## SYNOPSIS

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|---|---|
| Name of Sponsor/Company | Janssen Pharmaceutical K.K. |
| Name of Investigational Product | TMC278-FDC (rilpivirine/tenofovir disoproxyl fumarate/emtricitabine) |

**Status:** Approved
**Date:** 4 February 2016
**Prepared by:** Janssen Pharmaceutical K.K.

**Protocol No.:** TMC278FDCHIV4001

**Title of Study:** An Open-Label Study to Evaluate the Pharmacokinetics of Rilpivirine/Tenofovir/Emtricitabine After a Single-Oral Administration of a Rilpivirine/Tenofovir Disoproxil Fumarate/Emtricitabine Fixed-Dose Combination Tablet in Healthy Japanese Adult Male Subjects

**NCT No.:** NCT02530060

**Clinical Registry No.:** CR107748

**Principal Investigator:** Masanari Shiramoto, MD

**Study Center(s):** Medical Co. LTA [redacted] Clinic

**Publication (Reference):** Not applicable

**Study Period:** 20 August 2015 (date of first subject enrolled [informed consent]) to 24 September 2015 (date of last observation for last subject); 26 October 2015 (database lock)

**Phase of Development:** Phase 4

**Objectives:**

***Primary Objective***

To evaluate the pharmacokinetics (PK) of rilpivirine/tenofovir/emtricitabine after a single-oral administration of TMC278-FDC (COMPLERA®) under fed condition to healthy Japanese adult male subjects.

***Secondary Objective***

To investigate the safety after a single-oral administration of COMPLERA to healthy Japanese adult male subjects.

**Hypothesis:**

No formal statistical hypothesis testing was planned for this study. This study was designed to collect PK data in healthy Japanese subjects after a single-oral administration of COMPLERA under fed condition.

**Methodology:**

This was a single center, open-label, single-oral dose study in healthy Japanese adult male subjects. The study consisted of 3 phases; a screening phase up to 27 days (Day -28 to Day -2), an in-patient phase from Day -1 to Day 3 (dosing day was Day 1), and a follow-up assessment phase from Day 4 to the last follow-up assessment scheduled on Day 15 or at the time of early withdrawal.

Subjects who met the selection criteria at screening were admitted to the investigational institute on the day before the dose (Day -1). All enrolled subjects received a single-oral dose of one COMPLERA tablet on Day 1 within 5 minutes after completion of the standardized breakfast. All the subjects remained in the investigational institute for the entire duration of the in-patient phase. Subjects were discharged on Day 3 after the completion of all required assessments. Subjects visited the investigational institute on the days as scheduled until the last follow-up assessment on Day 15. Serial blood samples for the determination of plasma tenofovir and emtricitabine concentrations were collected over a period of 96 hours (4 days), and those for plasma rilpivirine concentrations were collected over a period of 192 hours (8 days).

**Number of Subjects (planned and analyzed):**

A total of 8 subjects were planned to be enrolled in the study to ensure that at least 6 subjects complete the PK sample collection. Eight subjects were enrolled in the study. All of the 8 subjects completed the study and were included in the PK and safety analysis population.

Subject Disposition and Number of Subjects per Analysis Set; Safety

| | COMPLERA |
|---|---|
| Total Number of Subjects with Administration | 8 (100.0%) |
| Completed | 8 (100.0%) |
| Discontinued After Administration | 0 |
| Evaluable Subjects | |
| Pharmacokinetic Analysis Set | 8 (100.0%) |
| Safety Analysis Set | 8 (100.0%) |

**Diagnosis and Main Criteria for Inclusion:**

Healthy Japanese men between 20 and 55 years of age, inclusive; body mass index (BMI) between 18.0 and 30.0 $kg/m^2$, inclusive; and a body weight of not less than 50 kg.

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

COMPLERA tablet (study drug), provided as marketed tablet, contains 25 mg of rilpivirine, 300 mg of tenofovir disoproxil fumarate and 200 mg of emtricitabine. The lot number of the COMPLERA tablet was 0001A.

One COMPLERA tablet was taken in the morning on Day 1. COMPLERA tablet was taken orally with 150 mL of noncarbonated water within 5 minutes after completion of a standardized breakfast. COMPLERA tablet was swallowed whole, not chewed, divided, dissolved, or crushed.

