Title: A Phase 1, Double-Blind, Parallel Group Study to Evaluate the Safety and Pharmacokinetics of Quadruple Therapy (Bismuth, Clarithromycin, and Amoxicillin) With TAK-438 Versus Quadruple Therapy With Lansoprazole.

NCT Number: NCT02892409

SAP Approve Date: 15MAY2017

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TAKEDA DEVELOPMENT CENTER

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-438_115

A Phase 1, Double-Blind, Parallel Group Study to Evaluate the Safety and Pharmacokinetics of Quadruple Therapy (Bismuth, Clarithromycin, and Amoxicillin) With TAK-438 Versus Quadruple Therapy With Lansoprazole.

PHASE 1

Version: 2.0
Date: 15MAY2017

Prepared by:

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Study Title: A Phase 1, Double-Blind, Parallel Group Study to Evaluate the Safety and Pharmacokinetics of Quadruple Therapy (Bismuth, Clarithromycin, and Amoxicillin) With TAK-438 Versus Quadruple Therapy With Lansoprazole.

TDC Approvals:

PPD [Signature] Date

PPD [Signature] Date

PPD [Signature] Date

PPD [Signature] Date

PPD [Signature] Date
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3.0 LIST OF ABBREVIATIONS

AE        adverse event
Ae        amount of drug excreted in urine during a dosing interval
ALT       alanine aminotransferase
ALP       alkaline phosphatase
AUC        area under the concentration-time curve during a dosing interval
AUC∞      area under the plasma concentration-time curve from time 0 to infinity
AST       aspartate aminotransferase
BID       twice daily
BMI       body mass index
CAL       clarithromycin (500 mg BID), amoxicillin (1000 mg BID), and lansoprazole (30 mg BID)
CAT       clarithromycin (500 mg BID), amoxicillin (1000 mg BID), and TAK-438 (20 mg BID)
CL/F      apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration
CLR       renal clearance
Cmax      maximum observed plasma concentration
CRF       case report form
CV        coefficient of variation
CYP       cytochrome P450
ECG       electrocardiogram
f(0, t)   Fraction of administered dose of drug excreted in urine during a dosing interval. Molecular weight adjustment needed for metabolites.
GGT       γ-glutamyl transferase
HP        Helicobacter pylori
LDH       lactate dehydrogenase
LLN       lower limit of normal
λz        terminal disposition phase rate constant
MAV       markedly abnormal values
MedDRA    Medical Dictionary for Regulatory Activities
PD        pharmacodynamics
PK        pharmacokinetics
PTE       pretreatment event
QTcF      QT interval corrected by Fridericia's method
SAP       statistical analysis plan
TAK-438F  freebase of TAK-438
TEAE      treatment-emergent adverse event
t(1/2)z    terminal disposition phase half-life
<table>
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<th>Term</th>
<th>Definition</th>
</tr>
</thead>
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<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>time of first occurrence of C&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>V&lt;sub&gt;a&lt;/sub&gt;/F</td>
<td>apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration</td>
</tr>
<tr>
<td>WHO Drug</td>
<td>World Health Organization Drug Dictionary</td>
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4.0 OBJECTIVES

4.1 PRIMARY OBJECTIVES

The primary objective is to evaluate the safety, tolerability, and PK of quadruple therapy BID with tripotassium bismuth dicitrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and TAK-438 (20 mg) versus quadruple therapy BID with tripotassium bismuth dicitrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and lansoprazole (30 mg).

4.2 SECONDARY OBJECTIVES

Not applicable

4.3 ADDITIONAL OBJECTIVES

Not applicable

4.4 STUDY DESIGN

This is a phase 1, double-blind, parallel group study in HP positive subjects to evaluate the safety, tolerability, and PK of quadruple therapy with bismuth, clarithromycin, amoxicillin, and TAK-438 versus quadruple therapy with bismuth, clarithromycin, amoxicillin, and lansoprazole.

Thirty HP positive male or female subjects aged 19 to 60 years, inclusive, considered eligible based on the inclusion and exclusion criteria, will participate in this study. All subjects will be enrolled and will be randomized to 1 of 2 treatment groups as indicated in Figure 1. One site in Asia will be selected to conduct this study.

The treatment phase consists of quadruple therapy BID with tripotassium bismuth dicitrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and TAK-438 (20 mg) or quadruple therapy BID with tripotassium bismuth dicitrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and lansoprazole (30 mg) for 14 days (Days 1 to 14). Subjects will be discharged on Day 15 after final PK blood samples are collected and all procedures performed.

Screening for potential subjects will occur between Days -28 and -2 prior to confinement at the phase 1 unit. Eligibility will be reconfirmed on Day -1. Having fasted for a minimum of 8 hours, oral doses of tripotassium bismuth dicitrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and TAK-438 (20 mg) or tripotassium bismuth dicitrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and lansoprazole (30 mg) will be administered BID from Days 1 to 14. The last dose will be on the evening of Day 14. Blood sampling for TAK-438 and lansoprazole PK measurements will be taken on Days 12 to 14 (predose evening and morning) and for bismuth PK measurements on Day 14 (pre–morning dose to 12 hours post–morning dose). Urine sampling for bismuth PK measurements will be taken on Day 14 (pre–morning dose to 12 hours post–morning dose). The subject will be confined to the phase 1 unit from Day -1 (Check-in) through to Day 15 (Check-out), and will be required to contact the study site once again for a follow-up call on Day 17 and a clinic visit on Day 42 for a HP breath test.

