SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals Ltd, now Tibotec Pharmaceuticals **Trade Name**: Darunavir **Indication**: HIV-1 infection	**Drug Substance**: TMC114 **Trial no**.: TMC114-C208 **Clinical Phase**: II
Title: An open-label trial of TMC114/RTV in HIV-1 infected subjects who were randomized in the trials TMC114-C201, TMC114-C207 or in sponsor-selected Phase I trials. Final analysis with cut-off date 12 March 2009.	
Investigator: C. Workman, MD, AIDS Research Initiative, 48 Little Oxford Street, 2010 Darlinghurst, Australia	**Country**: Australia, Austria, Belgium, Denmark, Germany, Italy, Poland, Russian Federation, UK
Trial Period: Start: 14-Jan-2005 End: 12-Mar-2009	**No. of Investigators**: 16 **No. of Subjects**: 51

Objectives: The primary objective of the trial was to evaluate the long-term safety and tolerability of DRV/rtv 600/100 mg b.i.d. The secondary objectives were to evaluate the antiviral activity over time and to evaluate the immunologic effect over time.

Design: Trial TMC114-C208 was an open-label trial in HIV-1 infected subjects who were randomized in the Phase IIa trials TMC114-C201 or TMC114-C207, or in sponsor-selected Phase I trials, and who might derive benefit from darunavir/ritonavir (DRV [TMC114]/rtv), as judged by the investigator. The long-term safety and tolerability of DRV/rtv combined with an optimized background regimen (OBR) (≥ 2 ARVs including approved nucleoside/ nucleotide analogue reverse transcriptase inhibitors [N(t)RTIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs], and/or the fusion inhibitor enfuvirtide [ENF]) have been assessed. In addition, antiviral activity and immunologic effect were evaluated.

Subjects who were randomized in trials TMC114-C201, TMC114-C207, or sponsor-selected Phase I trials were eligible for screening. The trial included a screening period of at most 4 weeks, a 96- week treatment period, followed by a follow-up period of 4 weeks. At baseline, subjects started treatment with DRV/rtv combined with an OBR. Initially, subjects started treatment with DRV/rtv 400/100 mg b.i.d. (n = 14). After the selection of the recommended dose (based on the dose-finding trials), all subjects who initiated treatment with DRV/rtv 400/100 mg b.i.d. were asked to switch to the recommended dose of DRV/rtv 600/100 mg b.i.d., and all additional subjects (n = 37) who entered the trial started treatment immediately with DRV/rtv 600/100 mg b.i.d. All subjects received DRV/rtv orally.

Tibotec provided follow-up treatment with DRV for all subjects who continued to benefit from treatment with DRV/rtv until it was commercially available for the subject. Subjects who completed 96 weeks of treatment with DRV, had the opportunity to roll over to the extension of trial TMC114-C208, if DRV was not locally commercially available. Subjects who no longer benefitted from DRV/rtv therapy, as judged by the investigator, or who met 1 of the withdrawal criteria were withdrawn from the trial.

This report describes the results of the final analysis of trial TMC114-C208, including data from the start of the trial (14 January 2005) up to the cut-off date (last patient last visit [LPLV]) of 12 March 2009, at which time all subjects had completed the trial or discontinued earlier.

Subject Selection

For the original part of the trial

Inclusion Criteria

1. Subject had signed the informed consent form voluntarily.
2. Male or female subjects aged ≥ 18 years.
3. Previous randomization to 1 of the treatment groups (including control) in trials TMC114-C201, TMC114-C207, or sponsor-selected Phase I trials.
4. Subject agreed to take ≥ 2 ARVs including approved N(t)RTIs, NNRTIs, and/or ENF in combination with the trial medication (DRV/rtv) from baseline onwards.
5. Subject could comply with the protocol requirements.

6. Subject's general medical condition was, in the investigator's opinion, not interfering with the assessments and the conduct of the trial.

