Title: A Phase 1, Single-Center, Open-Label, 2-Arm Parallel Group, Single-Dose Study to Evaluate the Pharmacokinetics of Dexlansoprazole 30 mg and 60 mg Delayed-Release Capsules in Healthy Chinese Subjects

NCT Number: NCT03316976

SAP Approve Date: 22 March 2018

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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.

TAKEDA DEVELOPMENT CENTER

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-390MR_106

A Phase 1, Single-Center, Open-Label, 2-Arm Parallel Group, Single-Dose Study to Evaluate the Pharmacokinetics of Dexlansoprazole 30 mg and 60 mg Delayed-Release Capsules in Healthy Chinese Subjects

Phase 1 Dexlansoprazole PK Study in Healthy Chinese Subjects

Version**:** Final

Date**:** 22 March 2018

SPONSOR APPROVAL PAGE

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Version: Final

Date: 22 March 2018

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Date: _____

Date: _____

Date: _____

Date: _____

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

λ_z	terminal disposition phase rate constant
AE	adverse event
AUC	area under the plasma concentration-time curve
AUC_{last}	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
BMI	body mass index
bpm	beats per minute
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed concentration
CS	clinically significant
CYP	cytochrome P450
ECG	electrocardiogram
FSH	follicle stimulating hormone
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
MedDRA	Medical Dictionary for Regulatory Activities
NCS	not clinically significant
PK	pharmacokinetics
PT	preferred term
PTE	pretreatment event
SAE	serious adverse event
SOC	system organ class
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
V_z/F	volume of distribution during the terminal disposition phase after extravascular administration
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of this study is to assess the PK after a single dose of dexlansoprazole 30 and 60 mg delayed-release capsules in healthy Chinese subjects.

4.2 Secondary Objectives

The secondary objective of this study is to evaluate the safety and tolerability of dexlansoprazole following oral administration of a single 30 or 60 mg dexlansoprazole delayed-release capsule.

4.3 Study Design

This is a phase 1, open-label, single dose, 2-arm parallel study to assess the PK of a single oral dose of dexlansoprazole 30 and 60 mg delayed-release capsules. Forty subjects will be enrolled in the study, 20 subjects in Group 1 and 20 subjects in Group 2 (Table 4.a).

Table 4.a Parallel Groups

Group	Regimen
1	A single oral dose of dexlansoprazole 30 mg delayed-release capsule
2	A single oral dose of dexlansoprazole 60 mg delayed-release capsule

A schematic of the study design is included as Figure 4.a.

Figure 4.a Schematic of Study Design

Pretreatment Period		Treatment Period		Follow-Up
Screening	Check-in	Dexlansoprazole Delayed-Release Capsule Single Dose (30 or 60 mg)	Discharge/Study Exit/Premature Termination	Follow-up Site/ Telephone Visit
Days -28 to -2	Day -1	Day 1	Day 2	5 to 10 days postdose
	←——Confinement to Clinic——→			

Note: A follow-up site/telephone visit will be made for collection of adverse events, serious adverse events, and concomitant medications taken since final dose.

Subjects will fast for a minimum of 8 hours prior to dosing. On Day 1, breakfast will be served 1 hour postdose. Subjects may consume water ad libitum except for 1 hour before and 1 hour after drug administration. Dosing will commence at approximately 8:00 am on Day 1. Study drug will be administered with 240 mL of water. Subjects must drink all of the water provided with the dose.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

The primary endpoints for this study are the PK parameters of dexlansoprazole following a single oral dose of dexlansoprazole 30 and 60 mg delayed-release capsules:

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

5.2 Additional Endpoints

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

5.3 Safety Endpoints

Safety endpoints include treatment-related AEs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital sign measurements, electrocardiograms (ECGs), and physical examinations.

6.0 DETERMINATION OF SAMPLE SIZE

No formal sample size calculations were conducted. A sample size of 40 subjects, 20 subjects per parallel group, will be used in this study. This sample size is deemed to be sufficient for the assessment of the PK of dexlansoprazole 30 and 60 mg delayed-release capsules in the Chinese population.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Considerations

Statistical analysis will be performed using SAS® software (SAS Institute, Inc., Cary, North Carolina) Version 9.2, or later.

