Title: A Randomized, Double-Blind, Double-Dummy Phase 3 Study to Evaluate the Efficacy and Safety of Oral Once-Daily administration of TAK-438 20 mg compared to Lansoprazole 30 mg in the Treatment of Subjects with Erosive Esophagitis

NCT Number: NCT02388724

SAP Approve Date: 23 August 2017

TAKEDA DEVELOPMENT CENTER

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-438_303

A Randomized, Double-Blind, Double-Dummy Phase 3 Study to Evaluate the Efficacy and Safety of Oral Once-Daily administration of TAK-438 20 mg compared to Lansoprazole 30 mg in the Treatment of Subjects with Erosive Esophagitis

PHASE 3

Version**:** 2

Date**:** 23 August 2017

Prepared by:

PPD

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CROSS-REGIONAL TEMPLATE

Template Number:	C-TMPL-DO-801	**Page:**	**2 of 51**
Version Number:	1.0	**Effective Date:**	**02 Apr 2014**
This version replaces:	TMPL-104		
Template Title:	Statistical Analysis Plan (Legacy Takeda)		

1.0 APPROVAL SIGNATURES

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

Study Title: A Randomized, Double-Blind, Double-Dummy Phase 3 Study to Evaluate the Efficacy and Safety of Oral Once-Daily administration of TAK-438 20 mg compared to Lansoprazole 30 mg in the Treatment of Subjects with Erosive Esophagitis

TDC Approvals:

PPD _____ Date

PPD _____ Date

PPD _____ Date

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CROSS-REGIONAL TEMPLATE

Template Number:	C-TMPL-DO-801	Page:	3 of 51
Version Number:	1.0	Effective Date:	02 Apr 2014
This version replaces:	TMPL-104		
Template Title:	Statistical Analysis Plan (Legacy Takeda)		

2.0   TABLE OF CONTENTS

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**4 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**5 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

Printed or downloaded documents must be verified against the effective version.

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**6 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

3.0   LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CMH	Cochran-Mantel-Haenszel
CPK	creatine phosphokinase
ECG	electrocardiogram
EQ-5D-5L	the 5-level version of the EuroQOL five dimensions questionnaire
FAS	full analysis set
GGT	γ-glutamyl transferase
H. pylori	Helicobacter pylori
HRQoL	Health-Related Quality of Life
LA classification	Los Angeles classification
LDH	lactate dehydrogenase
LLN	lower limit of normal
LS means	least square means
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
PPS	per protocol set
QOL	quality-of-life
QTcF	QT interval corrected by Fridericia's method
SAP	statistical analysis plan
Tbili	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO Drug	World Health Organization Drug Dictionary
WMWodds	Wilcoxon-Mann-Whitney odds

CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**7 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

4.0   OBJECTIVES

4.1.   PRIMARY OBJECTIVES

The primary objective is to demonstrate the non-inferior efficacy of TAK-438 versus Lansoprazole in the treatment of subjects with erosive esophagitis classified as LA classification grades A to D during the 8-week treatment.

4.2.   SECONDARY OBJECTIVES

To compare the efficacy of TAK-438 versus Lansoprazole in the healing of subjects with erosive esophagitis classified as LA classification grades A to D during the 2-week treatment.

To compare the efficacy of TAK-438 versus Lansoprazole in the healing of subjects with erosive esophagitis classified as LA classification grades A to D during the 4-week treatment.

To compare the safety of TAK-438 versus Lansoprazole in subjects with erosive esophagitis classified as LA classification grades A to D.

4.3.   ADDITIONAL OBJECTIVES

CCI

4.4.   STUDY DESIGN

A phase III, multi-center, double-blind, non-inferiority study of TAK-438 20 mg versus Lansoprazole 30 mg given once daily for up to 8 weeks in subjects with erosive esophagitis, with the LA classification grade A/B or C/D serving as the stratification factors at randomization, where all subjects with endoscopic healing of erosive esophagitis 2, 4, or 8 weeks after the start of the study will be construed as "completed cases" who then may be invited to participate with further informed consent in the planned, ensuing, maintenance trial (TAK-438_305).

Upon randomization subjects will be assigned (at a 1:1 ratio) to receive either oral TAK-438 20 mg or Lansoprazole 30 mg all study medication will once daily after breakfast except on Day 1 when it will be administered at the study site before the subject's visit is concluded.

This study will be conducted at a total of around 50 sites across Asia with an estimated total of 240 subjects randomized to each treatment group totaling 480 for the study.

The study will consist of a Screening Phase of up to 28 days, including an Observation Phase of 3-7 days prior to the randomization visit (Day 1), during which a baseline observation of EE symptoms will be completed, and then a Treatment Phase of up to 8 weeks. There will be 6 subject visits scheduled: the start of the Observation Phase (Visit 1), the start of the Treatment Phase (Visit 2), after 2 weeks of treatment (Visit 3), after 4 weeks of treatment (Visit 4), after 6 weeks of treatment (Visit 5), after 8 weeks of treatment (Visit 6), and a phone call during the Follow-up phase (only for those not participating in TAK-438_305 study).

Dosing will commence on Day 1 after randomization at Visit 2 (after completion of all required assessments scheduled on the Day 1).

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**8 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		
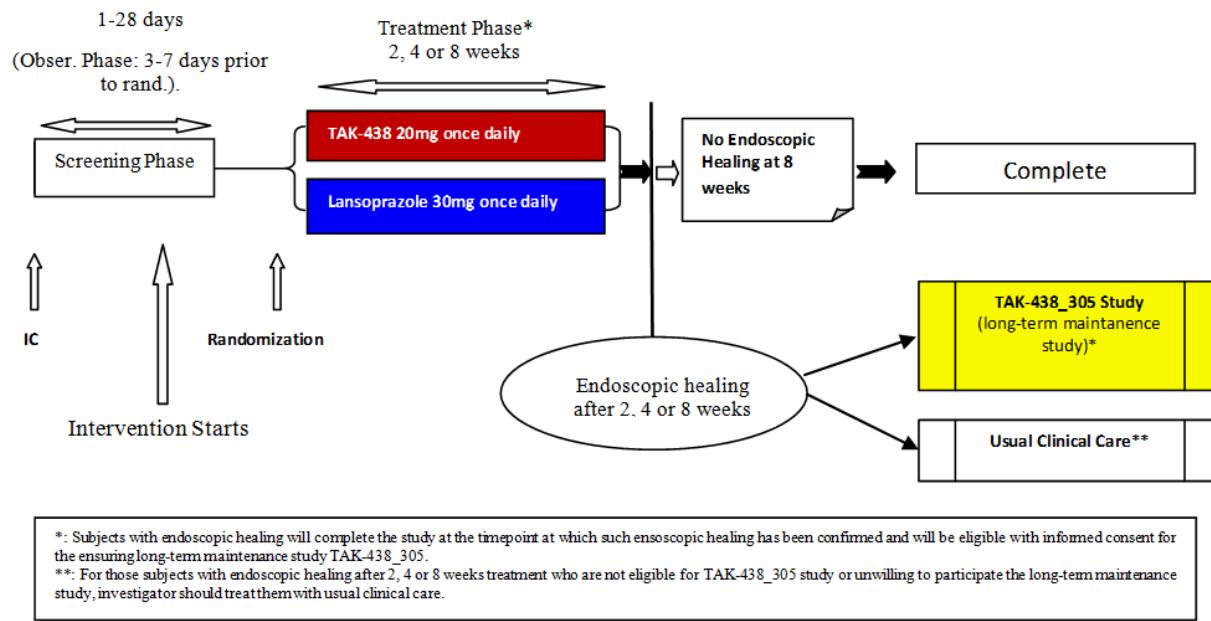
Figure 4.a Schematic of Study Design

CROSS-REGIONAL TEMPLATE

Template Number:	C-TMPL-DO-801	Page:	9 of 51
Version Number:	1.0	Effective Date:	02 Apr 2014
This version replaces:	TMPL-104		
Template Title:	Statistical Analysis Plan (Legacy Takeda)		

5.0 ANALYSIS ENDPOINTS

Primary Endpoint

The primary efficacy endpoint of this study is the rate of endoscopic healing* of erosive esophagitis during the 8-week treatment.

Endoscopic healing: defined as subjects endoscopically diagnosed as LA classification grade O during the treatment phase

Secondary Endpoints

The secondary efficacy endpoints of this study are

- the rate of endoscopic healing of erosive esophagitis during the 2-week treatment,

- the rate of endoscopic healing of erosive esophagitis during the 4-week treatment.

The safety endpoints of this study include adverse events, laboratory test values, ECG, vital signs, serum gastrin values, and pepsinogen I/II values.

Additional Endpoints

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CROSS-REGIONAL TEMPLATE

Template Number:	C-TMPL-DO-801	**Page:**	**10 of 51**
Version Number:	1.0	**Effective Date:**	**02 Apr 2014**
This version replaces:	TMPL-104		
Template Title:	Statistical Analysis Plan (Legacy Takeda)		

6.0 DETERMINATION OF SAMPLE SIZE

Assuming that the true Week 8 healing rate is 94.7% for both TAK-438 and Lansoprazole, and assuming that the dropout rate is up to 20%, a sample size of 160 subjects per group will provide 90% power to establish non-inferiority using a 2-sided 95% CI with a -10% non-inferiority margin. A sample size of 240 subjects per group is planned in order to provide more subjects with healed EE to the subsequent maintenance study TAK-438_305 and to provide adequate subjects for regulatory requirements in various countries.

The assumption of the 94.7% true healing rate is based on Phase 2 studies TAK-438/CCT-001 and TAK-390MR/CCT-001.

In a randomized, double-blind study in US (M87-092), the difference in Week 8 EE healing rate between lansoprazole 30 mg and placebo groups was 42.9% with a lower limit of 27.8% for the 2-sided 95% confidence interval. Based on this study, the non-inferiority margin is specified as -10%.

CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**11 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

7.0   METHODS OF ANALYSIS AND PRESENTATION

7.1 GENERAL CONSIDERATIONS

7.1.1 DEFINITIONS

The following definitions and calculation formulas will be used.

- TEAE: An adverse event whose date of onset occurs on or after the start of study drug. A TEAE whose relationship to study drug is missing will be considered drug-related. A TEAE whose intensity is missing will be considered severe.

- Descriptive statistics: number of subjects, mean, standard deviation, maximum, minimum, and quartiles

- Study Day: The day before the first dose of the study medication will be defined as Study Day -1 and the day of the first dose will be defined as Study Day 1. Other study days are defined relative to Study Day 1, e.g., the day prior to Study Day 1 is Day -1 and the day after Study Day 1 is Day 2.