A schematic of the study design is included as Figure 1.

Figure 1. Schematic of Study Design
### CROSS-REGIONAL TEMPLATE

**Template Number:** C-TMPL-DO-801  
**Version Number:** 1.2  
**Effective Date:** 14 Sep 2015

**Parent Document:** C-SOP-DO-800  
**Template Title:** Statistical Analysis Plan (Legacy Takeda)

---

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<td>Screening</td>
<td>Check-in Baseline</td>
<td>Confinement</td>
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<tr>
<td>Days -28 to -2</td>
<td>Day -1</td>
<td>Day 1-11</td>
</tr>
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</table>

- **Group A:** CA + bismuth + lansoprazole dosing
- **Group B:** CA + bismuth + TAK-438 dosing
- **TAK-438 PK or lansoprazole PK in plasma**
- **Bismuth PK in plasma and urine**
- **HP breath test**

---

Bismuth: tripotassium bismuth dicitrate (600 mg BID, equivalent to bismuth 220 mg BID); CA: clarithromycin (500 mg BID), amoxicillin (1000 mg BID); TAK-438: 20 mg BID; lansoprazole: 30 mg BID.

**Blood PK samples** for Bismuth: Day 14 predose (0 hours), 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, and 12.0 hours after morning dose.

**Urine PK samples** for Bismuth: Day 14 at 0 to 12 hours post–morning dose.

**Blood PK samples** for TAK-438 and lansoprazole: Day 12-14 predose (morning and evening)

**Analyte:** bismuth, TAK-438F, and lansoprazole.

Comparison of Group A and Group B: C<sub>max</sub> and AUC<sub>r</sub>.
5.0 ANALYSIS ENDPOINTS

- Percentage of subjects who experience at least 1 treatment-emergent adverse event (TEAE).
- Percentage of subjects who discontinue due to an adverse event (AE).
- Percentage of subjects who meet the markedly abnormal criteria for safety laboratory tests at least once postdose.
- Percentage of subjects who meet the markedly abnormal criteria for vital sign measurements at least once postdose.
- Percentage of subjects who meet the markedly abnormal criteria for safety electrocardiogram (ECG) parameters at least once postdose.
- Plasma PK parameters of tripotassium bismuth dicitrate (600 mg) when coadministered with clarithromycin (500 mg BID), amoxicillin (1000 mg BID), and TAK-438 (20 mg BID) (CAT), and coadministered with clarithromycin (500 mg BID), amoxicillin (1000 mg BID), and lansoprazole (30 mg BID) (CAL):
  - $C_{\text{max}}$ at Day 14.
  - The area under the plasma concentration-time curve during a dosing interval ($\text{AUC}_{\tau}$) at Day 14.
  - The amount of drug excreted in urine during a dosing interval ($\text{Ae}_{\tau}$) at Day 14.
6.0 DETERMINATION OF SAMPLE SIZE

A sample size of 30 (15 subjects per group) will be used in this exploratory study. Although this planned sample size is not primarily based on statistical considerations, it will allow precise estimation of the relative treatment effect of TAK-438 versus lansoprazole on bismuth exposure as follows:

<table>
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<th>Estimated Ratio</th>
<th>CV</th>
<th>Expected 90% CI</th>
<th>Expected 95% CI</th>
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</thead>
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<td>TAK-438/Lansoprazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>0.40</td>
<td>1.15, 1.96</td>
<td>1.09, 2.07</td>
</tr>
<tr>
<td>1.5</td>
<td>0.50</td>
<td>1.07, 2.10</td>
<td>1.00, 2.25</td>
</tr>
<tr>
<td>1.5</td>
<td>0.60</td>
<td>1.00, 2.24</td>
<td>0.92, 2.44</td>
</tr>
<tr>
<td>2.0</td>
<td>0.40</td>
<td>1.53, 2.62</td>
<td>1.45, 2.76</td>
</tr>
<tr>
<td>2.0</td>
<td>0.50</td>
<td>1.43, 2.80</td>
<td>1.33, 3.00</td>
</tr>
<tr>
<td>2.0</td>
<td>0.60</td>
<td>1.34, 2.99</td>
<td>1.23, 3.25</td>
</tr>
</tbody>
</table>

CV = coefficient of variation.

These calculations allow for up to 2 dropouts per group and are based on estimates of CV of 0.40 to 0.60 for PK parameters (area under the plasma concentration-time curve from time 0 to infinity [AUC∞] and Cmax).
7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 GENERAL PRINCIPLES

7.1.1 Definitions

The following definitions and calculation formulas will be used.

- TEAE: An AE whose date of onset occurs on or after the start of study drug.
- PTE: An AE whose date of onset occurs before the start of study drug.
- Significant TEAE: any AEs (not including serious TEAEs) that led to an intervention, including withdrawal of drug treatment or significant additional concomitant therapy.

