Study Protocol

This is the translated version of the Study Protocol (Version 4) written in Japanese

Study title:	Phase-3 clinical study of duloxetine hydrochloride in children and adolescent patients with depressive disorder: An open-label extension study
Study No.:	1702A3632
Development phase:	3
Product No.:	LY248686
Sponsor:	Shionogi & Co., Ltd. (Head Office) 3-1-8 Doshomachi, Chuo-ku, Osaka, 541-0045, Japan
Contact information for the sponsor:	[redacted]
Emergency contact:	[redacted]

Preparation dates

First version (Version 1):	September 25, 2017
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Version 4	August 8, 2018

Overview of the study

Study title:	Phase-3 clinical study of duloxetine hydrochloride in children and adolescent patients with depressive disorder: An open-label extension study
Study No.:	1702A3632
Development phase:	3
Primary objective:	To evaluate the long-term safety of duloxetine in children and adolescent patients with depressive disorder.
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 compare the plasma duloxetine concentrations at steady state obtained at 5 time points (including at least one predose level [trough]) in children and adolescent patients with depressive disorder with those of adult patients with depressive disorder. - To examine the potential factors that affect the pharmacokinetic properties of duloxetine (e.g., age, body weight, and sex) and their effects in the population pharmacokinetics analysis. • 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.
Study design:	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. 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.

Study subjects:

The subjects must meet the following criteria: (i) aged ≥9 to <18 at the time of obtaining consent and assent (consecutive subjects are allowed to be enrolled if they are aged ≥9 to <18 in the preceding study); (ii) diagnosed as having depression or persistent depressive disorder as defined in the Diagnostic and Statistical Manual of Mental Disorders, version 5 (DSM-5), with onset at the age of ≥7; and (iii) fully meeting the criteria for a depressive episode. The Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID; version 7.0.2) will be used for diagnosis on the basis of DSM-5.

Inclusion/exclusion criteria:

Subjects must meet all the following criteria:

Inclusion criteria	Consecutive subjects	New subjects
1) Have completed 7-week treatment in the preceding study and wish to continue treatment with duloxetine.	X	
2) Have been diagnosed with depression or persistent depressive disorder, as defined in DSM-5, and fully meet the criteria for a depressive episode. MINI-KID (version 7.0.2) should be used for diagnosis of depression.		X
3) Are aged ≥9 to <18 at the time of obtaining consent and assent, and must have been ≥7 at the initial onset of depression episode. Are male or female and are hospitalized or out-patients.		X
4) Have a legal representative capable of providing written informed consent for this study. In addition, for patients aged ≥13, a written, informed assent must also be obtained from the patient him/herself. For patients aged ≥9 to <13, a written, informed assent should also be obtained from the patient him/herself if possible.	X	X
5) For post-menarchic females, a pregnancy test result must be negative at Visit 1 (or Visit 2 for consecutive subjects). In addition, the patient must agree to use one	X	X

of the following contraceptive methods from Visit 1 (or Visit 2 for consecutive subjects) until 1 month after the final administration. However, this requirement does not apply to females for whom it can be confirmed in writing that 6 weeks or more has passed since bilateral ovariectomy. Estrogen- and progesterone-containing, combined-hormonal contraceptive agents with ovulation-suppressing effects (administered orally, intravaginally, subcutaneously, etc.), progesterone-containing hormonal contraceptive agents (administered orally, intravenously, by implantation, etc.), intrauterine device, intrauterine system, bilateral tubal ligation, male partner's vasectomy, or sexual abstinence.		
6) The principal investigator or sub-investigator judges that the subject's legal representative can ensure that the subject him/herself will comply with all hospital visits, tests, and other procedures stipulated in this protocol. In addition, the principal investigator or sub-investigator judges that the subject him/herself will be able to comply with all the hospital visits, tests, and other procedures stipulated in this protocol.		X
7) The principal investigator or sub-investigator judges that the subject's legal representative has sufficient comprehension and cognitive ability to communicate as appropriate with the principal investigator or sub-investigator, and other persons involved with the study. In addition, the principal investigator or sub-investigator confirms that the subject him/herself has a cognitive level appropriate to his/her age, and judges that he/she has sufficient comprehension and cognitive ability to communicate as appropriate with the principal investigator or sub-investigator, and other persons involved with the study.		X
8) Have ability to swallow the capsules without opening, crushing, dissolving, or breaking them. In addition,		X

he/she can take up to three capsules per day.		

Patients who meet any of the following criteria will be excluded:

Exclusion criteria	Consecutive subjects	New subjects
1) Judged by the principal investigator or sub-investigator to have complications diagnosed as belonging to one or more of the following categories in DSM-5, or to have a history of such disorders: • Neurodevelopmental disorders • Schizophrenia-spectrum disorder or other psychotic disorders • Bipolar or related disorders • Trauma and stressor-related disorders • Disruptive, impulse–control, and conduct disorders	X	X
2) Judged by the principal investigator or sub-investigator to have complications diagnosed as belonging to one or more of the following categories in DSM-5: • Obsessive-compulsive disorder or related disorders • Anorexia nervosa, bulimia nervosa, or binge-eating disorder • Sleep-wake disorders • Neurocognitive disorders • Disruptive mood dysregulation disorder	X	X
3) Judged by the principal investigator or sub-investigator to have a personality disorder.	X	X
4) Treatment with two or more antidepressants has previously been tried, and, despite treatment of a single depressive episode with the optimal clinical dose for 4 weeks or more, there has been no response. Alternatively, the depressive episode has been treated previously or is currently being treated with duloxetine, but without response.		X
5) The principal investigator or sub-investigator judges	X	X

that systematic psychotherapy must be initiated between Visits 1 and 18.		
6) One or more of the patient's parents and/or siblings has been diagnosed with bipolar disorder.	X	X
7) A history of epileptic or other convulsive attacks. However, patients with a history of febrile convulsions can be enrolled.	X	X
8) Administered electroconvulsive therapy within 1 year before Visit 1.		X
9) Uncontrolled diabetes or collagen disease.		X
10) Have initiated, changed or discontinued hormonal therapy within 3 months before Visit 1. Patients with thyroid dysfunction are excluded. But patients can be enrolled if they (i) have undergone thyroid hormone supplementation at a consistent dose for at least 3 months as of Visit 1; (ii) show medically appropriate thyroid hormone (TSH, FT_3, FT_4) concentrations; and (iii) have clinically normal thyroid function.		X
11) Currently have or have a history of malignant tumors/cancer.	X	X
12) For new subjects, either (i) suicidal ideation and/or suicidal attempt within 1 year before Visit 1; or (ii) at Visits 1 and 2 (or Visit 2 for consecutive subjects), answer "Yes" to questions 4 and/or 5 about suicidal ideation, and/or any of the questions about suicidal behaviors (except those about non-suicidal self-injurious behavior), on the Columbia suicide severity rating scale (C-SSRS).	X	X
13) Body weight below 20 kg at Visit 2.	X	X
14) Serious[*1] or medically unstable[*2] disease (cardiovascular disease, hepatic disease, respiratory disease, hematologic disease, endocrine disease, peripheral vascular disorder, neuropsychiatric disease, renal disease), or clinically problematic abnormal laboratory test results or abnormal electrocardiography (ECG) findings[*3]. *1: Grade 3 in "Concerning classification criteria for	X	X

seriousness of adverse drug reactions to pharmaceutical products, etc." (Drug Safety Notification no. 80; June 29, 1992). *2: Judged by the principal investigator or sub-investigator to have the potential to disrupt study participation, or to necessitate hospitalization during the study period. *3: Judged by the principal investigator or sub-investigator to suggest serious medical problems, or to necessitate aggressive therapy.		
15) Meeting one or more of the following criteria: • At Visit 2, latest ALT or AST of 100 U/L or higher, or latest total bilirubin of 1.6 mg/dL or higher. • Latest serum creatinine level of 2.0 mg/dL or higher at Visit 2. Or have severe renal impairment, history of renal transplantation, and/or currently undergoing renal dialysis.	X	X
16) Glaucoma, elevated intraocular pressure, and/or prostatic hypertrophy or other types of dysuria.	X	X
17) Depression or depressive state due to organic brain disorder.	X	X
18) Hemorrhagic tendency or hemorrhagic diathesis.	X	X
19) Treatment with monoamine oxidase (MAO) inhibitor within 14 days before Visit 2, and/or potential for MAO inhibitor treatment during the study period or within 5 days after completion of study drug administration.	X	X
20) Hypersensitivity to duloxetine or inactive ingredients of duloxetine formulation.	X	X
21) Allergic to two or more drugs, or a history of serious allergic reactions to one or more drugs.	X	X
22) Judged by the principal investigator or sub-investigator to have the complication of substance-related and/or addictive disorders, as defined in DSM-5, or a history of such disorders. However, patients with caffeine-related disorder can be enrolled.		X
23) One or more substances of abuse (phencyclidines,		X

benzodiazepines, cocaine-type drugs, stimulants, cannabis, opioids, barbiturates, tricyclic antidepressants, etc.) detected by urinary drug screening at Visit 2.		
24) Intension to travel overseas between Visit 1 (or Visit 2 for consecutive subjects) and Visit 6.	X	X
25) Pregnant* or possibly pregnant, breastfeeding, hoping to become pregnant during the study period. Or recently given birth. * Pregnancy: Pregnancy tests (blood or urine human chorionic gonadotropin) will be performed in all post-menarche females.	X	X
26) Previously administered the study drug during participation in this study, or during participation in a different clinical study on duloxetine.		X
27) Have received another study drug within 30 days before Visit 1 or are currently receiving it.		X
28) Participation judged to be inappropriate for any other reason by the principal investigator or sub-investigator.	X	X

Study drug dosage and administration method:

All subjects will receive 1 to 3 oral capsules of duloxetine 20 mg once daily after breakfast from the day after the registration (Visit 2).

During the treatment period, subjects will receive duloxetine 20 mg/day for one week then 40 mg/day for one week, and subsequently receive 40 mg/day or 60 mg/day for 48 weeks depending on the symptoms.

During the tapering period, the subjects whose duloxetine dose at discontinuation or completion of the treatment period is 60 mg/day will receive 40 mg/day for one week then 20 mg/day for one week. The subjects whose duloxetine dose at discontinuation or completion of the treatment period is 40 mg/day will receive 20 mg/day for one week.

Administration period:

51 or 52 weeks (50-week treatment period and 1- to 2-week tapering period)

Prohibited drugs and therapies:

Use of the below drugs, or over-the-counter drugs with equivalent effects, is prohibited from Visit 1 (or after completing the observation period at the completion of the tapering period in the preceding study for consecutive subjects) through to Visit 18 (completion of the tapering period):

Prohibited drugs that may affect therapeutic evaluation:

1) Antidepressants

2) Anxiolytics
3) Soporific agents, other than the "Permitted soporific agents" in Section 6.2.2
4) Antipsychotics
5) Antiparkinsonian agents
6) Anticonvulsants
7) Mood-stabilizers (lithium carbonate, carbamazepine, sodium valproate)
8) Psychostimulants
9) Adrenal corticosteroids (excluding topical agents, such as ear drops, nose drops, eye drops, topical skin formulations, and inhaled formulations).
10) Interferon formulations
11) Any of the following drugs, which might affect the metabolic/agonistic activities of serotonin or noradrenaline:
    Cyproheptadine hydrochloride (Periactin®, etc.)
    Dimetotiazine mesilate (Migristene®)
    Ifenprodil tartrate (Cerocral®, etc.)
    5-HT_3 inhibitors (Zofran®, etc.)
    5-HT_4 stimulants (Gasmotin®, etc.)
    5-$HT_{1B/1D}$ receptor agonists (Imigran®, etc.)
    Adrenergic agents (Noradrenaline®, etc.)
12) St. John's wort
13) Chinese herbal medicines administered to treat central nervous conditions such as insomnia, neurosis or anxiety.
14) Other agents judged to act on the central nervous system, and thus affect therapeutic evaluation.

Prohibited drugs that present safety-related problems:

1) MAO inhibitors** (FP®, Azilect®, etc.)