- Follow-up Day: The day after the last dose of the study medication will be defined as Follow-up Day 1. Other follow-up days are defined relative to Follow-up Day 1.

- Duration of exposure to study medication (days): date of last dose of study medication - date of first dose of study medication + 1

- Study drug compliance (%): (number of days the subject answered "Yes" in the subject diary to the question "Study medication taken?") / duration of exposure to study medication * 100 (rounded to 1 decimal place)

- Age (years): The following only applies to subjects from countries other than Korea. If the date informed consent obtained or the date of birth is missing, then age will be missing. If the month and the day of the date informed consent obtained is before the month and the day of the date of birth, then age will be calculated as follows: the year of the date informed consent obtained - the year of the date of birth - 1. For all others, age will be calculated as follows: the year of the date informed consent obtained - the year of the date of birth.

- BMI (kg/m^2): weight (kg) / (height (m))^2 (rounded to 1 decimal place)

- Pepsinogen I/II Ratio: Pepsinogen I (μg/L) / Pepsinogen II (μg/L) (rounded to 1 decimal place)

- QTcF interval (msec): QT interval (msec) / (RR interval (sec))$^{0.33}$ (rounded to the nearest whole number)

- Confidence interval for one sample proportion: Exact (Clopper-Pearson) confidence interval will be used.

- Confidence interval for two sample proportion difference: Wald confidence interval will be used.

- Significant TEAE: Any TEAE (not including serious TEAEs) that led to an intervention, including withdrawal of drug treatment, dose increase, dose reduction or significant additional concomitant therapy.

7.1.2 ANALYSIS SETS

Analysis of efficacy variables will be conducted in the full analysis set defined as all randomized subjects who receive at least 1 dose of study medication and have at least 1 post-baseline endoscopy, and will be based on the randomized treatment.

The primary efficacy endpoint and the secondary efficacy endpoints will also be analyzed in the per protocol set defined as all FAS subjects who did not have any of the major protocol deviations listed below. Analyses will be based on the randomized treatment.

- Subjects who did not meet inclusion criteria #3

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**12 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

- Subjects who met exclusion criteria #8, #11, #12, #13, or #14

- Subjects with study medication compliance of less than 70%

- Subjects who have been unblinded prior to database lock

- Subjects who have violated the rules specified in section 7.3 of the protocol

Analysis of safety variables will be conducted in the safety analysis set defined as all subjects who take at least 1 dose of study medication and will be based on the treatment received.

7.1.3 HANDLING OF RATE OF ENDOSCOPIC HEALING OF EROSIVE ESOPHAGITIS

7.1.3.1 RATE OF ENDOSCOPIC HEALING OF EROSIVE ESOPHAGITIS DURING THE 2-WEEK TREATMENT

A subject who is diagnosed as LA classification grade O from endoscopy tests performed between Study Day 2 and Study Day 21 will be considered as a healed subject. Subjects who do not have any endoscopy data during this period will be treated as missing. Subjects who do not meet this requirement will be considered as 'not healed'. Healing rate will be calculated from the healed and not healed subjects, however, any subjects diagnosed as LA classification grade O from endoscopy tests performed before the study medication administration will be excluded from the analysis.

7.1.3.2 RATE OF ENDOSCOPIC HEALING OF EROSIVE ESOPHAGITIS DURING THE 4-WEEK TREATMENT

A subject who is diagnosed as LA classification grade O from endoscopy tests performed between Study Day 2 and Study Day 42 will be considered as a healed subject. Subjects who do not have any endoscopy data during this period will be treated as missing. Subjects who do not meet this requirement will be considered as 'not healed'. Healing rate will be calculated from the healed and not healed subjects, however, any subjects diagnosed as LA classification grade O from endoscopy tests performed before the study medication administration will be excluded from the analysis.

7.1.3.3 RATE OF ENDOSCOPIC HEALING OF EROSIVE ESOPHAGITIS DURING THE 8-WEEK TREATMENT

A subject who is diagnosed as LA classification grade O from any of the endoscopy tests performed after Study Day 2 will be considered as a healed subject. Subjects who do not meet this requirement will be considered as 'not healed'. Healing rate will be calculated from the healed and not healed subjects, however, any subjects diagnosed as LA classification grade O from endoscopy tests performed before the study medication administration will be excluded from the analysis.

7.1.4 HANDLING OF DATA WHEN CALCULATING PROPORTION OF DAYS WITHOUT SUBJECTIVE SYMPTOMS ACCORDING TO SUBJECT DIARY

Each subjective symptom of erosive esophagitis as recorded in subject diaries (i.e., heartburn, gastric acid regurgitation) will be handled as below.

For each subject, the proportion of days without subjective symptoms will be calculated as follows at each visit. If the denominator of the following formula is missing, then the calculated result should also be missing.

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**13 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

Proportion of days without subjective symptoms (%) = (number of days where "None" is recorded as the severity of symptom for the visit) / (number of days the severity of symptom is recorded) * 100 (rounded to 1 decimal place)

(Note: Severity recorded as "Not Completed" will be treated as missing.)

The following visits will be used.

Visit	Time Interval (days)	
	Study Day	Follow-up Day
Baseline	Day -6 – Day 1	
Week 1	Day 2 – Day 8	up to and including Follow-up Day 1
Week 2	Day 9 – Day 15	up to and including Follow-up Day 1
Week 4	Day 16 – Day 29	up to and including Follow-up Day 1
Week 8	Day 30 – Day 57	up to and including Follow-up Day 1
Treatment Phase	on and after Day 2	up to and including Follow-up Day 1

7.1.5 HANDLING OF DATA WHEN CALCULATING MEAN SEVERITY ACCORDING TO SUBJECT DIARY

Each subjective symptom of erosive esophagitis as recorded in subject diaries (i.e., heartburn, gastric acid regurgitation) will be handled as below.

Severity will be scored as follows. None: 0, Mild: 1, Moderate: 2, Severe: 3.

For each subject, the mean severity will be calculated as follows at each visit. If the denominator is missing, then the calculated result should also be missing.

Mean severity = (total score of the severity recorded for the visit) / (number of days the severity of symptom is recorded) (rounded to 2 decimal places)

(Note: Severity recorded as "Not Completed" will be treated as missing.)

The following visits will be used.

Visit	Time Interval (days)	
	Study Day	Follow-up Day
Baseline	Day -6 – Day 1	
Week 1	Day 2 – Day 8	up to and including Follow-up Day 1
Week 2	Day 9 – Day 15	up to and including Follow-up Day 1
Week 4	Day 16 – Day 29	up to and including Follow-up Day 1
Week 8	Day 30 – Day 57	up to and including Follow-up Day 1
Treatment Phase	on and after Day 2	up to and including Follow-up Day 1

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**14 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

7.1.6 HANDLING OF PARTIALLY SUSTAINED RESOLUTION ACCORDING TO SUBJECT DIARY

Analysis will be performed on data obtained from Day 2 to the day after the last dose of the study medication (treatment phase). If there are no records concerning subjective symptoms in the subject diary during the treatment phase, then the subject will be excluded from the analysis. Severity recorded as "Not Completed" will be treated as missing.

An event will have occurred if "None" is recorded as the severity of the subjective symptom for seven days in a row or more. The event date will be defined as the first day of the 7-day period of the first event confirmed. A subject will be censored if there are records concerning subjective symptoms in the subject diary during the treatment phase but an event has not occurred. The censoring date will be defined as below.

If the entries concerning subjective symptoms in the subject diary do not continue for seven days in a row, then Day 2 will be the censoring date.

If there are records concerning subjective symptoms in the subject diary for at least seven days in a row, then six days before the last day of the last 7-day period will be the censoring date.

7.1.7 HANDLING OF SUSTAINED RESOLUTION ACCORDING TO SUBJECT DIARY

Analysis will be performed on data obtained from Day 2 to the day after the last dose of the study medication (treatment phase). If there are no records concerning subjective symptoms in the subject diary during the treatment phase, then the subject will be excluded from the analysis. Severity recorded as "Not Completed" will be treated as missing.

An event will have occurred if "None" is recorded as the severity of the subjective symptom for seven days in a row or more until the day after the last dose of study medication. The event date will be defined as the first day of the 7-day period when the event is confirmed. A subject will be censored if there are records concerning subjective symptoms in the subject diary during the treatment phase but an event has not occurred. The censoring date will be defined as below.

If there are no records in the subject diary concerning subjective symptoms on Day 8 or after, then Day 2 will be the censoring date.

If there is an entry in the subject diary concerning subjective symptoms on Day 8 or after, then six days before the last entry will be the censoring date.

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CROSS-REGIONAL TEMPLATE

Template Number:	C-TMPL-DO-801	Page:	15 of 51
Version Number:	1.0	Effective Date:	02 Apr 2014
This version replaces:	TMPL-104		
Template Title:	Statistical Analysis Plan (Legacy Takeda)		

7.1.8   HRQoL (EQ-5D-5L)

All evaluable data (i.e., non-missing) obtained in the corresponding time interval will be used in evaluating the EQ-5D-5L index value and EQ VAS score. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day, the later observation will be used.

The EQ-5D-5L index values will be calculated from the EQ-5D-5L descriptive system scores based on the EQ-5D-5L Crosswalk value sets. If any of the questions are not answered, the EQ-5D-5L index value of the day will be treated as missing.

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-28 – 1	
Week 2	Study Day: 15	2 – 21	up to and including Follow-up Day 14
Week 4	Study Day: 29	22 – 42	up to and including Follow-up Day 14
Week 8	Study Day: 57	43 – 71	up to and including Follow-up Day 14

7.1.9   HANDLING OF DATA WHEN CALCULATING PROPORTION OF DAYS WITHOUT RESCUE MEDICATION

For each subject, the proportion of days without rescue medication will be calculated as follows at each visit. If the denominator is missing, then the calculated result should also be missing.

Proportion of days without rescue medication (%) = (number of days in the visit where the subject answered "No" in the subject diary to the question "Any antacid taken?") / (number of days in the visit where the question "Any antacid taken?" was answered in the subject diary) * 100 (rounded to 1 decimal place)

(Note: Records entered as "Not Completed" will be treated as missing.)

The following visits will be used.

