SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals Ltd. **Trade Name**: Prezista™ **Indication**: HIV-1 infection	**Drug Substance**: TMC114 **Trial no**.: TMC114-C151 **Clinical Phase**: I
Title: The pharmacokinetic interaction between TMC114, lopinavir and ritonavir, in HIV-1 infected subjects.	
Investigator: International, multicenter	**Country**: Australia, Denmark, Germany, Italy United Kingdom
Trial Period: Start: 18-Apr-2005 End: 30-Sep-2005	**No. of Investigators**: 8 **No. of Subjects**: 33
Objectives: The objectives of this trial were to determine the effect of steady-state concentrations of DRV, administered alone or in the presence of low-dose ritonavir, on the steady-state pharmacokinetics of LPV/rtv (Kaletra®); to determine the effects of steady-state concentrations of LPV/rtv on the steady-state pharmacokinetics of DRV, administered alone or in the presence of low-dose ritonavir; to determine the short term safety and tolerability of coadministration of DRV, LPV and low-dose ritonavir and to determine the potential impact of DRV on virologic response in HIV-1 infected subjects on a LPV/rtv based regimen.	
Design: This was a Phase I, open-label, randomized, crossover trial in HIV-1 infected subjects to investigate the pharmacokinetic interaction at steady-state between darunavir (DRV, TMC114), administered alone or in the presence of low-dose ritonavir, and lopinavir (LPV)/ritonavir (rtv) (Kaletra®). The trial population was planned to consist of 2 panels of 16 HIV-1 infected subjects each, who were on an ARV therapy that included LPV/rtv (400/100 mg b.i.d.) in combination with at least 2 NRTIs with or without enfuvirtide, and had a screening viral load between 1000 and 10000 HIV-1 RNA copies/mL. After the implementation of country-specific Amendment I (all countries but Italy), subjects with a viral load < 1000 HIV-1 RNA copies/mL, could also be included in the trial. Rescreening was allowed for subjects who had a viral load < 1000 HIV-1 RNA copies/mL at the initial screening visit, before the implementation of the country-specific Amendment I and if their ARV regimen had not been changed. Subjects who received a double PI combination that included LPV/rtv were eligible to participate after Amendment I as long as they were willing to discontinue the other PI in the regimen at screening. For the other PI a washout period of at least 2 weeks was necessary before the start of Session 1. No changes were made to all other ARVs in the regimen except for those related to the different treatment periods in this trial. In 3 sessions, Panel 1 received Treatments A, B and D and Panel 2 received Treatments A, C and D. In Treatment A, subjects continued their usual HIV therapy consisting of LPV/rtv (400/100 mg b.i.d.) and 2 or more NRTIs with or without enfuvirtide. In Treatment B, subjects received DRV/rtv 1200/100 mg b.i.d. for 14 days, as add-on to their usual LPV/rtv (400/100 mg b.i.d.) therapy and at least 2 NRTIs with or without enfuvirtide. In Treatment C, subjects received DRV 1200 mg b.i.d. and an additional capsule of LPV/rtv (133.3/33.3 mg b.i.d.) for 14 days, as add-on to their usual therapy consisting of LPV/rtv (400/100 mg b.i.d.) and at least 2 NRTIs with or without enfuvirtide. In Treatment D, LPV/rtv was substituted by DRV/rtv 600/100 mg b.i.d. in combination with baseline NRTI with or without enfuvirtide for 14 days. Subsequent sessions were not separated by a washout period. On Day 14 of each treatment, 12-hour pharmacokinetic profiles of ritonavir, DRV and/or LPV were determined. Safety and tolerability were also assessed. Subjects who, after the last treatment in the current trial, wanted to continue on DRV/rtv as the only PI component of their new ARV therapy had the opportunity to participate in a follow-up trial with DRV (TMC114-C208).	
Subject Selection Inclusion Criteria 1. Male or female subject, aged 18 years or older. 2. Documented HIV-1 infection and plasma viral load at the screening visit between 1000 and 10000 HIV–1 RNA copies/mL (a viral load <1000 HIV-1 RNA copies/mL was allowed after the implementation of country-specific Amendment I, in all countries except Italy) (assayed by Roche Amplicor® HIV-1 (Version 1.5), ultrasensitive method). ***Note*:** Retesting of screening viral load falling outside of this range was allowed only once using an unscheduled visit.	