- Descriptive statistics: number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- Study Day: The day before the first dose of the study medication will be defined as Study Day -1 and the day of the first dose will be defined as Study Day 1. Other study days are defined relative to Study Day 1, e.g., the day prior to Study Day 1 is Day -1 and the day after Study Day 1 is Day 2.
- Duration of exposure to study medication (days): date of last dose of study medication - date of first dose of study medication + 1
- Study drug compliance (%): (number of times “Dose Start Time” was collected) / (2* Duration of exposure to study medication) *100 (rounded to 1 decimal place). Study drug compliance will be calculated each group of study drugs, 1)TAK438/ lansoprazole and bismuth or 2)clarithromycin and amoxicillin.
- QTcF interval (msec): QT interval (msec) / (RR interval (msec)/1000)^0.33 (rounded to the nearest whole number)
- Baseline and Screening values: The last evaluable observation (i.e., non-missing) before the first dose of study medication. If no evaluable observation is obtained before the first dose, the baseline value will be missing.

7.1.2 Handling of Plasma Bismuth Concentrations at Day 14

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

<table>
<thead>
<tr>
<th>Time</th>
<th>Scheduled Time From Morning Dose at Day 14 (min)</th>
<th>Time Interval (min) Sampling Time From Morning Dose at Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre–morning dose (0 hours)</td>
<td>0</td>
<td>-10 – 0</td>
</tr>
<tr>
<td>0.25 hours post–morning dose</td>
<td>15</td>
<td>10 - 20</td>
</tr>
</tbody>
</table>
### Statistical Analysis Plan (Legacy Takeda)

<table>
<thead>
<tr>
<th>Time Post-Morning Dose</th>
<th>Concentration</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 hours</td>
<td>30</td>
<td>25 - 35</td>
<td></td>
</tr>
<tr>
<td>0.75 hours</td>
<td>45</td>
<td>40 - 50</td>
<td></td>
</tr>
<tr>
<td>1.0 hour</td>
<td>60</td>
<td>55 - 65</td>
<td></td>
</tr>
<tr>
<td>1.5 hours</td>
<td>90</td>
<td>85 - 95</td>
<td></td>
</tr>
<tr>
<td>2.0 hours</td>
<td>120</td>
<td>115 - 125</td>
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</tr>
<tr>
<td>3.0 hours</td>
<td>180</td>
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</tr>
<tr>
<td>4.0 hours</td>
<td>240</td>
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<td>5.0 hours</td>
<td>300</td>
<td>295 - 305</td>
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</tr>
<tr>
<td>6.0 hours</td>
<td>360</td>
<td>355 - 365</td>
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<tr>
<td>8.0 hours</td>
<td>480</td>
<td>470 - 490</td>
<td></td>
</tr>
<tr>
<td>10.0 hours</td>
<td>600</td>
<td>590 - 610</td>
<td></td>
</tr>
<tr>
<td>12.0 hours</td>
<td>720</td>
<td>710 - 730</td>
<td></td>
</tr>
</tbody>
</table>

*Start Time of Bismuth, TAK-438, Lansoprazole at morning*

Concentrations below the lower limit of quantification will be treated as zero in the analysis of concentration-time data.
### 7.1.3 Handling of Plasma TAK-438F/ Lansoprazole Concentrations

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

<table>
<thead>
<tr>
<th>Visit</th>
<th>Time</th>
<th>Scheduled Time From Dose&lt;sup&gt;*&lt;/sup&gt; (min)</th>
<th>Time Interval (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 12</td>
<td>Pre-morning dose</td>
<td>Morning 0</td>
<td>-10 – 0</td>
</tr>
<tr>
<td>Day 12</td>
<td>Pre-evening dose</td>
<td>Evening 0</td>
<td>-10 – 0</td>
</tr>
<tr>
<td>Day 13</td>
<td>Pre-morning dose</td>
<td>Morning 0</td>
<td>-10 – 0</td>
</tr>
<tr>
<td>Day 13</td>
<td>Pre-evening dose</td>
<td>Evening 0</td>
<td>-10 – 0</td>
</tr>
<tr>
<td>Day 14</td>
<td>Pre-morning dose</td>
<td>Morning 0</td>
<td>-10 – 0</td>
</tr>
<tr>
<td>Day 14</td>
<td>Pre-evening dose</td>
<td>Evening 0</td>
<td>-10 – 0</td>
</tr>
</tbody>
</table>

<sup>*</sup> Start Time of Bismuth, TAK-438, Lansoprazole

Concentrations below the lower quantifiable concentration will be treated as zero in the analysis of concentration-time data.

