Clinical Research Report Addendum I

Project no:	TMC114		
Department:	Clinical R&D	**Nonproprietary name:**	Darunavir
Status:	Approved	**Issued Date:**	26-Feb-2013

Trial no:	TMC114-C211 (CR002800) **Clinical Phase:** III
Addendum 1 to:	TMC114-C211-W192-CRR dated 11 October 2010 A randomized, controlled, open-label trial to compare the efficacy, safety and tolerability of darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve HIV-1 infected subjects. Week-192 analysis. This trial is referred to as ARTEMIS.
Sponser:	Janssen Research & Development*
Prepared by:	Janssen Infectious Diseases - Diagnostics BVBA

GCP STATEMENT

The study was performed in compliance with Good Clinical Practices, including the archiving of essential documents.

CONFIDENTIALITY STATEMENT

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LIST OF ABBREVIATIONS

AE	adverse event
ARV	antiretroviral
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CRR	Clinical Research Report
DRV	darunavir
DRV/rtv	darunavir in combination with low-dose ritonavir
FTC	emtricitabine
HIV-1	human immunodeficiency virus - type 1
LPV	lopinavir
LPV/rtv	lopinavir in combination with low-dose ritonavir
rtv	ritonavir
SAE	serious adverse event
TDF	tenofovir disoproxil fumarate

1 INTRODUCTION

TMC114-C211 was a randomized, controlled (lopinavir [LPV]/ritonavir [rtv]), open-label Phase III study to determine the efficacy, safety and tolerability of darunavir (DRV, formerly TMC114), formulated as an oral tablet, and administered with a 100 mg dose of rtv and other antiretroviral (ARV) drugs over a 192-week treatment period in human immunodeficiency virus – type 1 (HIV-1) infected subjects who never received treatment with an ARV. At baseline, the eligible subjects started ARV therapy that consisted of a protease inhibitor (randomized in a 1:1 ratio to DRV/rtv 800/100 mg once daily, or LPV/rtv 800/200 mg daily dose) combined with a fixed background regimen consisting of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC).

This document is an addendum to the Week-192 report of study TMC114-C211 (TMC114-C211-W192-CRR[1]) and describes the results from the extension phase of this study. Data available up to and including 8 May 2012 ('last patient last visit') are included in the final analysis.

The primary objective of the extension phase was to provide DRV/rtv access to subjects living in a region where DRV was not yet commercially available, not yet reimbursed by the public and/or private health system, or could not be accessed from another source (e.g., access program, government program).

Subjects who completed the 192 weeks of treatment with DRV/rtv in the main phase of the study (or who received treatment with DRV/rtv in the rollover phase, if applicable) and who continued to benefit from this treatment, had the opportunity to continue DRV/rtv treatment in the extension phase. In addition, subjects randomized to LPV/rtv in the main phase of the study, who met the virologic failure criteria, or who experienced intolerance on LPV/rtv could also enter the extension phase of the study to switch to a DRV/rtv-containing regimen (See Figure 1).

The DRV switch/extension visit took place on the same day as the Week-192 visit (main phase), or, if applicable, the same day as a last visit of the main phase for subjects on LPV/rtv in that phase, who switched to DRV/rtv in the extension phase, or the same day as the last visit for subjects on DRV/rtv in the previously existing rollover phase, who continued DRV/rtv in the extension phase. The subjects were seen at Week 204 (or 12 weeks after the DRV switch/extension visit) and preferably every 12 weeks thereafter. The investigator conducted a final/withdrawal visit (and a Week-4 follow-up visit in case the subject had an ongoing adverse event [AE] at withdrawal) when the subject withdrew or stopped treatment for any reason.

The performed analysis included the subject treatment information (subject disposition and study completion, protocol deviations, and extent of exposure) and safety (AEs, including deaths). Demographic parameters, baseline disease characteristics, laboratory safety, physical examination, ECG, pharmacokinetics, and pharmacokinetic/pharmacodynamic parameters were not reanalyzed.

For details on the previous analyses, see the Clinical Research Report (CRR) of the Week-192 analysis of this study[1].