3. Receiving a stable ARV regimen that included LPV/rtv, given at a dose level of LPV/rtv 400/100 mg b.i.d. for at least 12 weeks before screening in combination with at least 2 NRTIs with or without enfuvirtide.
   ***Note*:** Subjects who received a double PI combination that included LPV/rtv were eligible to participate, after the implementation of Amendement I, as long as they were willing to discontinue the other PI in the regimen at screening. A washout period of at least 2 weeks was necessary before the start of Session 1. No changes were made to all other ARVs in the regimen except for those related to the different treatment periods in this trial.
4. Agreeing not to change LPV/rtv and NRTI combination with or without enfuvirtide (including dosages) from screening until the end of the treatment period (except for the dose changes of LPV/rtv as described per Clinical Trial Protocol), unless this was medically indicated as decided by the treating physician and after having checked with the sponsor.
5. Informed Consent Form (ICF) signed voluntarily before first trial related activity.

Exclusion Criteria

1. Presence of any currently active AIDS defining illness (Category C conditions according to the CDC Classification System for HIV Infection 1993), with the following exceptions:
   - stable cutaneous Kaposi's Sarcoma (i.e., no internal organ involvement other than oral lesions) that was unlikely to require any form of systemic therapy during the trial time period.
   - wasting syndrome.

   ***Note*:** Primary and secondary prophylaxis for an AIDS defining illness was allowed in case the medication used was not part of the disallowed medication.
2. History or suspicion of alcohol, barbiturate, amphetamine, recreational or narcotic drug use that could impact compliance to protocol requirements and/or safety.
3. Positive drug screening at two consecutive drug screenings (a positive drug screening at screening was repeated between screening and baseline). The drug screening involved analysis for amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids and opioids.
   Note: Positive drug screening tests resulting from the following were not considered exclusionary:
   - prescription use of temazepam, oxazepam, lorazepam, chlordiazepoxide, codeine and/or methadone was allowed
   - cannabinoids
4. Use of disallowed concomitant therapy.
5. Current use of NNRTI(s) and investigational ARVs, except for tenofovir, emtricitabine, if applicable.
6. Previous use of tipranavir and DRV.
7. Use of any non ARV investigational agents within 90 days prior to screening.
8. Life expectancy of less than 6 months.
9. Pregnant or breast feeding.
10. Female subject of childbearing potential without use of effective non-hormonal birth control methods or not willing to continue practicing these birth control methods for at least 14 days after the end of the treatment period.
    Note: Hormonal based contraception may not be reliable when taking DRV, therefore to be eligible for this trial women of childbearing potential had to either:
    1) use a double barrier method to prevent pregnancy (i.e. using a condom with either diaphragm or cervical cap) or
    2) use hormonal based contraceptives in combination with a barrier contraceptive (i.e. male condom, diaphragm or cervical cap or female condom) or
    3) use a intra uterine device in combination with a barrier contraceptive (i.e. male condom, diaphragm or cervical cap or female condom) or
    4) be non-heterosexually active, practice heterosexual abstinence or have a vasectomized partner (confirmed sterile)

    Note: Women who were postmenopausal for at least 2 years, women with total hysterectomy and women with tubular ligation were considered of non-childbearing potential.
11. Any active clinically significant disease (e.g., tuberculosis, cardiac dysfunction, pancreatitis, acute viral infections) or findings during screening of medical history or physical examination that, in the investigator's opinion, would compromise the subject's safety or outcome of the trial.
12. Allergy to any of the constituents of the pharmaceuticals administered in this trial.

