SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals Ltd. **Trade Name**: Prezista **Indication**: HIV-1 infection	**Drug Substance**: Darunavir **Trial no.**: TMC114-C209 **Clinical Phase**: III
Title: Open-label safety study of TMC114 in combination with low dose RTV and other ARVs in highly experienced HIV-1 infected subjects with limited or no treatment options.	
Principal Investigator: A. Lazzarin, M.D., Ospedale S. Raffaele, Dipartimento di Malattie Infettive, Via Stamira D'Ancona 20, 20127 Milano, Italy	**Countries**: United States, Australia, Belgium, Canada, Germany, Spain, France, Italy
Trial Period: Start: 18-Jul-2005 End: 06-Jun-2007	**No. of Investigators**: 46 **No. of Subjects**: 312 screened, 262 included
Objectives: The primary objective of this trial was to provide early access to darunavir (DRV) for highly antiretroviral (ARV) experienced human immunodeficiency virus (HIV)-1 infected subjects who had failed and exhausted treatment options based on commercially available ARVs. The secondary objective was to gather additional information on the safety and tolerability of DRV in combination with low dose ritonavir and other ARVs.	
Design: This was an open-label safety trial to provide early access to darunavir (DRV[TMC114]) to human immunodeficiency virus (HIV-1) infected subjects, who had failed and exhausted regimens based on commercially available antiretroviral (ARV) therapy and who were ineligible for participation in any other Tibotec-sponsored trial. The safety and tolerability of DRV in combination with low dose ritonavir and other ARVs in highly ARV-experienced HIV-1 infected subjects with limited or no treatment options were assessed. The trial involved a screening period of a maximum of 4 weeks. Eligible subjects then started treatment with DRV in combination with low dose ritonavir and other ARVs based on local resistance testing and previous ARV history. No protease inhibitor (PI) combinations other than DRV/ritonavir were to be used in this trial. Treatment was to be continued until treatment limiting toxicity, loss to follow-up, withdrawal, pregnancy, discontinuation of DRV development or when DRV became commercially available or until the subject rolled over into the Expanded Access Program (EAP).	
Subject Selection Inclusion Criteria 1. Subject had voluntarily signed the informed consent before initiation of trial procedures. 2. Subject with documented HIV-1 infection. 3. Male or female subject over 18 years of age. 4. Subject had limited or no treatment options because of multiple treatment failures. ***Note:*** Documentation of limited or no treatment options related to ARVs including PIs had to be based on previous treatment history and resistance testing, where available. 5. Negative pregnancy test for females of childbearing potential. 6. CD4 cell count ≤ 100 cells/mm^3. 7. Viral load ≥ 10000 copies/mL.	

Exclusion Criteria

1. Primary HIV-infection.
2. Subject was eligible for other Tibotec-sponsored trials.
3. Prior or current participation in a trial with DRV (except for Phase I studies conducted in HIV-infected subjects).
4. Use of disallowed concomitant therapy.
5. Participation in any other protocols, including cohort studies, without prior approval by the sponsor.
6. Use of investigational medication within the last 90 days. The following exceptions applied:
   - abacavir/lamivudine and tenofovir/emtricitabine fixed dose combinations (if applicable, based on the status of local approval) within the last 30 days;
   - tipranavir (if applicable, based on the status of local approval) within the last 14 days.
7. Pregnant or breast-feeding female.
8. Female subject of child bearing potential without the use of effective non-hormonal birth control methods or not willing to continue practicing those birth control methods from screening until the last trial related activity.

   Note: Hormonal-based contraception might not have been reliable when taking DRV, therefore to be eligible for this trial, woman of childbearing potential had to either:
   - use a double barrier method to prevent pregnancy (i.e., using a condom with either diaphragm or cervical cap) or
   - use hormonal based contraceptives in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap or female condom) or
   - use an intra uterine device in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap or female condom) or
   - 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-child bearing potential.
9. Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the investigational medication (DRV) or ritonavir.

   Note: DRV is a sulfonamide. Subjects who previously experienced a sulfonamide allergy were allowed to enter the trial. 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.
10. Subjects with the following laboratory abnormalities as defined by a standardized grading scheme based on the Division of Acquired Immunodeficiency Syndrome table (updated version from December 2004):
    - Any grade 3 or 4 toxicity with the following exceptions:
      - Subjects with pre-existing diabetes or asymptomatic glucose elevations of grade 3 or 4;
      - Subjects with asymptomatic triglyceride elevations of grade 3 or 4 or cholesterol elevations ≥ grade 3.
11. Subject 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 clinically stable. Subjects diagnosed with acute viral hepatitis at screening were not allowed to enroll.

