Non-Interventional Study Protocol
B2411278

DRUG USE INVESTIGATION OF EFFEXOR® SR CAPSULES

STATISTICAL ANALYSIS PLAN

Version: 5.0.

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Date: 11-May-2020

1. CHANGES FROM PREVIOUS VERSION

Version/ Date/ Author	Summary of Changes/Comments
1.0 14-Jun-2016 PPD	Initial version
2.0 30-Sep-2016 PPD	**Study status: Before the start of the study** • Complications, gender, depression phase, duration of the latest episode of depression/depressive state, previous therapies for depression/depressive state, duration of depression/depressive state and baseline CGI-S were added as subgroups in Section 5.4.1 Safety assessment • Baseline HAM-D_{17} anxiety/somatization factor total score was added to subgroups in Section 5.4.2 Efficacy assessment • Item numbers for HAM-D_{17} anxiety/somatization factor score were amended in Section 6.2 • Definition of the timing for tabulation of the number of discontinued subjects was changed in Section 8.2.1 • Definitions of the treatment period and the highest dose category were changed in Section 8.2.2 Status of treatment with this product • Subgroup analysis was added to the tabulation of all adverse reactions, definition of the time of onset was changed and subgroup analysis was added to the tabulation of adverse reactions by time of onset in Section 8.2.3.2 • Tabulation of anxiety/somatization factor total score was added, figures showing changes over time were added for evaluation over time, description was adjusted and instruction to prepare figures was added to responder analysis in Section 8.2.4.1 • Figures showing changes over time were added for evaluation over time in Section 8.2.4.2 • Instruction to prepare figures was added in Section 8.2.4.4 • List of additional patient background factors in subjects with ischemic heart disease was added in Section 9 • Definition of post-dose increase for safety assessment was changed in Section 10.1 • Precautions for the design of figures were added in Section 10.3 • Other description adjustment
3.0 24-May-2018 PPD	**Study status: Ongoing** • "1200 as registered subjects" was deleted from Section 2.1 Planned sample size • Conditions for the safety analysis set were added in Section 5.1 • "≤37.5 mg/day" and ">225 mg/day" were added to the subgroups in dose classification 1 for the highest dose in Sections 5.4.1 and 5.4.2 • Safety subgroup analysis of potentially contraindicated subjects was added in Section 5.4.1

Version/ Date/ Author	Summary of Changes/Comments
	• Definitions of adverse reactions, serious adverse events or adverse reactions were amended and added in Section 6.1 • Definitions of the major investigation items, withdrawal syndrome and noradrenaline effect potentiation by increase in dosage (insomnia, blood pressure increased etc.) were added in Section 6.1 • Highest dose category and dose-increase pattern were added, and categories for the initial and highest doses were specified for the tabulation of the status of treatment in Section 8.2.2 • Summary of the number and percentage of subjects by severity of renal impairment at baseline, categorized by the initial and highest daily doses was added to the tabulation of the status of treatment in Section 8.2.2 • Data collection period was specified in Sections 8.2.3 and 8.2.4 • Statement was added to Section 8.2.3.1 to exclude safety in subjects with mild or moderate hepatic impairment and safety in subjects with mild or moderate renal impairment from the major investigation items • Populations were added to subgroup analysis of all adverse reactions in Section 8.2.3.2 • ">225 mg/day" was added to the categories of the dose at the onset of adverse reactions for the analysis of first-onset adverse reactions (all adverse reactions, adverse reactions by period) in Section 8.2.3.2 • Subgroup analysis by the highest dose was deleted from the analysis of adverse reactions by time of onset in Section 8.2.3.2 • Date of censoring was changed for the analysis of adverse reactions by time of onset in Section 8.2.3.2 • Exceptions were specified for the calculation of risk ratios in Section 8.2.3.5 • Analysis of potentially contraindicated subjects was added in Section 8.2.3.5 • Policy for handling was specified for cases where there are multiple relevant data for the analysis targeting all dose increased time points in Section 8.2.4 • Score category was specified for the preparation of cross tables for tabulation of HAM-D at each evaluation time point in Section 8.2.4.1 • Time points were changed for the preparation of scatter plots for tabulation of HAM-D before and after the dose increase in Section 8.2.4.1 • Target analysis population was specified for the calculation of HAM-D_{17} remission rate in Section 8.2.4.1 • Score category was specified for the preparation of cross tables for tabulation of MADRS total score before and after the dose increase of MADRAS in Section 8.2.4.2 • Time points were changed for the preparation of scatter plots for tabulation of MADRS total score before and after the dose increase of MADRAS • List of subjects with adverse reactions among contraindicated subjects was added in Section 9 • References were added

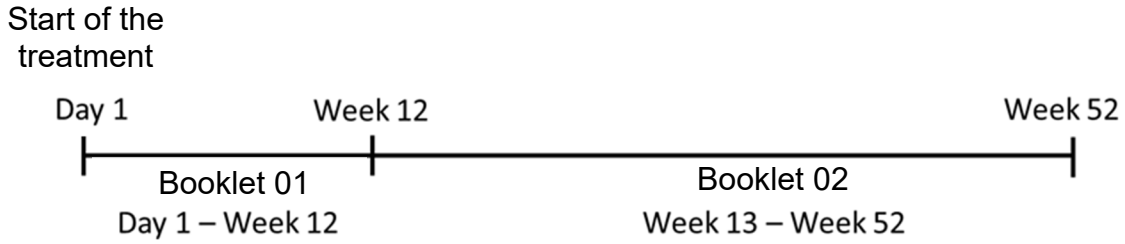
Version/ Date/ Author	Summary of Changes/Comments
	• Conditions were added to the acceptable window for the date of discontinuation (date of start of tapering or date of last treatment) in Section 10.1 • Revision associated with the update (Version 3) of the statistical analysis plan template • Other description adjustment
4.0 18-Apr-2019 PPD	**Study status: Ongoing** • Subgroup in the dose classification 2 for the highest dose, "≤75 mg/day" was changed to "≥37.5 mg/day to ≤75 mg/day" in Sections 5.4.1 Safety assessment and 5.4.2 Efficacy assessment • Definitions were specified for each of other safety investigation items in Section 6.1 Safety endpoints • Tabulation by phenotype of CYP2D6 metabolizing enzyme was added in Section 8.2.2 Patient background • Other safety investigation items was added in Section 8.2.3.2 • Calculation of the percentage was deleted from the tabulation by dose category at the onset of adverse reactions for first-onset adverse reactions in Section 8.2.3.3 Adverse reactions • (Obsolete) Section 8.2.3.4 Other assessments (Analysis of laboratory values) was deleted • Analysis by phenotype of CYP2D6 metabolizing enzyme was added to the tabulation of changes before and after the dose increase in Sections 8.2.4.1 HAM-D and 8.2.4.2 MADRS • List of laboratory test values was added in Section 9 LISTINGS • Other description adjustment
5.0 11-May-2020 PPD	**Study status: Ongoing** • Exploratory analysis set was added in Section 5.3 Other analysis set • Tabulation of the number of study sites and subjects by founders was deleted from Section 8.2.1 • Tabulation of patient background factors for the exploratory analysis set was added in Section 8.2.2 Patient background and treatment history • Analyses to be performed on the exploratory analysis set were specified in Section 8.2.4 Efficacy analysis • Subgroup analysis of each item was added in Section 8.2.4.2 MADRS • List of status of treatment with this product and list of reasons for discontinuation (others) were added in Section 9 LISTINGS • Other description adjustment

2. INTRODUCTION

This statistical analysis plan describes the statistical analysis plan for the drug use investigation of Effexor® SR Capsules 37.5 mg and 75 mg (this product).

