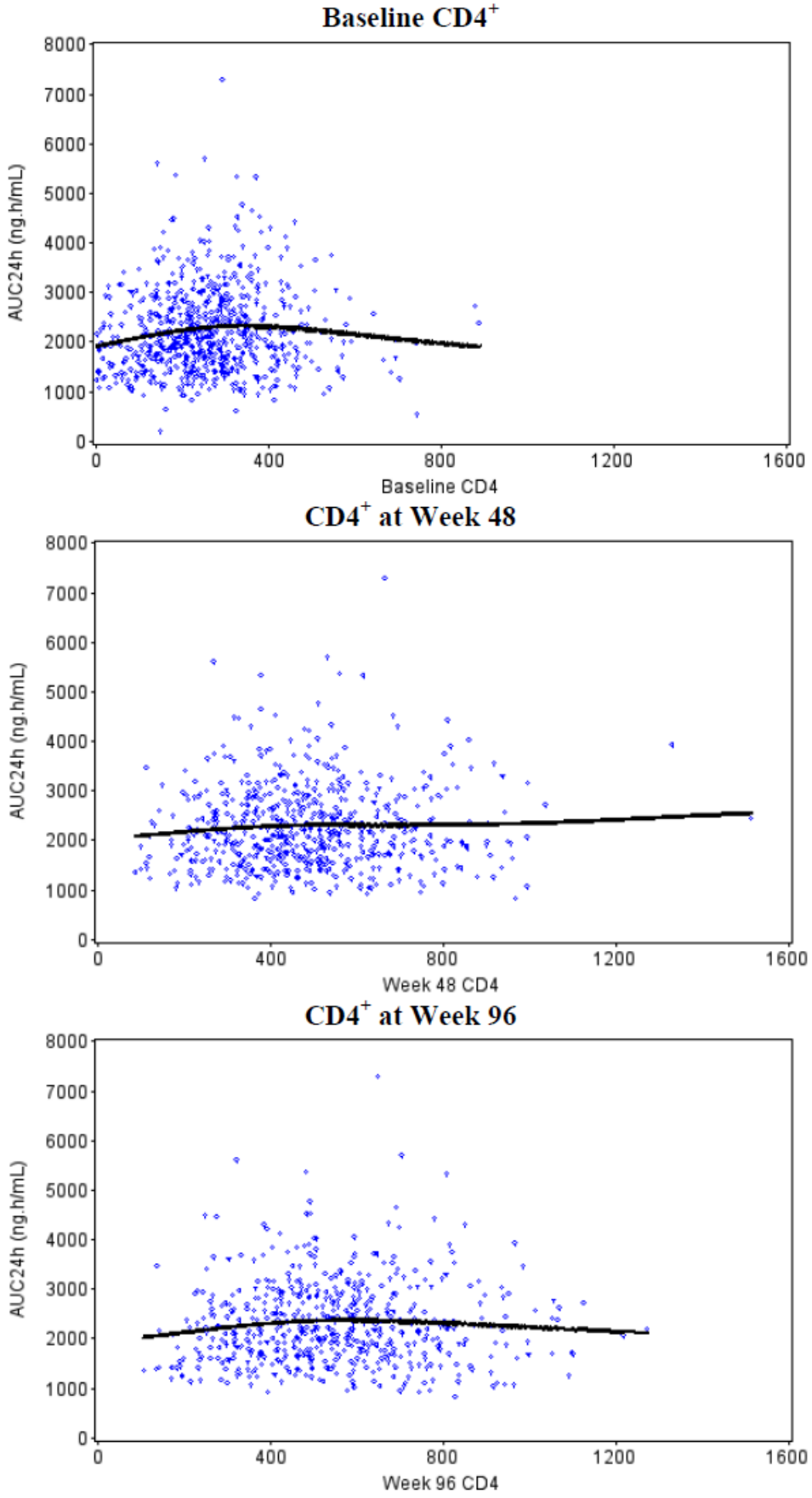


Figure 1 Scatter Plots of Estimated RPV Exposure (AUC24h) by CD4+ Cell Count Value at Baseline (top), week 48 (middle) and week 96 (bottom) – All subjects

The analysis was started from the non-virologic failure (non-VF) censored population in the Week 96 analysis (i.e., subjects who discontinued for reasons other than virologic failure were excluded).

In addition, for the virologic failures, only subjects with a primary virologic response (i.e., confirmed viral load <50 HIV-1 RNA copies/mL) but subsequent failure at any time during the study (i.e., rebounders) were retained, excluding the never suppressed subjects.

Figure 2 shows rebounders and responders (indicated in the figure as 'not VF') separately. No obvious relationship between AUC24h values and CD4+ cell count (at baseline, at Week 48, and at Week 96) could be observed, across the non-VF censored population (responders and rebounders) or specifically in the rebounders.

Figure 3 shows a scatter plot of AUC24h values for responders and rebounders by baseline viral load categories (i.e., ≤100,000 HIV-1 RNA copies/mL and >100,000 HIV-1 RNA copies/mL) and by CD4+ cell count categories (i.e., <200 cells/mL and ≥200 cells/mL). In both baseline viral load categories, the ranges of exposures observed were similar across the CD4+ cell count categories; this is true for the responders, as well as for the rebounders.

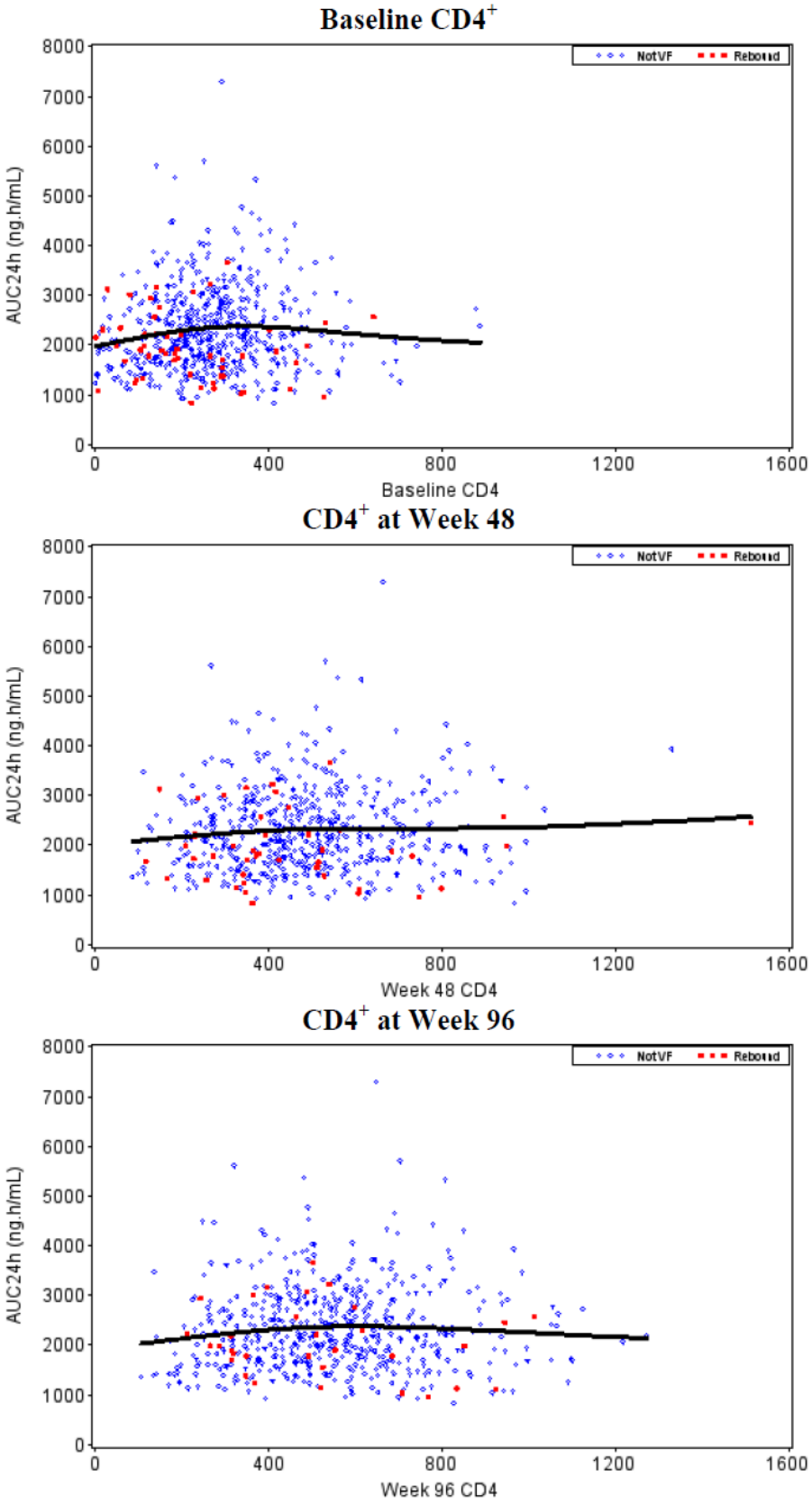
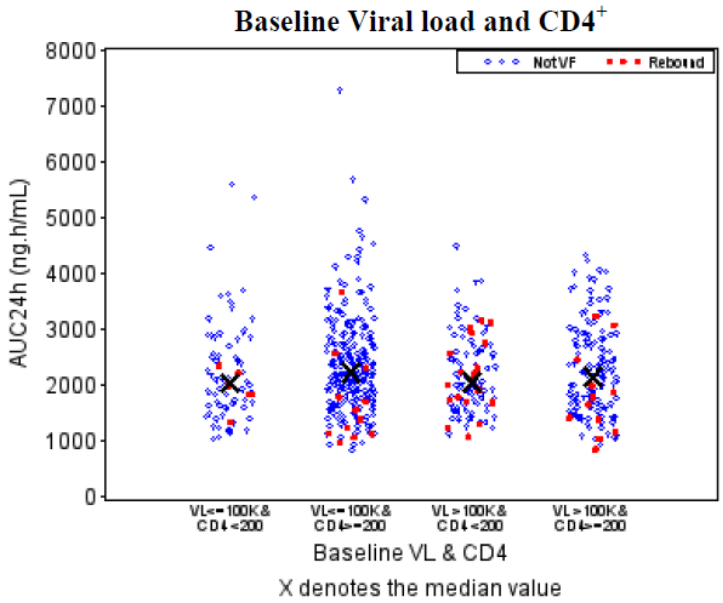


Figure 2 Scatter Plots of Estimated RPV Exposure (AUC24h) by CD4+ Cell Count Value at Baseline (top), week 48 (middle) and week 96 (bottom) – Non-VF Censored, Rebounders at Any Time Point

Figure 3 Scatter Plot of Estimated RPV Exposure (AUC24h) by Baseline Viral Load and CD4+ Cell Count Categories at Baseline– Non-VF Censored, Rebounders at Any Time Point



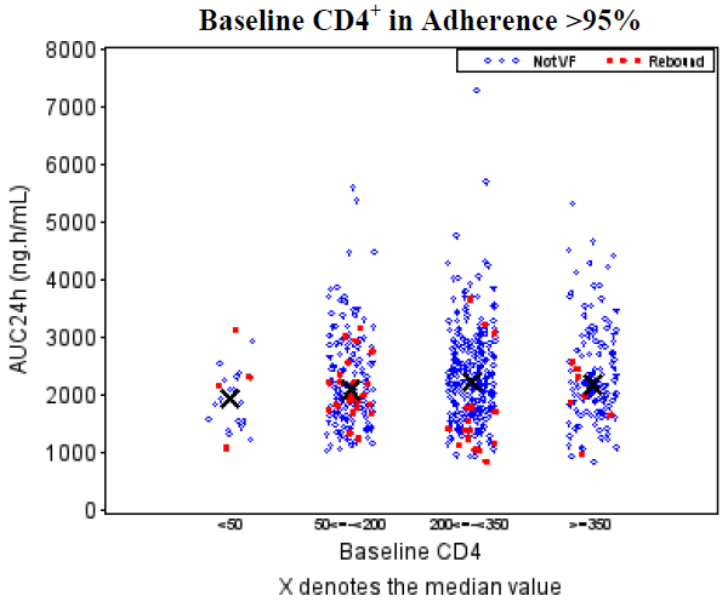


Figure 4 Scatter Plot of Estimated RPV Exposure (AUC24h) by CD4+ Cell Count Categories at Baseline in Subjects with Good Adherence (>95% [Investigator-Reported Compliance]) – Non-VF Censored, Rebounders at Any Time Point

Figure 4 presents these data in the adherent group of patients (i.e., >95% [investigator-reported compliance]). This latter graph shows that exposure is similar across the different CD4+ cell count categories (i.e., <50, ≥50-<200, ≥200-<350, ≥350 cells/mL).

A multivariable analysis looking at the effect on exposure for the rebounders only, also indicated that the baseline CD4+ cell count did not affect RPV exposure (p=0.22).

Patients failing virologically between Week 48 and Week 96

The analysis was started from the non-VF censored population in the Week 96 analysis. In addition, for the virologic failures, only subjects with a primary virologic response but subsequent failure between Week 48 and Week 96 (i.e., late rebounders) were retained.
Figure 5 shows scatter plots of AUC_{24h} by CD4+ cell count at baseline, at Week 48, and at Week 96 for late rebounders and responders separately. From this graph it appears that RPV exposure is not correlated with CD4+ cell count across the non-VF censored population or specifically in the late rebounders.

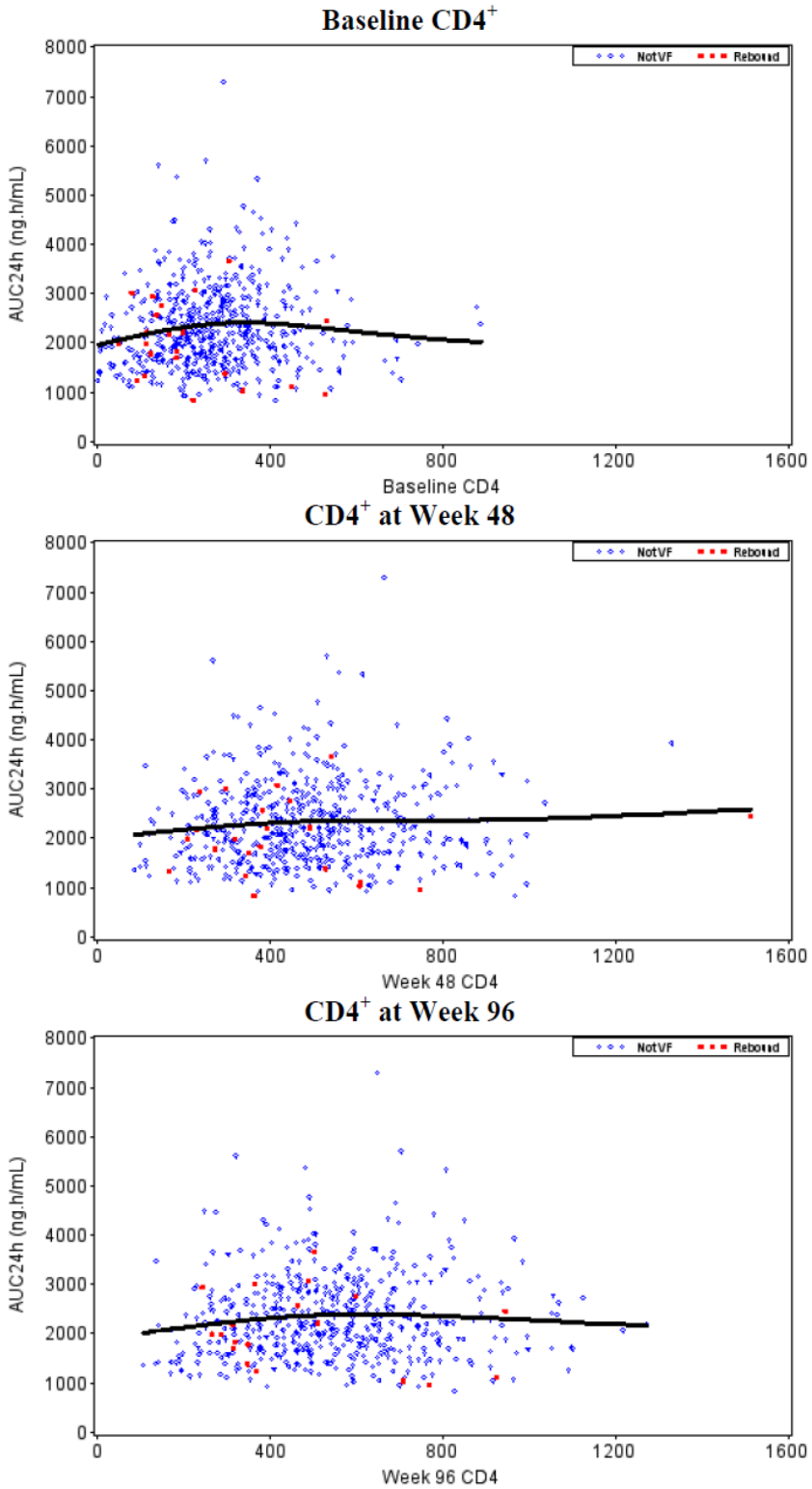


Figure 5 Scatter Plots of Estimated RPV Exposure (AUC24h) by CD4+ Cell Count Value at Baseline (top), week 48 (middle) and week 96 (bottom) – Non-VF Censored, Late Rebounders

2.3.3. Discussion on clinical pharmacology

RPV dose after switching from EFV

After the switch from EV, the RPV concentrations are initially low. Due to the decline in EFV plasma levels, the inductive effect decreases and RPV concentrations starts to normalize. As a result, and as shown by the MAH in figures A – H, at day 4 after switching from EFV to RPV, RPV concentrations are all above EC50 and at day 14 all above the EC90. This continues till day 28 (and expected to be thereafter). At day 28 one subject had RPV concentrations below EC50; however, this observation is considered an outlier, because concentrations for this subject were above EC50 before day 28.

For EFV, up to day 4, all EFV concentrations were above EC90. At day 7, 2 subjects had concentrations below EC90, and this number increases, as expected over the following weeks.

The most important observation from these data is that during the time period of declining EFV plasma levels and increasing RPV plasma levels, during the 28 day period after switching, none of the subjects had EFV neither RPV plasma levels below their respective EC90 levels at the same time.

In NNRTIs EC90 levels and required therapeutic drug levels used for TDM do not coincide, for example therapeutic range of EFV is 1-4 ug/ml that is much higher than the EC90 (figure H). Effectively, only the interval from day 2 to day 7 after switch may have sub-therapeutic drug concentrations of the combined NNRTIs, since EFV is below the therapeutic range (but still above the EC90) and RPV has not even achieved its EC90. A period of less than 7 days which has been accepted even for functional monotherapy studies in HIV infected individuals with detectable viral load. In the subjects in this switch study, therapeutic drug concentrations of the backbone ARVs (TDF+FTC) in virally suppressed individuals will give additional viral suppression. This provides assurance that efficacy is likely not to be affected after switching.

RPV exposure and CD4+ cell count

The scatter plots provided by the MAH do not indicate a clear relationship between CD4+ counts and RPV exposure at baseline, week 48 or week 96 and AUC_{24h}.

The conclusion therefore is that in all subjects, regardless of CD4 count, low C0h and AUC_{24h} can occur.

The analytical results also indicate that for successfully suppressed patients at week 48 and 96, compared to rebounders no apparent relationship between RPV exposures and CD4 count is apparent.

However, the distribution of data points both of lower values of AUC_{24} h and of C0h seems to occur among all CD4 counts. As a consequence, in rebounders no relationship between CD4 count and RPV exposure can be established.

Similarly, baseline Viral Load or Adherence >95% did not show a clear relationship between the different strata baseline CD4 and RPV exposures.

The CHMP concluded that patients with low CD4 count are not more prone to low exposures, also not in patients who fail while on treatment (i.e. rebounders).

Considering the spread of data points of the 2 subgroups over all values of CD4 counts, no relationship can be seen for patients failing virologically between Week 48 and Week 96.

In late rebounders after week 48 lower RPV exposures could be found in patients with both high and low CD4 cell counts, and as such this seems not to make an impact.

2.3.4. Conclusions on clinical pharmacology

RPV dose after switching from EFV

The MAH submitted the requested data on concentrations of EFV en RPV in relation to the EC50 and EC90 values and these data confirm that during all days after switch the EC90 values of either drug are reached and that sub-therapeutic drug concentrations will be present during a period of < 1 week which is unlikely to influence viral suppression.

RPV exposure and CD4+ cell count

CD4 count did not seem to influence RPV exposure (both AUC24h and C0h) in all subjects, in subjects with both low CD4 count and low baseline viral load, in subjects with good adherence, in rebounders and in late rebounders, and therefore the hypothesis that patients with low CD4 cell count might have considerably lower rilpivirine exposure due to gastric hypoacidity is not supported by the available data.

The initial assessment already demonstrated that individuals with low CD4 count experienced higher virologic failure rates.

From these provided data at 3 time points it cannot be derived that lower RPV exposure contributed to higher failure rates in this subgroup.

No outstanding issues remain for the clinical pharmacology regarding the requested extension of the indication.

2.4. Clinical efficacy aspects

Two new clinical studies in virologically suppressed adult HIV patients have been submitted in this application, both to support the extension of the indication.

- **GS-US-264-0106** (A Phase 3 Randomized, Open-Label Study to Evaluate Switching from Regimens Consisting of a Ritonavir-boosted Protease Inhibitor and Two Nucleoside Reverse Transcriptase Inhibitors to Emtricitabine/Rilpivirine/ Tenofovir Disoproxil Fumarate (FTC/RPV/TDF) Fixed-dose Regimen in Virologically-Suppressed, HIV-1 Infected Patients).
- **GS-US-264-0111** (A Phase 2B Open Label Pilot Study to Evaluate Switching From a Regimen Consisting of a Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF) Single Tablet Regimen (STR) to Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate (FTC/RPV/TDF) STR in Virologically Suppressed, HIV 1 Infected Subjects).

2.5. Main studies

GS-US-264-0106: switch to 25 mg Eviplera (FTC/RPV/TDF) after PI-based regimen in HIV-infected patients ("PI switchers")

Methods

Study design

In this randomized, open-label, multicentre study during 48 weeks in total 476 virologically suppressed patients were randomized in a 2:1 ratio to the following groups:

- FTC/RPV/TDF: Switch to FTC 200 mg/RPV 25 mg/TDF 300 mg STR

- SBR: Delayed switch to FTC/RPV/TDF STR after remaining on current antiretroviral (ARV) regimen consisting of a PI/r and 2 NRTIs for the first 24 weeks after baseline followed by 24 weeks of FTC/RPV/TDF.