**Administration of these is contraindicated from 14 days before Visit 2 (or after completing the observation period at the completion of the tapering period in the preceding study for consecutive subjects) until 5 days after completion of study drug administration.

2) Other investigational drugs

Unless specifically stated otherwise, use of the following treatments is contraindicated from Visit 1 (or after completing the observation period at the completion of the tapering period in the preceding study for consecutive subjects) through to Visit 18 (completion of the tapering period):

1) Electroconvulsive therapy
2) Bright-light therapy, i.e. therapy using irradiation devices approved as medical devices.
3) Systematic psychotherapy, such as systematically organized cognitive therapy, cognitive behavioral therapy, and interpersonal psychotherapy. For new subjects, this study will use educational tools, consistently in all institutions, for the psycho-education of subjects and guardians.
4) Exercise therapy
5) Hormone therapy is contraindicated. However, in accordance with exclusion criterion 10, treatment can be continued at the same dose in thyroid dysfunction patients who meet the following three criteria: (i) having undergone thyroid hormone supplementation for at least 3 months as of Visit 1 (or Visit 2 for consecutive subjects); (ii) showing medically appropriate concentrations of thyroid hormones (TSH, FT_3 and FT_4); and (iii) having attained a clinically normal state of thyroid function.

Efficacy endpoints:	CDRS-R, Clinical Global Impression of Severity (CGI-S)
Pharmacokinetic endpoint:	Plasma duloxetine concentrations
Safety endpoints:	Adverse events, adverse drug reactions, C-SSRS score, laboratory test results, blood pressure, pulse rate, body weight, ECG
Statistical methods:	The summary statistics will be calculated for the observed efficacy endpoints (CDRS-R total score and CGI-S) and their changes from baseline at each time-point after study drug administration. In principle, the baseline for each endpoint is defined as the subject's initiation of this study (Visit 2).
Study period:	Study period for each subject: Up to 56 weeks (consisting of a 1- to 3-week Screening period, a 50-week treatment period, a 1- to 2-week tapering period, and a 1-week follow-up period). Scheduled study period: From November 2017 to March 2021.
Date of preparation of the first version:	September 25, 2017
Date of preparation of the latest version:	August 8, 2018 (Version 4):

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List of abbreviations and definitions of terms

Abbreviation and terms	Definition
5-HT	5-hydroxytryptamine (serotonin)
CDRS-R	Children's Depression Rating Scale-Revised
CGI-S	Clinical Global Impression of Severity
C-SSRS	Columbia Suicide Severity Rating Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition – Text Revision
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
EDC	electronic data capture
FAS	full analysis set
FDA	Food and Drug Administration
FT_3	free triiodothyronine
FT_4	free thyroxine
IRB	institutional review board
LOCF	last observation carried forward
MAO	monoamine oxidase
MINI-KID	Mini International Neuropsychiatric Interview for children and adolescents
NA	noradrenaline
SNRI	serotonin noradrenaline reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TSH	thyroid stimulating hormone

1. Background information

Depression is a psychiatric disorder, with the principal symptoms being depressive mood, and mood/affective disorders such as anxiety and irritation, and it is often associated with volitional and behavioral disorders, and also generalized symptoms such as sleep disorders, anorexia, and fatigue. The etiology and pathology of depression have not been fully elucidated (1), but one fundamental concept of the mechanism of onset of depression is the monoamine hypothesis, according to which deficiency of monoamines, such as serotonin and noradrenaline, which are neurotransmitters at cerebral nerve terminals, results in decreased synaptic transmission (2).

Before 1980, very little attention was given to pediatric depression, and it was thought to be a very rare condition. However, when the operational diagnostic criteria in DSM Version 3 (DSM-III), published by the American Psychiatric Association in 1980, were applied, it was found that there are children with depressive symptoms just as there are adults, and it is now clear that pediatric depression patients are far more numerous than previously thought (3). Overseas epidemiological studies have shown that the frequency of initial depressive episodes increases rapidly from the age of 12, and from that age the incidence of depression is approximately the same as in adults (4, 5). In addition, although the symptoms of depression change with developmental stage, it has been reported that from the age of 10 they increasingly resemble those of adults (6). In recent years, considerable attention has been given to pediatric/adolescent depression in Japan, and the number of patients diagnosed has increased (7). The progression and prognosis of pediatric depression are not good, as, according to a prognostic survey of 65 patients by Kovacs (1984), 92% showed recovery within 18 months after onset, but with 40% of these the condition recurred within 2 years after recovery, and with 70% it recurred within 5 years after onset (8, 9). According to Fombonne (2001), a 20-year outcome survey of 149 patients with depression onset before the age of 18 showed recurrence of major depression with 62.4% (10). In other words, pediatric depression is readily cured, but also recurs readily (11); it is a condition showing both high incidence and ready recurrence. In addition, it is considered that it results in considerable psychosocial dysfunction, and also has major effects on family members (3). For these reasons, as with adult depression, prompt and appropriate diagnosis and treatment are important for pediatric depression. However, it cannot really be said that appropriate, evidence-based drug therapy is currently in use (7). In Japan, clinical studies of children and adolescent depression have not shown any safe and effective antidepressants, and no drugs are currently indicated for pediatric depression. However, based on the results of overseas clinical studies, the package insert of escitalopram has no description of careful administration to patients aged 12 to 17.

The latest version of Treatment Guideline II: Major Depressive Disorder, amended from the previous version (amended 2013) by the Japanese Society of Mood Disorders in July 2016 (7) includes a new section, titled “Pediatric/adolescent depression”, which is an area of ongoing research, and the unmet medical needs for pediatric/adolescent antidepressants are thus proposed. In the USA also, on the basis of observational research on and reanalysis of clinical studies on serotonin/noradrenaline reuptake inhibitors and selective serotonin reuptake inhibitors, several reports have suggested that the risks of not prescribing antidepressants to juveniles are higher than the risks of prescribing them. Therefore, in July 2016, the

American Academy of Pediatrics amended its treatment guidance (Guidance for the Clinician in Rendering Pediatric Care) to recommend appropriate antidepressant treatment even for juveniles (12).

Duloxetine is a compound that is classified as a serotonin/noradrenaline reuptake inhibitor and shows marked inhibition of both serotonin (5-HT) and noradrenaline reuptake. In Japan, after approval for treatment of depression and depressive state was achieved in January 2010, approval was achieved for the following indications: (i) pain associated with diabetic neuropathy; (ii) pain associated with fibromyalgia; (iii) pain associated with chronic low back pain; and (iv) pain associated with osteoarthritis. In worldwide terms, since approval for major depressive disorder was achieved in the USA in August 2004, it has been approved in more than 100 countries, including Japan, and is now in wide use. In addition, as of May 2017, in addition to major depressive disorder, it has been approved for numerous indications, including (i) pain associated with diabetic neuropathy; (ii) fibromyalgia; (iii) chronic musculoskeletal pain, including chronic low back pain and chronic osteoarthritis; (iv) stress urinary incontinence; and (v) generalized anxiety disorder. Most of the above indications are for adults, but in October 2014 generalized anxiety disorder was achieved as a pediatric indication in the USA. In addition, in March 2015 the Duloxetine Pediatric-Focused Safety Review (Cymbalta® [Duloxetine] Pediatric Advisory Committee Meeting) was held in the USA, no new safety-related concerns were identified, and the Food and Drug Administration (FDA)'s conclusion was that the usual safety monitoring should be continued (13).

On the other hand, in the HMCK and HMCL studies, which were overseas, Phase-3, double-blind, parallel-group, comparative studies with pediatric/adolescent major depressive disorder patients diagnosed on the basis of DSM Version 4 (amended version; DSM-IV-TR), although no particular safety-related problems were found, there were high placebo responses in both studies, and superiority over the placebo was not found with either duloxetine or the positive control, fluoxetine. However, on the basis of the results of a supplementary analysis performed before a Japanese study was planned, in a population of patients with treatment initiation at the age of ≥9 and depression onset at the age of ≥7, the changes in CDRS-R total scores in the duloxetine 30- and 60-mg groups were significantly higher than in the placebo group (in the HMCL study, this was the change at the final evaluation time-point, at week 10, by the LOCF method). In addition, as a tendency toward differences in placebo response between institutions was found, it is considered that performance of the study with a relatively small number of subjects, at an institution selected as having a low placebo response, is a method that is appropriate from the point of view of a clinical study, and that it should increase the probability of success. In addition, both the pediatric subjects enrolled in the study and their guardians are to be given basic psycho-education about treatment of depression, which will be systematic, and have the same contents, and this is expected to minimize the variation between subjects, thus increasing the detection power. At the same time, the psycho-education is to be provided consistently from the screening period, and subjects with high placebo response are to be excluded, thus reducing the mean placebo response.

Under such background, 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) will be conducted to evaluate the efficacy and safety of duloxetine in children and adolescent

patients with depressive disorder. Additionally, an extended long-term treatment study is planned in participants of the preceding study and new patients in order to confirm the long-term safety and efficacy of duloxetine.

The duloxetine package insert includes, as drug-class labeling, the following requirement to take care: “There have been reports of an increased risk for suicidal ideation and/or suicidal attempt in antidepressant-treated patients aged 24 years or younger, so consideration should be given to the risk/benefit relationship when this drug is to be administered”. Therefore, the intention is to take great care during performance of this study with the followings. Sufficient warning, especially about suicide-related adverse events is to be given to the principal investigator or sub-investigator. In addition, information about adverse events, especially those relating to suicide, as well as the evaluation by C-SSRS is to be gathered, and the Safety Evaluation Committee is to assess them.

2. Study objectives

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

2.1 Primary objective

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

2.2 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 compare the plasma duloxetine concentrations at steady state obtained at 5 time points (including at least one predose level [trough]) from children and adolescent patients with depressive disorder with those of adult patients with depressive disorder.
  - To examine the potential factors that affect the pharmacokinetic properties of duloxetine (e.g., age, body weight, and sex) and their effects in the population pharmacokinetics analysis.
- 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.

3. Study plan

3.1 Study design

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 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.

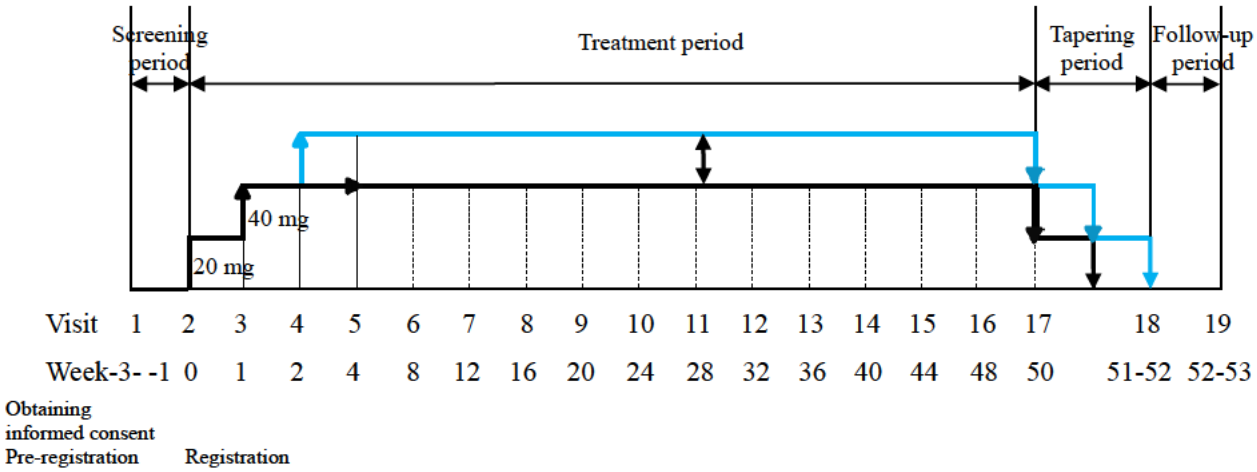
As shown below, this study will consist of the following four periods (a total of 53 to 56 weeks): screening period (1 to 3 weeks), treatment period (50 weeks), tapering period (1 to 2 weeks), and follow-up period (1 week). Note that consecutive subjects will undergo three periods (a total of 52 to 53 weeks) excluding the screening period.

