Electronic Signature Page

Full Title
Long-term, open-label, flexible-dose, extension study of vortioxetine in child and adolescent patients with Major Depressive Disorder (MDD) from 7 to 18 years of age.

Short Title
12712A Protocol Edition 3.0

Study Number 12712A

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Clinical Study Protocol

Long-term, open-label, flexible-dose, extension study of vortioxetine in child and adolescent patients with Major Depressive Disorder (MDD) from 7 to 18 years of age

Vortioxetine

Study No.:	12712A
EudraCT No./IND:	2008-005356-25 / 112581
Sponsor:	H. Lundbeck A/S (Lundbeck) 2500 Valby (Copenhagen), Denmark
Edition No.:	3.0 (including PA2) (the version No. in the footer is the system version No.)
Date of edition:	16 January 2017
Edition history:	Edition 2.0, 18 January 2016 (including PA1) Edition 1.0 (original protocol), 6 November 2015

Synopsis – Study 12712A

Sponsor	**Investigational Medicinal Product**	**EudraCT No./IND No.**
H. Lundbeck A/S	Vortioxetine	2008-005356-25/ 112581

Title of Study

Long-term, open-label, flexible-dose, extension study of vortioxetine in child and adolescent patients with Major Depressive Disorder (MDD) from 7 to 18 years of age

Study Sites and Number of Patients Planned

Sites involved in studies 12709A and 12710A. Approximately 120 sites are planned in approximately 20 countries worldwide (specialists, mainly outpatient clinics)

Objectives

- Primary objective:
  - to evaluate the long-term safety and tolerability of vortioxetine in child and adolescent patients with a DSM-5™/diagnosis of MDD
- Secondary objectives:
  - to evaluate the long-term effectiveness of flexible doses of vortioxetine in a range of 5 mg/day to 20 mg/day on:
    - depressive symptoms
    - clinical global impression
    - cognitive function
    - functionality

Study Methodology

- Interventional, multi-national, multi-site, open-label, flexible-dose, long-term extension study in child and adolescent patients with MDD who completed one of the double-blind, placebo-controlled, active-reference studies 12709A and 12710A.
- The Baseline Visit of this extension study hereafter referred to as Baseline Extension A, will be Visit 12 (Completion Visit) of lead-in Study 12709A or 12710A.
- The dosage of vortioxetine will be initiated at 5 mg/day for the first 2 days prior to receiving 10 mg/day.
- The target dose is 10 mg/day; however the investigator has the possibility to adjust the dose in case of unsatisfactory response up to 20 mg or in case of dose-limiting adverse events. The dose can be up or down titrated with 5 mg/day. The patient should receive the same dose for 2 days before being up-titrated to a new dose. Changes in dosing may occur at any site visit during the treatment course at the investigator's discretion but the maximum dose may not exceed 20 mg/day.
- The treatment period is 26 weeks. The total study duration per patient from Baseline Extension A to the end of follow-up will be approximately 30 weeks.
- If possible, patients who withdraw are to be seen for a withdrawal visit as soon as possible and they will be contacted for a safety follow-up visit 4 weeks after withdrawal.
- The study design is presented in Panel 1 and the scheduled assessments are summarised in Panel 2.
- Investigators will not be informed about which treatment their patients received during the 12709A or 12710A study at the time of enrolling them into this open-label extension study.
- For ethical and equity reasons patients who turned 18 years during the lead-in study 12710A can be enrolled into this extension study.

Target Patient Population

- The patient is a male or female, child aged ≥7 and <12 years or adolescent aged ≥12 and ≤18 years at Baseline Extension A.
- The patient must have completed Study 12709A or 12710A (Visit 12, Completion Visit) immediately prior to enrolment into this extension study.
- The patient had a primary diagnosis of a Major Depressive Disorder (MDD) at entry in study 12709A or 12710A, diagnosed according to DSM-5™.
- The patient is indicated for long-term treatment with vortioxetine according to the clinical opinion of the investigator.

Investigational Medicinal Products, Doses and Mode of Administration

- Vortioxetine – 5 mg/day, tablets, orally
- Vortioxetine – 10 mg/day, tablets, orally
- Vortioxetine – 15 mg/day, tablets, orally
- Vortioxetine – 20 mg/day, tablets, orally

The treatment should be given once a day, preferably in the morning.

Efficacy Assessments

- Assessment of depressive symptoms:
  - Investigator rated
    - Children Depression Rating Scale Revised version (CDRS-R)
- Assessment of Global Impression:
  - Investigator rated
    - Clinical Global Impression Scale – Severity of Illness (CGI-S)
    - Clinical Global Impression Scale – Global Improvement (CGI-I)
- Assessment of cognitive function:
  - Parent rated (children aged 7-11 years at Baseline Extension A)
    - Behaviour Rating Inventory of Executive Function (BRIEF) – Global Executive Composite (overall summary score) – Subscales (initiate, working memory, plan/organize, organization of materials, monitor, inhibit, shift and emotional control)
    - BRIEF – Metacognition Index – Subscales (initiate, working memory, plan/organize, self-monitor, organization of materials)
  - Patient rated (adolescents aged 12-18 years at Baseline Extension A)
    - Behaviour Rating Inventory of Executive Function – Adolescent version- (BRIEF-SR) – Global Executive Composite (overall summary score) – Subscales (working memory, plan/organize, organization of materials, task completion, monitor, inhibit, shift and emotional control)
    - BRIEF-SR – Metacognition Index – Subscales (working memory, plan/organize, organization of materials and task completion)
- Assessment of functionality:
  - Investigator rated
    - Children's Global Assessment Scale (CGAS)
  - Patient rated
    - The PedsQL Present Functioning Visual Analogue Scales (PedsQL VAS)

Safety Assessments

- Adverse Events (AEs)
- Paediatric Adverse Event Rating Scale (PAERS)
- Clinical safety laboratory tests, including reproductive hormones
- Vital signs
- Menstrual cycle (age of menarche, the length of the menstrual cycle)
- Weight/Height
- Electrocardiograms (ECGs)
- Physical examinations including Tanner scoring
- Columbia Suicide Severity Rating Scale (C-SSRS)

Endpoints

- Primary endpoint:
  - description of safety parameters, see safety endpoints below.
- Secondary endpoints:
  - depressive symptoms:
    - change from Baseline Extension A to Week 26 in CDRS-R total score
    - time to first relapse (CDRS-R value of ≥40)
    - time to first loss of remission (CDRS-R >28)
  - Global Clinical Impression:
    - change from Baseline Extension A to Week 26 in CGI-S score
    - CGI-I score at Week 26. The assessment of the CGI-I should be in reference to Baseline A in the lead-in studies
  - cognitive function:

    Children (7-11 years)
    - change from Baseline Extension A to Week 26 in BRIEF using the Global Executive Composite score
    - change from Baseline Extension A to Week 26 in BRIEF using the Metacognition Index

    Adolescents (12-18 years)
    - change from Baseline Extension A to Week 26 in BRIEF-SR using the Global Executive Composite score
    - change from Baseline Extension A to Week 26 in BRIEF-SR using the Metacognition Index
  - functionality:
    - change from Baseline Extension A to Week 26 in CGAS score
    - change from Baseline Extension A to Week 26 in PedsQL VAS score
- Safety endpoints:
  - adverse events (AEs)
  - tolerability including assessment based on PAERS
  - Tanner score
  - absolute values and changes from Baseline Extension A in clinical safety laboratory tests, vital signs, weight, height, and ECG parameters
  - length of menstrual cycle
  - potentially clinically significant clinical safety laboratory test values, vital signs, weight, and ECG parameter values relative to Baseline Extension A
  - C-SSRS categorisation based on C-CASA definitions (1, 2, 3, 4, and 7)

Statistical Methodology

- The following analysis sets will be used to analyse and present the data:
  - *all-patients-treated set* (APTS) – all patients who took at least one dose of vortioxetine in the extension study.
  - *full-analysis set* (FAS) – all patients in the APTS with at least one valid post-Baseline Extension A assessment of the CDRS-R total score.
- The safety analyses will be based on the APTS.
- Descriptive statistics for all patients and by lead-in study and by treatment (n, arithmetic mean, standard deviation, median, minimum and maximum values) will be presented for continuous variables (values at each visit and, if relevant, changes from Baseline Extension A) and counts. If relevant, percentages will be presented for categorical variables.
- Analyses of safety endpoints:
  - Adverse events, PAERS items, Tanner scores, clinical safety laboratory tests, vital signs, height, weight, BMI, and ECG parameters will be summarised, and observed potentially clinically significant (PCS) safety laboratory test values will be flagged and summarised. The length of menstrual cycle and C-SSRS scores will be summarised using descriptive statistics.
  - The change from baseline will be derived with respect both to baseline in the lead-in studies and baseline in extension Study 12712A.
- The primary objective will be addressed with an overall clinical evaluation of the safety results.
- Adverse events occurring in the first two weeks of the study will be reported separately.
- The efficacy analyses will be based on the FAS.
- Analyses of efficacy endpoints:
  - Change from Baseline Extension A in CDRS-R, CGI-S, BRIEF, CGAS, and PedsQL VAS using descriptive statistics by lead-in study and by lead-in treatment.
  - CGI-I score at week 26 using descriptive statistics by lead-in study and by lead-in treatment.
  - Time to first relapse (CDRS-R value of ≥40) using Kaplan-Meier estimates.
  - Time to first loss of remission (CDRS-R >28) using Kaplan-Meier estimates.
- For exploratory use a random effects slope and intercept model on safety and efficacy parameters will be applied using Mixed Model Repeated Measurements (MMRM) to study long-term development in safety and efficacy parameters (e.g. weight and CDRS-R).
- Summaries and analyses will be performed with respect to the Baseline in the lead-in studies.
- No interim analyses for efficacy are planned. A DMC will monitor safety data at regular intervals to be specified in the Data Monitoring Committee Charter.

Pharmacokinetic Analysis

Sparse PK samples (2) will be collected to measure vortioxetine plasma concentration. The population PK of vortioxetine will be assessed by means of nonlinear mixed effect modelling and the results from the analysis will be reported in a separate population PK report.

Sample Size Considerations

No formal sample size calculation has been performed for the present study, which includes patients who have completed the studies 12709A or 12710A and are eligible for enrolment for this study. Sample size is based on an expected withdrawal of 15-20% of the 1200 patients randomised to the lead-in studies. A maximum of 85% of these lead-in completers are expected to accept to continue into this extension study. This gives approximately 850 patients.

Ethical Rationale for Study and Study Design

In May 2014, WHO's "Health for the world's adolescents" report reveals that "depression is the predominant cause of illness and disability for both boys and girls aged 10 to 19 years" and adds that the "top 3 causes of adolescent deaths globally are road traffic injuries, HIV/AIDS, and suicide. Worldwide, an estimated 1.3 million adolescents died in 2012". The prevalence of Major Depressive Disorder (MDD) is estimated to be approximately 2% in children and 4% to 8% in adolescents.

Only one antidepressant, fluoxetine, is currently approved in Europe for the treatment of MDD in children and adolescents. In the US only fluoxetine is approved for use in children and fluoxetine and escitalopram for use in the adolescent population. Development of a new antidepressant will increase and strengthen the pharmacological treatment options for this patient population. This study is an extension study to Studies 12709A and 12710A and part of the agreed EMA Paediatric Investigational Plan (PIP) and the US Pediatric Written Request (PWR) for vortioxetine with the purpose to investigate the long-term safety and tolerability of vortioxetine in paediatric patients aged 7-17 years. It is the expectation that this study will demonstrate a favourable safety and tolerability profile, and therefore a positive benefit-risk ratio for the use of vortioxetine in the paediatric population.

Vortioxetine is approved in the US, EU and a number of other countries for the treatment of MDE/MDD in the adult population. The evaluation of the safety and tolerability of vortioxetine is based on data from a large clinical development programme in adult and elderly patients. In the overall clinical development programme treatment with vortioxetine at the therapeutic doses (5-20 mg/day) was safe and well tolerated. The approved recommended dose range of 5-20 mg/day for adults was evaluated in a pharmacokinetic and tolerability study performed in the paediatric population (aged 7 to 17 years) designed to guide the choice of doses to be used in the planned paediatric programme. Hence the chosen doses of vortioxetine (5, 10, 15 and 20 mg/day) for this study is based on the results from the paediatric pharmacokinetic and tolerability study and the knowledge from the adult studies.

As extrapolation of adult safety data is not considered appropriate for the paediatric population; a specific paediatric study is warranted to thoroughly address the long-term safety/tolerability of vortioxetine in the paediatric population. The 26-week treatment period is in alignment with treatment guidelines in EU and US that recommend continuation therapy with an antidepressant for at least 6 months in children and adolescents. Patients will be asked to attend the investigational clinic at regular intervals to ensure an adequate follow-up. The visits will be performed either as a visit in an outpatient clinic or as a phone call. In order to minimize potential pain, distress, and fear, patients will be seen in facilities which will be appropriate for childcare; the study personnel who interact with the patients will be experienced health care professionals (physicians with paediatric qualification, qualified paediatric nurses or psychologists); their education, training and experience will be documented. Age-appropriate explanations will be given to the child/adolescent prior to any investigation or procedure, in order to decrease anxiety and anticipation of pain. Potentially painful procedures such as venepuncture will be minimised with the use of topical anaesthesia before venepuncture. Blood sampling will be limited to the minimum required for obtaining valid data for evaluation. The number of blood samples and visits has been carefully evaluated against the value for the overall objectives of the study.

