Rifapentine Once-Weekly Dosing Effect on Efavirenz, Emtricitabine and Tenofovir Pharmacokinetics.

Farenc C[1], Doroumian S[1], Cantalloube C[1], Perrin L[3], Esposito V[3], Cieren-Puiseux[2], Boulenc X[1], Maroni M[2]

[1] Drug Disposition, Disposition Safety Animal Research, Research & Development, Sanofi; [2] Access To Medicine, Sanofi [3] Clinical Exploratory Pharmacology, Research & Development, Sanofi

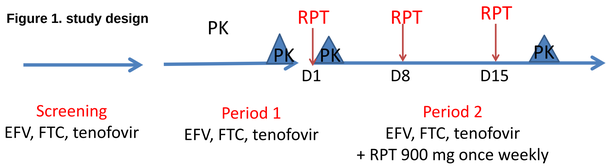
INTRODUCTION

A large Phase 3 trial (Prevent TB TBTC Study 26) indicated that rifapentine (RPT) plus isoniazid (900 mg each once a week) for 3 months was effective and well tolerated for the treatment of latent tuberculosis infection (LTBI) (1). RPT, an inducer of both CYP3A4 and CYP2B6, is expected to affect the efavirenz (EFV) PK which is of potential concern for DDI if RPT is administered in HIV infected subjects on treatment with EFV-based antiretroviral therapy (ART). Interaction towards emtricitabine (FTC) and tenofovir cannot not be ruled out, since these compounds are substrates of transporters and rifamycins, such as RPT may lead to up-regulation of transporters via PXR activation. In this context, a clinical interaction study between RPT (Priftin™) and Atripla™ fixed-dose combination of EFV 600 mg, FTC 200 mg, and tenofovir disoproxil fumarate 300 mg, was conducted. Since EFV has a narrow therapeutic range and one part of the PK variability is explained by the inter-subject variability of CYP2B6 activity (2) , main part of this poster is focused on the results for EFV

METHODS

- An open-label, non-randomized, single sequence, two periods, two-treatments
- Subjects : HIV infected subjects with CD4 cell count ≥ 350 and viral load <LOQ, TB free receiving Atripla ™, as background therapy (as of before the screening)
- Treatments
  - Atripla ™ : fixed dose combination of EFV 600 mg, FTC 200 mg, and tenofovir disoproxil fumarate 300 mg, administered daily, at least 2 hours after the dinner (at bedtime)
  - RPT 900 mg once weekly for 3 weekly administrations in fed conditions in the morning.
- PK samplings were performed over 24 h, 2 days before the first administration of RPT, after the first administration of RPT and 38h after the 3rd administration of RPT (time course for maximum CYP3A4 and CYP2B6 induction determined using a Physiological Based PK model) for assays of EFV, FTC and tenofovir plasma concentrations;
- Plasma concentrations were measured simultaneously using a validated HPLC-MS method with LOQ of 10, 5, and 2.5 ng/mL for EFV, FTC and tenofovir, respectively.
- PK parameters were determined by non-compartmental analysis
- Genotyping: a blood sample was collected to investigate variants of enzymes and transporters expected to be involved in EFV, TFC, and tenofovir clearance (eg, CYP2B6 for efavirenz).
- Statistical analysis :
  For EFV, TFC, and tenofovir, C_{max}, C_{min} and AUC_{0-24}, estimates and 90% CIs for the geometric mean ratios [EFV ,TFC and tenofovir respectively) coadministered with RPT versus administered alone] were computing with a linear mixed effects model.

Figure 1. study design



RESULTS

Study Population

12 subjects completed the study :
- ❑ 10 males/2 females;
- ❑ 5 caucasian /7 blacks;
- ❑ Mean weight 78 kg;
- ❑ mean age 34 years.

Table 1 Distribution in the different CYP2B6 genotypes groups

CYP2B6 Genotype	Number of patients
*1/*1	1
*2/*2	1
*1/*6	4
*4/*4;*4/*6;*6/*6	5

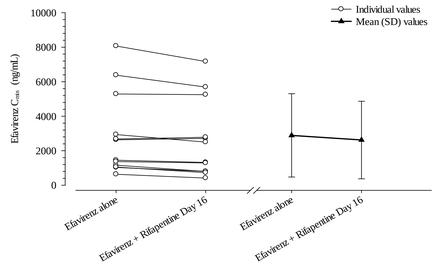
Table 1 : Treatment ratio estimates for EFV, FTC and tenofovir after a single dose of RPT versus administered alone

GMR (with/without single dose of RPT)						
	EFV		FTC		tenofovir	
Parameter	Estimate	90% CI	Estimate	90% CI	Estimate	90% CI
C_{max}	1.01	(0.94 -1.08)	1.03	(0.93 -1.14)	1.23	(1.00 - 1.51)
C_{min}	1.00	(0.95 -1.05)	1.07	(0.99 - 1.15)	0.93	(0.84 - 1.03)
AUC_{0-24}	0.97	(0.93 - 1.01)	0.96	(0.92 - 1.01)	1.02	(0.91 -1.15)

