SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals, Formerly Tibotec Pharmaceuticals Ltd. **Trade Name**: Prezista® **Indication**: HIV-1 infection	**Drug Substance**: Darunavir (DRV, TMC114) **Trial no**.: TMC114-C226 **Clinical Phase**: NA
Title: Early access of darunavir (TMC114) in combination with low-dose ritonavir and other antiretrovirals in highly treatment-experienced HIV-1 infected subjects with limited to no treatment options.	
Investigator: A. Lazzarin, Ospedale S. Raffaele, Dipartimento di Malattie Infettive, Via Stamira D'Ancona 20, 20127 Milano, Italy	**Country**: Multicenter
Trial Period: Start: 13-Oct-2005 End: 29-Sep-2009	**No. of Subjects**: 2966

Objectives: The primary objective of this trial was to provide early access to darunavir (DRV, formerly TMC114) for highly treatment- experienced HIV-1 infected subjects who had failed multiple antiretroviral (ARV) regimens. The secondary objective was to gather information on the safety and tolerability of DRV in combination with low-dose rtv and other ARVs. The safety assessment focussed on serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation.

Design: This was an open-label trial to provide early access to DRV for HIV-1 infected subjects, who failed multiple ARV regimens and who were ineligible for participation in any other Tibotec-sponsored HIV-1 trial. In addition, information was collected on the safety and tolerability of DRV in combination with low-dose ritonavir (rtv) and other ARVs in these highly treatment-experienced HIV-1 infected subjects with limited to no treatment options. The safety assessment focussed on SAEs and on AEs leading to discontinuation.
Once trial treatment was initiated, subjects were instructed to follow the visit schedule based on routine clinical care. Recommended visits were planned 4 and 12 weeks after initiation of treatment with DRV in combination with low-dose rtv and other ARVs, and every 12 weeks thereafter while on trial treatment. Treatment with trial medication was continued until treatment-limiting toxicity, loss to follow-up, withdrawal from the trial, pregnancy, discontinuation of DRV development, or when DRV became commercially available to the subject.

Subject Selection

Inclusion Criteria

1. Having voluntarily signed the Informed Consent Form before initiation of trial procedures.
2. Documented HIV-1 infection.
3. 18 years of age or older.
4. Having limited or no treatment options due to virologic failure or intolerance to multiple ARV regimens.
5. At least 3-class experienced and previously received 2 different protease inhibitor (PI)-based regimens.
6. Not achieving virologic suppression on the current regimen and at risk of clinical or immunologic progression (could have been not applicable, if the subject was a roll over subject, without treatment interruption, from trials TMC114-C202, TMC114-C209, TMC114-C213, TMC114-C215, or any other sponsor-selected trial with DRV).

Exclusion Criteria

1. Primary HIV-1 infection.
   Note: Subjects with primary HIV-1 infection were only allowed in the trial if they had documented resistance to all currently approved PIs. For these subjects, it was possible that Inclusion Criteria 4, 5 and 6 did not apply.
2. Eligibility for other Tibotec-sponsored HIV-1 trials.
   Note: Subjects who were eligible for any other Tibotec-sponsored HIV-1 trial, but located more than 100 km away from a site participating in such trial, were considered eligible for trial TMC114-C226.
   Note: This criterion was not applicable for Tibotec-sponsored HIV-1 trials that had as primary objective the provision of early access to ART.