Inclusion criteria

Subjects of ≥ 18 years with life expectancy of ≥ 1 year that could be included,

- Were currently receiving ARV therapy with a PI/r and 2 NRTIs continuously for ≥ 6 months preceding the screening visit
- Had plasma HIV-1 RNA concentrations (at least 2 measurements) at undetectable levels for ≥ 6 months prior to the screening visit and had HIV RNA < 50 copies/mL at the screening visit
- Were on their first or second ARV drug regimen; if on their second regimen, the subject could not have had HIV-1 RNA > 50 copies/mL at the time of the change in ARV drugs, nor ever have had 2 consecutive HIV-1 RNA results ≥ 50 copies/mL after first achieving HIV RNA < 50 copies/mL
- Had not previously used any approved or experimental NNRTI drug for any length of time
- Had a genotype determination prior to starting initial ARV therapy and had no known resistance to any of the study agents at any time in the past including, but not limited to the reverse transcriptase (RT) resistance mutations K65R, K101E/P, E138G/K/R/Q, Y181C/I/V, M184V/I, or H221Y
- Had normal electrocardiogram (ECG) results (or if abnormal, determined by the investigator to be not clinically significant)
- Had hepatic transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) ≤ 5 × the upper limit of the normal range (ULN)
- Had total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin
- Had adequate hematologic function (absolute neutrophil count ≥ 1000/mm3, platelets ≥ 50,000/mm3; and haemoglobin ≥ 8.5 g/dL)
- Had serum amylase ≤ 5 × ULN (subjects with serum amylase > 5 × ULN were eligible if serum lipase was ≤ 5 × ULN)
- Had adequate renal function: eGFR ≥ 70 mL/min
- Used adequate contraceptive methods

Exclusion criteria:

- Had a new acquired immunodeficiency syndrome (AIDS)-defining condition diagnosed within the 30 days prior to screening
- Was a female currently breastfeeding or a female with positive serum pregnancy test
- Had proven or suspected acute hepatitis in the 30 days prior to study entry
- Had current alcohol/substance abuse that could potentially interfere with compliance
- Had a history of malignancy within the past 5 years (prior to screening) or on-going malignancy other than cutaneous Kaposi sarcoma (KS), basal cell carcinoma, or resected,
- noninvasive cutaneous squamous carcinoma.

- Had active, serious infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days prior to study baseline
- Were anticipated to need to initiate drugs during the study that were contraindicated including drugs not to be used with FTC, TDF, RPV or subjects with known allergies
- Had been treated with immunosuppressant therapies or chemotherapeutic agents within 3 months of study screening, or was expected to receive these agents or systemic steroids during the study (eg, corticosteroids, immunoglobulins, and other immune- or cytokine-based therapies)
- Had a history of liver disease, including Gilbert disease

Sample Size and Power

A total of 420 subjects were planned to be randomized in a 2:1 ratio to 1 of 2 treatment groups. With 280 subjects randomized to switch to the FTC/RPV/TDF STR on Day 1 and 140 subjects randomized to the SBR group, with a non-inferiority margin of 12%) and > 95% power when the proportion of responders in both treatment groups for the primary endpoint was 90% at Week 24 (the 90% estimate is based on data from Study GSUS-177-0107).

Outcomes/Endpoints

The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA < 50 copies/mL at week 24, and was analysed using the (US FDA) snapshot algorithm.

Statistical Methods

Non-inferiority: it was to be concluded that the FTC/RPV/TDF STR group was not inferior to the SBR group if the lower bound of the 2-sided 95% CI of the difference (FTC/RPV/TDF STR – SBR) in the response rate was greater than −12%.

The secondary objectives of this study were as follows:

- To evaluate the change from baseline in fasting lipid parameters (total cholesterol, low-density lipoprotein [LDL] and high-density lipoprotein [HDL] cholesterol, and triglycerides) over 24 and 48 weeks
- To evaluate the safety and tolerability of each treatment over 24 and 48 weeks
- To evaluate the change from baseline in CD4+ cell count in each treatment group at 24 and 48 weeks

Results

Recruitment

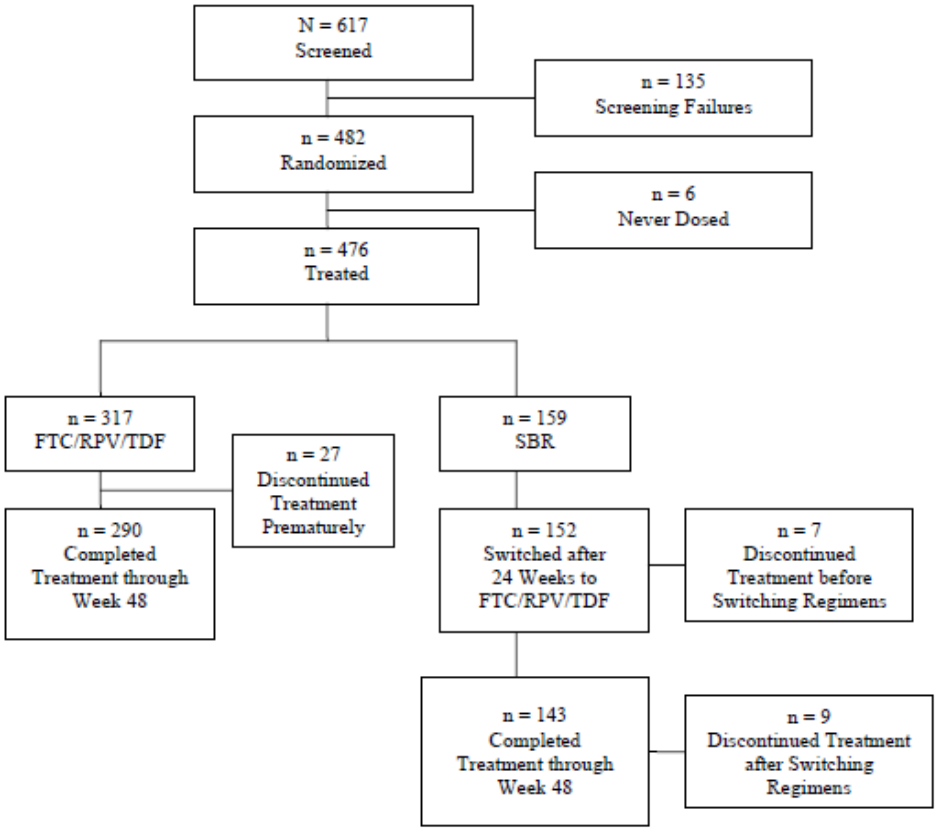
The study was overenrolled in the last days of screening:

- for the FTC/RPV/TDF group, 317 subjects were treated with study drug, 290 subjects completed 48 weeks of study drug treatment, and 294 completed 48 weeks of the study.
- for the SBR group, 159 subjects were treated with their baseline regimen and 152 switched to FTC/RPV/TDF at Week 24; 143 subjects completed 48 weeks of treatment, and 146 subjects completed 48 weeks of the study.

Enrolment took place in 110 enrolling sites in Austria, Belgium, Canada, France, Germany, Italy, Puerto Rico, Spain, United Kingdom, and United States.

Participant flow

Figure 6 Disposition of Subjects in study GS-US-264-0106



Discontinuations

Table 2. GS-US-264-0106: Reasons for Discontinuation of Study Drug or Discontinuation from the Study by Week 48 (Safety Analysis Set)

Discontinuation Reasons	FTC/RPV/TDF (N = 317)	SBR[a] (N = 159)	Delayed Switch to RPV/FTC/TDF (N = 152)	Total RPV/FTC/TDF (N = 469)
Reasons for Discontinuation of Study Drug by Week 48				
Adverse Event	7 (2.2%)	0	5 (3.3%)	12 (2.6%)
Lack of Efficacy	2 (0.6%)	0	1 (0.7%)	3 (0.6%)
Investigator's Discretion	1 (0.3%)	1 (0.6%)	0	1 (0.2%)
Withdrawal by Subject	6 (1.9%)	3 (1.9%)	2 (1.3%)	8 (1.7%)
Lost to Follow-up	6 (1.9%)	1 (0.6%)	0	6 (1.3%)
Subject Noncompliance	1 (0.3%)	1 (0.6%)	0	1 (0.2%)
Protocol Violation	4 (1.3%)	1 (0.6%)	1 (0.7%)	5 (1.1%)

Baseline characteristics

The following table summarizes these characteristics and the most common reason that subjects enrolled in this study was the desire to simplify their current ARV regimen (88.2%).

Table 3. GS-US-264-0106: Key Demographic and Baseline Characteristics (Safety Analysis Set)

Demographics and Baseline Characteristics	FTC/RPV/TDF (N=317)	SBR (N=159)	Total (N=476)
CD4+ (cells/μL)			
N	317	159	476
Mean (SD)	576 (236.6)	600 (258.8)	584 (244.2)
Median	554	561	558
Q1, Q3	412, 713	401, 744	409, 727
Min, Max	42, 1484	50, 1423	42, 1484
CD4+ Categories (cells/μL)			
≤ 50	1 (0.3%)	1 (0.6%)	2 (0.4%)
51 to ≤ 200	14 (4.4%)	6 (3.8%)	20 (4.2%)
201 to ≤ 350	31 (9.8%)	15 (9.4%)	46 (9.7%)
351 to ≤500	88 (27.8%)	37 (23.3%)	125 (26.3%)
> 500	183 (57.7%)	100 (62.9%)	283 (59.5%)
Creatinine Clearance - Cockcroft-Gault (mL/min) (using observed weight)[b]			
N	317	159	476
Mean (SD)	109.5 (28.38)	108.6 (29.94)	109.2 (28.88)
Median	104.2	103.8	104.1
Q1, Q3	90.0, 123.2	88.9, 124.3	89.8, 123.7
Min, Max	56.3, 224.1	50.2, 250.9	50.2, 250.9
Stratification (based on ARV use data from CRF)			
Either TDF or Fixed Dose FTC/TDF + LPV/r	82 (25.9%)	49 (30.8%)	131 (27.5%)
Either TDF or Fixed Dose FTC/TDF + Other PI/r	178 (56.2%)	81 (50.9%)	259 (54.4%)
Non-TDF Containing Regimen + LPV/r	15 (4.7%)	9 (5.7%)	24 (5.0%)
Non-TDF Containing Regimen + Other PI/r	42 (13.2%)	20 (12.6%)	62 (13.0%)
Hepatitis B Infection Status at Screening			
Positive	4 (1.3%)	4 (2.5%)	8 (1.7%)
Negative	313 (98.7%)	155 (97.5%)	468 (98.3%)
Hepatitis C Infection Status at Screening			
Positive	14 (4.4%)	7 (4.4%)	21 (4.4%)
Negative	303 (95.6%)	152 (95.6%)	455 (95.6%)
Lipid-Modifying Agent Use at Baseline			
Yes	37 (11.7%)	29 (18.2%)	66 (13.9%)
No	280 (88.3%)	130 (81.8%)	410 (86.1%)
Time Since First Antiretroviral Medication (Years)			
N	317	159	476
Mean (SD)	3.4 (2.25)	3.3 (2.20)	3.3 (2.24)
Median	2.9	2.6	2.8
Q1, Q3	1.9, 4.4	1.7, 4.8	1.8, 4.5
Min, Max	0.5, 21.6	0.4, 16.0	0.4, 21.6
Enrollment Survey (Reasons Subject Enrolled in Study)			
Desire to simplify current anti-HIV regimen	284 (89.6%)	136 (85.5%)	420 (88.2%)
Not tolerating current regimen well because of side effects	27 (8.5%)	17 (10.7%)	44 (9.2%)
Concerned about the long-term side effects of current anti-HIV regimen	44 (13.9%)	34 (21.4%)	78 (16.4%)
Having trouble taking current regimen on a regular basis	21 (6.6%)	7 (4.4%)	28 (5.9%)

(Continued) GS-US-264-0106: Key Demographic and Baseline Characteristics (Safety Analysis Set)

Demographics and Baseline Characteristics	FTC/RPV/TDF (N=317)	SBR (N=159)	Total (N=476)
Age (Years)			
N	317	159	476
Mean (SD)	41 (9.2)	43 (9.7)	42 (9.4)
Median	42	43	42
Q1, Q3	35, 48	36, 49	35, 48
Min, Max	19, 73	20, 71	19, 73
Sex			
Male	273 (86.1%)	144 (90.6%)	417 (87.6%)
Female	44 (13.9%)	15 (9.4%)	59 (12.4%)
Race			
White	241 (76.0%)	124 (78.0%)	365 (76.7%)
Black or African American	61 (19.2%)	22 (13.8%)	83 (17.4%)
American Indian or Alaska Native	3 (0.9%)	2 (1.3%)	5 (1.1%)
Asian	6 (1.9%)	2 (1.3%)	8 (1.7%)
Native Hawaiian or Pacific Islander	0	0	0
Other	6 (1.9%)	9 (5.7%)	15 (3.2%)
Ethnicity			
Hispanic or Latino	51 (16.1%)	31 (19.5%)	82 (17.2%)
Not Hispanic or Latino	264 (83.3%)	128 (80.5%)	392 (82.4%)
Not Permitted	2 (0.6%)	0	2 (0.4%)
Body Mass Index (kg/m^2)*			
N	316	159	475
Mean (SD)	25.8 (4.88)	26.2 (5.65)	25.9 (5.15)
Median	25.2	25.1	25.1
Q1, Q3	22.2, 27.7	22.9, 28.5	22.5, 27.9
Min, Max	17.3, 53.7	17.3, 66.3	17.3, 66.3
Screening HIV-1 RNA Category			
< 50 copies/mL	317 (100.0%)	159 (100.0%)	476 (100.0%)
50 to < 200 copies/mL	0	0	0
200 to < 400 copies/mL	0	0	0
400 to < 1000 copies/mL	0	0	0
≥ 1000 copies/mL	0	0	0
Baseline HIV-1 RNA Category			
< 50 copies/mL	299 (94.3%)	152 (95.6%)	451 (94.7%)
50 to < 200 copies/mL	10 (3.2%)	6 (3.8%)	16 (3.4%)
200 to < 400 copies/mL	2 (0.6%)	0	2 (0.4%)
400 to < 1000 copies/mL	2 (0.6%)	0	2 (0.4%)
≥ 1000 copies/mL	4 (1.3%)	1 (0.6%)	5 (1.1%)

Patients were mostly white males in their 40s, with HIV viral load <50 copies/ml at screening, but in the window phase until treatment initiation 25 subjects had increased viral loads, including 7 with loads>400 copies/mL.

Most patients had been treated for several years; mean 3.3 years, from which at least in the last months with a protease inhibitor. However, some patients had been treated only shortly, since a minimum of 0.4 year was reported and 4.7% and 4.4% had baseline CD4 < 200 in the FTC/RPV/TDF group and SBR group, respectively.

Current treatment: NRTIs

The majority of subjects were receiving FTC/TDF (Truvada) at screening (80.4% in the FTC/RPV/TDF group and 81.8% in the SBR group). Approximately 13% of subjects in both groups were receiving abacavir + lamivudine (Kivexa/Epzicom) at screening.

Current treatment: Protease inhibitors

Protease inhibitors taken at screening included the following:

- ritonavir (68.8% in the FTC/RPV/TDF group and 62.9% in the SBR group),
- atazanavir (38.5% in the FTC/RPV/TDF group and 34.0% in the SBR group),

- lopinavir + ritonavir (Kaletra; 30.6% in the FTC/RPV/TDF group and 36.5% in the SBR group),
- darunavir (19.9% in the FTC/RPV/TDF group and 20.8% in the SBR group),
- fosamprenavir (7.9% in the FTC/RPV/TDF group and 7.5% in the SBR group),
- saquinavir (1.9% in the FTC/RPV/TDF group and 1.3% in the SBR group),
- amprenavir (0.3% in the FTC/RPV/TDF group).

Adherence

Self-reported Adherence: A total of 51 of 469 subjects (about 10% in both groups) self-reported adherence and it was similar between groups.

Pill counts were only collected for FTC/RPV/TDF. Based on pill counts mean (SD) adherence was identical in the FTC/RPV/TDF and Delayed Switch treatment groups (99% [2.8%]), and similar proportions of subjects in both treatment groups were > 95% adherent to the study drug regimen (89.9% FTC/RPV/TDF group and 92.8% Delayed Switch group). For the total FTC/RPV/TDF group, 90.8% were > 95% adherent to the study drug regimen.

Adherence questionnaire: showed a significant increase in mean adherence from baseline to week 4, to week 8 and week 12 in the FTC/RPV/TDF group compared to the SBR group, that were not significantly different after week 12.

Primary outcome

The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 24 (snapshot analysis) was similar in the FTC/RPV/TDF (93.7%) and SBR (89.9%) treatment groups (3.8% treatment difference; 95% CI: −1.6%, 9.1%). The lower bound of the 95% CI was within the predefined 12% margin for non-inferiority of FTC/RPV/TDF to SBR at Week 24.

In the Delayed Switch group, 92.1% of subjects had HIV-1 RNA < 50 copies/mL after 24 weeks of treatment, consistent with the FTC/RPV/TDF group at Week 24.

The TLOVR analysis results were generally consistent with the snapshot analysis, with 88.3% of those in the FTC/RPV/TDF group having HIV-1 RNA < 50 copies/mL through 48 weeks (95% CI: 84.3%, 91.6%).

One subject (0.3%) in the FTC/RPV/TDF group and 8 subjects (5.0%) in the SBR group had HIV-1 RNA ≥ 50 copies/mL at Week 24 (defined as virologic failure). Two additional subjects in the FTC/RPV/TDF group were classified as virologic failures; 1 subject discontinued study drug due to lack of efficacy, and 1 subject discontinued due to other reasons and their last HIV-1 RNA result was ≥ 50 copies/mL.

As a consequence, 3 subjects experienced VF in the first 24 weeks in FTC/RPV/TDF versus 8 subjects in the SBR arm.

Also the sensitivity analyses M = F and M = E and the LOCF analyses (both on-treatment and on-study analyses) were consistent with primary snapshot analysis.

Table 4. GS-US-264-0106: Virologic Outcomes at Weeks 24 and 48 (Snapshot Analysis) Full Analysis Set

	FTC/RPV/TDF (N=317)	SBR (N=159)	Delayed Switch to FTC/RPV/TDF (N=152)	Treatment Difference	95% CI[a]
Virologic Success at Week 24					
HIV-1 RNA < 50 copies/mL	297 (93.7%)	143 (89.9%)	140 (92.1%)	3.8%	(–1.6%, 9.1%)
Virologic Failure (VF) at Week 24	3 (0.9%)	8 (5.0%)	2 (1.3%)		
HIV-1 RNA ≥ 50 copies/mL	1 (0.3%)	8 (5.0%)	1 (0.7%)		
VF - Discontinued Study Drug Due to Lack of Efficacy	1 (0.3%)	0	1 (0.7%)		
VF - Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL	1 (0.3%)	0	0		
No Virologic Data in Week 24 Window	17 (5.4%)	8 (5.0%)	10 (6.6%)		
Discontinued Study Drug Due to AE or Death	6 (1.9%)	0	5 (3.3%)		
Discontinued Study Drug Due to Other Reasons[b] and Last Available HIV-1 RNA < 50 copies/mL	11 (3.5%)	5 (3.1%)	3 (2.0%)		
Missing Data During Window But on Study Drug	0	3 (1.9%)	2 (1.3%)		
Virologic Success at Week 48					
HIV-1 RNA < 50 copies/mL	283 (89.3%)	—	—		
Virologic Failure (VF) at Week 48	8 (2.5%)	—	—		
HIV-1 RNA ≥ 50 copies/mL	4 (1.3%)	—	—		
VF - Discontinued Study Drug Due to Lack of Efficacy	2 (0.6%)	—	—		
VF - Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL	2 (0.6%)	—	—		
No Virologic Data in Week 48 Window	26 (8.2%)	—	—		
Discontinued Study Drug Due to AE or Death	7 (2.2%)	—	—		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	16 (5.0%)	—	—		
Missing Data During Window But on Study Drug	3 (0.9%)	—	—		

a The 95% confidence interval (CI) for the treatment difference (FTC/RPV/TDF vs. SBR) is based on normal approximation.

b Discontinuation due to other reasons includes subjects who discontinued study drug due to lost to follow-up, subject withdrawal, noncompliance, protocol violation, and other reasons.

Secondary endpoints

48 week data

HIV-1 RNA suppression below 50 copies/mL was maintained for those receiving FTC/RPV/TDF for 48 weeks (89.3%) (full analysis set, snapshot algorithm).

Four subjects (1.3%) in the FTC/RPV/TDF group had HIV-1 RNA ≥ 50 copies/mL at Week 48, 2 subjects (0.6%) discontinued study drug due to lack of efficacy, and 2 subjects (0.6%) discontinued study drug for other reasons and their last HIV-1 RNA result was ≥ 50 copies/mL.

The results from the TLOVR analysis and per-protocol analysis were consistent with these results.

Table 5. GS-US-264-0106: Proportion of Subjects with HIV-1 RNA <50 copies/mL and HIV-1 RNA by Category through Week 48, Full Analysis Set

HIV-1 RNA < 50 copies/mL	FTC/RPV/TDF (N=317)	SBR (N=159)	Delayed Switch to FTC/RPV/TDF (N=152)	Total FTC/RPV/TDF (N=469)[a]
On-Treatment Analysis[b]				
Missing = Failure				
Baseline	299/317 (94.3%)	152/159 (95.6%)	144/152 (94.7%)	443/469 (94.5%)
Week 24	297/317 (93.7%)	143/159 (89.9%)	140/152 (92.1%)	437/469 (93.2%)
95% CI[c]	90.4%, 96.1%	84.2%, 94.1%	86.6%, 95.9%	90.5%, 95.3%
Week 48	283/317 (89.3%)	—	—	283/317 (89.3%)
Missing = Excluded				
Baseline	299/317 (94.3%)	152/159 (95.6%)	144/152 (94.7%)	443/469 (94.5%)
Week 24	297/298 (99.7%)	143/151 (94.7%)	140/141 (99.3%)	437/439 (99.5%)
95% CI[c]	98.1%, 100.0%	89.8%, 97.7%	96.1%, 100.0%	98.4%, 99.9%
Week 48	283/287 (98.6%)	—	—	283/287 (98.6%)
Last Observation Carried Forward				
Baseline	—	—	—	—
Week 24	311/314 (99.0%)	150/158 (94.9%)	149/151 (98.7%)	460/465 (98.9%)
95% CI[c]	97.2%, 99.8%	90.3%, 97.8%	95.3%, 99.8%	97.5%, 99.6%
Week 48	306/314 (97.5%)	—	—	306/314 (97.5%)
On-Study Analysis				
Missing = Failure				
Baseline	299/317 (94.3%)	152/159 (95.6%)	144/152 (94.7%)	443/469 (94.5%)
Week 24	302/317 (95.3%)	143/159 (89.9%)	143/152 (94.1%)	445/469 (94.9%)
95% CI[c]	92.3%, 97.3%	84.2%, 94.1%	89.1%, 97.3%	92.5, 96.7
Week 48	287/317 (90.5%)	—	—	287/317 (90.5%)
Missing = Excluded				
Baseline	299/317 (94.3%)	152/159 (95.6%)	144/152 (94.7%)	443/469 (98.7%)
Week 24	302/303 (99.7%)	143/151 (94.7%)	143/146 (97.9%)	445/449 (99.1%)
95% CI[c]	98.2%, 100.0%	89.8%, 97.7%	94.1%, 99.6%	97.7%, 99.8%
Week 48	287/293 (98.0%)	—	—	287/293 (98.0%)
Last Observation Carried Forward				
Baseline	—	—	—	—
Week 24	312/315 (99.0%)	150/158 (94.9%)	149/152 (98.0%)	461/467 (98.7%)
95% CI[c]	97.2%, 99.8%	90.3%, 97.8%	94.3%, 99.6%	97.2%, 99.5%
Week 48	306/315 (97.1%)	—	—	306/315 (97.1%)
TLOVR Analysis[d]				
Week 48 Responders	280/317 (88.3%)	—	—	—
95% CI[c]	84.3%, 91.6%	—	—	—
HIV-1 RNA Categories, On-Treatment Analysis[b]				
Week 24				
< 50 copies/mL	297/317 (93.7%)	143/159 (89.9%)	140/152 (92.1%)	437/469 (93.2%)
50 to < 200 copies/mL	1/317 (0.3%)	7/159 (4.4%)	1/152 (0.7%)	2/469 (0.4%)
200 to < 400 copies/mL	0	0	0	0
400 to < 1000 copies/mL	0	0	0	0
≥ 1000 copies/mL	0	1/159 (0.6%)	0	0
Noncompleters[e]	17/317 (5.4%)	5/159 (3.1%)	9/152 (5.9%)	26/469 (5.5%)
Missing	2/317 (0.6%)	3/159 (1.9%)	2/152 (1.3%)	4/469 (0.9%)
Week 48				
< 50 copies/mL	283/317 (89.3%)	—	—	283/317 (89.3%)
50 to < 200 copies/mL	1/317 (0.3%)	—	—	1/317 (0.3%)
200 to < 400 copies/mL	0	—	—	0
400 to < 1000 copies/mL	0	—	—	0
≥ 1000 copies/mL	3/317 (0.9%)	—	—	3/317 (0.9%)
Noncompleters[e]	26/317 (8.2%)	—	—	26/317 (8.2%)
Missing	4/317 (1.3%)	—	—	4/317 (1.3%)

CI = confidence interval, TLOVR = time to loss of virologic response

a Total TC/RPV/TDF group includes subjects from the FTC/RPV/TDF and Delayed Switch to FTC/RPV/TDF groups.

b The on-treatment analysis includes data for subjects on study drug at the time point of interest; the on-study analysis includes all subjects still in the study (even if no longer on treatment) at the time point of interest.

c 95% CI is the 2-sided exact 95% CI for binomial proportions.

d Subjects were considered nonresponders in the TLOVR analysis if they experienced virologic rebound prior to or at Week 48 or discontinued study drug prior to Week 48. Virologic rebound was defined as 2 consecutive HIV-1 RNA values ≥ 50 copies/mL or the last value ≥ 50 copies/mL followed by premature discontinuation of study drug.

e Non-completers are subjects who prematurely discontinued from the study prior to the beginning of the visit window corresponding to the summarized visit.