### 7.1.4 Handling of Laboratory Test

For each visit, all evaluable observation (i.e., non-missing) obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest sampling 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.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Scheduled Study Day (days)</th>
<th>Time Interval (days)</th>
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<tr>
<td>Baseline</td>
<td>Study Day: -1</td>
<td>-28 – -1</td>
</tr>
<tr>
<td>Day 5</td>
<td>Study Day: 5</td>
<td>1 – 6</td>
</tr>
<tr>
<td>Day 8</td>
<td>Study Day: 8</td>
<td>7 – 9</td>
</tr>
<tr>
<td>Day 12</td>
<td>Study Day: 12</td>
<td>10 – 12</td>
</tr>
<tr>
<td>Day 13</td>
<td>Study Day: 13</td>
<td>13</td>
</tr>
<tr>
<td>Day 14</td>
<td>Study Day: 14</td>
<td>14</td>
</tr>
</tbody>
</table>
### 7.1.5 Handling of Vital Signs

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

<table>
<thead>
<tr>
<th>Visit</th>
<th>Time</th>
<th>Scheduled Study Day (days)</th>
<th>Scheduled Time From Dose* (min)</th>
<th>Time Interval (min) / Study Day (days)</th>
<th>Assessment Time From Dose*</th>
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<td>Pre-morning dose</td>
<td>Study Day: 1</td>
<td>Morning</td>
<td>Study Day: -28 – 1</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>Pre–evening dose</td>
<td>Study Day: 1</td>
<td>Evening</td>
<td>Time: -60 – 0</td>
<td></td>
</tr>
<tr>
<td>Day 2 to 14</td>
<td>Pre-morning dose</td>
<td>Study Day: 2 to 14</td>
<td>Morning</td>
<td>Time: -60 – 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre-evening dose</td>
<td>Study Day: 2 to 14</td>
<td>Evening</td>
<td>Time: -60 – 0</td>
<td></td>
</tr>
<tr>
<td>Day 15</td>
<td></td>
<td>Study Day: 15</td>
<td></td>
<td></td>
<td>Study Day: Post-dose – 15</td>
</tr>
</tbody>
</table>

* Start Time of Bismuth, TAK-438, Lansoprazole

### 7.1.6 Handling of 12-Lead ECGs

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

<table>
<thead>
<tr>
<th>Visit</th>
<th>Time</th>
<th>Scheduled Study Day (days)</th>
<th>Scheduled Time From Dose* (min)</th>
<th>Time Interval (min) / Study Day (days)</th>
<th>Assessment Time From Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Pre-morning dose</td>
<td>Study Day: 1</td>
<td>Morning</td>
<td>Study Day: -28 – 1</td>
<td></td>
</tr>
</tbody>
</table>
### Cross-Regional Template

**Template Number:** C-TMPL-DO-801  
**Version Number:** 1.2  
**Effective Date:** 14 Sep 2015

**This version replaces:** 1.1  
**Parent Document:** C-SOP-DO-800  
**Template Title:** Statistical Analysis Plan (Legacy Takeda)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Time</th>
<th>Scheduled Study Day (days)</th>
<th>Scheduled Time From Dose* (min)</th>
<th>Time Interval (min) / Study Day (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3</td>
<td>Pre-morning dose</td>
<td>Study Day: 3</td>
<td>Morning 0</td>
<td>Time: -60 – 0</td>
</tr>
<tr>
<td>Day 7</td>
<td>Pre-morning dose</td>
<td>Study Day: 7</td>
<td>Morning 0</td>
<td>Time: -60 – 0</td>
</tr>
<tr>
<td>Day 14</td>
<td>Pre-morning dose</td>
<td>Study Day: 14</td>
<td>Morning 0</td>
<td>Time: -60 – 0</td>
</tr>
<tr>
<td></td>
<td>1 hour post-morning dose</td>
<td></td>
<td>Morning 60</td>
<td>Time: 0&lt; – 90</td>
</tr>
<tr>
<td></td>
<td>2 hours post-morning dose</td>
<td></td>
<td>Morning 120</td>
<td>Time: 90&lt; – 180</td>
</tr>
<tr>
<td></td>
<td>4 hours post-morning dose</td>
<td></td>
<td>Morning 240</td>
<td>Time: 180&lt; – 300</td>
</tr>
<tr>
<td>Day 15</td>
<td>Study Day: 15</td>
<td></td>
<td></td>
<td>Study Day: Post-dose – 15</td>
</tr>
</tbody>
</table>

* Start Time of Bismuth, TAK-438, Lansoprazole

### 7.1.7 Handling of HP Breath Test

For each visit, all evaluable observation (i.e., non-missing) obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest sampling 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.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Scheduled Study Day (days)</th>
<th>Time Interval (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>-2</td>
<td>-28 – -2</td>
</tr>
<tr>
<td>Day 42</td>
<td>42</td>
<td>Post-dose – 48</td>
</tr>
</tbody>
</table>

### 7.2 Analysis Sets

The safety analysis set used for primary analysis will consist of subjects who received at least 1 dose of the study drug.
The PK analysis set will consist of subjects who received the study drug, who have sufficient plasma/urine concentration data to calculate at least 1 pharmacokinetic parameter, and completed the minimum protocol specified procedures with no significant protocol deviations listed below:

- Subjects who did not meet inclusion criteria #3, #4 or #5
- Subjects who met exclusion criteria #1, #4, #6, #7, #8, #10, #11, #13, #14, #15, #16, #17, #21, or #22
- Subjects who have violated the rules specified in section 7.3 (excluded medications and dietary products) of the protocol up to end of Day 14
- Subjects with study medication compliance of less than 100%