2.1. Study design

This is a multicenter open-label study conducted in patients who received this product. This study is conducted using the separate-type case report forms. The results of observation from the start date until Week 12 are entered to Booklet 01. Patients who complete the 12-week treatment are followed up until Week 52, and the results of observation from Week 13 are entered to Booklet 02. However, the information from the date of last treatment until 28 days later are collected for patients who discontinue this product.



Observation period for each booklet

Study subjects
Patients who have never used this product and are receiving this product for the first time, who are registered to this study within 14 days including the start date of treatment with this product are included in this study.

Planned sample size
The target sample size is 900 as subjects who complete the 12-week treatment with this product.

Data source
The case report forms are filled out with required information by physicians according to the protocol based on the medical charts which contain the data obtained from usual daily medical practice.

2.2. Research objective

To confirm the safety and efficacy of this product under actual medical practice.

3. INTERIM AND FINAL ANALYSES

In this study, regular interim analysis is performed for periodic safety reports. In the interim analysis, only the items required for periodic safety reports are analyzed among statistical analyses specified in this statistical analysis plan. Also, a final analysis is performed for application for re-examination. In the final analysis, all analyses specified in this statistical analysis plan are performed.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical hypotheses

Since this study is not a confirmatory study, tests are performed as exploratory measures. Unless otherwise stated, all statistical tests will be two-sided with a significance level of 5%.

4.2. Statistical decision rules

Not applicable.

5. ANALYSIS SETS

5.1. Safety analysis set

The safety analysis set is the full analysis set, which is as close as possible to all subjects who have received treatment with this product. Specifically, it is a group of registered or reported subjects excluding those who meet any one of the following conditions:

a. Complete failure in collecting case report forms (description in the report: “Case report form not collected”)

b. Contract violation or defect (description in the report: “Contract violation/defect”)

c. Violation in registration (description in the report: “Registration violation”)

d. Total absence of reporting on administration of the drug to be studied (description in the report: “No dosing information”)

e. Total absence of reporting of adverse event information - failure to visit after the date of initial prescription (description in the report: “No adverse event information - failure to revisit”)

f. Total absence of reporting of adverse event information - information missing despite visits made after the date of initial prescription (description in the report: “No adverse event information - missing information”)

For the details of each condition, follow the “Guidance on Analysis Sets and Handling of Data in Drug Use Investigations”.

5.2. Efficacy analysis set

The efficacy analysis set consists of subjects in the safety analysis set excluding those who meet any of the following conditions:

g. Total absence of reporting on efficacy assessment (description in the report: “No efficacy information”)

h. Disease not subject to the study (description in the report: “Disease not subject to study”)
Subjects whose disease to be studied is recorded only as “others” and not diagnosed as “depression/depressive state”

5.3. Other analysis set

5.3.1. Exploratory analysis set

The exploratory analysis set consists of subjects in the efficacy analysis set excluding those who have received this product at dosage and administration different from those specified in the package insert. The details are specified separately.

5.4. Subgroups

5.4.1. Safety assessment

Regarding the safety, subgroup analyses are performed by the following patient background factors: For each subgroup, the standard category for the calculation of the risk ratio is shown in parentheses.

- Name of the disease to be studied
  - “Depression/depressive state” only
- Presence or absence of hepatic impairment (standard: absent)
- Presence or absence of renal impairment (standard: absent)
- Age classification 1 (standard: ≥15 years to <65 years)
  - <15 years
  - ≥15 years to <65 years
  - ≥65 years
- Age classification 2 (standard: ≥25 years)
  - <25 years
  - ≥25 years
- Dose classification 1 for the highest dose (standard: >37.5 mg/day to ≤75 mg/day)
  - ≤37.5 mg/day
  - >37.5 mg/day to ≤75 mg/day
  - >75 mg/day to ≤150 mg/day
  - >150 mg/day to ≤225 mg/day
  - >225 mg/day
- Dose classification 2 for the highest dose (standard: ≥37.5 mg/day to ≤75 mg/day)
  - ≥37.5 mg/day to ≤75 mg/day
  - >75 mg/day to ≤225 mg/day

- Presence or absence of pregnancy (standard: absent)
- Presence or absence of complications (standard: absent)
- Presence or absence of concomitant drug therapies for depression/depressive state (standard: absent)
- Gender (standard: female)
  - Male
  - Female
- Depression phase (standard: initial onset)
  - Initial onset
  - Relapse
- Duration of the latest episode of depression/depressive state (standard: ≤ median)
  - ≤ median
  - > median
- Presence or absence of previous drug therapies for depression/depressive state (standard: absent)
- Duration of depression/depressive state (standard: ≤ median)
  - ≤ median
  - > median
- CGI-S rating at baseline (standard: <4)
  - <4
  - ≥4

Subjects who may be contraindicated in the package insert of this product ("contraindicated subjects") will be extracted based on separately specified criteria, and a safety subgroup analysis will be performed on these subjects.

5.4.2. Efficacy assessment

Regarding the efficacy, subgroup analyses are performed by the following patient background factors:

- Name of the disease to be studied
  - "Depression/depressive state" only
- Presence or absence of hepatic impairment
- Presence or absence of renal impairment
- Gender
  - Male

- Female

– Depression phase
  - Initial onset
  - Relapse

– Duration of the latest episode of depression/depressive state
  - ≤ median
  - > median

– Age classification 3
  - <18 years
  - ≥18 years to <65 years
  - ≥65 years

– Dose classification 1 for the highest dose
  - ≤37.5 mg/day
  - >37.5 mg/day to ≤75 mg/day
  - >75 mg/day to ≤150 mg/day
  - >150 mg/day to ≤225 mg/day
  - >225 mg/day

– Dose classification 2 for the highest dose
  - ≥37.5 mg/day to ≤75 mg/day
  - >75 mg/day to ≤225 mg/day

– Presence or absence of previous drug therapies for depression/depressive state

– Presence or absence of concomitant drug therapies for depression/depressive state

– Duration of depression/depressive state
  - ≤ median
  - > median

– HAM-D_{17} total score at baseline
  - ≤ median
  - > median

– MADRS total score at baseline
  - ≤ median
  - > median

– HAM-D_{17} anxiety/somatization factor total score at baseline
  - ≤ median
  - > median

- MADRS total score at baseline
  - <26
  - ≥26

- CGI-S rating at baseline
  - <4
  - ≥4

6. ENDPOINTS AND COVARIATES

6.1. Safety endpoints

- Adverse reactions: Adverse events for which the causal relationship with this product cannot be ruled out by physicians

- Adverse events: Adverse events regardless of the causal relationship with this product

- Serious adverse events or adverse reactions: Adverse events or adverse reactions assessed as serious by physicians

- Major investigation items: Events to be handled as major investigation items are listed below:

Serotonin syndrome, Convulsion, Withdrawal syndrome, Increased blood pressure/Hypertensive crisis/Increased heart rate, QT prolongation/Torsade de Pointes (TdP), Lipid effects, Hyponatremia/Syndrome of inappropriate secretion of antidiuretic hormone (SIADH), Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN)/Erythema multiforme, Anaphylaxis, Urinary retention, Suicidal ideation/Suicide attempt, Mania/Hypomania, Abnormal bleeding: ecchymoses/hematomas/epistaxis/petechiae leading to life-threatening hemorrhage, Hostility/Aggression, Ischaemic heart disease, Agranulocytosis/Aplastic anaemia/Pancytopenia/Neutrophil count decreased/Platelet count decreased, Interstitial lung disease (ILD), Noradrenaline effect potentiation by increase in dosage (Insomnia, Blood pressure increased, etc.), Safety in the patient with mild or moderate hepatic impairment, Safety in the patient with mild or moderate renal impairment.

