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 Following a High-Fat Meal

NCT Number: NCT03801148

SAP Approve Date: 29 January 2019

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 (PPD) information or company confidential information (CCI).

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-1002
CELERION STUDY NUMBER: CA24021

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 Following a High-Fat Meal

PHASE 1

Version: Final

Date**:** 29 January 2019

Prepared by:

PPD
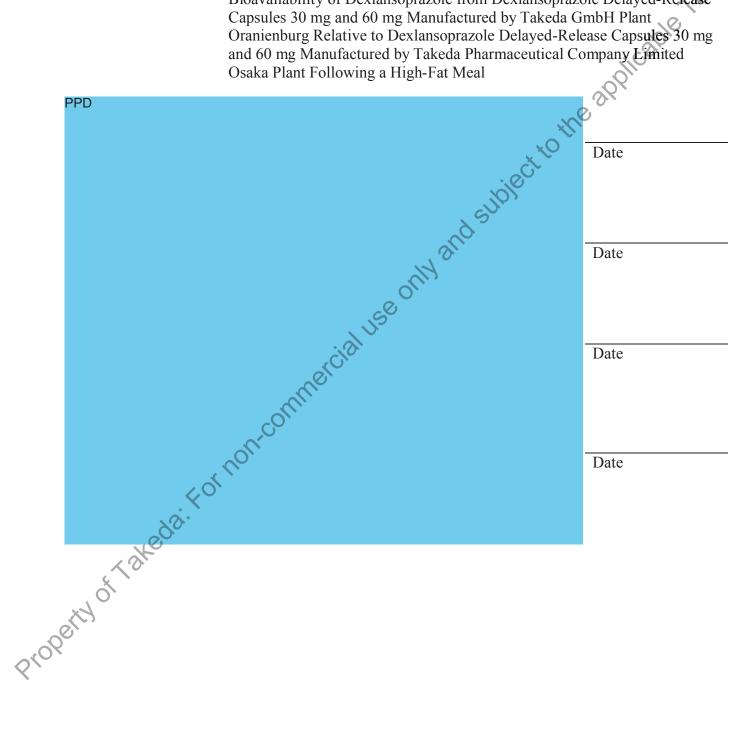
Based on:

Protocol Dated: 17 December 2018
Protocol Amendment 1: 09 January 2019

1.1 Approval Signatures

Study 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 Following a High-Fat Meal

PPD

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2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
AUC	area under the curve
AUC_∞	area under the plasma concentration-time curve from time 0 to infinity
AUC_{last}	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
C_{max}	maximum observed plasma concentration
CPAP	Clinical Pharmacology Analysis Plan
CRF	case report form
CS	clinically significant
CSR	clinical study report
CV	coefficient of variation
DMP	Data Management Plan
ECG	electrocardiogram
eCRF	electronic case report form
Geom CV	geometric coefficient of variation
Geom Mean	geometric mean
ICF	informed consent form
ICH	International Conference on Harmonisation
λ_z	Terminal disposition phase rate constant
ln	natural log
LSM	least-square means
Mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
PK	pharmacokinetics
SAE	serious adverse event
SD	standard deviation
SEM	standard error of the mean
SOC	system organ class
$t_{\frac{1}{2}z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
TFL	tables, figures and listings
t_{max}	time to first occurrence of C_{max}
WHO	World Health Organisation

4.0   OBJECTIVES

4.1   Hypothesis

A conclusion of bioequivalence (BE) in the pharmacokinetics (PK) of dexlansoprazole between test products (dexlansoprazole capsule – Takeda GmbH Plant Oranienburg (TOB)) and the reference product (dexlansoprazole capsule – Takeda Pharmaceutical Company Ltd. (TPC)) will be reached if the 90% confidence interval (CI) for the ratio of C_{max} TOB to C_{max} TPC and the 90% CI for the ratio of AUC TOB to AUC TPC are each within the (0.80, 1.25) interval.

4.2   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.

4.3   Secondary Objective

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

4.4   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 under fed conditions. The study will be conducted in 2 parts. In Part 1, 60 healthy subjects will receive dexlansoprazole 30 mg capsules manufactured by TOB and TPC in a crossover fashion. In Part 2, an additional 60 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.

At Check-in (Day -1 of Period 1), approximately 120 subjects in total (60 in Part 1, 60 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 predose and 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	30	A	B
2	30	B	A

Regimen A (test): A single dexlansoprazole 30 mg capsule manufactured at TOB administered orally on Day 1 30 minutes following the beginning of a high-fat/high calorie breakfast.
Regimen B (reference): A single dexlansoprazole 30 mg capsule manufactured at TPC administered orally on Day 1 30 minutes following the beginning of a high-fat/high calorie breakfast.

