Shionogi Study Title:	Phase-3 clinical study of duloxetine hydrochloride in children's and adolescent patients with depressive disorder: Superiority study versus placebo
Shionogi Study Number:	1701A3631
ClinicalTrials.gov Registration No.	NCT03315793
Study Document	Protocol Version 5 (Amendment 4) August 8, 2018

History of Protocol Amendments

Version 1 (Original)	July 18, 2017
• Adds contract monitoring organization to the monitoring process	
Version 2	August 30, 2017
• Improves the description for the use of antihistamine agents prior to the Children's Depression Rating Scale-Revised (CDRS-R) or Clinical Global Impression-Severity (CGI-S) evaluation • Changes the CDRS-R description to include the original English	
Version 3	October 20, 2017
• Improves the description of the exclusion criteria for suicidal ideation • Clarifies the use of ramelteon (Rozerem®)	
Version 4	February 23, 2018
• Adds prohibited drugs from the revised package insert for Cymbalta (duloxetine) • Adds new duloxetine package insert reference on the use of ramelteon (Rozerem®)	
Version 5	August 8, 2018

Study Protocol

This is the translated version of the Study Protocol (Version 5.0) written in Japanese

Study title:	Phase-3 clinical study of duloxetine hydrochloride in children and adolescent patients with depressive disorder: Superiority study versus placebo
Study No.:	1701A3631 (NCT03315793)
Development phase:	3
Product No.:	LY248686
Sponsor:	Shionogi & Co., Ltd. 3-1-8 Doshomachi, Chuo-ku, Osaka, 541-0045, Japan
Contact information for the sponsor:	[redacted]
Emergency contact:	[redacted]

Preparation dates

Initial version (Version 1):	July 18, 2017
Version 2	August 30, 2017
Version 3	October 20, 2017
Version 4	February 23, 2018
Version 5	August 8, 2018

Overview of the study

Study title:	Phase-3 clinical study of duloxetine hydrochloride in children and adolescent patients with depressive disorder: Superiority study versus placebo
Study No.:	1701A3631
Development phase:	3
Primary objective:	To verify the superiority of duloxetine over placebo, using change from baseline in Children's Depression Rating Scale-Revised (CDRS-R) total score as the index.
Secondary objectives:	● To evaluate the efficacy of duloxetine compared with placebo on the basis of the following indices: - 30% response rate: Proportion of subjects showing CDRS-R total score decreases of 30% or more from baseline. - 50% response rate: Proportion of subjects showing CDRS-R total score decreases of 50% or more from baseline. - Remission rate: Proportion of subjects with CDRS-R total scores of 28 or lower - Change from baseline in CDRS-R subscales and item 13 (suicidal ideation) - Change from baseline in clinical global impression: severity (CGI-S) ● To evaluate the safety of duloxetine, with occurrence or non-occurrence and frequency of adverse events and adverse drug reactions as indices.
Study design:	This study is to be a multicenter, randomized, placebo-controlled, double-blind, parallel-group comparative study with children and adolescent patients with depressive disorder, with the target number being 148. It will consist of the following four periods: Screening period (1-3 weeks), treatment period (6 weeks), Tapering period (1 week), Follow-up period (1 week), (total: up to 11 weeks). Patients 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). Registered patients will be allocated randomly to either the duloxetine group or the placebo group, in a 1:1 ratio, and will be orally administered duloxetine or placebo once daily after breakfast, under double-blind conditions.
Study subjects:	The subjects must meet the following criteria: (i) aged ≥9 to <18 at the

time of obtaining consent and assent; (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 with a CDRS-R total score of ≥40 and a CGI-S score of ≥4. 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:

1) At Visit 1, they have been diagnosed as having 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) is used for diagnosis of depression.
2) They must be aged ≥9 to <18 at the time of obtaining consent and assent, and must have been ≥7 at the initial onset of depression episode. They can be of either sex, and be either hospitalized or out-patients, but patients for whom the principal investigator or sub-investigator judges change in hospitalization status to be necessary between Visits 1 and 8 are excluded.
3) At Visits 1 and 2, the CDRS-R total score is ≥40, and the CGI-S score is ≥4.
4) By Visit 1, freely given, written, informed consent for participation in the study has been obtained from the patient's legal representative. In addition, in the case of patients aged ≥13, written, informed assent has also been obtained from the patient him/herself. In the case of patients aged ≥9 to <13, written, informed assent is obtained from the patient him/herself if possible.
5) In the case of post-menarchic females, a pregnancy test must give a negative result at Visit 1. In addition, the subject must agree to use the below contraceptive methods from Visit 1 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 (oral, intravaginal, subcutaneous, etc.), progesterone-containing hormonal contraceptive agents (orally, injective, implanted, 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 as far as possible be able to comply with all hospital visits, tests, and other procedures stipulated in this protocol.
7) The principal investigator or sub-investigator judges that the subject's legal representative has sufficient comprehension ability 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/he age, and as far as possible judges that he/she has sufficient comprehension ability and cognitive ability to communicate as appropriate with the principal investigator or sub-investigator, and other persons involved with the study.
8) The subject can swallow the capsules without opening, crushing, dissolving, or breaking them. In addition, he/she can take up to three capsules per day.

Patients who meet one or more of the following criteria are excluded:

1) Between Visits 1 and 2, the CDRS-R total score improves by 30% or more.
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, 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
3) 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

4) Judged by the principal investigator or sub-investigator to have a personality disorder.
5) 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, no response was found. Alternatively, the depressive episode was previously treated with duloxetine, and no response was found.
6) The depressive episode is currently being treated with duloxetine.
7) The principal investigator or sub-investigator judges that systematic psychotherapy must be initiated between Visits 1 and 9.
8) One or more of the patient's parents and/or siblings has been diagnosed as having bipolar disorder.
9) A history of epileptic or other convulsive attacks. However, patients with a history of febrile convulsions can be enrolled.
10) Administered electroconvulsive therapy within 1 year before Visit 1.
11) Used contraindicated drugs or therapies between Visit 1 (pre-registration) and Visit 2 (registration).
12) Uncontrolled diabetes or collagen disease.
13) Hormonal therapy initiated, changed or discontinued 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, FT3, FT4) concentrations; and (iii) have clinically normal thyroid function.
14) Currently have or have a history of malignant tumors/cancer.
15) Either (i) suicidal ideation and/or suicidal attempt within 1 year before Visit 1; or (ii) at Visits 1 and 2, answer "Yes" on 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).
16) Body weight below 20 kg at Visit 2.
17) 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 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.

