

Title: A Randomized, Double-Blind, Double-Dummy, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of Oral Once-Daily Administration of TAK-438 10 or 20 mg Compared to Lansoprazole 15 mg in the Maintenance Treatment of Subjects With Endoscopic Healing of Erosive Esophagitis

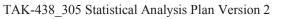
NCT Number: NCT02388737

SAP Approve Date: 08 January 2019

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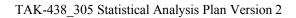




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3.0	LIST OF AB	BREVIATIONS		
AE		adverse event		الم
ALT		alanine aminotransferase		XO
ALP		alkaline phosphatase		
ANCOVA	L	analysis of covariance		2010
AST		aspartate aminotransferase		
BMI		body mass index		
BUN		blood urea nitrogen	2	
CMH		Cochran-Mantel-Haenszel	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	
СРК		creatine phosphokinase	N/	
ECG		electrocardiogram	χ×Ο	
EQ-5D-5I		the 5-level version of the EuroQOL	five dimensions questionnair	e
FAS		full analysis set	101	
GGT		γ-glutamyl transferase	SUL	
H. pylori		Helicobacter pylori	6	
HRQoL		Health-Related Quality of Life		
LA classif	ication	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		
MMRM		mixed model repeated measures ana	llysis	
PPI		proton pump inhibitor		
PPS		per protocol set		
QOL	0	quality-of-life		
QTcF	. (1	Fridericia's corrected QT		
SAP	1.01	statistical analysis plan		
Tbili TEAE	oda. For he	total bilirubin		
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		inferiority of TAK-438 to Lansop			

4.0 OBJECTIVES

4.1 **PRIMARY OBJECTIVES**

- To demonstrate the non-inferiority of TAK-438 to Lansoprazole in the reduction of relapse of erosive esophagitis in subjects in the Maintenance Phase (24 weeks) in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a PPI.
- To determine the clinically recommended dose of TAK-438 for maintenance therapy in erosive esophagitis in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a PPI.

4.2 SECONDARY OBJECTIVES

- To evaluate the efficacy of TAK-438 during the first 12-weeks of treatment in the Maintenance Phase in subjects with endoscopically confirmed healed erosive esophagitis receiving TAK-438 or a PPI.
- To evaluate the safety of TAK-438 versus Lansoprazole in subjects in the Maintenance Phase (24 weeks) in • whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a PPI.

ADDITIONAL OBJECTIVES 4.3

To evaluate the effect of TAK-438 on subjective symptoms of erosive esophagitis (heartburn and regurgitation) • and improvement in Health Related Quality of Life using the EuroQol (EQ-5D-5L).

4.4 STUDY DESIGN

This is a phase 3, multicenter, randomized double-blind, parallel-group study to demonstrate the non-inferiority of TAK-438 (10 mg or 20 mg) to Lansoprazole 15 mg in preventing the recurrence of erosive esophagitis in subjects with endoscopically confirmed healing of erosive esophagitis. This study also aims to determine the clinically recommended dose of TAK-438 for maintenance therapy of erosive esophagitis.

This study is comprised of 2 treatment periods: An open-label, single-arm period in which subjects receive Lansoprazole 30 mg for up to 8 weeks (Healing Phase), and a double-blind, parallel-group period in which subjects are randomized at a 1:1:1 ratio to TAK-438 10 mg, 20 mg or Lansoprazole 15 mg once daily for up to 24 weeks (Maintenance Phase). To entoil in the study subjects must have ongoing erosive esophagitis or have completed Study TAK-438 303. Subjects with ongoing erosive esophagitis are required to undergo the Healing Phase. Once erosive esophagitis healing is confirmed by endoscopy, these subjects may be randomized to 1 of 3 treatments in the Maintenance Phase. Subjects with endoscopic-confirmed healing of erosive esophagitis following the completion of Study TAK-438 303 will be randomized into the Maintenance Phase without carrying out the open-label Healing Phase. Subjects who previously entered the study (prior to Protocol Amendment 06) after confirmation of healed erosive esophagitis following treatment with a proton pump inhibitor (termed "de novo" subjects) are no longer eligible to enter the study; any ongoing subjects may continue being treated in the Maintenance Phase. A schematic of the study design is included in Figure 4.a.

If relapse of erosive esophagitis has been endoscopically confirmed in any subject, the subject will complete the study at that time point (to be construed as "complete cases in the Maintenance Phase"), regardless of the time point where relapse of disease is confirmed.

This study will be conducted at a total of around 70 sites across Asia with an estimated total of 231 subjects randomized to each treatment group during the Maintenance Phase (totaling 693 subjects entering the Maintenance Phase for the study).



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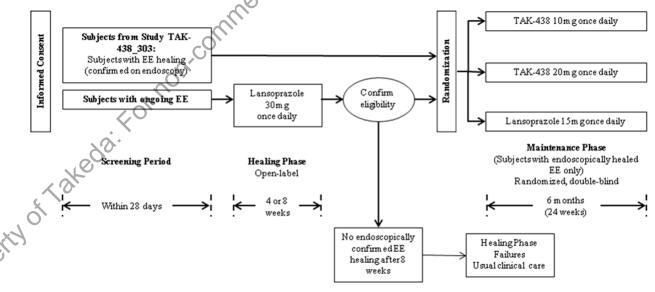
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The study will consist of a Screening Phase of up to 28 days duration (Visit 1), a Healing Phase (for those subjects with ongoing erosive esophagitis only) of 4 or 8 weeks duration (Visits 2_{HP} and 3_{HP}), followed by a Maintenance Phase of up to 24 weeks (Visits 2-8), and a Follow-up Period of up to 14 days duration. With the exception of the Follow-up (which will be carried out by phone), all visits will occur at the clinic. The total duration of treatment is up to 6 months (24 weeks) in subjects entering from Study TAK-438_303, and up to 8 months (32 weeks) in subjects entering the study with ongoing erosive esophagitis.

Subjects with ongoing erosive esophagitis: Subjects who have ongoing erosive esophagitis will enter the Healing Phase and administration of Lansoprazole 30 mg once daily will commence following the completion of all required assessments at Visit 2_{HP}. Subjects will then undergo a visit at Week -4 (Visit 3_{HP}), where the subject may undergo endoscopy to confirm healing of erosive esophagitis. This is an optional procedure where the decision to perform endoscopic healing at Visit 3_{HP} may continue in the Healing Phase and undergo endoscopy at Day 1 (Visit 2). Subjects with endoscopically confirmed healing of erosive esophagitis at Week -4 or at Day 1 will be eligible to enter the Maintenance Phase. Where the results from clinical laboratory tests confirming eligibility for the Maintenance Phase at Week -4 are not immediately available, subjects should continue to receive Lansoprazole 30 mg for up to 14 days. Subjects healed at Day 1 should be immediately randomized. Subjects who do not have endoscopic-confirmed healed erosive esophagitis after 8 weeks treatment (Healing Phase Failures) will not be randomized into the Maintenance Phase and should be treated using routine clinical care.

Subjects with healed erosive esophagitis: Subjects with healed erosive esophagitis will undergo a randomization visit (Visit 2), and dosing for the Maintenance Phase will commence following the completion of all required assessments on Day 1. Visits will then occur at 2 week intervals after the initiation of treatment in the Maintenance Phase. As a result of Protocol Amendment 06, subjects with healed erosive esophagitis following treatment with a proton pump inhibitor outside Study TAK-438_303 or the Healing Phase of the current study (*de novo* subjects) are no longer eligible to enter the study; any ongoing subjects may continue to be treated in the Maintenance Phase.

All subjects receiving TAK-438 must undergo a total of 8 weeks of LFT monitoring visits with visits occurring every 2 weeks. For subjects entering the Maintenance Phase of the current study within 7 days of completing Study TAK-438_303, the requirement for 8 weeks of monitoring can be totalled across the 2 studies.







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5.0 ANALYSIS EN	IDPOINTS			SOL
Primary Endpoint			x orn	*
The primary efficacy endpoin ndoscopy during the 24-week	t for this study is the rate of recurren k Maintenance Phase	ce* of erosive esophagitis as co	nfirmed on	

5.0 ANALYSIS ENDPOINTS

Primary Endpoint

The primary efficacy endpoint for this study is the rate of recurrence* of erosive esophagitis as confirmed on endoscopy during the 24-week Maintenance Phase.

*Recurrence: defined as subjects endoscopically confirmed to have erosive esophagitis (LA classification grades A to D) during the Maintenance Phase (24 weeks).

Secondary Endpoint

The secondary efficacy endpoint for this study is the rate of recurrence* of erosive esophagitis during the first 12 weeks of treatment in the Maintenance Phase. Safety endpoints for this study include adverse events (AEs), clinical laboratory test results, ECG, vital signs, serum gastrin and pepsinogen I/II levels

*Recurrence: defined as subjects endoscopically confirmed to have erosive esophagitis (LA classification grades A to D) during the Maintenance Phase (12 weeks). SU

Additional Endpoints

eropethor takeda. For non-commercial use Other efficacy endpoints include subjective symptoms of erosive sophagitis (heartburn and regurgitation) as recorded in subject diaries and Health-Related Quality of Life measures.



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JETERMINATION OF SAMPLE SIZE Assuming that the true Week 24 recurrence rate is 30.4% for Lansoprazole, 22.0% for TAK-438 10 mg, and 13.6% for TAK-438 20 mg, and assuming that the dropout rate is approximately 30%, a sample size of 208 subjects per group will provide an overall power of 90% to establish non-inferiority using a 2-sided 050/ CT TAK-438 10 mg and 13.6% for the included to all requirements of various countries.

The assumption of the true recurrence rate is based on a phase 3 study that showed a Week 24 recurrence rate of 30.4% for Lansoprazole 15 mg and 13.6% for Lansoprazole 30 mg.

fore s-30.7%. The supervise on and supervise property of takeda. For non-commercial use on wand supervised as the supervised of the superv Based on results from an earlier study of Lansoprazole as maintenance therapy for erosive esophagitis (AG-1749/CCT-202), the point estimate for the difference (Lansoprazole 15 mg group - famotidine group) was calculated as -57.6% with the upper limit of the confidence interval being -30.7%. Therefore, the non-inferiority



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.1	GENERAL CONS	IDERATIONS		1 ern	
.1.1	Definitions				
he follo	wing definitions and c	calculation formulas will be used.		C. C	

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 **GENERAL CONSIDERATIONS**

7.1.1 Definitions

- TEAE: An adverse event whose date of onset occurs on or after the start of the Maintenance Phase drug. A TEAE whose relationship to the Maintenance Phase 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 Maintenance Phase drug 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, eg, 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 Maintenance Phase drug 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 drug (days): date of last dose of Maintenance Phase drug date of first dose of Maintenance Phase drug + 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 drug * 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.

Analysis Sets 7.1.2

Analysis of efficacy variables will be conducted in the full analysis set (FAS) defined as all randomized subjects who receive at least 1 dose of the Maintenance Phase drug and have at least 1 post-baseline endoscopy, and will be based on the randomized treatment. Randomized subjects who were accidentally unblinded due to IWRS system error will be excluded.

The primary efficacy endpoint and the secondary efficacy endpoint 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.



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- Subjects who met exclu	usion criteria #8, #11, #12, #13, or #	414	~	S
- Subjects with study dru	g compliance of less than 70%		X OLL	
- Subjects who have beer	n unblinded prior to database lock		0	
- Subjects who have viol	ated the rules specified in section 7.	3 of the protocol	2016	
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- Subjects with study drug 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 the Maintenance Phase drug and will be based on the treatment received in the Maintenance Phase.

Handling of Rate of Endoscopic Recurrence of Erosive Esophagitis 7.1.3

7.1.3.1 Rate of Endoscopic Recurrence of Erosive Esophagitis During the first 12 Weeks of Treatment in the Maintenance Phase

A subject who is diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed between Study Day 2 and Study Day 127 (up to and including Follow-up Day 14) will be considered as a relapsed 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 relapsed'. Recurrence rate will be calculated from the relapsed and not relapsed subjects, however, any subjects diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed before the Maintenance Phase drug administration will be excluded from the analysis.

