These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi Drug substance(s): M000473 (rifapentine) and ATRIPLA™	Study Identifiers: NCT01690403, UTN U1111-1131-1992 Study code: INT12291
Title of the study: An open-label, non-randomized, single sequence, two periods, four-treatment, three parallel groups pharmacokinetic interaction study of repeated oral doses (daily or weekly regimen) of rifapentine on ATRIPLA™ (fixed dose combination of efavirenz, emtricitabine, and tenofovir disoproxil fumarate) given to HIV+ patients	
Study center(s): 1 center in the United States of America	
Study period: Date first patient enrolled: 14/Dec/2012 Date last patient completed: 14/Mar/2014	
Phase of development: Phase 1	
Objectives: • Primary: To evaluate the effect of single and repeated administration of rifapentine given as daily or weekly regimen on steady-state pharmacokinetic (PK) parameters of efavirenz, emtricitabine, and tenofovir given as a fixed-dose combination (ATRIPLA). • Secondary: To evaluate the safety and tolerability of concomitant administration of rifapentine and ATRIPLA given to human immunodeficiency virus-positive (HIV+) patients.	
Methodology: Open-label, non-randomized, 2-period, 4-treatment, 3 parallel cohorts in a single sequence study: • 1st cohort: ATRIPLA in Period 1 (15 days) and ATRIPLA + 15 mg/kg once daily (OD) × 21 days of oral rifapentine in Period 2. • 2nd cohort: ATRIPLA in Period 1 (15 days) and ATRIPLA + 900 mg oral of rifapentine (once weekly - 3 weekly administrations) in Period 2. • 3rd cohort (optional & not studied): ATRIPLA in Period 1 (15 days) and ATRIPLA + 10 mg/kg twice daily 21 days of oral rifapentine in Period 2.	
Number of patients: Planned: 36 (12 patients per cohort) Enrolled: 25 (13 patients in Cohort 1 and 12 patients in Cohort 2) Treated: 25 (13 patients in Cohort 1 and 12 patients in Cohort 2) Evaluated: Pharmacokinetics: 24 (12 patients per cohort) Safety: 25 (13 patients in Cohort 1 and 12 patients in Cohort 2)	
Diagnosis and criteria for inclusion: Human immunodeficiency virus-infected male and female patients (treated by ATRIPLA) between 18 and 55 years of age, inclusive, with a cluster of differentiation 4 (CD4) cell count of at least 350 cells/mm^3 and with a viral load below the limit of detection.	
Study treatments Investigational medicinal product: Rifapentine (PRIFTIN™)	

Formulation: 150-mg film-coated tablet

Route(s) of administration: oral

Dose regimen:

- Daily regimen: 15 mg/kg OD for 21 days in fed conditions in the morning

- Weekly regimen: 900 mg once weekly (Day 1, Day 8, and Day 15) for 3 weekly administrations in fed conditions in the morning.

Investigational medicinal product: ATRIPLA

Formulation: film-coated tablet (600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate corresponding to 245 mg tenofovir disoproxil given as a fixed-dose combination)

Route of administration: oral

Dose regimen: All patients were on the same dose and dosing schedule for ATRIPLA during all study periods. All patients had received ATRIPLA before screening (background therapy) and received 1 tablet at least 2 hours after the evening meal (fasting conditions), at night (bedtime) on each day of the study.

Duration of treatment: Patients received ATRIPLA in Period 1 (15 days) and ATRIPLA + rifapentine (daily for 21 days or once weekly for 3 weeks) in Period 2.

Duration of observation: Up to 65 days (including a screening period of up to 21 days prior to dosing, 15 days in Treatment Period 1, up to 23 days in Treatment Period 2, and followup visits up to 5 days after last dosing)

Criteria for evaluation:

Pharmacokinetics:

Primary endpoints:

Efavirenz, emtricitabine, and tenofovir: minimum plasma concentration observed (C_{min}), maximum plasma concentration observed (C_{max}), area under the plasma concentration versus time curve from time 0 to 24 hours postdose (AUC_{0-24}).

Secondary endpoints:

Efavirenz, emtricitabine, and tenofovir: time to reach C_{max} (t_{max}), $t_{1/2z}$ (terminal half-life), CL_{ss}/F (apparent total body clearance of the drugs at steady state from plasma). For Cohort 1 only, area under the plasma concentration versus time curve from time 0 to 10 hours postdose (AUC_{0-10}) on Day -2 and Day 1.

