SYNOPSIS

Name of Sponsor/Company	Janssen Pharmaceutical K.K.
Name of Finished Product	EDURANT tablets
Name of Active Ingredient	TMC278 (rilpivirine)

Status: Final

Date: 21 AUG 2013

Prepared by: Janssen Pharmaceutical K.K.

Protocol No.: TMC278IFD4005

Title of Study: An Open-label, Single-dose Study to Investigate the Pharmacokinetics and Safety of TMC278 After Oral Administration of TMC278 25 mg Tablet Under Fed Condition in Healthy Japanese Adult Male Subjects

NCT No.: NCT01804244

Principal Investigator: Yoichiro Ogama, MD, PhD

Study Center: Medical Co. LTA Sumida Hospital

Publication (Reference): Not applicable

Study Period: 19 February 2013 (date of first subject enrolled [informed consent]) to 22 March 2013 (date of last observation for last subject); 7 May 2013 (database lock)

Phase of Development: Phase 4

Objectives:

Primary objective

To evaluate the pharmacokinetics (PK) of TMC278 after a single oral dose of TMC278 25 mg tablet (27.5 mg as the hydrochloride salt) under fed condition in healthy Japanese adult male subjects.

Secondary objective

To evaluate safety after a single oral dose of TMC278 25 mg tablet under fed condition in healthy Japanese adult male subjects.

Hypothesis:

No formal statistical hypothesis testing was planned for this study. This study was designed only to collect plasma TMC278 PK profiles in healthy Japanese adult male subjects, not to explore or generate any hypotheses.

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 26 days (Day -28 to Day -3), an inpatient phase from Day -2 to Day 8, and a follow-up assessment phase on Day 15 (±2 days) or at the time of early withdrawal.

Subjects who met the selection criteria were admitted to the investigational institute 2 days before receiving the study drug (Day -2). All enrolled subjects received a single oral dose of one TMC278 25 mg

tablet on Day 1 within 10 minutes after completion of a standardized breakfast. Enrolled subjects remained in the investigational institute for the entire duration of the inpatient phase. Subjects were discharged on Day 8 after the completion of all required assessments. Serial blood samples for determination of plasma concentrations of TMC278 were collected over a period of 168 hours (7 days).

Standardized Breakfast

Japanese breakfast. Total energy was approximately 450 kcal, with percentages of energy from carbohydrates, protein, and fat of about 60%, 15%, and 25%, respectively.

Number of Subjects (planned and analyzed):

Eight subjects were enrolled to ensure that at least 6 subjects completed the planned collection of PK samples. All of the 8 subjects completed the study and were included in the safety and PK analysis population (Table 1).

Table 1: Subject Disposition and Number of Subjects Per Analysis Set; Safety

		Number of subjects
Total number of subjects who were administered the study drug		8
	Completed	8
	Discontinued after administration	0
Evaluable subjects		
	PK analysis set	8
	Safety analysis set	8
Subjects excluded from analysis set		
	PK analysis set	0
	Safety analysis set	0

Cross-reference: Attachment TSIDISP

Diagnosis and Main Criteria for Inclusion:

Healthy Japanese men aged 20 to 40 years, inclusive; BMI between 18.5 and 25.0 kg/m^2, inclusive; body weight of at least 50 kg.

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

TMC278 25 mg tablet containing 25 mg of TMC278 as the hydrochloride salt (27.5 mg). The batch number of the TMC278 25 mg tablet was 0002A.

The TMC278 25 mg tablet was taken between approximately 9:00 AM and 10:00 AM within 10 minutes after completion of a standardized breakfast as an oral dose with 150 mL of noncarbonated water and was swallowed whole, not chewed, divided, dissolved, or crushed.

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

Duration of Treatment:

The maximum study duration for each subject was 45 days, including the screening phase, inpatient period, and follow-up visit. If it was considered necessary, the study duration could be prolonged for additional follow-up.

Criteria for Evaluation:

Pharmacokinetics

Venous blood samples (4 mL each) were collected for the measurement of plasma TMC278 concentrations at the following time points:

Predose, 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 16, 24, 48, 72, 120, and 168 hours postdose.

