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Full Title

A double-blind, randomized, placebo-controlled, multicentre, relapse-prevention study of vortioxetine in paediatric patients aged 7 to 11 years with Major Depressive Disorder

Short Title

13546A - Protocol - Edition 1.0

Study Number 13546A

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Clinical Study Protocol

A double-blind, randomized, placebo-controlled, multicentre, relapse-prevention study of vortioxetine in paediatric patients aged 7 to 11 years with Major Depressive Disorder

Vortioxetine

Study No.:	13546A
EudraCT No/IND.:	2010-020493-42/112581
Sponsor:	H. Lundbeck A/S (Lundbeck) 2500 Valby (Copenhagen), Denmark
Edition No.:	1.0
Date of edition:	7 January 2021

Synopsis – Study 13546A

Sponsor H. Lundbeck A/S	**Investigational Medicinal Product** Vortioxetine
Study Title A double-blind, randomized, placebo-controlled, multicentre, relapse-prevention study of vortioxetine in paediatric patients aged 7 to 11 years with Major Depressive Disorder (MDD)	
Objectives and Endpoints **Objectives**	**Endpoints**
Primary Objective • to evaluate the efficacy of vortioxetine in the prevention of relapse of major depressive episodes in paediatric patients with MDD	**Depressive Symptoms** • Primary endpoint: – time to relapse in the double-blind period • Secondary endpoint: – relapse rate in the double-blind period
Secondary Objectives • to evaluate efficacy of vortioxetine during continuation treatment of paediatric patients with MDD • to evaluate the efficacy of vortioxetine on: – clinical global impression – quality of life • to assess adherence to investigational medicinal product (IMP) through pharmacokinetic analysis	**Depressive Symptoms** • Secondary endpoint: – change from baseline to Week 26 in the Children Depression Rating Scale Revised Version (CDRS-R) total score **Global Clinical Impression** • Secondary endpoints: – change from baseline to Week 26 in the Clinical Global Impression – Severity of Illness (CGI-S) score – Clinical Global Impression – Global Improvement (CGI-I) score at Week 26 **Quality of life** • Secondary endpoint: – Change from baseline to Week 26 in Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) – Patient rated **Pharmacokinetics** • Secondary endpoints: – plasma exposure to vortioxetine – population pharmacokinetic parameter values

Safety Objectives	Safety Endpoints
• to evaluate long-term safety and tolerability of vortioxetine in paediatric patients with MDD	• adverse events • absolute values and changes from baseline in clinical safety laboratory test values (including estradiol [girls only], and luteinising hormone [LH], follicle-stimulating hormone [FSH]), vital signs, height, weight, Tanner staging, electrocardiogram (ECG) parameter values. Effects on menstrual cycle will be assessed. • potentially clinically significant clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values • Columbia-Suicide Severity Rating Scale (C-SSRS) score • General Behaviour Inventory (GBI) using the 10-item mania subscale (parental version)

Study Methodology

- This is an interventional, multi-national, multi-site, randomized, parallel-group, placebo-controlled, relapse-prevention study in paediatric patients with MDD from 7 to 11 years of age.
- The study consists of a 12-week, open-label, flexible-dose treatment period with vortioxetine followed by a 26-week, randomized, double-blind, fixed-dose, placebo-controlled relapse-prevention period.
- The study population will include *de novo* patients as well as rollover patients from other paediatric vortioxetine studies (Studies 12709A and 12712A), who, in the investigator's opinion, could benefit from continued treatment with vortioxetine.

***De novo* patients**

- Patients meeting eligibility criteria for *de novo* patients will be enrolled in the 12-week, open-label, flexible-dose treatment period.

Rollover patients from Study 12709A (enrolled to the open-label period)

- Patients may participate in the present study after completion of the randomized, 8-week, double-blind, placebo-controlled treatment period of Study 12709A.
- Eligible patients will be enrolled in the 12-week, open-label, flexible-dose treatment period.
- The Baseline Visit of this study (Study 13546A) will take place at the same visit as Visit 12 (Completion Visit) of Study 12709A. Participation in Study 12709A is considered completed when all assessments required at Visit 12 are completed.

Rollover patients (remitters) from Study 12712A (randomized to the double-blind period)

- Patients who have received 8 to 12 weeks of treatment with vortioxetine in the open-label extension study 12712A may participate in the present study if they have remitted (CDRS-R total score ≤28) at the last 2 visits in Study 12712A prior to the rollover. In addition, the dose of vortioxetine must have been fixed for the last 4 weeks in Study 12712A prior to randomization in the present study.
- Eligible patients will be randomized directly to the 26-week, double-blind treatment period.

- The study design is presented in Panel 1 (including the study periods) and the scheduled study procedures and assessments are summarized in Panel 2 and Panel 3.

Open-label Period (for *de novo* patients and rollover patients from Study 12709A)

- The duration of the open-label, flexible-dose treatment period will be 12 weeks.
- 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 increase the dose to a maximum of 20 mg/day in case of unsatisfactory response or decrease the dose to 5 mg/day 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- or down-titrated to a new dose. Changes in dosing may occur at any visit during the first 8 weeks at the investigator's discretion. In addition, between Week 2 and Week 8, the patient and/or parent(s)/legal representative(s) can request an unscheduled visit to discuss their current dose.
- From Week 8 onwards the dose has to remain fixed.
- Patients in remission (CDRS-R total score ≤28) at both Weeks 10 and 12 or with an adequate clinical response (defined as ≥50% reduction in the CDRS-R total score compared to the baseline score in this study [subtracted 17 to avoid flooring effect] and a CDRS-R total score ≤35) at both Weeks 10 and 12 will be randomized in the double-blind, placebo-controlled, fixed-dose period.
- Patients who do not fulfil the randomization criteria at Week 10 and/or Week 12 will be withdrawn from the study and will complete an early Withdrawal Visit. Non-remitters who leave the study will be treated at the investigator's discretion.
- A Safety Follow-up Visit will be performed approximately 4 weeks after withdrawal from the open-label period.

Double-Blind Period (for all patients)

- A total of 80 patients who fulfil the randomization criteria will be randomly assigned via a centralized randomization system to receive vortioxetine or placebo in a 1:1 ratio. Randomization will be stratified by patient inclusion source (*de novo* patients, rollover patients from 12709A, or from 12712A).
- Patients randomized to vortioxetine will continue on their final dose from the open-label period or the dose they had on their last visit in Study 12712A, as applicable.
- The duration of the double-blind, fixed-dose treatment period will be 26 weeks.
- Patients who relapse during the double-blind period must be withdrawn from the study. The criterion for a relapse is a CDRS-R total score of ≥40 with a history of 2 weeks of clinical deterioration, or a clinical deterioration that in the investigator's opinion warrants alteration of treatment to prevent full relapse.
- A Safety Follow-up Visit will be performed 4 weeks after withdrawal from or completion of the double-blind period.
- An independent Data Monitoring Committee (DMC) will monitor safety data at regular intervals as specified in the DMC Charter.
- This study will be terminated if the result of the currently ongoing placebo-controlled, short-term study (12709A) in children is negative (that is, if vortioxetine fails to show a significant difference from placebo in acute treatment). In case of study termination, the participating patients will be treated at the discretion of the investigator in line with clinical practice.

Number of Patients Planned

Eighty (80) patients are planned for randomization to the 26-week double-blind period (including those who rollover from study 12712A): 40 in the vortioxetine group and 40 in the placebo group.

One-hundred fifty (150) patients recruited from specialist settings, mainly outpatient clinics, either as *de novo* patients or rollover patients from Study 12709A, are estimated to be enrolled into the study. The exact number of enrolled patients will depend on the number and randomization rate of *de novo* and rollover patients.

Approximately 40 psychiatric centres are planned for recruitment in approximately 10 countries worldwide.

Target Patient Population

Main Inclusion Criteria

***De novo* patients**

- The patient has MDD, diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5™) and confirmed by The Kiddie-Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime version (K-SADS-PL).
- The patient has a CDRS-R total score ≥45 at the Screening and Baseline Visits.
- The patient has a CGI-S ≥4 at the Screening and Baseline Visits.
- The patient has a primary diagnosis of MDD, although co-morbid anxiety disorders will be permitted except Post Traumatic Stress Disorder (PTSD) and Obsessive-Compulsive Disorder (OCD).
- The patient is aged ≥7 and <12 years at screening. Patients who turn 12 years during this study will be allowed to continue in the study.

Rollover patients from Study 12709A (enrolled to the open-label period)

- The patient has completed Study 12709A (Visit 12, Completion Visit) immediately prior to enrolment into this study.
- In the investigator's opinion, the patient could benefit from participation in a study which includes continued treatment with vortioxetine.
- The patient is a child aged ≥7 and <12 years at screening of Study 12709A.

Rollover patients (remitters) from Study 12712A (randomized to the double-blind period)

- The patient has received 8 to 12 weeks of open-label treatment with vortioxetine in Study 12712A and completed Visit 7 (Week 8), or Visit 8 (Week 10), or Visit 9 (Week 12) immediately prior to enrolment into this study.
- In the investigator's opinion, the patient could benefit from participation in a study which includes continued treatment with vortioxetine.
- The patient is in remission at the last 2 visits in Study 12712A, in which the CDRS-R is assessed every 4 weeks. Hence
  a) If the patient rolls over at Visit 7 or Visit 8 (Week 8 or Week 10): the patient has a CDRS-R total score ≤28 at Visit 5 (Week 4) and Visit 7 (Week 8) in Study 12712A
  b) If the patient rolls over at Visit 9 (Week 12): the patient has a CDRS-R total score ≤28 at Visit 7 (Week 8) and Visit 9 (Week 12) in Study 12712A
- The patient has been on a stable dose of vortioxetine for the past 4 weeks prior to rollover to this study.
- The patient is a child aged ≥7 and <12 years at Baseline of Study 12712A.

Main Exclusion Criteria

- The patient presents with, or has a history of, an Axis I (DSM-5™) diagnosis of Bipolar Disorder, PTSD, OCD, Autism, Pervasive Developmental Disorder (PDD), or Schizophrenia or Schizoaffective Disorder.
- The patient has a diagnosis of attention-deficit/hyperactivity disorder (ADHD) and is not maintained on a stable dose of a methylphenidate or amphetamine for a minimum of 4 weeks prior to the study treatment.
- One of the parents or siblings of the patient has a history of Bipolar Disorder.
- The patient has attempted 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 within the last 12 months).
- The patient has a known intellectual disability (as suggested by an intelligence quotient [IQ] <70), or, clinical evidence or known social or school history indicative of intellectual disability.).
- The patient has been treated with any antidepressant or anxiolytic medication within 2 weeks prior to Visit 2 (only *de novo* patients).
- The patient is unable to swallow capsules.
- The patient has previously been treated with vortioxetine in a clinical study (only *de novo* patients).

Investigational Medicinal Product, Reference Therapy, Doses and Mode of Administration

Open-label Period

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

  The treatment should be taken once daily, preferably at the same time each day.
- Patients will receive a targeted dose of 10 mg/day vortioxetine, however the investigator has the possibility to adjust the dose in case of unsatisfactory response or in case of dose-limiting AEs. The patient will receive a lower initial dose (5 mg/day for 2 days) prior to receiving 10 mg/day. 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- or down-titrated to a new dose.

Double-blind Period

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

The treatment should be taken once daily, preferably at the same time each day.

Statistical Methodology

- The following analysis sets will be used to analyse and present the data:
  - *all-patients-enrolled set* (APES) – all patients enrolled to the 12-week open-label, flexible-dose treatment period who took at least one dose of IMP
  - *all-patients-randomized set* (APRS) – all patients randomized to the 26-week double-blind treatment period
  - *full-analysis set* (FAS) – all patients randomized to the 26-week double-blind treatment period who took at least one dose of double-blind IMP

The efficacy analyses will be based on the FAS.

- Primary analysis:
  - Primary efficacy analysis will compare the time to relapse (defined as either a total score ≥40 on the CDRS-R with a history of 2 weeks of clinical deterioration, or clinical deterioration as judged by the clinician) between Vortioxetine and placebo using a Cox regression model with exact adjustment for ties. A one-sided 5% level of significance will be used. Patients not relapsing before Week 26 will be censored at Week 26 and patients withdrawing due to other reasons than relapse will be censored at time of withdrawal.
- Sensitivity analysis of the primary endpoint:
  - Primary analysis will be repeated ignoring relapses occurring during the first week, two weeks and four weeks of the double-blind period, respectively.
  - The number of relapses will be summarized according to relapse criteria: CDRS-R total score ≥40 with 2 weeks of clinical deterioration, investigator's judgement, or both.
  - Primary analysis will be repeated for the *de novo* patients and for the (pooled) 12709A patients and 12712A patients.
- Analyses of secondary endpoints:
  - Relapse over 26 weeks will be analysed using logistic regression.
  - Secondary efficacy variables (CDRS-R, PQ-LES-Q, CGI-S, CGI-I) will, on an exploratory basis be analysed over the 26-week double-blind period by Mixed Model Repeated Measurements (MMRM) and analysis of covariance (ANCOVA) (observed cases [OC] and last observation carried forward [LOCF]).
  - The population pharmacokinetics (popPK) of vortioxetine in children will be analysed through non-linear mixed effect analysis and will be described in a separate popPK analysis plan.
- Analyses of other endpoints:
  - On an exploratory basis, potential use of psychotherapy in the double-blind period, severity of illness, gender, and age will be assessed as covariates or to generate subgroups for the Cox regression model.
  - Descriptive statistics will be used to compare patient populations and treatment outcome between the geographical regions.
- The safety analyses will be based on the APES and the FAS.
- Analyses of safety endpoints:
  - AEs, absolute and change from baseline in clinical safety laboratory tests (estradiol for girls, LH, FSH), Tanner staging, ECG, and effects on menstrual cycle, vital signs, height, weight, and ECG parameters will be summarized, and observed potentially clinically significant (PCS) safety laboratory test values will be flagged and summarized. GBI scores (using the 10-item mania subscale), and C-SSRS scores will be summarized using descriptive statistics.
  - AEs and other safety endpoints will be reported separately for the 12-week open-label period and the 26-week double-blind period.
- Patient disposition and demographics will be summarized using descriptive statistics.

