Title: A Phase 1, Randomized, Open-Label, Single-Center, Single-Dose, Two-Period Two Part Crossover Study in Healthy Subjects to Compare the Bioavailability of Dexlansoprazole from Dexlansoprazole Delayed-Release Capsules 30 mg and 60 mg Manufactured by Takeda GmbH Plant Oranienburg Relative to Dexlansoprazole Delayed-Release Capsules 30 mg and 60 mg Manufactured by Takeda Pharmaceutical Company Limited Osaka Plant

NCT Number: NCT03131895

SAP Approve Date: 28 June 2017

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-390MR-1001

A Phase 1, Randomized, Open-Label, Single-Center, Single-Dose, Two-Period Two Part Crossover Study in Healthy Subjects to Compare the Bioavailability of Dexlansoprazole from Dexlansoprazole Delayed-Release Capsules 30 mg and 60 mg Manufactured by Takeda GmbH Plant Oranienburg Relative to Dexlansoprazole Delayed-Release Capsules 30 mg and 60 mg Manufactured by Takeda Pharmaceutical Company Limited Osaka Plant

Phase 1 Bioequivalence Study of Dexlansoprazole Capsules from Two Manufacturing Plants

Version**:** Final

Date**:** 28 June 2017

Based on:

Protocol Version: Protocol Amendment 02

Protocol Date: 6 June 2017

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

%CV	percent coefficient of variation
λ_z	terminal disposition rate constant
AE	adverse event
ANOVA	analysis of variance
AUC_∞	area under the plasma concentration-time curve from time 0 to infinity
AUC_t	area under the plasma concentration-time curve from time 0 to the time of last quantifiable concentration
BMI	body mass index
C_{max}	maximum observed plasma concentration
CI	confidence interval
CL/F	apparent clearance after extravascular administration
ECG	electrocardiogram
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Drug Regulatory Activities
PK	pharmacokinetic(s)
PT	preferred term
PTE	pretreatment event
SD	standard deviation
SAE	serious adverse event
SI	International System of Units
SOC	system organ class
$t_{1/2z}$	terminal elimination half-life
t_{max}	time to reach C_{max}
TEAE	treatment-emergent adverse event
Vz/F	apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration.
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

- To assess the bioavailability (BA) of dexlansoprazole from a 30 mg capsule manufactured at TOB relative to that of dexlansoprazole from a 30 mg capsule manufactured at TPC.
- To assess the BA of dexlansoprazole from a 60 mg capsule manufactured at TOB relative to that of dexlansoprazole from a 60 mg capsule manufactured at TPC.

4.2 Additional Objectives

- To evaluate the safety and tolerability of dexlansoprazole following oral administration of a single 30 mg or 60 mg dexlansoprazole capsule.

4.3 Study Design

This is a phase 1, randomized, open-label, single-center, single-dose, 2-part, 2-way crossover study in healthy subjects to assess the BA of 30 or 60 mg dexlansoprazole capsules manufactured at TOB relative to the corresponding 30 or 60 mg dexlansoprazole capsules manufactured at TPC. The study will be conducted in 2 parts. In Part 1, 52 healthy subjects will receive dexlansoprazole 30 mg capsules manufactured by TOB and TPC in a crossover fashion. In Part 2, an additional 52 healthy subjects will receive dexlansoprazole 60 mg capsules manufactured by TOB and TPC in a crossover fashion. Due to the difference between the Granules-L used in the 30 mg (Granules-LL) and 60 mg (Granules-LS) capsules, the relative BA of both dosage strengths will be assessed. If BE is not achieved with the first TOB formulation, the study may be repeated for one or both dose strengths in new subjects who will receive the same TOB formulation or a different TOB formulation. The same study design will be used if additional formulation assessments are needed.