Consecutive subjects will give consent to 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 to this study from Visit 2 (registration).

- Screening period (for new subjects only): After obtaining informed consent, subjects for whom eligibility is confirmed will be pre-registered (at Visit 1) and the first session of psycho-education will be provided in addition to the subjects' condition assessment.
- Treatment period: Subjects for whom eligibility is confirmed will be registered (at Visit 2) and the study drug will be administered orally, once daily after breakfast, for 50 weeks. The administration of duloxetine will be initiated at 20 mg/day, then the dose will be increased to 40 mg/day from 1 week after treatment initiation. From 2 weeks after treatment initiation, if there are no concerns about safety, the dose may be increased to 60 mg/day. Subsequently, 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.
- Tapering period: In order to minimize the occurrence of adverse events due to discontinuation of administration, a 1- to 2-week tapering period is set for subjects who complete the treatment period, or who withdraw from it during the second week or later. Subjects whose duloxetine dose at discontinuation or completion of the treatment period is 60 mg/day will receive 40 mg/day for one week then 20 mg/day for one week. If the dose at discontinuation or completion is 40 mg/day, 20 mg/day will be administered for one week.
- Follow-up period: No study drugs will be administered during the 1-week follow-up period. This period is set to enable evaluation of any adverse events during the week after completion of study drug administration, irrespective of whether or not the dose was tapered. If administration is discontinued during the treatment period, and there is then no administration during the tapering period, a 1-week follow-up period will be set after administration discontinuation.

The study design is shown in Fig. 3-1. The study schedule is shown in Appendix 1.

Fig. 3-1. Schematic diagram of study schedule



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.

3.2 Rationale for setting the study design

As in the preceding study, the planned dosing regimen in this study will be either 40 mg/day or 60 mg/day of duloxetine for 51 or 52 weeks in order to evaluate the long-term safety and efficacy of duloxetine in children and adolescent patients with depressive disorder, based on "The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions (ICH E1)" (Notification No. 592 of the Evaluation and Licensing Division, PAB dated May 24, 1995).

3.3 Study period:

3.3.1 Study period for each subject

Up to a total of 56 weeks, consisting of a 1- to 3-week screening period, a 50-week treatment period, a 1- to 2-week tapering period, and a 1-week follow-up period.

3.3.2 Scheduled period of entire study

From November 2017 to March 2021.

4. Eligibility of subjects and discontinuation of study

4.1 Study subjects

Children and adolescent patients with depressive disorder who meet all of the following inclusion criteria and do not meet any of the exclusion criteria will be included in this study.

4.2 Inclusion criteria

Subjects must meet all the following criteria:

Inclusion criteria	Consecutive subjects	New subjects
1) Have completed a 7-week treatment in the preceding study and wish to continue treatment with duloxetine.	X	
2) Have been diagnosed with depression or persistent depressive disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders, version 5 (DSM-5), and fully meet the criteria for a depressive episode. MINI-KID (version 7.0.2) is used for diagnosis of depression.		X
3) Are aged ≥9 to <18 at the time of obtaining consent and assent, and must have been ≥7 at the initial onset of depression episode. Are male or female and are hospitalized or out-patients.		X
4) Have a legal representative capable of providing written informed consent for this study. In addition, for patients aged ≥13, a written, informed assent must also be obtained from the patient him/herself. For patients aged ≥9 to <13, a written, informed assent should also be obtained from the patient him/herself if possible.	X	X
5) For post-menarchic females, a pregnancy test result must be negative at Visit 1 (or Visit 2 for consecutive subjects). In addition, the patient must agree to use one of the following contraceptive methods from Visit 1 (or Visit 2 for consecutive subjects) until 1 month after the final administration. However, this requirement does not apply to females for whom it can be confirmed in writing that 6 weeks or more has passed since bilateral ovariectomy. Estrogen- and progesterone-containing, combined-hormonal contraceptive agents with ovulation-suppressing effects (administered orally, intravaginally, subcutaneously, etc.), progesterone-containing hormonal contraceptive agents (administered orally, intravenously, by implantation, etc.), intrauterine device, intrauterine system, bilateral tubal ligation, male	X	X

Inclusion criteria	Consecutive subjects	New subjects
partner's vasectomy, or sexual abstinence.		
6) The principal investigator or sub-investigator judges that the subject's legal representative can ensure that the subject him/herself will comply with all hospital visits, tests, and other procedures stipulated in this protocol. In addition, the principal investigator or sub-investigator judges that the subject him/herself will be able to comply with all the hospital visits, tests, and other procedures stipulated in this protocol.		X
7) The principal investigator or sub-investigator judges that the subject's legal representative has sufficient comprehension and cognitive ability to communicate as appropriate with the principal investigator or sub-investigator, and other persons involved with the study. In addition, the principal investigator or sub-investigator confirms that the subject him/herself has a cognitive level appropriate to his/her age, and judges that he/she has sufficient comprehension and cognitive ability to communicate as appropriate with the principal investigator or sub-investigator, and other persons involved with the study.		X
8) Have ability to swallow the capsules without opening, crushing, dissolving, or breaking them. In addition, he/she can take up to three capsules per day.		X

4.3 Exclusion criteria

Patients who meet any of the following criteria will be excluded:

Exclusion criteria	Consecutive subjects	New subjects
1) Judged by the principal investigator or sub-investigator to have complications diagnosed as belonging to one or more of the following categories in DSM-5, or to have a history of such disorders: • Neurodevelopmental disorders • Schizophrenia-spectrum disorder or other psychotic disorders • Bipolar or related disorders • Trauma and stressor-related disorders • Disruptive, impulse–control, and conduct disorders	X	X
2) Judged by the principal investigator or sub-investigator to have complications diagnosed as belonging to one or more of the following categories in DSM-5:	X	X

Exclusion criteria	Consecutive subjects	New subjects
• Obsessive-compulsive disorder or related disorders • Anorexia nervosa, bulimia nervosa, or binge-eating disorder • Sleep-wake disorders • Neurocognitive disorders • Disruptive mood dysregulation disorder		
3) Judged by the principal investigator or sub-investigator to have a personality disorder.	X	X
4) Treatment with two or more antidepressants has previously been tried, and, despite treatment of a single depressive episode with the optimal clinical dose for 4 weeks or more, there has been no response. Alternatively, the depressive episode has been treated previously or is currently being treated with duloxetine, but without response.		X
5) The principal investigator or sub-investigator judges that systematic psychotherapy must be initiated between Visits 1 and 18.	X	X
6) One or more of the patient's parents and/or siblings has been diagnosed with bipolar disorder.	X	X
7) A history of epileptic or other convulsive attacks. However, patients with a history of febrile convulsions can be enrolled.	X	X
8) Administered electroconvulsive therapy within 1 year before Visit 1.		X
9) Uncontrolled diabetes or collagen disease.		X
10) Have initiated, changed or discontinued hormone replacement therapy within 3 months before Visit 1. Patients with thyroid dysfunction are excluded. But patients can be enrolled if they (i) have undergone thyroid hormone supplementation at a consistent dose for at least 3 months as of Visit 1; (ii) show medically appropriate thyroid hormone (TSH, FT_3, FT_4) concentrations; and (iii) have clinically normal thyroid function.		X
11) Currently have or have a history of malignant tumors/cancer.	X	X
12) For new subjects, either (i) suicidal ideation and/or suicidal attempt within 1 year before Visit 1; or (ii) at Visits 1 and 2 (or Visit 2 for consecutive subjects), answer "Yes" to questions 4 and/or 5 about suicidal ideation, and/or any of the questions about suicidal behaviors (except those about non-suicidal self-injurious behavior), on the Columbia suicide severity rating scale (C-SSRS).	X	X
13) Body weight below 20 kg at Visit 2.	X	X
14) Serious[*1] or medically unstable[*2] disease (cardiovascular disease, hepatic	X	X

Exclusion criteria	Consecutive subjects	New subjects
disease, respiratory disease, hematologic disease, endocrine disease, peripheral vascular disorder, neuropsychiatric disease, renal disease), or clinically problematic abnormal laboratory test results or abnormal electrocardiography (ECG) findings*3. *1: Grade 3 in "Concerning classification criteria for seriousness of adverse drug reactions to pharmaceutical products, etc." (Drug Safety Notification no. 80; June 29, 1992). *2: Judged by the principal investigator or sub-investigator to have the potential to disrupt study participation, or to necessitate hospitalization during the study period. *3: Judged by the principal investigator or sub-investigator to suggest serious medical problems, or to necessitate aggressive therapy.		
15) Meeting one or more of the following criteria: • At Visit 2, latest ALT or AST of 100 U/L or higher, or latest total bilirubin of 1.6 mg/dL or higher. • Latest serum creatinine level of 2.0 mg/dL or higher at Visit 2. Or have severe renal impairment, history of renal transplantation, and/or currently undergoing renal dialysis.	X	X
16) Glaucoma, elevated intraocular pressure, and/or prostatic hypertrophy or other types of dysuria.	X	X
17) Depression or depressive state due to organic brain disorder.	X	X
18) Hemorrhagic tendency or hemorrhagic diathesis.	X	X
19) Treatment with monoamine oxidase (MAO) inhibitor within 14 days before Visit 2, and/or potential for MAO inhibitor treatment during the study period or within 5 days after completion of study drug administration.	X	X
20) Hypersensitivity to duloxetine or inactive ingredients of duloxetine formulation.	X	X
21) Allergic to two or more drugs, or a history of serious allergic reactions to one or more drugs.	X	X
22) Judged by the principal investigator or sub-investigator to have the complication of substance-related and/or addictive disorders, as defined in DSM-5, or a history of such disorders. However, patients with caffeine-related disorder can be enrolled.		X
23) One or more substances of abuse (phencyclidines, benzodiazepines,		X

Exclusion criteria	Consecutive subjects	New subjects
cocaine-type drugs, stimulants, cannabis, opioids, barbiturates, tricyclic antidepressants, etc.) detected by urinary drug screening at Visit 2.		
24) Intension to travel overseas between Visit 1 (or Visit 2 for consecutive subjects) and Visit 6.	X	X
25) Pregnant* or possibly pregnant, breastfeeding, hoping to become pregnant during the study period. Or recently given birth. * Pregnancy: Pregnancy tests (blood or urine human chorionic gonadotropin) will be performed in all post-menarchic females.	X	X
26) Previously administered the study drug during participation in this study, or during participation in a different clinical study on duloxetine.		X
27) Have received another study drug within 30 days before Visit 1 or are currently receiving it.		X
28) Participation judged to be inappropriate for any other reason by the principal investigator or sub-investigator.	X	X

4.4 Screening dropouts

A subject who gives informed consent to participate in the study but is not registered in the study will be considered as a screening dropout. The following are entered in these patients' case report forms (CRFs): date of obtaining legal representative's written, informed consent; date of obtaining the patient's written assent (if applicable); demographic factors; information about meeting inclusion criteria and violating exclusion criteria; dropout date; reasons for dropping out; and adverse events leading to dropping out and serious adverse events.

4.5 Withdrawal from study or discontinuation of administration

The principal investigator or sub-investigator will as far as possibly encourage subjects to complete the study, but subjects can withdraw for any reason. The principal investigator or sub-investigator will notify the sponsor about all discontinuations. If one or more of the following is applicable, the principal investigator or sub-investigator will discontinue study drug administration to the subject, and then discontinue the study. Note that the study will be considered completed when administrations and observations up to Visit 19 are completed.

- The principal investigator or sub-investigator judges discontinuation to be necessary due to one or more serious or intolerable adverse events.
- The principal investigator or sub-investigator judges that insufficient efficacy of the study drug has resulted in aggravation of the primary disease, making discontinuation necessary.
- Pregnancy of the subject.