CD4 count

By Week 24, median (Q1, Q3) CD4+ cell counts had increased significantly from baseline in both the FTC/RPV/TDF group and the SBR group in the on-treatment analysis of absolute cell counts. The difference between the FTC/RPV/TDF and SBR treatment groups was not statistically significant at Week 24 (p = 0.28).

Table 6. GS-US-264-0106: CD4+ Cell Count by Visit and Change from Baseline through Week 48, On-Treatment Analysis (Full Analysis Set)

CD4+ Cell Results	FTC/RPV/TDF (N=317)	SBR (N=159)	Delayed Switch to FTC/RPV/TDF (N=152)	Total FTC/RPV/TDF (N=469)
Median (Q1, Q3) CD4+ Cell Count (cells/μL)				
Baseline	554 (412, 713)	561 (401, 744)	601 (436, 810)	568 (420, 740)
Week 24	569 (445, 731)	601 (436, 810)	591 (422, 789)	570 (436, 752)
Week 48	583 (431, 718)	—	—	583 (431, 718)
Median (Q1, Q3) Change from Baseline (cells/μL)				
Week 24	10 (–61, 82)	22 (–40, 106)	–11 (–65, 46)	1 (–62, 72)
P-value 1[b]	0.046	0.008	0.23	0.31
P-value 2[c]	0.28			
Week 48	17 (–56, 84)	—	—	17 (–56, 84)
P-value 1[b]	0.072	—	—	0.072
Median (Q1, Q3) CD4+ Cells (%)				
Baseline	31.1 (24.3, 37.9)	32.3 (25.5, 37.8)	32.1 (24.9, 38.8)	31.4 (24.3, 38.5)
Week 24	32.0 (25.7, 38.7)	32.1 (25.3, 38.9)	33.1 (27.2, 39.5)	32.3 (26.1, 39.4)
Week 48	31.9 (25.8, 38.5)	—	—	31.9 (25.8, 38.5)
Median (Q1, Q3) Change from Baseline (%)				
Week 24	1.1 (–0.7, 3.3)	0.2 (–1.6, 2.9)	1.1 (–0.8, 2.7)	1.1 (–0.8, 3.1)
P-value 1[b]	< 0.001	0.024	< 0.001	< 0.001
P-value 2[c]	0.057		—	—
Week 48	1.3 (–1.2, 3.9)	—	—	1.3 (–1.2, 3.9)
P-value 1[b]	< 0.001	—	—	< 0.001

SD = standard deviation

Note: Results collected while subjects are on study drug are included.

a Total TC/RPV/TDF group includes subjects from the FTC/RPV/TDF and Delayed Switch to FTC/RPV/TDF groups.

b P-value for comparison to baseline within each treatment group is from Wilcoxon signed rank test.

c P-value for comparison between FTC/RPV/TDF STR and SBR at Week 24 is from Wilcoxon rank sum test.

For the Delayed Switch group after 24 weeks of treatment with FTC/RPV/TDF, median (Q1, Q3) CD4+ cell counts had decreased from baseline (−11 cells/μL [−65, 46]).

Virology

The HIV-1 subtype was determined for 65% of subjects (309 of 475) by the historical genotype. Most subjects with an HIV-1 subtype listed had subtype B (275 of 475, 58%).

Other subtypes present were subtypes AG (12 of 475, 2.5%), AE (4 of 475, 0.8%), C (4 of 475, 0.8%), A (3 of 475, 0.6%), G (3 of 475, 0.6%) and mixtures or other subtypes (8 of 475, 1.7%). The remaining 166 of 475 subjects with historical genotype data available did not have an HIV-1 subtype listed in their report.

Virologic rebound was defined as having 2 consecutive visits with HIV-1 RNA ≥ 400 copies/mL. In addition, subjects who were on study drugs and had not been analysed previously, and who had HIV-1 RNA ≥ 400 copies/mL at Week 48 or their last visit were also analysed for resistance at their last visit.

A total of 8 subjects in either group met the criteria for inclusion in the resistance analysis (8 of 476, 1.7%). Two subjects (2 of 317, 0.6%) were included from the baseline switch to FTC/RPV/TDF group

through Week 24, 7 subjects (7 of 317, 2.2%) were in the FTC/RPV/TDF group through Week 48, and 1 subject (1 of 159, 0.6%) was in the SBR group through Week 24.

Resistance

Resistance development to one or more components of the FTC/RPV/TDF STR or a PI-based regimen was infrequent through Week 48 of this study

- 0.6% of subjects in the FTC/RPV/TDF group through Week 24,
- 1.3% of subjects in the FTC/RPV/TDF group through Week 48,
- no subjects with delayed switch to FTC/RPV/TDF at Week 24,
- 0.6% in the SBR group

The most common emergent resistance mutations in the FTC/RPV/TDF-treated subjects were M184V/I and E138K in RT.

Of the 469 FTC/RPV/TDF-treated subjects, a total of 7 subjects were analysed for resistance development and had postbaseline genotypic and phenotypic data for PR and RT.

- Two subjects who switched to FTC/RPV/TDF at baseline (2 of 317, 0.6%) developed primary NRTI or NNRTI resistance mutations and reduced susceptibility to FTC and/or RPV by Week 24,
- 2 additional subjects in the FTC/RPV/TDF group developed resistance between Weeks 24 and 48 (total of 4 of 317 from baseline to Week 48, 1.3%),
- no subjects in the delayed switch group (0 of 152, 0%) developed resistance after switching to FTC/RPV/TDF at Week 24 through Week 48.

All 4 subjects with emergent resistance had an M184V/I substitution and 3 of the 4 also had emergent resistance mutations to RPV (L100I and K103N with pre-existing V90V/I; E138K; and V108V/I and E138K with pre-existing K103N and V179I).

Subjects who developed genotypic resistance to RPV showed a mean of 9-fold reduced susceptibility to RPV compared to wild-type. Subjects who developed phenotypic resistance to RPV also showed reduced phenotypic susceptibility to the other NNRTIs delavirdine, EFV, and nevirapine, but remained susceptible to etravirine in 1 of 2 cases.

In the SBR group, 1 subject was included in the resistance analysis population and was analysed for resistance development (1/159, 0.6%). This subject developed the K70E/K and M184V mutations and reduced susceptibility to FTC while on their PI-based regimen (atazanavir + ritonavir + FTC/TDF) at Week 24. After switch to Eviplera at week 24 after initial suppression from 23,400 copies to 181 copies/ml, the patient discontinued due to lack of efficacy at day 43.

All subjects remained susceptible to tenofovir.

Table 7. GS-US-264-0106: Development of HIV-1 Genotypic Resistance at Week 48

	Number of Subjects (% of Subjects; % RAP)				
	FTC/RPV/TDF (N=317)		SBR (N=159)	Delayed Switch to FTC/RPV/TDF (N=152)	Total FTC/RPV/TDF[a] (N=469)
Resistance Development Category	Baseline to Week 24	Baseline to Week 48	Baseline to Week 24	Week 24 to Week 48	Baseline to Week 48
Resistance Analysis Population	2 (0.6%)	7 (2.2%)	1 (0.6%)	0	7 (1.5%)
Subjects with Data	2	7	1	0	7
Developed Resistance Mutations to Study Drugs[b]	2 (0.6%; 100%)	4 (1.3%; 57%)[c]	1 (0.6%; 100%)	0	4 (0.9%; 57%)
No Change from Baseline (Primary Mutations[d])	0	3 (0.9%; 43%)	0	0	3 (0.6%; 43%)
Any NNRTI-R[e]	1 (0.3%; 50%)	3 (0.9%; 43%)	0	0	3 (0.6%; 43%)
L100I	1 (0.3%; 50%)	1 (0.3%; 14%)	0	0	1 (0.2%; 14%)
K103N	1 (0.3%; 50%)	1 (0.3%; 14%)	0	0	1 (0.2%; 14%)
V108I	0	1 (0.3%; 14%)	0	0	1 (0.2%; 14%)
E138K	0	2 (0.6%; 29%)	0	0	2 (0.4%; 29%)
Any NRTI-R[f]	2 (0.6%; 100%)	4 (1.3%; 57%)	1 (0.6%; 100%)	0	4 (0.9%; 57%)
M184V/I	2 (0.6%; 100%)	4 (1.3%; 57%)	1 (0.6%; 100%)	0	4 (0.9%; 57%)
K70E/K	0	0	1 (0.6%; 100%)	0	0
K65R/N	0	0	0	0	0
Developed Primary PI-R[g]	0	0	0	0	0

a Includes all FTC/RPV/TDF-treated subjects with follow-up through 24 or 48 weeks of treatment.

b Denominators for the percentages given are 1) the number of subjects in the treatment group and 2) the number of subjects in the resistance analysis population.

c Two subjects in the FTC/RPV/TDF group developed resistance from baseline to Week 24, and 2 subjects developed resistance between Weeks 24 and 48.

d No change from baseline at NNRTI-R, NRTI-R, or primary PI-R sites.

e Nonnucleoside reverse transcriptase inhibitor resistance (NNRTI-R) mutations are V90I, A98G, L100I, K101E/H/P, K103N/S, V106A/I/M, V108I, E138A/G/K/Q/R, V179D/F/I/L/T, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, and M230I/L in RT.

f Nucleoside/nucleotide reverse transcriptase inhibitor resistance (NRTI-R) mutations are M41L, E44D, A62V, K65N/R, D67N, T69D, T69 Insertions; K70E/R, L74I/V, V75I, F77L, Y115F, F116Y, V118I, Q151M, M184I/V, L210W, T215F/Y, and K219E/N/Q/R in RT.

g Primary protease inhibitor resistance (PI-R) mutations are D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, Q58E, T74P, L76V, V82A/F/L/S/T, I84V, N88S, and L90M in PR.

Other outcome measures

HIV Symptom Index Questionnaire

For 12 items of the 20-item HIV Symptom Index, subject-reported symptoms were significantly reduced compared to baseline in the FTC/RPV/TDF group at Week 24 ($p \leq 0.031$).

The difference between the FTC/RPV/TDF group and the SBR group at Week 24 in the presence of HIV symptoms was statistically significant for

- diarrhoea or loose bowel movements (17.4% FTC/RPV/TDF vs. 45.3% in the SBR group; $p < 0.001$);
- bloating, pain, or gas in the stomach (18.6% FTC/RPV/TDF group vs. 32.1% in the SBR group; $p = 0.001$);
- problems having sex (20.8% in the FTC/RPV/TDF vs. 32.7% in the SBR group; $p = 0.005$).

After 24 weeks of FTC/RPV/TDF treatment in the Delayed Switch group, subject-reported symptoms were significantly reduced compared to baseline for only 2 of the 20 items on the HIV Symptom Index (diarrhoea or loose bowel movements and difficulty falling or staying asleep) ($p \leq 0.034$).

HIV Treatment Satisfaction Questionnaire

At Week 24, mean (SD) total HIVTSQ change scores (sum of the 10 questionnaire items) were significantly higher for the FTC/RPV/TDF group (24 [SD 8.4]) ($p < 0.001$) than for the SBR group (15 [12.8]) indicating more subjects were satisfied with their FTC/RPV/TDF than those on their baseline regimen.

GS-US-264-0111: switch to 25 mg Eviplera after EFV/FTC/TDF in HIV-infected patients

Methods

This study was a Phase 2B open-label pilot study to evaluate switching from a regimen consisting of an Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF) single tablet regimen (STR) to Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate (FTC/RPV/TDF) STR in 49 virologically-suppressed, HIV-1 infected subjects. This study evaluated efficacy, safety and pharmacokinetics of RPV after switching from EFV during a period of 48 weeks in subjects that did not tolerate EFV.

Study design

Open-label, multicentre (18 centres in the US) study to evaluate switching from EFV/FTC/TDF to FTC/RPV/TDF STR in virologically-suppressed HIV-1 infected subjects who had been on EFV/FTC/TDF for $\geq$ 3 months at screening and had decided on a change in regimen due to EFV intolerance. All subjects switched from EFV/FTC/TDF to FTC/RPV/TDF STR at baseline. After 48 weeks of treatment with FTC/RPV/TDF, all subjects completed a 30-day follow-up visit or telephone call.

Objectives

The primary objective of this study was to evaluate the efficacy of FTC/RPV/TDF STR after switching from EFV/FTC/TDF at baseline in maintaining HIV-1 RNA < 50 copies/mL at Week 12

The primary endpoint was the proportion (%) of subjects who had HIV-1 RNA < 50 copies/mL at Week 12 as defined by the Food and Drug Administration (FDA) snapshot analysis.

The secondary objectives with subsequent endpoints of this study were as follows:

1. To evaluate the safety and tolerability of FTC/RPV/TDF STR over 24 and 48 weeks
2. To evaluate the efficacy of FTC/RPV/TDF STR after switching from EFV/FTC/TDF at baseline in maintaining HIV-1 RNA , 50 copies/mL at Week 24 and Week 48
3. To explore the pharmacokinetics of RPV after switching from EFV
4. To determine CD4 counts and changes during 48 weeks

Inclusion Criteria

Subjects who met all of the following criteria were eligible for participation in the study:

- Received ARV therapy consisting only of EFV/FTC/TDF (as Atripla) continuously for $\geq$3 months preceding the screening visit

- Plasma HIV-1 RNA concentrations (at least 2 measurements) at undetectable levels while on treatment for ≥ 8 weeks prior to the screening visit and RNA < 50 copies/mL at the screening visit
- Be on their first ARV drug regimen and not have HIV-1 RNA > 50 copies/mL at 2 consecutive time points after first achieving HIV RNA < 50 copies/mL
- A genotype prior to starting FTC/RPV/TDF and no known resistance to any of the study agents at any time in the past including, but not limited to the RT mutations K65R, K101E/P, E138G/K/Q/R, Y181C/I/V, M184V/I, and H221Y
- A normal ECG (or if abnormal, determined by the investigator as not clinically significant)
- Hepatic transaminase levels (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) ≤ 5 x upper limit of normal (ULN) / Total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin / Adequate hematologic function (absolute neutrophil count ≥ 1,000/mm3, platelets, ≥ 50,000/mm3, haemoglobin ≥ 8.5 g/dL) / Serum amylase ≤ 5 x ULN
- Adequate renal function: estimated glomerular filtration rate (eGFR) ≥ 50 mL/min
- Age ≥ 18 years

Exclusion Criteria

Subjects who met any of the following criteria were excluded from participation in the study:

- A new acquired immunodeficiency syndrome (AIDS)-defining condition diagnosed within the 21 days prior to screening
- Females who were breastfeeding
- Positive serum pregnancy test (females of childbearing potential)
- Proven or suspected acute hepatitis in the 21 days prior to study entry
- Subjects who received drug treatment for hepatitis C, or subjects who were anticipated to receive treatment for hepatitis C during the course of the study or who had a history of liver disease / Subjects who experienced decompensated cirrhosis
- Implanted defibrillator or pacemaker
- Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance
- A history of malignancy within the past 5 years (prior to screening) or on-going malignancy other than cutaneous Kaposi's sarcoma (KS), basal cell carcinoma, or resected, noninvasive cutaneous squamous carcinoma.
- Active, serious infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 21 days prior to baseline
- Treated with immunosuppressant therapies or chemotherapeutic agents within 3 months of study screening, or was expected to receive those agents or systemic steroids during the study (eg, corticosteroids, immunoglobulins, and other immune- or cytokine-based therapies)

Sample Size and Power

Sample size of this one-arm pilot study was selected based on the feasibility of the study conduct.

PK data

Blood samples for trough pharmacokinetic analyses were obtained pre-dose at Weeks 1, 2, 4, 6, 8, 12, 24, and 48. A single post-dose blood sample was collected from each subject at Week 36 (any time post-dose).

Rilpivirine and efavirenz concentrations were measured by validated LC-MS/MS methods.

Results

The study started on 27 January 2011, first subject screened, and the last observation took place at 19 April 2012.

Subjects

63 subjects were screened, 50 were enrolled at 18 sites in the US. One subject withdrew consent before the start of FTC/RPV/TDF dosing.

Table 8. GS-US-264-0111: Disposition of Subjects (Enrolled Subjects)

	FTC/RPV/TDF (N = 50)
Subject Disposition	**N (%)**
Enrolled	50
Treated	49
Completed Study	48 (98.0)
Discontinued Study Drug Prematurely	1 (2.0%)
Protocol Violation	1 (2.0%)

Note: Percentages are based on the number of subjects in the treated (safety) analysis set.

A total of 48 subjects completed both the protocol-defined period of study drug dosing and the whole study. One subject did not complete study drug dosing or the study because of a protocol violation (low adherence; stopped taking study medication due to incarceration, his last Viral Load was < 50 copies/ml).

Baseline data

The majority of subjects in the safety analysis set were male (91.8%), with an overall mean age of 38 years (range, 24 to 57 years); most were white (81.6%).

At baseline, mean CD4+ cell count was 656/uL (range, 188 to 1528/uL). The mean time since first taking ARV medication (EFV/FTC/TDF) was 2.7 years (range, 0.5 to 7.5 years).

Table 9. GS-US-264-0111: Key Demographic and Baseline Characteristics (Safety Analysis Set)

Characteristic	FTC/RPV/TDF (N = 49)
Age (years)	
Mean (SD)	38 (8.3)
Median (Q1, Q3)	39 (31, 43)
Min, Max	24, 57
Sex (n, %)	
Male	45 (91.8%)
Female	4 (8.2%)
Race n (%)	
White	40 (81.6%)
Black or African American	6 (12.2%)
Asian	3 (6.1%)
Ethnicity	
Hispanic or Latino	10 (20.4%)
Not Hispanic or Latino	39 (79.6%)
Weight (kg)	
Mean (SD)	83.1 (15.50)
Median (Q1, Q3)	81.0 (75.8, 91.6)
Min, Max	50.0, 116.6
Height (cm)	
Mean (SD)	176.0 (7.32)
Median (Q1, Q3)	175.3 (172.7, 181.6)
Min, Max	160.0, 190.5
BMI (kg/m^2) [a]	
Mean (SD)	26.9 (5.48)
Median (Q1, Q3)	25.7 (24.0, 28.2)
Min, Max	18.9, 42.5
CD4+ (/µL)	
Mean (SD)	656 (239.2)
Median (Q1, Q3)	653 (513, 766)
Min, Max	188, 1528
≤ 50	0
51 to ≤ 200	1 (2.0%)
201 to ≤ 350	3 (6.1%)
351 to 500	7 (14.3%)
> 500	38 (77.6%)

Treatment Adherence

Adherence to FTC/RPV/TDF was measured by pill count. Overall, 91.8% (45 of 49 subjects) had an adherence rate of ≥ 95%.

Outcomes and estimation

Primary Efficacy Endpoint

All 49 subjects (100%) maintained an HIV-1 RNA viral load of < 50 copies/mL at the Week 12 visit (FDA snapshot analysis).

Secondary efficacy endpoints

Week 24: Virologic suppression was maintained in all 49 subjects (100%)

Week 48: 93.9% of subjects (46 of 49 subjects; 95% CI: 83.1%, 98.7%) had HIV-1 RNA < 50 copies/mL and were defined as virologic successes according to the snapshot analysis.

Virologic failures

Two subjects had HIV-1 RNA > 50 copies/mL at Week 48 and were considered virologic failures:

- 1 subject had low-level viral loads of 63 copies/mL (Day 245 [Week **36**]) and 95 copies/mL (Day 335 [Week 48]). After switching the subject back to prestudy EFV/FTC/TDF by the investigator on Day 336, viral load became undetectable (ie, < 50 copies/mL) by Day 356.
- Another subject had viral loads of 330,000 (Week 48), 1890 (Week 51), and 991 copies/mL (Week 54). This subject was noted to have poor study-drug adherence prior to Week 48, lacked a detectable RPV trough level at Week 48, and had HIV-1 with no resistance to study drugs at Weeks 48 and 51.

Table 10. GS-US-264-0111: Treatment Outcomes at Week 48 for HIV-1 RNA at a Cut off of 50 copies/mL (Snapshot Analysis; Full Analysis Set)

	FTC/RPV/TDF (N=49)	95% CI [a]
Virologic Success at Week 48, n (%)		
HIV-1RNA < 50 copies/mL	46 (93.9%)	(83.1%, 98.7%)
Virologic Failure (VF) at Week 48, n (%)	2 (4.1%)	
HIV-1RNA ≥ 50 copies/mL	2 (4.1%)	
VF: Discontinued Study Drug Due to Lack of Efficacy	0	
VF: Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL	0	
No Virologic Data in Week 48 Window	1 (2.0%)	
Discontinued Study Drug Due to AE or Death	0	
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	1 (2.0%)	
Missing Data During Window but On Study Drug	0	

a 95% CI is the 2-sided exact 95% CI for binomial proportions.

Other analyses confirmed the results of the snapshot analysis for virologic success: TLOVR 93.9%, M=F analysis 93.9%, M=E analysis 95.8%, LOCF analysis 100% at week 12 and 95.9% at week 48.

CD4 count

Median (Q1, Q3) baseline CD4+ cell counts were 653 (513, 766) cells/mL. Median (Q1, Q3) change from baseline in CD4+ cell counts were not statistically significant at Week 48 (-2 [–76, 104] cells/uL; p = 0.87, Wilcoxon signed rank test).

Virology

Baseline virologic data

No subject had evidence of protocol-defined exclusion mutations in their historical genotype. In total, 7 subjects had a documented NNRTI resistance mutation (14.3%, 7/49 subjects), 3 subjects had an NRTI resistance mutation (6.1%, 3/49 subjects), and 2 subjects had a primary protease inhibitor resistance mutation (4.1%, 2/49 subjects). One subject had the RPV resistance-associated mutation

E138A, which was not an exclusion mutation at the time of this study; this subject maintained virologic suppression through Week 48.

Genotype

The HIV-1 subtype was determined for 67% of subjects (33/49) by the historical genotype.
All subjects with an HIV-1 subtype listed had subtype B (67%, 33/49 subjects). The remaining 16 subjects did not have an HIV-1 subtype listed in their report.

