# Phase-3 clinical study of duloxetine hydrochloride in children and adolescent patients with depressive disorder: An open-label extension study

Protocol No. 1702A3632

## Statistical Analysis Plan

Version 1.1

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*This is the translated version of the Statistical Analysis Plan (Version 1.1) written in Japanese*

Signatures

| Company name and roles | Approver | Date |
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Preparation and amendment history

| Version | Date | Author, amender | Comments |
|---|---|---|---|
| 1.0 | January 22, 2018 | [redacted] | New preparation |
| 1.1 | August 25, 2020 | [redacted] | Addition of abbreviations; revision of handling of the tests at discontinuation and at the final evaluation; addition of categories in the maximum and final doses during the treatment period; deletion of “consecutive from the preceding study” from onset timing category for adverse events during the treatment period; addition of CGI-S score category distribution analysis; addition of status of occurrence of adverse events and adverse drug reactions, classified by dosage at onset; addition of shift tables for the analyses of Columbia suicide severity rating scale; deletion of “performance of interim analysis”. |

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List of abbreviations and terms

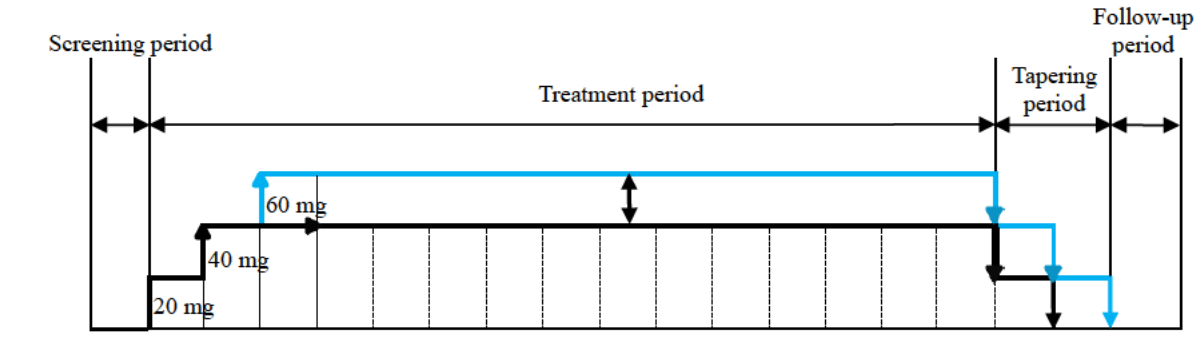
| Abbreviation and terms | Definition |
|---|---|
| BOCF | baseline observation carried forward |
| CDRS-R | Children’s Depression Rating Scale-Revised |
| CGI-S | Clinical Global Impression of Severity |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders Fifth Edition |
| FAS | Full Analysis Set |
| FT3 | free triiodothyronine |
| FT4 | free thyroxine |
| LOCF | last observation carried forward |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MINI-KID | Mini International Neuropsychiatric Interview for children and adolescents |
| SMQ | Standardised MedDRA Queries |

# 1. Introduction

This document presents in concrete terms the contents of Section 8 (Statistical analysis) of the study protocol (study no.: 1702A3632). The details of the pharmacokinetic analysis will be specified separately in "pharmacokinetic analysis plan". With respect to the details of the output from the analysis results stated in the statistical analysis plan, the analysis figures and tables output plan (mock tables, listings and figures) will be prepared separately.

# 2. Study summary

This study is a multicenter, open-label, uncontrolled, long-term treatment study in children and adolescent patients with depressive disorder. This study will include a total of 135 patients; consecutive subjects who have completed the preceding study "Phase-3 clinical study of duloxetine hydrochloride in children and adolescent patients with depressive disorder: Superiority study versus placebo" (Study No.: 1701A3631) then wish to continue the study treatment will be enrolled, as well as additional subjects who have child and adolescent depressive disorder, with a target of 100 subjects completing a 1-year treatment. As shown below, this study will consist of the following four periods (a total of 53 to 56 weeks): screening period (1 to 3 weeks), treatment period (50 weeks), tapering period (1 to 2 weeks), and follow-up period (1 week). Note that consecutive subjects will undergo three periods (a total of 52 to 53 weeks) excluding the screening period. New subjects whose eligibility has been confirmed after obtaining informed consent will be pre-registered (Visit 1), and, after completion of the 1- to 3-week screening period, their eligibility will be confirmed again and they will be registered (Visit 2). Consecutive subjects will give consent for this study before completing the observation at Visit 9 in the preceding study, and, after completing the observation at Visit 9 in the preceding study and the eligibility of this study is confirmed, be enrolled in this study from Visit 2 (registration). After registration, the study drug will be administered orally, once daily after breakfast.




| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Obtaining informed consent | | | | | | | | | | | | | | | | | | |
| | Pre-registration | Registration | | | | | | | | | | | | | | | | | |
| Week-3to-1 | 0 | 1 | 2 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 50 | | 51-52 | 52-53 |

Until 50 weeks after treatment initiation, the dose may be increased to 40 mg/day or 60 mg/day as appropriate, depending on the symptoms.
Consecutive subjects will start this study from Visit 2 after completing Visit 9 in the preceding study.

# 3. Study objectives

## 3.1 Primary objective

To evaluate the long-term safety of duloxetine in children and adolescent patients with depressive disorder.

## 3.2 Secondary objectives

- To evaluate the long-term efficacy of duloxetine in children and adolescent patients with depressive disorder.
- To evaluate the pharmacokinetics of duloxetine in Japanese children and adolescent patients with depressive disorder.
- To evaluate the relationship between duloxetine exposure at steady state and Children's Depression Rating Scale-Revised (CDRS-R) total score, one of the efficacy endpoints.

# 4. Study design

## 4.1 Observation schedule

A schedule table is presented in Appendix 1.

## 4.2 Allocation method

This study is not a randomized study and all enrolled subjects will receive duloxetine.

## 4.3 Target number of subjects

135 subjects (targeting 100 subjects complete one year-administration)

Rationale for the target sample size:

In this study, the target number of subjects is set as at least 100 subjects to collect data from, who will receive duloxetine for one year. Assuming that 25% of subjects drop out of this study, the target total number of registered subjects is 135, including consecutive subjects and new subjects.

# 5. Analysis sets

The efficacy analysis set is defined as the full-analysis set (FAS). In addition, the safety-analysis set will be defined for the analysis of safety.

## 5.1 FAS

This comprises all subjects to whom the study drug has been administered at least once, and with whom the CDRS-R total score has been determined at baseline and at least once after initiation of study drug administration.

## 5.2 Safety-analysis set

This comprises all subjects to whom the study drug is administered at least once.

# 6. Issues with statistical analysis, and data handling

## 6.1 Reporting of analysis results

The numbers of subjects, arithmetic means, standard deviations, minima, medians, and maxima will in principle be calculated as summary statistics for the endpoints measured as continuous data. Items observed as discrete values will be summarized as the number and proportion of subjects in each category. While the results of the analysis will be presented using the entire analysis sets, unless otherwise specified, the analysis of data from the initiation of the preceding study throughout this study will include the consecutive subjects and the results will be presented by the treatment group in the preceding study.

The software used for statistical analyses in this study will be SAS, Version 9.4.

## 6.2 Statistical tests

If a statistical test is performed, the level of significance will be 0.05 (two-sided), unless stated otherwise. There will be no multiplicity adjustment for the statistical tests.

## 6.3 Assessments, observations and tests: Permitted timing and handling in statistical analyses

In principle, data obtained at the time-points shown in the case report forms, and collected in accordance with the performance schedule shown in the study protocol, will be used for the statistical analysis. In the case of data reported at the discontinuation visit, the time-points for use in analyses will be determined on the basis of the permitted ranges in the performance schedule. If there is duplication by data obtained at the scheduled visits and data obtained at the discontinuation tests, the data obtained closest to the scheduled date will be used. If this does not eliminate duplication, data from the scheduled visit will be used. Unscheduled visits will not be included in the time-points for analysis. For the permitted ranges for the observation, test, and evaluation time-points shown in the study protocol, refer to Appendix 2.

For the final evaluation, data obtained at weeks 51 to 52 or at discontinuation of the treatment/tapering period will be used, except for CDRS-R and CGI-S scores, for which those obtained at week 50 or at discontinuation of the treatment period are used. However, if none of the above data are available, the latest data among reported data collected at scheduled visits are used for the final evaluation.

## 6.4 Handling of missing data

In principle, missing data will not be imputed. However, if missing data is imputed for analysis at the final evaluation time point, LOCF may be used.

## 6.5 Baseline

Data obtained before initiation of study drug administration (Visit 2) in this study will be used as baseline data, unless otherwise specified. As with laboratory test results of new subjects, if data from Visit 2 are missing, data from Visit 1 (screening period) will be used as baseline data. The baseline for the analysis of

data from the preceding study throughout this study will be the observed values obtained before initiation of study drug administration in the preceding study.