At Check-in (Day -1 of Period 1), approximately 104 subjects in total (52 in Part 1, 52 in Part 2), including both men and women, aged 18 to 55 years, inclusive, will be selected to participate in the study. Subjects who satisfy the Screening evaluation and selection criteria may be enrolled in the study. For each part, eligible subjects will be randomized on Day 1 of Period 1 in a 1:1 ratio to 1 of 2 sequences, which defines the order in which they will receive dexlansoprazole regimens in Periods 1 and 2. The dosing between periods will be separated by a minimum 5-day washout interval. During Periods 1 and 2, blood samples will be collected over 24 hours postdose to measure dexlansoprazole plasma concentrations.

The treatment sequences are outlined in Table 4.a (Part 1) and Table 4.b (Part 2).

Table 4.a Part 1 Sequences

Sequences	Number of Subjects	Period 1	Period 2
1	26	A	B
2	26	B	A

Regimen A (test): A single dexlansoprazole 30 mg capsule manufactured at TOB administered orally on Day 1 following a 10-hour fast.
Regimen B (reference): A single dexlansoprazole 30 mg capsule manufactured at TPC administered orally on Day 1 following a 10-hour fast.

Table 4.b Part 2 Sequences

Sequences	Number of Subjects	Period 1	Period 2
3	26	C	D
4	26	D	C

Regimen C (test): A single dexlansoprazole 60 mg capsule manufactured at TOB administered orally on Day 1 following a 10-hour fast.
Regimen D (reference): A single dexlansoprazole 60 mg capsule manufactured at TPC administered orally on Day 1 following a 10-hour fast.

In each period of each part, subjects will be confined from Check-in Day -1 until all study procedures have been completed on Day 2. Study drug will be administered on Day 1 of each period at approximately 0800 hours, following a 10-hour fast. Dosing may be staggered to help facilitate logistics at the site. Subjects will be instructed to swallow the intact capsule with 240 mL of water. On Day 1 of each period, breakfast will not be served. During Periods 1 and 2, blood samples will be collected over 24 hours postdose to measure dexlansoprazole plasma concentrations.

A blood sample for pharmacogenomics (PGx) will also be collected on Day 1 of Period 1. The cytochrome P-450 (CYP)2C19 isozyme is a polymorphic enzyme that is involved in the metabolism of dexlansoprazole. A genotype test for CYP2C19 will determine the subject's metabolizer status.

Subjects will be discharged from the study site on Day 2 of each period (subjects will exit the study on Day 2 of Period 2 within each part), and the dosing between periods within each part will be separated by a minimum 5-day washout interval.

A follow-up phone call will be made 10 (±2) days post last dose of study drug to inquire for any ongoing AEs or serious adverse events (SAEs), new AEs or SAEs, and concomitant medications taken since final dose. Any spontaneously reported AEs will continue to be collected for 30 days after the last dose of study drug. Subjects who withdraw their consent will still be contacted for a safety follow-up call. The contact will only be recorded in their source documents and the electronic case report forms (eCRFs), according to data protection regulations.

Primary completion date will be based on the final data collection for the primary endpoint, Day 2 of Period 2. End of trial (study completion date) will be based on the final data collection date for the entire study, which is the follow-up phone call.