- The subject or his/her legal representative expresses the wish to withdraw from the study.
- The ineligibility of the subject is revealed after registration.
- Administration of duloxetine at a dose of 40 mg/day or higher is difficult at or after Visit 3.
- The subject is unable to visit hospital due to moving home, transferring to a different hospital, etc.
- Death of the subject.
- It is judged that management of abnormal hepatic function test results is necessary, as is withdrawal on the basis of the discontinuation criteria (Appendix 2).
- Discontinuation is judged by the principal investigator or sub-investigator to be necessary for any other reason.

If a subject is withdrawn, the principal investigator will promptly report the withdrawal to the sponsor, and will as far as possible perform the assessments and tests for discontinuation of the treatment period or tapering period. Subjects withdrawn during the treatment period will be transferred to the tapering period. In the case of subjects withdrawn during the tapering period, the assessments for the follow-up period will be performed. All subjects withdrawn because of adverse events will be followed up until one of the following: (i) recovery from the adverse event to the state pertaining before administration initiation; (ii) the investigator or sub-investigator judges that the symptoms have stabilized or become chronic; and (iii) it is not possible to maintain communications with the subject. In addition, the date of completion or discontinuation of the treatment period or tapering period (as applicable), and the reasons for discontinuation (if applicable), will be recorded in the CRF.

5. Treatments

5.1 Study drug

5.1.1 Investigational product

- Product name: LY248686
- Nonproprietary name: Duloxetine hydrochloride (JAN)
- Chemical name: (+)-(S)-N-methyl-3-(1-naphthyloxy)-3-(2-thienyl)propylamine monohydrochloride
- Components, content, and dosage form: Dark brown, opaque, hard capsule, packed with enteric granules, containing 20 mg of duloxetine per capsule

5.2 Dosage and regimen

All subjects will receive oral duloxetine once daily after breakfast for 51 or 52 weeks (a 50-week treatment period and 1- to 2-week tapering period) from the day after registration (Visit 2). Note that, once or twice between Visits 5 and 17, the subjects should visit the study site without taking a dose to collect a blood sample for pre-dose PK (refer to Section 7.6). Table 5-1 shows the treatment regimens for the study drug. During the treatment period, the subjects will receive duloxetine 20 mg/day for one week then 40 mg/day for one week, and subsequently receive either 40 mg/day or 60 mg/day for 48 weeks as appropriate.

Subjects who complete the treatment period or who withdraw from it during Week 2 or later of treatment period will be transferred to the tapering period. During the tapering period, subjects whose duloxetine dose at discontinuation or completion of the treatment period is 60 mg/day will receive 40 mg/day for one week then 20 mg/day for one week. Subjects whose duloxetine dose at discontinuation or completion of the treatment period is 40 mg/day will receive 20 mg/day for one week. However, tapered administration may be omitted if serious adverse drug reactions occur, there are safety-related problems, or the subject or his/her legal representative refuses the tapered administration.

Table 5-1. Treatment Regimens

Treatment period			Tapering period	
Week 1	Week 2	Weeks 3 - 50	Week 51	Week 52
20 mg/day	40 mg/day	60 mg/day	40 mg/day	20 mg/day
1 x 20 mg LY248686 capsule	2 x 20 mg LY248686 capsule	3 x 20 mg LY248686 capsule	2 x 20 mg LY248686 capsule	1 x 20 mg LY248686 capsule
		40 mg/day	20 mg/day	-
		2 x 20 mg LY248686 capsule	1 x 20 mg LY248686 capsule	-

5.3 Selection of dose and timing of administration for each subject

During Weeks 3 to 50 of the treatment period, the subjects will receive duloxetine 40 mg/day or 60 mg/day for 48 weeks depending on symptoms. As described in Section 5.2 , the tapering period will be 1 or 2 weeks based on the dose at discontinuation or completion of the treatment period.

5.4 Allocation method for each subject

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

5.5 Blinding

This study is an open-label study in which no one is blinded.

5.6 Packaging and labeling

One Press Through Package (PTP) sheet contains 10 capsules of the study drug (LY248686 20 mg) and a box contains 10 PTP sheets. Each study drug box is labeled with the investigational material development number (LY248686), manufacturing number, expiration date, storage condition, a statement that it is for investigational use, and the sponsor's name and address.

5.7 Storage and management of study drug

LY248686 should be stored in a tight container at room temperature.

The sponsor will supply the study drug to the study drug manager designated by the director of the study site, in accordance with the contract between the sponsor and the study site. The study drug manager will store/manage the study drug according to the separately prepared procedures for handling/storage/management of the study drug, and record the use of study drug.

5.8 Study drug management at the study site

Unused study drug does not have to be stored under the conditions stipulated in this protocol, but all such materials will be stored at the study site. The study drug manager will accurately record the amount of unused study drug at study completion, place all unused study drug in appropriate boxes, and return it to the sponsor together with a photocopy of the study drug management table.

5.9 Treatment compliance

At each study site visit, the subjects should return unused study drugs to the study site. The investigator or sub-investigator will confirm treatment compliance, ascertaining the exact amount of the drug taken since the previous visit. At each visit, the duration of study drug administration, dosage, and a number of unused capsules will be entered in the CRF. If the prescription is changed, the change of prescription and its reason should also be entered. If unused study drug is found when checking the treatment compliance, the investigator or sub-investigator will instruct the subject about the importance of treatment compliance.

The subject is taken to be noncompliant when, since the previous visit, the proportion of days on which the drug has not been taken as stipulated exceeds 30%. On the other hand, if the drug taken exceeds the stipulated dose on even one occasion, this is taken to constitute noncompliance, and a Special Situations Report is submitted to the sponsor.

6. Restrictions on subjects

6.1 Prior treatment (prior drugs/therapies)

For new subjects, a treatment received prior to the observation of Visit 1 will be considered as a prior treatment (prior drug/therapy). The restrictions on prior treatment are stipulated in Section 4.3 .

For all depression treatments performed for new subjects within 2 weeks before Visit 1, including ethical drugs, over-the-counter drugs, and non-pharmaceutical therapies, the name of the drug or therapy, dosage, administration route, and duration of treatment will be recorded in the CRF. For consecutive subjects, the prior treatment will be based on the information obtained in the CRF of the preceding study.

6.2 Treatment during study treatment period (concomitant drugs/therapies)

Concomitant treatments (concomitant drugs/therapies) will include treatments performed after the observation at Visit 1 (or after completing the observation at the completion of the tapering period in the preceding study for consecutive subjects).

The investigator or sub-investigator will record in the CRF the following information about treatments (ethical drugs, over-the-counter drugs, and non-pharmaceutical therapies) administered to the relevant subject between Visit 1 (or after completing the observation at the completion of the tapering period in the preceding study for consecutive subjects) and Visit 19 (completion of the follow-up period):

- Name of the concomitant drug or non-pharmaceutical therapy
- Administration route
- Occurrence or non-occurrence of dosage changes, and whether use is as-needed basis or not
- Duration of treatment
- Reasons for use

However, the following drugs do not have to be recorded in the CRF unless they are the cause of adverse events:

- Drugs for diluting solutions, such as physiological saline solution
- Drugs used in medical procedures, etc., with the drug itself not being for treatment, such as alcohol disinfection, and heparin lock.
- Items that are not recognized as drugs, such as foods. However, health foods, etc., with ingredient of contraindicated drugs or restricted drugs have to be recorded in the CRF.
- Fluid replacement or infusion solution, unless used to treat adverse events.
- Drugs used for tests, such as contrast agents and pre- and post-medication

6.2.1 Prohibited drugs and therapies:

Use of the below drugs, or over-the-counter drugs with equivalent effects, is prohibited from Visit 1 (or after completing the observation at the completion of the tapering period in the preceding study for consecutive subjects) through to Visit 18 (completion of the tapering period):

Prohibited drugs that may affect therapeutic evaluation:

1) Antidepressants

2) Anxiolytics
3) Soporific agents, other than the "Permitted soporific agents" in Section 6.2.2
4) Antipsychotics
5) Antiparkinsonian agents
6) Anticonvulsants
7) Mood-stabilizers (lithium carbonate, carbamazepine, sodium valproate)
8) Psychostimulants
9) Adrenal corticosteroids (excluding topical agents, such as ear drops, nose drops, eye drops, topical skin formulations, and inhaled formulations).
10) Interferon formulations
11) Any of the following drugs, which might affect the metabolic/agonistic activities of serotonin or noradrenaline:

    Cyproheptadine hydrochloride (Periactin®, etc.)
    Dimetotiazine mesilate (Migristene®)
    Ifenprodil tartrate (Cerocral®, etc.)
    5-HT_3 inhibitors (Zofran®, etc.)
    5-HT_4 stimulants (Gasmotin®, etc.)
    5-$HT_{1B/1D}$ receptor agonists (Imigran®, etc.)
    Adrenergic agents (Noradrenaline®, etc.)
12) St. John's wort
13) Chinese herbal medicines administered to treat central nervous conditions such as insomnia, neurosis or anxiety.
14) Other agents judged to act on the central nervous system, and thus affect therapeutic evaluation.

Prohibited drugs that present safety-related problems:

1) MAO inhibitors (FP®, Azilect®, etc.)

   **Administration of these is contraindicated from 14 days before Visit 2 (or after completing the observation at the completion of the tapering period in the preceding study for consecutive subjects) until 5 days after completion of study drug administration.
2) Other investigational drugs

Unless specifically stated otherwise, use of the following treatments is contraindicated from Visit 1 (or after completing the observation at the completion of the tapering period in the preceding study for consecutive subjects) through to Visit 18 (completion of the tapering period):

1) Electroconvulsive therapy
2) Bright-light therapy, i.e. therapy using irradiation devices approved as medical devices.
3) Systematic psychotherapy, such as systematically organized cognitive therapy, cognitive behavioral therapy, and interpersonal psychotherapy. For new subjects, this study will use

educational tools, consistently in all institutions, for the psycho-education of subjects and guardians.

4) Exercise therapy
5) Hormone therapy is contraindicated. However, in accordance with exclusion criterion 10, treatment can be continued at the same dose with thyroid dysfunction patients show meet the following three criteria: (i) having undergone thyroid hormone supplementation for at least 3 months as of Visit 1 (or Visit 2 for consecutive subjects); (ii) showing medically appropriate concentrations of thyroid hormones (TSH, FT_3 and FT_4); and (iii) having attained a clinically normal state of thyroid function.

6.2.2 Restricted drugs and therapies

The following permitted soporific agents and restricted drugs and therapies may only be used under the stipulated conditions from Visit 1 (or after completing the observation at the completion of the tapering period in the preceding study for consecutive subjects) to Visit 18 (completion of the tapering period):

Permitted soporific agents:

The following soporific agent may be used in subjects aged ≥15:

Ramelteon (Rozerem ®)

Restricted drugs:

Antihistamine agents (e.g. pseudoephedrine, diphenhydramine) and commercially available drugs containing antihistamine agents should only be used 12 hours or more before CDRS-R or Clinical Global Impression of Severity (CGI-S) evaluation (except in the case of topical agents, such as ear drops, nose drops, eye drops, topical skin formulations, and inhaled formulations).

If antihistamine agents or commercially available drugs containing antihistamine agents are used, the time of use is confirmed with the subject, and at least 12 hours is allowed to pass after use of these drugs before the CDRS-R or CGI-S evaluation.

6.2.3 Drugs with which care required

Sufficient care about subjects' safety should be taken when using any of the following drugs between Visit 1 (or after completing the observation at the completion of the tapering period in the preceding study for consecutive subjects) and Visit 18 (completion of the tapering period):

1) Hypotensive agents (central sympathetic suppressors), such as clonidine hydrochloride.
2) Drugs with high protein-binding rates, such as warfarin potassium and clofibrate
3) CYP1A2-inhibitors, such as cimetidine.
4) CYP2D6-inhibitors and substrates, such as quinidine sulfate®, Pronon tablets®, and Tambocor tablets®
5) Formulations containing serotonin precursors such as L-tryptophan and 5-hydroxytryptophan
6) Tramadol
7) Linezolid
8) Nonsteroidal anti-inflammatory drugs

9) Pimozide
10) Alcohol
11) Ciprofloxacin
12) Triptan-based agents
13) Methylene blue

6.3 Other restrictions

It will be explained to subjects that they should comply with the following points from Visit 1 (or after completing the observation at the completion of the tapering period in the preceding study for consecutive subjects) to Visit 18 (completion of tapering period):

1) If an over-the-counter drug is to be taken, obtain approval by the investigator or sub-investigator first.
2) Do not drink alcohol.
3) Do not operate potentially dangerous machinery.
4) Use contraception (in the case of post-menarchic females only).