# 7. Subject composition and backgrounds

## 7.1 Disposition of patients

With registered subjects, the number who complete the treatment period and the number of withdrawals are calculated, and in the case of the withdrawals the disposition of the reasons for discontinuation is shown. Among subjects transferred to the tapering period, the number who complete the tapering period and the number of withdrawals are calculated, and the disposition of the reasons for discontinuation is summarized.

### 7.1.1 Patient composition in efficacy evaluation

With registered subjects, the numbers of subjects included in and excluded from the FAS will be calculated, and the disposition of the reasons for exclusion will be shown.

### 7.1.2 Patient composition in safety evaluation

With registered subjects, the numbers of subjects included in and excluded from the safety-analysis set will be calculated, and the disposition of the reasons for exclusion will be shown.

## 7.2 Analysis of demographic factors

With the safety-analysis set, summary statistics will be determined for the following continuous data items; and the frequencies and proportions of subjects in each category will be determined for discrete values: For the consecutive subjects, each demographic factor will also be summarized by the treatment group in the preceding study. Demographic factors will also be calculated separately for new subjects.

| Data type | Item |
|---|---|
| Continuous | Age on date of obtaining legal representative's informed consent,<br>age at initial onset of depression,<br>height, body weight,<br>CDRS-R total score baseline value,<br>CDRS-R subscale (mood, somatic, subjective, behavior) baseline values,<br>CGI-S score baseline value |
| Discrete | Sex (male, female), ethnicity, race,<br>age on date of obtaining legal representative's informed consent (<12, ≥12),<br>depressive episode ordinal number (first time, second time, third to seventh time, eighth time or more, not known),<br>duration of current depressive episode (0 to 2 weeks, 2 to 4 weeks, 4 to 8 weeks, more than 8 weeks, not known), disease class according to DSM-5 (depression, persistent depressive disorder),<br>hospitalization status category (hospitalized, out-patient),<br>medical and surgical history (present, absent),<br>complications (present, absent),<br>previous drug treatment (present, absent),<br>previous therapy (present, absent) |

The dispositions of medical and surgical history, complications, previous drug treatment, and previous therapy will be shown. Drugs used previously will be coded for using the WHO Drug Dictionary, and summarized on the basis of consistently selected noncommercial names.

# 8. Treatment course and compliance

## 8.1 Compliance

### 8.1.1 Duration of administration and total dose

The following analyses will be performed for the administration in this study with the safety-analysis set:

1) Summary statistics for study drug administration duration will be calculated. Administration duration is defined as follows:

   Administration duration (days)

   = (administration completion date) − (administration initiation date) + 1.

   In addition, times (days) will be converted to week units, and the distributions in the following categories will be summarized: 12 or less weeks; more than 12 to 24 weeks; more than 24 to 50 weeks; and more than 50 weeks.
2) Summary statistics will be calculated for the total dose of study drug.
3) For the maximum and final doses during the treatment period, the distribution in the following categories will be summarized: 20 mg, 40 mg, 60 mg, 80 mg, and 540 mg.

### 8.1.2 Compliance rate

In the safety-analysis set, summary statistics for compliance rate during the treatment period will be calculated. Distribution in the following categories will be summarized: less than 70%, and 70% or more. Compliance rate is defined as follows:

$$\text{Compliance rate [\%]} = \frac{\{Total\ Prescription\ -\ 20 \times (Total\ number\ of\ untaken\ capsules)\}}{(Total\ Prescription)} \times 100$$

## 8.2 Concomitant treatment

The following analyses will be performed with the safety-analysis set: Concomitant drugs will be coded for using the WHO Drug Dictionary, and then summarized on the basis of consistently selected noncommercial names.

1) The number and proportion of subjects who have taken any concomitant medication at least once during the study period will be calculated. In addition, the disposition of the concomitant medication(s) will be shown. If use of the same concomitant medication has been reported more than once with the same subject, this will be taken to be one concomitant medication.
2) The number and proportion of subjects who have had any concomitant therapy at least once during the study period will be calculated. In addition, the disposition will be shown by the name of concomitant therapy. If use of the same concomitant therapy has been reported more than once with the same subject, this will be taken to be one concomitant therapy.