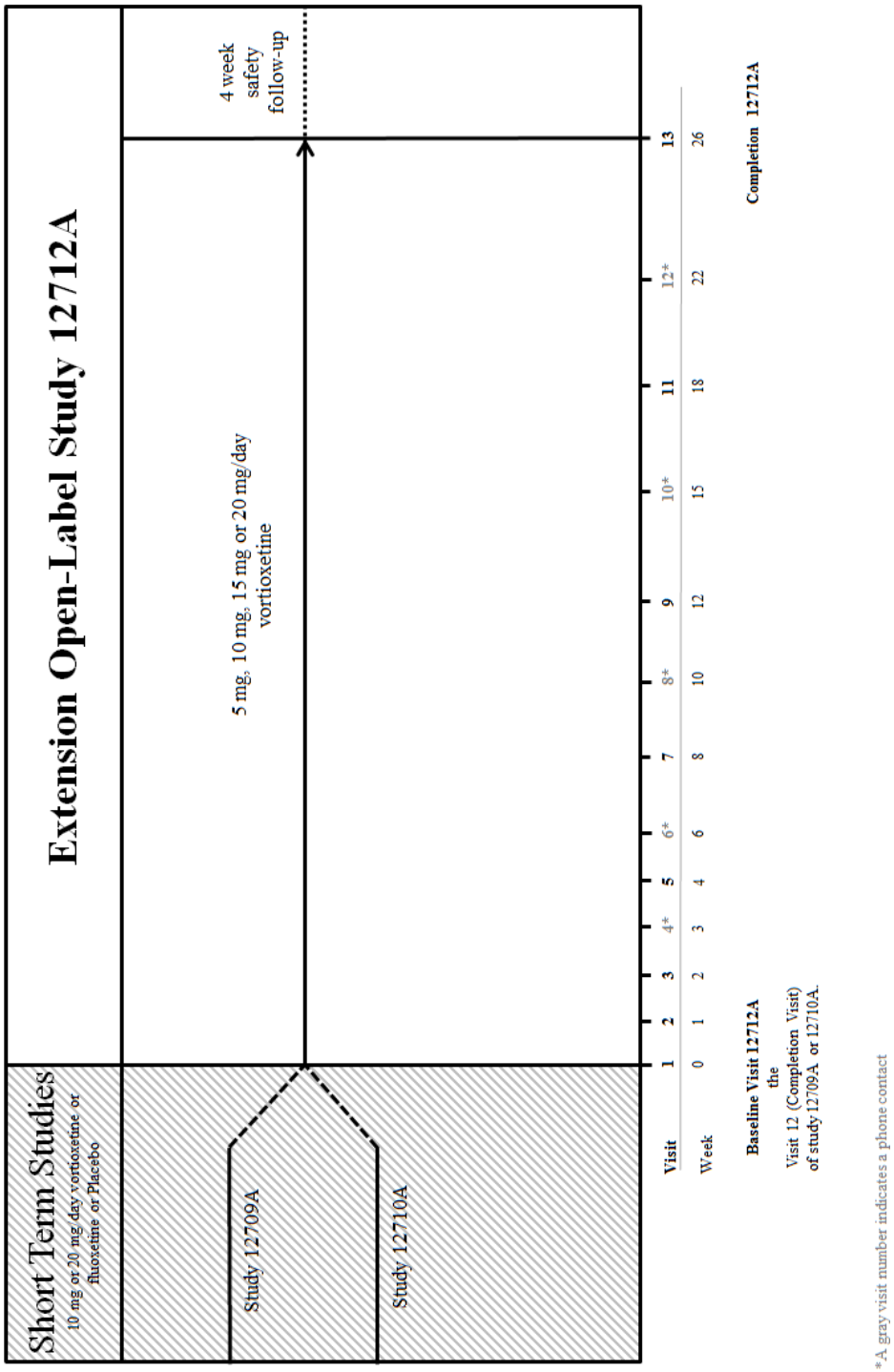
The investigator plays an important role in protecting the safety of the patient. The assessment of potential burden and risk is defined specifically in the clinical study protocol (safety rating scales, recording of adverse events, clinical safety laboratory tests (blood biochemistry, haematology and urine analysis), vital signs (blood pressure and pulse rate), weight, height, electrocardiogram and physical examination) and these will be evaluated by the investigator at each visit to ensure the patients' safety and well-being. If it does not remain in the patient's best interest to stay in the study, the investigator will ensure that the patient is withdrawn. Patients that are withdrawn from the study and do not complete, will be treated according to normal clinical practice.

In accordance with Good Clinical Practice, qualified medical personnel at Lundbeck will be available to advice on study-related medical questions. Medical monitoring and safety surveillance will be performed throughout the study according to Lundbeck standard procedures, and Lundbeck will regularly monitor and re-examine the balance of risks and benefit of the full clinical study, so that the health and well-being of paediatric patients enrolled will be safeguarded.

The selection criteria exclude the participation of patients at significant risk of suicide, and patients becoming at significant suicidal risk during the study will be withdrawn. Throughout the study, potential suicidal risk will be assessed both by rating scale (Columbia-Suicide Severity Rating Scale) and by the investigator's judgment.

An independent Data Monitoring Committee will be established in order to review the safety and tolerability data throughout this study. The same DMC will cover all the clinical studies in the paediatric vortioxetine program.

Panel 1 Study Design



Panel 2 Study Procedures and Assessments

Visit	Base-line Extension A	Treatment Period											Com-pletion /With-drawal[a]	Safety Follow-up[b]
Visit Number	**1**	**2**	**3**	**4[c]**	**5**	**6[c]**	**7**	**8[c]**	**9**	**10[c]**	**11**	**12[c]**	**13**	**14**
End of Week	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**15**	**18**	**22**	**26**	**30**
Visit Window[d] (days relative to nominal visit)	**0**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 5**	**± 5**	**± 5**
Baseline Extension A Procedures and Assessments														
Signed informed consent/assent	√													
Inclusion/exclusion criteria	√													
Efficacy Assessments														
CDRS-R	√[e]	√	√		√		√		√		√		√	
CGI-S	√[e]	√	√		√		√		√		√		√	
CGI-I[f]	√[e]	√	√		√		√		√		√		√	
BRIEF (7-11 years at Baseline Extension A)	√				√		√		√		√		√	
BRIEF-SR (12-18 years at Baseline Extension A)	√				√		√		√		√		√	
CGAS	√[e]				√		√		√		√		√	
PedsQL VAS (PRO)	√[e]				√		√		√		√		√	
Vortioxetine Quantification														
Blood sampling vortioxetine quantification	√[e]				√								√	
Safety Assessments														
Adverse events	√[g]	√	√	√	√	√	√	√	√	√	√	√	√	√[h]
Blood and urine sampling for clinical safety laboratory tests	√[e,i]				√								√	
Vital signs	√[e]	√	√		√		√		√		√		√	
Weight and height	√[e]								√				√	
Menstrual cycle and Tanner score	√								√				√	
ECGs	√[e]				√								√	
Examinations (physical and neurological)	√[e]								√				√	
PAERS	√[e]	√	√	√	√	√	√	√	√	√	√	√	√	
C-SSRS	√[e]	√	√	√	√	√	√	√	√	√	√	√	√	

Visit	Base-line Extension A	Treatment Period											Com-pletion /With-drawal[a]	Safety Follow-up[b]
Visit Number	**1**	**2**	**3**	**4[c]**	**5**	**6[c]**	**7**	**8[c]**	**9**	**10[c]**	**11**	**12[c]**	**13**	**14**
End of Week	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**15**	**18**	**22**	**26**	**30**
Visit Window[d] (days relative to nominal visit)	**0**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 5**	**± 5**	**± 5**
Other Study Procedures														
IMP dispensed	√	√	√		√		√		√		√			
Possible change in IMP dose		√	√		√		√		√		√			
IMP returned and IMP accountability		√	√		√		√		√		√		√	
Recent and concomitant medication	√[g]	√	√	√	√	√	√	√	√	√	√	√	√	
Pregnancy test[j]	√[e]				√								√	
Drug and alcohol screen[e,k]														

a This visit should take place as soon as possible after the patient withdraws from the study.

b This can be a telephone contact, unless an SAE has occurred since the last visit or unless there was a clinically significant abnormal safety laboratory test value at the last visit. In such cases, safety follow-up(s) must be scheduled to allow for a medical examination and/or blood/urine sampling. Further safety follow-up visits beyond 30 days may be needed as judged by the investigator (if further safety follow-up visits are performed, these must be recorded in the patient's medical record, and not in the eCRF).

c A telephone contact. The patient and/or legal representative and/or the investigator can request an unscheduled site visit to discuss their current dose. During such an unscheduled site visit, the CDRS-R, CGI-S, CGI-I, PAERS and C-SSRS must be performed.

d If the date of a patient visit does not conform to the study plan, subsequent visits should be planned to maintain the visit schedule relative to Baseline Extension A. The number of days between 2 visits must not exceed the number of days for which IMP is provided for in the drug kit.

e Values from assessments and procedures conducted at Visit 12 (Completion Visit) of Study 12709A or 12710A will be the Baseline Extension A Visit values for this study (12712A).

f The assessment of the CGI-I should be in reference to Baseline A in the lead-in studies.

g Ongoing adverse events and concomitant medications (at Completion Visit 12 in Study 12709A or 12710A) will be transcribed to the eCRF Adverse Event Form and Concomitant Medication Form.

h Only for adverse events ongoing at Completion/Withdrawal and new SAEs.

i The 12712A Hormones panel is to be collected using a separate study-specific kit

j Females >10 years of age or female patients at lower age judged by the investigator to be of childbearing potential. Additional pregnancy tests during the study will be performed according to local requirements. Females <11 years will be tested using a urine hCG test and females >11 years will be tested using a blood hCG test.

k It is not mandatory to screen for drugs and/or alcohol. However, it can be performed at any visit, at the discretion of the investigator.

Table of Contents

Appendices

List of Panels

List of Abbreviations and Definitions of Terms

AIDS	Acquired Immune Deficiency Syndrome
ALT	alanine aminotransferase
APTS	all-patients-treated set
AST	aspartate aminotransferase
BPCA	Best Pharmaceuticals for Children Act
BRIEF	Behaviour Rating Inventory of Executive Function
BRIEF-SR	Behaviour Rating Inventory of Executive Function self-report
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CDRS-R	Children Depression Rating Scale Revised Version
CGAS	Children's Global Assessment Scale
CGI-I	Clinical Global Impression – Global Improvement
CGI-S	Clinical Global Impression – Severity of Illness
CRA	clinical research associate
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450 isoenzyme
DMC	Data Monitoring Committee
DO	doctor of osteopathic medicine
DSM-5™	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSM-IV-TR™	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision
ECG	Electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	United States Food and Drug Administration
PV	Division of Pharmacovigilance, H. Lundbeck A/S
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
IND	Investigational New Drug Application
IRB	institutional review board
IVRS	interactive voice response system
IWRS	interactive web response system
Lu	Lundbeck

MDD	major depressive disorder
NA	not applicable
PAERS	Paediatric Adverse Event Rating Scale
PedsQL™ VAS	PedsQL Present Functioning Visual Analogue Scales
PIP	Paediatric Investigational Plan
PK	pharmacokinetic(s)
PREA	US Paediatric Research Equity Act
PRO	patient-reported outcome
QP	qualified person
SAE	serious adverse event
SD	standard deviation
SERT	serotonin (5-HT) transporter
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TMF	trial master file
TSH	thyroid stimulating hormone
US PREA	US Paediatric Research Equity Act
WHO	World Health Organization

1 Introduction

1.1 Background

1.1.1 Overview

Mood disorders in children and adolescents are among the most debilitating illnesses, exerting a major impact on family and social functioning, school performance and an increased risk of recurrence, substance abuse, psychiatric comorbidity and suicidality.[1,2,3,4] In May 2014, WHO's *Health for the world's adolescents*[5] report reveals that depression is the predominant cause of illness and disability for both boys and girls aged 10 to 19 years and adds that the top 3 causes of adolescent deaths globally are road traffic injuries, HIV/AIDS, and suicide. Worldwide, an estimated 1.3 million adolescents died in 2012. The prevalence of Major depressive disorder (MDD) is estimated to be approximately 2% in children and 4 to 8% in adolescents.[3,4,6,7]

Only one antidepressant, fluoxetine, is currently approved in Europe for the treatment of MDD in children and adolescents. In the US only fluoxetine is approved for children and fluoxetine and escitalopram for the adolescent population. Development of a new antidepressant will increase and strengthen the pharmacological treatment options for this patient population.