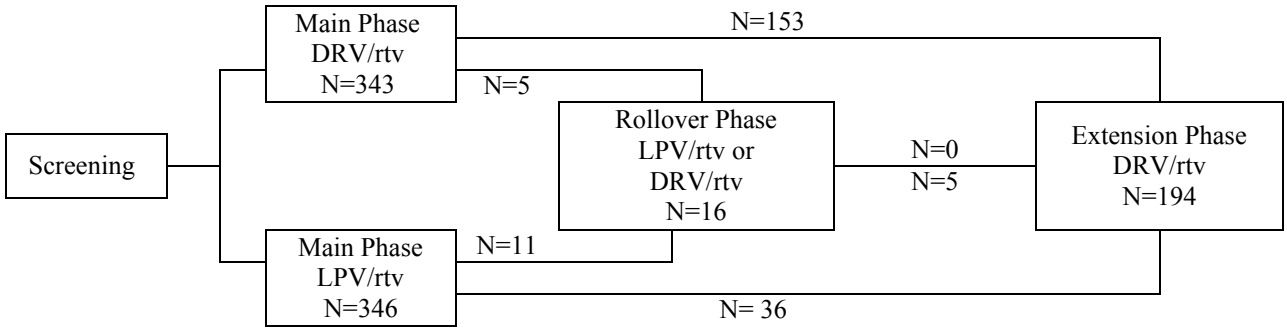

Figure 1: Study Design of TMC114-C211

2 SUBJECTS AND TREATMENT INFORMATION

2.1 SUBJECT DISPOSITION AND STUDY COMPLETION OR WITHDRAWAL INFORMATION

Subject disposition is provided in TSIDS01; individual subject data are provided in LSIDS02. An overview of the study termination is provided in TSDEM01 and LSDEM02.

In total, 843 subjects were screened, of which 689 subjects were randomized and treated, 343 subjects with DRV/rtv and 346 subjects with LPV/rtv. At the time of the Week-192 analysis, 199 (28.9%) subjects receiving treatment in study TMC114-C211 had prematurely discontinued (data from Week-192 CRR[1]). Of the 490 subjects who completed the study (258 and 232 in the DRV/rtv and LPV/rtv treatment group, respectively [data from Week-192 CRR[1]]), 296 subjects completed without continuing in the extension phase and 194 subjects continued or had switched to DRV/rtv treatment in the extension phase (153 and 41 subjects from DRV/rtv and LPV/rtv treatment in the main phase, respectively).

Fourteen (9.2%) DRV/rtv - DRV/rtv subjects and 2 (4.9%) LPV/rtv - DRV/rtv subjects withdrew consent. Other reasons for discontinuation, 133 (86.9%) and 35 (85.4%) subjects, respectively, included rollover to other studies (including TMC114IFD3001 which is the continued access study for HIV-1 infected adults) or switch to commercially available medications. The reasons for study discontinuation are summarized in Table 1.

A total of 124 subjects consented to poststudy follow-up on survival (source: footnote in LSFAE09).

Table 1: Subject Disposition

n (%)	DRV/rtv - DRV/rtv N = 153	LPV/rtv - DRV/rtv N = 41
Discontinued	**153 (100.0)**	**41 (100.0)**
Adverse Event/HIV Related Event	2 (1.3)	0
Other	133 (86.9)	35 (85.4)
Sponsor's Decision	1 (0.7)	0
Subject Lost to Follow-up	1 (0.7)	2 (4.9)
Subject Non-compliant	1 (0.7)	2 (4.9)
Subject Reached a Virologic Endpoint	1 (0.7)	0
Subject Withdrew Consent	14 (9.2)	2 (4.9)

N = number of subjects with data, n = number of observations
Source: TSIDEM01

2.2 PROTOCOL DEVIATIONS

An overview of the major protocol violations during the entire study and extension phase is provided in TSIDEM03 and LSIDEM04.

2.3 EXTENT OF EXPOSURE

An overview of the treatment duration during the extension phase is provided in TSIEXP01 and is summarized in Table 2. Individual subject data on study medication intake are provided in LSIEXP02.

The additional mean (standard error) exposure during the extension phase was 72.36 (2.694) weeks in the DRV/rtv - DRV/rtv group and 79.23 (3.920) weeks in the LPV/rtv - DRV/rtv group. The total patient years of exposure was 212.9 and 62.5 in the DRV/rtv - DRV/rtv and LPV/rtv - DRV/rtv groups, respectively.

Table 2: Duration of Medication Intake During the Extension Phase

	DRV/rtv - DRV/rtv	LPV/rtv - DRV/rtv
Total Duration (Weeks)		
N	153	41
Mean (SE)	72.36 (2.694)	79.23 (3.920)
Median (Range)	81.29 (4.6; 127.0)	80.43 (11.0; 162.7)
Patient Years of Exposure[a]	**212.9**	**62.5**

N = number of subjects

[a] Patient years exposure = mean number of weeks treated x N / 52 weeks (Source: Statistical Analysis Plan)

Source: TSIEXP01

3 SAFETY RESULTS

3.1 DATA SETS ANALYZED

The safety analysis was performed on the intent-to-treat population, i.e., all subjects with baseline or postbaseline data, regardless of their compliance with the protocol or their ineligibility.