Rifapentine and 25-desacetyl rifapentine (25-DR):

- For Cohort 1: plasma concentrations observed predose (C_{0h}) on Days 1, 5, 8, 15, 18, and 21, and 24 hours after the last dosing day (C_{24h}).
- For Cohort 2: on Day 1, plasma concentration observed predose (C_{0h}), 8 hours postdose (C_{8h}), and 24 hours postdose (C_{24h}). On Day 8, plasma concentration observed 8 hours postdose (C_{8h}) and on Day 15, plasma concentration observed 8 hours postdose (C_{8h}) and 48 hours postdose (C_{48h}).

Safety: Adverse events (AEs), physical examination, clinical laboratory evaluations (hematology, serum chemistry, and urinalysis), vital signs (supine and standing blood pressure, heart rate, and body temperature), 12-lead electrocardiograms (ECGs), CD4 cell counts, and viral load measurements.

Pharmacokinetic sampling times and bioanalytical methods:

Sampling times:

- ATRIPLA (efavirenz, emtricitabine and tenofovir):

  Plasma samples were collected predose, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 16, and 24 hours postdose of ATRIPLA on Day -2, Day 1, and Day 21 for Cohort 1 and on Day -2, Day 1, and Day 16 for Cohort 2.

- Rifapentine and 25-DR:

  - Daily regimen (Cohort 1)

  Plasma samples were collected at predose on Days 1, 5, 8, 15, 18, and 21, and 24 hours after last dosing.

  - Weekly regimen (Cohort 2)

  Plasma samples were collected at predose on Day 1 and then 8 and 24 hours postdose. On Day 8, samples were collected at 8 hours postdose and Day 15 at 8 and 48 hours postdose.

Assays:

- Plasma concentrations of efavirenz, emtricitabine, and tenofovir were determined simultaneously using a validated liquid chromatography-tandem mass spectrometry (LC MS/MS) method with lower limits of quantification (LLOQs) of 10 ng/mL, 5 ng/mL, and 2.5 ng/mL, respectively.
- Plasma concentrations of rifapentine and 25-DR were determined using a validated LC-MS/MS method with an LLOQ of 1.00 µg/mL for both analytes.

Genotyping:

A blood sample was collected to investigate variants of enzymes and transporters expected to be involved in efavirenz, emtricitabine, and tenofovir clearance (eg, cytochrome P450 [CYP] 2B6 for efavirenz).

Statistical methods:

Pharmacokinetics: Pharmacokinetics parameters of efavirenz, emtricitabine, and tenofovir were summarized using descriptive statistics by day, separately for each cohort. Plasma concentrations of efavirenz, emtricitabine, tenofovir, and rifapentine and 25-DR (metabolite) were also summarized using descriptive statistics by day and time, separately for each cohort.

- Effect of repeated doses of rifapentine on efavirenz, emtricitabine, and tenofovir PK parameters at steady state: For log-transformed C_{max}, C_{min}, AUC_{0-24}, and $t_{1/2z}$, the effect of rifapentine on PK parameters of efavirenz, emtricitabine, and tenofovir was assessed on Day -2 (ATRIPLA alone) and Day 21 for Cohort 1 (ATRIPLA + rifapentine) or Day 16 for Cohort 2 (ATRIPLA + rifapentine) using a linear mixed effects model with fixed terms for treatment ("ATRIPLA alone" or ATRIPLA + rifapentine) and gender, and with an unstructured 2-by-2 matrix of treatment-specific variances and covariances for patient-within-gender. Estimates and 90% confidence interval (CI) for the geometric means ratio of efavirenz, emtricitabine, and tenofovir coadministered with rifapentine versus administration alone were provided for C_{max}, C_{min}, AUC_{0-24}, and $t_{1/2z}$, separately for each cohort.
- Effect of a single dose of rifapentine on efavirenz, emtricitabine, and tenofovir PK parameters at steady state: The same statistical analysis was performed on log-transformed C_{max}, C_{min}, AUC_{0-24}, AUC_{0-10} (for Cohort 1), and $t_{1/2z}$, separately for each cohort. Pharmacokinetic parameters of efavirenz, emtricitabine, and tenofovir were obtained on Day -2 (ATRIPLA alone) and Day 1 (ATRIPLA + rifapentine) for Cohorts 1 and 2.