3. Prior or current participation in a trial with DRV.
   Note: This criterion did not apply to the following trials:
   - TMC114-C209.
   - TMC114-C202, TMC114-C213 and TMC114-C215 either if the subject had completed the 144-weeks treatment period or experienced a virologic failure as defined in the originating protocol and required treatment with DRV in combination with an ARV that was not allowed per the originating protocol.
   - Other trials with DRV after prior discussion with and approval from the sponsor.
4. Any condition (including but not limited to alcohol and drug use) that, in the opinion of the investigator, could compromise the subject's safety or adherence to the trial protocol.
5. Use of disallowed concomitant therapy.
6. Use of investigational medication within the last 30 days or during the trial, with the exception of:
   - the investigational fixed dose combinations abacavir/lamuvidine and tenofovir/emtricitabine (if applicable, based on the status of local approval);
   - tipranavir (if applicable, based on the status of local approval); tipranavir was allowed until the day before DRV intake (wash-out period of 30 days was not applicable for tipranavir);
   - investigational ARVs for which favorable pharmacokinetic interaction and safety data supported coadministration with DRV/rtv; investigational drugs that fulfilled this criterion were allowed only after the sponsor had informed the investigators, applicable Ethics Committees and Health Authorities.
7. Any active clinically significant disease (e.g., cardiac dysfunction, pancreatitis, acute viral infection), or findings during screening of medical history or physical examination, that was not either resolved or stabilized for at least 30 days before the screening phase of the trial.
8. Pregnant or breastfeeding female.
9. Female subject of childbearing potential not using effective nonhormonal birth-control methods or not willing to continue practicing these birth-control methods from screening until the last trial-related activity.
   Note: Hormonal based contraception may not be reliable when taking DRV, therefore to be eligible for this trial, women of childbearing potential who might have vaginal intercourse had to either:
   - use a double-barrier method to prevent pregnancy (i.e., condom without spermicide, with either diaphragm or cervical cap);
   - use hormonal based contraceptives in combination with a barrier contraceptive (i.e., male condom without spermicide, diaphragm or cervical cap or female condom);
   - use an intra uterine device (IUD) in combination with a barrier contraceptive (i.e., male condom without spermicide, diaphragm or cervical cap or female condom);
   - be non-heterosexually active, practice sexual 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.
10. Subjects with any grade 3 or 4 toxicity of selected laboratory parameters as defined by a standardized grading scheme based on the Division of Acquired Immunodeficiency Syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events.
11. Subjects with clinical or laboratory evidence of active liver disease, liver impairment/dysfunction or cirrhosis irrespective of liver enzyme levels.
    Note: Subjects coinfected with chronic hepatitis B or C were allowed to enter the trial if their condition was judged to be clinically stable; subjects diagnosed with acute viral hepatitis at screening were not allowed.
12. Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the investigational medication (DRV) or rtv.
    Note: DRV is a sulfonamide. Subjects who previously experienced a sulfonamide allergy were allowed. To date, no potential for cross-sensitivity between drugs in the sulfonamide class and DRV has been identified in subjects participating in Phase II trials.

Treatment	DRV	Ritonavir
Concentration Dosage Form (F No.) Usage	300-mg tablet F016 Oral	100-mg capsule - Oral
Dose Regimen	DRV/rtv 600/100 mg b.i.d.	
Duration of Treatment	Treatment with trial medication was continued until treatment-limiting toxicity, loss to follow-up, withdrawal from the trial, pregnancy, discontinuation of DRV development, or when DRV became commercially available to the subject.	
Duration of Trial	All subjects, except those who withdrew informed consent, could be followed for survival until the last follow-up visit of the last subject in this trial.	

Disallowed Medication	Non-ARVs
	- all products containing *Hypericum perforatum* (St John's Wort);
	- rifampin, rifapentin;
	- phenobarbital, phenytoin, carbamazepine;
	- systemic dexamethasone;
	- investigational medication.
	ARVs
	- PI(s), except for atazanavir and indinavir;
	- Investigational ARVs, with the following exceptions:
	  - the investigational fixed dose combinations abacavir/lamivudine and tenofovir disoproxil fumarate/emtricitabine;
	  - etravirine;
	  - investigational ARVs for which favorable pharmacokinetic interaction and safety data supported coadministration with DRV/rtv;
	  - MK-0518 (raltegravir).	