7.1.3.2 Rate of Endoscopic Recurrence of Prosive Esophagitis During the 24-Week Maintenance Phase

A subject who is diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed after Study Day 2 (up to and including Follow-up Day 14) will be considered as a relapsed 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 relapsed'. Recurrence rate will be calculated from the relapsed and not relapsed subjects, however, any subjects diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed before the Maintenance Phase drug administration will be excluded from the analysis.

Handling of Data When Calculating Mean Severity According to Subject 7.1.4 Diary

Each subjective symptom of erosive esophagitis as recorded in subject diaries (ie, 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.



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Visit	Study Day	Follow-up Day	able reims or
Baseline*	Day -6 – Day 1		LON.
Week 4	Day 2 – Day 29	up to and including Follow-up Day 1	
Week 8	Day 30 – Day 57	up to and including Follow-up Day 1	
Week 12	Day 58 – Day 85	up to and including Follow-up Day 1	, ,
Week 16	Day 86 – Day 113	up to and including Follow-up Day 1	
Week 20	Day 114 – Day 141	up to and including Follow-up Day 1	
Week 24	Day 142 – Day 169	up to and including Follow-up Day 1	

*: Will not be included in the analysis, however, data will be created.

7.1.5 HRQoL (EQ-5D-5L)

All evaluable data (ie, 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.

The following visits will be used.

	Visit	Scheduled Study Day			Time Interval (days)
	VISIC	(days)		Study Day	Follow-up Day
	Baseline	Study Day: 1		-28 - 1	
	Week 4	Study Day: 29		2-57	up to and including Follow-up Day 14
	Week 12	Study Day: 85		58 - 127	up to and including Follow-up Day 14
	Week 24	Study Day: 169		128 - 211	up to and including Follow-up Day 14
Property	Kakeda.				



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For each visit, all evaluable observation (ie, 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 will be used. If there are two observations equidistant to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day to the observation will be used. If there are two observations equidistant to the scheduled Study Day to the observation will be used. nicabl

Weight, BMI, Endoscopy	y (esophageal hiatal hernia)		
Visit	Scheduled Study Day	Time In	terval (days)
VISIL	(days)	Study Day	Follow-up Day
Baseline	Study Day: 1	up to and including Study Day 1	
Endoscopy (Barrett's muc	cosa), 12-lead ECG	SUD)	

	Endoscopy (Barren's mud	105a), 12-10au 100	2		
	Visit Scheduled Study Day (days)		Time Interval (days)		
	V ISIt	(days)	Study Day	Follow-up Day	
	Baseline	Study Day:	up to and including Study Day 1		
	Week 12	Study Day: 85	2 – 127	up to and including Follow-up Day 14	
	Week 24	Study Day: 169	128 – 211	up to and including Follow-up Day 14	
Property	Week 24				

Property



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•	(ALT, AST, total bilirubin, and direct		\$ C
Visit	Scheduled Study Day	Time I	Interval (days)
V ISIt	(days)	Study Day	Follow-up Day
Baseline*	Study Day: 1	-28 - 1	
Week 2	Study Day: 15	2 – 22	up to and including Follow-up Day 14
Week 4	Study Day 29	23 - 36	up to and including Follow-up Day 14
Week 6	Study Day: 43	37 - 50	up to and including Follow-up Day 14
Week 8	Study Day: 57	51-71	up to and including Follow-up Day 14
Week 12	Study Day: 85	1172 – 127	up to and including Follow-up Day 14
Week 24	Study Day: 169	128 - 211	up to and including Follow-up Day 14

*: For the clinical laboratory tests of the subjects who participated in the TAK-438_303 study, if the last study visit coincides with the first visit in the 305 study or if the subject was randomized in the 305 study within 7 days after completing the last visit in the 303 study, then the data obtained at the last visit can be used as the baseline data for the 305 study.

Clinical laboratory tests (other than ALT, AST, total bilirubin, and direct bilirubin), Gastrin, Pepsinogen I/II, Vital signs

Visit	Scheduled Study Day	Time Interval (days)		
v isit	(days)	Study Day	Follow-up Day	
Baseline*	Study Day: 1	-28 - 1		
Week 4	Study Day 29	2-57	up to and including Follow-up Day 14	
Week 12	Study Day: 85	58 – 127	up to and including Follow-up Day 14	
Week 24	Study Day: 169	128 - 211	up to and including Follow-up Day 14	

* For the clinical laboratory tests, gastrin, and pepsinogen I/II of the subjects who participated in the TAK-438_303 study, if the last study visit coincides with the first visit in the 305 study or if the subject was randomized in the 305 study within 7 days after completing the last visit in the 303 study, then the data obtained at the last visit can be used as the baseline data for the 305 study.



	Versio This v	ate Numbe n Number: ersion repl ate Title:	1.0 aces: TM	MPL-DO-801 PL-104 cal Analysis Plan (Legacy Tak	Page: Effective Date: eda)	16 of 58 02 Apr 2014
	7.2	STUDY S	JBJECTS, D	EMOGRAPHICS, AND OTHER	BASELINE CHARACTE	RISTICS
	7.2.1	Disposit	ion of Sub	ojects		enns
	7.2.1.1	Study Int	formation			
	Analysis Analysis	Set: Variables:	Date First Su Date of Last MedDRA Vo WHO Drug		Form rm	22 Apr 2014
	Analytica	ll Methods:	(1) Study In	_	iables section will be prov	rided.
	7.2.1.2	Screen F	ailures	6	50	
	Analysis Analysis	Set: Variables:	All Subjects Age (years) Gender Race	Who Were Not Randomized [Min<= - <65, 65<= <75, 75<= [Male, Female] [American Indian or Alaska Nat	tive, Asian, Black or Afric	
	Analytica	ll Methods:	-	Native Hawaiian or Other Pacifi ailures y distributions for categorical varia will be provided.	-	
	7.2.1.3	Subject I	Eliaibility	•		
	Analysis Analysis	Set:	All Subjects Eligibility St	Who Signed the Informed Consent atus ason for Subject Not Being Eligible	[Yes, No]	ation, al, ce Criteria,
Property	Analytica	ll Methods:	Frequenc primary r	y for Randomization by distributions will be provided. W reasons for subject not being eligibles the denominator.	hen calculating the percent	-



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Analysis Set: Randomized Set Analysis Variables: Randomization Status [Yes] Stratum: Country [China, Malaysia, South Korea, Taiwan Site Ste [Site numbers will be used as categories Analytical Methods: (1) Number of Subjects Randomized by Country, Site, and Treatmore Frequency distribution will be provided for each stratum by treatmore 7.2.1.5 Disposition of Subjects Analysis Set: Randomized Set Analysis Variables: Maintenance Phase Drug Administration [No] Status Reason for Not Being Treated [Pretreatment Event/Adv. Major Protocol Deviation Voluntary Withdrawal, Pregnancy, Lack of Effin Maintenance Phase Drug Completion Status [Completed Maintenance Prematurely Discontinue Drug]	nt Group and overall
Analysis Variables: Randomization Status [Yes] Stratum: Country [China, Malaysia, South Korea, Taiwan Site Analytical Methods: (1) Number of Subjects Randomized by Country, Site, and Treatmer Frequency distribution will be provided for each stratum by treatmer 7.2.1.5 Disposition of Subjects Analysis Set: Randomized Set Analysis Variables: Maintenance Phase Drug Administration Status Reason for Not Being Treated Pregnancy, Lack of Effi Maintenance Phase Drug Completion Status Image: Completed Maintenance Reason for Not Being Treated Pregnancy, Lack of Effi Maintenance Phase Drug Completion Status Image: Prematurely Discontinue Drug]	nt Group and overall
Analysis Set: Randomized Set Analysis Variables: Maintenance Phase Drug Administration [No] Status Reason for Not Being Treated [Pretreatment Event/Advention Voluntary Withdrawal, Pregnancy, Lack of Effit Maintenance Phase Drug Completion Status [Completed Maintenance Prematurely Discontinue Drug]	
Analysis Set: Analysis Variables: Reason for Not Being Treated Maintenance Phase Drug Administration Status Reason for Not Being Treated Major Protocol Deviation Voluntary Withdrawal, Pregnancy, Lack of Effi Maintenance Phase Drug Completion Status Maintenance Phase Drug Completion Status Drug]	and Freedo
Pregnancy, Lack of Effi Maintenance Phase Drug Completion Status [Completed Maintenance Prematurely Discontinu Drug]	n, Lost to Follow-Uj
	cacy, Other] Phase Drug,
Reason for Discontinuation of Maintenance [Pretreatment Event/Adv Phase Drug Major Protocol Deviation Voluntary Withdrawal, S Pregnancy, Lack of Effi	n, Lost to Follow-Uj udy Termination,
Analytical Methods: (1) Disposition of Subjects Frequency distributions will be provided for each treatment group a calculating percentages for the reasons for not being treated, the tota not treated by the maintenance phase drug will be used as the denor ealculating percentages for the reasons for discontinued the main the total number of subjects who prematurely discontinued the main will be used as the denominator. (2) Flow Chart of Subject Distribution Flow chart will be provided.	nd overall. When l number of subjects ninator. When mance phase drug,



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7.2.1.6 Protoco	I Deviations and Analysis Sets	;	02 Apr 2014
Protocol Deviati	ons		رو
Analysis Set:	Randomized Set		NO I
Analysis Variables:	-	try Criteria, Concomitant Medication	l, 0
		ocedure Not Performed Per Protocol,	
		udy Medication, Withdrawal Criteria	R,
Analytical Methods:	(1) Protocol Deviations		
	category. A subject who has seven	ovided by treatment group and overal ral deviations will be counted once in ral deviations that can be classified in re.	each appropriat
Analysis Sets		1101er	
Analysis Set: Analysis Variables:	Randomized Set Analysis Sets Full Analysis Set [Included]	e. and subject te	
	Per Protocol Set[Included]Safety Analysis Set[Included]		
Analytical Methods:	(1) Analysis Sets Frequency distributions will be p	provided by treatment group and over	all.
	ricia		
7.2.2 Demog	raphics and Other Baseline	Characteristics	
7.2.2.1 Summa	ry of Demographics and Other	Baseline Characteristics	
Analysis Set:	Randomized Set Full Analysis Set		
Analysis Variables:		[China, Malaysia, South Korea,	Taiwan]
	Participation in TAK-438_303 Study		
20.	Age (years)	[Min<= - <65, 65<= - <75, 75<	= - <=Max]
00-	Gender	[Male, Female]	-
A	Race	[American Indian or Alaska Na	tive, Asian,
×~~		Black or African American,	
0,		Native Hawaiian or Other Pac	ific Islander,
		White, Multiple]	
	Height (cm)	[Min<= - <150, 150<= - <160,	
		160<= - <170, 170<= - <=Max	x]
		·	-
	Weight (kg) (Baseline)	[Min<= - <50.0, 50.0<= - <60.0	
Analysis Variables:	Weight (kg) (Baseline)	·	

80.0<= - <=Max]



		CROSS-REGION	AL TEMPLATE
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		BMI (kg/m ²) (Baseline)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <=Max]
		Smoking Classification	[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]
		History of H. pylori Eradication	[Yes (End of Treatment: Within the Past 1 Year),
		Therapy	Yes (End of Treatment: More than 1 Year), No]
		LA Classification (Time of Diagnos	
			[Grade A/B, Grade C/D]
		Barrett's Mucosa (Baseline)	[Present (3 cm or Greater),
		Esophageal Hiatal Hernia (Baseline	Present (Less than 3 cm), Absent, Unknown] Present (2 cm or Greater),
		Esophageai matai menna (Basenne	Present (Less than 2 cm), Absent, Unknown]
		HRQoL (EQ-5D-5L)	riesent (Less than 2 ent), riesent, enthievit]
		EQ-5D-5L Index Value (Baseline	e)
		EQ VAS Score (Baseline)	·
	Analytical Methods:	(1) Summary of Demographics an	nd Other Baseline Characteristics
			gorical variables and descriptive statistics for continuous
		variables will be provided by tre	eatment group and overall.
		conti	
	7.2.2.2 Medical F	listory and Concurrent Medi	ical Conditions
	Analysis Set:	Safety Analysis Set	
	Analysis Variables: 🔿	Medical History	
		Concurrent Medical Conditions	
	Analytical Methods:	(1) Medical History by System On	-
Property	of allo	Frequency distributions will be will be used for coding. Summa will be sorted alphabetically and A subject with multiple occurre within a SOC will be counted or	ns by System Organ Class and Preferred Term provided for each treatment group. MedDRA dictionary aries will be provided using SOC and PT, where SOC d PT will be sorted in decreasing frequency. ences of medical history or concurrent medical condition nly once in that SOC. A subject with multiple or concurrent medical condition within a PT will be



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7 2 2 3 Medic	ation His	tory and Concomitant Med	dications	2	S
1.2.2.3 IVI C UIC	ali0111115		lications		
Analysis Set:	Safety	Analysis Set		\sim	

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.

			r -	will be counted only	everal medications with the same preferr once for that preferred medication name.	
	7.2.3	Treatmer	nt Compliance	ð	nd sub.	
	7.2.3.1	Study Dru	g Exposure and			
	Analysis	Set:	Safety Analysis Set Full Analysis Set	150		
	Analysis	Variables:	Duration of Exposur	e to Study Drug (day	ys) [1<= - <=84, 85<= - <=168, 169<= - <=Max]	
			Study Drug Complia	nce (%)	[Min<= - <50.0, 50.0<= - <70.0, 70.0<= - <90.0, 90.0<= - <=Max]	
	-	ll Methods:	Frequency distrib	outions for categorica	nce in Maintenance Phase al variables and descriptive statistics for l by treatment group and overall.	
	10	eda. For				
Property	Ŏ					



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7.3	EFFICACY ANAL	YSIS		~	SOL
		e main analysis set used. The per j icacy endpoint and secondary effi			*

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 applicable the results.

