Janssen Taiwan, Pharmaceutical Companies of Johnson & Johnson

Abbreviated Clinical Study Report

Early Access to TMC114 in Combination with Low-dose ritonavir (TMC114/r) and Other Antiretrovirals (ARVs) for Treatment-naïve or TMC114-naïve, Early Treatment-experienced in HIV-1 Infected Patients

Protocol TMC114HIV4073 (DRV-C-10-TW01-001); Phase [4]

TMC114 (PREZISTA) (Darunavir)

PRINCIPAL INVESTIGATOR:

Chien-Ching Hung, MD – National Taiwan University Hospital, Taipei, Taiwan

COORDINATING INVESTIGATOR:

Hsin-Yun Sun, MD – National Taiwan University Hospital, Taipei, Taiwan

Szu-Min Hsieh, MD – National Taiwan University Hospital, Taipei, Taiwan

Wang-Huei Sheng, MD – National Taiwan University Hospital, Taipei, Taiwan

SPONSOR'S RESPONSIBLE MEDICAL OFFICER:

Mee Mee Leong, MD - Medical Affairs, Janssen Taiwan, Pharmaceutical Companies of Johnson & Johnson

DATE STUDY INITIATED: 07-Dec-2011

DATE STUDY COMPLETED: 19-Jun-2012

Status:	Approved
Date:	23 July 2013
Prepared by:	Kookies Inc.
Document No.:	EDMS-ERI-67819511

GCP Compliance: This study was conducted in compliance with Good Clinical Practice, including the archival of essential documents.

SYNOPSIS

Name of Sponsor/Company	Janssen-Cilag Taiwan, Pharmaceutical Companies of Johnson & Johnson
Name of Finished Product	TMC114 (PREZISTA)
Name of Active Ingredient(s)	TMC114 (PREZISTA) (Darunavir)

Status: Approved
Date: 23 July 2013
Prepared by: Kookies Inc.

Protocol No.: TMC114HIV4073 (DRV-C-10-TW01-001)

Title of Study: Early Access to TMC114 in Combination with Low-dose ritonavir (TMC114/r) and Other Antiretrovirals (ARVs) for Treatment-naïve or TMC114-naïve, Early Treatment-experienced in HIV-1 Infected Patients

NCT No.: NCT01702090

Clinical Registry No.: CR100712

Principal Investigator(s):

Chien-Ching Hung, MD – National Taiwan University Hospital, Taipei, Taiwan

Coordinating Investigator(s):

Hsin-Yun Sun, MD – National Taiwan University Hospital, Taipei, Taiwan

Szu-Min Hsieh, MD – National Taiwan University Hospital, Taipei, Taiwan

Wang-Huei Sheng, MD – National Taiwan University Hospital, Taipei, Taiwan

Study Center(s): National Taiwan University Hospital

Publication (Reference): None

Study Period: 07-Dec-2011 - 19-Jun-2012

Phase of Development: Phase 4

Objectives:

The primary objective was to provide early access to TMC114 co-administered with low-dose ritonavir (TMC114/r) and other ARVs for HIV-1 infected patients who were treatment-naïve or were early treatment-experienced without TMC114 regimens.

The secondary objective was to gather information on the safety and tolerability of TMC114/r in combination with ARVs during the course of this study. Available efficacy data was also collected.

Methodology:

This was a single arm, open-label, non-randomized and single center study to provide early access to TMC114/r co-administered ARVs for HIV-1 infected patients who were treatment-naïve or TMC114-naïve, early treatment-experienced and who were ineligible for participation in any other

Tibotec-sponsored HIV-1 trial. Information on the safety and tolerability aspects of TMC114/r and other ARVs were assessed. Available data regarding the effectiveness of the drug was collected.

Patients must meet all inclusion and exclusion criteria to be eligible for this early access program. TMC114 800 mg once daily (q.d.) together with 100 mg ritonavir was provided to the patient confirmed eligible for entry. TMC114/r was administered in combination with an investigator-selected background of additional ARVs. TMC114/r was continued until virologic failure, treatment-limiting toxicity, loss to follow-up or study withdrawal, pregnancy, or until discontinuation of TMC114 development or when TMC114 became commercially available.

Eligible patients were evaluated at initiation of TMC114/r in combination with other ARVs (baseline), Week 4, and every 12 weeks during this trial. A final/withdrawal visit as well as a post-trial treatment follow-up (30 days after the final/withdrawal visit) was performed. If changes in the background regimen were made, it was recommended that a follow-up visit be planned 30 days after the change in therapy. Patients must be instructed to follow the recommended visit schedule base on routine clinical care.

In terms of study design limitations, the study was single arm and open label. In addition, the observation period of 16 weeks was relatively short.

Number of Subjects (planned and analyzed):

Thirty intent-to-treat (ITT) patients (ten treatment-naïve and twenty early treatment-experienced patients) were planned, and ten ITT patients (six treatment-naïve and four early treatment-experienced patients) were analyzed.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

Patients who met all of the following inclusion criteria were enrolled in the study:

a. Patients with documented HIV-1 infection who are ineligible for participation in any other Tibotec-sponsored HIV-1 trial.
b. Patients aged at least 20 years.
c. Patients have never been treated with antiretroviral (ARV) medications or had prior early treatment-experience without TMC114 regimens, including those limited or had no treatment options due to virological failure or intolerance to regimens.
   【Virological failure: losing (rebound) or never achieving (never suppressed) HIV-1 RNA <200 copies/mL in the previous ARV treatment.】
   【Early treatment-experienced patients: previous ARV medication intolerance or treatment failure patients. Antiretroviral treatment-experienced patients with no TMC114 resistance associated mutations and who have plasma HIV-1 RNA <100,000 copies/ml, except those patients who have ARV medication intolerance within 6 months.】*
d. Patient's general medical condition, as in the opinion of the investigator evaluating the patient's eligibility for TMC114-containing regimen, does not interfere with the assessments and the completion of the trial.
e. Ability to understand and willingly provide signed informed consent.