# 9. Efficacy evaluation

Efficacy analyses will be performed with the FAS. Efficacy endpoints are summarized in Table 1. The statistical analysis will be mainly descriptive; when changes from the initiation of the preceding study or from the initiation of the open-label extension study are evaluated, the 95% confidence interval for the mean will be calculated.

Table 1. Summary of endpoints and analysis methods

| | Observed values | | Changes | |
|---|---|---|---|---|
| | Summary statistics | 95% confidence interval for mean | Summary statistics | 95% confidence interval for mean |
| CDRS-R total score. | ○ | ○ | ○ | ○ |
| CGI-S | ○ | ○ | ○ | ○ |
| CDRS-R subscales and item 13 (suicidal ideation) | ○ | ○ | ○ | ○ |

○: to be calculated

## 9.1 Endpoints

1) CDRS-R total score.

   The CDRS-R total score will be calculated by adding together the scores for answers to all questions in the 17 items (refer to Appendix 3).

2) CDRS-R subscales and item 13 (suicidal ideation)

   The CDRS-R subscales are defined as mood, somatic, subjective and behavior (refer to Appendix 3).

3) CGI-S

   Disease severity will be evaluated on the basis of seven grades, from 1 (no disease or abnormality) to 7 (extremely severe disease). The analysis of CGI-S will be based on the score.

### 9.1.1 Analysis of efficacy endpoints

The following analyses will be performed for the efficacy endpoints.

1) Analysis of CDRS-R total score, CGI-S, CDRS-R subscales, and item 13 (suicidal ideation)
   A) Summary statistics will be calculated at each evaluation time-point in this study.
   B) Summary statistics for changes from baseline in this study will be calculated at each evaluation time-point and the 95% confidence interval for the mean will be calculated.
   C) Time-course graph for mean changes (standard deviation) from baseline will be prepared, where the baseline is Visit 2 of this study.
   D) The CGI-S score category distribution will be summarized at baseline (Visit 2 of this study) and at the final evaluation (week 50 of administration or discontinuation of the treatment period).
2) Analysis of CDRS-R total score, CGI-S, CDRS-R subscales, and item 13 (suicidal ideation) from the initiation of the preceding study throughout this study

The following analyses will be performed only in consecutive subjects:

A) Summary statistics will be calculated at each evaluation time-point in the preceding study and this study.
B) Summary statistics for changes from baseline in the preceding study will be calculated at each evaluation time-point in the preceding study and this study and the 95% confidence interval for the mean will be calculated.
C) Time-course graph for mean changes (standard deviation) from baseline in the preceding study will be prepared.
D) The CGI-S score category distribution will be summarized at baseline in the preceding study and at the final evaluation (week 50 of administration or discontinuation of the treatment period).

# 10. Safety evaluation

Safety analyses will be performed with the safety-analysis set.

## 10.1 Adverse events and adverse drug reactions

Adverse events occurring at or after the initiation of the open-label extension study and continuing from the preceding study will be evaluated. Reported adverse events will be converted to Medical Dictionary for Regulatory Activities (MedDRA) terms, and tabulated by system organ class and preferred term.

1) The number of subjects with a given adverse event and the number of cases will be determined, and the incidence rate and 95% confidence interval will be calculated. The incidence rate will be obtained as the proportion of subjects in the analysis set with a specific adverse event, and the confidence interval for the incidence rate will be determined by the Clopper-Pearson method. Totaling will be performed in a similar manner to above with deaths, other serious adverse events, adverse events leading to administration discontinuation, adverse events leading to dose reduction, adverse drug reactions, deaths as adverse drug reactions, other serious adverse drug reactions, adverse drug reactions leading to administration discontinuation, and adverse drug reactions leading to dose reduction. The relevant definitions are shown below.

| | |
|---|---|
| Death | Adverse event with “Death” as the outcome |
| Other serious adverse event | Adverse event in the seriousness category “Serious”, except for death |
| Adverse event leading to administration discontinuation | Adverse event for which the study drug action is “Administration discontinuation” |
| Adverse event leading to dose reduction | Adverse event for which the study drug action is “Dose reduction” |
| Adverse drug reaction | Adverse event with the causal relationship with the study drug judged to be other than “Not related” |
| Death as adverse drug reaction | Death, with the causal relationship with the study drug judged to be other than “Not related” |
| Other serious adverse drug reaction | Other serious adverse event with the causal relationship with the study drug judged to be other than “Not related” |
| Adverse drug reaction leading to administration discontinuation | Adverse event leading to administration discontinuation, with the causal relationship with the study drug judged to be other than “Not related” |
| Adverse drug reaction leading to dose reduction | Adverse event leading to dose reduction, with the causal relationship with the study drug judged to be other than “Not related” |