Resistance

Virologic rebound was defined as having 2 postbaseline visits with HIV-1 RNA $\geq$ 400 copies/mL, having HIV-1 RNA $\geq$ 400 copies/mL at Week 48 or their last visit (at or after Week 4), or having a single rebound of HIV-1 RNA $\geq$ 1000 copies/mL at Week 2, 4, or 6.

In this single-arm study, 1 subject was analysed for resistance development and had no evidence of genotypic and phenotypic resistance to any component of the FTC/RPV/TDF STR at Week 48 (Day 337 and Day 362 were analysed). This subject had an overall adherence rate by pill count of 95.2%, however, missed a minimum of 10 doses of study drug between Week 24 and Week 36, and at least 9 doses between Week 36 and Week 48. A viral rebound was recorded (> 100,000 copies/ml), that did not result in discontinuation of Eviplera.

Pharmacokinetics

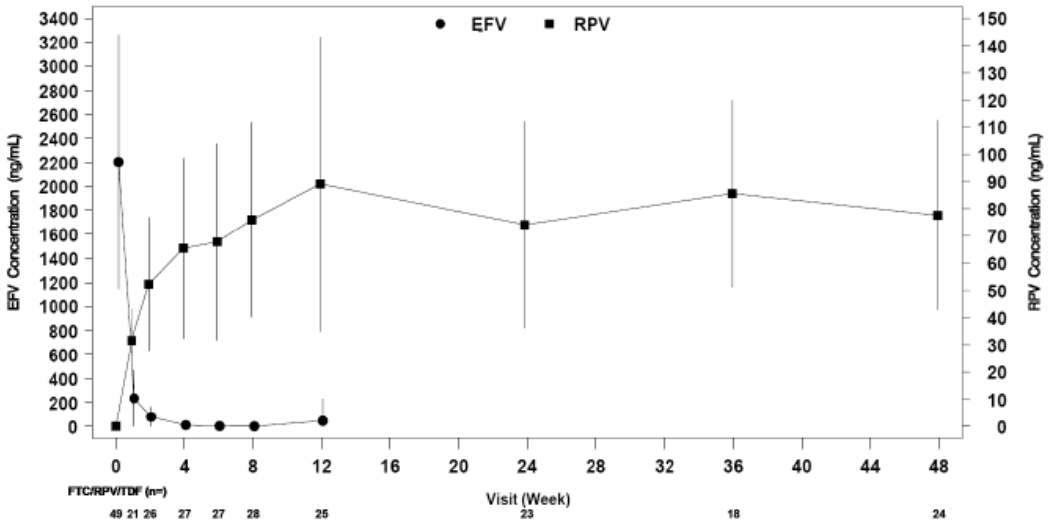
The mean observed rilpivirine trough concentrations are shown in the table below.

Visit (Week)	1	2	4	6	8	12	24	36	48
C_{trough} mean (%CV)	31.6 (36.2)	52.3 (46.7)	65.5 (50.7)	67.8 (53.3)	76.0 (47.1)	89.0 (60.8)	74.1 (51.2)	85.5 (40.1)	77.6 (44.9)

At week 1, the mean rilpivirine trough concentration of 31.6 ng/ml was lower than those observed in the Phase 3 trials in patients C209 and C215 (mean: 80 ± 37 ng/ml; median 74 (range 1 – 300 ng/ml) not on efavirenz therapy, indicative for the inductive effect of efavirenz on rilpivirine metabolism. Around week 4 – 6, plasma rilpivirine trough concentrations were in the normal range (see also the figure below).

Evafirenz trough plasma concentrations decreased slowly, which is expected as evafirenz has a long elimination half-life. After 4 weeks, in about half of the included patients, efavirenz trough concentrations were still measurable (see also figure below).

Figure 7 Mean &SD Graphic of Plasma Concentrations of Rilpivirine versus Efavirenz by Visit (PK analysis set)



2.5.1. Efficacy results - Additional analysis on baseline viral loads and CD4 counts

The CHMP requested to discuss the impact of baseline viral load and CD4 count on response to Eviplera.

The collection of pre-ART BLVL and CD4 counts was not mandatory for enrolment in the study hence this data is not available for all subjects who experienced VF.

The MAH performed a post-hoc analysis of pre-ART HIV-1 RNA levels on virologic response (Table 3). In this table the virologic failures are listed by pre-ART BLVL (≤100,000 copies/mL, >100,000 copies/mL and missing). The data do not indicate any association between virologic success (by the Snapshot method) and pre-ARV HIV-1 RNA in patients who are virologically suppressed on a PI/r based regimen and switch to Eviplera.

Table 11. Virologic Outcomes by pre-ART HIV-1 RNA Levels, FDA Snapshot Analysis - ITT Population

	FTC/RPV/TDF N=317		SBR N=159	Delayed Switch N=152	Total FTC/RPV/TDF N=469
	Week 24	Week 48[a]	Week 24	Week 24	Week 24[b]
Virologic Success HIV-1 RNA < 50 copies/mL By viral load while ART-naive					
≤100,000	95% (155/163)	90% (147/163)	89% (83/93)	98% (85/87)	96% (240/250)
> 100,000	95% (125/131)	94% (123/131)	92% (48/52)	86% (44/51)	93% (169/182)
Missing	*74% (17/23)*	*56% (13/23)*	86% (12/14)	79% (11/14)	76% (28/37)
Virologic Failure[c] By viral load while ART-naive					
≤100,000	0% (0/163)	2% (3/163)	3% (3/93)	0% (0/87)	0% (0/250)
> 100,000	1% (1/131)	2% (2/131)	6% (3/52)	4% (2/51)	2% (3/182)
Missing	*9% (2/23)*	*13% (3/23)*	*14% (2/14)*	0% (0/14)	*5% (2/37)*

ART = antiretroviral therapy; SBR = stay on background regimen; Delayed Switch= Switch to FTC/RPV/TDF at Week 24
a: HIV-1 RNA outcome 48 weeks after switch (p=0.29 by Fishers Exact test for association of pre-ART HIV-1 RNA category and virologic success). The analysis excludes subjects with missing pre-ART HIV-1 RNA.
b: Total FTC/RPV/TDF summarizes the HIV-1 RNA outcome 24 weeks after switch (p=0.19 by Fishers Exact test for association of pre-ART HIV-1 RNA category and virologic success). The analysis excludes subjects with missing pre-ART HIV-1 RNA.

c: Virologic Failure as defined by the Snapshot method (includes subjects with HIV-1 RNA >50 copies/mL, early discontinuation of study drug due to lack of efficacy or early discontinuation of study drug for other reason with last available HIV-1 RNA>50 copies/mL).

The MAH performed a post-hoc analysis of pre-ART CD4 counts on virologic response (Table 11). In this table the virologic failures are listed by pre-ART CD4 count (<100, >100 to .200, >200 to .350 and >350 counts/mL). The data do not indicate any association between virologic success (by the Snapshot method) and pre-ART CD4 levels in patients who are virologically suppressed on a PI/r based regimen and switch to Eviplera.

Table 12. Virologic Outcomes by pre-ART CD4+ Count, FDA Snapshot Analysis - ITT Population

	FTC/RPV/TDF N=317		SBR N=159[b]	Delayed Switch N=152	Total FTC/RPV/TDF N=469
	Week 24	Week 48[a]	Week 24	Week 24	Week 24[b]
Virologic Success HIV-1 RNA < 50 copies/mL By CD4+ while ART-naïve					
≤ 100	97% (73/75)	95% (71/75)	91% (30/33)	88% (29/33)	94% (102/108)
> 100 to ≤ 200	95% (58/61)	93% (57/61)	100% (20/20)	95% (19/20)	95% (77/81)
> 200 to ≤ 350	94% (88/94)	90% (85/94)	88% (43/49)	98% (46/47)	95% (134/141)
> 350	96% (65/68)	88% (60/68)	86% (38/44)	92% (36/39)	94% (101/107)
Missing	*68% (13/19)*	*53% (10/19)*	*92% (12/13)*	*77% (10/13)*	*72% (23/32)*
Virologic Failure[c] By Baseline viral load while ART-naïve					
≤ 100	0% (0/75)	3% (2/75)	9% (3/33)	3% (1/33)	1% (1/108)
> 100 to ≤ 200	2% (1/61)	2% (1/61)	0% (0/20)	5% (1/20)	2% (2/81)
> 200 to ≤ 350	0% (0/94)	0% (0/94)	6% (3/49)	0% (0/47)	0% (0/141)
> 350	0% (0/68)	3% (2/68)	2% (1/44)	0% (0/39)	0% (0/107)
Missing	*11% (2/19)*	*16% (3/19)*	*8% (1/13)*	*0% (0/13)*	*6% (2/32)*

ART = antiretroviral therapy; SBR = stay on background regimen; Delayed Switch= Switch to FTC/RPV/TDF at Week 24
a: HIV-1 RNA outcome 48 weeks after switch (p=0.51 by Fishers Exact test for association of pre-ART CD4 category and virologic success). The analysis excludes subjects with missing pre-ART CD4.
b: Total FTC/RPV/TDF summarizes the HIV-1 RNA outcome 24 weeks after switch (p=0.999 by Fishers Exact test for association of pre-ART CD4 category and virologic success). The analysis excludes subjects with missing pre-ART CD4.
c: Virologic Failure as defined by the Snapshot method (includes subjects with HIV-1 RNA >50 copies/mL, early discontinuation of study drug due to lack of efficacy or early discontinuation of study drug for other reason with last available HIV-1 RNA>50 copies/mL).

GS-US-264-0111

Pre-ART CD4 values were not collected for study GS-US-264-0111 so an analysis cannot be performed.

Pre-ART BLVL values were available for 35 of the 49 subjects (71.4%). Of these subjects, there were 57.1% (n = 20) of patients with BLVL <100,000 copies/mL and 42.9% (n = 15) with BLVL > 100,000 copies/mL. At Week 48, 94% (46/49) of patients remained virologically suppressed, and 4% (2/49) were considered VFs (HIV-1 RNA < 50 copies/mL). One subject (No. 3832) had a pre-ART BLVL HIV-1 RNA of .100,000 copies/mL and 1 subject (No. 3839) had a pre-ART BLVL HIV-1 RNA of slightly >100,000 copies/mL. In this latter subject, the RPV plasma concentration level was very low at Week 36 and was below the limit of quantitation (BLQ) at Week 48, corresponding to the time of VF and was consistent with subject's admission of non-adherence.

Serious questions about the accuracy of the database were raised, since the most essential data was missing for 23/317 in the Eviplera group and 14/159 in the SBR group: baseline characteristics of the subjects were apparently not adequately recorded. Similarly: in 19/317 patients receiving Eviplera and in 13/159 patients in the SBR group not even the initial CD4 count was recorded. The information that led to initiation of cART in the first place is missing in almost 10% of patients.

The MAH performed sensitivity analyses where the subjects with unknown pre-ART BLVL and CD4 were combined with the group of highest theoretical concern (i.e. BLVL >100,000 c/mL and CD4 ≤ 100) (Table 12 and Table 13). No trends are observed with the most conservative assumption.

Table 13. Virologic Outcomes by pre-ART HIV-1 RNA levels, FDA Snapshot Analysis - ITT Population

	FTC/RPV/TDF N=317		SBR N=159	Delayed Switch N=152	Total FTC/RPV/TDF N=469
	Week 24	Week 48[a]	Week 24	Week 24	Week 24[b]
Virologic Success HIV-1 RNA < 50 copies/mL By viral load while ART-naive					
≤100,000	95% (155/163)	90% (147/163)	89% (83/93)	98% (85/87)	96% (240/250)
> 100,000	95% (125/131)	94% (123/131)	92% (48/52)	86% (44/51)	93% (169/182)
Missing	*74% (17/23)*	*56% (13/23)*	*86% (12/14)*	*79% (11/14)*	*76% (28/37)*
Missing + >100,000 (sensitivity)	*92% (142/154)*	*88% (135/154)*	*91% (60/66)*	*85% (55/65)*	*90% (197/219)*
Virologic Failure[c] By viral load while ART-naive					
≤100,000	0% (0/163)	2% (3/163)	3% (3/93)	0% (0/87)	0% (0/250)
> 100,000	1% (1/131)	2% (2/131)	6% (3/52)	4% (2/51)	2% (3/182)
Missing	*9% (2/23)*	*13% (3/23)*	*14% (2/14)*	*0% (0/14)*	*5% (2/37)*
Missing + >100,000 (sensitivity)	*2% (3/154)*	*3% (5/154)*	*8% (5/66)*	*3% (2/65)*	*2% (5/219)*

ART = antiretroviral therapy; SBR = stay on background regimen; Delayed Switch= Switch to FTC/RPV/TDF at Week 24

a: HIV-1 RNA outcome 48 weeks after switch (p=0.29 by Fishers Exact test for association of pre-ART HIV-1 RNA category and virologic success). The analysis excludes subjects with missing pre-ART HIV-1 RNA.

b: Total FTC/RPV/TDF summarizes the HIV-1 RNA outcome 24 weeks after switch (p=0.19 by Fishers Exact test for association of pre-ART HIV-1 RNA category and virologic success). The analysis excludes subjects with missing pre-ART HIV-1 RNA.

c: Virologic Failure as defined by the Snapshot method (includes subjects with HIV-1 RNA >50 copies/mL, early discontinuation of study drug due to lack of efficacy or early discontinuation of study drug for other reason with last available HIV-1 RNA>50 copies/mL).

Table 14. Virologic Outcomes by pre-ART CD4+ count, FDA Snapshot Analysis - ITT Population

	FTC/RPV/TDF N=317		SBR N=159[b]	Delayed Switch N=152	Total FTC/RPV/TDF N=469
	Week 24	Week 48[a]	Week 24	Week 24	Week 24[b]
Virologic Success HIV-1 RNA < 50 copies/mL By CD4+ while ART-naïve					
≤ 100	97% (73/75)	95% (71/75)	91% (30/33)	88% (29/33)	94% (102/108)
> 100 to ≤ 200	95% (58/61)	93% (57/61)	100% (20/20)	95% (19/20)	95% (77/81)
> 200 to ≤ 350	94% (88/94)	90% (85/94)	88% (43/49)	98% (46/47)	95% (134/141)
> 350	96% (65/68)	88% (60/68)	86% (38/44)	92% (36/39)	94% (101/107)
Missing	*68% (13/19)*	*53% (10/19)*	*92% (12/13)*	*77% (10/13)*	*72% (23/32)*
Missing + ≤ 100 (sensitivity)	*91% (86/94)*	*87% (82/94)*	*91% (42/46)*	*85% (39/46)*	*89% (125/140)*
Virologic Failure[c] By Baseline viral load while ART-naïve					
≤ 100	0% (0/75)	3% (2/75)	9% (3/33)	3% (1/33)	1% (1/108)
> 100 to ≤ 200	2% (1/61)	2% (1/61)	0% (0/20)	5% (1/20)	2% (2/81)
> 200 to ≤ 350	0% (0/94)	0% (0/94)	6% (3/49)	0% (0/47)	0% (0/141)
> 350	0% (0/68)	3% (2/68)	2% (1/44)	0% (0/39)	0% (0/107)
Missing	*11% (2/19)*	*16% (3/19)*	*8% (1/13)*	*0% (0/13)*	*6% (2/32)*
Missing + ≤ 100 (sensitivity)	*2% (2/94)*	*5% (5/94)*	*9% (4/46)*	*2% (1/46)*	*2% (3/140)*

ART = antiretroviral therapy; SBR = stay on background regimen; Delayed Switch= Switch to FTC/RPV/TDF at Week 24
a: HIV-1 RNA outcome 48 weeks after switch (p=0.51 by Fishers Exact test for association of pre-ART CD4 category and virologic success). The analysis excludes subjects with missing pre-ART CD4.
b: Total FTC/RPV/TDF summarizes the HIV-1 RNA outcome 24 weeks after switch (p=0.999 by Fishers Exact test for association of pre-ART CD4 category and virologic success). The analysis excludes subjects with missing pre-ART CD4.
c: Virologic Failure as defined by the Snapshot method (includes subjects with HIV-1 RNA >50 copies/mL, early discontinuation of study drug due to lack of efficacy or early discontinuation of study drug for other reason with last available HIV-1 RNA>50 copies/mL).

2.5.2. Discussion on clinical efficacy

Study GS-US-264-0106

In this phase III randomized, open-label switch study from a PI-based regimen to RPV-based fixed dose combination a large sample size was collected with patients on PI-based regimens. The reason for switch in 88% of the cases was the desire to simplify the regimen. Some of the patients were relatively short on PI-based regimens (<6 months) with all having viral suppression at screening but not all at the moment of switch. Considering the desire to switch it comes as no surprise that in this open label study the results of a HIV Treatment Satisfaction Questionnaire were significantly better for the new regimen.

Efficacy was demonstrated, because introduction of a RPV-based regimen after switch from PI did not result in reductions of proportions of subjects with Viral Load < 50 copies/ml at week 24 when FTC/RPV/TDF was compared to PI-regimen continuation.

After 24 weeks 3 and 8 subjects in the FTC/RPV/TDF group and SBR group respectively developed virologic failure, and an additional 2 from week 24 to week 48 in the FTC/RPV/TDF group. Four from these 5 subjects in the FTC/RPV/TDF group developed mutations resulting not only in loss of RPV and other components of the NNRTI class (n=3 out of 4), but also in M184I/V substitution (n=4). This loss of therapeutic options/reduced sensitivity to NRTIs was also demonstrated in the registration studies of RPV.

Unknown is whether the cases that failed on RPV after switch were subjects who had a viral load > 100,000 copies/ml at the initiation of their very first regimen. That level of baseline viremia is a contraindication to start RPV in treatment-naïve patients, but after virologic suppression with a different regimen a safe switch is most likely to be anticipated. However, when irreversible physiological changes may have occurred due to an advanced stage of HIV infection with high baseline viral loads and low CD4 counts that in some way influence the response to RPV in treatment naïve patients, the switch to RPV even after viral suppression with a different regimen may result in

suboptimal results and loss of virologic suppression. An example of such a physiological change could be loss of gastric acidity in advanced HIV infection, which would decrease RPV plasma concentrations.

There was a long discussion on baseline viral loads and CD4 counts that is exposed separately in the section 2.3.2.2. Efficacy results - Additional analysis on baseline viral loads and CD4 counts.

Disappointingly, self-reported adherence did not improve with the once daily administration of Eviplera, even though 88% of subjects desired to simplify their regimen.

The switch did result in more frequent discontinuations with the new regimen: because of treatment – emergent AEs 2.8% in the FTC/RPV/TDF group discontinued versus 0% in the SBR group. Increases in ALT, AST, and both transaminases occurred more frequently in the RPV-based regimens, and resulted in 2 cases in permanent discontinuations in the Delayed switch group. However, in most switch studies there are more treatment emergent AEs in those that switch, since the population has been selected to tolerate their pre-switch regimen.

Study GS-US-264-0111

In single arm open label switch study GS-US-264-0111 from EFV/FTC/TDF to Eviplera in 48 subjects who did not tolerate EFV, 2 (4.2%) virologically suppressed subjects experienced virologic failure after week 24 following the switch.

This number of failures is relatively similar to that in the registration study TMC278-C209 (RPV/FTC/TDF vs EFV/FTC/TDF) that showed a 4.6% rebound percentage, albeit in subjects who were *not* virologically suppressed at baseline but who initiated cART as naïve patients.

It was unknown whether these failures in the RPV group after switch had baseline viral loads > 100,000 copies/ml when they initially started with EFV.

Although the AEs did not result in discontinuations the virologic failures are worrisome. RPV is sensitive to small PK disturbances e.g. due to lack of sufficient food concomitant with drug intake or due to use of concomitant PPI or due to lack of adherence. The latter factor was demonstrated once more in this study GS-US-264-0111, where 1 non-adherent subject lost virologic suppression.

Next to possible high baseline viral load at start of cART with EFV, another possible explanation could be that this subject and the subject experiencing repeated low level viremia from week 24 onwards developed resistant mutations due to prior underdosing of RPV directly after the switch from EFV due to the inductive effect of EFV on the RPV plasma levels in the weeks after the switch. It is unknown whether the 2 subjects experiencing virologic failure had particularly or extensively prolonged low RPV concentrations after switch due to prolonged induction of CYP3A4 by EFV.

However, resistance mutations were not found as demonstrated in the population sampling of the single subject with viral loads > 400 copies/ml. Follow up of these cases and the other subjects in this study was considered essential to determine whether relative underexposure to RPV in the post-EFV switch period results in more failures > 48 weeks after switch and also RPV-resistance mutations.

As such, lack of virological suppression was demonstrated in two cases, but most likely related late failures related to poor intake of the registered 25 mg dose, which is sensitive to non-compliance.

Indication

The extension of the indication as initially proposed implied the creation of a new patient category ('treatment experienced but not experiencing virologic failure') the appropriateness of which is questionable as it is more a patient management issue.

The current regulatory thinking and the state of the art of the HIV therapeutics (e.g. the EMA guideline released under consultation during this procedure[2]) are moving away from the terms 'treatment-naïve' or 'treatment-experienced', because it does not adequately reflect the susceptibility of the virus either before or during exposure to ARVs. Therefore the focus should be on antiviral activity of the medicinal product (i.e. the virus) and not on (prior) exposure history (i.e. the patient).

It would not be appropriate to indicate the product in ART experienced virologically suppressed patients without virological failure history as this would not adequately reflect viral susceptibility issues, because even patients experiencing virologic failure on ARVs from another class than the NNRTIs may benefit from initiation of NNRTI-based (i.e. Rilpivirine-based) ART if their viral load does not exceed 100,000 copies/ml and the virus population is susceptible to the 3 components.

In their studies the MAH has provided data on efficacy and safety in virologically suppressed patients that switch from other regimens to Eviplera. Reasons to switch are diverse and can be related to compliance, simplicity, tolerability, desire to switch, availability, reimbursement issues, taste or size of tablets, etc. expressed either by the patient or by the physician. This information is not relevant for SmPC section 4.1, but antiretroviral activity is.

The information from the studies should concisely be included in SmPC section 5.1 to demonstrate sustained viral suppression and discontinuations after switch and include information that switch studies were only done in virologically suppressed patients, that evidence of efficacy was obtained only for combination of RPV and Emtricitabine/tenofovir (not with other NRTIs) and that patients had viral suppression for at least 6 months (PI) or 3 months (emtricitabine/efavirenz/tenofovir disoproxil fumarate).

Studies in patients experiencing virologic failure on efavirenz in Atripla and subsequently switched to Eviplera have not been performed, therefore clinical evidence to support this switch is lacking. Rilpivirine has not been studied in patients with pre-selected NNRTI resistance either due to transmitted resistance or due to virologic failure on efavirenz which is also mentioned in the SmPC:

"Considering all of the available in vitro and in vivo data in treatment naïve subjects, the following resistance-associated mutations, when present at baseline, may affect the activity of Eviplera: K65R, K101E, K101P, E138A, E138G, E138K, E138Q, E138R, V179L, Y181C, Y181I, Y181V, M184I, M184V, Y188L, H221Y, F227C, M230I and M230L."

The K103N mutation, associated with failure on efavirenz, is not in this list. Claims that K103N will not result in virologic failure would be based on very limited numbers (n=17 in GS-US-264-0106) and cannot be supported.

It would not be justified to assume that the resistance-mutations associated with rilpivirine are distinct to those associated with other NNRTIs. This has either not been studied extensively or partial overlap was evident in vitro and vivo studies. In addition, the current dose of 25 mg rilpivirine in Eviplera has not been studied in virologic failure on efavirenz.

Therefore Eviplera should only be used in patients without known mutations associated with resistance to the NNRTI class.