7.3.1 **Primary Efficacy Endpoint**

7.3.1.1 Primary Analysis

Analysis Set:	Full Analysis Set
Analysis Variable:	Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-week Maintenance
	Phase (%)
Analytical Methods:	(1) Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-week
	Maintenance Phase
	Frequency distributions will be provided by treatment group along with rates and the
	two-sided 95% confidence intervals. The differences in the rates between each TAK-438
	group and the Lansoprazole group (each TAK-438 group – the Lansoprazole group) and
	the two-sided 95% confidence intervals using the Wald method will be provided. The
	non-inferiority margin will be set to 10%. Details concerning interpretation are described
	in section 7.3.4.5.

7.3.1.2 Secondary Analysis

Analysis Set: Per Protocol Set Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-week Maintenance Analysis Variable: Phase (%) 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.

Secondary Efficacy Endpoint 7.3.2

7.3.2.1 Rate of Endoscopic Recurrence of Erosive Esophagitis During the First 12 Weeks of Treatment in the Maintenance Phase

Analysis Set:	Full Analysis Set
Analysis Variable:	Rate of Endoscopic Recurrence of Erosive Esophagitis During the First 12 Weeks of
×	Treatment in the Maintenance Phase (%)
Property Analytical Methods:	(1) Rate of Endoscopic Recurrence of Erosive Esophagitis During the First 12 Weeks of Treatment in the Maintenance Phase Frequency distributions will be provided by treatment group along with rates and the two-sided 95% confidence intervals. The differences in the rates between each TAK-438 group and the Lansoprazole group (each TAK-438 group – the Lansoprazole group) and the two-sided 95% confidence intervals will also be provided.



 Analysis variable. Take of Encoderence of Encoder Encoderence of Encodere Explanging the First 12 Weeks of Treatment in the Maintenance Phase (%) Analytical Methods: (1) Sensitivity Analysis To check the robustness of the results, the same analyses as section 7.3.2.1 will be performed using the per protocol set. 7.3.3 Additional Efficacy Endpoints 7.3.3 Additional Efficacy Endpoints 7.3.3 Additional Efficacy Endpoints 7.3.3.1 Gastrointestinal Symptoms Based on Subject Diary Heartburn Symptoms Analysis Set: Full Analysis Set Analysis Variables: Mean Severity of Symptoms Subgroups: Barrett's Mucosa (Baseline) [Present, Absent] Visit: Week 4, Week 12, Week 16, Week 20, Week 24 Analytical Methods: The following summaries will be provided for each visit. ii) Descriptive statistics will be provided for each visit. ii) The difference in the medians between each TAK-438 group and the Lansoprazole group (ach TAK-438 group – the Lansoprazole group) and the two-sided 95% confidence intervals will be provided for each visit using the Hodges-Lehmann estimator. Wilcoron rank-sum tests will be used to test for treatment differences at e visit. iii) WMWodds of each TAK-438 group to the Lansoprazole group and the two-sided 95% confidence intervals will be provided for each visit based on Wilcoxon-Mann-Whith test statistics. Subgroup Analysis (Baseline Barrett's Mucosa) The same analyses as all of the above will be conducted for the defined subgroup 	Template Number Version Number This version repl Template Title:	1.0	Page: Effective Date:	22 of 58 02 Apr 2014
 Analysis variable. Take of Encoderence of Encoder Encoderence of Encodere Explanging the First 12 Weeks of Treatment in the Maintenance Phase (%) Analytical Methods: (1) Sensitivity Analysis To check the robustness of the results, the same analyses as section 7.3.2.1 will be performed using the per protocol set. 7.3.3 Additional Efficacy Endpoints 7.3.3 Additional Efficacy Endpoints 7.3.3 Additional Efficacy Endpoints 7.3.3.1 Gastrointestinal Symptoms Based on Subject Diary Heartburn Symptoms Analysis Set: Full Analysis Set Analysis Variables: Mean Severity of Symptoms Subgroups: Barrett's Mucosa (Baseline) [Present, Absent] Visit: Week 4, Week 12, Week 16, Week 20, Week 24 Analytical Methods: The following summaries will be provided for each visit. ii) Descriptive statistics will be provided for each visit. ii) The difference in the medians between each TAK-438 group and the Lansoprazole group (ach TAK-438 group – the Lansoprazole group) and the two-sided 95% confidence intervals will be provided for each visit using the Hodges-Lehmann estimator. Wilcoron rank-sum tests will be used to test for treatment differences at e visit. iii) WMWodds of each TAK-438 group to the Lansoprazole group and the two-sided 95% confidence intervals will be provided for each visit based on Wilcoxon-Mann-Whith test statistics. Subgroup Analysis (Baseline Barrett's Mucosa) The same analyses as all of the above will be conducted for the defined subgroup 	7.3.2.2 Sensitivi	ty Analysis		
To check the robustness of the results, the same analyses as section 7.3.2.1 will be performed using the per protocol set. 7.3.3 Additional Efficacy Endpoints 7.3.3.1 Gastrointestinal Symptoms Based on Subject Diary Heartburn Symptoms Analysis Set: Full Analysis Set Analysis Variables: Mean Severity of Symptoms Subgroups: Barrett's Mucosa (Baseline) (Present, Absent] Visit: Week 4, Week 8, Week 12, Week 16, Week 20, Week 24 Analytical Methods: The following summaries will be provided for each treatment group. i) Descriptive statistics will be provided for each visit. ii) The difference in the medians between each TAK-438 group and the Lansoprazole group (each 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 e visit. iii) WMWoods of each TAK-438 group to the Lansoprazole group and the two-sided 95% confidence intervals will be provided for each visit based on Wilcoxon-Mann-Whitn test statistics. Subgroup Analysis (Baseline Barrett's Mucosa) • The same analyses as all of the above will be conducted for the defined subgroup Gastric Acto Reegurgitation • The same analyses set all of the above will be conducted for the defined subgroup	•	Rate of Endoscopic Recurrence of Erosit		2 Weeks of
Heartburn Symptoms Analysis Set: Full Analysis Set Analysis Variables: Mean Severity of Symptoms Subgroups: Barrett's Mucosa (Baseline) [Present, Absent] Visit: Week 4, Week 8, Week 12, Week 16, Week 20, Week 24 Analysical Methods: The following summaries will be provided for each treatment group. i) Descriptive statistics will be provided for each visit. ii) The difference in the medians between each TAK-438 group and the Lansoprazole group (each 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 evisit. iii) WMWodds of each TAK-438 group to the Lansoprazole group and the two-sided 95 confidence intervals will be provided for each visit based on Wilcoxon-Mann-Whitm test statistics. Subgroup Analysis (Baseline Barrett's Mucosa) • The same analyses as all of the above will be conducted for the defined subgroup Gastric Acid Reejurgitation Analysis Set Full Analysis Set	Analytical Methods:	To check the robustness of the results	s, the same analyses as section 7.3	3.2.1 will be
Heartburn Symptoms Analysis Set: Full Analysis Set Analysis Variables: Mean Severity of Symptoms Subgroups: Barrett's Mucosa (Baseline) [Present, Absent] Visit: Week 4, Week 8, Week 12, Week 16, Week 20, Week 24 Analytical Methods: The following summaries will be provided for each treatment group. i) Descriptive statistics will be provided for each visit. ii) The difference in the medians between each TAK-438 group and the Lansoprazole group (each 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 evisit. iii) WMWodds of each TAK-438 group to the Lansoprazole group and the two-sided 95 confidence intervals will be provided for each visit based on Wilcoxon-Mann-Whitn test statistics. Subgroup Analysis (Baseline Barrett's Mucosa) • The same analyses as all of the above will be conducted for the defined subgroup Gastric Acid Recurgitation Analysis Set Full Analysis Set	7.3.3 Addition	al Efficacy Endpoints	20	X
Heartburn Symptoms Analysis Set: Full Analysis Set Analysis Variables: Mean Severity of Symptoms Subgroups: Barrett's Mucosa (Baseline) [Present, Absent] Visit: Week 4, Week 8, Week 12, Week 16, Week 20, Week 24 Analytical Methods: The following summaries will be provided for each treatment group. i) Descriptive statistics will be provided for each visit. ii) The difference in the medians between each TAK-438 group and the Lansoprazole group (each 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 evisit. iii) WMWodds of each TAK-438 group to the Lansoprazole group and the two-sided 95 confidence intervals will be provided for each visit based on Wilcoxon-Mann-Whitm test statistics. Subgroup Analysis (Baseline Barrett's Mucosa) • The same analyses as all of the above will be conducted for the defined subgroup Castric Acid Recurgitation Analysis Set: Full Analysis Set	7.3.3.1 Gastroin	testinal Symptoms Based on Su	biect Diary	
Analysis Set: Full Analysis Set Analysis Variables: Mean Severity of Symptoms Subgroups: Barrett's Mucosa (Baseline) [Present, Absent] Visit: Week 4, Week 8, Week 12, Week 16, Week 20, Week 24 Analytical Methods: The following summaries will be provided for each treatment group. i) Descriptive statistics will be provided for each AK-438 group and the Lansoprazole group (each 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 e visit. iii) WMWodds of each TAK-438 group to the Lansoprazole group and the two-sided 95 confidence intervals will be provided for each visit based on Wilcoxon-Mann-Whitm test statistics. Subgroup Analysis (Baseline Barrett's Mucosa) • The same analyses as all of the above will be conducted for the defined subgroup Analysis Set: Full Analysis Set			d'	
Analysis Set: Full Analysis Set	Analysis Set: Analysis Variables: Subgroups: Visit:	 Full Analysis Set Mean Severity of Symptoms Barrett's Mucosa (Baseline) Week 4, Week 8, Week 12, Week 16, We The following summaries will be provided i) Descriptive statistics will be provided ii) The difference in the medians betwee group (each TAK-438 group – the I confidence intervals will be provided estimator. Wilcoxon rank-sum tests visit. WMWodds of each TAK-438 group confidence intervals will be provided test statistics. Subgroup Analysis (Baseline Barrett's Statistics) 	ek 20, Week 24 ed for each treatment group. ed for each visit. een each TAK-438 group and the Lansoprazole group) and the two-sed for each visit using the Hodges will be used to test for treatment to to the Lansoprazole group and the ed for each visit based on Wilcoxo Mucosa)	sided 95% -Lehmann differences at each he two-sided 95% on-Mann-Whitney
	Gastric Acid Rec	jurgitation		
\checkmark		The same analyses as those in section 7.2	3.3.1 "Heartburn Symptoms" will	be conducted for