**TMC114 resistance associated mutations: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V*

Exclusion Criteria

Patients who meet any of the following exclusion criteria were not enrolled in the study:

a. Patients who uses disallowed concomitant therapy.
b. Patients suffers from any active clinically significant disease (e.g., cardiac dysfunction, pancreatitis) or findings during screening of medical history or physical examination that is either not resolved or stabilized for at least 30 days before the screening phase of the trial.
c. Patients has evidence of active liver disease, acute viral hepatitis, liver impairment/dysfunction or cirrhosis irrespective of liver enzyme levels; however, patients co-infected with hepatitis B or C will be included if their condition is judged to be clinically stable.
d. Patients has grade 3 or 4 laboratory abnormalities as defined by Division of AIDS (DAIDS) grading scheme or calculated creatinine clearance (CrCl) of less than 50 ml/min.
e. Female patients who are pregnant or breast-feeding, or of childbearing potential without using effective non-hormonal birth control methods or not willing to continue practicing these birth control methods from screening until the last 30 days after the end of the treatment period. All pregnancy events involving female patients and patients' female partners should be reported by the investigator through the adverse event (AE) reporting process even though they are not AEs.
   Note: Women who are postmenopausal for at least 2 years, women with total hysterectomy and women with tubular ligation are considered of non-childbearing potential.
f. Any condition (including but not limited to alcohol and/or drug abuse), which in the opinion of the investigator, could compromise the patient's safety or compliance to the study protocol procedures.
g. Allergy or hypersensitivity to TMC114, ritonavir or to any of their excipients.

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

Patients took oral doses of 800 mg of TMC114 q.d. co-administered with 100 mg of ritonavir q.d. within 30 minutes after completion of a meal, and in combination with other ARVs. The batch number of the study drug is 365264.

Reference Therapy, Dose and Mode of Administration, Batch No.:

Not applicable.

Duration of Treatment:

TMC114 was continued until virologic failure, treatment-limiting toxicity, loss to follow-up or study withdrawal, pregnancy, or until discontinuation of TMC114 development or when TMC114 became commercially available for the treatment-experienced patients.

Criteria for Evaluation:

Efficacy Evaluation

1 Change in plasma HIV-1 RNA
2 Change in cluster of differentiation 4 (CD4) cell count.

Safety Evaluation

Safety was assessed through the analysis of AEs, standard clinical chemistry and hematology findings.

Statistical Methods:

Descriptive statistics were provided for demographics, baseline characteristics, and safety results. Available efficacy measures including HIV-1 RNA level and CD4 cell count were summarized descriptively. Type and incidence of AEs, AIDS defining illnesses and AEs leading to treatment discontinuation or treatment interruption between baseline and trial termination were tabulated. In addition, the summary of clinical laboratory data and vital sign were tabulated.

RESULTS:

STUDY POPULATION:

Of the 15 subjects screened, ten were eligible for the study. All eligible subjects were males and treated with TMC114/r. There were four patients completing 16-week treatment period. The reasons for discontinuation were: TMC114 becoming commercially available (n=7), protocol violation (n=1), informed consent withdrawn (n=1), and intolerable AE (n=1). Data from these ten patients were included in efficacy and safety assessments.

The average age of the ten males in the study was 32.7 years. Seventy percent (7/10) of patients were diagnosed with HIV-1 infection. Three AIDS patients and one HIV-1 infection patient were treated with ARV drug in the past and during the study period.

EFFICACY RESULTS:

At final visit, there were 70% (7/10) of patients with plasma HIV-1 RNA < 40 copies/mL or HIV-1 RNA < 400 copies/mL and a decrease of 0.5 log10 or more in ITT population. In the PP population, it was 77.8% (7/9). Among the ITT population, mean (SD) CD4+ cell counts increased from the baseline value of 258.9 (147.81) cells/mm^3 to a final value of 324.0 (149.42) cells/mm^3, and the mean improvement on CD4+ cell count was 65.1 (105.29) cells/mm^3. The improvement of CD4+ cell counts in PP population was 65.4 (111.67) cells/mm^3.

SAFETY RESULTS:

During the study, there were six patients (60%) with at least one treatment-emergent adverse event (TEAE), and five patients (50%) underwent at least one TEAE. There were no SAEs. The common AEs reported were diarrhea (3/10, 30%) and rash (3/10, 30%). All three cases of diarrhea and two cases of rash were diagnosed as treatment-related.

Two patients discontinued the study medication because of AE. One patient underwent Grade 2 rash and Grade 2 diarrhea, and these were deemed related to study therapy. The other patient experienced grade 1 rash, and also diagnosed as treated-related.

STUDY LIMITATIONS:

There were some limitations, for example, the number of patients was relatively low and 16 weeks was a relatively short observation period. The other limitation was the single-arm and open-label design.

CONCLUSIONS:

The primary objective of providing early access to TMC114/r combined with other ARVs in HIV-1 infected patients were met. There were ten patients treated with TMC114/r, providing information on the efficacy, safety and tolerability of TMC114/r. This study showed that TMC114/r was efficacious for HIV-1 RNA suppression and CD4+ cell count improvement. The safety profile showed that TMC114/r was tolerable for HIV-1 infected patients who were treatment-naïve or were early treatment-experienced without TMC114 regimens.