Exclusion Criteria

1. Use of disallowed concomitant therapy.
2. Use of other investigational drugs (except for emtricitabine [FTC], fos-amprenavir [AMP], tipranavir [TPV] [see note below], ENF and atazanavir [ATV] where approval status may vary from country to country), within 30 days prior to the investigational medication administration (i.e., baseline visit).
   Note: DRV could not be used within 14 days following the use of TPV. A minimum 14-day washout period was required in which TPV had to be either interrupted or substituted to an investigator selected PI regimen until the baseline visit (Day 1).
3. Current or past history of active alcohol and/or drug use that in the investigator's opinion could compromise the subject's safety or compliance to the trial protocol procedures.
4. Pregnant or breastfeeding females.
5. Female subjects of childbearing potential without the use of effective birth control methods or not willing to continue practicing these birth control methods from screening until ≥30 days after the end of the treatment period.
   Note: Hormonal based contraception may be not reliable when taking DRV, therefore to be eligible for this trial, women of childbearing potential either had to:
   - use a double barrier method (i.e., use a male condom with either diaphragm or cervical cap),
   - use hormonal based contraceptives in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap or female condom),
   - use an intrauterine device (IUD) in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap or female condom),
   - be non-heterosexually active, practice heterosexual abstinence or have a vasectomized partner (confirmed sterile).

   Note: Women who were postmenopausal for ≥ 2 years, women with total hysterectomy and women with tubal ligation were considered of non-childbearing potential.
6. Any active or unstable medical condition (e.g., tuberculosis, cardiac dysfunction, pancreatitis, acute viral infections) or findings during physical examination that, in the investigator's opinion, could compromise the subject's safety.
7. Subject with the following laboratory abnormalities at screening as defined by the Division of AIDS (DAIDS) grading scale:
   - alanine aminotransferase (ALT)/aspartate aminotransferase (AST) > 3 x ULN;
   - any grade 3 or 4 toxicity with the following exceptions, 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 of grade 3 or 4.
8. Subject with clinical or laboratory evidence of active liver disease, liver impairment/dysfunction or cirrhosis irrespective of liver enzyme levels.
   Note: Subjects coinfected with hepatitis B or C were allowed to enter the trial if their condition was clinically stable and in case it was unlikely that they would require any form of anti-hepatitis therapy during the trial, as assessed by the investigator at screening. Subjects diagnosed with hepatitis A at screening were not allowed to take part in the trial.
9. Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the investigational medication (DRV/rtv) (per Exclusion Criterion 7, subjects with a grade 3 or 4 rash were excluded).
   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.

Note: Retesting of abnormal screening values that led to exclusion was allowed only once using an unscheduled visit.

For the extension part of the trial (i.e., subjects who completed the 96-weeks DRV/rtv treatment, where DRV was not yet commercially available)

Inclusion Criteria

1.A Male or female subject, ≥ 18 years.
2.A Subject completed 96 weeks of treatment with DRV/rtv in the original part of trial TMC114-C208 and DRV was not yet commercially available.
3.A Subject had signed the informed consent form voluntary.
4.A Subject could comply with the protocol requirements.
5.A Subject's general medical condition, in the investigator's opinion, did not interfere with the assessments and the conduct of the trial.

Exclusion Criteria

1.A Use of disallowed concomitant therapy.
2.A Pregnant or breastfeeding female.
3.A Female of childbearing potential without the use of effective birth control methods from screening until ≥ 30 days after the end of the treatment period.

Note: Hormonal based contraception may be not reliable when taking DRV, therefore to be eligible for this trial, women of childbearing potential either had to:

- use a double barrier method (i.e., use a male condom with either diaphragm or cervical cap),
- use hormonal based contraceptives in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap or female condom),
- use an IUD in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap or female condom),
- be non-heterosexually active, practice heterosexual abstinence or have a vasectomized partner (confirmed sterile).