Visit	Time Interval (days)	
	Study Day	Follow-up Day
Week 2	Day 2 – Day 15	up to and including Follow-up Day 1
Week 4	Day 16 – Day 29	up to and including Follow-up Day 1
Week 8	Day 30 – Day 57	up to and including Follow-up Day 1
One Month to the Day of Last Dose	27 days before the last dose – day of last dose	
Treatment Phase	on Day 2 or after	up to and including Follow-up Day 1

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CROSS-REGIONAL TEMPLATE

Template Number:	C-TMPL-DO-801	**Page:**	**16 of 51**
Version Number:	1.0	**Effective Date:**	02 Apr 2014
This version replaces:	TMPL-104		
Template Title:	Statistical Analysis Plan (Legacy Takeda)		

7.1.10 HANDLING OF OTHER ENDPOINTS

For each visit, all evaluable observation (i.e., non-missing) obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day, the later observation will be used. If there are two observations with the same Study Day, the earlier observation will be used.

Weight, BMI, ^{13}C or ^{14}C breath test (H. pylori infection status), Endoscopy (esophageal hiatal hernia)

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-28 – 1	

Endoscopy (Barrett's mucosa), Clinical laboratory tests (other than ALT, AST, total bilirubin, and direct bilirubin), Gastrin, Pepsinogen I/II, Vital signs, 12-lead ECG

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-28 – 1	
Week 2	Study Day: 15	2 – 21	up to and including Follow-up Day 14
Week 4	Study Day: 29	22 – 42	up to and including Follow-up Day 14
Week 8	Study Day: 57	43 – 71	up to and including Follow-up Day 14

Clinical laboratory tests (ALT, AST, total bilirubin, and direct bilirubin)

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-28 – 1	
Week 2	Study Day: 15	2 – 21	up to and including Follow-up Day 14
Week 4	Study Day: 29	22 – 35	up to and including Follow-up Day 14
Week 6	Study Day: 43	36 – 49	up to and including Follow-up Day 14
Week 8	Study Day: 57	50 – 71	up to and including Follow-up Day 14

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**17 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

7.2 STUDY SUBJECTS, DEMOGRAPHICS, AND OTHER BASELINE CHARACTERISTICS

7.2.1 DISPOSITION OF SUBJECTS

7.2.1.1 STUDY INFORMATION

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variables: Date First Subject Signed Informed Consent Form

Date of Last Subject's Last Visit/Contact

MedDRA Version

WHO Drug Version

SAS Version Used for Creating the Datasets

Analytical Methods: **(1) Study Information**

Study information shown in the analysis variables section will be provided.

7.2.1.2 SCREEN FAILURES

Analysis Set: All Subjects Who Were Not Randomized

Analysis Variables: Age (years)   [Min<= - <65, 65<= - <75, 75<= - <=Max]

Gender   [Male, Female]

Race   [American Indian or Alaska Native, Asian, Black or African American,

Native Hawaiian or Other Pacific Islander, White]

Analytical Methods: **(1) Screen Failures**

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.2.1.3 SUBJECT ELIGIBILITY

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variables: Eligibility Status   [Yes, No]

Primary Reason for Subject Not Being Eligible   [Pretreatment Event/Adverse Event,

Major Protocol Deviation,

Lost to Follow-Up,

Voluntary Withdrawal,

Study Termination,

Did Not Meet Entrance Criteria,

Other]

Analytical Methods: **(1) Eligibility for Randomization**

Frequency distributions will be provided. When calculating the percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**18 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

7.2.1.4 NUMBER OF SUBJECTS RANDOMIZED BY COUNTRY, SITE, AND TREATMENT GROUP

Analysis Set:	Randomized Set	
Analysis Variables:	Randomization Status	[Yes]
Stratum:	Country	[China, Malaysia, South Korea, Taiwan]
	Site	[Site numbers will be used as categories]
Analytical Methods:	**(1) Number of Subjects Randomized by Country, Site, and Treatment Group**	
	Frequency distribution will be provided for each stratum by treatment group and overall.	

7.2.1.5 DISPOSITION OF SUBJECTS

Analysis Set:	Randomized Set	
Analysis Variables:	Study Drug Administration Status	[No]
	Reason for Not Being Treated	[Pretreatment Event/Adverse Event, Major Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Pregnancy, Lack of Efficacy, Other]
	Study Drug Completion Status	[Completed Study Drug, Prematurely Discontinued Study Drug]
	Reason for Discontinuation of Study Drug	[Pretreatment Event/Adverse Event, Major Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Pregnancy, Lack of Efficacy, Other]
Analytical Methods:	**(1) Disposition of Subjects**	
	Frequency distributions will be provided for each treatment group and overall. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation of study drug, the total number of subjects who prematurely discontinued the study drug will be used as the denominator.	
	(2) Flow Chart of Subject Distribution	
	Flow chart will be provided.	

7.2.1.6 PROTOCOL DEVIATIONS AND ANALYSIS SETS

Protocol Deviations

Analysis Set:	Randomized Set	
Analysis Variables:	Protocol Deviation	[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria]
Analytical Methods:	**(1) Protocol Deviations**	
	Frequency distribution will be provided by treatment group and overall for each deviation category. A subject who has several deviations will be counted once in each appropriate	

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**19 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

category. A subject who has several deviations that can be classified into the same category will be counted only once.

Analysis Sets

Analysis Set:	Randomized Set
Analysis Variables:	Analysis Sets
	Full Analysis Set [Included]
	Per Protocol Set [Included]
	Safety Analysis Set [Included]
Analytical Methods:	**(1) Analysis Sets**
	Frequency distributions will be provided by treatment group and overall.

7.2.2 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

7.2.2.1 SUMMARY OF DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Analysis Set:	Randomized Set	
Analysis Variables:	Country	[China, Malaysia, South Korea, Taiwan]
	Age (years)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Gender	[Male, Female]
	Race	[American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White]
	Height (cm)	[Min<= - <150, 150<= - <160, 160<= - <170, 170<= - <=Max]
	Weight (kg) (Baseline)	[Min<= - <50.0, 50.0<= - <60.0, 60.0<= - <70.0, 70.0<= - <80.0, 80.0<= - <=Max]
	BMI (kg/m^2) (Baseline)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <=Max]
	Smoking Classification	[The Subject Has Never Smoked, The Subject Is a Current Smoker, The Subject Is an Ex-smoker]
	Consumption of Alcohol	[Drink Everyday, Drink a Couple of Days Per Week, Drink a Couple of Days Per Month, Never Drink]
	Consumption of Caffeine	[Yes, No]

CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**20 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

History of H.pylori Eradication Therapy	[Yes (End of Treatment: Within the Past 1 Year), Yes (End of Treatment: More than 1 Year), No]
H. pylori Infection Status	[Positive, Negative]
LA Classification (Baseline)	[Grade O, Grade A, Grade B, Grade C, Grade D] [Grade O, Grade A/B, Grade C/D]
Barrett's Mucosa (Baseline)	[Present (3 cm or Greater), Present (Less than 3 cm), Absent, Unknown]
Esophageal Hiatal Hernia (Baseline)	[Present (2 cm or Greater), Present (Less than 2 cm), Absent, Unknown]

Diary for Gastrointestinal Symptoms

Mean Severity of Heartburn Symptoms (Baseline)	[0.00, 0.00< - <=1.00, 1.00< - <=2.00, 2.00< - <=3.00]
Mean Severity of Gastric Acid Regurgitation (Baseline)	[0.00, 0.00< - <=1.00, 1.00< - <=2.00, 2.00< - <=3.00]

HRQoL (EQ-5D-5L)
EQ-5D-5L Index Value (Baseline)
EQ VAS Score (Baseline)

Analytical Methods: **(1) Summary of Demographics and Other Baseline Characteristics**

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by treatment group and overall.

7.2.2.2 MEDICAL HISTORY AND CONCURRENT MEDICAL CONDITIONS

Analysis Set: Safety Analysis Set

Analysis Variables: Medical History

Concurrent Medical Conditions

Analytical Methods: **(1) Medical History by System Organ Class and Preferred Term**

(2) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided for each treatment group. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency. A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**21 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

7.2.2.3 MEDICATION HISTORY AND CONCOMITANT MEDICATIONS

Analysis Set: Safety Analysis Set

Analysis Variables: Medication History

Concomitant Medications

Analytical Methods: **(1) Medication History by Preferred Medication Name**

(2) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Preferred Medication Name

Frequency distributions will be provided for each treatment group. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

7.2.3 TREATMENT COMPLIANCE

7.2.3.1 STUDY DRUG EXPOSURE AND COMPLIANCE

Analysis Set: Safety Analysis Set

Analysis Variables: Duration of Exposure to Study Drug (days) [1<= - <=14, 15<= - <=28, 29<= - <=56, 57<= - <=Max]

Study Drug Compliance (%)   [Min<= - <50.0, 50.0<= - <70.0, 70.0<= - <90.0, 90.0<= - <=Max]

Analytical Methods: **(1) Study Drug Exposure and Compliance**

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by treatment group and overall.

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**22 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

7.3 EFFICACY ANALYSIS

The full analysis set will be the main analysis set used. The per protocol set will be used for analyses performed secondarily on the primary efficacy endpoint and secondary efficacy endpoints in order to examine the robustness of the results.

7.3.1 PRIMARY EFFICACY ENDPOINT

7.3.1.1 PRIMARY ANALYSIS

Analysis Set: Full Analysis Set

Analysis Variable: Rate of Endoscopic Healing of Erosive Esophagitis During the 8-week Treatment (%)

Analytical Methods: **(1) Rate of Endoscopic Healing of Erosive Esophagitis During the 8-week Treatment**
Frequency distributions will be provided by treatment group along with rates and the two-sided 95% confidence intervals.
The differences in the rates between the TAK-438 group and the Lansoprazole group (the TAK-438 group – the Lansoprazole group) and the two-sided 95% confidence intervals using the Wald method will be provided. If the lower bound of this 95% confidence intervals is $\geq$-10%, non-inferiority for TAK-438 relative to Lansoprazole will be declared.

7.3.1.2 SECONDARY ANALYSIS

Analysis Set: Per Protocol Set

Analysis Variable: Rate of Endoscopic Healing of Erosive Esophagitis During the 8-week Treatment (%)

Analytical Methods: **(1) Sensitivity Analysis**
To check the robustness of the results, the same analyses as those in section 7.3.1.1 will be performed using the per protocol set.

7.3.2 SECONDARY EFFICACY ENDPOINTS

7.3.2.1 RATE OF ENDOSCOPIC HEALING OF EROSIVE ESOPHAGITIS DURING THE 2-WEEK TREATMENT

Analysis Set: Full Analysis Set

Analysis Variable: Rate of Endoscopic Healing of Erosive Esophagitis During the 2-week Treatment (%)

Analytical Methods: **(1) Rate of Endoscopic Healing of Erosive Esophagitis During the 2-week Treatment**
Frequency distributions will be provided by treatment group along with rates and the two-sided 95% confidence intervals. Also, the differences in the rates between the TAK-438 group and the Lansoprazole group (the TAK-438 group – the Lansoprazole group) and the two-sided 95% confidence intervals will be provided. Details concerning interpretation are described in section 7.3.4.5.

CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**23 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

7.3.2.2 RATE OF ENDOSCOPIC HEALING OF EROSIVE ESOPHAGITIS DURING THE 4-WEEK TREATMENT

Analysis Set: Full Analysis Set

Analysis Variable: Rate of Endoscopic Healing of Erosive Esophagitis During the 4-week Treatment (%)

Analytical Methods: **(1) Rate of Endoscopic Healing of Erosive Esophagitis During the 4-week Treatment**

Frequency distributions will be provided by treatment group along with rates and the two-sided 95% confidence intervals. Also, the differences in the rates between the TAK-438 group and the Lansoprazole group (the TAK-438 group – the Lansoprazole group) and the two-sided 95% confidence intervals will be provided. Details concerning interpretation are described in section 7.3.4.5.

7.3.2.3 SENSITIVITY ANALYSIS

Analysis Set: Per Protocol Set

Analysis Variable: Rate of Endoscopic Healing of Erosive Esophagitis During the 2-week Treatment (%)

Rate of Endoscopic Healing of Erosive Esophagitis During the 4-week Treatment (%)

Analytical Methods: **(1) Sensitivity Analysis**

To check the robustness of the results, the same analyses as section 7.3.2.1 and 7.3.2.2 will be performed using the per protocol set.

7.3.3 ADDITIONAL EFFICACY ENDPOINTS

7.3.3.1 CCI

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CONFIDENTIAL INFORMATION

CROSS-REGIONAL TEMPLATE

Template Number:	C-TMPL-DO-801	**Page:**	**24 of 51**
Version Number:	1.0	**Effective Date:**	02 Apr 2014
This version replaces:	TMPL-104		
Template Title:	Statistical Analysis Plan (Legacy Takeda)		

CCI

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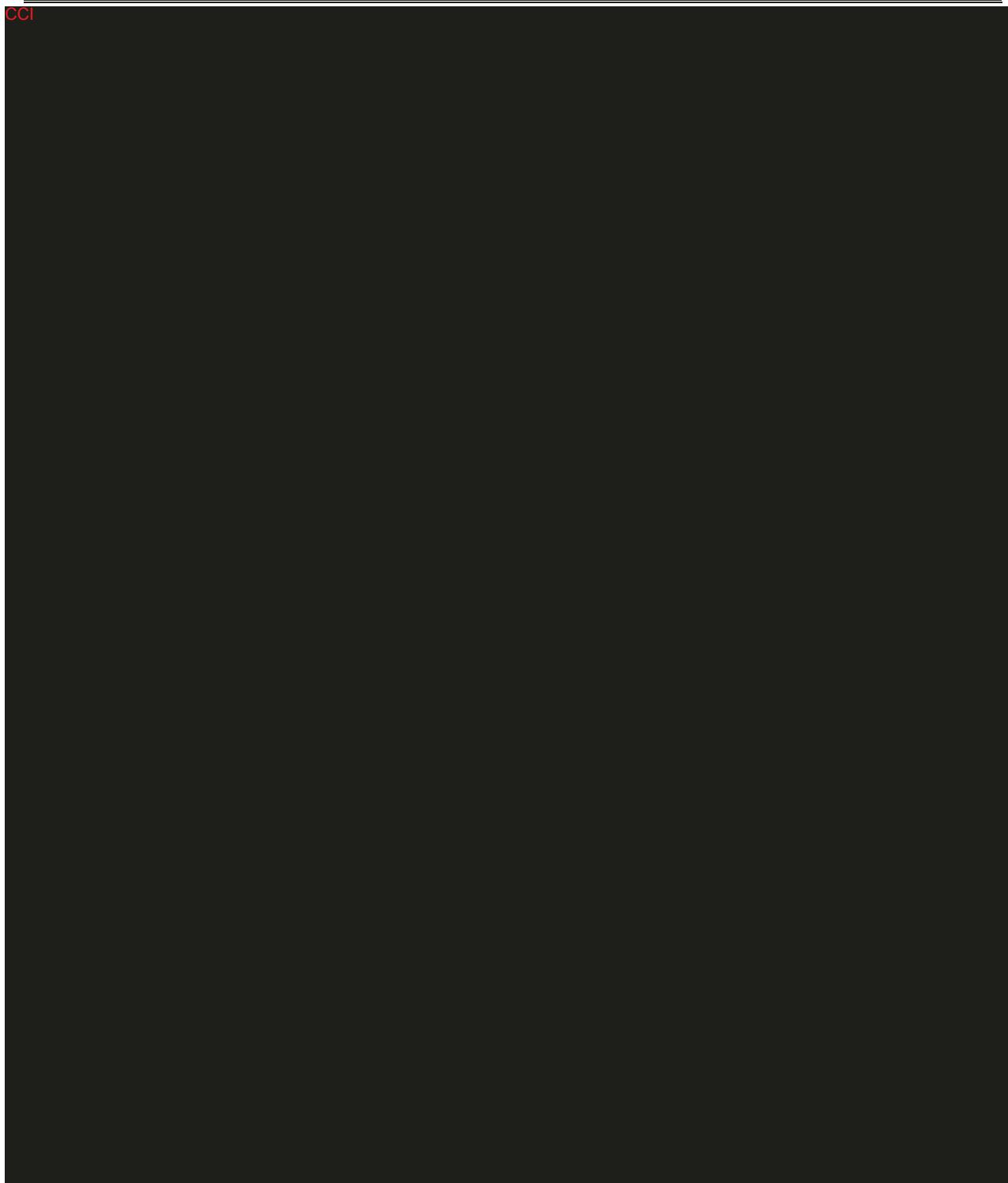
CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**25 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

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7.3.3.2   CCI

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**26 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

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7.3.3.3   PROPORTION OF DAYS WITHOUT RESCUE MEDICATIONS

Analysis Set:	Full Analysis Set
Analysis Variables:	Proportion of Days Without Rescue Medications (%)
Visit:	Week 2, Week 4, Week 8, One Month to the Day of Last Dose, Treatment Phase
Analytical Methods:	**(1) Proportion of Days Without Rescue Medications**

Descriptive statistics will be provided for each visit by treatment group. The difference in the medians between the TAK-438 group and the Lansoprazole group (the TAK-438 group – the Lansoprazole group) and the two-sided 95% confidence intervals will be provided for each visit using the Hodges-Lehmann estimator. Wilcoxon rank-sum tests will be used to test for treatment differences at each visit. WMWodds of the TAK-438 group to the Lansoprazole group and the two-sided 95% confidence intervals will also be provided for each visit based on Wilcoxon-Mann-Whitney test statistics.

7.3.3.4   BARRETT'S MUCOSA

Analysis Set:	Full Analysis Set	
Analysis Variables:	Barrett's Mucosa (Change)	[Increased, Unchanged, Reduced, Disappeared, Unknown]
Subgroups:	Barrett's Mucosa (Baseline)	[Present (3 cm or Greater), Present (Less than 3 cm), Absent, Unknown]
Visit:	Week 2, Week 4, Week 8	
Analytical Methods:	**(1) Frequency distribution of Barrett's Mucosa (Change) by Baseline Barrett's Mucosa**	

Frequency distribution will be provided for each subgroup and visit by treatment group.

CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**27 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

7.3.4 STATISTICAL/ANALYTICAL ISSUES

7.3.4.1 ADJUSTMENTS FOR COVARIATES

Analysis Set: Full Analysis Set

Analysis Variable: Rate of Endoscopic Healing of Erosive Esophagitis During the 8-week Treatment (%)
Rate of Endoscopic Healing of Erosive Esophagitis During the 2-week Treatment (%)
Rate of Endoscopic Healing of Erosive Esophagitis During the 4-week Treatment (%)

Stratified Variable: LA Classification (Baseline)   [Grade A/B, Grade C/D]

Analytical Methods: **(1) CMH Test for the Rate of Endoscopic Healing of Erosive Esophagitis During the 8-week Treatment** (%)

                    (2) CMH Test for the Rate of Endoscopic Healing of Erosive Esophagitis During the 2-week Treatment (%)

                    (3) CMH Test for the Rate of Endoscopic Healing of Erosive Esophagitis During the 4-week Treatment (%)

A CMH test with baseline LA Classification as a stratification factor will be used to compare the above analysis variable between the TAK-438 group and the Lansoprazole group for treatment differences. Mantel-Haenszel estimate of risk difference between the TAK-438 group and the Lansoprazole group (the TAK-438 group – the Lansoprazole group) and the two-sided 95% confidence interval using the Wald method will also be provided.

7.3.4.2 HANDLING OF DROPOUTS OR MISSING DATA

For the primary endpoint "rate of endoscopic healing of erosive esophagitis during the 8-week treatment" and the secondary efficacy endpoints "rate of endoscopic healing of erosive esophagitis during the 2-week treatment" and "rate of endoscopic healing of erosive esophagitis during the 4-week treatment", missing data will be handled according to section 7.1.3.

Values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. Values above the upper limit of quantification will be treated as the upper limit values when calculating the descriptive statistics.

7.3.4.3 INTERIM ANALYSES AND DATA MONITORING

No interim analysis is planned in this study.

7.3.4.4 MULTICENTER STUDIES

Treatment-by-center interaction will not be explored in this study.

7.3.4.5 MULTIPLE COMPARISON/MULTIPLICITY

Adjustment for multiplicity will be performed for the primary efficacy endpoint "The Rate of Endoscopic Healing of Erosive Esophagitis during the 8-week Treatment" and the secondary efficacy endpoints "The Rate of Endoscopic Healing of Erosive Esophagitis during the 2-week Treatment" and "The Rate of Endoscopic Healing of Erosive Esophagitis During the 4-week Treatment" in the following fashion. The following procedure is based on the closed testing principle and the analysis will be conducted using the full analysis set.

- The primary endpoint "The Rate of Endoscopic Healing of Erosive Esophagitis during the 8-week Treatment" will be tested for non-inferiority between the TAK-438 group and the Lansoprazole group. If the lower bound

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**28 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

of the 95% confidence interval of the treatment difference (the TAK-438 group – the Lansoprazole group) is ≥-10%, non-inferiority for TAK-438 relative to Lansoprazole will be declared.

- If the previous test is successful, the secondary endpoint "The Rate of Endoscopic Healing of Erosive Esophagitis during the 2-week Treatment" will be tested for superiority between the TAK-438 group and the Lansoprazole group. The lower bound of the 95% confidence interval of the treatment difference (the TAK-438 group – the Lansoprazole group) will be compared to 0%.