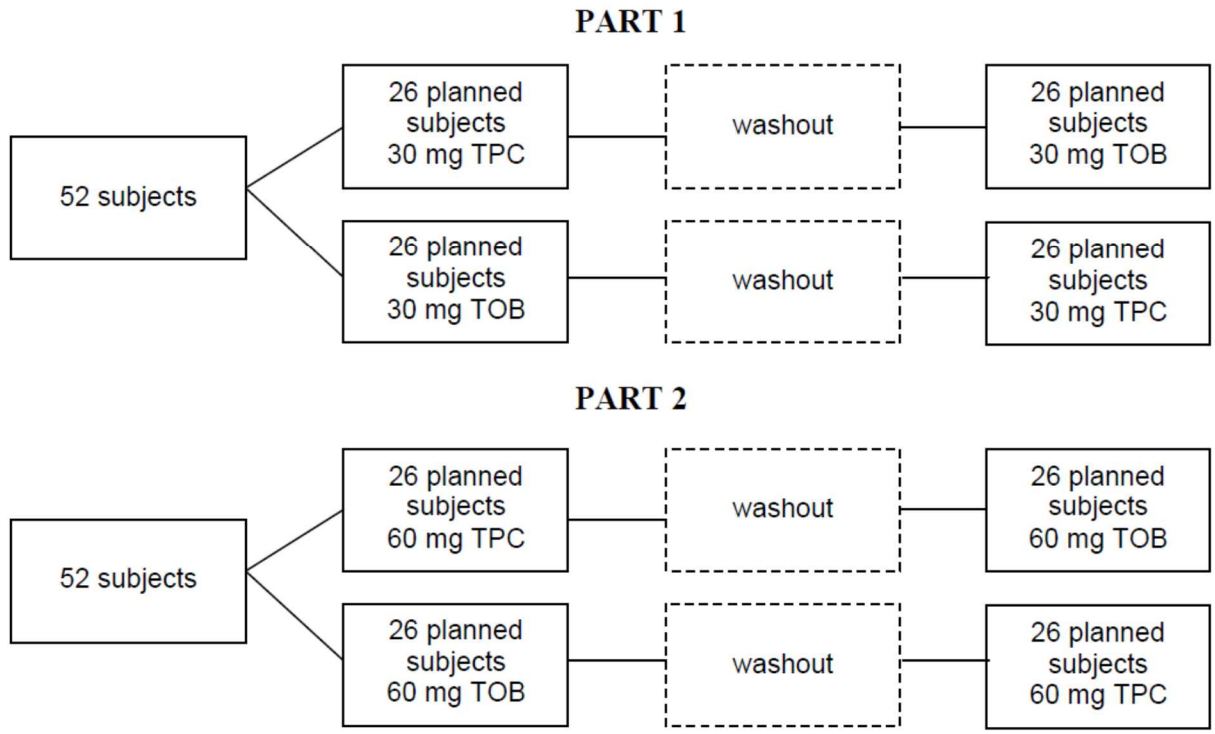
A schematic of the study design is included as Figure 4.a and Figure 4.b. A schedule of assessments is listed in Appendix A.

Figure 4.a Schematic of Study Design

Screening Period	**Check-in (Periods 1 and 2)**	**Treatment Periods 1 and 2**		**Study Exit (Period 2)**	**Follow-Up Phone Call**
		Dexlansoprazole 30 and 60 mg capsule Single Dose PK	Discharge (Period 1)		
Days -28 to -2	Day -1	Day 1	Day 2 Period 1	Day 2	Day 10±2
		←——Confinement ——→			

Note: There is a minimum 5-day washout period between the dose in Period 1 and the dose in Period 2. A follow-up phone call will be made for collection of AEs, SAEs, and concomitant medications taken since the final dose.

Figure 4.b Schematic of Crossover Design



5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The following plasma PK parameters of dexlansoprazole derived on Day 1 of each period:

- Maximum observed concentration (C_{max}).
- Area under the concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).
- Area under the concentration-time curve from time 0 to infinity (AUC_{∞}).

5.2 Additional Endpoints

- Time to first occurrence of C_{max} (t_{max}).
- Terminal disposition phase half-life ($t_{1/2z}$).
- Terminal disposition phase rate constant (λ_z).
- Apparent clearance after extravascular administration (CL/F).
- Apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F).

5.3 Safety Endpoints

Safety will be assessed by summarizing the incidence of adverse events (AEs), clinical laboratory values, physical examinations, electrocardiograms (ECGs), and vital signs.

6.0 DETERMINATION OF SAMPLE SIZE

For each part, a sample size of 52 (26 per sequence) will be used in this study. This sample size will allow for up to 6 dropouts (11.5% dropout rate) and provide 90% probability of concluding equivalence on dexlansoprazole C_{max} between the 2 regimens if the true difference between dexlansoprazole C_{max} central values from 2 regimens is no more than 5%. The power for concluding equivalence on dexlansoprazole AUC between 2 regimens would be over 90%. This sample size was based on the intrasubject variance of 0.075 for log(C_{max}) and 0.024 for log(AUC) from the TAK-390MR_107 study.