Testing Strategy

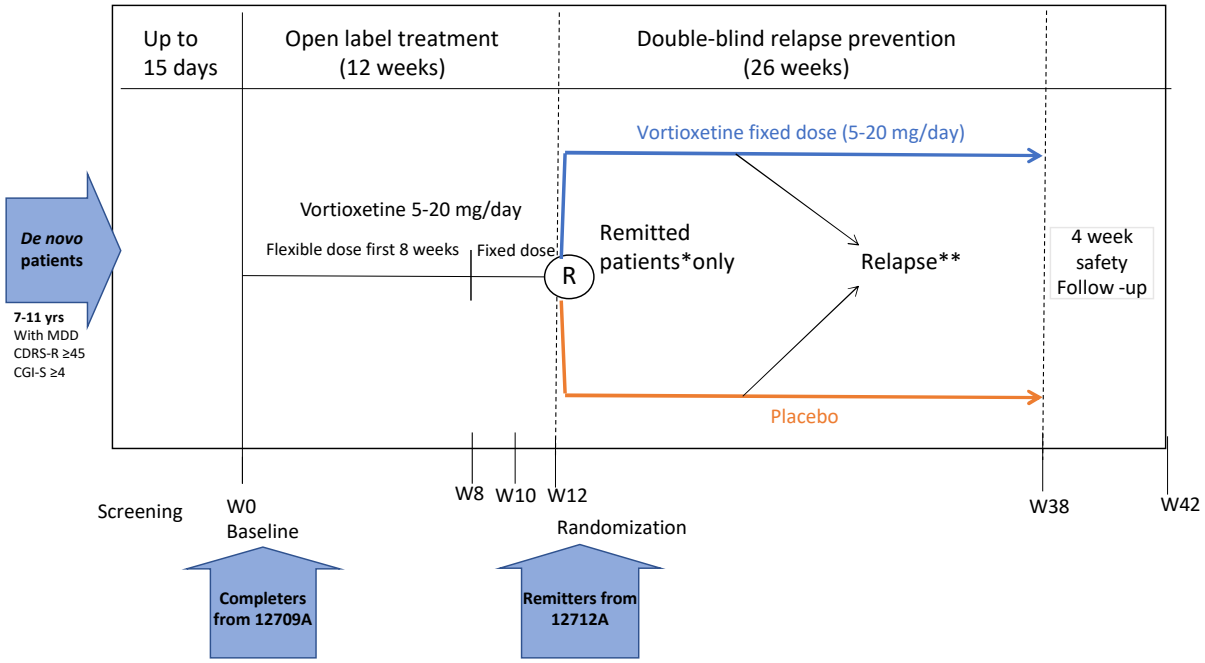
Not applicable

Sample Size Considerations

The calculation of power is based on a log-rank test for the time to relapse at a one-sided 5% level of significance using SAS® Proc Power. A sample size of 80 randomized patients (40 patients per treatment group) will provide at least 80% power to find a difference between vortioxetine and placebo as statistically significant, when expecting cumulative relapse rates at 0.42 and 0.69 over 26 weeks, respectively, corresponding to a hazard-ratio of 2.15.

It is anticipated that approximately 60% of *de novo* patients enrolled into the open-label period will qualify for the double-blind study period. One-hundred fifty (150) patients are estimated to be enrolled into the study (depending on number and randomization rate of *de novo* and rollover patients).

Panel 1 Study Design



* Patients in remission (CDRS total score ≤28) at the two last visits in the open-label treatment period / Study 12712A *OR* with an adequate clinical response (≥50% reduction in the CDRS-R total score compared to the baseline score and a CDRS-R total score ≤35) at the two last visits in the open-label treatment period
**Relapse: CDRS-R total score of ≥40 with a history of 2 weeks of clinical deterioration, or a clinical deterioration that in the investigator's opinion warrants alteration of treatment to prevent full relapse

Panel 2 Study Procedures and Assessments – Open-label Period for *de novo* Patients and Rollover Patients from Study 12709A

		Open-label Period									
Visit Name	**Screening[a] only *de novo***	**Baseline[b] *de novo***	**Baseline[c] 12709A rollover**						**Randomization**	**Withdrawal[d]**	**Safety Follow-up[e]**
Visit Number	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		
Day/End of Week	**d-5/d-15**	**0**	**0**	**W1**	**W2**	**W4**	**W8**	**W10**	**W12**		**W16**
Visit Window[f] (days relative to nominal visit)		**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±5**
Screening and Baseline Procedures and Assessments											
Signed Informed Assents/Consents	√		√								
Diagnosis (DSM-5™)	√		(√)[g]								
K-SADS-PL[h]	√		(√)[g]								
Disease-specific history	√		(√)[g]								
Relevant history (social, medical, psychiatric, neurological)	√		(√)[g]								
Demographics (age, sex, race)	√		(√)[g]								
Family psychiatric history	√		(√)[g]								
Traumatic life events	√		(√)[g]								
Inclusion/exclusion criteria	√	√	√								
Randomization criteria									√		
History of stimulant medication	√		(√)[g]								
Efficacy Assessments											
CDRS-R	√	√	(√)[i]	√	√	√	√	√	√	√	
CGI-S	√	√	(√)[i]	√	√	√	√	√	√	√	
PQ-LES-Q (PRO)		√	(√)[i]				√		√	√	
Pharmacokinetic Assessments											
Blood sampling for vortioxetine quantification						√			√	√	
Safety Assessments											
Adverse events	√	√	(√)[i]	√	√	√	√	√	√	√	√[j]
Blood and urine sampling for clinical safety laboratory tests	√[k]		(√)[i, l]			√			√	√	
Vital signs	√	√	(√)[i]	√	√	√	√	√	√	√	
Weight and height	√		(√)[i]						√	√	
ECG	√		(√)[i]			√			√	√	
Examinations (physical and neurological)	√		√							√	

		Open-label Period								
Visit Name	**Screening[a] only *de novo***	**Baseline[b] *de novo***	**Baseline[c] 12709A rollover**					**Randomization**	**Withdrawal[d]**	**Safety Follow-up[e]**
Visit Number	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		
Day/End of Week	**d-5/d-15**	**0**	**0**	**W1**	**W2**	**W4**	**W8**	**W10**	**W12**		**W16**
Visit Window[f] (days relative to nominal visit)		**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±5**
Tanner staging and menstrual cycle	√		√							√	
C-SSRS	√	√	(√)[i]	√	√	√	√	√	√	√	
GBI (Mania subscale)	√	√	(√)[i]	√	√	√	√	√	√	√	
Other Study Procedures and Assessments											
IMP dispensed		√	√	√	√	√	√	√	√		
Possible change in IMP dose[m]				√	√	√	√				
IMP returned and IMP accountability				√	√	√	√	√	√	√	
Recent and concomitant medication	√	√	(√)[i]	√	√	√	√	√	√	√	
Pregnancy test[n]	√		(√)[i]						√	√	
Drug and alcohol screen[o]											

AE = adverse event; CDRS-R = Children depression rating scale revised version; CGI-S = Clinical Global Impression – Severity of Illness; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic case report form; GBI= General Behaviour Inventory; IMP = investigational medicinal product; K-SADS-PL = The Kiddie-Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime version; PQ-LES-Q = Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire – Patient rated; SAE = serious AE

a Screening visit will be performed only for *de novo* patients. Patients rolling over from Study 12709A will proceed directly to the Baseline Visit (see 'Baseline Visit 12709A rollover' column). The Informed Assent/Consent Form must be signed before any study-related activities take place.

b Applicable only for *De novo* patients.

c Applicable only for 12709A rollover patients. Assessments marked with (√) in this column will be used from 12709A study and therefore not repeated.

d This visit should take place as soon as possible after the patient withdraws from the study. Any visit during the open-label treatment period can be converted into a Withdrawal Visit on the day of the visit.

e Applicable for patients withdrawn prior or at Visit 8: Safety follow-up should be scheduled approximately 30 days after the last dose of IMP. It 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 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).

f If the date of a visit does not conform to the schedule, subsequent visits should be planned to maintain the visit schedule relative to the Baseline Visit. Consider that the number of days between 2 visits must not exceed the number of days for which the patient has been dispensed IMP.

g The data from the Screening Visit in the Study 12709A eCRF will be used.

h The K-SADS-PL will be used to confirm diagnosis of MDD and to assess possible psychiatric co-morbidities.

i Values from all assessments and procedures (efficacy/safety, including blood/urine samples and use of concomitant medication) performed at the Completion Visit (Visit 12) in Study 12709A will be the Baseline Visit values in Study 13546A.

j Only for AEs ongoing at Withdrawal and new SAEs.

k The hormones panel is to be collected at Visit 1 (estradiol in females only).

l An extra tube of blood samples will be required for hormones at the Study 12709 Week 12 Visit.

m Between Week 2 and Week 8, the patient and/or parents /legal representative can request an unscheduled site visit to discuss their current dose. AEs will be collected and C-SSRS, GBI-mania and CGI-S will be done at the unscheduled visit.

n If the patient is a female subject of childbearing potential (defined as females aged ≥10 years old and younger girls who, at the discretion of the investigator, are deemed to be of reproductive potential), a urine pregnancy test is to be performed at screening and randomization, and at the Withdrawal Visit.

o 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.

Panel 3 Study Procedures and Assessments – Double-blind Period

Visit	Double-blind period (Relapse-prevention)										Safety Follow-up[b]
	Randomization[a]									Completion or Withdrawal	
Visit Number	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
End of Week (relative to Baseline)	**12**	**13**	**14**	**16**	**18**	**22**	**26**	**30**	**34**	**38**	**42**
End of Week (relative to Randomization)	**0**	**1**	**2**	**4**	**6**	**10**	**14**	**18**	**22**	**26**	**30**
Visit Window[c] (days relative to nominal visit)	**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	**±**	**±5**	**±5**	**±5**
Randomisation Procedures and Assessments											
Signed Informed Assent/Consent (rollover patients from 12712A only)	√										
Inclusion criteria	√										
Efficacy Assessments											
CDRS-R	√[d]	√	√	√	√	√	√	√	√	√	
CGI-S	√[d]	√	√	√	√	√	√	√	√	√	
CGI-I		√		√		√		√		√	
PQ-LES-Q (PRO)	√			√		√		√		√	
Pharmacokinetic Assessments											
Blood sampling for vortioxetine quantification	√					√				√	
Safety Assessments											
Adverse events	√[e]	√	√	√	√	√	√	√	√	√	√[f]
Blood and urine sampling for clinical safety laboratory tests[j]	√[i]					√				√	
Vital signs	√[d]	√	√	√	√	√		√		√	
Weight and height	√[d]					√				√	
ECGs	√					√				√	
Examinations (physical and neurological)	√[d]					√				√	
Menstrual cycle	√[d]									√	
Tanner staging	√[d]									√	
C-SSRS	√[d]	√	√	√	√	√	√	√	√	√	
GBI (mania subscale)	√		√		√	√		√		√	
Other Study Procedures											

IMP dispensed	√	√	√	√	√	√	√	√	√		
IMP returned and IMP accountability	√	√	√	√	√	√	√	√	√	√	
Recent and concomitant medication	√[e]	√	√	√	√	√	√	√	√	√	
Pregnancy test[g]	√					√				√	
Drug and alcohol screen[h]											

CDRS-R = Children depression rating scale revised version; CGI-I = Clinical Global Impression – Global Improvement; CGI-S = Clinical Global Impression – Severity of Illness; C-SSRS = Columbia-Suicide Severity Rating Scale; eCRF = electronic case report form; ECG = electrocardiogram; GBI: General Behaviour Inventory; IMP = investigational medicinal product; K-SADS-PL = The Kiddie-Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime version; PQ-LES-Q = Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire – Patient rated; SAE = serious adverse event

a Patients from Study 12712A who are in remission after 8 to 12 weeks of open-label treatment in study 12712A will enter directly into the Randomization Visit of this 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 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 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 the Randomization Visit (Visit 8). Consider that the number of days between 2 visits must not exceed the number of days for which the patient has been dispensed IMP.

d For 12712A-patients, last available values from assessments and procedures (efficacy/safety, and use of concomitant medication) performed at either Visit 7 (Week 8) and/or Visit 8 (Week 10), or Visit 9 (Week 12) in Study 12712A will be the Randomization Visit values for this study, when applicable. For patients who rollover at Visit 7 or Visit 8, weight, height, Tanner staging, menstrual cycle, and examinations should be done at the Randomization Visits.

e For 12712A-patients, ongoing AEs and concomitant medication from study 12712A will be used for eCRF.

f Only for AEs ongoing at Completion/Withdrawal and new SAEs

g If the patient is a female subject of childbearing potential (defined as females aged ≥10 years old and younger girls who, at the discretion of the investigator, were deemed to be of reproductive potential), a urine pregnancy test is to be performed at randomization, Visit 13 (double-blind period Week 10) and at Completion/Withdrawal Visit. Additional pregnancy tests during the study will be performed according to local requirements.

h 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.

i Only for 12712A-patients who rollover into double-blind phase.

j The hormones panel is to be collected at Visit 8 (for 12712A-patients) and Completion/Withdrawal (for all patients).