Gastric Acid Regurgitation

Full Analysis Set



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7.3.3.2 HRQoL ((EQ-5D-5L)		SOI
EQ-5D-5L Index	Value		erma
Analysis Set: Analysis Variables: Covariates: Visit: Analytical Methods:	 Full Analysis Set EQ-5D-5L Index Value LA Classification (Time of Diagnosis) EQ-5D-5L Index Value (Baseline) Baseline, Week 4, Week 12, Week 24 (1) Summary of EQ-5D-5L Index Value Descriptive statistics will be provided for post-baseline visit for the changes from be treatment group. The mean differences in 438 group and the Lansoprazole group (e and the two-sided 95% confidence interver. Two sample t-tests will be used to test for visit. (2) ANCOVA The changes from baseline (each post baswill be analyzed using an ANCOVA mod time of diagnosis as factors and baseline ANCOVA analysis will be performed at e sided 95% confidence intervals will be provided. The difference in the LS means between each TAK-438 438 group – the Lansoprazole group) and provided. The difference in the LS means (3) MMRM The changes from baseline (each post baswill be analyzed using a mixed model reputed to the state of the second second test for the changes from baseline (each post baswill be provided. The difference in the LS means 	aseline (each post-baseline w the changes from baseline b ach TAK-438 group – the La als will be provided for each treatment differences at eac seline visit - baseline) in the el with treatment and LA cla EQ-5D-5L index value as a c each post baseline visit. LS n rovided for each treatment gr group and the Lansoprazole the two-sided 95% confider s will be tested for treatment seline visit – baseline) in the beated measures analysis (MI variable as the response, and seline value of the analysis v y-visit interaction, and LA gr d the two-sided 95% confider p. The differences in the LS ble group (each TAK-438 gro 5% confidence intervals will ns will be tested for treatment	values and for each isit - baseline) by etween each TAK- insoprazole group) post-baseline visit. h post-baseline analysis variable ssification at the sovariate. The neans and the two- oup. The difference group (each TAK- ice interval will be differences. analysis variable MRM) model with I treatment, LA ariable, visit, ade-by-visit nce intervals will be means between up - the be provided for t differences. An hin-subject errors



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Template Title:	Statistical Analysis Pla	an (Legacy Takeda)		
EQ VAS Score				
Analysis Set:	Full Analysis Set			, es
Analysis Variables:	EQ VAS Score			\sim
Covariates:	LA Classification (Time of Di	agnosis) [Grade A/E	B, Grade C/D]	20
	EQ VAS Score (Baseline)			~ U
Analytical Methods:	The same analyses as those in the EQ VAS score.	section 7.3.3.2 "EQ-5D-5L	Index Value" wi	
7.3.3.3 Barrett's	Mucosa			
Analysis Set:	Full Analysis Set		H,	
Analysis Variables:	Barrett's Mucosa (Change)	[Increased, Unchanged, Re	duced. Disappe	ared. Unknown]
Subgroups:	Barrett's Mucosa (Baseline)	[Present (3 cm or Greater)] Unknown]		
Visit:	Week 12, Week 24	SU		
Analytical Methods:	(1) Frequency distribution o Frequency distribution will	f Barrett's Mucosa (Chang l be provided for each subgr		
7.3.4 Statistic	al/Analytical Issues	onit		
7.3.4.1 Adjustme	ents for Covariates			
Analysis Set:	Full Analysis Set			
Analysis Variable:	Rate of Endoscopic Recurrence	e of Erosive Esophagitis Du	ring the 24-wee	k Maintenance
	Phase (%)			
	Rate of Endoscopic Recurrence		ring the First 12	2 Weeks of
Stratified Variable:	Treatment in the Maintenance		ada C/Dl	
Stratified Variable: Analytical Methods:	LA Classification (Time of Di (1) CMH Test for the Rate o			hagitis During th
a maryticar ivictilous.	24-week Maintenance Ph	-	1 121 031 ve 1230 pi	agius During III
60	(2) CMH Test for the Rate of		f Erosive Esopl	hagitis During th
X	First 12 Weeks of Treatm	ent in the Maintenance Ph		
20	A CMH test with LA Clas	sification at the time of diag		ication factor will
Xe	be used to compare the ab	ove analysis variable betwee		
1º0	Lansoprazole group for tre	atment differences. Mantel-		
Š.	difference between each T	AK-438 group and the Lans		
7.3.4.2 Handling	group – the Lansoprazole Wald method will also be	group) and the two-sided 95 provided.	% confidence in	terval using the
7.3.4.2 Handlina	of Dropouts or Missing	Data		
Eastha miner			rin = 4k = 0.4	
	int "rate of endoscopic recurrent ary efficacy endpoint "rate of end		-	

7.3.4.2 Handling of Dropouts or Missing Data

For the primary endpoint "rate of endoscopic recurrence of erosive esophagitis during the 24-week maintenance phase" and the secondary efficacy endpoint "rate of endoscopic recurrence of erosive esophagitis during the first 12



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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. ect to the applicable

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 endpoint "rate of endoscopic recurrence of erosive esophagitis during the 24-week maintenance phase" and the secondary efficacy endpoint "rate of endoscopic recurrence of erosive esophagitis during the first 12 weeks of treatment in the maintenance phase" in the following order under the closed testing procedure and the analysis will be conducted using the full analysis set.

- The primary endpoint "rate of endoscopic recurrence of erosive esophagitis during the 24-week maintenance phase" will be tested for non-inferiority between the TAK-438 20 mg group and the Lansoprazole group. In other words, if the upper bound of the 95% confidence interval of the treatment difference (the TAK-438 20 mg group) the Lansoprazole group) is $\leq 10\%$, the non-inferiority for TAK-438 20 mg relative to Lansoprazole will be declared.
- If the previous test is successful, the primary endpoint will be tested for non-inferiority between the TAK-438 10 mg group and the Lansoprazole group. In other words, if the upper bound of the 95% confidence interval of the treatment difference (the TAK-438 10 mg group – the Lansoprazole group) is $\leq 10\%$, the non-inferiority for TAK-438 10 mg relative to Lansoprazole will be declared.
- If the previous test is successful, the primary endpoint will be tested for superiority between the TAK-438 20 mg group and the Lansoprazole group. The upper bound of the 95% confidence interval of the treatment difference (the TAK-438 20 mg group -the Lansoprazole group) will be compared to 0%.
- If the previous test is successful, the primary endpoint will be tested for superiority between the TAK-438 10 mg group and the Lansoprazole group.
- If the previous test is successful, the secondary endpoint "rate of endoscopic recurrence of erosive esophagitis during the first 12 weeks of treatment in the maintenance phase" will be tested for superiority between the TAK-438 20 mg group and the Lansoprazole group.
- If the previous test is successful, the secondary endpoint will be tested for superiority between the TAK-438 10 mg group and the Lansoprazole group.



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5	ill be done only for exploratory p	urposes and multiplicity adjustn	nents will not be	0
nade.			-54	ns
.3.4.6 Use of an "Effi	cacy Subset" of Subjects		\checkmark°	
addition to analyses on the	primary and secondary efficacy e	ndpoints using the full analysis	set, sensitivity	

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 each TAK-438 group relative to the Lansoprazole group will be confirmed in the full analysis set using a non-inferiority margin of 10%. X

7.3.4.8 Subgroup Analysis

be commined in	in the run analysis set using a non-interiority margin of 10%.
7.3.4.8 Sul	bgroup Analysis
Analysis Set:	Full Analysis Set
Analysis Varial	
	Phase (%)
	Rate of Endoscopic Recurrence of Erosive Esophagitis During the First 12 Weeks of
	Treatment in the Maintenance Phase (%)
Subgroups:	Age (years) [Min<= - <65, 65<= - <75, 75<= - <=Max]
	Gender [Male, Female]
	BMI (kg/m ²) (Baseline) [Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <=Max]
	LA Classification (Time of Diagnosis) [Grade A/B, Grade C/D]
	Barrett's Mucosa (Baseline) [Present, Absent]
	Esophageal Hiatal Hernia (Baseline) [Present (2 cm or Greater),
	Present (Less than 2 cm), Absent, Unknown]
Analytical Met	
	During the 24-week Maintenance Phase
	(2) Subgroup Analysis for the Rate of Endoscopic Recurrence of Erosive Esophagitis
	During the First 12 Weeks of Treatment in the Maintenance Phase
	The same analyses as those in section 7.3.1.1 will be performed for each of the above
	subgroups, except for non-inferiority testing.
X	\diamond
XOL	
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7.4 SAFETY	ANALYSIS		ASO'
7.4.1 Treatm	ent-Emergent Adverse I	Events	10th
7.4.1.1 Overvie	ew of Treatment-Emergen	t Adverse Events	0/6
Analysis Set: Analysis Variables: Categories:	 Safety Analysis Set TEAE Relationship to Study Drug Intensity The following summaries will b (1) Overview of Treatment-Emergent A subjects) 2) Relationship of Treatment number and percentage of 3) Intensity of Treatment-Emergent Adva of events, number and per 5) Relationship to Study Dru Drug Discontinuation (num 6) Serious Treatment-Emerge of subjects) 7) Relationship of Serious Tr events, number and percer 8) Serious Treatment-Emerge (number of events, number 	e provided for each treatment group. nergent Adverse Events Adverse Events (number of events, number -Emergent Adverse Events to Study Drug 'subjects) nergent Adverse Events (number of events, erse Events Leading to Study Drug Discom- centage of subjects) g of Treatment-Emergent Adverse Events mber of events, number and percentage of se ent Adverse Events (number of events, num- reatment-Emergent Adverse Events to Study ntage of subjects) ent Adverse Events Leading to Study Drug er and percentage of subjects) erse Events Resulting in Death (number of verse Events Corresponding to Liver Funct Cevents, number and percentage of subjects) erse the trules below. 7) s of TEAE in both categories (ie, Related at	(number of events, number and inuation (number Leading to Study subjects) nber and percentage y Drug (number of Discontinuation events, number and ion Test) , number and



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Version Numbe This version rep Template Title:	•
	r: 1.0 Effective Date: 02 Apr 2014 blaces: TMPL-104 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. s of Treatment-Emergent Adverse Events Safety Analysis Set TEAE Intensity [Mild, Moderate, Severe]
7.4.1.2 Display	s of Treatment-Emergent Adverse Events
Analysis Set: Analysis Variables: Categories:	Safety Analysis Set TEAE Intensity [Mild, Moderate, Severe] Time of Onset (day) [1<= - <=84, 85<= - <=168, 169<= - <=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
atty of Takeda. F	 Discontinuation by System Organ Class and Preferred Term (9) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
1 Ster	(10) Serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
NON T	 (11) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time (12) Most Energy on Treatment Emergent Adverse Events by System Organ Class and
8	(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
	(14) Drug-Related Treatment-Emergent Adverse Events Corresponding to Liver