Safety: Evaluation of safety was based on review of individual values and descriptive statistics. All AEs were coded using the Medical Dictionary for Regulatory Activities (version 16.1), and frequencies of treatment-emergent adverse events (TEAEs) were classified and tabulated (counts and percents) by primary system organ class (SOC), preferred term, and cohort (including treatment group). Potentially clinically significant abnormalities (PCSAs; definitions according to version 2 dated 14 September 2009) for clinical laboratory data, vital signs, and ECG data, and out-of-range values for clinical laboratory data were flagged and summarized by treatment group. In addition, raw data and changes from baseline for vital signs, ECGs, limited laboratory parameters, including CD4 counts, and viral loads were summarized in descriptive statistics by cohort and treatment group.

Summary:

Population characteristics: In Cohort 1, 13 patients (10 males and 3 females) were enrolled, and 11 completed the study period (1 patient discontinued due to elevated alanine aminotransferase [ALT] at Period 2 Day 18 and was replaced, and 1 patient withdrew from the study on Period Day -1 just before the start of the coadministration period ATRIPLA + rifapentine for personal reasons not related to the study). Twelve patients (10 males and 2 females) were enrolled in Cohort 2 and completed the study treatment period.

Pharmacokinetic results:

Cohort 1: Daily Regimen

1. Descriptive statistics on efavirenz, emtricitabine, and tenofovir steady state PK parameters when administered alone, administered after a single dose of rifapentine (Period 2, Day 1) or administered after 21 daily administrations of rifapentine (Period 2, Day 21) (n=12):

One patient received rifapentine OD for 21 days but was not correctly exposed to either the parent drug or its metabolite; more than half of its samples were nonquantifiable for rifapentine and 25-DR suggesting poor compliance to rifapentine. The effect of rifapentine on ATRIPLA PK was, thus, not evaluable for the patient. The patient's efavirenz, emtricitabine, and tenofovir PK was taken into account in Period 1, only (ATRIPLA alone). For this patient, no obvious compliance issue was reported by the Investigator.

1.1 Efavirenz

Efavirenz plasma concentrations for 2 patients were not validated due to the inability to show stability over the storage period. Two analyses were conducted for efavirenz (with and without the 2 patients) and led to similar results in term of PK parameters. Only the results without the 2 patients are reported.

Summary of pharmacokinetic parameters for efavirenz

Mean ± SD (Geometric Mean) [CV%]	**efavirenz alone**	**efavirenz with daily RPT**	
		Day 1	**Day 21**
N	10	9	8
C_{min}	3070 ± 3130	3310 ± 3150	2430 ± 2210
(ng/mL)	(1930) [101.7]	(2180) [95.1]	(1550) [90.7]
C_{max}	6050 ± 3660	6240 ± 3990	5410 ± 2640
(ng/mL)	(5110) [60.5]	(5210) [63.9]	(4750) [48.8]
t_{max}[a]	5.00	3.00	4.50
(hr)	(3.00 - 10.00)	(2.00 - 6.00)	(2.00 - 8.00)
AUC_{0-24}	100000 ± 85400	105000 ± 88100	80400 ± 61500
(ng.hr/mL)	(73600) [85.4]	(77500) [83.5]	(59200) [76.5]
AUC_{0-10}	46500 ± 35200	49700 ± 38200	NC
(ng.hr/mL)	(36600) [75.7]	(38600) [77.0]	NC
$t_{1/2z}$	29.2 ± 23.5	37.2 ± 20.4	27.2 ± 12.1
(hr)	(24.4) [80.4][b]	(32.1) [54.9][b]	(25.0) [44.3][c]
CL_{ss}/F	10.3 ± 6.12	9.94 ± 6.13	13.7 ± 10.4
(L/hr)	(8.16) [59.2]	(7.75) [61.7]	(10.1) [75.7]

[a] Median (Min - Max)