Reference to class resistance is in line with the within the current regulatory thinking and the state of the art of the HIV therapeutics as shown in evolving CHMP guidelines on HIV medicines which

[2] Draft guideline on the clinical development of medicinal products for the treatment of human-immunodeficiency-virus (HIV) infection (revision 3)

emphasizes that only with appropriate studies new agents in an existing class may be approved in case of treatment failure on agents in that class.

Uncertainties

With some levels of uncertainty is can be concluded from the available data that not the inclusion criteria (i.e. viral load above or below 100,000 or CD4 count above or below 100) at the very start of cART are important, but that failure is driven by other factors during treatment e.g., poor adherence or diminished concentrations due to insufficient food intake with RPV resulting in low concentrations.

Baseline data are missing from a proportion of patients: 7% of subjects in the FTC/RPV/TDF and 9% in the SBR arm had unknown pre-ART BLVL and 6% of subjects in the FTC/RPV/TDF arm and 8% of subjects in the SBR arm had unknown pre-ART CD4 counts.

However, in a sensitivity analysis that included these proportions in the group with high baseline viral load or low CD4 count, differences with the actually obtained data on success or failure were not substantial; therefore no issues arise regarding the potential impact of baseline viral load on CD4 count.

2.5.3. Conclusions on the clinical efficacy

Study GS-US-264-0106 showed that switch from PI to RPV-based regimens is efficacious from a virological and immunological perspective, but that the simplification of regimen is not a major stimulus in adherence.

The results from this study could be added to section 5.1 of the SmPC to demonstrate the results of the switch in virologically suppressed patients if baseline viral loads at start of their very first regimen have been reviewed and did not influence treatment outcomes after switch.

2.6. Clinical safety aspects

2.6.1. Study GS-US-264-0106

Patient exposure

A total of 469 subjects received at least 1 dose of FTC/RPV/TDF, including 317 subjects in the FTC/RPV/TDF group and 152 subjects in the Delayed Switch group. The mean (SD) duration of exposure to FTC/RPV/TDF was 45.6 (9.21) weeks in the FTC/RPV/TDF group and 23.2 (3.93) weeks in the Delayed Switch group

Adverse events

The percentage of subjects who reported a treatment-related AE that was considered by the investigator to be related to study drug was similar between the FTC/RPV/TDF group (24.9%) and the Delayed Switch group (23.0%) during 48 and 24 weeks of FTC/RPV/TDF therapy, respectively. The percentage of subjects who reported a treatment-related AE that was considered by the investigator to be related to study drug was lower among the subjects remaining on their current ARV regimen for the first 24 weeks of the study (2.5% in the SBR group).

Table 15. GS-US-264-0106: Overall Summary of Adverse Events (Safety Analysis Set)

	FTC/RPV/TDF (N=317)	SBR (N=159)	Delayed Switch to FTC/RPV/TDF (N=152)	Total FTC/RPV/TDF (N=469)[a]
Subjects Experiencing Any Treatment-Emergent Adverse Event	253 (79.8%)	91 (57.2%)	109 (71.7%)	362 (77.2%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event	18 (5.7%)	11 (6.9%)	12 (7.9%)	30 (6.4%)
Subjects Experiencing Any Grade 2, 3 or 4 Treatment-Emergent Adverse Event	138 (43.5%)	39 (24.5%)	47 (30.9%)	185 (39.4%)
Subjects Experiencing Any Treatment-Emergent Adverse Event Related to Study Drug	79 (24.9%)	4 (2.5%)	35 (23.0%)	114 (24.3%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event Related to Study Drug	3 (0.9%)	0	4 (2.6%)	7 (1.5%)
Subjects Experiencing Any Grade 2, 3 or 4 Treatment-Emergent Adverse Event Related to Study Drug	31 (9.8%)	1 (0.6%)	11 (7.2%)	42 (9.0%)
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	18 (5.7%)	8 (5.0%)	9 (5.9%)	27 (5.8%)
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event Related to Study Drug	3 (0.9%)	0	0	3 (0.6%)
Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Permanent Discontinuation of Study Drug	7 (2.2%)	0	6 (3.9%)	13 (2.8%)
Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Temporary Interruption of Study Drug	3 (0.9%)	0	2 (1.3%)	5 (1.1%)

Note: Safety Analysis Set includes subjects who were enrolled into the study and received at least one dose of study drug. Adverse events are mapped according to MedDRA Version 15.

a Total FTC/RPV/TDF group includes subjects from the FTC/RPV/TDF and Delayed Switch to FTC/RPV/TDF groups.

Grade 2, 3, or 4 treatment-emergent AEs were reported in

- 43.5% of subjects in the FTC/RPV/TDF group,
- 24.5% of subjects in the SBR group, and
- 30.9% of subjects in the Delayed Switch group.

Grade 3 or 4 treatment-emergent AEs were reported in

- 5.7% of subjects in the FTC/RPV/TDF group,
- 6.9% of subjects in the SBR group, and
- 7.9% of subjects in the Delayed Switch group.

Thirteen subjects permanently discontinued study drug due to treatment-emergent AEs (7 in the FTC/RPV/TDF group and 6 in the Delayed Switch group).

Treatment-emergent AEs

The only Grade 2, 3, or 4 treatment-emergent AEs reported in $\geq$ 2% of subjects in the FTC/RPV/TDF group receiving up to 48 weeks of treatment included depression (3.2%), diarrhoea (2.8%), back pain (2.5%), and headache (2.2%).

Grade 2, 3, or 4 treatment-emergent AEs reported in $\geq$ 2% of subjects the Delayed Switch group receiving up to 24 weeks of FTC/RPV/TDF included diarrhoea, nasopharyngitis, upper respiratory tract infection, gastroenteritis, procedural pain, depression, and insomnia (each reported in 2.0% of subjects).

There were no treatment-emergent AEs of Grade 2 severity or greater that occurred in ≥2% of subjects in the SBR group.

Table 16. GS-US-264-0106: Treatment-Emergent Adverse Events Reported in at Least 2% of Subjects in Any Treatment Group (Safety Analysis Set)

	FTC/RPV/TDF (N=317)	SBR (N=159)	Delayed Switch to FTC/RPV/ TDF (N=152)	Total FTC/RPV/ TDF (N=469)a
Subjects With Any Treatment-Emergent Adverse Event	253 (79.8%)	91 (57.2%)	109 (71.7%)	362 (77.2%)
Subjects With Any Treatment-Emergent Adverse Event By System Organ Class and Preferred Term				
GASTROINTESTINAL DISORDERS	86 (27.1%)	26 (16.4%)	43 (28.3%)	129 (27.5%)
DIARRHOEA	32 (10.1%)	8 (5.0%)	6 (3.9%)	38 (8.1%)
NAUSEA	12 (3.8%)	5 (3.1%)	10 (6.6%)	22 (4.7%)
ABDOMINAL PAIN	8 (2.5%)	2 (1.3%)	6 (3.9%)	14 (3.0%)
CONSTIPATION	7 (2.2%)	3 (1.9%)	5 (3.3%)	12 (2.6%)
HAEMORRHOIDS	5 (1.6%)	1 (0.6%)	3 (2.0%)	8 (1.7%)
DYSPEPSIA	2 (0.6%)	2 (1.3%)	5 (3.3%)	7 (1.5%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	52 (16.4%)	15 (9.4%)	10 (6.6%)	62 (13.2%)
FATIGUE	22 (6.9%)	5 (3.1%)	3 (2.0%)	25 (5.3%)
PYREXIA	11 (3.5%)	5 (3.1%)	3 (2.0%)	14 (3.0%)
CHEST PAIN	4 (1.3%)	2 (1.3%)	4 (2.6%)	8 (1.7%)
HEPATOBILIARY DISORDERS	7 (2.2%)	0	3 (2.0%)	10 (2.1%)
CYTOLYTIC HEPATITIS	1 (0.3%)	0	3 (2.0%)	4 (0.9%)
INFECTIONS AND INFESTATIONS	125 (39.4%)	47 (29.6%)	49 (32.2%)	174 (37.1%)
NASOPHARYNGITIS	28 (8.8%)	8 (5.0%)	8 (5.3%)	36 (7.7%)
UPPER RESPIRATORY TRACT INFECTION	11 (3.5%)	5 (3.1%)	13 (8.6%)	24 (5.1%)
BRONCHITIS	13 (4.1%)	4 (2.5%)	5 (3.3%)	18 (3.8%)
SINUSITIS	10 (3.2%)	4 (2.5%)	1 (0.7%)	11 (2.3%)
GASTROENTERITIS	4 (1.3%)	1 (0.6%)	5 (3.3%)	9 (1.9%)
ORAL HERPES	8 (2.5%)	1 (0.6%)	1 (0.7%)	9 (1.9%)
HERPES SIMPLEX	7 (2.2%)	1 (0.6%)	1 (0.7%)	8 (1.7%)
SYPHILIS	5 (1.6%)	2 (1.3%)	3 (2.0%)	8 (1.7%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	29 (9.1%)	10 (6.3%)	11 (7.2%)	40 (8.5%)
PROCEDURAL PAIN	2 (0.6%)	1 (0.6%)	3 (2.0%)	5 (1.1%)
INVESTIGATIONS	34 (10.7%)	5 (3.1%)	11 (7.2%)	45 (9.6%)
ALANINE AMINOTRANSFERASE INCREASED	4 (1.3%)	1 (0.6%)	4 (2.6%)	8 (1.7%)
METABOLISM AND NUTRITION DISORDERS	25 (7.9%)	6 (3.8%)	7 (4.6%)	32 (6.8%)
CELL DEATH	5 (1.6%)	0	3 (2.0%)	8 (1.7%)

	FTC/RPV/TDF (N=317)	SBR (N=159)	Delayed Switch to FTC/RPV/ TDF (N=152)	Total FTC/RPV/ TDF (N=469)a
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	54 (17.0%)	21 (13.2%)	26 (17.1%)	80 (17.1%)
ARTHRALGIA	16 (5.0%)	2 (1.3%)	3 (2.0%)	19 (4.1%)
BACK PAIN	9 (2.8%)	6 (3.8%)	6 (3.9%)	15 (3.2%)
PAIN IN EXTREMITY	6 (1.9%)	2 (1.3%)	3 (2.0%)	9 (1.9%)
MYALGIA	5 (1.6%)	2 (1.3%)	3 (2.0%)	8 (1.7%)
NECK PAIN	3 (0.9%)	1 (0.6%)	4 (2.6%)	7 (1.5%)
MUSCLE SPASMS	2 (0.6%)	0	3 (2.0%)	5 (1.1%)
NERVOUS SYSTEM DISORDERS	48 (15.1%)	15 (9.4%)	22 (14.5%)	70 (14.9%)
HEADACHE	28 (8.8%)	6 (3.8%)	5 (3.3%)	33 (7.0%)
DIZZINESS	7 (2.2%)	3 (1.9%)	5 (3.3%)	12 (2.6%)
PSYCHIATRIC DISORDERS	62 (19.6%)	10 (6.3%)	20 (13.2%)	82 (17.5%)
INSOMNIA	20 (6.3%)	3 (1.9%)	8 (5.3%)	28 (6.0%)
DEPRESSION	14 (4.4%)	4 (2.5%)	5 (3.3%)	19 (4.1%)9
ABNORMAL DREAMS	6 (1.9%)	0	3 (2.0%)	(1.9%)
SLEEP DISORDER	7 (2.2%)	1 (0.6%)	0	7 (1.5%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	38 (12.0%)	9 (5.7%)	13 (8.6%)	51 (10.9%)
COUGH	19 (6.0%)	1 (0.6%)	1 (0.7%)	20 (4.3%)
SINUS CONGESTION	1 (0.3%)	0	4 (2.6%)	5 (1.1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	60 (18.9%)	9 (5.7%)	16 (10.5%)	76 (16.2%)
RASH	7 (2.2%)	2 (1.3%)	4 (2.6%)	11 (2.3%)
ECZEMA	7 (2.2%)	1 (0.6%)	1 (0.7%)	8 (1.7%)
PRURITUS	5 (1.6%)	0	3 (2.0%)	8 (1.7%)

AEs related to study drug

The percentage of subjects who reported an AE that was considered by the investigator to be related to study drug was:

- 2.5% in the SBR group
- 24.9% in the Eviplera group
- 23.0% in the delayed switch group

The most frequently reported study drug-related AEs included

- nausea (2.2% in the FTC/RPV/TDF group and 5.9% in the Delayed Switch group)
- diarrhoea (3.2% in FTC/RPV/TDF, 0.6% in SBR , 2.6% in the Delayed Switch group)
- fatigue (3.5% in the FTC/RPV/TDF group).

Study drug-related AEs of Grade 2 or higher reported in more than 2 subjects included

- nausea (3 subjects in the FTC/RPV/TDF group and 2 subjects in the Delayed Switch group),
- diarrhoea (3 subjects in the FTC/RPV/TDF group and 1 subject in the Delayed Switch group),
- abdominal pain (1 subject in the FTC/RPV/TDF group and 2 subjects in the Delayed Switch group),
- fatigue (3 subjects in the FTC/RPV/TDF group),
- ALT increased (2 subjects in the FTC/RPV/TDF group and 1 subject in the Delayed Switch group),
- cell death (3 subjects in the FTC/RPV/TDF group and 1 subject in the Delayed Switch group),
- insomnia (2 subjects in the FTC/RPV/TDF group and 1 subject in the Delayed Switch group).

Grade 3 study drug-related AEs occurred in 1 subject each and included the following: fatigue, ALT increased, AST increased, blood creatine phosphokinase increased, decreased appetite, rhabdomyolysis, amnesia, depression, insomnia, renal impairment, and dyspnoea. No Grade 4 study drug related AEs were reported.

Psychiatric disorders

Psychiatric disorders that were considered to be related to study drug occurred much more frequently in the FTC/RPV/TDF group:

Table 17. GS-US-264-0106: Treatment-Emergent Adverse Events Related to Study Drug (Safety Analysis Set)

	FTC/RPV/TDF (N=317)	SBR (N=159)	Delayed Switch to FTC/RPV/TDF (N=152)	Total FTC/RPV/TDF (N=469)
PSYCHIATRIC DISORDERS	19 (6.0%)	0	5 (3.3%)	24 (5.1%)
ABNORMAL DREAMS	6 (1.9%)	0	3 (2.0%)	9 (1.9%)
INSOMNIA	7 (2.2%)	0	2 (1.3%)	9 (1.9%)
SLEEP DISORDER	5 (1.6%)	0	0	5 (1.1%)
AGITATION	1 (0.3%)	0	1 (0.7%)	2 (0.4%)
DEPRESSION	2 (0.6%)	0	0	2 (0.4%)
RESTLESSNESS	2 (0.6%)	0	0	2 (0.4%)
ANXIETY	1 (0.3%)	0	0	1 (0.2%)
ANXIETY DISORDER	1 (0.3%)	0	0	1 (0.2%)
LIBIDO DECREASED	1 (0.3%)	0	0	1 (0.2%)
NERVOUSNESS	1 (0.3%)	0	0	1 (0.2%)

There were no study drug-related AEs in the psychiatric disorders in the SBR group during the first 24 weeks of the study.

In the group receiving FTC/RPV/TDF study drug-related disorders were

- abnormal dreams: 6 (1.9%)
- sleep disorder: 5 (1.6%)
- insomnia: 7 (2.2%)
- and other disorders in single subjects: agitation, depression/restlessness (in 2 subjects), anxiety, libido decreased, nervousness

Suicidal ideation was reported by 2 subjects, 1 in the FTC/RPV/TDF and 1 subject in the Delayed Switch group, but both of these SAEs of suicidal ideation resolved while study drug was on-going. Also in the FTC/RPV/TDF group 1 subject temporarily interrupted treatment due to affective disorder during 6 days and 1 subject experienced an exacerbation of bipolar disorder.

Nervous system disorders

Twelve of 317 subjects (3.8%) in the FTC/RPV/TDF group and 8 of 152 subjects (5.3%) in the Delayed Switch group reported AEs in the nervous system disorders (headache, disturbance of attention, dizziness, paraesthesia, lethargy, and ageusia, amnesia, memory impairment and somnolence) that were considered by the investigator to be related to study drug, but in the SBR group only one (hyperesthesia) was reported.

Also 3 SAE were reported (hypaesthesia, peripheral neuropathy, sensory loss) in the FTC/RPV/TDF group, there resolved and in two cases resulted in temporary interruption of cART.

Hepatobiliary disorders

Seven subjects in the FTC/RPV/TDF group, 3 in the delayed switch and 0 in the SBR group experienced hepatobiliary disorders: 2 hypertransaminasaemia and other events in single cases in FTC/RPV/TDF and 3 in the delayed switch (cytolytic hepatitis), steatosis (2 subjects in FTC/RPV/TDF.

Four subjects (1.3%) in the FTC/RPV/TDF group and 3 subjects (2.0%) in the Delayed Switch group reported AEs of cell death (cytolysis) that were considered by the investigator to be related to study drug No subjects reported an AE in the hepatobiliary disorders SOC or PT cell death while remaining on their baseline ARV regimen (SBR group) during the first 24 weeks of the study.

Two subjects experienced AEs of liver-related laboratory abnormalities (transaminase increase) resulting in permanent discontinuation of study drug; both in the Delayed Switch group.

Rash

Seven of 317 subjects (2.2%) in the FTC/RPV/TDF group and 4 of 152 subjects (2.6%) in the Delayed Switch group reported rash during the study. Two subjects (1.3%) remaining on their baseline ARV regimen (SBR group) during the first 24 weeks of the study reported AEs of rash. All were non-serious and 3 were considered related to study drug, all in RPV-receiving subjects, that resulted in temporary interruption of study medication in 1 subject.

Serious adverse event / deaths / other significant events

No subjects died during the study.

Table 18. GS-US-264-0106: Treatment-Emergent Serious Adverse Events Reported in at Least 2 Subjects (Safety Analysis Set)

	FTC/RPV/TDF (N=317)	SBR (N=159)	Delayed Switch to FTC/RPV/TDF (N=152)	Total FTC/RPV/TDF (N=469)[a]
Subjects With Any Treatment-Emergent Serious Adverse Event	18 (5.7%)	8 (5.0%)	9 (5.9%)	27 (5.8%)
Subjects With Any Treatment-Emergent Serious Adverse Event By System Organ Class and Preferred Term				
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (0.6%)	1 (0.6%)	1 (0.7%)	3 (0.6%)
CHEST PAIN	1 (0.3%)	0	1 (0.7%)	2 (0.4%)
PYREXIA	1 (0.3%)	1 (0.6%)	0	1 (0.2%)
INFECTIONS AND INFESTATIONS	6 (1.9%)	5 (3.1%)	1 (0.7%)	7 (1.5%)
PNEUMONIA	3 (0.9%)	0	0	3 (0.6%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 (0.9%)	1 (0.6%)	1 (0.7%)	4 (0.9%)
POLYARTHRITIS	0	1 (0.6%)[b]	1 (0.7%)[b]	1 (0.2%)
PSYCHIATRIC DISORDERS	3 (0.9%)	0	1 (0.7%)	4 (0.9%)
SUICIDAL IDEATION	1 (0.3%)	0	1 (0.7%)	2 (0.4%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (0.9%)	0	1 (0.7%)	4 (0.9%)
DYSPNOEA	1 (0.3%)	0	1 (0.7%)	2 (0.4%)

Three subjects (all in the FTC/RPV/TDF group) experienced treatment-emergent SAEs that were considered by the investigator to be related to study drug: toxic nephropathy due to TDF without treatment interruption & renal impairment and dyspnoea the latter two resulting in permanent discontinuation.

Discontinuation due to adverse events

Thirteen subjects permanently discontinued study drug due to a treatment-emergent AE (7 in the FTC/RPV/TDF group and 6 in the Delayed Switch group). Of these 13 subjects, 12 subjects discontinued study drug due to an AE before Week 48 and 1 subject discontinued study drug due to an AE that occurred after Week 48 during the extension phase. No subjects discontinued from the study due to a treatment-emergent AE while remaining on their baseline ARV regimen (SBR group).

Reasons for discontinuation were:

- 2 cases of depression in the FTC/RPV/TDF group
- 2 cases of insomnia, one in each group with RPV
- one: abdominal distension or pain, dyspepsia, fatigue, cytolytic hepatitis, ALT or AST or both transaminases increased, back pain, osteoporosis, headache, agitation, anxiety, glycosuria, proteinuria, renal impairment, cough, dyspnoea, respiratory tract congestion, throat tightness, hyperhidrosis, and hot flush.

Grade 3 treatment-emergent AEs that resulted in permanent discontinuation of study drug included headache in 1 subject (FTC/RPV/TDF group); ALT and AST increased in 1 subject (Delayed Switch); agitation, anxiety, and depression in 1 Subject (FTC/RPV/TDF); depression in 1 Subject (FTC/RPV/TDF group); and dyspnoea (SAE) in 1 Subject (FTC/RPV/TDF group).

Grade 4 treatment-emergent AEs reported during the study included suicidal ideation (Delayed Switch group), pyrexia (SBR group), blood creatine phosphokinase increased (Delayed Switch group), and acute respiratory failure and asthma (FTC/RPV/TDF group) . None of these events were considered by the investigator to be related to study drug. All of these Grade 4 treatment-emergent AEs were considered to be SAEs.

No Grade 4 treatment-emergent AE resulted in permanent discontinuation of study drug.

Temporary interruptions

Five subjects had treatment-emergent AEs resulting in temporary interruption of study drug (3 subjects [0.9%] in the FTC/RPV/TDF group and 2 subjects [1.3%] in the Delayed Switch group), but none in the SBR group. Only one case was considered related to study drug: rash and decreased appetite in 1 subject.

Laboratory findings

The severity of laboratory abnormalities was graded on a 4-point scale: mild (Grade 1), moderate (Grade 2), severe (Grade 3), and possibly life threatening (Grade 4).

Treatment emergent laboratory abnormalities were reported in

- FTC/RPV/TDF: Grade 1 in 47.6% of subjects, Grade 2 in 25.6% of subjects, Grade 3 in 6.6%, Grade 4 in 2.2%
- SBR group: Grade 1 in 39.6% , Grade 2 in 27.7%, Grade 3 in 8.2%, Grade 4 in 3.1%
- Delayed Switch group: Grade 1 in 45.4%, Grade 2 in 23.7%, Grade 3 in 13.2%, Grade 4 in 2.0%

Treatment emergent laboratory abnormalities

FTC/RPV/TDF group
Grade 3 or 4 treatment-emergent laboratory abnormalities reported in more than 1 subject in the FTC/RPV/TDF group included increased creatine kinase (8 subjects), elevated ALT (5 subjects), elevated AST (5 subjects), decreased absolute neutrophil count (3 subjects), increased amylase (3 subjects), increased lipase (3 subjects), and haematuria (5 subjects).

SBR group

Grade 3 or 4 treatment-emergent laboratory abnormalities reported in more than 1 subject in the SBR group included increased bilirubin (10 subjects), increased creatine kinase (3 subjects), elevated AST (3 subjects), and increased triglycerides (2 subjects).

Delayed switch group

Grade 3 or 4 treatment-emergent laboratory abnormalities reported in more than 1 subject (Weeks 24–48) included increased creatine kinase (7 subjects), elevated ALT (7 subjects), elevated AST (3 subjects), decreased absolute neutrophil count (2 subjects), and glycosuria (2 subjects).

No SAEs of individual laboratory abnormalities were reported during the study, other than high CPK in the delayed switch group, that was considered to be not related to study drug and did not result in discontinuation and resolved partly.