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	Function Test Abnormalities by	System Organ Class and Preferre	d Term
	(15) Significant Treatment-Emergent	Adverse Events by System Organ	n Class and
	Preferred Term		XON
	(16) Drug-Related Significant Treatm	nent-Emergent Adverse Events by	System Organ
	Class and Preferred Term		
	(17) Most Frequent Non Serious Trea	atment-Emergent Adverse Events	by System Organ
	Class and Preferred Term		
	The frequency distribution will be prov	ided according to the rules below.	
	Number of subjects	(11)	
	• Summary tables other than (5), (6)		unted only encoded
		es of TEAE within a SOC will be co occurrences of TEAE within a PT v	
	· · ·	will be based on the number of subj	
	analysis set.	will be based on the number of subj	cets in the safety
	 Summary tables for (5) and (6) 	CUL.	
	• • • • • • •	es of TEAE within a SOC or a PT w	vill be counted only
		num intensity. Percentages will be b	
	number of subjects in the safety a		
	Summary table for (11)		
		s in more than one interval is counte	d in all the
		or each time interval, a subject with	
		C or a PT will be counted only once	
	When calculating percentages for	each time interval, the number of su	bjects at risk
	(ie, subjects who either have an ex	posure or have an occurrence of TE	AE, during or after
		vill be used as the denominator. The	-
	whose onset of any one of the TEA	AEs is within the time interval will b	be used as the
	numerator.		
	• Summary table for (12)		
. (Most frequent TEAEs refer to PTs	s whose percentages are at least 2%	in any one of the
$\langle \cdot \rangle$	treatment groups.		
\$.	• Summary table for (17)		
600	Most frequent non-serious TEAEs	refer to PTs that are not serious wh	
X	at least 5% in any one of the treatr	nent groups. If there are no PTs who	1 0
	exceed 5%, the threshold is lower	ed to 2%. When calculating the perc	-
Ó	"Subjects With Any TEAEs", the	number of subjects with at least one	of these most
B	frequent non-serious TEAEs will	be used as the numerator.	
ty of takeda. Fo			



	tment Events and Adverse Events	ents in the Healing Phas	02 Apr 2014
	All Subjects Who Signed the Informed Co PTE The following summaries will be provided PTEs will be coded using the MedDRA at be sorted alphabetically and PT will be so (1) Pretreatment Events by System Org (2) Serious Pretreatment Events by Sys The frequency distribution will be provided <u>Number of subjects</u> A subject with multiple occurrences of PT SOC. A subject with multiple occurrences that PT. s of Adverse Events in the Healing	d using frequency distribution. ad will be summarized using SOC rted in decreasing frequency. can Class and Preferred Term tem Organ Class and Preferred ed according to the rules below. TE within a SOC will be counted of a of PTE within a PT will be count	and PT. SOC will Term nly once in that
Analysis Set: Analysis Variables: Analytical Methods:	All Subjects Who Entered the Healing Ph AE in the Healing Phase The following summaries will be provided AEs will be coded using the MedDRA and be sorted alphabetically and PT will be so (1) Adverse Events in the Healing Phase (2) Serious Adverse Events in the Healing The frequency distribution will be provided <u>Number of subjects</u> A subject with multiple occurrences of All SOC. A subject with multiple occurrences PT.	ase d using frequency distribution.	eferred Term s and Preferred ly once in that d only once in that



CROSS-REGIONAL TEMPLATE Template Number: C-TMPL-DO-801 31 of 58 Page: icable terms of Use **Version Number:** 1.0 **Effective Date:** 02 Apr 2014 This version replaces: **TMPL-104 Template Title:** Statistical Analysis Plan (Legacy Takeda) 7.4.3 Laboratory and Other Safety Data 7.4.3.1 Laboratory Test Results Hematology and Serum Chemistry 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) Platelets ($\times 10^{9}/L$) Hematocrit (%) White Blood Cell Fractions (Neutrophils (%), Eosinophils (%), Basophils (%), Monocytes (%), Lymphocytes (%)) Serum Chemistry ALT (U/L) ALP (U/L) AST (U/L) Total Bilirubin (umol/L) GGT (U/L) Direct Bilirubin (µmol/L) CK (CPK) (U/L) LDH (U/L) Albumin (g/L) Creatinine (µmol/L) Total Protein (g/L) BUN (mmol/L) Uric Acid (mmol/L) Total Cholesterol (mmol/L) Triglycerides (mmol/L) Potassium (mmol/L) Sodium (mmol/L) Glucose (mmol/L) Magnesium (mmol/L) Calcium (mmol/L) Inorganic Phosphorus (mmol/L) Chloride (mmol/L) Serum Iron (µmol/L) Vitamin B₁₂ (pmol/L) ALT, AST, Total Bilirubin, and Direct Bilirubin: Visit: Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 24 Variables other than ALT, AST, Total Bilirubin, and Direct Bilirubin: Baseline, Week 4, Week 12, Week 24 Analytical Methods: For each variable, summaries (1) and (2) will be provided by treatment group. Property of Takeda. 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. (2) Summary of Shifts of Laboratory Test Results Shift tables showing the number of subjects in each category at baseline and each postbaseline 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 maintenance phase will be provided. If a



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	laborator for each. (4) Number Paramet Overall f	ry parameter has both lower and up Further details are given in Appen and Percentage of Subjects with	per MAV criteria, analysis w dix. Elevated Liver Enzyme La hepatic parameters during m	boratory
<u>Urinalysis</u>				SIIC
Analysis Set:	Safety Analy	ysis Set	2	
Analysis Variables :	Protein	[Neg, Trace, 30 mg/dL, 100 n	ng/dL, 300 mg/dL, >=2000 r	ng/dL]
	Sugar	[Neg, 100 mg/dL, 250 mg/dL	, 500 mg/dL, 1000 mg/dL, >	=2000 mg/dL]
Visit:	Baseline, We	eek 4, Week 12, Week 24	Č.	
Analytical Methods:	The followin	ng summaries will be provided for e	each treatment group.	
Serum Gastrin, Analysis Set: Analysis Variables :	Safety Analy	ysis Set in (pmol/L) I (µg/L)		
	Pepsinogen I			
Visit:	C	eek 4, Week 12, Week 24		
	(1) Summer	Ig summaries will be provided for e y of Serum Gastrin and Pepsinon visit, descriptive statistics for obse eline visit - baseline) will be provid	gen I/II Results rved values and changes from	n baseline (each
of takeda. Fo				

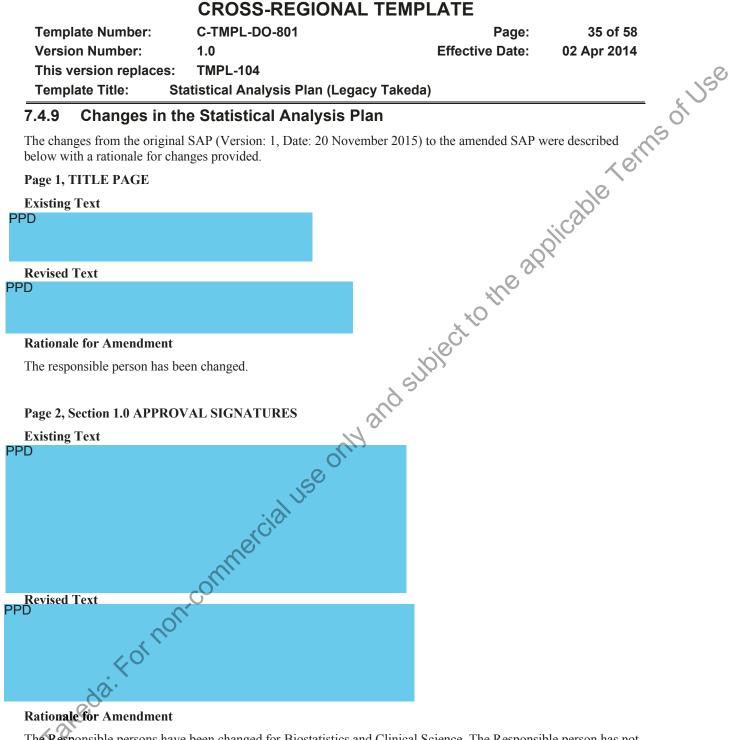


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7.4.4 Vital Si	gns, Physical Findings, and Ot	her Observations Relat	ed to Safety of Terms of	USE
Vital Signs			1 Chi	
Analysis Set:	Safety Analysis Set		NO Ì	
Analysis Variables:	Body Temperature (C)		2010	
	Systolic Blood Pressure (mmHg)		100	
	Diastolic Blood Pressure (mmHg)		<i>5,,</i>	
	Pulse (bpm)	2		
Visit:	Baseline, Week 4, Week 12, Week 24	0		
Analytical Methods:	For each variable, summaries (1) and (2) w	vill be provided by treatment grou	p.	
	(1) Summary of Vital Signs Parameters	and Change from Baseline by V	isit	
	Descriptive statistics for observed value	- (Z,	ch post-baseline	
	visit – baseline) will be provided for ea			
	(2) Number and Percentage of Subjects	with Markedly Abnormal Valu	es of Vital Signs	
	Parameters	6		
	Overall frequency distributions of MA		•	
	vital sign parameter has both lower and		ll be performed for	
	each. Further details are given in Appe	ndıx.		
12 load ECC	C ^O			
<u>12-lead ECG</u>	, J ³			
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)	in Normal Lincital		
		in Normal Limits", ormal, Not Clinically Significant'		
<' <'	-	ormal, Clinically Significant"]	,	
Visit:	Baseline, Week 12, Week 24	official, Chinearly Significant		
Analytica Methods:	For each variable other than interpretation,	summary (1) will be provided by	treatment groun	
Analyte an Diethous.	For applicable variables, summary (2) will		treatment group.	
	For interpretation, summary (3) will be pro-			
0	(1) Summary of ECG Parameters and C			
Ex.	Descriptive statistics for observed value		ch post-baseline	
ON IN	visit – baseline) will be provided for ea		1	
Property of the second	(2) Number and Percentage of Subjects		es of ECG	
<i>Q</i> `	Parameters			
	Overall frequency distributions of MA	V during maintenance phase will	be provided. If an	



ECG 1 perfor (3) Summ Shift t baselin 7.4.5 Subgroup Anal Analysis Population: Subjects in Subjects in Analytical Methods: (1) The s China (2) The s	in China in Countries other than Chi same analyses as those in s	both lower and upp ails are given in Ap prameters r of subjects in each nina section 7.2 to 7.4.4	er MAV criteria, anal opendix. h category at baseline	and each post-of
Template Title:StatECG I perfor(3) Summer Shift t baselin7.4.5Subgroup AnalAnalysis Population:Subjects in Subjects in Subjects in (1)Analytical Methods:(1)The s China (2)The s	atistical Analysis Plan (laboratory parameter has b rmed for each. Further deta nary of Shifts of ECG Part tables showing the number ine visit will be provided. Alysis for China in China in Countries other than Chi same analyses as those in s a. same analyses as those in s	both lower and upp ails are given in Ap prameters r of subjects in each nina section 7.2 to 7.4.4	er MAV criteria, anal opendix. h category at baseline	plicable
perfor (3) Summ Shift t baselin 7.4.5 Subgroup Anal Analysis Population: Subjects in Subjects in Analytical Methods: (1) The s China (2) The s	rmed for each. Further deta nary of Shifts of ECG Part tables showing the number ine visit will be provided. Alysis for China in China in Countries other than Chi same analyses as those in s a. same analyses as those in s	ails are given in Ap arameters r of subjects in each nina section 7.2 to 7.4.4	opendix. h category at baseline	plicable
Analysis Population: Subjects in Subjects in Analytical Methods: (1) The s China (2) The s	in China in Countries other than Chi same analyses as those in s a. same analyses as those in s	section 7.2 to 7.4.4		
Subjects in Analytical Methods: (1) The s China (2) The s	in Countries other than Chi same analyses as those in s a. same analyses as those in s	section 7.2 to 7.4.4		
	-			
	unes outer than Clilla.	section /.2 to /.4.4	will be conducted for	the subjects in
7.4.6 Subgroup Anal	Ilysis for Taiwan	SUL	Ô,	
Analysis Population: Subjects in		ano.		
Analytical Methods: (1) The s Taiwa		section 72 to 7.4.4	will be conducted for	the subjects in
7.4.7 Subgroup Anal Unblinded Sub	Ilysis for Safety Ana ojects	alysis Set Ex	cluding Accide	ntally
Safety An China	nalysis Set Excluding the A nalysis Set Excluding the A nalysis Set Excluding the A nalysis Set Excluding the A	Accidentally Unblin Accidentally Unblin	nded Subjects in Chin nded Subjects in Cour	tries other than
system err	ety analysis set that exclude	des subjects who we ed for the subjects i	ere accidentally unbli	nded due to IWRS
7.4.8 Significance Le	evel and Confidence	ce Coefficient	t	
• Significance level: 5% (tw	vo-sided test)			
Confidence coefficient: 95	5% (two-sided)			





The Responsible persons have been changed for Biostatistics and Clinical Science. The Responsible person has not been needed for Pharmacovigilance.