[b] n=8; [c] n=6

NC : not calculated

Profile of one patient was excluded for efavirenz + rifapentine treatment

1.2 Emtricitabine

Summary of pharmacokinetic parameters for emtricitabine

Mean ± SD (Geometric Mean) [CV%]	emtricitabine alone	emtricitabine with daily RPT	
		Day 1	Day 21
N	12	11	10
C_{min}	51.7 ± 23.3	64.0 ± 20.8	61.8 ± 19.8
(ng/mL)	(45.8) [45.1]	(61.2) [32.4]	(59.0) [32.0]
C_{max}	1450 ± 474	1520 ± 442	1670 ± 441
(ng/mL)	(1380) [32.8]	(1470) [29.1]	(1620) [26.4]
t_{max}[a]	2.00	1.53	2.00
(hr)	(1.50 - 6.00)	(1.00 - 3.00)	(1.50 - 4.00)
AUC_{0-24}	9260 ± 2040	9120 ± 1600	9760 ± 1780
(ng.hr/mL)	(9060) [22.0]	(9000) [17.6]	(9620) [18.2]
AUC_{0-10}	7320 ± 1910	7210 ± 1530	NC
(ng.hr/mL)	(7110) [26.1]	(7070) [21.2]	NC
$t_{1/2z}$	6.09 ± 0.719	7.02 ± 1.84	6.39 ± 1.09
(hr)	(6.05) [11.8]	(6.82) [26.2]	(6.31) [17.1]
CL_{ss}/F	22.5 ± 4.75	22.5 ± 3.76	21.1 ± 3.79
(L/hr)	(22.1) [21.1]	(22.2) [16.7]	(20.8) [18.0]

[a] Median (Min - Max)

NC: not calculated

Profile of one patient was excluded for emtricitabine + rifapentine treatment

1.3 Tenofovir

Summary of pharmacokinetic parameters for tenofovir

Mean ± SD (Geometric Mean) [CV%]	tenofovir alone	tenofovir with daily RPT	
		Day 1	Day 21
N	12	11	10
C_{min}	46.1 ± 18.3	55.3 ± 11.4	50.8 ± 13.4
(ng/mL)	(39.4) [39.7]	(54.2) [20.6]	(49.1) [26.5]
C_{max}	293 ± 90.5	405 ± 141	352 ± 67.3
(ng/mL)	(281) [30.8]	(384) [34.9]	(346) [19.1]
t_{max}[a]	2.00	1.50	2.00
(hr)	(1.00 - 6.00)	(0.75 - 3.00)	(1.00 - 4.00)
AUC_{0-24}	2380 ± 662	2720 ± 690	2540 ± 465
(ng.hr/mL)	(2290) [27.9]	(2660) [25.4]	(2500) [18.3]
AUC_{0-10}	1430 ± 432	1720 ± 541	NC
(ng.hr/mL)	(1380) [30.1]	(1660) [31.4]	NC
$t_{1/2z}$	16.8 ± 3.11	23.0 ± 7.67	19.9 ± 5.66
(hr)	(16.6) [18.5]	(21.9) [33.4]	(19.3) [28.5]
CL_{ss}/F	61.4 ± 17.2	52.2 ± 10.5	55.0 ± 10.5
(L/hr)	(59.2) [28.1]	(51.1) [20.1]	(54.1) [19.2]

[a] Median (Min - Max)

NC: not calculated

Profile of one patient was excluded for tenofovir + rifapentine treatment

2. Interaction of single and repeated administration of rifapentine on ATRIPLA

2.1 Efavirenz

Two statistical analyses were conducted for efavirenz (with and without 2 patients) and led to similar results in term of ratio estimates and 90% CI. Only the results without the 2 patients are reported.

Treatment ratio estimates with 90% CI for efavirenz administered after a single dose of rifapentine versus efavirenz administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Efavirenz	ATRIPLA + rifapentine vs ATRIPLA alone	C_{max}	1.00	(0.94 to 1.06)
		C_{min}	1.01	(0.95 to 1.06)
		AUC_{0-24}	0.99	(0.94 to 1.04)
		AUC_{0-10}	1.00	(0.94 to 1.06)

Cohort n°1: ATRIPLA™ in Period 1 (15 days) and ATRIPLA™ + 15 mg/kg OD x 21 days of oral rifapentine in Period 2

One patient: PK parameters calculated at Period 2 (ATRIPLA+RPT) were excluded due to plasma concentrations of RPT and its metabolite unquantifiable

*Two patients were excluded due to plasma concentrations of efavirenz not covered by the stability study

Efavirenz C_{min}, C_{max}, AUC_{0-24}, and AUC_{0-10} treatment ratios are close to 1, indicating a lack of interaction of a single dose of rifapentine on efavirenz C_{min}, C_{max}, AUC_{0-24}, and AUC_{0-10} at steady state.