Preferred terms (PTs) of events to be handled as major investigation items are specified separately.

For withdrawal syndrome, events that occur within 3 days[1] after dose reduction will be included. For noradrenaline effect potentiation by increase in dosage (insomnia, blood pressure increased, etc.), events that occur within 28 days after dose increase will be included.

- Other safety investigation items

Adverse events of central nervous system, adverse events of gastrointestinal system, sexual dysfunction, safety in highly accumulated sites (liver, urinary organ, lung, eye, and skin), sites, safety of CYP2D6 by UM/EM/PM/IM, effect on weight.

Events corresponding to each safety investigation item are defined as follows:

Adverse events of central nervous system:	Events corresponding to MedDRA SOCs “Nervous system disorders” and “Psychiatric disorders”
Adverse events of gastrointestinal system:	Events corresponding to MedDRA SMQs “Gastrointestinal nonspecific inflammation and dysfunctional conditions (narrow)” and “Gastrointestinal perforation, ulceration, haemorrhage or obstruction (narrow)”, as well as PTs “Decreased appetite” and “Weight decreased”
Sexual dysfunction:	Events included in MedDRA SOC “Reproductive system and breast disorders” or HLT “Reproductive hormone analyses”
Safety in highly accumulated sites (liver, urinary organ, lung, eye and skin):	Events included in MedDRA SMQ “Drug related hepatic disorders - comprehensive search”, events included in MedDRA SMQ “Acute renal failure (narrow)” and HLGT “Bladder and bladder neck disorders (excluding calculi)”, events included in MedDRA SMQs “Interstitial lung disease (narrow)” and “Eosinophilic pneumonia (narrow)” and HLGT “Respiratory disorders NEC”, events included in MedDRA SOC “Eye disorders” and events included in MedDRA SOC “Skin and subcutaneous tissue disorders”
Effect on weight:	Events included in MedDRA PTs “Weight decreased” and “Weight increased”

- Laboratory tests

White blood cell count, platelet count, hemoglobin, AST (GOT), ALT (GPT), LDH, GGT (γ-GTP), Al-P, CK (CPK), total bilirubin, BUN, serum creatinine, Na, triglyceride (TG), total cholesterol, HDL cholesterol, LDL cholesterol, fasting blood glucose, HbA1c

6.2. Efficacy endpoints

- Hamilton Rating Scale for Depression (HAM-D_{17})

HAM-D_{17} is a scale for assessing the symptoms of depression such as depressed mood, work and activities, sleep, suicide, psychomotor retardation, appetite, sexual interest, anxiety, and general somatic symptoms. It is scored from 0 to 2 (8 items) or from 0 to 4 (9 items). The total score ranges from 0 to 52. The higher the score, the more severe the depression. HAM-D_6, a subscale of HAM-D_{17}, consists of items 1, 2, 7, 8, 10 and 13. Anxiety/somatization factor score consists of items 10, 11, 12, 13, 15 and 17, and sleep disorder score consists of items 4, 5 and 6.

- Montgomery - Asberg Depression Rating Scale (MADRS)

MADRS is a scale for assessing the overall severity of depression. It is a physician-rated scale consisting of 10 items: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. It is sensitive to changes brought by the treatment. Each MADRS item is rated on a 7-point scale (0 - 6) with anchor points provided at 2-point intervals. The total score ranges from 0 to 60. The higher the score, the more severe the depression.

- Clinical Global Impressions - Severity of Illness (CGI-S)

CGI-S is a 7-point rating scale that rates the overall severity of an illness. The rater will select one rating based on the following question: “Considering your total clinical experience with this particular population (major depressive disorder), how mentally ill is the patient at this time?” The rating points are as follows: “1=Normal, not at all ill”, “2=Borderline mentally ill”, “3=Mildly ill”, “4=Moderately ill”, “5=Markedly ill”, “6=Severely ill”, “7=Among the most extremely ill patients”.

- Clinical Global Impressions - Improvement (CGI-I)

CGI-I is a 7-point rating scale that rates the overall improvement of an illness regardless of whether or not the change is attributed to drug therapy. The rater will select one rating based on the following question: “Compared to the patient's condition at baseline (Week 0, CGI-S), how much the patient's condition has changed?” The rating points are as follows: “1=Markedly improved”, “2=Moderately improved”, “3=Mildly improved”, “4=No change”, “5=Slightly worsened”, “6=Worsened”, “7=Severely worsened”.

6.3. Other endpoints

Not applicable.

6.4. Covariates

There are no covariates identified based on the clinical study data obtained to date or potential covariates that are related to the safety and efficacy of this product.

7. HANDLING OF MISSING DATA

- Safety endpoints

If the seriousness, treatment or outcome of an adverse event is missing, it will be handled as “unknown” in the tabulation.

If laboratory tests shown in Section 10.1 are not measured within the acceptable window for each evaluation time point, it will be handled as missing and not imputed.

The policy for handling uncleaned data is described below:

1. Missing data: Handled as missing data in both tabulation and listing (classified as “Unknown” in cases of categorical variables).

2. Inconsistent data: Inconsistent data will be handled as missing data in both tabulation and listing. However, a list of data handling will be prepared separately.

3. Missing signature: The part of the case report form without the signature of the contract physician (including the case where it is only signed by those other than the contract physician) will be handled as missing data in both tabulation and listing.

- Efficacy endpoints

Missing data within the same evaluation time point will not be imputed. For HAM-D_{17} or MADRS, completed survey forms will be collected. On the other hand, if efficacy endpoints are missing at each post-baseline evaluation time point, the last observation carried forward (LOCF) may be used for imputation. Cases where LOCF is used for imputation are listed in Section 8.2.4.

8. STATISTICAL METHODS AND ANALYSES

8.1. Statistical methods

8.1.1. Analysis of continuous data

Summary statistics

Summary statistics (number of subjects, mean, standard deviation, median, first quartile, third quartile, maximum and minimum) will be calculated.

8.1.2. Analysis of categorical data

Summary statistics

The number and percentage of subjects falling under each category will be calculated.

8.1.3. Analysis of binary data

Summary statistics

The frequency and percentage will be calculated. When calculating the confidence interval of the percentage, two-sided 95% confidence interval (exact method) will be calculated.