Signs and symptoms of MDD in children and adolescents are similar to the adult population, but depressive disorders meeting the diagnostic criteria rarely is present before the age of seven years.[8,9] The clinical picture may differ according to age at presentation. Children may have mood liability, irritability, low frustration tolerance, somatic complaints, and/or social withdrawal instead of verbalising feelings of depression, whilst adolescents are more likely than children to complain of feelings of hopelessness/helplessness, lack of energy and to have a higher rate of suicidal thoughts.[1,10] As extrapolation of adult safety data is not considered appropriate for the paediatric population; a specific paediatric study is warranted to thoroughly address the long-term safety/tolerability of vortioxetine in the paediatric population. The 26-week treatment period is in alignment with treatment guidelines in EU and US that recommend continuation therapy with an antidepressant for at least 6 months in children and adolescents.[1,9]

The following sections provide an overview of the nonclinical and clinical data currently available for vortioxetine. For further information please refer to the current version of the *Investigator's Brochure.*[11]

1.1.2 Nonclinical Data

The mechanism of action of vortioxetine is thought to be related to its direct modulation of serotonergic receptor activity and inhibition of the serotonin (5-HT) transporter (SERT). Nonclinical data indicate that vortioxetine is a 5-HT3, 5-HT7, and 5-HT1D receptor

antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist and inhibitor of the SERT, leading to modulation of neurotransmission in several systems. This multimodal activity is considered to be responsible for the antidepressant and anxiolytic-like effects and the improvement of cognitive function, learning and memory observed with vortioxetine in animal studies.[12]

Average exposures to vortioxetine and metabolites at the relevant human therapeutic doses are below the toxicity levels (NOAEL) determined in animals. In support of the paediatric program, 3 juvenile toxicity studies were completed. These studies concluded that no new or critical vortioxetine treatment-related findings were seen in juvenile rats compared to the repeat-dose toxicity and reproductive studies in adult rats.

1.1.3 Clinical Data

1.1.3.1 Pharmacokinetics

In adults, vortioxetine has shown to be a compound with slow absorption, large volume of distribution and medium clearance. Vortioxetine is slowly, but well absorbed after oral administration and the peak plasma concentration is reached within 7 to 11 hours. Following multiple dosing of 5, 10, or 20 mg/day, mean C_{max} values of 9 to 33 ng/mL were observed. The absolute bioavailability is 75%. No effect of food on the pharmacokinetics was observed. The mean volume of distribution (V_{ss}) is 2,600 L, indicating extensive extravascular distribution. Vortioxetine is highly bound to plasma proteins (98 to 99%) and the binding appears to be independent of vortioxetine plasma concentrations. Vortioxetine is extensively metabolised in the liver, primarily through oxidation catalysed by CYP2D6 and to a minor extent CYP3A4/5 and CYP2C9, and subsequent glucuronic acid conjugation. No inhibitory or inducing effect of vortioxetine was observed in the drug-drug interaction studies for the CYP isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5. Vortioxetine is a poor P-gp substrate and inhibitor. The major metabolite (Lu AA34443) of vortioxetine is pharmacologically inactive. The mean elimination half-life and oral clearance are 66 hours and 33 L/h, respectively. The pharmacokinetics is linear and time independent in the dose range studied (2.5 to 60 mg/day).[11]

In study 12708A, entitled *An open-label study evaluating the pharmacokinetics and tolerability of Lu AA21004 in connection with multiple oral dosing of Lu AA21004 in child and adolescent patients with a DSM-IV-TR™ diagnosis of depressive or anxiety disorder*, the pharmacokinetic properties of vortioxetine in the children and adolescent population after 14 days of dosing with 5, 10, 15 and 20 mg were investigated. Data showed that the exposures to vortioxetine and its metabolite Lu AA34443, in terms of C_{max} and AUC, increased in a dose-proportional manner and were generally lower in the adolescent patients than in the children, but data suggests that the doses tested (5 to 20 mg/day vortioxetine) and the up-titration scheme employed in this study are appropriate for the paediatric population.

1.1.3.2 Efficacy

Vortioxetine has been approved in the US, EU and a number of other countries for the treatment of MDD in the adult population. Broad efficacy on depressive symptoms has been proven in an extensive clinical development program. Vortioxetine was efficacious, safe, and well tolerated in adults and in the elderly with MDD in short-term treatment and long-term maintenance. This also includes proven effect of vortioxetine on cognitive dysfunction in adult patients with MDD, assessed using a range of objective neuropsychological tests.

To date, the efficacy of vortioxetine has not yet been investigated in children with MDD.

1.1.3.3 Safety

The evaluation of the safety and tolerability of vortioxetine is based on data from a large clinical development programme. In the completed Phase II to IV short- and long-term studies in adults, more than 8000 patients with MDD or Generalized Anxiety Disorder (GAD) received vortioxetine at doses of 1 to 20 mg/day, corresponding to an overall exposure >3200 patient-years. Overall short- and long-term treatment with vortioxetine at the therapeutic doses (5-20 mg/day) was safe and well tolerated in adults and in the elderly. The incidence of nausea, the most common adverse event (AE), showed a trend towards a dose-response relationship. For vortioxetine, at the therapeutic doses, the incidences of adverse events such as insomnia, somnolence, fatigue, and hyperhidrosis, were at placebo level, as was the incidence of sexual dysfunction. The changes in body weight, vital signs, ECGs (including the QTc interval), and clinical safety laboratory tests (including liver and renal tests) were at placebo level for all therapeutic doses of vortioxetine. Abrupt discontinuation of vortioxetine after short, as well as after long-term treatment was well tolerated. Based on an 8-week vortioxetine study, the direct switch from ≥6-week treatment with selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor (SSRI/SNRI) to vortioxetine was well tolerated.

The tolerability of vortioxetine in multiple oral doses of 5 to 20 mg/day was also evaluated in an open label study among children and adolescent patients (aged 7 to 17 years) with a DSM-IV-TR™ diagnosis of depressive or anxiety disorder. The purpose of this, open-label study was to assess the safety, tolerability, and pharmacokinetics of vortioxetine in children and adolescents with depressive or anxiety disorder and to provide supportive information for its dose regimen in paediatric efficacy and safety studies. In total 24 children and 24 adolescents received vortioxetine. Based on the data from this study, no concerns were raised on the safety and tolerability profile of vortioxetine among paediatric patients with depression or anxiety. Vortioxetine was safe and well tolerated following 14 days of dosing as well as during an initial up-titration period. Overall, the adverse event profile in adolescents and children appeared similar to that of the adult population. Nausea, headache and sedation were the TEAEs with the overall highest incidence in this study. Nausea is also the most common TEAE in studies with adult patients, with an incidence of approximately 20 to 30% following 5 to 20 mg vortioxetine. Other common TEAEs were sedation, abdominal pain upper, fatigue, and vomiting. There was no apparent relationship between dose and the incidence of these adverse events.

1.2 Rationale for the Study

Mood disorders in children and adolescents are among the most debilitating illnesses, exerting a major impact on family and social functioning, school performance and an increased risk of recurrence, substance abuse, psychiatric comorbidity and suicidality.[1,2,3,4]

As outlined in the EMA *Assessment of the Paediatric Needs in psychiatry* there is a therapeutic need in the paediatric population of depressed patients.[13] Although several acute treatment studies of antidepressants have been completed in the MDD patient population, only two antidepressants have shown replicate efficacy in two or more trials, and have received regulatory approval for the treatment of MDD in paediatric patients. Fluoxetine in the treatment of children and adolescents with MDD,[14,15] and escitalopram in the treatment of adolescents with MDD.[16,17]

Specific studies are necessary in the paediatric population and separate studies should generally be conducted in children and adolescents.[18] This study is an extension study to Studies 12709A and 12710A and part of the agreed EMA Paediatric Investigational Plan (PIP) and the US Pediatric Written Request (PWR) for vortioxetine with the purpose to investigate the long-term safety and tolerability of vortioxetine in paediatric patients aged 7-17 years. It is the expectation that this study will demonstrate a favourable safety and tolerability profile, and therefore a positive benefit-risk ratio for the use of vortioxetine in the paediatric population.

2 Objectives

Primary Objective

- Primary objective:
  - to evaluate the long-term safety and tolerability of vortioxetine in child and adolescent patients with a DSM-5™/diagnosis of MDD

Secondary Objectives

- Secondary objectives:
  - to evaluate the long-term effectiveness of flexible doses of vortioxetine in a range of 5 mg/day to 20 mg/day on:
    - depressive symptoms
    - clinical global impression
    - cognitive function
    - functionality

3 Study Design

3.1 Overview of the Study Design

This study has been designed in accordance with the *Declaration of Helsinki.*[19]

This is an interventional, multi-national, multi-site, open-label, flexible-dose, long-term extension study in child and adolescent patients with MDD who completed one of the double-blind, placebo-controlled, active-reference Studies 12709A and 12710A.

This study will be conducted in compliance with the protocol, *Good Clinical Practice*,[20] and applicable regulatory requirements.

An overview of the study is presented in Panel 1.

The Baseline Visit of this extension study, hereafter referred to as Baseline Extension A, will be Visit 12 (Completion Visit) of lead-in Study 12709A or 12710A.

The dosage of vortioxetine will be initiated at 5 mg/day for the first 2 days prior to receiving 10 mg/day.

The target dose is 10 mg/day; however the investigator has the possibility to adjust the dose in case of unsatisfactory response up to 20 mg or in case of dose-limiting adverse events. The dose can be up or down titrated with 5 mg/day. The patient should receive the same dose for 2 days before being up-titrated to a new dose. Changes in dosing may occur at any site visit during the treatment course at the investigator's discretion but the maximum dose may not exceed 20 mg/day.

The treatment period is 26 weeks. The total study duration per patient from Baseline Extension A to the end of follow-up will be approximately 30 weeks.

If possible, patients who withdraw are to be seen for a withdrawal visit as soon as possible and they will be contacted for a safety follow-up visit 4 weeks after withdrawal.

Investigators will not be informed about which treatment their patients received during the 12709A or 12710A study at the time of enrolling them into this open-label extension study.

For ethical and equity reasons patients who turned 18 years during the lead-in study 12710A can be enrolled into this extension study.

Approximately 850 patients at approximately 120 sites from 12709A and 12710A are planned for enrolment.

An independent Data Monitoring Committee will be established in order to review the safety and tolerability data throughout this study. The same DMC will cover all the clinical studies in the pediatric vortioxetine program.

An internal safety committee at H. Lundbeck A/S has been set up for vortioxetine, who will perform regular evaluations of blinded safety data.

3.2 Rationale for the Study Design

The proposed study 12712A is an interventional, open-label, flexible-dose, long-term extension study with the primary objective to evaluate the long-term safety and tolerability of vortioxetine in children and adolescents with a DSM-5™ diagnosis of MDD who completed studies 12709A or 12710A. Secondary objectives are to evaluate the long-term effectiveness of flexible doses of vortioxetine in a range of 5 mg/day to 20 mg/day on depressive symptoms, clinical global impression, cognitive function and functionality.

In the overall adult clinical development programme, treatment with vortioxetine at the therapeutic doses (5-20 mg/day) was safe and well tolerated. It has been suggested that a failure to conduct and use information from appropriately designed preliminary pharmacokinetic and dose-finding studies has contributed to the failure of several large scale antidepressant studies in the paediatric MDD population.[21] The chosen doses of vortioxetine for this study are based on the knowledge from the clinical development programme in adult patients and from the paediatric pharmacokinetic and tolerability study performed in the paediatric population (aged 7 to 17 years) designed to guide the choice of doses to be used in the planned paediatric investigation plan.

The primary efficacy endpoint will be the CDRS-R total score. The CDRS-R[22] is the most widely used rating scale in clinical trials for assessing severity of depression and change in depressive symptoms in children and adolescents with depression. The CDRS-R is based on the adult Hamilton Depression Rating Scale. The Psychometric analyses provide evidence that the CDRS-R is a valid measure of severity and improvement of depressive symptoms in paediatric patients. A score of ≥40 is indicative of depression, whereas a score ≤28 is often used to define remission (minimal or no symptoms).

The CGI-S and CGI-I will be used for assessing disorder severity and improvement.[23]

The Behaviour Rating Inventory of Executive Function (BRIEF)[24] will be used to assess cognitive function for the children aged 7-11 years and the BRIEF-SR will be used for the adolescents aged 12-18 years. The BRIEF was designed to be used for a range of childhood disorders to assess executive function behaviors in the school and home environments. Children's Global Assessment Scale (CGAS) and the PedsQL Present Functioning Visual Analogue Scales (PedsQL™ VAS) will be used to assess functionality. Children and adolescents with MDD are at high risk of having severe difficulties in various domains of functioning and in quality of life.[1,25] Both the BRIEF, CGAS and PedsQL™ VAS are validated scales appropriate for use in children and adolescents with psychiatric disorders.[24,25,26]

4 Ethics

4.1 Ethical Rationale

Patients will be fully informed about the study including the risks and benefits of his or her participation. The patient may withdraw from the study at any time, for any reason. Unscheduled visits can be made and immediate withdrawal is possible. Throughout the study, signs of suicidal risk will be assessed and patients at risk will be withdrawn.

The risks associated with the study are considered, well controlled by cautionary measures in the study design, and well balanced with the potential benefits of the treatment. Vortioxetine is approved in the US, EU and a number of other countries for the treatment of MDE/MDD in the adult population. The evaluation of the safety and tolerability of vortioxetine is based on data from a large clinical development programme in adult and elderly patients. In the overall clinical development programme treatment with vortioxetine at the therapeutic doses (5-20 mg/day) was safe and well tolerated. The approved recommended dose range of 5-20 mg/day for adults was evaluated in a pharmacokinetic and tolerability study performed in the paediatric population (aged 7 to 17 years) designed to guide the choice of doses to be used in the planned paediatric programme. Hence the chosen doses of vortioxetine (5, 10, 15, and 20 mg/day) for this study is based on the results from the paediatric pharmacokinetic and tolerability study and the knowledge from the adult studies.