2) The number of subjects with a given adverse event, the number of cases, and the incidence rate will be determined by adverse event system organ class and preferred term. However, when calculating the number of subjects with a given adverse event and the incidence rate, if the same adverse event occurs more than once with the same subject, these events will be taken to be have affected one subject. Adverse drug reactions will be tabulated similarly.
3) With respect to adverse events with an incidence of 2% or more, the number of subjects, number of cases, and incidence rate will be calculated for each adverse event preferred term. Adverse drug reactions will be tabulated similarly.
4) The number of subjects and incidence rate will be calculated for each severity and outcome category, by adverse event system organ class and preferred term. If the same adverse event occurs more than once in different categories with the same subject, it will be taken to have occurred once, in the category with the highest of the below priority ranks. Adverse drug reactions will be tabulated similarly.

| | Survey item category | |
|---|---|---|
| Priority rank | Severity | Outcome |
| 1 | Severe | Death |
| 2 | Moderate | Recovery with sequelae |
| 3 | Mild | No improvement |
| 4 | | Partial recovery |
| 5 | | Recovery |
| 6 | | Unknown |

5) The number of subjects and the incidence rate will be calculated for each onset timing category (weeks 0 to 8; weeks 8 to 16, weeks 16 to 24, weeks 24 to 32; weeks 32 to 40; weeks 40 to 48; weeks 48 to 50; later than week 50) for adverse events during the treatment period, by system organ class and preferred term. The denominator of the incidence rate will be the number of subjects with administration duration no shorter than the lower limit of each onset time category. The onset timing will be calculated as follows:

Onset timing [day]

= (onset date) − (administration initiation date in the open-label extension study) + 1

When calculating the number of subjects and the incidence rate, if the same adverse event occurs in different categories more than once in the same subject, it will be taken to have occurred with one subject in each of the relevant categories. Adverse drug reactions will be tabulated similarly.

6) With subjects in the safety analysis set who are transferred to the tapering period, adverse events that occur during the tapering period will be summarized. The number of subjects with a given adverse event, the number of cases, and the incidence rate will be determined by adverse event system organ class and preferred term. However, when calculating the number of subjects with a given adverse event and the incidence rate, if the same adverse event occurs more than once with the same subject, these events will be taken to be have affected one subject. Adverse drug reactions will be tabulated similarly.

7) With respect to adverse events for which the following standard MedDRA queries (SMQ) are applicable, the number of subjects, number of cases, and incidence rate will be determined by system organ class and preferred term. However, when calculating the number of subjects with a given adverse event and the incidence rate, if the same adverse event occurs more than once with the same subject, these events will be taken to be have affected one subject.

| SMQ | Range |
|---|---|
| Suicide/self-injury | Broad search |
| Hostility/aggression | Broad search |

8) The number of subjects and incidence rate will be calculated for each study drug dose category (20 mg, 40 mg, 60 mg, 540 mg) at the onset date of adverse event occurring after the initiation of the open-label extension study, by system organ class and preferred term. When calculating the number of subjects and the incidence rate, if the same adverse event occurs in different categories

more than once in the same subject, it will be taken to have occurred with one subject in each of the relevant categories. Adverse drug reactions will be tabulated similarly.

## 10.2 Analyses of vital signs and body weight

Blood pressure (systolic and diastolic), pulse rate, and body weight will be analyzed. The time-points for evaluation of vital signs and body weight are taken to be the baseline, weeks 4, 16, 28, 40, and 50 after administration initiation, and the final evaluation time (weeks 51 to 52, or at discontinuation of the treatment period or tapering period).

1) With respect to blood pressure (systolic and diastolic), pulse rate, and body weight, summary statistics of observed values at each evaluation time-point and changes from baseline will be calculated.
2) For consecutive subjects, summary statistics of observed values at each evaluation time-point in the preceding study and this study and changes from baseline in the preceding study will be calculated.