Table 4.b   Part 2 Sequences

Sequences	Number of Subjects	Period 1	Period 2
3	30	C	D
4	30	D	C

Regimen C (test): A single dexlansoprazole 60 mg capsule manufactured at TOB administered orally on Day 1 30 minutes following the beginning of a high-fat/high calorie breakfast.
Regimen D (reference): A single dexlansoprazole 60 mg capsule manufactured at TPC administered orally on Day 1 30 minutes following the beginning of a high-fat/high calorie breakfast.

Subjects were screened up to 28 days prior to dosing, to determine eligibility before randomization. Eligible subjects returned to the clinic at Check-in (Day -1).

A schematic of the study design is included as Figure 4.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 days)
		←——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 adverse events (AEs), serious adverse events (SAEs), and concomitant medications taken since the final dose.

A schematic of the crossover design is included as Figure 4.b.

Figure 4.b   Schematic

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 in the morning of Day 1 of each period 30 minutes following the beginning of a high-fat/high calorie breakfast. The entire standardized breakfast is to be consumed within 25 minutes. 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.

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).

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), as well as new AEs or SAEs, and concomitant medications taken since final dose. Subjects who received at least one dose of study drug and terminate from the study early will still be contacted for a safety follow-up call. The contact will only be recorded in their source documents and the case report forms (CRFs), 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.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

The primary endpoints of the study are the following plasma PK parameters of dexlansoprazole derived on Day 1 of each period:

- Maximum observed concentration (C_{max}).

- Area under the plasma concentration-time curve (AUC) from time 0 to time of the last quantifiable concentration (AUC_{last}).

- AUC from time 0 to infinity (AUC_∞).

5.2 Additional Endpoints

The following additional plasma PK parameters for dexlansoprazole will be calculated:

- Percent of AUC_∞ extrapolated ($AUC_{\%extrap}$).

- Time to first occurrence of C_{max} (t_{max}).

- Terminal disposition phase half-life ($t_{\frac{1}{2}z}$).

- 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 AEs, clinical laboratory values, physical examinations, ECGs, and vital signs.

6.0   DETERMINATION OF SAMPLE SIZE

For each part, a sample size of 60 (30 per sequence) will be used in this study. This sample size will allow for up to 6 dropouts (10.0% dropout rate) and provide 90% probability of concluding bioequivalence 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 95%. This sample size was based on the intrasubject variance of 0.0884 for $\log(C_{max})$ and 0.0365 for $\log(AUC)$ from the Part 1 (30 mg) of the TAK-390MR-1001 study. Part 1 was used because the intrasubject variance of $\log(C_{max})$ was higher than in Part 2 (60 mg).

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All PK analyses will be conducted using Phoenix® WinNonlin® Version 7.0, or higher. All statistical analyses will be conducted using SAS® Version 9.3, or higher. All analyses will be performed by study part separately. All data recorded on the CRF will be listed by subject. All tables, figures and listings (TFLs) shells and numbering list will be included in the Clinical Pharmacology Analysis Plan (CPAP).

Arithmetic mean (mean), median, and geometric mean (Geom Mean) values will be presented to 1 more level of precision than the individual values. Standard deviation (SD) and standard error of the mean (SEM) will be presented to 2 more levels of precision than the individual values. Minimum and maximum values will be presented to the same precision as the individual values. Arithmetic percent coefficient of variation (CV%) and geometric percent coefficient of variation (Geom CV%) will be presented to 1 decimal place.

Geometric least-squares means (LSMs) will be reported with 1 more level of precision than the recorded data. Geometric LSMs are least-squares means derived from the analysis of variance (ANOVA) model for the analyses of ln-transformed AUC_{last}, AUC_{∞}, and C_{max} which have been exponentiated to provide estimates on the original scale. The difference in the LSM on the ln-scale and associated 90% CIs will be exponentiated to produce geometric mean ratios (GMRs) and 90% CIs around the ratio and will be reported using 2 decimal places. These ratios will be expressed relative to the reference treatment (i.e., Treatments B and D, for Parts 1 and 2, respectively).

Concentration values below the limit of quantitation (BLQ) will be presented as 'BLQ' in the concentration table listings and footnoted accordingly. BLQ values will be treated as zero for the calculation of summary statistics, the generation of concentration plots, and the calculation of PK parameters, unless they are obvious outliers (e.g. BLQ value between 2 measurable values), in which case they will be treated as missing.

For the calculation of PK parameters, if actual times are missing, nominal times will be used instead.