Estimation

When comparing percentages, percentages, risk ratios and their 95% confidence intervals will be calculated. Sample codes are shown in Section 10.2. Also, risk ratios and 95% confidence intervals will be presented in figures. Sample figures are shown in Section 10.3.

8.1.4. Analysis of period data (time to event onset)

The median, first quartile and third quartile will be calculated using the Kaplan-Meier method. In addition, Kaplan-Meier plots will be prepared as required.

8.2. Statistical analyses

8.2.1. Summary of subjects

- **Subject disposition**

For enrolled subjects, the number of enrolled subjects, the number of subjects who completed the study, the number of subjects included in the safety analysis, and the number of subjects included in the efficacy analysis will be counted. In addition, the number of subjects for whom case report forms have not been collected, the number of subjects who are excluded from the safety analysis, the number of subjects who are excluded from the efficacy analysis, and the number of subjects by reason for exclusion will be counted.

- **List of discontinued/dropped-out subjects**

For the safety analysis set, the number and percentage of subjects who discontinued the study will be summarized by period (≤1 week, >1 week to ≤2 weeks, >2 weeks to ≤4 weeks, >4 weeks to ≤12 weeks, >12 weeks to ≤24 weeks, and >24 weeks). In addition, the number and percentage of subjects will be summarized by reason for discontinuation. Subjects who have not visited the hospital during and after the relevant evaluation period without a reason for discontinuation will also be considered as discontinued subjects and included in the tabulation as "reason for discontinuation not specified".

- **List of excluded subjects**

A list of subjects excluded from safety analysis and subjects excluded from efficacy analysis as well as reasons for exclusion will be prepared.

8.2.2. Patient background and treatment history

- **Patient background**

Unless otherwise specified, the following patient background factors will be summarized for the 3 analysis sets (safety analysis set, efficacy analysis set and exploratory analysis set) in accordance with Section 8.1:

- Disease to be studied [depression/depressive state only, depression/depressive state and others, others only] (the category of "others only" will be included in the tabulation only for the safety analysis set)
- Gender [male, female]
- Age (continuous data)
- Hospitalization status at the initial prescription [inpatient, outpatient]
- Age [<15 years, ≥15 years] (only tabulated for the safety analysis set)
- Age [<65 years, ≥65 years] (only tabulated for the safety analysis set)
- Age [<15 years, ≥15 years to <65 years, ≥65 years] (only tabulated for the safety analysis set)
- Age [<18 years, ≥18 years to <65 years, ≥65 years] (only tabulated for the efficacy analysis set)
- Age [<25 years, ≥25 years] (only tabulated for the safety analysis set)
- Height (continuous data)

- Weight (continuous data)
- BMI (continuous data)
- BMI [<18.5, ≥18.5 to <25.0, ≥25.0]
- CYP2D6 [UM, EM, PM, IM, no information]
- Diagnosis [depression/depressive state only, depression/depressive state and others]
- Duration of depression/depressive state (continuous data)
- Depression phase (initial onset, relapse)
- Duration of the latest episode of depression/depressive state (continuous data)
- Hepatic impairment [absent, present]
- Severity of hepatic impairment [mild, moderate, severe, unknown]
- Renal impairment [absent, present]
- Severity of renal impairment [mild, moderate, severe, unknown]
- Frequency of drinking (daily, occasional, rarely [unable to drink])
- Amount of drinking per day [<180 mL, 180 to <360 mL, 360 to <540 mL, ≥540 mL]
- Pregnancy [absent, present]
- Medical history [absent, present]
- Complications [absent, present]
- HAM-D_{17} total score at baseline (continuous data)
- MADRS total score at baseline (continuous data)
- MADRS total score at baseline [<26, ≥26]
- CGI-S rating at baseline [<4, ≥4]
- CGI-S rating at baseline [1, 2, 3, 4, 5, 6, 7]
- Previous drug therapies for depression/depressive state [absent, present]
- Concomitant drug therapies for depression/depressive state [absent, present]
- Other concomitant drug therapies [absent, present]
- Previous non-drug therapies for depression/depressive state [absent, present]
- Concomitant non-drug therapies for depression/depressive state [absent, present]

For the safety analysis set, the number and percentage of subjects will be summarized by system organ class (SOC) and preferred term (PT) based on the following factors:

- Detailed medical history
- Detailed complications

For the safety analysis set, the number and percentage of subjects will be summarized based on the following factors:

- Detailed previous drug therapies
- Detailed previous non-drug therapies
- Detailed concomitant drug therapies
- Detailed concomitant non-drug therapies
  - If ≥10% of the subjects in the safety analysis set are receiving the same concomitant non-drug therapy, summary statistics of the duration of the relevant concomitant non-drug therapy will be calculated according to Section 8.1.1.

- **Status of treatment with this product**

For the safety analysis set, the status of treatment with this product will be summarized based on the following factors in accordance with Section 8.1.2:

- Summary of the number and percentage of subjects by treatment period
  [≤1 week, >1 week to ≤2 weeks, >2 weeks to ≤4 weeks, >4 weeks to ≤12 weeks, >12 weeks to ≤24 weeks, >24 weeks to ≤52 weeks, >52 weeks]

- Summary of the number and percentage of subjects by the highest dose category in each treatment period above
  [≤37.5 mg/day, >37.5 mg/day to ≤75 mg/day, >75 mg/day to ≤150 mg/day, >150 mg/day to ≤225 mg/day, >225 mg/day]

- Summary of the number and percentage of subjects by all dose-increase patterns during the treatment period of ≤12 weeks, ≤52 weeks, and each treatment period above
  - Each subject will be counted once for each dose-increase pattern
  - If administration is performed after >7-day withdrawal, it will be considered that the dose is increased from 0 mg/day

- Summary of the number and percentage of subjects categorized by the initial dose
  [≤37.5 mg/day, >37.5 mg/day to ≤75 mg/day, >75 mg/day to ≤150 mg/day, >150 mg/day to ≤225 mg/day, >225 mg/day]

- Summary of the number and percentage of subjects categorized by the highest dose
  [≤37.5 mg/day, >37.5 mg/day to ≤75 mg/day, >75 mg/day to ≤150 mg/day, >150 mg/day to ≤225 mg/day, >225 mg/day]

- The following analyses in discontinued subjects:
  1. Figure showing individual changes in the dose (vertical axis, dose taken; horizontal axis, time)
  2. Summary of the dose on the last day of treatment (Section 8.1.1)
  3. Summary of the highest dose during the period from 28 days before the last day of treatment to the last day of treatment (Section 8.1.1)
  4. Summary of the number and percentage of subjects in whom the dose on the last day of treatment is different from the highest dose during the period from 28 days before the last day of treatment to the last day of treatment

- Summary of the number and percentage of subjects by severity of hepatic impairment at baseline, categorized by the initial and highest daily doses
  [≤37.5 mg/day, >37.5 mg/day to ≤75 mg/day, >75 mg/day to ≤150 mg/day, >150 mg/day to ≤225 mg/day, >225 mg/day], [≤112.5 mg/day, >112.5 mg/day]

- Summary of the number and percentage of subjects by severity of renal impairment at baseline, categorized by the initial and highest daily doses

[≤37.5 mg/day, >37.5 mg/day to ≤75 mg/day, >75 mg/day to ≤150 mg/day, >150 mg/day to ≤225 mg/day, >225 mg/day]

The treatment period is defined as the period from the day of the first dose to the day of the last confirmed dose in this study, including the treatment interruption period.