- If the previous test is successful, the primary endpoint "The Rate of Endoscopic Healing of Erosive Esophagitis during the 8-week Treatment" will be tested for superiority between the TAK-438 group and the Lansoprazole group.

- If the previous test is successful, the secondary endpoint "The Rate of Endoscopic Healing of Erosive Esophagitis during the 4-week Treatment" will be tested for superiority between the TAK-438 group and the Lansoprazole group.

7.3.4.6 USE OF AN "EFFICACY SUBSET" OF SUBJECTS

In addition to analyses on the primary and secondary efficacy endpoints using the full analysis set, sensitivity analyses will also be performed using the per protocol set to examine the robustness of the results.

7.3.4.7 ACTIVE-CONTROL STUDIES INTENDED TO SHOW EQUIVALENCE OR NON-INFERIORITY

For the primary efficacy endpoint, non-inferiority for TAK-438 relative to Lansoprazole will be confirmed in the full analysis set using a non-inferiority margin of 10% as described in section 7.3.1.1 "Primary Analysis".

7.3.4.8 SUBGROUP ANALYSIS

Analysis Set:	Full Analysis Set
Analysis Variable:	Rate of Endoscopic Healing of Erosive Esophagitis During the 8-week Treatment (%)
	Rate of Endoscopic Healing of Erosive Esophagitis During the 2-week Treatment (%)
	Rate of Endoscopic Healing of Erosive Esophagitis During the 4-week Treatment (%)

Subgroups:	Age (years)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Gender	[Male, Female]
	H. pylori Infection Status	[Positive, Negative]
	LA Classification (Baseline)	[Grade A/B, Grade C/D]
	Barrett's Mucosa (Baseline)	[Present, Absent]
	Version of Informed Consent Form	[Protocol Amendment No.3 or Later]

Analytical Methods:

(1) Subgroup Analysis for the Rate of Endoscopic Healing of Erosive Esophagitis During the 8-week Treatment (%)

(2) Subgroup Analysis for the Rate of Endoscopic Healing of Erosive Esophagitis During the 2-week Treatment (%)

(3) Subgroup Analysis for the Rate of Endoscopic Healing of Erosive Esophagitis During the 4-week Treatment (%)

The same analyses as those in section 7.3.2.2 will be performed for each of the above subgroups.

CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**29 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

7.4 SAFETY ANALYSIS

7.4.1 TREATMENT-EMERGENT ADVERSE EVENTS

7.4.1.1 OVERVIEW OF TREATMENT-EMERGENT ADVERSE EVENTS

Analysis Set: Safety Analysis Set

Analysis Variables: TEAE

Categories: Relationship to Study Drug   [Related, Not Related]

                  Intensity   [Mild, Moderate, Severe]

Analytical Methods: The following summaries will be provided for each treatment group.

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)

2) Relationship of Treatment-Emergent Adverse Events to Study Drug (number of events, number and percentage of subjects)

3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)

4) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (number of events, number and percentage of subjects)

5) Relationship to Study Drug of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (number of events, number and percentage of subjects)

6) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)

7) Relationship of Serious Treatment-Emergent Adverse Events to Study Drug (number of events, number and percentage of subjects)

8) Serious Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (number of events, number and percentage of subjects)

9) Treatment-Emergent Adverse Events Resulting in Death (number of events, number and percentage of subjects)

10) Treatment-Emergent Adverse Events Corresponding to Liver Function Test Abnormalities (number of events, number and percentage of subjects)

11) Significant Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

<u>Number of subjects</u>

- Summaries for 2), 5) and 7)
  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.

- Summary for 3)
  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**30 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

· Summaries other than 2), 3), 5) and 7)

A subject with multiple occurrences of TEAE will be counted only once.

<u>Number of events</u>

For each summary, the total number of events will be calculated.

7.4.1.2 DISPLAYS OF TREATMENT-EMERGENT ADVERSE EVENTS

Analysis Set: Safety Analysis Set

Analysis Variables: TEAE

Categories: Intensity   [Mild, Moderate, Severe]

Time of Onset (day)   [1<= - <=14, 15<= - <=28, 29<= - <=56, 57<= - <=Max]

Analytical Methods: The following summaries will be provided using frequency distribution for each treatment group.

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by SOC only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(2) Treatment-Emergent Adverse Events by System Organ Class

(3) Treatment-Emergent Adverse Events by Preferred Term

(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term

(7) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term

(8) Drug-Related Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term

(9) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(10) Serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(11) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time

(12) Most Frequent Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(13) Treatment-Emergent Adverse Events Corresponding to Liver Function Test Abnormalities by System Organ Class and Preferred Term

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**31 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

(14) **Drug-Related Treatment-Emergent Adverse Events Corresponding to Liver Function Test Abnormalities by System Organ Class and Preferred Term**

(15) **Significant Treatment-Emergent Adverse Events by System Organ Class and Preferred Term**

(16) **Drug-Related Significant Treatment-Emergent Adverse Events by System Organ Class and Preferred Term**

(17) **Most Frequent Non Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term**

The frequency distribution will be provided according to the rules below.

Number of subjects

- Summary tables other than (5), (6) and (11)

  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set.

- Summary tables for (5) and (6)

  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages will be based on the number of subjects in the safety analysis set.

- Summary table for (11)

  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT. When calculating percentages for each time interval, the number of subjects at risk (i.e., subjects who either have an exposure or have an occurrence of TEAE, during or after the corresponding time interval) will be used as the denominator. The number of subjects whose onset of any one of the TEAEs is within the time interval will be used as the numerator.

- Summary table for (12)

  Most frequent TEAEs refer to PTs whose percentages are at least 2% in any one of the treatment groups.

- Summary table for (17)

  Most frequent non-serious TEAEs refer to PTs that are not serious whose percentages are at least 5% in any one of the treatment groups. If there are no PTs whose percentages exceed 5%, the threshold is lowered to 2%. When counting the number of "Subjects With Any TEAEs", subjects with at least one of these most frequent non-serious TEAEs will be counted.

7.4.2   PRETREATMENT EVENTS

7.4.2.1   DISPLAYS OF PRETREATMENT EVENTS

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variables: PTE

Analytical Methods: The following summaries will be provided using frequency distribution.

PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**32 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term
(2) Serious Pretreatment Events by System Organ Class and Preferred Term
The frequency distribution will be provided according to the rules below.
<u>Number of subjects</u>
A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

7.4.3 LABORATORY AND OTHER SAFETY DATA

7.4.3.1 LABORATORY TEST RESULTS

<u>Hematology and Serum Chemistry</u>

Analysis Set: Safety Analysis Set

Analysis Variables : Hematology

Red Blood Cells ($\times 10^{12}$/L)	White Blood Cells ($\times 10^9$/L)	Hemoglobin (g/L)
Hematocrit (%)	Platelets ($\times 10^9$/L)	

White Blood Cell Fractions (Neutrophils (%), Eosinophils (%), Basophils (%), Monocytes (%), Lymphocytes (%))

Serum Chemistry

ALT (U/L)	ALP (U/L)	AST (U/L)
GGT (U/L)	Total Bilirubin (μmol/L)	Direct Bilirubin (μmol/L)
LDH (U/L)	CK (CPK) (U/L)	Albumin (g/L)
Total Protein (g/L)	Creatinine (μmol/L)	BUN (mmol/L)
Uric Acid (mmol/L)	Total Cholesterol (mmol/L)	Triglycerides (mmol/L)
Glucose (mmol/L)	Potassium (mmol/L)	Sodium (mmol/L)
Magnesium (mmol/L)	Calcium (mmol/L)	Inorganic Phosphorus (mmol/L)
Chloride (mmol/L)	Serum Iron (μmol/L)	Vitamin B_{12} (pmol/L)

Visit: ALT, AST, Total Bilirubin, and Direct Bilirubin:
Baseline, Week 2, Week 4, Week 6, Week 8
Variables other than ALT, AST, Total Bilirubin, and Direct Bilirubin:
Baseline, Week 2, Week 4, Week 8

Analytical Methods: For each variable, summaries (1) and (2) will be provided by treatment group.
For applicable variables, summaries (3) and (4) will be provided by treatment group.
(1) Summary of Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each post-baseline visit - baseline) will be provided for each visit.

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**33 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

(2) Summary of Shifts of Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided. For each laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" relative to the normal reference range provided by the central laboratory. The shift tables will be based on these classifications.

(3) Number and Percentage of Subjects with Markedly Abnormal Values of Laboratory Parameters

Overall frequency distributions of MAV during treatment phase will be provided. If a laboratory parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

(4) Number and Percentage of Subjects with Elevated Liver Enzyme Laboratory Parameters

Overall frequency distributions of elevated hepatic parameters during treatment phase will be provided. Further details are given in Appendix.

Urinalysis

Analysis Set:	Safety Analysis Set
Analysis Variables :	Protein [Neg, Trace, 30 mg/dL, 100 mg/dL, 300 mg/dL, >=2000 mg/dL]
	Sugar [Neg, 100 mg/dL, 250 mg/dL, 500 mg/dL, 1000 mg/dL, >=2000 mg/dL]
Visit:	Baseline, Week 2, Week 4, Week 8
Analytical Methods:	The following summaries will be provided for each treatment group.

(1) Summary of Shifts of Urine Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

Serum Gastrin, Pepsinogen I/II

Analysis Set:	Safety Analysis Set
Analysis Variables :	Serum Gastrin (pmol/L)
	Pepsinogen I (µg/L)
	Pepsinogen II (µg/L)
	Pepsinogen I/II Ratio
Visit:	Baseline, Week 2, Week 4, Week 8
Analytical Methods:	The following summaries will be provided for each treatment group.

(1) Summary of Serum Gastrin and Pepsinogen I/II Results

For each visit, descriptive statistics for observed values and changes from baseline (each post-baseline visit - baseline) will be provided.

CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**34 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

7.4.4 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Vital Signs

Analysis Set:	Safety Analysis Set
Analysis Variables:	Body Temperature (C)
	Systolic Blood Pressure (mmHg)
	Diastolic Blood Pressure (mmHg)
	Pulse (bpm)
Visit:	Baseline, Week 2, Week 4, Week 8
Analytical Methods:	For each variable, summaries (1) and (2) will be provided by treatment group.

(1) Summary of Vital Signs Parameters and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline (each post-baseline visit – baseline) will be provided for each visit.