Table of Contents

Appendices

List of Panels

List of Abbreviations and Definitions of Terms

ADHD	attention-deficit/hyperactivity disorder
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APES	all-patients-enrolled
APRS	all-patients-randomized set
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	Area under the curve
B	blood
BMI	body mass index
bpm	beats per minute
CDRS-R	Children Depression Rating Scale Revised Version
CGI-I	Clinical Global Impression – Global Improvement
CGI-S	Clinical Global Impression – Severity of Illness
CHMP	Committee for Medicinal Products for Human Use (European Union)
CI	confidence interval
C_{max}	maximum observed concentration
COA	Clinical Outcome Assessments
COVID	Coronavirus disease
CBT	cognitive behavioural therapy
CRA	clinical research associate
CRO	Contract Research Organisation
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450 isoenzyme
DMC	Data Monitoring Committee
DO	Doctor of osteopathy/osteopathic medicine
DSM-5™	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	electrocardiogram
eCRF	electronic case report form
eCOA	Electronic COA
EDTA	ethylenediamine tetra acetic acid
EMA	European Medicines Agency
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	full-analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GBI	General Behaviour Inventory

HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
5-HT	serotonin
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IPT	interpersonal psychotherapy
IQ	intelligence quotient
IRB	institutional review board
IRT	interactive response technology
K-SADS-PL	The Kiddie-Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime version
LH	luteinising hormone
LOCF	last observation carried forward
Lu	Lundbeck
MDD	major depressive disorder
MMRM	mixed model for repeated measurements
NOAEL	no-observed-adverse-effect level
OC	observed cases
OCD	Obsessive Compulsive Disorder
P	plasma
PCS	potentially clinically significant
PDD	Pervasive Developmental Disorder
PIP	Paediatric Investigational Plan
PK	pharmacokinetic(s)
PKS	pharmacokinetic set
popPK	population pharmacokinetics
PPS	per protocol set
PQ	specific ECG interval describing atrioventricular conduction
PQ-LES-Q	Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire
PR	specific ECG interval describing atrioventricular conduction
PRO	patient-reported outcome
PROLCTN	prolactin
PTSD	Post Traumatic Stress Disorder
QP	qualified person
QRS	specific ECG interval describing ventricular depolarization
QT	specific ECG interval describing ventricular depolarization/repolarization

QT_c	heart rate corrected QT interval
QT_{cF}	heart rate corrected QT interval using Fridericia's correction formula
RR	specific ECG interval describing the ventricular depolarization/repolarization cycle
SAE	serious adverse event
SAS®	statistical software package from the SAS® Institute
SERT	serotonergic receptor activity and inhibition of the serotonin (5-HT) transporter
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TMF	trial master file
TSH	thyroid stimulating hormone
U	urine
US	United States
Vss	volume of distribution

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]

The prevalence of Major depressive disorder (MDD) is estimated to be approximately 2% in children and 4 to 8% in adolescents.[3,4,5,6]

Signs and symptoms of MDD are similar to the adult population, but depressive disorders meeting the diagnostic criteria are rarely present before the age of seven years.[7,8] 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 to complain of feelings of hopelessness/helplessness, lack of energy and to have a higher rate of suicidal thoughts.[9,10]

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 is currently approved in both Europe and the US for the treatment of children and adolescents with MDD [11,12] and escitalopram is approved in the US for the treatment of adolescents with MDD.[13,14] Thus, there is a critical need to broaden current pharmacological treatment options for this patient population.

The aim of this study is to evaluate the efficacy of vortioxetine versus placebo in preventing relapse of depressive symptoms in children aged 7 to 11 years with a DSM-5™ diagnosis of MDD.

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* (IB).[15]

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.[16]

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

This relapse-prevention study is part of agreed European Medicines Agency (EMA) Paediatric Investigational Plan (PIP) to evaluate vortioxetine in the treatment of MDD in children and adolescents. The PIP includes a total of 6 studies:

- Study 12708A that investigated pharmacokinetics (PK) and safety in children and adolescents
- 2 short-term efficacy studies: Study 12709A in children and Study 12710A in adolescents
- 2 open-label extension studies to Studies 12709A and 12710A: 12712A (6 months) and 12712B (extension to 12712A; 18 months)
- Relapse-prevention study 13546A

The PK study, 2 short-term studies, and the 6- month extension study are also part of the paediatric programme for vortioxetine agreed with the US Food and Drug Administration (FDA). Of the 2 short-term efficacy and safety studies, Study 12710A in adolescents has been completed with a negative outcome, whereas Study 12709A in children is still ongoing. Of the 2 open-label extension studies of 6 and 18 months' duration that enrol completers from the short-term studies, Study 12712A (6-month extension) is ongoing and enrolling patients from 12709A. Study 12712B which enrolled completers from Study 12712A has been completed. The data available from these studies are described in the following sections.

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 maximum observed concentration (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).[15]

In the paediatric PK study (12708A), 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 area under the curve (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 uptitration scheme employed in this study are appropriate for the paediatric population.

In the short-term efficacy study for adolescents (12710A), vortioxetine steady-state exposures in adolescents were similar to those previously reported in adults both for vortioxetine 10 mg and 20 mg. Regarding PK/PD, no apparent relationships could be found between the efficacy variables and plasma exposure of vortioxetine at the end of the double-blind period, which was in line with the primary analysis showing negative results for vortioxetine. Based on PK data, 16% of the vortioxetine-treated patients (11% in the 10 mg group and 20% in the 20 mg group) and 14% of the vortioxetine and fluoxetine treated patients, could be regarded as non-compliant in this study.

1.1.3.2 Efficacy

Adults

Vortioxetine has been approved in the United States (US), European Union (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.

Paediatrics

An 8-week, randomized, double-blind, placebo-controlled, active-reference, fixed-dose, study (Study 12710A) was conducted in adolescent patients with MDD aged 12 to 17 years. The study included a 4-week, single-blind, placebo lead-in period with standardized psychosocial intervention (N=777); only non-responders from the lead-in period were randomized (N=616). The study was concluded negative: similar improvements in depressive symptoms were observed over 8 weeks for vortioxetine and placebo-treated patients, with no statistically significant differences between vortioxetine and placebo on the primary endpoint (mean change from baseline to end-point [8 weeks] on the CDRS-R total score). The active reference (fluoxetine 20 mg/day) separated from placebo on the CDRS-R total score, however, a substantial placebo response was still observed.

In a similarly designed study in children with MDD aged 7 to 11 years (Study 12709A), an interim analysis was conducted based on data from 271 randomized patients to potentially terminate the study, if there was sufficient evidence of an effect of vortioxetine, or a clear lack thereof. As the results of the interim analysis met neither the efficacy nor the futility criterion, and no safety concerns have been raised, the study should continue as planned until the prespecified sample size of 539 patients has been reached. A review of unblinded efficacy data from the interim analysis by an independent data monitoring committee (DMC) indicated no concerns that would preclude continuation of studies of vortioxetine in children.

The efficacy data from the open-label extension studies (ongoing Study 12A and completed Study 12B) indicate continuous improvements on depressive symptoms in patients who continued to receive vortioxetine for up to 6 months or 24 months, respectively.

1.1.3.3 Safety

Adults

The evaluation of the safety and tolerability of vortioxetine is based on data from a large clinical development programme and extensive post-approval experience (see IB[15]). Overall short- and long-term treatment with vortioxetine at the therapeutic doses (5 to 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 AEs 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, electrocardiograms (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.

Paediatrics

The dose range of vortioxetine (5 to 20 mg/day) was chosen based on the knowledge from the clinical development programme in adult patients and the results of a paediatric pharmacokinetic and tolerability study (Study 12708A), which indicated that no dose adjustment was needed in the paediatric population. Hence, the doses known to be efficacious in the adult population (5 to 20 mg/day) and used in the paediatric development programme are confirmed as well tolerated based on the current large paediatric database.

Study 12708A, 24 children and 24 adolescents (aged 7 to 17 years) with a depressive or anxiety disorder were treated with vortioxetine 5 to 20 mg/day. Based on the data from this study, no concerns were raised on the safety and tolerability profile of vortioxetine. Vortioxetine was safe and well tolerated following 14 days of dosing, as well as during an initial up-titration period and following 6 months of treatment. Overall, the tolerability profile in adolescents and children in this study was similar to that in adults with no new types of AEs.

Study 12710A, 308 adolescents (aged 12 to 17 years) with MDD were treated with vortioxetine 10 or 20 mg/day. In general, the adverse reaction profile of vortioxetine in

adolescents was similar to that in adults. The AEs with an incidence ≥5% in the vortioxetine groups were nausea, headache, vomiting, nasopharyngitis, diarrhoea, and dizziness. In particular, the incidences were higher in the vortioxetine groups than in the placebo group for nausea, headache, and vomiting. The mean changes from randomization in the clinical safety laboratory tests; vital signs; weight, body mass index (BMI), and height; and ECG parameters were small, comparable between treatment groups, and not clinically relevant.

Study 12712B, an open-label, flexible-dose, 18-month extension study to Study 12712A, (a 6-month, open-label extension study), 94 children and adolescents (aged 7 to 17 years) with MDD were treated with vortioxetine 5 to 20 mg/day. None of the patients had a serious AE or an AE leading to withdrawal. Overall, the AE profile was similar in children and adolescents. The AEs with an incidence ≥5% were headache, nausea, nasopharyngitis, abdominal pain upper, hyperprolactinaemia, respiratory tract infection viral and vomiting. All the patients with hyperprolactinaemia were asymptomatic. Except for prolactin, the mean changes from baseline in all the other safety laboratory tests, vital signs, and ECG parameters were small and not clinically relevant.

Based on the completed paediatric studies, no new important risks have been identified in the paediatric population beyond those established for the adult population. In the paediatric patients, the safety and tolerability profile of vortioxetine after long-term use was comparable to that observed after short-term use. This conclusion is also supported by data emerging from the ongoing 6-month extension study 12712A that to date enrolled nearly 600 patients. For the ongoing, blinded study in children, continuous review of unblinded safety data by the DMC did not raise any safety concerns. Overall, there are no findings that would preclude continuation of studies of vortioxetine in children.

1.2 Rationale for the Study

This study is part of the agreed EMA PIP for vortioxetine with the purpose to investigate the antidepressant effect of vortioxetine in paediatric patients with MDD. The study is designed to evaluate maintenance of antidepressant effect in children aged 7 to 11 years who continue to receive vortioxetine compared with children switched to placebo after response to vortioxetine treatment.

1.3 COVID 19 Related Risk Assessment and Mitigation

Appropriate risk assessment has been performed and mitigations to be done in case of restrictions due to COVID-19 are described in detail in a separate “COVID-19 Mitigation Plan”.

2 Objectives and Endpoints

The study objectives and endpoints are summarized in Panel 4.

Panel 4 Objectives and Endpoints

Objectives	Endpoints
Primary Objective • to evaluate the efficacy of vortioxetine in the prevention of relapse of major depressive episodes in paediatric patients with MDD	**Depressive Symptoms** • Primary endpoint: – time to relapse in the double-blind period • Secondary endpoint: – relapse rate in the double-blind period
Secondary Objectives • to evaluate efficacy of vortioxetine during continuation treatment of paediatric patients with MDD • to evaluate the efficacy of vortioxetine on: – clinical global impression – quality of life • to assess adherence to investigational medicinal product (IMP) through pharmacokinetic analysis	**Depressive Symptoms** • Secondary endpoint: – change from baseline to Week 26 in the Children Depression Rating Scale Revised Version (CDRS-R) total score **Global Clinical Impression** • Secondary endpoints: – change from baseline to Week 26 in the Clinical Global Impression – Severity of Illness (CGI-S) score – Clinical Global Impression – Global Improvement (CGI-I) score at Week 26 **Quality of life** • Secondary endpoint: – Change from baseline to Week 26 in Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) – Patient rated **Pharmacokinetics** • Secondary endpoints: – plasma exposure to vortioxetine – population pharmacokinetic parameter values
Safety Objectives • to evaluate long-term safety and tolerability of vortioxetine in paediatric patients with MDD	**Safety Endpoints** • adverse events • absolute values and changes from baseline in clinical safety laboratory test values (including estradiol [girls only], and luteinising hormone [LH], follicle-stimulating hormone [FSH]), vital signs, height, weight, Tanner staging, electrocardiogram (ECG) parameter values. Effects on menstrual cycle will be assessed. • potentially clinically significant clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values • Columbia-Suicide Severity Rating Scale (C-SSRS) score • General Behaviour Inventory (GBI) using the 10-item mania subscale (parental version)

3 Study Design

3.1 Overview of the Study Design

This study has been designed in accordance with the *Declaration of Helsinki*[17] and will be conducted in compliance with the protocol, *Good Clinical Practice*,[18] and applicable regulatory requirements.