3.2 ADVERSE EVENTS

The AEs discussed in this section are those that were reported during the extension phase, unless otherwise specified. All AEs are reported by preferred term, unless otherwise specified. For events where a relationship to the investigational medication (DRV/rtv) is provided, the assessment is based on the judgment of the investigator. All AE summary tables are ordered alphabetically, both by System Organ Class and by preferred term.

During the extension phase, the following AEs were collected:

- AEs leading to discontinuations;
- Serious adverse events (SAEs) and pregnancies;
- AEs considered to be at least possibly related to DRV/rtv.

3.2.1 Summary of Adverse Events

A tabulation of all SAEs during the extension phase and follow-up is provided in TSFAE01. A tabulation of SAEs at least possibly related to DRV/rtv during the extension phase is provided in TSFAE04. A tabulation of AEs leading to permanent discontinuation of DRV/rtv and AEs at least possibly related to DRV/rtv is provided in TSFAE02 and TSFAE03, respectively. A tabulation of AEs leading to permanent discontinuation of DRV/rtv that were considered at least possibly related to DRV/rtv is provided in TSFAE05.

Individual subject data for reported AEs, SAEs and AEs leading to permanent discontinuation of DRV/rtv are provided in LSFAE06, LSFAE07 and LSFAE10, respectively. Individual data for subjects who died and who died poststudy are provided in LSFAE08 and LSFAE09, respectively.

One (0.5%) subject died of respiratory failure (not related to DRV/rtv) during the extension phase. In addition, there were also 2 subjects who had not entered the extension phase but died after having discontinued in the main phase for an AE and who were followed-up for survival. One of these subjects died due to an HIV-related illness (lymphoma) and the other subject due to a middle cerebral artery stroke.

Eight (4.1%) subjects had 1 or more SAEs during the extension phase, all in the DRV/rtv - DRV/rtv group. All SAEs occurred in at most 1 subject. No SAEs were considered at least possibly related to DRV/rtv except for the SAE diabetes mellitus which was considered possibly related to DRV/rtv by the investigator. Two (1.0%) subjects had an SAE leading to permanent discontinuation.

During the extension phase, 2 (1.3%) subjects had an AE leading to permanent discontinuation of DRV/rtv in the DRV/rtv – DRV/rtv group. One (0.5%) subject experienced respiratory failure and one (0.5%) subject developed diabetes mellitus. Both were reported as SAEs.

Four (2.6%) subjects in the DRV/rtv – DRV/rtv group and 1 (2.4%) subject in the LPV/rtv – DRV/rtv group experienced an AE that was considered at least possibly related to DRV/rtv. All AEs at least possibly related to DRV/rtv occurred in only one subject (transaminases increased, diabetes mellitus, dyslipidemia, hypertriglyceridemia, and subcutaneous nodule).

3.2.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Individual narratives for AEs with fatal outcome, SAEs at least possibly related to the study medication, AEs leading to discontinuation that are at least possibly related to the study medication, and AEs of special interest (cardiac events) that are either SAEs or AEs of grade 3 or 4 are provided in TMC114-C211-final-narratives. The data presented in the narratives principally reflect those available in the extension phase analysis. Nevertheless, whenever the pharmacovigilance database (i.e., the Council for International Organizations of Medical Sciences [CIOMS] reports) contained additional information that was considered relevant to understand the events leading to death or other SAEs, this information was added to the narratives. Consequently, the narratives included with this report can contain more information compared to the data included in the extension phase analysis.

3.2.2.1 Deaths During the Extension Phase

One subject (Case Report Form [CRF] ID 211-0447, treatment group DRV/rtv - DRV/rtv) died during the extension phase of grade 4 respiratory failure on 31 May 2010 (LSFAE08). The investigator considered this death as not related to DRV/rtv. The duration of the subject's extension phase was 143 days or approximately 20 weeks. DRV/rtv was permanently discontinued due to the SAE.

3.2.2.2 Deaths During Follow-up of Main Phase

Two subjects who had not entered the extension phase died after the study (source: LSFAE09 and TMC114-C211-W192-CRR [SAF.1, SAF.3 and GEN.4]).