Note: Women who were postmenopausal for ≥ 2 years, women with total hysterectomy and women with tubal ligation were considered of non-childbearing potential.

4.A Any active or unstable medical condition (e.g., tuberculosis, cardiac dysfunction, pancreatitis, acute viral infections) or findings during physical examination that, in the investigator's opinion, could compromise the subject's safety.

Treatment	**Darunavir**		**Ritonavir**
Concentration	400-mg tablets	300-mg tablets	100-mg capsules
Dosage Form (TF No.)	F001	F016 (commercial formulation)	
Usage	oral	oral	oral
Batch Number	See Appendix 7.1.5		
Dose Regimen	Original: DRV/rtv 400/100 mg b.i.d. After switch to the recommended dose: DRV/rtv 600/100 mg b.i.d.		
Duration of Treatment	96 weeks. Subjects who completed the 96-weeks DRV/rtv treatment, had the opportunity to roll over to the extension phase (> 96 weeks), if DRV was not locally commercially available.		
Duration of Trial	Screening: ≤ 4 weeks; Treatment period: 96 weeks (> 96 weeks for subjects in the extension phase); Follow-up (FU): 4 weeks		
Disallowed Medication	*Antiretroviral medication:* - From baseline until the end of the treatment period: all PIs other than DRV/rtv, investigational N(t)RTIs, delavirdine, and investigational NNRTIs *Other disallowed medication (non-ARV):* - From screening until the end of the treatment period: amphetamines and amphetamine derivatives, all products containing *Hypericum perforatum* (St John's Wort), rifampin, rifapentine, phenobarbital, phenytoin, carbamazepine, modafinil, and investigational vaccines		

	- From baseline until the end of the treatment period: systemic use of ketoconazole and itraconazole at > 200 mg/day, amiodarone, bepridil, flecainide, propafenone, quinidine, systemic lidocaine, mexiletine, disopyramide, astemizole, terfenadine, ergot derivatives (dihydroergotamine, ergonovine [ergometrine], ergotamine, methylergonovine), cisapride, pimozide, midazolam, triazolam, clonazepam, lovastatin, simvastatin, pravastatin, cholestyramine and colestipol, telithromycin, cyclosporine, tacrolimus, rapamycin, serolimus, calcium channel blockers (e.g., felodipine, nifedipine, nicardipine, amlodipine, verapamil etc.), meperidine (pethidine), and dexamethasone (topical applications allowed)
Assessments	
Antiviral Activity Plasma Viral Load	Samples for plasma viral load determinations were taken: - at screening and baseline, - at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, and 96 (or early withdrawal), - at both FU visits. For subjects entering the extension phase (> 96 weeks): - at the roll-over visit, - at Week 108 and every 12 weeks thereafter (or early withdrawal)
Immunology	Samples for immunology assessment were taken: - at screening and baseline, - at Weeks 4, 8, 12, 20, 32, 40, 48, 60, 72, 84, and 96 (or early withdrawal). For subjects entering the extension phase (> 96 weeks) (only CD4 cell count): - at the roll-over visit, - at Week 108 and every 12 weeks thereafter (or early withdrawal)
Resistance Determinations	Samples for phenotype and genotype determinations were taken: - at screening and baseline, - at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, and 96 (or early withdrawal), - at both FU visits. Analysis of samples taken at Weeks 2, 4, 8, 12, 16, 20, 32, 40, 60, 72, 84, and at both FU visits (1 and 4 weeks after last intake of trial medication) depended on the judgement of the Protocol Virologist based on HIV-1 plasma viral load. A peripheral blood mononuclear cells (PBMC) sample was taken at baseline and Week 96 (or early withdrawal).
Safety Adverse Events	Adverse events (AEs) and HIV-related events were checked at every visit and reported from screening onwards until the last trial-related activity.

