SYNOPSIS

Issue Date: 28 April 2008

Name of Sponsor/Company	Janssen-Cilag International N.V
Name of Finished Product	Prezista
Name of Active Ingredient(s)	**TMC114HIV3017 (Darunavir)**

Protocol No.: 289/07-01

Title of Study: A randomized, controlled, open-label trial to compare brachial artery reactivity and cardiovascular risk of a treatment simplification by darunavir/ritonavir (DRV/r) 800/100 mg O.D. versus a triple combination therapy containing DRV/r in HIV-1 infected subjects with undetectable plasma HIV-1 RNA on their current treatments. Monarch Study.

Study Name: Monarch Study

EudraCT Number: 2008-002383-34

Principal Investigator: Giovanni Guaraldi, M.D. - Clinica Malattie Infettive e Tropicali. Azienda Ospedaliera Policlinico Universitario. Via del Pozzo 71. 41100 Modena-Italy

Publication (Reference): Not Applicable.

Study Period: 28/05/2009-15/04/2011

Phase of Development: Phase II

Objectives:

Primary Objectives: To compare the change in brachial artery flow mediated vasodilatation (FMD) from baseline to week 24 in the two study arms (DRV/r monotherapy versus a triple combination therapy containing DRV/r and 2 Nucleoside reverse transcriptase inhibitor (NRTIs).

Important Secondary Study Objectives:

1. To compare the change in brachial artery flow mediated vasodilatation (FMD) from baseline to week 48 in the two study arms.
2. To evaluate and compare the efficacy of a treatment simplification by a DRV/r monotherapy versus a triple combination therapy with DRV/r at 48 weeks.
3. To compare the change in circulating endothelial cells and their precursors from baseline to week 48.
4. To compare the change in mean Low density Lipoprotein (LDL)-cholesterol, High density Lipoprotein (HDL)-cholesterol, triglycerides, HOMA-IR and Framingham risk score from baseline to week 24 and 48 in the two study arms.
5. To compare body fat changes by means of leg fat content analyzed by DEXA and visceral fat content in abdomen by TC in the two study arms from baseline to week 48.
6. To compare the measure of drug toxicity on mithocondrial DNA (mtDNA) and soluble factors involved in mitochondrial/metabolic alterations (leptin, adiponectin) from baseline to week 48 in the two study arms.
7. To compare lumbar and femoral neck T and Z score from baseline to week 48.
8. To compare the virologic response in terms of change in HIV-DNA in isolated CD4+ T cells from baseline over 48 weeks of both treatment regimens.
9. To determine the evolution in the CD4+ T cell count from baseline to week of patients from both study group.

Methods: Patients were randomised in a 1:1 ratio to one of the two treatment arm based on a computer-generated randomization schedule: DRV/r 800/100 mg Once Daily (O.D) plus 2 Nucleoside reverse transcriptase inhibitor (NRTIs), or, DRV/r 800/100 mg O.D. The treatment duration was 48 weeks (with a further follow-up visit 4 weeks later). Both the investigator and the subject knew to which treatment group the subject has been assigned to.

The study population were 30 treatment-experienced HIV-1 positive patients who were virologically suppressed on their current HAART treatment, but, who intend to switch their current regimen for tolerability, simplification or convenience.
allowed antiretroviral medications:

-DRV/r triple combination group: all approved NRTIs.

-DRV/r monotherapy arm: only DRV/r

Excluded antiretroviral medications:

DRV/r triple combination group: All other PI, Investigational NRTIs, all approved and investigational NNRTIs, T20

DRV/r monotherapy arm: All other PI, All NRTIs; All NNRTIs, T-20

Number of Subjects (planned and analyzed): As planned, 30 patients were enrolled with 15 individuals assigned to each arm and all subjects continued the assigned treatment until week 48.

Diagnosis and Main Criteria for Inclusion:

Main Inclusion Criteria: HIV-1 naïve patients virologically suppressed who have been receiving HAART for at least 24 weeks and were taking the same ARV combination for at least 8 weeks before screening. At screening, patients should have CD4 > 200/mm^3 and at the start of HAART > 100/mm^3 and being healthy on the basis of physical examination, medical history, vital signs, clinical laboratory tests performed at screening. Woman must be: Postmenopausal for at least 2 years, surgically sterile, abstinent or if sexually active, be practicing an effective method of birth control.

Main Exclusion Criteria: Patients with history of: cardiovascular disease, virological failure on HAART, any PI mutations for DRV, allergy or hypersensitivity to any of the ingredients found in DRV or ritonavir. Patients co-infected with hepatitis B (HBV), heavy smokers, with active drug or alcohol dependence, using the disallowed concomitant therapy, who had initiated certain drugs prior to study entry.