It will be explained to subjects that they should comply with the following points after completion of study drug administration:

1) MAO inhibitor should not be used within 5 days of completion of dosing of the study drug.
2) Use reliable contraception until 1 month after completion of study drug administration (in the case of post-menarchic females only).

7. Study procedures and evaluation methods

The performance times are shown in Appendix 1.

7.1 Obtaining informed consent

The principal investigator or sub-investigator will give a sufficient explanation about the details of this study to subjects and their legal representatives, using informed consent explanatory documents and assent documents approved by the Institutional Review Board (IRB), and will obtain written, informed consent from the legal representatives before initiation of the study. Subjects will be given explanations about the details and duration of the study, using information, words and technical terms appropriate to their comprehension ability, and signatures on assent forms will be obtained from those aged ≥13. Written assent will also be obtained from subjects <13 years old if possible, but oral assent is acceptable if obtaining written assent is difficult. Each subject's legal representative will, after signing the informed consent form, enter a statement that written or oral assent has been obtained from the subject. Photocopies of the signed or sealed informed consent form and assent form will be provided to the relevant subject or his/her legal representative, and the principal investigator will store the original. Informed consent must be obtained from all subjects' legal representatives. Subjects can be enrolled in this study once their legal representatives have signed or sealed the informed consent forms. The following will be entered in the patients' case report forms (CRFs): date of obtaining legal representative's written, informed consent; and date of obtaining the patient's written assent (if applicable).

The principal investigator or sub-investigator must enable the subject and his/her legal representative to understand the risks and benefits associated with participation in the study, not only when giving an explanation before study initiation, but also in response to questions from the subject or his/her legal representative at any time during the study. If any information that may affect the wish of a subject and/or his legal representative to continue with study participation is obtained during the study, this information must be promptly explained to the subject and his/her legal representative.

7.2 Confirmation of demographic factors and medical history

(1) Baseline subject characteristic and medical history

For new subjects, the following baseline subject characteristics will be obtained at Visit 1 and entered in the CRF: date of birth; sex; height; ethnicity; race; hospitalization status; history of current condition (age at onset of depression, number of depressive episodes to date, timing of onset of current episode); disease category according to DSM-5; and medical history. As to medical history, important aspects of medical history necessitating hospitalization and/or surgery, all complications continuing as of the time of obtaining informed consent, and surgical history are determined.

For consecutive subjects, the baseline subject characteristics and medical history will be based on the information obtained in the CRF of the preceding study.

(2) Urinary drug screening

For new subjects, urinary drug tests will be performed at Visit 2, and the presence or absence of substances of abuse (phencyclidine, benzodiazepines, cocaine-type drugs, stimulants, cannabis, opioids, barbiturates, tricyclic antidepressants, etc.) will be determined.

7.3 Registration of subjects and prescription of study drug

After confirming the eligibility of subjects on the basis of the inclusion and exclusion criteria, the principal investigator, sub-investigator, or study collaborators will enter the necessary information in Electronic Data Capture (EDC) then pre-register and register subjects at Visits 1 (new subjects only) and 2, respectively. After enrolling subjects in the study, the principal investigator, sub-investigator, or study drug manager will prescribe the study drug in accordance with the stipulations in Section 5.

7.4 Psycho-education

Fundamental psycho-education about depression treatment will be provided systematically, with the same contents, to new subjects only (consecutive subjects have taken the sessions in the preceding study). The principal investigator, sub-investigator, or clinical psychologist will hold sessions with the subjects and guardians at Visits 1, 2, 5, and 6. Psycho-education is provided after evaluation of CDRS-R and CGI-S. At each session, the subjects and guardians will watch a DVD, followed by a question and answer session with the principal investigator or sub-investigator, and a clinical psychologist or similar. The session date and name will be recorded in the CRF. The details of the psycho-education are stipulated in a separately specified procedures.

7.5 Efficacy evaluation

7.5.1 Children's Depression Rating Scale-Revised (CDRS-R)

At Visits 1 (or Visit 2 for consecutive subjects) to 17 (or at discontinuation of treatment), the severity of symptoms for the below 17 items will be judged using CDRS-R (Table 7-1). The date and results of evaluation will be recorded in the CRF. At discontinuation of treatment, evaluation will be performed if possible, and recorded in the CRF.

Table 7-1. Children's Depression Rating Scale-Revised

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

7.5.2 Clinical Global Impression of Severity (CGI-S)

At Visits 1 (or Visit 2 for consecutive subjects) to 17 (or at discontinuation of treatment), the principal investigator or sub-investigator will evaluate the disease severity in terms of the below grades 1 to 7. The date and results of evaluation will be recorded in the CRF. At discontinuation of treatment, evaluation will be performed if possible, and recorded in the CRF.

1. Normal / no disease
2. Bordering on disease
3. Mild disease
4. Moderate disease
5. Marked disease
6. Severe disease
7. Extremely severe disease

7.6 Pharmacokinetic evaluation

Random blood samples for quantitation of plasma concentrations of duloxetine will be collected from all subjects five times between Visit 5 and the completion of study drug administration during the treatment period. Note that, for one or two of the five collections, subjects should visit the study site without taking the study drug to collect pre-dose blood samples. If the dose is increased or decreased, blood samples should be collected at least 2 weeks after the dose adjustment. The date and time of blood collection and the date and time of the last dose of study drug prior to blood collection will be recorded in the CRF.

A 2 mL blood sample will be collected in a heparin containing tube and should be centrifuged at 3,000 x g for 15 minutes at room temperature or 4°C within 30 minutes after collection. The separated blood plasma will be dispensed into two polypropylene tubes at approximately 0.3 mL each and stored at −20°C or below. Samples will be collected by [redacted] (refer to Section 7.7.6.2).

[redacted] will store samples (0.3 mL each) at −20°C or below and send to the drug concentration laboratory ([redacted]) with dry ice.

The drug concentration laboratory will analyze the plasma samples within 13 months after collection.

[redacted]

7.7 Safety evaluation

7.7.1 Physical examination

At Visits 1 (or Visit 2 for consecutive subjects) to 18 (or discontinuation of the treatment or tapering period) and Visit 19, the principal investigator or sub-investigator will examine the subject by the standard methods in use at the relevant institution, and will ascertain the occurrence or non-occurrence of adverse events. When an adverse event is found, the details will be recorded in the CRF. If necessary, examination appropriate to the signs and symptoms will also be performed, as judged appropriate by a physician. For 2 weeks after the initial administration of the study drug, the subject's progression will be monitored with special care.

7.7.2 Columbia Suicide Severity Rating Scale (C-SSRS)

At Visits 1 (or Visit 2 for consecutive subjects) to 18 (or discontinuation of the treatment or tapering period), the principal investigator or sub-investigator will evaluate suicidal thinking using a questionnaire. For consecutive subjects, a measurement at Visit 9 in the preceding study may be used as a measurement at Visit 2 of this study. The date and results of evaluation will be recorded in the CRF. The principal investigator or sub-investigator will judge whether any abnormal change from baseline (Visit 2) is clinically significant (refer to Section 7.7.7.7) and will record any changes judged to be clinically significant as adverse events.

7.7.3 Body weight

Body weight (kg) will be measured at Visits 2, 5, 8, 11, 14, 17 (or at discontinuation of the treatment period) and Visit 18 (or at discontinuation of the tapering period). For consecutive subjects, a measurement at Visit 9 in the preceding study may be used as a measurement at Visit 2 of this study. The date and result of measurement will be recorded in the CRF. The principal investigator or sub-investigator will judge whether any abnormal change from baseline (Visit 2) is clinically significant (refer to Section 7.7.7.7) and will record any changes judged to be clinically significant as adverse events.

7.7.4 Blood pressure and pulse rate

The blood pressure (systolic and diastolic) and pulse rate, at rest, will be measured at Visits 1 (new subjects only), 2, 5, 8, 11, 14, 17 (or at discontinuation of the treatment period) and Visit 18 (or at discontinuation of the tapering period). For consecutive subjects, a measurement at Visit 9 in the preceding study may be used as a measurement at Visit 2 of this study. The date and result of measurement will be recorded in the CRF. The principal investigator or sub-investigator will judge whether any abnormal change from baseline (Visit 2) is clinically significant (refer to Section 7.7.7.7) and will record any changes judged to be clinically significant as adverse events.

7.7.5 Electrocardiogram

Standard, 12-lead electrocardiogram (ECG) will be performed at Visits 1 (or Visit 2 for consecutive subjects), 5, 11, and 18 (or at discontinuation of the tapering period; if not transferred to the tapering period, at completion or discontinuation [Visit 17] of the treatment period). For consecutive subjects, a measurement at Visit 9 in the preceding study may be used as a measurement at Visit 2 of this study. The principal investigator or sub-investigator will judge whether ECG results are normal or abnormal, and will record the date of ECG, the judgment, and any abnormal findings in the CRF.

If there are abnormal findings, the principal investigator or sub-investigator will judge whether the abnormal change from baseline (i.e., Visit 1 for new subjects or Visit 2 for consecutive subjects) is clinically significant (refer to Section 7.7.7.7), and will record any changes judged to be clinically significant as adverse events.

7.7.6 Laboratory tests

7.7.6.1 Laboratory test items

At Visits 1 (or Visit 2 for consecutive subjects), 5, 8, 11, 14, and 18 (or at discontinuation of the tapering period; if not transferred to the tapering period, at completion or discontinuation [Visit 17] of the treatment period), blood samples will be collected for laboratory tests, the volumes being 2 mL for hematology tests, and 8 mL and 5 mL for blood chemistry tests, at Visit 1 and other visits, respectively; and urine samples will also be collected. The samples will then be sent to the clinical laboratory facility specified in Section 7.7.6.2 . Details of the collection, handling, storage, and shipment of samples are stipulated in a separate document. For new subjects, blood samples and urine samples at Visit 1 will be collected after obtaining informed consent, between 3 weeks before the initial administration of the study drug and Visit 2. For consecutive subjects, a measurement at Visit 9 in the preceding study may be used as a measurement at Visit 2 of this study. Both new subjects and consecutive subjects will be registered after the latest measurements at Visit 2 are confirmed.

The principal investigator or sub-investigator will judge whether the abnormal change from baseline (i.e., Visit 1 for new subjects or Visit 2 for consecutive subjects) is clinically significant (refer to Section 7.7.7.7), and will record any changes judged to be clinically significant as adverse events. The sample collection dates will be recorded in the CRF for each sample type (blood or urine).

7.7.6.1.1 Routine tests

Table 7-2 shows the routine hematology test, blood chemistry test, and urinalysis parameters.

Table 7-2. Routine laboratory tests

Classification	Parameter
Hematology	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, HbA1c[a], TSH[a], $FT3_3$[a], $FT4_4$[a]
Urinalysis (qualitative)	Urinary protein, urinary glucose, urobilinogen, urinary occult blood

a For new subjects, measurements will be obtained at Visit 1 only.

7.7.6.1.2 Pregnancy test

Pregnancy will be determined by the test for human chorionic gonadotropin (HCG) in urine or serum (only with post-menarchic females) at Visits 1 (or Visit 2 for consecutive subjects) and 18 (or at discontinuation of the tapering period; if not transferred to the tapering period, at completion or discontinuation of the treatment period [Visit 17]). For consecutive subjects, a measurement at Visit 9 in the preceding study may be used as a measurement at Visit 2 of this study.

7.7.6.2 Methods for collection, storage, and shipment of samples

An principal investigator, sub-investigator, nurse, or medical technician will collect blood and urine samples at the stipulated times, and send them to the below clinical laboratory facility. Details of the collection, handling, storage, and shipment of samples are specified in a separate document.