Clinical Laboratory	Samples for hematology, biochemistry (fasted), and coagulation testing were taken at every visit, i.e., - at screening and baseline, - at Weeks 2, 4, 6, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, and 96 (or early withdrawal), - at both FU visits. At Week 6, samples were only taken for subjects with sulfonamide allergy: eosinophil count and percentage were assessed. An hepatitis A, B and C test was performed at screening and thereafter only upon request of the investigator if clinically indicated. Urinalysis was performed: - at screening and baseline, - at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, and 96 (or early withdrawal). - A urine pregnancy test was also performed at these visits, except at screening and Week 2 (for women of childbearing potential only). For subjects entering the extension phase (> 96 weeks): - A pregnancy test (urine or serum, depending on the local laboratory facilities) was performed at the roll-over visit, Week 108 and every 12 weeks thereafter (or early withdrawal).
Cardiovascular Safety	Vital signs (pulse and blood pressure [BP]) were assessed: - at screening and baseline, - at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, and 96 (or early withdrawal). Central electrocardiogram (ECG) readings were performed: - at screening and baseline, - at Weeks 4, 12, 24, 48, 72, and 96 (or early withdrawal).
Physical Examination	Physical examination was performed: - at screening and baseline, - at Weeks 12, 24, 48, 72, and 96 (or early withdrawal).
Anthropometric Measurements	Height was measured at screening. Weight, and waist and hip circumference were determined: - at screening and baseline, - at Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, and 96 (or early withdrawal).
Pharmacokinetics	The time points of sample collection were: - at Weeks 4, 12, 24, 48, 72, and 96 (or early withdrawal). Samples were taken and were only analyzed upon the sponsor's specific request. In case of hepatic toxicity (grade 3 or 4 elevations in liver function tests or bilirubin), an extra pharmacokinetic sample was taken at the time of the observed toxicity.
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**[a]
Number of Subjects Entered (M/F)	51 (45/6)
Age: median (range), yrs	42.0 (26; 64)
Race	
Caucasian/White	47 (92.2)
Hispanic	3 (5.9)
Other	1 (2.0)
Plasma viral load: mean (SD), $\log_{10}$ copies/mL	3.56 (1.554)
CD4 cell count: median (range), x 10^6 cells/L	233 (7; 1193)
Time since HIV infection diagnosis: median (range), years	12.1 (2; 22)
CDC Class at time of screening	
A	9 (17.6)
B	20 (39.2)
C	22 (43.1)
Hepatitis B or C coinfection status	
Coinfected	2 (3.9)
Previous ARV experience, n (%)	
PI : ≥ 2	44 (86.3)
NNRTI : ≥ 1	40 (78.4)
NRTI : ≥ 4	45 (88.2)
Fusion Inhibitor[b] : 1	7 (13.7)
ARVs in the OBR (i.e., initial OBR, defined as therapy taken 7 days after initiation of DRV/rtv treatment)	Most frequently used NRTIs were lamivudine (72.5%) and tenofovir (62.7%); 15 subjects (29.4%) used ENF (of these subjects, 10 [19.6%] were considered naïve to ENF; 1 subject used an NNRTI.
Discontinuations - Reason, n (%)	7 (13.7)
AE/HIV-related event	2 (3.9)[c]
Subject withdrew consent	2 (3.9)
Other	2 (3.9)
Subject non-compliant	1 (2.0)

[a] The DRV/rtv group included all subjects rolling over from a DRV/rtv or control arm in the original trial TMC114-C201 (10 subjects), trial TMC114-C207 (17 subjects), or sponsor-selected Phase I trials (24 subjects from TMC114-C151). Some of the subjects (14 out of 51) started treatment in TMC114-C208 with DRV/rtv 400/100 mg b.i.d. and, except for 1 subject who had discontinued, later switched to the recommended dose of DRV/rtv 600/100 mg b.i.d. The other 37 subjects started immediately at the recommended dose.

[b] ENF was the only fusion inhibitor used.