Test Product, Dose and Mode of Administration, Batch No.:

Drug	*Dose*	*Batch No*	*Expiry date*
NORVIR	100 mg	72648VA	10/2010
DARUNAVIR	400 mg	360412-8ITK001	09/2010
DARUNAVIR	400 mg	362155-9FTK017	06/2011
NORVIR	100 mg	6008303	01/2012
DARUNAVIR	400 mg	363551-9FTK02D	06/2011

Duration of Treatment: The treatment duration was 48 weeks, with a 4-week screening period prior to commencing treatment and a 4-week follow-up period after completing the 48-week treatment period.

Criteria for Evaluation:

- The primary efficacy objective was to evaluate and compare the brachial artery reactivity through FMD of a monotherapy regimen of DRV/r against a triple drug combination using DRV/r.
- A physical examination, safety bloods (haematology, chemistry, and urinalysis), metabolic and morphologic measurements and vital signs have been performed at protocol-scheduled visits and monitored at each study visit. In addition, at each study visit, every subject has been asked about the occurrence of or change in adverse events (AE) since they were last seen by the investigator. Pregnancy test has been done at each visit for female participants of child-bearing potential. Any

possible clinically significant abnormalities persisting at the end of the study should have been followed by the investigator until resolution or until reaching a clinically stable endpoint.

Statistical Methods: The comparison between treatment groups from baseline (BL) to week 24 or 48 for all continuous parameters was made using a nonparametric Wilcoxon rank sum test. For binary/categorical parameters differences in the distribution of frequency between the two arms were evaluated using Chi square test. Efficacy and safety analysis have been conducted.

RESULTS: During the 48 weeks of the study period, the median FMD (%) decreased in both group with no significant differences between arms, Cholesterol significantly increased at 48 weeks more in the DRV/r monotherapy arm, circulating endothelial cells and their precursors increased at week 48, a significant reduction of HOMA-IR was observed in the whole population. An increase of lumbar T and Z scores was present especially in the monotherapy arm at week 48. No difference in CD4 cell count were observed between groups and no virological failure at week 48. Furthermore there was the absence of deaths or AEs in both study arms. All 30 patients continued the assigned treatment until week 48 without any major protocol deviation.
At baseline, median age was 44.6 years, 77% were males and 46,7% were smokers, HIV-RNA was <40 copies/ml in all patients but one, many patients were clinically asymptomatic and CD4 and CD8 count were substantially good. One patient was Hepatitis C (HCV)-positive and none was HBV-positive. In the arm of triple therapy, 10 patients combined DRV/r with TDF+Emtricitabine (FTC) and 6 with Abacavir (ABC) + Lamivudine (3TC). The two arms were substantially balanced with regard to demographics variables.

EFFICACY RESULTS: Primary and secondary efficacy analysis data were based on 30 subjects, 15 individuals assigned to each arm. The median FMD (%) and median change of FMD (%) decreased in both arms in the study period with no significant differences between arms, both at 24 and at 48 weeks, see table 1. There were statistically significant differences at week 48 between the two arms with higher median changes from BL for total and LDL-cholesterol in the monotherapy arm. A significant reduction of HOMA-IR was observed in the whole population. (median change of -0.5, p=0.013), see table 2. Circulating endothelial cells and their precursors increased at week 48 with respect to their value at BL (p<0.01) with no significant differences between the study arms. Compared to BL values, there was a significant difference with the triple therapy group in the values at week 48 for increase in lumb t and z scores, see table 3 There were no significant differences between the treatment arms for HDL-cholesterol and triglycerides values and Framingham score, either at baseline or week 48. There were no particular changes in mass fat parameters and CT values from baseline to week 48 and there were no statistically significant differences between the study arms. In both arms, on average, there was a decrease of mtDNA at week 48 with no differences between the treatment arms both for the values at week 48 and the changes from BL at week 48. Only in few cases the HIV-RNA was above the detectability but no statistically significant differences among study arms were found. On average, in both arms an increase of CD4 count was observed, but there were not statistically significant differences between treatment arms.

Table 1: Median values at week 24 and 48 and changes in FMD from BL to week 24 and 48 in the two study arms.

		DRV/r 800/100mg OD			***DRV/r 800/100mg OD + 2 NRTIs***			**p-values**	
		Median	**Median change**	**IQR change**	**Median**	**Median change**	**IQR change**	*** Values at 24**	****Changes from 0**
BL	**FMD (%)**	11.1			10.7				
W24	**FMD (%)**	8.9	-4.8	(-7.0;0.3)	8.5	-0.6	(-4.7;3.3)	0.55	0.08
W48	**FMD (%)**	8.8	-4.4	(-6.2;2.6)	6.7	-3	(-4.5;4.0)	0.52	0.88

** Comparison of values between treatment arms at weeks 24 & 48; ** Comparison of changes from baseline to week 24 & 48 between treatment arms*

Table 2: Median values and changes of total cholesterol and LDL-cholesterol from BL to week 48 in the two study arms.