If BE is not achieved with the first TOB formulation assessed, the study may be repeated in new subjects who will receive the same TOB formulation or a different TOB formulation. The same study design will be utilized if additional formulation assessments are needed.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Continuous data will be summarized using descriptive statistics, including the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. The coefficient of variation (%CV) and geometric mean will be included in the summary of continuous data where indicated. Categorical data will be summarized as the number and percentage of subjects in each category.

Arithmetic means, geometric means, and medians will be presented to 1 more decimal place than the recorded data, and SDs will be presented to 2 more decimal places than the recorded data, where appropriate. Where applicable, confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate and p-values will be rounded to 3 decimal places prior to assessment of statistical significance.

All study-related raw data for enrolled subjects, including derived data, will be presented in data listings. In addition, the actual day relative to the first dose will be presented, where applicable.

All statistical analyses will be performed using the SAS System® Version 9.4.

7.1.1 Study Definitions

There are no study-specific definitions.

7.1.2 Definition of Study Days

Study Day 1 is defined as the date of the first dose of study drug, as recorded on the electronic case report form (eCRF) dosing page. Other study days are defined relative to Study Day 1, with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1. Study days prior to the first dose of study drug will be calculated as: {date of assessment/event – date of first dose of study drug}. Study days on or after the first dose of study drug will be calculated as: {date of assessment/event – date of first dose of study drug + 1}.The calculation of day within a period will be similar to study day but relative to the date of administration of the first dose of study drug within the period.

All protocol-specified study visit dates are defined relative to Study Day 1.

7.1.3 Definition of Study Visit Windows

There will be no visit windowing.

7.1.4 Conventions for Missing Adverse Event Dates

There will be no imputation of incomplete or missing adverse event dates.

7.1.5 Conventions for Missing Concomitant Medication Dates

There will be no imputation of incomplete or missing concomitant medication dates.

7.1.6 Conventions for Missing Data

There will be no imputation of incomplete or missing data.

Plasma concentrations that are below the lower limit of quantification (< LLOQ) will be treated as zero in the summarization of concentration values and derivation of PK parameters.

7.2 Analysis Sets

The following analysis sets will be used for analysis and presentation of the study data:

- Safety Analysis Set: The safety analysis set will consist of all subjects who are randomized and received at least 1 dose of study drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.
- Pharmacokinetic Set: The PK set will consist of all subjects who received at least 1 dose of study drug and have at least 1 measurable plasma concentration.

If any subjects are found to be noncompliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis but will be presented in the subject listings.

Number of subjects in each analysis set will be tabulated by randomization sequence and overall for each part.

7.3 Disposition of Subjects

Study Information, including date of first subject signing Informed Consent Form (ICF), date of first/last study drug, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, Medical Dictionary for Drug Regulatory Activities (MedDRA) Version, World Health Organization Drug Dictionary (WHODrug) Version, and SAS Version, will be tabulated for each part.

The eligibility of subjects will be summarized, along with the primary reasons of screen failure as recorded in eCRF.

Number of subjects randomized will be tabulated by randomization sequence (ie AB or BA, CD or DC) and overall for each part.

Disposition of all enrolled subjects will be tabulated for each part. Categories will include:

- Subjects who were randomized but not treated.
- Subjects who completed the study.
- Subjects who prematurely discontinued study.

Primary reasons for discontinuing study, as entered on the eCRF will be tabulated for each part.

7.4 Demographic and Other Baseline Characteristics

Demographic and study baseline characteristics, including age at informed consent, gender, ethnicity, race, height (cm), weight (kg), body mass index (kg/m^2), smoking status, alcohol use, caffeine/xanthine consumption, and female reproductive status, will be summarized by sequence and overall for each part.

There will be no inferential analysis of demographic and baseline characteristics.

7.5 Medical History and Concurrent Medical Conditions

Medical history is defined as significant conditions or diseases that resolved at or prior to the time of informed consent. Concurrent medical conditions are defined as significant conditions or diseases that are present at signing of informed consent.

Medical history and concurrent medical conditions will be coded using the MedDRA coding system.