18) Meeting one or more of the following criteria:
    - At Visit 1, 100 U/L or higher ALT or AST, or 1.6 mg/dL or higher total bilirubin.
    - Serum creatinine level of 2.0 mg/dL or higher at Visit 1, or severe renal impairment, history of renal transplantation, and/or currently undergoing renal dialysis.
19) Glaucoma, elevated intraocular pressure, and/or prostatic hypertrophy or other types of dysuria.
20) Depression or depressive state due to organic brain disorder.
21) Hemorrhagic tendency or hemorrhagic diathesis.
22) 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.
23) Hypersensitivity to duloxetine or inactive ingredients of duloxetine formulation.
24) Allergic to two or more drugs, or a history of serious allergic reactions to one or more drugs.
25) 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 enroll.
26) One or more substances of abuse (phencyclidines, benzodiazepines, cocaine-type drugs, stimulants, cannabis, opioids, barbiturates, tricyclic antidepressants, etc.) detected by urinary drug screening at Visit 2.
27) Intention to travel overseas between Visit 1 (pre-registration) and Visit 10 (or Visit 9 in the case of transfer to the extended long-term

	treatment study). 28) Pregnant* or possibly pregnant, breastfeeding, hoping to become pregnant during the study period, or recently given birth. * Pregnancy: At Visit 1, pregnancy tests (blood or urine human chorionic gonadotropin) are performed with all post-menarchic females. 29) Previously administered the study drug during participation in this study, or during participation in a different clinical study on duloxetine. 30) Administered a different study drug either currently or within 30 days before Visit 1. 31) Participation judged by the principal investigator or sub-investigator to be inappropriate for any other reason.
Study drug dosage and administration method:	Duloxetine (20-mg capsules) is administered orally, once daily after breakfast, for 7 weeks, this consisting of a 6-week treatment period and a 1-week tapering period. During the treatment period, administration is initiated at 20 mg/day, and increased to 40 mg/day at Visit 3, 1 week later. From Visit 4, 1 week after Visit 3, if the CGI-S score is 3 or higher, and there are no concerns about safety, the dose is increased to 60 mg/day. In addition, from Visit 5, after the dose has been temporarily increased to 60 mg/day, if there are safety-related problems, it can be reduced again to 40 mg/day. If the CGI-S score is ≥3, and there are no safety-related problems, after confirming the subject's clinical condition and safety, the dose can be increased again. 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. During the 1-week tapering period, if the duloxetine dose at discontinuation or completion of the treatment period was 60 mg/day, 40 mg/day is administered for the first 3 days of the week, and 20 mg/day is administered for the remaining 4 days. On the other hand, if the dose at discontinuation or completion was 40 mg/day, 20 mg/day is administered for the entire week.
Control drug dosage and administration method:	Placebo for 20-mg duloxetine capsules is administered orally, once daily after breakfast, for 7 weeks, this consisting of a 6-week treatment period and a 1-week tapering period as is the administration way in active drug.
Administration period:	7 weeks (6-week treatment period and 1-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 through Visit 9. (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 externally administered 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 until 5 days after completion of study drug administration.
2) Other study drugs

Unless specifically stated otherwise, use of the following treatments is prohibited from Visit 1 through Visit 9 (completion of the tapering period):

1) Electroconvulsive therapy

2) Bright-light therapy, i.e. therapy using irradiation devices approved for medical use.
3) Systematic psychotherapy, such as systematically organized cognitive therapy, cognitive behavioral therapy, and interpersonal psychotherapy. In this study, educational tools will be used, 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 13, treatment can be continued at the same dose with thyroid dysfunction patients who (i) have undergone thyroid hormone supplementation at the same dose for at least 3 months as of Visit 1; (ii) show medically appropriate thyroid hormone (TSH, FT3, FT4) concentrations; and (iii) have a clinically normal state of thyroid function.

Efficacy endpoints:

Primary endpoint:

- Change from baseline in CDRS-R total score.

Secondary endpoints:

- 30% response rate: Proportion of subjects showing CDRS-R total score decreases of 30% or more from baseline.
- 50% response rate: Proportion of subjects showing CDRS-R total score decreases of 50% or more from baseline.
- Remission rate: Proportion of subjects with CDRS-R total scores of 28 or lower
- Changes from baseline in CDRS-R subscales and item 13 (suicidal ideation)
- Change from baseline in CGI-S score.

Safety endpoints: Adverse events, adverse drug reactions, C-SSRS score, blood pressure, pulse rate, body weight, ECG, laboratory test results

Statistical methods: The mixed-effects model repeated measures (MMRM) method is used for the primary analysis of efficacy. All usable data obtained at stipulated observation time-points after study drug administration are used, and a linear model is applied, with change in CDRS-R total score from baseline taken to be a response variable; treatment group, observation time-points, and interaction between treatment group and observation time-points taken to be fixed effects; baseline CDRS-R total score and age (<12, ≥ 12) taken to be covariates; and the covariance structure of error variance taken to be unstructured. On the basis of this model, the superiority of the

	duloxetine group over the placebo group is evaluated in terms of change in CDRS-R score after administration for 6 weeks. In addition, as secondary analysis of the primary endpoint, analysis of covariance is performed by the last observation carried forward (LOCF) method.
Study period:	Study period for each subject: Up to 11 weeks (1- to 3-week Screening period, 6-week Treatment period, 1-week Tapering period, 1-week Follow-up period) Scheduled study period: October 2017 to February 2020
Date of preparation of the first version:	July 18, 2017
Date of preparation of the latest version:	August 8, 2018 (Version 5):

Table of contents

Tables

Figures

List of abbreviations and terms

Abbreviation	Full term
5-HT	5-hydroxytryptamine (serotonin)
AUC	area under the plasma concentration-time curve
CDRS-R	Children's Depression Rating Scale-Revised
CGI-S	Clinical Global Impression of Severity
C_{max}	maximum plasma concentration
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
EDC	electronic data capture
FAS	full analysis set
FT3	free triiodothyronine
FT4	free thyroxine
IRB	institutional review board
IWRS	interactive web response system
LOCF	last observation carried forward
MAO	monoamine oxidase
MINI-KID	Mini International Neuropsychiatric Interview for children and adolescents
MMRM	mixed-effects model repeated measures
NA	noradrenaline
PPS	per protocol set
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 children and 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, escitalopram is no description of careful administration to patients aged 12 to 18.

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 “Children and adolescent depression”, which is an area of ongoing research, and the unmet medical needs for children and 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).

For the above reasons, a Phase-3 study is to be performed to verify the superiority of duloxetine hydrochloride (referred to below as "duloxetine") over placebo, for children and adolescent depression patients in Japan, and it is considered that this will provide evidence for the efficacy and safety of duloxetine, and thus help to achieve the additional indication of pediatric depression.

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 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 children and 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 the present 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

viriation 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. Furthermore, 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.

On the basis of the above, it is judged that it is appropriate to perform this study.

2. Study objectives

To evaluate the efficacy and safety of duloxetine for children and adolescent patients with depressive disorder in a placebo-controlled, double-blind, parallel-group, comparative study.

2.1 Primary objective

To verify the superiority of duloxetine over placebo, using change from baseline in CDRS-R total score as the index.

2.2 Secondary objectives

- To evaluate the efficacy of duloxetine compared with placebo on the basis of the following indices:
  - 30% response rate: Proportion of subjects showing CDRS-R total score decreases of 30% or more from baseline.
  - 50% response rate: Proportion of subjects showing CDRS-R total score decreases of 50% or more from baseline.
  - Remission rate: Proportion of subjects with CDRS-R total scores of 28 or lower
  - Change from baseline in CDRS-R subscales and item 13 (suicidal ideation)
  - Change from baseline in CGI-S score
- To evaluate the safety of duloxetine, with occurrence or non-occurrence and frequency of adverse events and adverse drug reactions as indices.