### 7.3 Disposition of Subjects

#### 7.3.1 Study Information

**Analysis Set:** All Subjects Who Signed the Informed Consent Form

**Analysis Variables:** Date First Subject Signed Informed Consent Form, Date of Last Subject’s Last Visit/Contact, MedDRA Version, WHO Drug Version, SAS Version Used for Creating the Datasets

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

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

#### 7.3.2 Screen Failures

**Analysis Set:** All Subjects Who Were Not Randomized

**Analysis Variables:** Age (years) [Min<= - <30, 30<= - <50, 50<= - <=Max], Gender [Male, Female], Race [American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White]

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

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

#### 7.3.3 Subject Eligibility

**Analysis Set:** All Subjects Who Signed the Informed Consent Form

**Analysis Variables:** Eligibility Status [Yes, No], Primary Reason for Subject Not Being Eligible [Pretreatment Event/Adverse Event, Significant Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal]
Analytical Methods: **(1) Eligibility for Randomization**

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

### 7.3.4 Disposition of Subjects

**Analysis Set:** Randomized Set

**Analysis Variables:**
- Study Drug Administration Status: [No]
- Reason for Not Being Treated: [Pretreatment Event/Adverse Event, Significant Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Pregnancy, Other]
- Study Drug Completion Status: [Completed Study Drug, Prematurely Discontinued Study Drug]
- Reason for Discontinuation of Study Drug: [Pretreatment Event/Adverse Event, Significant Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Pregnancy, Other]

**Analytical Methods:** (1) **Disposition of Subjects**

Frequency distributions will be provided for each treatment group and overall. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation of study drug, the total number of subjects who prematurely discontinued the study drug will be used as the denominator.

### 7.3.5 Protocol Deviations and Analysis Sets

**Protocol Deviations**

**Analysis Set:** Randomized Set

**Analysis Variables:** Protocol Deviation: [Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria]

**Analytical Methods:** (1) **Protocol Deviations**

Frequency distribution will be provided by treatment group and overall for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.
Analysis Sets

Analysis Set: Randomized Set
Analysis Variables: Analysis Sets
PK Analysis Set [Included]
Safety Analysis Set [Included]

Analytical Methods: (1) Analysis Sets
Frequency distributions will be provided by treatment group and overall.

7.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Analysis Set: PK Analysis Set
Safety Analysis Set

Analysis Variables: Age (years)
[Min<= - <30, 30<= - <50, 50<= - <=Max]
Gender
[Male, Female]
Race
[American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White]
Height (cm)
[Min<= - <150, 150<= - <160, 160<= - <170, 170<= - <=Max]
Weight (kg) (Baseline)
[Min<= - <50.0, 50.0<= - <60.0, 60.0<= - <70.0, 70.0<= - <80.0, 80.0<= - <=Max]
BMI (kg/m²) (Baseline)
[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <=Max]
Smoking Classification
[The Subject Has Never Smoked, The Subject Is a Current Smoker, The Subject Is an Ex-smoker]
Consumption of Alcohol
[Drink Every day, Drink a Couple of Days Per Week, Drink a Couple of Days Per Month, Never Drink]
Consumption of Caffeine
[Yes, No]
CYP2C19 Genotype
[*1/*1, *1/*2, *1/*3, *2/*2, *2/*3, *3/*3]

Analytical Methods: (1) Summary of Demographics and Other Baseline Characteristics
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by treatment group and overall.
7.5 MEDICAL HISTORY AND CONCURRENT MEDICAL CONDITIONS

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

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 19.0 or higher) coding system.

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

7.6 MEDICATION HISTORY AND CONCOMITANT MEDICATIONS

Medication history information includes any medication relevant to eligibility criteria stopped prior to signing of informed consent. Concomitant medications are recorded on the eCRF and include any medications, other than the study drug, taken at any time between informed consent and on or prior to the last dose of study drug.

Medication history and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO Drug) version 2016Q1 or higher.

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

7.7 STUDY DRUG EXPOSURE AND COMPLIANCE

TAK-438/ Lansoprazole and Bismuth Exposure and Compliance

Analysis Set: Safety Analysis Set
Analysis Variables: Duration of Exposure to Study Drug (days)
Study Drug Compliance (%) [Min<= - <50.0, 50.0<= - <70.0, 70.0<= - <90.0, 90.0<= - <=Max]
Analytical Methods: (1) Study Drug Exposure and Compliance
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by treatment group and overall.

Clarithromycin and Amoxicillin Exposure and Compliance

Analysis Set: Safety Analysis Set
Analysis Variables: Duration of Exposure to Study Drug (days)
Study Drug Compliance (%) [Min<= - <50.0, 50.0<= - <70.0, 70.0<= - <90.0, 90.0<= - <=Max]
Analytical Methods: (1) Study Drug Exposure and Compliance
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by treatment group and overall.
7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic Analysis

Plasma Bismuth Concentration

Analysis Set: PK Analysis Set
Analysis Variable: Plasma Bismuth Concentrations
Time Point: Pre–morning dose (0 hours) and 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0 hours post–morning dose during Day 14
Analytical Methods: Following analysis will be provided by treatment group.