Treatment	DRV	Ritonavir
Concentration	2 x 300 mg tablets	100 mg tablets
Dosage Form (TF No.)	F016	-
Usage	Oral	Oral
Dose Regimen	DRV and ritonavir 600/100 mg twice-daily (b.i.d.).	
Duration of Treatment	See below.	
Duration of Trial	Screening period: maximum 4 weeks, treatment phase: treatment continued until the subject developed a treatment-limiting toxicity, was lost to follow-up, withdrew consent, became pregnant, stopped taking DRV, when DRV became commercially available, or until the subject rolled over into the EAP. Follow-up period: 4 weeks post-treatment. Subjects who discontinued early, except for withdrawal of consent, were followed for survival until the trial ended in the country in which they participated.	
Disallowed Medication	**Non-ARV Medications** *From screening until the end of the treatment phase:* - all products containing *Hypericum perforatum* (St John's Wort); - rifampin, rifapentine; - phenobarbital, phenytoin, carbamazepine, modafinil; - systemic dexamethasone (topical use was allowed); - investigational medication. **ARV Medications** *During treatment with DRV:* - PI(s); - investigational ARVs (country dependent). The following exceptions applied: - abacavir/lamivudine and tenofovir/emtricitabine fixed dose combinations.	
Assessments		
Safety		
Adverse Events	Adverse events were checked at every visit and reported from signing of the informed consent onwards until the last trial-related activity (Week 4 follow-up visit).	
Clinical Laboratory	Samples for hematology and biochemistry (fasted) and coagulation testing were taken at every visit, i.e., - at screening and baseline; - at Weeks 4 and 12 and every 3 months thereafter; - at the final/withdrawal visit.	

Cardiovascular Safety	Vital signs (body temperature [nonaxillary], heart rate, and blood pressure) were assessed at every visit, i.e., - at screening and baseline; - at Weeks 4 and 12 and every 3 months thereafter; - at the final/withdrawal visit. Local electrocardiogram (ECG) was performed at screening if the site did not have ECG results from an assessment performed within 2 months prior to the screening visit.
Physical Examination	Physical examination was performed - at screening and baseline; - at Week 12 and every 3 months thereafter; - at the final/withdrawal visit.
Efficacy	
Plasma viral load and immunology	Plasma viral load and immune function assessments were performed - at screening and baseline; - at Week 12 and every 3 months thereafter; - at the final/withdrawal visit.
Resistance Determination	Samples for resistance determination were taken at the baseline and final/withdrawal visits and kept in a central laboratory. Analysis depended on the opinion of the Protocol Virologist.
Statistical Methods	Descriptive statistics, frequency tabulations, intent-to-treat analysis, Wilcoxon matched pairs signed ranks test.

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics - Subject Disposition	DRV/rtv
Number of subjects entered (M/F)	262 (225/37)
Age (Years), Median (Range)	44.0 (19; 71)
Log_{10} plasma viral load (Copies/mL), Mean (SD)	5.1 (0.70)
CD4+ cell count ($\times 10^6$/L), Median (Range)	22 (0; 382)
Time since HIV infection diagnosis (Years), Median (Range)	14.1 (4; 26)
Previous ARV Experience, n (%)	
PI: ≥ 2	255 (98.1)
NNRTI: ≥ 1	244 (93.8)
NRTI: ≥ 4	249 (95.8)
Fusion inhibitor	148 (56.9)
Discontinuations - Reason, n (%)[c]	**262 (100)**
Adverse event/HIV related[a]	21 (8.0)[a]
Subject reached a virologic endpoint	15 (5.7)
Subject lost to follow-up	8 (3.1)
Subject withdrew consent	7 (2.7)
Sponsor's decision	4 (1.5)
Subject non-compliant[b]	3 (1.1)[b]
Subject ineligible to continue the trial	2 (0.8)
Other[d]	202 (77.1)

PI=protease inhibitor, NNRTI=non-nucleoside reverse transcriptase inhibitor, NRTI=nucleoside reverse transcriptase inhibitor.
[a] One subject (CRF ID 209-0244) who died after the date of last contact, is not included.
[b] Includes 1 subject (CRF ID 209-0244) who died after the date of last contact.
[c] Three subjects were recorded as 'completed' but actually switched to use of commercially available DRV.
[d] The majority of subjects recorded as discontinuing the trial for 'Other' reasons was due to enrollment into the EAP or switching to commercially available DRV.