**Reference Therapy, Dose and Mode of Administration, Batch No.:** Not applicable

**Duration of Treatment:**

The study consisted of 3 phases; a screening phase up to 27 days (Day -28 to Day -2), an in-patient phase of 4 days (Day -1 to Day 3), and a follow-up assessment phase of approximately 12 days (Day 4 to Day 15 or at the time of early withdrawal).

**Criteria for Evaluation:**

***Pharmacokinetics***

Venous blood samples of approximately 4 mL were collected for the determination of plasma concentrations for each component of rilpivirine/tenofovir/emtricitabine at the following time points;

Predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 168, and 192 hours postdose (120, 168, and 192 hours postdose samplings were only for the determination of plasma rilpivirine concentrations).

For each subject, the following PK parameters for each analyte were estimated by noncompartmental analysis: maximum plasma concentration ($C_{max}$), time to reach the maximum plasma concentration ($t_{max}$), area under the plasma concentration-time curve from time zero to time the last quantifiable time, calculated by linear trapezoidal summation ($AUC_{last}$), area under the plasma concentration-time curve from time zero to infinite time ($AUC_{\infty}$), elimination half-life ($t_{1/2}$), elimination rate constant associated with the terminal phase ($\lambda_z$), apparent volume of distribution at the terminal phase after extravascular administration ($Vd_z/F$), and apparent total body clearance of drug at the terminal phase after extravascular administration (CL/F).

***Safety***

The safety of COMPLERA was to be monitored by adverse events (AEs), clinical laboratory tests (hematology, biochemistry, and urinalysis), vital signs, physical examinations, and 12-lead electrocardiogram (ECG).

**Statistical Methods:**

***Sample Size Determination***

Eight subjects were to be enrolled in the study to ensure that at least 6 subjects complete the study assessments up to Day 9. Based on a previous study, GS-US-264-0103,[2] the maximum observed value of intersubject coefficient of variation (CV) for $C_{max}$, $AUC_{last}$, and $AUC_{\infty}$ of rilpivirine/tenofovir/emtricitabine was 38% in healthy white adult subjects. Using an estimate of approximately 38% for intersubject CV and a sample size of 6 subjects, all the true mean $C_{max}$, $AUC_{last}$, and $AUC_{\infty}$ for each component of rilpivirine/tenofovir/emtricitabine were estimated to be within 68% to 147% of the observed geometric means with 95% confidence.

***Subject Information***

For all subjects who received at least one dose of COMPLERA, descriptive statistics were provided. All demographic (age, height, weight, and BMI) and other initial subject characteristics (eg, medical history, physical examination) were tabulated and analyzed descriptively.

***Pharmacokinetics***

All subjects who received the study drug and had at least one plasma concentration data after administration were included in the PK analysis.

Plasma concentration data were tabulated for each analyte. Individual and mean concentration-time profiles for each analyte were visually presented on a linear scale.

PK parameters for each analyte were estimated for all subjects with sufficient concentration data for PK analysis (ie, whose concentration-time profiles allowed accurate calculation of PK parameters). For the population, concentrations data and PK parameters were summarized using descriptive statistics (eg, number of collected data, mean, standard deviation, median, minimum, maximum, and CV) of plasma concentrations of each analyte at each time point. Individual and descriptive statistics of PK parameters of each analyte were tabulated.

The PK parameters and those descriptive statistics obtained from this study and the previous study in non-Japanese healthy adult subjects (GS-US-264-0103[2]) were tabulated for comparison.

***Safety***

All subjects who received the study drug were included in the safety analysis.

Baseline laboratory evaluations, vital signs, and ECG assessments were defined as the last evaluation done before the study drug administration. Safety data were summarized using descriptive statistics and frequency tables.

**RESULTS:**

***STUDY POPULATION:***

Eight healthy Japanese male subjects aged 20 to 34 years were enrolled in the study. All of the 8 subjects received a single dose of the study drug, and all subjects completed the study.

***PHARMACOKINETIC RESULTS:***

The estimated PK parameters of rilpivirine/tenofovir/emtricitabine following a single-oral administration of study drug under fed condition are summarized in the table below.