This is an interventional, multi-national, multi-site, randomized, parallel-group, placebo-controlled, relapse-prevention study in paediatric patients with MDD from 7 to 11 years of age.

The study consists of a 12-week, open-label, flexible-dose treatment period with vortioxetine followed by a 26-week, randomized, double-blind, fixed-dose, placebo-controlled relapse-prevention period.

The study population will include *de novo* patients as well as rollover patients from other paediatric vortioxetine studies (Studies 12709A and 12712A), who, in the investigator's opinion, could benefit from continued treatment with vortioxetine. To reach 80 randomized patients, approximately 150 patients recruited, either as *de novo* patients or rollover patients from Study 12709A, are estimated to be enrolled into the study.

De novo patients

- Patients meeting eligibility criteria for *de novo* patients will be enrolled in the 12-week, open-label, flexible-dose treatment period.

Rollover patients from Study 12709A (enrolled to the open-label period)

- Patients may participate in the present study after completion of the randomized, 8-week, double-blind, placebo-controlled treatment period of Study 12709A.
- Eligible patients will be enrolled in the 12-week, open-label, flexible-dose treatment period.
- The Baseline Visit of this study (Study 13546A) will take place at the same visit as Visit 12 (Completion Visit) of Study 12709A. Participation in Study 12709A is considered completed when all assessments required at Visit 12 are completed.

Rollover patients (remitters) from Study 12712A (randomized to the double-blind period)

- Patients who have received 8 to 12 weeks of treatment with vortioxetine in the open-label extension study 12712A may participate in the present study if they have remitted (CDRS-R total score ≤28) at the last 2 visits in Study 12712A prior to the rollover. In addition, the dose of vortioxetine must have been fixed for the last 4 weeks in Study 12712A prior to randomization in the present study.
- Eligible patients will be randomized directly to the 26-week, double-blind treatment period.

An overview of the study is presented in Panel 1 (including the study periods) and the scheduled study procedures and assessments are summarized in Panel 2 and Panel 3.

Open-label Period (for de novo patients and rollover patients from Study 12709A)

- The duration of the open-label, flexible-dose treatment period will be 12 weeks.
- 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 increase the dose to a maximum of 20 mg/day in case of unsatisfactory response or decrease the dose to 5 mg/day in case of dose-limiting AEs. 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- or down-titrated to a new dose. Changes in dosing may occur at any visit during the first 8 weeks at the investigator's discretion. In addition, between Week 2 and Week 8, the patient and/or parent(s)/legal representative(s) can request an unscheduled visit to discuss their current dose. The maximum dose may not exceed 20 mg/day. The minimum dose is 5 mg/day.
- From Week 8 and onwards the dose has to remain fixed.
- Patients in remission (CDRS-R total score ≤28) at both Weeks 10 and 12 or with an adequate clinical response (defined as ≥50% reduction in the CDRS-R total score compared to the baseline score in this study [subtracted 17 to avoid flooring effect] and a CDRS-R total score ≤35) at both Weeks 10 and 12 will be randomized in the double-blind, placebo-controlled, fixed-dose period.
- Patients who do not fulfil randomization criteria for remission or adequate response at Week 10 and/or Week 12 will be withdrawn from the study and will complete an early Withdrawal Visit. Non-remitters/non-responders who leave the study will be treated at the investigator's discretion.
- A Safety Follow-up Visit will be performed approximately 4 weeks after withdrawal from the open-label period.

Double-blind Period (for all patients)

- Patients who fulfil the randomization criteria and do not meet any of the withdrawal criteria will be randomly assigned via a centralized randomization system to receive vortioxetine or placebo in a 1:1 ratio. Randomization will be stratified by patient inclusion sources (*de novo* patients, rollover patients from 12709A, or from 12712A).
- Patients randomized to vortioxetine will continue on their final dose from the open-label period or the dose they had on their last visit in Study 12712A, as applicable.
- The duration of the double-blind period will be 26 weeks.
- Patients who relapse during the double-blind period must be withdrawn from the study. The criterion for a relapse is a CDRS-R total score of ≥40 with a history of 2 weeks of clinical deterioration, or a clinical deterioration that in the investigator's opinion warrants alteration of treatment to prevent full relapse.
- A Safety Follow-up Visit will be performed 4 weeks after withdrawal or completion of the double-blind period.

3.2 Rationale for the Study Design

This relapse-prevention study is part of the agreed EMA PIP to evaluate the PK, efficacy and safety of vortioxetine in the treatment of MDD in children and adolescents (section 1.1.3).

Due to the character of the disorder, long-term studies are necessary to demonstrate that the short-term effect is maintained during an episode. This study will evaluate the antidepressant effect of vortioxetine in decreasing the rate of relapse using a randomised withdrawal design, which is the design of choice to establish maintenance of effect of long-term treatment within the episode.[19] In this design, responders to an open-label course of the studied antidepressant are randomized to continue on the study drug or be switched to placebo and are observed for relapse over a defined period of time.

This study will enrol children 7 to 11 years of age. Adolescents will not be included in this study due to the negative results of the short-term efficacy and safety study in adolescents (Study 12710A).

Recruitment of young children with MDD into clinical studies is challenging for multiple reasons, including low prevalence of depression in this age group, difficulties in diagnosing MDD, reluctance to participate in a placebo-controlled study, and the burden on families associated with participation in a research study. To minimize the challenges associated with recruitment of *de novo* patients and to optimize the study design and feasibility, without compromising the validity or integrity of the study, children who complete 8 weeks of double-blind treatment in the short-term study (12709A) and who could benefit from continued treatment with vortioxetine will be invited to participate in this study. The same approach was applied in a previous fluoxetine relapse-prevention study.[20] In addition, patients who have received vortioxetine for 8 to 12 weeks in the open-label extension study (Study 12712A; 6 months extension) and achieved stable remission may be enrolled. These patients will be randomized directly to the double-blind randomized treatment phase, as they have already stabilized on vortioxetine treatment. Inclusion of rollover patients who may have received vortioxetine for more than 12 weeks is supported by the results of an FDA review of relapse-prevention studies in adults which found no relationship between the length of the open-label phase and relapse rates in the placebo or drug arms.[21]

The duration of the double-blind treatment phase of 26 weeks is considered sufficient based on the experience from previous relapse-prevention studies in children[22].

While acute studies in MDD tend to suffer from lack of sensitivity, placebo response appears to be of lesser concern in studies using this randomized withdrawal design which enrol only patients who tolerate and respond to a studied drug in the acute phase into the maintenance phase. Because it is “enriched” with responders/remitters, the differences between the two groups are typically larger than in the acute, parallel design studies. Virtually all antidepressants, irrespective of the class, that demonstrated efficacy in short-term studies have also demonstrated efficacy in relapse-prevention studies.

The dose range of vortioxetine (5 to 20 mg/day) was chosen based on the knowledge from the clinical development programme in adult patients and the results of a paediatric pharmacokinetic and tolerability study (Study 12708A), which indicated that no dose adjustment was needed in the paediatric population. Hence, the doses known to be efficacious in the adult population (5 to 20 mg/day) are used in the paediatric development programme and are confirmed as well tolerated based on the current large paediatric database.

4 Ethics

4.1 Ethical Rationale

Patients and their parent(s)/legal representative(s) 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 88 countries worldwide, including the US and EU, for the treatment of MDD in the adult population. As summarized in section 1.1.3, in the 3 completed paediatric studies, vortioxetine was safe and well-tolerated in paediatric patients with MDD aged 7-17 years and the safety and tolerability profile of vortioxetine after long-term use was comparable to that observed after short-term use. Overall, based on the data from 3 completed paediatric studies and data available to date from the ongoing studies in children aged 7-11 years, no new important risks have been identified in the paediatric population beyond those established for the adult population.

Vortioxetine did not separate from placebo in the short-term study in adolescents (12710A), however, the results of the interim analysis in a similarly designed study in children found no evidence of futility. Furthermore, a review by an independent data monitoring committee (DMC) of unblinded efficacy as well as continuous review of safety data from the children study (12709A) and the OLE 12712A data indicate no concerns that would preclude continuation of studies of vortioxetine in children.

The present study will permit the investigation of the efficacy - in particular maintenance of antidepressant effect - of a new potential treatment of MDD in children. The inclusion of a placebo group has major scientific importance in this evaluation to ensure adequate evaluation of efficacy.

As stated in section 3.2 above, to address the challenges associated with recruitment of *de novo* patients and to minimize the number of patients exposed to IMP, the study will also enrol rollover patients from Studies 12709A and 12712A.

The definition of relapse (CDRS-R score of ≥40 with a history of 2 weeks of clinical deterioration, or clinical deterioration as judged by the clinician) has been carefully considered and aligned with the previous study of fluoxetine [23], to avoid participants becoming too ill before declaring a relapse, but also to avoid counting minor worsening (which might improve spontaneously) as a sign of relapse. 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 children; 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 prior to any investigation or procedure, in order to decrease anxiety and anticipation of pain. Potentially painful procedures such as venepuncture will be minimized with the use of for example 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.

Because the duration of the study (9 months) precludes withholding appropriate treatment for attention-deficit/hyperactivity disorder (ADHD), participants are allowed to be on stimulant treatment during the study if they have been on a stable dose for at least 4 weeks prior to study entry. The addition of stimulant treatment is not allowed during the study.

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 by using the Columbia-Suicide Severity Rating Scale and by the investigator's judgement. The GBI 10-item mania is included to screen for manic symptoms in children.

In accordance with *Good Clinical Practice*[18], qualified medical personnel at Lundbeck and the contract research organisation (CRO) will be readily available to advise 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 benefits of the full clinical study so that the health and wellbeing of the paediatric patients enrolled will be safeguarded.

The independent DMC for the paediatric vortioxetine programme will be continued throughout this study in order to review the safety and tolerability data (section 10.6).

In accordance with *Good Clinical Practice*,[18] the investigator will be responsible for all study-related medical decisions.

4.2 Informed Consent

No study-related procedures, including any screening procedures, may be performed before the investigator has obtained written assent from the patient and written informed consent from his or her parent(s)/legal representative(s).

Changing (for example, discontinuing or down-tapering) a patient's concomitant medications prior to the Screening Visit to ensure that the patient meets the selection criteria is a study-related activity and must not occur before the Informed Assent/Consent Forms have been signed.

Minors are dependent on their parent(s)/legal representative(s) (typically their parent[s]) to assume responsibility for their participation in clinical studies.[24]

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 their parent(s)/legal representative(s) the aims and methods of the study and any reasonably expected benefits and foreseeable risks or inconveniences to the patients.

The patients and their parent(s)/legal representative(s) 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
- of the possibility of withdrawing consent (section 8.5)
- of their right to request a copy of their personal data from the study via the investigator
- of their right to be informed by the investigator, after the study has been reported, about which treatment they received
- of their right to receive information about the study results from the investigator on the patient's own initiative; the results will be available approximately 1 year after the end of the study

The patients and their parent(s)/legal representative(s) must be informed that persons authorized by Lundbeck and authorized personnel from certain authorities (domestic, foreign, data protection agencies, or independent ethics committees (IECs)/institutional review boards (IRBs) may view their medical records. The patients and their parent(s)/legal representative(s) must also be informed that de-personalized copies of parts of their medical records may be requested by authorized personnel from certain authorities (domestic, foreign, data protection agencies, or IECs/IRBs) for verification of study procedures and/or data. The confidentiality of the patients will in all cases be respected.

The patients and their parent(s)/legal representative(s) 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 parent(s)/legal representative(s). Prior to allowing a patient to participate in the study, an *Informed Assent/Consent Form* must be signed and dated (including the time) by the patient and the patient's parent(s)/legal

representative(s) and/or (co-)signed by an impartial witness (if applicable) and signed and dated by the investigator or a designee on the same day. If the patient and/or the patient's parent(s)/legal representative(s) (if applicable) is/are able to understand the nature and potential consequences of the interventions and is/are able to give consent, but not in writing, an impartial witness, in addition to the informing physician, must sign the *Informed Consent Form*. The patients and their parent(s)/legal representative(s) (if applicable) must be given a copy of the written information (*Patient Information Sheet*) as well as a copy of the signed *Informed Assent/Consent Form*.

The consent procedures described above will only be implemented if allowed by local laws and regulations and will only be initiated after approval by the relevant IECs/IRBs.

4.3 Personal Data Protection

The data collected in this study will be processed in accordance with the specifications outlined in the Danish Data Protection Act and the European Union legislation[25] to ensure that requirements regarding personal data protection are met. If an external organization will process data on behalf of Lundbeck, a contractual procedure will be signed between Lundbeck and the external organization to ensure compliance with the above-mentioned legislation.

4.4 Ethics Committee(s) and Institutional Review Board(s)

This study will be conducted only after Lundbeck has received confirmation that the regulatory authorities have approved or confirmed notification of the study and that written approval of the protocol has been granted by the appropriate IEC or IRB.

The investigator must not allow any patients to participate in the study before receiving confirmation from Lundbeck or the CRO that the required approvals and/or notifications have been received.

The IEC or IRB must be informed when specific types of protocol amendments have been made and written approval must be obtained before implementation of each amendment, if required by local law.

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 Number of Patients and Countries

Planned countries and regions:

- Patients from the European Union, Europe outside the European Union, North America and Latin America.