8.2.3. Safety analysis

Data will be collected up to Week 52 (Day 364) for subjects who have completed the study, and up to the last day of treatment + 28 days for discontinued subjects. Data beyond the above cut-off date will also be summarized as necessary. The listings will include all data reported in this study.

8.2.3.1. Major investigation items

The number and percentage of subjects with the major investigation items will be summarized by the causal relationship with this product. Furthermore, the number and percentage of subjects with adverse reactions of major investigation items will be summarized based on SOC and PT by treatment and outcome.

For each major investigation item, the patient background factors and concomitant drug therapies will be summarized by the presence or absence of adverse reactions of major investigation items.

Furthermore, for subjects with adverse events of major investigation items, a list will be prepared including the disease to be studied, name of the major investigation item, number of days to onset, dose at onset, seriousness, expectedness, treatment, outcome, causal relationship with this product, patient background, and concomitant drugs.

Also, for each major investigation item, the time to event onset will be summarized according to Section 8.1.4, considering the first onset of the adverse reaction as an event. Subjects without adverse reactions will be censored at Week 52 (Day 364) if they have completed the study, or at the last day of treatment + 28 days if they have discontinued the study. The Kaplan-Meier plots will be prepared for events that are observed in 10% or more of the subjects in the safety analysis set (each subject is counted once).

However, safety in subjects with mild or moderate hepatic impairment and safety in subjects with mild or moderate renal impairment will be excluded.

8.2.3.2. Other safety investigation items

The following analyses will be performed for the adverse events of central nervous system, adverse events of gastrointestinal system, sexual dysfunction, safety in highly accumulated sites (liver, urinary organ, lung, eye and skin) and effect on weight:

- The number and percentage of subjects with events will be summarized by the causal relationship with this product.
- For subjects in whom the dose is increased by >75 mg/day, the number and percentage of subjects with adverse reactions within the acceptable window after the dose increase and during

the entire period after the dose increase will be summarized by SOC and PT for each dose-increase pattern (dose increase within the range from 75 mg/day to 150 mg/day or from 150 mg/day to 225 mg/day) with respect to the first dose increase (e.g. the first dose increase if the dose is increased more than once within the range from 75 mg/day to 150 mg/day). Also, the number and percentage of subjects with adverse reactions during the period before the first dose increase will be summarized by SOC and PT for each dose-increase pattern.

The same analyses as above will also be performed by type of CYP2D6. However, it will not be performed if the number of subjects in whom CYP2D6 is measured is less than 10.

8.2.3.3. Adverse reactions

- **All adverse reactions**

The number and percentage of subjects with adverse reactions will be summarized by SOC and PT.

Also, the same analysis as above will be performed for each of the populations or categories shown below:

- Pediatric subjects (<15 years), elderly subjects (≥65 years), pregnant women, subjects with hepatic impairment, subjects with renal impairment, each subgroup based on the doses defined in Section 5.4.1 (dose classifications 1 and 2 for the highest dose)

In addition, the number of subjects with adverse reactions will be summarized by SOC and PT based on the following categories:

- Categories of the dose at the onset of adverse reactions for the first-onset adverse reactions (≤37.5 mg/day, >37.5 mg/day to ≤75 mg/day, >75 mg/day to ≤150 mg/day, >150 mg/day to ≤225 mg/day, >225 mg/day)

- **Serious adverse reactions**

The number and percentage of subjects with serious adverse reactions will be summarized by SOC and PT.

- **Details of adverse reactions**

The number and percentage of subjects with adverse reactions will be summarized by SOC and PT based on the following factors:

- Seriousness [serious, non-serious]
- Expectedness [expected, unexpected]
- Treatment [discontinued, temporary interrupted or dose reduction, others (none, dose increase)]
- Outcome [not recovered, recovered with sequelae, recovering, recovered/resolved, unknown]

If one subject experience the same adverse reaction (the same PT) for multiple times, it will be handled as follows in tabulation of the number of subjects with events:

- Seriousness: If both serious and non-serious events have occurred, the event will be assessed as serious
- Expectedness: If both expected and unexpected events have occurred, the event will be considered unexpected
- Number of days to onset: The number of days to the first event
- Treatment: If several measures have been taken, one treatment will be adopted in the following priority: discontinued, temporary interrupted or dose decrease, others (none, dose increase)
- Outcome: The outcome of the last event will be used

- **Time of onset of adverse reactions**

For adverse reactions, the number of subjects with adverse reactions will be summarized by SOC and PT based on the time of first onset (≤1 week, >1 week to ≤2 weeks, >2 weeks to ≤4 weeks, >4 weeks to ≤12 weeks, >12 weeks).

Also, the same analysis as above will be performed based on the following categories:

- Categories of the dose at the onset of adverse reactions for first-onset adverse reactions (≤37.5 mg/day, >37.5 mg/day to ≤75 mg/day, >75 mg/day to ≤150 mg/day, >150 mg/day to ≤225 mg/day, >225 mg/day)

- **Relationship between previous/concomitant drug therapies for depression/depressive state and occurrence of adverse reactions**

In order to evaluate the relationship between previous/concomitant drug therapies for depression/depressive state and occurrence of adverse reactions, the number of subjects with adverse reactions will be summarized by PT for each of the previous and concomitant drug therapies, and common adverse reactions will be reported. However, concomitant drug therapies used after the first onset of the relevant event will be excluded from the tabulation.

- **Occurrence of adverse reactions by inclusion or exclusion from the safety analysis set**

A list of adverse reactions will be prepared for subjects from whom the case report forms have been collected who are excluded from the safety analysis set. Furthermore, the number of subjects with adverse reactions will be summarized by SOC and PT.

- **Occurrence of adverse reactions after dose increase**

For subjects in whom the dose is increased by >75 mg/day, the number and percentage of subjects with adverse reactions within the acceptable window after the dose increase and during the entire period after the dose increase will be summarized by SOC and PT for each dose-increase pattern (dose increase within the range from 75 mg/day to 150 mg/day or from 150 mg/day to 225 mg/day) with respect to the first dose increase (e.g. the first dose increase if the dose is increased more than once within the range from 75 mg/day to 150 mg/day). Also, the number and percentage of subjects with adverse reactions during the period before the first dose increase will be summarized by SOC and PT for each dose-increase pattern.

8.2.3.4. Adverse events

- **All adverse events**

The number and percentage of subjects with adverse events will be summarized by SOC and PT.

- **Adverse events by seriousness**

The number and percentage of subjects with serious adverse events will be summarized by SOC and PT. The same tabulation will be performed for non-serious adverse events.

- **Occurrence of adverse events after dose increase**

For subjects in whom the dose is increased by >75 mg/day, the number and percentage of subjects with adverse events within the acceptable window after the dose increase and during the entire period after the dose increase will be summarized by SOC and PT for each dose-increase pattern (dose increase within the range from 75 mg/day to 150 mg/day or from 150 mg/day to 225 mg/day) with respect to the first dose increase. Also, the number and percentage of subjects with adverse events during the period before the first dose increase will be summarized by SOC and PT for each dose-increase pattern.