Assessments		
Safety		
Adverse Events	From signing the Informed Consent Form onwards until the last trial-related activity, SAEs (with the exception of most non-fatal AIDS defining illnesses) and AEs leading to discontinuation or treatment interruption were collected per protocol. Other AEs were only requested to be reported if required per local regulations.	
Clinical Laboratory[a]	Samples for hematology and biochemistry (fasted): at screening, and further recommended at baseline, Week 4, Week 12, subsequently at 12-week intervals, and the final/withdrawal visit (coagulation at the same time points except screening). Samples for hepatitis A, B, C: recommended at screening Pregnancy testing: at screening, baseline, Week 4, Week 12, subsequently at 12-week intervals, and the final/withdrawal visit.	
HIV-1 Surrogate Markers[a]: Plasma Viral Load and Immunology	Samples at screening and further recommended at baseline, Week 4, Week 12, subsequently at 12-week intervals, and the final/withdrawal visit.	
Statistical Methods	Descriptive analyses, generation of data listings	

[a] All tests were performed by local laboratories.

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics	
Number of Subjects Entered: N (M/F)	2966 (2504/462)
Age (years): mean (SE)	45.5 (0.15)
Log_{10} plasma viral load (copies/mL), mean (SE)	4.25 (0.022)
CD4+ cell count (x 10^6/L), mean (SE)	241 (48.2)
Known duration of HIV infection (yrs), mean (SE)	14.6 (0.09)
WHO Clinical stage of HIV infection, n (%)	
A	723 (24.4)
B	704 (23.7)
C	1537 (51.8)
Missing	2 (0.1)
Trial Termination (According to the Trial Termination Page)	
Completed	698 (23.5)
Switch to commercially available DRV	1835 (61.9)
Adverse Event/HIV related	146 (4.9)
Other	95 (3.2)
Subject lost to follow-up	69 (2.3)
Subject withdrew consent	40 (1.3)
Subject did not fulfill all inclusion/exclusion criteria	21 (0.7)
Subject noncompliant	20 (0.7)
Subject reached a virologic endpoint	17 (0.6)
Subject ineligible to continue the trial	10 (0.3)
Sponsor's decision	5 (0.2)
Missing	10 (0.3)

Exposure based on Visit Data	
Visit, n (%)	**DRV/rtv 600/mg b.i.d.**
Baseline[a]	2815 (94.9)[a]
Week 24	1951 (65.8)
Week 48	998 (33.6)
Week 72	322 (10.9)
Week 96	114 (3.8)
Week 120	33 (1.1)

a Not all subjects had a registered baseline visit.

Safety	
Adverse Events, n (%)	
Deaths	74
Subjects with ≥ 1 SAEs	327 (11.0)
Subjects with ≥ 1 SAEs at least possibly related	43 (1.4)
Subjects with ≥ 1 AEs leading to permanent discontinuation	138 (4.7)
Subjects with ≥ 1 AEs leading to permanent discontinuation at least possibly related	56 (1.9)
There were no new clinically relevant findings compared to the known AE profile of DRV/rtv. The most frequent (> 2 subjects) SAEs at least possibly related (preferred term) were diarrhea (4 subjects, 0.1%), and nausea, pancreatitis, hepatitis, and immune reconstitution syndrome (all in 3 subjects, 0.1%). The most frequent (> 3 subjects) AEs leading to permanent discontinuation and at least possibly related (preferred term) were diarrhea (8 subjects, 0.3%), nausea and rash (each in 7 subjects, 0.2%), and transaminases increased (4 subjects, 0.1%).	

Plasma Viral Load	**DRV/rtv N = 2966**	
Virologic response (proportion of subjects with undetectable[a] plasma viral load)	**N**	**n (%)**
Week 24	1636	970 (59.3)
Week 48	783	482 (61.6)
Week 96	100	79 (79.0)
Immunology		
Change versus baseline in CD4+ cell count	**N**	**Mean (SE)**
Week 24	1528	-4 (85.8)
Week 48	682	115 (5.3)
Week 96	49	126 (25.4)

N = number of subjects, number of observations

[a] Plasma viral load below the threshold used by the local test.

Conclusions

Evaluation of the safety and tolerability data of treatment with DRV/rtv 600/100 mg b.i.d. in highly treatment-experienced subjects in trial TMC114-C226 did not identify new clinically relevant safety findings compared with the currently known safety profile of DRV/rtv.

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