The PK parameters determined for each subject included (but were not limited to) the following: maximum plasma concentration (C_{max}), time to reach the maximum plasma concentration (t_{max}), area under the plasma concentration-time curve from time 0 to the last quantifiable time, calculated by linear trapezoidal summation (AUC_{last}), area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}), elimination rate constant associated with the terminal phase (λ_z), elimination half-life ($t_{1/2}$), apparent total body clearance of drug at the terminal phase after extravascular administration (CL/F), and apparent volume of distribution at the terminal phase after extravascular administration (Vd_z/F), estimated by non-compartmental analysis using WinNonlin® (Version 6.2.1).

Safety

Safety was evaluated throughout the study by examining incidence, severity, type of adverse events (AEs), changes in clinical laboratory results (hematology, biochemistry, and urinalysis), vital signs, physical examinations, and 12-lead ECGs.

Statistical Methods:

Sample Size Determination

Eight subjects were enrolled in the study to ensure that at least 6 subjects completed the study assessments up to Day 8. Based on a previous study (TMC278-TiDP38-C145), the intersubject coefficients of variation (CVs) for AUC_{last} and C_{max} of a single dose of TMC278 were estimated to be less than or equal to 42% in healthy non-Japanese adult subjects. Using an estimate of approximately 42% for intersubject CVs and a sample size of 6 subjects, the true mean AUC_{last} and C_{max} of TMC278 were estimated to be within 72% to 139% of the observed geometric means with 95% confidence.

Subject Information

For all subjects who had received at least one dose of study drug, 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

For all subjects with at least one available plasma TMC278 concentration, plasma TMC278 concentration data were tabulated. Individual plasma TMC278 concentration-time profiles were visually presented.

All subjects who completed the treatment with sufficient TMC278 plasma concentration data for the estimation of the PK parameters were included in the PK analysis population. Descriptive statistics (eg, number of collected data, mean, standard deviation, median, minimum, maximum, CV) of plasma TMC278 concentration data at each time point were reported. Mean plasma TMC278 concentration-time profile data was visually presented on a linear scale.

PK parameters of plasma TMC278 were estimated using a non-compartmental analysis method with WinNonlin® (Version 6.2.1). Individual and descriptive statistics of plasma PK parameters of TMC278 were tabulated.

Safety

All subjects who received at least one dose of the study drug were included in the safety analysis.

Baseline laboratory evaluations, vital signs, and ECG measurements 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 37 years, inclusive, 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 are shown in Table 2.

Table 2: Summary of Plasma Pharmacokinetic Parameters After a Single Oral Dose of TMC278 25 mg Under Fed Condition (Number of Subjects=8)

Parameters (unit)	C_{max} (ng/mL)	t_{max} (h)	AUC_{last} (ng·h/mL)	AUC_{∞} (ng·h/mL)	$t_{1/2}$ (h)	λ_z (1/h)	Vd_z/F (L)	CL/F (L/h)
Mean	144.3	4.50	4,246	4,542	43.0	0.01695	397.4	6.389
SD	49.660	1.20	1,911.8	2,001.2	10.9	0.0038610	183.32	2.3964
Minimum	91.3	2.00	2,513	2,574	31.7	0.0109	178	3.27
Median	129.0	5.00	3,565	3,840	39.2	0.01770	361.6	6.559
Maximum	244	6.00	7,287	7,653	63.4	0.0219	665	9.71
%CV	34.4		45.0	44.1	25.4	22.8	46.1	37.5
Geo Mean	137.8		3,917	4,199	41.9	0.01654	360.1	5.954

h = hour(s), Geo Mean = geometric mean.
Cross-reference: Attachment TPKPARAM

Safety Results:

No death, serious adverse event (SAE), or withdrawal from the study due to an AE occurred in this study (Table 3).

Table 3: Subjects With Adverse Events/Reactions

	TMC278 25 mg (N=8)	
	N	(%)
One or more AEs	0	(0)
One or more SAEs	0	(0)
Deaths	0	(0)
Treatment stopped due to AEs	0	(0)

N = Number of subjects.
Cross-reference: Attachment TSFAE01

No consistent changes in mean laboratory values over time were observed. All laboratory values outside the reference range were considered clinically insignificant by the investigator.

One subject experienced a change in QT corrected according to Bazett's formula (QTcB) from baseline of >30 ms at 24 hours postdose. The finding was considered not clinically relevant. No other abnormal findings were reported in 12-lead ECGs, physical examination, and vital signs.

Study Limitations:

No notable study limitations were identified by the sponsor.

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