(1) Summary of Plasma Concentrations by Time Point
Descriptive statistics for observed values will be provided for each time point. In addition, geometric mean, and %CV will be provided.

(2) Concentration-time Profiles of Bismuth for Individual Subjects
Observed values will be plotted using individual case plot.

(3) Mean Concentration-time Profiles with Standard Deviations
Mean of plasma concentration will be plotted by time point using linear scale and natural log scale.

Plasma TAK-438F/ Lansoprazole Concentration

Analysis Set: PK Analysis Set
Analysis Variable: Plasma TAK-438F Concentrations
Plasma Lansoprazole Concentrations
Analytical Methods: (1) Summary of Plasma Concentrations by Time Point
Descriptive statistics for observed values will be provided for each visit and time point. In addition, geometric mean, and %CV will be provided.
Plasma PK Parameters of Bismuth

Analysis Set: PK Analysis Set
Analysis Variable: Plasma PK Parameters of Bismuth

- $C_{\text{max}}$
- $\text{AUC}_1$
- $\text{CL} / \text{F}$
- $\lambda_z$
- $t_{1/2z}$
- $t_{\text{max}}$

Visit: Day 14
Analytical Methods: For all variables, Summary (1) will be provided by treatment group. For $C_{\text{max}}$ and $\text{AUC}_1$, Summary (2) will be provided.

1. **Summary of Plasma PK Parameters**
   - Descriptive statistics for PK parameters will be provided. In addition, geometric mean and %CV will be computed for $C_{\text{max}}$ and $\text{AUC}_1$.

2. **Analysis of Variance with Natural log-transformed $\text{AUC}_1$ and $C_{\text{max}}$**
   - Two-sided confidence intervals (90% and 95% confidence level) of the ratio between administration conditions (bismuth with CAL and bismuth with CAT) will be calculated using an analysis of variance with natural log-transformed $\text{AUC}_1$ and $C_{\text{max}}$ of bismuth.

Urine PK parameters of Bismuth

Analysis Set: PK Analysis Set
Analysis Variable: Urine PK parameters of Bismuth

- $Ae_\tau$
- $f_{e,t}$
- $\text{CL}_R$

Visit: Day 14
Analytical Methods: (1) **Summary of Urine PK Parameters**
   - Descriptive statistics for PK parameters will be provided.

7.10 **OTHER OUTCOMES**

**HP Breath Test**

Analysis Set: Safety Analysis Set
Analysis Variable: HP Breath Test
Visit: Screening and Day 42
Analytical Methods: (1) **Summary of HP Breath Test**
   - Frequency distributions will be provided by treatment group and overall.
7.11 SAFETY ANALYSIS

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set: Safety Analysis Set
Analysis Variables: TEAE
Categories: Relationship to Study Drug
  Relationship to TAK-438/
  Lansoprazole
  Relationship to Bismuth
  Relationship to Clarithromycin
  Relationship to Amoxicillin
Intensity [Mild, Moderate, Severe]

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

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
2) Relationship of Treatment-Emergent Adverse Events to Study Drug (number of events, number and percentage of subjects)
3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
4) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (number of events, number and percentage of subjects)
5) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
6) Relationship of Serious Treatment-Emergent Adverse Events to Study Drug (number of events, number and percentage of subjects)
7) Serious Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (number of events, number and percentage of subjects)
8) Treatment-Emergent Adverse Events Resulting in Death (number of events, number and percentage of subjects)
9) Significant Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
10) Relationship of Significant Treatment-Emergent Adverse Events to Study Drug (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

Number of subjects
  • Summaries for 2), 6) and 10)
    A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.
  • Summary for 3)
A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.

- Summaries other than 2), 3), 6) and 10)
  A subject with multiple occurrences of TEAE will be counted only once.

**Number of events**

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

### 7.11.1.2 Displays of Treatment-Emergent Adverse Events

**Analysis Set:** Safety Analysis Set  
**Analysis Variables:** TEAE  
**Categories:** Intensity [Mild, Moderate, Severe]  
**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.

Drug-related TEAEs will be summarized for TAK-438/ Lansoprazole, Bismuth, Clarithromycin and Amoxicillin, respectively.

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. **Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term**  
9. **Significant Treatment-Emergent Adverse Events by System Organ Class and Preferred Term**  
10. **Drug-Related Significant Treatment-Emergent Adverse Events by System Organ Class and Preferred Term**

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

**Number of subjects**

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

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7.11.1.3 Displays of Pretreatment Events

Analysis Set: All Subjects Who Signed the Informed Consent Form
Analysis Variables: PTE
Analytical Methods: The following summaries will be provided using frequency distribution.

PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term
(2) Serious Pretreatment Events by System Organ Class and Preferred Term

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

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

7.11.2 Clinical Laboratory Evaluations

Hematology and Serum Chemistry

Analysis Set: Safety Analysis Set
Analysis Variables:

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Serum Chemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBCs (×10^{12}/L)</td>
<td>ALT (U/L)</td>
</tr>
<tr>
<td>WBCs (×10^{9}/L)</td>
<td>GGT (U/L)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>Creatine kinase (U/L)</td>
</tr>
<tr>
<td>Platelets (×10^{9}/L)</td>
<td>Total Bilirubin (μmol/L)</td>
</tr>
<tr>
<td>White Blood Cell Fractions (Neutrophils (%), Eosinophils (%), Basophils (%), Monocytes (%), Lymphocytes (%))</td>
<td></td>
</tr>
<tr>
<td>PT/INR</td>
<td>Creatine kinase MB (μg/L)</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>Albumin (g/L)</td>
</tr>
<tr>
<td>Reticulocyte count (×10^{9}/L)</td>
<td></td>
</tr>
</tbody>
</table>
Printed or downloaded documents must be verified against the effective version.

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CROSS-REGIONAL TEMPLATE

Template Number: C-TMPL-DO-801
Version Number: 1.2
This version replaces: 1.1
Parent Document: C-SOP-DO-800
Template Title: Statistical Analysis Plan (Legacy Takeda)

Total Protein (g/L) Serum creatinine (umol/L) Blood urea nitrogen (mmol/L)
Uric Acid (mmol/L) HDL Cholesterol (mmol/L) LDL Cholesterol (mmol/L)
Triglycerides (mmol/L) Glucose (mmol/L) Potassium (mmol/L)
Sodium (mmol/L) Magnesium (mmol/L) Calcium (mmol/L)
Chloride (mmol/L) Amylase (U/L)

Visit: Baseline, Day 5, 8, 12, 13, 14, 15
Analytical Methods: The following summaries will be provided for each 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 post-baseline visit will be provided. For each laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" relative to the normal reference range provided by the central laboratory. The shift tables will be based on these classifications.

3) Number and Percentage of Subjects with Markedly Abnormal Values of Laboratory Test results
Overall frequency distributions of MAV during treatment phase will be provided. If a laboratory test result has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

Urinalysis

Analysis Set: Safety Analysis Set
Analysis Variables:
- pH: [Min<= -5.0, 5.0<= - <=8.5, 8.5< - <=Max]
- Specific gravity: [Min<= -1.005, 1.005<= - <=1.030, 1.030< - <=Max]
- Protein: [Negative, Positive]
- Glucose: [Negative, Positive]
- Nitrites: [Negative, Positive]
- Bilirubin: [Negative, Positive]
- Hemoglobin: [Negative, Positive]
- Ketones: [Negative, Positive]
- Leucocytes: [Negative, Positive]
- Urobilinogen: [Negative, Positive]

Visit: Baseline, Day 5, 8, 12, 13, 14, 15
Analytical Methods: The following summaries will be provided for each treatment group.

1) Summary of Shifts of Urine Laboratory Test Results
7.11.3 Vital Signs

Analysis Set: Safety Analysis Set
Analysis Variables: Body Temperature (°C)
Systolic Blood Pressure (mmHg)
Diastolic Blood Pressure (mmHg)
Respiratory Rate (bpm)
Pulse (bpm)
Visit: Baseline, Day 1 at Pre–evening dose, Day 2 to 14 at Pre–morning dose, Day 2 to 14 Pre–evening dose, Day 15
Analytical Methods: For each variable, following summary will be provided by treatment group.

1) Summary of Vital Signs Parameters and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each post-baseline visit – baseline) will be provided for each visit.

2) Number and Percentage of Subjects with Markedly Abnormal Values of Vital Signs Parameters
Overall frequency distributions of MAV during treatment phase will be provided. If a vital sign parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

7.11.4 12-Lead ECGs

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)
12-Lead ECG Interpretation ["Within Normal Limits",
"Abnormal, Not Clinically Significant",
"Abnormal, Clinically Significant"]
Visit: Baseline, Day 3, Day 7 at Pre–morning dose, Day 14 at Pre–morning dose, 1, 2, 4 hour Post–morning dose, Day 15
Analytical Methods: For each variable other than 12-lead ECG interpretations, summary (1) will be provided by treatment group.
For 12-lead ECG interpretations, summary (3) will be provided by treatment group.
(1) Summary of ECG Parameters and Change from Baseline by Visit
   Descriptive statistics for observed values and changes from baseline (each post-baseline visit – baseline) will be provided for each visit.

(2) Number and Percentage of Subjects with Markedly Abnormal Values of ECG Parameters
   Overall frequency distributions of MAV during treatment phase will be provided. If an ECG parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

(3) Summary of Shifts of ECG Parameters
   Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

7.11.5 Other Observations Related to Safety
Not applicable

7.12 INTERIM ANALYSIS
Not applicable

7.13 CHANGES IN THE STATISTICAL ANALYSIS PLAN
Time intervals in 7.1.5 and 7.1.6 were modified from SAP version 1.0 to include all records for pre-morning dose, pre-evening dose, and Day 15 as well as to correct misspecification for post-morning dose.
8.0  REFERENCES

Not applicable
9.0 APPENDIX

9.1 CRITERIA FOR MARKEDLY ABNORMAL VALUES

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

For each parameter, all evaluable data (i.e., non-missing data) obtained up to Day 15 will be classified as a MAV or not. The criteria in the table below will be used.