Medical history and concurrent medical conditions will be listed by site and subject number.

There will be no summary or inferential analysis of medical history and concurrent medical conditions.

7.6 Medication History and Concomitant Medications

Medication history information includes any medication relevant to eligibility criteria stopped at or within 28 days prior to signing of informed consent. Concomitant medication is any drug given in addition to the study drug, taken at any time from signing of informed consent through the end of study.

Medication history and concomitant medications will be coded using the WHODrug.

Listings for medication history and concomitant medications will be produced by site and subject number.

There will be no summary or inferential analysis of medication history and concomitant medications.

7.7 Study Drug Exposure and Compliance

All doses of study medication will be administered during confinement. Dosing data, including dosing time will be provided by subject and visit in the listings.

7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

The schedule for blood samples for PK analysis of dexlansoprazole is listed in Table 7.a.

The concentration of dexlansoprazole in plasma will be summarized by regimen over each scheduled sampling time point using descriptive statistics (arithmetic mean, SD, CV%, median, minimum and maximum). Individual plasma concentration data versus time will be presented in a data listing.

In addition, the figures for mean plasma concentrations of dexlansoprazole versus time (linear and semi-log scale) will be generated.

PK parameters will be estimated using non-compartmental methods with WinNonlin® (version 6.3). Actual sampling times, rather than scheduled (nominal) sampling times, will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameter. Determination of points to be included in λ_z range will follow the Guideline for Defining, Calculating, and Summarizing Pharmacokinetic / Pharmacodynamic Parameters (EDSREP 009 R 01). All AUC values will be determined by the linear trapezoidal linear interpolation method of calculation.

Descriptive statistics (N, mean, SD, CV%, median, minimum and maximum) will be used to summarize the PK parameters for dexlansoprazole by regimen. In addition, geometric mean will be computed for AUCs and C_{max}. The PK parameters of dexlansoprazole are listed in Table 7.b.

Box plots for C_{max} and AUC_{∞} will be generated by regimen.

Table 7.a Collection of Blood Samples for Pharmacokinetic Analysis

Sample Type	Dosing Day (Periods 1 and 2)	Time (hours)
Plasma	1	Predose (within 15 minutes prior to dose) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours postdose.

Table 7.b Plasma PK Parameters

Symbol/Term	Definition
Plasma	
AUC_{last}	Area under the concentration-time curve from time 0 to time of the last quantifiable concentration.
AUC_{∞}	Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.
C_{max}	Maximum observed concentration.
CL/F	Apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration.
λ_z	Terminal disposition phase rate constant.
$t_{1/2z}$	Terminal disposition phase half-life.
t_{max}	Time of first occurrence of C_{max}.
V_z/F	Apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration.

For each part, analysis of variance (ANOVA) will be performed on natural logarithms of dexlansoprazole C_{max} and AUC with factors for sequence, the subject nested within sequence, period and regimen. The factor of the subject nested within sequence will be the error term for testing the sequence effect. Other factors will be tested with the residual as the error term. For the relative BA determination, pairwise comparisons will be performed to assess the relative BA of dexlansoprazole via point estimates and 90% confidence interval (CI) for the ratio of C_{max} and AUC central values of the dexlansoprazole 30 mg or 60 mg capsules manufactured at TOB compared with the respective dexlansoprazole 30 mg or 60 mg capsules manufactured at TPC. A conclusion of BE in the PK of dexlansoprazole between test regimen (dexlansoprazole capsule - TOB) and the reference regimen (dexlansoprazole capsule - TPC) will be reached if the 90% CIs for C_{max} and AUC are within the (0.80-1.25) interval.

All pharmacokinetic parameters calculated will be provided in a listing.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Daily meals during confinement in each period will be reported in the data listing.

7.11 Safety Analysis

Safety analyses include adverse events (AEs), clinical laboratory parameters, vital sign parameters, and 12-lead electrocardiogram (ECG) results.

All summaries of safety data are based on subjects in the Safety Analysis Set.