7.7.7 Evaluation of adverse events

7.7.7.1 Evaluation methods for adverse events

An adverse event is any unfavorable medical event suffered by someone administered a pharmaceutical product (including a study drug) and does not necessarily have a causal relationship with the relevant pharmaceutical product. In other words, an adverse event is any unfavorable and/or unexpected sign (including abnormal laboratory test result), symptom, or disease associated with the administration of a drug, irrespective of any causal relationship with that drug. Surgery that was already planned is not considered to be an adverse event, unless it leads to exacerbation of an existing disease, and is therefore not considered to be a serious adverse event even if it necessitates hospitalization. However, if an additional surgery is performed in connection with the planned surgery, this is taken to be an adverse event, and to be a serious adverse event if prolongation of hospitalization is required, or if any other criterion for being a serious adverse event is met. Hospitalization or prolongation of hospitalization for reasons other than adverse events is not considered to constitute a serious adverse event.

The presence or absence of an adverse event will be confirmed on the basis of the subject's spontaneous complaint, non-inductive questions, examination, C-SSRS, blood pressure, pulse rate, body weight, and ECG or laboratory test results. Adverse events include new onset of an event, increase in the severity or frequency of an event since administration initiation, and diagnostic abnormality, including abnormal laboratory test results. A symptom recorded as a medical history at study initiation will be handled as an adverse event only when symptoms are aggravated. In addition, loss of efficacy, and changes in the primary disease (depression) or scores for any of the CDRS-R items, will not be handled as adverse events in this study, unless judged to be serious adverse events.

The principal investigator or sub-investigator will evaluate adverse events. The principal investigator or sub-investigator will carefully investigate each adverse event, and record in the CRF the date of onset, time of onset, date of cessation (if the outcome is recovery or death), severity, seriousness (including the reason for judging seriousness), causal relationship with the study drug, actions taken for the adverse event, and outcome of the adverse event.

7.7.7.2 Assessment period

Adverse events occurring between obtaining the legal representative's informed consent (for new subjects) or initiation of study drug administration in this study (for consecutive subjects) and 7 days after the final administration of study drug (the follow-up period) as well as adverse events consecutive from the preceding study at the initiation of study drug administration in this study (only if applicable) will be assessed. For consecutive subjects, adverse events that occurred between obtaining informed consent for this study and initiation of study drug administration in this study will be assessed in the preceding study. In the case of withdrawn subjects, the principal investigator or sub-investigator will assess adverse events up to 7 days after final administration of the study drug. Appropriate follow-up will be continued until one of the following, and the outcome will be determined on that basis: (i) the relevant adverse event recovers to the pre-administration state (if consecutive from the preceding study, it should be recovered to the pre-administration of the preceding study); (ii) the subject's condition stabilizes or becomes chronic; (iii) the subject is lost to follow-up; or (iv) the principal investigator or sub-investigator judges further assessment to be unnecessary. In addition, if the subject stops visiting hospital during the study, he/she will be followed up by an appropriate method such as by telephone, and the findings will be entered in the CRF.

If the above adverse event follow-up has to be continued for 28 days or more after completion of administration, the outcome at the earliest date after 28 days after completion of administration will be recorded in the CRF.

7.7.7.3 Severity

The principal investigator or sub-investigator will judge the severity of adverse events in accordance with the below definitions. The highest severity of each event during its period of occurrence will be recorded as the severity in the CRF.

- Mild: Signs or symptoms are found, but activities of daily life are not disturbed.
- Moderate: Activities of daily life are disturbed due to discomfort, and/or abnormality is clinically demonstrated.
- Severe: Activities of daily life are impossible, and/or major clinical effects are demonstrated.

7.7.7.4 Causal relationship with study drug

The principal investigator or sub-investigator will judge the causal relationship with the study drug in accordance with the following criteria:

- Not related: The adverse event can be clearly explained by a factor other than the study drug, and/or there is no valid chronological relationship between the study drug and the adverse event.
- Possibly related: The adverse event may have been caused by a factor other than the study drug, but a causal relationship with the study drug cannot be ruled out.

- Probably related: It is unlikely that the adverse event was caused by a factor other than the study drug.
- Related: There is a valid chronological relationship between administration of the study drug and onset of the adverse event, and the event cannot be explained by a factor other than the study drug

Adverse events judged to be “Possibly related”, “Probably related” or “Related” are taken to be adverse drug reactions.

7.7.7.5 Predictable adverse drug reactions

Adverse drug reactions listed in the most recent investigator’s brochure for duloxetine, or in any reports about adverse drug reactions submitted separately to the IRB, study site, or the principal investigator, are taken to be predictable adverse drug reactions.

7.7.7.6 Adverse events of special concern

7.7.7.6.1 Suicide-related adverse events

The duloxetine package insert, includes, as drug-class labeling, the following requirement to take great care: “There have been reports of increases in the risks of suicidal ideation and suicidal planning in patients aged under 24 administered antidepressants, so consideration should be given to the risk/benefit relationship when this drug is to be administered”. Therefore, the principal investigator or sub-investigator will evaluate any suicidal thinking using the C-SSRS questionnaire, as detailed in Section 7.7.2 , and will record any suicide-related adverse events.

The principal investigator or sub-investigator will perform sufficient monitoring of subjects who suffer from adverse events that are clearly or possibly suicide-related.

If a subject suffers a suicide-related adverse event, and/or if requested by the sponsor, the principal investigator will report the details of the relevant adverse event to the sponsor, by fax, email or telephone, or orally. After the sponsor has received the relevant information, he/she will promptly request the Safety Evaluation Committee to perform a review. If necessary, the sponsor can also request the principal investigator to provide additional information.

7.7.7.7 Adverse events such as laboratory test results

The principal investigator or sub-investigator will judge whether or not any changes from the baseline by laboratory test results (hematology, blood chemistry, and urinalysis) and abnormalities in other safety endpoints (e.g. examination findings, body weight, blood pressure, pulse rate, ECG findings) are clinically significant. Laboratory test results that deviate from the reference range will be handled as abnormal values.

If a baseline value is abnormal, but worsens after study initiation, the principal investigator or sub-investigator will judge whether or not this is clinically significant. Events judged by the principal investigator or sub-investigator to be clinically significant will be recorded as adverse events. When an

abnormal test result is accompanied by disease or other toxicity, the disease name and/or details of toxicity will be reported as an adverse event.

An event will be considered clinically significant if one or more of the following criteria is met, and judgment about clinical significance in other situations will be at the discretion of the principal investigator or sub-investigator:

- The criterion for a serious adverse event is met (refer to Section 7.7.7.8).
- Study drug discontinuation or dose reduction is required.
- Drug administration or another procedure is required for treatment.
- An additional test or other medical procedure is required.
- Management of abnormal hepatic function test results is necessary, and the discontinuation criteria (Appendix 2) are met.

If management of abnormal hepatic function test results is necessary, and the discontinuation criteria (Appendix 2) are met, evaluation and additional assessment will be performed, and records will be made in the follow-up assessment form for abnormal hepatic function.

7.7.7.8 Serious adverse events

7.7.7.8.1 Definition

Of the adverse events observed after study initiation, an adverse event meeting one or more of the following criteria will be handled as a serious adverse event:

- Leading to death.
- Life-threatening.
- Requiring hospitalization or prolongation of hospitalization.
- Leading to permanent and/or significant disability or dysfunction (according to the opinion of the reporting physician).
- Leading to congenital anomaly.
- Other medically major event.

If an adverse event exposes a subject to danger, or requires medical procedures to prevent one of the results defined above, even if the event does not lead to death, is not life-threatening, and does not require hospitalization, it will be handled as a serious adverse event on the basis of appropriate medical judgment. For example, bronchial asthma which requires intensive therapy at emergency department, etc., vascular disorder or convulsion not requiring hospitalization, drug dependency or abuse are included. In addition, all events meeting the below criterion are taken to be serious adverse events. The principal investigator or sub-investigator will judge the seriousness of adverse events.

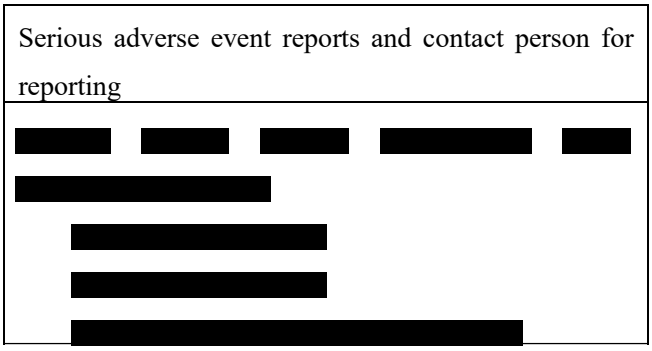
- AST and/or ALT >3 times the upper limit of the respective reference values, and total bilirubin >2 times the upper limit of the reference values.

7.7.7.8.2 Reports of serious adverse events

The principal investigator will report the details of all serious adverse events to the sponsor, using the

serious adverse event report form, within 24 hours after the relevant events are judged to be serious. All serious adverse events will be reported, irrespective of the causal relationship with the study drug. The sponsor can also request additional information about serious adverse events.

As far as possible, the principal investigator will report all serious adverse events using the diagnostic names. If the diagnostic name has not been fixed at the time of reporting, the report will state the individual signs and symptoms.



If the sponsor judges follow-up to be necessary, the principal investigator will report to the above contact person by fax or email, using a serious adverse event form, and will provide any new information to the sponsor. The principal investigator will evaluate photocopies of relevant documents, such as discharge summaries, medical records from other departments and institutions, and autopsy reports, and will include any relevant information in a supplementary serious adverse event report. The sponsor can also request photocopies of such reports.

The principal investigator will establish appropriate measures for medical treatment of serious adverse events, on the basis of medical judgment. Measures taken with serious adverse events, and their results, will be recorded. The principal investigator will establish the necessary measures, and will also elucidate the causes of serious adverse events as far as possible.

If a serious adverse event during or after the assessment period stipulated in Section 7.7.7.2 is judged by the principal investigator to have a causal relationship with study drug, he will report it to the sponsor.

The principal investigator will also report all serious adverse events to the IRB in accordance with the regulatory requirements. The sponsor will report all reported serious adverse events to the regulatory authority, in accordance with the regulatory requirements.

7.7.7.9 Abuse, misuse, overdose, and medication error (special situations)

In the event of abuse, misuse, overdose, or medication error associated with the study drug (special situations), as defined below, the principal investigator will promptly report it to the sponsor by fax or email, using the form stipulated by the sponsor (Special Situation Report Form). The principal investigator will also submit reports to the sponsor about any serious adverse events associated with the special situation.

- Abuse: Intentional overdose of the study drug, associated with adverse physical or mental effects,

irrespective of whether this is continuous or sporadic.

- Misuse: Inappropriate use of the study drug at doses other than those instructed or on the label, intentionally by the subject.
- Overdose: Accidental or intentional use of the study drug at a dose exceeding that prescribed.
- Medication error: An accidental medication error, including cases that have been prevented from occurring, during the process of prescription, dispensing or administration. A medication error due to the subject forgetting to take one or more doses is not reportable.

7.7.7.10 Pregnancy

The principal investigator or sub-investigator will instruct female subjects that, if they become pregnant during the study, they must stop taking the study drug, and immediately inform the principal investigator or sub-investigator. If a subject is found to be pregnant, the principal investigator or sub-investigator will withdraw her form the study. Information about the pregnancy will be reported to the sponsor as detailed below.

For all pregnancies that occur between initiation of study drug administration and completion of the follow-up period, the principal investigator will send a pregnancy follow-up report to the sponsor by fax or email within 24 hours after the pregnancy comes to light. Pregnancy complications and terminations for medical reasons will be reported appropriately, as adverse events or serious adverse events. Miscarriages will be reported as serious adverse events. In addition, pregnancies will be followed, and pregnancy follow-up reports will be submitted to the sponsor by fax or email. Even after completion of the follow-up period, if a pregnancy comes to light within 1 month after the final study drug administration, the study site will report it to the sponsor. At completion of pregnancy, by birth, miscarriage or termination, the outcome will be reported to the sponsor.