A subject's PK parameter data will be included in the listings but excluded from the descriptive statistics and statistical evaluation if one or more of the following criteria are met:

- A predose (0 hr) concentration is greater than 5% of that subject's C_{max} value in that period.

- A subject did not meet inclusion/exclusion criteria that may have an effect on the PK (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist).

- A subject deviates substantially from the protocol defined study procedures including but not limited to dosing, dose timing, sample collection, meal timing, etc. (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist).

The details on PK parameter calculations will be outlined in the CPAP including specifics on the following:

- Insufficient data to determine a reliable $t_{1/2}$ value and other terminal disposition phase rate constant dependent parameters.

- PK parameters presented by treatment, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables.

- Concentration data presented by treatment, including the units, precision, and summary statistics that will be presented in end-of-text tables.

- Concentration data file used for PK analysis.

- PK parameter WinNonlin® output file used to generate the TFLs.

- ANOVA results presented in in-text and end-of-text tables.

- Arithmetic mean concentration-time figures presented as in-text and end-of-text figures.

- Individual concentration-time figures presented in Appendix 16.2.6.

For demographic data where appropriate, variables will be summarized descriptively by treatment sequence and overall for each part. For the categorical variables, the count and proportions of each possible value will be tabulated by treatment sequence, and overall for each part, where applicable. The denominator for the proportion will be based on the number of subjects who provided non missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, SD, minimum, median, and maximum values will be tabulated.

7.1.1 Study Definitions

7.1.2 Definition of Study Days

Day 1 for each period of each part is defined as the date on which a subject is administered their first dose of the study drug(s) in each period. Other study days are defined relative to Day 1 with Day -1 being the day prior to Day 1 of each period. Study day prior to the first dose of each treatment will be calculated as: date of assessment/event-date of treatment; study day on or after the date of first dose will be calculated as: date of assessment/event-date of treatment +1.

7.2 Analysis Sets

Safety Set:

All subjects who enrolled into the study and received at least one dose of the study drug(s) will be included in the safety set. Subjects in this analysis set will be used for demographic, baseline characteristics and safety summaries.

PK Set:

Samples from all subjects will be assayed even if the subjects did not complete the study. All subjects in the safety set who have at least 1 valid plasma concentration of dexlansoprazole will be in the PK set. All subjects who comply sufficiently with the protocol and display an evaluable PK profile (eg, exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the statistical analyses. In terms of criteria for evaluable subjects, please see CPAP.

7.3 Disposition of Subjects

For each study part, disposition of subjects (number of subjects dosed, completed the study, discontinued from the study, and reason(s) for discontinuation) will be summarized for each treatment sequence and overall. Study completion status, including reason for discontinuation, will also be listed by subject.

7.4 Demographic and Other Baseline Characteristics

For each study part, demographic and baseline characteristics will be summarized by treatment sequence and overall. Summary statistics (number of subjects [n], mean, SD, minimum, median, and maximum) will be generated for continuous variables (age [calculated from the date of signed Informed Consent Form [ICF], weight, height and body mass index [BMI]) and the number and percentage of subjects within each category will be presented for categorical variables (sex, race, and ethnicity). Height, weight, and BMI collected at screening will be used in the baseline summaries. Height will be recorded without decimals and weight will be recorded with one decimal place. BMI will be calculated using the following formula: weight (kg)/[height (m)]^2 and will be recorded with one decimal place by rounding. Demographics data will also be listed as recorded on the CRF, including the date of informed consent.

7.5 Medical History and Concurrent Medical Conditions

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or before signing the ICF. Ongoing conditions are considered concurrent medical conditions. Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing the ICF. Each subject's medical history and concurrent medical conditions will be listed. Any medical condition started after taking the study drug will be classified as an adverse event. The medical history listing will include whether the event was medical or surgical, the body system or organ class involved, start date (if known) and end date or whether the condition was ongoing, and a description of the condition or event. There will be no statistical analysis of medical history.

7.6 Medication History and Concomitant Medications

Medication history to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 28 days prior to signing the ICF. Concomitant

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medication includes any medication other than study drug taken at any time between time of signing the ICF through the end of the study (including follow-up visit). All medication history and concomitant medications recorded during the study will be coded with the World Health Organization (WHO) Dictionary, as described in the Data Management Plan (DMP), and listed. If appropriate, the listing will include the medication name, coded term, dosage, route of administration, start date and time (if known), end date and time, or whether it continued after study completion, and indication for use.

7.7 Study Drug Exposure and Compliance

Not applicable.