The patients will be asked to attend the investigational clinic at regular intervals to ensure an adequate follow-up. The visits will be performed either as a visit in an outpatient clinic or as a phone call. In order to minimize potential pain, distress, and fear, patients will be seen in facilities which will be appropriate for childcare. The study personnel who interact with the patients will be experienced health care professionals (physicians with paediatric qualification, qualified paediatric nurses or psychologists) and their education, training and experience will be documented. Age-appropriate explanations will be given to the child/adolescent prior to any investigation or procedure, in order to decrease anxiety and anticipation of pain. Potentially painful procedures such as venepuncture will be minimised with the use of topical anaesthesia before venepuncture. Blood sampling will be limited to the minimum required for obtaining valid data for evaluation. The number of blood samples and visits has been carefully evaluated against the value for the overall objectives of the study.

The investigator plays an important role in protecting the safety of the patient. The assessment of potential burden and risk is defined specifically in the clinical study protocol (safety rating scales, recording of adverse events, clinical safety laboratory tests [blood biochemistry, haematology, reproductive hormones and urine analysis], vital signs [blood pressure and pulse rate], weight, electrocardiogram and physical examination) and these will be evaluated by the investigator at each visit to ensure study the patients' safety and well-being. If it does not remain in the patient's best interest to stay in the study, the investigator will ensure that the patient is excluded. If the patient is not completing the study, a treatment will be offered to the patient at the discretion of the investigator in line with clinical practice.

In accordance with *Good Clinical Practice,*[20] qualified medical personnel at Lundbeck or a delegate will be readily available to advise on study-related medical questions. Medical monitoring will be performed throughout the study. Safety data will be reviewed regularly by the Lundbeck Vortioxetine Safety Committee to ensure that prompt action is taken, if needed, to maximise patient safety.

The selection criteria exclude the participation of patients at significant risk of suicide, and patients becoming at significant suicidal risk during the study will be withdrawn. Throughout the study, potential suicidal risk will be assessed both by rating scale *The Columbia-Suicide Severity Rating Scale* and/or by the investigator's judgment.

An independent Data Monitoring Committee will be established in order to review the safety and tolerability data throughout this study. The same DMC will cover all the clinical studies in the pediatric vortioxetine program.

In accordance with *Good Clinical Practice*,[20] the investigator will be responsible for all study-related medical decisions.

4.2 Informed Assent/Consent

No study-related procedures may be performed before the investigator has obtained written assent from the patient and written informed consent from his or her parents/legal representative, or written informed assent/consent from the patient (if applicable).

Minors are dependent on their legal representative(s) (typically their parent[s]) to assume responsibility for their participation in clinical studies.[27]

If the informed assent/consent process may be delegated, the requirements for the delegates must be documented prior to the start of the study. National laws must always be adhered to when allowing potential delegation. Any delegation must be documented in the site delegation log.

The investigator must identify vulnerable patients, that is, patients whose willingness to participate in this study might be unduly influenced by the expectation, regardless of whether it is justified, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Patients thus identified must be excluded from participation in the study.

Prior to obtaining written informed assent/consent, the investigator or a designee must explain to the patients and/or their legal representatives (if applicable) the aims, methods, and potential hazards of the study and any discomfort it may entail. The patients and their legal representatives (if applicable) must be informed that their participation in the study is voluntary and that they are free to withdraw from the study at any time without justifying their decision. The patients and their legal representatives (if applicable) must be informed of the possibility of withdrawing assent/consent (section 8.3).

The patients and their legal representatives (if applicable) must be given ample time and opportunity to enquire about details of the study prior to deciding whether to participate in the study.

It is the responsibility of the investigator to ensure that all questions about the study are answered to the satisfaction of the patients and their legal representatives. Prior to including a patient in the study, an *Informed Assent Form* must be signed and dated by the patient and an *Informed Consent Form* signed by his or her parent and/or legal representative and signed and dated by the investigator or a designee. The patients and their legal representatives must receive a copy of the written information (*Patient Information Sheet*) as well as a copy of the signed *Informed Assent/Consent Forms*.

The consent procedures described above will only be implemented if allowed by local law and regulations and will only be initiated after approval by the relevant ethics committees.

4.3 Personal Data Protection

In accordance with European Union Directive 95/46/EC,[28] the data will be processed in accordance with the specifications outlined by the Danish Data Protection Agency to ensure that requirements regarding personal data protection are met. If an external organisation will process data on behalf of Lundbeck, a contractual procedure will be signed between Lundbeck and the external organisation to ensure compliance with the above-mentioned legislation.

If applicable, the participation of patients in this study will be reported to the appropriate local data protection agencies, in accordance with European Union Directive 95/46/EC and country-specific guidelines and laws.

4.4 Independent Ethics Committees (IECs) and Institutional Review Boards (IRBs)

This study will be conducted only after approval of the protocol has been granted by the appropriate IEC or IRB and a copy of the written approval has been received by Lundbeck.

The investigator must not include any patients before receiving written approval from the IEC or IRB.

The IEC or IRB must be informed when specific types of protocol amendments have been made and must be asked whether a re-evaluation of the ethical aspects of the study is necessary.

If applicable, interim reports on the study and reviews of its progress will be submitted to the IEC or IRB by the investigator at intervals stipulated in its guidelines.

4.5 Regulatory Approval/Notification Requirements

In accordance with local requirements, this study will be submitted to the regulatory authorities for approval or notification. The study will only be undertaken when Lundbeck has received written approval or confirmation of notification from the regulatory authorities.

5 Study Population

5.1 Numbers of Patients and Sites

Planned countries and regions:

A global study with patients from the US, EU and other geographic regions

Planned number of patients:

to be enrolled (approximately):	850

Planned number of:

study sites (approximately):	120

5.2 Selection Criteria

Patients will be recruited among those who complete treatment in Study 12709A or 12710A.

Patient selection is based on the inclusion and exclusion criteria listed below.

Patients who meet each of the inclusion criteria and none of the exclusion criteria at the Baseline Extension A Visit of this extension study are eligible to participate in this study. However, the sponsor reserves the right to utilise quality oversight methods to determine appropriateness of patient enrolment into the study.

Inclusion Criteria

1. The patient is a male or female child aged ≥7 and <12 years or adolescent aged ≥12 and ≤18 years at Baseline Extension A.
2. For patients aged ≥7 and ≤17 years at the Baseline Extension A visit; the patient is able to understand the Informed Assent Form, and parent(s)/legal representative(s)/ are able to read and understand the Informed Consent Form.
3. For patients aged ≥7 and ≤17 years at the Baseline Extension A visit; The patient has provided a new assent to participation (signed the new informed assent form) and parent(s)/legal representative(s) signed the new Informed Consent Form which are separate from the informed assent/consent obtained from patient and parent(s)/legal representative(s) for Study 12709A or 12710A.
4. For patients aged 18 at the Baseline Extension A visit; the patient is able to read and understand the Informed Consent Form.

5. For patients who turned 18 years during the lead-in study 12710A; the patient has signed the Informed Consent Form.
6. The patient and parent(s)/ legal representative(s) are willing and able to attend study appointments within the specified time windows. For patients who turned 18 years during the lead-in study 12710A; the patient is willing and able to attend study appointments within the specified time windows.
7. The patient must have completed Study 12709A or 12710A (Visit 12, Completion Visit) immediately prior to enrolment into this extension study.
8. The patient had a primary diagnosis of a Major Depressive Disorder (MDD) at entry in Study 12709A or 12710A, diagnosed according to DSM-5™.
9. The patient is indicated for long-term treatment with vortioxetine according to the clinical opinion of the investigator.
10. The patient, if a female of childbearing potential (defined as girls aged ≥10 years old and younger girls who, at the discretion of the investigator, are deemed to be of reproductive potential) and sexually active, must:
    - use adequate, highly effective contraception (defined as those that result in a low failure rate [that is, <1% per year] when used consistently and correctly, for example, implants, injectables, combined oral contraceptives in combination with a double barrier method, some intrauterine devices, sexual abstinence, vasectomised partner); this should be used from the Screening Visit of the lead in study 12709A or 12710A to 30 days after the last dose of IMP.
11. The patient, if a male patient and sexually active, must:
    - use two methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from the Screening Visit of the lead in study 12709A or 12710A to 30 days after the last dose of IMP, OR
    - if applicable have been surgically sterilised prior to the Baseline Extension A Visit.

Exclusion Criteria

1. The patient has been diagnosed with another psychiatric disorder (for example mania, bipolar disorder, schizophrenia or any psychotic disorder) during study 12709A or 12710A.
2. The patient has an attention-deficit/hyperactivity disorder (ADHD) that requires a pharmacological treatment other than a stimulant medication.
3. The patient has, moderate or severe on-going adverse event, related to study medication in Study 12709A or 12710A considered a potential safety risk by the investigator.
4. The patient has previously been enrolled in this study.
5. The patient is a member of the study personnel or of their immediate families, or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.
6. The patient is under forced treatment.
7. The patient is pregnant or breast-feeding.
8. The patient has a history of severe drug allergy or hypersensitivity, or known hypersensitivity to any of the IMP(s) or their excipients.

9. The patient has hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrose-isomaltase insufficiency.
10. The patient has a current diagnosis or history of substance dependence (excluding nicotine, and caffeine) or alcohol dependence (DSM-5™ criteria) <6 months prior to the Baseline Visit of the lead in study 12709A or 12710A.
11. The patient has reported current use of, or at the discretion of the investigator has tested positive for drugs of abuse (opiates, cocaine, amphetamines [including ecstasy], barbiturates, benzodiazepines, and cannabinoids) at the Baseline Extension A visit. If a patient tests positive for amphetamines due to his/her ADHD current treatment, as confirmed by a clinical interview, the patient is eligible for the study.
12. The patient suffers from intellectual disability, organic mental disorders, or mental disorders due to a general medical condition (DSM-5™ criteria).
13. The patient has a known intellectual disability (as suggested by an IQ <70), or, clinical evidence or known social or school history indicative of intellectual disability.
14. The patient has any other disorder for which the treatment takes priority over treatment of MDD or is likely to interfere with study treatment or impair treatment compliance.
15. The patient has a history of moderate or severe head trauma or other neurological disorders or systemic medical diseases that are, in the investigator's opinion, likely to affect central nervous system functioning.
16. The patient has a known first degree relative with a history of Bipolar Disorder.
17. The patient is unable to swallow tablets.
18. The patient has a history of cancer that has not been in remission for >5 years prior to the first dose of IMP.
19. The patient has or has had one or more of the following conditions diagnosed during Study 12709A or 12710A that is/are considered clinically relevant in the context of the study:
    - neurological disorder
    - other psychiatric disorder
    - cardiovascular disease
    - seizure disorder or encephalopathy
    - congestive heart failure
    - cardiac hypertrophy
    - arrhythmia
    - bradycardia (pulse <50 bpm)
    - respiratory disease
    - hepatic impairment or renal insufficiency
    - metabolic disorder
    - endocrinological disorder
    - gastrointestinal disorder
    - haematological disorder
    - infectious disorder
    - any clinically significant immunological condition

- dermatological disorder
- congenital or juvenile glaucoma or is at risk of acute narrow-angle glaucoma

20. The patient takes or has taken disallowed recent or concomitant medication (specified in Appendix II or it is anticipated that the patient will require treatment with at least one of the disallowed concomitant medications during the study.
21. The patient has clinically significant abnormal vital signs at the Completion Visit (Visit 12) of Study 12709A or 12710A and considered a potential safety risk by the investigator.
22. The patient has one or more clinical laboratory test values outside the reference range, based on the latest blood and urine sample results in the lead-in study, that are of potential risk to the patient's safety, or the patient has, according to the latest blood sample:
    - a serum creatinine value >1.5 times the upper limit of the reference range
    - a serum total bilirubin value >1.5 times the upper limit of the reference range
    - a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2 times the upper limit of the reference range
23. The patient has an abnormal thyroid stimulating hormone (TSH) level based on the latest blood sample results in the lead-in study. Patients with thyroid disease may be enrolled in the study provided they are stable and euthyroid.
24. The patient has, at the Completion Visit (Visit 12) of Study 12709A or 12710A:
    - an abnormal ECG that is, in the investigator's opinion, clinically significant
    - a QTcF interval >450 ms (based on the Fridericia correction where $QT_{cF} = QT/RR^{0.33}$)
25. The patient has a disease or takes medication that could, in the investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with the conduct or interpretation of the study.
26. The patient is, in the investigator's opinion, unlikely to comply with the protocol or is unsuitable for any reason.
27. The patient has in the investigator's clinical judgement a significant risk of suicide OR
    - answers "yes" to the C-SSRS suicidal ideation questions 4 or 5 OR
    - answers "yes" to suicidal behaviour on the C-SSRS within the last 12 months)
28. The patient receives on-going current psychotherapy that is planned to be intensified. Interpersonal psychotherapy (IPT) or cognitive behavioural therapies (CBT) are not allowed.