7.7.7.11 Adverse events during study drug administration

Adverse events with onset after the initial study drug administration are taken to be treatment-emergent adverse events (TEAE). For consecutive subjects, of adverse events consecutive from the preceding study at initiation of study drug administration in this study, adverse events that started after initiation of study drug administration in the preceding study are also taken to be TEAEs of this study.

7.8 Appropriateness of test items

Efficacy endpoints chosen in this study are similar to those in the preceding study in order to study and examine various aspects of long-term efficacy.

Safety endpoints chosen in this study are also similar to that in the preceding study.

7.9 Permitted range of test times

Examination, observation and tests will be performed in accordance with Appendix 1. If performance at the date and time shown in Appendix 1 is impossible, for unavoidable reasons, performance within the

permitted range shown in Table 7-3 will be acceptable. Data collected outside the permitted range will be taken to be missing for that visit. When the dose is to be increased from 20 to 40 mg/day, or from 40 to 60 mg/day for the first time, the pre-increase dose must be administered for at least 7 days.

Table 7-3. Permitted range of time of examinations, observations and tests

	Visit	Week	Stipulated date of visit	Permitted range (days)	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 administration in treatment period	+3	-
Tapering period	18	51 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 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	-	Final administration in tapering period	+3	-
Follow-up period	19	52 to 53	On day 7 or later, taking the final administration date to be day 0.		-

8. Statistical analysis

8.1 Statistical analysis methods

The sponsor will commission a contract organization to perform the statistical analysis. The sponsor will perform the pharmacokinetic analysis. The details of the analysis will be stipulated in the "Statistical analysis plan" and "Pharmacokinetic analysis plan", which will be prepared on the basis of this section. When any change is made to the analysis planned in the protocol, reason for a change will be specified in the statistical analysis plan or pharmacokinetic analysis plan without fail.

Number of subjects, arithmetic mean, standard deviation, minimum, median, and maximum will be calculated as summary statistics for the items measured by continuous data in principle. Number of subjects and proportion of each category will be calculated as summary statistics for the items measured by discrete value.

Level of significance at 0.05 (two-sided) will be used for statistical tests in this study unless otherwise specified. There will be no multiplicity adjustment for the statistical tests.

SAS of Version 9.2 or higher will be used for all analyses and for creation of tables.

8.2 Target number of subjects

The target number of subjects is set as at least 100 subjects to collect data from, who receive duloxetine for one year. Assuming that 25% of subjects dropout from this study, the target total number of registered subjects is 135, including consecutive subjects and new subjects. Blood samples for plasma drug concentration measurements will be collected five times for each subject to evaluate the pharmacokinetics in Japanese children and adolescent patients with depressive disorder.

8.3 Analysis sets

The following analysis sets are defined:

(1) Full-analysis set (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.

(2) Safety-analysis set

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

(3) Pharmacokinetic analysis set

This comprises all subjects to whom the study drug is administered at least once and the plasma duloxetine concentration is measured at least once. The pharmacokinetic analysis set will be used for preparing and summarizing the list of drug concentrations.

8.4 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.

8.5 Subject characteristics

Of the subjects registered, the number and proportion who complete the study, and the number and proportion withdrawn will be summarized. In addition, the reasons for withdrawal will be summarized. The number and proportion of subjects included in each analysis set will also be shown.

8.6 Demographic and baseline characteristics

The summary statistics will be used to summarize the demographic and baseline characteristics of the safety analysis set.

8.7 Study drug administration period, dosage, and treatment compliance

The study drug administration period, administration rate, and total dose will be summarized on the safety analysis set.

8.8 Prior treatment

Drugs used in prior treatment will be coded for using the WHO Drug Dictionary. With the safety analysis set, the subjects who received prior treatment will be tabulated.

8.9 Concomitant treatment

Drugs used in concomitant treatment will be coded for using the WHO Drug Dictionary. For the safety analysis set, the subjects who receive concomitant therapy will be tabulated.

8.10 Analysis of efficacy

The summary statistics will be calculated using the FAS for the observed efficacy endpoints (CDRS-R total score and CGI-S) and their changes from baseline at each time-point after study drug administration. The baseline for each endpoint is defined as the subject's initiation of this study (Visit 2). Changes from the start of the preceding study will be summarized similarly by treatment group in the preceding study.

8.11 Safety analysis

Safety analysis will be conducted on the safety analysis sets.

8.11.1 Adverse events

Adverse events will be classified by system organ class and preferred term, in accordance with MedDRA. Of the adverse events reported using CRFs, TEAEs will be used for safety analysis. TEAEs are defined in Section 7.7.7.11 .

The number of subjects suffering TEAEs, and the numbers suffering death, other serious TEAEs, TEAEs leading to discontinuation of administration, and TEAEs leading to dose reduction will be determined. The TEAE rate and 95% confidence interval will be calculated by the Clopper-Pearson method. The number

of adverse events will also be included. Adverse drug reactions will be summarized in the same manner as TEAEs. Adverse drug reactions are defined in Section 7.7.7.4 .

As summarization of TEAEs by system organ class and preferred term, the number and proportion of subjects suffering these events will be shown. In addition, TEAEs will be summarized by severity, onset timing, and outcome. Adverse drug reactions will be summarized similarly.

8.11.2 Blood pressure, pulse rate, and body weight

Summary statistics will be calculated for the measurements and change from baseline at each time-point. The baseline is defined as the subject's initiation of this study (Visit 2).

8.11.3 Laboratory test results

Summary statistics will be calculated for the measurements and change from baseline at each time-point. The baseline is defined as Visit 1 for new subjects or Visit 2 for consecutive subjects.

The category distribution of the qualitative laboratory test data at each time-point will be summarized.

8.11.4 ECG

The distribution of ECG findings (normal or abnormal) will be summarized for observation time-point.

8.11.5 Columbia Suicide Severity Rating Scale (C-SSRS)

The distribution of the presence or absence of suicidal ideation and suicidal behavior will be summarized for observation time-point.

8.12 Pharmacokinetic analysis

Plasma duloxetine concentrations and time from the last administration will be listed for each subject. Trough plasma concentrations, which are 18 to 30 hours after the last administration of duloxetine, for each subject will be collected and summarized for each dose group by the number of subjects with measurements, arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV% = SD/Mean × 100), median, minimum (Min), and maximum (Max). The plasma concentration below quantifiable limit will be substituted with 0. The plasma duloxetine concentrations at steady state from children and adolescent patients with depressive disorder will be compared with those of adult patients with depressive disorder. The relationship between the trough concentration of duloxetine and CDRS-R total score will be displayed in a graph.

Data considered by the pharmacokinetic analysts to be clearly inappropriate to include in the analysis will be excluded from the analysis. If excluded, the reason for exclusion shall be described in the clinical study report.

The population pharmacokinetic analysis will be conducted using a nonlinear mixed effect model, with NONMEM version 7.3 or higher. The report of population pharmacokinetic analysis will be prepared separately.

8.13 Interim analysis

After completing registration of subjects, once all subjects complete (or withdraw) observation at Visit 11 (Week 28), an interim analysis may be performed to assess the safety and efficacy of duloxetine administered for 6 months. The method of interim analysis should follow that of the analysis at the end of study.

9. Management-related items requiring attention

9.1 Principal investigator and study management system

Sponsor	Shionogi & Co., Ltd. (Head Office) 3-1-8 Doshomachi, Chuo-ku, Osaka, 541-0045, Japan
Contact information of sponsor	[redacted]
[redacted]	[redacted]
Medical Expert	[redacted]
Coordinating investigator	[redacted]
Safety Monitoring committee members	[redacted]

Study sites and principal investigators	See separate sheet
Clinical research associate (CRA)	See separate sheet
Emergency contact	[redacted]
Clinical research organization (CRO)	[redacted]
Clinical laboratory facility	[redacted]
Drug Concentration Laboratory	[redacted]
Data management	[redacted]
Statistical analysis	[redacted]

9.2 Institutional review board (IRB)

The IRB will protect the human rights, safety and welfare of subjects by reviewing study-related documents (including revised versions when any important amendments are made to these documents) such as the protocol, informed consent form and explanatory documents (or assent documents), materials

relating to subject recruitment (when applicable), other documents provided to subjects, the investigator's brochure, safety information, and annual reports of study performance (when applicable), as submitted by the principal investigator or sponsor. The IRB will be established on the basis of the GCP and various regulations. This study will be initiated after the principal investigator has obtained written approval by the IRB.

Revision of the protocol should be deliberated as done for the initial deliberation. The principal investigator will submit all periodic reports and updated information upon request by the IRB. The principal investigator will report all the applicable adverse events to the IRB.

9.3 Ethics

The clinical study will be performed in accordance with the appropriate regulatory requirements and the protocol approved by the IRB, and in compliance with the latest GCP, all appropriate requirements for protection of subjects' confidentiality, and ethical principles based on the Declaration of Helsinki.

9.4 Providing information to patients and obtaining informed consent

After accepting the sponsor's proposal about the explanatory documents and informed consent form, or assent document, in accordance with GCP and the regulatory requirements, the principal investigator will prepare the explanatory documents and informed consent form, or assent document. The sponsor must agree with the revisions pointed out by the principal investigator in relation to the explanatory documents and informed consent form, or assent document, before submitting these documents to the IRB. The principal investigator must provide the sponsor with the explanatory documents and informed consent form, or assent document, after the documents have been appropriately reviewed and approved by the IRB.

The principal investigator or sub-investigator will use the explanatory documents and informed consent form, or assent document, approved by the IRB to explain the quality, purpose, methods, foreseeable benefits, and potential risks to subjects before study participation, using readily understandable vocabulary. The method for obtaining written consent or assent should be in accordance with the GCP and appropriate regulatory requirements.

9.5 Protection of subjects' confidentiality

Laws about appropriate data privacy protection must be complied with in relation to subjects' personal information. CRFs, study drug management table, reports, letters, etc. should be identified by subject code to protect the personal information of subjects. The principal investigator will permit access to all source documents for monitors of the sponsor, auditors, and regulatory authority to confirm data of the CRF and verify procedures of data collection. However, personal information of subjects will be protected within the scope of appropriate laws and regulations. The principal investigator and sponsor must ensure that handling of confidential information is in accordance with any local regulatory requirements. If there is potential for anonymized subjects' information to be used, made public, or transferred, appropriate consent or approval must be obtained.

The information of subjects will be identified by subject ID code during the study and coded information will be recorded in the CRF. Personal information of subjects will be protected even when a subject must be identified for reasons such as safe conduct of a clinical study or instructions of regulatory authority.

9.6 Monitoring

The sponsor and contract monitoring organization will perform monitoring to ensure that the study is performed in compliance with the GCP requirements and the protocol. Monitoring will be performed by the sponsor or by monitors who are representatives of the contract monitoring organization, by means of on-site monitoring, at the appropriate frequency, and with frequent communication by e-mail, mail, telephone, or fax. Monitors will check the data recorded in the CRF; verify the items recorded in the CRF by direct access to source documents; collect information on the safety and efficacy of subjects; perform inspections to ensure that the quantity of unused study drug is accurate; and confirm that the source documents and essential documents have been stored.

9.7 Case report forms and source documents

9.7.1 Case Report forms

The sponsor will provide the CRF. The CRF will be prepared using an EDC system. A CRF will be prepared for each new subject who has signed informed consent or for each consecutive subject who has registered to this study, and subjects' demographic information stipulated in the protocol and data relating to the study will be recorded. Subjects' data relating to the study will be recorded in the source documents, and then promptly recorded in the CRF in accordance with the procedures relating to the CRF. The principal investigator or sub-investigator, and other study collaborators designated in writing, will make entries in the CRF.

If the sponsor has uncertainties about data from a study site, either the data in the CRF will be revised in accordance with the appropriate procedures, or a response to the question will be recorded. The principal investigator will ensure that the data recorded in CRF are accurate, complete, and legible and that the timing of submission is appropriate. The principal investigator will sign CRF to verify completeness of the recorded data.