Table 19. GS-US-264-0106: Grade 3 or 4 Treatment-Emergent Laboratory Abnormalities (Safety Analysis Set)

	FTC/RPV/TDF (N=317)	SBR (N=159)	Delayed Switch to FTC/RPV/TDF (N=152)	Total FTC/RPV/TDF (N=469)[a]
Subjects With a Maximum Postdose Toxicity Grade 3 or 4 Treatment-Emergent Laboratory Abnormality, n (%)				
Grade 3	21 (6.6)	13 (8.2)	20 (13.2)	41 (8.7)
Grade 4	7 (2.2)	5 (3.1)	3 (2.0)	10 (2.1)
Absolute Neutrophil Count				
Grade 3	3 (0.9)	1 (0.6)	2 (1.3)	5 (1.1)
ALT				
Grade 3	4 (1.3)	1 (0.6)	6 (3.9)	10 (2.1)
Grade 4	1 (0.3)	0	1 (0.7)	2 (0.4)
Amylase (Total Amylase)				
Grade 3	2 (0.6)	1 (0.6)	1 (0.7)	3 (0.6)
Grade 4	1 (0.3)	0	0	1 (0.2)
AST				
Grade 3	4 (1.3)	1 (0.6)	2 (1.3)	6 (1.3)
Grade 4	1 (0.3)	2 (1.3)	1 (0.7)	2 (0.4)
Bilirubin (Hyperbilirubinemia)				
Grade 3	0	9 (5.7)	1 (0.7)	1 (0.2)
Grade 4	0	1 (0.6)	0	0
Cholesterol (Hypercholesterolemia)				
Grade 3	0	1 (0.7)	0	0
Creatine Kinase				
Grade 3	3 (0.9)	1 (0.6)	5 (3.3)	8 (1.7)
Grade 4	5 (1.6)	2 (1.3)	2 (1.3)	7 (1.5)
Gamma Glutamyl Transferase				
Grade 3	1 (0.3)	0	1 (0.7)	2 (0.4)
Glucose (Hyperglycemia)				
Grade 3	1 (0.3)	1 (0.6)	1 (0.7)	2 (0.4)
Lipase				
Grade 3	3 (18.8)	0	0	3 (16.7)
Triglycerides				
Grade 3	1 (0.3)	0	0	1 (0.2)
Grade 4	0	2 (1.3)	0	0
Urine Glucose (Glycosuria)				
Grade 3	1 (0.3)	1 (0.6)	2 (1.3)	3 (0.6)
Urine Occult Blood (Hematuria)				
Grade 3	5 (1.6)	1 (0.6)	1 (0.7)	6 (1.3)
Urine Protein (Proteinuria)				
Grade 3	0	0	1 (0.7)	1 (0.2)

Study drug related laboratory abnormalities

Study drug-related AEs of laboratory abnormalities that were reported in at least 2 subjects in any treatment group included:

- ALT increased (3 subjects [0.9%] in the FTC/RPV/TDF group and 2 subjects [1.3%] in the Delayed Switch group),
- AST increased (1 subject [0.3%] in the FTC/RPV/TDF group and 1 subject [0.7%] in the Delayed Switch group)
- transaminases increased (2 subjects [1.3%] in the Delayed Switch group),
- liver function test abnormal (4 subjects [1.3%] in the FTC/RPV/TDF group and 1 subject [0.7%] in the Delayed Switch group),
- proteinuria (4 subjects [1.3%] in the FTC/RPV/TDF group and 1 subject [0.7%] in the Delayed Switch group).

Quantitative change of laboratory abnormalities: worsening by 3 grades

Treatment-emergent marked laboratory abnormalities were defined as values that worsened by at least 3 toxicity grades from baseline to any postbaseline time point up to 30 days after the last dose date.

FTC/RPV/TDF group

Treatment-emergent marked laboratory abnormalities were reported in 28 subjects:

- increased creatine kinase (8 subjects),
- elevated ALT (4 subjects),
- elevated AST (5 subjects),
- haematuria (5 subjects),
- increased amylase (3 subjects),
- increased lipase (2 subjects),
- decreased absolute neutrophil count (2 subjects),
- elevated GGT (1 subject),
- increased triglycerides (1 subject),
- glycosuria (1 subject).

SBR group

Nine subjects in the SBR group had at least 1 marked clinical laboratory abnormality during the first 24 weeks of the study:

- increased creatine kinase (3 subjects),
- elevated AST (3 subjects),
- elevated ALT (1 subject),
- elevated triglycerides (2 subjects),
- hyperbilirubinemia (1 subject),
- decreased absolute neutrophil count (1 subject),
- urine glucose (1 subject),

- haematuria (1 subject).

Delayed Switch group

In this group 16 subjects had a marked clinical laboratory abnormality:

- creatine kinase (6 subjects),
- elevated ALT (5 subjects),
- elevated AST (3 subjects),
- glycosuria (2 subjects),
- haematuria (1 subject),
- proteinuria (1 subject),
- hyperbilirubinemia (1 subject)

Renal parameters

In vitro, RPV has been shown to inhibit organic cation transporter 2 (OCT2), a renal transporter involved in creatinine tubular secretion. Overall, serum creatinine elevations were evident by Week 4 and stable through Week 24 in subjects receiving FTC/RPV/TDF compared to subjects remaining on their baseline ARV regimen (SBR group).

At Week 24, the mean increase in serum creatinine was statistically significantly greater in the FTC/RPV/TDF group compared with the SBR group (mean [SD] increase of 0.05 [0.119] mg/dL vs. 0.01 [0.103] mg/dL, respectively; $p < 0.001$). The increase in serum creatinine was generally maintained through Week 48 in the FTC/RPV/TDF group (mean [SD] increase of 0.05 [0.115) mg/dL at Week 48). An increase in serum creatinine was also observed in the Delayed Switch group over 24 weeks of FTC/RPV/TDF therapy.

This increase was not worse in case of co-administration of TDF in the regimen, because in RPV-containing regimens similar trends were demonstrated with or without concomitant TDF.

Accordingly, decreases in estimated CLcr using Cockcroft-Gault were evident by Week 4 and stable through Week 24 in subjects receiving FTC/RPV/TDF compared to subjects in the SBR group: mean -3.5 versus -0.7 mL/min, respectively, which was evident also in the 24 weeks after delayed switch to Eviplera. No further decrease was observed in the period from week 24-48.

TDF in background regimen did not result in more decrease of eGFR compared to values obtained in subjects without TDF.

Study drug related renal SAE

One Subject in the FTC/RPV/TDF group had a study drug-related SAE of renal impairment (Grade 2) on Day 60 that was on-going at the end of the study. Concurrent AEs included glycosuria and proteinuria (both Grade 1). The subject was permanently discontinued from the study due to the events of renal impairment and proteinuria.

Another SAE was also considered to be related to study drug: on-going Nephropathy toxic (Grade 2) in 1 subject in the FTC/RPV/TDF group on Day 262, but no action was taken with the study drug.

Glucose

There were no clinically relevant changes from baseline in mean values for fasting glucose during the study.

Lipids

At study entry, 11.7% of subjects in the randomized FTC/RPV/TDF group and 18.2% of subjects in the SBR group reported use of a lipid-modifying agent. Few subjects (≤ 2.8% in each treatment group) added or modified the use of lipid-modifying agents during the study.

Overall, fasting total cholesterol, HDL cholesterol, direct LDL cholesterol, fasting triglycerides, and the ratio of total cholesterol/HDL cholesterol decreased to a greater extent through Week 24 among subjects switching to FTC/RPV/TDF at study baseline (randomized FTC/RPV/TDF group) versus those maintaining their baseline PI + 2 NRTIs regimen (SBR group). Overall differences between these treatment groups for all 5 of these lipid parameters were statistically significant at Week 24 ($p < 0.001$). At Week 24, the mean (SD) changes from baseline were as follows:

- Fasting total cholesterol: −25 (30.2) mg/dL in the FTC/RPV/TDF group and −1 (25.9) mg/dL in the SBR group
- Fasting HDL cholesterol: −4 (10.3) mg/dL in the FTC/RPV/TDF group and −1 (8.2) mg/dL in the SBR group
- Fasting direct LDL cholesterol: −16 (25.6) mg/dL in the FTC/RPV/TDF group and 0 (23.7) mg/dL in the SBR group
- Fasting triglycerides: −53 (110.1) mg/dL in the FTC/RPV/TDF group and 3 (100.1) mg/dL in the SBR group
- Ratio of fasting total cholesterol/HDL cholesterol: −0.27 (0.913) in the FTC/RPV/TDF group and 0.08 (0.771) mg/dL in the SBR group

After subjects in the SBR group switched to FTC/RPV/TDF therapy at Week 24 (i.e. entered the Delayed Switch group), similar decreases in lipid parameters were observed in the Delayed Switch group over Weeks 24 to 48 of the study as were observed during the first 24 weeks of therapy in the randomized FTC/RPV/TDF group.

In general, mean decreases from baseline to Week 24 of FTC/RPV/TDF therapy were larger in subjects with prior LPV/r use at study entry compared with those without prior LPV/r use.

When the mean values and mean changes from baseline in fasting glucose and lipid parameters were analysed excluding subjects who started/modified lipid-lowering agents during the study, results were very similar to those described above for the analyses including these subjects.

<u>Increase in percentage of subjects with normal total cholesterol, LDL and triglycerides</u>

The increase in the percentage of subjects with desirable total cholesterol levels observed at Weeks 12 and 24 in the randomized FTC/RPV/TDF group were generally maintained through Week 48 of therapy. After subjects in the SBR group switched to FTC/RPV/TDF therapy at Week 24 (ie, entered the Delayed Switch group), similar fasting total cholesterol category results were observed in the Delayed Switch group over Weeks 24 to 48 of the study as were observed during the first 24 weeks of therapy in the randomized FTC/RPV/TDF group described above.

HDL levels were not significantly affected in the 3 groups.

LDL cholesterol: more subjects in the FTC/RPV/TDF group obtained optimal categories of LDL after 12 and 24 weeks than in the SBR group. The increases in the percentage of subjects with optimal and near optimal fasting direct LDL levels and the decreases in the percentages of subjects with borderline high, high, and very high levels observed at Weeks 12 and 24 in the randomized FTC/RPV/TDF group were generally maintained through Week 48 of therapy and the Delayed switch group mimicked these trends after switch from PI.

These trends were the same in the different triglyceride categories and for different categories of ratio of fasting total cholesterol:HDL.

Vital signs

Vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature) showed no consistent pattern of change during the course of therapy that would be suggestive of any clinically significant treatment-emergent effect.

2.6.2. Study GS-US-264-0111

Table 20. GS-US-264-0111: Overall Summary of Adverse Events (Safety Analysis Set)

Adverse Event Category, n (%)	FTC/RPV/TDF (N = 49)
Any Treatment-Emergent AE	43 (87.8%)
Any Grade 3 or 4 Treatment-Emergent AE	3 (6.1%)
Any Grade 2, 3, or 4 Treatment-Emergent AE	21 (42.9%)
Any Treatment-Emergent AE Related to Study Drug	12 (24.5%)
Any Grade 3 or 4 Treatment-Emergent AE Related to Study Drug	0
Any Grade 2, 3, or 4 Treatment-Emergent AE Related to Study Drug	3 (6.1%)
Any Treatment-Emergent SAE	1 (2.0%)
Any Treatment-Emergent SAE Related to Study Drug	0
Any Treatment-Emergent AE That Caused Permanent Discontinuation or Temporary Interruption From Study Drug	0
Death	0

AEs in at least 2 subjects

Diarrhoea was the most frequently occurring treatment-emergent AE (8 subjects [16.3%]), followed by upper respiratory tract infection (7 subjects [14.3%]) and insomnia (6 subjects [12.2%].

Grade 3 events: There were four Grade 3 events reported in 3 subjects during the study:

1. bradycardia and dyspnoea in 1 subject (both SAEs),
2. haematuria in 1 subject,
3. nephrolithiasis in 1 subject.

The haematuria and nephrolithiasis were nonserious AEs and both resolved during the study. None of the Grade 3 AEs were considered by the investigator to be related to study drug. Both events did not result in discontinuation of study drug.

No subject experienced a Grade 4 AE.

Study drug related AEs: All other AEs were Grade 1 and 2 AEs, and 12 subjects (24.5%) experienced AEs during the study that were considered by the investigator to be related to study drug. The highest incidence of treatment-related AEs was in the SOC of gastrointestinal disorders (7 subjects [14.3%].

Table 21. GS-US-264-0111: Treatment-Emergent Serious Adverse Events Reported in at Least 2 Subjects (Safety Analysis Set)

Adverse Events[a] by System Organ Class and Preferred Term	FTC/RPV/TDF (N = 49)	
	n	%
Any Treatment-Emergent AE	43	87.8%
Endocrine Disorders	2	4.1%
Hypogonadism	2	4.1%
Gastrointestinal Disorders	20	40.8%
Diarrhoea	8	16.3%
Abdominal Pain	4	8.2%
Nausea	3	6.1%
Flatulence	2	4.1%
Rectal haemorrhage	2	4.1%
Vomiting	2	4.1%
General Disorders and Administration Site Conditions	9	18.4%
Fatigue	4	8.2%
Infections and Infestations	22	44.9%
Upper respiratory tract infection	7	14.3%
Sinusitis	5	10.2%
Pharyngitis	4	8.2%
Syphilis	3	6.1%
Urethritis	3	6.1%
Bronchitis	2	4.1%
Influenza	2	4.1%
Investigations	5	10.2%
Anal pap smear abnormal	2	4.1%
Metabolism and Nutrition Disorders	4	8.2%
Vitamin D Deficiency	2	4.1%
Musculoskeletal and Connective Tissue Disorders	11	22.4%
Back pain	4	8.2%
Psychiatric Disorders	14	28.6%
Insomnia	6	12.2%
Anxiety	3	6.1%
Depression	3	6.1%
Abnormal Dreams	2	4.1%

Psychiatric disorders: Adverse events in the psychiatric disorders SOC were reported in 14 subjects (28.6%), with the most frequently occurring AE in that SOC being insomnia (6 subjects [12.2%]). Anxiety and depression were reported in 3 subjects (6.1%) each and abnormal dreams were reported in 2 subjects (4.1%). Attention deficit/hyperactivity disorder and stress were reported in 1 subject (2.0%) each.

Nervous system disorders: Adverse events reported in the nervous system disorders SOC occurred in 7 subjects (14.3%). The following events were reported in 1 subject (2.0%) each: amnesia, cervicobrachial syndrome, disturbance in attention, dizziness, headache, poor quality sleep, and psychomotor hyperactivity.

Rash: Two subjects (4.1%) experienced a rash during the study, both of which were Grade 1; 1 of the rash AEs was considered related to study drug by the investigator.

Laboratory findings

Two subjects each had a Grade 3 increased creatine kinase value, and a Grade 4 increased creatine kinase value was reported in 1 subject. No other Grade 3 or 4 laboratory abnormalities were reported for any other parameter during the study.

Two subjects with increased serum amylase had elevated values at screening and baseline.

Creatinine

Serum creatinine elevations were evident by Week 4 (mean change of +0.07 mg/dL) and stable through Week 48 (mean change of +0.08 mg/dL; this effect has been known since the development of RPV and has been associated with creatinine secretion inhibition.

Lipids

There were statistically significant decreases in fasting total cholesterol, triglycerides, and direct LDL cholesterol at Week 48, that started as early as week 12.

Table 22. GS-US-264-0111: Median (Q1,Q2) of Observed Fasting Lipid Parameters and Change from Baseline (Safety Analysis Set)

Fasting Lipid Parameter	Baseline Median (Q1, Q3)	Week 48 Median (Q1, Q3)	Median Change from Baseline at Week 48 (Q1, Q3)	p-value [a]
Total Cholesterol	177 (159, 210)	159 (147, 194)	–17 (–38, 1)	< 0.001
	N = 48	N = 47	N = 46	
Direct LDL Cholesterol	113 (93, 132)	103 (82, 121)	–8 (–29, 7)	0.016
	N = 49	N = 47	N = 47	
HDL Cholesterol	49 (41, 58)	45 (40, 53)	–2 (–6, 2)	0.077
	N = 48	N = 47	N = 46	
Triglycerides	114 (86, 147)	92 (72, 136)	–26 (–50, –2)	< 0.001
	N = 48	N = 47	N = 46	

a P-value for comparison to baseline within treatment group is from Wilcoxon signed rank test.

2.6.3. Other safety results

Adverse events of interest

Elevated CPK

Data from Antiretroviral Treatment-Naive HIV-1 Infected Patients

In the ECHO/THRIVE studies in treatment-naive patients, no TEAEs relevant to elevated CPK were reported through 96 weeks of treatment; no CPK laboratory abnormality data were available from ECHO/ THRIVE. In Study GS-US-264-0110, similar frequencies of TEAEs and laboratory abnormalities relevant to elevated CPK were observed in the FTC/RPV/TDF and EFV/FTC/TDF arms ('blood creatine phosphokinase increased' as a TEAE occurred in 2.3% of subjects in the FTC/RPV/TDF arm and in 1.3% of subjects in the EFV/FTC/TDF arm; Grades 3 to 4 laboratory abnormalities involving CPK occurred in 5.1% of subjects in both arms; and marked laboratory abnormalities involving CPK occurred in 4.8% of subjects in the FTC/RPV/TDF arm and in 4.1% of subjects in the EFV/FTC/TDF arm).

Rhabdomyolysis as a TEAE was not reported in any of the studies in treatment-naive patients (through 96 weeks of treatment in ECHO/THRIVE and through 48 weeks of treatment in Study GS-US-264-0110).

Data from Antiretroviral Treatment-Experienced HIV-1 Infected Patients

In Study GS-US-264-0106, 'blood creatine phosphokinase increased' as a TEAE occurred at similar and low frequencies in all groups analysed in the study (0.6% over 24 weeks and 0.6% over 48 weeks in the FTC/RPV/TDF group, 0.6% over 24 weeks in the SBR group, and 1.3% over 24 weeks in the Delayed Switch to FTC/RPV/TDF group). Two subjects (No. 0369-3203 and No. 0369-3223) in the Delayed Switch to FTC/RPV/TDF group of Study GS-US-264-0106 experienced non-serious TEAEs of rhabdomyolysis. Both cases were reported by the same investigator in France and the non-serious nature of the events was confirmed by the investigator upon querying. One of the cases was considered to be Grade 3 in severity. In both subjects, the events resolved with FTC/RPV/TDF on-going and, per the investigator, the events were likely related to muscular exercise. In both cases, the reported event of rhabdomyolysis was associated with increased CPK levels, but no other muscle symptoms or laboratory abnormalities were reported.

No TEAEs involving elevated CPK or rhabdomyolysis were observed in Study GS-US-264-0111.

The frequency of elevated CPK as a Grade 3 to 4 laboratory abnormality and as a marked laboratory abnormality (defined as increasing by at least 3 toxicity grades from baseline) did not show a consistent effect in the FTC/RPV/TDF and Delayed Switch arms of Study GS-US-264-0106 (frequencies of 1.6% and 1.6% over 24 weeks in the FTC/RPV/TDF group, 2.5% and 2.5% over 48 weeks in the FTC/RPV/TDF group, 1.9% and 1.9% over 24 weeks in the SBR group, and 4.6% and 3.9% over 24 weeks in the Delayed Switch to FTC/RPV/TDF group for Grades 3 to 4 and for marked laboratory abnormalities, respectively). In Study GS-US-264-0111, the frequency of elevated CPK as a Grade 3 to 4 laboratory abnormality was 6.1% and as a marked laboratory abnormality was also 6.1%.

In 4 of 5 subjects who experienced increased CPK over 48 weeks of treatment in Study GS-US-264-0106 (2 in the FTC/RPV/TDF group, 1 in the SBR group, and 1 in the Delayed Switch group), the events resolved with continuing therapy, suggesting alternative aetiology. One subject (No. 5464-3272) in the FTC/RPV/TDF arm of Study GS-US-264-0106 who experienced a TEAE of ☐'blood creat
phosphokinase increased' and a Grade 4 laboratory abnormality of increased CPK was receiving a statin (atorvastatin calcium) during the study. In this subject, the event resolved with continuing

FTC/RPV/TDF therapy. In 1 subject in the Delayed Switch to FTC/RPV/TDF group, the event had not resolved at the time of the reporting, with on-going FTC/RPV/TDF treatment.

The MAH position was that elevated CPK can be caused by many factors, including, but not limited to, strenuous exercise, use of statins and viral infections. In Study GS-US-264-0106, 11.7% of subjects in the FTC/RPV/TDF group and 18.2% of subjects in the SBR group were using lipid-modifying medications (including statins) at baseline.

The MAH considered that in the light of the variety of alternative explanations for elevated CPK, the fact that the frequencies of CPK elevations in antiretroviral treatment-naive and antiretroviral treatment-experienced patients were low in patients receiving an RPV-containing regimen in clinical studies, and because elevated CPK is already described in the SmPC as an ADR for FTC, elevated CPK should not be included in the Eviplera SmPC as an ADR for RPV.

Diarrhoea

According to the MAH, the Phase 2b and 3 studies of RPV consistently showed a lower frequency of diarrhoea in the RPV arm compared to EFV, at the incidences previously shown. In the reported cases from the Phase 3 studies, time to onset was variable, there were no grade 4 events and only 1 grade 3 event of diarrhoea, and these events did not lead to permanent treatment discontinuation. A low proportion (4.2%) of subjects had events of diarrhoea considered at least possibly related to RPV by the investigators in the Phase 3 studies.

The MAH noted that the emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) background regimen, for which diarrhoea is listed as a very common ADR in the SmPC of both drugs, was associated with a higher incidence of diarrhoea than the other 2 background regimens (zidovudine (AZT)/lamivudine (3TC), and abacavir (ABC)/3TC) used in the registrational Phase 3 studies. The pattern of the lower incidence in the RPV arm compared to the EFV arm is observed with each background regimen. In the Week 96 subgroup analysis by background regimen, the incidence of diarrhoea with FTC/TDF was 15.6% (86/550) in the RPV arm versus 16.7% (91/546) for EFV the incidence of diarrhoea with AZT/3TC was 5.9% (6/101) versus 10.7%.(11/103); while the incidence of diarrhoea with ABC/3TC was 5.7% (2/35) compared to 27.3% (9/33). The observed frequency with the FTC/TDF background regimen was consistent with the known incidence of diarrhoea as a very common ADR (incidence ≥ 10.0%) for FTC/TDF. According to the MAH, this shows that RPV is unlikely to have contributed to the observed cases of diarrhoea in the RPV arm when the FTC/TDF background regimen was used. In addition, diarrhoea is listed as a common ADR to ABC, AZT, and 3TC providing an explanation for the observed cases of diarrhoea with the other background regimens. To exclude contributory effect of these background regimens, the MAH also considered data from a placebo-controlled Phase 1 study (TMC278-TiDP6-C152), where healthy subjects (N=60) received 11 days of treatment with RPV 25 mg qd or placebo. In this study, the frequency of diarrhoea was very low, occurring in 1/58 (1.7%) of subjects in the RPV arm and 2/59 (3.4%) on placebo.

2.6.4. Discussion on clinical safety

GS-US-264-0106

According to the results the new regimen was not an improvement compared to their old regimen in some specific areas:

- Any AE study drug related: 24% vs 2.5% (RPV vs continuation of PI-based regimen, respectively)

- Grade 2-4 study drug related: 9.9% vs 0%
- More nervous system disorders: 14.9% vs 9.4%
- More psychiatric disorders: 17.5% vs 6.3%
- More gastrointestinal disorders: 27.5% vs 16.4% (mostly diarrhoea and nausea)
- More frequent CK elevations are noticed while taking RPV

On the contrary, lipids were favourably affected by the switch to RPV, because significant decreases were noticed in cholesterol, LDL and triglycerides. However, these decreases did not seem to benefit patients in the short term, because only rarely did these decrease result in cessation of statin therapy (< 2.8%).