## 10.3 Analysis of laboratory test results

The below laboratory test results will be analyzed. The time-points for evaluation of laboratory test results are taken to be baseline (Visit 1 for new subjects, Visit 2 for consecutive subjects), weeks 4, 16, 28, and 40 after administration initiation, and the final evaluation time (weeks 51-52, or at discontinuation of the treatment period or tapering period). However, for $HbA_{1c}$ TSH, FT3 and FT4, evaluation is solely during the screening period.

| Classification | Parameter |
|---|---|
| Hematology tests | Leukocyte count, erythrocyte count, hemoglobin, hematocrit, leukocyte fractions (eosinophils, basophils, neutrophils, monocytes, lymphocytes), platelet count |
| Blood chemistry | AST, ALT, LDH, γ-GTP, ALP, creatine kinase, total bilirubin, total protein, blood urea nitrogen, serum creatinine, uric acid, total cholesterol, triglycerides, Na, K, Cl, Ca, blood glucose, $HbA_{1c}$, TSH, FT3, FT4 |
| Urinalysis (qualitative) | Urinary protein, urinary glucose, urobilinogen, urinary occult blood |

1) With respect to laboratory test results obtained as continuous values, summary statistics of observed values at each evaluation time-point and changes from baseline will be calculated.
2) With respect to urinalysis parameters obtained as qualitative values, the number and proportion of subjects in each category at each evaluation time-point will be determined.
3) As evaluation of liver function, the numbers and proportions of subjects meeting the following criteria at each evaluation time-point, and the numbers and proportions meeting these criteria at least one evaluation time-point after administration initiation, will be determined:
   - AST >5 times the upper limit of the reference values.
   - ALT >5 times the upper limit of the reference values.
   - AST or ALT >3 times the upper limit of the reference values, and total bilirubin >2 times the

upper limit of the reference values

- AST >3 times the upper limit of the reference values.
- ALT >3 times the upper limit of the reference values.

4) For consecutive subjects, summary statistics of observed values at each evaluation time-point in the preceding study and this study and changes from baseline in the preceding study will be calculated.

## 10.4 Analysis of ECG

The presence or absence of ECG abnormalities will be analyzed. The time-points for evaluation of ECG are taken to be baseline (Visit 1 for new subjects, Visit 2 for consecutive subjects), weeks 4 and 28 after administration initiation, and the final evaluation time (weeks 51-52, or at discontinuation of the tapering period).

1) With respect to the presence or absence of ECG abnormalities, the frequency of each category before and after administration initiation as well as before administration initiation and the final evaluation time (weeks 51-52, or at discontinuation of the treatment period or tapering period) will be summarized in the form of a shift table. With respect to categories after administration initiation, events will be taken to have occurred once, in the category with the highest of the below priority ranks.

| | Survey item category |
|---|---|
| Priority rank | Judgment |
| 1 | Abnormal, clinically significant |
| 2 | Abnormal, not clinically significant |
| 3 | Normal |
| 4 | Not observed |

2) With respect to the presence or absence of ECG abnormalities, the number and proportion of subjects in each category at each evaluation time-point will be determined.

## 10.5 Analysis of Columbia suicide severity rating scale

Columbia Suicide Severity Rating Scale (C-SSRS) will be analyzed. The time-points for evaluation of C-SSRS are taken to be the screening period and all scheduled visits during the treatment period, and the final evaluation time (weeks 51-52 or at discontinuation of the treatment period or tapering period).

1) The distribution of categories (yes, no) on the below evaluation scale will be summarized in the form of a shift table before and after administration initiation as well as before administration initiation and the final evaluation time (weeks 51-52, or at discontinuation of the treatment period or tapering period). For categories before administration initiation, subjects with at least one “yes” assessment at any one evaluation time-point in the screening period or before administration initiation will be classified as ”yes”, and other subjects will be classified as “no”. For categories

after administration initiation, subjects with at least one “yes” assessment at any one evaluation time-point after administration initiation will be classified as “yes”, and other subjects will be classified as “no”. Both before and after administration initiation as well as the final evaluation time, subjects with missing observed values at all evaluation time-points will be classified as “non-assessed subjects”.

2) The number and proportion of subjects in each category at each evaluation time-point will be determined.

| Columbia suicide severity rating scale | |
|---|---|
| Suicidal ideation | 1. Wish to be dead<br>2. Non-specific Active suicidal thoughts. |
| Suicidal behavior | 1. Actual attempt<br>2. Non-Suicidal Self-Injurious Behavior<br>3. Self-Injurious Behavior, intent unknown<br>4. Interrupted attempt<br>5. Aborted attempt<br>6. Preparatory Act or Behavior<br>7. Suicidal behavior<br>8. Completed suicide |

3) For the following five questions about suicidal ideation, the distribution on the highest question number with at least one “yes” answer will be summarized in the form of a shift table of before versus after administration initiation.