13. Subjects with clinical or laboratory evidence of significantly decreased hepatic function or decompensation, irrespective of liver enzyme levels.
Note: Subjects coinfected with chronic hepatitis B or C were allowed to enter the trial if their condition was clinically stable, and were not expected to require treatment during the trial period and had transaminase levels ≤ 3 x upper limit of normal (ULN). Subjects diagnosed with acute hepatitis A at screening were allowed in the trial.
14. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 3 x ULN.
15. Subjects with any grade 3 or 4 laboratory abnormality as defined by ACTG grading scheme. The following exceptions could be included unless clinical assessment foresaw an immediate health risk to the subject:
    - subjects with pre-existing diabetes or asymptomatic glucose elevations of grade 3 or 4.
    - subjects with asymptomatic triglyceride or cholesterol elevations grade 3 or 4.
    - subjects with asymptomatic and isolated lactate dehydrogenase (LDH) or gamma glutamyltransferase (GGT) elevations of grade 3 or 4 with all other liver function tests (LFT) including bilirubin within normal ranges (≤ 3 x ULN).

Retesting of abnormal screening values that lead to exclusion was allowed only once and using an unscheduled visit.

Treatment	**Darunavir**	**Ritonavir**	**LPV/rtv**
Concentration	200 mg/tablet 400 mg/tablet	100 mg/capsule	133.3/33.3 mg/capsule
Dosage Form (TF No.)	tablet (F014/F015)	capsule (Norvir®)	capsule (Kaletra®)
Usage	oral	oral	oral
Batch Number	PD1220/PD1243	21336VA	23293VA
Dose Regimen	In 3 sessions, subjects of Panel 1 received Treatments A, B and D, and subjects of Panel 2 received Treatments A, C and D. ARV therapy at screening consisted of LPV/rtv (400/100 mg b.i.d.) in combination with at least 2 NRTIs with or without enfuvirtide. Treatment A: Usual ARV therapy, including LPV/rtv 400/100 mg b.i.d. Treatment B: Usual ARV therapy, including LPV/rtv 400/100 mg b.i.d., and DRV/rtv 1200/100 mg b.i.d. on Days 1-14. Treatment C: Usual ARV therapy, including LPV/rtv 400/100 mg b.i.d., DRV 1200 mg b.i.d. and LPV/rtv 133.3/33.3 mg b.i.d. on Days 1-14. Treatment D: Usual ARV therapy was continued, but LPV/rtv was substituted by DRV/rtv 600/100 mg b.i.d. on Days 1-14.		
Duration of Treatment	6 weeks		
Duration of Trial	10 weeks (excluding screening, including follow-up)		
Disallowed Medication	The following medications were not allowed from 2 days before start of treatment (2 days before Day 1 of Session 1) until end of treatment (the last day of Session 3, after all assessments had been performed): any anti-HIV therapy (including hydroxyurea) not in agreement with the inclusion criteria or prohibited based on the exclusion criteria; HIV- vaccines, cytochrome P450 3A4 inhibitors and - substrates with small therapeutic index; cholestyramine, colestipol, lovastatin and pravastatin. The following cytochrome P450 3A4 inducers were not allowed from 14 days before the start of the treatment (14 days before Day 1 of Session 1) until the end of the treatment (the last day of Session 3, after all assessments have been performed): rifamycins, anticonvulsants, all products containing *Hypericum perforatum* (St John's Wort). Amphetamines and amphetamine derivatives could not be used for the duration of the whole trial period (i.e., from screening up to the last follow-up visit). In the event that rash and/or pruritus occurred, treatment with cetirizine (Zyrtec®), levocetirizine (Xyzal®), topical corticosteroids or antipruritic agents, as medically indicated, could be prescribed, taking into account the above-mentioned disallowed medication.		