[c] 2 discontinuations due to AE were subjects who died, see below.

Efficacy

The antiviral activity results of this trial show that the recommended dose of DRV/rtv 600/100 mg b.i.d. coadministered with an OBR was associated with a clinically relevant sustained virologic response and immunologic improvement over 96 weeks of treatment.

Parameters	**Time Point**	**N**	**DRV/rtv**
Virologic response: Viral load < 50 copies/mL, n (%) (ITT – TLOVR [non-VF censored])	Week 24	50	38 (76.0)
	Week 48	49	40 (81.6)
	Week 96	46	37 (80.4)
Change versus baseline in $\log_{10}$ viral load (copies/mL), mean (SE) (ITT – NC = F [non-VF censored])	Week 24	49	-1.48 (0.195)
	Week 48	48	-1.44 (0.215)
	Week 96	45	-1.38 (0.228)
Change versus baseline in CD4 cell count (x 10^6/L), mean (SE) (ITT – NC = F [non-VF censored])	Week 20	49	96 (17.4)
	Week 48	48	151 (20.3)
	Week 96	45	139 (23.4)

Safety (n = number of subjects with data)	**DRV/rtv** **N = 51**
Mean (SD) Exposure (Weeks)	*119.3 (37.63)*
Adverse Events	
Most frequently reported AEs (in > 15%), n (%)	
Back pain	11 (21.6)
Headache	10 (19.6)
Injection site reaction (associated with ENF adminstration)	10 (19.6)
Cough	9 (17.6)
Nasopharyngitis	9 (17.6)
Diarrhea	8 (15.7)
Oral candidiasis	8 (15.7)
Pain in extremity	8 (15.7)
n (%) with 1 or more AEs	49 (96.1)
n (%) of deaths	2 (3.9)[a]
n (%) with 1 or more other SAEs	6 (11.8)[a]
n (%) of treatment discontinued due to AEs	2 (3.9)[a]
n (%) with 1 or more grade 3 or 4 AEs	16 (31.4)[a]
[a] The 2 cases of death were considered related to the underlying HIV disease. There were no other discontinuations due to an AE(s) with onset during the treatment period. All SAEs were reported in only 1 subject. The majority of individual grade 3 or 4 AEs were reported in ≤ 1 subject.	
Clinical Laboratory Tests	Most graded laboratory abnormalities were grade 1 or 2 in severity. The most common grade 3 or 4 abnormalities related to laboratory parameters of interest were increased total cholesterol (15.7%), LDL cholesterol (23.5%), lipase and amylase (7.8% each).
Cardiovascular Safety	No clinically relevant changes over time versus baseline were observed for any of the cardiovascular parameters. No treatment-emergent QTc values > 500 ms were observed, and no QTcF increases by > 60 ms. Two subjects had a QTcB increase by > 60 ms (resulting in an abnormal value of 468 ms and 469 ms, respectively). The most common grade 2 vital sign abnormality was increased standing DBP (23.5%), all other grade 2 vital sign abnormalities were observed in at most 11.8% subjects.
Other Safety Observations	A small increase in mean weight versus baseline was observed at Week 24 (+ 1.4 kg), which was sustained up to Week 96 (+ 1.2 kg). No clinically relevant changes versus baseline in BMI or hip- and waist circumference, or physical examinations were observed.

Conclusions

The antiviral activity and immunologic effects observed in trial TMC114-C208 showed that DRV/rtv 600/100 mg b.i.d. with an OBR was effective both clinically and virologically in this population of treatment-experienced HIV-1 infected subjects.The efficacy results demonstrated a sustained viral load reduction and increase in CD4 cell count over a period of 96 weeks.

The evaluation of the safety data in trial TMC114-C208 confirmed the long-term safety and tolerability of DRV/rtv 600/100 mg b.i.d in this patient population. The overall safety profile was similar to that observed in other (controlled) trials with DRV/rtv and published data.

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