5.3 Withdrawal Criteria

A patient must be withdrawn from the study if:

- the patient and/or his or her parent(s)/legal representative(s) withdraw(s) his or her assent/consent (defined as a patient and/or his or her parent(s)/legal representative(s) who explicitly take back his or her assent/consent); section 8.4 states how the patient's data will be handled
- the investigator considers it, for safety, lack of efficacy, and/or study compliance reasons, in the best interests of the patient that he or she be withdrawn

- the patient becomes pregnant
- the patient has a serum ALT or AST value >3 times the upper limit of the reference range and a serum total bilirubin value >2 times the upper limit of the reference range
- the patient has a serum ALT or AST value >5 times the upper limit of the reference range that is confirmed by testing <2 weeks later
- • the patient has a QTcF interval >500 ms; the decision to withdraw a patient may be postponed until a repeat ECG is taken, if it is taken within 24 hours the patient is lost to follow-up (defined as a patient who fails to comply with scheduled study visits or contact, who has not actively withdrawn from the study, and for whom no alternative contact information is available [this implies that at least two documented attempts have been made to contact the patient])
- the patient and his or her parent(s)/legal representative(s) fails to comply with study procedures
- the patient attempts suicide or is at significant risk of suicide (either in the opinion of the Investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behaviour on the C-SSRS during the study)

Patients who withdraw will not be replaced.

6 Investigational Medicinal Products

6.1 Treatment Regimen

The dosage of vortioxetine will be initiated at 5 mg/day for the first 2 days prior to receiving 10 mg/day. The target dose is 10 mg/day; however the investigator has the possibility to adjust the dose in case of unsatisfactory response or in case of dose-limiting adverse events. The dose can be up or down titrated with 5 mg/day. The patient should receive the same dose for 2 days before being up-titrated to a new dose.

Changes in dosing may occur at any site visit during the treatment course at the investigator's discretion but the maximum dose may not exceed 20 mg/day. At telephone visits the patient and/or legal representative can request an unscheduled site visit to discuss their current dose.

The treatment period is 26 weeks. The total study duration per patient from Baseline Extension A to the end of follow-up will be approximately 30 weeks.

The tablets should be taken orally once daily, preferably in the morning.

Panel 3 Dose Titration Schedules

Visit	IMP
1	Up-titration
2-12	Maintenance*

*IMP dose may be changed

6.2 IMPs, Formulations, and Strengths

The IMPs supplied by Lundbeck in this study are:

- Vortioxetine : 5 mg, 10 mg, 15 mg and 20 mg tablets.

6.3 Manufacturing, Packaging, Labelling, and Storage of IMPs

The IMPs will be manufactured, packaged, labelled, released (by a qualified person [QP]), and distributed in accordance with the principles of *Good Manufacturing Practice*, under the responsibility of Lundbeck.

The IMPs will be provided in wallet cards.

The wording on the labels will be in accordance with *Good Manufacturing Practice* regarding labelling and national and/or local regulatory requirements. If additional information is to be added when the IMP is dispensed to patients, this will be clearly stated on the labels, and the investigator will be instructed to do so.

No manipulation, repackaging, or relabelling of IMP is permitted after QP release by Lundbeck, unless a repackaging/relabelling agreement exists, and the documentation is available to the Department of Clinical Supply, H. Lundbeck A/S, and, where necessary, new QP releases are made.

The IMPs will be identified using a unique IMP number.

The IMPs must be stored in a safe and secure location, and in accordance with the storage conditions specified on the labels.

6.4 Method of Assigning Patients to Treatment

The patients' screening numbers from the lead-in studies will be used to identify them in the extension study.

An interactive voice/web response system (IVRS/IWRS) will be used to dispense IMP to patients.

6.5 IMP Accountability

The IMP is tracked in IVRS.

- IMP shipped to site (and returned)
- IMP allocated to patients and returned by patient

Paper log

- A patient-specific paper log for IMP tear off label to document the kit dispensed to patient at dispensing visits

The investigator and the pharmacist (if applicable) must agree to only dispense IMP to patients enrolled in the study. The investigator or the pharmacist (if applicable) must maintain an adequate record of the receipt and distribution of the IMP (confirmation email from IVRS system). This record must be available for inspection at any time.

6.6 Post-study Access to IMP

Post-study access to the IMP will not be available. Patients in the study will have access to appropriate medical care after they complete or withdraw from the study.

7 Concomitant Medication

Concomitant medication is any medication other than the IMP that is taken during the study.

The concomitant medications that are disallowed or allowed with restrictions during the study are summarised in Appendix II.

Details of all concomitant medication (prescription and over-the-counter) taken at the time of the Final Visit in studies 12709A or 12710A must be recorded in the eCRF at the first visit. Any changes (including reason for changes) in concomitant medication must be recorded at each subsequent visit. For any concomitant medication initiated or for which the dose has changed due to a new disorder or worsening of a concurrent disorder, the disorder must be recorded as an adverse event.

Concomitant medication initiated after the last dose of IMP must only be recorded if associated with an SAE.

8 Study Visit Plan

8.1 Overview

An overview of the procedures and assessments to be conducted during the study and their timing is presented in Panel 2. Further details are in chapter 9.

After completing or withdrawing from the study, the patient must be treated in accordance with usual clinical practice.

8.2 Baseline Extension A Visit (Visit 1)

The Baseline Extension A Visit (Visit 1) is the Final Visit (Visit 12) of study 12709A or 12710A. Assessments are described in Panel 2.

8.2.1 Patient Identification Card

Each patient will be provided with a patient identification card that states, at a minimum, the name of the IMP, the study number, the patient identification number, the investigator's name, and an emergency telephone number providing 24-hour service.

The patient identification card should be returned to the investigator upon completion of the patient's participation in the study.

8.3 Visits 4, 6, 8, 10 and 12

Visits 4, 6, 8, 10 and 12 are a telephone contacts where following assessments and procedures will be conducted - Adverse events, PAERS, C-SSRS, recent and concomitant medication. The patient and/or legal representative and/or the investigator can during the telephone contact request an unscheduled site visit to discuss their current dose. During such an unscheduled site visit, the CDRS-R, CGI-S, CGI-I, PAERS and C-SSRS must be performed.

8.4 Withdrawal Visit

Patients who withdraw from the study prior to the Completion Visit will be asked to attend a Withdrawal Visit, if at all possible. The visit must be scheduled as soon as possible after withdrawal.

No new information will be collected from patients who withdraw, except information collected in relation to the scheduled Withdrawal Visit or needed for the follow-up of adverse events (section 10.5).

The reason for withdrawal must be recorded on the *Reason for Withdrawal Form*.

For a patient and/or his or her legal representative (if applicable) who withdraw assent/consent:

- if the patient and/or his or her legal representative (if applicable) withdraw assent/consent during a visit and then agrees to it being the final visit, the investigator will complete the visit as a Withdrawal Visit and all the data collected up to and including this visit will be used
- if the patient and/or his or her legal representative (if applicable) withdraw assent/consent during a telephone conversation, the investigator will ask the patient if he or she will attend a Withdrawal Visit. If the patient:
  - agrees to attend a Withdrawal Visit, all the data collected up to and including this visit will be used
  - refuses to attend a Withdrawal Visit, the investigator should attempt to follow the patient's safety and future treatment; any information collected will only be recorded in the patient's medical record

- if the patient and/or his or her legal representative (if applicable) explicitly request that his or her data collected from the time of withdrawal of assent/consent onwards not be used, this will be respected

8.5 Safety Follow-up Visit/Contact (Visit 14)

The safety follow-up is conducted to capture serious adverse events (SAEs) that occur during the Safety Follow-up Period as well as to follow up on the outcome of adverse events ongoing at the end of the Treatment Period. The safety follow-up may either be conducted as a visit to the site or as a telephone contact. The safety follow-up must be conducted approximately 30 days after the last dose of IMP.

If any new SAEs have occurred since the last assessment at which the patient received IMP, the safety follow-up must, when possible, be a visit to the site.

For adverse events that were ongoing at the end of the Treatment Period and that resolved during the Safety Follow-up Period, the stop date must be recorded. For non-serious adverse events still ongoing at the safety follow-up, the stop date must be recorded as “ongoing”. SAEs must be followed until resolution or the outcome is known.

Patients with a clinical safety laboratory test value that was out-of-range at the Completion or Withdrawal Visit and judged clinically significant must be followed according to accepted medical standards for up to 30 days or until the value normalises or stabilises or a diagnosis or a reasonable explanation has been established. For these patients, safety follow-up visits must be scheduled to allow for a medical examination and/or blood sampling. The investigator must decide whether further safety follow-up visits are required after 30 days. If further safety follow-up visits are made, these must be documented in the patient’s medical record and not in the eCRF.

Patients who withdrew due to elevated AST or ALT values (see section 5.3) should be followed until the values normalise or stabilise or a diagnosis or a reasonable explanation has been established (see section 10.5).

The safety follow-up for patients who withdraw assent/consent must be performed, if at all possible; any information collected will be recorded in the patients’ medical records.

8.6 End-of-study Definition

The end of the study for an individual patient is defined as the last protocol-specified contact with that patient. The overall end of the study is defined as the last protocol-specified contact with the last patient ongoing in the study.

9 Assessments

Timing and frequency of all assessments are specified in Panel 2.

Lundbeck reserves the right to use external quality oversight methods of all study assessment tools to ensure the validity of the diagnosis and severity of illness.

9.1 Baseline Extension A Procedures and Assessments

9.1.1 Demographics and Other Baseline Characteristics

Prior to enrolling a patient in the study, the investigator must ascertain that the patient meets the selection criteria.

The following data from the Ongoing Logs in the lead-in study (12709A or 12710A) must be entered by site staff into the eCRF's of the Baseline Extension A.

- Ongoing Adverse Advents
- Ongoing Recent and concomitant medications

All other study related data can be found in the eCRFs of the lead-in studies.

Latest laboratory and ECG results available from the lead-in studies will be used for eligibility assessment.

9.1.2 Drug and Alcohol Screen

It is not mandatory to screen for drugs and/or alcohol. However, it can be performed at any visit, at the discretion of the investigator.

If a patient tests positive for amphetamines due to his/her ADHD current treatment, as confirmed by a clinical interview, the patient can continue in the study. Patients may continue in the study if they have a positive blood alcohol result or have tested positive for opiates due to incidental use of codeine-containing medication, as assessed in a clinical interview, but only after consultation and approval by the medical monitor. Patients whose urine drug screen is positive for cocaine or other illicit drugs should be considered for withdrawal from the study after consultation and approval with the medical monitor.

Urine drug and blood alcohol screening kits will be supplied by a central laboratory.

9.2 Efficacy Assessments

9.2.1 Clinician-rated Scales

9.2.1.1 Use of Clinician-rated Scales

The following assessment tools will be used:

- CDRS-R – assessing depressive symptoms
- CGI – assessing global impression
- CGAS – assessing functionality

Detailed instructions on how to administer the scales and how to score using the scales will be provided to the site in a *Rater Station Site Manual.*

The CDRS-R and CGAS will be administered in the local language. Only scales provided by Lundbeck that have been validated in the language to which they have been translated will be used in this study. The CGI will be administered in English.

9.2.1.2 Children Depression Rating Scale Revised Version (CDRS-R)

The CDRS-R[22] is a clinician-rated scale to measure the severity of depression of children and adolescents. The CDRS-R consists of 17 items: 14 items rate verbal observations, and three items rate nonverbal observations (tempo of language, hypoactivity, and nonverbal expression of depressed affect). Depression symptoms are rated on a 5-point scale from 1 to 5 for the verbal observations, and a 7-point scale from 1 to 7 for the nonverbal observations. The total score ranges from 17 (normal) to 113 (severe depression). The CDRS-R can be administered by a clinician after a training session. It takes approximately 20 to 30 minutes to administer and rate the CDRS-R.

9.2.1.3 Clinical Global Impression scales (CGI-S/I)

The CGI[23] was developed to provide global measures of the severity of a patient's clinical condition and improvement or worsening during clinical studies.

The clinician will use the scale to assess depressive symptoms.

The CGI consists of two clinician-rated subscales: severity of illness (CGI-S) and global improvement (CGI-I).

The CGI-S provides the clinician's impression of the patient's current state of mental illness. The clinician uses his or her clinical experience of this patient population to rate the severity of the patient's current mental illness on a 7-point scale ranging from 1 (*Normal - not at all ill*) to 7 (*among the most extremely ill patients*).

The CGI-I provides the clinician's impression of the patient's improvement (or worsening) from Baseline A in the lead-in studies. The clinician assesses the patient's condition relative to a baseline on a 7-point scale ranging from 1 (*very much improved*) to 7 (*very much worse*). In all cases, the assessment should be made independent of whether the rater believes the improvement is drug-related or not.

An experienced clinician can use the CGI after a short training session. It takes 1 to 2 minutes to score the CGI after a clinical interview.

9.2.1.4 Children's Global Assessment Scale (CGAS)

The CGAS[29] is a clinician-rated global scale to measure the lowest level of functioning for a child (4 to 16 years) during a specified time period. The CGAS contains behaviourally-oriented descriptors at each anchor point that depict behaviours and life situations applicable to a child. The items range in value from 1 (most functionally impaired child) to 100 (the healthiest). A total score above 70 indicates normal function. The CGAS can be administered by a clinician after a training session. It takes approximately 2 minutes to administer CGAS.