(2) Number and Percentage of Subjects with Markedly Abnormal Values of Vital Signs Parameters

Overall frequency distributions of MAV during treatment phase will be provided. If a vital sign parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

12-lead ECG

Analysis Set:	Safety Analysis Set
Analysis Variables:	Heart Rate (bpm)
	RR Interval (msec)
	PR Interval (msec)
	QT Interval (msec)
	QTcF Interval (msec)
	QRS Interval (msec)
	Interpretation ["Within Normal Limits",
	"Abnormal, Not Clinically Significant",
	"Abnormal, Clinically Significant"]
Visit:	Baseline, Week 2, Week 4, Week 8
Analytical Methods:	For each variable other than interpretations, summary (1) will be provided by treatment group.
	For applicable variables, summary (2) will be provided by treatment group.
	For interpretation, summary (3) will be provided by treatment group.

(1) Summary of ECG Parameters and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline (each post-baseline visit – baseline) will be provided for each visit.

(2) Number and Percentage of Subjects with Markedly Abnormal Values of ECG Parameters

Overall frequency distributions of MAV during treatment phase will be provided. If an

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**35 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

ECG laboratory parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

(3) Summary of Shifts of ECG Parameters

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

7.4.5 SUBGROUP ANALYSIS FOR CHINA

Analysis Population: Subjects in China

Analytical Methods: The same analyses as those in section 7.2 to 7.4.4 will be conducted for the subjects in China.

7.4.6 SUBGROUP ANALYSIS FOR KOREA

Analysis Population: Subjects in Korea

Subjects in Countries other than Korea

Analytical Methods: (1) The same analyses as those in the following sections will be conducted for the subjects in Korea.

- Section 7.2.1.5, 7.2.2.1, 7.2.3.1
- Section 7.3.1.1, 7.3.2.1, 7.3.2.2, 7.3.3.1 ("Heartburn Symptom" (Analysis Variables (1), (2), (3), (5), (8)), "Gastric Acid Regurgitation" (Analysis Variables (1), (2), (3), (5), (8))), 7.3.3.4, 7.3.4.8
- Section 7.4.1.1, 7.4.1.2 ((1), (4) – (17)), 7.4.3, 7.4.4

(2) The same analyses as those in the following sections will be conducted for the subjects in countries other than Korea.

- Section 7.2.1.5, 7.2.2.1, 7.2.3.1
- Section 7.3.1.1, 7.3.2.1, 7.3.2.2, 7.3.3.1 ("Heartburn Symptom" (Analysis Variables (1), (2), (3), (5), (8)), "Gastric Acid Regurgitation" (Analysis Variables (1), (2), (3), (5), (8))), 7.3.3.4, 7.3.4.8
- Section 7.4.1.1, 7.4.1.2 ((1), (4) – (17)), 7.4.3, 7.4.4

7.4.7 SUBGROUP ANALYSIS FOR TAIWAN

Analysis Population: Subjects in Taiwan

Subjects in Countries other than Taiwan

Analytical Methods: (1) The same analyses as those in the following sections will be conducted for the subjects in Taiwan.

- Section 7.2.1.5, 7.2.2.1, 7.2.3.1
- Section 7.3.1.1, 7.3.2.1, 7.3.2.2, 7.3.3.1 ("Heartburn Symptom" (Analysis Variables (1), (2), (3), (5), (8)), "Gastric Acid Regurgitation" (Analysis Variables (1), (2), (3), (5), (8))), 7.3.3.4, 7.3.4.8
- Section 7.4.1.1, 7.4.1.2 ((1), (4) – (17)), 7.4.3, 7.4.4

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**36 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

(2) The same analyses as those in the following sections will be conducted for the subjects in countries other than Taiwan.

- Section 7.2.1.5, 7.2.2.1, 7.2.3.1
- Section 7.3.1.1, 7.3.2.1, 7.3.2.2, 7.3.3.1 ("Heartburn Symptom" (Analysis Variables (1), (2), (3), (5), (8)), "Gastric Acid Regurgitation" (Analysis Variables (1), (2), (3), (5), (8))), 7.3.3.4, 7.3.4.8
- Section 7.4.1.1, 7.4.1.2 ((1), (4) – (17)), 7.4.3, 7.4.4

7.4.8 SIGNIFICANCE LEVEL AND CONFIDENCE COEFFICIENT

- Significance level: 5% (two-sided test)
- Confidence coefficient: 95% (two-sided)

No statistical testing will be performed if there are less than 5 subjects.

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**37 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

7.4.9 CHANGES IN THE STATISTICAL ANALYSIS PLAN

The changes from the original SAP (Version: 1, Date: 01 September 2015) to the amended SAP were described below with a rationale for changes provided.
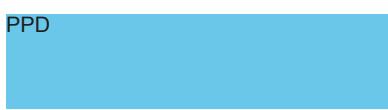
Page 1, TITLE PAGE

Existing Text

PPD

Revised Text

PPD

Rationale for Amendment

The department and position of the responsible person have been changed.

Page 2, Section 1.0 APPROVAL SIGNATURES

Existing Text

PPD

Revised Text

PPD

Rationale for Amendment

The Responsible persons have been changed.

Page 7, Section 4.4. STUDY DESIGN

Existing Text

The study will consist of a Screening Phase of up to 28 days including an Observation Phase of 3-7 days prior to the randomization visit (Day 1), during which a baseline observation of EE symptoms will be completed, and then a Treatment Phase of up to 8 weeks. There will be 5 subject visits scheduled: the start of the Observation Phase (Visit 1), the start of the Treatment Phase (Visit 2), after 2 weeks of treatment (Visit 3), after 4 weeks of treatment (Visit 4), after 8 weeks of treatment (Visit 5), and a phone call during the Follow-up phase (only for those not participate in TAK-438_305 study).

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**38 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

Revised Text

The study will consist of a Screening Phase of up to 28 days, including an Observation Phase of 3-7 days prior to the randomization visit (Day 1), during which a baseline observation of EE symptoms will be completed, and then a Treatment Phase of up to 8 weeks. There will be 6 subject visits scheduled: the start of the Observation Phase (Visit 1), the start of the Treatment Phase (Visit 2), after 2 weeks of treatment (Visit 3), after 4 weeks of treatment (Visit 4), after 6 weeks of treatment (Visit 5), after 8 weeks of treatment (Visit 6), and a phone call during the Follow-up phase (only for those not participating in TAK-438_305 study).

Rationale for Amendment

Visit 5 (6 weeks of treatment) has been added in the protocol.

Page 11, Section 7.1.1 DEFINITIONS

Added Text

A TEAE whose relationship to study drug is missing will be considered drug-related. A TEAE whose intensity is missing will be considered severe.

Rationale for Amendment

The handling rules for missing data for TEAE have been added.

Page 11, Section 7.1.1 DEFINITIONS

Added Text

Pepsinogen I/II Ratio: Pepsinogen I (µg/L) / Pepsinogen II (µg/L) (rounded to 1 decimal place)

Rationale for Amendment

The calculation formula for the above variable has been added with the number of decimal places.

Page 11, Section 7.1.1 DEFINITIONS

Added Text

Significant TEAE: Any TEAE (not including serious TEAEs) that led to an intervention, including withdrawal of drug treatment, dose increase, dose reduction or significant additional concomitant therapy.

Rationale for Amendment

The significant TEAE should be analyzed and the definition of this type of TEAE has been added.

Page 13, Section 7.1.5 HANDLING OF DATA WHEN CALCULATING MEAN SEVERITY ACCORDING TO SUBJECT DIARY

Existing Text

Mean severity = (total score of the severity recorded for the visit) / (number of days the severity of symptom is recorded) * 100 (rounded to 2 decimal places)

CROSS-REGIONAL TEMPLATE

Template Number:	C-TMPL-DO-801	**Page:**	**39 of 51**
Version Number:	1.0	**Effective Date:**	**02 Apr 2014**
This version replaces:	TMPL-104		
Template Title:	Statistical Analysis Plan (Legacy Takeda)		

Revised Text

Mean severity = (total score of the severity recorded for the visit) / (number of days the severity of symptom is recorded) (rounded to 2 decimal places)

Rationale for Amendment

The expression "* 100" has been deleted because of clerical error.

Page 15, Section 7.1.9 HANDLING OF DATA WHEN CALCULATING PROPORTION OF DAYS WITHOUT RESCUE MEDICATION

Existing Text

One month to the Day of Last Dose	27 days before the last dose – day of last dose	up to and including Follow-up Day 1

Revised Text

One Month to the Day of Last Dose	27 days before the last dose – day of last dose	

Rationale for Amendment

The expression "m" has been replaced with "M". The condition "up to and including Follow-up Day 1" was not a clerical error, but the condition was not necessary because there was the condition "27 days before the last dose - day of last dose".

Page 16, Section 7.1.10 HANDLING OF OTHER ENDPOINTS

Added Text

If there are two observations with the same Study Day, the earlier observation will be used.

Rationale for Amendment

The handling rules of multiple observations with the same Study Day have been added.

Page 16, Section 7.1.10 HANDLING OF OTHER ENDPOINTS

Existing Text

Endoscopy (Barrett's mucosa), Clinical laboratory tests, Gastrin, Pepsinogen I/II, Vital signs, 12-lead ECG

Revised Text

Endoscopy (Barrett's mucosa), Clinical laboratory tests (other than ALT, AST, total bilirubin, and direct bilirubin), Gastrin, Pepsinogen I/II, Vital signs, 12-lead ECG

(omitted)

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**40 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

Clinical laboratory tests (ALT, AST, total bilirubin, and direct bilirubin)

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-28 – 1	
Week 2	Study Day: 15	2 – 21	up to and including Follow-up Day 14
Week 4	Study Day: 29	22 – 35	up to and including Follow-up Day 14
Week 6	Study Day: 43	36 – 49	up to and including Follow-up Day 14
Week 8	Study Day: 57	50 – 71	up to and including Follow-up Day 14

Rationale for Amendment

Visit 5 (6 weeks of treatment) has been added in the protocol for evaluating liver function tests (ALT, AST, total bilirubin, and direct bilirubin).

Page 18, Section 7.2.1.5 DISPOSITION OF SUBJECTS

Added Text

(2) Flow Chart of Subject Distribution

Flow chart will be provided.

Rationale for Amendment

The analysis for providing a flow chart has been added.

Page 22, Section 7.3.2.1 RATE OF ENDOSCOPIC HEALING OF EROSIVE ESOPHAGITIS DURING THE 2-WEEK TREATMENT

Existing Text

The primary efficacy endpoint will be first tested for non-inferiority. If non-inferiority with regard to the primary efficacy endpoint is established, then the secondary efficacy endpoint "The Rate of Endoscopic Healing of Erosive Esophagitis during the 2-week Treatment" will be tested for superiority.

Revised Text

Details concerning interpretation are described in section 7.3.4.5.