- Subject 211-0212 received DRV/rtv during the main phase of the study. The subject prematurely discontinued treatment due to the AE lymphoma on 12 June 2008. The lymphoma was considered doubtfully related to DRV/rtv by the investigator. On 24 July 2008, the subject died of an HIV-related illness (lymphoma).
- Subject 211-0527 received LPV/rtv during the main phase of the study. The subject prematurely discontinued treatment on 17 October 2007 due to the AEs parasthesia (hands and feet) and nausea. The parasthesia was considered very likely related to LPV/rtv and the nausea was considered doubtfully related to LPV/rtv by the investigator. On 23 June 2009, the subject died of a middle cerebral artery stroke.

3.2.2.3 Serious Adverse Events

A tabulation of all SAEs (including a death) is provided in TSFAE01 and is summarized in Table 3. Individual subject data for SAEs are provided in LSFAE07.

Eight (4.1%) subjects had one or more SAEs during the extension phase, i.e., 8 (5.2%) subjects in the DRV/rtv - DRV/rtv treatment group and no subjects in the LPV/rtv - DRV/rtv treatment group. All SAEs occurred in at most 1 subject. No SAEs were considered related to DRV/rtv except for the SAE diabetes mellitus which was considered possibly related to DRV/rtv by the investigator (see Table 4).

One non-fatal SAE led to permanent discontinuation of DRV/rtv, i.e., diabetes mellitus. Subject 211-0041 was reported with grade 3 diabetes mellitus on 24 March 2011 which was considered serious and possibly related to DRV/rtv. The subject permanently discontinued treatment due to this SAE on 1 April 2011.

Table 3: Serious Adverse Events During the Extension Phase

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv - DRV/rtv N = 153	LPV/rtv - DRV/rtv N = 41
Adverse Event	**8 (5.2)**	**0**
Blood and Lymphatic System Disorders	**1 (0.7)**	**0**
Anaemia	1 (0.7)	0
Cardiac Disorders	**2 (1.3)**	**0**
Acute Myocardial Infarction	1 (0.7)	0
Arteriosclerosis Coronary Artery	1 (0.7)	0
Atrial Fibrillation	1 (0.7)	0
Hepatobiliary Disorders	**1 (0.7)**	**0**
Bile Duct Stone	1 (0.7)	0
Infections and Infestations	**1 (0.7)**	**0**
Subcutaneous Abscess	1 (0.7)	0
Metabolism and Nutrition Disorders	**1 (0.7)**	**0**
Diabetes Mellitus	1 (0.7)	0
Nervous System Disorders	**1 (0.7)**	**0**
Cerebrovascular Accident	1 (0.7)	0
Respiratory, Thoracic and Mediastinal Disorders	**1 (0.7)**	**0**
Respiratory Failure	1 (0.7)	0

N = number of subjects; n = numbers of observations.
Source: TSFAE01

Table 4: Serious Adverse Events Considered at Least Possibly Related to DRV/rtv During the Extension Phase

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv - DRV/rtv N = 153	LPV/rtv - DRV/rtv N = 41
Adverse Event	**1 (0.7)**	**0**
Metabolism and Nutrition Disorders	**1 (0.7)**	**0**
Diabetes Mellitus	1 (0.7)	0

N = number of subjects; n = numbers of observations.
Source: TSFAE04

3.2.2.4 Adverse Events Leading to Permanent Treatment Discontinuation

An overview of all AEs leading to permanent discontinuation (summarized in Table 5) and AEs leading to permanent discontinuation that were considered at least possibly related to study medication occurring during the extension phase is provided in TSFAE02 and TSFAE05, respectively. Individual subject data for AEs leading to permanent discontinuation are provided in LSFAE10.

During the extension phase, 2 (1.3%) subjects in the DRV/rtv - DRV/rtv treatment group and no subjects in the LPV/rtv - DRV/rtv treatment group had an AE leading to permanent discontinuation of DRV/rtv. One (0.7%) subject experienced respiratory failure (CRF ID 211-0447; see Section 3.2.2.1) and one (0.7%) subject developed diabetes mellitus (CRF ID 211-0041). The latter was considered possibly related to DRV/rtv (see Section 3.2.2.3).

Table 5: Adverse Events Leading to Permanent Discontinuation of DRV/rtv During the Extension Phase

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv - DRV/rtv N = 153	LPV/rtv - DRV/rtv N = 41
Adverse Event	**2 (1.3)**	**0**
Metabolism and Nutrition Disorders	**1 (0.7)**	**0**
Diabetes Mellitus[a]	1 (0.7)	0
Respiratory, Thoracic and Mediastinal Disorders	**1 (0.7)**	**0**
Respiratory Failure	1 (0.7)	0

N = number of subjects; n = numbers of observations.
[a] considered at least possibly related to DRV/rtv
Source: TSFAE02

3.2.2.5 PREGNANCY

An overview of individual subject data on pregnancy tests is provided in LSFLAB01.