9.2.1.5 CDRS-R, CGI, CGAS Rater Qualification and Certification

The CDRS-R, CGI and CGAS scales should only be administered by a rater who has adequate experience with paediatric patients with MDD and who has adequate experience in rating scales. The rater should be a psychiatrist or DO specialised in child and adolescent psychiatry, or a clinical paediatric (neuro-) psychologist involved in clinical practice.

The CGI should be administered by the investigator responsible for the patient. The investigator must be psychiatrists or DO specialised in child and adolescent psychiatry that has adequate experience with paediatric patients with MDD.

Any exceptions must be discussed and approved by Lundbeck.

Only raters who have been already trained and certified in Study 12709A or Study 12710A are allowed to rate the patients in Study 12712A. The certificate(s) issued during Study 12709A or Study 12710A cover the extension study and no additional certificate will be issued.

New raters joining Study 12712A will be trained and certified using the same certification processes as in Study 12709A and Study 12710A. Documentation of training and certification will be delivered to the raters for arching in the investigator trial master file (TMF). No patient may be rated before the documentation has been delivered.

For each individual patient, the same certified rater should rate the patient, and preferably the same as in Study 12709A or Study 12710A study. For unforeseen circumstances, certified back-up raters should be available throughout the study.

9.2.2 Patient and/or Parent Reported Outcomes (PROs)

9.2.2.1 Use of PROs

The following PRO will be used:

- BRIEF – Assessing cognitive function
- PedsQL VAS – assessing functionality

9.2.2.1.1 Behavioural Rating Inventory of Executive Function® (BRIEF®)

The BRIEF[30] is a patient and carer-rated scale designed to measure executive function behaviour in children and adolescents in an everyday environment. We use BRIEF (parent form) for the children aged 7 to 11 years and BRIEF-SR (self-report) for the adolescents aged 12 to 18 years. Both versions of the BRIEF contain 86 items. Items are rated on a 3-point scale, from N (never) to O (often). These items cover 8 non-overlapping clinical scales: 3 scales in the Behavioural Regulation Index (inhibit, shift and emotional control), and 5 scales in the Metacognition Index (initiate, working memory, plan/organize, organisation of materials, and monitor). The clinical scales also provide the Global Executive Composite score, which represents the child's overall executive function behaviour. There are 2 validity scales: negativity and inconsistency. It takes approximately 30 minutes to complete and score the BRIEF.

9.2.2.1.2 PedsQL Present Functioning Visual Analogue Scales (PedsQL™ VAS)

The PedsQL™ VAS[31] is designed to measure at-that-moment functioning in children and adolescents. The PedsQL VAS consists of 6 domains: anxiety, sadness, anger, worry, fatigue and pain using visual analogue scales. The functionality for each domain is measured on a 10 cm line with a happy face at one end and a sad face at the other. The patients are asked to mark on the line how they feel. The total score is the average of all 6 items, and the emotional distress summary score is the mean of the anxiety, sadness, anger, and worry items. It takes 2 to 5 minutes to administer and rate the PedsQL VAS.

9.3 Blood Sampling for Vortioxetine Quantification

Blood samples (2 x 1 mL) for IMP analysis will be collected in EDTA tubes simultaneously with clinical safety lab samples. The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual*.

The blood samples will be analysed for vortioxetine using a method validated in accordance with the EMA *Guideline on Bioanalytical Method Validation*[32] and the FDA *Guidance for Industry*.[33] A bioanalytical protocol will be prepared by Lundbeck before the plasma samples are analysed.

The results of the bioassay will be given will be given in the bioanalytical study report that will be prepared by the Department of Bioanalysis, H. Lundbeck A/S.

9.4 Safety Assessments

9.4.1 Adverse Events

The patients will be asked a non-leading question (for example, “how do you feel?”, “how have you felt since your last visit?”) at each visit, starting at the Baseline Extension A Visit. Adverse events (including worsening of concurrent disorders, new disorders, and pregnancies) either observed by the investigator or reported spontaneously by the patient will be recorded, and the investigator will assess the seriousness and the intensity of the adverse event and its relationship to the IMP. Results from relevant tests and examinations, such as clinical safety laboratory tests, vital signs, and ECGs, or their corresponding conditions will also be recorded as adverse events if considered by the investigator to be clinically significant.

See chapter 10 for further information on adverse events.

9.4.2 Clinical Safety Laboratory Tests

The clinical safety laboratory tests are listed in Panel 4.

Results of safety laboratory tests for Visit 12 (Completion Visit) of the lead-in studies 12709A or 12710A will be transcribed to Visit 1 (Baseline Extension A) of 12712A study (i.e. these tests should not be collected at Visit 1). However, the Hormones laboratory tests are specific for the 12712A study and will be collected at the 12712A Visit 1 using a separate kit.

Panel 4 Clinical Safety Laboratory Tests

Haematology	**Electrolytes**[a]	**Urine**[b]
B-haemoglobin	S-sodium	U-protein (dipstick)
B-erythrocyte count	S-potassium	U-glucose (dipstick)
B-haematocrit	S-calcium (total)	U-blood (dipstick)
B-total leucocyte count	**Endocrine and Metabolic**[a]	U-ketones (dipstick)
B-neutrophils (% of total leucocytes)	S-albumin	**Pregnancy**[d] **(women only)**
B-eosinophils (% of total leucocytes)	S-glucose (non fasting)	U-hCG
B-basophils (% of total leucocytes)	**Kidney**[a]	B-hCG
B-lymphocytes (% of total leucocytes)	S-creatinine	**Urine Drug Screen**[e]
B-monocytes (% of total leucocytes)	S-urea nitrogen (BUN)	U-amphetamines (incl. methamphetamine)
B-thrombocyte count	**Hormones**	U-barbiturates
Liver[a]	S-estradiol (girls)	U-benzodiazepines
S-total bilirubin	S-total testosterone (boys)	U-cannabinoids
S-conjugated bilirubin	S-LH	U-cocaine
S-alkaline phosphatase (AP)	S-FSH	U-opiates
S-alanine aminotransferase (ALT)	S-LHRH	U-phencyclidine
S-aspartate aminotransferase (AST)	S-prolactin	**Blood Alcohol Screen**[e]
S-lactate dehydrogenase (LDH)	S-TSH[c]	B-ethanol
S-γ-glutamyl transferase (γGT)	**Infection**	
Lipids[a]	S-C-reactive protein (CRP)	
S-cholesterol (total) (non fasting)	**Serology**[c]	
S-triglycerides (non fasting)	B-HBsAg	
S-low density lipoprotein (LDL)	B-anti HCV	
S-high density lipoprotein (HDL)		

B – blood; P – plasma; S – serum; U – urine

a. Clinical chemistry
b. Microscopic examination (leucocytes, erythrocytes, and casts) will be performed only if any of the urine evaluations are abnormal.
c. TSH and hepatitis B and C panels are optional and may be performed at the investigator's discretion if there is clinical justification.
d. Females >10 years of age or female patients at lower age judged by the investigator to be of childbearing potential. Additional pregnancy tests during the study will be performed according to local requirements. Females under 11 years will be tested with a urine hCG test and females over 11 years will be tested with using a blood hCG test.
e. It is not mandatory to screen for drugs and/or alcohol. However, it can be performed at any visit, at the discretion of the investigator.

Blood samples for the clinical safety laboratory tests will be collected as outlined in Panel 2. The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual*.

The blood and urine drug screen samples will be analysed at the central laboratory.

The additional urine samples will be collected and analysed at the site using dipsticks. If the dipstick evaluation is positive or abnormal, further analysis will be performed at the central laboratory.

The investigator must review (initial and date) the results of the clinical safety laboratory tests as soon as possible after receipt of those results. Out-of-range values must be interpreted by the investigator as "not clinically significant" or "clinically significant" with a comment concerning the planned follow-up. Tests for clinically significant out-of-range values must be repeated, or an appropriate clinical follow-up must be arranged by the investigator and documented on the laboratory report, until the value has stabilised or until the value has returned to a clinically acceptable value (regardless of relationship to IMP). Any value that is out-of-range at the Completion or Withdrawal Visit and judged clinically significant must be followed according to accepted medical standards for up to 30 days or until the value normalises or stabilises or a diagnosis or reasonable explanation has been established. Any out-of-range values followed after the last protocol-specified contact with the patient will be documented in the patient's medical record.

Clinically significant out-of-range values must be recorded as an adverse event on an *Adverse Event Form*.

The central laboratory will be notified by the sponsor when the biological samples may be destroyed.

9.4.3 Vital Signs

Blood pressure (BP) and pulse rate will be measured using a standard digital meter after the patient has rested for at least 5 minutes in a supine position.

The patient must then be instructed to change from a supine to a standing position in a manner that includes passing through a sitting position before assuming an upright position. Blood pressure and pulse rate will be measured after the patient has been standing for at least 1 minute but no longer than 5 minutes.

Vital signs should be assessed prior to blood sampling.

Abnormalities of clinical significance must be recorded as an adverse event on an *Adverse Event Form*.

9.4.4 Height and Weight

Height will be measured with a stadiometer, without shoes.

Patients will be weighed wearing light clothing and no shoes. A similar amount of clothing must be worn on each occasion.

Abnormalities of clinical significance must be recorded as an adverse event on an Adverse Event Form.

9.4.5 Menstrual Cycle

The following will be recorded:

- Age of menarche
- The length of the menstrual cycle (number of days from the first day of menstruation to the day before the first day of the next menstrual period)
- Menstrual cycle regularity

9.4.6 Tanner Staging

Tanner staging is a scale for assessing physical development and sexual maturity during onset and progress of puberty.

The scale includes five stages of pubertal changes (called Tanner stages) separate for males and for females.

For females, the 5 stages of maturation are recognized by assessing pubic hair and breast development. For males, the 5 stages of maturation are recognized by assessing pubic hair, growth of penis and testicles. Post-puberty is defined as a Tanner stage = 5 in both of observed criteria.

The evaluation of Tanner stage will be performed by a physician or trained nurse; they will be provided with figures depicting the somatic changes and tables describing these changes in words to facilitate the staging.

9.4.7 Electrocardiograms (ECGs)

A standard 12-lead electronic ECG (eECG) will be performed using digital ECG recording equipment provided to the investigator or, upon agreement, to an external cardiology centre. The ECGs will be transferred digitally to a central ECG laboratory for evaluation, and the results from the central ECG laboratory will include the RR, PR, QRS, QT, and QTc intervals.

The investigator will, during the study be provided with the results and a cardiological interpretation of the ECG performed by a paediatric cardiologist from the central ECG laboratory.

The investigator has the final decision on the clinical significance of the ECG evaluation.

Abnormalities of clinical significance must be recorded as an adverse event on an *Adverse Event Form*.

9.4.8 Physical and Neurological Examinations

The physical examination must, at a minimum, include an examination of appearance, extremities, skin, head, neck, eyes, ears, nose, throat, lungs, chest, heart, abdomen, and

musculoskeletal system. The investigator may appoint a designee to be primarily responsible for performing the physical examinations provided this is permitted according to local regulations. The investigator must take responsibility for reviewing the findings.

The neurological examination must be performed by a physician.

Abnormalities of clinical significance must be recorded as an adverse event on an *Adverse Event Form*.

9.4.9 Assessment Tools

9.4.10 Paediatric Adverse Event Rating Scale (PAERS)

The PAERS[34] is a clinician-rated scale designed and validated to assess adverse events occurring in paediatric patients who are treated with psychotropic medication in clinical studies.

The PAERS consists of 45 items: 43 specific signs and symptoms and two to be specified. Each item specifies if the adverse event was present recently, if it was resolved (*No, Yes*), related to drug (*No, Study drug, Other drug, Drug-drug interaction*), its severity (*Mild, Moderate, Severe, Extreme*) and if it impaired function (*No, Yes*).

The PAERS can be administered by a clinician after a short training session. It takes approximately 10 minutes to administer and score the PAERS.

The PAERS must be applied after the non-leading, open questions on any adverse events (see section 9.4.1). As this recording of adverse events should precede the use of the PAERS, the numbers of adverse events captured by these two methods potentially differ.

9.4.10.1 Columbia-Suicide Severity Rating Scale

The C-SSRS[35] is a semi-structured interview developed to systematically assess suicidal ideation and behaviour of patients participating in a clinical study. The C-SSRS has 4 questions addressing suicidal behaviour, 5 questions addressing suicidal ideation, and sub-questions assessing the severity.

In this study, the “Since last visit” version will be applied.

An age-appropriate version of the C-SSRS will be used.

An experienced clinician can use the C-SSRS after a short training session. It takes approximately 5 minutes to administer and rate the C-SSRS.

9.4.11 Rater Qualification and Certification

The PAERS and C-SSRS should only be administered by a rater who has adequate experience with paediatric patients and who has adequate experience in rating scales. The rater should be a psychiatrist or DO specialised in child and adolescent psychiatry, or a clinical paediatric (neuro-) psychologist involved in clinical practice. Any exceptions must be discussed with and approved by Lundbeck.

Only raters who have been already trained and certified in Study 12709A or Study 12710A are allowed to rate the patients in Study 12712A. The certificate(s) issued during Study 12709A or Study 12710A cover the extension study and no additional certificate will be issued.

New raters joining Study 12712A will be trained and certified using the same certification processes as in Study 12709A and Study 12710A. Documentation of training and certification will be delivered to the raters for arching in the investigator trial master file (TMF). No patient may be rated before the documentation has been delivered.