Planned number of patients:

- to be screened (approximately): 170
- to be enrolled (approximately): 150
- to be randomized: 80

Planned number of:

- study sites (approximately): 40

5.2 Patient Recruitment

Competitive patient recruitment between countries and sites will be used during the entire recruitment period to ensure that the required number of patients are randomized within the planned recruitment period.

The investigators will be notified immediately when the recruitment period comes to an end.

5.3 Selection Criteria

Patients will be recruited *de novo* (enrolled to the open-label period) as well among those who complete treatment in lead-in Study 12709A (enrolled to the open-label period) or remitters from Study 12712A (randomized to the double-blind period).

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

Patients who meet each of the inclusion criteria at the Screening Visit and Baseline (unless otherwise specified) and none of the exclusion criteria at the Screening Visit and Baseline (unless otherwise specified) are eligible to participate in this study.

For patients rolling over from Studies 12709A or 12712A, their data from Studies 12709A and 12712A - including Inclusion Criteria - will be used for this study (see also section 11.1.2).

Inclusion Criteria for *de novo* patients

1. The patient is capable of communicating with the site personnel.
2. The patient and/or the patient's parent(s)/legal representative(s) are able to read and understand the *Informed Assent/Consent Form.*

3. The patient and the patient's parent(s)/legal representative(s) have signed the *Informed Assent/Consent Form*.
4. The patient and the patient's parent(s)/legal representative(s) are willing and able to attend study appointments within the specified time windows.
5. The patient is an outpatient consulting a clinician.
6. The patient has a primary diagnosis of MDD according to DSM-5™ although co-morbid anxiety disorders will be permitted (except Post Traumatic Stress Disorder (PTSD) and Obsessive Compulsive Disorder (OCD)). The diagnoses will be confirmed using the K-SADS-PL.
7. The patient has a CDRS-R total score ≥45 at the Screening and Baseline Visits.
8. The patient has a CGI-S ≥4 at the Screening and Baseline Visits.
9. The patient is boy or girl aged ≥7 and <12 years at screening. Patients who turn 12 years during this study will be allowed to continue in the study.
10. Contraception criterion, if applicable: The patient, if a girl who is sexually active and of childbearing potential (defined as girls aged ≥10 years and younger girls who, at the discretion of the investigator, are deemed to be of reproductive potential), must use adequate contraception from the Screening Visit until 30 days after the last dose of IMP.
11. The patient, if a girl aged ≥10 years, or if a younger girl who, at the discretion of the investigator, is deemed to be of reproductive potential, must have a confirmed negative urine pregnancy test at the Screening Visit.
12. Contraception criterion, if applicable: The patient, if a boy who is sexually active, must use adequate contraception from the Screening Visit until 30 days after the last dose of IMP.

Inclusion criteria for rollover patients from Studies 12709A and 12712A

For rollover patients from Studies 12709A and 12712A:

1. The patient and the patient's parent(s)/legal representative(s) are able to read and understand the *Informed Assent/Consent Form.*
2. The patient and the patient's parent(s)/legal representative(s) have signed the *Informed Assent/Consent Form*.
3. The patient and the patient's parent(s)/legal representative(s) /are willing and able to attend study appointments within the specified time windows.
4. Contraception criterion, if applicable: The patient, if a girl who is sexually active and of childbearing potential (defined as girls aged ≥10 years and younger girls who, at the discretion of the investigator, are deemed to be of reproductive potential), must use adequate contraception from the Screening Visit until 30 days after the last dose of IMP.
5. The patient, if a girl aged ≥10 years, or if a younger girl who, at the discretion of the investigator, is deemed to be of reproductive potential, must have a confirmed negative urine pregnancy test at the Screening Visit.
6. Contraception criterion, if applicable: The patient, if a boy who is sexually active, must use adequate contraception from the Screening Visit until 30 days after the last dose of IMP.

For rollover patients from Study 12709A:

1. The patient has completed Study 12709A (Visit 12, Completion Visit) immediately prior to enrolment into this study.
2. In the investigator's opinion, the patient could benefit from participation in a study which includes continued treatment with vortioxetine.
3. The patient is a child aged ≥7 and <12 years at Baseline of Study 12709A.

For rollover patients from Study 12712A (randomized to the double-blind period):

1. The patient has received 8 to 12 weeks of open-label treatment with vortioxetine in Study 12712A and completed Visit 7 (Week 8), or Visit 8 (Week 10), or Visit 9 (Week 12) immediately prior to enrolment into this study
2. In the investigator's opinion, the patient could benefit from participation in a study which includes continued treatment with vortioxetine.
3. The patient is in remission at the last 2 visits in Study 12712A, in which the CDRS-R is assessed every 4 weeks. Hence
    a. If the patient rolls over at Visit 7 or Visit 8 (Week 8 or Week 10): the patient has a CDRS-R total score ≤28 at Visit 5 (Week 4) and Visit 7 (Week 8) in Study 12712A
    b. If the patient rolls over at Visit 9 (Week 12): the patient has a CDRS-R total score ≤28 at Visit 7 (Week 8) and Visit 9 (Week 12) in Study 12712A
4. The patient has been on a stable dose of vortioxetine for the past 4 weeks prior to rollover to this study.
5. The patient is a child aged ≥7 and <12 years at Baseline of Study 12712A.

Exclusion Criteria (*de novo* patients, rollover patients from Studies 12709A and 12712A)

1. The patient has previously been enrolled in this study.
2. 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.
3. The patient is pregnant or breastfeeding.
4. The patient has a history of severe drug allergy or hypersensitivity, or known hypersensitivity or intolerance to any of the IMP(s) or its/their excipients.
5. The patient has previously been treated with vortioxetine in a clinical study (applicable only to *de novo* patients). Patients who previously participated in 12709 study and were withdrawn prior to randomization may participate.
6. The patient is under forced treatment.
7. The patient receives ongoing current psychotherapy that is planned to be intensified. Interpersonal psychotherapy (IPT) or cognitive behavioural therapy (CBT) are not allowed.
8. The patient has hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrose-isomaltase insufficiency.
9. The patient has any current psychiatric disorder (DSM-5™ criteria) different from MDD, established as the primary diagnosis, as assessed using The Kiddie-Schedule for Affective

Disorders and Schizophrenia for School-aged Children, Present and Lifetime version (K-SADS-PL).

10. The patient suffers from intellectual disability, organic mental disorders, or mental disorders due to a general medical condition (DSM-5™ criteria).
11. The patient has a known intellectual disability (as suggested by a known intelligence quotient [IQ] <70), or, clinical evidence or known social or school history indicative of intellectual disability.
12. 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.
13. 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.
14. The patient has a diagnosis of ADHD that requires a pharmacological treatment that cannot be maintained on a stable dose of an appropriate stimulant medication for a minimum of 4 weeks prior to the Baseline Visit.
15. The patient has a known first degree relative with a history of Bipolar Disorder.
16. The patient is unable to swallow capsules.
17. The patient has a history of cancer, other than basal cell or Stage 1 squamous cell carcinoma of the skin, that has not been in remission for >5 years prior to the first dose of IMP.
18. The patient has or has had one or more of the following conditions 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 (heart rate <50 beats per minute [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
    - venereal disease

- elevated intra-ocular pressure or is at risk of acute narrow-angle glaucoma

19. The patient takes or has taken recent or concomitant medication that is disallowed or allowed with restrictions (specified in Appendix II) or it is anticipated that the patient will require treatment with at least one of these medications during the study.
20. The patient has one or more clinically significant out-of-range vital signs at the Screening Visit (*de novo* patients, or at the last visit of Studies 12709A or 12712A for rollover patients).
21. The patient has one or more clinical laboratory test values outside the reference range, based on the blood and urine samples taken at the Screening Visit, that are of potential risk to the patient's safety, or the patient has, at the Screening Visit (*de novo* patients, or at last visit of Studies12709A or 12712A for rollover patients):
    - 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
22. The patient has a thyroid stimulating hormone (TSH) value outside the reference range. Patients with thyroid disease may be enrolled in the study provided they are stable and euthyroid.
23. The patient has, at the Screening Visit (*de novo* patients, or at last visit of Studies 12709A or 12712A for rollover patients):
    - an abnormal ECG that is, in the investigator's opinion, clinically significant
    - a QT_{cF} interval >450 ms (based on the Fridericia correction where $QT_{cF} = QT/RR^{0.33}$)
24. 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.
25. The patient is, in the investigator's opinion, unlikely to comply with the protocol or is unsuitable for any reason.
26. The patient has been treated with any antidepressant or anxiolytic medication within 2 weeks prior to Visit 2 (only *de novo* patients).
27. The patient has attempted 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 within the last 12 months).

5.4 Randomization Criteria

Randomization Criteria for *de novo* patients and rollover patients from Study 12709A

1. The patients is in remission (CDRS-R total score ≤28) at both Weeks 10 and 12 or with an adequate clinical response (defined as ≥50% reduction in the CDRS-R total score compared to the baseline score in this study [subtracted 17 to avoid flooring effect] and a CDRS-R total score ≤35) at both Weeks 10 and 12.
2. The patient has been on a stable dose of vortioxetine for the last 4 weeks prior to randomization.

Randomization Criteria for rollover patients from Study 12712A

At the Randomization Visit, the inclusion/exclusion criteria will be checked and all patients included will be randomised (see inclusion criteria for rollover patients from Study 12712A in section 5.3).

5.5 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 8.5 states how the patient's data will be handled
- the patient has been randomized in error and has not taken IMP
- 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])

A patient must be withdrawn from treatment if:

- 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 from treatment
- any site personnel break the randomization code for that patient
- 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
- 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 the patient may be postponed until a repeat ECG is taken, if it is taken within 24 hours
- 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)

A patient may be withdrawn from the study if:

- the patient and/or his or her parent(s)/legal representative (s) fails to comply with study procedures
- the patient did not take IMP on the assigned dose level for 6 consecutive days

Patients who withdraw will not be replaced.

6 Investigational Medicinal Products (IMPs)

6.1 Treatment Regimen

Open-label period:

The dosage of vortioxetine will be initiated at 5 mg/day for the first 2 days prior to receiving 10 mg/day. The vortioxetine target dose is 10 mg/day, however the investigator has the possibility to increase the dose to a maximum of 20 mg/day in case of unsatisfactory response or decrease the dose to 5 mg/day in case of dose-limiting AEs. 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- or down-titrated to a new dose. Changes in dosing may occur at any visit during the first 8 weeks at the investigator's discretion. From Week 8 onwards the dose has to remain fixed.

The tablets should be taken once daily, preferably at the same time each day.

Double-blind period:

Patients who fulfil the randomization criteria will be randomly assigned via a centralized randomization system to receive vortioxetine or placebo in a 1:1 ratio. Randomization will be stratified by patient inclusion sources (*de novo* patients, rollover patients from 12709A, or from 12712A).

Patients randomized to vortioxetine will continue on their final dose from the open-label period or the dose they had on their last visit in Study 12712A, as applicable.

The capsules should be taken once daily, preferably at the same time each day.

6.2 IMPs, Formulations, and Strengths

The IMPs supplied by Lundbeck in this study are:

Open-label period
- Vortioxetine film-coated tablets 5 mg, orally
- Vortioxetine film-coated tablets 10 mg, orally
- Vortioxetine film-coated tablets 15 mg, orally
- Vortioxetine film-coated tablets 20 mg, orally

Double-blind period
- Encapsulated vortioxetine film-coated tablets 5 mg, orally
- Encapsulated vortioxetine film-coated tablets 10 mg, orally
- Encapsulated vortioxetine film-coated tablets 15 mg, orally
- Encapsulated vortioxetine film-coated tablets 20 mg, orally
- Encapsulated placebo to vortioxetine film-coated tablets, orally

The IMPs will be identical in appearance.

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.

For the open-label period, the IMP will be provided in 1-week wallet cards, containing 10 tablets of vortioxetine 5 mg, 10 mg, 15 mg or 20 mg, respectively. At the baseline visit (Visit 2), an up-titration wallet card containing 2 × 5 mg vortioxetine tablets and 8 × 10 mg vortioxetine tablets will be provided.

For the double-blind period, the IMP will be provided in 1-week wallet cards, containing 10 capsules vortioxetine (5 mg, 10 mg, 15 mg or 20 mg) or placebo.

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 the 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 Clinical Supply, H. Lundbeck A/S, and, where necessary, new QP releases are made.

The IMPs will be identified using a unique medication 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

Interactive response technology (IRT) will be used in this study. The patient's screening number from the lead-in studies will be used to identify the rollover patients in this study. *De novo* patients will be assigned a screening number by the IRT, and that number will be used to identify *de novo* patients throughout the study. When a patient is to be randomized, the investigator uses the IRT. The IRT allocates the patient to a treatment group during the call and assigns the patient a randomization number in accordance with the specifications from Biostatistics, H. Lundbeck A/S.

6.5 IMP Accountability

IMP accountability is documented in the IRT.

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 IMPs. This record must be available for inspection at any time.

6.6 Unblinding Procedures

Pharmacovigilance, H. Lundbeck A/S, and the investigator or the pharmacist (if applicable), and the DMC will have access to the unblinded information for the double-blind treatment for each patient. Access to these details will be via IRT.

The IRT unblinding procedure is described in the *IRT User Guide*.