	DRV/r 800/100mg OD			*DRV/r 800/100mg OD + 2 NRTIs*			p-values	
	Median	**Median change**	**IQR change**	**Median**	**Median change**	**IQR change**	***Values**	****Changes from BL**
Total cholesterol (mg/dl)	232	26	(14;68)	210	9	(-16;18)	0.22	0.01
LDL (mg/dl)	137	14	(7;42)	117	5	(-12;19)	0.23	0.02

** Comparison of values between treatment arms at weeks 24 & 48; ** Comparison of changes from baseline to week 24 & 48 between treatment arms*

Table 3: Dexa: Median values and changes from BL to week 48 of Lumb T and Z scores in the two study arms.

	Median (IQR) values at week 48			**Median (IQR) changes from BL to week 48**		
	DRV/r 800/100mg OD	**DRV/r 800/100mg OD + 2 NRTIs**	**Between arms**	**DRV/r 800/100mg OD**	**DRV/r 800/100mg OD + 2 NRTIs**	**Between arms**
Lumb T	-0.7 (-1.2;-0.2)	-1.4 (-2.1;-0.5)	0.16	0.1 (0.0;0.3)	0.0 (-0.2;0.1)	0.03
Lumb Z	-0.4 (-0.8;0.3)	-0.9 (-2.1;0.0)	0.21	0.1 (0.0;0.3)	0.0 (-0.2;0.1)	0.04

SAFETY RESULTS:

Table 4: Adverse events summary table.

Patients with AEs	**DRV (N=15)**	**DRV+2NRTIs (N=15)**	**Total (N=30)**
One or more AE	10 (66.7%)	11 (73.3%)	21 (70.0%)
One or more SAE	0	0	0
Deaths	0	0	0
Treatment stopped due to adverse events	0	0	0

Table 5: Tabulation of AEs occurred in at least 5% of study subjects in any treatment group.

System organ class \Preferred term	**DRV/r 800/100mg OD plus 2 NRTIs (N=15)**		**DRV/r 800/100mg OD (N=15)**		**Total (N=30)**	
	N events	**n(%) patients**	**N events**	**n(%) patients**	**N events**	**n(%) patients**
Gastrointestinal disorders						
Diarrhoea	3	3 (20.0)	1	1(6.7)	4	4 (13.3)
General disorders and administration site conditions						
Malaise	1	1(6.7)	1	1(6.7)	2	2 (6.7)
Pyrexia	1	1(6.7)	3	3 (20.0)	4	4 (13.3)
Infections and infestations						
Influenza	1	1(6.7)	2	2 (13.3)	3	3 (10.0)
Investigations						
Blood cholesterol increased	0	0	4	4	4	4(13.3)
Blood creatine phosphokinase increased	2	2(13.3)	0	0	2	2 (6.7)
Blood triglycerides increased	1	1(6.7)	1	1(6.7)	2	2 (6.7)

System organ class \Preferred term	DRV/r 800/100mg OD plus 2 NRTIs (N=15)		DRV/r 800/100mg OD (N=15)		Total (N=30)	
	N events	n(%) patients	N events	n(%) patients	N events	n(%) patients
Low density lipoprotein increased	0	0	4	4 (26.7)	4	4 (13.3)
Nervous system disorders						
Headache	1	1(6.7)	1	1(6.7)	2	2 (6.7)
Psychiatric disorders					2	
Insomnia	0	0	2	2 (13.3)	2	2 (6.7)
Vascular disorders					2	
Hypertension	1	1(6.7)	1	1(6.7)	2	2 (6.7)

During the course of the 48 weeks of the study there was the absence of deaths and serious adverse events in both regimen arms. The most commons AEs were gastrointestinal disorders and the most frequent laboratory abnormalities were elevations of lipids (total and LDL-cholesterol) especially in the DRV/r monotherapy arm.

CONCLUSION: In this small, pilot study, the expected increase in lipid levels (TC and LDL-C) especially in the DRV/r monotherapy, did not correlated with an increase in cardiovascular risk of the patients as measured by FMD change (%) and insulin levels. Furthermore a less reduction in bone loss in both arms, at week 48, has been reported. An increase in circulating endothelial cells and their precursors at week 48 without significant differences between the study arms has been found. The role of increased levels of circulating endothelial cells and their precursors form baseline deserves further investigations.

Disclaimer

Disclaimer Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.