Assessments	
Pharmacokinetics	
	Blood samples were taken on: – In each session on Days 1, 7, 12, 13 (predose) and 14 (predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9 and 12 hours after drug intake). – At the time of discontinuation (or the following morning), for subjects who prematurely discontinued the trial.
Efficacy	
Virology	Samples for plasma viral load determination were taken: – At screening. – On Day 1 (predose) of Session 1. – On Days 7 and 14 (predose) of each session. – At the time of discontinuation (or the following morning), and at the follow-up visits 1 and 4-5 weeks after the last drug intake or early discontinuation.
Immunology	Immunologic CD4+ count was done: – At screening. – On Day 14 (predose) of each session. – At the time of discontinuation (or the following morning), and at the follow-up visits 1 and 4-5 weeks after the last drug intake or early discontinuation.
Resistance determinations	
	Samples for pheno-/genotyping were taken (only if VL was >1000 HIV-1 RNA copies/mL): – On Day 1 (predose) in Session 1. – On Day 14 (predose) in Session 3. – At the time of discontinuation (or the following morning).
Safety	
Adverse Events	Adverse events were checked at every visit and reported from signing the ICF onwards until the last trial related activity.
Clinical Laboratory	Samples for biochemistry, hematology and coagulation testing were taken: – At screening (fasted). – On Day 1, 4, 7, 10, 12 and 14 (predose, fasted) and Days 14, 12 hours postdose. – At the time of discontinuation (or the following morning) (fasted, if possible), and at the follow-up visit 1 and 4-5 weeks after the last drug intake (fasted) or early discontinuation. Peripheral blood mononuclear cell (PBMC) samples for immunologic assessments were taken: – On Day 1 (predose) in Session 1. – On Day 14 (predose) in Session 3. – At the time of discontinuation (or the following morning).
	Urinalysis was performed: – At screening. – On Day 1, 4, 7, 10, 12 and 14 (predose, 3 and 5 hours postdose) of each session. – At the time of discontinuation (or the following morning), and at the follow-up visit 1 and 4-5 weeks after the last drug intake or early discontinuation.
Cardiovascular safety	ECG and vital signs were performed: – At screening. – On Day 1, 7 and 14 (predose) of each session. – On Day 14 (3 and 5 hours postdose) of each session. – At the time of discontinuation (or the following morning), and at the follow-up visit 1 and 4-5 weeks after the last drug intake.

Physical examination	At screening, at time of discontinuation for subjects who discontinued prematurely, and at the follow-up visits 1 and 4-5 weeks after the last drug intake.
Statistical Methods	Descriptive statistics, linear mixed effect modeling, frequency tabulations Intent-to-Treat (ITT) analysis, Wilcoxon matched-pairs signed-ranks test

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics - Subject Disposition	Panel 1		Panel 2	
	Treatment A/B/D N = 9	Treatment A/D/B N = 8	Treatment A/C/D N = 8	Treatment A/D/C N = 8
Number of Subjects Entered by Gender (M/F)	7/2	8/0	8/0	7/1
Age: median (range), yrs	44.0 (32-52)	47.0 (36-59)	41.5 (36-52)	43.5 (25-64)
Baseline log_{10} viral load, median (range), HIV-1 RNA copies/mL	4.17 (3.1-4.6)	4.04 (3.2-4.8)	1.69 (1.7-4.5)	1.80 (1.7-4.1)
Screening CD4+ count, median (range), 10^6 cells/L	375.00 (176.0-581.0)	260.50 (159.0-422.0)	508.00 (149.0-1195.0)	426.50 (253.0-1086.0)
Duration of HIV infection, median (range), yrs	13.0 (10-21)	14.5 (5-20)	13.5 (3-19)	10.5 (2-21)
Discontinuations- Reason, n (%)				
Sponsor's decision	1	0	0	0
Adverse event	0	2	0	0
Non compliant	0	0	0	1