3. Study plan

3.1 Study design

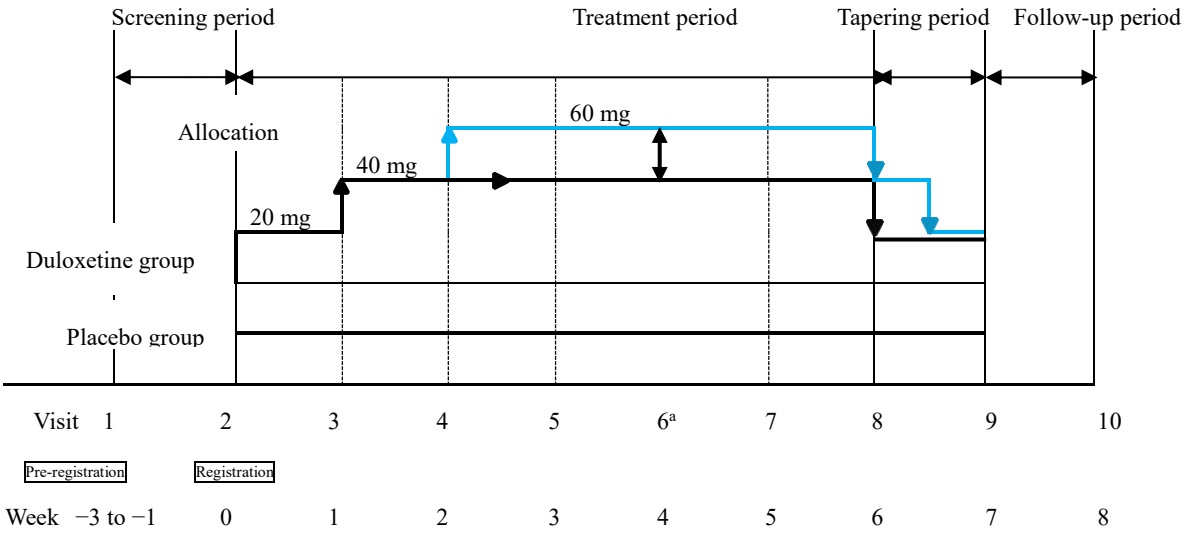
This study is to be a multicenter, randomized, placebo-controlled, double-blind, parallel-group, comparative study with children and adolescent patients with depressive disorder, with the target number of subjects being 148. It will consist of the following four periods: Screening period (1-3 weeks), treatment period(6 weeks), Tapering period(1 week), Follow-up period(1 week), (total: up to 11 weeks). During the treatment and tapering periods (total: 7 weeks), duloxetine or placebo will be administered orally, once daily after breakfast. Subjects who transfer to the extended long-term treatment study [study no.: 1702A3632 (NCT03395353)] will transfer to the extended study after completion of the tapering period.

- Screening period: After obtaining informed consent, eligibility has to be confirmed at Visit 1, and subjects for whom this is confirmed will then be pre-registered In addition, the first session of psycho-education will be provided, and the subjects' conditions will be assessed.
- Treatment period: Eligibility will be confirmed again at Visit 2, and subjects for whom this is confirmed will then be registered. The subjects will then be allocated randomly, with double-blinding, to the duloxetine and placebo groups, in a 1:1 ratio, and will be orally administered duloxetine or placebo once daily after breakfast, for 6 weeks. With the duloxetine group, administration will be initiated at 20 mg/day, and increased to 40 mg/day at Visit 3, 1 week later. From Visit 4, 1 week after Visit 3, if the CGI-S score is 3 or higher, and there are no concerns about safety, the dose will be increased to 60 mg/day. In addition, from Visit 5, after the dose has been temporarily increased to 60 mg/day, if there are safety-related problems, it can be reduced again to 40 mg/day. If the CGI-S score is ≥3, and there are no safety-related problems, after confirming the subject's clinical condition and safety, the dose can be increased again. 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. Visit 6 is a visit that can be made to the hospital in connection with dose increase, decrease, etc.
- Tapering period: In order to minimize the occurrence of adverse events due to discontinuation of administration, a 1-week tapering period is set for subjects who complete the treatment period, or who withdraw from it during the second week or later, and during this time duloxetine or placebo will be administered orally, once daily after breakfast, with double-blinding. If the duloxetine dose at discontinuation or completion of the treatment period is 60 mg/day, 40 mg/day will be administered for the first 3 days of the 1-week tapering period, and 20 mg/day will be administered for the remaining 4 days. On the other hand, if the dose at discontinuation or completion is 40 mg/day, 20 mg/day will be administered for the entire week (for details about the tapering method at discontinuation of the treatment period, refer to Section 5.2).
- 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 run-out period will be set after administration discontinuation.

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

Fig. 3-1. Schematic diagram of study schedule



a Visit 6 is a visit that can be made to the hospital in connection with dose increase, decrease, etc.

3.2 Rationale for setting the study design

(1) Rationale for setting the screening period

This period is set for the following reasons:

- In order to select appropriate patients for study participation, on the basis of the results of observation and tests before initial administration.
- In order to eliminate carry-over effects if contraindicated drugs and/or therapies were being used at the time of joining the study.
- So that diagnoses are made twice, before the pre-registration and registration, enabling selection of the most appropriate subjects.

(2) Rationale for setting placebo as the control drug

A double-blind, parallel-group, comparative study is the standard design for evaluation of the efficacy of antidepressants in acute-phase depression. No drugs are currently indicated for pediatric depression in Japan, so placebo is set as the control.

(3) Rationale for setting the doses (the same as for adults with depression or depressive state in Japan)

Three overseas studies, the HMFN, HMCK and HMCL studies, have been performed with children and adolescent major depressive disorder patients, diagnosed in accordance with DSM-IV and DSM-IV-TR, and the plasma duloxetine concentrations measured in these studies were compared with those in overseas adult patients. The ratios in the median plasma duloxetine concentrations in children subjects (7 to 11 years old) and adolescent subjects (12 to 17 years old) compared with the dose-corrected plasma duloxetine concentration in adult patients were 0.829 and 0.686, respectively. Although the values were thus somewhat lower in children and adolescent patients, the ratios were not great enough to necessitate dose adjustment. In addition, plasma duloxetine concentration shows widevariation in children, adolescent and

adult patients, and no differences between these three groups were found in the distribution range of dose-corrected plasma concentration measurements. Furthermore, on the basis of a steady-state plasma concentration simulation, it has been predicted that similar plasma concentration time-courses will be shown with pediatric and adult patients when the same doses are administered. For these reasons, it is considered that administration of the same dose to children and adolescent patients as to adult patients will result in approximately the same level of exposure.

The pharmacokinetic parameters for duloxetine, that is, the maximum plasma concentration (C_{max}) and the area under the curve for plasma concentration against time (AUC), have been compared between Japanese and non-Japanese (Caucasian and black) healthy adults, and no statistically significant ethnic differences have been found. It has thus been confirmed that, with the same duloxetine dose, the plasma concentration is approximately the same in overseas adults and children, and in overseas and Japanese adults, and the dose in this study has thus been set the same as that used in Japan for adult depression and depressive state patients.

(4) Rationale for setting administration period (6-week treatment period)

The administration period set for clinical studies on antidepressants is 6 to 8 weeks in the Japanese guidelines (1), and at least 4 and approximately 6 weeks in the European Medicines Agency guidelines (14). The study drug administration period set for the present study, 6 weeks, is within the range set by the Japanese guidelines, and the administration period after reaching the maintenance dose, 4 to 5 weeks, complies with the European Medicines Agency guidelines.

In practice, even the Phase-3 duloxetine verification study results, which were included in the Japanese approval application data package for adult depression and depressive state patients, verified superiority over the placebo group with a 6-week administration period.