The sponsor will obtain in writing a list of site reference values for all laboratory test items before study initiation. When the site reference values are changed after study initiation, the list will be obtained in writing. If all or some tests are performed at a central laboratory, reference values will be obtained for all items measured by that laboratory.

9.7.2 Source documents and raw data

Source documents are the basic materials for data recorded in the CRF. Participation of subjects in the study, details and date of study performance, adverse events, and the condition of subjects will be recorded.

However, for the following types of data, the data recorded in the CRFs may be used as raw data:

Reasons for use of prior and concomitant treatment.

Adverse events: severity, seriousness, and causal relationships with the study drug

Comments recorded in CRFs.

In addition, for data managed solely with CRFs (calculated automatically by the EDC), there is the following item:

Age at the time of obtaining informed consent (new subjects only)

Age at the time of obtaining assent (new subjects only)

CDRS-R total score.

The principal investigator will store source documents, such as laboratory test reports, and detailed subjects' medical history and medical records. All source documents should be made available for direct access by monitors, auditors, and IRB and inspection by regulatory authorities. Therefore, the principal investigator, sub-investigator, or study collaborators must make arrangements enabling appropriate direct access. The sponsor and study site personnel will ascertain the source documents in which information required for completing CRFs is recorded, and where they are stored. In the case of storage by electronic recording, the access method for verification must be stipulated in a document stipulated by the study site.

9.7.3 External data

The following data will be reported separately from CRFs:

- Plasma concentrations of duloxetine (measured at [redacted] according to the separately prepared procedures)
- Results of pharmacokinetic analysis
- Laboratory test results

9.8 Committees, meetings, etc.

9.8.1 Case review committee

Before the database lock, at a case review meeting, the sponsor, together with a medical expert, will check all data for all subjects recorded in CRFs. The subjects to be included in the analysis set will be decided upon on the basis of the outcome of the case review meeting and the definition of the analysis set in the protocol. Appropriateness of medical judgment of the principal investigator for the significant data affecting the safety or efficacy endpoint will also be evaluated during a case review meeting.

9.8.2 Safety monitoring committee

Depending upon the sponsor's requirements, reported interim safety data will be evaluated, and the sponsor will be notified as to whether the study should be continued, modified or discontinued. The evaluation will be performed in accordance with the Safety Monitoring Committee's standard operating procedures, which are set separately.

9.9 Study discontinuation or suspension

9.9.1 Discontinuation or suspension of entire study

The sponsor may discontinue or suspend the study when one or more of the following conditions is applicable:

- Ensuring the safety of the study is difficult, for reasons such as multiple occurrence of serious adverse drug reactions.
- It is not considered possible to achieve the study objectives, for reasons such as not being able to enroll a sufficient number of subjects.

When disconsecutive or suspending the study, the sponsor must report promptly to the principal investigator. The principal investigator or sub-investigator must promptly explain about study discontinuation or suspension to the participating subjects, and transfer them to other appropriate treatment. Discontinuation criteria for each subject are shown in Section 4.5 .

9.9.2 Discontinuation or suspension of study at each study site

When ensuring the safety of the study is difficult, for reasons such as multiple occurrence of serious adverse drug reactions, the principal investigator may discontinue or suspend the study at the relevant study site after obtaining approval by the sponsor. If a major deviation from the protocol (including other procedures) and/or the GCP occurs, and is not resolved, the sponsor may request the principal investigator to discontinue or suspend the study at the relevant study site.

If the study is discontinued or suspended, the principal investigator or sub-investigator must promptly explain about the discontinuation or suspension to the participating subjects and the IRB, and transfer the subjects to other appropriate treatment.

9.10 Modifications to and deviations from the protocol

The principal investigator will perform the study in accordance with the study protocol approved by the IRB and regulatory authority, and provided by the sponsor. Protocol amendments require agreement by the principal investigator and sponsor. For any protocol amendment, written approval must be obtained from the IRB beforehand, unless such amendments are medically essential for avoiding immediate risk to the subject.

The principal investigator or sub-investigator must record deviations from the protocol and the reasons for these. In the event of an amendment to or deviation from the protocol in order to avoid immediate risk to the subject, the principal investigator must immediately submit a record of the deviation or amendment to the sponsor, study site, and IRB, and promptly obtain approval by the IRB. After obtaining approval by the IRB, the principal investigator will obtain written agreement by the sponsor, via the study site.

If deviation from the protocol is required as an emergency, in a medically unavoidable situation, such as in order to avoid immediate risk to the subject, the principal investigator will contact the sponsor in advance wherever possible to discuss how this should be handled. All deviations from the protocol should

be recorded in the source documents.

9.11 Data management

The sponsor will commission data management tasks to a contract data management organization. Details of data management tasks will be defined in a separately specified procedure.

9.12 Storage of records

Study-related documents must be stored in accordance with the GCP and regulatory requirements. The principal investigator and study site must take measures to prevent accidental or premature disposal of the documents. When manufacture and marketing of the study drug has been approved, the sponsor will promptly report this in writing to the director of the study site.

The duration of storage of records will be until the later of the following:

- Three years after the date of achieving study drug marketing approval or after the decision to discontinue study drug development.
- Three years after study discontinuation or completion.

The above period of storage can be extended if necessary, as agreed upon with the sponsor. If the principal investigator cannot be responsible for storage of study-related records, this responsibility will be transferred to an appropriate successor.

9.13 Study quality control and quality assurance

The sponsor will define the procedures for quality control and quality assurance in the standard operation procedures in order to ensure that the study is performed, and that data, documents and reports are prepared in accordance with the protocol, GCP, and appropriate regulatory requirements. This study will be performed in accordance with ethical principles based on the Declaration of Helsinki, GCP, and other appropriate regulatory requirements.

The sponsor will hold explanatory meetings with the principal investigator and each study site before study initiation, and will provide education and training as required for study performance.

9.14 Decisions relating to publication

All information about duloxetine provided by the sponsor to the principal investigator is confidential information, and must not be disclosed to any third party. The principal investigator must not use this information for purposes other than the study without obtaining the consent of the sponsor. All the information obtained during the study should be provided to the sponsor. The information obtained during the study will be used for development of duloxetine and will be disclosed to the regulatory authority, other principal investigators, joint development company, and consulting company, etc. as necessary. The sponsor possesses the right to all data. Approval of the sponsor should be obtained before making public the information obtained in this study.

Overview of this protocol is made available on the clinical study registry site.

10. References

1. Guideline for clinical evaluation of antidepressants. Pharmaceutical and Food Safety Bureau notification no. 1116-1. November 16, 2010
2. Tanabe A, Nomura S. Pathology and pathophysiology. Jpn J Clin Med 2007; 65: 1585-90.
3. Denda K. Current status of pediatric depression in Japan. Jpn J Clin Psychopharmacol 2004; 7: 1567-77.
4. Zisook S, Lesser I, Stewart JW, et al. Effect of age at onset on the course of major depressive disorder. Am J Psychiatry 2007; 164: 1539-46.
5. Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Arch Gen Psychiatry 2005; 62: 1097-106.
6. Carlson GA, Kashani JH. Phenomenology of major depression from childhood through adulthood: analysis of three studies. Am J Psychiatry 1988; 145: 1222-5.
7. Japanese Society of Mood Disorders Guidelines (II): Depression (DSM-5) and major depressive disorder, 2016.
8. Kovacs M, Feinberg TL, Crouse-Novak MA, Paulauskas SL, Finkelstein R. Depressive disorders in childhood. I. A longitudinal prospective study of characteristics and recovery. Arch Gen Psychiatry 1984; 41: 229-37.
9. Kovacs M, Feinberg TL, Crouse-Novak M, Paulauskas SL, Pollock M, Finkelstein R. Depressive disorders in childhood. II. A longitudinal study of the risk for a subsequent major depression. Arch Gen Psychiatry 1984; 41: 643-9.
10. Fombonne E, Wostear G, Cooper V, Harrington R, Rutter M. The Maudsley long-term follow-up of child and adolescent depression. 1. Psychiatric outcomes in adulthood. Br J Psychiatry 2001; 179: 210-7.
11. Denda K. Epidemiology, diagnosis and treatment of pediatric/adolescent depression. Jpn J Clin Psychopharmacol 2006; 9: 780-90.
12. Shain B. American Academy of Pediatrics Committee on Adolescence. Clinical report: Guidance for the Clinician in Rendering Pediatric Care. Suicide and suicide attempts in adolescents. Pediatrics 2016; 138 (1) (accessed 2016-10-13).
13. U.S. Food and Drug Administration (FDA). MINUTES OF THE PEDIATRIC ADVISORY COMMITTEE March 24, 2015.

Appendix 1: Study 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, pulse 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] (5 times)											
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 for 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: Management of abnormal hepatic function test results, and discontinuation criteria

In order to ensure subjects' safety , as well as to evaluate the causes of any hepatic dysfunction found, management on the basis of abnormal hepatic function test results, and the discontinuation criteria, are defined, on the basis of the FDA's July 2009 guidance (Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation).

(1) Hepatic dysfunction criteria

The principal investigator or sub-investigator confirms whether or not the subject's laboratory test results meet any of the following criteria:

a. AST and/or ALT >5 times the upper limit of normal (ULN).
b. AST and/or ALT >3 times the upper limit of normal (ULN), and total bilirubin >2 times the upper limit of normal (ULN).
c. AST and/or ALT >3 times the upper limit of normal (ULN), and signs and/or symptoms consistent with hepatitis or hypersensitivity (e.g. fatigue, nausea, vomiting, right upper abdominal pain or tenderness, jaundice, fever, rash, eosinophil increase by more than 5%).

(2) Principal investigator's actions

If one or more of the above hepatic dysfunction criteria is met, the principal investigator or sub-investigator will act as follows:

- Immediately ensure that the subject stops taking the study drug.
- If possible, have the subject visit hospital within 72 hours after the abnormalities are first found, to repeat the hepatic function tests for a supplementary evaluation of hepatic function.
- Until the hepatic function test result (ALT, AST, ALP, and total bilirubin) abnormalities cease, stabilize, or return to within the reference range or to the baseline, the subject's progression is observed two to three times per week, if possible.
- Report to the sponsor using the hepatic dysfunction follow-up assessment form, within 72 hours after the relevant abnormalities coming to the principal investigator's attention.
- Look into the option of consulting a hepatologist or other specialist.
- Look into the option of performing hepatic imaging, such as ultrasonography, magnetic resonance imaging, or computed tomography.
- Report all events that meet criterion b (above) as serious adverse events.

(3) Follow-up assessment

If one or more of the above hepatic dysfunction criteria is met, items including the following will be assessed at the time of the follow-up assessment visit, and the results will be entered in the hepatic dysfunction follow-up assessment form:

- Clinical symptom.

- Alcohol intake.
- Risk factors for nonalcoholic steatohepatitis (NASH) (e.g. diabetes, obesity, and hypertriglyceridemia).
- Autoimmune hepatitis and cholangitis.
- Wilson's disease.
- Laboratory tests:
  - The following serum tests relating to viral hepatitis:
    - Hepatitis A IgM antibody
    - Hepatitis B surface antigen and hepatitis B core antibody
    - Hepatitis C RNA
    - Hepatitis E IgA antibody
    - Cytomegalovirus IgM antibody
    - Epstein-Barr virus capsid antigen IgM antibody
  - In the case of subjects with total bilirubin >1.5 times the upper limit of the reference values, conjugated bilirubin will be measured.
  - Blood cell measurement will be carried out, including leukocyte fractions.

Appendix 3: Sponsor's signature

Approval of the Protocol

Product Name: LY248686

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

Study Protocol Number: 1702A3632

Version Number: 4

Issue Date: 8 August 2018

Sponsor signatory:

This clinical study protocol was subject to critical review and has been approved by the sponsor:

Refer to electronic signature page

[redacted]

Refer to electronic signature page

Date: day-month-year

[redacted]

Final Approval	[redacted] [redacted] 08-Aug-2018 08:44:31 GMT+0000

[redacted]