Pharmacokinetics of DRV Panel 1 (mean ± SD, $t_{max:}$ median (range))	**Treatment D (reference)** DRV/rtv	**Treatment B (test)** DRV/rtv + LPV/rtv 400/100 mg b.i.d.
n	15	14[a]
t_{max}, h	3.00 (1.50 - 6.02)	3.00 (0.50 - 4.00)
C_{0h}, ng/mL	3167 ± 1155	2152 ± 1526
C_{min}, ng/mL	2770 ± 958.2	1438 ± 842.3
C_{max}, ng/mL	6701 ± 1920	5322 ± 1928
AUC_{12h}, ng.h/mL	55599 ± 19077	34640 ± 15210
$C_{ss,av,}$ ng/mL	4632 ± 1588	2891 ± 1261
FI, %	87.65 ± 28.10	142.2 ± 33.85
LSmean ratio (90% CI), %		
		B vs D
n	-	14 vs 15
C_{0h}	-	66.44 (53.34 - 82.76)[b]
C_{min}	-	49.31 (38.70 - 62.84)[b]
C_{max}	-	78.63 (67.27 - 91.92)[b]
AUC_{12h}	-	62.00 (52.58 - 73.11)[b]

[a] n = 13 for C_{0h}
[b] p-value < 0.05

Pharmacokinetics of DRV Panel 2 (mean ± SD, $t_{max:}$ median (range))	**Treatment D (reference)** DRV/rtv	**Treatment C (test)** DRV + LPV/rtv 533.3/133.3 mg b.i.d.
n	15	15
t_{max}, h	3.00 (1.50 - 4.00)	2.00 (1.50 - 5.02)
C_{0h}, ng/mL	3259 ± 1121	1715 ± 1154
C_{min}, ng/mL	2495 ± 663.5	1187 ± 517.7
C_{max}, ng/mL	6379 ± 1246	5471 ± 2875
AUC_{12h}, ng.h/mL	50399 ± 11140	31020 ± 12420
$C_{ss,av,}$ ng/mL	4203 ± 931.5	2590 ± 1035
FI, %	93.71 ± 19.17	161.2 ± 45.94
LSmean ratio (90% CI), %		
		C vs D
n	-	15 vs 15
C_{0h}	-	48.24 (39.59 - 58.79)[a]
C_{min}	-	44.68 (38.31 - 52.12)[a]
C_{max}	-	78.87 (64.06 - 97.10)
AUC_{12h}	-	59.08 (49.76 - 70.15)[a]

[a] p-value < 0.05

Pharmacokinetics of Lopinavir Panel 1 (mean ± SD, $t_{max:}$ median (range))	**Treatment A (reference)** LPV/rtv	**Treatment B (test)** DRV/rtv + LPV/rtv 400/100 mg b.i.d.
n	16	14[a]
t_{max}, h	4.00 (0.00 - 6.00)	5.00 (0.00 - 12.00)
C_{0h}, ng/mL	7362 ± 3451	8526 ± 3321
C_{min}, ng/mL	4701 ± 2322	6126 ± 3606
C_{max}, ng/mL	11097 ± 2900	11290 ± 4341
AUC_{12h}, ng.h/mL	92379 ± 29721	104800 ± 47850
$C_{ss,av,}$ ng/mL	7709 ± 2479	8775 ± 4046
FI, %	87.95 ± 28.55	66.13 ± 36.54
LSmean ratio (90% CI), %		
		B vs A
n	-	14 vs 16
C_{0h}	-	119.7 (88.26 - 162.3)
C_{min}	-	123.1 (89.65 - 169.1)
C_{max}	-	97.55 (77.76 - 122.4)
AUC_{12h}	-	108.5 (86.03 - 136.9)