In addition, in the HMCL study, which was the one of the overseas Phase-3 studies with which the results suggested efficacy, the adjusted mean CDRS-R change in patients aged ≥9 to <18 at the time of obtaining informed consent, and ≥7 at initial onset of depression, was consistent from 1 week after initiation of administration, and was greater with duloxetine than with placebo. Furthermore, no major change differences between duloxetine 60mg and placebo were found at any time from 1 week after administration initiation. For the above reasons, the administration duration has been set at 6 weeks.

(5) Rationale for setting the tapering period

The duloxetine package insert states that, if administration is to be discontinued, in order to avoid withdrawal symptoms, administration should be tapered off rather than discontinued suddenly. Therefore, taking subjects' safety into consideration, tapering of administration has been set after completion or discontinuation of the treatment period.

3.3 Study period:

3.3.1 Study period for each subject

Up to a total of 11 weeks, consisting of a 1- to 3-week screening period, a 6-week treatment period, a 1-week tapering period, and a 1-week follow-up period.

3.3.2 Scheduled period of entire study

October 2017 to February 2020

4. Inclusion of subjects and discontinuation of study

4.1 Study subjects

Children and adolescent patients with depressive disorder who meet 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:

1) At Visit 1, they have been diagnosed as having depression or persistent depressive disorder, as defined in DSM-5, and fully meet the criteria for depressive episodes. MINI-KID (version 7.0.2) is used for diagnosis of depression.
2) They must be aged ≥9 to <18 at the time of obtaining consent and assent, and must have been ≥7 at the initial onset of depression. They can be of either sex, and be either hospitalized or out-patients, but patients for whom the principal investigator or sub-investigator judges change in hospitalization status to be necessary between Visits 1 and 8 are excluded.
3) At Visits 1 and 2, the CDRS-R total score is ≥40, and the CGI-S score is ≥4.
4) By Visit 1, freely given, written, informed consent for participation in the study has been obtained from the patient's legal representative. In addition, in the case of patients aged ≥13, written, informed assent has also been obtained from the patient him/herself. In the case of patients aged ≥9 to <13, written, informed assent is obtained from the patient him/herself, if possible.
5) In the case of post-menarchic females, a pregnancy test must give a negative result at Visit 1. In addition, the patient must consent to use one of the below contraceptive methods from Visit 1 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 patient's legal representative can ensure that the patient him/herself will comply with all the hospital visits, tests, and other procedures stipulated in this protocol. In addition, the principal investigator or sub-investigator judges that the patient him/herself will be able to comply with all the hospital visits, tests, and other procedures stipulated in this protocol.
7) The principal investigator or sub-investigator judges that the patient's legal representative has sufficient comprehension ability 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 ability and

cognitive ability to communicate as appropriate with the principal investigator or sub-investigator, and other persons involved with the study.

8) The patient can swallow the capsules without opening, crushing, dissolving, or breaking them. In addition, he/she can take up to three capsules per day.

4.3 Exclusion criteria

Patients who meet one or more of the following criteria are excluded:

1) Between Visits 1 and 2, the CDRS-R total score improves by 30% or more.
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, or to have a history of such disorders:
   - Neurodevelopmental disorders
   - Schizophrenia-spectrum disorder or other psychotic disorders
   - Bipolar or related disorders
   - Emotional trauma or stress disorders
   - Disruptive, impulse–control, and conduct disorders
3) Judged by the principal investigator or sub-investigator to have complications diagnosed as belonging to one or more of the following categories in the DSM-5:
   - Obsessive-compulsive disorder or related disorders
   - Anorexia nervosa, bulimia nervosa, or binge-eating disorders
   - Sleep-wake disorders
   - Neurocognitive disorders
   - Disruptive mood dysregulation disorders
4) Judged by the principal investigator or sub-investigator to have a personality disorder.
5) Treatment with two or more antidepressants has previously been tried, and, despite administration of the optimal clinical dose for the depressive episode for 4 weeks or more, no response was seen. Alternatively, the depressive episodes were previously treated with duloxetine, and no response was seen.
6) Depressive episodes currently being treated with duloxetine.
7) The principal investigator or sub-investigator judges that systematic psychotherapy must be initiated between Visits 1 and 9.
8) One or more of the patient's parents and/or siblings has been diagnosed as having bipolar disorder.
9) A history of epileptic or other convulsive attacks. However, patients with a history of febrile convulsions can be enrolled.
10) Administered electroconvulsive therapy within 1 year before Visit 1.
11) Used contraindicated drugs or therapiesbetween Visit 1 (pre-registration) and Visit 2 (registration).
12) Uncontrolled diabetes or collagen disease.
13) Hormonal therapy initiated, changed or discontinued within 3 months before Visit 1. Patients with

thyroid dysfunction are excluded, unless they (i) have undergone thyroid hormone supplementation for at least 3 months as of Visit 1; (ii) show medically appropriate concentrations of thyroid hormones (TSH, FT3 and FT4); and (iii) have attained a clinically normal state of thyroid function.

14) Currently have or have a history of malignant tumors/cancer.
15) Suicidal ideation and/or suicidal attempt within 1 year before Visit 1; and/or, at Visits 1 and 2, answer "Yes" on C-SSRS questions 4 and/or 5 about suicidal ideation, and/or any of the questions about suicidal behaviors (except for questions about non-suicidal self-injurious behabvior).
16) Body weight below 20 kg at Visit 2.
17) Serious[*1] or medically unstable disease[*2] (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 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 issues, or to necessitate aggressive therapy.

18) Meeting one or more of the following criteria:
    - At Visit 1, 100 U/L or higher ALT or AST, or 1.6 mg/dL or higher total bilirubin.
    - Serum creatinine level of 2.0 mg/dL or higher at Visit 1, severe renal impairment, history of renal transplantation, and/or currently undergoing renal dialysis.
19) Glaucoma, elevated intraocular pressure, and/or prostatic hypertrophy or other types of dysuria.
20) Depression or depressive state due to organic brain disorder.
21) Hemorrhagic tendency or hemorrhagic diathesis.
22) 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
23) Hypersensitivity to duloxetine or active ingredients of duloxetine.
24) Allergic to two or more drugs, or a history of serious allergic reaction to one or more drugs.
25) Judged by the principal investigator or sub-investigator to have his/her condition complicated by substance-related and/or addictive disorders, as defined in DSM-5, or to have a history of such disorders. However, patients with caffeine-related disorder can enroll.
26) One or more substances of abuse (phencyclidine, benzodiazepines, cocaine-type drugs, stimulants, cannabis, opioids, barbiturates, tricyclic antidepressants, etc.) detected by urinary drug screening at Visit 2.
27) Intention to travel overseas between Visit 1 (pre-registration) and Visit 10 (or Visit 9 in the case of transfer to the extended long-term treatment study).

28) Pregnant* or possibly pregnant, breastfeeding, hoping to become pregnant during the study period, or recently given birth.

    * Pregnancy: At Visit 1, pregnancy tests (blood or urine human chorionic gonadotropin) are performed with all post-menarchic females.

29) Previously administered the study drug during participation in this study, or during participation in a different clinical study on duloxetine.
30) Administered a different study drug either currently or within 30 days before Visit 1.
31) Participation judged by the principal investigator or sub-investigator to be inappropriate for any other reason.