Page 7, Section 4.1 PRIMARY OBJECTIVES

Existing Text

To demonstrate the non-inferiority of TAK-438 to Lansoprazole in the reduction of relapse of erosive esophagitis in subjects in the Maintenance Phase (24 weeks) in whom endoscopic healing of erosive esophagitis has been



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confirmed after treatment w 438 for maintenance therapy	ith TAK-438 or a PPI <u>, as well as to</u> d v in erosive esophagitis.	letermine the clinically recomme	nded dose of TAK-	SOT
Revised Text			erth.	
	n-inferiority of TAK-438 to Lansopra in the Maintenance Phase (24 weeks			

Revised Text

- To demonstrate the non-inferiority of TAK-438 to Lansoprazole in the reduction of relapse of erosive esophagitis in subjects in the Maintenance Phase (24 weeks) in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a PPI.
- To determine the clinically recommended dose of TAK-438 for maintenance therapy in erosive esophagitis in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a PPI. ect to the

Rationale for Amendment

The description has been revised in the protocol.

Page 7, Section 4.2 SECONDARY OBJECTIVES

Existing Text

To evaluate the efficacy of TAK-438 during the 12-week treatment and the safety of TAK-438 versus Lansoprazole in subjects in the Maintenance Phase (24 weeks) in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a PPI.

Revised Text

- To evaluate the efficacy of TAK-438 during the first 12-weeks of treatment in the Maintenance Phase in subjects with endoscopically confirmed healed erosive esophagitis receiving TAK-438 or a PPI.
- To evaluate the safety of TAK-438 versus Lansoprazole in subjects in the Maintenance Phase (24 weeks) in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a PPI.

Rationale for Amendment

The description has been revised in the protocol.

Page 7~8, Section 4.4 STUDY DESIGN

Existing Text

This is a phase III, multicenter, double-blind, parallel-group comparative study of TAK-438 (10 mg or 20 mg) in subjects in whom endoscopic healing of erosive esophagitis has been confirmed with TAK-438 or following proton pump inhibitor (PPI) treatment, to demonstrate the non-inferiority of TAK-438 to Lansoprazole in their maintenance treatment (6 months or 24 weeks) as well as to determine the clinically recommended dose for TAK-438 for maintenance therapy in erosive esophagitis.

All subjects who have been confirmed on endoscopy to have healing of erosive esophagitis will be randomized at a CC: 1 ratio to oral TAK-438 10 mg, 20 mg or Lansoprazole 15 mg once daily given in the Maintenance Phase lasting 24 weeks.

If relapse of erosive esophagitis has been endoscopically confirmed in any subject, the subject will complete the study at that time point (to be construed as "complete cases in the Maintenance Phase", regardless of the time point where relapse of disease is confirmed).

This study will be conducted at a total of around 60 sites across Asia with an estimated total of 200 subjects randomized to each treatment group totaling 600 for the study.



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This version replaces:	TMPL-104			~0
Template Title: Sta	atistical Analysis Plan (Legacy Ta	keda)		, SS
The study will consist of a Scr	eening Phase of up to 28 days followed	by a Treatment Phase of up	to 24 weeks.	õ
There will be 5 subject visits s	cheduled: the start of the Screening Pha	ase (Visit 1), the start of the	Freatment Phase	5
Visit 2), after 4 weeks of treat	tment (Visit 3), after 12 weeks of treatm	nent (Visit 4), after 24 weeks	of treatment	0
Visit 5), and a Follow-up pha	<u>se.</u>		101	
Dosing will commence on Day	y 1 after randomization at Visit 2 (after	completion of all required as	ssessments	
1 1 1 1 1 1 1			<u></u>	

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

Revised Text

This is a phase 3, multicenter, randomized double-blind, parallel-group study to demonstrate the non-inferiority of TAK-438 (10 mg or 20 mg) to Lansoprazole 15 mg in preventing the recurrence of erosive esophagitis in subjects with endoscopically confirmed healing of erosive esophagitis. This study also aims to determine the clinically recommended dose of TAK-438 for maintenance therapy of erosive esophagitis.

This study is comprised of 2 treatment periods: An open-label, single-arm period in which subjects receive Lansoprazole 30 mg for up to 8 weeks (Healing Phase), and a double-blind, parallel-group period in which subjects are randomized at a 1:1:1 ratio to TAK-438 10 mg, 20 mg or Lansoprazole 15 mg once daily for up to 24 weeks (Maintenance Phase). To enroll in the study subjects must have ongoing erosive esophagitis or have completed Study TAK-438 303. Subjects with ongoing erosive esophagitis are required to undergo the Healing Phase. Once erosive esophagitis healing is confirmed by endoscopy, these subjects may be randomized to 1 of 3 treatments in the Maintenance Phase. Subjects with endoscopic-confirmed healing of erosive esophagitis following the completion of Study TAK-438 303 will be randomized into the Maintenance Phase without carrying out the open-label Healing Phase. Subjects who previously entered the study (prior to Protocol Amendment 06) after confirmation of healed erosive esophagitis following treatment with a proton pump inhibitor (termed "de novo" subjects) are no longer eligible to enter the study; any ongoing subjects may continue being treated in the Maintenance Phase. A schematic 5 of the study design is included in Figure 4.a.

If relapse of erosive esophagitis has been endoscopically confirmed in any subject, the subject will complete the study at that time point (to be construed as "complete cases in the Maintenance Phase"), regardless of the time point where relapse of disease is confirmed.

This study will be conducted at a total of around 70 sites across Asia with an estimated total of 231 subjects randomized to each treatment group during the Maintenance Phase (totaling 693 subjects entering the Maintenance Phase for the study).

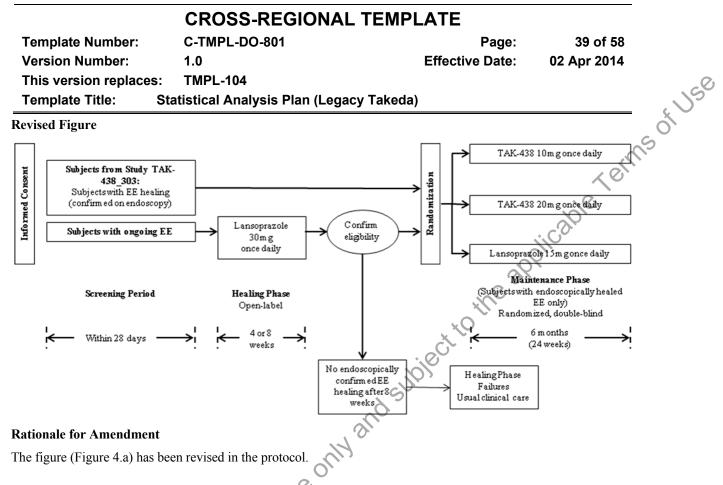
The study will consist of a Screening Phase of up to 28 days duration (Visit 1), a Healing Phase (for those subjects with ongoing erosive esophagitis only) of 4 or 8 weeks duration (Visits 2_{HP} and 3_{HP}), followed by a Maintenance Phase of up to 24 weeks (Visits 2-8), and a Follow-up Period of up to 14 days duration. With the exception of the Follow-up (which will be carried out by phone), all visits will occur at the clinic. The total duration of treatment is up to 6 months (24 weeks) in subjects entering from Study TAK-438 303, and up to 8 months (32 weeks) in subjects entering the study with ongoing erosive esophagitis.

Subjects with ongoing erosive esophagitis: Subjects who have ongoing erosive esophagitis will enter the Healing Phase and administration of Lansoprazole 30 mg once daily will commence following the completion of all required assessments at Visit 2_{HP} . Subjects will then undergo a visit at Week -4 (Visit 3_{HP}), where the subject may undergo endoscopy to confirm healing of erosive esophagitis. This is an optional procedure where the decision to perform endoscopy is based on the investigator's clinical judgment of a subject's symptoms of healing. Subjects who do not show endoscopic healing at Visit 3_{HP} may continue in the Healing Phase and undergo endoscopy at Day 1 (Visit 2). Subjects with endoscopically confirmed healing of erosive esophagitis at Week -4 or at Day 1 will be eligible to enter the Maintenance Phase. Where the results from clinical laboratory tests confirming eligibility for the Maintenance Phase at Week -4 are not immediately available, subjects should continue to receive Lansoprazole 30 mg for up to 14 days. Subjects healed at Day 1 should be immediately randomized. Subjects who do not have



CROSS-REGIONAL TEMPLATE Template Number: C-TMPL-DO-801 Page: 38 of 58 Version Number: 1.0 **Effective Date:** 02 Apr 2014 Subjects with healed erosive esophagitis: Subjects with healed erosive esophagitis will undergo a randomization visit (Visit 2), and dosing for the Maintenance Phase will commence following the completion of all required assessments on Day 1. Visits will then occur at 2 week intervals after the initiation of treatment. Phase. As a result of Protocol Amendment 06, subjects with healed to proton pump inhibitor outside Study TAV 400 no longer eligible t no longer eligible to enter the study; any ongoing subjects may continue to be treated in the Maintenance Phase. All subjects receiving TAK-438 must undergo a total of 8 weeks of LFT monitoring visits with visits occurring every 2 weeks. For subjects entering the Maintenance Phase of the current study within 7 days of completing Study TAK-438 303, the requirement for 8 weeks of monitoring can be totalled across the 2 studies. d subject to **Rationale for Amendment** The descriptions have been revised in the protocol. Page 8, Section 4.4 STUDY DESIGN **Existing Figure** Maintenance Treatment Up to 24 weeks Screening Within 28 days TAK-438 10mg once daily Follow-up Phase 7-14 days Subjects with Endoscopic confirmed erosive esophagitis TAK-438 20mg once daily healing after TAK-438 or PPIs Property of takeda. For normalization treatment Follow-up phone call Lansoprazole 15mg once daily





Page 9, Section 5.0 ANALYSIS ENDPOINTS

Existing Text

The secondary efficacy endpoint for this study is the rate of recurrence* of erosive esophagitis during the 12 weeks of treatment in the Maintenance Phase. Safety endpoints for this study include adverse events, clinical laboratory test results, ECG, vital signs, serum gastrin and pepsinogen I/II levels.

Revised Text

The secondary efficacy endpoint for this study is the rate of recurrence* of erosive esophagitis during the <u>first 12</u> weeks of treatment in the Maintenance Phase. Safety endpoints for this study include adverse events (AEs), clinical laboratory test results, ECG, vital signs, serum gastrin and pepsinogen I/II levels.

Rationale for Amendment

The description has been revised in the protocol.

Page 10, Section 6.0 DETERMINATION OF SAMPLE SIZE

Existing Text

Assuming that the true Week 24 recurrence rate is 30.4% for <u>lansoprazole</u>, 22.0% for TAK-438 10 mg, and 13.6% for TAK-438 20 mg, and assuming that the dropout rate is <u>up to 20%</u>, a sample size of <u>185</u> subjects per group will provide an overall power of 90% to establish non-inferiority using a 2-sided 95% CI with a 10% non-inferiority margin. <u>200</u> subjects per group will be included to allow adequate numbers for the regulatory requirements of various countries.



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The assumption of the true re	currence rate is based on a <u>Phase</u> 3 g and 13.6% for <u>lansoprazole</u> 30 mg	study that showed a Week 24 re	currence rate of	SOL
1749/CCT-202), the point est	ier study of Lansoprazole as mainte imate for the difference (Lansopraz- upper limit of the confidence interv	ole 15 mg group – <u>Famotidine</u> g	roup) was	

Based on results from an earlier study of Lansoprazole as maintenance therapy for erosive esophagitis (AG-1749/CCT-202), the point estimate for the difference (Lansoprazole 15 mg group - Famotidine group) was calculated as -57.6% with the upper limit of the confidence interval being -30.7%. Therefore, the non-inferiority margin is specified as 10%.

Revised Text

Assuming that the true Week 24 recurrence rate is 30.4% for Lansoprazole, 22.0% for TAK-438 0 mg, and 13.6% for TAK-438 20 mg, and assuming that the dropout rate is approximately 30%, a sample size of 208 subjects per group will provide an overall power of 90% to establish non-inferiority using a 2-sided 95% CI with a 10% noninferiority margin. 231 subjects per group will be included to allow adequate numbers for the regulatory requirements of various countries.