GS-US-264-0111

Safety issues were not prominent in study GS-US-264-0111 except the frequent occurrence of diarrhoea (16.3%) and insomnia (12.2%), and elevations in CK at least grade 3 (3/48; 6.3%). The observed improvement in lipids was not considered clinically relevant.

Tolerability

The proposed extension of the indication - treatment switch - is motivated by tolerability issues of the previous regimen, which suggests superiority of rilpivirine (RPV) on matters of tolerability, but that has not been subject of evaluation in well-designed studies. Findings from study GS-US-264-0106 demonstrated more treatment-emergent discontinuations due to RPV compared to continuation of initial PI-based regimens.

In addition to GS-US-264-0106, tolerability has been evaluated in the Phase III studies ECHO, THRIVE and GS-US-264-0110 according to the MAH. FTC/RPV/TDF was found to be well tolerated in all of these studies, and showed a differentiated safety profile compared to the control regimen.

It is recognised that there is an inherent bias in the design of any switch study (against the switch group) in virologically suppressed patients, because such studies select for enrolment those subjects who have been tolerating their baseline regimen.

The discontinuation rates due to TEAEs in Study GS-US-264-0106 for the subjects switching to Eviplera were comparable with the previous clinical experience of Eviplera:

- In study GS-US-264-0106 13 subjects permanently discontinued study drug due to a TEAE (7 of 317 subjects [2.2%] in the FTC/RPV/TDF group and 6 of 152 subjects [3.9%] in the Delayed Switch group).
- Pooled ECHO/THRIVE, Week 48 results reported discontinuation due to a TEAE of 2.2% (12/550) of subjects in the RPV + FTC/TDF subset versus 7.1% (39/546) of subjects in the EFV + FTC/TDF subset. Week 96 results reported discontinuation due to a TEAE of 3.6% (20/550) of subjects in the RPV + FTC/TDF subset versus 8.1% (44/546) of subjects in the EFV + FTC/TDF subset.
- In GS-US-264-0110, Week 48 results reported discontinuations due to a TEAE of 2.5% (10/394) of subjects in the FTC/RPV/TDF arm versus 8.7% (34/392) or subjects in the EFV/FTC/TDF arm.

The patient-reported symptom data (HIV symptom index) and lipid results from study GS-US-264-0106 for subjects suppressed on a PI-based regimen switching to FTC/RPV/TDF shows an improvement in these PI-mediated side effects.

It is also recognised that treatment switch could be motivated not only by tolerability issues with the previous regimen, but also for reasons of simplification of the ART to a single-tablet regimen.

The tolerability features of RPV-based regimens at initiation of cART or after switch have never been evaluated as primary endpoints in comparative and adequately powered studies, but physicians and patients can decide on the selection of any guideline-recommended ARV based on anticipated tolerability issues (e.g. known negative cardiovascular risk profile, renal impairment or history of psychiatric disorder etc) or perceived TEAEs on their current regimen. This could imply switching from PI to NNRTI as was done in study GS-US-264-0106, or any other change as considered clinically relevant in the management of that particular patient. As long as the ARV has demonstrated antiretroviral activity in that patient group, the decision on the selection of that particular ARV can be accepted. This has been demonstrated in the submitted studies.

Therefore while the concerns regarding tolerability of Eviplera have been only partly addressed, they should not prevent its use in the proposed target population.

The MAH considered that CPK elevations should be attributed to the other ARVs in the combination and not to RPV. Being more uncommon than diarrhoea, possible association between RPV and CK elevations become difficult to establish and various explanations can be provided including statin use. Because most elevations resolved without treatment discontinuation the link is debatable.

The occurrence of diarrhoea in different cohorts of patients receiving RPV, RPV in combination with other ARVs and comparison with occurrence of diarrhoea in subjects receiving either placebo or EFV was reported by the MAH. Increases in occurrence of diarrhoea in patients receiving RPV are considered minimal or largely influenced by co-administered ARVs.

2.6.5. Conclusions on clinical safety

Study GS-US-264-0106 showed that switch from PI to RPV-based regimen results in more intolerability and safety issues, including more RPV-related discontinuations. These AEs can be anticipated because most are known AEs.

Most patients stayed on Eviplera in study GS-US-264-0111 after switching from EFV/FTC/TDF, but considering the rapid virologic failure in 2/48 subjects after 24 weeks most likely associated with non-adherence and the reported gastrointestinal and psychiatric AEs the actual benefit of this switch in clinical practice is not evident. Since no patient satisfaction was examined, no data is available how the switch from EFV to RPV was appreciated by patients.

2.7. Risk management plan

2.7.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

The RMP v4.0 submitted to support this variation could be acceptable if the following issues were resolved:

- The RMP should be updated with the information that Eviplera might have a drug-drug interaction with other medications more sensitive to P-glycoprotein (P gp) activity than digoxin, as a result of CHMP opinion reached on 21 February 2013 (EMA/CHMP/99443/2013) related to variation (EMEA/H/C/002312/II/0020) following results from study TMC278IFD1001
- The MAH was requested to include as important potential risk:
    - Off-label use in patients with a viral load between 100,000 and 500,000 copies/ML
    - Off-label use in treatment experienced patients without virologic suppression

These issues should be monitored with routine pharmacovigilance including discussions in coming PSURs and in the Drug Utilization Study: Observational cohort study including a nested case-control study to assess rilpivirine (RPV) utilization according to the European SmPC, in line with current measures related to off-label use

- Concerning the *in vitro* studies on human colonic cell line, caco 2, to evaluate a potential inhibitory effect of tenofovir DF on absorption of phosphate in the gastrointestinal tract, the MAH is requested to inform authorities if new information becomes available, especially because the currently approved SmPC includes hypophosphatemia as a listed adverse event and the following statement *"This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil fumarate in the absence of this condition."*, which might not be appropriate if an inhibitory effect of TDF on gastrointestinal phosphate absorption would be found.

The CHMP endorsed this advice without changes.

The changes required in the RMP are either not applicable due to the withdrawal of the variation II/0023 or the rewording of the indication initially proposed for variation II/0021, or have already addressed in a subsequent RMP submission:

- RMP Version 5 Dated April 2013 (submitted with PSUR)
- RMP Version 6 dated September 2013 (submitted with PSUR)

The CHMP endorsed the Risk Management Plan with the following summary of the content:

2.7.2. Safety concerns

Table 23. Summary of the Safety Concerns (from MAH v5.0 RMP module SVIII)

Important Identified Risks	FTC, TDF	Post-treatment hepatic flares in HIV-1/HBV coinfected patients
	FTC, TDF	Lactic acidosis and severe hepatomegaly with steatosis
	FTC, TDF	Lipodystrophy
	RPV	Development of drug resistance
	TDF	Renal toxicity
	TDF	Bone events due to proximal renal tubulopathy/loss of BMD
	TDF	Interaction with didanosine
	TDF	Pancreatitis
Important Potential Risks	Eviplera, RPV	Overdose (including overdose through accidental concurrent use of Eviplera with any of its active components)
	Eviplera, RPV	Off-label use (in paediatric patients [< 18 years of age], treatment-naïve patients with a baseline viral load > 100,000 HIV-1 RNA copies/mL, or in ART-treatment-experienced patients for Eviplera; in adult and paediatric subjects for RPV)
	RPV	QT interval prolongation
	RPV	Hepatotoxicity
	RPV	Severe skin reactions
	RPV	Major depressive disorder
	RPV	Lipodystrophy
	RPV	Bleeding disorders
	RPV	Blood cortisol decreased
Missing Information	Eviplera	Safety information for Eviplera
	RPV, TDF	Safety in children (including long-term safety for TDF)
	FTC, RPV, TDF	Safety in elderly patients
	FTC, RPV, TDF	Safety in pregnancy
	FTC, RPV, TDF	Safety in lactation
	RPV, TDF	Safety in patients with renal impairment ($eGFR_{creat}$ <50 mL/min/1.73 m^2 for RPV)
	RPV	Safety in patients with severe hepatic impairment (CPT score C)
	RPV	Drug-drug interactions

2.7.3. Pharmacovigilance plans

On-going and Planned Additional Pharmacovigilance Studies / Activities in the Pharmacovigilance Plan

An overview of all on-going and planned studies in Categories 1-3 are described in below.

Table 24. On-going and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan (Categories 1-3)

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Interventional clinical studies (Category 3)				
GS-US-264-0110 A Phase 3B, Randomized, Open-label Study to Evaluate the Safety and Efficacy of a Single-Tablet Regimen of Emtricitabine/Rilpivirine/ Tenofovir Disoproxil Fumarate Compared with a Single-Tablet Regimen of Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults	To evaluate the safety and efficacy of FTC/RPV/TDF STR compared with EFV/FTC/TDF STR in HIV-1 infected, antiretroviral treatment-naïve adults	*Missing information*: Safety information for Eviplera (Eviplera)	Started	Final Week 96 report planned February 2014
TMC278IFD1003 A Phase 1, open-label trial in healthy subjects, to explore the pharmacokinetics of different dosing regimens of rilpivirine in combination with rifabutin, at steady-state.	To evaluate the effect of rifabutin on the pharmacokinetics of rilpivirine and evaluate potential alternative dosing regimens to overcome the interaction	*Missing information*: Drug-drug interactions (RPV)	Started	Final report planned Q2 2013
TMC278IFD1004 A Phase 1, open-label trial in healthy subjects to explore the potential for a pharmacokinetic interaction between steady-state rilpivirine and a single dose of metformin.	To evaluate the effect of rilpivirine on the pharmacokinetics of metformin and vice versa	*Missing information*: Drug-drug interactions (RPV)	Started	Final report planned Q3 2013

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
GS-99-903 A Phase 3, randomized, double-blind, multicentre study of the treatment of antiretroviral-naïve, HIV-1 infected patients comparing tenofovir disoproxil fumarate administered in combination with lamivudine and efavirenz versus stavudine, lamivudine, and efavirenz.	To evaluate the efficacy and safety of tenofovir DF versus stavudine, each administered in combination with lamivudine and efavirenz, in antiretroviral-naïve HIV-1 infected patients	*Important identified risk*: Bone events due to proximal renal tubulopathy/ loss of BMD (TDF)	Started	Final report planned 31 March 2014
GS-US-236-0103 A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Emtricitabine/ Tenofovir Disoproxil Fumarate/GS-9350 Versus Ritonavir-Boosted Atazanavir Plus Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults	To evaluate the safety and efficacy of Stribild versus ritonavir-boosted atazanavir plus emtricitabine/tenofovir DF in HIV-1 infected, antiretroviral treatment-naïve adults	*Important identified risk*: Bone events due to proximal renal tubulopathy/ loss of BMD (TDF)	Started	Interim Week 96 report planned Q2 2013
GS-US-104-0321 Phase 3, Randomized, Double-blind, Placebo-Controlled Study of the Safety and Efficacy of Tenofovir DF as Part of an Optimized Antiretroviral Regimen in HIV-1 Infected Adolescents	To evaluate the safety and efficacy of tenofovir DF as part of an optimized antiretroviral regimen in HIV-1 infected adolescents	*Important identified risk*: Bone events due to proximal renal tubulopathy/loss of BMD (TDF) *Missing information*: Safety in children (including long-term safety) (TDF)	Started	Final Week 336 report planned December 2014
GS-US-104-0352 A Phase 3, Randomized, Open-Label Study Comparing the Safety and Efficacy of Switching Stavudine or Zidovudine to Tenofovir Disoproxil Fumarate versus Continuing Stavudine or Zidovudine in Virologically Suppressed HIV-Infected Children Taking Highly Active Antiretroviral Therapy	To compare the safety and efficacy of switching stavudine or zidovudine to tenofovir DF versus continuing stavudine or zidovudine in virologically suppressed HIV-1 infected children taking HAART	*Important identified risk*: Bone events due to proximal renal tubulopathy/loss of BMD (TDF) *Missing information*: Safety in children (including long-term safety) (TDF)	Started	Final Week 336 report planned May 2015

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
GS-US-174-0102 A Randomized, Double-Blind, Controlled Evaluation of Tenofovir DF versus Adefovir Dipivoxil for the Treatment of Presumed Pre-Core Mutant Chronic Hepatitis B	To evaluate tenofovir DF versus adefovir dipivoxil for the treatment of presumed pre-core mutant chronic hepatitis B	*Important identified risk*: Bone events due to proximal renal tubulopathy/loss of BMD (TDF)	Started	Final report planned Q3 2014
GS-US-174-0103 A Randomized, Double-Blind, Controlled Evaluation of Tenofovir DF versus Adefovir Dipivoxil for the Treatment of HBeAg Positive Chronic Hepatitis B	To evaluate tenofovir DF versus adefovir dipivoxil for the treatment of HBeAg positive chronic hepatitis B	*Important identified risk*: Bone events due to proximal renal tubulopathy/loss of BMD (TDF)	Started	Final report planned Q3 2014
GS-US-174-0115 A Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Adolescents with Chronic Hepatitis B Infection	To evaluate the antiviral efficacy, safety and tolerability of tenofovir DF versus placebo in adolescents with chronic hepatitis B infection	*Important identified risk*: Bone events due to proximal renal tubulopathy/loss of BMD (TDF)	Started	Interim Week 192 report planned Q4 2013
GS-US-174-0121 A Randomized, Double-Blind, Double-Dummy Study Evaluating the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate (DF) Monotherapy Versus Emtricitabine plus Tenofovir DF Fixed-Dose Combination Therapy in Subjects with Chronic Hepatitis B who are Resistant to Lamivudine	To evaluate the antiviral efficacy, safety and tolerability of tenofovir DF monotherapy versus emtricitabine/tenofovir DF combination therapy in subjects with chronic hepatitis B who are resistant to lamivudine	*Important identified risk*: Bone events due to proximal renal tubulopathy/loss of BMD (TDF) *Missing information*: Safety in patients with renal impairment (TDF)	Started	Final report planned Q2 2015
GS-US-174-0127 A Phase 2, Multi-center, Open-label Study of Tenofovir Disoproxil Fumarate (DF) for the Treatment of Chronic Hepatitis B Subjects with Compensated or Decompensated Liver Disease and Moderate to Severe Renal Impairment	To evaluate tenofovir DF for the treatment of chronic hepatitis B subjects with compensated or decompensated liver disease and moderate to severe renal impairment	*Missing information*: Safety in patients with renal impairment (TDF)	Planned	To be confirmed

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
GS-US-174-0144 A Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Paediatric Patients with Chronic Hepatitis B Infection	To evaluate the antiviral efficacy, safety and tolerability of tenofovir DF versus placebo in paediatric patients with chronic hepatitis B infection	*Important identified risk*: Bone events due to proximal renal tubulopathy/loss of BMD (TDF) *Missing information*: Safety in children (including long-term safety) (TDF)	Planned	Interim Week 24 report planned Q2 2015 (PK data expected to be submitted by 30 June 2014)
GS-US-104-0427 A Phase 1 Pharmacokinetic Study Evaluating the Relative Bioavailability Between Tenofovir Disoproxil Fumarate (TDF) Oral Powder and Oral Tablet Formulation Under Fed Conditions	To evaluate the relative bioavailability between tenofovir DF oral powder and oral tablet formulation under fed conditions	*Missing information*: Safety in children (including long-term safety) (TDF)	Started	Final report planned 31 August 2013

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Noninterventional studies (Category 3)				
DUS Observational cohort study including a nested case-control study to assess RPV utilization according to the European SmPC	To assess the use of rilpivirine according to the SmPC for rilpivirine and the development of resistance in routine clinical practice	*Important identified risk*: Development of drug resistance (RPV) *Important potential risk:* Off-label use (in paediatric patients [< 18 years of age], treatment-naïve patients with a viral load > 100,000 HIV-1 RNA copies/mL, or in ART-treatment-experienced patients for Eviplera; in adult and paediatric subjects for RPV) (Eviplera, RPV) *Missing information*: Safety information for Eviplera (Eviplera)	Started	Final report planned Q2 2019

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Post-authorization safety study of HIV-1 infected paediatric patients Pharmacoepidemiology study to define the long-term safety profile of tenofovir disoproxil fumarate (TDF, Viread) and explore the management of TDF-associated renal and bone toxicity in HIV-infected children aged 2 to <18 years in Europe	To define the long-term safety profile of tenofovir DF and explore management of TDF-associated renal and bone toxicity in HIV infected children aged 2 to < 18 years in Europe	*Important identified risk*: Renal toxicity (TDF); Bone events due to proximal renal tubulopathy/loss of BMD (TDF) *Missing information*: Safety in children (including long-term safety) (TDF)	Planned	Interim report for HIV study (European Pharmaco-vigilance Study) planned 30 September 2014. Final report for HIV study (UK/Ireland Retrospective Cohort Study) planned 31 December 2014. Final report for HIV study (European Pharmaco-vigilance Study) planned 30 September 2016
GS-US-104-0353 A Preliminary Evaluation of Fanconi Syndrome Due to Antiretroviral Therapies in HIV Infected Persons	To collect information on potential genetic susceptibility for proximal renal tubulopathy with tenofovir DF	*Important identified risk*: Renal toxicity (TDF)	Started	Final report on genetic analyses planned Q2 2013
GS-US-104-0423 A Phase 4 Cross-Sectional Study of Bone Mineral Density in HIV-1 Infected Subjects	To characterize the profile of low BMD in ≥ 50 years old male HIV-1 infected subjects and post-menopausal female HIV-1 infected subjects taking TDF-based regimens relative to those taking non-TDF-based regimens for HIV infection	*Important identified risk*: Bone events due to proximal renal tubulopathy/loss of BMD (TDF)	Planned	Final report planned 21 August 2014

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
GS-EU-104-0433 (Drug Utilization Study of Viread in HIV-1 infected paediatric patients) An observational, drug utilization study of Viread in children and adolescents with HIV-1 infection	To assess the effectiveness of the risk minimization measures (EU SmPC and educational brochures) that have been implemented post-approval of Viread in the paediatric population, by describing the characteristics and management in accordance with the EU SmPC of HIV-1 infected paediatric patients being treated with Viread prior to and post-approval of the paediatric indication	*Important identified risk*: Renal toxicity (TDF); Bone events due to proximal renal tubulopathy/loss of BMD (TDF) *Missing information*: Safety in children (including long-term safety) (TDF)	Planned	Interim HIV reports anticipated 31 December 2015 and 31 December 2016. Final report anticipated 31 December 2017.
Antiretroviral Pregnancy Registry	To collect information on the risk of birth defects in patients exposed to FTC, RPV or TDF during pregnancy	*Missing information*: Safety in pregnancy (FTC, RPV, TDF)	Started	Interim reports produced 6-monthly (June and December each year)
Mitochondrial Collaborative Committee (MITOC) Mitochondrial toxicity in children with in utero / post-natal exposure to NRTIs	To investigate the association of NRTI exposure during pregnancy and/or post-natally with mitochondrial dysfunction	*Missing information*: Safety in pregnancy (FTC, RPV, TDF)	Started	Final report planned Q4 2014
Nonclinical studies (Category 3)				
In vitro study evaluating MATE inhibition	To evaluate the MATE inhibitory potential of rilpivirine in vitro	*Missing information*: Drug-drug interactions (RPV)	Planned	Final report planned Q3 2013
In vitro studies on intestinal phosphate absorption	To collect information on whether TDF has an inhibitory effect on intestinal absorption of phosphate, which may contribute to the understanding of the observed effects of TDF on BMD	*Important identified risk*: Bone events due to proximal renal tubulopathy/loss of BMD (TDF)	Planned	Final report planned Q3 2013

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Other data (Category 3)				
Monitoring of reversibility of renal tubulopathy in clinical trials	To collect information on the reversibility of renal tubulopathy following the discontinuation of tenofovir DF in adult and paediatric patients	*Important identified risk*: Renal toxicity (TDF) *Missing information*: Safety in children (including long-term safety) (TDF)	Planned	EU-RMP to be updated with reversibility data when available from clinical study reports
Retrospective analyses of paediatric BMD Z-scores adjusted by height	To collect information on BMD Z-scores adjusted by height in paediatric patients	*Important identified risk*: Bone events due to proximal renal tubulopathy/loss of BMD (TDF)	Planned	Submission of analysis planned Q1 2013

Completed Studies / Activities from the Pharmacovigilance Plan

An overview of all completed studies in Categories 1-3, completed since submission of the last EU-RMP, is shown below.

Table 25. Completed Studies/Activities from the Pharmacovigilance Plan (Categories 1-3)

Study / Title	Objectives	Safety Concerns Addressed	Status (Completed)	Date for Submission of Final Study Report
Interventional clinical studies (Category 3)				
TMC278IFD1005 A Phase I, open-label study in healthy subjects, to explore the pharmacokinetics, safety and tolerability of rilpivirine 50 mg once daily following a two-week efavirenz intake period	To evaluate the pharmacokinetics, safety and tolerability of rilpivirine 50 mg QD following a two-week efavirenz intake period	*missing information*: Drug-drug interactions (RPV)	Completed	Final report submitted 09 January 2013.