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

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

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

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

### Hematology

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MAV Criteria</th>
<th>Lower Criteria</th>
<th>Upper Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBCs (×10^12/L)</td>
<td>MAV Criteria</td>
<td>&lt;0.8×LLN</td>
<td>&gt;1.2×ULN</td>
</tr>
<tr>
<td>WBCs (×10^9/L)</td>
<td>MAV Criteria</td>
<td>&lt;0.5×LLN</td>
<td>&gt;1.5×ULN</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>MAV Criteria</td>
<td>&lt;0.8×LLN</td>
<td>&gt;1.2×ULN</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>MAV Criteria</td>
<td>&lt;0.8×LLN</td>
<td>&gt;1.2×ULN</td>
</tr>
<tr>
<td>Platelets (×10^9/L)</td>
<td>MAV Criteria</td>
<td>&lt;75</td>
<td>&gt;600</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>MAV Criteria</td>
<td>&lt;0.5×LLN</td>
<td>&gt;1.5×ULN</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>MAV Criteria</td>
<td>-</td>
<td>&gt;2×ULN</td>
</tr>
<tr>
<td>Basophils (%)</td>
<td>MAV Criteria</td>
<td>-</td>
<td>&gt;3×ULN</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>MAV Criteria</td>
<td>-</td>
<td>&gt;2×ULN</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>MAV Criteria</td>
<td>&lt;0.5×LLN</td>
<td>&gt;1.5×ULN</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>MAV Criteria</td>
<td>-</td>
<td>&gt;1.5</td>
</tr>
<tr>
<td>PT/INR</td>
<td>MAV Criteria</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Serum Chemistry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MAV Criteria</th>
<th>Lower Criteria</th>
<th>Upper Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (U/L)</td>
<td>MAV Criteria</td>
<td>-</td>
<td>&gt;3×ULN</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>MAV Criteria</td>
<td>-</td>
<td>&gt;3×ULN</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>MAV Criteria</td>
<td>-</td>
<td>&gt;3×ULN</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>MAV Criteria</td>
<td>-</td>
<td>&gt;3×ULN</td>
</tr>
<tr>
<td>Total Bilirubin (μmol/L)</td>
<td>MAV Criteria</td>
<td>-</td>
<td>&gt;34.2</td>
</tr>
<tr>
<td>Creatine kinase (U/L)</td>
<td>MAV Criteria</td>
<td>-</td>
<td>&gt;5×ULN</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>MAV Criteria</td>
<td>&lt;25</td>
<td>-</td>
</tr>
</tbody>
</table>

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

CONFIDENTIAL INFORMATION

Do not distribute outside of Takeda without a confidentiality agreement.
### Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MAV Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Protein (g/L)</td>
<td>&lt;0.8×LLN</td>
</tr>
<tr>
<td>Blood urea nitrogen (mmol/L)</td>
<td>-</td>
</tr>
<tr>
<td>Uric acid (mmol/L)</td>
<td>-</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>-</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>&lt;3.0</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Magnesium (mmol/L)</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>&lt;1.75</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>&lt;75</td>
</tr>
<tr>
<td>Amylase (U/L)</td>
<td>-</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>-</td>
</tr>
</tbody>
</table>

### Vital Signs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MAV Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Temperature (°C)</td>
<td>&lt;35.6</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>&lt;85</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Pulse (bpm)</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>

### 12-lead ECG

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MAV Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate (bpm)</td>
<td>&lt;50</td>
</tr>
<tr>
<td>QT Interval (msec)</td>
<td>&lt;=50</td>
</tr>
<tr>
<td>QTcF Interval (msec)</td>
<td>&lt;=50</td>
</tr>
</tbody>
</table>

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

All evaluable data (i.e., non-missing data) obtained up to Day 15 will be classified as a MAV or not. The criteria in the table below will be used. Note that the observed value and the change from baseline used for classification should be measurements taken on the same day.

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

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

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

iii) A subject who does not meet conditions i) or ii) will be excluded from the analysis of MAV.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>MAV Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTcF Interval (msec)</td>
<td>If either of the following conditions is met:</td>
</tr>
<tr>
<td></td>
<td>• observed value &gt;=500</td>
</tr>
<tr>
<td></td>
<td>• change from baseline &gt;= 30 and observed value &gt;=450</td>
</tr>
</tbody>
</table>
## Electronic Signatures

<table>
<thead>
<tr>
<th>Signed by</th>
<th>Meaning of Signature</th>
<th>Server Date (dd-MMM-yyyy HH:mm ‘UTC’)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD</td>
<td>Clinical Pharmacology Approval</td>
<td>17-May-2017 08:17 UTC</td>
</tr>
<tr>
<td></td>
<td>Pharmacovigilance Approval</td>
<td>17-May-2017 13:37 UTC</td>
</tr>
<tr>
<td></td>
<td>Clinical Science Approval</td>
<td>18-May-2017 00:51 UTC</td>
</tr>
<tr>
<td></td>
<td>Biostatistics Approval</td>
<td>19-May-2017 08:39 UTC</td>
</tr>
<tr>
<td></td>
<td>Biostatistics Approval</td>
<td>22-May-2017 01:59 UTC</td>
</tr>
</tbody>
</table>