The assumption of the true recurrence rate is based on a phase 3 study that showed a Week 24 recurrence rate of 30.4% for Lansoprazole 15 mg and 13.6% for Lansoprazole 30 mg.

Based on results from an earlier study of Lansoprazole as maintenance therapy for erosive esophagitis (AG-1749/CCT-202), the point estimate for the difference (Lansoprazole 15 mg group - famotidine group) was calculated as -57.6% with the upper limit of the confidence interval being -30.7%. Therefore, the non-inferiority margin is specified as 10%.

Rationale for Amendment

The description with the targeted sample size has been revised in the protocol.

Page 11, Section 7.1.1 Definitions

Existing Text

TEAE: An adverse event whose date of onset occurs on or after the start of study drug.

Revised Text

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

Rationale for Amendment

The Maintenance Phase has been added in the protocol, and the handling rules for missing data for TEAE have been added.

Page 11, Section 7.1.1 Definitions

Existing Text

- 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, eg, 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.



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

Revised Text

- Study Day: The day before the first dose of the Maintenance Phase drug 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 eg, 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 Maintenance Phase drug 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 drug (days): date of last dose of Maintenance Phase drug date of first dose of lect to the Maintenance Phase drug + 1

Rationale for Amendment

The Maintenance Phase has been added in the protocol.

Page 11, Section 7.1.1 Definitions

Added Text

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

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 calculation formula for the above variable has been added with the number of decimal places. The significant TEAE should be analyzed and the definition of this type of TEAE has been added.

Page 11~12, Section 7.1.2 Analysis Set

Existing Text

Analysis of efficacy variables will be conducted in the full analysis set (FAS) 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 endpoint 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 or #4

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.



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Revised Text

Analysis of efficacy variables will be conducted in the full analysis set (FAS) defined as all randomized subjects who receive at least 1 dose of the Maintenance Phase drug and have at least 1 post-baseline endoscopy, and will be based on the randomized treatment. Randomized subjects who were accidentally unblinded due to IWRS system error will be excluded.

The primary efficacy endpoint and the secondary efficacy endpoint 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. to the al

- Subjects who did not meet inclusion criteria #3 or #4
- Subjects who met exclusion criteria #8, #11, #12, #13, or #14
- Subjects with study drug 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 the Maintenance Phase drug and will be based on the treatment received in the Maintenance Phase.

Rationale for Amendment

The Maintenance Phase has been added in the protocol. Accidental unblinding was identified in the study on Dec 16, 2015. It was confirmed that the treatment details of 93 subjects randomized in the study were accidentally unblinded to the site investigators, clinical project managers, and the CRA team through the IWRS subject visit notification emails. The accidental unblinding was caused by an WRS system error. The randomized subjects who were accidentally unblinded due to IWRS system error should be excluded from the FAS and the PPS.

Page 12, Section 7.1.3 Handling of Rate of Endoscopic Recurrence of Erosive Esophagitis

Existing Text

7.1.3.1 Rate of Endoscopic Recurrence of Erosive Esophagitis During the 12-Week Treatment

A subject who is diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed between Study Day 2 and Study Day 127 up to and including Follow-up Day 14) will be considered as a relapsed 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 relapsed'. Recurrence rate will be calculated from the relapsed and not relapsed subjects, however, any subjects diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed before the study medication administration will be excluded from the analysis.

7.1.3.2 Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-Week Treatment

A subject who is diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed after Study Day 2 (up to and including Follow-up Day 14) will be considered as a relapsed 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 relapsed'. Recurrence rate will be calculated from the relapsed and not relapsed subjects, however, any subjects diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed before the study medication administration will be excluded from the analysis.



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Revised Text				- Č
.1.3.1 Rate of Endoscopic Jaintenance Phase	Recurrence of Erosive Esophagitis During th	he <u>first 12 Weeks of</u> Tree	utment <u>in the</u>	ns

Revised Text

7.1.3.1 Rate of Endoscopic Recurrence of Erosive Esophagitis During the first 12 Weeks of Treatment in the Maintenance Phase

A subject who is diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed between Study Day 2 and Study Day 127 (up to and including Follow-up Day 14) will be considered as a relapsed 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 relapsed'. Recurrence rate will be calculated from the relapsed and not relapsed subjects, however, any subjects diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed before the Maintenance Phase drug administration will be excluded from the analysis,

7.1.3.2 Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-Week Maintenance Phase

A subject who is diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed after Study Day 2 (up to and including Follow-up Day 14) will be considered as a relapsed 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 relapsed'. Recurrence rate will be calculated from the relapsed and not relapsed subjects, however, any subjects diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed before the Maintenance Phase drug administration will be excluded from the analysis

Rationale for Amendment

The Maintenance Phase has been added, and the description has been revised in the protocol.

Page 12, Section 7.1.4 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)

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 14, Section 7.1.6 Handling of Other Endpoints

Existing Text

Study Day: <u>-28 – 1</u> (2 places)

Revised Text

Study Day: up to and including Study Day 1 (2 places)

Rationale for Amendment

The time intervals should be changed because the Healing Phase has been added in the protocol.



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Existing Text

Revised Text

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ev	vised Text			NO Ì	
ir	nical laboratory tests (ALT	Γ, AST, total bilirubin, and direct bilirubi	<u>n)</u>		
	Visit	Scheduled Study Day	<u>Time In</u>	<u>terval (days)</u>	
	<u></u>	<u>(days)</u>	Study Day	Follow-up Day	
	Baseline [*]	Study Day: 1	<u>-28 - 1</u>)	
	Week 2	Study Day: 15	$\frac{2-22}{2}$	up to and including Follow-up Day 14	
	Week 4	Study Day 29	23-36	up to and including Follow-up Day 14	
	Week 6	Study Day: 43	<u>37 - 50</u>	up to and including Follow-up Day 14	
	Week 8	Study Day: 57	<u>51 - 71</u>	up to and including Follow-up Day 14	
	Week 12	Study Day: 85	<u>72 – 127</u>	up to and including Follow-up Day 14	
	Week 24	<u>Study Day:</u> <u>169</u>	<u>128 – 211</u>	up to and including Follow-up Day 14	

: For the clinical laboratory tests of the subjects who participated in the TAK-438 303 study, if the last study visit coincides with the first visit in the 305 study or if the subject was randomized in the 305 study within 7 days after completing the last visit in the 303 study, then the data obtained at the last visit can be used as the baseline data for the 305 study.

Clinical laboratory tests (other than ALT, AST, total bilirubin, and direct bilirubin), Gastrin, Pepsinogen I/II, Vital signs

Rationale for Amendment

Visit 3 (Week 2), Visit 5 (Week 6) and Visit 6 (Week 8) has been added in the protocol for evaluating liver function tests (ALT, AST, total bilirubin, and direct bilirubin).

Page 15, Section 7.1.6 Handling of Other Endpoints

Existing Text

For the clinical laboratory tests, gastrin and pepsinogen I/II, for the subjects who participated in the TAK-438 303 study

Revised Text

For the clinical laboratory tests, gastrin, and pepsinogen I/II of the subjects who participated in the TAK-438 303 study



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Did Not Meet Entrance Criteria, <u>Healing Phase</u>	



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Page 17, Section 7.2.1.5 D	Disposition of Subjects			0 ¹
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1) Disposition of Subjects	5		1 off	*

Page 17, Section 7.2.1.5 Disposition of Subjects

Existing Text

(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.

Revised Text

(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 maintenance phase drug will be used as the denominator. When calculating percentages for the reasons for discontinuation of maintenance phase drug, the total number of subjects who prematurely discontinued the maintenance phase drug will be used as the denominator.

(2) Flow Chart of Subject Distribution Flow chart will be provided.

Rationale for Amendment

The Maintenance Phase has been added in the protocol. The analysis for providing a flow chart has been added in this SAP.

Page 18, Section 7.2.2.1 Summary of Demographics and Other Baseline Characteristics

Existing Text

Analysis Set: Randomized Set

Revised Text

Analysis Set: Randomized Set. Full Analysis Set

Rationale for Amendment

The analysis for the full analysis set has been added.

Page 18, Section 7.2.2.1 Summary of Demographics and Other Baseline Characteristics

Existing Text

Race [American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White]

Revised Text

Race [American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple]

Rationale for Amendment

There have been subjects whose race were "Multiple".



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•	tatistical Analysis Plan (Legacy	y Takeda)	
Page 20, Section 7.2.3.1 Stud	dy Drug Exposure and Complianc	ce	
Existing Text			
Analysis Set: Safety Analysis	Set		10
Revised Text			
Analysis Set: Safety Analysis	Set <u>, Full Analysis Set</u>		2010
Rationale for Amendment			il.co.
The analysis for the full analy	vsis set has been added.	Ó	5.
		0	
Page 20, Section 7.2.3.1 Stud	dy Drug Exposure and Complianc	e XV-	
Existing Text		A VO	
(1) Study Drug Exposure and	Compliance	ieu	
Revised Text			
(1) Study Drug Exposure and	Compliance in Maintenance Phase	23	
Rationale for Amendment			
The Maintenance Phase has b	een added in the protocol.		
Page 21, Section 7.3.1 Prima	ary Efficacy Endpoint		
Existing Text	in		
Rate of Endoscopic Recurren	ce of Erosive Esophagitis During th	e 24-week <u>Treatment</u> (3 places)	
Revised Text	ane		
Rate of Endoscopic Recurrent	ce of Erosive Esophagitis During th	e 24-week <u>Maintenance Phase</u> (3	g places)
Rationale for Amendment	L'O		
The Maintenance Phase has b	een added in the protocol.		
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Page 21~22, Section 7.3.2 Se	econdary Efficacy Endpoint		
Existing Text			
	ce of Erosive Esophagitis During th	e <u>12-week Treatment</u> (4 places)	
Revised Text			
Rate of Endoscopic Recurrent Phase (4 places)	ce of Erosive Esophagitis During th	e First 12 Weeks of Treatment in	the Maintenance
Rationale for Amendment			
The Maintenance Phase has b	been added in the protocol and the de	escription has been revised in the	protocol.



Hermitate Number: C-TMPL-DO-801 Effective Date: 02 Apr 2014 Hersion Number: 1.0 Effective Date: 02 Apr 2014 His version replaces: TMPL-104 Hersion 1.3.3.3 Barrett's Mucosa Hersion 1.3.3.3 Barrett's Mucosa Factoria 7.3.3.3 Barrett's Mucosa Hersion 1.3.3.3 Barrett's Mucosa Factoria 7.3.4 Gravity Mucosa Hersion 1.3.4 Construction 1.3.4 Constructio
Rate of Endoscopic Recurrence of Erosive Esophagitis During the <u>12-week Treatment</u> (7 places) Revised Text Rate of Endoscopic Recurrence of Erosive Esophagitis During the <u>24-week Maintenance Phase</u> (7 places) Rate of Endoscopic Recurrence of Erosive Esophagitis During the <u>First 12 Weeks of Treatment in the Maintenance Phase</u> (7 places) Rationale for Amendment The Maintenance Phase has been added in the protocol and the description has been revised in the protocol. Page 25, 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. Values below the lower limit of quantification will be treated as the upper limit values 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. Values above the upper limit of quantification will be treated as the upper limit values 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. Values above the upper limit of quantification will be treated as the upper limit values when calculating the descriptive statistics. Values below the lower or upper limit values for calculating the descripti
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Page 25, 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. Values above the upper limit of quantification will be treated as the upper limit values 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
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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
The handling rules of values below the lower or upper limit values for calculating the descriptive statistics have been
So.
Page 27, Section 7.4.1.1 Overview of Treatment-Emergent Adverse Events Added Text
S 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 have been added.