Table 2. Treatment ratio estimates for EFV, FTC and tenofovir after 3 weekly doses of RPT versus administered alone

GMR (with/without repeated doses of RPT)						
	EFV		FTC		tenofovir	
Parameter	Estimate	90% CI	Estimate	90% CI	Estimate	90% CI
C_{max}	0.92	(0.82 -1.03)	0.95	(0.81- 1.10)	1.00	(0.82 -1.22)
C_{min}	0.85	(0.79- 0.93)	0.97	(0.90- 1.05)	0.87	(0.73 - 1.05)
AUC_{0-24}	0.86	(0.79- 0.93)	0.93	(0.89- 0.98)	0.91	(0.85 -0.98)

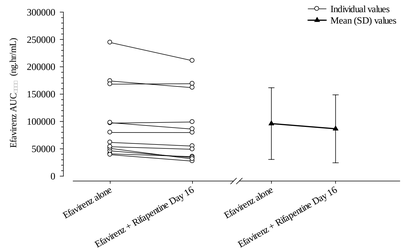
Figure2. Individual and mean (SD) EFV C_{min} values when administered alone and after 3 weekly doses of RPT (n=12)



EFV C_{min} values <1µg/mL

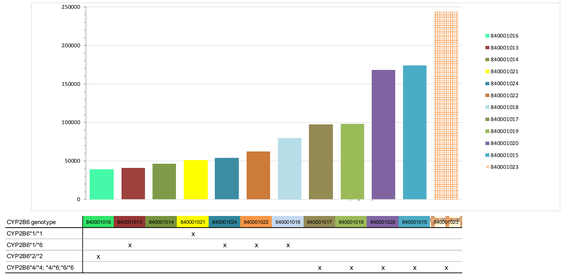
- Atripla administered alone
  1 subject (*2/*2 CYP2B6 genotype) had EFV C_{min} <1 µg/mL (C_{min} = 634 ng/mL)
- Atripla administered after repeated doses of RPT
  3 more subjects (*1/*6; and *1/*1 CYP2B6 genotypes) had EFV C_{min} <1 µg/mL (C_{min} .416 to 803 ng/mL)

Figure3 : Individual and mean (SD) EFV AUC_{0-24} values when administered alone and after 3 weekly doses of RPT (n=12)



Source = PKS Study : INT12291-EF; Scenario: P-EF-B-EV, Version 7
Date/Time = 7/19/2013 130:42 PM

Figure 4 :EFV AUC_{0-24} values versus CYP2B6 genotype (Atripla alone)



Interaction magnitude versus CYP2B6 genotypes

individual treatment ratio estimates for EFV-AUC_{0-24} co-administered with RPT (repeated doses)
- for the group with *1/*1, *1/*6 and *2/*2 ranged from 0.62 and 1 (n=6)
- for the group with *4/*4 or*4/*6 or*6/*6 ranged from 0.86 and 1.02 (n=5)

Table 4 : Descriptive statistics on CD4 count

			Raw data					
		N	Mean	SD	SEM	Median	Min	Max
Atripla alone								
P1D-15	Baseline	12	0.754	0.294	0.0847	0.786	0.32	1.18
P1D-2	Baseline	12	0.708	0.291	0.0841	0.729	0.29	1.12
Atripla + RPT 900 mg o.w								
P2D15	T0H	12	0.720	0.242	0.0698	0.652	0.33	1.12
EOS		12	0.643	0.227	0.0655	0.625	0.34	1.03

viral loads remained below LOQ throughout the study in all subjects (N=12)

Adverse Events

The coadministration of Atripla with weekly RPT 900mg was well tolerated. The majority of AEs reported were of mild intensity. No unexpected clinically relevant AEs or laboratory abnormalities were observed in this study (in particular liver function tests).

CONCLUSIONS

- Overall the steady state exposures of EFV, FTC and tenofovir were comparable with and without weekly RPT in HIV infected subjects
- The co-administration of Atripla with weekly RPT was well tolerated and no clinically significant modifications of CD4 cell counts or viral loads were observed
- Thus, the concomitant use of RPT according to LTBI regimen (900 mg weekly) and EFV-based ART is possible with no dose adjustment.

REFERENCES

1. Sterling T, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med 2011; 365:2155-66.
2. Kwara A1, Tashima KT, Dumond JB, et al. Modest but variable effect of rifampin on steady-state plasma pharmacokinetics of efavirenz in healthy African-American and Caucasian volunteers. Antimicrob Agents Chemother. 2011 Jul;55(7):3527-33.