For each individual patient, the same certified rater should rate the patient, and preferably the same as in Study 12709A or Study 12710A study. For unforeseen circumstances, certified back-up raters should be available throughout the study.

An electronic version of the PAERS and C-SSRS will be used in this study.

9.5 Order of Assessments

The scales should preferably be administered in the following order:

- CDRS-R
- CGAS
- BRIEF (7-11 years), BRIEF-SR (12-18 years), PedsQL VAS (PRO)
- PAERS
- C-SSRS
- CGI-S, CGI-I

The PAERS must be applied after the non-leading, open questions on any adverse events.

9.6 Total Volume of Blood Drawn and Destruction of Biological Material

The volume of blood drawn from each patient will be approximately 13 ml at the required study visits.

Safety blood test drawn at the Visit 12 of the lead-in Study 12709A or 12710A will be used as the safety blood test for Baseline Extension A Visit (excluding the additional Hormones panel of approximately 5 ml). Hence, the total volume of the blood drawn for the entire study is approximately 31 ml.

Additional blood samples may be required if the original blood samples are not viable or if re-testing is required.

9.7 Treatment Compliance

It is the responsibility of the investigator to account for all IMP (refer to IMP accountability section 6.5). The investigator or her/his designee must agree not to dispense any IMP to any person, except patient/parents included in the study and he/she/they must further agree only to use IMP in accordance with protocol.

10 Adverse Events

10.1 Definitions

10.1.1 Adverse Event Definitions[36]

Adverse event – is any untoward medical occurrence in a clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including clinically significant out-of-range values from relevant tests, such as clinical safety laboratory tests, vital signs, ECGs), symptom, or disease temporally associated with the use of a medicinal product, regardless of whether it is considered related to the medicinal product.

Serious adverse event (SAE) – is any adverse event that:

- results in death
- is life-threatening (this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe)
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent any of the SAEs defined above)

Examples of medically important events are intensive treatment for allergic bronchospasm; blood dyscrasia or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

Planned hospitalisations or surgical interventions for a condition that existed before the patient signed the *Informed Assent/Consent Form* and that did not change in intensity are not SAEs. Emergency room visits that do not result in admission to the hospital are not

necessarily SAEs; however, they must be evaluated to determine whether they meet any of the SAE definitions (for example, life-threatening or other serious [medically important] event).

The C-SSRS has 5 questions addressing suicidal ideation. If level 4 or 5 has been answered "yes", a corresponding SAE should be reported.

Non-serious adverse event – is any adverse event that does not meet the definition of an SAE.

If there is any doubt as to whether an adverse event meets the definition of an SAE, a conservative viewpoint must be taken, and the adverse event must be reported as an SAE.

Suspected unexpected serious adverse reaction (SUSAR) – is any adverse event that is assessed as serious, unexpected (its nature or intensity is not consistent with the current version of the *Investigator's Brochure* for vortioxetine),[11] and related to an investigational product by either the investigator or the sponsor.

Overdose – is a dose taken by a patient that exceeds the dose prescribed to that patient. Any overdose (and associated symptoms) must, at a minimum, be recorded as a non-serious adverse event.

10.1.2 Adverse Event Assessment Definitions

Assessment of Intensity

The investigator must assess the *intensity* of the adverse event using the following definitions, and record it on the *Adverse Event Form*:

- *Mild* – the adverse event causes minimal discomfort and does not interfere in a significant manner with the patient's normal activities.
- *Moderate* – the adverse event is sufficiently uncomfortable to produce some impairment of the patient's normal activities.
- *Severe* – the adverse event is incapacitating, preventing the patient from participating in his or her normal activities.

Assessment of Causality

The investigator must assess the *causal relationship* between the adverse event and the IMP using the following definitions, and record it on the *Adverse Event Form* and the *Serious Adverse Event Form* (if applicable):

- *Probable* – the adverse event has a strong temporal relationship to the IMP or recurs on rechallenge, and another aetiology is unlikely or significantly less likely.
- *Possible* – the adverse event has a suggestive temporal relationship to the IMP, and an alternative aetiology is equally or less likely.

- *Not related* – the adverse event has no temporal relationship to the IMP or is due to underlying/concurrent illness or effect of another drug (that is, there is no causal relationship between the IMP and the adverse event).

An adverse event is considered causally related to the use of the IMP when the causality assessment is *probable* or *possible*.

Assessment of Outcome

The investigator must assess the *outcome* of the adverse event using the following definitions, and record it on the *Adverse Event Form* and the *Serious Adverse Event Form* (if applicable):

- *Recovered* – the patient has recovered completely, and no symptoms remain.
- *Recovering* – the patient's condition is improving, but symptoms still remain.
- *Recovered with sequelae* – the patient has recovered, but some symptoms remain (for example, the patient had a stroke and is functioning normally, but has some motor impairment).
- *Not recovered* – the patient's condition has not improved and the symptoms are unchanged (for example, an atrial fibrillation has become chronic).
- *Death*

10.2 Pregnancy

Although not necessarily considered an adverse event, a pregnancy in a patient in the study must be recorded on an *Adverse Event Form*, as well as on a *Pregnancy Form* (paper), even if no adverse event associated with the pregnancy has occurred. Pregnancies must be reported to Lundbeck using the same expedited reporting timelines as those for SAEs.

An uncomplicated pregnancy should not be considered an SAE. If, however, the pregnancy is associated with an SAE, the appropriate serious criterion (for example, hospitalisation) must be indicated on the Serious Adverse Event Form. Examples of pregnancies to be reported as SAEs (medically important) are spontaneous abortions, stillbirths, and malformations.

The investigator must follow up on the outcome of the pregnancy and report it on a *Pregnancy Form* (paper). The follow-up must include information on the neonate at least up until the age of 1 month.

10.3 Recording Adverse Events

Adverse events must be recorded on an *Adverse Event Form*. The investigator must provide information on the adverse event, preferably with a diagnosis, or at least with signs and symptoms; start and stop dates (and start and stop time if the adverse event lasts less than 24 hours); intensity; causal relationship to IMP; action taken; and outcome. If the adverse event is an overdose, the nature of the overdose must be stated (for example, medication error, accidental overdose, or intentional overdose). If the intensity changes during the course of the adverse event, this must be recorded on the *AE Intensity Log*.

If the adverse event is *serious*, this must be indicated on the *Adverse Event Form*. Furthermore, the investigator must fill out a *Serious Adverse Event Form* and report the SAE to Lundbeck immediately (within 24 hours) after becoming aware of it (section 10.4).

Adverse events, including clinically significant out-of-range clinical safety laboratory test values and findings from for example, ECGs, must be recorded individually, except when considered manifestations of the same medical condition or disease state; in such cases, they must be recorded under a single diagnosis.

10.4 Reporting Serious Adverse Events

The investigator must report SAEs to Lundbeck immediately (within 24 hours) after becoming aware of them by completing a *Serious Adverse Event Form*.

The initial report must contain as much information as possible and, if more information about the patient's condition becomes available, the *Serious Adverse Event Form* must be updated with the additional information.

If the investigator cannot report the SAE in Rave®, then he or she must complete and sign the *Serious Adverse Event Fallback Form* and send it to:

Pharmacovigilance (PV)
Fax: [redacted]
e-mail: [redacted]

Lundbeck will assume responsibility for reporting SAEs to the authorities in accordance with local regulations.

It is the investigator's responsibility to be familiar with local requirements regarding reporting SAEs to the IEC or IRB and to act accordingly.

Lundbeck will assume responsibility for reporting SUSARs to the authorities in accordance with local regulations. In those Member States of the European Union that have implemented the *European Union Clinical Trials Directive*[37] and in Norway, Liechtenstein, and Iceland, that is, in the countries where unblinded expedited safety reporting is required, Lundbeck will also assume responsibility for reporting SUSARs to the ethics committees.

Lundbeck will assess the expectedness of SAEs and inform the investigator(s) about SUSARs, at a minimum, in the 6-monthly, blinded SUSAR listings. CIOMS-I reports for SUSARS are not normally distributed to investigators in those countries where SUSAR listings are sufficient. However, if the CIOMS-I reports are required (for example, by the local EC/IRB/REB), they will be sent to the investigator.

10.5 Treatment and Follow-up of Adverse Events

Patients with adverse events must be treated in accordance with usual clinical practice at the discretion of the investigator.

Non-serious adverse events must be followed up until resolution or the safety follow-up assessment, whichever comes first. At the safety follow-up, information on new SAEs, if any, and stop dates for previously reported adverse events must be recorded.

It is the responsibility of the investigator to follow up on all SAEs until the patient has recovered, stabilised, or recovered with sequelae, and to report to Lundbeck all relevant new information using the same procedures and timelines as those for the initial report. Relevant information includes discharge summaries, autopsy reports, and medical consultations.

SAEs that are spontaneously reported by a patient to the investigator after the safety follow-up assessment must be handled in the same manner as SAEs that occur during the study. These SAEs will be captured in the GPV database.

Patients with clinically significant out-of-range clinical safety laboratory test values at the Completion or Withdrawal Visit must be followed in accordance with usual clinical practice and be scheduled for a Safety Follow-up Visit to allow for a medical examination and/or blood sampling (see section 8.5).

Patients who withdraw due to elevated AST or ALT values (see section 5.3) must be followed until the values normalise or stabilise or a diagnosis or a reasonable explanation has been established. Additional medical examinations (for example, ultrasound scanning and/or sampling for serology, conjugated bilirubin, INR) should be considered. A gastroenterology or hepatology consultation should also be considered.

10.5.1 Data Monitoring Committee

The Data Monitoring Committee (DMC) includes child and adolescent psychiatrists. The DMC ensures that the ethical principles are observed and monitors the safety of the patients. The DMC will be informed to what extent the data and analyses provided to them have been quality controlled. Members of the DMC will not be involved in other study-related tasks. The details of the DMC procedures are described in the Data Monitoring Committee Charter.

11 Data Handling and Record Keeping

11.1 Data Collection

11.1.1 Electronic Case Report Forms (eCRFs)

eCRFs will be used to collect all the data related to the study, except the external data described in section 11.1.3.

The eCRFs use third party software (Rave®) to capture data via an on-line system on a computer. Data related to the study will be recorded electronically in a central database over encrypted lines, and all entries and modifications to the data will be logged in an audit trail.

Access to the system will only be granted after appropriate and documented training. Written instructions for using the system will be provided along with the training.

Electronic signatures will be used where signatures are required on pages and/or visits. Automated data entry checks will be implemented where appropriate; other data will be reviewed and evaluated for accuracy by the CRA. All entries, corrections, and changes must be made by the investigator or a delegate.

11.1.2 Patient Binders

11.1.2.1 Use of Patient Binders

Lundbeck will provide a *Patient Binder* for each patient. The *Patient Binder* contains different types of source documents, organised by visit and type. A ballpoint pen with waterproof ink must be used to enter information in the *Patient Binder*.

11.1.2.2 Rating Scales and Patient-reported Outcomes (PROs)

The *Patient Binder* contains paper versions of the rating scales and PROs. The rater(s) must verify that all the entries in the *Scale Section* are accurate and correct by signing and dating the relevant pages.

The patients will be asked to complete the PRO in their local language. The patient's responses may only be corrected by the patient.

11.1.2.3 Serious Adverse Event Fallback Forms

Serious Adverse Event Fallback Forms must be used when the eCRF cannot be accessed.

11.1.3 External Data

All electronic data will be transferred using a secure method accepted by Lundbeck.

The clinical safety laboratory test results will be transferred by the central laboratory.

The electronic data received from the following vendors will be kept in a secure designated storage area outside the eCRF:

- In case of any electronic Assessment(s) /PRO(s) the results will be transferred by designated vendor.
- The ECG results will be transferred by the central ECG laboratory.

11.2 Retention of Study Documents at the Site

11.2.1 eCRF Data

If a site closes before the study has been completed, the investigator will continue to have read-only access to the eCRF. If a site closes after the study has been completed, the investigator will no longer have read access to the eCRF. Instead, each site will be provided with a CD-ROM containing the data related to the site (including eCRF data, queries, and the audit trail). As a CD-ROM is not considered a durable medium and may therefore not be readable for the full retention period (for example, 15 years [if required by the applicable regulatory requirements]), it is possible for the investigator to request a new CD-ROM with the data related to the site.

11.2.2 Other Study Documents

The investigator must keep the investigator's set of documents in the investigator TMF for at least 15 years after the *Clinical Study Report* has been approved or in accordance with national requirements, whichever is longer.

If off-site storage is used, a study-specific binder will remain at the site after the other study-specific documents have been shipped for off-site storage. This binder is considered part of the investigator TMF and must be kept in a secure place by the site for the required period of time. The binder must contain, at a minimum, the following documents: a copy of the *Investigator TMF Index*, a certified copy of the *Patient Identification Code List*, and a *Retrieval Form*.

Lundbeck will notify the investigator in writing when the required storage period has expired and when the documents may be destroyed according to regulations.

12 Monitoring Procedures

Prior to including patients in the study, the investigator must sign a source data agreement that identifies the source documents (original documents, data, and records) at the site. The document will also list which data may be recorded directly on the eCRFs.

During the study, the CRA will visit the site to ensure that the protocol is being adhered to and that all issues are being recorded, to perform source data verification, and to monitor IMP accountability. The visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the site's recruitment rate, and the compliance of the site to the protocol and *Good Clinical Practice*. In addition, the CRA will be available for discussions by telephone.