[a] n=13 for C_{0h}

Pharmacokinetics of Lopinavir Panel 2 (mean ± SD, $t_{max:}$ median (range))	**Treatment A (reference)** LPV/rtv	**Treatment C (test)** DRV + LPV/rtv 533.3 + 133.3 mg b.i.d.
n	15[a]	15
t_{max}, h	4.92 (0.00 - 6.02)	5.00 (0.00 - 12.00)
C_{0h}, ng/mL	5720 ± 3001	6568 ± 2667
C_{min}, ng/mL	4175 ± 2375	4290 ± 1911
C_{max}, ng/mL	10301 ± 3047	11230 ± 2414
AUC_{12h}, ng.h/mL	85193 ± 28805	90480 ± 22630
$C_{ss,av,}$ ng/mL	7091 ± 2379	7554 ± 1887
FI, %	92.45 ± 38.24	95.47 ± 36.27
LSmean ratio (90% CI), %		
		C vs A
n	-	15 vs 15[b]
C_{0h}	-	122.1 (97.81 - 152.5)
C_{min}	-	113.1 (89.81 - 142.3)
C_{max}	-	111.5 (95.96 - 129.7)
AUC_{12h}	-	109.1 (95.89 - 124.1)

[a] n=14 for C_{0h}
[b] 15 vs 14 for C_{0h}

Pharmacokinetics of ritonavir Panel 1 (mean ± SD, $t_{max:}$ median (range))	**Treatment A** LPV/rtv	**Treatment B** DRV/rtv + LPV/rtv 400/100 mg b.i.d.	**Treatment D** DRV/rtv
n	16	14[a]	15
t_{max}, h	4.00 (0.00 - 9.00)	4.50 (1.00 - 6.00)	4.97 (0.00 - 6.00)
C_{0h}, ng/mL	295.8 ± 162.9	1000 ± 635.1	386.1 ± 189.8
C_{min}, ng/mL	162.4 ± 87.53	575.9 ± 324.6	262.4 ± 122.3
C_{max}, ng/mL	725.5 ± 321.6	2137 ± 798.3	809.5 ± 402.4
AUC_{12h}, ng.h/mL	4640 ± 1888	13890 ± 5211	5952 ± 2674
$C_{ss,av,}$ ng/mL	387.2 ± 157.3	1159 ± 430.8	495.8 ± 222.7
FI, %	151.6 ± 55.28	140.3 ± 57.87	107.9 ± 22.19

[a] n = 13 for C_{0h}

Pharmacokinetics of ritonavir Panel 2 (mean ± SD, $t_{max:}$ median (range))	**Treatment A** LPV/rtv	**Treatment C** DRV + LPV/rtv 533.3/133.3 mg b.i.d.	**Treatment D** DRV/rtv
n	15[a]	15	15
t_{max}, h	5.00 (1.50 - 9.00)	5.00 (0.00 - 6.00)	4.02 (2.00 - 6.00)
C_{0h}, ng/mL	343.8 ± 251.2	388.1 ± 239.4	416.7 ± 207.9
C_{min}, ng/mL	194.2 ± 141.1	205.8 ± 116.8	268.5 ± 137.5
C_{max}, ng/mL	1052 ± 694.4	1373 ± 929.4	1006 ± 402.4
AUC_{12h}, ng.h/mL	5780 ± 2998	6919 ± 3595	6550 ± 2470
$C_{ss,av}$, ng/mL	481.1 ± 248.3	577.4 ± 299.3	545.9 ± 205.6
FI, %	169.9 ± 66.25	189.5 ± 61.45	138.0 ± 31.93