7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Blood samples (one 4 mL sample per scheduled time) for PK analysis of dexlansoprazole will be collected as specified in Table 7.a following administration of different formulations on Day 1 of each period of each part under fed conditions.

Table 7.a   Collection of Blood Samples for Pharmacokinetic Analysis

Sample Type	Dosing Day (Periods 1 and 2)	Time (hours)
Plasma	1	Predose (within 1 hour prior to dose) and at 1, 2, 3, 4, 5, 6, 6.5, 7, 8, 10, 12, 14, 16, and 24 hours postdose.

The actual date and time of sample collection will be recorded on the source document and electronic case report form (eCRF).

The PK parameters of dexlansoprazole will be listed in the CPAP for this study and will be determined from the concentration-time profiles for subjects in the PK set using a noncompartmental analysis method. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If actual sample times are missing, nominal times may be used.

Concentrations will be listed and summarized descriptively by PK sampling time. Summary will be done by treatment using the summary statistics listed in the CPAP. Excluded concentrations will be presented and footnoted as such in the concentration table listings, and those values will be excluded from the descriptive summary statistics. Individual subject and arithmetic mean profiles of the concentration-time data will be plotted by treatment on linear (with and without SD) and semi-log scales. For summary statistics and arithmetic mean plots by sampling time, the

nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

PK parameters will be summarized descriptively by treatment using the summary statistics listed in the CPAP. Excluded parameters will be presented and footnoted as such in the PK parameter table listings, and those values will be excluded from the descriptive summary statistics.

Relative Bioavailability (Treatments A-D)

For each study part, natural log (ln)-transformed AUC_{last}, AUC_{∞}, and C_{max} will be analyzed using an ANOVA model to assess the relative bioavailability of dexlansoprazole 30 mg or 60 mg capsules manufactured at TOB compared with the respective dexlansoprazole 30 mg or 60 mg capsules manufactured at TPC. The model will include sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. Each ANOVA will include calculation of LSM as well as the difference between treatment LSM. Geometric LSM ratios will be calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed AUC_{last}, AUC_{∞}, and C_{max}. These ratios will be expressed relative to the reference treatments (ie, Treatments B and D, for Parts 1 and 2, respectively). The following SAS® code will be used by study part for the analysis:

```
PROC MIXED DATA=XXXX;
CLASS Sequence Treatment Period Subject;
MODEL <PK_Parameter> = Sequence Treatment Period / DDFM=KR;
RANDOM Subject(Sequence);
/*For Part 1*/
ESTIMATE 'Treatment A vs B ' Treatment 1 -1 / CL ALPHA = 0.10 E;
/*For Part 2*/
ESTIMATE 'Treatment C vs D 'Treatment 1 -1 / CL ALPHA = 0.10 E;
LSMEANS Treatment;
Run;
```

Consistent with the two one-sided test, 90% CIs for the ratios will be derived by exponentiation of the CIs obtained for the difference between treatment LSM resulting from the analyses on the ln-transformed AUC_{last}, AUC_{∞}, and C_{max}. The CIs will be expressed as a ratio relative to the reference treatments (ie, Treatments B and D, for study parts 1 and 2, respectively). Bioequivalence (Treatment A versus Treatment B and Treatment C versus Treatment D) will be claimed if the 90% CIs of the ratios of geometric LSMs of PK parameters AUC_{last}, AUC_{∞}, and C_{max} of TAK-831 fall entirely within (0.80, 1.25).

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

For each study part, safety will be evaluated by the incidence of treatment-emergent adverse events (TEAEs), severity and type of TEAEs, changes from baseline in the subjects' clinical laboratory results, vital signs, and ECG's using the safety set. Reasons for discontinuation will be tabulated. All clinical safety data will be listed by subject and assessment time points, including rechecks, unscheduled assessments, and early termination, chronologically.

Continuous variables will be summarized using n, mean, SD, minimum, median, and maximum. Frequency counts and percentages will be reported for categorical data when appropriate. Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

7.11.1 Adverse Events

For each study part, all AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, severity (mild, moderate or severe), relationship to study drug (s) (related or not related), action relative to the study drug(s), and procedures. All AEs occurring during this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), as described in the DMP. However, only TEAEs occurring after administration of the first dose of study drug and through the end of the study (approximately 10 (± 2) days after the last dose of investigational product administration) will be summarized. A TEAE is defined as an AE that is starting or worsening at the time of or after study drug administration.

For each study part and treatment, TEAEs will be coded using MedDRA® and tabulated by System Organ Class (SOC) and Preferred Term. Summary tables will include number of subjects reporting the AE and as percent of safety set by treatment. The most commonly reported TEAEs (i.e., those events reported by >5% of all subjects in each treatment group or at least 2 subjects, excluding SAEs) will also be summarized. For the list of all AE summary tables see CPAP.