Rationale for Amendment

The details concerning interpretation has been moved to section 7.3.4.5.

Page 23, Section 7.3.2.2 RATE OF ENDOSCOPIC HEALING OF EROSIVE ESOPHAGITIS DURING THE 4-WEEK TREATMENT

Added Text

Details concerning interpretation are described in section 7.3.4.5.

CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**41 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

Rationale for Amendment

The interpretation for the test of "The Rate of Endoscopic Healing of Erosive Esophagitis During the 4-week Treatment" has been added to section 7.3.4.5 to be clarified.

Page 26, Section 7.3.3.4 BARRETT'S MUCOSA

Existing Text

Present (3 cm or greater)

Revised Text

Present (3 cm or Greater)

Rationale for Amendment

The expression "greater" has been replaced with "Greater" because of clerical error.

Page 27, Section 7.3.4.2 HANDLING OF DROPOUTS OR MISSING DATA

Added Text

Values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. Values above the upper limit of quantification will be treated as the upper limit values when calculating the descriptive statistics.

Rationale for Amendment

The handling rules of values below the lower or upper limit values for calculating the descriptive statistics have been added.

Page 27, Section 7.3.4.5 MULTIPLE COMPARISON/MULTIPLICITY

Existing Text

Adjustment for multiplicity will be performed for the primary efficacy endpoint "The Rate of Endoscopic Healing of Erosive Esophagitis during the 8-week Treatment" and the secondary efficacy endpoint "The Rate of Endoscopic Healing of Erosive Esophagitis during the 2-week Treatment" in the following fashion. The primary endpoint will be first tested for non-inferiority. If non-inferiority with regard to the primary endpoint is established, then the secondary endpoint will be tested for superiority. This procedure is based on the closed testing principle and the analysis will be conducted using the full analysis set.

Revised Text

Adjustment for multiplicity will be performed for the primary efficacy endpoint "The Rate of Endoscopic Healing of Erosive Esophagitis during the 8-week Treatment" and the secondary efficacy endpoints "The Rate of Endoscopic Healing of Erosive Esophagitis during the 2-week Treatment" and "The Rate of Endoscopic Healing of Erosive Esophagitis During the 4-week Treatment" in the following fashion. The following procedure is based on the closed testing principle and the analysis will be conducted using the full analysis set.

- The primary endpoint "The Rate of Endoscopic Healing of Erosive Esophagitis during the 8-week Treatment" will be tested for non-inferiority between the TAK-438 group and the Lansoprazole group. If the lower bound of the 95% confidence interval of the treatment difference (the TAK-438 group – the Lansoprazole group) is ≥-10%, non-inferiority for TAK-438 relative to Lansoprazole will be declared.

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CROSS-REGIONAL TEMPLATE

Template Number:	C-TMPL-DO-801	**Page:**	**42 of 51**
Version Number:	1.0	**Effective Date:**	**02 Apr 2014**
This version replaces:	TMPL-104		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

- If the previous test is successful, the secondary endpoint "The Rate of Endoscopic Healing of Erosive Esophagitis during the 2-week Treatment" will be tested for superiority between the TAK-438 group and the Lansoprazole group. The lower bound of the 95% confidence interval of the treatment difference (the TAK-438 group – the Lansoprazole group) will be compared to 0%.

- If the previous test is successful, the primary endpoint "The Rate of Endoscopic Healing of Erosive Esophagitis during the 8-week Treatment" will be tested for superiority between the TAK-438 group and the Lansoprazole group.

- If the previous test is successful, the secondary endpoint "The Rate of Endoscopic Healing of Erosive Esophagitis during the 4-week Treatment" will be tested for superiority between the TAK-438 group and the Lansoprazole group.

Rationale for Amendment

The interpretation for the superiority tests of "The Rate of Endoscopic Healing of Erosive Esophagitis During the 8-week Treatment" and "The Rate of Endoscopic Healing of Erosive Esophagitis During the 4-week Treatment" has been explicitly added to the procedure already defined in the protocol. The revised procedure is still based on the closed testing principle and maintains maintain a Type 1 error rate at 5%.

Page 29, Section 7.4.1.1 OVERVIEW OF TREATMENT-EMERGENT ADVERSE EVENTS

Added Text

5) Relationship to Study Drug of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (number of events, number and percentage of subjects)

11) Significant Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)

Rationale for Amendment

The analyses for these types of TEAEs has been added.

Page 30, Section 7.4.1.2 DISPLAYS OF TREATMENT-EMERGENT ADVERSE EVENTS

Existing Text

System Organ Class

Revised Text

SOC

Rationale for Amendment

The expression "System Organ Class" has been replaced with "SOC" for expression consistency.

Page 30, Section 7.4.1.2 DISPLAYS OF TREATMENT-EMERGENT ADVERSE EVENTS

Added Text

(8) Drug-Related Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term

(10) Serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

CROSS-REGIONAL TEMPLATE

Template Number:	C-TMPL-DO-801	**Page:**	**43 of 51**
Version Number:	1.0	**Effective Date:**	02 Apr 2014
This version replaces:	TMPL-104		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

(15) Significant Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(16) Drug-Related Significant Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(17) Most Frequent Non Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

Summary table for (17)

Most frequent non-serious TEAEs refer to PTs that are not serious whose percentages are at least 5% in any one of the treatment groups. If there are no PTs whose percentages exceed 5%, the threshold is lowered to 2%. When counting the number of "Subjects With Any TEAEs", subjects with at least one of these most frequent non-serious TEAEs will be counted.

Rationale for Amendment

The analyses for these types of TEAEs has been added.

Page 32, Section 7.4.3.1 LABORATORY TEST RESULTS (Hematology and Serum Chemistry)

Existing Text

Visit: Baseline, Week 2, Week 4, Week 8

Revised Text

Visit: ALT, AST, Total Bilirubin, and Direct Bilirubin:
          Baseline, Week 2, Week 4, Week 6, Week 8
         Variables other than ALT, AST, Total Bilirubin, and Direct Bilirubin:
          Baseline, Week 2, Week 4, Week 8

Rationale for Amendment

Week 6 has been added in the protocol for evaluating liver function tests (ALT, AST, total bilirubin, and direct bilirubin).

Page 33, Section 7.4.3.1 LABORATORY TEST RESULTS (Serum Gastrin, Pepsinogen I/II)

Existing Text

Pepsinogen I (mcg/L), Pepsinogen II (mcg/L)

Revised Text

Pepsinogen I (μg/L), Pepsinogen II (μg/L)

Rationale for Amendment

The expression "mcg" has been replaced with "μg" for using more suitable expression.

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**44 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

Page 34, Section 7.4.4 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY (Vital Signs)

Existing Text

Body Temperature (°C)

Revised Text

Body Temperature (C)

Rationale for Amendment

The expression "°C" has been replaced with "C" for using more suitable expression.

Page 34, Section 7.4.4 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY (12-lead ECG)

Existing Text

Visit: Baseline, Week 2, Week 8
Revised Text

Visit: Baseline, Week 2, Week 4, Week 8
Rationale for Amendment

Week 4 has been added because of clerical error.

Page 34, Section 7.4.4 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY (12-lead ECG)

Existing Text

12-lead ECG interpretations (3 places)

Revised Text

interpretations (3 places)

Rationale for Amendment

The expression "12-lead ECG" has been deleted for expression consistency with TFLs.

Page 35, Section 7.4.6 SUBGROUP ANALYSIS FOR KOREA

Existing Text

· Section 7.3.1.1, 7.3.2.1, 7.3.2.2, 7.3.3.1 ("Heartburn Symptom" (Analysis Variables (1), (2), (5), (8)), "Gastric Acid Regurgitation" (Analysis Variables (1), (2), (5), (8))), 7.3.4.8
· Section 7.4.1.1, 7.4.1.2 ((1), (4) – (12)), 7.4.3.1 ("Hematology and Serum Chemistry" (3) and "Serum Gastrin, Pepsinogen I/II (1)"), 7.4.4 ("Vital Signs" (2) and "12-lead ECG " (2))   (2 places)

Revised Text

· Section 7.3.1.1, 7.3.2.1, 7.3.2.2, 7.3.3.1 ("Heartburn Symptom" (Analysis Variables (1), (2), (3), (5), (8)), "Gastric Acid Regurgitation" (Analysis Variables (1), (2), (3), (5), (8))), 7.3.3.4, 7.3.4.8

CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**45 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

- Section 7.4.1.1, 7.4.1.2 ((1), (4) – (17)), 7.4.3, 7.4.4   (2 places)

Rationale for Amendment

The analyses for the underlined part have been added.

Page 35

Added Text

7.4.7 SUBGROUP ANALYSIS FOR TAIWAN

Analysis Population: Subjects in Taiwan

Subjects in Countries other than Taiwan

Analytical Methods: (1) The same analyses as those in the following sections will be conducted for the subjects in Taiwan.
- Section 7.2.1.5, 7.2.2.1, 7,2,3,1
- Section 7.3.1.1, 7.3.2.1, 7.3.2.2, 7.3.3.1 ("Heartburn Symptom" (Analysis Variables (1), (2), (3), (5), (8)), "Gastric Acid Regurgitation" (Analysis Variables (1), (2), (3), (5), (8))), 7.3.3.4, 7.3.4.8
- Section 7.4.1.1, 7.4.1.2 ((1), (4) – (17)), 7.4.3, 7.4.4

(2) The same analyses as those in the following sections will be conducted for the subjects in countries other than Taiwan.
- Section 7.2.1.5, 7.2.2.1, 7,2,3,1
- Section 7.3.1.1, 7.3.2.1, 7.3.2.2, 7.3.3.1 ("Heartburn Symptom" (Analysis Variables (1), (2), (3), (5), (8)), "Gastric Acid Regurgitation" (Analysis Variables (1), (2), (3), (5), (8))), 7.3.3.4, 7.3.4.8
- Section 7.4.1.1, 7.4.1.2 ((1), (4) – (17)), 7.4.3, 7.4.4

Rationale for Amendment

The analyses for the underlined part have been added.

Page 47, Section 8.0 REFERENCES

Added Text

Luo N, et. al. (2017) "Estimating an EQ-5D-5L Value Set for China", Value in Health, Volume 20(4): 662-669.

Rationale for Amendment

The above reference has been added.

Page 49, Section 9.1.1 HEMATOLOGY, SERUM CHEMISTRY, URINALYSIS, VITAL SIGNS, AND 12-LEAD ECG (EXCEPT UPPER MAV CRITERIA OF QTCF INTERVAL) (Vital Signs)

Existing Text

Body Temperature (°C)

Revised Text

Body Temperature (C)

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**46 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

Rationale for Amendment

The expression "°C" has been replaced with "C" for using more suitable expression.

CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**47 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

8.0   REFERENCES

- DeLong ER, et. al. (1988) "Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach", Biometrics, Volume 44(3): 837-45.

- Divine G, et al. (2013) "A review of analysis and sample size calculation considerations for Wilcoxon tests", Anesth Analg, Volume 117(3): 699-710.

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- Mason SJ, et. al. (2002) "Areas beneath the relative operating characteristics (ROC) and relative operating levels (ROL) curves: Statistical significance and interpretation", Quarterly Journal of the Royal Meteorological Society (128): 2145-2166.

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- Luo N, et. al. (2017) "Estimating an EQ-5D-5L Value Set for China", Value in Health, Volume 20(4): 662-669.

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CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:**	**48 of 51**
Version Number:	**1.0**	**Effective Date:**	**02 Apr 2014**
This version replaces:	**TMPL-104**		
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**		

9.0 APPENDIX

9.1 CRITERIA FOR MARKEDLY ABNORMAL VALUES

9.1.1 HEMATOLOGY, SERUM CHEMISTRY, URINALYSIS, VITAL SIGNS, AND 12-LEAD ECG (EXCEPT UPPER MAV CRITERIA OF QTCF INTERVAL)

For each parameter, all evaluable data (i.e., non-missing data) obtained up to Follow-up Day 14 will be classified as a MAV or not. The criteria in the table below will be used.

For each parameter and subject, classifications will be made according to the conditions i) to iii) provided below. The lower and the upper criteria will be considered separately.

i) A subject with at least one evaluable data after baseline that meets the MAV criteria will be classified as a subject with MAV.

ii) A subject who does not meet condition i) and has at least one evaluable data after baseline that doesn't meet the MAV criteria will be considered as a subject without MAV.

iii) A subject who does not meet conditions i) or ii) will be excluded from the analysis of MAV for that parameter.

Hematology

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
Red Blood Cells ($\times 10^{12}$/L)	<0.8×LLN	>1.2×ULN
White Blood Cells ($\times 10^{9}$/L)	<0.5×LLN	>1.5×ULN
Hemoglobin (g/L)	<0.8×LLN	>1.2×ULN
Hematocrit (%)	<0.8×LLN	>1.2×ULN
Platelets ($\times 10^{9}$/L)	<75	>600
Neutrophils (%)	<0.5×LLN	>1.5×ULN
Eosinophils (%)	-	>2×ULN
Basophils (%)	-	>3×ULN
Monocytes (%)	-	>2×ULN
Lymphocytes (%)	<0.5×LLN	>1.5×ULN

Serum Chemistry

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
ALT (U/L)	-	>3×ULN
ALP (U/L)	-	>3×ULN
AST (U/L)	-	>3×ULN
GGT (U/L)	-	>3×ULN
Total Bilirubin (μmol/L)	-	>34.2
Direct Bilirubin (μmol/L)	-	>2×ULN
CK (CPK) (U/L)	-	>5×ULN
Albumin (g/L)	<25	-
Total Protein (g/L)	<0.8×LLN	>1.2×ULN
Creatinine (μmol/L)	-	>177
BUN (mmol/L)	-	>10.7

CROSS-REGIONAL TEMPLATE

Template Number:	C-TMPL-DO-801	Page:	49 of 51
Version Number:	1.0	Effective Date:	02 Apr 2014
This version replaces:	TMPL-104		
Template Title:	Statistical Analysis Plan (Legacy Takeda)		

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
Uric Acid (mmol/L)	-	>0.773
Total Cholesterol (mmol/L)	-	>7.72
Triglycerides (mmol/L)	-	>2.5×ULN
Glucose (mmol/L)	<2.8	>19.4
Potassium (mmol/L)	<3.0	>6.0
Sodium (mmol/L)	<130	>150
Magnesium (mmol/L)	<0.5	>1.2
Calcium (mmol/L)	<1.75	>2.88
Inorganic Phosphorus (mmol/L)	<0.52	>2.00
Chloride (mmol/L)	<75	>126
Vitamin B$_{12}$ (pmol/L)	<92	-

Vital Signs

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
Body Temperature (C)	<35.6	>37.7
Systolic Blood Pressure (mmHg)	<85	>180
Diastolic Blood Pressure (mmHg)	<50	>110
Pulse (bpm)	<50	>120

12-lead ECG

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
Heart Rate (bpm)	<50	>120
QT Interval (msec)	<=50	>=460
QTcF Interval (msec)	<=50	-

9.1.2 12-LEAD ECG (UPPER MAV CRITERIA OF QTcF INTERVAL)

All evaluable data (i.e., non-missing data) obtained up to Follow-up Day 14 will be classified as a MAV or not. The criteria in the table below will be used. Note that the observed value and the change from baseline used for classification should be measurements taken on the same day.

For each subject, classifications will be made according to the conditions i) to iii) provided below.

i) A subject with at least one evaluable data after baseline that meets the MAV criteria will be classified as a subject with MAV.

ii) A subject who does not meet condition i) and has at least one evaluable data after baseline that meets any of the following will be considered as a subject without MAV.
   · Observed value is less than 450 msec and not missing.
   · Change from baseline is less than 30 msec and not missing, and observed value is less than 500 msec and not missing.

iii) A subject who does not meet conditions i) or ii) will be excluded from the analysis of MAV.

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CROSS-REGIONAL TEMPLATE

Template Number:	C-TMPL-DO-801	Page:	50 of 51
Version Number:	1.0	Effective Date:	02 Apr 2014
This version replaces:	TMPL-104		
Template Title:	Statistical Analysis Plan (Legacy Takeda)		

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
QTcF Interval (msec)	-	If either of the following conditions is met: • observed value >=500 • change from baseline >= 30 and observed value >=450

9.2 CRITERIA FOR ELEVATED LIVER ENZYME

All evaluable data (i.e., non-missing data) obtained up to Follow-up Day 14 will be used to determine whether each criteria for elevated liver enzyme in the table below is met or not. If there is more than one parameter that need to be considered for a criteria, parameter measurements taken on the same day will be used. For each criteria and subject, classifications will be made according to the conditions i) to iii) provided below.

i) A subject who met criteria (a) at least once after baseline will be considered to have met the criteria for elevated liver enzyme.

ii) If condition i) is not met but if criteria (b) is met at least once after baseline, then the subject will be considered to have not met the criteria for elevated liver enzyme.

iii) If neither i) nor ii) is met, then the subject will be excluded from the analysis for the criteria for elevated liver enzyme.

Label	Criteria for Elevated Liver Enzyme	
	(a) Elevated	(b) Not Elevated
ALT > 3xULN	ALT is greater than 3 times the ULN	ALT is non-missing and less than or equal to 3 times the ULN
ALT > 5xULN	ALT is greater than 5 times the ULN	ALT is non-missing and less than or equal to 5 times the ULN
ALT > 8xULN	ALT is greater than 8 times the ULN	ALT is non-missing and less than or equal to 8 times the ULN
ALT > 3xULN with Tbili > 2xULN	ALT is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	Either ALT is non-missing and less than or equal to 3 times the ULN, or the total bilirubin is non-missing and less than or equal to twice the ULN
AST > 3xULN	AST is greater than 3 times the ULN	AST is non-missing and less than or equal to 3 times the ULN
AST > 5xULN	AST is greater than 5 times the ULN	AST is non-missing and less than or equal to 5 times the ULN
AST > 8xULN	AST is greater than 8 times the ULN	AST is non-missing and less than or equal to 8 times the ULN
AST > 3xULN with Tbili > 2xULN	AST is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	Either AST is non-missing and less than or equal to 3 times the ULN, or the total bilirubin is non-missing and less than or equal to twice the ULN
ALT or AST > 3xULN	Either ALT or AST is greater than 3 times the ULN	Both ALT and AST are non-missing and less than or equal to 3 times the ULN
ALT or AST > 5xULN	Either ALT or AST is greater than 5 times the ULN	Both ALT and AST are non-missing and less than or equal to 5 times the ULN

CROSS-REGIONAL TEMPLATE

Template Number:	**C-TMPL-DO-801**	**Page:** 51 of 51
Version Number:	**1.0**	**Effective Date:** 02 Apr 2014
This version replaces:	**TMPL-104**	
Template Title:	**Statistical Analysis Plan (Legacy Takeda)**	

Label	Criteria for Elevated Liver Enzyme	
	(a) Elevated	(b) Not Elevated
ALT or AST > 8xULN	Either ALT or AST is greater than 8 times the ULN	Both ALT and AST are non-missing and less than or equal to 8 times the ULN
ALT or AST > 3xULN with Tbili > 2xULN	Either ALT or AST is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	If any of the following conditions is met: - Both ALT and AST are non-missing and less than or equal to 3 times the ULN. - Total bilirubin is non-missing and less than or equal to twice the ULN.
ALT and AST > 3xULN	Both ALT and AST are greater than 3 times the ULN	Either ALT is non-missing and less than or equal to 3 times the ULN, or AST is non-missing and less than or equal to 3 times the ULN
ALT and AST > 5xULN	Both ALT and AST are greater than 5 times the ULN	Either ALT is non-missing and less than or equal to 5 times the ULN, or AST is non-missing and less than or equal to 5 times the ULN
ALT and AST > 8xULN	Both ALT and AST are greater than 8 times the ULN	Either ALT is non-missing and less than or equal to 8 times the ULN, or AST is non-missing and less than or equal to 8 times the ULN
ALT and AST > 3xULN with Tbili > 2xULN	Both ALT and AST are greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	If any of the following conditions is met: - ALT is non-missing and less than or equal to 3 times the ULN - AST is non-missing and less than or equal to 3 times the ULN - Total bilirubin is non-missing and less than or equal to twice the ULN
ALP > 3xULN	ALP is greater than 3 times the ULN	ALP is non-missing and less than or equal to 3 times the ULN
ALP > 3xULN with ALT > 3xULN	Both ALP and ALT are greater than 3 time the ULN	Either ALP is non-missing and less than or equal to 3 times the ULN, or ALT is non-missing and less than or equal to 3 times the ULN
ALP > 3xULN with AST > 3xULN	Both ALP and AST are greater than 3 times the ULN	Either ALP is non-missing and less than or equal to 3 times the ULN, or AST is non-missing and less than or equal to 3 times the ULN

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Statistical Approval	25-Aug-2017 00:59 UTC
	Biostatistics Approval	25-Aug-2017 09:49 UTC
	Pharmacovigilance Approval	25-Aug-2017 10:01 UTC
	Clinical Science Approval	30-Aug-2017 08:30 UTC