Treatment ratio estimates with 90% CI for efavirenz administered after 21 daily administrations of rifapentine versus efavirenz administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Efavirenz	ATRIPLA + rifapentine vs ATRIPLA alone	C_{max}	0.83	(0.72 to 0.94)
		C_{min}	0.63	(0.52 to 0.76)
		AUC_{0-24}	0.67	(0.59 to 0.78)

Cohort n°1: ATRIPLA™ in Period 1 (15 days) and ATRIPLA™ + 15 mg/kg OD x 21 days of oral rifapentine in Period 2

One patient: PK parameters calculated at Period 2 (ATRIPLA + RPT) were excluded due to plasma concentrations of RPT and its metabolite unquantifiable

*Two patients were excluded due to plasma concentrations of efavirenz not covered by the stability study

Treatment ratio estimates indicated a decrease in efavirenz C_{max} of 17%, C_{min} of 37%, and AUC_{0-24} of 33% after repeated daily doses of rifapentine.

2.2 Emtricitabine

Treatment ratio estimates with 90% CI for emtricitabine administered after a single dose of rifapentine versus emtricitabine administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Emtricitabine	ATRIPLA + rifapentine vs ATRIPLA alone	C_{max}	1.06	(0.94 to 1.19)
		C_{min}	1.23	(1.07 to 1.43)
		AUC_{0-24}	0.98	(0.92 to 1.04)
		AUC_{0-10}	0.98	(0.94 to 1.04)

Cohort n°1: ATRIPLA™ in Period 1 (15 days) and ATRIPLA™ + 15 mg/kg OD x 21 days of oral rifapentine in Period 2

One patient: PK parameters calculated at Period 2 (ATRIPLA + RPT) were excluded due to plasma concentrations of RPT and its metabolite unquantifiable

One patient stopped the study at P2D18 and had PK parameters calculated only at Day 1 of Period 2, another patient withdrew the study for personal reasons at P1D-2 and had no PK parameters calculated for both periods

Treatment ratio estimates (with associated 90% CI) indicated an increase in emtricitabine C_{min} of 23% after a single dose of rifapentine while emtricitabine C_{max}, AUC_{0-24}, and AUC_{0-10} were not affected.

Treatment ratio estimates with 90% CI for emtricitabine administered after 21 daily administrations of rifapentine versus emtricitabine administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Emtricitabine	ATRIPLA + rifapentine vs ATRIPLA alone	C_{max}	1.11	(0.99 to 1.24)
		C_{min}	1.14	(0.99 to 1.31)
		AUC_{0-24}	1.01	(0.97 to 1.06)

Cohort n°1: ATRIPLA™ in Period 1 (15 days) and ATRIPLA™ + 15 mg/kg OD x 21 days of oral rifapentine in Period 2

One patient: PK parameters calculated at Period 2 (ATRIPLA + RPT) were excluded due to plasma concentrations of RPT and its metabolite unquantifiable

One patient stopped the study at P2D18 and had PK parameters calculated only at Day 1 of Period 2; another patient withdrew from the study for personal reasons at P1D-2 and had no PK parameters calculated for both periods

Treatment ratio estimates indicated an increase in emtricitabine C_{max} and C_{min} of 11% and 14%, respectively, after repeated daily doses of rifapentine, while emtricitabine AUC_{0-24} at steady state was not affected.

2.3 Tenofovir

Treatment ratio estimates with 90% CI for tenofovir administered after a single dose of rifapentine versus tenofovir administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Tenofovir	ATRIPLA + rifapentine vs ATRIPLA alone	C_{max}	1.34	(1.15 to 1.57)
		C_{min}	1.22	(1.00 to 1.48)
		AUC_{0-24}	1.13	(1.00 to 1.28)
		AUC_{0-10}	1.18	(1.03 to 1.34)

Cohort n°1: ATRIPLA™ in Period 1 (15 days) and ATRIPLA™ + 15 mg/kg OD x 21 days of oral rifapentine in Period 2

One patient: PK parameters calculated at Period 2 (ATRIPLA + RPT) were excluded due to plasma concentrations of RPT and its metabolite unquantifiable

One patient stopped the study at P2D18 and had PK parameters calculated only at Day 1 of Period 2; another patient withdrew from the study for personal reasons at P1D-2 and had no PK parameters calculated for both periods

Treatment ratio estimates indicated an increase in tenofovir steady-state C_{max} of 34%, C_{min} of 22%, AUC_{0-24} of 13%, and AUC_{0-10} of 18% after a single dose of rifapentine.