7.11.1 Adverse Events

A treatment-emergent adverse event (TEAE) will be defined as an AE or serious adverse event (SAE) that started or worsened after first study drug administration and within 30 days of last dose of study drug (onset date – date of last dose + 1 ≤ 30). A TEAE will be attributed to a regimen if the TEAE occurs after administration of the study drug in a period and up to just prior to study drug administration in the next period. A TEAE that occurs after administration of the study drug in the last period and up to 30 days after the last study drug dose is attributed to the regimen received in the last period. All AE verbatim terms will be coded by system organ class (SOC) and preferred term using (PT) the MedDRA coding system.

TEAEs will be summarized by regimen and overall. The tables will include the number and percentage (N [%]) of subjects reporting any event for that term. The following TEAE tables will be summarized by part.

- Overview of TEAEs.
- TEAEs by SOC and PT at subject and event level.
- Subject Mappings for TEAEs.
- TEAEs by PT.
- Most Frequent TEAEs by PT term
- Most Frequent Non-Serious TEAEs by PT term at subject and event level
- Relationship of TEAEs to Study Drug by SOC and PT.
- Drug-Related TEAEs by SOC and PT.
- Severity of TEAEs by SOC and PT.
- Severity of Drug-Related TEAEs by SOC and PT.

In addition, pretreatment events (PTEs) will be summarized overall by SOC and PT.

For each regimen and overall, subjects reporting more than one occurrence for a term (SOC or PT) being summarized will be counted only once using the most extreme incident (most severe for the severity tables and related for the relationship to study drug tables).

Most frequent TEAEs are those events occurred in at least ≥ 5% (before any rounding) of subjects in a regimen.

Data listings will be provided for all TEAEs, PTEs, TEAEs that led to study discontinuation, TEAEs that led to abnormal liver functions, SAEs, AEs that resulted in death, and AEs occurring more than 30 days after the last dose of study medication.

7.11.2 Clinical Laboratory Evaluations

Clinical safety laboratory tests include hematology, chemistry, urinalysis, and diagnostic screening. Refer to Appendix A for scheduled clinical laboratory test measurements and to Table 7.c for the list of all clinical laboratory tests.

Individual results for hematology and chemistry laboratory tests that meet the Takeda predefined laboratory markedly abnormal value (MAV) criteria in Appendix B will be presented in a data listing. If a subject has an MAV for a particular laboratory test, all visits for that subject for that parameter will be listed.

All clinical laboratory data will be presented in both SI and conventional units in the data listings. Laboratory data outside of the normal reference range will be listed. Out of normal range values and MAVs will be flagged in data listings.

Table 7.c Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBC	Alanine aminotransferase	Specific gravity
WBC with differential	Albumin	pH
Hemoglobin	Alkaline phosphatase	Protein
Hematocrit	Aspartate aminotransferase	Ketones
Platelets	Glucose	Glucose
	Total bilirubin	Bilirubin
	Total protein	Red blood cells and white blood cells
	Total cholesterol	
	Triglycerides	
	Serum creatinine	Microscopic battery (RBCs, WBCs, epithelial cells, casts) if significant findings on dipstick urinalysis
	Blood urea nitrogen	
	Uric acid	
	gamma-glutamyl transferase	
	Calcium	
	Phosphorus	
	Potassium	
	Sodium	
	Chloride	
	Bicarbonate or carbon dioxide	

Diagnostic Screenings:

Serum	Urine/Blood	Breath
Hepatitis panel, including HBsAg and anti-HCV	Drug screen, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine and opiates.	Alcohol
Women subjects only:		
Serum hCG for pregnancy		
Serum FSH *If postmenopausal women defined as amenorrhea >1 year*		

FSH=follicle stimulating hormone, hCG= human chorionic gonadotropin, RBC=red blood cells, WBC=white blood cells.

7.11.3 Vital Signs

Refer to Appendix A for scheduled vital signs measurement visits.

Individual results for vital sign measurements that meet the Takeda predefined vital signs MAV criteria in Appendix C will be presented in a data listing. If a subject has an MAV for a particular vital sign parameter, all visits for that subject for that parameter will be listed.