8.2.3.5. Subgroup analyses

The number and percentage of subjects with at least 1 adverse reaction will be summarized based on the subgroup factors specified in Section 5.4. For subgroups listed in Section 5.4 for which the standard categories are specified, the incidence of adverse reactions, risk ratio and the 95% confidence interval will be calculated by categories and presented in figures in accordance with Section 8.1.3. However, risk ratio will not be calculated for categories with <10 subjects.

For subjects in whom the dose is increased by >75 mg/day, the number and percentage of subjects with at least 1 adverse reactions will be summarized based on the subgroup factors specified in Section 5.4, for first-onset adverse reactions that have occurred within the acceptable window after the first dose increase.

For serious adverse reactions and serious adverse events, the number and percentage of subjects will be summarized based on the factors specified in Section 5.4.

A list of adverse reactions will be prepared for the contraindicated subjects. Furthermore, the number and percentage of subjects with adverse reactions will be summarized by SOC and PT as required.

8.2.3.6. Exploratory analysis

Exploratory analysis may be performed as necessary for factors that may affect safety. Exploratory analysis will be reported only if results that provide important interpretation are obtained.

8.2.4. Efficacy analysis

Data will be collected until 12 weeks after the end of the observation period for subjects who have completed the study, and up to the last day of treatment + 14 days for discontinued subjects. Data beyond

the above cut-off date will also be summarized as necessary. The listings will include all data reported in this study.

If one subject has multiple evaluable data of the same dose-increase pattern within the same acceptable window for the same evaluation time point in the analysis of all dose increases, the data which day of dose increase is closest to the target day (before the target day if there are multiple closest dates) will be used.

8.2.4.1. HAM-D

- Summary by evaluation time point

  - For actual values and changes from baseline in HAM-D_{17} total score, HAM-D_6 total score, anxiety/somatization factor total score, and total sleep disorder score, summary statistics will be calculated and figures showing changes over time will be plotted in accordance with Section 8.1.1. If there is at least one post-baseline measurement, missing data at each evaluation time point will be imputed by LOCF and the same analysis will be performed (no figure is required). The same analysis will also be performed on the exploratory analysis set (no figure is required).

  - For actual values and changes from baseline in each of the 17 items, the relevant number and percentage of subjects will be summarized in accordance with Section 8.1.2, using the actual values and changes as categories. In addition, the actual values and changes will be summarized in accordance with Section 8.1.1. The same analysis will also be performed on the exploratory analysis set. Furthermore, the actual values at baseline and each evaluation time point will be summarized in a cross table (categories[2]: ≤7, 8 to 13, 14 to 18, 19 to 22, ≥23).

  - For HAM-D_{17} total score, HAM-D_6 total score, anxiety/somatization factor total score, and total sleep disorder score, as well as for each items of anxiety/somatization factor score and sleep disorder score, the same analysis as above will be performed by subgroups in Section 5.4 (no figure is required). For the HAM-D_{17} total score, HAM-D_6 total score, anxiety/somatization factor total score, and total sleep disorder score, the same analysis as above will also be performed on the exploratory analysis set by subgroups based on the highest dose category (1), HAM-D_{17} total score at baseline, and HAM-D_{17} anxiety/somatization factor total score at baseline. For each of anxiety/somatization factor score and sleep disorder score, the same analysis as above will also be performed on the exploratory analysis set by subgroups based on the highest dose category (1) (no figure is required).

- Summary before and after the dose increase (for subjects in whom the dose is increased by >75 mg/day)

  - For the HAM-D_{17} total score, HAM-D_6 total score, anxiety/somatization factor total score, and total sleep disorder score, the following procedures will be performed for each dose-increase pattern at each evaluation time point (dose increase within the range from 75 mg/day to 150 mg/day or from 150 mg/day to 225 mg/day):

- ✧ For the first dose increase, changes before and after the dose increase will be summarized in accordance with Section 8.1.1, and the actual values before and after the dose increase will be presented in a scatter plot. A scatter plot will be prepared for each evaluation time point. Furthermore, the actual HAM-D_{17} total scores before and after the dose increase will be summarized in a cross table.

- ✧ For all dose increases, intrasubject mean changes before and after the dose increase will be summarized in accordance with Section 8.1.1, combining all evaluation time points. The intrasubject means before and after the dose increase will be presented in a scatter plot. The same analysis will also be performed on the exploratory analysis set.

- ✧ For all dose increases, changes before and after the dose increase will be summarized in accordance with Section 8.1.1, and the actual values before and after the dose increase will be presented in a scatter plot. A scatter plot will be prepared for each evaluation time point.

- ✧ For the first and all dose increases, changes before and after the dose increase will be summarized by type of CYP2D6 in accordance with Section 8.1.1. However, it will not be performed if the number of subjects in whom CYP2D6 is measured is less than 10.

- For each of the 17 items, the following procedures will be performed for each dose-increase pattern up to each evaluation time point (dose increase within the range from 75 mg/day to 150 mg/day or from 150 mg/day to 225 mg/day):

  - ✧ For the first dose increase, changes before and after the dose increase will be summarized as categories in accordance with Section 8.1.2, and the actual values before and after the dose increase will be presented in a scatter plot. A scatter plot will be prepared for each evaluation time point. Furthermore, the actual values before and after the dose increase will be summarized in a cross table. In addition, the actual values before and after the dose increase and changes before and after the dose increase will be summarized in accordance with Section 8.1.1.

  - ✧ For all dose increases, changes before and after the dose increase will be summarized as categories in accordance with Section 8.1.2, and the actual values before and after the dose increase will be presented in a scatter plot. A scatter plot will be prepared for each evaluation time point. In addition, the actual values before and after the dose increase and changes before and after the dose increase will be summarized in accordance with Section 8.1.1.

➢ Responders

- For the percentage of subjects with a ≥50% decrease in HAM-D_{17} total score from baseline (HAM-D_{17} response rate), summary statistics shown in Section 8.1.3 will be calculated for each evaluation time point, and the percentage and the confidence interval at each evaluation time point will be plotted. The same analysis will also be performed on the exploratory analysis set.

- For the percentage of subjects with a HAM-D_{17} total score of ≤7 (a value defined as remission) among those with a baseline HAM-D_{17} total score of >7 (HAM-D_{17} remission rate), summary statistics shown in Section 8.1.3 will be calculated for each evaluation time point, and the percentage and the confidence interval at each evaluation time point will be plotted. If there is at least one post-baseline measurement, missing data at each evaluation time point will be imputed by LOCF and the same analysis will be performed (no figure is required). The same analysis will also be performed on the exploratory analysis set.

- The same analysis as above will also be performed by subgroups in Section 5.4 (no figure is required).

8.2.4.2. MADRS

➢ Summary by evaluation time point

- For actual values and changes from baseline in the MADRS total score at each evaluation time point, summary statistics will be calculated and figures showing changes over time will be prepared in accordance with Section 8.1.1. If there is at least one post-baseline measurement, missing data at each evaluation time point will be imputed by LOCF and the same analysis will be performed (no figure is required). The same analysis will also be performed on the exploratory analysis set (no figure is required).