All study-related raw data for enrolled subjects, including derived data, will be presented in data listings. Continuous data will be summarized using number of subjects, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized using the number and percentage of subjects for each category where appropriate.

7.2 Data Handling Conventions

7.2.1 Premature Withdrawal

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded. Discontinued or withdrawn subjects will not be replaced after enrollment. All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary.

7.2.2 Handling of Missing Data

No imputation will be used for Missing data.

7.2.3 Handling of Missing/Partial Date

Completed missing start or end dates will remain missing, with no imputation applied.

Partial dates will be imputed using below convention:

- If the partial date is a start date, impute as the first day as the month (only missing day) /year (missing both month and day).
- If the partial date is an end date, impute as the last day as the month (only missing day) /year (missing both month and day).
- If the partial date is in the same month (only missing day) or same year (missing both month and day) as the study treatment, and the imputed start date of an adverse event (not pretreatment event) is prior to the start of study treatment, then the start date of study treatment will be assumed to be the start date. The AE will then be considered as start on treatment (worst case scenario).

The recorded partial date will be displayed in the listings.

7.2.4 Definition of Baseline and Change from Baseline

Baseline is defined as the last non-missing measurement prior to first dose of study drug.

The change from baseline will be calculated by subtracting the baseline values from the individual post-baseline values. If either the baseline or post-baseline value is missing, the change from baseline is set to missing as well.

7.2.5 Definition of Study Days

Study day will be calculated relative to the date of the first dose of study drug in the study. The study day prior to the first dose of study drug will be calculated as:

Date of assessment/event – date of first dose of study drug

The study day 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.

AEs that start more than 30 days after the last dose of study drug will be listed, but excluded from the summaries and analyses.

7.3 Analysis Sets

Enrolled Subjects Set (EPS): All enrolled subjects who are enrolled will be included, which will be used in the analysis of disposition, medical history, protocol deviation, etc.

Safety Analysis Set (SS): All subjects who are enrolled in the study and take at least 1 dose of study drug will be included, which will be used in the demographic summary and safety data analysis.

PK Analysis Set (PAS): All subjects who receive at least 1 dose of study drug and have at least 1 measureable plasma concentration of dexlansoprazole will be included, which will be used in PK data analysis.

7.4 Disposition of Subjects

Disposition of all screened subjects will be tabulated (count and percent). Primary reasons for screen failure will be summarized and will be presented in a data listing. There will be no inferential analysis of subject disposition data.

Disposition of all enrolled subjects will be tabulated by dexlansoprazole dose groups and overall:

- All subjects received at least one dose of study drug.
- Subjects who completed the study.
- Subjects who prematurely discontinued study.

Primary reasons for discontinuation of study, as entered on the electronic case report form (eCRF), will be tabulated. The date of first dose, date of last dose, duration of treatment and the reason for premature discontinuation of study drug/study visit will be presented for each subject in listings.

7.5 Protocol Deviation

A summary of the number and percentage of subjects with a significant protocol deviation by type of deviation will be provided using enrolled subjects set by dexlansoparzole dose groups and overall. Individual subject listings of significant protocol deviations will be provided.

7.6 Demographic and Baseline Characteristics

Demographic and baseline characteristics variables will be summarized by dose group and overall using the safety analysis set.

For continuous variables (age, weight, height, and body mass index [BMI]), summary statistics will be generated.

For categorical variables (gender, ethnicity, race, smoking status of the subject at Screening, caffeine consumption and alcohol history), the number and percentage of subjects in each category will be presented.

7.7 Medical History and Concurrent Medical Conditions

Medical history include any significant conditions or diseases that stopped at or prior to signing of informed consent. Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed.

Medical history and concurrent medical conditions will be presented in a data listing only.

7.8 Medication History and Concomitant Medications

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 28 days prior to signing of informed consent. Concomitant medications are recorded on the eCRF and include any medications, other than study drug, taken at any time between informed consent and the end of the study. They may be prescribed by a physician or obtained by the subject over the counter.

All medication history and concomitant medications will be coded by therapeutic classification, sub-classification, and medication using the World Health Organization Drug Dictionary (WHO Drug).

All medication history and concomitant medications will be listed by site (study center) and subject number. The listings will contain subject identifier, treatment, World Health Organization Drug Dictionary (WHODrug) preferred medication name, dose, unit, frequency, route, start date, stop date, whether the medication was ongoing, and reason for use. No summary or inferential statistics will be presented.