4.4 Screening dropouts

Patients who give informed consent to participate in the study, but are not then allocated to groups are considered to be screening dropouts. 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 possible 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. Completion of the study means completion of administration and observation up to Visit 9, or up to Visit 10 in the case of subjects who do not transfer to the extended long-term treatment study [study no.: 1702A3632 (NCT03395353)].

- 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 during the screening period.
- The ineligibility of the subject is revealed after initiation of study drug administration.
- Administration of duloxetine at a dose of 40 mg/day or higher is difficult at or after Visit 3.
- Change in hospitalization status is necessary between Visits 1 and 8.
- 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. Study drug regimen

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

5.1.2 Placebo or control

- Placebo capsules: Capsules indistinguishable from LY248686, manufactured by Shionogi and Co., Ltd.

5.2 Dosage and regimen

Subjects who are formally enrolled after confirmation of eligibility will be randomly allocated to the duloxetine and placebo groups in accordance with the allocation method stipulated in Section 5.4 . The two groups are shown in Table 5-1. Oral administration of duloxetine or placebo will be initiated the day after the registration (Visit 2), with administration once daily after breakfast for 7 weeks, in a 6-week treatment period and a 1-week tapering period. Treatments by methods other than the study drug administration are detailed in Section 6. .

Table 5-1. Study drug regimen for each group

Treatment group	Treatment period			Tapering period	
	Week 1	Week 2	Weeks 3 - 6	Week 7	
				First 3 days	Latter 4 days
Duloxetine group	20 mg/day	40 mg/day	40 or 60[a] mg/day	20[b] or 40[c] mg/day	20 mg/day
	One 20-mg LY248686 capsule and one placebo capsule	Two 20-mg LY248686 capsules	Two 20-mg LY248686 capsules or three 20-mg LY248686 capsules	One 20-mg LY248686 capsule or two 20-mg LY248686 capsules	One 20-mg LY248686 capsule
Placebo group	0 mg/day	0 mg/day	0 mg/day	0 mg/day	0 mg/day
	Two 20-mg placebo capsules	Two 20-mg placebo capsule	Two 20-mg placebo capsules or Three 20-mg placebo capsules	One 20-mg placebo capsules or Two 20-mg placebo capsules	One 20-mg placebo capsules

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.

a When the CGI-S score is ≥3, and there are no concerns about safety. If there are safety-related problems, as judged by the principal investigator, the dose can be reduced to 40 mg/day. If the CGI-S score is ≥3, and there are no safety-related problems, after confirming the subject's clinical condition and safety, the dose can be increased again.

b If the duloxetine dose at discontinuation or completion of the treatment period was 40 mg/day.

c If the duloxetine dose at discontinuation or completion of the treatment period was 60 mg/day.

One of the following measures will be taken if administration is discontinued during the treatment period:

1) Discontinuation during week 1 of treatment period: Promptly discontinue administration.
2) Discontinuation during week 2 of treatment period: Discontinue after administration of the study drug at 20 mg/day for a tapering period of 7 days.
3) Discontinuation during week 3 to 6 of treatment period: If the duloxetine dose at administration discontinuation is 60 mg/day, discontinue after tapering-period administration of the study drug, at 40 mg/day for 3 days, and 20 mg/day for 4 days.
   If the duloxetine dose at administration discontinuation is 40 mg/day, discontinue after tapering-period administration of the study drug at 20 mg/day for 7 days.

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.

5.3 Selection of dose and timing of administration for each subject

Subjects will be randomly allocated to the duloxetine and placebo groups. With the duloxetine group, administration will be initiated at 20 mg/day, and increased to 40 mg/day at Visit 3, 1 week later. From Visit 4, 1 week after Visit 3, if the CGI-S score is 3 or higher, and there are no concerns about safety, the dose will be increased to 60 mg/day. In addition, from Visit 5, after the dose has been temporarily increased to 60 mg/day, if there are safety-related problems, it can be reduced again to 40 mg/day. If the CGI-S score is ≥3, and there are no safety-related problems, after confirming the subject's clinical condition and safety, the dose can be increased again. 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. During the 1-week tapering period, if the duloxetine dose at discontinuation or completion of the treatment period was 60 mg/day, 40 mg/day will be administered for the first 3 days of the week, and 20 mg/day will be administered for the remaining 4 days. On the other hand, if the dose at discontinuation or completion was 40 mg/day, 20 mg/day will be administered for the entire week.

5.4 Allocation method for each subject

After completion of the screening period, subjects for whom eligibility has been confirmed will be randomly allocated to the duloxetine and placebo groups in a 1:1 ratio using the interactive web response system (IWRS). Allocation will be by the stochastic minimization method, with age (<12, ≥12) and study site as the allocation factors. So that the number of subjects in each treatment group at the same study site is as far as possible equal, at each medical institution consideration should be given to not allowing the maximum inter-group difference to exceed two subjects.

The allocation manager/organization will prepare random allocation procedures, and then comply with them.

5.5 Blinding

This is a double-blind study using a placebo that is indistinguishable in terms of appearance, labeling, and packaging. After allocation of the study drug, the study drug allocation manager will seal the study drug allocation table to be retained during the study period. The study drug allocation manager will store the study drug allocation table to maintain blindness to all involved persons other than the study drug allocation manager. The study drug allocation manager will open the study drug allocation table after all data in the CRF have been locked. The study drug allocation manager will submit the record of preparation and maintenance of the study drug allocation table to the sponsor. These procedures are determined in the separately specified procedures.

The study drug allocation manager will prepare and store the study drug allocation code for emergency. When it becomes necessary, as an emergency, to obtain knowledge about the administered drug due to occurrence of a serious adverse event, etc., the principal investigator may open the emergency study drug allocation code. The principal investigator will specify the reason for requiring emergency key break and all records up to key break, and submit them to the sponsor. Details about the broken emergency study-drug allocation code will be passed to the principal investigator via the IWRS at the Registration Center (available 24 hr everyday). If there is no need to break the emergency study-drug allocation code, the study drug allocation manager will record that the emergency study-drug allocation code was not broken before key break. These procedures are determined in the separately specified procedures.

In an emergency, or in the event of adverse events to which an appropriate measures cannot be made without knowing the subject's allocation details (but not in other situations), the principal investigator can request key opening. If the principal investigator judges that certain allocation details for specific subjects must be ascertained, he/she will notify the study drug allocation manager about this requirement.

Before ascertaining the allocation details, if possible, the principal investigator should contact the sponsor with the aim of obtaining more information about the study drug. If the prioncipal investigator is unable to contact the sponsor beforehand, he/she will notify the sponsor about the key opening as soon as possible afterward. However, the allocation details will not be clarified. The principal investigator will record the relevant subject's identification no. and unblinding date, and must also provide a clear explanation about the reasons for unblinding. This information must be entered in a form stipulated by the sponsor, and then provided to the sponsor. Details of the procedures relating to emergency key break are shown in a separately specified procedures.

The study drug allocation manager will confirm indistinguishability of the study drug and control in terms of appearance, dosage form, smell, etc., before study drug allocation, after completion of study drug administration to all subjects, and before key break, in accordance with the separately specified procedures. Indistinguishability of packaging and labeling will be confirmed after completion of study drug administration to all subjects.

The study drug allocation manager will prepare the record of confirming indistinguishability and submit it to the sponsor.