	CROSS-REGIONAL TEMPLATE			
	Template Number: Version Number: This version replaces: Template Title: St	C-TMPL-DO-801 1.0 TMPL-104 atistical Analysis Plan (Legacy	Page: Effective Date: 7 Takeda)	49 of 58 02 Apr 2014
	Page 28, Section 7.4.1.2 Dis	olays of Treatment-Emergent Adv	erse Events	Ő
	Existing Text			ans.
	System Organ Class			x official
	Revised Text			Ø
	SOC			2010
	Rationale for Amendment			lico
	The expression "System Orga	n Class" has been replaced with "SC	OC" for expression consistency.	R
			0	
	Page 28~29, Section 7.4.1.2	Displays of Treatment-Emergent A	Adverse Events	
	Added Text			
	(8) Drug-Related Treatment-I Class and Preferred Term	Emergent Adverse Events Leading to	Study Drug Discontinuation b	y System Organ
	(10) Serious Drug-Related Tr	eatment-Emergent Adverse Events b	by System Organ Class and Pref	erred Term
	(15) Significant Treatment-En	nergent Adverse Events by System	Organ Class and Preferred Term	1
	(16) Drug-Related Significant	Treatment-Emergent Adverse Even	ts by System Organ Class and I	Preferred Term
	(17) Most Frequent Non Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred			
	the treatment groups. If there	AEs refer to PTs that are not serious are no PTs whose percentages excee r "Subjects With Any TEAEs", the r will be used as the numerator.	ed 5%, the threshold is lowered	to 2%. When
	Rationale for Amendment	con.		
	The analyses for these types	TEAEs has been added.		
	Page 30, Section 7,4,2 Pretro	eatment Events and Adverse Even	ts in the Healing Phase	
	Existing Text			
	7.4.2 Pretreatment Events			
	Revised Text			
	7.4.2 Pretreatment Events and	Adverse Events in the Healing Phase	se	
X	(omitted)			
200	7.4.2.2 Displays of Adverse E	events in the Healing Phase		
5,00		ects Who Entered the Healing Phase the Healing Phase	2	



	CROSS-REGIONAL	_ TEMPLATE		
Template Number:	C-TMPL-DO-801	Page:	50 of 58	
Version Number:	1.0	Effective Date:	02 Apr 2014	
This version replaces:	TMPL-104			
Template Title: S	Statistical Analysis Plan (Lega	cy Takeda)		\mathcal{S}
Analytical Methods: The fol	llowing summaries will be provided	d using frequency distribution.	, C	5
AEs wi	ill be coded using the MedDRA and	d will be summarized using SOC a	nd PT. SOC will	
be sorte	ed alphabetically and PT will be so	rted in decreasing frequency.		
<u>(1) Adv</u>	verse Events in the Healing Phase b	by System Organ Class and Preferr	ed Term	
<u>(2) Seri</u>	ious Adverse Events in the Healing	Phase by System Organ Class and	l Preferred Term	
The fre	equency distribution will be provide	ed according to the rules below.	<i>p</i>	
Numbe	er of subjects			
<u>A subje</u>	ect with multiple occurrences of AI	E within a SOC will be counted on	ly once in that	
SOC. A	A subject with multiple occurrences	s of AE within a PT will be counted	d only once in that	
<u>PT.</u>		*he		

Rationale for Amendment

The Healing Phase has been added in the protocol and the analyses for adverse events in the Healing Phase have been added in this SAP.

Page 31~33, Section 7.4.3 Laboratory and Other Safety Data, Section 7.4.4 Vital Signs, Physical Findings, and USEONIY **Other Observations Related to Safety** \mathcal{O}

Existing Text

treatment phase (4 places)

Revised Text

maintenance phase (4 places)

Rationale for Amendment

The Maintenance Phase has been added in the protocol.

Page 31, Section 7.4.3.1 Laboratory Test Results

Existing Text

Visit: Baseline, Week 4, Week 12, Week 24

Revised Text

ALT, AST, Total Bilirubin, and Direct Bilirubin: Visit:

Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 24

Variables other than ALT, AST, Total Bilirubin, and Direct Bilirubin:

Baseline, Week 4, Week 12, Week 24

Rationale for Amendment

Visit 3 (Week 2), Visit 5 (Week 6) and Visit 6 (Week 8) has been added in the protocol for evaluating liver function tests (ALT, AST, total bilirubin, and direct bilirubin).



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Version Number:			
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Template Title:	Statistical Analysis Plan (Lega	cy Takeda)	02 Apr 2014
Page 32, Section 7.4.	3.1 Laboratory Test Results (Serum Ga	strin, Pepsinogen I/II)	
Existing Text			
Pepsinogen I (mcg/L)	, Pepsinogen II (<u>mcg</u> /L)		λÔ
Revised Text			0
Pepsinogen I (<u>µg</u> /L), I	Pepsinogen II (<u>μg</u> /L)		201
Rationale for Amend	lment		ilou
The expression "mcg"	has been replaced with " μ g" for using me	ore suitable expression.	X
		NO NO	
Page 33, Section 7.4.	4 Vital Signs, Physical Findings, and Ot	ther Observations Related to Sat	fety (Vital Signs)
Existing Text			
Body Temperature (°C	<i>C</i>)	ieu	
Revised Text		culo,	
Body Temperature (C)	23	
Rationale for Amend	lment	all	
The expression "°C" h	as been replaced with "C" for using more	suitable expression.	
	O`		
Page 33, Section 7.4. ECG)	4 Vital Signs, Physical Findings, and O	ther Observations Related to Sat	fety (12-lead
Existing Text	(D)		
<u>12-lead ECG</u> interpret	ations (3 places)		
Revised Text			
interpretations (3 plac	es)		
Rationale for Amend			
	ad ECG" has been deleted for expression	consistency with TFLs.	
¢C			
Page 34. Section 7.4.	5 Subgroup Analysis for China		
Existing Text			
Analysis Population:	Subjects in China		
	The same analyses as those in section 7.2	to 7.4 will be conducted for the su	bjects in China.
			-
Revised Text			
Analysis Population:			
-	Subjects in Countries other than China	7) to 7 / / will be seedent of for	the aubients in
Anarytical Methods:	 The same analyses as those in section China. 	1.2 to $1.4.4$ will be conducted for	the subjects in



	CROSS-REGIONAL	TEMPLATE	
Template Numbe Version Number: This version repl	1.0 aces: TMPL-104	Page: Effective Date:	52 of 58 02 Apr 2014
Template Title:	Statistical Analysis Plan (Legac	y Takeda)	
(The same analyses as those in section countries other than China. 	7.2 to 7.4.4 will be conducted for	02 Apr 2014
Rationale for Amend	ment		\mathbf{X}^{\otimes}
The analyses for the u	nderlined part have been added.		cable
	5 Subgroup Analysis for Taiwan, Section lly Unblinded Subjects	1 7.4.7 Subgroup Analysis for S	afety Analysis Set
Added Text			
7.4.6 Subgroup Analy	sis for Taiwan		
Analysis Population: S	Subjects in Taiwan	A.V.	
Analytical Methods: (1) The same analyses as those in section 7	7.2 to 7.4.4 will be conducted for	the subjects in
	<u>Taiwan.</u>	culo,	
		03	
	sis for Safety Analysis Set Excluding Acci	0.	
	Safety Analysis Set Excluding the Accident		_
	Safety Analysis Set Excluding the Accident Safety Analysis Set Excluding the Accident		
	<u>China</u>	·····, · · · · · · · · · · · · · · · ·	
	Safety Analysis Set Excluding the Acciden		
	The same analyses as those in sections 7.4. n the safety analysis set that excludes subject that excludes subj		
	system error.	cets who were accidentary unon	
	The same analyses will be conducted for th The same analyses will be conducted for th		other than China.
-	ine same analyses will be conducted for th	e subjects in Taiwan.	
Rationale for Amend			
The analyses for the u	nderlined part have been added.		
Page 34, Section 7.4.0	5 Significance Level and Confidence Coe	fficient	
Existing Text			
Significance leve	el: 5% (two-sided test)		
Confidence coeff	icient: 95% (two-sided)		
No statistical testing w	vill be performed if there are less than 5 sul	bjects.	
Revised Text			
)X	el: 5% (two-sided test)		
-	icient: 95% (two-sided)		



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Template Title:	Statistical Analysis Plan (Leg	acy Takeda)	
Rationale for Amendme		<u> </u>	
The analysis plan has bee	en changed that statistical testing will	be performed even if there are less	than 5 subjects.
			than 5 subjects.
Page 54, Section 8.0 RE	FERENCES		
Added Text			2015
Luo N, et. al. (2017) "Est	imating an EQ-5D-5L Value Set for		
Rationale for Amendme	ent	20	< compared with the second sec
The above reference has	been added.	*11° 319	
Page 56, Section 9.1.1 H MAV Criteria of QTcF	ematology, Serum Chemistry, Uriı Interval)	alysis, Vital Signs, and 12-lead E	CG (except Upper
Existing Text	····)	.0)	
Body Temperature (<u>°</u> C)		alysis, Vital Signs, and 12-lead E	
Revised Text		ano	
Body Temperature (C)		1.0.	
Rationale for Amendme	ent of	, ð	
The expression "°C" has			
	been replaced with "C" for asing mor		
perty of Takeda. For the	comme		
~	on		
al al			
8a.			
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A CONTRACTOR			
*10.			
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3.0	REFERENCE	S			SOL
•		8) "Comparing the areas under two approach", Biometrics, Volume 44		ting characteristic	
•	Divine G, et al. (2013) " Anesth Analg, Volume	A review of analysis and sample si 117(3): 699-710.	ize calculation considerations for	Wilcoxon tests",	
•	Lehmann FL et al (19	75) "Nonnarametrics: statistical me	thods based on ranks" Springer	. 0.	

8.0

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- •
- Lehmann EL, et. al. (1975) "Nonparametrics: statistical methods based on ranks", Springer. •
- 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.
- and ap Inter a China", Va a China China a China a China China China C O'Brien RG, et. al. (2006) "Exploiting the link between the Wilcoxon-Mann-Whitney test and a simple odds • statistic", Proceedings of the Thirty-First Annual SAS Users Group International Conference.
 - 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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	•	atistical Analysis Plan (Legacy Tak	(eda)		USO
.0	APPENDIX				SOL
.1	CRITERIA FOR	ARKEDLY ABNORMAL VALUES		X OTT	
.1.1	Hematology,	Serum Chemistry, Urinalysis	, Vital Signs, and 12	2-lead ECG	

9.0 APPENDIX

9.1 **CRITERIA FOR MARKEDLY ABNORMAL VALUES**

Hematology, Serum Chemistry, Urinalysis, Vital Signs, and 12-lead ECG 9.1.1 (except Upper MAV Criteria of QTcF Interval)

For each parameter, all evaluable data (ie, 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.

- A subject with at least one evaluable data after baseline that meets the MAV criteria will be classified as a i) subject with MAV.
- A subject who does not meet condition i) and has at least one evaluable data after baseline that doesn't meet the ii) 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.

<u>Hematology</u>	·O.		
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		
Farameter	Lower Criteria	Upper Criteria	
ALT (U/L)	-	>3×ULN	
ALP (Q/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	



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Template Title: Statistical Analysis	Plan (Legacy Takeda)	
Parameter	MAV	Criteria
T drameter	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		
Falanietei	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	
	0,		

12-lead ECG	6		
Parameter	MAV	MAV Criteria	
Falanciel	Lower Criteria	Upper Criteria	
Heart Rate (bpm)	<50	>120	
QT Interval (msec)	<=50	>=460	
QTcF Interval (msec)	<=50	-	

12-lead ECG (Upper MAV Criteria of QTcF Interval) 9.1.2

All evaluable data (ie, 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.

- A subject with at least one evaluable data after baseline that meets the MAV criteria will be classified as a i) 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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		O ^N
Donomotor		MAV Criteria
Parameter	Lower Criteria	Upper Criteria
		If either of the following conditions is met:
QTcF Interval (msec)	-	observed value >= 500
		• change from baseline \geq 30 and observed value \geq 450

9.2 **CRITERIA FOR ELEVATED LIVER ENZYME**

All evaluable data (ie, 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

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

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Label	Criteria for Eleva	ted Liver Enzyme
Label	(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



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Label		ated Liver Enzyme
Laber	(a) Elevated	(b) Not Elevated
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
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 equa to 3 times the ULN
ALP > 3xULN with ALT > 3xULNO	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

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