7.9 Study Drug Exposure and Overdose

Study drug administration and overdose information will be listed. Standard meal information will also be presented. Summaries of PK data will be provided by dose group. No other summary statistics for the extent of exposure to study drug or compliance calculations will be performed for this study.

7.10 Pharmacokinetic Analysis

All PK summaries will be based on the PK set. PK parameters of dexlansoprazole will be derived using non-compartmental analysis methods. They will be determined from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

Serial blood samples for determination of dexlansoprazole concentrations will be collected on Day 1 (within 30 minutes before dosing) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours post dose. The concentration of dexlansoprazole in plasma will be summarized by scheduled sampling time points and dose group using descriptive statistics. Individual plasma concentration data will be presented in a data listing. Subject phenotypes will be listed with the concentrations.

The PK parameters of dexlansoprazole will be determined below from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be calculated:

Symbol/Term	Definition
Plasma	
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity.
C_{max}	Maximum observed concentration.
CL/F	Apparent clearance after extravascular administration.
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.

Descriptive statistics (number of subjects, arithmetic mean, SD, %CV, median, minimum and maximum) by dose groups will be provided for dexlansoprazole plasma PK parameters. Geometric means will be calculated for Cmax and AUCs. Individual plasma PK parameters will be presented in a data listing. Subject phenotypes will be listed with the PK parameters.

No inferential statistical analysis will be performed. Additional summaries by phenotypes may be performed if there are sufficient number of subjects for each phenotype. More information please refer to separate clinical pharmacology analysis plan (CPAP).

7.11 Safety Analysis

All safety analyses will be performed using the safety analysis set.

7.11.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug. All AEs will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Agencies (MedDRA 20.0).

A treatment-emergent adverse event (TEAE) will be defined as an AE that starts or worsens on or after Study Day 1 (defined as day first dosed), and no more than 30 days after the last dose of study drug (onset date – last date of dose +1≤30).

In an TEAE overview table, the number and percentage of subjects who experience AEs, TEAEs, TEAEs by severity and relationship, SAEs, discontinued from study treatment due to an AEs, death will be summarized by dose groups and overall.

In addition, the number and percentage of subjects with AEs will be summarized in several different tables:

- All TEAEs by system organ class (SOC) and preferred term (PT).
- TEAE by PT.
- Most frequent TEAEs (>5% or >2 subjects in any dose group).
- Most frequent non-serious TEAEs (>5% or >2 subjects in any dose group).
- Drug-related TEAEs by SOC and PT.
- Relationship to study drug for all TEAEs by SOC and PT (related vs not related).
- All SAEs by SOC and PT.
- Severity of all TEAEs by SOC and PT (mild, moderate, or severe).
- Severity of drug-related TEAEs by SOC and PT (mild, moderate, or severe).

A subject with 2 or more AEs within the same level of the MedDRA term will be counted only once in that level using the most extreme incident (most severe for the severity tables and related for the relationship to study drug tables).

Additionally, treatment-emergent serious adverse events, deaths, and TEAEs resulting in premature discontinuation from study drug will be listed.

A pretreatment event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug.

Data listings will be provided for all AEs including PTEs, TEAEs, AEs leading to study drug discontinuation, and SAEs.

7.11.2 Physical Examination

The physical examination findings will be presented in data listings.

7.11.3 Clinical Laboratory Evaluations

All laboratory test parameters will be displayed in individual subject data listings in both SI units and conventional (CV) units. For test results not in SI units, the conversion to SI units will be done in the derived analysis datasets using the known conversion factors. If necessary, SI units from the central laboratory may be converted to Takeda's preferred SI units in the derived analysis datasets. All summaries will be based on the values using these preferred SI units.

Clinical laboratory values (hematology, serum chemistry, and urinalysis) will be summarized (N, mean, SD, median, minimum, and maximum) by dose group using descriptive statistics for baseline, postdose, and change from baseline to postdose values. Only observations within 7 days of the last dose of study drug will be included in the summaries. No inferential statistics will be presented unless otherwise stated.