5.6 Packaging and labeling

The study drug is packaged in a single book of capsules for each 7-day period, consisting of one book for week 1 of the treatment period, one book for week 2 of the treatment period, four books for week 3 of the treatment period and later, one book for the tapering period, and one spare book, making a total of eight books, which are packed in a single box as a one-subject unit. Four of these boxes are packed in a large box, as a one-group unit. Each of the one-subject boxes is labeled with the investigational material development number (LY248686), drug ID ., 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 and placebo are stored in airtight containers 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. If the sponsor's monitor retrieves unused drug before the key break, this will be after the study drug has been sealed by the study drug manager.

5.9 Treatment compliance

At each study site visit, subjects will bring study drug books (containing unused drug) with them, and will return the books that are no longer needed. However, the 1-week book containing spare study drug will be returned at Visit 8. The investigator or sub-investigator will confirm treatment compliance from the study drug books, ascertaining the exact amount of the drug taken since the previous visit. At each visit, the duration of study drug administration, dosage, reasons for prescription change or continuation, a number of unused capsules will be entered in the CRF. Other items entered in the CRF will be whether prescription has been in accordance with the allocation no. released by the Registration Center, and, if not, the prescribed drug ID, and the study drug administration initiation and completion dates for each dose. 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)

Treatment before Visit 1 (pre-registration) is taken to be prior treatment (prior drugs/therapies). The restrictions on prior treatment are stipulated in Section 4.3 .

For all treatments for depression performed 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 treatment period will be recorded in the CRF.

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

Treatment after Visit 1 is taken to be concomitant treatment (concomitant drugs/therapies).

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 during the treatment period, that is, between Visit 1 and Visit 10 (completion of the follow-up period), or Visit 9 (completion of the tapering period) if the subject is transferred to the extended long-term treatment study [study no.: 1702A3632 (NCT03395353)]:

- 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
- Treatment period
- 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 through Visit 9. (completion of the tapering period):

The first group of contraindicated drugs 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.

The second group of contraindicated drugs present safety-related problems:

1) MAO inhibitors (FP®, Azilect®,etc.)
   Administration of these is contraindicated from 14 days before Visit 2 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 through Visit 9 (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. In this study, educational tools will be used, 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 13, 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;

(ii) showing medically appropriate concentrations of thyroid hormones (TSH, FT3 and FT4); and
(iii) having attained a clinically normal state of thyroid function.

6.2.2 Restricted drugs and therapies

The following restricted drugs and therapies may only be used under the stipulated conditions from Visit 1 to Visit 9 (completion of the tapering period):

Permitted soporific agents:

The following soporific agent may be used during the study period with subjects aged ≥15, if the same dosage can be maintained:

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 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 and Visit 9 (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 to Visit 9 (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 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

The following baseline subject characteristics are obtained at initiation of the study, and entered in the CRF: date of obtaining the legal representative's written, informed consent; date of obtaining the subject's written assent (if applicable); 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.

(2) Urinary drug tests

At Visit 2, urinary drug tests will be performed, 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 or sub-investigator will pre-register and register subjects at Visits 1 and 2, respectively, via IWRS at the Registration Center. At Visit 2, the study drug will be allocated , and drug ID for each subject notified . 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. . The drug ID allocated will be recorded in the CRF.

7.4 Psycho-education

Fundamental psycho-education about depression treatment will be provided systematically, with the same contents at each institution, and sessions with the subjects and guardians will therefore be held by a clinical psychologist or similar, and the principal investigator or sub-investigator, at Visits 1, 2 and 5, and at Visit 8 (or at discontinuation of treatment). At Visits 1, 2 and 5, psycho-education will be provided after evaluation of CDRS-R and CGI-S. At Visit 8 or treatment discontinuation, psycho-education will if possible be 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 to 5, Visit 7, and Visit 8 or 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. The baseline is defined as Visit 2.

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 to 8 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 (if the subject visits hospital for Visit 6, it will be performed if possible). 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. The baseline is defined as Visit 2.

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 Safety evaluation

7.6.1 Physical examination

At Visits 1 to 9, or discontinuation of the treatment or tapering period, and Visit 10, 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 (if the subject visits hospital for Visit 6, it will be performed if possible). 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.

7.6.2 Columbia Suicide Severity Rating Scale (C-SSRS)

At Visits 1 to 9, or at discontinuation of the treatment or tapering period, the principal investigator or sub-investigator will evaluate suicidal thinking using a questionnaire (if the subject visits hospital for Visit 6, it will be performed if possible). 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 7.6.7.7) and will record any changes judged to be clinically significant as adverse events.

7.6.3 Body weight

Body weight (kg) will be measured at Visits 2 and 8, and Visit 9 (or at discontinuation of the treatment period or tapering period). 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 7.6.7.7) and will record any changes judged to be clinically significant as adverse events.

7.6.4 Blood pressure and pulse rate

The blood pressure (systolic and diastolic) and pulse rate, at rest, will be measured at Visits 1 to 9 (or at discontinuation of the treatment period or tapering period). If possible, this will be performed if the subject arrives at hospital for Visit 6. The date and results 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 7.6.7.7), and will record any changes judged to be clinically significant as adverse events.

7.6.5 Electrocardiogram

Standard, 12-lead electrocardiogram (ECG) will be performed at Visits 1, 8 and 9 (or at discontinuation of the treatment period or tapering period). 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 (Visit 1) is clinically significant (refer to Section 7.6.7.7), and will record any changes judged to be clinically significant as adverse events.

7.6.6 Laboratory tests

7.6.6.1 Laboratory test items

At Visits 1, 5, 8 and 9, or at discontinuation of the treatment period or tapering period, blood samples will be collected for laboratory tests, the volumes being 2 mL for hematology tests, and 8 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 7.6.6.2. Details of the collection, handling, storage, and shipment of samples are stipulated in a separate document.

The principal investigator or sub-investigator will judge whether any abnormal change from baseline (Visit 1) is clinically significant (see Section 7.6.7.7) 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).

7.6.6.1.1 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[a], FT4[a]
Urinalysis (qualitative)	Urinary protein, urinary glucose, urobilinogen, urinary occult blood

a: Only at Visit 1

7.6.6.1.2 Pregnancy test

At Visits 1 and 9, or at discontinuation of the treatment or tapering period, pregnancy will be determined

by the test for human chorionic gonadotropin in urine or serum (only with post-menarchic females).

7.6.6.2 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.

7.6.7 Evaluation of adverse events

7.6.7.1 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.

7.6.7.2 Assessment period

Adverse events occurring between obtaining the legal representative's informed consent and 7 days after the final administration of study drug (the follow-up period) will be assessed. Adverse events that occur before initiation of administration in the extended long-term treatment study (study no.: 1702A3632), in subjects transferred to that study, will also be assessed. 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; (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. If the relevant subject transfers to the extended long-term treatment study (study no.: 1702A3632), follow-up of the adverse event will be continued after initiation of administration in that study, and it will be recorded in the CRF that the relevant adverse event continued after initiation of administration in the extended long-term treatment study. 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.

7.6.7.3 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.

7.6.7.4 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.

7.6.7.5 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.

7.6.7.6 Adverse events of special concern

7.6.7.6.1 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 エラー! 参照元が見つかりません。, 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.

7.6.7.7 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 7.6.7.8).
- 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.

7.6.7.8 Serious adverse events

7.6.7.8.1 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.