| Question No. | Questions |
|---|---|
| 1 | Wish to be dead |
| 2 | Non-specific Active suicidal thoughts. |
| 3 | Active suicidal ideation with any methods (not plans) but without intent to act |
| 4 | Active suicidal ideation with some intent to act, without specific plan |
| 5 | Active suicidal ideation with specific plan and intent |

4) For the following six questions about suicidal behavior, the distribution of yes/no will be summarized in the form of a shift table of before versus after administration initiation, where “yes” represents there is at least one answer of “yes” to a question, and “no” represents there is no answer of “yes” to a question.

| Questions |
|---|
| Actual attempt |
| Interrupted attempt |
| Aborted attempt |
| Preparatory Act or Behavior |
| Suicidal behavior |
| Completed suicide |

# 11. Performance of interim analysis

In this study, no interim analysis will be performed.

# 12. Data handling in analyses

## 12.1 Number of decimal places for calculated values

In principle, the number of decimal places to which calculated summary statistics and proportions are expressed will be as shown below.

| Index | Rules for data expression |
|---|---|
| p-Value | Rounded off to the fourth decimal place. If below 0.0001, expressed as "<.0001". |
| Mean, standard deviation, median | Rounded off to one significant figure of the raw data. |
| Maximum, minimum | The same number of significant figures as the raw data. |
| Proportion (%) | Rounded off to the first decimal place. |

## Appendix 1. Schedule

| | Screening period | Treatment period | | | | | | | | | | | | | Tapering period | Follow-up period |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9, 10 | 11 | 12, 13 | 14 | 15,16 | 17/discontinuation | 18/discontinuation | 19 |
| Week | − 3 to −1 | 0 | 1 | 2 | 4 | 8 | 12 | 16 | 20, 24 | 28 | 32, 36 | 40 | 44, 48 | 50 | 51 to 52 | 52 to 53 |
| Visit date | | 0 | 7 | 14 | 28 | 56 | 84 | 112 | 140, 168 | 196 | 224, 252 | 280 | 308, 336 | 350 | 364 | 371 |
| Obtaining informed consent or assent | X[a] | X[b] | | | | | | | | | | | | | | |
| Demographic factors | X[a] | | | | | | | | | | | | | | | |
| MINI-KID | X[a] | | | | | | | | | | | | | | | |
| Confirmation of inclusion/exclusion criteria: | X[a] | X | | | | | | | | | | | | | | |
| Physical Examination | X[a] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[j] |
| Registration | X[a] (pre-Registration) | X[c] (Registration) | | | | | | | | | | | | | | |
| CDRS-R | X[a] | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Psycho-education | X[a, d] | X[a, d] | | | X[a, d, g] | X[a, d, g] | | | | | | | | | | |
| CGI-S | X[a] | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| C-SSRS | X[a] | X[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Study drug administered | | X | X | X | X | X | X | X | X | X | X | X | X | X[k] | | |
| Adherence of drug administration | | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Laboratory tests[e] | X[a] | X[b, f] | | | X | | | X | | X | | X | | | X[l] | |
| Blood pressure and heart rate | X[a] | X[f] | | | X | | | X | | X | | X | | X | X | |
| ECG | X[a] | X[b, f] | | | X | | | | | X | | | | | X[l] | |
| Body weight | | X[f] | | | X | | | X | | X | | X | | X | X | |
| Urinary drug screening | | X[a] | | | | | | | | | | | | | | |
| Pregnancy test[h] | X[a] | X[b, f] | | | | | | | | | | | | | X[l] | |
| Plasma concentration | | | | | X[i] (5times) | | | | | | | | | | | |
| Adverse events | X | | | | | | | | | | | | | | | |

a Will be performed only in new subjects.

b Will be performed only in consecutive subjects. Informed consent/assent will be obtained before completing the observation at Visit 9 in the preceding study.
c Consecutive subjects should be enrolled (registered) in this study within 3 days after the final administration of study drug in the preceding study.
d Psycho-education is provided after evaluation of CDRS-R and CGI-S.
e Hematology tests, blood chemistry tests, and urinalysis. HbA1c, TSH, $FT_3$, and $FT_4$ will also be measured at Visit 1 for new subjects only.
f For consecutive subjects, results at Visit 9 in the preceding study may be used.
g Will be performed at discontinuation if a subject discontinues the study before Visit 6.
h Will be performed only in post-menarche females.
i Blood samples for quantitation of plasma concentrations of duloxetine will be collected five times at any timing between Visit 5 and the completion of study drug administration during the treatment period. If the dose is increased or decreased, blood samples should be collected at least 2 weeks after the dose adjustment. Of five random blood samples, one or two samples should be collected before dosing.
j Adverse events occurring within 7 days after the final administration of the study drug will be investigated. The subject is checked by telephone or other appropriate method, even if he/she fails to make a visit.
k Dispense study drugs for tapering period.
l If the tapering period is not conducted, the pregnancy test will be performed at Visit 17 or at the time of discontinuation during the treatment period.