Efficacy (ITT Population-Observed Case Analysis)	N	Time Point	DRV/rtv N=262
Virologic response: decrease of at least 1.0 log_{10} in VL, n (%)	212	Week 24	136 (64)
	121	Week 48	78 (65)
	45	Week 72	29 (64)
Virologic response: VL below 50 copies/mL, n (%)	212	Week 24	79 (37)
	121	Week 48	53 (44)
	45	Week 72	21 (47)
Virologic response: VL below 400 copies/mL, n (%)	212	Week 24	114 (54)
	121	Week 48	66 (55)
	45	Week 72	25 (56)

N=total number of subjects with data, n=number of observations, VL=viral load, ITT=intent-to-treat.

The antiviral activity results of this trial show that the recommended dose of DRV/rtv 600/100 mg b.i.d. coadministered with other ARVs was associated with a clinically relevant sustained virologic response and immunologic improvement over at least 72 weeks of treatment. Virologic response rates (observed) at Week 48 (n=121) were 44% (viral load < 50 copies/mL), 55% (viral load < 400 copies/mL) and 65% (≥ l log_{10} drop in viral load) respectively, and at Week 72 (n=45) were 47% (viral load < 50 copies/mL), 56% (viral load < 400 copies/mL) and 64% (≥ l log_{10} drop in viral load), respectively. The mean change from baseline in log_{10} viral load at Week 48 was -1.92 and at Week 72 was -1.99. The mean change from baseline in CD4+ cell count

(x 10^6/L) at Week 48 (observed case) was 121 and at Week 72 (observed case) was 155. Little can be concluded at Week 84 since there were a low number of subjects with data at this time point as a result of subject discontinuations from the trial, mainly due to rollover to the EAP and to commercially available DRV.

Safety (N=number of subjects with data)	**DRV/rtv N=262**
Mean Exposure (Weeks)	***45.60***
Adverse Events (AEs) During the Treatment Phase	
Most frequently reported AEs[a], n (%)	
Diarrhea	41 (15.6)
Injection site reaction	39 (14.9)
Nausea	31 (11.8)
Pyrexia	28 (10.7)
Oral candidiasis	28 (10.7)
Cough	25 (9.5)
Asthenia	21 (8.0)
Herpes simplex	20 (7.6)
Vomiting	19 (7.3)
Headache	17 (6.5)
Rash	17 (6.5)
Bronchitis	17 (6.5)
Sinusitis	16 (6.1)
Anemia	15 (5.7)
Neutropenia	15 (5.7)
Abdominal pain	15 (5.7)
n (%) with at least 1 AE	247 (94.3)
n (%) of deaths	18 (6.9)
N (%) with at least 1 SAE	68 (26.0)
Most frequently reported SAEs	
Pyrexia	5 (1.9)
Diarrhea	4 (1.5)
N (%) with at least 1 AE leading to treatment discontinuation	22 (8.4)[b]
N (%) with at least 1 grade 3 AE	90 (34.4)
N (%) with at least 1 grade 4 AE	38 (14.5)
Most frequently reported grade 3 or 4 AEs	
Neutropenia	14 (5.3)
Injection site reaction	8 (3.1)

[a] >5% of subjects during the treatment phase.
[b] An additional 4 subjects are included who experienced an AE with fatal outcome, but were not reported as having drug withdrawn with a permanent stop.

Clinical Laboratory Tests	Most graded laboratory abnormalities were grade 1 or 2 in severity. The most common graded abnormalities related to laboratory parameters of interest were alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and hyperbiliruninemia. Overall, the incidence of AEs related to laboratory parameters was low. These events were rarely reported as SAEs and none led to treatment discontinuation.
Cardiovascular Safety	The most common cardiac-related AE was tachycardia. The most common reported abnormalities in vital signs were grade 1 or mild abnormalities in diastolic blood pressure and systolic blood pressure. The most common AE related to vital signs was hypertension.
Other Safety Parameters	The incidence of AEs related to anthropometric measurements was low. The most common AEs were

	weight decreased, cachexia and lipodystrophy acquired. One SAE (weight decreased) related to changes in anthropometric measurements was reported. The majority of AEs related to changes in anthropometric measurements were grade 1 or 2 in severity. An increase in mean weight and body mass index was observed at up to Week 72 (+4.8 kg compared to baseline).

Conclusions

The results of the present trial demonstrate that the antiviral and immunologic effects of DRV/rtv 600/100 mg b.i.d. coadministered with other ARVs were associated with a clinically relevant sustained virologic response and immunologic improvement over at least 72 weeks of treatment. Considering the well-defined advanced baseline characteristics of these subjects, the efficacy results, although open-label and non-randomized, demonstrate a substantial sustained clinical benefit of DRV in this population with little or no remaining treatment options. The evaluation of safety data in trial TMC114-C209 indicate that DRV/rtv 600/100 mg b.i.d. treatment was generally safe and well tolerated. The safety profile was similar to that observed in other trials with DRV.

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