[a] n = 14 for C_{0h}

Safety (Panel 1) (N = number of subjects with data)	Treatment A LPV/rtv N = 17	Treatment B DRV/rtv + LPV/rtv 400/100 mg b.i.d. N = 15	Treatment D DRV/rtv N = 15	FU N = 10
Adverse Events (AEs)				
Most frequently reported AEs (reported in ≥ 2 subjects during any treatment), n (%)				
- GI Disorders	**1 (5.9)**	**6 (40.0)**	**3 (20.0)**	**2 (20.0)**
Diarrhea	0	2 (13.3)	1 (6.7)	1 (10.0)
Nausea	0	3 (20.0)	0	0
Vomiting	0	0	2 (13.3)	1 (10.0)
- Renal and urinary disorders	**2 (11.8)**	**2 (13.3)**	**0**	**0**
Hematuria	2 (11.8)	0	0	0
- Respiratory, thoracic and mediastinal disorders	**0**	**1 (6.7)**	**0**	**2 (20.0)**
Pharyngolaryngeal pain	0	1 (6.7)	0	2 (20.0)
n (%) with 1 or more AEs	7 (41.2)	11 (73.3)	7 (46.7)	5 (50.0)
n (%) of deaths	0	1 (6.7)	0	0
n (%) with 1 or more other serious AEs	1 (5.9)	1 (6.7)	0	1 (10.0)
n (%) of treatment stopped due to AEs	0	1 (6.7)	0	1 (10.0)
n (%) with 1 or more grade 3 or 4 AEs	0	1 (6.7)	1 (6.7)	0

Two subjects of Panel 1, assigned to treatment schedule A/D/B, discontinued due to AEs. One subject (151-00014) discontinued after the first treatment period due to grade 2 lower respiratory tract infection. The second subject (151-0026) discontinued due to acute renal failure on Day 4 of Session 3 (bladder cancer was later diagnosed) , and died during follow-up (approximately 2 months after last drug intake) due to a cardiogenic shock. Apart from this death, no other SAEs were reported during this trial.

Safety (Panel 2) (N = number of subjects with data)	Treatment A LPV/rtv N = 16	Treatment C DRV + LPV/rtv 533.3/133.3 mg b.i.d. N = 15	Treatment D DRV/rtv N = 15	FU N = 15
Adverse Events (AEs)				
Most frequently reported AEs (reported in ≥ 2 subjects, during any treatment), n (%)				
- GI disorders	**0**	**5 (33.3)**	**0**	**0**
Diarrhea	0	2 (13.3)	0	0
Flatulence	0	2 (13.3)	0	0
Gastrointestinal motility disorder	0	2 (13.3)	0	0
- Psychiatric disorders	**0**	**2 (13.3)**	**0**	**0**
Anxiety	0	2 (13.3)	0	0
n (%) with 1 or more AEs	4 (25.0)	9 (60.0)	5 (33.3)	1 (6.7)
n (%) of deaths	0	0	0	0
n (%) with 1 or more other serious AEs	0	0	0	0
n (%) of treatment stopped due to AEs	0	0	0	0
n (%) with 1 or more grade 3 or 4 AEs	0	0	0	0