- The same analysis as above will also be performed by subgroups in Section 5.4 (no figure is required).

- For actual values and changes from baseline in each items, the relevant number and percentage of subjects will be summarized in accordance with Section 8.1.2, using the actual values and changes as categories. In addition, the actual values and changes will be summarized and figures showing changes over time will be prepared in accordance with Section 8.1.1. The same analysis will also be performed on the exploratory analysis set (no figure is required). In addition, the actual values at baseline and each evaluation time point will be summarized in a cross table.

- The same analysis as above will also be performed by subgroups in Section 5.4 (no figure is required). For the MADRS total score, the same analysis as above will be performed on the exploratory analysis set by subgroups based on the highest dose category (1) (no figure is required).

➢ Summary of MADRS total score before and after the dose increase (for subjects in whom the dose is increased by >75 mg/day)

- The following procedures will be performed for each dose-increase pattern at each evaluation time point (dose increase within the range from 75 mg/day to 150 mg/day or from 150 mg/day to 225 mg/day):

  ✧ For the first dose increase, changes before and after the dose increase will be summarized in accordance with Section 8.1.1, and the actual values before and after the dose increase

will be presented in a scatter plot. A scatter plot will be prepared for each evaluation time point. Furthermore, the actual values before and after the dose increase will be summarized in a cross table (categories[3]: ≤10, 11 to 34, ≥35).

- ✧ For all dose-increase time points, intrasubject mean changes before and after the dose increase will be summarized in accordance with Section 8.1.1, combining all evaluation time points. The means before and after the dose increase will be presented in a scatter plot.

- ✧ For all dose increases, changes before and after the dose increase will be summarized in accordance with Section 8.1.1, and the actual values before and after the dose increase will be presented in a scatter plot. A scatter plot will be prepared for each evaluation time point.

- ✧ For the first and all dose increases, changes before and after the dose increase will be summarized by type of CYP2D6 in accordance with Section 8.1.1. However, it will not be performed if the number of subjects in whom CYP2D6 is measured is less than 10.

- For each items, the following procedures will be performed for each dose-increase pattern at each evaluation time point (dose increase within the range from 75 mg/day to 150 mg/day or from 150 mg/day to 225 mg/day):

  - ✧ For the first dose increase, changes before and after the dose increase will be summarized as categories in accordance with Section 8.1.2, and the actual values before and after the dose increase will be presented in a scatter plot. A scatter plot will be prepared for each evaluation time point. Furthermore, the actual values before and after the dose increase will be summarized in a cross table. In addition, the actual values before and after the dose increase and changes before and after the dose increase will be summarized in accordance with Section 8.1.1.

  - ✧ For all dose increases, changes before and after the dose increase will be summarized as categories in accordance with Section 8.1.2, and the actual values before and after the dose increase will be presented in a scatter plot. A scatter plot will be prepared for each evaluation time point. Furthermore, the actual values before and after the dose increase will be summarized in a cross table. In addition, the actual values before and after the dose increase and changes before and after the dose increase will be summarized in accordance with Section 8.1.1.

8.2.4.3. CGI-S

➢ Summary by evaluation time point

- Scores at each evaluation time point will be summarized in a cross table using baseline as a control.

- The same analysis as above will also be performed by subgroups in Section 5.4. (Excluding subgroups based on the CGI-S rating at baseline)

- Summary before and after the dose increase (for subjects in whom the dose is increased by >75 mg/day)

  - For the first dose increase, scores before and after the dose increase will be summarized in a cross table for each dose-increase pattern at each evaluation time point (dose increase within the range from 75 mg/day to 150 mg/day or from 150 mg/day to 225 mg/day).

  - For all dose increases, scores before and after the dose increase will be summarized in a cross table for each dose-increase pattern at each evaluation time point (dose increase within the range from 75 mg/day to 150 mg/day or from 150 mg/day to 225 mg/day).

8.2.4.4. CGI-I

- Summary by evaluation time point

  - Using the score as a category, the number of subjects with the relevant score will be summarized for each evaluation time point in accordance with Section 8.1.2. The same analysis will also be performed on the exploratory analysis set. In addition, the breakdown of scores at each evaluation time point (number and percentage of subjects) will be plotted.

  - The same analysis as above will also be performed by subgroups in Section 5.4 (no figure is required).

- Summary before and after the dose increase (for subjects in whom the dose is increased by >75 mg/day)

  - For the first dose increase, scores before and after the dose increase will be summarized in a cross table for each dose-increase pattern at each evaluation time point (dose increase within the range from 75 mg/day to 150 mg/day or from 150 mg/day to 225 mg/day).

  - For all dose increases, scores before and after the dose increase will be summarized in a cross table for each dose-increase pattern at each evaluation time point (dose increase within the range from 75 mg/day to 150 mg/day or from 150 mg/day to 225 mg/day).

8.2.4.5. Exploratory analysis

Additional analysis may be performed as necessary for factors that may affect efficacy. Exploratory analysis will be reported only if results that provide important interpretation are obtained.

9. LISTINGS

The following listings will be prepared:

- List of subjects (subjects who have completed the study)
- List of subjects with adverse events
- List of subjects with adverse reactions

- List of subjects excluded from safety analysis and subjects excluded from efficacy analysis and reasons for exclusion
- List of subjects with adverse reactions among those who have been excluded from safety analysis
- List of patient background and concomitant drugs related to commonly reported major investigation items
- List of subjects with adverse reactions among contraindicated subjects
- List of subjects with serious adverse reactions
- List of subjects with serious adverse events
- List of subjects with adverse reactions among those with hepatic impairment
- List of subjects with adverse reactions among those with renal impairment
- List of events corresponding to major investigation items
- List of subjects with adverse reactions of major investigation items
- List of additional patient background factors in subjects with ischemic heart disease
- List of efficacy endpoints in children (<15 years)
- List of laboratory test values
- List of status of treatment with this product
- List of reasons for discontinuation (others)

Furthermore, the following tables will be prepared based on the attached forms of the periodic safety report:

- Attached form 3 (List of summary of subjects)
- Attached form 2 (List of status of occurrence of adverse reactions/infections)
- Attached form 10 (Attached form 2-2) (List of status of occurrence of serious adverse events)

REFERENCES

[1]: Hsiao, M. C., & Liu, C. Y. (2008). Successful duloxetine use to prevent venlafaxine withdrawal symptoms. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 32*(2), 576.

[2]: National Institute for Clinical Excellence. (2009). Depression: the treatment and management of depression in adults (update). *Clinical guidelines, CG90*.

[3]: Otsubo, T. (2006). Structured interview and evaluation of symptoms of major depressive disorder. (Special issue: How to measure a mind). *Japanese Journal of Psychiat*ry, 8(1), 22-29.