A table with predefined criteria for markedly abnormal values for laboratory variables (Appendix A) will be presented. If a subject has a MAV for a particular laboratory test, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 postdose markedly abnormal laboratory test result will be summarized. The mapping of the subjects who meet the MAV criteria will be listed as a table. All observations, including ones at unscheduled visits, will be included in the MAV evaluation and summaries.

All clinical laboratory data will be displayed in data listing. Laboratory data outside of the normal reference range will be indicated in the listings. In addition, MAVs will be flagged. The listing will include site number, subject identifier, age, gender, treatment group, study visit, and sample collection date and time. MAV listings will be presented in the unit specified in the MAV criteria in Appendix A.

7.11.4 Vital Signs

Vital signs will include weight, oral or axillary body temperature measurement, sitting blood pressure (after 5 minutes resting), respiration rate and pulse beats per minute (bpm). Only blood pressure and pulse will be taken on Check-in (Day -1) through Day 2.

Vital signs will be summarized (N, mean, SD, median, minimum, and maximum) for each dose group by presenting descriptive statistics for baseline, postdose, and change from baseline to postdose values.

Vital signs that meet predefined markedly abnormal criteria (Appendix B) will be presented. If a subject has a MAV for a particular vital sign, all visits for that subject for that vital sign will be listed. The number and percentage of subjects with at least 1 postdose markedly abnormal vital signs measurement will be summarized. The mapping of the subjects who meet the MAV criteria will be listed as a table. All observations, including ones at unscheduled visits, will be included in the MAV evaluation and summaries.

All vital sign data will be provided in the data listings. Vital sign MAVs will be flagged in the listings. The listing will include site number, subject identifier, age, gender, treatment group, study visit, and sample collection date and time.

7.11.5 12-Lead ECGs

ECG results will be interpreted using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. Shift tables for ECG evaluation will be provided by dose groups. All ECG data will be listed in the data listings.

7.11.6 Other Observations Related to Safety

Below information will be presented in data listing:

- Child bearing potential;
- Serum FSH test;
- Pregnancy test results;
- Hepatitis results;
- HIV results;
- Urine drug screen;
- Alcohol test.

7.12 Genotype Analysis

Genotype test will be summarized by Genotype and phenotype, and Blood samples collected for genotype test will be presented in data listing.

7.13 Interim Analysis

Not applicable.

7.14 Changes in the Statistical Analysis Plan

None.

8.0 REFERENCES

1. Dexilant (dexlansoprazole) Delayed Release Capsules. Full Prescribing Information. Deerfield, IL: Takeda Pharmaceuticals America, Inc., Revised 16 January 2016.
2. Vakily M, Zhang W, Wu J, Atkinson SN, Mulford D. Pharmacokinetics and pharmacodynamics of a known active PPI with a novel dual delayed release technology, dexlansoprazole MR: a combined analysis of randomized controlled clinical trials. Curr Med Res Opin 2009;25(3):627-38.
3. Yin OQ, Tomlinson B, Chow AH, Waye MM, Chow MS. Omeprazole as a CYP2C19 marker in Chinese subjects: assessment of its gene-dose effect and intrasubject variability. J Clin Pharmacol 2004;44(6):582-9.

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

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

RBC=red blood cell, WBC=white blood cell.

Chemistry—Criteria for Markedly Abnormal Values

Parameter	Low Abnormal	High Abnormal
ALT	--	>3x ULN
AST	--	>3x ULN
GGT	--	>3x ULN
Alkaline phosphatase	--	>3x ULN
Total bilirubin	--	>2.0 mg/dL
Albumin	<2.5 g/dL	--
Total protein	<0.8x LLN	>1.2x ULN
Creatinine		>2.0 mg/dL
Blood Urea Nitrogen	--	>30 mg/dl
Sodium	<130 mEq/L	>150 mEq/L
Potassium	<3.0 mEq/L	>6.0 mEq/L
CPK	--	>5x ULN

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

Appendix B Criteria for Markedly Abnormal Values for 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 (axillary)	^{o}C	<35.6	>37.7

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
Personally Protected Data	Biostatistics Approval	22-Mar-2018 16:11 UTC
	Clinical Operations Approval	22-Mar-2018 16:37 UTC
	Pharmacovigilance Approval	23-Mar-2018 00:34 UTC
	Clinical Science Approval	23-Mar-2018 09:59 UTC