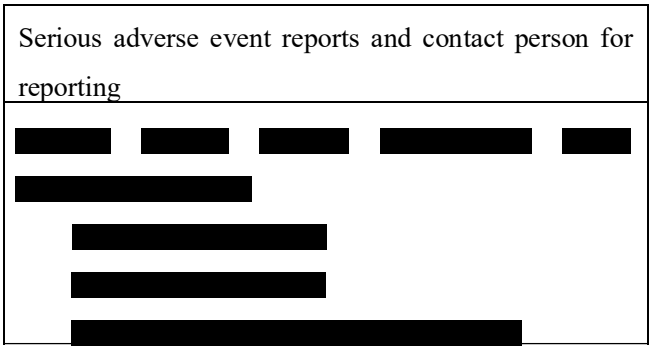
If an adverse event exposes a subject to danger, or requires medical procedures to prevent one of the results defined above, even if the event does not lead to death, is not life-threatening, and does not require hospitalization, it will be handled as a serious adverse event on the basis of appropriate 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.

7.6.7.8.2 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 7.6.7.2 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.

7.6.7.9 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.

7.6.7.10 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.

7.6.7.11 Adverse events during study drug administration

Adverse events with onset after the initial study drug administration are taken to be treatment-emergent adverse events.

7.7 Appropriateness of test items

CDRS-R, which is the primary efficacy endpoint in this study, is in widespread overseas use as an index of therapeutic efficacy against pediatric depression, and was selected as the primary endpoint in the HMCK and HMCL studies, which were overseas, Phase-3, double-blind, parallel-group, comparative studies on children and adolescent major depressive disorders (DSM-IV-TR). In addition, CGI-S is in general use in clinical studies on adult as well as pediatric depression.

Among safety endpoints, C-SSRS is in general, international use for assessing the presence or absence of suicide-related adverse events, about which there is widespread concern in relation to pediatric

antidepressant use. The other items are in standard use in clinical studies, and are widely accepted.

7.8 Permitted range of test times

Examination, observation and tests will be performed in accordance with Appemdix 1. If performance at the date and time shown in Appemdix 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)
Screening period	1	−3 to −1	−21 to −7	–
Treatment period	2	0	0	0
	3	1	7	±3
	4	2	14	±3
	5	3	21	±3
	6[a]	4	28	±3
	7	5	35	±3
	8	6	42	−3 to +1
	At discontinuation	–	Date of final administration in treatment period	0 to +3
Tapering period	9	7	On day 7, taking Visit 8 (or the time of discontinuation during the treatment period) to be day 0.	0 to +3
	At discontinuation	–	Final administration in tapering period	0 to +3
Follow-up period	10	8	On day 7 or later, taking the final administration date to be day 0.	–

a: Visit 6 is a visit that can be made to the hospital in connection with dose increase, decrease, etc.

8. Statistical analysis

8.1 Statistical analysis methods

The sponsor will commission a contract organization to perform the statistical analysis. The details of the analysis will be stipulated in the "Statistical 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 without fail. Statistical analysis plan will be fixed prior to unblinding of data.

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 all statistical tests unless otherwise specified. The primary endpoint in this study will be only change in CDRS-R total score from the baseline, so there will be no multiplicity adjustment for the statistical tests.

Subjects' data will be shown in separate tables for each subject. Table will be tabulated for each group as a rule and a list of data of each subject will be shown by group and subject. 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 number of subjects has been set with reference to the results obtained in two overseas, Phase-3 studies, the HMCL and HMCK studies, with the target population planned for the present study, that is, patients who were aged ≥9 when informed consent was obtained, and ≥7 at initial onset of depressive symptoms.

In the HMCL study, the inter-group difference (placebo - study drug 60 mg) in change in CDRS-R total score at week 7 between the 60-mg-study-drug group and the placebo group (CDRS-R change) was 4.66, so the efficacy of the study drug was suggested on the basis of point estimates. On the other hand, the inter-group difference in the HMCK study was -1.95, but the result with the positive control, fluoxetine, was also inferior to the placebo, and the HMCK study is therefore not considered to show analytical sensitivity. It was therefore decided to refer to the results of the HMCL study only for estimating the inter-group difference in the present study. In addition, it is hoped that in the present study more accurate selection of institutions and subjects will enable minimization of the placebo response, and thus increase in inter-group difference. In overseas studies also, when the analysis was performed with the above age restrictions applied, and institutions with marked placebo responses excluded, the inter-group difference tended to be greater than in the entire study. It is therefore considered that the inter-group difference will be greater than the 4.66 found in the HMCL study, and is assumed to be 5.9 (approximately 4.66 × 1.25).

With reference to information about CDRS-R change at week 7, in the 60-mg-study-drug and placebo groups in the HMCL study, and in the 60/120-mg-study-drug and placebo groups in the HMCK study, a common standard deviation of 13.2 was estimated for all four groups. In addition, if the above measures to increase study quality make a sufficient contribution, it is expected that the precision of CDS-R

evaluation will increase, and the standard deviation of the changes will decrease. It has been assumed that the standard deviation of the changes will be 12.0.

As explained above, in this study, the inter-group difference (placebo - duloxetine) between the duloxetine group and the placebo group in CDSRS-R change up to week 6 of treatment period is assumed to be 5.9, the standard deviation in CDRS-R change is assumed to be 12.0 in both groups, and the effect size is predicted to be 0.49. It is thus estimated that 66 subjects per group (total: 132) are required to achieve a detection power of 80% or higher in a two-sample t-test at a two-sided significance level of 0.05. Therefore, predicting the dropout rate to be 10%, the target total number of subjects has been set at 148 (74 per group).

8.3 Analysis sets

The following analysis sets are defined:

Full-analysis set (FAS)

This comprises all randomized 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. Even in the event of an incorrect prescription during the study, analysis of the FAS will be performed with the allocated group.

Safety-analysis set

This comprises all randomized subjects to whom the study drug is administered at least once. Analysis of this set will be performed with subjects actually administered the study drug, rather than allocated group.

Per-protocol set (PPS)

This comprises all randomized subjects who are included in the FAS, and to whom neither of the following conditions apply:

- Not meeting the inclusion criteria, and/or violating the exclusion criteria, in the protocol
- Insufficient compliance in study drug use.
- Violation of restrictions on concomitant treatment.

8.4 Handling of missing data

In principle, missing data will not be imputed. If missing data are nevertheless imputed for the secondary efficacy analyses, the LOCF method or baseline observation carried forward (BOCF) method will be used.

8.5 Subject characteristics

Of the subjects allocated to each group, the number and proportion who complete the study, and the number and proportion withdrawn will be summarized. The reasons for withdrawal will be summarized for each group. The number of subjects included in each analysis set, and the proportion of subjects allocated to each group 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 FAS.

8.7 Study drug administration period, dosage, and treatment compliance

With the safety analysis set, summary statistics for the study drug administration period and administration rate will be presented for each group. Summary statistics will also be presented for exposure in the duloxetine group.

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 FAS will be the primary efficacy analysis set. PPS will be used for sensitivity analysis of the primary efficacy analysis.

8.10.1 Primary efficacy endpoint

The primary efficacy endpoint is change from baseline in CDRS-R total score. In the primary efficacy analysis, the superiority of duloxetine over placebo will be verified for change from baseline to week 6 of administration (Visit 8). Baseline is defined as the data obtained at Visit 2, before randomization.