Source data verification requires that the CRA be given direct access to all the source documents. Direct access includes permission to examine, analyse, and verify any records and reports that are important for the evaluation of the study.

In this study a Risk Based Monitoring approach will be applied.

13 Audits and Inspections

Authorised personnel from Global Clinical Quality Assurance at Lundbeck and quality assurance personnel from business partners may audit the study at any time to assess compliance with the protocol and the principles of *Good Clinical Practice* and all other relevant regulations.

The patients must be informed that authorised personnel from Lundbeck may wish to review their medical records. The investigator must be aware and the patients must be informed that representatives from regulatory authorities may also wish to inspect source data, such as medical records.

The investigator must notify Lundbeck, without delay, of an announced inspection by a regulatory authority.

During audits and inspections, the investigator must permit direct access to all the source documents, including medical records and other documents pertinent to the study.

During audits and inspections, the auditors and inspectors may copy relevant parts of medical records. No personal identification apart from the screening number will appear on these copies.

Patient data will not be disclosed to unauthorised third parties, and patient confidentiality will be maintained at all times.

14 Protocol Compliance

Lundbeck has a “no-waiver” policy, which means that permission will not be given to deviate from the protocol.

If deviations occur, the investigator must inform the CRA and they must review, discuss, and document the implications of the deviation.

15 Study Termination

Lundbeck or a pertinent regulatory authority may terminate the study or part of the study at any time. The reasons for such action may include, but are not limited to:

- safety concerns
- proven lack of efficacy of the IMP in other studies

If the study is terminated or suspended, the investigator must promptly inform the patients and ensure appropriate therapy and follow-up. Furthermore, the investigator and/or sponsor

must promptly inform the IEC or IRB and provide a detailed written explanation. The pertinent regulatory authorities must be informed in accordance with national regulations.

If the risk/benefit analysis changes after the termination of the study, the new evaluation must be provided to the IEC or IRB if it will have an impact on the planned follow-up of the patients who participated in the study. If so, the actions needed to protect the patients must be described.

16 Endpoints

16.1 Primary Endpoint

Safety:
- adverse events (AEs)
- tolerability including assessment based on PAERS
- Tanner score
- absolute values and changes from Baseline Extension A in clinical safety laboratory tests, vital signs, weight, height, and ECG parameters
- length of menstrual cycle
- potentially clinically significant clinical safety laboratory test values, vital signs, weight, and ECG parameter values relative to Baseline Extension A
- C-SSRS categorisation based on C-CASA definitions (1, 2, 3, 4, and 7)

16.2 Secondary Endpoints

Depressive symptoms:
- change from Baseline Extension A to Week 26 in CDRS-R total score
- time to first relapse (CDRS-R value of ≥40)
- time to first loss of remission (CDRS-R >28)

Global Clinical Impression:
- change from Baseline Extension A to Week 26 in CGI-S score
- CGI-I score at Week 26. The assessment of the CGI-I should be in reference to Baseline A in the lead-in studies.

Cognitive function:
Children (7-11 years)
- change from Baseline Extension A to Week 26 in BRIEF using the Global Executive Composite score
- change from Baseline Extension A to Week 26 in BRIEF using the Metacognition Index

Adolescents (12-18 years)
- change from Baseline Extension A to Week 26 in BRIEF-SR using the Global Executive Composite score
- change from Baseline Extension A to Week 26 in BRIEF-SR using the Metacognition Index

Functionality:
- change from Baseline Extension A to Week 26 in CGAS score
- change from Baseline Extension A to Week 26 in PedsQL VAS

17 Statistical Methodology

17.1 Responsibilities

The Department of Biostatistics, H. Lundbeck A/S will perform the statistical analyses described below.

17.2 Analysis Sets

The following analysis sets will be used to analyse and present the data:
- all-patients-treated set (APTS) – all patients who took at least one dose of vortioxetine in the extension study.
- full-analysis set (FAS) –all patients in the APTS with at least one valid post-Baseline Extension A assessment of the CDRS-R total score.

The safety analyses will be based on the APTS.

The efficacy analyses will be based on the FAS.

17.3 Descriptive Statistics

In general, summary statistics (n, arithmetic mean, standard deviation, median, minimum and maximum values) will be presented for continuous variables and counts and, if relevant, percentages will be presented for categorical variables.

The data will be summarised for all patients, and by lead-in study and by lead-in treatment (lead-in Study 12709A and Study 12710A).

For some variables summaries will include data from the lead-in study.

17.4 Patient Disposition

Patient disposition will be summarised and include the number of patients who completed and the number of patients who withdrew from treatment, as well as the number of patients in each analysis set (APTS and FAS).

The number of patients who withdrew from treatment will be summarised by primary reason for withdrawal as well as by all reasons for withdrawal.

17.5 Demographics and Other Baseline Characteristics

Demographics (sex, age, race), other baseline (Baseline Extension A) characteristics (height, weight, BMI) for the extension study, and baseline efficacy variables for the extension study will be summarised.

17.6 Recent and Concomitant Medication

Recent and concomitant medication will be summarised by anatomical therapeutic chemical (ATC) code and generic drug name.

17.7 Exposure and Compliance

Exposure and compliance will be calculated per patient and summarised.

17.8 Efficacy Analyses

17.8.1 General Efficacy Analysis Methodology

Change from Baseline Extension A in CDRS-R, CGI-S, BRIEF, CGAS, and PedsQL VAS using descriptive statistics by lead-in study and by lead-in treatment.

CGI-I score at Week 26 using descriptive statistics by lead-in study and by lead-in treatment.

Time to first loss of remission and time to first relapse will be analysed using Kaplan-Meier estimates.

For exploratory use a random effects slope and intercept model will be applied using Mixed Model Repeated Measurements (MMRM) to study long-term development in efficacy parameters such as CDRS-R.

17.9 Pharmacokinetic Analyses

Sparse sampling (2 time points) for vortioxetine quantification will be performed. The population PK of vortioxetine will be assessed by means of nonlinear mixed effect modelling and the results from the analysis will be reported in a separate population PK report.

17.10 Safety Analyses

17.10.1 Analysis of Adverse Events

Adverse events will be classified according to the time of onset of the adverse event:

- *lead-in adverse event* – an adverse event ongoing from lead-in study 12709A or study 12710A and prior to the date of first dose of IMP in study 12712A
- *treatment-emergent adverse event* (TEAE) – an adverse event that starts or increases in intensity on or after the date of first dose of IMP in study 12712A.

Adverse events, sorted by system organ class (SOC) and preferred term, will be summarised.

TEAEs may be allocated into study periods (these will be defined in the *Statistical Analysis Plan*).

The primary objective will be addressed with an overall clinical evaluation of the safety results.

17.10.2 Analyses of Safety Endpoints

Adverse events, PAERS items, Tanner scores, clinical safety laboratory tests, vital signs, height, weight, BMI, and ECG parameters will be summarised, and observed potentially clinically significant (PCS) safety laboratory test values will be flagged and summarised. Length of menstrual cycle and C-SSRS scores will be summarised using descriptive statistics.

For variables that are heavily dependent on sex and age (such as Tanner and menstrual cycle length) further exploratory descriptions will be made.

Analyses will be performed with respect to the baseline in lead-in study 12709A or 12710A and Baseline Extension A.

For exploratory use a random effects slope and intercept model will be applied using Mixed Model Repeated Measurements (MMRM) to study long-term development in safety parameters such as weight.

17.11 Interim Analyses

No interim analyses for efficacy are planned. A DMC will monitor safety data at regular intervals to be specified in the Data Monitoring Committee Charter.

17.12 Sample Size and Power

No formal sample size calculation has been performed for the present study, which includes patients who have completed the studies 12709A or 12710A and are eligible for enrolment for this study. Sample size is based on an expected withdrawal of 15-20% of the 1200 patients randomised to the lead-in studies. A maximum of 85% of these lead-in completers are

expected to accept to continue into this extension study. This gives approximately 850 patients.

17.13 Statistical Analysis Plan

A *Statistical Analysis Plan* describing the handling of data issues and the planned statistical analyses in more detail will be prepared by the Department of Biostatistics, H. Lundbeck A/S.

18 Clinical Study Report and Publications

18.1 Clinical Study Report

Upon completion of the study, a *Clinical Study Report* will be prepared by the Department of Medical Writing, H. Lundbeck A/S.

18.2 Data Ownership

The data collected in this study are the property of H. Lundbeck A/S.

18.3 Publications

The results of this study will be submitted for publication.

The primary publication based on this study must be published before any secondary publications are submitted for publication.

Authors of the primary publication must fulfil the criteria defined by the International Committee of Medical Journal Editors (ICMJE).[38]

19 Indemnity and Insurance

In the event of study-related injuries or deaths, insurance for the patients and indemnity of the investigators and those of their employees, servants, or agents whose participation in this study has been documented are provided. Insurance and liability will be in accordance with applicable laws and *Good Clinical Practice*.

20 Finance

20.1 Site Agreement

The financial agreements for the site are addressed in one or more documents. Both parties must sign the agreements before the site is initiated.

20.2 Financial Disclosure

All the investigators, including sub-investigators, and raters participating in the study must complete a *Financial Disclosure Form* in order to comply with the United States Food and Drug Administration (FDA) *Financial Disclosure* requirements.

20.3 Equipment

Equipment owned or rented by Lundbeck that has been provided to the site for use during the study must be returned at the end of the study.

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Appendix I

Clinical Study Protocol Authentication and Authorisation

Clinical Study Protocol
Authentication and Authorisation

Study title:	Long-term, open-label, flexible-dose, extension study of vortioxetine in child and adolescent patients with Major Depressive Disorder (MDD) from 7 to 18 years of age
Study No.:	12712A
Edition No.:	3.0
Date of edition:	16 January 2017

This document has been signed electronically. The signatories are listed below.

Authentication

I hereby confirm that I am of the opinion that the ethical and scientific basis of this study is sound.

International study manager: [redacted]

Clinical research scientist: [redacted]

Head, Biostatistics: [redacted]

Divisional Director, GPV: [redacted]

Authorisation

I hereby confirm that I am of the opinion that the ethical and scientific basis of this study is sound.

Director,
Clinical Research - Paediatrics: [redacted]

Appendix II
Recent and Concomitant Medication:
Disallowed or Allowed with Restrictions

Recent and Concomitant Medication: Disallowed or Allowed with Restrictions

In the table below disallowed recent and concomitant medications are listed, including any restrictions with respect to their use prior to and during the study.

Drug Class		**Disallowed (X) During the Study for**		
		Chronic Use	**Episodic Use**	**Comments or Exceptions**
Agents used for ADHD (non stimulant e.g. atomoxetine, guanfacine, and clonidine)		X	X	Psychostimulant agents (e.g. methylphenidate and amphetamine), are allowed.
Anaesthetics	General	X	X	General anaesthetics are disallowed during the study except in case of emergency procedures requiring anaesthesia
	Local	X		
Analgesics	Narcotic analgesics	X	X	
	NSAIDs[a]	X		
Anorexics		X	X	
Antiacne agents		X	X	Agents for topical use are allowed
Antibiotics				Only rifampicin is disallowed
Anticoagulants		X	X	Only low-molecular weight heparins are allowed for episodic use
Anticonvulsants		X	X	
Antidepressants		X	X	Monoamine oxidase inhibitors (MAOs) are contraindicated.
Antidiarrhoeal agents		X	X	Only loperamide, bismuth and kaolin preparations are allowed
Antihistamines		X	X	Only loratadine, desloratadine, cetirizine, levocetirizine, mizolastine and fexofenadine are allowed
Antimigraine agents – triptans, dopamine antagonists		X	X	
Antinauseants (including dopamine antagonists)		X	X	Only phosphoric acid preparations, bismuth and cola syrup are allowed
Antineoplastics		X	X	
Antiobesity agents		X	X	
Antiplatelet treatment (including low dose aspirin)		X	X	
Antipsychotics		X	X	
Anxiolytics		X	X	

Drug Class	Disallowed (X) During the Study for		
	Chronic Use	Episodic Use	Comments or Exceptions
Cough/cold agents	X		Preparations containing ephedrine, pseudoephedrine and codeine are allowed for episodic treatment for a maximum of 1 week
Herbal remedies, which are psychoactive (e.g. St. John's Wort, kava kava, valerian, ginkgo biloba)	X	X	
Hormones	X	X	Only thyroid hormone replacement, contraceptives and progesterone replacement therapy are allowed.
Hypoglycaemic agents		X	
Insulin		X	
Mood stabilisers (including lithium, valproate, valpromide)	X	X	
Muscle relaxant	X	X	
Psychotropic agents not otherwise specified (including, tryptophan, and dopamine agonists)	X	X	
Sedatives/hypnotics[b]	X	X	Zolpidem, zopiclone or zaleplon allowed, for severe insomnia, with a maximum of 2 nights per week. Melatonin is allowed with a maximum of 3 nights per week. The patient is not allowed to take any sleeping aid the night before a study visit.
Systemic steroids	X	X	

a. Both start and stop dates for each use are to be reported in the eCRF

b. Both start and stop dates for each use are to be reported in the eCRF. Every tablet/capsule should be reported for this type of medication from the Baseline Extension A Visit until Visit 13.