Treatment ratio estimates with 90% CI for tenofovir administered after 21 daily administrations of rifapentine versus tenofovir administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Tenofovir	ATRIPLA +rifapentine vs ATRIPLA alone	C_{max}	1.20	(1.02 to 1.40)
		C_{min}	1.05	(0.92 to 1.20)
		AUC_{0-24}	1.04	(0.97 to 1.11)

Cohort n°1: ATRIPLA™ in Period 1 (15 days) and ATRIPLA™ + 15 mg/kg OD x 21 days of oral rifapentine in Period 2

One patient: PK parameters calculated at Period 2 (ATRIPLA + RPT) were excluded due to plasma concentrations of RPT and its metabolite unquantifiable

One patient stopped the study at P2D18 and had PK parameters calculated only at Day 1 of Period 2; another patient withdrew from the study for personal reasons at P1D-2 and had no PK parameters calculated for both periods

Treatment ratio estimates (with associated 90% CI) indicated an increase in tenofovir C_{max} of 20% after repeated daily doses of rifapentine, while tenofovir C_{min} and AUC_{0-24} were not affected.

Cohort 2: Weekly regimen

3. Descriptive statistics on efavirenz, emtricitabine and tenofovir steady state PK parameters when administered alone, administered after a single dose of rifapentine (Period 2, Day 1) or administered after 3 weekly administrations of rifapentine (Period 2, Day 16) (n=12):

3.1 Efavirenz

Summary of pharmacokinetic parameters for efavirenz

Mean ± SD	**Efavirenz alone**	**Efavirenz + Rifapentine**	
(Geometric mean) [CV%]		**Day 1**	**Day 16**
C_{min}	2890 ± 2420	3000 ± 2630	2620 ± 2250
(ng/mL)	(2130) [83.6]	(2130) [87.7]	(1820) [85.8]
C_{max}	5960 ± 2830	6020 ± 2940	5500 ± 2500
(ng/mL)	(5470) [47.5]	(5510) [48.8]	(5020) [45.5]
t_{max}[a]	4.00	3.00	4.00
(h)	(1.50 - 10.00)	(1.50 - 8.00)	(2.00 - 10.00)
AUC_{0-24}	96100 ± 65600	95600 ± 68400	86600 ± 62200
(ng.h/mL)	(79900) [68.3]	(77600) [71.6]	(68600) [71.8]
$t_{1/2z}$	24.3 ± 14.6	32.3 ± 20.6	30.9 ± 20.6
(h)	(21.2) [59.9][b]	(27.2) [63.9][c]	(25.8) [66.7][d]
CL_{ss}/F	8.75 ± 4.49	9.19 ± 4.95	10.8 ± 6.70
(L/h)	(7.51) [51.3]	(7.74) [53.9]	(8.74) [62.1]

[a] Median (Min - Max)

[b] n=10, 2 patients not included in calculation of summary statistics

[c] n=11, 1 patient not included in calculation of summary statistics

[d] n=10, 2 patients not included in calculation of summary statistics

3.2 Emtricitabine

Summary of pharmacokinetic parameters for emtricitabine

Mean ± SD (Geometric mean) [CV%]	Emtricitabine alone	Emtricitabine + Rifapentine	
		Day 1	Day 16
C_{min}	52.6 ± 11.6	56.1 ± 12.9	51.7 ± 14.8
(ng/mL)	(51.4) [22.1]	(54.8) [22.9]	(50.0) [28.6]
C_{max}	1620 ± 357	1660 ± 318	1540 ± 371
(ng/mL)	(1580) [22.1]	(1630) [19.2]	(1490) [24.2]
t_{max}[a]	2.00	2.00	2.00
(h)	(1.00 - 6.00)	(0.75 - 4.00)	(1.00 - 4.00)
AUC_{0-24}	9440 ± 1160	9130 ± 1430	8860 ± 1570
(ng.h/mL)	(9370) [12.3]	(9030) [15.7]	(8740) [17.8]
$t_{1/2z}$	5.88 ± 1.08	6.49 ± 1.01	6.14 ± 1.34
(h)	(5.79) [18.4]	(6.42) [15.6]	(6.02) [21.8]
CLss/F	21.5 ± 2.70	22.4 ± 3.51	23.2 ± 4.12
(L/h)	(21.3) [12.6]	(22.2) [15.6]	(22.9) [17.7]