The investigator may only break the code for a patient if knowledge of the IMP is necessary to provide optimal treatment to the patient in an emergency. If possible, the investigator must consult the medical monitor before breaking the code. The investigator must record the date and reason for breaking the code on the IMP Code Break Form. If the emergency was an AE, it must be recorded on an Adverse Event Form. The medical monitor must be notified immediately. The IRT will capture the date and time of the code break call. Information on the allocated treatment will be provided during the call and by fax or email, depending on availability/preference. When the code is broken for a patient, the patient must be immediately withdrawn from the study. If this occurs during a visit, the investigator must complete the visit as a Withdrawal Visit; otherwise, the patient will be asked to attend a Withdrawal Visit.

6.7 Post-study Access to IMP

Post-study access to the IMPs 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 IMPs that are taken during the study, including the Screening Period up to Safety Follow-up.

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

Details of all concomitant medication (prescription and over-the-counter) taken <3 months prior to the Screening Visit must be recorded in the electronic case report form (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 or worsening must be recorded as an adverse event.

Concomitant medication initiated after the last dose of IMP must only be recorded if associated with a 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 and Panel 3. 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 Screening Visit (Visit 1)

The Screening visit will be performed only for *de novo* patients. Patients rolling over from Study 12709A will proceed directly to the Baseline Visit.

The screening period begins when the first screening assessment is done, after written Informed Assent/Consent has been obtained. If there is a need for washout of disallowed medication, it should be completed before any Baseline (Visit 2) assessment is done and must comply with the required washout periods in Appendix II.

The Baseline visit should be scheduled 5 to 15 days after the Screening Visit. However, in exceptional cases, the visit interval between the Screening and Baseline Visits may be extended up to 30 days with consent from the Medical Monitor, provided the Medical Monitor accepts the rationale provided for the extension.

8.2.1 Pre-screening

Each site must record in a pre-screening log which patients attended the Screening Visit.

Preferably within 24 hours from the Screening Visit, a study-specific Pre-Enrolment Form needs to be completed for *de novo* patients by the site and transmitted to the CRO for their review. A confirmation that *de novo* patients can continue further with the study procedures is required before enrolment.

8.2.2 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.

8.2.3 Re-screening

Re-screening is only allowed for *de novo* patients with a *complete* Screening Visit and who fail to attend the Baseline Visit within the planned window due to e.g., logistical constraints.

Only the sponsor's medical expert (or the CRO's medical monitor) may give permission to re-screen a patient.

Authorization for re-screening may only be granted by the CRO's medical monitor after a thorough review of all data from the original Screening Visit.

At the new Screening Visit, the patient (and/or his or her parent(s)/legal representative(s) [if applicable] and/or the responsible caregiver) must sign new *Informed Assent/Consent Forms* At the new Screening Visit, the patient will be assigned a new screening number. A re-screened patient must have a complete new Screening Visit, and all the eligibility criteria must be re-assessed at the new Screening Visit.

The following information will also be recorded in the eCRF at the new Screening Visit:

- that the patient has previously been screened for the study
- that re-screening has been authorized by the CRO's medical monitor
- the screening number that was assigned to the patient at the original Screening Visit

If a patient is re-screened, no data from the original Screening Visit will be used.

A patient may only be re-screened once.

8.3 Baseline Visit Open-label Period (Visit 2)

De novo patients who continue to meet all inclusion criteria and none of the exclusion criteria (see section 5.3) will be enrolled into a 12-week open-label treatment period.

For patients rolling over from Study 12709A, the Baseline Visit will be performed the same day as the Week 12 (Completion) Visit of Study 12709A. The ICF must be signed before any Study 13546A-related activities take place. The eligibility criteria should be confirmed based on the evaluation of the latest data available in Study 12709A.

For 12709A patients, values from assessments and procedures (efficacy/safety, including blood/urine samples and use of concomitant medication) performed at the Completion Visit (Visit 12) in Study 12709A will be the Baseline Visit values in Study 13546A (detailed in Panel 2 and section 11.1.2). Please note that the hormones laboratory tests are specific for the 13546A study and will have to be collected using a separate kit at the same time as collecting the blood samples required by the 12709A protocol. Assessments that are not part of the Completion visit in 12709A (that is, examinations, Tanner staging, and menstrual cycle) will

be performed as part of the 13546A Baseline Visit. Patients eligible for entering the open-label period will start IMP (vortioxetine) at the Baseline Visit. Patients will start with 5 mg/day as detailed in section 6.1.

The schedule of assessments during the open-label period is described in Panel 2.

8.4 Randomization Visit (Visit 8)

The double-blind period starts with the Randomization Visit (8) at Week 12. Patients who fulfil the randomization criteria (section 5.4) will be randomly assigned via a centralized randomization system to receive vortioxetine or placebo in a 1:1 ratio.

Patients rolling over from Study 12712A need to fulfil inclusion/exclusion criteria detailed in sections 5.3. At the Randomization Visit, *de novo* patients and rollover patients from Study 12709A undergo evaluation of randomization criteria, and evaluation of efficacy and safety assessments as per Panel 3. Patients who do not meet the randomization criteria will be withdrawn from the study and complete an early withdrawal visit.

For 12712A-patients, last available values from assessments and procedures (efficacy/safety, and use of concomitant medication) performed at either Visit 7 (Week 8) and/or Visit 8 (Week 10), or Visit 9 (Week 12) in Study 12712A will be the Randomization Visit values for this study. For patients who rollover at Visit 7 or Visit 8, weight, height, Tanner staging, menstrual cycle, and examinations should be done at the Randomization Visits (detailed in Panel 3 and section 11.1.2).

The schedule of assessments during the Double-blind Period is described in Panel 3.

8.5 Withdrawal Visit

Open-label Period: Patients who withdraw from the study prior to Visit 8 will be asked to attend a Withdrawal Visit, if at all possible. The visit must be scheduled as soon as possible after withdrawal. Patients who withdraw from treatment will also be asked to attend a Safety Follow-up Visit.

Patients who do not fulfil randomization criteria for remission or adequate response at Week 10 and/or Week 12 will be withdrawn from the study and will complete an early Withdrawal Visit.

Double-blind Period: Patients who withdraw from the study prior to the Completion Visit after 26 weeks of treatment in the double-blind period will be asked to attend a Withdrawal Visit, if at all possible. The visit must be scheduled as soon as possible after withdrawal. Patients who withdraw from the study will also be asked to attend a Withdrawal Visit (Visit 17, where both efficacy and safety are assessed).

No new information will be collected from patients who withdraw from the study, 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 in the eCRF.

For a patient and/or the patient's parent(s)/legal representative(s) who withdraw consent:

- if the patient and/or the patient's parent(s)/legal representative(s) withdraw consent during a visit and then agree(s) 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 that visit will be used
- if the patient and/or the patient's parent(s)/legal representative(s) withdraw(s) 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 that 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 records
- if the patient and/or the patient's patients/legal representative explicitly request(s) that the patient's data collected from the time of withdrawal of consent onwards not be used, this will be respected

8.6 Safety Follow-up Visit

A safety follow-up is conducted to capture 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.

Safety follow-up for the open-label period is applicable for patients who are withdrawn or do not continue to the double-blind period: 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 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).

Safety follow-up for the double-blind period: This visit should be scheduled approximately 30 days after the last dose of IMP. 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 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).

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 *Ongoing Adverse Event* checkbox on the *Adverse Event Form* must be ticked. 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/ Withdrawal Visit and judged clinically significant must be followed according to accepted medical standards for up to 30 days or until the value normalizes or stabilizes 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 5.5) should be followed until the values normalize or stabilize or a diagnosis or a reasonable explanation has been established (see section 10.5).

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

8.7 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.

This study will be terminated if the result of the currently ongoing placebo-controlled, short-term study (12709A) in children is negative (that is, if vortioxetine fails to show a significant difference from placebo in acute treatment). In case of study termination, the participating patients will be treated at the discretion of the investigator in line with clinical practice.

9 Assessments

Timing and frequency of all assessments are specified in Panel 2 (open-label period) and Panel 3 (double-blind period).

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

9.1 Screening and Baseline Procedures and Assessments

9.1.1 Demographics and Baseline Characteristics

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

At the Screening Visit (concerns *de novo* patients only), the following will be recorded or assessed:

- Relevant medical, social, psychiatric and neurological history including MDD history, time of diagnosis, treatment type and outcome (response and tolerability)
- History of stimulant medication, if any
- Demographics: age, sex, and race. In order to determine the exact age at any point in the study, full date of birth will be collected where permitted by local regulations.
- Family psychiatric history
- Traumatic life events
- Height, weight
- Puberty status (Tanner staging)
- Menstrual cycle

9.1.2 Diagnostic Assessments

The K-SADS-PL will be used as screening assessment. The diagnosis of MDD (according to DSM-5™) will be established via a psychiatric evaluation. The K-SADS-PL will be used to confirm the diagnosis of MDD and to assess possible psychiatric co-morbidities.

The K-SADL-PL will be administered in 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.

9.1.3 The Kiddie-Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime version (K-SADS-PL).

The K-SADS-PL[26] is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents. The K-SADS-PL consists of interviews with the parent(s), the child, and information from other sources (for example, school report). The unstructured introductory interview establishes a rapport with the parent(s) and the child, the screening interview (comprising 82-items to survey key symptoms for current and past episodes of 20 different diagnostic areas) provides a diagnosis, and responses to skip-out criteria determine whether additional interviewing is necessary. If necessary, the additional interview consists of a maximum of five diagnostic supplements (affective disorders, psychotic disorders, anxiety disorders, behavioural disorders, and substance abuse, eating, and tic disorders). The K-SADS-PL items are scored using a 2-point or a 3-point scale

from 1 (no symptoms) to 3 (threshold levels of symptomatology). It takes approximately 180 minutes to complete both K-SADS-PL interviews (parent(s) and child).

9.1.4 K-SADS-PL Rater Qualification and Certification

The K-SADS-PL should be administered by a rater who has adequate experience with paediatric patients with MDD. The rater should be a psychiatrist or doctor of osteopathy (DO) specialised in child and adolescent psychiatry, or a clinical paediatric (neuro-) psychologist involved in clinical practice.

Any exceptions must be discussed and approved by Lundbeck.

Only raters who have been certified in a study-specific Rater Certification Programme will be authorized to rate in this study. Documentation of training and certification will be delivered to the raters for archiving in the investigator trial master file (TMF). No patient may be rated before the documentation has been delivered.

New raters joining the study will be trained and certified locally using the same certification processes.

9.1.5 Drug and Alcohol Screen

It is not mandatory to screen for drugs and/or alcohol. However, it can be performed at any visit during the open-label and double-blind periods, at the discretion of the investigator. The blood and urine drug screen samples will be analysed at the central laboratory.

9.2 Efficacy Assessments

9.2.1 Clinical Outcome Assessments (COAs)

9.2.1.1 Use of COA Tools

The following clinician-rated electronic assessment tools will be used and accessed via a tablet provided by Signant Health, called a Rater Station:

- CDRS-R – assessing depressive symptoms
- CGI-S/I – assessing clinical global impression

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 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.

9.2.1.2 Children depression rating scale revised version (CDRS-R)

The CDRS-R[27] is a clinician-rated scale to measure the severity of depression of children and adolescents. The CDRS-R is rated by a clinician following interviews with the child and parent(s) and consists of 17 items: 14 items rate verbal observations, and 3 items rate nonverbal observations (tempo of language, hypoactivity, and nonverbal expression of depressed affect). Items are rated for severity on a 7-point scale (1 to 7) for 14 items, and on a 5-point scale (1 to 5) for 3 items (sleep disturbance, appetite disturbance, and listless speech). 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[28] 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). The clinician assesses the patient's condition relative to Randomization (as the CGI-I only will be assessed in the Double-blind period) 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 Rater Qualification

The CDRS-R and CGI-S/I 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-S/I should be administered by the investigator responsible for the patient. The investigator must be a psychiatrist 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 certified in a study-specific Rater Certification Programme will be authorized to rate in this study. Documentation of training and certification will be delivered to the raters for archiving in the investigator TMF. No patient may be rated before the documentation has been delivered.

The individual scores from the primary scale rater qualification session will be used to document inter-rater reliability and filed in the sponsor TMF.

New raters joining the study will be trained and certified locally using the same certification processes. Rater training and certification will be conducted by Signant Health.

For each individual patient, the same certified rater should rate the patient. For unforeseen circumstances, certified back-up raters should be available throughout the study.

9.2.2 Patient and/or Parent Reported Outcomes (PROs)

The following electronic PRO will be completed by the patient on the Rater Station:

- PQ-LES-Q[29]: designed to assess patient's satisfaction with life

9.2.2.1 Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)

The PQ-LES-Q[29] is a patient-rated scale designed to assess satisfaction with life. It is an adaptation of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), which is used to measure quality of life in adults. The PQ-LES-Q consist of 15 items, item 1 to 14 assess the degree of satisfaction experienced by patients in various areas of daily functioning and item 15 allows subjects to summarize their experience in a global rating.

Each item is rated on a 5-point scale from 1 (*very poor*) to 5 (*very good*). The total score range of item 1 to 14 is 14 to 70, with higher scores indicating greater satisfaction. It takes 5 to 10 minutes to complete the scale.

The site staff should instruct patients on how to use the Rater Station. On-screen instructions on how to complete the scale will be available in the Rater Station.