Summary of Pharmacokinetic Parameters

| PK Parameters (unit) | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $AUC_{last}$ (ng*h/mL) | $AUC_{\infty}$ (ng*h/mL) | $t_{1/2}$ (h) | $\lambda_z$ (1/h) | $Vd_z/F$ (mL) | CL/F (mL/h) |
|---|---|---|---|---|---|---|---|---|
| Rilpivirine (N=8) | | | | | | | | |
| Arithmetic Mean | 194.0 | 3.813 | 4780.0 | 5028.9 | 35.11 | 0.02291 | 264541.8 | 5815.6 |
| SD | 52.88 | 0.8839 | 1699.72 | 1899.03 | 15.210 | 0.009005 | 87196.34 | 2705.73 |
| CV% | 27.3 | 23.2 | 35.6 | 37.8 | 43.3 | 39.3 | 33.0 | 46.5 |
| Geo Mean | 187.6 | 3.698 | 4477.6 | 4675.2 | 32.52 | 0.02132 | 250777.1 | 5347.2 |
| Median | 189.0 | 4.000 | 4917.0 | 5048.5 | 30.90 | 0.02255 | 275435.5 | 4956.0 |
| Minimum | 125 | 2.00 | 2205 | 2254 | 17.7 | 0.0115 | 132709 | 3312 |
| Maximum | 263 | 4.50 | 6819 | 7549 | 60.3 | 0.0393 | 400798 | 11093 |
| Tenofovir (N=8) | | | | | | | | |
| Arithmetic Mean | 334.6 | 2.125 | 3155.1 | 3265.9 | 22.18 | 0.03164 | 3079294.8 | 96974.8 |
| SD | 107.36 | 1.1260 | 747.23 | 775.51 | 2.578 | 0.003607 | 795648.67 | 25089.07 |
| CV% | 32.1 | 53.0 | 23.7 | 23.7 | 11.6 | 11.4 | 25.8 | 25.9 |
| Geo Mean | 319.2 | 1.851 | 3073.6 | 3181.0 | 22.05 | 0.03146 | 2998656.1 | 94309.8 |
| Median | 335.0 | 2.000 | 3143.5 | 3281.0 | 22.35 | 0.03110 | 3037465.0 | 91604.5 |
| Minimum | 195 | 1.00 | 2037 | 2119 | 19.1 | 0.0264 | 2160860 | 70173 |
| Maximum | 489 | 3.50 | 4117 | 4275 | 26.3 | 0.0363 | 4745542 | 141574 |
| Emtricitabine (N=8) | | | | | | | | |
| Arithmetic Mean | 2476.3 | 2.313 | 10771.4 | 11032.5 | 22.26 | 0.03374 | 576223.5 | 18236.0 |
| SD | 534.15 | 1.0670 | 914.71 | 920.44 | 7.714 | 0.009038 | 171251.14 | 1482.00 |
| CV% | 21.6 | 46.1 | 8.5 | 8.3 | 34.7 | 26.8 | 29.7 | 8.1 |
| Geo Mean | 2431.4 | 2.065 | 10738.1 | 10999.5 | 21.32 | 0.03253 | 559028.9 | 18182.5 |
| Median | 2250.0 | 2.500 | 10752.0 | 10946.0 | 20.70 | 0.03355 | 544806.5 | 18274.0 |
| Minimum | 1970 | 1.00 | 9726 | 9976 | 14.7 | 0.0175 | 425747 | 15786 |
| Maximum | 3550 | 3.50 | 12420 | 12670 | 39.6 | 0.0470 | 982506 | 20047 |

GeoMean: Geometric Mean
CV%: Coefficient of Variation

***SAFETY RESULTS:***

No AEs or deaths occurred in this study. No consistent changes in mean laboratory values over time were observed. All laboratory values outside the reference range were considered clinically insignificant. No clinically significant abnormal findings were reported in vital signs, physical examination, or 12-lead ECGs.

***STUDY LIMITATIONS:***

No notable study limitations were identified by the Sponsor.

**CONCLUSION(S):**

Plasma concentrations of rilpivirine, tenofovir, and emtricitabine reached $C_{max}$ at 4.0, 2.0, and 2.5 hours postdose (median), and then declined with a mean $t_{1/2}$ of 35.1, 22.2, and 22.3 hours after a single oral administration of COMPLERA under fed condition in healthy Japanese adult male subjects.

A single-oral dose of COMPLERA was generally well tolerated in Japanese subjects. There were no AEs or deaths. No clinically significant findings were observed for laboratory results (hematology, biochemistry, and urinalysis), vital signs, physical examination, or 12-lead ECGs.

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