[a] Median (Min - Max)

3.3 Tenofovir

Summary of pharmacokinetic parameters for tenofovir

Mean ± SD (Geometric mean) [CV%]	Tenofovir alone	Tenofovir + Rifapentine	
		Day 1	Day 16
C_{min}	49.7 ± 8.40	46.6 ± 9.18	45.3 ± 15.0
(ng/mL)	(49.1) [16.9]	(45.8) [19.7]	(42.9) [33.1]
C_{max}	278 ± 85.3	347 ± 135	277 ± 81.9
(ng/mL)	(266) [30.7]	(326) [39.0]	(266) [29.5]
t_{max}[a]	1.75	1.75	2.00
(h)	(1.00 - 5.00)	(0.50 - 4.00)	(1.00 - 4.00)
AUC_{0-24}	2260 ± 310	2370 ± 652	2090 ± 423
(ng.h/mL)	(2240) [13.7]	(2290) [27.5]	(2050) [20.3]
$t_{1/2z}$	21.0 ± 6.99	19.2 ± 4.70	19.0 ± 4.44
(h)	(20.1) [33.2]	(18.8) [24.4]	(18.5) [23.3]
CLss/F	61.1 ± 9.09	61.1 ± 15.5	67.6 ± 14.3
(L/h)	(60.5) [14.9]	(59.2) [25.3]	(66.3) [21.2]

[a] Median (Min - Max)

4. Interaction of single and repeated administration of rifapentine on ATRIPLA

4.1 Efavirenz

Treatment ratio estimates with 90% CI for efavirenz administered after a single dose of rifapentine versus efavirenz administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Efavirenz	ATRIPLA + rifapentine vs ATRIPLA alone	C_{max}	1.01	(0.94 to 1.08)
		C_{min}	1.00	(0.95 to 1.05)
		AUC_{0-24}	0.97	(0.93 to 1.01)

Cohort n°2: ATRIPLA™ in Period 1 (15 days) and ATRIPLA™ + 900 mg oral of rifapentine (once weekly - 3 weekly administrations) in Period 2

Efavirenz C_{min}, C_{max}, and AUC_{0-24} treatment ratio estimates were close to 1, indicating a lack of interaction of a single dose of rifapentine on efavirenz C_{min}, C_{max}, and AUC_{0-24} at steady state.

Treatment ratio estimates with 90% CI for efavirenz administered after three weekly administrations of rifapentine versus efavirenz administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Efavirenz	ATRIPLA + rifapentine vs ATRIPLA alone	C_{max}	0.92	(0.82 to 1.03)
		C_{min}	0.85	(0.79 to 0.93)
		AUC_{0-24}	0.86	(0.79 to 0.93)

Cohort n°2: ATRIPLA™ in Period 1 (15 days) and ATRIPLA™ + 900mg oral of rifapentine (once weekly - 3 weekly administrations) in Period 2

Treatment ratio estimates indicated a decrease in efavirenz C_{min} and AUC_{0-24} of around 15% after repeated doses of rifapentine, while efavirenz C_{max} at steady state was not affected by repeated doses of rifapentine.

4.2 Emtricitabine

Treatment ratio estimates with 90% CI for emtricitabine administered after a single dose of rifapentine versus emtricitabine administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Emtricitabine	ATRIPLA + rifapentine vs ATRIPLA alone	C_{max}	1.03	(0.93 to 1.14)
		C_{min}	1.07	(0.99 to 1.15)
		AUC_{0-24}	0.96	(0.92 to 1.01)

Cohort n°2: ATRIPLA™ in Period 1 (15 days) and ATRIPLA™ + 900mg oral of rifapentine (once weekly - 3 weekly administrations) in Period 2

Emtricitabine C_{min}, C_{max}, and AUC_{0-24} treatment ratio estimates were close to 1, indicating a lack of interaction of a single dose of rifapentine on emtricitabine C_{min}, C_{max}, and AUC_{0-24} at steady state.