## Appendix 2. Permitted range of timing of examinations, observations and tests

| | Visit | Week | Stipulated date of visit | Permitted range (day) | Range (Day) |
|---|---|---|---|---|---|
| Screening period | 1 | −3 to −1 | −21 to −7 | - | - |
| Treatment period | 2 | 0 | 0 (Registration) | 0 | - |
| | 3 | 1 | 7 | ±3 | 4 to 10 |
| | 4 | 2 | 14 | ±3 | 11 to 17 |
| | 5 | 4 | 28 | ±7 | 21 to 35 |
| | 6 | 8 | 56 | ±7 | 49 to 63 |
| | 7 | 12 | 84 | ±7 | 77 to 91 |
| | 8 | 16 | 112 | ±7 | 105 to 119 |
| | 9 | 20 | 140 | ±7 | 133 to 147 |
| | 10 | 24 | 168 | ±7 | 161 to 175 |
| | 11 | 28 | 196 | ±7 | 189 to 203 |
| | 12 | 32 | 224 | ±7 | 217 to 231 |
| | 13 | 36 | 252 | ±7 | 245 to 259 |
| | 14 | 40 | 280 | ±7 | 273 to 287 |
| | 15 | 44 | 308 | ±7 | 301 to 315 |
| | 16 | 48 | 336 | ±7 | 329 to 343 |
| | 17 | 50 | 350 | ±3 | 347 to 353 |
| | At discontinuation | - | Date of final dosing of treatment period | +3 | - |
| Tapering period | 18 | 51<br>If the last dose is 40 mg | On Day 7, taking Visit 17 (or the time of discontinuation during the treatment period) to be Day 0. | ±3 | - |
| | | 52<br>If the last dose is 60 mg | On Day 14, taking Visit 17 (or the time of discontinuation during the treatment period) to be Day 0. | ±3 | - |
| | At discontinuation | - | Date of final dosing of tapering period | +3 | - |
| Follow-up period | 19 | 52 to 53 | On day 7 or later, taking final administration date to be day 0. | | - |

## Appendix 3: Endpoint Scoring

### 1. Calculation methods for CDRS-R total score and subscale scores

The scores for items 1 to 17 will be totaled, and the CDRS-R total score calculated.

| Endpoints | Score range | Endpoints | Score range |
|---|---|---|---|
| 1. Impaired Schoolwork | 1～7 | 11. Depressed Feelings | 1～7 |
| 2. Difficulty Having Fun | 1～7 | 12. Morbid Ideation | 1～7 |
| 3. Social Withdrawal | 1～7 | 13. Suicidal Ideation | 1～7 |
| 4. Sleep Disturbance | 1～5 | 14. Excessive Weeping | 1～7 |
| 5. Appetite Disturbance | 1～5 | 15. Depressed Facial Affect | 1～7 |
| 6. Excessive Fatigue | 1～7 | 16. Listless Speech | 1～5 |
| 7. Physical Complaints | 1～7 | 17. Hypoactivity | 1～7 |
| 8. Irritability | 1～7 | | |
| 9. Excessive Guilt | 1～7 | | |
| 10. Low Self-Esteem | 1～7 | Total | 17～113 |

The CDRS-R subscale scores will be calculated as shown below.

| Subscale | Calculation method |
|---|---|
| Mood | Total of items 8, 11, 14 and 15 |
| Somatic | Total of items 4, 5, 6, 7, 16 and 17 |
| Subjective | Total of items 9, 10, 12 and 13 |
| Behavior | Total of items 1, 2 and 3 |

[redacted]

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| Reason for signing: Approved | Name: [redacted]<br>[redacted]<br>Role: Approver<br>Date of signature: 01-Sep-2020 06:57:05 GMT+0000 |

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| Reason for signing: Approved | Name: [redacted]<br>[redacted]<br>Role: Approver<br>Date of signature: 01-Sep-2020 08:22:57 GMT+0000 |

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