10. APPENDIX

10.1. Definition of evaluation time points

The evaluation time points for HAM-D_{17} (including subscales), MADRS, CGI-S, CGI-I, vital signs, and laboratory tests are defined as follows:

Visit	[Acceptable window]
Baseline	[-28,1] , Target Day=1
Week 4	[2, 42] , Target Day=28
Week 8	[43, 70] , Target Day=56
Week 12	[71, 98] , Target Day=84
Week 16	[99, 140] , Target Day=112
Week 24	[141, 210] , Target Day=168
Week 36	[211, 308] , Target Day=252
Week 52	[309, 419], Target Day=364
Date of discontinuation (date of start of tapering or date of last treatment)	[Date of last treatment - 28, date of last treatment + 14], Target day=Date of last treatment - 14 (assuming the date of start of tapering); however, it must be after Day 1.
At the end of study or date of discontinuation	1. There is no upper limit for the end of the study. The acceptable window is as follows: • For Week 12 [71, ∞], Target Day=84 • For Week 52 [309, ∞], Target Day=364 2. The date of discontinuation should be within the acceptable window for date of discontinuation above.

When multiple data are available within the acceptable window, the date closest to the target day should be prioritized. When there are multiple closest dates, the date before the target day should be prioritized. However, the date after the target day should be prioritized if there are multiple closest dates in relation to the end of the study.

When LOCF is used in the evaluation, the last observed value obtained after the baseline will be used regardless of the acceptable window for each visit.

For the efficacy assessment, the evaluation time points before and after the dose increase are defined as follows. The evaluation before and after the dose increase will be performed only if it is specified.

Visit	[Acceptable window]
Before the dose increase	[Date of dose increase - 28, date of dose increase], Target Day=Date of dose increase
After the dose increase	[Date of dose increase + 1, date of dose increase + 42], Target Day=Date of dose increase + 28

When multiple data are available within the acceptable window, the date closest to the target day should be prioritized. When there are multiple closest dates, the date before the target day should be prioritized.

For the safety assessment, the evaluation time points before and after the dose increase are defined as follows. The evaluation before and after the dose increase will be performed only if it is specified.

Visit	[Acceptable window]
Before the dose increase	[Date of dose increase - 28, date of dose increase - 1], Target Day=Date of dose increase - 1
After the dose increase	[Date of dose increase, date of dose increase + 28], Target Day=Date of dose increase

When multiple data are available within the acceptable window, the date closest to the target day should be prioritized. When there are multiple closest dates, the date before the target day should be prioritized.

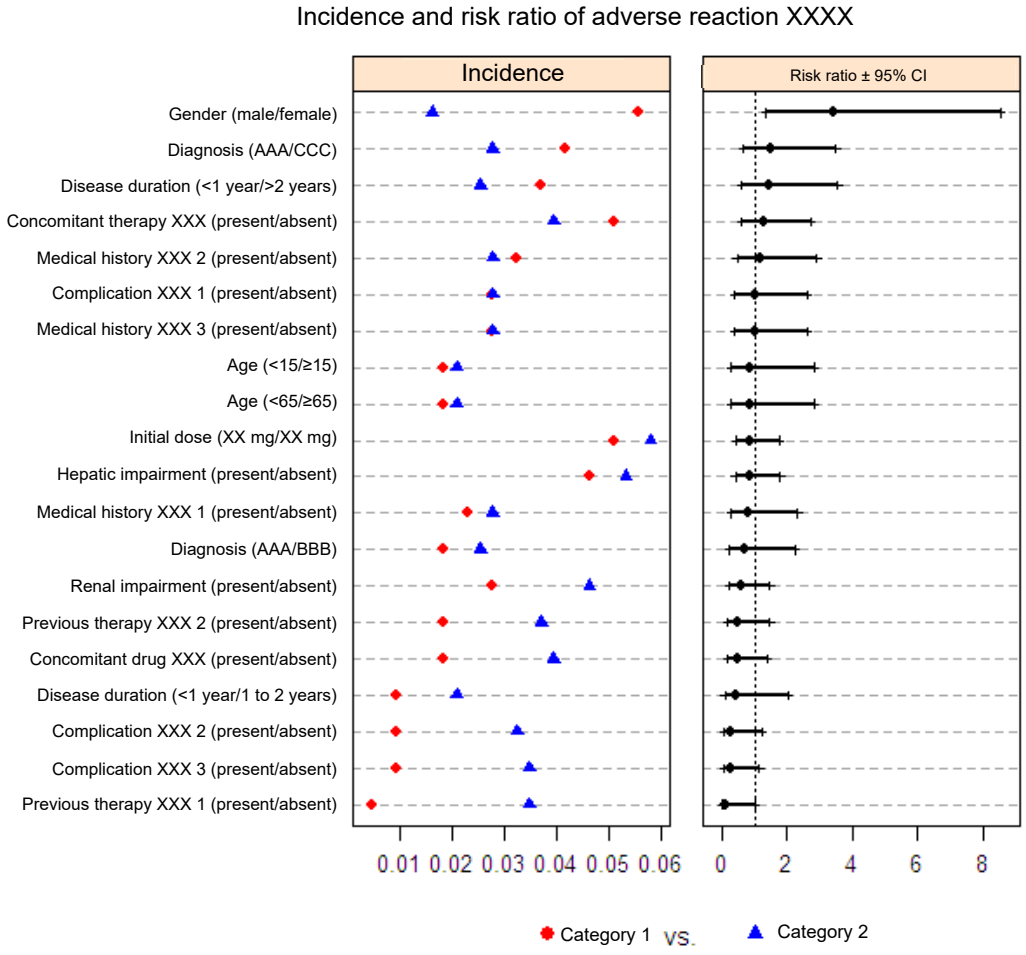
10.2. SAS sample code

SAS sample code for calculation of risk ratios and their 95% confidence intervals (exact method) are shown below. However, the method of calculation should be changed as required if it takes time to calculate the confidence interval due to a problem with calculation capacity.

```
proc freq data=Data;
   tables Variable*Response / relrisk(cl=exact printall);
   exact relrisk;
   weight Count;
   title 'Calculate Relative Risk Ratio';
run;
```

10.3. Sample table and figure for risk ratios among subgroups for the incidence of adverse reactions

Event name: Increase in XXX	Category 1		Category 2		Risk ratio (RR)	
	Number of subjects/N	(%)	Number of subjects/N	(%)	RR	95%CI
Gender (male/female)	18/2220	(0.8)	3/1099	(0.3)	2.97	(0.88-10.06)
Age (≥65 years/<65 years)	19/2788	(0.7)	2/531	(0.4)	1.81	(0.42-7.74)
Diagnosis (disease A/disease B)	3/221	(1.4)	18/3098	(0.6)	2.34	(0.69-7.87)
Disease duration (<1 year/≥1 year)	9/771	(1.2)	7/866	(0.8)	1.44	(0.54-3.86)
Concomitant drug A (present/absent)	9/798	(1.1)	12/2521	(0.5)	2.37	(1.00-5.60)
Previous therapy with drug A (present/absent)	1/148	(0.7)	20/3171	(0.6)	1.07	(0.14-7.93)
Complication with disease B (present/absent)	16/1614	(1.0)	5/1703	(0.3)	3.38	(1.24-9.20)
Medical history of disease B (present/absent)	7/674	(1.0)	14/2643	(0.5)	1.96	(0.79-4.84)
Hepatic impairment (present/absent)	0/80		18/2056	(0.9)		
Renal impairment (present/absent)	1/140	(0.7)	17/2004	(0.8)	0.84	(0.11-6.28)



The breakdown of the number of subjects should be included in the figure for the incidence and risk ratio in this study.