In addition, TEAEs will be summarized as number of AEs and percentage of AEs for each treatment for the overview of TEAEs.

Additional TEAE summary tables will be presented by severity and relationship to study drug. If a subject has multiple AEs with different severity levels within the same term, the subject will be counted in the most severe category only. If a subject has both related and unrelated AEs with the same term, the subject will be counted as having related TEAEs only.

Should any SAEs occur they will be summarized the same way as TEAE. All AEs will be displayed in the data listings and TEAEs will be discussed in the text of the study report. AEs leading to study drug discontinuation and SAEs will also be listed.

7.11.2 Clinical Laboratory Evaluations

Hematology, serum chemistry, and urinalysis will be performed at screening, check-in (Day -1) and Day 2 in each period, or upon early termination. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Principal Investigator (PI).

For all laboratory values that are numeric, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for each laboratory test by treatment and assessment time points, by study part. Change from baseline will be summarized. Baseline is defined as the last assessment including rechecks taken prior to dosing in each period (Day -1).

For each laboratory test, a shift table will be developed comparing the frequency of the results at treatment baseline (above normal (H), normal (N), or below normal (L)) with those postdose time points for each regimen. For urinalysis tests, the categories are normal (N) and abnormal (A). Out-of-range values and corresponding recheck results will be listed.

Out-of-normal range flags will be recorded as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results. If a value fails the reference range, it will automatically be compared to a clinically significant (CS) range. If the value falls within the CS range, it will be noted as "N" for not clinical significant. If the value fails the CS range, it will be flagged with a "Y" which prompts the PI to determine how the out-of-range value should be followed using 4 Investigator flags: "N", not clinically significant, "R", requesting a recheck, "^", checking at the next scheduled visit, or "Y", clinically significant. All clinically significant laboratory tests and the corresponding values will be listed by subject. All clinical laboratory data will be presented in by-subject data listings.

7.11.3 Vital Signs

Single measurements of heart rate and blood pressure will be obtained at screening, check-in (Day -1), Day 1 predose, Day 1 Hour 8, and Day 2 in each period, or upon early termination. Respiration rate, temperature, and orthostatic vital signs are collected at screening only. Additional unscheduled vital signs measurements may be taken at other times, if deemed necessary by the PI.

For each study part, summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for vital sign results (blood pressure and heart rate) and change from baseline by treatment and time point of collection. Baseline is defined as the last assessment including rechecks taken prior to dosing in each period (Day 1 Predose). Vital signs will also be displayed in a data listing by subject.

7.11.4 12-Lead ECGs

Standard 12-lead ECGs will be recorded at screening, check-in (Day -1 of Period 1), Day 2 in each period or upon early termination. Additional unscheduled ECGs may be recorded at other times if deemed necessary by the PI.

For each study part, summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for ECG results and change from baseline by treatment and time point of collection. Baseline is defined as the last assessment including rechecks taken prior to dosing in Period 1 (Day -1 of Period 1). ECG data will also be displayed in a data listing by subject.

7.11.5 Physical Exams

A full physical exam will be performed at screening, check-in in each period (Day -1 of Periods 1 and 2), and Day 2 of Period 2 or upon early termination. Symptom driven physical exams may be performed at other times at the discretion of the PI. Physical exam findings, as recorded on the CRF, will be presented in a data listing by subject. Reproductive system findings will also be listed by subject.

7.11.6 Overdose

All cases of overdose will be presented in a data listing by subject. Any AEs associated with overdose will be documented as AEs.

7.12 Interim Analysis

No interim analysis was performed.

7.13 Preliminary Analysis

Analysis will be completed as described in the CPAP and Section 7.9.1 of the SAP, with the following changes: (1) QCed data will be used (not QAed); (2) nominal times will be used for the calculation of PK parameters (not actual sampling times); (3) tables and figures will be created using Phoenix® WinNonlin® Version 7.0.

7.14 Changes in the Statistical Analysis Plan

The protocol states that values of subjects with markedly abnormal values for clinical laboratory tests and vital signs will be presented and tabulated. However, after agreement between Celerion and Takeda, it was decided that these would not be presented.

There are no other changes in the statistical analysis plan.

8.0   REFERENCES

Not applicable.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	29-Jan-2019 21:46 UTC
	Clinical Science Approval	29-Jan-2019 21:53 UTC
	Clinical Pharmacology Approval	29-Jan-2019 22:34 UTC
	Biostatistics Approval	30-Jan-2019 00:15 UTC