Treatment ratio estimates with 90% CI for emtricitabine administered after three weekly administrations of rifapentine versus emtricitabine administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Emtricitabine	ATRIPLA + rifapentine vs ATRIPLA alone	Cmax	0.95	(0.81 to 1.10)
		Cmin	0.97	(0.90 to 1.05)
		AUC0-24	0.93	(0.89 to 0.98)

Cohort n°2: ATRIPLA™ in Period 1 (15 days) and ATRIPLA™ + 900mg oral of rifapentine (once weekly - 3 weekly administrations) in Period 2

Emtricitabine C_{min}, C_{max}, and AUC_{0-24} treatment ratio estimates were close to 1 and, therefore, were not affected by repeated doses of rifapentine.

4.3 Tenofovir

Treatment ratio estimates with 90% CI for tenofovir administered after a single dose of rifapentine versus tenofovir administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Tenofovir	ATRIPLA + rifapentine vs ATRIPLA alone	C_{max}	1.23	(1.00 to 1.51)
		C_{min}	0.93	(0.84 to 1.03)
		AUC_{0-24}	1.02	(0.91 to 1.15)

Cohort n°2: ATRIPLA™ in Period 1 (15 days) and ATRIPLA™ + 900mg oral of rifapentine (once weekly - 3 weekly administrations) in Period 2

The C_{max} treatment ratio estimate (with associated 90%CI) indicated an increase in tenofovir C_{max} of 23% after a single dose of rifapentine while tenofovir C_{min} and AUC_{0-24} were not affected.

Treatment ratio estimates with 90% CI for tenofovir administered after three weekly administrations of rifapentine versus tenofovir administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Tenofovir	ATRIPLA + rifapentine vs ATRIPLA alone	C_{max}	1.00	(0.82 to 1.22)
		C_{min}	0.87	(0.73 to 1.05)
		AUC_{0-24}	0.91	(0.85 to 0.98)

Cohort n°2: ATRIPLA™ in Period 1 (15 days) and ATRIPLA™ + 900mg oral of rifapentine (once weekly - 3 weekly administrations) in Period 2

Tenofovir C_{max} and AUC_{0-24} treatment ratio estimates were close to 1, indicating that C_{max} and AUC_{0-24} were not affected after repeated administration of rifapentine. The treatment ratio estimate for C_{min} was lower (0.87) with a 90% CI of 0.73 to 1.05.

Safety results: There were no serious AEs or severe TEAEs reported during the study. In Cohort 1 (coadministration of ATRIPLA with daily regimen of rifapentine), 1 patient discontinued from the study during the coadministration period on Day 18 due to a TEAE of isolated elevated ALT (4.0 upper limit of normal [ULN] with a maximum increase of 5.9 ULN at end-of-study), without any associated symptoms (aspartate aminotransferase values were 1.7 ULN with no change in alkaline phosphatase and bilirubin). The ALT values returned to normal values during followup assessments, 2 weeks after rifapentine discontinuation. In Cohort 2, no patient was discontinued from the study treatment.

All TEAEs were of mild intensity and were reported in the majority of patients during the coadministration of ATRIPLA with rifapentine (10/12 patients and 11/12 patients for Cohort 1 and 2, respectively) as compared to ATRIPLA alone (5/13 and 3/12 patients for Cohorts 1 and 2, respectively).

Renal and urinary disorders (chromaturia) reported by 8/12 patients [66.7%] and 10/12 patients [83%] in Cohorts 1 and 2, respectively, and nervous system disorders (mainly headache and somnolence) were the most frequent SOCs affected during the coadministration period (6/12 patients [50%] and 5/12 patients [42%] for Cohorts 1 and 2, respectively).

Except for the ALT increase leading to discontinuation of 1 patient in Cohort 1, few isolated and no clinically relevant PCSAs were reported for laboratory parameters, vital signs, and ECG for either cohort.

Of note, 1 patient enrolled in Cohort 2 presented PCSA values for platelet count (minimum value of 55 Giga/L on Day 15 Period 2) with an already low value at baseline (57 Giga/L), and 1 patient who had an elevated baseline triglycerides value (7.1 mmol/L) presented PCSA for triglycerides (maximum value of 14.1 mmol/L on Day 15 Period 2).

For both cohorts, no clinically significant modification was reported throughout the study on the CD4 cell counts and the viral loads in any of the patients as compared to baseline. Of note, 1 patient was enrolled in Cohort 1 by error despite a viral load above the limit of detection at baseline; however, the patient's viral load significantly decreased during the study due to better compliance with ATRIPLA during the trial.

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