All vital sign data will be presented in the listings. Vital sign MAVs will be flagged in the listings.

7.11.4 12-Lead ECGs

The scheduled 12-lead ECG data will be collected according to Appendix A. The ECG parameters include heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval (Fredericia's and Bazett's corrections).

Individual results for 12-lead ECG measurements that meet the Takeda predefined 12-lead ECG MAV criteria in Appendix D will be presented in a data listing. If a subject has an MAV for a particular ECG parameter, all visits for that subject for that parameter will be listed.

All ECG data will be presented in the listings. ECG MAVs will be flagged in the listings.

7.11.5 Other Observations Related to Safety

Physical examination information will be presented in the listings. No summary tables will be provided.

All cases of overdose will be listed.

Follow-up phone call information will be listed.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

None.

8.0 REFERENCES

1. A Phase 1, Randomized, Open-Label, Single-Center, Single-Dose, Two-Period Two Part Crossover Study in Healthy Subjects to Compare the Bioavailability of Dexlansoprazole from Dexlansoprazole Delayed-Release Capsules 30 mg and 60 mg Manufactured by Takeda GmbH Plant Oranienburg Relative to Dexlansoprazole Delayed-Release Capsules 30 mg and 60 mg Manufactured by Takeda Pharmaceutical Company Limited Osaka Plant. Protocol No. TAK-390MR-1001 Amendment 02, dated 6 June, 2017.

Appendix A Schedule of Study Procedures

Study Day:	Pretreatment Period	Treatment Periods 1 and 2 (a)			Study Exit (Day 2 of Period 2)/ Early Termination Visit	Follow-up Phone Call (d)
	Days -28 to -2 (screening) (b)	Day -1 (Check-in)	Day 1 (c)	Day 2		
Confinement		X	X	X (e)	X (f)	
Informed consent	X					
Inclusion/exclusion criteria	X	X (g)				
Demographics and medical history	X					
Medication history	X					
Physical examination	X	X			X	
Height, Weight, and BMI (h)	X					
Vital signs (i)	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X
Concurrent medical conditions	X					
Clinical laboratory tests (j)	X	X		X	X	
Hepatitis panel	X					
Pregnancy test (hCG) (k)	X	X			X	
FSH (l)	X					
Urine drug screen	X	X				
ECG (m)	X	X		X	X	
Administration of study drug (n)			X			
PGx DNA sample collection (o)			X			
PK blood collection (p)			X	X	X (q)	
AE assessment (r)	X	X	X	X	X	X

Footnotes are on last table page.

(a) There will be at least 5 days between the dose in 1 period and the dose in a subsequent period.
(b) Screening procedures must be performed within 28 days prior to administration of investigational product.
(c) Day 1 of each treatment period.
(d) Follow-up phone call will be made 10±2 days after last dose of study drug to inquire about any TEAE or SAEs, and concomitant medications taken since final dose. Any TEAE/SAE spontaneously reported within 30 days postdose will be included within the database as a TEAE.
(e) Following study procedure completion on Day 2 of Period 1, subjects will be discharged from the clinic to begin the washout period.
(f) Following study procedure completion on Day 2 of Period 2, subjects will be discharged from the clinic. Early termination procedures are explained in Section 9.3.6.
(g) Assessment of inclusion and exclusion criteria will be done on Day -1, Period 1 only.
(h) The BMI is calculated using metric units as follows: Metric: BMI = weight (kg)/[height (m)]^2.
(i) Vital signs: oral body temperature, sitting blood pressure (after resting 5 minutes), respiratory rate, and pulse (beats per minute) at Screening. Only blood pressure and pulse will be collected on Check-in (Day -1) through Day 2 of each period prior to dose and 8 hours postdose, or if the subject terminated early from study. When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 30 minutes before or after the scheduled blood draw.
(j) Hematology, serum chemistries, and urinalysis tests. Clinical laboratory samples will be collected after a minimum of an 8 hour fast on Screening, Check-in (Day -1) of Periods 1 and 2; Day 2 of Period 1, and Study Exit (Day 2 of Period 2)/Early termination. If an 8-hour fast is not possible at Early termination, laboratory samples will still be collected.
(k) A serum pregnancy test will be done at Screening and Day -1 of each period, Study Exit (Day 2 of Period 2), or if a subject prematurely terminates from the study.
(l) For women where menopause is suspected (see Section 9.1.9).
(m) ECG performed at Screening, Check-in (Day -1 of Period 1), and Study Day 2 of each period, or if a subject terminates early from the study.
(n) Study drug will be administered on Day 1 of each period at approximately 0800 hours, following a 10-hour fast. Dosing may be staggered to help facilitate logistics at the site.
(o) One 6 mL whole-blood sample will be collected for DNA analysis prior to dosing on Day 1 of Period 1 only.
(p) Blood samples for PK obtained predose (within 15 minutes prior to dose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours post Day 1 dosing in each period.
(q) The PK sample should not be collected at the Early Termination Visit if a PK collection is not scheduled.
(r) Pretreatment AEs will be captured immediately following the signing of the informed consent at Screening until dosing on Day 1 of Period 1. The routine collection of AEs will continue after dosing through the follow-up phone call.