9.3 Pharmacokinetic Assessments

Blood samples (1 mL) for IMP analysis will be collected in ethylenediamine tetra acetic acid (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 methods validated in accordance with the EMA Guideline on Bioanalytical Method Validation[30] and the FDA Guidance for Industry.[31]

The bioanalysis of Lu AA21004 will be conducted by the contract laboratory PRA Health Sciences on behalf of Department of LC-MS Bioanalysis, H. Lundbeck A/S. A dedicated protocol for the bioanalytical study and a bioanalytical study report will be prepared by the contract laboratory.

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 Screening Visit. AEs (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 each AE 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 AEs if considered by the investigator to be clinically significant.

See chapter 10 for further information on AEs.

9.4.2 Clinical Safety Laboratory Tests

The clinical safety laboratory tests are listed in Panel 5.

Panel 5 Clinical Safety Laboratory Tests

<table>
<tr><td>Haematology

B-haemoglobin
B-erythrocyte count
B-total leucocyte count
B-neutrophils[a]
B-eosinophils[a]
B-basophils[a]
B-lymphocytes[a]
B-monocytes[a]
B-thrombocyte count</td><td>Liver[b]

S-total bilirubin
S-conjugated bilirubin
S-alkaline phosphatase
S-alanine aminotransferase
S-aspartate aminotransferase
S-gamma-glutamyl transferase</td><td>Serology[c]

S-HBsAg
S-anti HCV

Infection[c]

S-C-reactive protein</td></tr>
<tr><td>Electrolytes[b]

S-sodium
S-potassium
S-calcium (total)</td><td>Kidney[b]

S-creatinine
S-urea nitrogen</td><td>Urine[d]

U-protein (dipstick)
U-glucose (dipstick)
U-blood (dipstick)</td></tr>
<tr><td>Endocrine and Metabolic[b]

S-albumin
S-estradiol [girls only]
S-luteinising hormone [LH]
S-follicle-stimulating hormone [FSH])
S-prolactin [PROLCTN]
S-glucose[d]
S-thyroid-stimulating hormone[c]</td><td>Lipids[b,e]

S-low density lipoprotein
S-high density lipoprotein
S-triglycerides
S-cholesterol (total)</td><td>Pregnancy[f]

U-hCG
B-hCG (confirmatory for positive urine test only)</td></tr>
<tr><td colspan="3">B = blood; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; P = plasma; S = serum; U = urine</td></tr>
</table>

a Count and % of total leucocytes

b Clinical chemistry

c Performed at the Screening Visit only

d Microscopic examination (leucocytes, erythrocytes, and casts) will be performed only if any of the urine evaluations are abnormal Fasting, when possible

e Fasting, when possible

f Performed at the Screening Visit only. Only for female patients aged ≥10 years or female patients at lower age judged by the investigator to be of childbearing potential

Blood samples for the clinical safety laboratory tests will be collected as outlined in Panel 2 and Panel 3.

The blood and urine drug screen samples will be analysed at the central laboratory. Urine drug screen requires an additional tube, but ethanol is part of the urine drug screen panel so will be optional as a check box on the requisition form without a need for another additional tube.

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 stabilized or until the value has returned to a clinically acceptable value (regardless of relationship to the IMP). A patient with a value that is out-of-range at the Completion Visit (Week 26 of double-blind period) or Withdrawal Visit and considered clinically significant must be followed in accordance with usual clinical practice for up to 30 days or until the value normalizes or stabilizes 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 records.

Any out-of-range clinical safety laboratory test value considered clinically significant by the investigator must be recorded as an AE 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

The investigator may appoint a designee to measure vital signs, provided this is permitted according to local regulations and provided the investigator has trained the designee how to measure vital signs. The investigator must take responsibility for reviewing the findings.

Blood pressure and pulse rate will be measured using a standard digital meter with adequate cuff size 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.

Any out-of-range vital sign considered clinically significant by the investigator must be recorded as an AE on an *Adverse Event Form*.

9.4.4 Height and Weight

The patient's height will be measured, without shoes.

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

Any weight change considered clinically significant by the investigator must be recorded as an AE on an *Adverse Event Form*.

9.4.5 Electrocardiograms (ECGs)

A standard 12-lead ECG will be recorded 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, where they will be reviewed by a paediatric cardiologist. The investigator will be provided with the results and a cardiologic interpretation of the ECG from the central ECG laboratory.

The results from the central ECG laboratory will include the RR, PR, QRS, QT, QT_c, and QTc_F intervals.

The investigator has the final decision on the interpretation of the ECG results. Any abnormal ECG result or out-of-range ECG parameter value considered clinically significant by the investigator must be recorded as an AE on an *Adverse Event Form*.

9.4.6 Physical and Neurological Examinations

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. Whenever possible, the same individual should perform all the physical 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 and must be performed by a physician or physician assistant. If there is no physical examination at the Baseline Visit, the examination at the Screening Visit will be considered the baseline physical examination.

The neurological examination must be performed by a physician.

Any abnormal finding or out-of-range value considered clinically significant by the investigator must be recorded as an AE on an *Adverse Event Form*.

9.4.7 Tanner Staging

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

The scale includes 5 stages of pubertal changes (called Tanner stages) separate for males and for females.

For female the 5 stages of maturation are recognized by assessing pubic hair and breast development. For male 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 physician or trained nurse - they will be provided with figures depicting the somatic changes and tables describe these changes in words to facilitate the staging.

Tanner staging will be performed in conjunction with the physical examination according to the schedule displayed in Panel 2 and Panel 3.

9.4.8 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

9.4.9 General Behaviour Inventory (GBI) 10-Item Mania Scale

The GBI 10-item mania scale[32] is a parent- and subject-rated scale designed to screen for manic symptoms in children and adolescents. The ten items are rated on a 4-point scale from 0 (never or hardly ever) to 3 (very often or almost constantly). The total score ranges from 0 to 30, with higher scores indicating greater pathology. It takes approximately 5 minutes to complete the GBI 10-item mania scale.

The parent-rated scale is validated and appropriate for the use in children and adolescents with psychiatric disorders.[33] The subject-rated scale is validated only for patients in the age group 10 to 17 years.[34] Therefore, only the parent-rated scale will be used in this study.

The GBI 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 site staff should instruct patients and parents/caregivers on how to use the Rater Station, On-screen instructions on how to complete the scale will be available in the Rater Station.

9.4.10 Columbia-Suicide Severity Rating Scale (C-SSRS)

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.

Different versions of the scale are available: in this study, the “Baseline Screening” version will be applied at the Screening Visit and the “Since last visit” version will be applied other visits including the C-SSRS.

A version of the C-SSRS specifically developed for the use in children will be applied in the study population of children aged 7 to 11 years.

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.

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

If the electronic C-SSRS (eC-SSRS) system™ is temporarily unavailable on the Rater Station, a paper version of the C-SSRS (*C-SSRS Fallback Form – Baseline/Screening Version*) should be administered by the investigator. If the eC-SSRS is unavailable at the Screening Visit, the paper version should be used; however, the patient will have to return to the site to complete the eC-SSRS before he or she may be enrolled in the study. When a *C-SSRS Fallback Form* has been used, it must be kept as a source document in the Patient Binder. Data from the *C-SSRS Fallback Form* will not be transcribed in the eCRF.

9.4.10.1 Rater Qualification and Certification

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 certified through the scale author's website will be authorized to rate in this study. Documentation of training and certification will be delivered to the raters for archiving in the investigator TMF. No patient may be rated before the documentation has been delivered.

New raters joining the study will be trained and certified locally using the same certification process.

9.5 Order of Assessments

The scales should preferably be administered in the following order:

Screening Visit:
- K-SADS-PL
- CDRS-R
- GBI
- C-SSRS
- CGI-S

At visits other than the Screening Visit:

- CDRS-R
- PQ-LES-Q
- GBI
- C-SSRS
- CGI-S, CGI-I

9.6 Total Volume of Blood Drawn and Destruction of Biological Material

The total volume of blood drawn during the study will be approximately 39.5 mL (20 mL in the open-label period and 19.5 ml in the double blind period) for *de novo* patients.

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.

In addition, measures of the blood concentration of vortioxetine will indicate whether patient has been overall compliant throughout the study.

10 Adverse Events

10.1 Definitions

10.1.1 Adverse Event Definitions[36]

Adverse event – is any untoward medical occurrence in a patient or 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.

It is Lundbeck policy to collect and record all adverse events, including pre-treatment adverse events, that is, those that start after the patient has signed the *Assent Form*/*Informed Consent Form* and prior to the first dose of IMP.

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 hospitalization or prolongation of existing hospitalization
- 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 hospitalization, but may jeopardize 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 hospitalization; or development of drug dependency or drug abuse.

Planned hospitalizations 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 adverse events. 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).

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 AE meets the definition of an SAE, a conservative viewpoint must be taken, and the AE must be reported as an SAE.

Suspected unexpected serious adverse reaction (SUSAR) – is any AE that is assessed as serious, unexpected (its nature or intensity is not consistent with the current version of the *Investigator's Brochure* for vortioxetine[15] and related to a medicinal product by either the investigator or Lundbeck.

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

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 the patient's normal activities.

Assessment of Causal Relationship

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 disorder 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 reported as an SAE; hospitalization for a normal birth should not be reported as an SAE. If, however, the pregnancy is associated with an SAE, the appropriate serious criterion 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 (including pre-treatment 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 the IMP; action taken; and outcome. If the adverse event is not related to the IMP, an alternative aetiology must be recorded, if available. 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 (see section 10.4).

If individual adverse events are later linked to a specific diagnosis, the diagnosis should be reported and linked to the previously reported adverse events.

10.4 Reporting Serious Adverse Events (SAEs)

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 *Serious Adverse Event Form* 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:

<u>For H. Lundbeck A/S studies:</u>
Fax: [redacted]
email: [redacted]

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

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 requirements. 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 IECs.

Lundbeck will assess the expectedness of SAEs and inform the investigator(s) about SUSARs in the blinded SUSAR listings.

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.

The investigator must follow-up on non-serious adverse events until resolution or the Safety Follow-up Visit/Contact, whichever comes first. At the Safety Follow-up Visit/Contact, information on new SAEs, if any, and stop dates for previously reported adverse events must be recorded.

The investigator must follow-up on all SAEs until the patient has recovered, stabilized, or recovered with sequelae, and report to Lundbeck all relevant new information using the same procedures and timelines as those for the initial *Serious Adverse Event Form*.

SAEs that are spontaneously reported by a patient to the investigator after the Safety Follow-up Visit/Contact must be handled in the same manner as SAEs that occur during the study. These SAEs will be recorded in the Lundbeck safety database.

The investigator must follow-up on patients with a clinically significant out-of-range clinical safety laboratory test value at the Primary Outcome (Week 26 of double-blind period) or Withdrawal Visit in accordance with usual clinical practice be scheduled for a Safety Follow-up Visit to allow for a medical examination and/or blood sampling (see section 8.6). If further follow-up visits are made, these must be documented in the patient's medical records and not in the eCRF.

Patients who withdraw due to an elevated AST or ALT value (see section 5.5) must be followed until the values normalize or stabilize or a diagnosis or a reasonable explanation has been established. Additional medical examinations (for example, ultrasound scanning and/or sampling for serology, conjugated bilirubin, prothrombin time) should be considered. A gastroenterology or hepatology consultation should also be considered.

10.6 Study Monitoring Committee

10.6.1 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) has been established to cover all the clinical studies in the paediatric vortioxetine programme.

The DMC is an independent, external committee which includes child and adolescent psychiatrists. The DMC review and evaluate safety data on an ongoing basis in addition to cumulative safety data. The DMC will have access to unblinded data and will provide recommendations on study continuation, modification or termination. Members of the DMC will not be involved in other study-related tasks. 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 11.1.5.

The eCRFs use third party software (Rave®) to capture data via an online system on a computer. When the investigator enters data in the eCRF (ideally during the visit or as soon as possible, <3 days thereafter), the data 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 sponsor and/or representatives from specify CRO. All entries, corrections, and changes must be made by the investigator or a delegate.

11.1.2 Data Transfer for Rollover Patients (Studies 12709A and 12712A)

Data available in the eCRF for Studies 12709A and 12712A will be transferred to the Study 13546A eCRF where possible, in accordance with Panel 2 and Panel 3. The data to be transferred from Studies 12709A and 12712A eCRF to the Study13546A eCRF will be specified in the *eCRF Completion Guidelines*.

11.1.3 External Data From Study 12709A and Study 12712A

All external data pertaining to the rollover visit assessments (as detailed in Panel 2 and Panel 3) will be transferred to the 13546A Study.

11.1.4 Patient Binders eCRF

11.1.4.1 Use of Patient Binders

The *Patient Binder* contains different types of source documents, including paper versions of any COAs and PROs completed as a fall-back solution (see below). A ballpoint pen with waterproof ink must be used to enter information in the *Patient Binder*.

11.1.4.2 Clinical Outcome Assessments (COAs)

The *Patient Binder* contains the paper version of the following COA tool: K-SADS-PL, to be completed by the raters. The data will be transcribed to the *Scoring Sheets* in the eCRF by the investigator or a delegate; the raters must verify that all the entries are accurate and correct by signing and dating the relevant pages.

A paper version of any electronic clinical outcome assessments (eCOAs) (other than K-SADS-PL) or ePRO will only be completed as a fall-back solution if the electronic Rater Station system is not available.

In case when paper scales are used, the patients and parents will be asked to complete the PROs in their local language. The responses may only be corrected by the patient/parent.