Subject 211-0385 (treatment group DRV/rtv - DRV/rtv) had become pregnant in May 2011 as a result of a rape (Source: CIOMS; no exact date specified). The pregnancy was reported as AE and was considered not related to DRV/rtv. Treatment with DRV/rtv was temporarily discontinued. On 29 May 2011, at 3 weeks of gestation, the pregnancy was terminated on the subject's own request (Source: CIOMS).

4 DISCUSSION AND OVERALL CONCLUSIONS

[This section of the document was removed before posting to ClinicalTrials.gov as text could be considered promotional in nature].

5 REFERENCES

1. Spinosa-Guzman S., Van De Casteele T., Lathouwers E. A randomized, controlled, open-label trial to compare the efficacy, safety and tolerability of darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve HIV-1 infected subjects. Week-192 analysis. This trial is referred to as ARTEMIS. Tibotec Pharmaceuticals, Clinical Research Report TMC114-C211-W192-CRR, Oct 2010.

6 SIGNATURES

SIGNATURE OF COORDINATING INVESTIGATOR

Title:	Addendum 1 to: A randomized, controlled, open-label trial to compare the efficacy, safety and tolerability of darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve HIV-1 infected subjects. Week-192 analysis. This trial is referred to as ARTEMIS.
Author(s):	M. Opsomer, T. Van De Casteele

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the trial.

Name:	R. Ortiz
Affiliation:	Orlando Immunology Center, 1701 N Mills Ave, Orlando FL, 32803 US

Signature & Date:

SIGNATURE OF RESPONSIBLE MEDICAL OFFICER

Title:	Addendum 1 to: A randomized, controlled, open-label trial to compare the efficacy, safety and tolerability of darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve HIV-1 infected subjects. Week-192 analysis. This trial is referred to as ARTEMIS.
Author(s):	M. Opsomer, T. Van De Casteele

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the trial.

Name:	M. Opsomer
Affiliation:	Janssen Research & Development

See appended electronic signature page

7 APPENDICES

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Listing and display in TMC114-C211-EXT-Anal-Gen

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Listing and display in TMC114-C211-EXT-Anal-Gen

7.2.3 Demographic and Other Baseline Information (not applicable)

7.2.4 Concomitant Therapies (not applicable)

7.2.5 Compliance and/or Drug (not applicable)

7.2.6 Pharmacokinetic Data (not applicable)

7.2.7 Subjects Excluded From the Efficacy Analysis (not applicable)

7.2.8 Efficacy Response Data (not applicable)

7.2.9 Resistance Determination Data (not applicable)

7.2.10 Pharmacokinetic/Pharmacodynamic Data (not applicable)

7.2.11 Adverse Events

Listing and display in TMC114-C211-EXT-Anal-Saf-AE

7.2.12 Clinical Laboratory Data (not applicable)

7.2.13 Cardiovascular Safety (not applicable)

7.2.14 Vital Signs (not applicable)

7.2.15 ECG (not applicable)

7.2.16 Other Safety Evaluations (not applicable)

7.2.17 Physical Examination Data (not applicable)

7.2.18 Other Evaluations (not applicable)

7.3 Case Report Forms

7.3.1 Case Report Forms for Deaths, Other Serious Adverse Events and Withdrawal for Adverse Events

Deaths: CRF ID 211-0005, 211-0182, 211-0183, 211-0212, 211-0275, 211-0447, 211-0510, 211-0584, 211-0611, 211-0635, 211-0685, and 211-0746

Other SAEs: CRF ID 211-0041, 221-0045, 211-0216, 211-0223, 211-0234, 211-0249, 211-0259, 211-0269, 211-0318, 211-0336, 211-0344, 211-0418, 211-0448, 211-0539, 211-0571, 211-0585, 211-0595, 211-0628, 211-0683, 211-0686, 211-0792, and 211-0845

Withdrawal for AE: CRF ID 211-0017, 211-0080, 211-0099, 211-0114, 211-0117, 211-0127, 211-0154, 211-0167, 211-0190, 211-0207, 211-0208, 211-0266, 211-0300, 211-0340, 211-0361, 211-0454, 211-0463, 211-0503, 211-0504, 211-0527, 211-0599, 211-0610, and 211-0723

7.3.2 Other Case Report Forms (not applicable)

SIGNATURES

Signed by	Date	Justification
Magda Opsomer	27Feb2013, 06:11:29 AM, UTC	Document Approval

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