Appendix B Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	< 0.8 × LLN	> 1.2 × ULN
Hematocrit	Both	< 0.8 × LLN	> 1.2 × ULN
RBC count	Both	< 0.8 × LLN	> 1.2 × ULN
WBC count	Both	<0.5 x LLN	>1.5 x ULN
Platelet count	Conventional	$<75 \times 10^3/\mu L$	$>600 \times 10^3/\mu L$
	SI	$<75 \times 10^9/L$	$>600 \times 10^9/L$

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	≥3x ULN
AST	Both	--	≥3x ULN
GGT	Both	--	≥3x ULN
Alkaline phosphatase	Both	--	≥3x ULN
Total bilirubin	Conventional	--	>2.0 mg/dL
	SI	--	>34.2 μmol/L
Albumin	Conventional	<2.5 g/dL	--
	SI	<25 g/L	--
Total protein	Both	<0.8x LLN	>1.2x ULN
Creatinine	Conventional	--	>2.0 mg/dL
	SI		>177 μmol/L
Blood urea nitrogen	Conventional		>30 mg/dL
	SI		>10.7 mmol/L
Sodium	Conventional	<130 mEq/L	>150 mEq/L
	SI	<130 mmol/L	>150 mmol/L
Potassium	Conventional	<3.0 mEq/L	>6.0 mEq/L
	SI	<3.0 mmol/L	>6.0 mmol/L
Glucose	Conventional	< 50 mg/dL	>350 mg/dL
	SI	< 2.8 mmol/L	>19.4 mmol/L
Chloride	Conventional	< 75 mEq/L	>126 mmol/L
	SI	< 75 mmol/L	>126 mmol/L
Bicarbonate	Conventional	< 8.0 mEq/L	
	SI	< 8.0 mmol/L	
Phosphorous	Conventional	< 1.6 mg/dL	>6.2 mg/dL
	SI	< 0.52 mmol/L	>2.000 mmol/L
Total Cholesterol	Conventional	--	>300 mg/dL
	SI	--	>7.72 mmol/L
Triglycerides	Both	--	>2.5x ULN
		--	

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix C Criteria for Abnormal Changes from Baseline of Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	bpm	<50	>120
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	^{o}C	< 35.6	>37.7

Appendix D Criteria for Markedly Abnormal Values for the 12-Lead ECG Parameters

Parameter	Lower Criteria	Upper Criteria
Heart rate	<50 beats per minute	>120 beats per minute
QT Interval	≤50 milliseconds	≥460 milliseconds
QTcB Interval	≤50 milliseconds	≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds
QTcF Interval	≤50 milliseconds	≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
Personal Protected Data	Statistical Approval	28-Jun-2017 19:56 UTC
	Pharmacovigilance Approval	28-Jun-2017 20:01 UTC
	Clinical Pharmacology Approval	28-Jun-2017 20:16 UTC
	Clinical Science Approval	29-Jun-2017 00:40 UTC