11.1.4.3 Serious Adverse Event Fallback Forms

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

11.1.5 External Data

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

The clinical safety laboratory test data will be transferred by ICON laboratory.

The following electronic data will be transferred by ICON and kept in a secure designated storage area outside the eCRF:

- PRO data
- eCOA data
- IMP quantification results
- ECG results

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 until the study has been completed. After the study has been completed, all user access to the eCRF will be revoked. Renewed access to the eCRF will be given if corrections or updates to the database are required.

At the end of the study, the site will be provided with all data related to the site (including eCRF data, queries, and the audit trail) using a secure electronic medium; the secure storage of these data at the site is the responsibility of the investigator. When confirmation of receipt of the data has been received from all sites, all user access to the eCRF will be revoked. If, for some reason, the data are not readable for the full retention period (25 years or in accordance with national requirements, whichever is longer), the investigator may request that the data be re-sent.

11.2.2 Other Study Documents

The investigator must keep the investigator's set of documents in the investigator TMF for at least 25 years after the *Clinical Study Report* has been approved or in accordance with national requirements, whichever is longer. Lundbeck will remind the investigator in writing of this obligation when the *Clinical Study Report Synopsis* is distributed to the site.

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*.

When the required storage period has expired, the documents may be destroyed in accordance with regulations.

12 Monitoring Procedures

The monitoring strategy for the study foresees a risk-based monitoring approach, in line with the relevant FDA and EMA recommendations, and will be described in detail by the study-specific risk-based Monitoring Plan, including remote eCRF review and centralised monitoring of study data.

Prior to allowing patients to participate 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.

If the investigator does not have a patient's medical records, the investigator must attempt to obtain copies or a written summary of relevant medical records from the doctor who had treated the patient earlier and include the pertinent documentation in the patient's medical records at the site. The investigator must obtain medical records documenting the patient's lifetime MDD episodes and general medical history for the 3 months prior to the study.

During the study, the clinical research associate (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 and verify any records that are important for the evaluation of the study.

13 Audits and Inspections

Authorized personnel from Medical, Regulatory and Clinical Quality Assurance, H. Lundbeck A/S, 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 investigator must be aware 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 request relevant parts of medical records. No personal identification apart from the screening or randomization numbers will appear on these copies.

Patient data will not be disclosed to unauthorized third parties, and patient confidentiality will be respected 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 a deviation occurs, 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 the children's study (12709A)

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 evaluation changes after the study is terminated, 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 Statistical Methodology

16.1 Responsibilities

ICON Plc will perform the statistical analyses described below.

16.2 Analysis Sets

The following analysis sets will be used to analyse and present the data:

- *all-patients-enrolled* (APES) – all-patients-enrolled to the 12-week open-label, flexible-dose treatment period who took at least one dose of IMP
- *all-patients-randomized set* (APRS) – all patients randomized to the 26-week double-blind treatment period
- *full-analysis set* (FAS) – all patients randomized to the 26-week double-blind treatment period who took at least one dose of double-blind IMP

The patients and data will be classified into the analysis sets according to these definitions at a *Classification Meeting* held after the study database has been released, but before the blind has been broken.

16.3 Descriptive Statistics

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

16.4 Patient Disposition

Patient disposition will be summarized by treatment group and in total and will include the number of patients in the FAS who completed or withdrew from treatment and from study, as well as the number of patients in each analysis set (APES, APRS and FAS).

The disposition data will be summarized for the open-label period (split out by *de novo* patients and rollover patients from Study 12709A), and the double-blind period separately.

The number of patients who completed or withdrew from the study will also be summarized per period.

The number of patients who withdrew from treatment and from study will be summarized by treatment group and primary reason for withdrawal as well as all reasons for withdrawal will be presented per period.

16.5 Demographics and Baseline Characteristics

Demographics (sex, age, and race), baseline characteristics (height, weight and BMI), baseline efficacy variables, and other disease characteristics will be summarized by treatment group and in total. Patient disposition and demographics will be summarized using descriptive statistics.

16.6 Recent and Concomitant Medication

Recent and concomitant medication will be summarized by anatomical therapeutic chemical (ATC) code and generic drug name by treatment group and in total.

16.7 Exposure and Compliance

Exposure and compliance will be calculated per patient and summarized by treatment group.

Exposure will be defined as the number of days between the date the last dose of IMP was taken and first dose of IMP was taken. Compliance will be defined as the number of days in which a dose was taken related to the number of days the patient was expected to take IMP as per the protocol.

Exposure will be calculated for the open label period, the double-blind relapse period and in total.

16.8 Efficacy Analyses

16.8.1 General Efficacy Analysis Methodology

All the statistical tests of the efficacy endpoints will be two-sided tests performed at the 5% significance level and all confidence intervals (CIs) will be 95% CIs, unless otherwise specified.

The efficacy analyses will be based on the FAS.

16.8.2 Primary Analysis of the Primary Endpoint

The primary efficacy analysis will compare the time to relapse in the double-blind period between vortioxetine and placebo treated patients. Relapse will be defined as either a total score ≥40 on the CDRS-R with a history of 2 weeks of clinical deterioration, or clinical deterioration as judged by the clinician and documented in the eCRF.

The two treatment groups will be compared using a Cox regression model with exact adjustment for ties.

The regression model will have treatment as fixed factor, CDRS-R Total Score at randomization as covariate, and separate baseline hazards for the stratification factor, i.e. the patient inclusion source (*de novo* patients, rollover patients from 12709A, or from 12712A). Further details will be given in the SAP.

A one-sided 5% level of significance will be used. Patients not relapsing before Week 26 will be censored at Week 26 and patients withdrawing due to other reasons than relapse will be censored at time of withdrawal.

16.8.3 Sensitivity Analyses of the Primary Endpoint

The following sensitivity analyses will be performed:

1. The primary analysis will be repeated ignoring relapses occurring during the first week, two weeks and four weeks of the double-blind period, respectively.
2. The number of relapses will be summarized according to relapse criteria: CDRS-R total score ≥40 with 2 weeks of clinical deterioration, investigator's judgement, or both.
3. Primary analysis will be repeated for the *de novo* patients and for the (pooled) 12709A patients and 12712A patients.

16.8.4 Analysis of the Secondary Endpoint(s)

The number of relapses will be summarized according to relapse criteria (see section 16.8.2) and the relapse over the 26 weeks double-blind period will be analysed using logistic

regression, with treatment and inclusion source as fixed factors and CDRS-R Total Score at randomization as covariate.

Secondary efficacy variables (CDRS-R total score, PQ-LES-Q scores, CGI-S and CGI-I) will be analysed on an exploratory basis over the 26-week double-blind period by Mixed Model Repeated Measurements (MMRM) and analysis of covariance (ANCOVA). For the purpose of the analysis the change from baseline in CDRS-R total score, PQ-LES-Q scores, and in CGI-S score will be computed. In this respect, baseline will be defined as the start of the double-blind period.

For both the MMRM and the ANCOVA, the dependent variable will be the change from baseline in CDRS-R total score, change from baseline in PQ-LES-Q scores, change from baseline in CGI-S score and the absolute CGI-I score, respectively. In this respect, baseline will be defined as the start of the double-blind period.

The MMRM will have treatment, week and inclusion source as fixed factors and the baseline score will be added as a covariate. For CGI-I, the score at randomization for the CGI-S will be used as covariate. In addition, the interaction between treatment and week and between baseline score and week will be included and an unstructured covariance matrix will be applied. In this respect, baseline will be defined as the start of the double-blind period.

In the ANCOVA treatment and inclusion source will be included as a fixed factors and the respective baseline score will be included as a covariate. For CGI-I, the score at randomization for the CGI-S will be used as covariate.

Both the observed cases (OC) and last observation carried forward (LOCF) approach will be used.

16.8.5 Testing Strategy

This section is not applicable.

16.8.6 Analysis of the Exploratory Endpoint(s)

No formal exploratory endpoints have been defined.

On an exploratory basis, severity of illness, gender and age will be assessed as covariates or to generate subgroups for the Cox regression model as described in section 16.8.2.

In addition, descriptive statistics will be used to compare patient populations and treatment outcome between the geographical regions.

16.8.7 Pharmacokinetic Analyses

The pharmacokinetic analyses will be based on the pharmacokinetic set (PKS).

The population pharmacokinetics (popPK) of vortioxetine in children will be analysed through non-linear mixed effect analysis and will be described in a separate popPK analysis plan.

16.8.8 Safety Analyses

The safety analyses will be based on the APES and the FAS.

All safety endpoints will be reported for the 12-week open-label period and the 26-week double-blind period separately.

16.8.9 Analysis of Adverse Events

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

- *pre-treatment adverse event* – an adverse event that starts on or after the date the patient signed the *Informed Consent Form* and prior to the date of first dose of IMP
- *treatment-emergent adverse event* (TEAE) – an adverse event that starts or increases in intensity on or after the date of first dose of IMP

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

Allocation of TEAEs to Study Periods

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

16.8.10 Analysis of Other Safety Endpoints

Absolute and change from baseline in clinical safety laboratory tests (estradiol for girls, LH, FSH), Tanner staging, and effects on menstrual cycle, vital signs, height, weight, BMI and ECG parameters will be summarized by treatment group. Potentially clinically significant (PCS) safety laboratory test values will be flagged and summarized.

GBI scores (using the 10-item mania subscale), and C-SSRS scores will be summarized using descriptive statistics.

16.9 Interim Analyses

No interim analysis is planned.

16.10 Sample Size and Power

The calculation of power is based on a log-rank test for the time to relapse at a one-sided 5% level of significance using SAS Proc Power. A sample size of 80 randomized patients (40 patients per treatment group) will provide at least 80% power to find a difference between

vortioxetine and placebo as statistically significant, when expecting cumulative relapse rates at 0.42 and 0.69 over 26 weeks, respectively corresponding to a hazard-ratio of 2.15. The assumption of relapse rates (42% and 69% over 6 months for vortioxetine and placebo, respectively) is based on observed rates from a similarly designed relapse-prevention study of fluoxetine in paediatric patients with MDD who had an adequate response after 12 weeks of acute treatment.[14]

It is anticipated that approximately 60% of *de novo* patients enrolled into the open-label period will qualify for the double-blind study period. To achieve 80 randomized patients, 150 patients are estimated to be enrolled into the study (depending on number and randomization rate of *de novo* and rollover patients).

16.11 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 ICON Plc.

The SAP will be finalised prior to the first subject enrolled in the study.

17 Clinical Study Report and Publications

17.1 Data Ownership

The data collected in this study are the property of Lundbeck.

17.2 Clinical Study Report

Upon completion of the study, a *Clinical Study Report* will be prepared by ICON.

17.3 Summary of Clinical Study Results

Upon completion of the study and when the study results are available, the patient has the right to be informed by the investigator about the overall study results.

17.4 Publications

The results of this study will be submitted for publication.

Lundbeck will submit results information to:

- ClinicalTrials.gov
- European Union Drug Regulating Authorities Clinical Trials (EudraCT)

The primary publication based on this study must be published before any secondary publications. Authors of the primary publication must fulfil the criteria defined by the International Committee of Medical Journal Editors (ICMJE).[38]

18 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*.

19 Finance

19.1 Site Agreements

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

19.2 Financial Disclosure

All the investigators, including sub-investigators, and raters participating in the study must complete a *Financial Disclosure Form*.

19.3 Equipment

Equipment rented by ICON on behalf of Lundbeck that has been provided to the sites 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 Authorization

Clinical Study Protocol
Authentication and Authorization

Study title: A double-blind, randomized, placebo-controlled, multicentre, relapse-prevention study of vortioxetine in paediatric patients aged 7 to 11 years with Major Depressive Disorder

Study No.: 13546A

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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 of Biostatistics: [redacted]

Head of GPS Medical Safety [redacted]

Authorization

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

Head of Clinical Development - 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, recent and concomitant medications that are disallowed or allowed with restrictions with respect to their use prior to or during the study are listed.

Drug Class		Disallowed prior to Baseline	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)		2 weeks	X	X	Psychostimulants agents (e.g. methylphenidate or amphetamine), are allowed if the patient as a minimum has had a 4-week stable dose period, prior to the study treatment.
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		2 weeks	X	X	
Antiacne agents		2 weeks	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		2 weeks	X	X	
Antidepressants		2 weeks (5 weeks for fluoxetine)	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		2 weeks	X	X	
Antinauseants (including dopamine antagonists)		2 weeks	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	

Drug Class	Disallowed prior to Baseline	Disallowed (X) During the Study for		
		Chronic Use	Episodic Use	Comments or Exceptions
Antipsychotics	6 weeks (6 months for depot)	X	X	
Anxiolytics	2 weeks	X	X	
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, valerian, ginkgo biloba)	2 weeks	X	X	
Hormones		X	X	Only thyroid hormone replacement, contraceptives and progesterone replacement therapy are al-
Hypoglycaemic agents			X	
Insuline			X	
Mood stabilisers (including lithium, valproate, valpromide)	6 weeks	X	X	
Muscle relaxant	2 weeks	X	X	
Psychotropic agents not otherwise specified (including, tryptophan, and dopamine agonists)	2 weeks	X	X	
Sedatives/hypnotics[b]	2 weeks	X	X	Only zolpidem, zopiclone or zaleplon allowed, for severe insomnia, with a maximum of 2 nights per week. Only 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 two weeks prior to Screening Visit, until Visit 17.