8.10.2 Secondary efficacy endpoints

The secondary efficacy endpoints will be as follows:

- 30% response rate: Proportion of subjects showing CDRS-R total score decreases of 30% or more from baseline.
- 50% response rate: Proportion of subjects showing CDRS-R total score decreases of 50% or more from baseline.
- Remission rate: Proportion of subjects with CDRS-R total scores of 28 or lower
- Change from baseline in CDRS-R subscales and item 13 (suicidal ideation)
- Change from baseline in CGI-S score.

8.10.3 Analysis of efficacy endpoints

(1) Analysis of primary efficacy endpoint

(A) Primary analysis

The MMRM method is used for primary analysis of efficacy. All usable data obtained at stipulated observation time-points after study drug administration will be used, and a linear model will be applied, with change in CDRS-R total score from baseline taken to be a response variable; treatment group,

observation time-points, and interaction between treatment group and observation time-points taken to be fixed effects; baseline total CDRS-R and age (<12, ≥12) taken to be covariates, and the covariance structure of error variance taken to be unstructured. When applying this linear model, the degree of freedom is adjusted using Kenward-Roger approximation. On the basis of this model, the superiority of the duloxetine group over the placebo group is evaluated in terms of change in CDRS-R score after administration for 6 weeks.

(B) Secondary analysis

1) Analysis of the PPS by the MMRM method

Change from baseline in CDRS-R total score is analyzed by the same method as used for the primary analysis of the PPS.

2) Change at week 6 of administration (analysis of covariance)

A) Analysis of covariance will be performed using the change from baseline up to week 6 of administration as the response variable, the treatment group as the fixed effect, and the baseline value and age (<12, ≥12) as covariates, to compare duloxetine and placebo. If the CDRS-R total score at week 6 of administration is not available, the missing data will be imputed by the LOCF method.

B) In addition to analysis of covariance using the LOCF (above), analyses of covariance using the BOCF and modified BOCF methods will be performed as exploratory investigation of the efficacy of this drug. The modified BOCF is defined as follows:

- For subjects withdrawn from the study due to adverse events or insufficient efficacy, the CDRS-R total score at week 6 of administration will be imputed using the BOCF method.
- For subjects withdrawn from the study for any reason other than the above, the CDRS-R total score at week 6 of administration will be imputed using the LOCF method.

3) Tipping-point analysis

Taking into consideration the potential for a situation in which the mechanism responsible for CDRS-R total score data being missing is “missing not at random”, tipping-point analysis will be performed on the basis of multiple imputation, and the effects of the missing data imputation method on the analysis results will be investigated.

(2) Analysis of secondary efficacy endpoints

The following analyses will be performed with the secondary efficacy endpoints:

1) 30% or 50% response rate, remission rate:

The number of responders and response rate will be obtained for each group, and the Cochran-Mantel-Haenszel test, with stratification by age (<12, ≥12), will be used to compare the duloxetine and placebo groups.

2) CDRS-R subscales and item 13 (suicidal ideation), and CGI-S:

The MMRM method will be used to compare the change from baseline to week 6 of administration in the duloxetine and placebo groups. A linear model with unstructured analysis of covariance of error variance will be applied, using change from baseline as the response variable; treatment groups, observation time-points, and interactions between treatment group and observation point as fixed effects; baseline value, and age (<12, ≥12) as the covariate.

8.11 Safety analysis

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, treatment-emergent adverse events will be used for safety analysis. Treatment-emergent adverse events are defined in Section 7.6.7.11 .

The number of subjects suffering treatment-emergent adverse events, and the numbers suffering death, other serious treatment-emergent adverse events, treatment-emergent adverse events leading to discontinuation of administration, and treatment-emergent adverse events leading to dose reduction, will be determined for each treatment group. The treatment-emergent adverse event 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 treatment-emergent adverse events. Adverse drug reactions are defined in Section 7.6.7.4 .

As summarization of treatment-emergent adverse events by system organ class and preferred term, the number and proportion of subjects suffering these events will be shown for each treatment group. In addition, treatment-emergent adverse events 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

Blood pressure and pulse rate summary statistics will be calculated for the measurements scheduled after randomization, and change from baseline at each time-point. The baseline is defined as the last value obtained before randomization. Summary statistics for body weight will be calculated similarly.

8.11.3 Laboratory test results

Laboratory test result summary statistics will be calculated for the measurements scheduled after randomization, and change from baseline at each time-point. The baseline is defined as the last value obtained before randomization.

For qualitative laboratory test results, the test category distribution will be summarized for the baseline and scheduled time-points.

8.11.4 ECG

The distribution of ECG findings (normal or abnormal) will be summarized for each group and 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 each assessment time-point scheduled after randomization.

8.12 Interim analysis

No design changes based on the interim results of this study are planned, so no interim analysis is scheduled.

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]

	[redacted]
Study sites and principal investigators	Appendix
Clinical research associate (CRA)	Appendix
Emergency contact	[redacted]
Allocation manager	[redacted]
Registration Center	[redacted]
Clinical laboratory facility	[redacted]
Clinical research organization (CRO)	[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. An electronic data-capture (EDC) system will be used to prepare the CRF. A CRF will be prepared for each subject from whom informed consent has been obtained, 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, CRFs can 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:

- 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:

- 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 discontinuing 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 procedures.

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 registory 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.
14. European Medicines Agency (EMA). Guideline on clinical investigation of medicinal products in the treatment of depression. 30 May 2013.

Appendix 1: Study Schedule

	Screening period	Treatment period								Tapering period	Follow-up period
Visit	1	2	3	4	5	6[b]	7	8	discontinuation	9/discontinuation	10
Evaluation week	−3 to −1	0	1	2	3	4	5	6	–	7	8
Obtaining informed consent or assent	X										
Demographic factors	X										
MINI-KID	X										
Inclusion/exclusion criteria:	X	X									
Physical Examination	X	X	X	X	X	(X)	X	X	X	X	X[f]
Registration	X Pre-registration 1	X Registration									
CDRS-R	X	X	X	X	X		X	X	X		
CGI-S	X	X	X	X	X	(X)	X	X	X		
Psycho-education	X[c]	X[c]			X[c]			X[c]	X[c]		
C-SSRS	X	X	X	X	X	(X)	X	X	X	X	
Study drug administered		X	X	X	X	(X)	X	X[d]	X[d]		
Adherence of drug administration			X	X	X	(X)	X	X	X	X	
Randomization		X									
Laboratory tests[a]	X				X			X	X	X	
Blood pressure, pulse rate	X	X	X	X	X	(X)	X	X	X	X	
ECG	X							X	X	X	
Body weight		X						X	X	X	
Urinary drug screening		X									
Pregnancy test (post-menarche females only)	X								X[e]	X	
Adverse events	X										

a Hematology tests, blood chemistry tests, and urinalysis. HbA1c, TSH, FT3 and FT4 measurements are only performed at Visit 1.

b Visit 6 is a visit that can be made to the hospital in connection with dose increase, decrease, etc. If Visit 6 is made, observations and tests are performed as far as possible.

c Psycho-education is provided after evaluation of CDRS-R and CGI-S.

d Tapering-period prescription.

e Performed at discontinuation if not performed during the tapering period.

f Adverse events up to 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.

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: Superiority study versus placebo

Study Protocol Number: 1701A3631

Version Number: 5

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 08:43:42 GMT +0000

[redacted]