Risk minimisation measures

Table 26. Summary of Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Post-treatment hepatic flares in HIV/HBV coinfected patients (FTC, TDF)	Sections 4.2, 4.4 and 4.8 of the Eviplera SmPC warn about the risk of exacerbation of hepatitis in HIV-1/HBV coinfected patients following discontinuation of Eviplera.	None
Lactic acidosis and severe hepatomegaly with steatosis (FTC, TDF)	Sections 4.4 and 4.8 of the Eviplera SmPC warn that lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues, and that lactic acidosis is an ADR for the TDF component of Eviplera.	None
Lipodystrophy (FTC, TDF)	Sections 4.4 and 4.8 of the Eviplera SmPC warn that lipodystrophy has been associated combination antiretroviral therapy in HIV infected patients.	None
Development of drug resistance (RPV)	Sections 4.1, 4.4 and 5.1 of the Eviplera SmPC recommend that genotypic resistance testing should guide the use of Eviplera and information regarding virologic failure and resistance, particularly in patients with a viral load > 100,000 HIV-1 RNA copies/mL, in Sections 4.4 and 5.1 of the Eviplera SmPC.	None
Renal toxicity (TDF)	Section 4.2 of the Eviplera SmPC warns that Eviplera should only be used in patients with mild renal impairment if the benefits outweigh the risk and Sections 4.2 and 4.4 advise that Eviplera is not recommended for use in patients with moderate and severe renal impairment (creatinine clearance < 50 mL/min). Further recommendations are provided in Section 4.4 regarding renal monitoring at baseline and while receiving Eviplera. Section 4.5 of the Eviplera SmPC provides information on interactions due to elimination of FTC and TDF by the kidneys and provides recommendations against the use of Eviplera with nephrotoxic medications. Renal ADRs associated with the TDF component of Eviplera are provided in Section 4.8 of the Eviplera SmPC.	None
Bone events due to proximal renal tubulopathy/loss of BMD (TDF)	Section 4.4 of the Eviplera SmPC warn about loss of BMD associated with TDF and description of bone events associated with TDF-associated proximal renal tubulopathy in Sections 4.4 and 4.8 of the Eviplera SmPC.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Interaction with didanosine (TDF)	Sections 4.4 and 4.5 of the Eviplera SmPC warn that coadministration of Eviplera and didanosine is not recommended and there is a statement in Section 4.8 of the Eviplera SmPC regarding the risk of lactic acidosis and pancreatitis associated with the interaction between TDF and didanosine.	None
Pancreatitis (TDF)	Sections 4.4, 4.5 and 4.8 of the Eviplera SmPC warn about the risk of pancreatitis associated with the interaction between TDF and didanosine. Pancreatitis is included as an ADR to TDF in Section 4.8 of the Eviplera SmPC.	None
Important Potential Risks		
Overdose (including overdose through accidental concurrent use of Eviplera with any of its active components) (Eviplera, RPV)	Section 4.2 of the Eviplera SmPC recommends that the dose is one tablet, once daily, and warnings in Sections 4.4 and 4.5 of the Eviplera SmPC that Eviplera should not be administered concomitantly with other medicinal products containing FTC, RPV or TDF. Section 4.9 of the Eviplera SmPC provides guidance on patient monitoring and treatment in the event of overdose.	None
Off-label use (in paediatric patients [< 18 years of age], treatment-naïve patients with a baseline viral load > 100,000 HIV-1 RNA copies/mL, or in ART treatment-experienced patients for Eviplera; in adult and paediatric patients for RPV) (Eviplera, RPV)	Section 4.1 of the Eviplera SmPC clearly indicates the use of Eviplera in antiretroviral treatment-naïve adult patients with a viral load ≤ 100,000 HIV-1 RNA copies/mL. Sections 4.2, 4.8 and 5.2 of the Eviplera SmPC note that Eviplera is not recommended for use in paediatric patients due to insufficient data. Section 4.4 of the Eviplera SmPC provides information on the increased risk of virologic failure and resistance in patients with a viral load > 100,000 HIV-1 RNA copies/mL at baseline.	None
QT interval prolongation (RPV)	Sections 4.4 and 4.5 of the Eviplera SmPC warn that RPV has been associated with prolongation of QTc interval at supratherapeutic doses and should be used with caution in combination with medicinal products with a known risk of Torsade de Pointes. Section 4.9 of the Eviplera SmPC recommends monitoring of ECG (QT interval) in the event of overdose.	None
Hepatotoxicity (RPV)	Section 4.8 of the Eviplera SmPC describes increased transaminases (AST and/or ALT) as ADRs to RPV and notes that patients coinfected with HBV and/or HCV are at increased risk of transaminase elevations.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Severe skin reactions (RPV)	Section 4.8 of the Eviplera SmPC describes rash as an ADR to RPV.	None
Major depressive disorder (RPV)	Section 4.8 of the Eviplera SmPC describes depression as an ADR to RPV.	None
Lipodystrophy (RPV)	Sections 4.4 and 4.8 of the Eviplera SmPC warn that lipodystrophy has been associated with combination antiretroviral therapy in HIV infected patients.	None
Bleeding disorders (RPV)	No information with regard to bleeding disorders is included in the Eviplera SmPC.	None
Blood cortisol decreased (RPV)	Section 4.8 of the Eviplera SmPC describes changes in basal and ACTH-stimulated cortisol associated with RPV at Week 96 in pooled C209 and C215 studies. It is noted that the changes in adrenal safety parameters are not considered clinically relevant and that there were no clinical signs or symptoms suggestive of adrenal or gonadal dysfunction in adults.	None
Missing Information		
Safety information for Eviplera (Eviplera)	It is noted in Section 4.8 of the Eviplera SmPC that the safety profile of Eviplera is based on Week 96 pooled data from studies C209 and C215, in which RPV and FTC/TDF were studied.	None
Safety in children (including long-term safety for TDF) (RPV, TDF)	Sections 4.2, 4.8 and 5.2 of the Eviplera SmPC note that the safety and efficacy of Eviplera has not been studied in children < 18 years old and therefore Eviplera is not recommended in this population.	None
Safety in elderly patients (FTC, RPV, TDF)	Sections 4.2, 4.4 and 4.8 of the Eviplera SmPC note that Eviplera has not been studied in elderly patients (> 65 years), and should be administered with caution in this patient population.	None
Safety in pregnancy (FTC, RPV, TDF)	Section 4.6 of the Eviplera SmPC provides information on pregnancy in humans for the FTC and TDF components and in animals for all components of Eviplera and notes that Eviplera should not be used in pregnancy unless clearly needed.	None
Safety in lactation (FTC, RPV, TDF)	Section 4.6 of the Eviplera SmPC provides information on secretion of FTC and TDF in human milk, whereas it is unknown whether RPV is excreted in human milk, and notes that Eviplera should not be used during breastfeeding.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Safety in patients with renal impairment ($eGFR_{creat}$ < 50 mL/min/1.73 m^2 for RPV) (RPV, TDF)	Sections 4.2 and 5.2 of the Eviplera SmPC note that only limited data is available for patients with mild renal impairment (creatinine clearance 50-80 mL/min) and so Eviplera should only be used if the potential benefits outweigh the risks in patients with mild renal impairment. In patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min), Eviplera is not recommended. Section 5.2 of the SmPC also notes that RPV concentrations may be increased in patients with severe renal impairment or end-stage renal disease, despite negligible renal elimination of RPV.	None
Safety in patients with severe hepatic impairment (CPT score C) (RPV)	Section 4.2 of the Eviplera SmPC notes that Eviplera is not recommended for use in patients with severe hepatic impairment (CPT score C).	None
Drug-drug interactions (RPV)	Section 4.3 of the Eviplera SmPC provides a list of drugs contraindicated for use with Eviplera and Section 4.5 provides a list of drugs for which concurrent use is contraindicated, not recommended or should be used with caution.	None

2.8. Update of the Product information

During the procedure the MAH was requested to amend the proposed extension of indication as discussed in the clinical efficacy section.

The initial proposal of the MAH for the indication in SmPC section 4.1 was:

Section 4.1

Eviplera is indicated for treatment of HIV-1 infection in antiretroviral therapy (ART)-experienced adults who are virologically suppressed with no history of virologic failure

Following comments from the CHMP, the MAH proposed the following updates to the PI, which CHMP accepted.

Section 4.1:

Eviplera is indicated for the treatment of adults infected with human immunodeficiency virus type 1 (HIV-1) ~~infection~~ without known mutations associated with resistance to the NNRTI class, tenofovir or emtricitabine, and ~~in antiretroviral treatment naïve adult patients~~ with a viral load ≤ 100,000 HIV-1 RNA copies/mL (see sections 4.2, 4.4 and 5.1).

As with other *antiretroviral* medicinal products, genotypic resistance testing and/or historical resistance data should guide the use of Eviplera (see sections 4.4 and 5.1).

As a consequence of this new indication, sections 4.1, 4.4 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Section 4.4:

Virologic failure and development of resistance

Eviplera has not been evaluated in patients with previous virologic failure to any other antiretroviral therapy. There is not sufficient data to justify the use in patients with prior NNRTI failure. ~~Eviplera should be avoided in patients with HIV-1 harbouring the K65R mutation. The list of rilpivirine-associated mutations presented in section 5.1 should only guide the use of Eviplera in the treatment-naïve population.~~ (…)

Section 4.8

The combination of emtricitabine, rilpivirine and tenofovir disoproxil fumarate has been studied as the component products in treatment-naïve patients (Phase III studies C209 and C215). The single-tablet regimen (STR), Eviplera, has been studied in virologically suppressed patients who switched from a regimen containing a ritonavir-boosted protease inhibitor (Phase III study GS-US-264-0106) or from efavirenz/emtricitabine/tenofovir disoproxil fumarate (Phase IIb study GS-US-264-0111). In treatment-naïve patients, the most frequently reported adverse reactions considered possibly or probably related to rilpivirine hydrochloride and emtricitabine/tenofovir disoproxil fumarate were nausea (9%), dizziness (8%), abnormal dreams (8%), headache (6%), diarrhoea (5%) and insomnia (5%) (pooled data from the Phase III clinical studies C209 and C215, see section 5.1). No new adverse reaction terms were identified between 48 weeks and 96 weeks. In virologically suppressed patients switching to Eviplera, the most frequently reported adverse reactions considered possibly or probably related to Eviplera were fatigue (3%), diarrhoea (3%), nausea (2%) and insomnia (2%) (48 week data from the Phase III study GS-US-264-0106). No new adverse reactions to Eviplera were identified in virologically suppressed patients switching to Eviplera in clinical studies GS-US-264-0106 and GS-US-264-0111. The safety profile of emtricitabine and tenofovir disoproxil fumarate in these studies was consistent with the previous experience with these agents when each was administered with other antiretroviral agents.

(…)

Laboratory abnormalities

Lipids: At 96 weeks in the pooled Phase III C209 and C215 trials of treatment-naïve patients, in the rilpivirine arm the mean change from baseline in total cholesterol (fasted) was 5 mg/dL, in HDL cholesterol (fasted) 4 mg/dL, in LDL cholesterol (fasted) 1 mg/dL, and in triglycerides (fasted) -7 mg/dL. At 48 weeks in Phase III study GS-US-264-0106 of virologically suppressed patients switching to Eviplera from a regimen containing a ritonavir-boosted protease inhibitor, the mean change from baseline in total cholesterol (fasted) was -24 mg/dL, in HDL cholesterol (fasted) -2 mg/dL, in LDL cholesterol (fasted) -16 mg/dL, and in triglycerides (fasted) -64 mg/dL.

Creatinine: The pooled data from the Phase III C209 and C215 trials of treatment-naïve patients also demonstrate that serum creatinine increased and estimated glomerular filtration rate (eGFR) decreased over 96 weeks of treatment with rilpivirine. Most of this increase in creatinine and decrease in eGFR occurred within the first four weeks of treatment. Over 96 weeks of treatment with rilpivirine mean changes of 0.1 mg/dL (range: -0.3 mg/dL to 0.6 mg/dL) for creatinine and -13.3 mL/min/1.73 m2 (range: -63.7 mL/min/1.73 m2 to 40.1 mL/min/1.73 m2) for eGFR were observed. In patients who entered the studies with mild or moderate renal impairment, the serum creatinine increase observed was similar to that seen in patients with normal renal function. These

changes are not considered to be clinically relevant since they do not reflect a change in actual glomerular filtration rate ~~and no subject discontinued treatment due to increases in serum creatinine.~~ Changes in creatinine and eGFR observed at 48 weeks in Phase III study GS-US-264-0106 of virologically suppressed patients switching to Eviplera from a regimen containing a ritonavir-boosted protease inhibitor were consistent with those observed in studies C209 and C215.

Cortisol: In the pooled Phase III C209 and C215 trials of treatment-naïve patients, at week 96, there (…)

Section 5.1:

Resistance

Considering all of the available *in vitro* data and data generated in previously untreated patients, the following resistance-associated mutations in HIV-1 reverse transcriptase, when present at baseline, may affect the activity of Eviplera: K65R, K101E, K101P, E138A, E138G, E138K, E138Q, E138R, V179L, Y181C, Y181I, Y181V, M184I, M184V, Y188L, H221Y, F227C, M230I and M230L.

~~These resistance-associated mutations should only guide the use of Eviplera in the treatment-naïve population.~~ *A negative impact by NNRTI-mutations other than those listed above (e.g. mutations K103N or L100I as single mutations, or in combination) cannot be excluded, since this was not studied in vivo in a sufficient number of patients.*

As with other antiretroviral medicinal products, resistance testing and/or historical resistance data should guide the use of Eviplera (see section 4.4).

(…)

In virologically suppressed HIV-1 infected patients

Study GS-US-264-0106: Of the 469 Eviplera-treated patients [317 patients who switched to Eviplera at baseline (Eviplera arm) and 152 patients who switched at week 24 (Delayed Switch arm)], a total of 7 patients were analysed for resistance development and all had genotypic and phenotypic data available. Through week 24, two patients who switched to Eviplera at baseline (2 of 317 patients, 0.6%) and one patient who maintained their ritonavir-boosted protease inhibitor-based regimen [Stayed on Baseline Regimen (SBR) arm] (1 of 159 patients, 0.6%) developed genotypic and/or phenotypic resistance to study drugs. After week 24, the HIV-1 from 2 additional patients in the Eviplera arm developed resistance by week 48 (total of 4 of 469 patients, 0.9%). The remaining 3 Eviplera-treated patients did not have emergent resistance.

The most common emergent resistance mutations in Eviplera-treated patients were M184V/I and E138K in reverse transcriptase. All patients remained susceptible to tenofovir. Of the 24 patients treated with Eviplera that had the NNRTI-associated K103N substitution pre-existing at baseline in their HIV-1, 17 of 18 patients in the Eviplera arm and 5 of 6 patients in the SBR arm maintained virologic suppression after switching to Eviplera through 48 weeks and 24 weeks of treatment, respectively. One patient with pre-existing K103N at baseline had virologic failure with additional emergent resistance by week 48.

Study GS-US-264-0111: Through week 48, no emergent resistance developed in the 2 patients that failed virologically among patients that switched to Eviplera from efavirenz/emtricitabine/tenofovir disoproxil (0 of 49 patients).

~~Considering all of the available *in vitro* and *in vivo* data in treatment naïve subjects, the following resistance-associated mutations, when present at baseline, may affect the activity of Eviplera: K65R,~~

~~K101E, K101P, E138A, E138G, E138K, E138Q, E138R, V179L, Y181C, Y181I, Y181V, M184I, M184V, Y188L, H221Y, F227C, M230I and M230L. These resistance-associated mutations should only guide the use of Eviplera in the treatment-naïve population.~~

~~These resistance-associated mutations were derived from *in vivo* data involving treatment-naïve subjects only and therefore cannot be used to predict the activity of Eviplera in subjects who have virologically failed an antiretroviral-containing regimen.~~

~~As with other antiretroviral medicinal products resistance testing should guide the use of Eviplera (see section 4.4).~~

(...)

In virologically suppressed HIV-1 infected patients
In study GS-US-264-0106, 4 of the 469 patients who switched from a ritonavir-boosted protease inhibitor-based regimen to Eviplera had HIV-1 with reduced susceptibility to at least one component of Eviplera through week 48. De novo resistance to emtricitabine/lamivudine was seen in 4 cases, and also to rilpivirine in 2 cases, with a consequent cross resistance to efavirenz (2/2), nevirapine (2/2) and etravirine (1/2).

(...)

Virologically suppressed HIV-1 infected patients
Study GS-US-264-0106: The efficacy and safety of switching from a ritonavir-boosted protease inhibitor in combination with two NRTIs to Eviplera STR was evaluated in a randomised, open-label study in virologically suppressed HIV-1 infected adults. Patients had to be on either their first or second antiretroviral regimen with no history of virologic failure, have no current or past history of resistance to any of the three components of Eviplera, and must have been stably suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months prior to screening. Patients were randomised in a 2:1 ratio to either switch to Eviplera at baseline (Eviplera arm, n = 317), or stay on their baseline antiretroviral regimen for 24 weeks (SBR arm, n = 159) before switching to Eviplera for an additional 24 weeks (Delayed Switch arm, n = 152). Patients had a mean age of 42 years (range 19-73), 88% were male, 77% were White, 17% were Black, and 17% were Hispanic/Latino. The mean baseline CD4 cell count was 584 x 10^6 cells/L (range 42-1,484). Randomisation was stratified by use of tenofovir disoproxil fumarate and/or lopinavir/ritonavir in the baseline regimen.

Treatment outcomes through 24 weeks are presented in Table 7.

Table 7: Outcomes of randomised treatment in study GS-US-264-0106 at week 24[a]

	Eviplera arm n = 317	Stayed on Baseline Regimen (SBR) arm n = 159
Virologic success after 24 weeks of treatment[b] HIV-1 RNA < 50 copies/mL	94% (297/317)	90% (143/159)
Virologic failure[c]	1% (3/317)	5% (8/159)
No virologic data in week 24 window		
Discontinued study drug due to AE or death[d]	2% (6/317)	0%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[e]	3% (11/317)	3% (5/159)
Missing data during window but on study drug	0%	2% (3/159)
CD4 median increase from baseline (x 10^6 cells/L)	+10	+22

a Week 24 window is between day 127 and 210 (inclusive).
b Snapshot analysis.
c Includes patients who had HIV-1 RNA ≥ 50 copies/mL in the week 24 window, patients who discontinued early due to lack or loss of efficacy, patients who discontinued for reasons other than an adverse event or death, and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
d Includes patients who discontinued due to adverse event or death at any time point from day 1 through the week 24 window resulting in no virologic data on treatment during the specified window.
e Includes patients who discontinued for reasons other than an adverse event, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Switching to Eviplera was non-inferior in maintaining HIV-1 RNA < 50 copies/mL when compared to patients who stayed on a ritonavir-boosted protease inhibitor in combination with two NRTIs [Treatment difference (95% CI): + 3.8% (-1.6% to 9.1%)].

Among patients in the SBR arm who maintained their baseline regimen for 24 weeks and then switched to Eviplera, 92% (140/152) of patients had HIV-1 RNA < 50 copies/mL after 24 weeks of Eviplera, consistent with the week 24 results for patients who switched to Eviplera at baseline.

At week 48, 89% (283/317) of patients randomised to switch to Eviplera at baseline (Eviplera) had HIV-1 RNA < 50 copies/mL, 3% (8/317) were considered virologic failures (HIV RNA ≥ 50 copies/mL), and 8% (26/317) did not have data available in the week 48 window. Of the 26 patients without data available in the week 48 window, 7 patients discontinued due to adverse event or death, 16 patients discontinued for other reasons, and 3 patients were missing data but remained on study drug. The median change in CD4 cell count at week 48 was +17 x 10^6 cells/L, in the on-treatment analysis.

There were 7/317 patients (2%) in the Eviplera arm and 6/152 patients (4%) in the Delayed Switch arm who permanently discontinued study drug due to a treatment-emergent adverse events (TEAE). No patients discontinued from the study due to a TEAE in the SBR arm.

Study GS-US-264-0111: The efficacy, safety, and pharmacokinetics of switching from efavirenz/emtricitabine/tenofovir disoproxil STR to Eviplera STR was evaluated in an open-label study in virologically suppressed HIV-1 infected adults. Patients had to have previously only received efavirenz/emtricitabine/tenofovir disoproxil as their first antiretroviral regimen for at least three months, and wished to switch regimens due to efavirenz intolerance. Patients had to be stably suppressed for at least 8 weeks prior to study entry, have no current or past history of resistance to any of the three components of Eviplera, and have HIV-1 RNA < 50 copies/mL at screening. Patients

were switched from efavirenz/emtricitabine/tenofovir disoproxil to Eviplera without a washout period. Among 49 patients who received at least one dose of Eviplera, 100% of patients remained suppressed (HIV-1 RNA < 50 copies/mL) at week 12 and week 24. At week 48, 94% (46/49) of patients remained suppressed, and 4% (2/49) were considered virologic failures (HIV-1 RNA ≥ 50 copies/mL). One patient (2%) did not have data available in the week 48 window; study drug was discontinued due to a protocol violation (i.e. reason other than AE or death) and the last available HIV-1 RNA was < 50 copies/mL.

Section 5.2

Switching from an efavirenz-based regimen

The efficacy data from study GS-US-264-0111 (see section 5.1) indicates that the brief period of lower rilpivirine exposure does not impact antiviral efficacy of Eviplera. Due to the decline in efavirenz plasma levels, the inductive effect decreased and rilpivirine concentrations started to normalise. During the time period of declining efavirenz plasma levels and increasing rilpivirine plasma levels after switching, none of the patients had efavirenz or rilpivirine levels below their respective IC_{90} levels at the same time.No dose adjustment is required following the switch from an efavirenz-containing regimen.

Package Leaflet

1. What Eviplera is and what it is used for

Eviplera is a treatment for Human Immunodeficiency Virus (HIV) infection in adults aged 18 years and over ~~who have never been treated before with HIV medicines~~.

4. Possible side effects

Tests may also show:

[changed from uncommon to common]

- Low platelet count (a type of blood cell involved in clotting blood)

[deleted]

- ~~Increased cholesterol.~~

In addition the MAH took the opportunity tto implement corrections and mino editorial changes in Annexes I & IIIB.

3. Benefit-Risk Balance

Data from 2 switch studies in virologically suppressed adult HIV patients, GS-US-264-0106 and GS-US-264-0111, that evaluated efficacy and safety after switching from a PI-based regimen or Atripla (Efavirenz/ Emtricitabine/Tenofovir) to Eviplera once daily were submitted to support the use of this combination for other reasons than lack of efficacy of their initial regimen.

Benefits

Beneficial effects

Both studies demonstrated that switch to Eviplera did not result in accelerated immunological or virological deterioration, because most subjects maintained virologic suppression. Virologic suppression can be maintained in most patients, regardless whether initial HIV-RNA levels were below or above 100,000 copies/ml before they started their PI-based or efavirenz-based regimen.

The Eviplera FDC regimen implies in some cases a significant reduction of the pill burden, which is thought to help keeping treatment adherence.

The AE profile of RPV-based therapy was favourable compared to the PI-based regimen, due significant decreases observed in total cholesterol, LDL-cholesterol and triglycerides.

Uncertainty in the knowledge about the beneficial effects

Virologic failures (2/48 in GS-US-264-0111 and 8/317 in GS-US-264-0106) were observed in the switching studies and confirmed previous findings from registration studies in which non-adherence (i.e. low RPV plasma concentrations) could lead to an increased risk of loss of viral suppression with the registered dose of 25 mg RPV, and consequently to the development of RPV resistance associated mutations as well as concomitant NRTI mutations. In addition to non-adherence, RPV sensitive pharmacokinetic disturbances need to be taken into consideration. These include food intake as and concomitant use of proton pump inhibitors.

Low therapeutic levels of RPV might be present for at least one week, when switching from an EFV to a RPV containing regimen, due the inductive effect of efavirenz. As this period is limited to < 7 days, it can be considered acceptable as drug concentrations of the backbone ARVs (TDF+FTC) will not be affected. Therefore, it is not expected to compromise the efficacy of ARV therapy.

Risks

Unfavourable effects

Nervous system disorders (14.9% vs. 9.4%), psychiatric disorders (17.5% vs. 6.3%) and gastrointestinal disorders (27.5% vs. 16.4%) were observed more frequent in the RPV containing arm. However these adverse reactions are well characterised and therefore manageable by health care providers.

Due to the known inhibition of the organic cation transporter 2 (OCT2) by rilpivirine, a decrease of eGFR was observed after switching from a PI based regimen to Eviplera. These changes were consistent with the ones observed in the RPV pivotal studies.

Uncertainty in the knoledge about the unfavourable effects

Psychiatric disorders were observed while switching Eviplera, however no detailed comparisons to an EFV containing regimen could be done, as patient satisfaction was not evaluated.

More discontinuations occurred in the Eviplera study arm compared to the continued PI-based regimen. However, this effect is expected after the introduction of any new antiretroviral agent.

Importance of favourable and unfavourable effects

Most subjects maintained virologic suppression after switching from PI-based regimens or an efavirenz-based regimen to Eviplera. The reduction in pill burden compared to PI regimens or improvement of neuropsychiatric disorders associated with efavirenz, can be considered benefits which may increase adherence.

Although RPV adverse reactions (psychiatric disorders, decrease of eGFR) are well characterised, these require management and/or adequate monitoring.

Benefit-risk balance

The data show the benefits outweigh the risks if adherence to treatment is optimal in patients without resistant associated mutations emtricitabine, tenofovir and the NNRTI class. Eviplera provides a good and simple alternative in the ARV armamentarium for the switch for any reasons other than lack of efficacy of their initial regimen.

Benefit-risk balance discussion

Eviplera has a place in the armamentarium of anti HIV medicines in the proposed target population and should be used in line with resistance data, previous treatment success, individual tolerability profile and other clinical considerations.

4. Recommendations

Based on the review of the submitted data, the Committee considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**
C.1.6 a)	*Addition of a new therapeutic indication or modification of an approved one*	II

Extension of Indication to broaden the use of Eviplera to adults without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine (from the previous 'antiretroviral treatment-naïve') and with a viral load ≤ 100,000 HIV-1 RNA copies/ml, based on 2 clinical studies on patients switching from therapies based either on efavirenz or a Protease Inhibitor.

As a consequence, update of sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC to update the safety information. The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the SmPC and Package Leaflet.

The requested variation proposed amendments to the RMP.