Clinical Laboratory Tests	No consistent or clinically relevant changes over time in median laboratory parameters were observed. Most common graded laboratory abnormalities were hypertriglyceridemia, hyperglycemia, and hyperuricemia. Most graded laboratory parameters were grade 1 or 2 in severity. Grade 3 or 4 hypertriglyceridemia was observed in 5 subjects (33%) during Treatment B in Panel 1, compared to at most 1 subject (7%) during any other treatment in Panel 1. This increased incidence of grade 3 and 4 hypertriglyceridemia during coadministration of DRV and LPV/rtv was not observed in Panel 2. All other graded laboratory abnormalities of grade 3 or 4 were seen in at most 2 subjects during any treatment in any panel. Two laboratory abnormalities were reported as AE during DRV/rtv treatment phases, i.e., grade 1 blood creatinine increased (unrelated to DRV or LPV/rtv) and grade 4 hypertriglyceridaemia (doubtfully related to DRV, probably related to LPV/rtv).
Urinalysis	No clinically relevant urinalysis abnormalities related to DRV/rtv were reported.
Cardiovascular Safety	No clinically relevant changes in vital signs or ECG parameters were observed. The incidence of vital signs abnormalities was low and similar for all treatments. No pathologically prolonged QTcB or QTcF values were observed. The incidence of prolonged QTc values and increases by > 60 ms was generally low and similar for all treatments. No AEs related to ECG or vital signs abnormalities were reported during treatments including DRV.
Viral load and Immunologic Change	In Panel 1, none of the subjects had a viral load below 400 HIV-1 RNA copies/mL at baseline. In Panel 2, 10 subjects (63%) had a baseline viral load <400 HIV-1 RNA copies/mL, 8 of them had a viral load below the detection limit. These values were also reflected in the median log viral load at baseline, which was higher in Panel 1 (4.04 and 4.17 in treatment arms ADB and ABD, respectively) than in Panel 2 (1.69 and 1.80 in treatment arms ACD, and ADC, respectively). At the end of Session 3, 71 and 50% of subjects in Panel 1 (in treatment arms ABD, and ADB, respectively) had a viral load < 400 HIV-1 RNA copies/mL. In Panel 2, this was 100% and 85.7% of subjects in treatment arms ACD and ADC, respectively.

Conclusions

The results of this trial demonstrated that lopinavir AUC_{12h}, C_{min}, and C_{0h} after a 400 mg b.i.d. dose in combination with ritonavir 100 mg b.i.d. were slightly increased by coadministration of DRV/rtv 1200/100 mg b.i.d., i.e., LSmeans ratio [90% CI interval] for AUC_{12h}, C_{min} and C_{0h} was 108.5 [86.03-136.9], 123.1 [89.65-169.1], and 119.7 [88.26-162.3], respectively. C_{max} was unaltered. The increase in lopinavir exposure was similar when LPV/rtv 533.3/133.3 mg b.i.d. and DRV 1200 mg b.i.d (without low dose ritonavir) were coadministered, i.e., LSmeans ratio [90% CI] for AUC_{12h}, C_{min} and C_{0h} was 109.1 [95.89-124.1], 113.1 [89.81-142.3], and 122.1 [97.81-152.5], respectively.

Despite a two-fold increase in DRV dose (i.e., 1200 mg instead of the 600 mg recommended dose in treatment experienced subjects), AUC_{12h}, C_{max}, C_{0h} and C_{min} of DRV were considerably decreased when DRV/rtv 1200/100 mg b.i.d. was coadministered with LPV/rtv 400/100 mg b.i.d. (ratio of the LSmeans 62.00%, 78.63%, 66.44%, and 49.31%, respectively). Similar decreases in DRV exposure were also seen when DRV 1200 mg b.i.d. (without low-dose ritonavir) was coadministered with LPV/rtv 533.3/133.3 mg b.i.d. (ratio of the LSmeans 59.08%, 78.87%, 48.24%, and 44.68%, respectively).

In conclusion, the combination of LPV/rtv and DRV is not recommended for the following reasons:

- exposure to DRV is considerably decreased when combined with LPV/rtv, which is expected to be clinically relevant. Although initial virologic response may be observed with the coadministration of DRV and LPV/rtv as was shown in Panel 1, this considerable decrease in DRV exposure could lead to loss of response over time. Given the minimal increase in LPV exposure during the coadministration period, it can be stipulated that the additional antiviral effect was provided by DRV.
- gastrointestinal disorders were more common during coadministration of DRV/rtv and LPV/rtv compared to treatments where the drugs were administered alone. Such side-effects could impact quality of life and adherence to ART.

Therefore, patients not fully suppressed on LPV/rtv are more likely to benefit from a new regimen that includes DRV/rtv 600/100 mg b.i.d. as the PI component than from the coadministration of LPV/rtv and DRV. Maintaining a non-suppressive LPV/rtv containing regimen may lead to the development of additional PI mutations and an increase in DRV FC.

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